INSTITUTO NACIONAL DA PROPRIEDADE INDUSTRIAL

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Apresentação de subsídios ao exame técnico

Número do Processo: BR 11 2024 010162 2

Dados do Interessado

Interessado 1 de 8

Nome ou Razão Social: ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS
Tipo de Pessoa: Pessoa Jurídica
CPF/CNPJ: 29263068000145
Nacionalidade: Brasileira
Qualificação Jurídica: Associação com intuito não econômico
Endereço: Avenida Presidente Vargas, 446 - 13° andar
Cidade: Rio de Janeiro
Estado: RJ
CEP: 20071907
País: Brasil
Telefone: (21) 2223-1040
Fax:
Email: carolinne@abiaids.org.br

Interessado 2 de 8

Nome ou Razão Social: FEDERAÇÃO NACIONAL DOS FARMACÊUTICOS - FENAFAR
Tipo de Pessoa: Pessoa Jurídica
CPF/CNPJ: 00679357000148
Nacionalidade: Brasileira
Qualificação Jurídica: Associação com intuito não econômico
Endereço: Rua Barão de Itapetininga, 255, 11º andar, conjunto 1105, Centro
Cidade: São Paulo
Estado: SP
CEP:
País: BRASIL
Telefone:
Fax:
Email:

Interessado 3 de 8

Nome ou Razão Social: FÓRUM ONG AIDS RS - FOARS
Tipo de Pessoa: Pessoa Jurídica
CPF/CNPJ: 07959716000160
Nacionalidade: Brasileira
Qualificação Jurídica: Associação com intuito não econômico
Endereço: Rua dos Andradas, 1560, 6º andar, Centro Histórico
Cidade: Porto Alegre
Estado: RS
CEP:
País: BRASIL
Telefone:
Fax:
Email:

Interessado 4 de 8

Nome ou Razão Social: GRUPO DE RESISTÊNCIA ASA BRANCA - GRAB

Tipo de Pessoa: Pessoa Jurídica

CPF/CNPJ: 41302803000188

Nacionalidade: Brasileira

Qualificação Jurídica: Associação com intuito não econômico

Endereço: Rua K (Ipê Amarelo), 1022, Itaperi

Cidade: Fortaleza

Estado: CE

CEP:

País: BRASIL

Telefone:

Fax:

Email:

Interessado 5 de 8

Nome ou Razão Social: MOVIMENTO NACIONAL DE DOENÇAS NEGLIGENCIADAS - MNDN

Tipo de Pessoa: Pessoa Jurídica

CPF/CNPJ: 59935301000150

Nacionalidade: Brasileira

Qualificação Jurídica: Associação com intuito não econômico

Endereço: Rua Monte das Oliveiras, 104, quadra 01, Real Parque

Cidade: Cuiabá

Estado: MT

CEP:

País: BRASIL

Telefone:

Fax:

Email:

Interessado 6 de 8

Nome ou Razão Social: ASSOCIAÇÃO DE GAYS E AMIGOS DE NOVA IGUAÇU - AGANI
Tipo de Pessoa: Pessoa Jurídica
CPF/CNPJ: 00790968000169
Nacionalidade: Brasileira
Qualificação Jurídica: Associação com intuito não econômico
Endereço: Rua Marcial, 42, Juscelino
Cidade: Rio de Janeiro
Estado: RJ
CEP:
País: BRASIL
Telefone:
Fax:
Email:

Interessado 7 de 8

Nome ou Razão Social: REDE NACIONAL DAS PESSOAS QUE VIVEM COM HIV E AIDS - NÚCLEO PE - RNP+ PE
Tipo de Pessoa: Pessoa Fisica
CPF/CNPJ: 45021295420
Nacionalidade: Brasileira
Qualificação Física: Presidente, diretor, gerente e supervisor de organismo internacional e de organização não-governamental
Endereço: Rua dos Medicis, 68 - Boa Vista
Cidade: Recife
Estado: PE
CEP:
País: BRASIL
Telefone:
Fax:
Email:

Interessado 8 de 8

Nome ou Razão Social: REDE ESTADUAL DE ADOLESCENTES E JOVENS VIVENDO E CONVIVENDO COM HIV/AIDS DO RIO DE JANEIRO - REDE JOVEL RIO+
Tipo de Pessoa: Pessoa Fisica
CPF/CNPJ: 11270467727
Nacionalidade: Brasileira
Qualificação Física: Presidente, diretor, gerente e supervisor de organismo internacional e de organização não-governamental
Endereço: Rua Cinco de Julho, 335 - sala 301, Copacabana
Cidade: Rio de Janeiro
Estado: RJ
CEP:
País: BRASIL
Telefone:
Fax:
Email:

Referência Petição

Pedido : BR112024010162-2

Documentos anexados

Tipo Anexo	Nome
Esclarecimento	Subsidio BR112024010162.pdf
D1 (pág 1-200)	D1 (pág 1-200).pdf
D1 (pág 201-427)	D1 (pág 201-427).pdf
D2-D8	D2-D8.pdf
Procuração	Documentos Abia (anexos 9-11).pdf
Procuração	Documentos Fenafar (anexos 12-14).pdf
Procuração	Documentos FOARS (anexos 15-17).pdf
Procuração	Documentos GRAB (anexos 18-20).pdf
Procuração	Documentos MNDN (anexos 21-23).pdf
Procuração	Documentos Agani (anexos 24-26).pdf
Comprovante pagamento	Boleto+comprovante.pdf

Declaração de veracidade

☑ Declaro, sob as penas da lei, que todas as informações acima prestadas são completas e verdadeiras.

GRUPO DE TRABALHO SOBRE PROPRIEDADE INTELECTUAL
GTPI

ABIA

AO ILUSTRÍSSIMO SENHOR DIRETOR DE PATENTES DO INSTITUTO NACIONAL DA PROPRIEDADE INDUSTRIAL

Número do pedido: **BR112024010162-2 - WO2023102239 - PCT US2022051734**
Data de depósito: **02/12/2022**
Prioridade unionista: **US 63/356,889 29/06/2022**
US 63/285,730 03/12/2021
Depositante: **Gilead Sciences, Inc. (US)**
Título: **Compostos terapêuticos para infecção por vírus HIV**

ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS - ABIA, associação civil sem fins lucrativos, inscrita no CNPJ/MF sob no 29.263.068/0001-45, com sede na Avenida Presidente Vargas, 446, 13º andar, Centro - Rio de Janeiro - RJ CEP 20071-907, na pessoa de seu representante nos termos de seu Estatuto Social (anexos 9 e 10), por seu advogado (anexo 11);

FEDERAÇÃO NACIONAL DOS FARMACÊUTICOS - FENAFAR, pessoa jurídica de direito privado, sem fins lucrativos, inscrita no CNPJ sob o nº 00.679.357/0001-48, com sede à Rua Barão de Itapetininga, 255, 11º andar, Conjunto 1105, Centro, São Paulo - SP, na pessoa de seu representante legal nos termos de seu Estatuto Social (anexos 12 e 13), por sua advogada (anexo 14);

FÓRUM ONG AIDS RS - FOARS, pessoa jurídica de direito privado, sem fins lucrativos, inscrita no CNPJ sob o nº 07.959.716/0001-60, com sede à Rua dos Andradas, 1560, 6º andar, Centro Histórico, Porto Alegre - RS, na pessoa de seu representante legal nos termos de seu Estatuto Social (anexos 15 e 16), por sua advogada (anexo 17);

GRUPO DE RESISTÊNCIA ASA BRANCA - GRAB, pessoa jurídica de direito privado, sem fins lucrativos, inscrita no CNPJ sob o nº 41.302.803/0001-88, com sede à Rua K (Ipê Amarelo), 1022, Itaperi, Fortaleza - CE, na pessoa de seu representante legal nos termos de seu Estatuto Social (anexos 18 e 19), por sua advogada (anexo 20);

MOVIMENTO NACIONAL DE DOENÇAS NEGLIGENCIADAS - MNDN, pessoa jurídica de direito privado, sem fins lucrativos, inscrita no CNPJ sob o nº 59.935.301/0001-50, com sede à Rua Monte das Oliveiras, 104, quadra 01, Real

Parque, Cuiabá - MT, na pessoa de seu representante legal nos termos de seu Estatuto Social (anexos 21 e 22), por sua advogada (anexo 23);

ASSOCIAÇÃO DE GAYS E AMIGOS DE NOVA IGUAÇU - AGANI, pessoa jurídica de direito privado, sem fins lucrativos, inscrita no CNPJ sob o nº 00.790.968/0001-69, com sede à Rua Marcial, 42, Juscelino, Mesquita - RJ, na pessoa de seu representante legal nos termos de seu Estatuto Social (anexos 24 e 25), por sua advogada (anexo 26);

REDE NACIONAL DAS PESSOAS QUE VIVEM COM HIV E AIDS - NÚCLEO PE - RNP+ PE, pessoa física, representada por José Candido da Silva por meio do CPF nº 450.212.954-20, com sede à Rua dos Medicis, 68, Boa Vista, Recife - PE;

REDE ESTADUAL DE ADOLESCENTES E JOVENS VIVENDO E CONVIVENDO COM HIV/AIDS DO RIO DE JANEIRO - REDE JOVEM RIO+, pessoa física, representada por Lucas Barcellos dos Santos por meio do CPF nº 112.704.677-27, com sede à Rua Cinco de Julho, 335 - sala 301, Copacabana, Rio de Janeiro - RJ

vêm respeitosamente à presença de Vossa Senhoria, com fulcro no artigo 31 da Lei nº 9.279/1996 - Lei da Propriedade Industrial (LPI), apresentar o presente

SUBSÍDIO AO EXAME TÉCNICO

do pedido de patente **BR112024010162-2**, com base nos fatos e fundamentos a seguir.

1. DA LEGITIMIDADE DAS ORGANIZAÇÕES PROPONENTES, DA MOTIVAÇÃO E DA TEMPESTIVIDADE DO PRESENTE SUBSÍDIO AO EXAME TÉCNICO

A concessão de uma patente confere um privilégio temporário de exploração com exclusividade do seu objeto, durante o qual o titular da patente é o único autorizado a explorar a invenção. Essa situação de monopólio legal é excepcional e só deve existir nos casos em que o objeto da patente cumpra todos os requisitos e condições estabelecidos em lei para sua concessão. O objeto do presente pedido de patente, como será detalhado abaixo, é de extrema importância para saúde pública brasileira, uma vez que se trata de **compostos, composição e uso** para fabricação de medicamento para prevenção ou tratamento de HIV, entre eles o **pró-fármacos do lenacapavir**.

O artigo 31 da Lei nº 9.279/1996 (LPI)[1] estabelece que terceiros interessados podem enviar informações para subsidiar o exame de pedidos de patentes.

> Art. 31. Publicado o pedido de patente e até o final do exame, será facultada a apresentação, pelos interessados, de documentos e informações para subsidiarem o exame. Parágrafo único. O exame não será iniciado antes de decorridos 60 (sessenta) dias da publicação do pedido.

A **legitimidade das organizações** que apresentam o presente subsídio ao exame técnico, nos termos do artigo 31 da LPI, verifica-se diante de suas históricas e respeitadas trajetórias na defesa dos direitos humanos, com ênfase para o direito à saúde e acesso a tratamento e assistência farmacêutica de qualidade, além de ativa atuação no campo da implementação de políticas públicas na área de propriedade intelectual, com vistas à primazia do interesse público.

A **Associação Brasileira Interdisciplinar de Aids (Abia)** é uma associação civil, de natureza filantrópica, sem fins lucrativos. A Abia foi fundada em 12 de março de 1987 e é uma das mais antigas ONG dedicadas ao combate da epidemia de HIV no Brasil e à garantia de direitos às pessoas vivendo com HIV, tendo como um dos seus fundadores o sociólogo Herbert de Souza (o “Betinho”), figura de reconhecida importância na vida pública brasileira. A Abia segue como uma das mais conceituadas e reconhecidas entidades sobre a matéria no Brasil e com amplo reconhecimento entre seus pares no âmbito nacional e internacional, e conta, na sua composição, com pesquisadores, profissionais e ativistas de notório saber nessa temática, considerados referências em seus campos de atuação no Brasil. Mais informações em: www.abiaids.org.br.

A Abia coordena o **Grupo de Trabalho sobre Propriedade Intelectual (GTPI) da Rede Brasileira pela Integração dos Povos (Rebrip)**. A Rebrip congrega organizações da sociedade civil brasileira para acompanhar e monitorar os acordos comerciais nos quais o governo brasileiro está envolvido, a fim de avaliar e minimizar potenciais impactos no cotidiano da população e em políticas públicas que visam assegurar a efetivação dos direitos humanos no Brasil. Mais informações sobre a Rebrip estão disponíveis em www.rebrip.org.br. Um dos temas relevantes no âmbito da discussão sobre comércio e direitos humanos refere-se à propriedade intelectual, motivo pelo qual a Rebrip constituiu um grupo de trabalho para encaminhar as reivindicações da sociedade civil sobre esta questão, fundado em 2003. O GTPI reúne diversas entidades da sociedade civil e busca discutir, acompanhar e incidir no tema

[1] Brasil. Lei nº 9.279, de 14 de maio de 1996. Regula direitos e obrigações relativos à propriedade industrial. Brasília, DF: Presidência da República, 15 maio 1996.

da propriedade intelectual e, sobretudo, mitigar o impacto dos efeitos negativos do atual sistema de patente no acesso aos medicamentos essenciais da população brasileira. Mais informações sobre o GTPI/Rebrip podem ser consultadas em www.deolhonaspatentes.org.

A **Federação Nacional dos Farmacêuticos (Fenafar)** é uma entidade representativa da categoria farmacêutica a nível nacional. Fundada em 25 de outubro de 1974, possui hoje 22 sindicatos filiados. A Fenafar teve papel decisivo no processo de debate que culminou na constituição do Sistema Único de Saúde e na construção da Política Nacional de Assistência Farmacêutica. Nesses 49 anos, a Fenafar construiu uma história de lutas na promoção de ações que envolvem o medicamento, desde a sua produção até a orientação correta para o usuário sobre o seu uso racional. Essa luta sempre esteve vinculada à concepção da Saúde como direito de todos para a construção de um país menos desigual, mais soberano e desenvolvido. Mais informações em: www.fenafar.org.br.

O **Fórum ONG Aids - Rio Grande do Sul (FOARS)** foi fundado em 1999, reúne 48 organizações gaúchas voltadas à prevenção e conscientização acerca da epidemia de HIV. Com sede em Porto Alegre, atua em diferentes regiões do estado pela melhoria da qualidade de vida e pelos direitos das pessoas soropositivas. Algumas das suas ações são: articular a força das diversas ONGs que integram o Fórum para otimizar os resultados; conscientização acerca da prevenção; incentivo à aceitação dos portadores de si mesmos; desconstrução de tabus e preconceitos sobre a doença; melhora da qualidade de vida para pessoas vivendo com HIV; participar da formulação de políticas públicas inclusivas de prevenção e controle da aids; denunciar todas as formas de omissão, transgressão e violação dos direitos humanos, civis, políticos e sociais das pessoas que vivem com HIV. Mais informações em: https://www.forumongaidsrs.org/.

O **Grupo de Resistência Asa Branca (GRAB)** foi fundado em 1989 em Fortaleza, Ceará. Com o impacto da aids sobre a comunidade de gays, bissexuais e travestis na década de 1990, o apoio aos direitos das pessoas vivendo com HIV/aids (PVHA) tornou-se também uma das bandeiras de luta do GRAB. Essa bandeira foi incorporada à missão da organização. O GRAB é uma organização não governamental, sem fins lucrativos, reconhecida de utilidade pública municipal, que defende a livre orientação sexual e a defesa das identidades de gênero e desenvolve há 34 anos diversas ações comunitárias, *advocacy* e controle social em prol da cidadania de lésbicas, gays, bissexuais, travestis, transexuais e intersexo (LGBTI+), nas áreas da cultura, saúde, educação e direitos humanos. Mais informações em: www.grab.net.br.

O **Movimento Nacional de Doenças Negligenciadas (MNDN)** é uma iniciativa comprometida em transformar realidades, dar voz às comunidades afetadas e combater as desigualdades que perpetuam as doenças tropicais negligenciadas (DTN). O MNDN foi fundado em 2024, após o oitavo Fórum Social Brasileiro, como uma resposta à invisibilidade dessas enfermidades, que afetam milhões de pessoas no Brasil e no mundo, especialmente as populações mais vulneráveis. O MNDN atua na criação e monitoramento de políticas públicas voltadas ao enfrentamento das DTN, realiza campanhas e ações educativas para a sociedade, capacita pessoas afetadas para que se tornem agentes de mudança em suas comunidades, colabora com organizações nacionais e internacionais, setores públicos e privados e luta pelo acesso ao diagnóstico, tratamento e às condições básicas de vida, como moradia digna e saneamento básico. Mais informações em: https://movimentonacional.org/

A **Associação de Gays e Amigos de Nova Iguaçu (Agani)**, conhecida pelo nome fantasia de Associação de Gays e Amigos de Nova Iguaçu, Mesquita e Rio de Janeiro (Aganim) é uma organização não governamental sem fins lucrativos, criada em 17 de dezembro de 1988 no bairro Juscelino, até então município de Nova Iguaçu. Com atuação extensiva a vários municípios da baixada fluminense, o grupo procura manter um equilíbrio entre suas atividades nas áreas de prevenção das DST/Aids e garantir a construção de uma cultura em defesa dos direitos e do respeito às diversidades, afirmando a heterogeneidade e a pluralidade como valores da nossa sociedade.

A **Rede Nacional das Pessoas que vivem com HIV e Aids - Núcleo PE (RNP+ PE)** é uma organização estadual de pessoas vivendo com HIV/AIDS fundada em 1995, que atua na mobilização, integração e promoção do fortalecimento das pessoas sorologicamente positivas para o vírus HIV, independente de gênero, orientação sexual, credo, raça/cor ou etnia e nacionalidade. Além disso, atua na prevenção e promoção da saúde, por meio de orientações, disponibilização de preservativos, palestras, capacitações em saúde, e na participação social, por meio de *advocacy* e incidência política. A RNP-PE é uma organização reconhecidamente importante nas ações de enfrentamento da epidemia de Aids no Brasil junto aos gestores das três esferas de governo e participa ativamente do movimento nacional de luta contra a Aids, juntamente com outras redes, fóruns e parceiros.

A **Rede Estadual de Adolescentes e Jovens Vivendo e Convivendo com HIV/AIDS do Rio de Janeiro (Rede Jovem Rio+)** é um movimento social estadual, sem vínculo político-partidário ou religioso, construído prioritariamente por adolescentes e jovens entre 12 e 29 anos, atuando na inclusão social, na promoção

do fortalecimento biopsicossocial e do protagonismo destes, independentemente de sexo, identidade de gênero, sexualidade, credo, cor, etnia, nacionalidade, naturalidade, escolaridade, classe social e sorologias.

A presente **petição é motivada** pela apresentação das modificações ao pedido protocolada pela depositante sob n° 870250069985 em 06/08/2025, assim como pelo pedido de exame de invenção protocolado sob o n° 800250332581 na mesma data.

A presente subsidiante, verificando que o pedido de patente **BR112024010162-2** (doravante referido como **BR0162**) não é passível de patenteabilidade, utiliza-se da permissão dada pelo artigo 31 da Lei de Propriedade Industrial (LPI) n° 9.279/1996 e vem perante V. Sªs. apresentar apontamentos como forma de subsidiar o exame técnico do referido pedido de patente.

Ademais, a **presente petição é tempestiva** nos termos do aludido artigo 31 da LPI e artigo 32 da Instrução Normativa n° 30/2013[2].

2. DO PROCESSO ADMINISTRATIVO

Os principais eventos já ocorridos no processo administrativo do pedido BR0162 estão resumidos abaixo:

1. Em 02/12/2022, o pedido de patente BR112024010162-2 foi depositado pela Gilead Sciences, por meio da entrada em fase nacional do pedido PCT/US2022/051734, cuja data de prioridade mais antiga é 03/12/2021 referente ao pedido norte-americano US 63/285,730. O quadro reivindicatório depositado continha 83 reivindicações, sendo 21 independentes.
2. Em 06/08/2025, o quadro reivindicatório foi alterado e passou a conter 43 reivindicações, sendo 17 independentes em 3 categorias: composto (14 reivindicações independentes), composição e uso.
3. O pedido de exame foi peticionado em 06/08/2025.

[2] Instituto Nacional da Propriedade Industrial - INPI. Instrução Normativa nº 30, de 4 de dezembro de 2013. Estabelecimento de normas gerais de procedimentos para explicitar e cumprir dispositivos da Lei de Propriedade Industrial - Lei nº 9279, de 14 de maio de 1996, no que se refere às especificações dos pedidos de patente. [S. l.].

3. LENACAPAVIR, PRÓ-FÁRMACOS, PATENTES, PREÇO E ACESSO

O lenacapavir (GS-6207) é um inibidor do capsídeo do HIV-1, o primeiro desta classe, desenvolvido em formulações oral e injetável de longa duração, aprovado tanto para prevenção (Yeztugo®) quanto para tratamento de pessoas com HIV multirresistente com extensa experiência em tratamento (Sunlenca®).

Para o tratamento do HIV-1, o lenacapavir demonstrou excelente sinergia em combinação com outros antivirais e não apresentou resistência cruzada conhecida com nenhuma outra classe de antirretrovirais atualmente aprovada, além de possuir atividade antiviral em níveis picomolares. Ensaios clínicos como parte do tratamento de primeira linha e como parte de um regime de troca para pessoas com supressão viral estão em andamento.

Para a prevenção do HIV, em 2024, foram anunciadas análises interinas dos estudos de fase 3, demonstrando 100% de eficácia para o uso experimental na prevenção do HIV em mulheres cisgênero (PURPOSE 1), redução das infecções por HIV em 96% e superioridade em relação ao uso diário de Truvada®[3] na prevenção do HIV em homens cisgêneros e pessoas com diversidade de gênero (PURPOSE 2). Esses resultados indicaram o potencial para mudar o rumo da prevenção do HIV, razão pela qual se tornou em destaque durante a 25ª Conferência Internacional de Aids e foi reconhecido como descoberta do ano em 2024 pela revista Science[4].

Ainda em 2024, a farmacêutica Gilead apresentou novos dados sobre um estudo clínico em andamento envolvendo a combinação oral de um **pró-fármaco do lenacapavir (GS-4182)** e um novo inibidor de integrase (GS-1720) para o tratamento do HIV. Entretanto, esses estudos foram interrompidos por determinação da agência norte-americana *Food and Drug Administration* (FDA), que impôs *clinical hold* (suspensão clínica, em tradução livre) aos ensaios envolvendo GS-1720 e/ou GS-4182 após a identificação de um sinal de segurança consistente em queda de células CD4+ e redução absoluta da contagem de linfócitos em um subgrupo de participantes expostos à combinação dos dois compostos[5].

O lenacapavir já foi registrado em alguns países, entre eles nos Estados Unidos da América (EUA/FDA), na Europa (EMA), na África do Sul (SAHPRA) e na Zâmbia (ZAMRA), contudo ainda não há registro sanitário aprovado no Brasil pela Agência Nacional de Vigilância Sanitária (Anvisa) – por isso ainda não há um preço nacional definido pela Câmara de Regulação do Mercado de Medicamentos (Cmed).

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[3] Nome comercial da combinação entre fumarato de tenofovir disoproxila e entricitabina.

[4] Cohen J. 2024 Breakthrough of the year. Science, 2024. Disponível em: https://www.science.org/content/article/breakthrough-2024.

[5] Gilead Sciences. Gilead provides update on clinical studies evaluating GS-1720 and/or GS-4182 for the treatment of HIV-1 infection, 2025. Disponível em: https://www.gilead.com/company/company-statements/2025/gilead-provides-update-on-clinical-studies-evaluating-gs-1720-and-or-gs-4182-for-the-treatment-of-hiv-1-infection

Nos EUA, o lenacapavir custa aproximadamente US$ 42.250 por ano para tratamento (Sunlenca®) e US$ 28.000 por ano para prevenção (Yeztugo®). Em outubro de 2024, a Gilead anunciou uma licença voluntária para produção de genéricos de lenacapavir em 120 países de baixa renda ou alta incidência, afirmando tratar-se de uma estratégia para acelerar o acesso. No entanto, esse acordo excluiu países que participaram dos ensaios clínicos, como o Brasil, e impôs cláusulas restritivas, como a proibição de combinações com outras formulações e a vedação de importação por países sem patente concedida ou que optem por uma licença compulsória.

Em contraste com os preços praticados nos EUA, a versão genérica do lenacapavir recém-lançada confirma as estimativas de Hill *et al*.[6] ao chegar ao mercado por cerca de US$ 40 por pessoa/ano[7], valor que ainda poderia ser reduzido para US$ 25 por pessoa/ano de acordo com a análise de custos de produção apresentada por Fortunak *et al*.[8], demonstrando que os preços praticados pela Gilead são totalmente dissociados dos custos reais.

A situação de monopólio de comercialização, viabilizada pela proteção da propriedade intelectual, é um dos fatores que impactam nos altos preços e restrição do acesso. Em pesquisa realizada, em bases de dados privadas e públicas, e análise do conteúdo dos pedidos de patente identificados, foi possível identificar cinco pedidos de patentes relacionados ao lenacapavir no Brasil (Quadro 1), três dos quais foram concedidos (BR112015021027-9, BR112018071678-2 e BR122020001791-0), um foi indeferido (BR122019025799-0) e um ainda está pendente de análise e decisão (BR112024010162-2 - para o qual está sendo feito o presente subsídio ao exame técnico).

Quadro 1: Pedidos de patente relacionados ao lenacapavir no Brasil.

PEDIDO DE PATENTE	TÍTULO	SITUAÇÃO PATENTÁRIA	DEPOSITANTE
BR112015021027-9 WO2014134566 PCT US2014019663	Compostos terapêuticos, seus usos, e composições farmacêuticas	Depósito: 28/02/2014 Patente concedida	Gilead Sciences, Inc. (US)

[6] Hill A, Levi J, Fairhead C, Pilkington V, Wang J, Johnson M, Layne J, Roberts D, Fortunak J. Lenacapavir to prevent HIV infection: current prices versus estimated costs of production. J Antimicrob Chemother. 2024 Nov 4;79(11):2906-2915. doi: 10.1093/jac/dkae305. Erratum in: J Antimicrob Chemother. 2024 Nov 4;79(11):3052. doi: 10.1093/jac/dkae356. PMID: 39225016.

[7] Unitaid. Unitaid, CHAI, and wits RHI enter into a landmark agreement with Dr. Reddy's to make HIV prevention tool lenacapavir affordable in LMICs, 2025. Disponível em: https://unitaid.org/news-blog/lenacapavir-for-hiv-prevention/

[8] Fortunak, Joseph Marian and Layne, Jevon and Johnson, Madison and Smalley, Samyah and Lutterodt, Andrew and Roberts, David and Tadesse, Endalkachew and Lu, Jasmine and Pinheiro, Eloan and Wolde-mariam, Messay and Hill, Andrew and Fairhead, Cassandra and Pepperrel, Toby, Lenacapavir to Prevent HIV Infection: Updated Estimated Costs of Production for Generic Treatments. Available at SSRN: https://ssrn.com/abstract=5293409 or http://dx.doi.org/10.2139/ssrn.5293409

BR122019025799-0 WO2014134566 PCT US2014019663	Compostos terapêuticos	Depósito: 28/02/2014 Pedido indeferido	Gilead Sciences, Inc. (US)
BR112018071678-2 WO2018035359 PCT US2017047416	Compostos terapêuticos úteis para o tratamento profilático ou terapêutico de uma infecção por vírus HIV e suas composições farmacêuticas	Depósito: 17/08/2017 Patente concedida	Gilead Sciences, Inc. (US)
BR122020001791-0 WO2018035359 PCT US2017047416	Usos de compostos terapêuticos no tratamento profilático ou terapêutico de uma infecção por vírus HIV	Depósito: 17/08/2017 Patente concedida	Gilead Sciences, Inc. (US)
BR112024010162-2 WO2023102239 PCT US2022051734	Compostos terapêuticos para infecção por vírus HIV	Depósito: 02/12/2022 Pedido pendente	Gilead Sciences, Inc. (US)

A sobreposição de pedidos de patente (*evergreening*), seguindo abordagens bem conhecidas de patenteamento secundário, gera expectativa de direito para os objetos reivindicados. Caso todos os pedidos sejam concedidos, o lenacapavir pode ficar sob monopólio patentário pelo menos até o ano 2042.

De acordo com o documento “Diretrizes para o exame de pedidos de patentes relacionados a produtos farmacêuticos” (Correa, 2016)[9], vários medicamentos são comercializados na forma de pró-fármacos. Essa abordagem pode resultar em uma primeira opção de comercialização, como nos casos do fumarato de tenofovir disoproxil e do sofosbuvir, mas também como um produto de segunda geração, como a desloratadina, o pró-fármaco da loratadina, lançado após o composto ativo.

Os pró-fármacos são uma abordagem bem conhecida no campo farmacêutico e, ainda assim, essa estratégia de extensão do monopólio patentário foi utilizada pela Gilead oito anos após o primeiro pedido de patente. Conforme indicam as evidências iniciais, esse pedido de patente relacionado a pró-fármacos do lenacapavir está relacionado a formulações orais de longa duração, que podem representar a próxima geração de formulações de longa duração após as formulações injetáveis atualmente disponíveis.

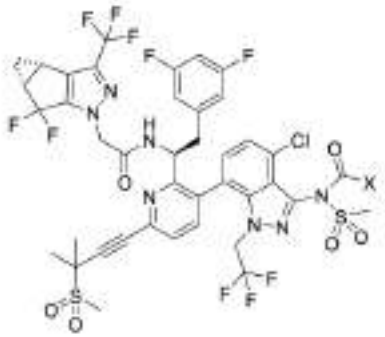
4. DA MATÉRIA REIVINDICADA NO PEDIDO BR112024010162-2

O pedido BR0162 é originário da entrada na fase nacional, via PCT, em 22/05/2024 apresentando um quadro reivindicatório contendo 83 reivindicações.

[9] Correa CM. Guidelines for the examination of patent applications relating to pharmaceuticals. United Nations Development Programme, 2016.

Em 06/08/2025, a depositante requereu o exame e apresentou modificação em seu quadro reivindicatório, que passou a ter as 43 reivindicações indicadas a seguir:

1. Composto caracterizado pelo fato de que apresenta a Fórmula I,



Fórmula I

ou um sal farmaceuticamente aceitável do mesmo, em que

X é $-NR_1R_2$, C_{1-10} alquila ou C_{2-6} alquenila,

sendo que a C_{1-10} alquila e a C_{2-6} alquenila são, cada uma independentemente, substituídas por 1 a 3 grupos Y;

cada Y é independentemente $-B(OH)_2$, -CN, halogênio, R_a, R_b, R_c, fenila, naftalenila, heteroarila monocíclica de 5 a 6 membros ou heteroarila bicíclica fundida de 8 a 10 membros,

sendo que a fenila, a naftalenila, a heteroarila monocíclica de 5 a 6 membros e a heteroarila bicíclica fundida de 8 a 10 membros são, cada uma independentemente, substituídas por 1 a 5 grupos R_3 ou

dois grupos Y no mesmo carbono, juntamente com o carbono ao qual estão fixados, formam uma C_{3-5} cicloalquila monocíclica;

R_1 é H ou C_{1-6} alquila, sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre -CN, halogênio, R_a, R_b e R_c;

R_2 é fenila ou heteroarila monocíclica de 5 a 6 membros, sendo que a fenila e a heteroarila monocíclica de 5 a 6 membros são, cada uma independentemente, opcionalmente substituídas por 1 a 3 grupos independentemente selecionados dentre -CN, halogênio, R_a, R_b, R_c e C_{1-6} alquila,

sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre -CN, halogênio, R_a, R_b e R_c;

cada R_3 independentemente é R_a, R_b, R_c, C_{1-6} alquila ou heteroarila monocíclica de 5 a 6 membros, sendo que a C_{1-6} alquila e a heteroarila monocíclica de 5 a 6 membros são, cada uma independentemente, opcionalmente substituídas por 1 a 3 grupos independentemente elecionados dentre -CN, halogênio, R_a, R_b e R_c;

cada R_a independentemente é $-P(O)(OH)_2$ ou $-OP(O)(OH)_2$;

cada R_b independentemente é $-C(O)R_4$, $-C(O)OR_4$, $-C(O)NR_5R_5$, $-C(O)C(O)OR_4$, $-S(O)_2R_4$, $-S(O)_2NR_5R_5$ ou $-S(O)_2OR_4$;

cada R_c independentemente é $-OR_4$, $-OC(O)R_4$, $-OC(O)C(O)OR_4$,$-(O\ (C_{1-4}\text{alquila}))_nOR_4$, $-NR_5R_5$, $-N^+R_5R_5R_{5a}$, $-NR_5C(O)R_4$, $-NR_5C(O)NR_5R_5$, $-NR_5C(O)OR_4$, $-NR_5C(O)C(O)OR_4$ ou $-NR_5S(O)_2R_4$;

cada R_4 independentemente é H ou C_{1-6} alquila, sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre -CN, halogênio, R_a, R_d e R_e;

cada R_5 independentemente é H, R_d, C_{1-6} alquila ou heteroarila monocíclica de 5 a 6 membros,

sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 3 grupos independentemente

selecionados dentre -CN, halogênio, =NR_{5a}, R_a, R_d, R_e, fenila, naftalenila e heteroarila bicíclica fundida de 8 a 10 membros,

sendo que a heteroarila monocíclica de 5 a 6 membros é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre -CN, halogênio, R_a, R_d e R_e;

cada R_{5a} independentemente é H ou C_{1-3} alquila;

cada R_d independentemente é $-C(O)R_6$, $-C(O)OR_6$, $-C(O)NR_7R_7$, $-C(O)C(O)OR_6$, $-S(O)_2R_6$, $-S(O)_2NR_7R_7$ ou $-S(O)_2OR_6$;

cada R_e independentemente é $-OR_6$, $-OC(O)R_6$, $-OC(O)C(O)OR_6$, $-NR_7R_7$, $-NR_7C(O)R_7$, $-NR_7C(O)NR_7R_7$, $-NR_7C(O)OR_6$, $-NR_7C(O)C(O)OR_6$ ou $-NR_7S(O)_2R_6$;

cada R_6 independentemente é H ou C_{1-6} alquila, sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados de CN, halogênio, R_a, R_f e R_g;

cada R_7 independentemente é H, R_f ou C_{1-6} alquila, sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre -CN, halogênio, R_a, R_f e R_g;

cada R_f independentemente é $-C(O)R_8$, $-C(O)OR_8$, $-C(O)NR_8R_8$, $-C(O)C(O)OR_8$, $-S(O)_2R_8$, $-S(O)_2NR_8R_8$, ou $-S(O)_2OR_8$;

cada R_g independentemente é $-OR_8$, $-OC(O)R_8$, $-OC(O)C(O)OR_8$, $-NR_8R_8$, $-NR_8C(O)R_8$, $-NR_8C(O)NR_8R_8$, $-NR_8C(O)OR_8$, $-NR_8C(O)C(O)OR_8$ ou $-NR_8S(O)_2R_8$;

cada R_8 independentemente é H ou C_{1-6} alquila, sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre OH, CN, halogênio, -C(O)OH e R_a;

n é 1, 2, 3, 4 ou 5; e

sendo que cada heteroarila monocíclica de 5 a 6 membros e heteroarila bicíclica fundida de 8 a 10 membros têm independentemente 1 a 4 heteroátomos de anel independentemente selecionados dentre N, O e S.

2. Composto, de acordo com a reivindicação 1, ou um sal farmaceuticamente aceitável do mesmo, caracterizado pelo fato de que

X é $-NR_1R_2$, C_{1-10}alquila ou C_{2-6} alquenila,

sendo que a C_{1-10} alquila e a C_{2-6} alquenila são, cada uma independentemente, substituídas por 1 a 3 grupos Y;

cada Y independentemente é -CN, halogênio, R_a, R_b, R_c, fenila ou naftalenila,

sendo que a fenila e a naftalenila são, cada uma independentemente, substituídas por 1 a 5 grupos R_3 ou

dois grupos Y no mesmo carbono, juntamente com o carbono ao qual estão fixados, formam uma C_{3-5} cicloalquila monocíclica;

R_1 é H ou C_{1-6} alquila, sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre -OH, CN, halogênio, -C(O)OH, e R_a;

R_2 é fenila ou heteroarila monocíclica de 5 a 6 membros, sendo que a fenila e a heteroarila monocíclica de 5 a 6 membros são, cada uma independentemente, opcionalmente substituídas por 1 a 3 grupos independentemente selecionados dentre -CN, halogênio, R_a, R_b, R_c e C_{1-6} alquila,

sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre -CN, halogênio, R_a, R_b e R_c;

cada R_3 independentemente é R_a, R_b, R_c, ou C_{1-6} alquila, sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre -CN, halogênio, R_a, R_b e R_c;

cada R_a independentemente é $-P(O)(OH)_2$ ou $-OP(O)(OH)_2$;

cada R_b independentemente é $-C(O)R_4$, $-C(O)OR_4$, $-C(O)NR_5R_5$, $-C(O)C(O)OR_4$, $-S(O)_2R_4$, $-S(O)_2NR_5R_5$ ou $-S(O)_2OR_4$;

cada R_c independentemente é $-OR_4$, $-OC(O)R_4$, $-OC(O)C(O)OR_4$,$-(O\ (C_{1-4}\text{alquila}))_nOR_4$, -

NR_5R_5, $-N^+R_5R_5R_{5a}$, $-NR_5C(O)R_4$, $-NR_5C(O)NR_5R_5$, $-NR_5C(O)OR_4$, $-NR_5C(O)C(O)OR_4$ ou $-NR_5S(O)_2R_4$;

cada R_4 independentemente é H ou C_{1-6} alquila, sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre -CN, halogênio, R_a, R_d e R_e;

cada R_5 independentemente é H, R_d ou C_{1-6} alquila, sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre -CN, halogênio, $=NR_{5a}$, R_a, R_d, R_e, fenila e naftalenila;

cada R_{5a} independentemente é H ou C_{1-3} alquila;

cada R_d independentemente é $-C(O)R_6$, $-C(O)OR_6$, $-C(O)NR_7R_7$, $-C(O)C(O)OR_6$, $-S(O)_2R_6$, $-S(O)_2NR_7R_7$ ou $-S(O)_2OR_6$;

cada R_e independentemente é $-OR_6$, $-OC(O)R_6$, $-OC(O)C(O)OR_6$, $-NR_7R_7$, $-NR_7C(O)R_7$, $-NR_7C(O)NR_7R_7$, $-NR_7C(O)OR_6$, $-NR_7C(O)C(O)OR_6$ ou $-NR_7S(O)_2R_6$;

cada R_6 independentemente é H ou C_{1-6} alquila, sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre OH, CN, halogênio, -C(O)OH e R_a;

cada R_7 independentemente é H ou C_{1-6} alquila, sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre -OH, -CN, halogênio, -C(O)OH e R_a;

n é 1, 2, 3, 4 ou 5; e

sendo que cada heteroarila monocíclica de 5 a 6 membros e heteroarila bicíclica fundida de 8 a 10 membros têm independentemente 1 a 4 heteroátomos de anel independentemente selecionados dentre N, O e S.

3. Composto, de acordo com qualquer uma das reivindicações 1 e 2, ou um sal farmaceuticamente aceitável do mesmo, caracterizado pelo fato de que:

X é $-NR_1R_2$, C_{1-10} alquila ou C_{2-4} alquenila,

sendo que a C_{1-10} alquila e a C_{2-4} alquenila são, cada uma independentemente, substituídas por 1 a 3 grupos Y;

cada Y é independentemente -OH, -CN, halogênio, R_a, $-NR_5R_5$, $-N^+R_5R_5R_{5a}$, $-C(O)NR_5R_5$, $-C(O)OR_4$, $-OC(O)R_4$,$-(O(C_{1-4}\text{ alquil})_nOR_4$ ou fenila,

sendo que a fenila é substituída por 1 a 5 grupos R_3 ou dois grupos Y no mesmo carbono, juntamente com o carbono ao qual estão fixados, formam uma C_{3-5} cicloalquila monocíclica;

R_1 é H ou C_{1-4} alquila, sendo que a C_{1-4} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre -OH, CN, halogênio, -C(O)OH, e R_a;

R_2 é fenila ou heteroarila monocíclica de 5 a 6 membros,

sendo que a fenila e a heteroarila monocíclica de 5 a 6 membros são, cada uma independentemente, opcionalmente substituídas por 1 a 3 grupos independentemente selecionados dentre -OH, -CN, halogênio, -C(O)OH, R_a e C_{1-6} alquila,

sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre -OH, -CN, halogênio, -C(O)OH, $-NR_5R_5$ e R_a;

cada R_3 independentemente é -OH, R_a, R_b ou C_{1-6} alquila, sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre -OH, -CN, halogênio, -C(O)OH, R_a e R_b;

cada R_a independentemente é $-P(O)(OH)_2$ ou $-OP(O)(OH)_2$;

cada R_b independentemente é $-C(O)OR_4$ ou $-C(O)NR_5R_5$;

cada R_4 independentemente é H ou C_{1-6} alquila, sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre -OH, -CN, halogênio, -(O)OH, $-NR_7R_7$ e R_a;

cada R_5 independentemente é H, $-C(O)OR_6$, $-C(O)C(O)OR_6$ ou C_{1-6} alquila, sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre -OH,

-CN, halogênio, -C(O)OR_6, =NR_{5a}, -NR_7R_7, R_a, R_b e fenila;

cada R_{5a} independentemente é H ou C_{1-3} alquila;

cada R_6 independentemente é H ou C_{1-6} alquila, sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre OH, CN, halogênio, -C(O)OH e R_a;

cada R_7 independentemente é H ou C_{1-3} alquila, sendo que a C_{1-3} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre -OH, -CN, halogênio, -C(O)OH e R_a;

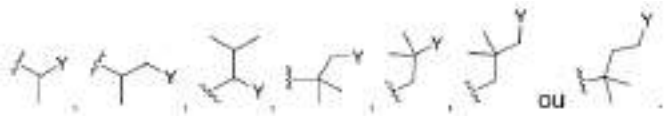
n é 1, 2, 3, 4 ou 5; e

sendo que cada heteroarila monocíclica de 5 a 6 membros e heteroarila bicíclica fundida de 8 a 10 membros têm independentemente 1 a 4 heteroátomos de anel independentemente selecionados dentre N, O e S.

4. Composto, de acordo com qualquer uma das reivindicações 1 a 3, ou um sal farmaceuticamente aceitável do mesmo, caracterizado pelo fato de que X é C_{1-10} alquila, sendo que a C_{1-10} alquila é substituída por 1 a 3 grupos Y.

5. Composto, de acordo com qualquer uma das reivindicações 1 a 4, ou um sal farmaceuticamente aceitável do mesmo, caracterizado pelo fato de que X é C_{1-6} alquila, sendo que a C_{1-6} alquila é substituída por um grupo Y.

6. Composto, de acordo com qualquer uma das reivindicações 1 a 5, ou um sal farmaceuticamente aceitável do mesmo, caracterizado pelo fato de que X substituído por Y é -CH_2Y, -CH_2CH_2Y, -$CH_2CH_2CH_2$Y, -$CH_2CH_2CH_2CH_2$Y,



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7. Composto, de acordo com qualquer uma das reivindicações 1 a 6, ou um sal farmaceuticamente aceitável do mesmo, caracterizado pelo fato de que X substituído por Y é

8. Composto, de acordo com qualquer uma das reivindicações 1 a 7, ou um sal farmaceuticamente aceitável do mesmo, caracterizado pelo fato de que um Y é fenila, sendo que a fenila é substituída por 1 a 5 grupos R_3.

9. Composto, de acordo com qualquer uma das reivindicações 1 a 8, ou um sal farmaceuticamente aceitável do mesmo, caracterizado pelo fato de que um Y é fenila, sendo que a fenila é substituída por 3 grupos R_3.

10. Composto, de acordo com qualquer uma das reivindicações 1 a 2 e 4 a 9, ou um sal farmaceuticamente aceitável do mesmo, caracterizado pelo fato de que cada R_3 independentemente é -C(O)OR_4, -C(O)NR_5R_5, -S(O)$_2R_4$, -S(O)$_2NR_5R_5$, -S(O)$_2OR_4$, -NR_5C(O)R_4, -NR_5C(O)NR_5R_5, -NR_5S(O)$_2R_4$, R_a ou C_{1-6} alquila,

sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre -OH, -CN, halogênio, -C(O)OR_4, -C(O)NR_5R_5 e R_a.

11. Composto, de acordo com qualquer uma das reivindicações 1 a 10, ou um sal farmaceuticamente aceitável do mesmo, caracterizado pelo fato de que cada R_3 independentemente é -OH, -C(O)OH, -C(O)NR_5R_5, R_a ou C_{1-3} alquila, sendo que a C_{1-3} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre -OH, -CN, halogênio, -C(O)OH, -C(O)NR_5R_5 e R_a.

12. Composto, de acordo com qualquer uma das reivindicações 1 a 11, ou um sal

farmaceuticamente aceitável do mesmo, caracterizado pelo fato de que cada R_3 independentemente é -OH, -C(O)OH, -C(O)NR_5R_5, R_a, metila, -$CH_2P(O)(OH)_2$, -$CH_2C(O)OH$ ou -$CH_2C(O)NR_5R_5$.

13. Composto, de acordo com qualquer um das reivindicações 1 a 12, ou um sal farmaceuticamente aceitável do mesmo, caracterizado pelo fato de que R_3 é -$OP(O)(OH)_2$ e 1 a 2 R_3 são C_{1-3} alquila, sendo que a C_{1-3} alquila é opcionalmente substituída por 1 a 3 grupos independentemente selecionados dentre -C(O)OH, -C(O)NR_5R_5 e R_a.

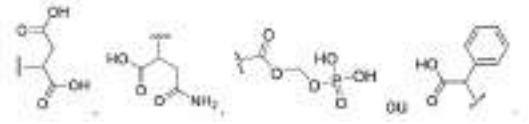
14. Composto, de acordo com qualquer uma das reivindicações 1 a 13, ou um sal farmaceuticamente aceitável do mesmo, caracterizado pelo fato de que um Y é fenila, sendo que a fenila é substituída por metila, -$OP(O)(OH)_2$ e -$CH_2C(O)OH$.

15. Composto, de acordo com qualquer uma das reivindicações 1 a 14, ou um sal farmaceuticamente aceitável do mesmo, caracterizado pelo fato de que R_4 independentemente é H ou C_{1-6} alquila, sendo que a C_{1-6} alquila é opcionalmente substituída por 1 a 2 grupos independentemente selecionados dentre -C(O)OH, -NR_7R_7 e R_a.

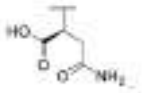
16. Composto, de acordo com qualquer uma das reivindicações 1 a 10 e 15, ou um sal farmaceuticamente aceitável do mesmo, caracterizado pelo fato de que cada R_5 independentemente é H, -C(O)OR_6, -C(O)C(O)OR_6 ou C_{1-4} alquila,

sendo que a C_{1-4} alquila é opcionalmente substituída por 1 a 2 grupos independentemente selecionados dentre -C(O)OH, -C(O)NH_2, =NR_{5a}, -NR_7R_7, R_a e fenila.

17. Composto, de acordo com qualquer uma das reivindicações 1 a 10 e 15 a 16, ou um sal farmaceuticamente aceitável do mesmo, caracterizado pelo fato de que cada R_5 independentemente é H, metila, -CH_2CO_2H, -$CH_2P(O)(OH)_2$, -$CH_2CH_2CO_2H$, -C(O)OCH_3, -C(=NH)NH_2, -C(O)C(O)OH,



18. Composto, de acordo com qualquer uma das reivindicações 1 a 10 e 15 a 17, ou um sal farmaceuticamente aceitável do mesmo, caracterizado pelo fato de que um R_5 é



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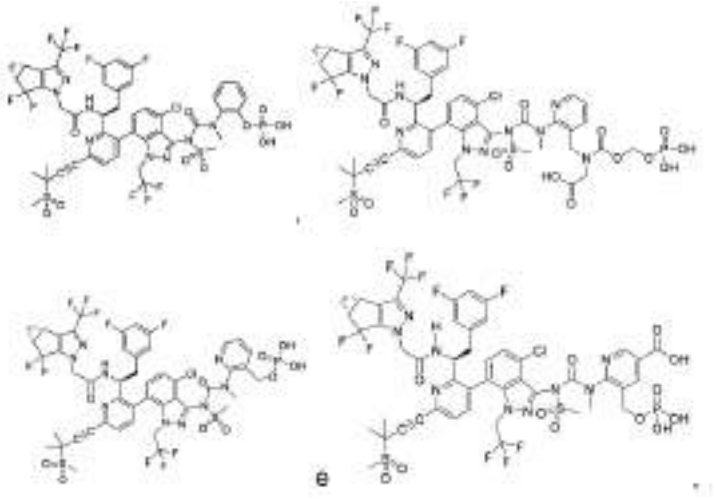
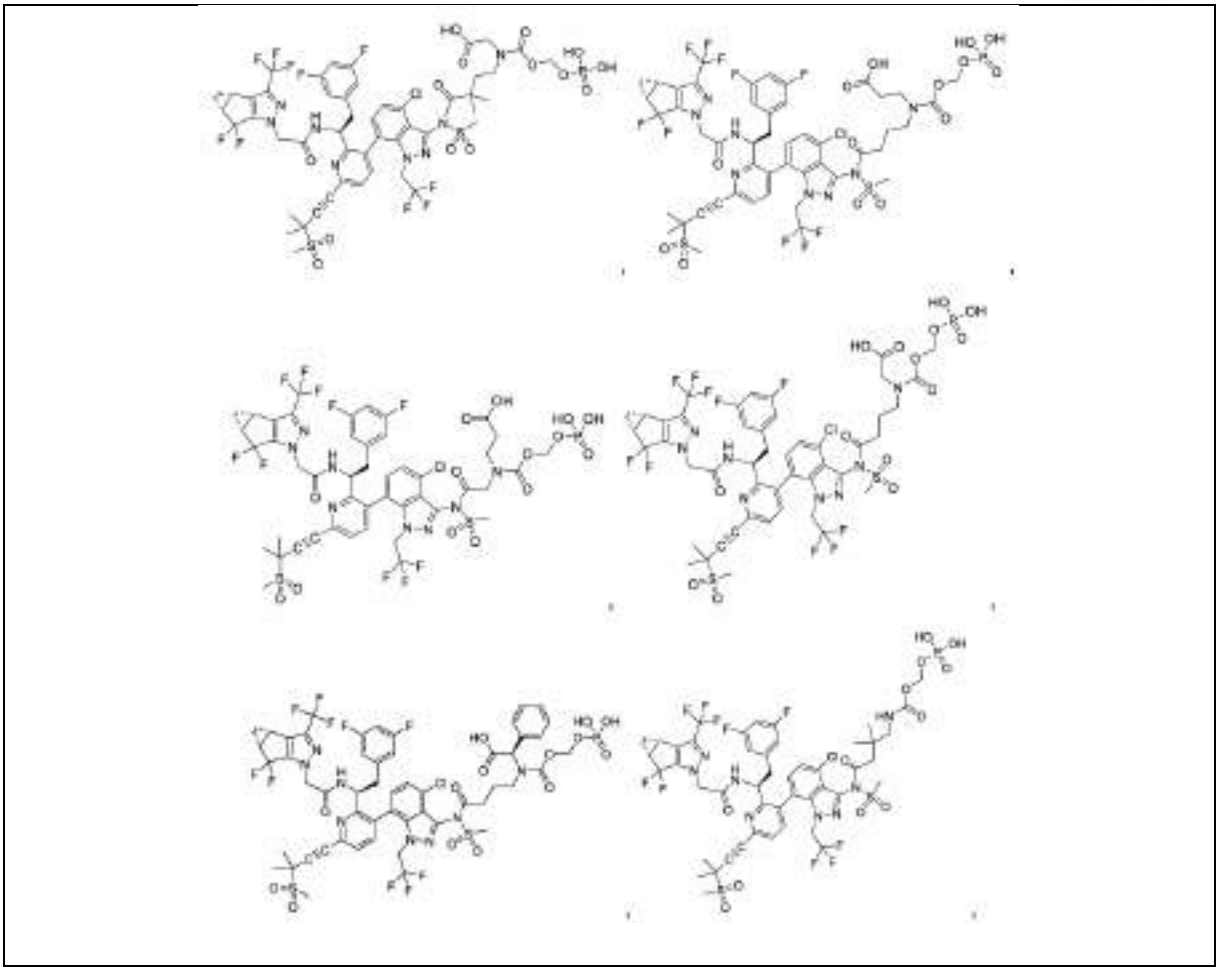
19. Composto caracterizado pelo fato de que é selecionado do grupo que consiste em:



ou um sal farmaceuticamente aceitável do mesmo.

20. Composto caracterizado pelo fato de que é selecionado do grupo que consiste em:



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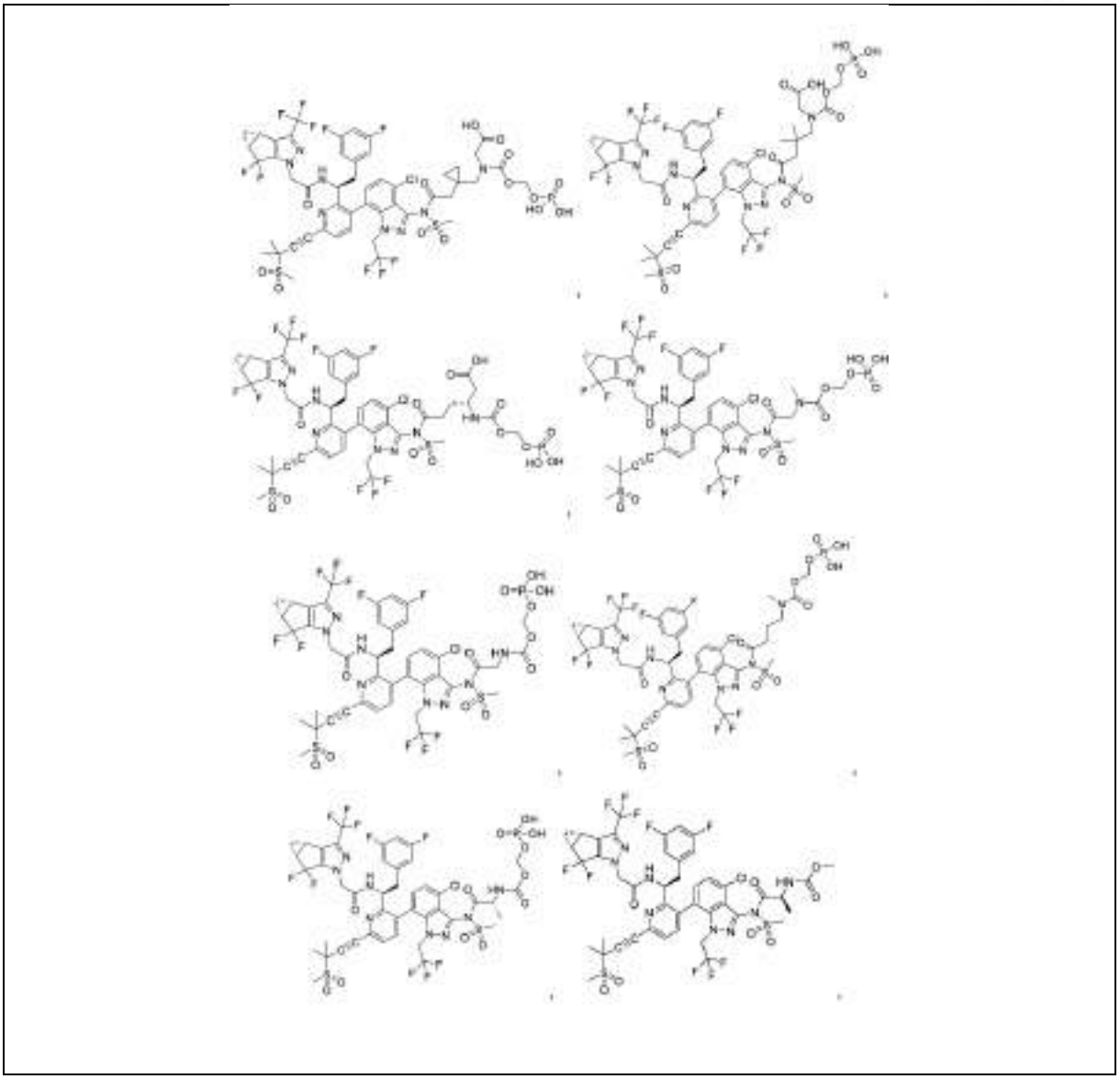

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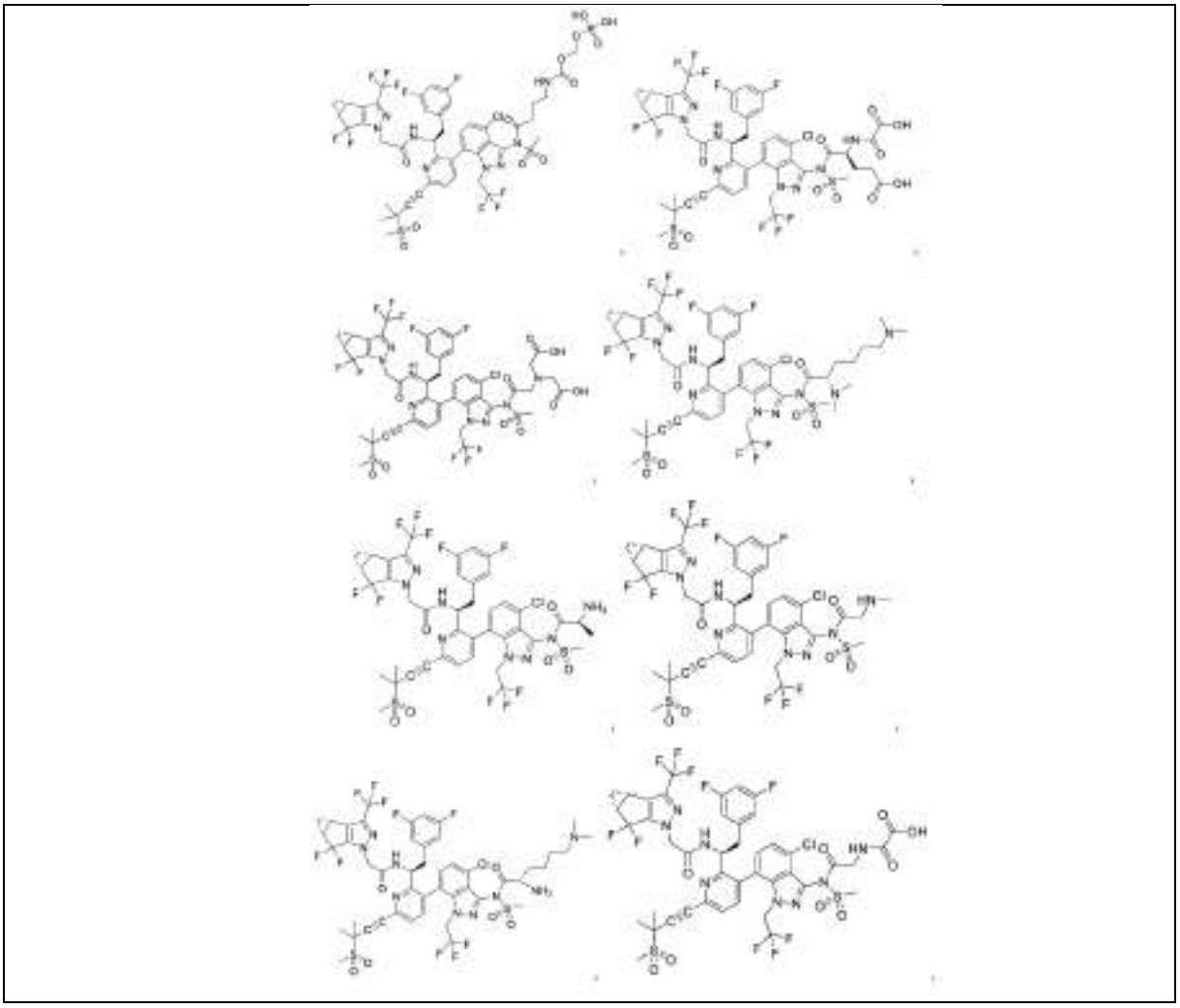

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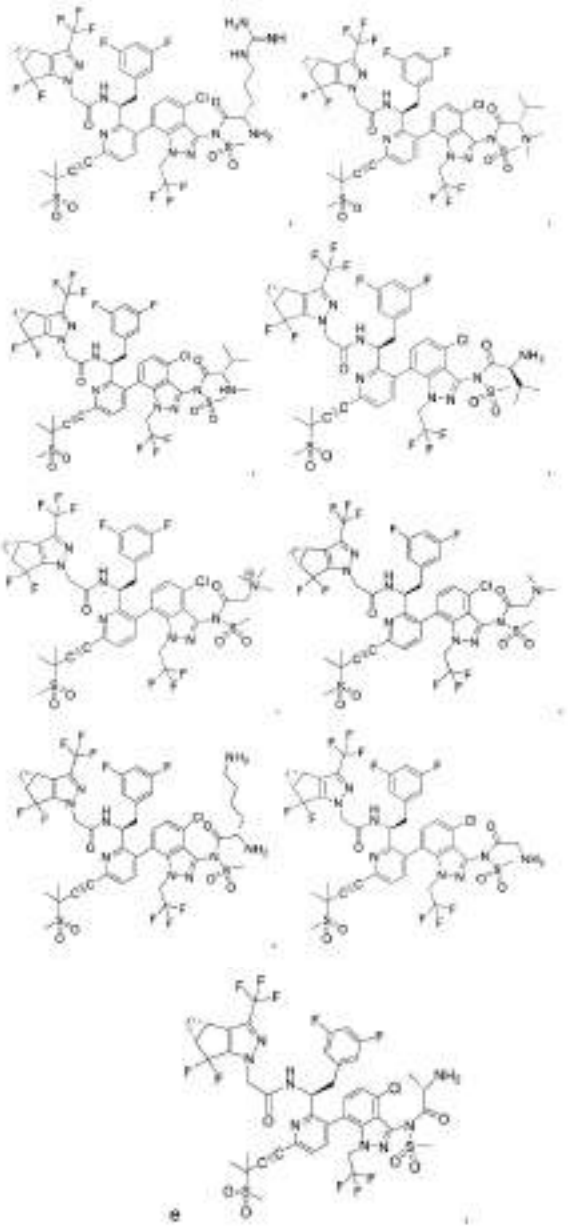

ou um sal farmaceuticamente aceitável do mesmo.

21. Composto caracterizado pelo fato de que é selecionado do grupo que consiste em:

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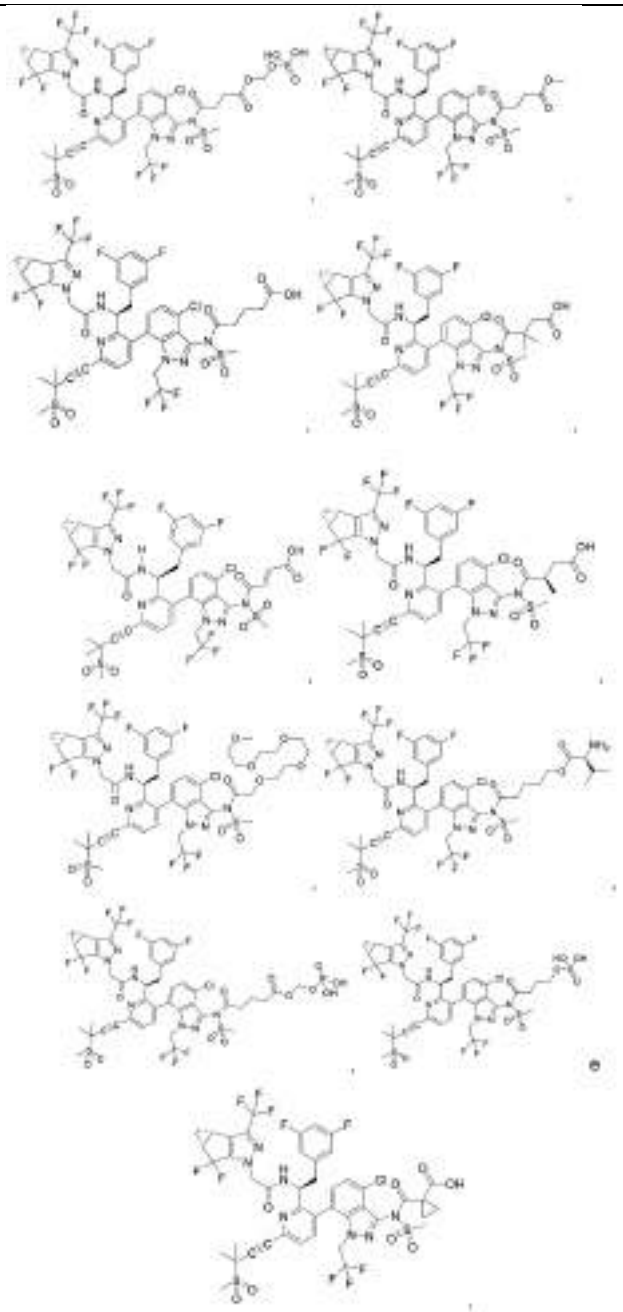

ou um sal farmaceuticamente aceitável do mesmo.

22. Composto caracterizado pelo fato de que é selecionado do grupo que consiste em:

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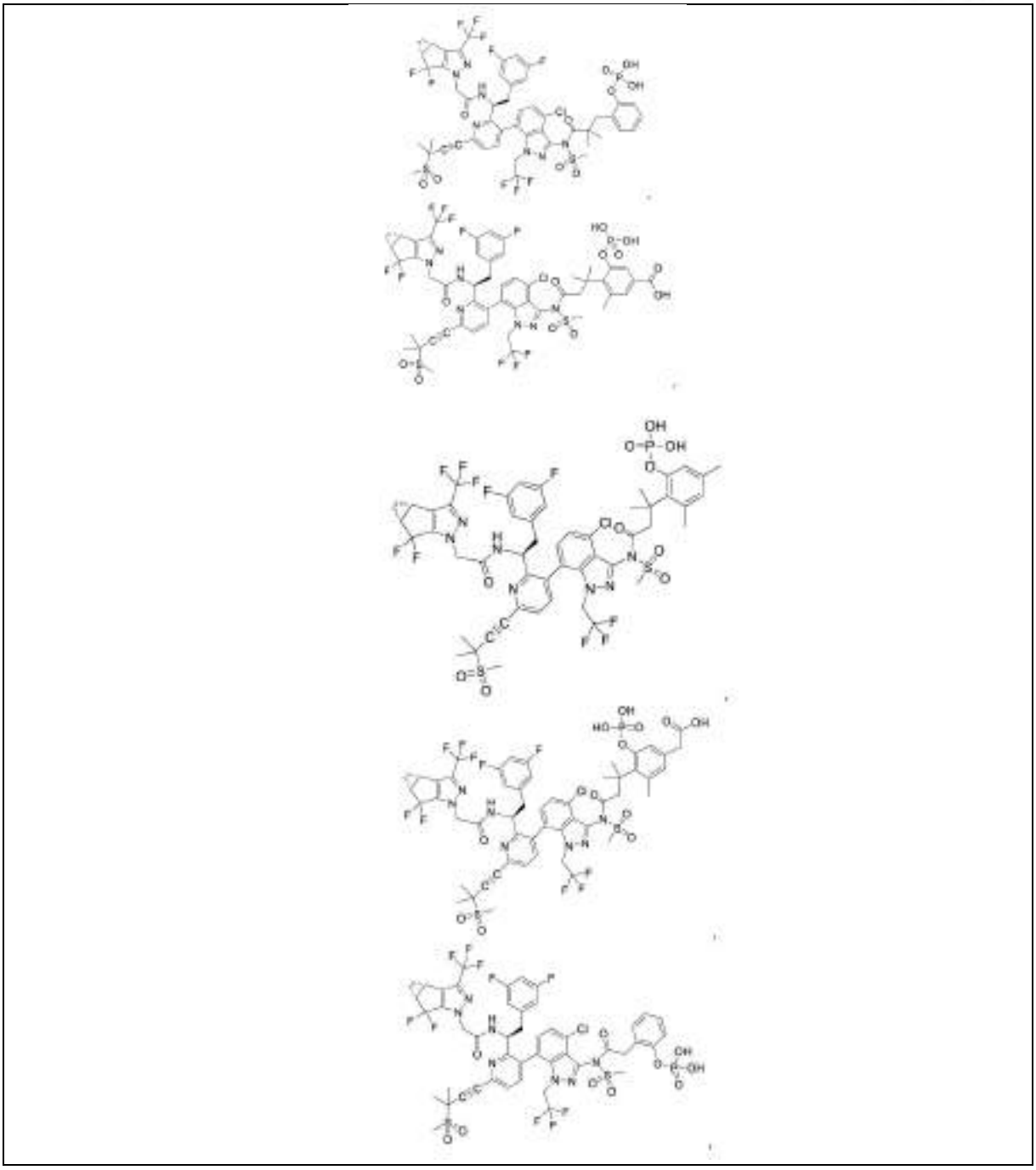

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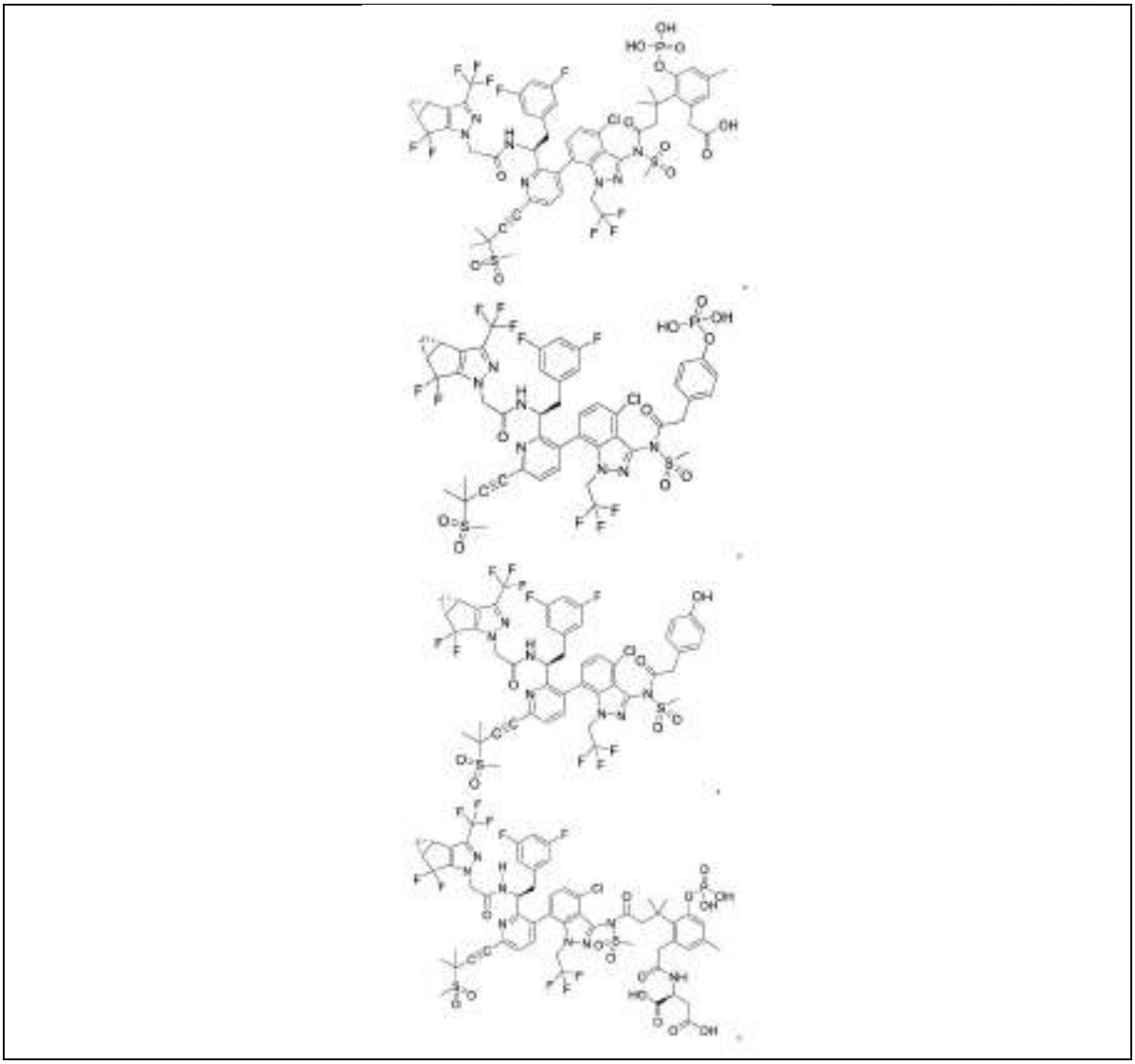

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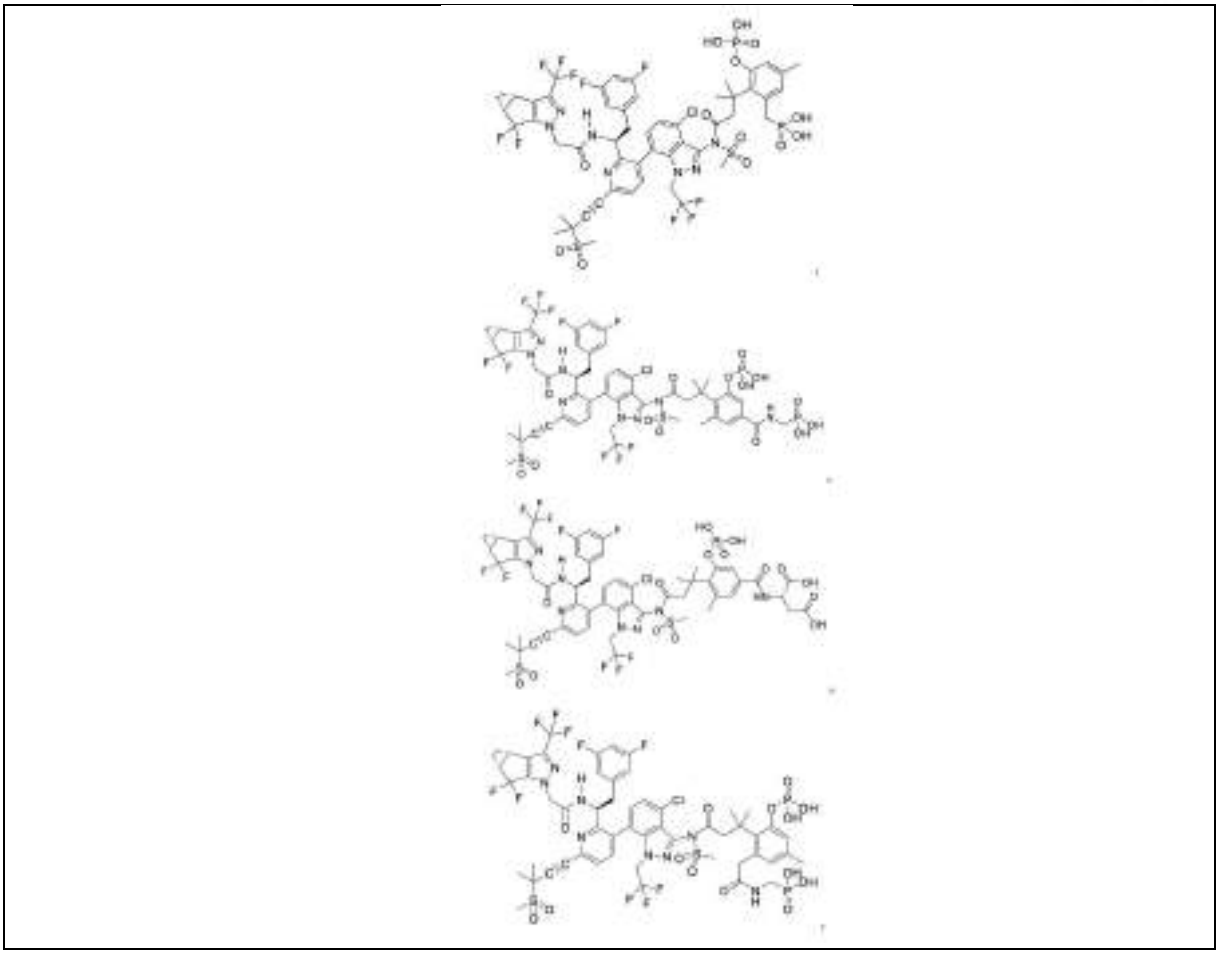

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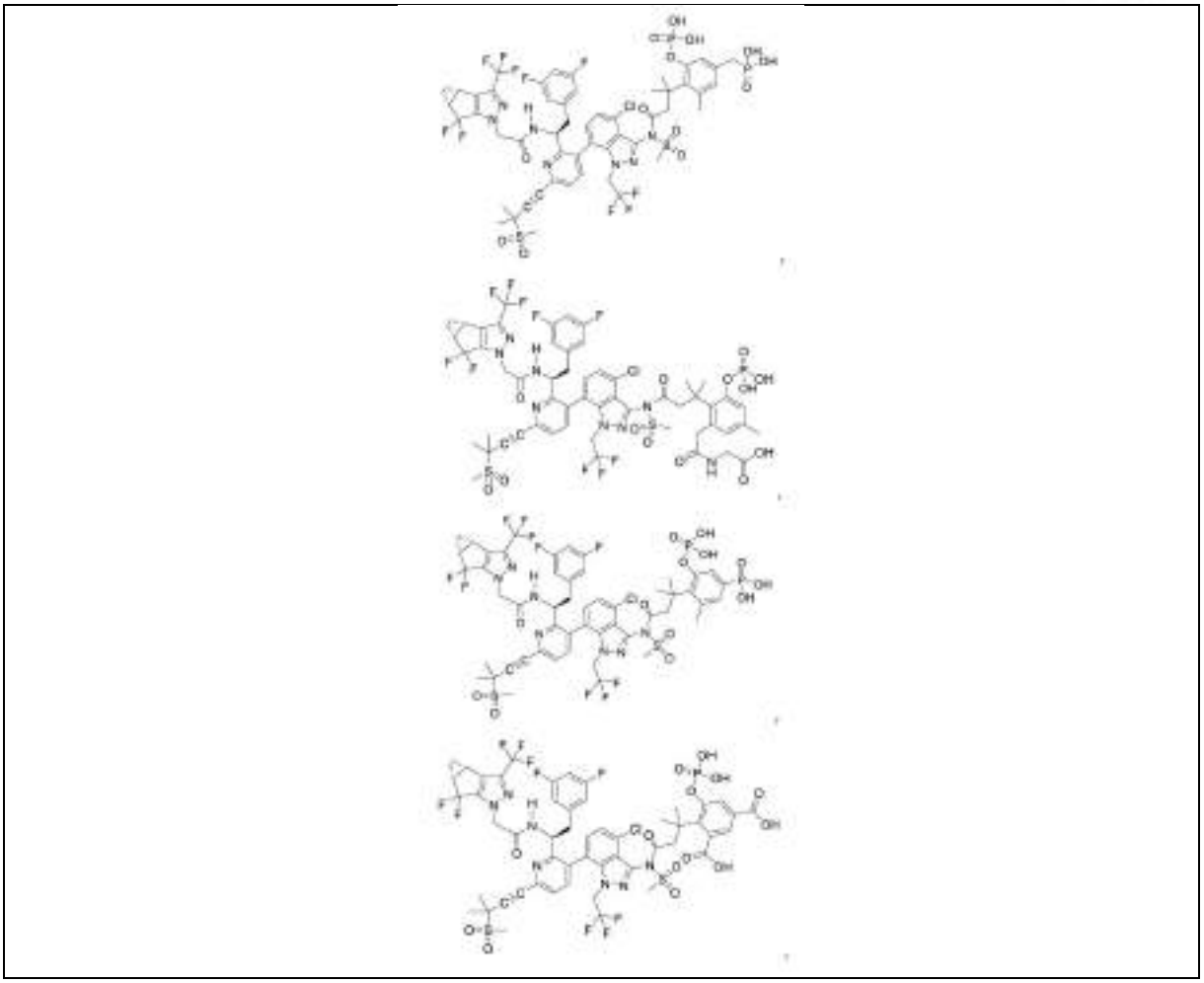

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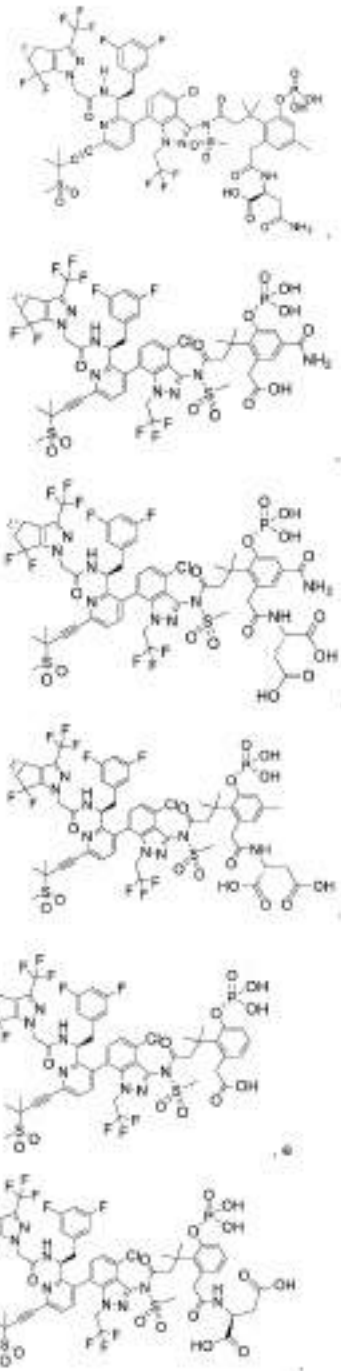

ou um sal farmaceuticamente aceitável do mesmo.

23. Composto caracterizado pelo fato de que é selecionado do grupo que consiste em:

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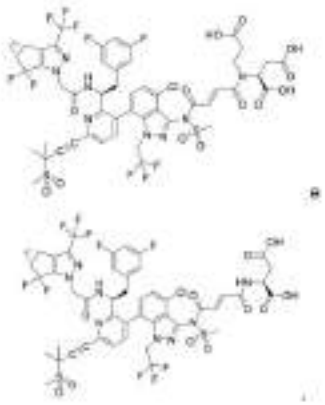
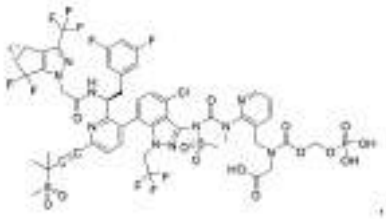


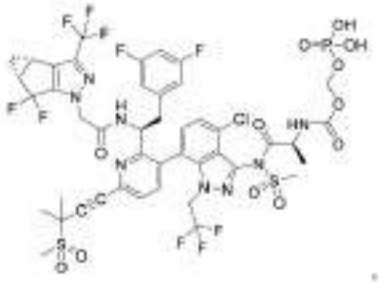
ou um sal farmaceuticamente aceitável do mesmo.

24. Composto caracterizado pelo fato de que é



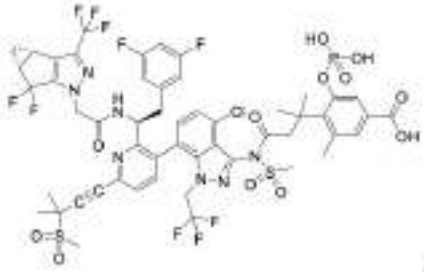
ou um sal farmaceuticamente aceitável do mesmo.

25. Composto caracterizado pelo fato de que é



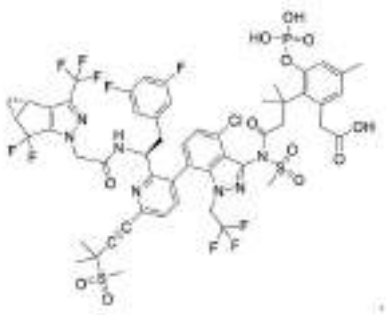
ou um sal farmaceuticamente aceitável do mesmo.

26. Composto caracterizado pelo fato de que é



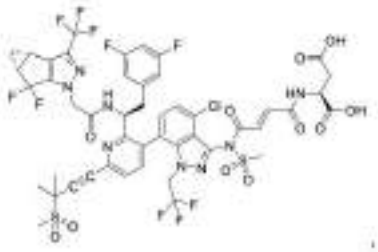
ou um sal farmaceuticamente aceitável do mesmo.

27. Composto caracterizado pelo fato de que é



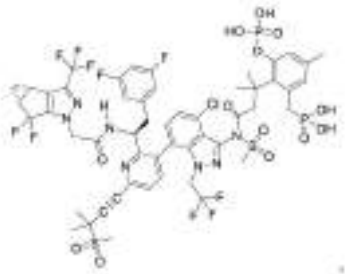
ou um sal farmaceuticamente aceitável do mesmo.

28. Composto caracterizado pelo fato de que é



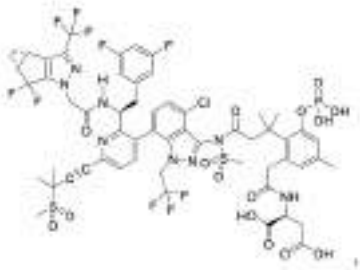
ou um sal farmaceuticamente aceitável do mesmo.

29. Composto caracterizado pelo fato de que é



ou um sal farmaceuticamente aceitável do mesmo.

30. Composto caracterizado pelo fato de que é



ou um sal farmaceuticamente aceitável do mesmo.

31. Composto caracterizado pelo fato de que é

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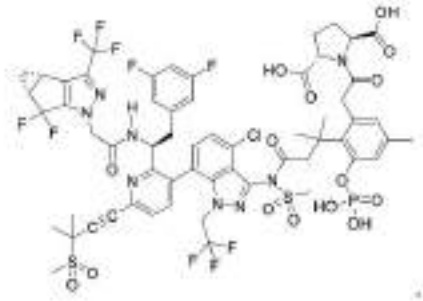

ou um sal farmaceuticamente aceitável do mesmo.

32. Composição farmacêutica caracterizada pelo fato de que compreende uma quantidade terapeuticamente eficaz de um composto como definido em qualquer uma das reivindicações 1 a 31, ou um sal farmaceuticamente aceitável do mesmo, e um excipiente farmaceuticamente aceitável.

33. Composição farmacêutica, de acordo com a reivindicação 32, caracterizada pelo fato de que compreende adicionalmente um, dois, três ou quatro agentes terapêuticos adicionais.

34. Composição farmacêutica, de acordo com a reivindicação 33, caracterizada pelo fato de que os agentes terapêuticos adicionais são selecionados do grupo que consiste em fármacos de combinação para HIV, outros fármacos para tratamento de HIV, inibidores da protease do HIV, inibidores não nucleosídicos ou não nucleotídicos da transcriptase reversa do HIV, inibidores nucleosídicos ou nucleotídicos da transcriptase reversa do HIV, inibidores da integrase do HIV, inibidores de sítio não catalítico (ou alostérico) da integrase do HIV, inibidores da entrada do HIV, inibidores da maturação do HIV, inibidores do capsídeo do HIV, inibidores da proteína 7 do nucleocapsídeo (NCVp7), inibidores de Tat ou Rev do HIV, inibidores de Tat-TAR-P-TEFb, imunomoduladores, agentes imunoterapêuticos, conjugados anticorpo-fármaco, modificadores de genes, editores de genes (como CRISPR/Cas9, nucleases de dedo de zinco, nucleases direcionadas ("homing nucleases"), nucleases sintéticas, TALENs), terapias com células (como células T com receptor de antígeno quimérico, CAR-T, e receptores de células T manipuladas, TCR-T, terapias com células T autólogas, células B manipuladas, células NK), agentes reversores de latência, imunoterapias, inibidores de fosfatidilinositol 3-quinase (PI3K), anticorpos para HIV, anticorpos biespecíficos e proteínas terapêuticas "semelhantes a anticorpos", inibidores da proteína de matriz p17 do HIV, antagonistas de IL-13, moduladores da peptidilprolil cis-trans-isomerase A, inibidores da proteína dissulfeto isomerase, antagonistas do receptor de complemento C5a, inibidor da DNA metiltransferase, inibidor da ácido graxo sintase, moduladores do gene vif do HIV, antagonistas de dimerização de Vif, inibidores do fator de infecciosidade viral do HIV-1, moduladores de Nef do HIV-1, inibidores do ligante do TNF alfa, inibidores de Nef do HIV-1, moduladores da tirosina quinase Hck, inibidores da quinase-3 de linhagem mista (MLK-3), inibidores de *splicing* de HIV-1, antagonistas de integrina, inibidores de nucleoproteína, moduladores do fator de *splicing*, moduladores da proteína 1 contendo domínio COMM, inibidores da ribonuclease H do HIV, antagonistas do IFN, moduladores da retrociclina, antagonistas de CD3, inibidores de CDK-4, inibidores de CDK-6, inibidores de CDK-9, inibidores de citocromo P450 3, moduladores de CXCR4, inibidores de não integrina 1 captadora de ICAM-3 específica de células dendríticas, inibidores da proteína GAG do HIV, inibidores da proteína POL do HIV, moduladores do fator H do complemento, inibidores da ubiquitina ligase, inibidores da desoxicitidina quinase, inibidores da quinase dependente de ciclina, inibidores de HPK1 (MAP4K1), estimuladores da pró-proteína convertase PC9, inibidores da RNA helicase DDX3X dependente de ATP, inibidores do complexo de iniciação de transcriptase reversa, inibidores de G6PD e NADH-oxidase, inibidores do complexo 1 mTOR, inibidores do complexo 2 mTOR, moduladores da P-glicoproteína, moduladores da RNA polimerase, inibidores da proteína TAT, inibidores da prolil endopeptidase, inibidores de fosfolipase A2, intensificadores

farmacocinéticos, terapia gênica contra HIV, vacinas contra HIV, peptídeos anti-HIV ou quaisquer combinações dos mesmos.

35. Composição farmacêutica, de acordo com qualquer uma das reivindicações 33 a 34, caracterizada pelo fato de que os agentes terapêuticos adicionais são selecionados do grupo que consiste em fármacos de combinação para HIV, outros fármacos para tratamento contra HIV, inibidores de protease de HIV, inibidores de transcriptase reversa de HIV, inibidores de integrase de HIV, inibidores de integrase (ou alostéricos) de sítio não catalítico de HIV, inibidores da entrada (fusão) do HIV, inibidores da maturação do HIV, agentes reversores de latência, inibidores de capsídeo, imunoterapias, inibidores de PI3K, anticorpos para HIV, anticorpos biespecíficos, proteínas terapêuticas "semelhantes a anticorpos" ou quaisquer combinações dos mesmos.

36. Composição farmacêutica, de acordo com qualquer uma das reivindicações 33 a 35, caracterizada pelo fato de que os agentes terapêuticos adicionais são selecionados do grupo que consiste em dolutegravir, cabotegravir, darunavir, bictegravir, elsulfavirina, rilpivirina, sulfato de abacavir, tenofovir, tenofovir desoproxila, fumarato de tenofovir desoproxila, hemifumarato de tenofovir desoproxila, tenofovir alafenamida e hemifumarato de tenofovir alafenamida, ou um sal farmaceuticamente aceitável dos mesmos.

37. Uso de um composto, como definido em qualquer uma das reivindicações 1 a 31, ou um sal farmaceuticamente aceitável do mesmo, ou composição farmacêutica, como definida em qualquer uma das reivindicações 32 a 35, caracterizado pelo fato de que é para a fabricação de um medicamento para tratamento ou prevenção de uma infecção por vírus da imunodeficiência humana (HIV) em um paciente em necessidade do mesmo.

38. Uso de um composto, como definido em qualquer uma das reivindicações 1 a 31, ou um sal farmaceuticamente aceitável do mesmo, ou composição farmacêutica, como definida em qualquer uma das reivindicações 32 a 35, caracterizado pelo fato de que é para a fabricação de um medicamento para tratamento de uma infecção por vírus da imunodeficiência humana (HIV) em um paciente muito experiente em tratamento.

39. Uso, de acordo com a reivindicação 37 ou 38, caracterizado pelo fato de que o método compreende adicionalmente administrar uma quantidade terapeuticamente eficaz de um, dois, três ou quatro agentes terapêuticos adicionais ou um sal farmaceuticamente aceitável dos mesmos.

40. Uso, de acordo com a reivindicação 39, caracterizado pelo fato de que o um, dois, três ou quatro agentes terapêuticos adicionais são selecionados do grupo que consiste em fármacos de combinação para HIV, outros fármacos para tratamento de HIV, inibidores da protease do HIV, inibidores não nucleosídicos ou não nucleotídicos da transcriptase reversa do HIV, inibidores nucleosídicos ou nucleotídicos da transcriptase reversa do HIV, inibidores da integrase do HIV, inibidores de sítio não catalítico (ou alostérico) da integrase do HIV, inibidores da entrada do HIV, inibidores da maturação do HIV, inibidores do capsídeo do HIV, inibidores da proteína 7 do nucleocapsídeo (NCVp7), inibidores de Tat ou Rev do HIV, inibidores de Tat-TAR-P-TEFb, imunomoduladores, agentes imunoterapêuticos, conjugados anticorpo-fármaco, modificadores de genes, editores de genes (como CRISPR/Cas9, nucleases de dedo de zinco, nucleases direcionadas ("homing nucleases"), nucleases sintéticas, TALENs), terapias com células (como células T com receptor de antígeno quimérico, CAR-T, e receptores de células T manipuladas, TCR-T, terapias com células T autólogas, células B manipuladas, células NK), agentes de reversão de latência, imunoterapias, inibidores de fosfatidilinositol 3-quinase (PI3K), anticorpos para HIV, anticorpos biespecíficos e proteínas terapêuticas "semelhantes a anticorpos", inibidores da proteína de matriz p17 do HIV, antagonistas de IL-13, moduladores da peptidilprolil cis-trans-isomerase A, inibidores da proteína dissulfeto isomera-se, antagonistas do receptor de complemento C5a, inibidor da DNA metiltransferase, inibidor da ácido graxo sintase, moduladores do gene vif do HIV, antagonistas de dimerização de Vif, inibidores do fator de infecciosidade viral do HIV-1, moduladores de Nef do HIV-

1, inibidores do ligante do TNF alfa, inibidores de Nef do HIV-1, moduladores da tirosina quinase Hck, inibidores da quinase-3 de linhagem mista (MLK-3), inibidores de splicing de HIV-1, antagonistas de integrina, inibidores de nucleoproteína, moduladores do fator de splicing, moduladores da proteína 1 contendo domínio COMM, inibidores da ribonuclease H do HIV, antagonistas do IFN, moduladores da retrociclina, antagonistas de CD3, inibidores de CDK-4, inibidores de CDK-6, inibidores de CDK-9, inibidores de citocromo P450 3, moduladores de CXCR4, inibidores não integrina 1 captadora de ICAM-3 específica de células dendríticas, inibidores da proteína GAG do HIV, inibidores da proteína POL do HIV, moduladores do fator H do complemento, inibidores da ubiquitina ligase, inibidores da desoxicitidina quinase, inibidores da quinase dependente de ciclina, inibidores de HPK1 (MAP4K1), estimuladores da pró-proteína convertase PC9, inibidores da RNA helicase DDX3X dependente de ATP, inibidores do complexo de iniciação de transcriptase reversa, inibidores de G6PD e NADH-oxidase, inibidores do complexo mTOR 1, inibidores do complexo mTOR 2, moduladores da P-glicoproteína, moduladores da RNA polimerase, inibidores da proteína TAT, inibidores da prolil endopeptidase, inibidores de fosfolipase A2, intensificadores farmacocinéticos, terapia gênica contra HIV, vacinas contra HIV, e peptídeos anti-HIV ou quaisquer combinações dos mesmos.

41. Uso, de acordo com qualquer uma das reivindicações 39 a 40, caracterizado pelo fato de que o um, dois, três ou quatro agentes terapêuticos adicionais são selecionados do grupo que consiste em fármacos de combinação para HIV, outros fármacos para tratamento contra HIV, inibidores de protease de HIV, inibidores de transcriptase reversa de HIV, inibidores de integrase de HIV, inibidores de integrase de sítio (ou alostérico) não catalítico de HIV, inibidores da entrada (fusão) do HIV, inibidores da maturação do HIV, agentes reversores de latência, inibidores de capsídeo, imunoterapias, inibidores de PI3K, anticorpos para HIV, anticorpos biespecíficos e proteínas terapêuticas "semelhantes a anticorpos" ou quaisquer combinações dos mesmos.

42. Uso, de acordo com qualquer uma das reivindicações 39 a 41, caracterizado pelo fato de que o um, dois, três ou quatro agentes terapêuticos adicionais são selecionados do grupo que consiste em dolutegravir, cabotegravir, darunavir, bictegravir, elsulfavirina, rilpivirina, sulfato de abacavir, tenofovir, tenofovir desoproxila, fumarato de tenofovir desoproxila, hemifumarato de tenofovir desoproxila, tenofovir alafenamida e hemifumarato de tenofovir alafenamida, ou um sal farmaceuticamente aceitável do mesmo.

43. Uso, de acordo com qualquer uma das reivindicações 37 a 42, caracterizado pelo fato de que o paciente é um é humano.

O Quadro 2 apresenta um resumo dos tipos de reivindicações do pedido de patente BR0162.

Quadro 2: Resumo dos tipos de reivindicações do pedido de patente BR0162.

TIPO DE PROTEÇÃO	REIVINDIDAÇÕES	DETALHES
Composto	1 a 18	Fórmula Markush I e substituintes
Composto	19 a 31	Compostos selecionados
Composição	32	Composição farmacêutica compreendendo uma quantidade eficaz dos compostos das reivindicações 1 a 31
Composição (combinação)	33 a 36	Composição farmacêutica da reivindicação 32, compreendendo um a quatro agentes terapêuticos adicionais
Uso	37, 38 e 43	Uso de um composto, definido nas reivindicações

		1 a 31, para a fabricação de um medicamento para tratamento ou prevenção do HIV
Uso (combinação)	39 a 42	Uso das reivindicações 37-38, em combinação com um a quatro agentes terapêuticos adicionais

5. DO ESTADO DA TÉCNICA DO PEDIDO BR112024010162-2

São citados, no presente subsídio ao exame técnico, os documentos do estado da técnica descritos no Quadro 3, todos publicados antes da data de prioridade mais antiga do pedido **BR112024010162-2**.

Quadro 3: Documentos do estado da técnica utilizado no presente subsídio ao exame técnico.

DENOMINAÇÃO	REFERÊNCIA	DATA DE PUBLICAÇÃO
D1	WO/2014/134566. Amide compounds for the treatment amide compounds for the treatment of HIV	04/09/2014
D2	WO/2018/035359. Therapeutic compounds useful for the prophylactic or therapeutic treatment of an HIV virus infection	22/02/2018
D3	Link JO, et al. Clinical targeting of HIV capsid protein with a long-acting small molecule. Nature, 584(7822):614-618, 2020. doi: 10.1038/s41586-020-2443-1.	2020
D4	Palombo MS, Singh Y, Sinko PJ. Prodrug and conjugate drug delivery strategies for improving HIV/AIDS therapy. J Drug Deliv Sci Technol., 19(1):3-14, 2009. doi: 10.1016/s1773-2247(09)50001-9.	2009
D5	Gomez-Orellana I. Strategies to improve oral drug bioavailability. Expert Opin Drug Deliv., 2(3):419-33, 2005. doi: 10.1517/17425247.2.3.419.	2005
D6	Rautio, J., Kumpulainen, H., Heimbach, T., Oliyai, R., Oh, D., Järvinen, T., & Savolainen, J. Prodrugs: design and clinical applications. Nature Reviews Drug Discovery, 7(3), 255-270, 2008. doi:10.1038/nrD4468	2008
D7	Krise, J.P., Oliyai, R. Prodrugs of Amines. In: Stella, V.J., Borchardt, R.T., Hageman, M.J., Oliyai, R., Maag, H., Tilley, J.W. (eds) Prodrugs. Biotechnology: Pharmaceutical Aspects, vol V. Springer, New York, NY, 2007. https://doi.org/10.1007/978-0-387-49785-3_22	2007
D8	Simplício AL, Clancy JM, Gilmer JF. Prodrugs for amines. Molecules, 13(3):519-47, 2008. doi: 10.3390/molecules13030519.	2008

D1 é uma patente sobre compostos amida (Fórmula IIId) para tratamento de HIV. O lenacapavir e derivados estão incluídos no escopo.

D2 divulga o lenacapavir ou seus sais farmacêuticos aceitáveis (incluindo pró-fármacos), formulações farmacêuticas, combinações com outros anti-HIV e métodos para tratamento ou prevenção da infecção por HIV.

D3 descreve o lenacapavir (GS-6207), seu desenho, atividade antiviral e características que o tornam promissor como agente de ação prolongada contra o HIV.

D4 faz uma revisão sobre estratégias de pró-fármacos e conjugados, aplicadas a compostos terapêuticos para HIV/AIDS.

D5 faz uma revisão de abordagens para melhorar a biodisponibilidade oral de fármacos, com foco em estratégias de pró-fármacos, otimização estrutural e desenho de formulações.

D6 descreve os grupos funcionais mais comuns usados no desenho de pró-fármacos, com exemplos já disponíveis no mercado ou em ensaios clínicos.

D7 enfoca pró-fármacos de aminas, exemplos de aplicação, desenho e grupos funcionais usados nessas estratégias.

D8 detalha estratégias para produção de pró-fármacos de aminas, dividindo entre os ativados enzimaticamente e aqueles que exploram condições químicas fisiológicas. Compara vantagens e desvantagens.

6. DA FALTA DE ATIVIDADE INVENTIVA

Para esta avaliação, emprega-se as etapas de avaliação de atividade inventiva da Resolução nº 169, de 15 de julho de 2016, que institui as Diretrizes de Exame de Pedidos de Patente – Bloco II – Patenteabilidade:

> 5.9 Três etapas são empregadas para determinar se uma invenção reivindicada é óbvia quando em comparação com o estado da técnica:
> (i) determinar o estado da técnica mais próximo;
> (ii) determinar as características distintivas da invenção e/ou o problema técnico de fato solucionado pela invenção; e
> (iii) determinar se, diante do problema técnico considerado, e partindo-se do estado da técnica mais próximo, a invenção é ou não óbvia para um técnico no assunto.

6.1 Reivindicações 1 a 31 (composto)

As reivindicações 1 a 31 referem-se a compostos da Fórmula Markush I, seus substituintes e compostos selecionados.

A depositante menciona, no relatório descritivo (RD), a necessidade de descobrir novos agentes antirretrovirais ativos contra variantes emergentes de HIV resistentes a fármacos; bem como fornecer esquemas terapêuticos a pacientes com propriedades farmacocinéticas aprimoradas. A descrição menciona que:

> (...) compostos da Fórmula I são mais solúveis do que lenacapavir e, portanto, são administrados por via oral em uma dose eficaz mais baixa do que a dose oral necessária para o lenacapavir alcançar o mesmo nível de exposição de lenacapavir *in vivo.* (página 87/362 - Petição 870250069985, de 06/08/2025).

O composto lenacapavir é divulgado nos documentos **D1** e **D2**. O documento **D1** descreve compostos da Fórmula de Markush IIId, a qual inclui lenacapavir quando substituições apropriadas são selecionadas. Considera-se, portanto, **D1** como estado da técnica mais próximo das reivindicações 1 a 31 do pedido BR0162, referentes a compostos pró-fármacos do lenacapavir.

Inicialmente, é importante destacar que a descrição de **D2** também menciona especificamente que a divulgação abrange pró-fármacos do composto lenacapavir (páginas 19-20, D2). Além disso, divulga composições farmacêuticas que o compreendem, incluindo uma formulação oral (página 104 e reivindicação 87, D2), bem como seu perfil farmacocinético (Figura 13, D2), mostrando a concentração plasmática de lenacapavir ao longo do tempo após administração oral em cães.

O problema técnico a ser resolvido seria o fornecimento de novos agentes antirretrovirais ativos contra variantes emergentes de HIV resistentes a fármacos, bem como esquemas terapêuticos a pacientes com propriedades farmacocinéticas aprimoradas.

As propriedades químico-farmacológicas do composto de base, o lenacapavir, já eram conhecidas antes da data de prioridade reivindicada pelo presente pedido. O inibidor do capsídeo do HIV demonstrou potente atividade antiviral tanto contra o vírus do tipo selvagem quanto contra variantes resistentes aos antirretrovirais atuais. A exposição farmacocinética prolongada e a eficácia antiviral observada em humanos sustentam seu posicionamento como um agente antirretroviral de ação prolongada para o tratamento e prevenção da infecção por HIV-1 (**D3**).

Os compostos do pedido BR0162 são pró-fármacos aminados de lenacapavir, nos quais o hidrogênio é substituído por um promotor para criar um pró-fármaco. O grupo funcional utilizado para o desenho do pró-fármaco está destacado em vermelho na Figura 1.

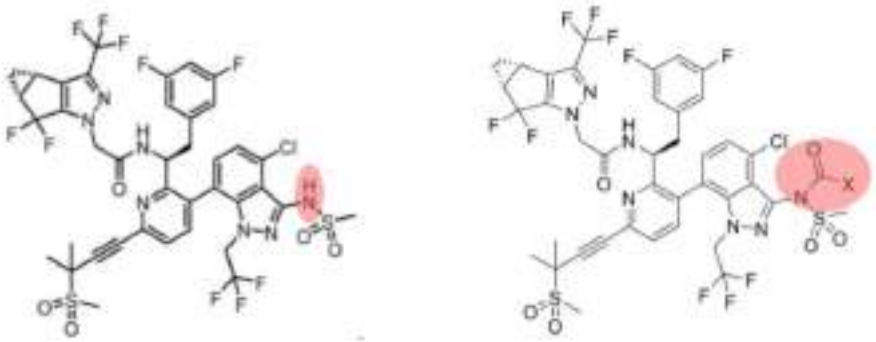

Figura 1: Lenacapavir e seu pró-fármaco, com destaque em vermelho para o grupo funcional substituído.

É necessário, portanto, avaliar se, diante do problema técnico considerado, e partindo-se do estado da técnica mais próximo, a invenção é ou não óbvia para um técnico no assunto. Em relação aos pró-fármacos especificamente pleiteados no pedido BR0162, o técnico no assunto chegaria com razoável expectativa de sucesso ao seu desenvolvimento, como ficará demonstrado a seguir.

Conforme **D1**, reivindicação 1, quando substituições apropriadas são selecionadas e Rn1 é H, o composto é lenacapavir, como apresentado na Figura 2.

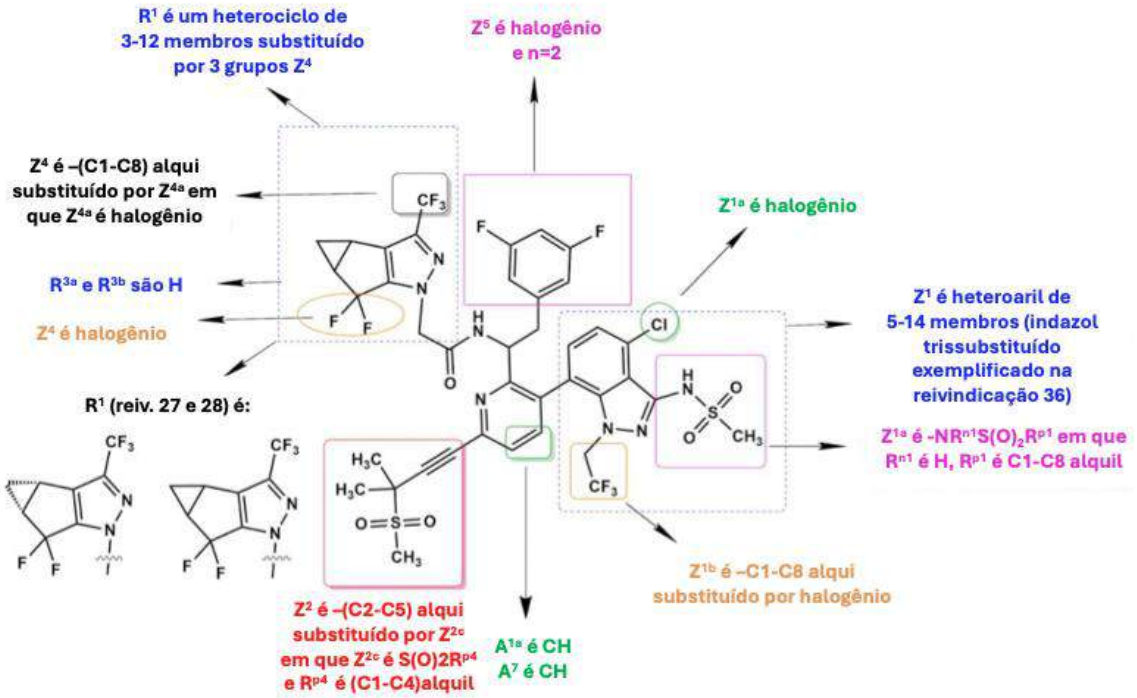

Figura 2: Substituições da Fórmula Markush IIId de **D1** para originar o composto lenacapavir

Ainda de acordo com **D1**, Rn1 pode ser outros grupos químicos, além de H:

- cada Rn1 é, independentemente, H, alquila C1-C8; carbociclo (C3-C7), heterociclo de 3 a 7 membros ou heteroarila monocíclica de 5 a 6 membros,

sendo que qualquer carbociclo (C3-C7), heterociclo de 3 a 7 membros ou heteroarila monocíclica de 5 a 6 membros de Rn1 é opcionalmente substituído com 1, 2, 3, 4 ou 5 grupos Z1c ou Z1d, podendo os grupos Z1c e Z1d serem iguais ou diferentes;

- e sendo que qualquer alquila (C1-C8) de Rn1 é opcionalmente substituída com 1, 2, 3, 4 ou 5 grupos Z1c, podendo os grupos Z1c serem iguais ou diferentes;
- cada Z1c é, independentemente, halogênio, -CN, -OH, -NH2, -C(0)NRq2Rr2 ou (C1-C8)heteroalquila;
- cada Rq2 e Rr2 é, independentemente, H, alquila (C1-C8), carbociclo (C3-C7), ou Rq2 e Rr2, juntamente com o nitrogênio ao qual estão ligados, formam um heterociclo de 5, 6 ou 7 membros.

Tendo em vista que os compostos derivados da Fórmula de Markush IIId de **D1** apresentam uma forte semelhança estrutural com os compostos da Fórmula de Markush I do presente pedido de patente, o técnico no assunto, buscando obter pró-fármacos do lenacapavir, teria razoável expectativa de sucesso na modificação química do radical Rn1 da Fórmula de Markush IIId de **D1**. Para ressaltar a semelhança, um possível composto derivado da Fórmula de Markush IIId de **D1** é comparado, na Figura 3, com um composto pleiteado no pedido BR0162 (reivindicação 20, 19° composto, página 13/31 – Petição 870250069985, de 06/08/2025).

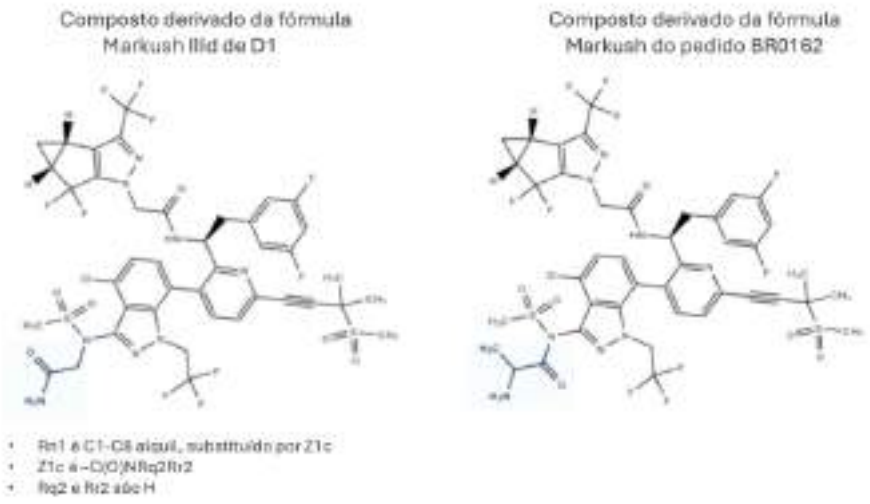

Figura 3: Comparação entre um composto **D1** (derivado da Fórmula Markush IIId) e um composto do presente pedido de patente (reivindicação 20, 19° composto). A porção comparativa está destacada em azul.

A abordagem de pró-fármacos foi previamente aplicada a compostos

antirretrovirais, como o fosamprenavir e o fumarato de tenofovir disoproxila. Esses pró-fármacos demonstraram melhora na absorção intestinal ao aumentarem a solubilidade em água e a lipofilicidade, para o fosamprenavir e o fumarato de tenofovir disoproxila, respectivamente, resultando em maior eficácia clínica em comparação com outras terapias antirretrovirais altamente ativas (**D4**, página 2).

Sabe-se que a biodisponibilidade oral de medicamentos depende de diversos fatores, principalmente da permeabilidade do fármaco, solubilidade aquosa, taxa de dissolução, metabolismo pré-sistêmico, metabolismo de primeira passagem e suscetibilidade a mecanismos de efluxo. Entre esses fatores, baixa permeabilidade e baixa solubilidade constituem as causas mais frequentes de baixa biodisponibilidade oral (**D5**, página 419), nesse sentido, pró-fármacos têm se mostrado uma abordagem eficaz para solucionar esse problema técnico. Além disso, pró-fármacos podem proporcionar perfis farmacocinéticos modificados para longa duração e maior meia-vida, por exemplo, ao direcionar mecanismos adequados de liberação do princípio ativo e/ou retardar o metabolismo e a eliminação. Nesses casos, os pró-fármacos oferecem vantagens tanto na redução da frequência de doses quanto na melhora da absorção (**D5**, página 422).

Aminas constituem um dos grupos funcionais mais comumente usados para o desenho de pró-fármacos (**D6**, página 256; **D7**, página 103). Abordagens para o desenvolvimento de pró-fármacos aminados foram revisadas, por exemplo, em **D7**, que menciona (página 104):

> *One important consideration is the influence of derivatization on the pKa of the parent drug. Typically, derivatizations of amines will result in reductions in both basicity and nucleophilicity. Reductions in basicity would be favorable for improving the rate of diffusion across biological membranes since at a given pH the percent of the molecule existing in the unionized state will increase. Reductions in nucleophilicity have been exploited in efforts to improve the chemical stability of parent amines that are prone to intermolecular aminolysis reactions.*
> *It is also important to focus on the physicochemical and structural properties of the promoiety itself. Some promoieties are considered hydrophilic and are designed to improve the water solubility of parent drugs. Conversely, others are lipophilic and are designed to improve membrane permeability. Another, less obvious, effect of amine derivatization is changes in intermolecular interactions between molecules in the crystalline state. Prodrugs that decrease the extent of these interactions will be expected to have increased dissolution rates and possibly higher water solubility. Therefore, it is conceivable that a prodrug could have both increased water solubility and membrane permeability relative to the parent amine.* (**D7**, página 104, grifos nossos)

Uma consideração importante é a influência da derivatização no pKa

> do fármaco original. Normalmente, as derivatizações de aminas resultam em reduções tanto na basicidade quanto na nucleofilicidade. Reduções na basicidade seriam favoráveis para melhorar a taxa de difusão através de membranas biológicas, uma vez que, em um determinado pH, a porcentagem da molécula existente no estado não ionizado aumentará. Reduções na nucleofilicidade têm sido exploradas em esforços para melhorar a estabilidade química de aminas originais que são propensas a reações de aminólise intermolecular.
>
> Também é importante focar nas propriedades físico-químicas e estruturais do próprio grupo promotor. Alguns grupos promotores são considerados hidrofílicos e são projetados para melhorar a solubilidade em água dos fármacos originais. Por outro lado, outros são lipofílicos e são projetados para melhorar a permeabilidade da membrana. Outro efeito, menos óbvio, da derivatização de aminas são as mudanças nas interações intermoleculares entre moléculas no estado cristalino. Espera-se que pró-fármacos que diminuam a extensão dessas interações tenham taxas de dissolução aumentadas e possivelmente maior solubilidade em água. Portanto, é concebível que um pró-fármaco possa apresentar maior solubilidade em água e permeabilidade da membrana em relação à amina original. (tradução livre, **D7**, página 104, grifos nossos)

As estratégias de pró-fármacos, revisadas em **D7**, são categorizadas de acordo com o tipo de promoção empregada, entre estas, aminas aciladas são definidas como a categoria de pró-fármacos que assumem a estrutura geral 1 (Figura 4), a qual compartilha a estrutura geral com os compostos da Fórmula I do presente pedido de patente.

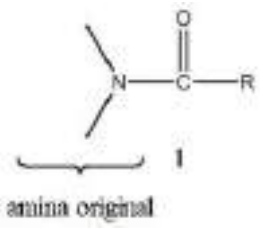

Figura 4: Estrutura geral das aminas aciladas como grupo promotor (**D7**, página 105)

Uma abordagem conhecida no desenvolvimento de pró-fármacos aminados é o sistema "*trimetil lock*", no qual amidas fenólicas derivadas de lactonas são utilizadas como promotores em pró-fármaco (**D7**, páginas 108-109; **D8**, página 536). O desenho foi modificado para produzir compostos sensíveis a esterases ou a processos redox. Pode-se notar que os grupos promotores mostrados na Figura 3 (**D1**) são muito semelhantes àqueles presentes nos compostos do pedido de patente BR0162, assim como os compostos dos exemplos 44 e 49 (Figura 5) e das reivindicações 1 a 18, 22,

25, 26 e 29.

D8

BR0162

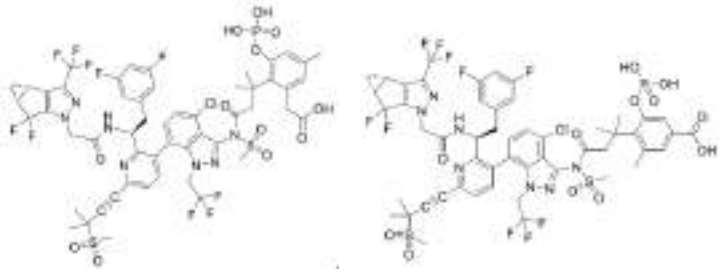

Figura 5: Comparação entre os grupos promotores de **D8** e compostos do presente pedido de patente (exemplos 44 e 49)

Em resumo, a abordagem de pró-fármacos é uma estratégia bem conhecida para melhorar as propriedades do composto original, tais como solubilidade e/ou biodisponibilidade. Em particular, pró-fármacos derivados de aminas e com os promotores utilizados no pedido de patente BR162 já foram divulgados no estado da técnica.

De forma ainda mais evidente, o próprio documento **D1** antecipa a possibilidade da inclusão de promotores de pró-fármacos na molécula do lenacapavir na mesma amina que foi modificada quimicamente para obtenção dos compostos do pedido de patente BR0162. O esquema sintético utilizado para a modificação é totalmente antecipado em **D7**.

Dessa forma, diante do problema técnico considerado, e partindo-se do estado da técnica mais próximo D1, combinado a D7, a matéria pleiteada nas reivindicações 1 a 31 do pedido BR0162 é óbvia para um técnico no assunto. As reivindicações 1 a 31 carecem de atividade inventiva, infringindo os artigos 8° e 13 da LPI.

Ademais, os ensaios biológicos descritos no presente pedido de patente são:

- Solubilidade em fluidos intestinais simulados (FaSSIF/FeSSIF);
- Análise de solubilidade cinética;
- Amostras farmacocinéticas de biodisponibilidade oral (em cães).

Os resultados são mostrados no relatório descritivo do presente pedido de patente (Tabela 1, páginas 359-361), que inclui 71 compostos selecionados da Fórmula I, comparados com o “intermediário 5” ou lenacapavir.

Primeiramente, a tabela parece estar incompleta, uma vez que apenas 43 compostos apresentam valores de solubilidade em FaSSIF/FeSSIF, e apenas 24 compostos apresentam dados de biodisponibilidade.

Em segundo lugar, dentre os compostos com dados disponíveis, vários não apresentam solubilidade e/ou biodisponibilidade aprimorada em comparação com lenacapavir (por exemplo, os compostos 18, 40, 41, 47, 53, 62).

Portanto, um suposto efeito técnico não pode ser atribuído aos compostos pleiteados no pedido de patente BR0162.

6.2 Reivindicações 32 a 36 (composição)

A reivindicação 32 do pedido BR0162 refere-se a uma composição farmacêutica que contém uma quantidade terapeuticamente eficaz de qualquer um dos compostos divulgados nas reivindicações 1-31 (ou um sal farmacêuticamente aceitável) e um excipiente farmacêuticamente aceitável. As reivindicações 33-36 referem-se à composição farmacêutica da reivindicação 32, compreendendo ainda um, dois, três ou quatro agentes terapêuticos adicionais, mencionando amplos grupos químicos/biológicos de fármacos anti-HIV.

De acordo com o depositante, há necessidade de descobrir novos agentes antirretrovirais que sejam ativos contra variantes emergentes de HIV resistentes a fármacos. O relatório descritivo menciona que há interesse em fornecer aos pacientes esquemas terapêuticos que apresentem propriedades farmacocinéticas aprimoradas. A requerente também afirma que seria benéfico dispor de terapias anti-HIV nas quais os pacientes precisem tomar a medicação menos de uma vez por dia ou tomar uma dose eficaz menor da(s) medicação(ões) diariamente, semanalmente, mensalmente ou por um período mais longo (RD, página 2, parágrafo 004).

O documento **D2** descreve composições farmacêuticas compreendendo lenacapavir (denominado composto Ib) ou um sal farmacêuticamente aceitável deste (reivindicação 3, D2); e opcionalmente em combinação com 1, 2, 3 ou 4 compostos pertencentes a amplos grupos químicos/biológicos de fármacos anti-HIV (reivindicações 4-8, D2). É importante notar que **D2** afirma que a divulgação também abrange pró-fármacos de lenacapavir (páginas 19-20, D2).

Como explicado na seção 6.1, os compostos da Fórmula I reivindicados na presente solicitação não são inventivos frente à técnica anterior (**D2/D1**, em combinação com **D7**).

A inclusão de um excipiente em uma composição farmacêutica é óbvia para um profissional da área. A combinação de diferentes compostos antivirais constitui uma estratégia conhecida e amplamente utilizada para o tratamento de infecções virais, incluindo aquelas causadas pelo HIV.

Dessa forma, a matéria pleiteada nas reivindicações 32 a 36 do pedido BR0162 é óbvia para um técnico no assunto. As reivindicações 32 a 36 carecem de atividade inventiva, infringindo os artigos 8° e 13 da LPI.

6.3 Reivindicações 37 a 43 (uso)

As reivindicações 37-43 têm como objetivo proteger o uso dos compostos ou das composições para obter um medicamento para tratamento ou prevenção de uma infecção por vírus da imunodeficiência humana (HIV) em um paciente em necessidade do mesmo (reivindicação 37) ou ainda em um paciente muito experiente em tratamento (reivindicação 38). O relatório descritivo do pedido BR0162 complementa que:

> [00183] Em algumas modalidades, a dosagem dos compostos da Fórmula I resulta na formação de lenacapavir, que é conhecido por ser ativo contra HIV, conforme revelado, por exemplo, na patente US nº 10.071.985. Em algumas modalidades, os compostos da Fórmula I são convertidos em lenacapavir no trato gastrointestinal. Em algumas modalidades,os compostos da Fórmula I são mais solúveis do que o lenacapavir e, portanto, são administrados por via oral em uma dose eficaz mais baixa do que a dose eficaz oral necessária para o lenacapavir alcançar o mesmo nível de exposição de lenacapavir in vivo. (Relatório descritivo, página 86/362, grifo nosso)

Desta forma, os compostos pleiteados no pedido BR0162 são utilizados no tratamento ou prevenção de infecção por HIV apenas por serem convertidos em lenacapavir.

O documento **D2** descreve composições farmacêuticas compreendendo lenacapavir (denominado composto Ib) ou um sal farmacêuticamente aceitável deste (reivindicação 3, D2); e opcionalmente em combinação com 1, 2, 3 ou 4 compostos pertencentes a amplos grupos químicos/biológicos de fármacos anti-HIV (reivindicações 4-8, D2). Na descrição de **D2**, também são divulgados pró-fármacos do composto Ib, ou seja, do lenacapavir (páginas 19-20, D2).

Além disso, **D2** divulga um método para produzir medicamentos para tratar ou prevenir uma infecção por HIV compreendendo lenacapavir (reivindicação 9 de D2) ou seus pró-fármacos e, opcionalmente compreendendo 1, 2, 3 ou 4 agentes terapêuticos adicionais (reivindicações 10-14 de D2), divulgando as mesmas classes de compostos e também os mesmos compostos específicos daqueles pleiteados no pedido BR0162.

Portanto, os uso dos compostos ou das composições descritas para tratar ou prevenir uma infecção por HIV compreendendo a administração de pró-fármacos de

lenacapavir, isoladamente ou em combinação com outros compostos pertencentes a amplos grupos químicos/biológicos de fármacos anti-HIV, já foram divulgados em **D2**.

As reivindicações 37-43 têm como objetivo proteger o uso dos compostos ou das composições para tratamento ou prevenção de uma infecção por vírus da imunodeficiência humana (HIV) em um paciente em necessidade do mesmo (reivindicação 37 e 39-43) ou ainda em um paciente muito experiente em tratamento (reivindicação 38 a 43).

Como mencionado anteriormente (seções 5.1 e 5.2), os compostos e as composições farmacêuticas que os compreendem carecem de atividade inventiva frente à técnica anterior.

Portanto, o uso dos compostos ou das composições para tratamento ou prevenção de uma infecção por vírus da imunodeficiência humana (HIV) com pró-fármacos de lenacapavir e suas combinações são óbvios para um profissional da área frente ao documento D2. As reivindicações 37 a 43 carecem de atividade inventiva, infringindo os artigos 8° e 13 da LPI.

7. DO PEDIDO

Estes fatos evidenciam que a matéria reivindicada no pedido **BR112024010162-2** não pode ser concedida por **falta de atividade inventiva, estando em desacordo com os artigos 8° e 13 da LPI**.

A subsidiante, acredita haver demonstrado à que a matéria para qual se requer proteção no pedido **BR112024010162-2** não é dotada de atividade inventiva, razão pela qual aguarda que o pedido de patente seja prontamente **INDEFERIDO**.

Rio de Janeiro, 01 de dezembro de 2025

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LISTA DE DOCUMENTOS ANEXOS

ANEXO 1: WO/2014/134566. Amide compounds for the treatment amide compounds for the treatment of HIV. Data de publicação: 04/09/2014. (**D1**)
ANEXO 2: WO/2018/035359. Therapeutic compounds useful for the prophylactic or therapeutic treatment of an HIV virus infection. Data de publicação: 22/02/2018. (**D2**)
ANEXO 3: Link JO, et al. Clinical targeting of HIV capsid protein with a long-acting small molecule. Nature, 584(7822):614-618, 2020. (**D3**)
ANEXO 4: Palombo MS, Singh Y, Sinko PJ. Prodrug and conjugate drug delivery strategies for improving HIV/AIDS therapy. J Drug Deliv Sci Technol, 19(1):3-14, 2009. (**D4**)
ANEXO 5: Gomez-Orellana I. Strategies to improve oral drug bioavailability. Expert Opin Drug Deliv, 2(3):419-33, 2005. (**D5**)
ANEXO 6: Rautio, J., Kumpulainen, H., Heimbach, T., Oliyai, R., Oh, D., Järvinen, T., & Savolainen, J. Prodrugs: design and clinical applications. Nature Reviews Drug Discovery, 7(3): 255-270, 2008. (**D6**)
ANEXO 7: Krise, J.P., Oliyai, R. Prodrugs of Amines. In: Stella, V.J., Borchardt, R.T., Hageman, M.J., Oliyai, R., Maag, H., Tilley, J.W. (eds) Prodrugs. Biotechnology: Pharmaceutical Aspects, vol V. Springer, New York, NY, 2007. (**D7**)
ANEXO 8: Simplício AL, Clancy JM, Gilmer JF. Prodrugs for amines. Molecules, 13(3):519-47, 2008. (**D8**)

ANEXO 9: Estatuto Social da ABIA
ANEXO 10: Ata de eleição de Diretoria da ABIA
ANEXO 11: Procuração da ABIA

ANEXO 12: Estatuto Social da Fenafar
ANEXO 13: Ata de eleição de Diretoria da Fenafar
ANEXO 14: Procuração da Fenafar

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ANEXO 24: Estatuto Social da Agani
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ANEXO 26: Procuração da Agani

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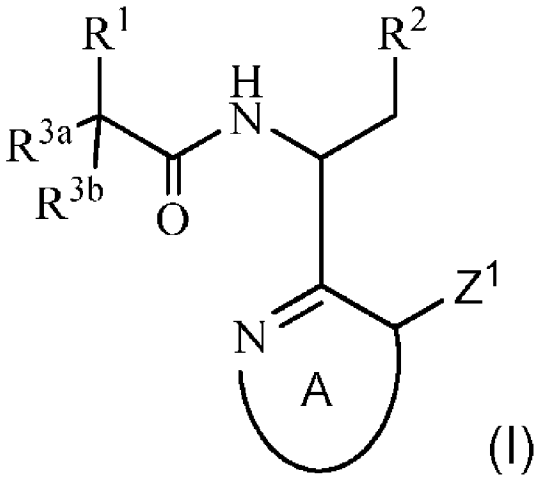
[Continued on next page]

(54) Title: THERAPEUTIC COMPOUNDS

(57) Abstract: Compounds of formula (I) or salts thereof are disclosed. Also disclosed are pharmaceutical compositions comprising a compound of formula I, processes for preparing compounds of formula I, intermediates useful for preparing compounds of formula I and therapeutic methods for treating a Retroviridae viral infection including an infection caused by the HIV virus.



(I)

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THERAPEUTIC COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Patent Application Serial Nos. 61/771,655, filed March 1, 2013 and 61/857,636, filed July 23, 2013, the disclosures of each of which are hereby incorporated herein by reference in their entirety.

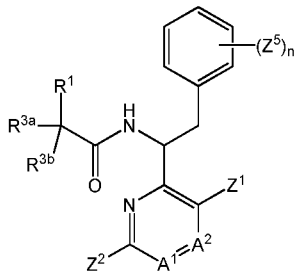
BACKGROUND

[0002] Positive-single stranded RNA viruses comprising the *Retroviridae* family include those of the subfamily *Orthoretrovirinae* and genera *Alpharetrovirus*, *Betaretrovirus*, *Gamaretrovirus*, *Deltaretrovirus*, *Epsilonretrovirus*, *Lentivirus*, and *Spumavirus* which cause many human and animal diseases. Among the *Lentivirus*, HIV-1 infection in humans leads to depletion of T helper cells and immune dysfunction, producing immunodeficiency and vulnerability to opportunistic infections. Treating HIV-1 infections with highly active antiretroviral therapies (HAART) has proven to be effective at reducing viral load and significantly delaying disease progression (Hammer, S.M., et al.; *JAMA* 2008, 300: 555-570). However, these treatments could lead to the emergence of HIV strains that are resistant to current therapies (Taiwo, B., *International Journal of Infectious Diseases* 2009, 13:552-559; Smith, R. J., et al., *Science* 2010, 327:697-701). Therefore, there is a pressing need to discover new antiretroviral agents that are active against emerging drug-resistant HIV variants.

SUMMARY

[0003] Provided herein are compounds and methods for the treatment of HIV (i.e., human immunodeficiency virus) infection.

[0004] One embodiment provides a compound of formula IIId:



IIId

wherein

A^1 is CH, C-Z^3, or nitrogen;

A^2 is CH or nitrogen;

R^1 is 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle, wherein any 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle of R^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, wherein the Z^4 groups are the same or different;

each R^{3a} and R^{3b} is independently H or (C_1-C_3)alkyl;

Z^1 is 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle, wherein any 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b}, wherein the Z^{1a} and Z^{1b} groups are the same or different;

each Z^{1a} is independently (C_3-C_7)carbocycle, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, -OR^{n1}, -$OC(O)R^{p1}$, -$OC(O)NR^{q1}R^{r1}$, -SR^{n1}, -$S(O)R^{p1}$, -$S(O)_2OH$, -$S(O)_2R^{p1}$, -$S(O)_2NR^{q1}R^{r1}$, -$NR^{q1}R^{r1}$, -$NR^{n1}COR^{p1}$, -$NR^{n1}CO_2R^{p1}$, -$NR^{n1}CONR^{q1}R^{r1}$, -$NR^{n1}S(O)_2R^{p1}$, -$NR^{n1}S(O)_2OR^{p1}$, -$NR^{n1}S(O)_2NR^{q1}R^{r1}$, -$C(O)R^{n1}$, -$C(O)OR^{n1}$, -$C(O)NR^{q1}R^{r1}$ and -$S(O)_2NR^{n1}COR^{p1}$, wherein any (C_3-C_7)carbocycle, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{1a} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different;

each Z^{1b} is independently (C_1-C_8)alkyl optionally substituted with 1, 2, 3, 4 or 5 halogen, which are the same or different;

each Z^{1c} is independently halogen, -CN, -OH, -NH_2, -$C(O)NR^{q2}R^{r2}$, or (C_1-C_8)heteroalkyl;

each Z^{1d} is independently (C_1-C_8)alkyl or (C_1-C_8)haloalkyl;

each R^{n1} is independently H, (C_1-C_8)alkyl, (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{n1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any (C_1-C_8)alkyl of R^{n1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different;

each R^{p1} is independently (C_1-C_8)alkyl, (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C_3-C_7)carbocycle, 3-7 membered

heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any $(C_1\text{-}C_8)$alkyl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different;

each R^{q1} and R^{r1} is independently H, $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any $(C_1\text{-}C_8)$alkyl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different, or R^{q1} and R^{r1} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or 7-membered heterocycle is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different;

each R^{q2} and R^{r2} is independently H, $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_7)$carbocycle, or R^{q2} and R^{r2} together with the nitrogen to which they are attached form a 5, 6, or 7-membered heterocycle;

Z^2 is $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, $-C(O)R^{n3}$, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, wherein the Z^{2b} and Z^{2c} groups are the same or different, and wherein any $(C_2\text{-}C_8)$alkenyl or $(C_2\text{-}C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4, or 5 Z^{2c} groups, wherein the Z^{2c} groups are the same or different;

each R^{n3} is independently H or $(C_1\text{-}C_4)$alkyl;

each R^{q3} and R^{r3} is independently H or $(C_1\text{-}C_4)$alkyl;

each Z^{2b} is independently oxo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$heteroalkyl or $(C_1\text{-}C_4)$haloalkyl;

each Z^{2c} is independently oxo, halogen, -CN, $-OR^{n4}$, $-OC(O)R^{p4}$, $-OC(O)NR^{q4}R^{r4}$, $-SR^{n4}$, $-S(O)R^{p4}$, $-S(O)_2OH$, $-S(O)_2R^{p4}$, $-S(O)_2NR^{q4}R^{r4}$, $-NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}CONR^{q4}R^{r4}$, $-NR^{n4}S(O)_2R^{p4}$, $-NR^{n4}S(O)_2OR^{p4}$, $-NR^{n4}S(O)_2NR^{q4}R^{r4}$, $-NO_2$, $-C(O)R^{n4}$, $-C(O)OR^{n4}$, or $-C(O)NR^{q4}R^{r4}$;

each R^{n4} is independently H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, or $(C_1\text{-}C_4)$heteroalkyl;

each R^{p4} is independently $(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_4)$haloalkyl, or $(C_1\text{-}C_4)$heteroalkyl;

each R^{q4} and R^{r4} is independently H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, or $(C_1\text{-}C_4)$heteroalkyl;

each Z^3 is independently a $(C_1\text{-}C_4)$heteroalkyl;

each Z^4 is independently oxo, $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_7)$carbocycle, halogen, -CN, $-OR^{n5}$, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-C(O)R^{n5}$, $-C(O)OR^{n5}$, or $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3\text{-}C_7)$carbocycle or $(C_1\text{-}C_8)$alkyl of Z^4 is optionally substituted with 1, 2, 3, 4 or 5 Z^{4a} groups, wherein the Z^{4a} groups are the same or different;

each Z^{4a} is independently halogen, -CN, or $-OR^{n6}$;

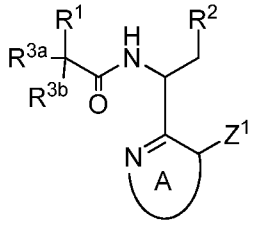
each R^{n5}, R^{p5}, R^{q5}, R^{r5}, and R^{n6} is independently H or $(C_1\text{-}C_4)$alkyl;

each Z^5 is independently halogen, which may be same or different; and

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof.

[0005] One embodiment provides a compound of formula III:



III

wherein

A is a 6-membered monocyclic-heteroaryl with one or two nitrogen atoms, wherein the 6-membered monocyclic-heteroaryl is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with 1 or 2 Z^3 groups, wherein the Z^3 groups are the same or different;

R^1 is 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle, wherein any 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle of R^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, wherein the Z^4 groups are the same or different;

R^2 is phenyl optionally substituted with 1, 2, 3, 4 or 5 halogen, which are the same or different;

each R^{3a} and R^{3b} is independently H or $(C_1\text{-}C_3)$alkyl;

Z^1 is 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle, wherein any 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b}, wherein the Z^{1a} and Z^{1b} groups are the same or different;

each Z^{1a} is independently (C_3-C_7)carbocycle, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, -OR^{n1}, -$OC(O)R^{p1}$, -$OC(O)NR^{q1}R^{r1}$, -SR^{n1}, -$S(O)R^{p1}$, -$S(O)_2OH$, -$S(O)_2R^{p1}$, -$S(O)_2NR^{q1}R^{r1}$, -$NR^{q1}R^{r1}$, -$NR^{n1}COR^{p1}$, -$NR^{n1}CO_2R^{p1}$, -$NR^{n1}CONR^{q1}R^{r1}$, -$NR^{n1}S(O)_2R^{p1}$, -$NR^{n1}S(O)_2OR^{p1}$, -$NR^{n1}S(O)_2NR^{q1}R^{r1}$, -$C(O)R^{n1}$, -$C(O)OR^{n1}$, -$C(O)NR^{q1}R^{r1}$ and -$S(O)_2NR^{n1}COR^{p1}$, wherein any (C_3-C_7)carbocycle, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{1a} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different;

each Z^{1b} is independently (C_1-C_8)alkyl optionally substituted with 1, 2, 3, 4 or 5 halogen, which are the same or different;

each Z^{1c} is independently halogen, -CN, -OH, -NH_2, -$C(O)NR^{q2}R^{r2}$, or (C_1-C_8)heteroalkyl;

each Z^{1d} is independently (C_1-C_8)alkyl or (C_1-C_8)haloalkyl;

each R^{n1} is independently H, (C_1-C_8)alkyl, (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{n1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any (C_1-C_8)alkyl of R^{n1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different;

each R^{p1} is independently (C_1-C_8)alkyl, (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any (C_1-C_8)alkyl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different;

each R^{q1} and R^{r1} is independently H, (C_1-C_8)alkyl, (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any (C_1-C_8)alkyl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different, or R^{q1} and R^{r1} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or

7-membered heterocycle is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different;

each R^{q2} and R^{r2} is independently H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, or R^{q2} and R^{r2} together with the nitrogen to which they are attached form a 5, 6, or 7-membered heterocycle;

Z^2 is $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, $-C(O)R^{n3}$, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, wherein the Z^{2b} and Z^{2c} groups are the same or different, and wherein any $(C_2$-$C_8)$alkenyl or $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4, or 5 Z^{2c} groups, wherein the Z^{2c} groups are the same or different;

each R^{n3} is independently H or $(C_1$-$C_4)$alkyl;

each R^{q3} and R^{r3} is independently H or $(C_1$-$C_4)$alkyl;

each Z^{2b} is independently oxo, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$heteroalkyl, or $(C_1$-$C_4)$haloalkyl;

each Z^{2c} is independently oxo, halogen, -CN, $-OR^{n4}$, $-OC(O)R^{p4}$, $-OC(O)NR^{q4}R^{r4}$, $-SR^{n4}$, $-S(O)R^{p4}$, $-S(O)_2OH$, $-S(O)_2R^{p4}$, $-S(O)_2NR^{q4}R^{r4}$, $-NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}CONR^{q4}R^{r4}$, $-NR^{n4}S(O)_2R^{p4}$, $-NR^{n4}S(O)_2OR^{p4}$, $-NR^{n4}S(O)_2NR^{q4}R^{r4}$, $-NO_2$, $-C(O)R^{n4}$, $-C(O)OR^{n4}$, or $-C(O)NR^{q4}R^{r4}$;

each R^{n4} is independently H, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, or $(C_1$-$C_4)$heteroalkyl;

each R^{p4} is independently $(C_1$-$C_8)$alkyl, $(C_1$-$C_4)$haloalkyl, or $(C_1$-$C_4)$heteroalkyl;

each R^{q4} and R^{r4} is independently H, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, or $(C_1$-$C_4)$heteroalkyl;

each Z^3 is independently a $(C_1$-$C_4)$heteroalkyl or halogen;

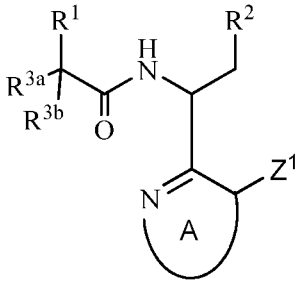
each Z^4 is independently oxo, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, halogen, -CN, $-OR^{n5}$, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-C(O)R^{n5}$, $-C(O)OR^{n5}$, or $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3$-$C_7)$carbocycle or $(C_1$-$C_8)$alkyl of Z^4 is optionally substituted with 1, 2, 3, 4 or 5 Z^{4a} groups, wherein the Z^{4a} groups are the same or different;

each Z^{4a} is independently halogen, -CN, or $-OR^{n6}$; and

each R^{n5}, R^{p5}, R^{q5}, R^{r5}, and R^{n6} is independently H or $(C_1$-$C_4)$alkyl;

or a pharmaceutically acceptable salt thereof.

[0006] One embodiment provides a compound of formula I



I

wherein:

A is a 6-membered monocyclic-heteroaryl with one or two nitrogen atoms, wherein the 6-membered monocyclic-heteroaryl is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with one or more (e.g., 1 or 2) Z^3 groups;

R^1 is 6-12 membered aryl, 5-12 membered heteroaryl or 3-12 membered heterocycle, wherein any 6-12 membered aryl, 5-12 membered heteroaryl or 3-12 membered heterocycle of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups;

R^2 is phenyl, 5-membered monocyclic-heteroaryl, 6-membered monocyclic-heteroaryl or $(C_3$-$C_7)$carbocycle, wherein any phenyl, 5-membered monocyclic-heteroaryl, 6-membered monocyclic-heteroaryl or $(C_3$-$C_7)$carbocycle of R^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^5 groups;

each R^{3a} and R^{3b} is independently selected from H, halogen, $(C_1$-$C_3)$alkyl and $(C_1$-$C_3)$haloalkyl, or R^{3a} is selected from H, $(C_1$-$C_3)$alkyl and $(C_1$-$C_3)$haloalkyl and R^{3b} is selected from -OH and -CN;

Z^1 is selected from 6-12 membered aryl, 5-14 membered heteroaryl and 3-14 membered heterocycle, wherein any 6-12 membered aryl, 5-14 membered heteroaryl and 3-14 membered heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b};

each Z^{1a} is independently selected from $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, $-OR^{n1}$, $-OC(O)R^{p1}$, $-OC(O)NR^{q1}R^{r1}$, $-SR^{n1}$, $-S(O)R^{p1}$, $-S(O)_2OH$, $-S(O)_2R^{p1}$, $-S(O)_2NR^{q1}R^{r1}$, $-NR^{q1}R^{r1}$, $-NR^{n1}COR^{p1}$, $-NR^{n1}CO_2R^{p1}$, $-NR^{n1}CONR^{q1}R^{r1}$, $-NR^{n1}S(O)_2R^{p1}$, $-NR^{n1}S(O)_2OR^{p1}$, $-NR^{n1}S(O)_2NR^{q1}R^{r1}$, NO_2, $-C(O)R^{n1}$, $-C(O)OR^{n1}$, $-C(O)NR^{q1}R^{r1}$ and $-S(O)_2NR^{n1}COR^{p1}$, wherein any $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{1a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups;

each Z^{1b} is independently selected from $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl and $(C_2\text{-}C_8)$alkynyl, wherein any $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl and $(C_2\text{-}C_8)$alkynyl of Z^{1b} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

each Z^{1c} is independently selected from $(C_3\text{-}C_7)$carbocycle, phenyl, 5-6 membered monocyclic-heteroaryl, 3-7 membered heterocycle, halogen, -CN, $-OR^{n2}$, $-OC(O)R^{p2}$, $-OC(O)NR^{q2}R^{r2}$, $-SR^{n2}$, $-S(O)R^{p2}$, $-S(O)_2OH$, $-S(O)_2R^{p2}$, $-S(O)_2NR^{q2}R^{r2}$, $-NR^{q2}R^{r2}$, $-NR^{n2}COR^{p2}$, $-NR^{n2}CO_2R^{p2}$, $-NR^{n2}CONR^{q2}R^{r2}$, $-NR^{n2}S(O)_2R^{p2}$, $-NR^{n2}S(O)_2OR^{p2}$, $-NR^{n2}S(O_2NR^{q2}R^{r2}$, NO_2, $-C(O)R^{n2}$, $-C(O)OR^{n2}$, $-C(O)NR^{q2}R^{r2}$, halophenyl, 5-6 membered haloheteroaryl, 3-7 membered haloheterocycle and $(C_1\text{-}C_8)$heteroalkyl;

each Z^{1d} is independently selected from $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl and $(C_1\text{-}C_8)$haloalkyl;

each R^{n1} is independently selected from H, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R^{n1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl and $(C_2\text{-}C_8)$alkynyl of R^{n1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

each R^{p1} is independently selected from $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R^{p1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl and $(C_2\text{-}C_8)$alkynyl of R^{p1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

R^{q1} and R^{r1} are each independently selected from H, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R^{q1} or R^{r1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl and $(C_2\text{-}C_8)$alkynyl of R^{q1} or R^{r1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups, or R^{q1} and R^{r1} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or 7-membered heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups;

each R^{n2} is independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, $(C_1$-$C_8)$haloalkyl and $(C_1$-$C_8)$heteroalkyl;

each R^{p2} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, $(C_1$-$C_8)$haloalkyl and $(C_1$-$C_8)$heteroalkyl;

R^{q2} and R^{r2} are each independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, $(C_1$-$C_8)$haloalkyl and $(C_1$-$C_8)$heteroalkyl, or R^{q2} and R^{r2} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

Z^2 is selected from $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, $-C(O)R^{n3}$ and $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl and 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with one or more (e.g.,1, 2, 3, 4, or 5) Z^{2c} groups;

each Z^{2a} is independently selected from $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, $-CN$, $-OR^{n4}$, $-OC(O)R^{p4}$, $-OC(O)NR^{q4}R^{r4}$, $-SR^{n4}$, $-S(O)R^{p4}$, $-S(O)_2OH$, $-S(O)_2R^{p4}$, $-S(O)_2NR^{q4}R^{r4}$, $-NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}CONR^{q4}R^{r4}$, $-NR^{n4}S(O)_2R^{p4}$, $-NR^{n4}S(O)_2OR^{p4}$, $-NR^{n4}S(O)_2NR^{q4}R^{r4}$, NO_2, $-C(O)R^{n4}$, $-C(O)OR^{n4}$ and $-C(O)NR^{q4}R^{r4}$, wherein any $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{2a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups;

each Z^{2b} is independently selected from $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$heteroalkyl and $(C_1$-$C_4)$haloalkyl;

each Z^{2c} is independently selected from halogen, $-CN$, $-OR^{n4}$, $-OC(O)R^{p4}$, $-OC(O)NR^{q4}R^{r4}$, $-SR^{n4}$, $-S(O)R^{p4}$, $-S(O)_2OH$, $-S(O)_2R^{p4}$, $-S(O)_2NR^{q4}R^{r4}$, $-NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}CONR^{q4}R^{r4}$, $-NR^{n4}S(O)_2R^{p4}$, $-NR^{n4}S(O)_2OR^{p4}$, $-NR^{n4}S(O)_2NR^{q4}R^{r4}$, NO_2, $-C(O)R^{n4}$, $-C(O)OR^{n4}$ and $-C(O)NR^{q4}R^{r4}$;

each R^{n3} is independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl, wherein any $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl of R^{n3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl and $(C_2$-$C_4)$alkynyl of R^{n3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups;

R^{q3} and R^{r3} are each independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl, wherein any $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl of R^{q3} or R^{r3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_1$-$C_4)$alkyl and $(C_2$-$C_4)$alkenyl of R^{q3} or R^{r3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups, or R^{q3} and R^{r3} together with the nitrogen to which they are attached form a heterocycle or heteroaryl, wherein the heterocycle or heteroaryl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups;

each R^{n4} is independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_4)$haloalkyl and $(C_1$-$C_4)$heteroalkyl;

each R^{p4} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_2$-$C_4)$alkynyl, $(C_1$-$C_4)$haloalkyl and $(C_1$-$C_4)$heteroalkyl;

R^{q4} and R^{r4} are each independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_2$-$C_4)$alkynyl, $(C_1$-$C_4)$haloalkyl and $(C_1$-$C_4)$heteroalkyl;

each Z^3 is independently selected from halogen, $(C_1$-$C_4)$alkyl, -OH, -CN, $(C_1$-$C_4)$heteroalkyl and $(C_1$-$C_4)$haloalkyl;

each Z^4 is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, halogen, -CN, $-OR^{n5}$, $-OC(O)R^{p5}$, $-OC(O)NR^{q5}R^{r5}$, $-SR^{n5}$, $-S(O)R^{p5}$, $-S(O)_2OH$, $-S(O)_2R^{p5}$, $-S(O)_2NR^{q5}R^{r5}$, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-NR^{n5}CONR^{q5}R^{r5}$, $-NR^{n5}S(O)_2R^{p5}$, $-NR^{n5}S(O)_2OR^{p5}$, $-NR^{n5}S(O)_2NR^{q5}R^{r5}$, NO_2, $-C(O)R^{n5}$, $-C(O)OR^{n5}$ and $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3$-$C_7)$carbocycle, of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} or Z^{4b} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} groups;

each Z^{4a} is independently selected from halogen, -CN, $-OR^{n6}$, $-OC(O)R^{p6}$, $-OC(O)NR^{q6}R^{r6}$, $-SR^{n6}$, $-S(O)R^{p6}$, $-S(O)_2OH$, $-S(O)_2R^{p6}$, $-S(O)_2NR^{q6}R^{r6}$, $-NR^{q6}R^{r6}$, $-NR^{n6}COR^{p6}$,

$-NR^{n6}CO_2R^{p6}$, $-NR^{n6}CONR^{q6}R^{r6}$, $-NR^{n6}S(O)_2R^{p6}$, $-NR^{n6}S(O)_2OR^{p6}$, $-NR^{n6}S(O)_2NR^{q6}R^{r6}$, NO_2, $-C(O)R^{n6}$, $-C(O)OR^{n6}$ and $-C(O)NR^{q6}R^{r6}$;

each Z^{4b} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl $(C_2\text{-}C_4)$alkynyl and $(C_1\text{-}C_4)$haloalkyl;

each R^{n5} is independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

each R^{p5} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

R^{q5} and R^{r5} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

each R^{n6} is independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

each R^{p6} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

R^{q6} and R^{r6} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

each Z^5 is independently selected from $(C_1\text{-}C_6)$alkyl, halogen, -CN and $-OR^{n7}$, wherein any $(C_1\text{-}C_6)$alkyl of Z^5 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen; and

each R^{n7} is independently selected from H, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$haloalkyl and $(C_3\text{-}C_7)$carbocycle;

or a pharmaceutically acceptable salt thereof.

[0007] One embodiment provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. Another embodiment provides a pharmaceutical composition comprising a compound as detailed herein, including a compound of any one of formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, III, IIIa, IIIb, IIIc, IIId, IIIe, IIIf, IIIg, IIIh, IIIi, IIIj, and IIIk, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0008] One embodiment provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof; and an additional therapeutic agent, wherein the additional therapeutic agent is an HIV protease inhibiting compound, an HIV non-nucleoside inhibitor of reverse transcriptase, an HIV nucleoside inhibitor of reverse

transcriptase, an HIV nucleotide inhibitor of reverse transcriptase, an HIV integrase inhibitor, a gp41 inhibitor, a CXCR4 inhibitor, a gp120 inhibitor, a CCR5 inhibitor, a capsid polymerization inhibitor, or a non-catalytic site HIV integrase inhibitor and combinations thereof. Another embodiment provides a pharmaceutical composition comprising a compound of anty one of formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, III, IIIa, IIIb, IIIc, IIId, IIIe, IIIf, IIIg, IIIh, IIIi, IIIj, and IIIk, or a pharmaceutically acceptable salt thereof; and an additional therapeutic agent, wherein the additional therapeutic agent is an HIV protease inhibiting compound, an HIV non-nucleoside inhibitor of reverse transcriptase, an HIV nucleoside inhibitor of reverse transcriptase, an HIV nucleotide inhibitor of reverse transcriptase, an HIV integrase inhibitor, a gp41 inhibitor, a CXCR4 inhibitor, a gp120 inhibitor, a CCR5 inhibitor, a capsid polymerization inhibitor, or a non-catalytic site HIV integrase inhibitor and combinations thereof.

[0009] One embodiment provides a method for treating a *Retroviridae* viral infection (e.g., an HIV viral infection) in a mammal (e.g., a human), comprising administering a compound of formula I, or a pharmaceutically acceptable salt thereof, to the mammal. Another embodiment provides a method for treating a *Retroviridae* viral infection (e.g., an HIV viral infection) in a mammal (e.g., a human), comprising administering a compound as detailed herein, including a compound of any one of formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, III, IIIa, IIIb, IIIc, IIId, IIIe, IIIf, IIIg, IIIh, IIIi, IIIj, and IIIk, or a pharmaceutically acceptable salt thereof, to the mammal. Another embodiment provides a method for treating a HIV infection in a patient in need thereof comprising administering a therapeutically effective amount of a compound as detailed herein, or a pharmaceutically acceptable salt thereof, to the patient.

[0010] One embodiment provides a method for inhibiting the proliferation of the HIV virus, treating AIDS or delaying the onset of AIDS or ARC symptoms in a mammal (e.g., a human), comprising administering a compound of formula I, or a pharmaceutically acceptable salt thereof, to the mammal. Another embodiment provides a method for inhibiting the proliferation of the HIV virus, treating AIDS or delaying the onset of AIDS or ARC symptoms in a mammal (e.g., a human), comprising administering a compound as detailed herein, including a compound of any one of formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, III, IIIa, IIIb, IIIc, IIId, IIIe, IIIf, IIIg, IIIh, IIIi, IIIj, and IIIk, or a pharmaceutically acceptable salt thereof, to the mammal.

[0011] One embodiment provides a method for treating an HIV infection in a mammal (e.g., a human), comprising administering a compound of formula I, or a pharmaceutically acceptable salt thereof, to the mammal. Another embodiment provides a method for treating an HIV

infection in a mammal (e.g., a human), comprising administering a compound as detailed herein, including a compound of any one of formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, III, IIIa, IIIb, IIIc, IIId, IIIe, IIIf, IIIg, IIIh, IIIi, IIIj, and IIIk, or a pharmaceutically acceptable salt thereof, to the mammal.

[0012] One embodiment provides a method for treating an HIV infection in a mammal (e.g., a human), comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and other drugs for treating HIV, and combinations thereof. Another embodiment provides a method for treating an HIV infection in a mammal (e.g., a human), comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of any one of formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, III, IIIa, IIIb, IIIc, IIId, IIIe, IIIf, IIIg, IIIh, IIIi, IIIj, and IIIk, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and other drugs for treating HIV, and combinations thereof. Another embodiment provides a method for treating an HIV infection in a patient in need thereof comprising administering to the patient a therapeutically effective amount of a compound as described herein, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of an additional therapeutic agent, wherein the additional therapeutic agent is an HIV protease inhibiting compound, an HIV non-nucleoside inhibitor of reverse transcriptase, an HIV nucleoside inhibitor of reverse transcriptase, an HIV nucleotide inhibitor of reverse transcriptase, an HIV integrase inhibitor, a gp41 inhibitor, a CXCR4 inhibitor, a gp120 inhibitor, a CCR5 inhibitor, a capsid polymerization inhibitor, or a non-catalytic site HIV integrase site inhibitor and combinations thereof.

[0013] One embodiment provides a method for treating an HIV infection in a mammal (e.g., a human), comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and non-catalytic site HIV integrase inhibitors, and combinations thereof. Another embodiment provides a method for treating an HIV infection in a mammal (e.g., a human), comprising administering to the mammal in need thereof a therapeutically effective amount of a compound as detailed herein, including a compound of any one of formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, III, IIIa, IIIb, IIIc, IIId, IIIe, IIIf, IIIg, IIIh, IIIi, IIIj, and IIIk, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and non-catalytic site HIV integrase inhibitors, and combinations thereof.

[0014] One embodiment provides a compound of formula I, or a pharmaceutically acceptable salt thereof for use in medical therapy (e.g., for use in treating a *Retroviridae* viral infection (e.g., an HIV viral infection) or the proliferation of the HIV virus or AIDS or delaying the onset of AIDS or ARC symptoms in a mammal (e.g., a human)). Another embodiment provides a compound as detailed herein, including a compound of any one of formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, III, IIIa, IIIb, IIIc, IIId, IIIe, IIIf, IIIg, IIIh, IIIi, IIIj, and IIIk, or a pharmaceutically acceptable salt thereof, for use in medical therapy (e.g., for use in treating a *Retroviridae* viral infection (e.g., an HIV viral infection) or the proliferation of the HIV virus or AIDS or delaying the onset of AIDS or ARC symptoms in a mammal (e.g., a human)).

[0015] One embodiment provides a compound of formula I, or a pharmaceutically acceptable salt thereof for use in the manufacture of a medicament for treating a *Retroviridae* viral infection (e.g., an HIV viral infection) or the proliferation of the HIV virus or AIDS or delaying the onset of AIDS or ARC symptoms in a mammal (e.g., a human). Another embodiment provides a

compound as detailed herein, including a compound of any one of formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, III, IIIa, IIIb, IIIc, IIId, IIIe, IIIf, IIIg, IIIh, IIIi, IIIj, and IIIk, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for treating a *Retroviridae* viral infection (e.g., an HIV viral infection) or the proliferation of the HIV virus or AIDS or delaying the onset of AIDS or ARC symptoms in a mammal (e.g., a human).

[0016] One embodiment provides a compound of formula I, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of the proliferation of a *Retroviridae* virus, an HIV virus or AIDS or for use in the therapeutic treatment of delaying the onset of AIDS or ARC symptoms. Another embodiment provides a compound as detailed herein, including a compound of any one of formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, III, IIIa, IIIb, IIIc, IIId, IIIe, IIIf, IIIg, IIIh, IIIi, IIIj, and IIIk, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of the proliferation of a *Retroviridae* virus, an HIV virus or AIDS or for use in the therapeutic treatment of delaying the onset of AIDS or ARC symptoms.

[0017] One embodiment provides a compound of formula I, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of a *Retroviridae* virus infection (e.g., an HIV virus infection). Another embodiment provides a compound as detailed herein, including a compound of any one of formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, III, IIIa, IIIb, IIIc, IIId, IIIe, IIIf, IIIg, IIIh, IIIi, IIIj, and IIIk, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of a *Retroviridae* virus infection (e.g., an HIV virus infection).

[0018] One embodiment provides the use of a compound of formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for a *Retroviridae* virus infection (e.g., an HIV virus infection) in a mammal (e.g., a human). Another embodiment provides a compound as detailed herein, including a compound of any one of formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, III, IIIa, IIIb, IIIc, IIId, IIIe, IIIf, IIIg, IIIh, IIIi, IIIj, and IIIk, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for a *Retroviridae* virus infection (e.g., an HIV virus infection) in a mammal (e.g., a human).

[0019] One embodiment provides processes and intermediates disclosed herein that are useful for preparing compounds of formula I or salts thereof. Another embodiment provides processes and intermediates disclosed herein that are useful for preparing compounds of any one of

formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, III, IIIa, IIIb, IIIc, IIId, IIIe, IIIf, IIIg, IIIh, IIIi, IIIj, and IIIk, or salts thereof.

[0020] Other embodiments, objects, features and advantages will be set forth in the detailed description of the embodiments that follows, and in part will be apparent from the description, or may be learned by practice, of the claimed invention. These objects and advantages will be realized and attained by the processes and compositions particularly pointed out in the written description and claims hereof. The foregoing Summary has been made with the understanding that it is to be considered as a brief and general synopsis of some of the embodiments disclosed herein, is provided solely for the benefit and convenience of the reader, and is not intended to limit in any manner the scope, or range of equivalents, to which the appended claims are lawfully entitled.

DETAILED DESCRIPTION

[0021] The description below is made with the understanding that the present disclosure is to be considered as an exemplification of the claimed subject matter, and is not intended to limit the appended claims to the specific embodiments illustrated. The headings used throughout this disclosure are provided for convenience only and are not to be construed to limit the claims in any way. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

Definitions

[0022] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. A dash at the front or end of a chemical group is a matter of convenience; chemical groups may be depicted with or without one or more dashes without losing their ordinary meaning. A wavy line drawn through a line in a structure indicates a point of attachment of a group. A dashed line indicates an optional bond. A prefix such as "C_{u-v}" or (C_u-C_v) indicates that the following group has from u to v carbon atoms. For example, "C_{1-6}alkyl" indicates that the alkyl group has from 1 to 6 carbon atoms.

[0023] Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

[0024] When trade names are used herein, applicants intend to independently include the tradename product and the active pharmaceutical ingredient(s) of the tradename product.

[0025] "Alkyl" is a straight or branched saturated hydrocarbon. For example, an alkyl group can have 1 to 8 carbon atoms (i.e., $(C_1$-$C_8)$alkyl) or 1 to 6 carbon atoms (i.e., $(C_1$-C_6 alkyl) or 1 to 4 carbon atoms (i.e., $(C_1$-$C_4)$alkyl). Examples of suitable alkyl groups include, but are not limited to, methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$, and octyl ($-(CH_2)_7CH_3$).

[0026] "Alkenyl" is a straight or branched hydrocarbon with at least one carbon-carbon, sp^2 double bond. For example, an alkenyl group can have 2 to 8 carbon atoms (i.e., C_2-C_8 alkenyl), or 2 to 6 carbon atoms (i.e., C_2-C_6 alkenyl). Examples of suitable alkenyl groups include, but are not limited to, ethylene or vinyl ($-CH=CH_2$), allyl ($-CH_2CH=CH_2$) and 5-hexenyl ($-CH_2CH_2CH_2CH_2CH=CH_2$).

[0027] "Alkynyl" is a straight or branched hydrocarbon with at least one carbon-carbon, *sp* triple bond. For example, an alkynyl group can have 2 to 8 carbon atoms (i.e., C_2-C_8 alkyne,) or 2 to 6 carbon atoms (i.e., C_2-C_6 alkynyl). Examples of suitable alkynyl groups include, but are not limited to, acetylenic ($-C\equiv CH$), propargyl ($-CH_2C\equiv CH$), and the like.

[0028] The term "halo" or "halogen" as used herein refers to fluoro, chloro, bromo and iodo.

[0029] The term "haloalkyl" as used herein refers to an alkyl as defined herein, wherein one or more hydrogen atoms of the alkyl are each independently replaced by a halo substituent. For example, $(C_1$-$C_6)$haloalkyl is a $(C_1$-$C_6)$alkyl wherein one or more of the hydrogen atoms of the $(C_1$-$C_6)$alkyl have been replaced by a halo substituent. Examples of haloalkyls include but are not limited to fluoromethyl, fluorochloromethyl, difluoromethyl, difluorochloromethyl, trifluoromethyl, 1,1,1, trifluoroethyl and pentafluoroethyl.

[0030] The term "heteroalkyl" as used herein refers to an alkyl as defined herein, wherein one or more of the carbon atoms of the alkyl are replaced by an O, S, or NR^q, (or if the carbon atom being replaced is a terminal carbon with an OH, SH or $N(R^q)_2$) wherein each R^q is independently H or $(C_1\text{-}C_6)$alkyl. For example, $(C_1\text{-}C_8)$heteroalkyl includes a heteroalkyl of one to eight carbons and one or more heteroatoms (e.g., O, S, NR^q, OH, SH or $N(R^q)_2$). Thus, for example, a C_1 heteroalkyl encompasses, e.g., $-CH_2\text{-}NH_2$. Examples of heteroalkyls include but are not limited to methoxymethyl, ethoxymethyl, methoxy, 2-hydroxyethyl and N,N'-dimethylpropylamine.

[0031] The term "aryl" as used herein refers to a single all carbon aromatic ring or a multiple condensed all carbon ring system wherein at least one of the rings is aromatic. For example, in certain embodiments, an aryl group has 6 to 20 carbon atoms, 6 to 14 carbon atoms, or 6 to 12 carbon atoms. Aryl includes a phenyl radical. Aryl also includes multiple condensed ring systems (e.g., ring systems comprising 2, 3 or 4 rings) having about 9 to 20 carbon atoms in which at least one ring is aromatic and wherein the other rings may be aromatic or not aromatic (i.e., carbocycle). Such multiple condensed ring systems are optionally substituted with one or more (e.g., 1, 2 or 3) oxo groups on any carbocycle portion of the multiple condensed ring system. The rings of the multiple condensed ring system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. It is to be understood that the point of attachment of a multiple condensed ring system, as defined above, can be at any position of the ring system including an aromatic or a carbocycle portion of the ring. It is also to be understood that when reference is made to a certain atom-range membered aryl (e.g., 6-12 membered aryl), the atom range is for the total ring atoms of the aryl. For example, a 6-membered aryl would include phenyl and a 10-membered aryl would include naphthyl and 1, 2, 3, 4-tetrahydronaphthyl. Non-limiting examples of aryl groups include, but are not limited to, phenyl, indenyl, naphthyl, 1, 2, 3, 4-tetrahydronaphthyl, anthracenyl, and the like.

[0032] The term "heteroaryl" as used herein refers to a single aromatic ring that has at least one atom other than carbon in the ring, wherein the atom is selected from the group consisting of oxygen, nitrogen and sulfur; "heteroaryl" also includes multiple condensed ring systems that have at least one such aromatic ring, which multiple condensed ring systems are further described below. Thus, "heteroaryl" includes single aromatic rings of from about 1 to 6 carbon atoms and about 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur. The sulfur and nitrogen atoms may also be present in an oxidized form provided the ring

is aromatic. Exemplary heteroaryl ring systems include but are not limited to pyridyl, pyrimidinyl, oxazolyl or furyl. "Heteroaryl" also includes multiple condensed ring systems (e.g., ring systems comprising 2, 3 or 4 rings) wherein a heteroaryl group, as defined above, is condensed with one or more rings selected from heteroaryls (to form for example 1,8-naphthyridinyl), heterocycles, (to form for example 1,2,3,4-tetrahydro-1,8-naphthyridinyl), carbocycles (to form for example 5,6,7,8-tetrahydroquinolyl) and aryls (to form for example indazolyl) to form the multiple condensed ring system. Thus, a heteroaryl (a single aromatic ring or multiple condensed ring system) has about 1-20 carbon atoms and about 1-6 heteroatoms within the heteroaryl ring. Such multiple condensed ring systems may be optionally substituted with one or more (e.g., 1, 2, 3 or 4) oxo groups on the carbocycle or heterocycle portions of the condensed ring. The rings of the multiple condensed ring system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. It is to be understood that the individual rings of the multiple condensed ring system may be connected in any order relative to one another. It is also to be understood that the point of attachment of a multiple condensed ring system (as defined above for a heteroaryl) can be at any position of the multiple condensed ring system including a heteroaryl, heterocycle, aryl or carbocycle portion of the multiple condensed ring system. It is also to be understood that the point of attachment for a heteroaryl or heteroaryl multiple condensed ring system can be at any suitable atom of the heteroaryl or heteroaryl multiple condensed ring system including a carbon atom and a heteroatom (e.g., a nitrogen). It also to be understood that when a reference is made to a certain atom-range membered heteroaryl (e.g., a 5-14 membered heteroaryl), the atom range is for the total ring atoms of the heteroaryl and includes carbon atoms and heteroatoms. For example, a 5-membered heteroaryl would include a thiazolyl and a 10-membered heteroaryl would include a quinolinyl. Exemplary heteroaryls include but are not limited to pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, thienyl, indolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, furyl, oxadiazolyl, thiadiazolyl, quinolyl, isoquinolyl, benzothiazolyl, benzoxazolyl, indazolyl, quinoxalyl, quinazolyl, 5,6,7,8-tetrahydroisoquinolinyl benzofuranyl, benzimidazolyl, thianaphthenyl, pyrrolo[2,3-b]pyridinyl, quinazolinyl-4(3H)-one, triazolyl, 4,5,6,7-tetrahydro-1H-indazole and 3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole.

[0033] The term "C-linked-heteroaryl" (carbon-linked heteroaryl) as used herein refers to a heteroaryl that is linked at a carbon atom of the heteroaryl to the remainder of the compound of

formula I (e.g., a C-linked-heteroaryl of Z^2 bonded to the A ring of formula I through a carbon atom of the C-linked-heteroaryl).

[0034] The term "heterocyclyl" or "heterocycle" as used herein refers to a single saturated or partially unsaturated ring that has at least one atom other than carbon in the ring, wherein the atom is selected from the group consisting of oxygen, nitrogen and sulfur; the term also includes multiple condensed ring systems that have at least one such saturated or partially unsaturated ring, which multiple condensed ring systems are further described below. Thus, the term includes single saturated or partially unsaturated rings (e.g., 3, 4, 5, 6 or 7-membered rings) from about 1 to 6 carbon atoms and from about 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur in the ring. The ring may be substituted with one or more (e.g., 1, 2 or 3) oxo groups and the sulfur and nitrogen atoms may also be present in their oxidized forms. Exemplary heterocycles include but are not limited to azetidinyl, tetrahydrofuranyl and piperidinyl. The term "heterocycle" also includes multiple condensed ring systems (e.g., ring systems comprising 2, 3 or 4 rings) wherein a single heterocycle ring (as defined above) can be condensed with one or more groups selected from heterocycles (to form for example a 1,8-decahydronapthyridinyl), carbocycles (to form for example a decahydroquinolyl) and aryls to form the multiple condensed ring system. Thus, a heterocycle (a single saturated or single partially unsaturated ring or multiple condensed ring system) has about 2-20 carbon atoms and 1-6 heteroatoms within the heterocycle ring. Such multiple condensed ring systems may be optionally substituted with one or more (e.g., 1, 2, 3 or 4) oxo groups on the carbocycle or heterocycle portions of the multiple condensed ring. The rings of the multiple condensed ring system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. It is to be understood that the individual rings of the multiple condensed ring system may be connected in any order relative to one another. It is also to be understood that the point of attachment of a multiple condensed ring system (as defined above for a heterocycle) can be at any position of the multiple condensed ring system including a heterocycle, aryl and carbocycle portion of the ring. It is also to be understood that the point of attachment for a heterocycle or heterocycle multiple condensed ring system can be at any suitable atom of the heterocycle or heterocycle multiple condensed ring system including a carbon atom and a heteroatom (e.g., a nitrogen). It is also to be understood that when reference is made to a certain atom-range membered heterocycle (e.g., a 3-14 membered heterocycle), the atom range is for the total ring atoms of the heterocycle and includes carbon atoms and

heteroatoms. For example, a 3-membered heterocycle would include an aziridinyl and a 10-membered heterocycle would include a 1,2,3,4- tetrahydroquinolyl. Exemplary heterocycles include, but are not limited to aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydrofuranyl, dihydrooxazolyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,2,3,4- tetrahydroquinolyl, benzoxazinyl, dihydrooxazolyl, chromanyl, 1,2-dihydropyridinyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl, spiro[cyclopropane-1,1'-isoindolinyl]-3'-one, isoindolinyl-1-one, 2-oxa-6-azaspiro[3.3]heptanyl, imidazolidin-2-one and pyrrolidin-2-one.

[0035] The term "C-linked-heterocycle" (carbon-linked heterocycle) as used herein refers to a "heterocycle that is linked at a carbon atom of the heterocycle to the remainder of the compound of formula I (e.g., a C-linked-heterocycle of Z^2 bonded to the A ring of formula I through a carbon atom of the C-linked-heterocycle).

[0036] The term "carbocycle" or "carbocyclyl" refers to a single saturated (i.e., cycloalkyl) or a single partially unsaturated (e.g., cycloalkenyl, cycloalkadienyl, etc.) all carbon ring having 3 to 7 carbon atoms (i.e., (C_3-C_7)carbocycle). The term "carbocycle" or "carbocyclyl" also includes multiple condensed, saturated and partially unsaturated all carbon ring systems (e.g., ring systems comprising 2, 3 or 4 carbocyclic rings). Accordingly, carbocycle includes multicyclic carbocyles such as a bicyclic carbocycles (e.g., bicyclic carbocycles having about 6 to 12 carbon atoms such as bicyclo[3.1.0]hexane and bicyclo[2.1.1]hexane), and polycyclic carbocycles (e.g tricyclic and tetracyclic carbocycles with up to about 20 carbon atoms). The rings of the multiple condensed ring system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. For example, multicyclic carbocyles can be connected to each other via a single carbon atom to form a spiro connection (e.g., spiropentane, spiro[4,5]decane, etc), via two adjacent carbon atoms to form a fused connection (e.g., carbocycles such as decahydronaphthalene, norsabinane, norcarane) or via two non-adjacent carbon atoms to form a bridged connection (e.g., norbornane, bicyclo[2.2.2]octane, etc). The "carbocycle" or "carbocyclyl" can also be optionally substituted with one or more (e.g., 1, 2 or 3) oxo groups. Non-limiting examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl and 1-cyclohex-3-enyl.

[0037] The term "halophenyl" as used herein refers to phenyl, wherein one or more (e.g., 1, 2, 3, 4 or 5) hydrogen atoms of the phenyl are each replaced independently by a halo substituent.

Examples of halophenyl include but are not limited to fluorophenyl, 2,3-dichlorophenyl, 3-bromo-4-fluorophenyl and pentafluorophenyl.

[0038] The term "haloheteroaryl" as used herein refers to a heteroaryl, wherein one or more (e.g., 1, 2, 3, 4 or 5) hydrogen atoms of the heteroaryl are each replaced independently by a halo substituent. Examples of haloheteroaryl include but are not limited to 2-fluorofuryl, 2,3-dichloropyridinyl and 8-chloro-3-fluoroquinolinyl.

[0039] The term "haloheterocycle" as used herein refers to a heterocycle, wherein one or more (e.g., 1, 2, 3, 4 or 5) hydrogen atoms of the heterocycle are each replaced independently by a halo substituent. Examples of haloheteroaryl include but are not limited to 2-fluoropiperidinyl, 2-chloro-3-fluoropiperazinyl and 3-bromopyrrolidinyl.

[0040] One skilled in the art will recognize that substituents and other moieties of the compounds of formula I should be selected in order to provide a compound which is sufficiently stable to provide a pharmaceutically useful compound which can be formulated into an acceptably stable pharmaceutical composition. Compounds of formula I which have such stability are contemplated as falling within the scope of the present invention. Similarly, one skilled in the art will recognize that substituents and other moieties of the compounds detailed herein, including a compound of any one of formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, III, IIIa, IIIb, IIIc, IIId, IIIe, IIIf, IIIg, IIIh, IIIi, IIIj, and IIIk, or a pharmaceutically acceptable salt thereof, should be selected in order to provide a compound which is sufficiently stable to provide a pharmaceutically useful compound which can be formulated into an acceptably stable pharmaceutical composition. Compounds as detailed herein which have such stability are contemplated as falling within the scope of the present invention.

[0041] The modifier "about" used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (e.g., includes the degree of error associated with measurement of the particular quantity). The word "about" may also be represented symbolically by "~" in the context of a chemical measurement (e.g., ~ 50 mg or pH ~ 7).

[0042] The term "treatment" or "treating," to the extent it relates to a disease or condition includes preventing the disease or condition from occurring, inhibiting the disease or condition, eliminating the disease or condition, and/or relieving one or more symptoms of the disease or condition.

[0043] In one embodiment, "treatment" or "treating" include one or more of the following: a) inhibiting the disease or condition (*e.g.*, decreasing one or more symptoms resulting from the

disease or condition, and/or diminishing the extent of the disease or condition); b) slowing or arresting the development of one or more symptoms associated with the disease or condition (*e.g.*, stabilizing the disease or condition, delaying the worsening or progression of the disease or condition); and c) relieving the disease or condition, e.g., causing the regression of clinical symptoms, ameliorating the disease state, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival.

Stereoisomers

[0044] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York.

[0045] The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

[0046] The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

[0047] "Diastereomer" refers to a stereoisomer with two or more centers or axes of chirality and whose molecules are not mirror images of one another. Diastereomers typically have different physical properties, e.g., melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

[0048] "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

[0049] The compounds disclosed herein may have chiral centers, e.g., chiral carbon atoms. Such compounds thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds disclosed herein include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. Similarly, compositions disclosed herein also include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers of compounds disclosed herein. In addition, the compounds and compositions disclosed herein include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures,

as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures can be separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g., acids or bases followed by conversion back to the optically active substances. The desired optical isomer can also be synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

[0050] The invention includes any or all of the stereochemical forms, including any enantiomeric or diastereomeric forms and geometric isomers of the compounds described, or mixtures thereof. Unless stereochemistry is explicitly indicated in a chemical structure or name, the structure or name is intended to embrace all possible stereoisomers, including geometric isomers, of a compound depicted. Compositions comprising a compound of the invention are also intended, such as a composition of substantially pure compound, including a specific stereochemical form, including a specific geometric isomer, thereof. Compositions comprising a mixture of compounds of the invention in any ratio are also embraced by the invention, including mixtures of two or more stereochemical forms of a compound of the invention in any ratio, such that racemic, non-racemic, enantio-enriched and scalemic mixtures of a compound are embraced, or mixtures thereof.

[0051] It is to be understood that for compounds disclosed herein when a bond is drawn in a non-stereochemical manner (e.g., flat) the atom to which the bond is attached includes all stereochemical possibilities. It is also to be understood that when a bond is drawn in a stereochemical manner (e.g., bold, bold-wedge, dashed or dashed-wedge) the atom to which the stereochemical bond is attached has the stereochemistry as shown unless otherwise noted. Accordingly, in one embodiment, a compound disclosed herein is greater than 50% a single enantiomer. In another embodiment, a compound disclosed herein is at least 80% a single enantiomer. In another embodiment, a compound disclosed herein is at least 90% a single enantiomer. In another embodiment, a compound disclosed herein is at least 98% a single enantiomer. In another embodiment, a compound disclosed herein is at least 99% a single enantiomer. In another embodiment, a compound disclosed herein is greater than 50% a single diastereomer. In another embodiment, a compound disclosed herein is at least 80% a single diastereomer. In another embodiment, a compound disclosed herein is at least 90% a single diastereomer. In another embodiment, a compound disclosed herein is at least 98% a single

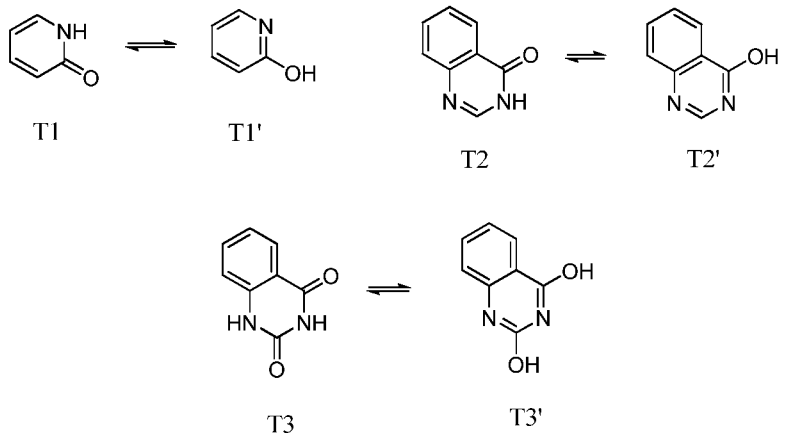
diastereomer. In another embodiment, a compound disclosed herein is at least 99% a single diastereomer.

[0052] Accordingly, in one embodiment, a composition disclosed herein is greater than 50% a single enantiomer. In another embodiment, a composition disclosed herein is at least 80% a single enantiomer. In another embodiment, a composition disclosed herein is at least 90% a single enantiomer. In another embodiment, a composition disclosed herein is at least 98% a single enantiomer. In another embodiment, a composition disclosed herein is at least 99% a single enantiomer. In another embodiment, a composition disclosed herein is greater than 50% a single diastereomer. In another embodiment, a composition disclosed herein is at least 80% a single diastereomer. In another embodiment, a composition disclosed herein is at least 90% a single diastereomer. In another embodiment, a composition disclosed herein is at least 98% a single diastereomer. In another embodiment, a composition disclosed herein is at least 99% a single diastereomer.

[0053] In certain embodiments, the compounds disclosed herein display atropisomerism resulting from steric hindrance affecting the axial rotation rate around a single bond. In certain circumstances, the resultant conformational isomers are observed as distinct entities by characterization techniques such as NMR and HPLC. In certain embodiments, the compounds disclosed herein exist as a mixture of atropisomers. The synthetic examples provided herein note where such mixtures of atropisomers have been observed. However, the detection of atropisomers is dependent on factors such as temperature, solvent, conditions of purification, and timescale of spectroscopic technique. Characterization data presented herein may not represent the equilibrium state depending on the conditions of purification, isolation, handling, solvents used, and temperature.

Tautomers

[0054] The compounds disclosed herein can also exist as tautomeric isomers in certain cases. Although only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the invention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention. Another non-limiting example includes keto-enol tautomers of heteroaryls. Such tautomers are exemplified by T1/T1', T2/T2' and T3/T3'. All such tautomeric forms are also within the scope of the invention.



T1 T1' T2 T2' T3 T3'

Protecting Groups

[0055] "Protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. Chemical protecting groups and strategies for protection/deprotection are well known in the art. See e.g., Protective Groups in Organic Chemistry, Theodora W. Greene, John Wiley & Sons, Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, e.g., making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

Salts and Hydrates

[0056] "Pharmaceutically acceptable salt" refers to a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Pharmaceutically acceptable salts are generally regarded as safe and suitable for use without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio. Examples of "pharmaceutically acceptable salts" of the compounds disclosed herein include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth metal (for example, magnesium), ammonium and NX_4^+ (wherein X is C_1–C_4 alkyl). Pharmaceutically acceptable salts of a nitrogen atom or an amino group include for example salts of organic carboxylic acids such as acetic, benzoic, camphorsulfonic, citric, glucoheptonic, gluconic, lactic, fumaric, tartaric, maleic, malonic, malic, mandelic, isethionic, lactobionic, succinic, 2-

napththalenesulfonic, oleic, palmitic, propionic, stearic, and trimethylacetic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric and sulfamic acids. Pharmaceutically acceptable salts of a compound of a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NX_4^+ (wherein X is independently selected from H or a C_1–C_4 alkyl group). Pharmaceutically acceptable salts also include salts formed when an acidic proton present in the parent compound is replaced by either a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as diethanolamine, triethanolamine, N-methylglucamine and the like. Also included in this definition are ammonium and substituted or quaternized ammonium salts. Representative non-limiting lists of pharmaceutically acceptable salts can be found in S.M. Berge et al., J. Pharma Sci., 66(1), 1-19 (1977), and Remington: The Science and Practice of Pharmacy, R. Hendrickson, ed., 21st edition, Lippincott, Williams & Wilkins, Philadelphia, PA, (2005), at p. 732, Table 38-5, both of which are hereby incorporated by reference herein.

[0057] For therapeutic use, salts of active ingredients of the compounds disclosed herein will typically be pharmaceutically acceptable, i.e., they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not pharmaceutically acceptable may also find use, for example, in the preparation or purification of a compound of formula I or another compound disclosed herein. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

[0058] Metal salts typically are prepared by reacting the metal hydroxide with a compound disclosed herein. Examples of metal salts which are prepared in this way are salts containing Li^+, Na^+, and K^+. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

[0059] In addition, salts may be formed from acid addition of certain organic and inorganic acids, e.g., HCl, HBr, H_2SO_4, H_3PO_4 or organic sulfonic acids, to basic centers, such as amines. Finally, it is to be understood that the compositions herein comprise compounds disclosed herein in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

[0060] Often crystallizations produce a solvate of the compound of the invention. As used herein, the term “solvate” refers to an aggregate that comprises one or more molecules of a compound of the invention with one or more molecules of solvent. The solvent may be water, in

which case the solvate may be a hydrate. Alternatively, the solvent may be an organic solvent. Thus, the compounds of the present invention may exist as a hydrate, including a monohydrate, dihydrate, hemihydrate, sesquihydrate, trihydrate, tetrahydrate and the like, as well as the corresponding solvated forms. The compound of the invention may be true solvates, while in other cases, the compound of the invention may merely retain adventitious water or be a mixture of water plus some adventitious solvent.

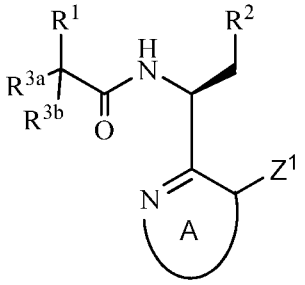
Isotopes

[0061] It is understood by one skilled in the art that this invention also includes any compound claimed that may be enriched at any or all atoms above naturally occurring isotopic ratios with one or more isotopes such as, but not limited to, deuterium (^{2}H or D). As a non-limiting example, in certain embodiments, a -CH_3 group is replaced with -CD_3.

[0062] Specific values listed below for radicals, substituents, and ranges in the embodiments of the invention are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

Compounds of formula I.

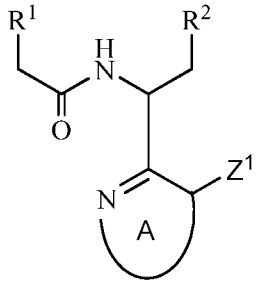
[0063] A specific group of compounds of formula I are compounds of formula Ia.



Ia

or a pharmaceutically acceptable salt thereof.

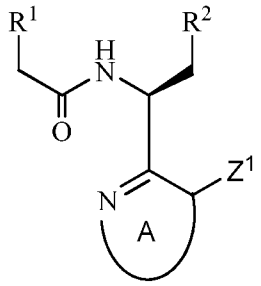
[0064] Another specific group of compounds of formula I are compounds of formula Ib.



Ib

or a pharmaceutically acceptable thereof.

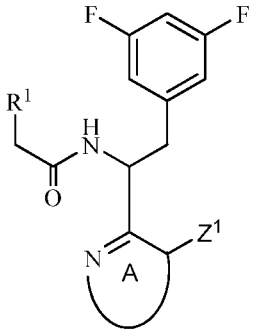
[0065] Another specific group of compounds of formula I are compounds of formula Ic.



Ic

or a pharmaceutically acceptable thereof.

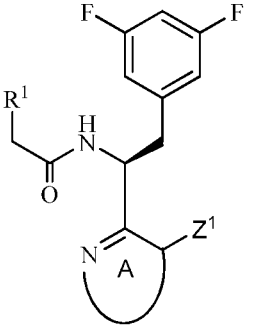
[0066] Another specific group of compounds of formula I are compounds of formula Id.



Id

or a pharmaceutically acceptable thereof.

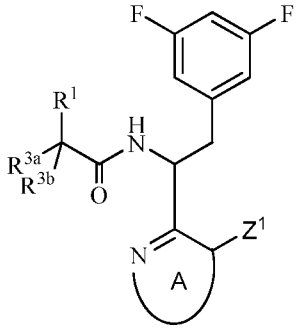
[0067] Another specific group of compounds of formula I are compounds of formula Ie.



Ie

or a pharmaceutically acceptable thereof.

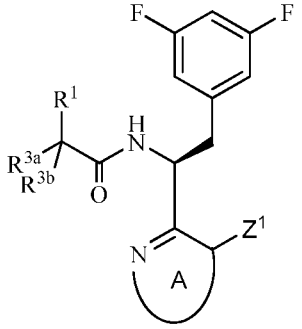
[0068] Another specific group of compounds of formula I are compounds of formula If.



If

or a pharmaceutically acceptable thereof.

[0069] Another specific group of compounds of formula I are compounds of formula Ig.



Ig

or a pharmaceutically acceptable thereof.

[0070] Specific values listed below are values for compounds of formula I as well as all related formulas (e.g., formulas Ia, Ib, Ic, Id, Ie, If, Ig). It is to be understood that two or more values may combined. Thus, it is to be understood that any variable for compounds of formula I may be combined with any other variable for compounds of formula I the same as if each and every combination of variables were specifically and individually listed. For example, it is understood that any specific value of R^1 detailed herein for compounds of formula I may be combined with any other specific value for one or more of the variables A, Z^1, R^2, R^{3a} or R^{3b} the same as if each and every combination were specifically and individually listed.

[0071] Specific values listed for compounds of formula I may apply equally to compounds of formula III and all related formulas (e.g., formulas IIIa, IIIb, IIIc, IIId, IIIe, IIIf, IIIg, IIIh, IIIi, IIIj, and IIIk) as applicable. For example, specific values for ring A of formula I may apply equally to ring A of formula III provided that the ring A of formula III encompasses within its scope the specific values. It is also understood that any combination of variables for compounds of formula I may apply equally to compounds of formula III and all related formulas (e.g., formulas IIIa, IIIb, IIIc, IIId, IIIe, IIIf, IIIg, IIIh, IIIi, IIIj, and IIIk) as applicable, the same

as if each and every combination were specifically and individually listed. For example, specific values for ring A and Z^1 may apply equally to the A-Z^1 moiety of formula III provided that the scope of the A-Z^1 moiety of formula III encompasses the specific value.

[0072] A specific group of compounds of formula I are compounds wherein each R^{3a} and R^{3b} is independently selected from H, halogen, (C_1-C_3)alkyl, and (C_1-C_3)haloalkyl.

[0073] A specific group of compounds of formula I are compounds wherein each R^{3a} and R^{3b} is independently selected from H, (C_1-C_3)alkyl, and (C_1-C_3)haloalkyl.

[0074] A specific group of compounds of formula I are compounds wherein each R^{3a} and R^{3b} is independently selected from H and (C_1-C_3)alkyl.

[0075] A specific group of compounds of formula I are compounds wherein each R^{3a} and R^{3b} is independently selected from H, methyl and ethyl.

[0076] A specific group of compounds of formula I are compounds wherein each R^{3a} and R^{3b} is independently selected from H and methyl.

[0077] A specific group of compounds of formula I are compounds wherein R^{3a} is H and R^{3b} is (C_1-C_3)alkyl.

[0078] A specific group of compounds of formula I are compounds wherein R^{3a} is H and R^{3b} is methyl or ethyl.

[0079] A specific group of compounds of formula I are compounds wherein R^{3a} is H and R^{3b} is methyl.

[0080] A specific value for R^{3a} and R^{3b} is H.

[0081] A specific value for R^2 is phenyl or a 5-membered monocyclic-heteroaryl, wherein any phenyl or 5-membered monocyclic-heteroaryl of R^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^5 groups.

[0082] A specific value for R^2 is phenyl or a 5-membered monocyclic-heteroaryl, wherein any phenyl or 5-membered monocyclic-heteroaryl of R^2 is substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^5 groups.

[0083] A specific value for R^2 is phenyl optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^5 groups.

[0084] A specific value for R^2 is phenyl substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^5 groups.

[0085] A specific value for Z^5 is halogen.

[0086] A specific value for Z^5 is fluoro.

[0087] A specific value for R^2 is 3,5-difluorophenyl.

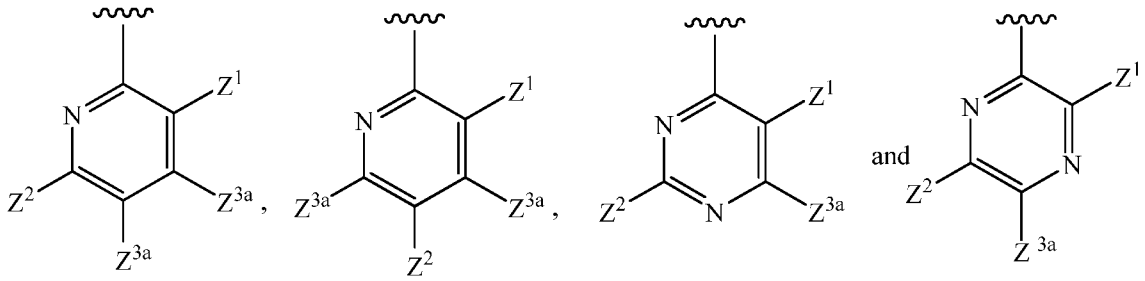
[0088] A specific value for A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein any pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl of A is substituted with one Z^1 group at the position shown, one Z^2 group and optionally substituted with one or more (e.g., 1 or 2) Z^3 groups.

[0089] A specific value for A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein any pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl of A is substituted with one Z^1 group at the position shown and one Z^2 group.

[0090] A specific value for A is pyridinyl, wherein any pyridinyl of A is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with one or more (e.g., 1 or 2) Z^3 groups.

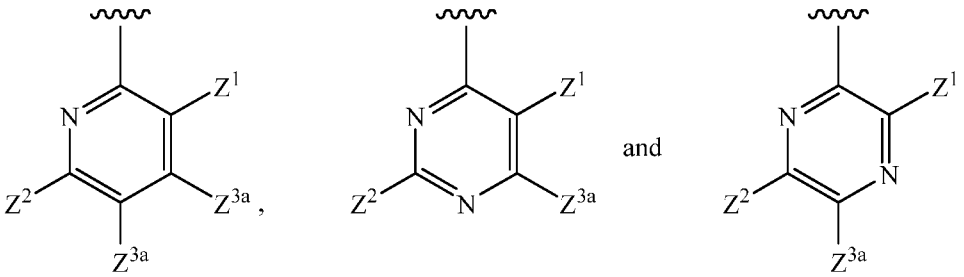
[0091] A specific value for A is pyridinyl, wherein any pyridinyl of A is substituted with one Z^1 group at the position shown and one Z^2 group

[0092] A specific value for A is selected from:



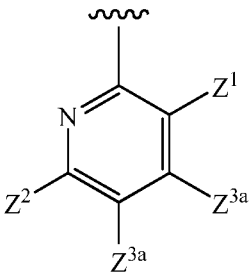
wherein each Z^{3a} is independently selected from H and Z^3.

[0093] A specific value for A is selected from:

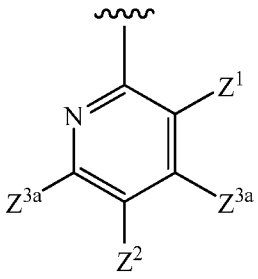


wherein each Z^{3a} is independently selected from H and Z^3.

[0094] A specific value for A is selected from:

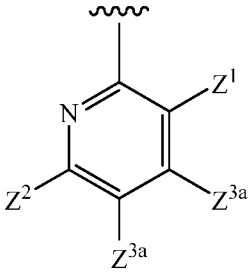


and



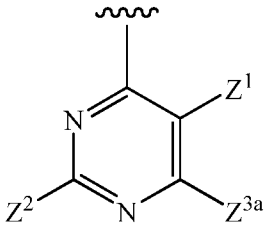
wherein each Z^{3a} is independently selected from H and Z^3.

[0095] A specific value for A is:



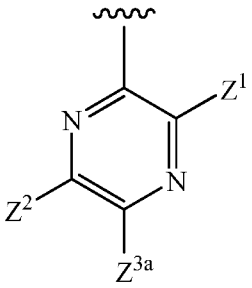
wherein each Z^{3a} is independently selected from H and Z^3.

[0096] A specific value for A is:



wherein each Z^{3a} is independently selected from H and Z^3.

[0097] A specific value for A is:



wherein each Z^{3a} is independently selected from H and Z^3.

[0098] A specific value for Z^{3a} is H.

[0099] A specific value for Z^1 is selected from phenyl, 5-14 membered heteroaryl and 3-14 membered heterocycle, wherein any phenyl, 5-14 membered heteroaryl and 3-14 membered

heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups.

[0100] A specific value for Z^1 is selected from phenyl, 5-12 membered heteroaryl and 3-12 membered heterocycle, wherein any phenyl, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups.

[0101] A specific value for Z^1 is selected from phenyl, 5-14 membered heteroaryl and 3-14 membered heterocycle, wherein any phenyl, 5-14 membered heteroaryl and 3-14 membered heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups.

[0102] A specific value for Z^1 is selected from phenyl, 5-12 membered heteroaryl and 3-12 membered heterocycle, wherein any phenyl, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups.

[0103] A specific value for Z^1 is selected from phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups.

[0104] A specific value for Z^1 is selected from phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups.

[0105] A specific value for Z^1 is selected from phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle, wherein the 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle have 1-11 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups.

[0106] A specific value for Z^1 is selected from phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle, wherein the 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle have 1-11 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups.

[0107] A specific value for Z^1 is selected from phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle, wherein the 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle have 4-11 carbon atoms and 1-3 heteroatoms in the ring system, and wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups.

[0108] A specific value for Z^1 is selected from phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle, wherein the 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle have 4-11 carbon atoms and 1-3 heteroatoms in the ring system, and wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups.

[0109] A specific value for Z^1 is selected from 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle, wherein any from 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups.

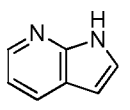
[0110] A specific value for Z^1 is selected from 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle, wherein any from 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle of Z^1 is optionally substituted with one or more Z^{1a} groups.

[0111] A specific value for Z^1 is selected from 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle, wherein the 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle have 3-9 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups.

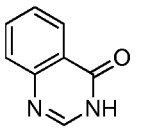
[0112] A specific value for Z^1 is selected from 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle, wherein the 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle have 3-9 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle of Z^1 is optionally substituted with one or more Z^{1a} groups.

[0113] A specific value for Z^1 is selected from phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 4-oxo-3,4-dihydroquinazolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, 1H-2-oxo-pyridinyl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolinyl, wherein any phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 4-oxo-3,4-dihydroquinazolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, 1H-2-oxo-pyridinyl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolinyl of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups. A specific value for Z^1 is 1H-indazol-7-yl, wherein Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups.

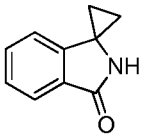
[0114] A specific value for Z^1 is selected from phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 4-oxo-3,4-dihydroquinazolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, 1H-2-oxo-pyridinyl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolinyl as shown by the following formulas;



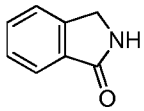
1*H*-pyrrolo[2,3-*b*]pyridinyl



4-oxo-3,4-dihydroquinazolinyl

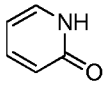


3-oxospiro[cyclopropane-1,1'-isoindolin]-yl



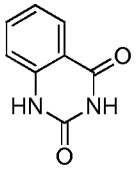
1-oxoisoindolinyl

phenyl

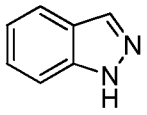
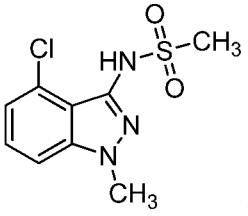
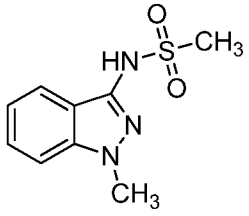


1H-2-oxo-pyridinyl

and



2,4-dioxo-1,2,3,4-tetrahydroquinazolinyl

wherein any phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 4-oxo-3,4-dihydroquinazolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, 1H-2-oxo-pyridinyl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolinyl of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups. A specific value for Z^1 is  . A specific value for Z^1 is  or  .

[0115] A specific value for Z^1 is selected from phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, pyridinyl and quinazolinyl, wherein any phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, pyridinyl and quinazolinyl of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups.

[0116] A specific value for Z^1 is selected from phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 4-oxo-3,4-dihydroquinazolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, 1H-2-oxo-pyridinyl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolinyl, wherein any phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 4-oxo-3,4-dihydroquinazolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, 1H-2-oxo-pyridinyl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolinyl of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups.

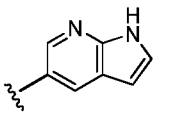
[0117] A specific value for Z^1 is selected from phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, pyridinyl and quinazolinyl, wherein any phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, pyridinyl and quinazolinyl of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups.

[0118] A specific value for Z^1 is selected from phenyl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1-oxoisoindolin-5-yl, 1-oxoisoindolin-4-yl, 4-oxo-3,4-dihydroquinazolin-8-yl, 3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl, 1H-2-oxo-pyridin-4-yl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolin-8-yl, wherein any phenyl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1-oxoisoindolin-5-yl, 1-oxoisoindolin-4-yl, 4-oxo-3,4-dihydroquinazolin-8-yl, 3'-oxospiro[cyclopropane-1,1'-

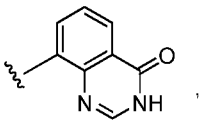
isoindolin]-5'-yl, 1H-2-oxo-pyridin-4-yl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolin-8-yl of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups.

[0119] A specific value for Z^1 is selected from phenyl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1-oxoisoindolin-5-yl, 1-oxoisoindolin-4-yl, 3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl, pyridin-4-yl and quinazolin-8-yl, wherein any phenyl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1-oxoisoindolin-5-yl, 1-oxoisoindolin-4-yl, 3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl, pyridin-4-yl and quinazolin-8-yl of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups.

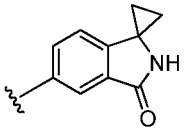
[0120] A specific value for Z^1 is selected from phenyl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1-oxoisoindolin-5-yl, 1-oxoisoindolin-4-yl, 4-oxo-3,4-dihydroquinazolin-8-yl, 3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl, 1H-2-oxo-pyridin-4-yl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolin-8-yl as shown by the following formulas;



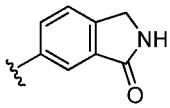
1*H*-pyrrolo[2,3-*b*]pyridin-5-yl



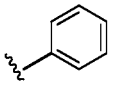
4-oxo-3,4-dihydroquinazolin-8-yl



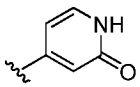
3-oxospiro[cyclopropane-1,1'-isoindolin]-5-yl



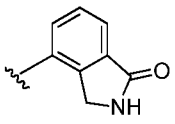
1-oxoisoindolin-6-yl



phenyl

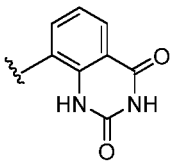


1H-2-oxo-pyridin-4-yl

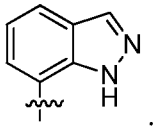
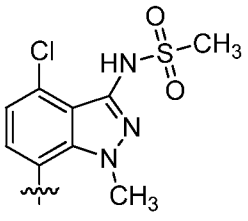
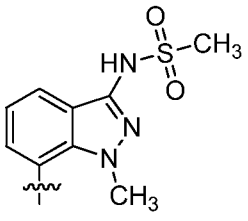


1-oxoisoindolin-4-yl

and



2,4-dioxo-1,2,3,4-tetrahydroquinazolin-8-yl

wherein any phenyl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1-oxoisoindolin-5-yl, 1-oxoisoindolin-4-yl, 4-oxo-3,4-dihydroquinazolin-8-yl, 3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl, 1H-2-oxo-pyridin-4-yl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolin-8-yl of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups. A specific value for Z^1 is  . A specific value for Z^1 is  or  .

[0121] A specific value for Z^1 is selected from phenyl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1-oxoisoindolin-5-yl, 1-oxoisoindolin-4-yl, 4-oxo-3,4-dihydroquinazolin-8-yl, 3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl, 1H-2-oxo-pyridin-4-yl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolin-8-yl, wherein any phenyl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1-oxoisoindolin-5-yl, 1-oxoisoindolin-4-yl, 4-oxo-3,4-dihydroquinazolin-8-yl, 3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl, 1H-2-oxo-pyridin-4-yl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolin-8-yl of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups.

[0122] A specific value for Z^1 is selected from phenyl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1-oxoisoindolin-5-yl, 1-oxoisoindolin-4-yl, 3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl, pyridin-4-yl and quinazolin-8-yl, wherein any phenyl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1-oxoisoindolin-5-yl, 1-oxoisoindolin-4-yl, 3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl, pyridin-4-yl and quinazolin-8-yl of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups.

[0123] A specific group of compounds of formula I are compounds wherein Z^1 is not substituted with Z^{1b}.

[0124] A specific value for each Z^{1a} is independently selected from halogen, $-OR^{n1}$ and $-C(O)NR^{q1}R^{r1}$.

[0125] A specific value for each Z^{1a} is independently selected from halogen and $-C(O)NR^{q1}R^{r1}$.

[0126] A specific value for each R^{n1}, R^{q1} and R^{r1} are each H.

[0127] A specific value for each Z^{1a} is independently selected from halogen, -OH and $-C(O)NH_2$.

[0128] A specific value for each Z^{1a} is independently selected from fluoro, -OH and $-C(O)NH_2$.

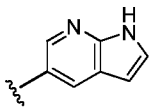
[0129] A specific value for R_{q1} and R_{r1} is H.

[0130] A specific value for each Z^{1a} is independently selected from halogen and $-NR^{n1}S(O)_2R^{p1}$.

[0131] A specific value for each Z^{1b} is $(C_1\text{-}C_8)$alkyl, which may be same or different.

[0132] In certain embodiments, each Z^{1a} is independently selected from halogen and $-NR^{n1}S(O)_2R^{p1}$ and each Z^{1b} is $(C_1\text{-}C_8)$alkyl, which may be same or different..

[0133] A specific value for Z^1 is selected from: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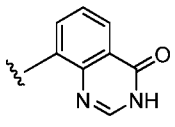
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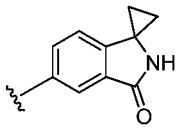
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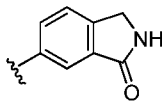
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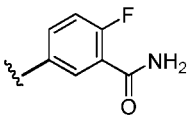
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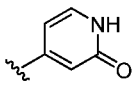
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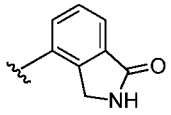
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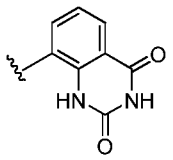
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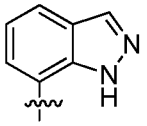
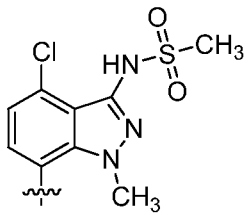
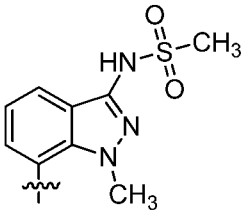
[0134] A specific value for Z^1 is  . A specific value for Z^1 is  or  .

[0135] A specific value for Z^2 is selected from $(C_2\text{-}C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle and $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl and 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_2\text{-}C_8)$alkynyl of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2c} groups.

[0136] A specific value for Z^2 is selected from $(C_2\text{-}C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle and $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl and 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2c} groups, and wherein any $(C_2\text{-}C_8)$alkynyl of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2c} groups.

[0137] A specific value for Z^2 is selected from $(C_2\text{-}C_8)$alkynyl, phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heterocycle and $-C(O)NR^{q3}R^{r3}$, wherein any phenyl, 5-6 membered C-linked-

monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl and 8-10 membered C-linked-bicyclic-heterocycle of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any (C_2-C_8)alkynyl of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2c} groups.

[0138] A specific value for Z^2 is selected from (C_2-C_8)alkynyl, phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heterocycle and -C(O)$NR^{q3}R^{r3}$, wherein any phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl and 8-10 membered C-linked-bicyclic-heterocycle of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2c} groups, and wherein any (C_2-C_8)alkynyl of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2c} groups.

[0139] A specific value for Z^2 is selected from (C_2-C_8)alkynyl, phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heterocycle and -C(O)$NR^{q3}R^{r3}$, wherein the 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl and 8-10 membered C-linked-bicyclic-heterocycle have 1-9 carbon atoms and 1-4 heteroatoms in the ring system, and wherein any phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered and C-linked-bicyclic-heterocycle of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any (C_2-C_8)alkynyl of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2c} groups.

[0140] A specific value for Z^2 is selected from (C_2-C_8)alkynyl, phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heterocycle and -C(O)$NR^{q3}R^{r3}$, wherein the 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl and 8-10 membered C-linked-bicyclic-heterocycle have 1-9 carbon atoms and 1-4 heteroatoms in the ring system, and wherein any phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered and C-linked-bicyclic-heterocycle of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2c} groups, and wherein any (C_2-C_8)alkynyl of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2c} groups.

[0141] A specific value for Z^2 is selected from 4-methylpentynyl, phenyl, pyridinyl, 1H-2-oxo-pyridinyl, triazolyl, 1-oxoisoindolinyl, 1H-pyrrolo[2,3-b]pyridinyl and -C(O)$NR^{q3}R^{r3}$, wherein any phenyl, pyridinyl, 1H-2-oxo-pyridinyl, triazolyl, 1-oxoisoindolinyl and 1H-

pyrrolo[2,3-b]pyridinyl of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any 4-methylpentynyl of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2c} groups.

[0142] A specific value for Z^2 is selected from 4-methylpentynyl, phenyl, pyridinyl, 1H-2-oxo-pyridinyl, triazolyl, 1-oxoisoindolinyl, 1H-pyrrolo[2,3-b]pyridinyl and $-C(O)NR^{q3}R^{r3}$, wherein any phenyl, pyridinyl, 2-oxopyridinyl, triazolyl, 1-oxoisoindolinyl and 1H-pyrrolo[2,3-b]pyridinyl of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2c} groups, and wherein any 4-methylpentynyl of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2c} groups.

[0143] A specific value for Z^2 is selected from 4-methylpentyn-1-yl, phenyl, pyridin-4-yl, 1H-2-oxo-pyridin-2-yl, triazol-4-yl, 1-oxoisoindolin-6-yl, 1H-pyrrolo[2,3-b]pyridine-5-yl and $-C(O)NR^{q3}R^{r3}$, wherein any phenyl, pyridin-4-yl, 1H-2-oxo-pyridin-2-yl, triazol-4-yl, 1-oxoisoindolin-6-yl and 1H-pyrrolo[2,3-b]pyridine-5-yl of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any 4-methylpentyn-1-yl of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2c} groups.

[0144] A specific value for Z^2 is selected from 4-methylpentyn-1-yl, phenyl, pyridin-4-yl, 1H-2-oxo-pyridin-2-yl, triazol-4-yl, 1-oxoisoindolin-6-yl, 1H-pyrrolo[2,3-b]pyridine-5-yl and $-C(O)NR^{q3}R^{r3}$, wherein any phenyl, pyridin-4-yl, 1H-2-oxo-pyridin-2-yl, triazol-4-yl, 1-oxoisoindolin-6-yl and 1H-pyrrolo[2,3-b]pyridine-5-yl of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2c} groups, and wherein any 4-methylpentyn-1-yl of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2c} groups.

[0145] A specific group of compounds of formula I are compounds wherein each Z^2 is not substituted with Z^{2b}.

[0146] A specific group of compounds of formula I are compounds wherein each Z^2 is optionally substituted with one or more Z^{2c} groups.

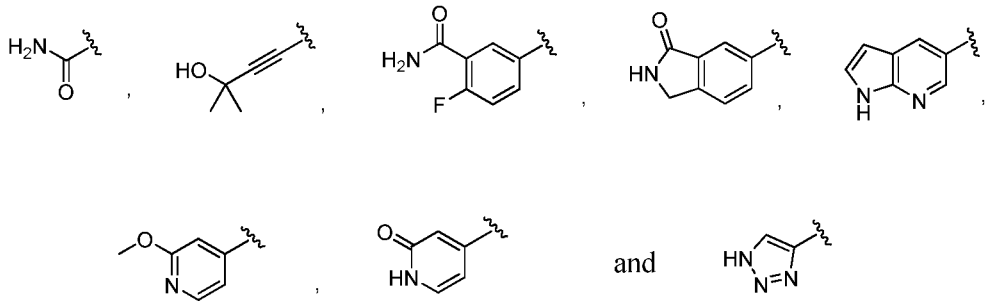
[0147] A specific value for each Z^{2c} is independently selected from halogen, $-OR_{n4}$ and $-C(O)NR_{q4}R_{r4}$.

[0148] A specific group of compounds of formula I are compounds wherein R^{n4} is H or methyl, and R^{q4} and R^{r4} are each H.

[0149] A specific value for R^{n4} is H or methyl.

[0150] A specific value for each R^{q4} and R^{r4} is H.

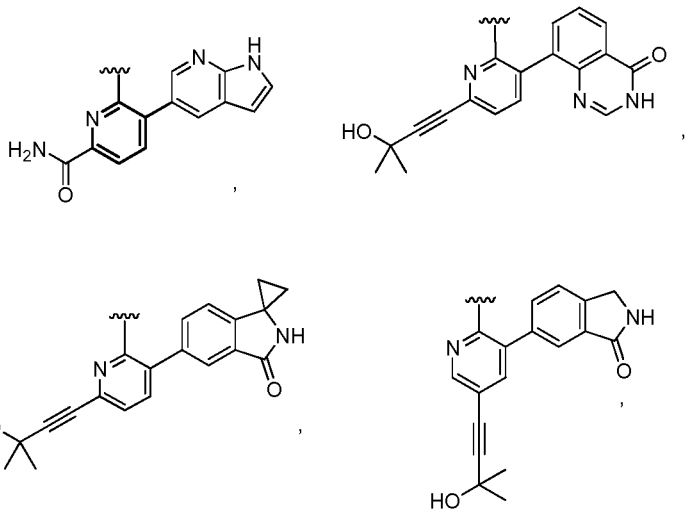
[0151] A specific value for Z^2 is selected from:

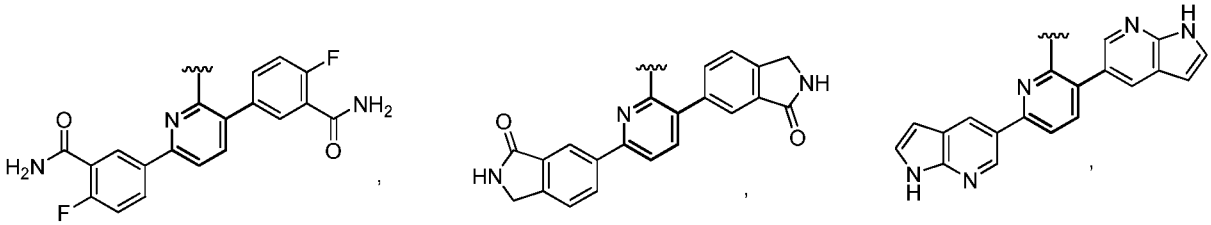


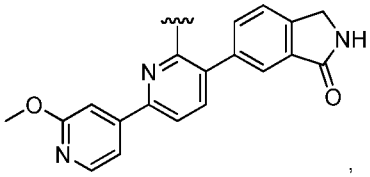
and

.

[0152] A specific value for A-Z^1 is selected from:



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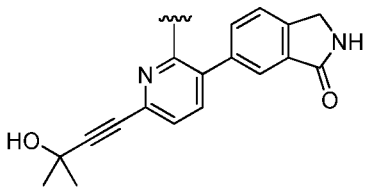
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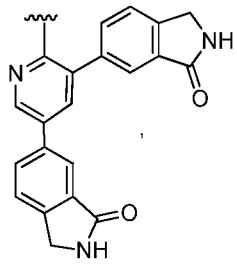
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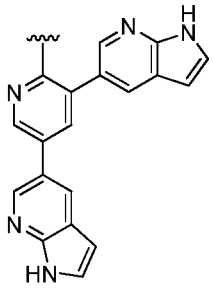
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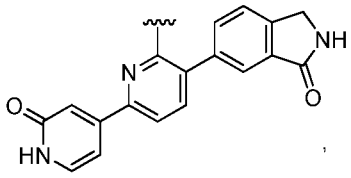
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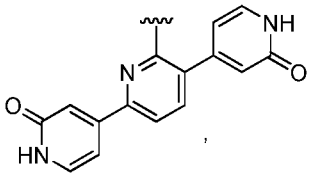
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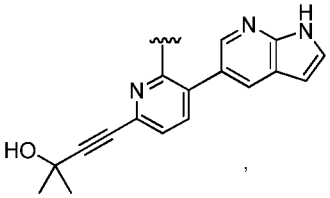
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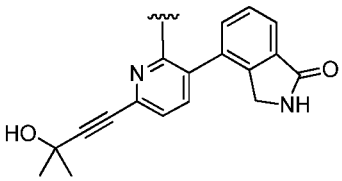
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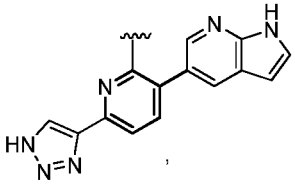
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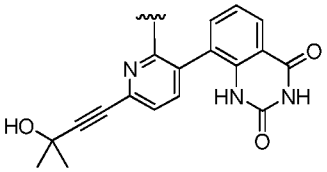
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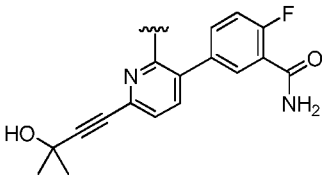
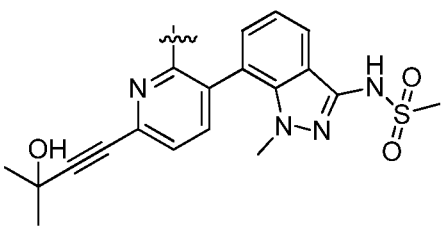
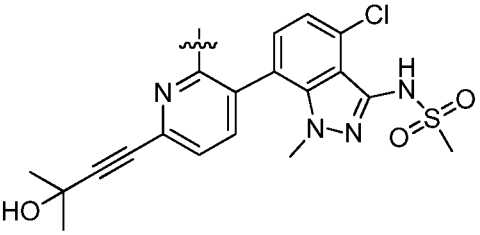

.

[0153] A specific value for A-Z^1 is selected from:


and.

.

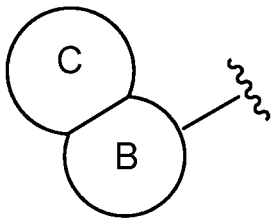
[0154] A specific value for R^1 is a 5-12 membered heteroaryl, wherein any 5-12 membered heteroaryl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) Z^4 groups.

[0155] A specific value for R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) Z^4 groups.

[0156] A specific value for R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein the 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl have 4-10 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) Z^4 groups.

[0157] A specific value for R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein the 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl contains at least one partially unsaturated ring, and wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

[0158] A specific value for R^1 has the following formula IIa:



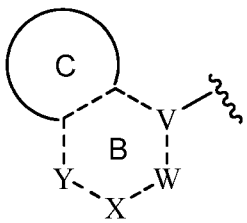
IIa

wherein:

C together with the two carbon atoms of ring B to which it is attached forms a 3-7 membered monocyclic-carbocycle, 5-8 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-8 membered bicyclic heterocycle, wherein any 3-7 membered monocyclic-carbocycle, 5-8 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-8 membered bicyclic heterocycle of C is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^4 groups; and

B is a 5 or 6 membered monocyclic-heteroaryl with 1, 2 or 3 nitrogen atoms, wherein B is optionally substituted with one or more or (e.g. 1, 2, 3, 4 or 5) Z^4 groups.

[0159] A specific value for R^1 has the following IIb:



IIb

wherein:

C together with the two carbon atoms of ring B to which it is attached forms a 3-7 membered monocyclic-carbocycle, 5-8 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-8 membered bicyclic heterocycle, wherein any 3-7 membered monocyclic-carbocycle, 5-8 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-8 membered bicyclic heterocycle of C is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^4 groups; and

B is a 5 or 6 membered monocyclic-heteroaryl having 1, 2 or 3 nitrogen atoms;

V is C or N;

W is CZ^{4c}, NZ^{4c} or N;

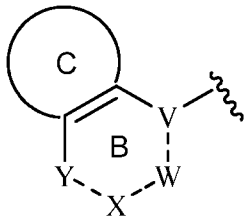
X is CZ^{4c}, NZ^{4c} or N;

Y is CZ^{4c}, N or absent;

the dashed bonds are selected from single bonds and double bonds, wherein the dashed bonds, V, W, X and Y are selected so that the 5 or 6 membered monocyclic-heteroaryl B is aromatic; and

each Z^{4c} is independently selected from H or Z^4.

[0160] A specific value for R^1 has the following formula IIc:



IIc

wherein:

C together with the two carbon atoms of ring B to which it is attached forms a 3-7 membered monocyclic-carbocycle, 5-8 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-8 membered bicyclic heterocycle, wherein any 3-7 membered monocyclic-carbocycle, 5-8 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-8 membered bicyclic heterocycle of C is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^4 groups; and

B is a 5 or 6 membered monocyclic-heteroaryl having 1, 2 or 3 nitrogen atoms;

V is C or N;

W is CZ^{4c} or N;

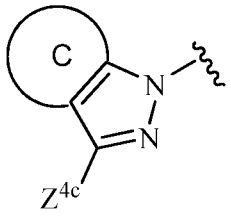
X is CZ^{4c}, NZ^{4c} or N;

Y is CZ^{4c}, N or absent;

the dashed bonds are selected from single bonds and double bonds, wherein the dashed bonds, V, W, X and Y are selected so that the 5 or 6 membered monocyclic-heteroaryl B is aromatic; and

each Z^{4c} is independently selected from H or Z^4.

[0161] A specific value for R^1 has the following R^1 has the following formula IId:



IId

wherein:

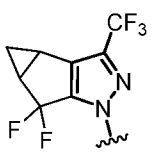
C together with the two carbon atoms to which it is attached forms a 3-7 membered monocyclic-carbocycle, 5-9 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-9 membered bicyclic heterocycle, wherein any 3-7 membered monocyclic-carbocycle, 5-9 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-9 membered bicyclic heterocycle of C is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^4 groups; and

each Z^{4c} is independently selected from H or Z^4.

[0162] A specific value for each Z^4 is independently selected from $(C_1\text{-}C_6)$alkyl and halogen, wherein any $(C_1\text{-}C_6)$alkyl of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) halogen.

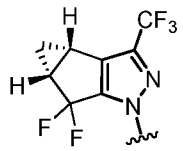
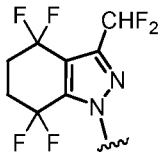
[0163] A specific value for each Z^4 is independently selected from fluoro, trifluoromethyl and difluoromethyl.

[0164] A specific value for R^1 is selected from:

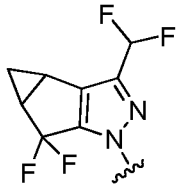
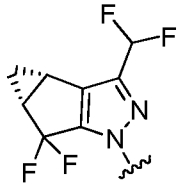


and

[0165] A specific value for R^1 is selected from:


and


.

[0166] A specific value for R^1 is  . A specific value for R^1 is  .

[0167] A specific value for R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein the 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl has 4-9 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

[0168] A specific value for R^1 is a 8-12 membered bicyclic-heteroaryl, wherein the 8-12 membered bicyclic-heteroaryl has 6-9 carbon atoms and 1-3 heteroatoms in the ring system, and wherein any 8-12 membered bicyclic-heteroaryl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

[0169] A specific value for R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein the 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl has 6-9 carbon atoms and 1-3 heteroatoms in the ring system, and wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

[0170] A specific value for R^1 is selected from indolyl and 4,5,6,7-tetrahydro-indazolyl, wherein any indolyl and 4,5,6,7-tetrahydro-indazolyl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

[0171] A specific value for R^1 is selected from indolyl, 4,5,6,7-tetrahydro-indazolyl, 3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole and 1,4,5,5a,6,6a-hexahydrocyclopropa[g]indazole, wherein any indolyl, 4,5,6,7-tetrahydro-indazolyl, 3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole and 1,4,5,5a,6,6a-

hexahydrocyclopropa[g]indazole of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

[0172] A specific value for R^1 is selected from indol-3-yl and 4,5,6,7-tetrahydro-1H-indazol-1-yl, wherein any indol-3-yl and 4,5,6,7-tetrahydro-1H-indazol-1-yl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

[0173] A specific value for R^1 is selected from indol-3-yl, 4,5,6,7-tetrahydro-1H-indazol-1-yl, 3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl and 1,4,5,5a,6,6a-hexahydrocyclopropa[g]indazol-1-yl, wherein any indol-3-yl, 4,5,6,7-tetrahydro-1H-indazol-1-yl, 3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl and 1,4,5,5a,6,6a-hexahydrocyclopropa[g]indazol-1-yl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

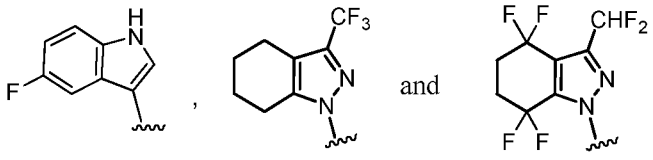
[0174] A specific value for each Z^4 is independently selected from $(C_1\text{-}C_6)$alkyl and halogen, wherein any $(C_1\text{-}C_6)$alkyl of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen.

[0175] A specific value for each Z^4 is independently selected from $(C_1\text{-}C_6)$alkyl, -CN and halogen, wherein any $(C_1\text{-}C_6)$alkyl of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen.

[0176] A specific value for each Z^4 is independently selected from fluoro, trifluoromethyl and difluoromethyl.

[0177] A specific value for each Z^4 is independently selected from fluoro, trifluoromethyl, -CN and difluoromethyl.

[0178] A specific value for R^1 is selected from:



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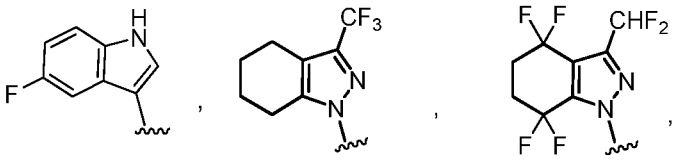
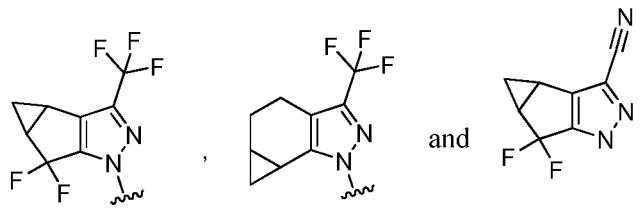
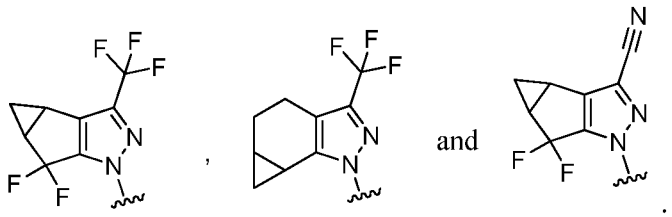
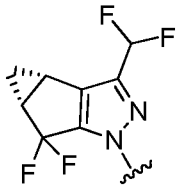
[0179] A specific value for R^1 is selected from:





[0180] A specific value for R^1 is selected from:



[0181] A specific value for R^1 is  . A specific value for R^1 is  .

[0182] In one variation of formula I, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and R^1 is a 5-12 membered heteroaryl, optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, which may be the same or different. In another variation, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups. In another variation, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups; and each Z^4 is independently fluoro, trifluoromethyl, or difluoromethyl.

[0183] In one variation of formula I, A is pyridinyl; and R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups.

[0184] In one variation of formula I, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and R^2 is 3,5-difluorophenyl. In another variation, A is pyridinyl; and R^2 is 3,5-difluorophenyl. In another variation, A is pyrimidinyl; and R^2 is 3,5-difluorophenyl. In another variation, A is pyrazinyl; and R^2 is 3,5-difluorophenyl. In another variation, A is pyridazinyl; and R^2 is 3,5-difluorophenyl.

[0185] In one variation of formula I, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and Z^1 is phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups. In another variation, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and Z^1 is phenyl, optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups. In another variation, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and Z^1 is 5-6 membered monocyclic-heteroaryl or 8-10 membered bicyclic-heteroaryl, wherein any 5-6 membered monocyclic-heteroaryl or 8-10 membered bicyclic-heteroaryl of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups. In another variation, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and Z^1 is 8-10 membered bicyclic-heterocycle or 9-12 membered tricyclic-heterocycle wherein any 8-10 membered bicyclic-heterocycle or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups.

[0186] In one variation of formula I, A is pyridinyl; and Z^1 is phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups. In another variation, A is pyridinyl; and Z^1 is phenyl, optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups. In another variation, A is pyridinyl; and Z^1 is 5-6 membered monocyclic-heteroaryl or 8-10 membered bicyclic-heteroaryl, wherein any 5-6 membered monocyclic-heteroaryl or 8-10 membered bicyclic-heteroaryl of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups. In another variation, A is pyridinyl; and Z^1 is 8-10 membered bicyclic-heterocycle or 9-12 membered tricyclic-heterocycle wherein any 8-10 membered bicyclic-heterocycle or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups.

[0187] In one variation of formula I, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and Z^2 is $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups. In another variation, A is pyridinyl; and Z^2 is $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups. In another variation, A is pyrimidinyl; and Z^2 is $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups. In another variation, A is pyrazinyl; and Z^2 is $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups. In another variation, A is pyridazinyl; and Z^2 is $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups.

[0188] In one variation of formula I, A is pyridinyl substituted with one Z^1 moiety, one Z^2 moiety and no (zero) Z^3 moieties; and Z^2 is $(C_2$-$C_8)$alkynyl or aryl, which Z^2 may be optionally substituted as provided by formula I. In another variation, A is pyridinyl substituted with one Z^1 moiety, one Z^2 moiety and no (zero) Z^3 moieties; and Z^2 is $(C_2$-$C_8)$alkynyl, which Z^2 may be optionally substituted as provided by formula I. In a particular variation, A is pyridinyl substituted with one Z^1 moiety, one Z^2 moiety at the position alpha to the nitrogen atom of the

pyridinyl ring, and no (zero) Z^3 moieties, wherein Z^2 is $(C_2$-$C_8)$alkynyl, which Z^2 may be optionally substituted as provided by formula I.

[0189] In one variation of formula I, R^1 is a 5-12 membered heteroaryl optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, which may be the same or different; and Z^1 is phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups. In another variation, R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups; and Z^1 is phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups.

[0190] In one variation of formula I, R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups; and Z^1 is 8-10 membered bicyclic-heteroaryl or 8-10 membered bicyclic-heterocycle wherein any 8-10 membered bicyclic-heteroaryl or 8-10 membered bicyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups.

[0191] In one variation of formula I, R^1 is a 5-12 membered heteroaryl optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, which may be the same or different; and Z^2 is $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups. In another variation, R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups; and Z^2 is $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle,

or -C(O)$NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, and wherein any (C_2-C_8)alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} group.

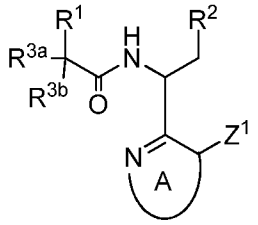
[0192] In one variation of formula I, Z^1 is phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups; and Z^2 is (C_2-C_8)alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, or -C(O)$NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, and wherein any (C_2-C_8)alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups.

[0193] In one variation of formula I, Z^1 is bicyclic-heteroaryl optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups; and Z^2 is (C_2-C_8)alkynyl optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups.

[0194] In one variation of formula I, R^1 is a 5-12 membered heteroaryl; Z^1 is phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups; and Z^2 is (C_2-C_8)alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, or -C(O)$NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, and wherein any (C_2-C_8)alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups.

Compounds of formula III.

[0195] The present disclosure provides compounds of formula III:



III

wherein

A is a 6-membered monocyclic-heteroaryl with one or two nitrogen atoms, wherein the 6-membered monocyclic-heteroaryl is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with 1 or 2 Z^3 groups, wherein the Z^3 groups are the same or different;

R^1 is 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle, wherein any 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle of R^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, wherein the Z^4 groups are the same or different;

R^2 is phenyl optionally substituted with 1, 2, 3, 4 or 5 halogen, which are the same or different;

each R^{3a} and R^{3b} is independently H or $(C_1$-$C_3)$alkyl;

Z^1 is 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle, wherein any 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b}, wherein the Z^{1a} and Z^{1b} groups are the same or different;

each Z^{1a} is independently $(C_3$-$C_7)$carbocycle, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, $-OR^{n1}$, $-OC(O)R^{p1}$, $-OC(O)NR^{q1}R^{r1}$, $-SR^{n1}$, $-S(O)R^{p1}$, $-S(O)_2OH$, $-S(O)_2R^{p1}$, $-S(O)_2NR^{q1}R^{r1}$, $-NR^{q1}R^{r1}$, $-NR^{n1}COR^{p1}$, $-NR^{n1}CO_2R^{p1}$, $-NR^{n1}CONR^{q1}R^{r1}$, $-NR^{n1}S(O)_2R^{p1}$, $-NR^{n1}S(O)_2OR^{p1}$, $-NR^{n1}S(O)_2NR^{q1}R^{r1}$, $-C(O)R^{n1}$, $-C(O)OR^{n1}$, $-C(O)NR^{q1}R^{r1}$ and $-S(O)_2NR^{n1}COR^{p1}$, wherein any $(C_3$-$C_7)$carbocycle, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{1a} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different;

each Z^{1b} is independently $(C_1$-$C_8)$alkyl optionally substituted with 1, 2, 3, 4 or 5 halogen, which are the same or different;

each Z^{1c} is independently halogen, -CN, -OH, $-NH_2$, $-C(O)NR^{q2}R^{r2}$, or $(C_1$-$C_8)$heteroalkyl;

each Z^{1d} is independently $(C_1\text{-}C_8)$alkyl or $(C_1\text{-}C_8)$haloalkyl;

each R^{n1} is independently H, $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{n1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any $(C_1\text{-}C_8)$alkyl of R^{n1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different;

each R^{p1} is independently $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any $(C_1\text{-}C_8)$alkyl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different;

each R^{q1} and R^{r1} is independently H, $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any $(C_1\text{-}C_8)$alkyl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different, or R^{q1} and R^{r1} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or 7-membered heterocycle is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different;

each R^{q2} and R^{r2} is independently H, $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_7)$carbocycle, or R^{q2} and R^{r2} together with the nitrogen to which they are attached form a 5, 6, or 7-membered heterocycle;

Z^2 is $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, $-C(O)R^{n3}$, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, wherein the Z^{2b} and Z^{2c} groups are the same or different, and wherein any $(C_2\text{-}C_8)$alkenyl or $(C_2\text{-}C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4, or 5 Z^{2c} groups, wherein the Z^{2c} groups are the same or different;

each R^{n3} is independently H or $(C_1\text{-}C_4)$alkyl;

each R^{q3} and R^{r3} is independently H or $(C_1\text{-}C_4)$alkyl;

each Z^{2b} is independently oxo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$heteroalkyl, or $(C_1\text{-}C_4)$haloalkyl;

each Z^{2c} is independently oxo, halogen, -CN, $-OR^{n4}$, $-OC(O)R^{p4}$, $-OC(O)NR^{q4}R^{r4}$, $-SR^{n4}$, $-S(O)R^{p4}$, $-S(O)_2OH$, $-S(O)_2R^{p4}$, $-S(O)_2NR^{q4}R^{r4}$, $-NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}CONR^{q4}R^{r4}$, $-NR^{n4}S(O)_2R^{p4}$, $-NR^{n4}S(O)_2OR^{p4}$, $-NR^{n4}S(O)_2NR^{q4}R^{r4}$, $-NO_2$, $-C(O)R^{n4}$, $-C(O)OR^{n4}$, or $-C(O)NR^{q4}R^{r4}$;

each R^{n4} is independently H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, or $(C_1\text{-}C_4)$heteroalkyl;

each R^{p4} is independently $(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_4)$haloalkyl, or $(C_1\text{-}C_4)$heteroalkyl;

each R^{q4} and R^{r4} is independently H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, or $(C_1\text{-}C_4)$heteroalkyl;

each Z^3 is independently a $(C_1\text{-}C_4)$heteroalkyl or halogen;

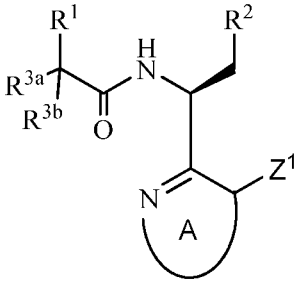
each Z^4 is independently oxo, $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_7)$carbocycle, halogen, -CN, $-OR^{n5}$, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-C(O)R^{n5}$, $-C(O)OR^{n5}$, or $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3\text{-}C_7)$carbocycle or $(C_1\text{-}C_8)$alkyl of Z^4 is optionally substituted with 1, 2, 3, 4 or 5 Z^{4a} groups, wherein the Z^{4a} groups are the same or different;

each Z^{4a} is independently halogen, -CN, or $-OR^{n6}$; and

each R^{n5}, R^{p5}, R^{q5}, R^{r5}, and R^{n6} is independently H or $(C_1\text{-}C_4)$alkyl;

or a pharmaceutically acceptable salt thereof.

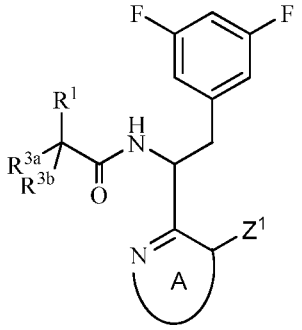
[0196] In certain embodiments, a compound of formula III is a compound of formula IIIa.



IIIa

or a pharmaceutically acceptable salt thereof.

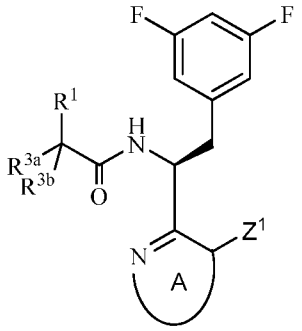
[0197] In certain embodiments, a compound of formula III is a compound of formula IIIb.



IIIb

or a pharmaceutically acceptable thereof.

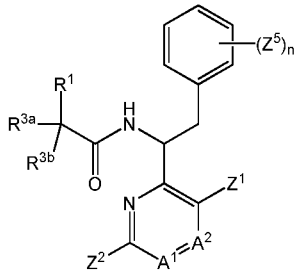
[0198] In certain embodiments, a compound of formula III is a compound of formula IIIc.



IIIc

or a pharmaceutically acceptable thereof.

[0199] The present disclosure provides compounds of formula IIId:



IIId

wherein

A^1 is CH, C-Z^3, or nitrogen;

A^2 is CH or nitrogen;

R^1 is 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle, wherein any 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle of R^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, wherein the Z^4 groups are the same or different;

each R^{3a} and R^{3b} is independently H or $(C_1$-$C_3)$alkyl;

Z^1 is 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle, wherein any 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b}, wherein the Z^{1a} and Z^{1b} groups are the same or different;

each Z^{1a} is independently $(C_3$-$C_7)$carbocycle, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, $-OR^{n1}$, $-OC(O)R^{p1}$, $-OC(O)NR^{q1}R^{r1}$, $-SR^{n1}$, $-S(O)R^{p1}$, $-S(O)_2OH$, $-S(O)_2R^{p1}$, $-S(O)_2NR^{q1}R^{r1}$, $-NR^{q1}R^{r1}$, $-NR^{n1}COR^{p1}$, $-NR^{n1}CO_2R^{p1}$, $-NR^{n1}CONR^{q1}R^{r1}$, $-NR^{n1}S(O)_2R^{p1}$, $-NR^{n1}S(O)_2OR^{p1}$, $-NR^{n1}S(O)_2NR^{q1}R^{r1}$, $-C(O)R^{n1}$, $-C(O)OR^{n1}$, $-C(O)NR^{q1}R^{r1}$ and $-S(O)_2NR^{n1}COR^{p1}$, wherein any $(C_3$-$C_7)$carbocycle, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{1a} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different;

each Z^{1b} is independently $(C_1$-$C_8)$alkyl optionally substituted with 1, 2, 3, 4 or 5 halogen, which are the same or different;

each Z^{1c} is independently halogen, -CN, -OH, $-NH_2$, $-C(O)NR^{q2}R^{r2}$, or $(C_1$-$C_8)$heteroalkyl;

each Z^{1d} is independently $(C_1$-$C_8)$alkyl or $(C_1$-$C_8)$haloalkyl;

each R^{n1} is independently H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{n1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any $(C_1$-$C_8)$alkyl of R^{n1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different;

each R^{p1} is independently $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any $(C_1$-$C_8)$alkyl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different;

each R^{q1} and R^{r1} is independently H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{q1} or R^{r1} is optionally

substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any $(C_1$-$C_8)$alkyl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different, or R^{q1} and R^{r1} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or 7-membered heterocycle is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different;

each R^{q2} and R^{r2} is independently H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, or R^{q2} and R^{r2} together with the nitrogen to which they are attached form a 5, 6, or 7-membered heterocycle;

Z^2 is $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, $-C(O)R^{n3}$, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, wherein the Z^{2b} and Z^{2c} groups are the same or different, and wherein any $(C_2$-$C_8)$alkenyl or $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4, or 5 Z^{2c} groups, wherein the Z^{2c} groups are the same or different;

each R^{n3} is independently H or $(C_1$-$C_4)$alkyl;

each R^{q3} and R^{r3} is independently H or $(C_1$-$C_4)$alkyl;

each Z^{2b} is independently oxo, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$heteroalkyl or $(C_1$-$C_4)$haloalkyl;

each Z^{2c} is independently oxo, halogen, -CN, $-OR^{n4}$, $-OC(O)R^{p4}$, $-OC(O)NR^{q4}R^{r4}$, $-SR^{n4}$, $-S(O)R^{p4}$, $-S(O)_2OH$, $-S(O)_2R^{p4}$, $-S(O)_2NR^{q4}R^{r4}$, $-NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}CONR^{q4}R^{r4}$, $-NR^{n4}S(O)_2R^{p4}$, $-NR^{n4}S(O)_2OR^{p4}$, $-NR^{n4}S(O)_2NR^{q4}R^{r4}$, $-NO_2$, $-C(O)R^{n4}$, $-C(O)OR^{n4}$, or $-C(O)NR^{q4}R^{r4}$;

each R^{n4} is independently H, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, or $(C_1$-$C_4)$heteroalkyl;

each R^{p4} is independently $(C_1$-$C_8)$alkyl, $(C_1$-$C_4)$haloalkyl, or $(C_1$-$C_4)$heteroalkyl;

each R^{q4} and R^{r4} is independently H, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, or $(C_1$-$C_4)$heteroalkyl;

each Z^3 is independently a $(C_1$-$C_4)$heteroalkyl;

each Z^4 is independently oxo, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, halogen, -CN, $-OR^{n5}$, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-C(O)R^{n5}$, $-C(O)OR^{n5}$, or $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3$-$C_7)$carbocycle or $(C_1$-$C_8)$alkyl of Z^4 is optionally substituted with 1, 2, 3, 4 or 5 Z^{4a} groups, wherein the Z^{4a} groups are the same or different;

each Z^{4a} is independently halogen, -CN, or $-OR^{n6}$;

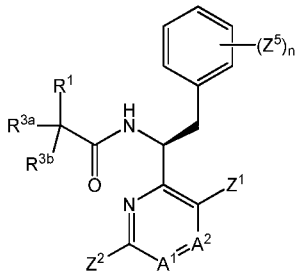
each R^{n5}, R^{p5}, R^{q5}, R^{r5}, and R^{n6} is independently H or $(C_1$-$C_4)$alkyl;

each Z^5 is independently halogen, which may be same or different; and

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof.

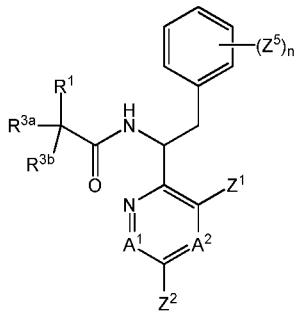
[0200] In certain embodiments, a compound of formula IIId is a compound of formula IIIe.



IIIe

or a pharmaceutically acceptable salt thereof.

[0201] The present disclosure provides compounds of formula IIIf:



IIIf

wherein

A^1 is CH, C-Z^3, or nitrogen;

A^2 is CH or nitrogen;

R^1 is 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle, wherein any 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle of R^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, wherein the Z^4 groups are the same or different;

each R^{3a} and R^{3b} is independently H or (C_1-C_3)alkyl;

Z^1 is 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle, wherein any 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b}, wherein the Z^{1a} and Z^{1b} groups are the same or different;

each Z^{1a} is independently (C_3-C_7)carbocycle, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, -OR^{n1}, -$OC(O)R^{p1}$, -$OC(O)NR^{q1}R^{r1}$, -SR^{n1}, -$S(O)R^{p1}$, -$S(O)_2OH$, -$S(O)_2R^{p1}$, -$S(O)_2NR^{q1}R^{r1}$, -$NR^{q1}R^{r1}$, -$NR^{n1}COR^{p1}$, -$NR^{n1}CO_2R^{p1}$, -$NR^{n1}CONR^{q1}R^{r1}$, -$NR^{n1}S(O)_2R^{p1}$, -$NR^{n1}S(O)_2OR^{p1}$, -$NR^{n1}S(O)_2NR^{q1}R^{r1}$, -$C(O)R^{n1}$, -$C(O)OR^{n1}$, -$C(O)NR^{q1}R^{r1}$ and -$S(O)_2NR^{n1}COR^{p1}$, wherein any (C_3-C_7)carbocycle, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{1a} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different;

each Z^{1b} is independently (C_1-C_8)alkyl optionally substituted with 1, 2, 3, 4 or 5 halogen, which are the same or different;

each Z^{1c} is independently halogen, -CN, -OH, -NH_2, -$C(O)NR^{q2}R^{r2}$, or (C_1-C_8)heteroalkyl;

each Z^{1d} is independently (C_1-C_8)alkyl or (C_1-C_8)haloalkyl;

each R^{n1} is independently H, (C_1-C_8)alkyl, (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{n1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any (C_1-C_8)alkyl of R^{n1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different;

each R^{p1} is independently (C_1-C_8)alkyl, (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any (C_1-C_8)alkyl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different;

each R^{q1} and R^{r1} is independently H, (C_1-C_8)alkyl, (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any (C_1-C_8)alkyl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different, or R^{q1} and R^{r1} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or

7-membered heterocycle is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different;

each R^{q2} and R^{r2} is independently H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, or R^{q2} and R^{r2} together with the nitrogen to which they are attached form a 5, 6, or 7-membered heterocycle;

Z^2 is $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, $-C(O)R^{n3}$, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, wherein the Z^{2b} and Z^{2c} groups are the same or different, and wherein any $(C_2$-$C_8)$alkenyl or $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4, or 5 Z^{2c} groups, wherein the Z^{2c} groups are the same or different;

each R^{n3} is independently H or $(C_1$-$C_4)$alkyl;

each R^{q3} and R^{r3} is independently H or $(C_1$-$C_4)$alkyl;

each Z^{2b} is independently oxo, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$heteroalkyl or $(C_1$-$C_4)$haloalkyl;

each Z^{2c} is independently oxo, halogen, -CN, $-OR^{n4}$, $-OC(O)R^{p4}$, $-OC(O)NR^{q4}R^{r4}$, $-SR^{n4}$, $-S(O)R^{p4}$, $-S(O)_2OH$, $-S(O)_2R^{p4}$, $-S(O)_2NR^{q4}R^{r4}$, $-NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}CONR^{q4}R^{r4}$, $-NR^{n4}S(O)_2R^{p4}$, $-NR^{n4}S(O)_2OR^{p4}$, $-NR^{n4}S(O)_2NR^{q4}R^{r4}$, $-NO_2$, $-C(O)R^{n4}$, $-C(O)OR^{n4}$, or $-C(O)NR^{q4}R^{r4}$;

each R^{n4} is independently H, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, or $(C_1$-$C_4)$heteroalkyl;

each R^{p4} is independently $(C_1$-$C_8)$alkyl, $(C_1$-$C_4)$haloalkyl, or $(C_1$-$C_4)$heteroalkyl;

each R^{q4} and R^{r4} is independently H, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, or $(C_1$-$C_4)$heteroalkyl;

each Z^3 is independently a $(C_1$-$C_4)$heteroalkyl;

each Z^4 is independently oxo, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, halogen, -CN, $-OR^{n5}$, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-C(O)R^{n5}$, $-C(O)OR^{n5}$, or $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3$-$C_7)$carbocycle or $(C_1$-$C_8)$alkyl of Z^4 is optionally substituted with 1, 2, 3, 4 or 5 Z^{4a} groups, wherein the Z^{4a} groups are the same or different;

each Z^{4a} is independently halogen, -CN, or $-OR^{n6}$;

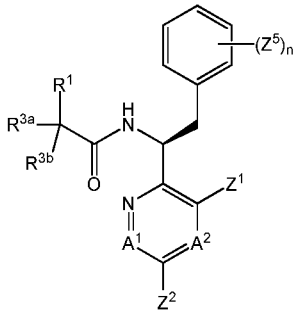
each R^{n5}, R^{p5}, R^{q5}, R^{r5}, and R^{n6} is independently H or $(C_1$-$C_4)$alkyl;

each Z^5 is independently halogen, which may be same or different; and

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof.

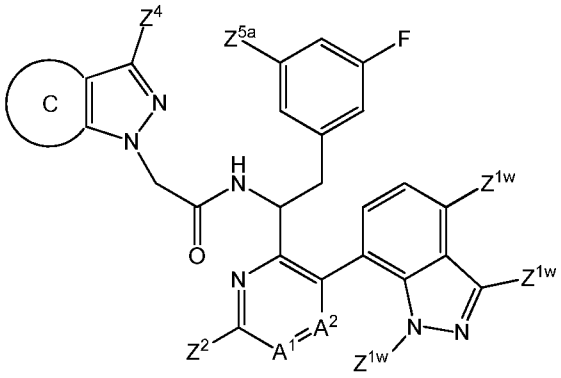
[0202] In certain embodiments, a compound of formula IIIf is a compound of formula IIIg.



IIIg

or a pharmaceutically acceptable salt thereof.

[0203] The present disclosure provides compounds of formula IIIh:



IIIh

wherein

A^1 is CH, C-Z^3, or nitrogen;

A^2 is CH or nitrogen;

C together with the two carbon atoms to which it is attached forms a 3-7 membered monocyclic-carbocycle or 5-9 membered bicyclic-carbocycle, wherein any 3-7 membered monocyclic-carbocycle or 5-9 membered bicyclic-carbocycle of C is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, wherein the Z^4 groups are the same or different;

each Z^{1w} is independently Z^{1a}, Z^{1b} or H;

each Z^{1a} is independently (C_3-C_7)carbocycle, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, -OR^{n1}, -$OC(O)R^{p1}$, -$OC(O)NR^{q1}R^{r1}$, -SR^{n1}, -$S(O)R^{p1}$, -$S(O)_2OH$, -$S(O)_2R^{p1}$, -$S(O)_2NR^{q1}R^{r1}$, -$NR^{q1}R^{r1}$, -$NR^{n1}COR^{p1}$, -$NR^{n1}CO_2R^{p1}$, -$NR^{n1}CONR^{q1}R^{r1}$, -$NR^{n1}S(O)_2R^{p1}$, -$NR^{n1}S(O)_2OR^{p1}$, -$NR^{n1}S(O)_2NR^{q1}R^{r1}$, -$C(O)R^{n1}$, -$C(O)OR^{n1}$, -$C(O)NR^{q1}R^{r1}$ and -$S(O)_2NR^{n1}COR^{p1}$, wherein any (C_3-C_7)carbocycle, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{1a} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different;

each Z^{1b} is independently (C_1-C_8)alkyl optionally substituted with 1, 2, 3, 4 or 5 halogen, which are the same or different;

each Z^{1c} is independently halogen, -CN, -OH, -NH_2, -C(O)$NR^{q2}R^{r2}$, or (C_1-C_8)heteroalkyl;

each Z^{1d} is independently (C_1-C_8)alkyl or (C_1-C_8)haloalkyl;

each R^{n1} is independently H, (C_1-C_8)alkyl, (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{n1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any (C_1-C_8)alkyl of R^{n1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different;

each R^{p1} is independently (C_1-C_8)alkyl, (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any (C_1-C_8)alkyl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different;

each R^{q1} and R^{r1} is independently H, (C_1-C_8)alkyl, (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any (C_1-C_8)alkyl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different, or R^{q1} and R^{r1} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or 7-membered heterocycle is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different;

each R^{q2} and R^{r2} is independently H, (C_1-C_8)alkyl, (C_3-C_7)carbocycle, or R^{q2} and R^{r2} together with the nitrogen to which they are attached form a 5, 6, or 7-membered heterocycle;

Z^2 is (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, -C(O)R^{n3}, or -C(O)$NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, wherein the Z^{2b} and Z^{2c} groups

are the same or different, and wherein any $(C_2$-$C_8)$alkenyl or $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4, or 5 Z^{2c} groups, wherein the Z^{2c} groups are the same or different;

each R^{n3} is independently H or $(C_1$-$C_4)$alkyl;

each R^{q3} and R^{r3} is independently H or $(C_1$-$C_4)$alkyl;

each Z^{2b} is independently oxo, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$heteroalkyl or $(C_1$-$C_4)$haloalkyl;

each Z^{2c} is independently oxo, halogen, -CN, $-OR^{n4}$, $-OC(O)R^{p4}$, $-OC(O)NR^{q4}R^{r4}$, $-SR^{n4}$, $-S(O)R^{p4}$, $-S(O)_2OH$, $-S(O)_2R^{p4}$, $-S(O)_2NR^{q4}R^{r4}$, $-NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}CONR^{q4}R^{r4}$, $-NR^{n4}S(O)_2R^{p4}$, $-NR^{n4}S(O)_2OR^{p4}$, $-NR^{n4}S(O)_2NR^{q4}R^{r4}$, $-NO_2$, $-C(O)R^{n4}$, $-C(O)OR^{n4}$, or $-C(O)NR^{q4}R^{r4}$;

each R^{n4} is independently H, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, or $(C_1$-$C_4)$heteroalkyl;

each R^{p4} is independently $(C_1$-$C_8)$alkyl, $(C_1$-$C_4)$haloalkyl, or $(C_1$-$C_4)$heteroalkyl;

each R^{q4} and R^{r4} is independently H, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, or $(C_1$-$C_4)$heteroalkyl;

Z^3 is independently a $(C_1$-$C_4)$heteroalkyl;

each Z^4 is independently oxo, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, halogen, -CN, $-OR^{n5}$, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-C(O)R^{n5}$, $-C(O)OR^{n5}$, or $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3$-$C_7)$carbocycle or $(C_1$-$C_8)$alkyl of Z^4 is optionally substituted with 1, 2, 3, 4 or 5 Z^{4a} groups, wherein the Z^{4a} groups are the same or different;

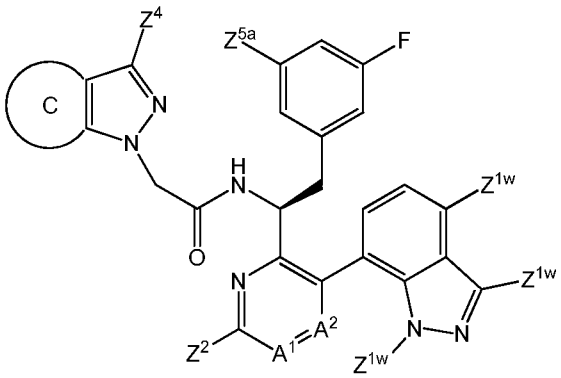
each Z^{4a} is independently halogen, -CN, or $-OR^{n6}$;

each R^{n5}, R^{p5}, R^{q5}, R^{r5}, and R^{n6} is independently H or $(C_1$-$C_4)$alkyl; and

Z^{5a} is H or halogen;

or a pharmaceutically acceptable salt thereof.

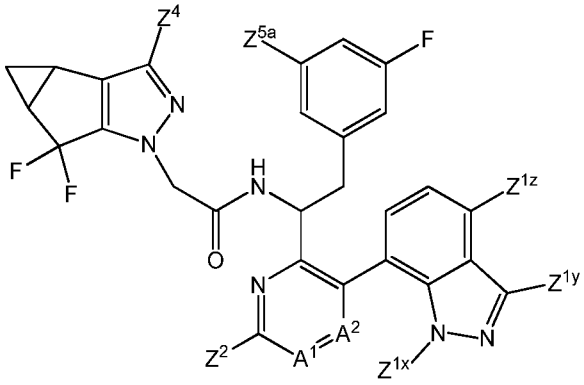
[0204] In certain embodiments, a compound of formula IIIh is a compound of formula IIIi.



IIIi

or a pharmaceutically acceptable salt thereof.

[0205] The present disclosure provides compounds of formula IIIj:



IIIj

wherein

A^1 is CH, C-Z^3, or nitrogen;

A^2 is CH or nitrogen;

Z^{1x} is H or (C_1-C_8)alkyl;

Z^{1y} is -$NR^{n1}S(O)_2R^{p1}$, -$NR^{n1}S(O)_2NR^{q1}R^{r1}$, -$NR^{q1}R^{r1}$, -$NR^{n1}COR^{p1}$, -$NR^{n1}CONR^{q1}R^{r1}$, or -$NR^{n1}CO_2R^{p1}$;

Z^{1z} is H, halogen, -CN, -OR^{n1}, (C_1-C_8)alkyl, wherein the (C_1-C_8)alkyl is optionally substituted with 1, 2, or 3 halogen, which are the same or different;

each R^{n1} is independently H or (C_1-C_8)alkyl;

each R^{p1} is independently (C_1-C_8)alkyl;

each R^{q1} and R^{r1} is independently H or (C_1-C_8)alkyl;

Z^3 is (C_1-C_4)heteroalkyl;

Z^2 is (C_2-C_8)alkynyl, optionally substituted with 1, 2, 3, 4, or 5 Z^{2c} group, wherein the Z^{2c} groups are the same or different; wherein Z^{2c} is independently halogen, -OR^{n4}, -$NR^{n4}CO_2R^{p4}$, -C(O)OR^{n4}, or -$NR^{q4}R^{r4}$;

each R^{n4} is independently H or (C_1-C_4)alkyl;

each R^{p4} is independently (C_1-C_4)alkyl;

each R^{q4} and R^{r4} is independently H, (C_1-C_4)alkyl, or (C_1-C_4)heteroalkyl;

Z^4 is hydrogen, (C_1-C_8)alkyl, halogen, -CN, C(O)R^{n5}, -C(O)OR^{n5}, -C(O)$NR^{q5}R^{r5}$, -$NR^{n5}COR^{p5}$, -$NR^{q5}R^{r5}$, or (C_3-C_7)carbocycle, wherein any (C_3-C_7)carbocycle or (C_1-C_8)alkyl of Z^4 is optionally substituted with halogen or hydroxyl;

each R^{n5} is independently H or (C_1-C_4)alkyl;

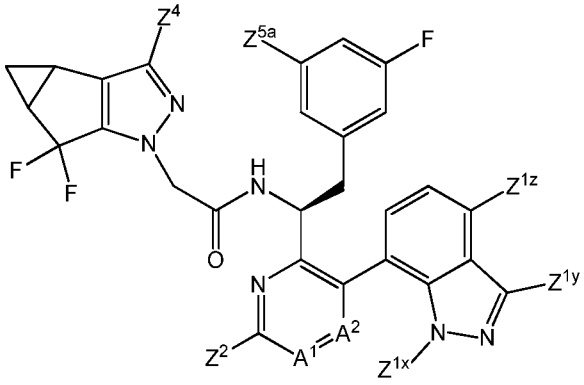
each R^{p5} is independently H or (C_1-C_4)alkyl;

each R^{q5} and R^{r5} is independently H or $(C_1$-$C_4)$alkyl; and

Z^{5a} is H or halogen;

or a pharmaceutically acceptable salt thereof.

[0206] In certain embodiments, a compound of formula IIIj is a compound of formula IIIk.



IIIk

or a pharmaceutically acceptable salt thereof.

[0207] Specific values listed below are values for compounds of formula III as well as all related formulas (e.g., formulas IIIa, IIIb, IIIc, IIId, IIIe, IIIf, IIIg, IIIh, IIIi, IIIj, and IIIk) where applicable. For example, values recited below as applying to formula III apply equally to all related formulas of formula III (e.g., formulas IIIa, IIIb, IIIc, IIId, IIIe, IIIf, IIIg, IIIh, IIIi, IIIj, and IIIk) that permit the presence of such variable. It is to be understood that two or more values may combined. Thus, it is to be understood that any variable for compounds of formula III may be combined with any other variable for compounds of formula III the same as if each and every combination of variables were specifically and individually listed. For example, it is understood that any specific value of R^1 detailed herein for compounds of formula III may be combined with any other specific value for one or more of the variables A, Z^1, R^2, R^{3a} or R^{3b} of formula III the same as if each and every combination were specifically and individually listed.

[0208] In certain embodiments of formula III, A^1 is CH. In certain embodiments, A^1 is C-Z^3. In certain embodiments, A^1 is nitrogen.

[0209] In certain embodiments of formula III, A^2 is CH. In certain embodiments, A^2 is nitrogen.

[0210] In certain embodiments of formula III, A^1 is CH; and A^2 is CH. In certain embodiments, A^1 is C-Z^3; and A^2 is CH. In certain embodiments, A^1 is nitrogen; and A^2 is CH.

[0211] In certain embodiments of formula III, A^1 is CH; and A^2 is nitrogen. In certain embodiments, A^1 is C-Z^3; and A^2 is nitrogen. In certain embodiments, A^1 is nitrogen; and A^2 is nitrogen.

[0212] In certain embodiments of formula III, Z^5 is F. In certain embodiments of formula III, n is one. In certain embodiments, n is two. In certain embodiments of formula III, n is one and Z^5 is F. In certain embodiments, n is two and each Z^5 is F.

[0213] In certain embodiments of formula III, Z^{5a} is H. In certain embodiments, Z^{5a} is F.

[0214] In certain embodiments of formula III, each Z^{1w} is independently Z^{1a} or Z^{1b}, wherein the Z^{1a} and Z^{1b} groups may be the same or different. In certain embodiments, each Z^{1w} is independently $(C_1$-$C_8)$alkyl, halogen, or $-NR^{n1}S(O)_2R^{p1}$, which may be same or different.

[0215] In certain embodiments of formula III, Z^{1x} is H. In certain embodiments, Z^{1x} is $(C_1$-$C_8)$alkyl. In certain embodiments, Z^{1x} is $(C_1$-$C_4)$alkyl. In certain embodiments, Z^{1x} is $(C_1$-$C_3)$alkyl. In certain embodiments, Z^{1x} is methyl.

[0216] In certain embodiments of formula III, Z^{1y} is $-NR^{n1}S(O)_2R^{p1}$, $-NR^{n1}S(O)_2NR^{q1}R^{r1}$, or $-NR^{q1}R^{r1}$. In certain embodiments, Z^{1y} is $-NR^{n1}S(O)_2R^{p1}$or $-NR^{n1}S(O)_2NR^{q1}R^{r1}$. In certain embodiments, Z^{1y} is $-NR^{n1}S(O)_2R^{p1}$. In certain embodiments, Z^{1y} is $-NR^{n1}S(O)_2NR^{q1}R^{r1}$. In certain embodiments, Z^{1y} is $-NR^{q1}R^{r1}$.

[0217] In certain embodiments of formula III, Z^{1z} is H or halogen. In certain embodiments, Z^{1z} is H. In certain embodiments, Z^{1z} is halogen. In certain embodiments, Z^{1z} is Cl. In certain embodiments, Z^{1z} is F. In certain embodiments, Z^{1z} is Br.

[0218] In certain embodiments of formula III, Z^{1y} is $-NR^{n1}S(O)_2R^{p1}$ or $-NR^{n1}S(O)_2NR^{q1}R^{r1}$ and Z^{1z} is halogen. In certain embodiments, Z^{1y} is $-NR^{n1}S(O)_2R^{p1}$ and Z^{1z} is halogen. In certain embodiments, Z^{1x} is $(C_1$-$C_4)$alkyl; Z^{1y} is $-NR^{n1}S(O)_2R^{p1}$ or $-NR^{n1}S(O)_2NR^{q1}R^{r1}$; and Z^{1z} is halogen. In certain embodiments, Z^{1x} is $(C_1$-$C_4)$alkyl; Z^{1y} is $-NR^{n1}S(O)_2R^{p1}$; and Z^{1z} is halogen.

[0219] In certain embodiments of formula III, A is pyridinyl, pyrimidinyl, pyrazinyl, or pyridazinyl, wherein any pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl of A is substituted with one Z^1 group at the position shown, one Z^2 group and optionally substituted with 1 or 2 Z^3 groups. In certain embodiments, A is pyridinyl, pyrimidinyl, pyrazinyl, or pyridazinyl, wherein any pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl of A is substituted with one Z^1 group at the position shown, one Z^2 group and optionally substituted with 1 Z^3 group.

[0220] In certain embodiments, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein any pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl of A is substituted with one Z^1 group at the position shown and one Z^2 group. In one aspect, A is not substituted with a Z^3 group.

[0221] In certain embodiments, A is pyridinyl, wherein any pyridinyl of A is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with 1 or 2 Z^3 groups. In certain embodiments, A is pyridinyl, wherein any pyridinyl of A is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with 1 Z^3 group.

[0222] In certain embodiments, A is pyridinyl, wherein any pyridinyl of A is substituted with one Z^1 group at the position shown and one Z^2 group. In one aspect, the Z^2 group attached at the position alpha to the nitrogen of the pyridinyl group. In a further aspect, A is not substituted with a Z^3 group.

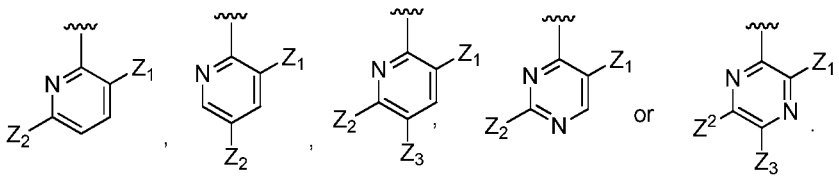
[0223] In certain embodiments, A is pyrimidinyl, wherein any pyridinyl of A is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with 1 or 2 Z^3 groups. In certain embodiments, A is pyrimidinyl, wherein any pyridinyl of A is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with 1 Z^3 group.

[0224] In certain embodiments, A is pyrimidinyl, wherein any pyridinyl of A is substituted with one Z^1 group at the position shown and one Z^2 group. In one aspect, A is not substituted with a Z^3 group.

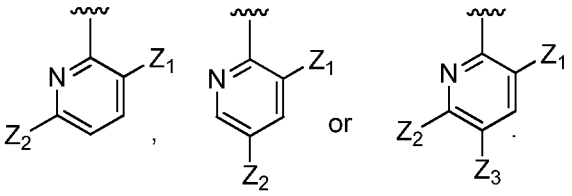
[0225] In certain embodiments, A is pyrazinyl, wherein any pyridinyl of A is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with 1 or 2 Z^3 groups. In certain embodiments, A is pyrazinyl, wherein any pyridinyl of A is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with 1 Z^3 group.

[0226] In certain embodiments, A is pyrazinyl, wherein any pyridinyl of A is substituted with one Z^1 group at the position shown and one Z^2 group. In one aspect, A is not substituted with a Z^3 group.

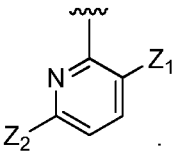
[0227] In certain embodiments, A is:



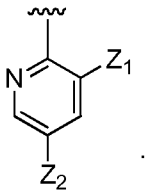
[0228] In certain embodiments, A is:



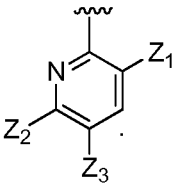
[0229] In certain embodiments, A is:



[0230] In certain embodiments, A is:

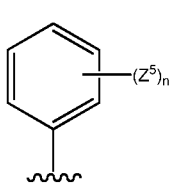
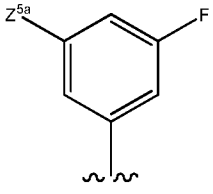


[0231] In certain embodiments, A is:



[0232] In certain embodiments of formula III, R^2 is phenyl optionally substituted with 1, 2, or 3 halogens, which may be the same or different. In certain embodiments, R^2 is phenyl optionally substituted with 1 or 2 halogens, which may be the same or different. In certain embodiments, R^2 is phenyl optionally substituted with 2 halogens, which may be the same or different. In certain embodiments, R^2 is phenyl optionally substituted with 1 halogen.

[0233] In certain embodiments, R^2 is 3,5-difluorophenyl or 3-fluorophenyl. In certain embodiments, R^2 is 3,5-difluorophenyl. In certain embodiments, R^2 is 3-fluorophenyl.

[0234] In certain embodiments, the moiety  is  wherein Z^{5a} is H or halogen.

[0235] In certain embodiments of formula III, each Z^3, where present, is independently methoxy, dimethylamino, or methylamino. In certain embodiments, Z^3, where present, is methoxy. In certain embodiments, Z^3, where present, is dimethylamino. In certain

embodiments, Z^3, where present, is methylamino. In certain embodiments, Z^3, where present, is halogen. In certain embodiments, Z^3, where present, is fluoro. In certain embodiments, Z^3, where present, is chloro. In certain embodiments, Z^3, where present, is bromo.

[0236] In certain embodiments of formula III, each R^{3a} and R^{3b} are each H. In certain embodiments, R^{3a} is methyl and R^{3b} is H.

[0237] In certain embodiments of formula III, Z^2 is $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups.

[0238] In certain embodiments, Z^2 is $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups.

[0239] In certain embodiments, Z^2 is $(C_2$-$C_8)$alkynyl, phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heterocycle, or $-C(O)NR^{q3}R^{r3}$, wherein any phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, or 8-10 membered C-linked-bicyclic-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups.

[0240] In certain embodiments, Z^2 is $(C_2$-$C_8)$alkynyl, phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heterocycle, or $-C(O)NR^{q3}R^{r3}$, wherein any phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, or 8-10 membered C-linked-bicyclic-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups.

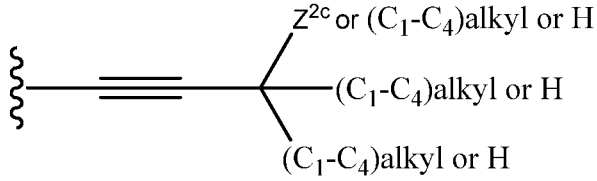
[0241] In certain embodiments, Z^2 is $(C_2$-$C_8)$alkynyl, phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heterocycle, or $-C(O)NR^{q3}R^{r3}$, wherein the 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, or 8-10 membered C-linked-bicyclic-heterocycle have 1-9 carbon atoms and 1-4 heteroatoms in the ring system, and wherein any

phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered and C-linked-bicyclic-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups.

[0242] In certain embodiments, Z^2 is $(C_2$-$C_8)$alkynyl, phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heterocycle, or $-C(O)NR^{q3}R^{r3}$, wherein the 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, or 8-10 membered C-linked-bicyclic-heterocycle have 1-9 carbon atoms and 1-4 heteroatoms in the ring system, and wherein any phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered, or C-linked-bicyclic-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups.

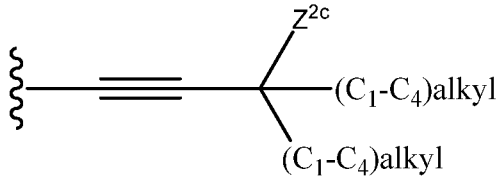
[0243] In certain embodiments of formula III, Z^2 is $(C_2$-$C_8)$alkynyl, optionally substituted with 1, 2, 3, 4, or 5 Z^{2c} groups. In certain embodiments, Z^2 is $(C_2$-$C_8)$alkynyl, optionally substituted with 1, 2, 3, or 4 Z^{2c} groups. In certain embodiments, Z^2 is $(C_2$-$C_8)$alkynyl, optionally substituted with 1, 2, or 3 Z^{2c} groups. In certain embodiments, Z^2 is $(C_2$-$C_8)$alkynyl, optionally substituted with 1 or 2 Z^{2c} groups.

[0244] In certain embodiments, Z^2 is of the formula:



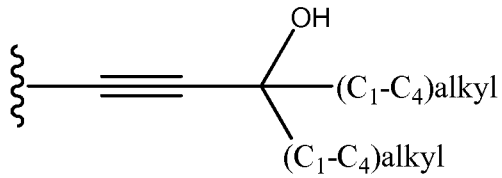
wherein each of the $(C_1$-$C_4)$alkyl moieties of Z^2, if present, is optionally substituted with 1, 2 or 3 Z^{2c} groups, wherein the Z^{2b} groups may be the same or different.

[0245] In certain embodiments, Z^2 is of the formula:



wherein each of the $(C_1$-$C_4)$alkyl moieties of Z^2 is optionally substituted with 1, 2 or 3 Z^{2c} groups, wherein the Z^{2b} groups may be the same or different.

[0246] In certain embodiments, Z^2 is of the formula:



wherein each of the $(C_1$-$C_4)$alkyl moieties of Z^2 is optionally substituted with 1, 2 or 3 Z^{2c} groups, wherein the Z^{2b} groups may be the same or different.

[0247] In certain embodiments of formula III, Z^2 is substituted with 1, 2, 3, or 4 Z^{2b} or Z^{2c} groups, wherein the Z^{2b} and Z^{2c} groups may be the same or different. In certain embodiments, Z^2 is substituted with 1, 2, or 3 Z^{2b} or Z^{2c} groups, wherein the Z^{2b} and Z^{2c} groups may be the same or different. In certain embodiments, Z^2 is substituted with 1 or 2 Z^{2b} or Z^{2c} groups, wherein the Z^{2b} and Z^{2c} groups may be the same or different. In certain embodiments, Z^2 is substituted with 1 Z^{2b} or Z^{2c} group.

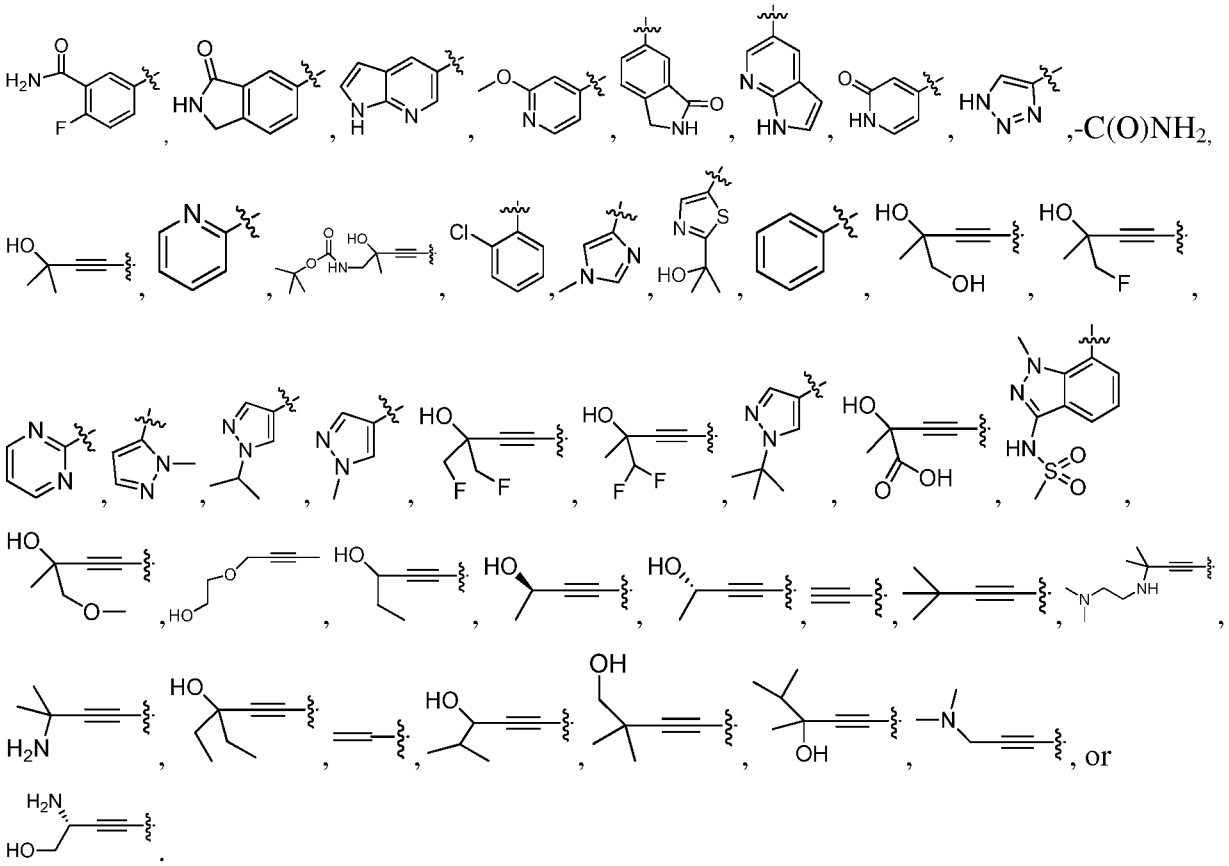
[0248] In certain embodiments of formula III, Z^2 is optionally substituted with 1, 2, or 3 Z^{2b} or Z^{2c} groups, wherein the Z^{2b} and Z^{2c} groups may be the same or different. In certain embodiments, Z^2 is substituted with 1 Z^{2b} or Z^{2c} group. In certain embodiments, Z^2 is substituted with 2 Z^{2b} or Z^{2c} groups, wherein the Z^{2b} and Z^{2c} groups may be the same or different. In certain embodiments, Z^2 is substituted with 3 Z^{2b} or Z^{2c} groups, wherein the Z^{2b} and Z^{2c} groups may be the same or different.

[0249] In certain embodiments of formula III, Z^2 is substituted with 1, 2, 3, or 4 Z^{2c} groups, wherein the Z^{2c} groups may be the same or different. In certain embodiments, Z^2 is substituted with 1, 2, or 3 Z^{2c} groups, wherein the Z^{2c} groups may be the same or different. In certain embodiments, Z^2 is substituted with 1 or 2 Z^{2c} groups, wherein the Z^{2c} groups may be the same or different. In certain embodiments, Z^2 is substituted with 1 Z^{2c} group.

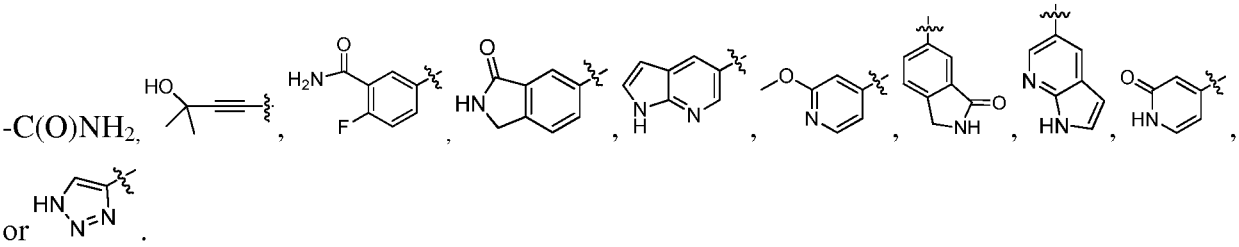
[0250] In certain embodiments of formula III, Z^2 is optionally substituted with 1, 2, or 3 Z^{2c} groups, wherein the Z^{2c} groups may be the same or different. In certain embodiments, Z^2 is substituted with 1 Z^{2c} group. In certain embodiments, Z^2 is substituted with 2 Z^{2c} groups, wherein the Z^{2c} groups may be the same or different. In certain embodiments, Z^2 is substituted with 3 Z^{2c} groups, wherein the Z^{2c} groups may be the same or different.

[0251] In certain embodiments, each Z^{2c} is independently halogen, $-OR^{n4}$, $NR^{q4}R^{r4}$, $-NR^{n4}CO_2R^{p4}$, $-C(O)OR^{n4}$, or $-C(O)NR^{q4}R^{r4}$. In certain embodiments, each Z^{2c} is independently halogen or $-OR^{n4}$.

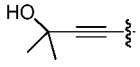
[0252] In certain embodiments, Z^2 optionally substituted with 1, 2, 3, 4, or 5 Z^{2b} or Z^{2c} groups is



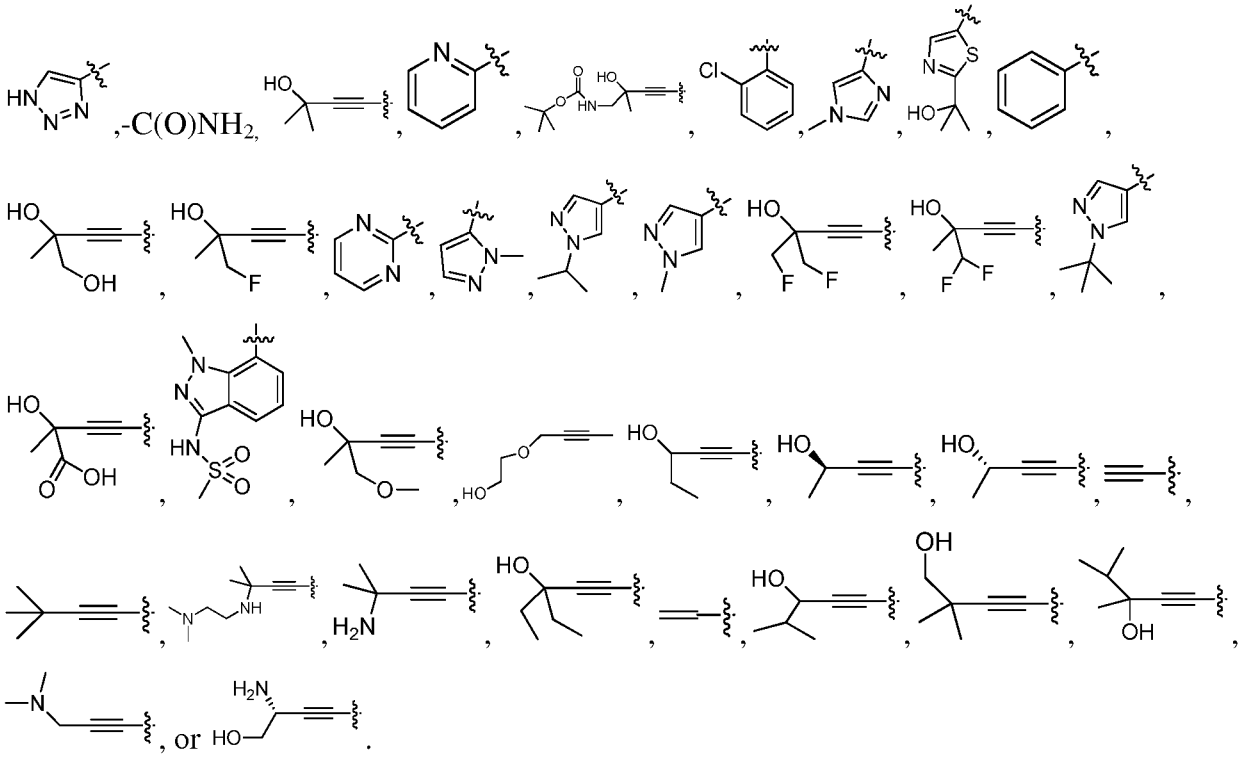
[0253] In certain embodiments, Z^2 optionally substituted with 1, 2, 3, 4, or 5 Z^{2b} or Z^{2c} groups is



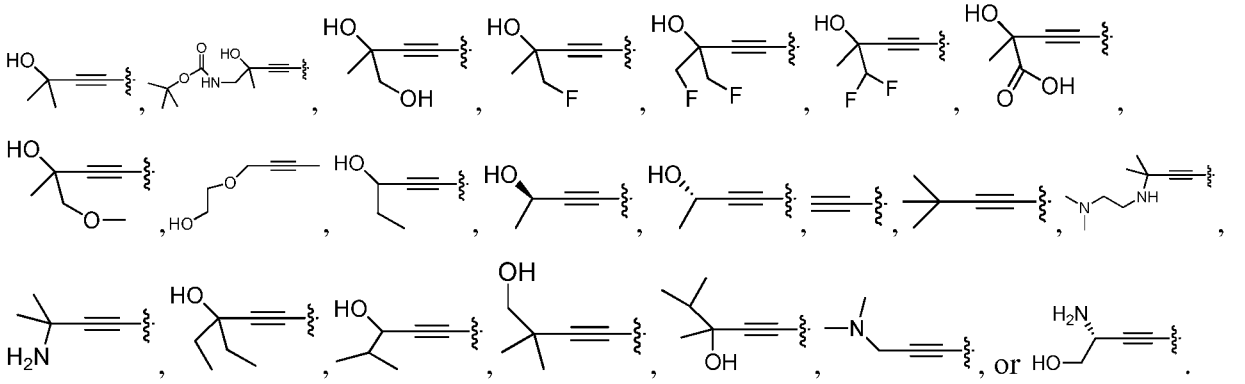
[0254] In certain embodiments, Z^2 optionally substituted with 1, 2, 3, 4, or 5 Z^{2b} or Z^{2c} groups is

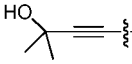


[0255] In certain embodiments, Z^2 optionally substituted with 1, 2, 3, 4, or 5 Z^{2b} or Z^{2c} groups is



[0256] In certain embodiments, Z^2 optionally substituted with 1, 2, 3, 4, or 5 Z^{2b} or Z^{2c} groups is



[0257] In certain embodiments, Z^2 optionally substituted with 1, 2, 3, 4, or 5 Z^{2b} or Z^{2c} groups is  .

[0258] In certain embodiments of formula III, R^1 is a 5-12 membered heteroaryl, wherein any 5-12 membered heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups.

[0259] In certain embodiments of formula III, R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups.

[0260] In certain embodiments, R^1 is a 8-12 membered tricyclic-heteroaryl, wherein the 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups.

[0261] In certain embodiments, R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein the 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl have 4-10 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups.

[0262] In certain embodiments, R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein the 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl contains at least one partially unsaturated ring, and wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups.

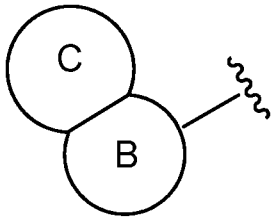
[0263] In certain embodiments, R^1 is a 8-12 membered tricyclic-heteroaryl, wherein the 8-12 membered tricyclic-heteroaryl contains at least one partially unsaturated ring, and wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups.

[0264] In certain embodiments of formula III, R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein the 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl has 4-9 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups.

[0265] In certain embodiments, R^1 is a 8-12 membered bicyclic-heteroaryl, wherein the 8-12 membered bicyclic-heteroaryl has 6-9 carbon atoms and 1-3 heteroatoms in the ring system, and wherein any 8-12 membered bicyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups.

[0266] In certain embodiments, R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein the 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl has 6-9 carbon atoms and 1-3 heteroatoms in the ring system, and wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups.

[0267] In certain embodiments of formula III, R^1 has the following formula IIa:



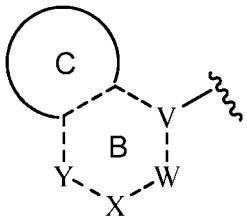
IIa

wherein:

C together with the two carbon atoms of ring B to which it is attached forms a 3-7 membered monocyclic-carbocycle, 5-8 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle, or 5-8 membered bicyclic heterocycle, wherein any 3-7 membered monocyclic-carbocycle, 5-8 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-8 membered bicyclic heterocycle of C is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, wherein the Z^4 groups are the same or different; and

B is a 5 or 6 membered monocyclic-heteroaryl with 1, 2 or 3 nitrogen atoms, wherein B is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, wherein the Z^4 groups are the same or different.

[0268] In certain embodiments of formula III, R^1 has the following formula IIb:



IIb

wherein:

C together with the two carbon atoms of ring B to which it is attached forms a 3-7 membered monocyclic-carbocycle, 5-8 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle, or 5-8 membered bicyclic heterocycle, wherein any 3-7 membered monocyclic-carbocycle, 5-8 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-8 membered bicyclic heterocycle of C is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, wherein the Z^4 groups are the same or different; and

B is a 5 or 6 membered monocyclic-heteroaryl having 1, 2 or 3 nitrogen atoms;

V is C or N;

W is CZ^{4c}, NZ^{4c} or N;

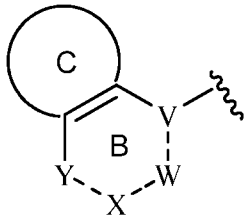
X is CZ^{4c}, NZ^{4c} or N;

Y is CZ^{4c}, N or absent;

the dashed bonds are selected from single bonds and double bonds, wherein the dashed bonds, V, W, X and Y are selected so that the 5 or 6 membered monocyclic-heteroaryl B is aromatic; and

each Z^{4c} is independently selected from H or Z^4, wherein the Z^4 groups are the same or different.

[0269] In certain embodiments of formula III, R^1 has the following formula IIc:



IIc

wherein:

C together with the two carbon atoms of ring B to which it is attached forms a 3-7 membered monocyclic-carbocycle, 5-8 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle, or 5-8 membered bicyclic heterocycle, wherein any 3-7 membered monocyclic-carbocycle, 5-8 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-8 membered bicyclic heterocycle of C is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, wherein the Z^4 groups are the same or different; and

B is a 5 or 6 membered monocyclic-heteroaryl having 1, 2 or 3 nitrogen atoms;

V is C or N;

W is CZ^{4c} or N;

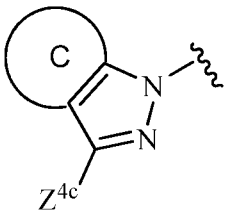
X is CZ^{4c}, NZ^{4c} or N;

Y is CZ^{4c}, N or absent;

the dashed bonds are selected from single bonds and double bonds, wherein the dashed bonds, V, W, X and Y are selected so that the 5 or 6 membered monocyclic-heteroaryl B is aromatic; and

each Z^{4c} is independently selected from H or Z^4, wherein the Z^4 groups are the same or different.

[0270] In certain embodiments of formula III, R^1 has the following formula IId:



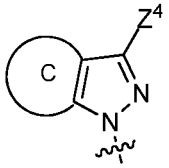
IId

wherein:

C together with the two carbon atoms to which it is attached forms a 3-7 membered monocyclic-carbocycle, 5-9 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle, or 5-9 membered bicyclic heterocycle, wherein any 3-7 membered monocyclic-carbocycle, 5-9 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-9 membered bicyclic heterocycle of C is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, wherein the Z^4 groups are the same or different; and

each Z^{4c} is independently selected from H or Z^4, wherein the Z^4 groups are the same or different.

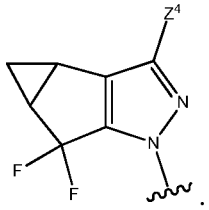
[0271] In certain embodiments of formula III, R^1 has the following formula:



wherein:

C together with the two carbon atoms to which it is attached forms a 3-7 membered monocyclic-carbocycle or 5-9 membered bicyclic-carbocycle, wherein any 3-7 membered monocyclic-carbocycle or 5-9 membered bicyclic-carbocycle of C is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, wherein the Z^4 groups are the same or different.

[0272] In certain embodiments of formula III, R^1 has the following formula:



[0273] In certain embodiments of formula III, C together with the two carbon atoms to which it is attached forms a 5-7 membered monocyclic-carbocycle or 5-7 membered bicyclic-

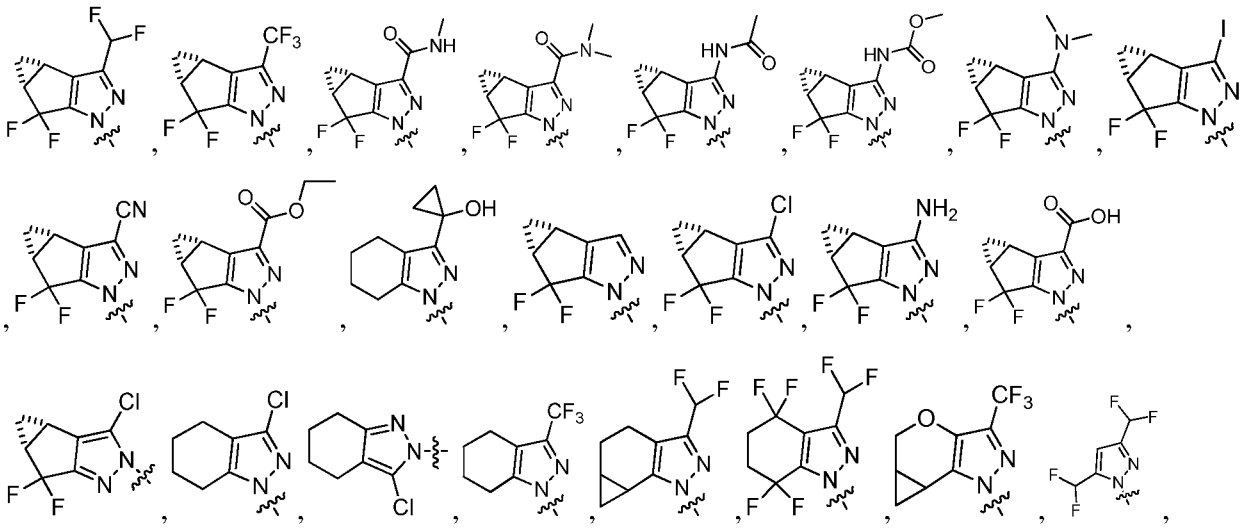
carbocycle, wherein any 5-7 membered monocyclic-carbocycle or 5-7 membered bicyclic-carbocycle of C is optionally substituted with 1, 2, 3, or 4 Z^4 groups, wherein the Z^4 groups are the same or different.

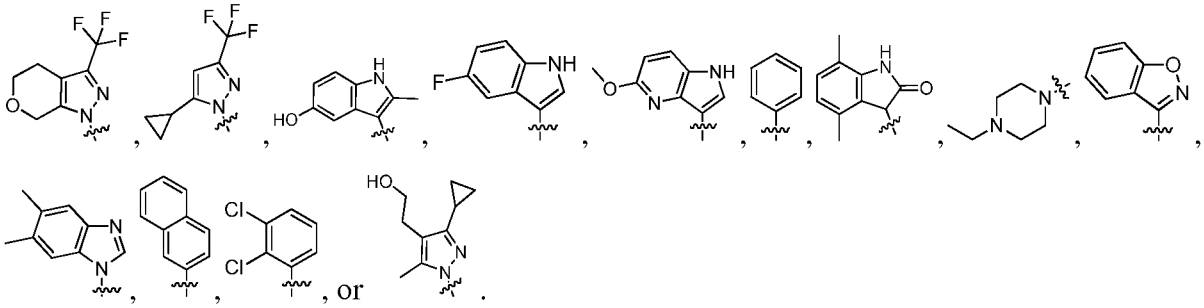
[0274] In certain embodiments of formula III, each Z^4 is independently $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, halogen, -CN, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-C(O)OR^{n5}$, or $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3$-$C_7)$carbocycle or $(C_1$-$C_8)$alkyl of Z^4 is optionally substituted with 1, 2, 3, 4 or 5 Z^{4a} groups.

[0275] In certain embodiments, each Z^4 is independently $(C_1$-$C_6)$alkyl or halogen, wherein any $(C_1$-$C_6)$alkyl of Z^4 is optionally substituted with 1, 2, 3, 4 or 5 halogen, which may be the same or different. In certain embodiments, each Z^4 is independently $(C_1$-$C_4)$alkyl or halogen, wherein any $(C_1$-$C_6)$alkyl of Z^4 is optionally substituted with 1, 2, 3, 4 or 5 halogen, which may be the same or different. In certain embodiments, each Z^4 is independently $(C_1$-$C_3)$alkyl or halogen, wherein any $(C_1$-$C_3)$alkyl of Z^4 is optionally substituted with 1, 2, 3, 4 or 5 halogen, which may be the same or different.

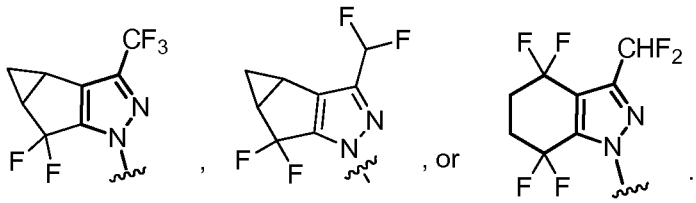
[0276] In certain embodiments, each Z^4 is independently fluoro, trifluoromethyl, or difluoromethyl.

[0277] In certain embodiments of formula III, R^1 optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups is

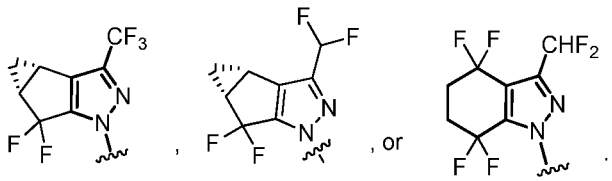




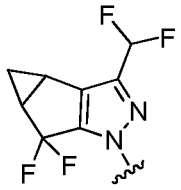
[0278] In certain embodiments, R^1 optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups is



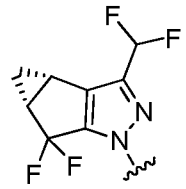
[0279] In certain embodiments, R^1 optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups is



[0280] In certain embodiments, R^1 optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups is

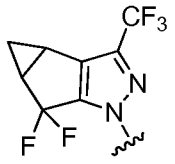


. In certain embodiments, R^1 optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups is

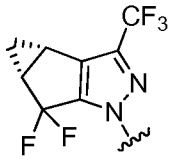


.

[0281] In certain embodiments, R^1 optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups is

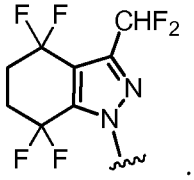


. In certain embodiments, R^1 optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups is



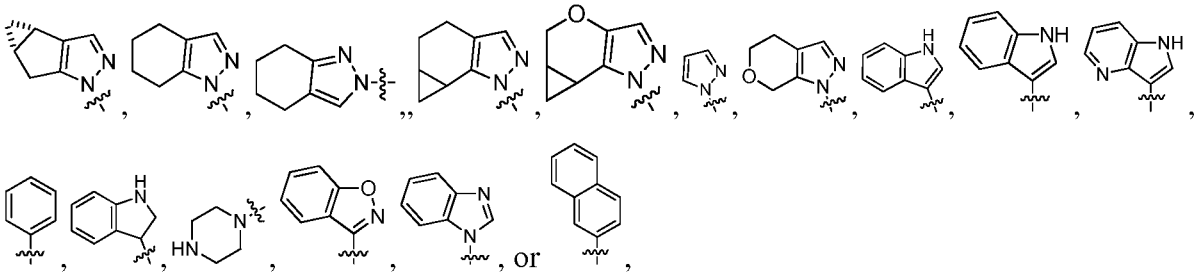
.

[0282] In certain embodiments, R^1 optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups is



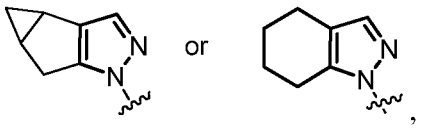
.

[0283] In certain embodiments, R^1 is



optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups.

[0284] In certain embodiments, R^1 is



optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups.

[0285] In certain embodiments of formula III, each Z^4 is independently $(C_1\text{-}C_6)$alkyl or halogen, wherein any $(C_1\text{-}C_6)$alkyl of Z^4 is optionally substituted with 1, 2, 3, 4 or 5 halogen, which may the same or different.

[0286] In certain embodiments, each Z^4 is independently $(C_1\text{-}C_6)$alkyl, -CN, or halogen, wherein any $(C_1\text{-}C_6)$alkyl of Z^4 is optionally substituted with 1, 2, 3, 4 or 5 halogen, which may the same or different.

[0287] In certain embodiments, each Z^4 is independently fluoro, trifluoromethyl, or difluoromethyl.

[0288] In certain embodiments, each Z^4 is independently fluoro, trifluoromethyl, -CN, or difluoromethyl.

[0289] In certain embodiments of Formula III, Z^1 is phenyl, 5-14 membered heteroaryl, or 3-14 membered heterocycle, wherein any phenyl, 5-14 membered heteroaryl, or 3-14 membered heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b} groups.

[0290] In certain embodiments, Z^1 is phenyl, 5-12 membered heteroaryl, or 3-12 membered heterocycle, wherein any phenyl, 5-12 membered heteroaryl, or 3-12 membered heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b} groups.

[0291] In certain embodiments, Z^1 is phenyl, 5-14 membered heteroaryl, or 3-14 membered heterocycle, wherein any phenyl, 5-14 membered heteroaryl, or 3-14 membered heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups.

[0292] In certain embodiments, Z^1 is phenyl, 5-12 membered heteroaryl, or 3-12 membered heterocycle, wherein any phenyl, 5-12 membered heteroaryl, or 3-12 membered heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups.

[0293] In certain embodiments, Z^1 is phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b} groups.

[0294] In certain embodiments, Z^1 is phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups.

[0295] In certain embodiments, Z^1 is phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle, wherein the 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle have 1-11 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b} groups.

[0296] In certain embodiments, Z^1 is phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle, wherein the 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle have 1-11 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups.

[0297] In certain embodiments, Z^1 is phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle, wherein the 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle have 4-11 carbon atoms and 1-3 heteroatoms in the ring system, and wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b} groups.

[0298] In certain embodiments, Z^1 is phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle, wherein the 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle have 4-11 carbon atoms and 1-3 heteroatoms in the ring system, and wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups.

[0299] In certain embodiments, Z^1 is 8-10 membered bicyclic-heteroaryl or 8-10 membered bicyclic-heterocycle, wherein any from 8-10 membered bicyclic-heteroaryl or 8-10 membered bicyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b} groups.

[0300] In certain embodiments, Z^1 is 8-10 membered bicyclic-heteroaryl or 8-10 membered bicyclic-heterocycle, wherein any from 8-10 membered bicyclic-heteroaryl or 8-10 membered bicyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups.

[0301] In certain embodiments, Z^1 is 8-10 membered bicyclic-heteroaryl or 8-10 membered bicyclic-heterocycle, wherein the 8-10 membered bicyclic-heteroaryl or 8-10 membered

bicyclic-heterocycle has 3-9 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any 8-10 membered bicyclic-heteroaryl or 8-10 membered bicyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b} groups.

[0302] In certain embodiments, Z^1 is 8-10 membered bicyclic-heteroaryl or 8-10 membered bicyclic-heterocycle, wherein the 8-10 membered bicyclic-heteroaryl or 8-10 membered bicyclic-heterocycle has 3-9 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any 8-10 membered bicyclic-heteroaryl or 8-10 membered bicyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups.

[0303] In certain embodiments of formula III, Z^1 is not substituted with Z^{1b}.

[0304] In certain embodiments of formula III, each Z^{1a} is independently oxo, $(C_3\text{-}C_7)$carbocycle, halogen, -CN, -O-$(C_1\text{-}C_8)$alkyl, $-NR^{q1}R^{r1}$, $-NR^{n1}COR^{p1}$, $-NR^{n1}CO_2R^{p1}$, $-NR^{n1}CONR^{q1}R^{r1}$, $-NR^{n1}S(O)_2R^{p1}$, $-NR^{n1}S(O)_2NR^{q1}R^{r1}$, or $-C(O)NR^{q1}R^{r1}$.

[0305] In certain embodiments, each Z^{1a} is independently $-NR^{n1}S(O)_2R^{p1}$, $-NR^{n1}S(O)_2NR^{q1}R^{r1}$, or halogen. In certain embodiments, each Z^{1a} is independently halogen or $-NR^{n1}S(O)_2R^{p1}$. In certain embodiments, each Z^{1a} is independently halogen or $-NR^{n1}S(O)_2NR^{q1}R^{r1}$.

[0306] In certain embodiments, Z^1 is substituted with 2 Z^{1a} groups, wherein each Z^{1a} is independently $-NR^{n1}S(O)_2R^{p1}$, $-NR^{n1}S(O)_2NR^{q1}R^{r1}$, or halogen.

[0307] In certain embodiments, each Z^{1a} is independently halogen or $-NR^{n1}S(O)_2R^{p1}$ and each Z^{1b} is $(C_1\text{-}C_8)$alkyl, which may be same or different.

[0308] In certain embodiments, Z^{1a} is $-NR^{n1}S(O)_2R^{p1}$ or $-NR^{n1}S(O)_2NR^{q1}R^{r1}$. In certain embodiments, Z^{1a} is halogen. In certain embodiments, Z^{1a} is $-NR^{q1}R^{r1}$, $-NR^{n1}COR^{p1}$, $-NR^{n1}CO_2R^{p1}$, or $-NR^{n1}CONR^{q1}R^{r1}$.

[0309] In certain embodiments, Z^{1a} is halogen, $-OR^{n1}$, or-$C(O)NR^{q1}R^{r1}$.

[0310] In certain embodiments, Z^{1a} is halogen or $-C(O)NR^{q1}R^{r1}$.

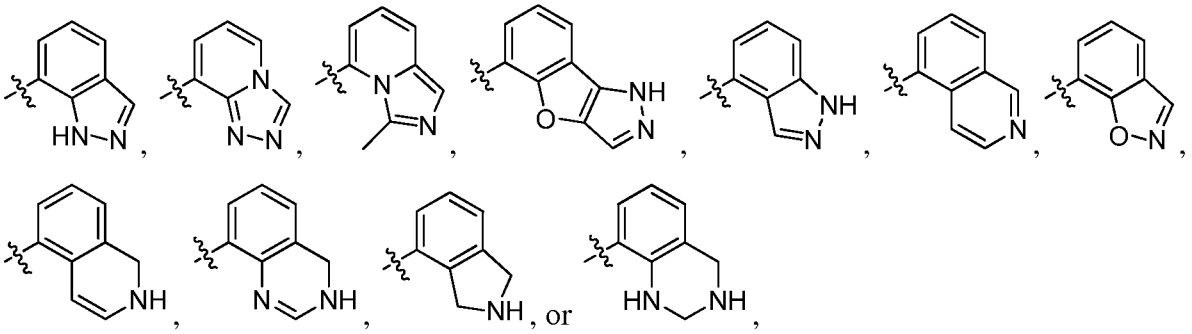
[0311] In certain embodiments, Z^{1a} is halogen, -OH, or $-C(O)NH_2$.

[0312] In certain embodiments, Z^{1a} is fluoro, -OH, or $-C(O)NH_2$.

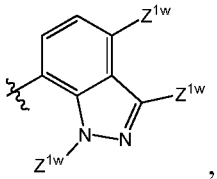
[0313] In certain embodiments, each Z^{1b} is $(C_1\text{-}C_8)$alkyl, which may be same or different.

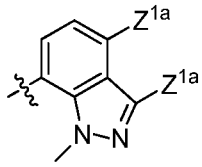
[0314] In certain embodiments, each Z^{1b} is independently methyl or difluoromethyl.

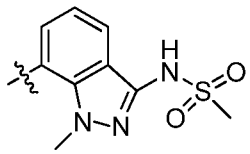
[0315] In certain embodiments of formula III, Z^1 is

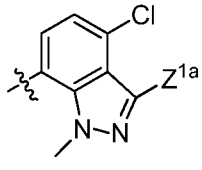


optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b}.

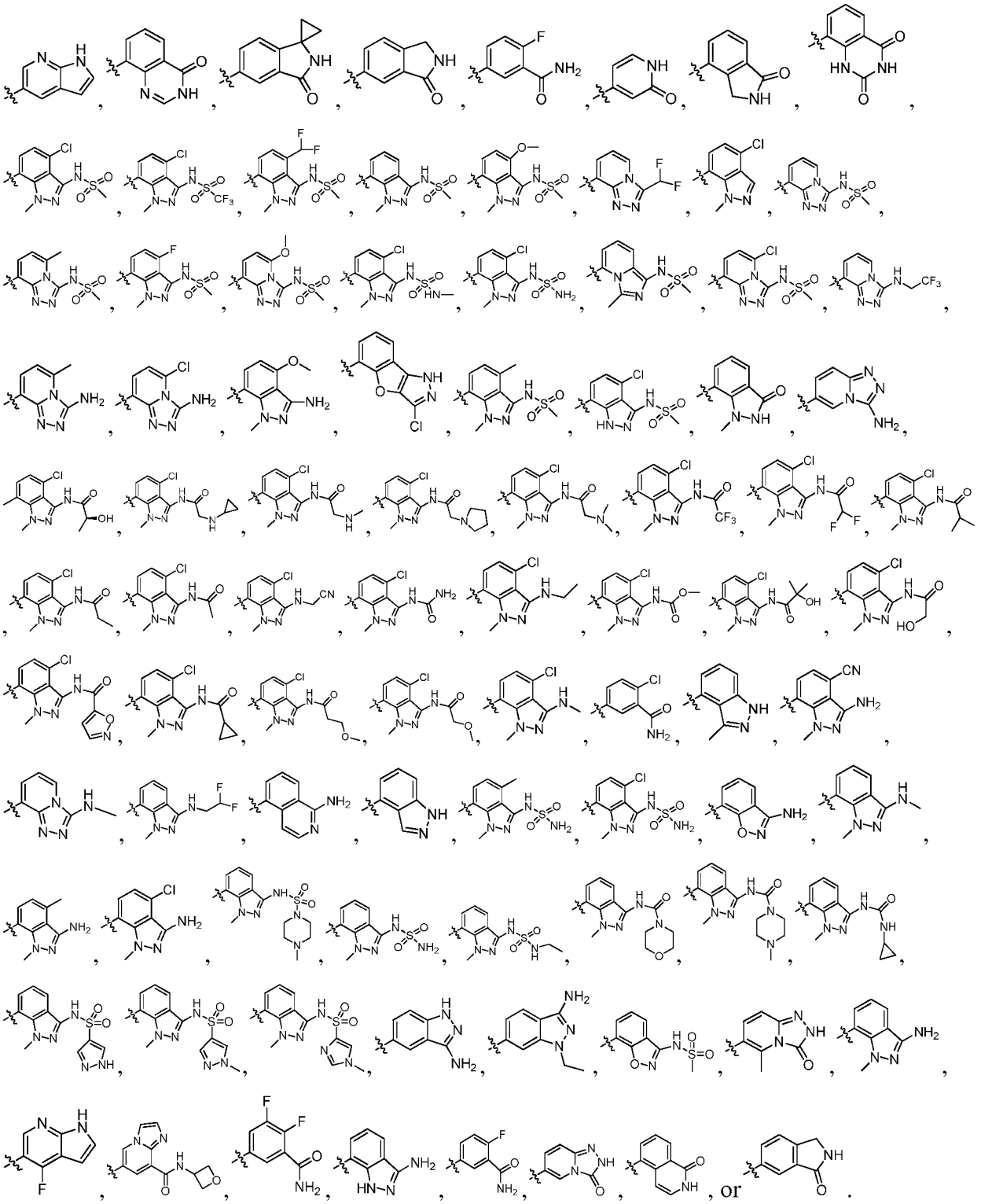
[0316] In certain embodiments, Z^1 is  , wherein each Z^{1w} is independently Z^{1a}, Z^{1b}, or H. In certain embodiments, each Z^{1a} is independently halogen, -CN, -OR^{n1}, -$NR^{n1}S(O)_2R^{p1}$, -$NR^{n1}S(O)_2NR^{q1}R^{r1}$, -$NR^{q1}R^{r1}$, -$NR^{n1}COR^{p1}$, -$NR^{n1}CONR^{q1}R^{r1}$, or -$NR^{n1}CO_2R^{p1}$; each Z^{1b} is independently (C_1-C_8alkyl), wherein the (C_1-C_8alkyl) is optionally substituted with 1, 2, or 3 halogen, which are the same or different; and at least one of Z^{1w} is Z^{1a} or Z^{1b}. In certain embodiments, at least two of Z^{1w} are independently Z^{1a}. In certain embodiments, each Z^{1a} is independently halogen, -$NR^{n1}S(O)_2R^{p1}$, or -$NR^{n1}S(O)_2NR^{q1}R^{r1}$.

[0317] In certain embodiments, Z^1 is  , wherein each Z^{1a} is independently halogen, -$NR^{n1}S(O)_2R^{p1}$ or -$NR^{n1}S(O)_2NR^{q1}R^{r1}$.

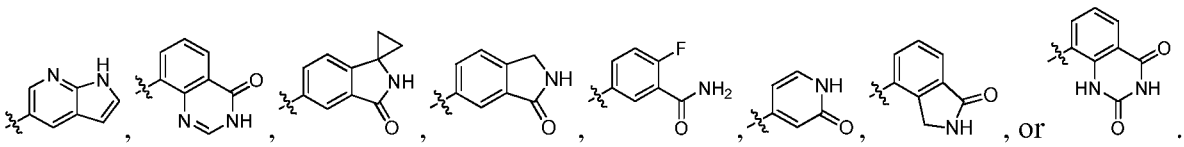
[0318] In certain embodiments, Z^1 is  , optionally substituted with 1, 2, 3, or 4 Z^{1a} or Z^{1b}.

[0319] In certain embodiments, Z^1 is  .

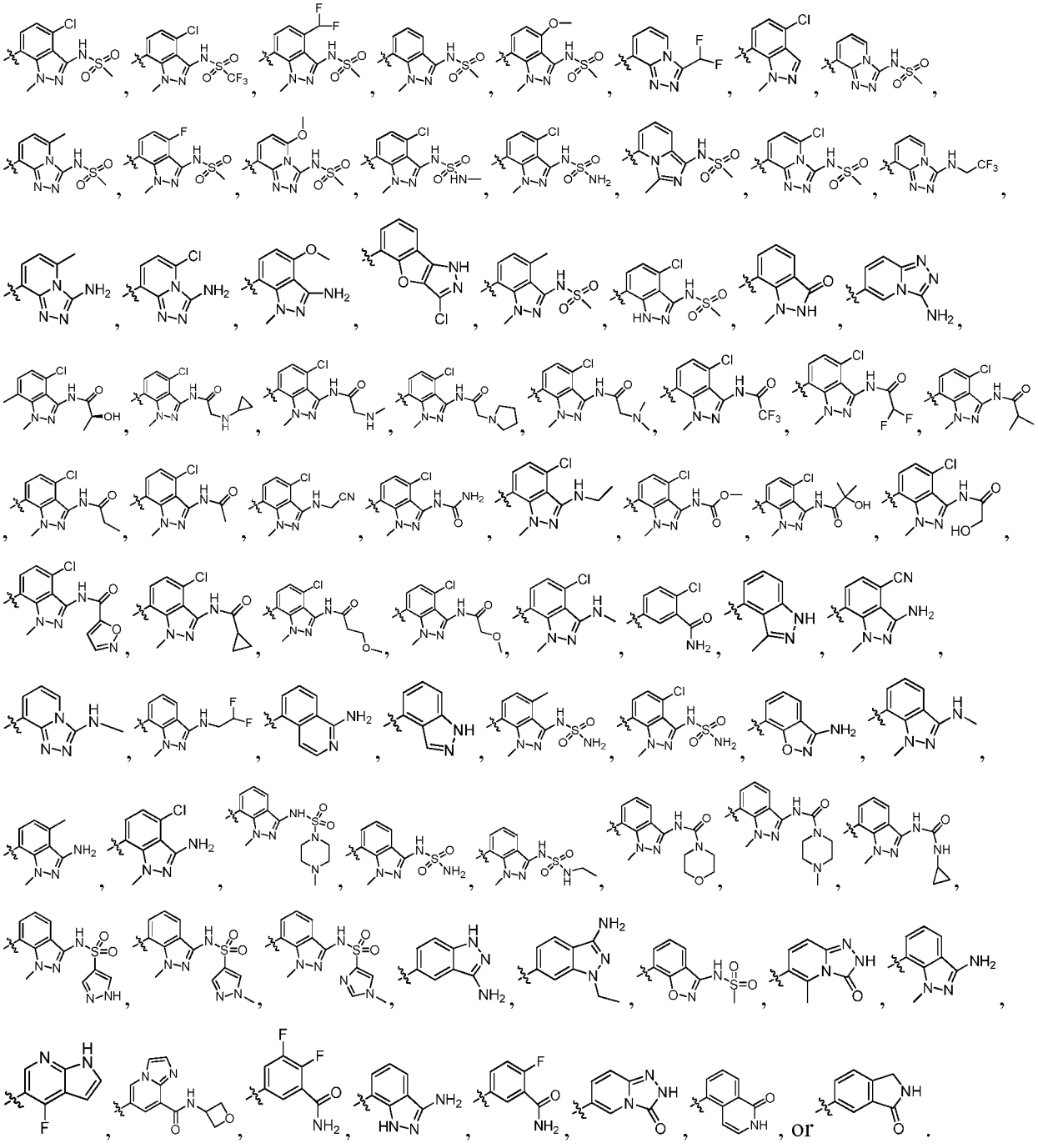
[0320] In certain embodiments, Z^1 optionally substituted with 1, 2, 3, 4, or 5 Z^{1a} or Z^{1b} groups is



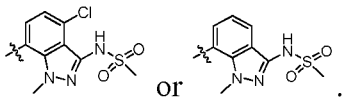
[0321] In certain embodiments, Z^1 optionally substituted with 1, 2, 3, 4, or 5 Z^{1a} or Z^{1b} groups is

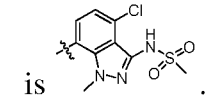


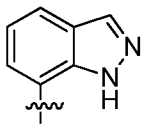
[0322] In certain embodiments, Z^1 optionally substituted with 1, 2, 3, 4, or 5 Z^{1a} or Z^{1b} groups is



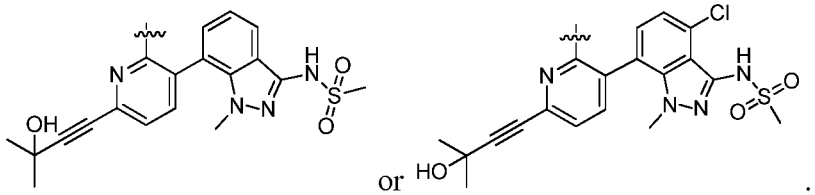
[0323] In certain embodiments, Z^1 optionally substituted with 1, 2, 3, 4, or 5 Z^{1a} or Z^{1b} groups is



[0324] In certain embodiments, Z^1 optionally substituted with 1, 2, 3, 4, or 5 Z^{1a} or Z^{1b} groups is  .

[0325] In certain embodiments, Z^1 is  .

[0326] In certain embodiments, Z^2-A-Z^1 is:



[0327] In one variation of formula III, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and R^1 is a 5-12 membered heteroaryl, optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, which may be the same or different. In another variation, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups. In another variation, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups; and each Z^4 is independently fluoro, trifluoromethyl, or difluoromethyl.

[0328] In one variation of formula III, A is pyridinyl; and R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups, which may be the same or different.

[0329] In one variation of formula III, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and R^2 is 3,5-difluorophenyl. In another variation, A is pyridinyl; and R^2 is 3,5-difluorophenyl. In another variation, A is pyrimidinyl; and R^2 is 3,5-difluorophenyl. In another variation, A is pyrazinyl; and R^2 is 3,5-difluorophenyl. In another variation, A is pyridazinyl; and R^2 is 3,5-difluorophenyl.

[0330] In one variation of formula III, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and Z^1 is phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups, which may be the same or different. In another variation, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and Z^1 is phenyl, optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups. In another variation, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and Z^1 is 5-6 membered monocyclic-heteroaryl or 8-10 membered bicyclic-heteroaryl, wherein any 5-6 membered monocyclic-heteroaryl or 8-10 membered bicyclic-heteroaryl of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups. In another variation, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and Z^1 is 8-10 membered bicyclic-heterocycle or 9-12 membered tricyclic-heterocycle wherein any 8-10 membered bicyclic-heterocycle or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups.

[0331] In one variation of formula III, A is pyridinyl; and Z^1 is phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups, which may be the same or different. In another variation, A is pyridinyl; and Z^1 is phenyl, optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups. In another variation, A is pyridinyl; and Z^1 is 5-6 membered monocyclic-heteroaryl or 8-10 membered bicyclic-heteroaryl, wherein any 5-6 membered monocyclic-heteroaryl or 8-10 membered bicyclic-heteroaryl of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups. In another variation, A is pyridinyl; and Z^1 is 8-10 membered bicyclic-heterocycle or 9-12 membered tricyclic-heterocycle wherein any 8-10 membered bicyclic-heterocycle or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups.

[0332] In one variation of formula III, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and Z^2 is $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally

substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, which may be the same or different, and wherein any (C_2-C_8)alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups, which may be the same or different. In another variation, A is pyridinyl; and Z^2 is (C_2-C_8)alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, or -C(O)$NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, and wherein any (C_2-C_8)alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups. In another variation, A is pyrimidinyl; and Z^2 is (C_2-C_8)alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, or -C(O)$NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, and wherein any (C_2-C_8)alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups. In another variation, A is pyrazinyl; and Z^2 is (C_2-C_8)alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, or -C(O)$NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, and wherein any (C_2-C_8)alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups. In another variation, A is pyridazinyl; and Z^2 is (C_2-C_8)alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, or -C(O)$NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, and wherein any (C_2-C_8)alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups.

[0333] In one variation of formula III, A is pyridinyl substituted with one Z^1 moiety, one Z^2 moiety and no (zero) Z^3 moieties; and Z^2 is (C_2-C_8)alkynyl or aryl, which Z^2 may be optionally substituted as provided by formula III. In another variation, A is pyridinyl substituted with one Z^1 moiety, one Z^2 moiety and no (zero) Z^3 moieties; and Z^2 is (C_2-C_8)alkynyl, which Z^2 may be optionally substituted as provided by formula III. In a particular variation, A is pyridinyl substituted with one Z^1 moiety, one Z^2 moiety at the position alpha to the nitrogen atom of the pyridinyl ring, and no (zero) Z^3 moieties, wherein Z^2 is (C_2-C_8)alkynyl, which Z^2 may be optionally substituted as provided by formula III.

[0334] In one variation of formula III, R^1 is a 5-12 membered heteroaryl optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, which may be the same or different; and Z^1 is phenyl, 5-6

membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups, which may be the same or different. In another variation, R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups; and Z^1 is phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups.

[0335] In one variation of formula III, R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups, which may be the same or different; and Z^1 is 8-10 membered bicyclic-heteroaryl or 8-10 membered bicyclic-heterocycle wherein any 8-10 membered bicyclic-heteroaryl or 8-10 membered bicyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups, which may be the same or different.

[0336] In one variation of formula III, R^1 is a 5-12 membered heteroaryl optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, which may be the same or different; and Z^2 is $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups, which may be the same or different. In another variation, R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups; and Z^2 is $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is

optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, and wherein any (C_2-C_8)alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} group.

[0337] In one variation of formula III, Z^1 is phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups, which may be the same or different; and Z^2 is (C_2-C_8)alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, or -C(O)$NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, which may be the same or different, and wherein any (C_2-C_8)alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups, which may be the same or different.

[0338] In one variation of formula III, Z^1 is bicyclic-heteroaryl optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups, which may be the same or different; and Z^2 is (C_2-C_8)alkynyl optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups, which may be the same or different.

[0339] In one variation of formula III, R^1 is a 5-12 membered heteroaryl; Z^1 is phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} groups, which may be the same or different; and Z^2 is (C_2-C_8)alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, or -C(O)$NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, which may be the same or different, and wherein any (C_2-C_8)alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups, which may be the same or different.

[0340] In certain embodiments of formula III,

A is a 6-membered monocyclic-heteroaryl with one or two nitrogen atoms, wherein the 6-membered monocyclic-heteroaryl is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with 1 or 2 Z^3 groups, which may be the same or different;

R^1 is 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle, wherein any 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle of R^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, which may be the same or different;

R^2 is phenyl optionally substituted with 1, 2, 3, 4 or 5 halogen, which may be the same or different;

each R^{3a} and R^{3b} is independently H or $(C_1$-$C_3)$alkyl;

Z^1 is 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle, wherein any 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b}, which may be the same or different;

each Z^{1a} is independently oxo, $(C_3$-$C_7)$carbocycle, halogen, -CN, -O-$(C_1$-$C_8)$alkyl, $-OC(O)R^{p1}$, $-OC(O)NR^{q1}R^{r1}$, $-NR^{q1}R^{r1}$, $-NR^{n1}COR^{p1}$, $-NR^{n1}CO_2R^{p1}$, $-NR^{n1}CONR^{q1}R^{r1}$, $-NR^{n1}S(O)_2R^{p1}$, $-NR^{n1}S(O)_2NR^{q1}R^{r1}$, $-C(O)R^{n1}$, $-C(O)OR^{n1}$, or $-C(O)NR^{q1}R^{r1}$;

each Z^{1b} is independently $(C_1$-$C_8)$alkyl optionally substituted with 1, 2, 3, 4 or 5 halogen, which may be the same or different;

each R^{n1} is independently H or $(C_1$-$C_8)$alkyl;

each R^{p1} is independently $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 $(C_1$-$C_8)$alkyl, which may be the same or different, and wherein any $(C_1$-$C_8)$alkyl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 halogen, hydroxyl, -O$(C_1$-$C_8)$alkyl, or $–NR^{q2}R^{r2}$, which may be the same or different;

each R^{q1} and R^{r1} is independently H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, or 3-7-membered heterocycle, wherein any $(C_1$-$C_8)$alkyl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 halogen or –CN, which may be the same or different, or R^{q1} and R^{r1} together with the nitrogen to which they are attached form a 5, 6, or 7-membered heterocycle, wherein the 5, 6, or 7-membered heterocycle is optionally substituted with 1, 2, 3, 4 or 5 $(C_1$-$C_8)$alkyl, which may be the same or different;

each R^{q2} and R^{r2} is independently H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, or R^{q2} and R^{r2} together with the nitrogen to which they are attached form a 5, 6, or 7-membered heterocycle;

Z^2 is $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, $-C(O)R^{n3}$, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of

Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, which may be the same or different, and wherein any $(C_2$-$C_8)$alkenyl or $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4, or 5 Z^{2c} groups, which may be the same or different;

each R^{n3} is independently H or $(C_1$-$C_4)$alkyl;

each R^{q3} and R^{r3} is independently H or $(C_1$-$C_4)$alkyl;

each Z^{2b} is independently oxo, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$heteroalkyl or $(C_1$-$C_4)$haloalkyl;

each Z^{2c} is independently oxo, halogen, -CN, $-OR^{n4}$, $NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}S(O)_2R^{p4}$, $-C(O)R^{n4}$, $-C(O)OR^{n4}$ or $-C(O)NR^{q4}R^{r4}$;

each R^{n4} is independently H, $(C_1$-$C_4)$alkyl, or $(C_1$-$C_4)$heteroalkyl;

each R^{p4} is independently $(C_1$-$C_8)$alkyl;

each R^{q4} and R^{r4} is independently H, $(C_1$-$C_4)$alkyl, or $(C_1$-$C_4)$heteroalkyl;

each Z^3 is independently a $(C_1$-$C_4)$heteroalkyl or halogen;

each Z^4 is independently oxo, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, halogen, -CN, $-OR^{n5}$, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-C(O)R^{n5}$, $-C(O)OR^{n5}$, or $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3$-$C_7)$carbocycle or $(C_1$-$C_8)$alkyl of Z^4 is optionally substituted with 1, 2, 3, 4 or 5 Z^{4a} groups, which may be the same or different;

each Z^{4a} is independently halogen, -CN, or $-OR^{n6}$; and

each R^{n5}, R^{p5}, R^{q5}, R^{r5}, and R^{n6} is independently H or $(C_1$-$C_4)$alkyl.

[0341] In certain embodiments of formula III,

A^1 is CH, C-Z^3, or nitrogen;

A^2 is CH or nitrogen;

R^1 is 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle, wherein any 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle of R^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, which may be the same or different;

each R^{3a} and R^{3b} is independently H or $(C_1$-$C_3)$alkyl;

Z^1 is 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle, wherein any 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b}, which may be the same or different;

each Z^{1a} is independently oxo, $(C_3$-$C_7)$carbocycle, halogen, -CN, -O-$(C_1$-$C_8)$alkyl, $-OC(O)R^{p1}$, $-OC(O)NR^{q1}R^{r1}$, $-NR^{q1}R^{r1}$, $-NR^{n1}COR^{p1}$, $-NR^{n1}CO_2R^{p1}$, $-NR^{n1}CONR^{q1}R^{r1}$, $-NR^{n1}S(O)_2R^{p1}$, $-NR^{n1}S(O)_2NR^{q1}R^{r1}$, $-C(O)R^{n1}$, $-C(O)OR^{n1}$, or $-C(O)NR^{q1}R^{r1}$;

each Z^{1b} is independently $(C_1\text{-}C_8)$alkyl optionally substituted with 1, 2, 3, 4 or 5 halogen, which may be the same or different;

each R^{n1} is independently H or $(C_1\text{-}C_8)$alkyl;

each R^{p1} is independently $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 $(C_1\text{-}C_8)$alkyl, which may be the same or different, and wherein any $(C_1\text{-}C_8)$alkyl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 halogen, hydroxyl, $-O(C_1\text{-}C_8)$alkyl, or $–NR^{q2}R^{r2}$, which may be the same or different;

each R^{q1} and R^{r1} is independently H, $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_7)$carbocycle, or 3-7-membered heterocycle, wherein any $(C_1\text{-}C_8)$alkyl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 halogen or –CN, which may be the same or different, or R^{q1} and R^{r1} together with the nitrogen to which they are attached form a 5, 6, or 7-membered heterocycle, wherein the 5, 6, or 7-membered heterocycle is optionally substituted with 1, 2, 3, 4 or 5 $(C_1\text{-}C_8)$alkyl, which may be the same or different;

each R^{q2} and R^{r2} is independently H, $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_7)$carbocycle, or R^{q2} and R^{r2} together with the nitrogen to which they are attached form a 5, 6, or 7-membered heterocycle;

Z^2 is $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, $-C(O)R^{n3}$, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, which may be the same or different, and wherein any $(C_2\text{-}C_8)$alkenyl or $(C_2\text{-}C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4, or 5 Z^{2c} groups, which may be the same or different;

each R^{n3} is independently H or $(C_1\text{-}C_4)$alkyl;

each R^{q3} and R^{r3} is independently H or $(C_1\text{-}C_4)$alkyl;

each Z^{2b} is independently oxo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$heteroalkyl or $(C_1\text{-}C_4)$haloalkyl;

each Z^{2c} is independently oxo, halogen, -CN, $-OR^{n4}$, $NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}S(O)_2R^{p4}$, $-C(O)R^{n4}$, $-C(O)OR^{n4}$ or $-C(O)NR^{q4}R^{r4}$;

each R^{n4} is independently H, $(C_1\text{-}C_4)$alkyl, or $(C_1\text{-}C_4)$heteroalkyl;

each R^{p4} is independently $(C_1\text{-}C_8)$alkyl;

each R^{q4} and R^{r4} is independently H, $(C_1\text{-}C_4)$alkyl, or $(C_1\text{-}C_4)$heteroalkyl;

Z^3 is independently a $(C_1\text{-}C_4)$heteroalkyl or halogen;

each Z^4 is independently oxo, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, halogen, -CN, $-OR^{n5}$, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-C(O)R^{n5}$, $-C(O)OR^{n5}$, or $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3$-$C_7)$carbocycle or $(C_1$-$C_8)$alkyl of Z^4 is optionally substituted with 1, 2, 3, 4 or 5 Z^{4a} groups, which may be the same or different;

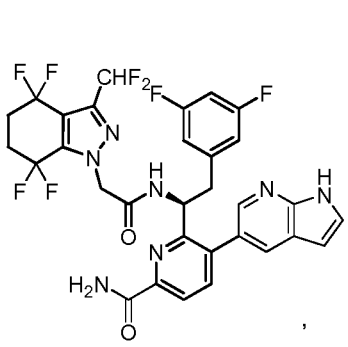
each Z^{4a} is independently halogen, -CN, or $-OR^{n6}$; and

each R^{n5}, R^{p5}, R^{q5}, R^{r5}, and R^{n6} is independently H or $(C_1$-$C_4)$alkyl;

each Z^5 is independently halogen, which may be same or different; and

n is 0, 1, 2, or 3.

[0342] In one embodiment the compound of formula I is selected from:



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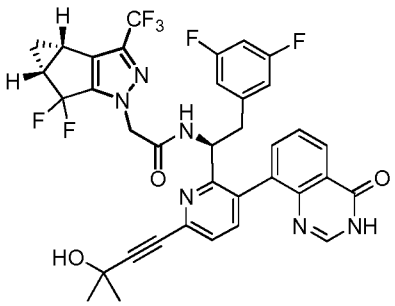

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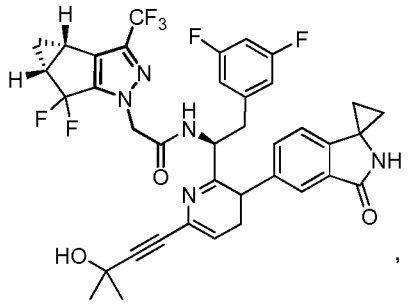

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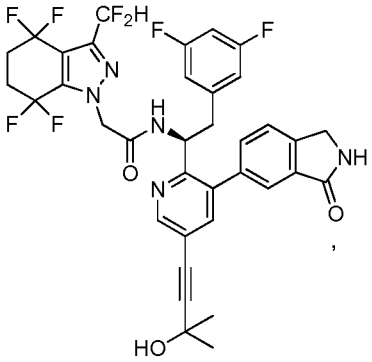

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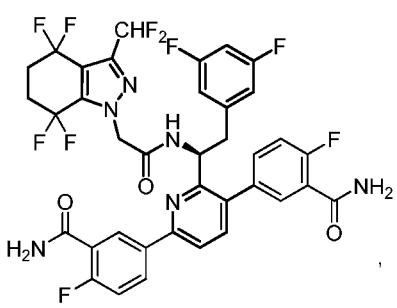

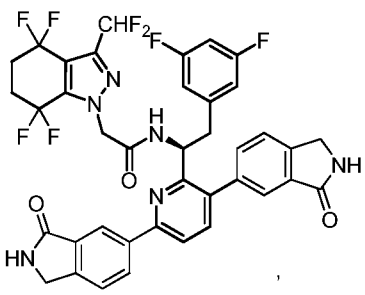

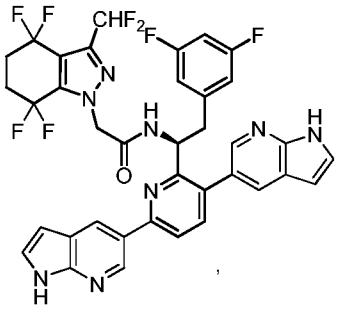

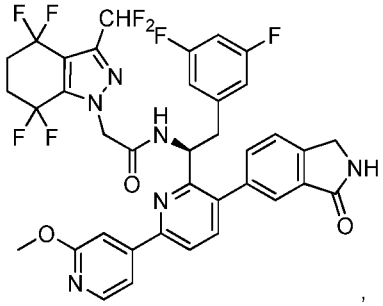

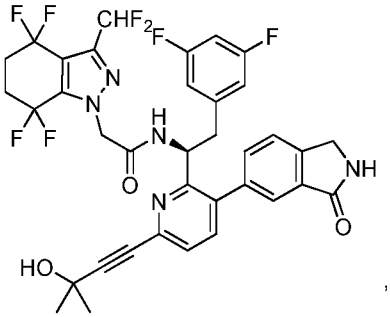

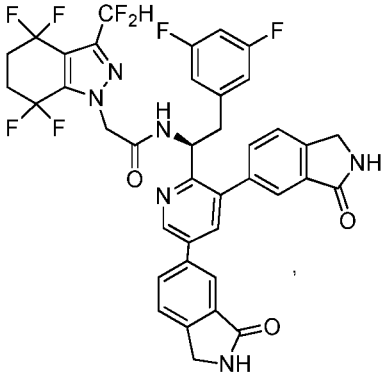

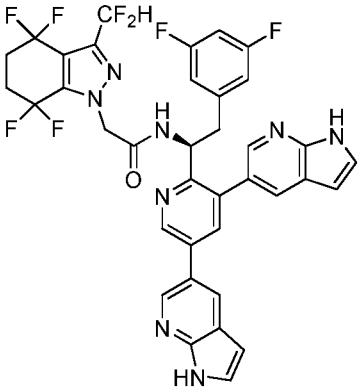

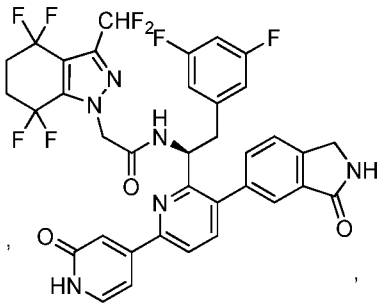

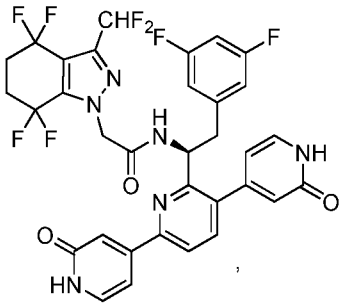

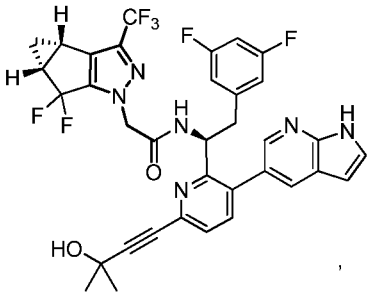

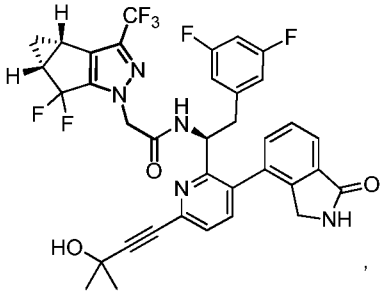

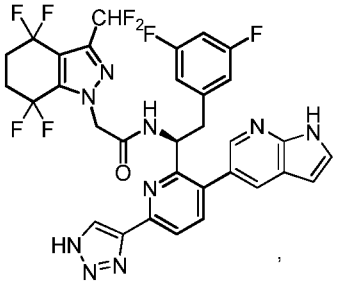

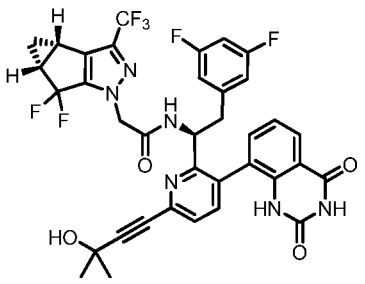
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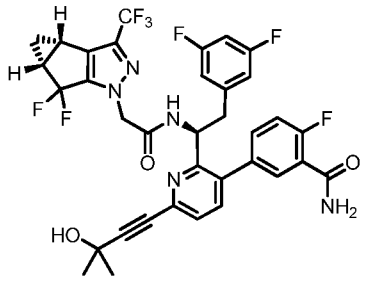
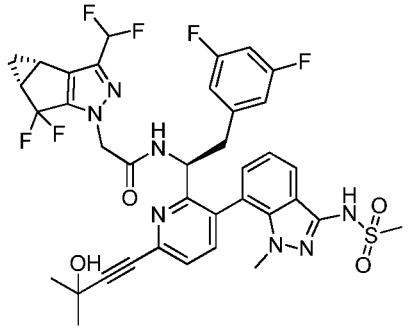


and pharmaceutically acceptable salts thereof.

[0343] In certain embodiments, a compound is: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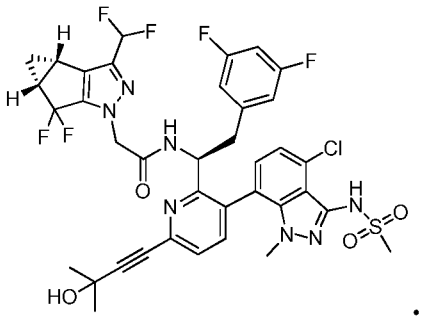
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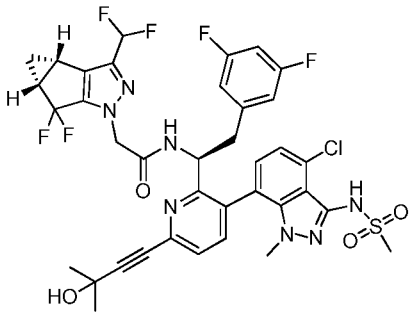
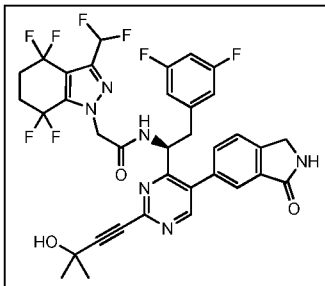
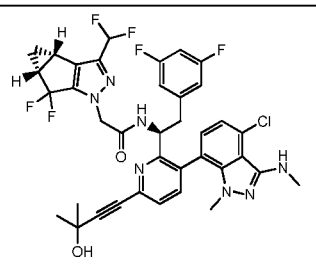
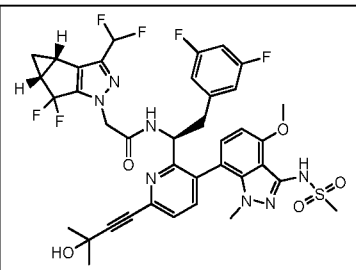
or a pharmaceutically acceptable salt thereof.

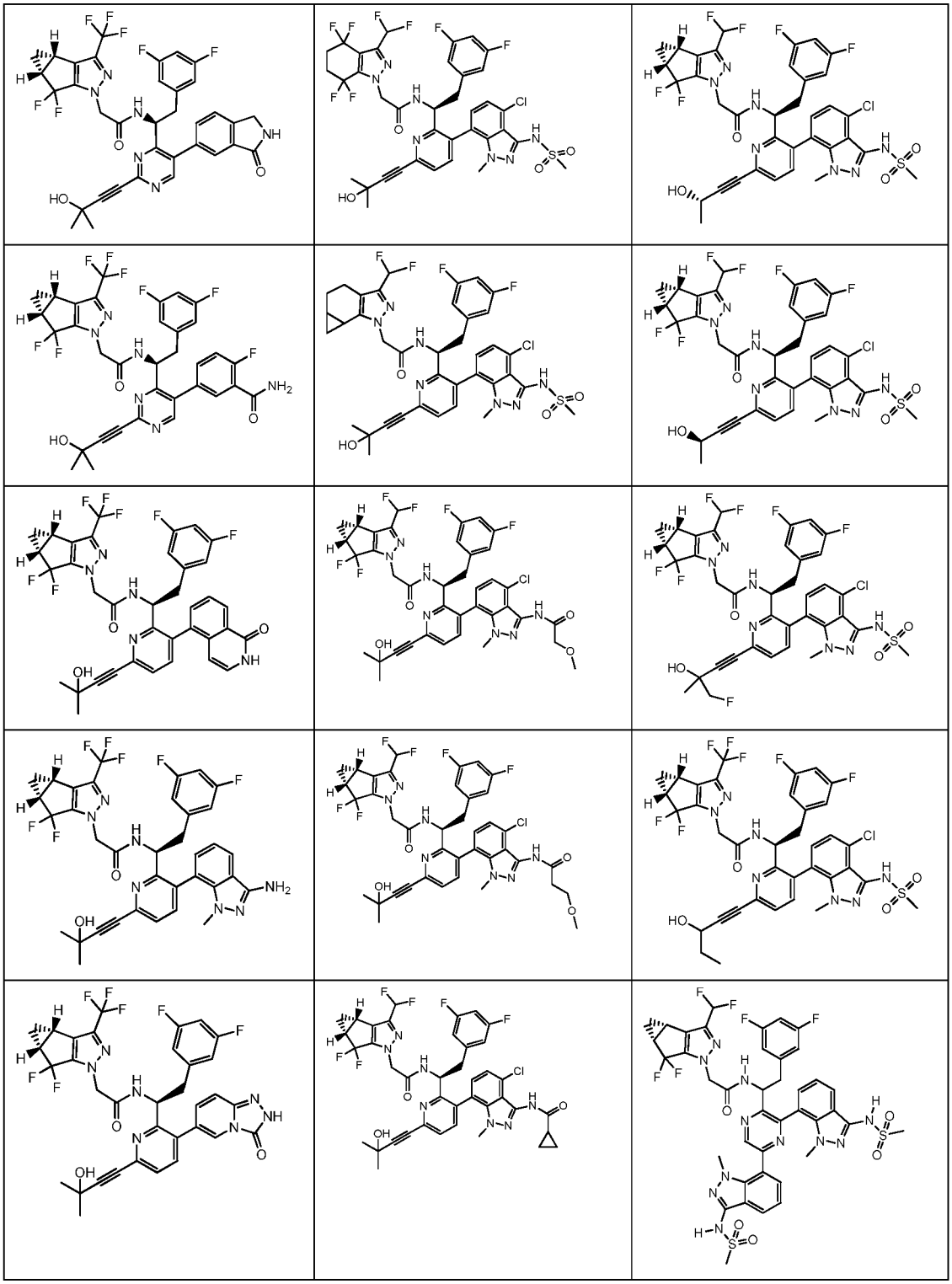
[0344] In certain embodiments, a compound is:

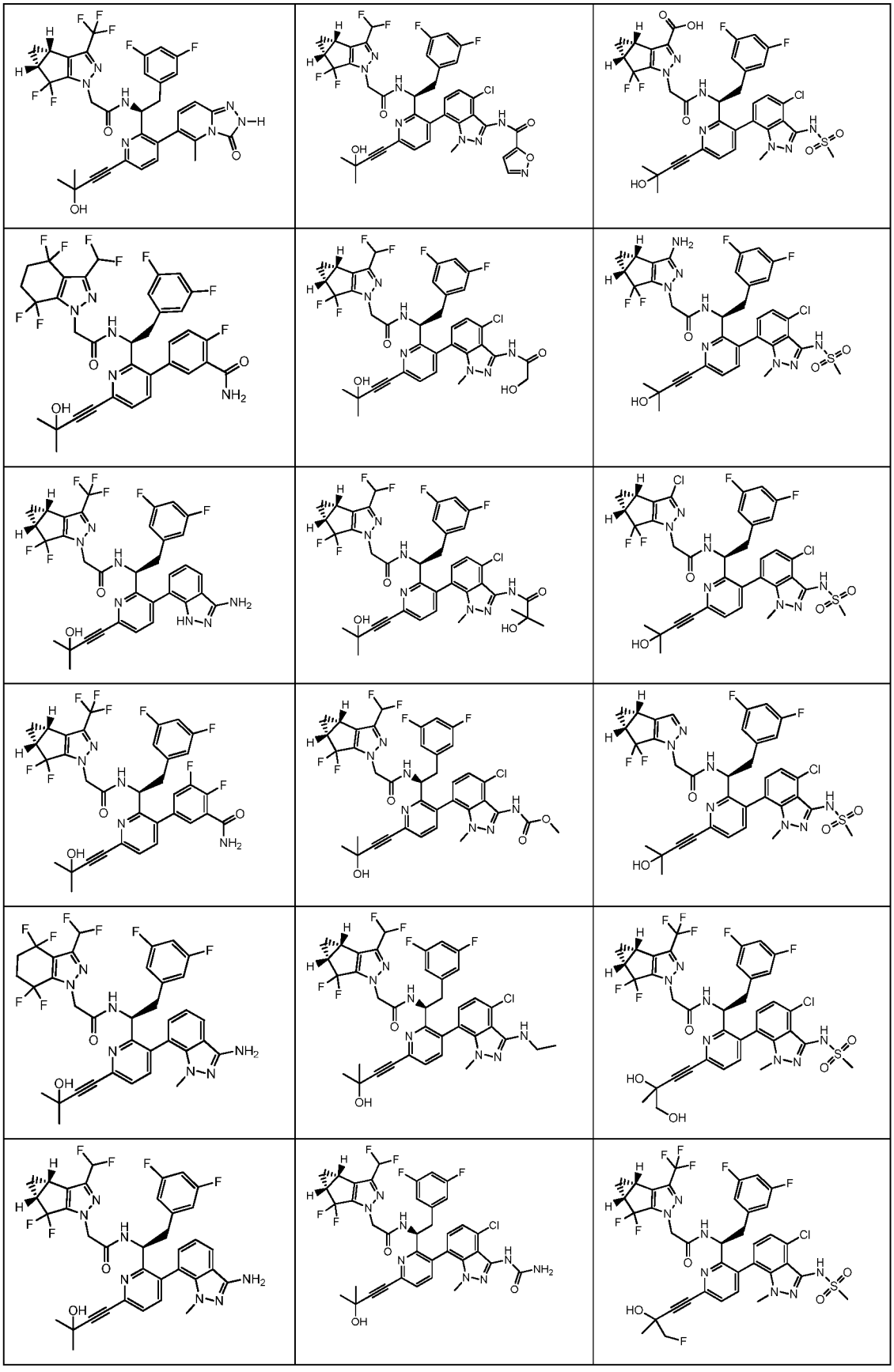


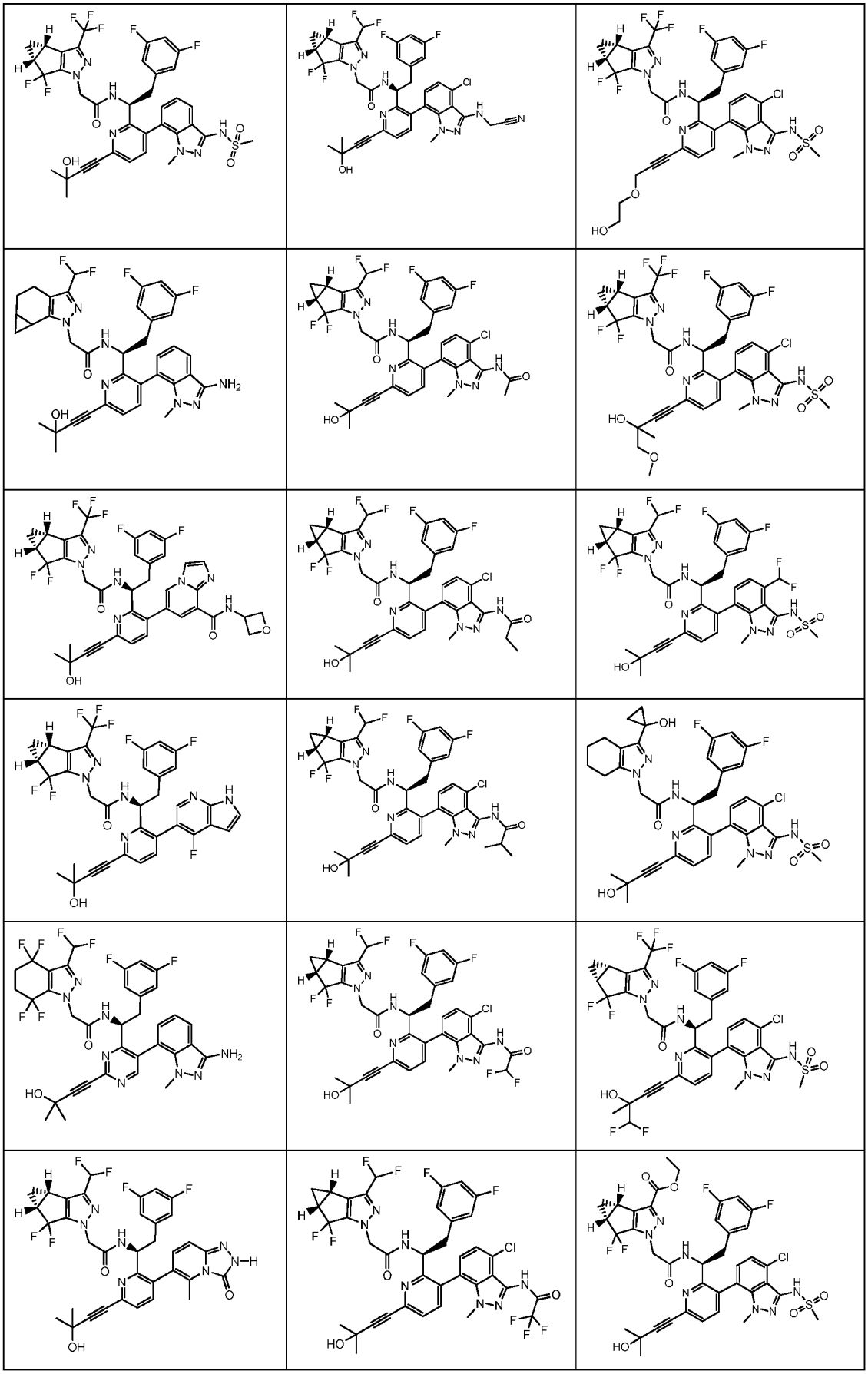
or a pharmaceutically acceptable salt thereof.

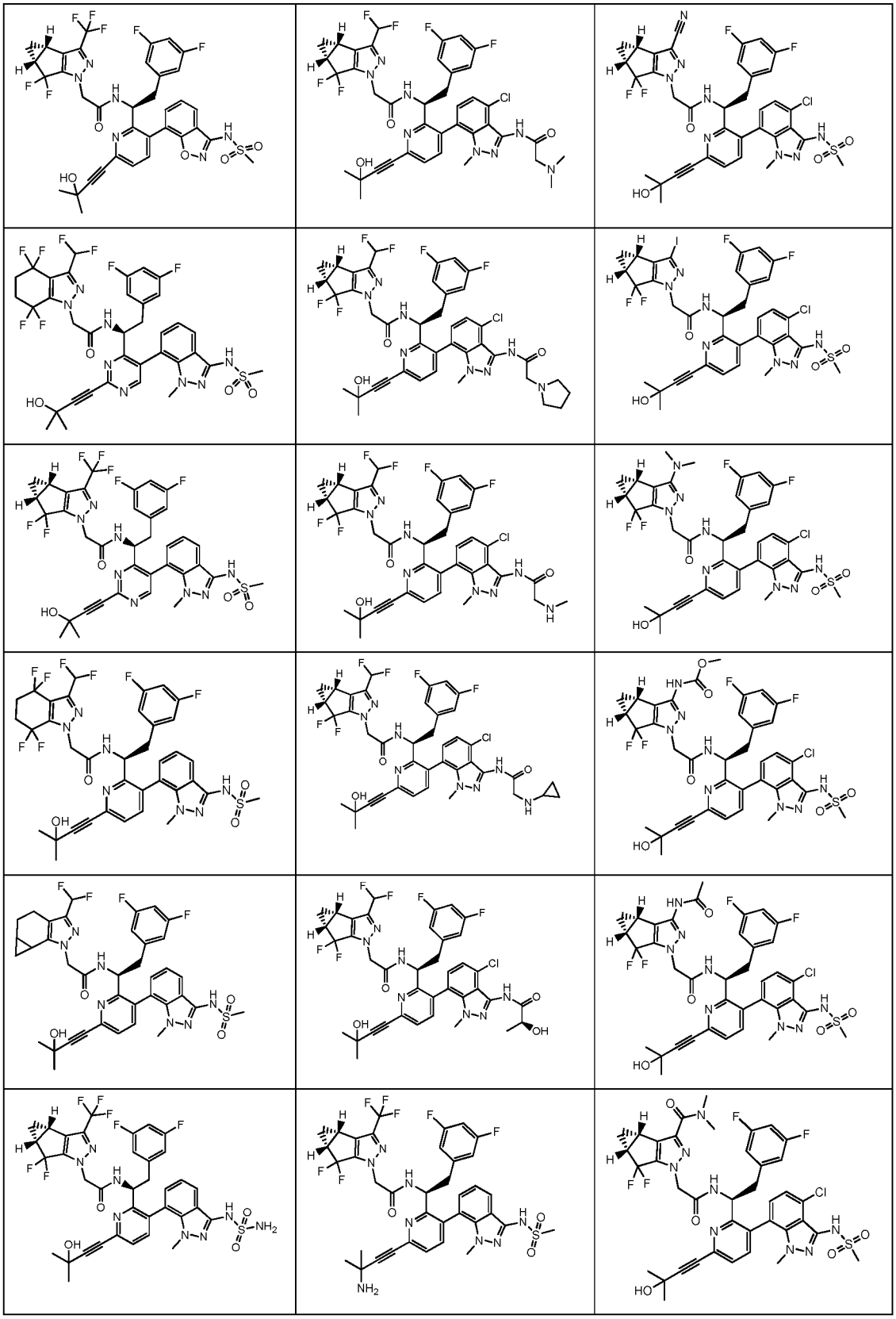
[0345] In certain embodiments, a compound or a pharmaceutically acceptable salt thereof is:

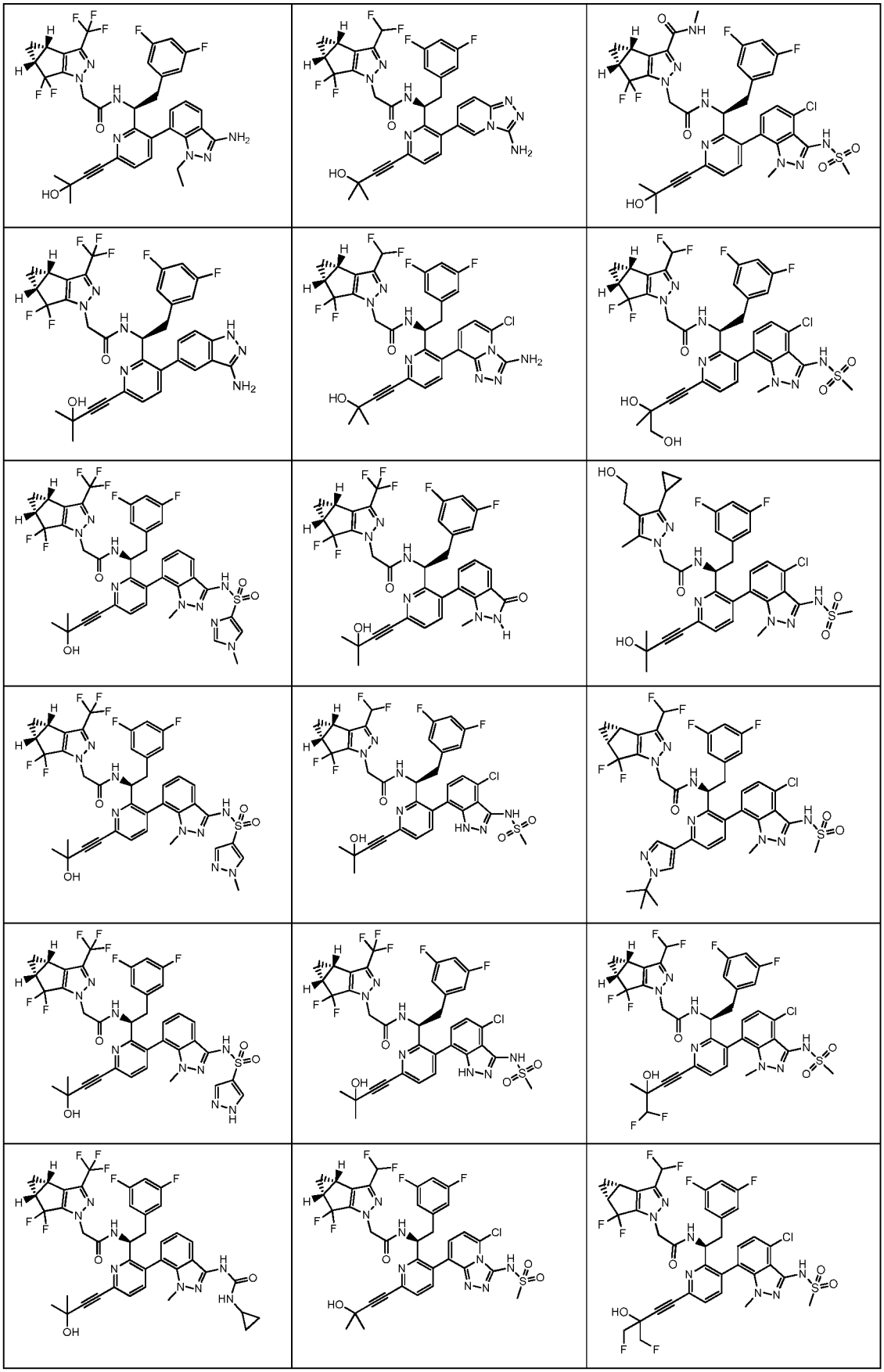
		

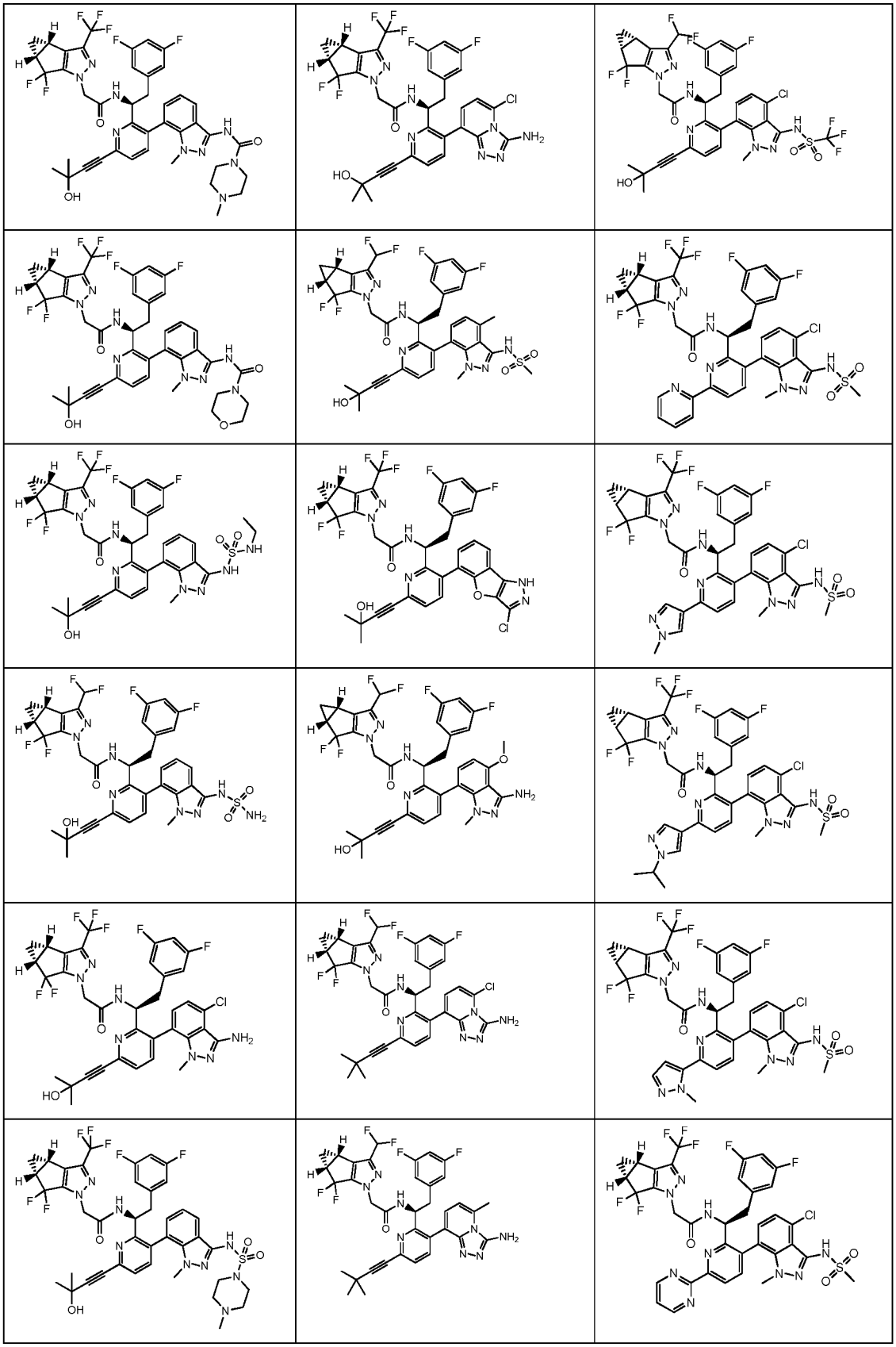


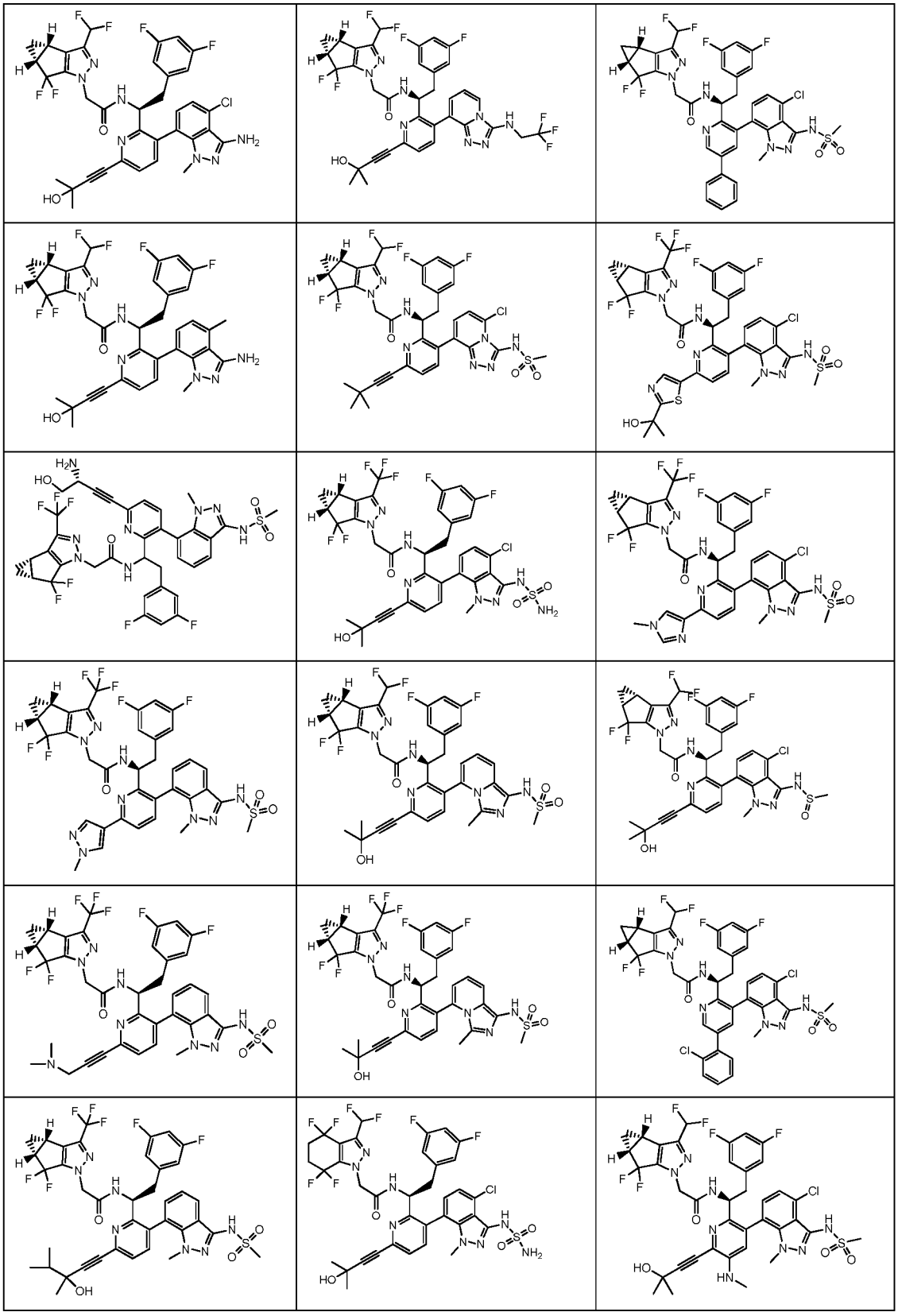


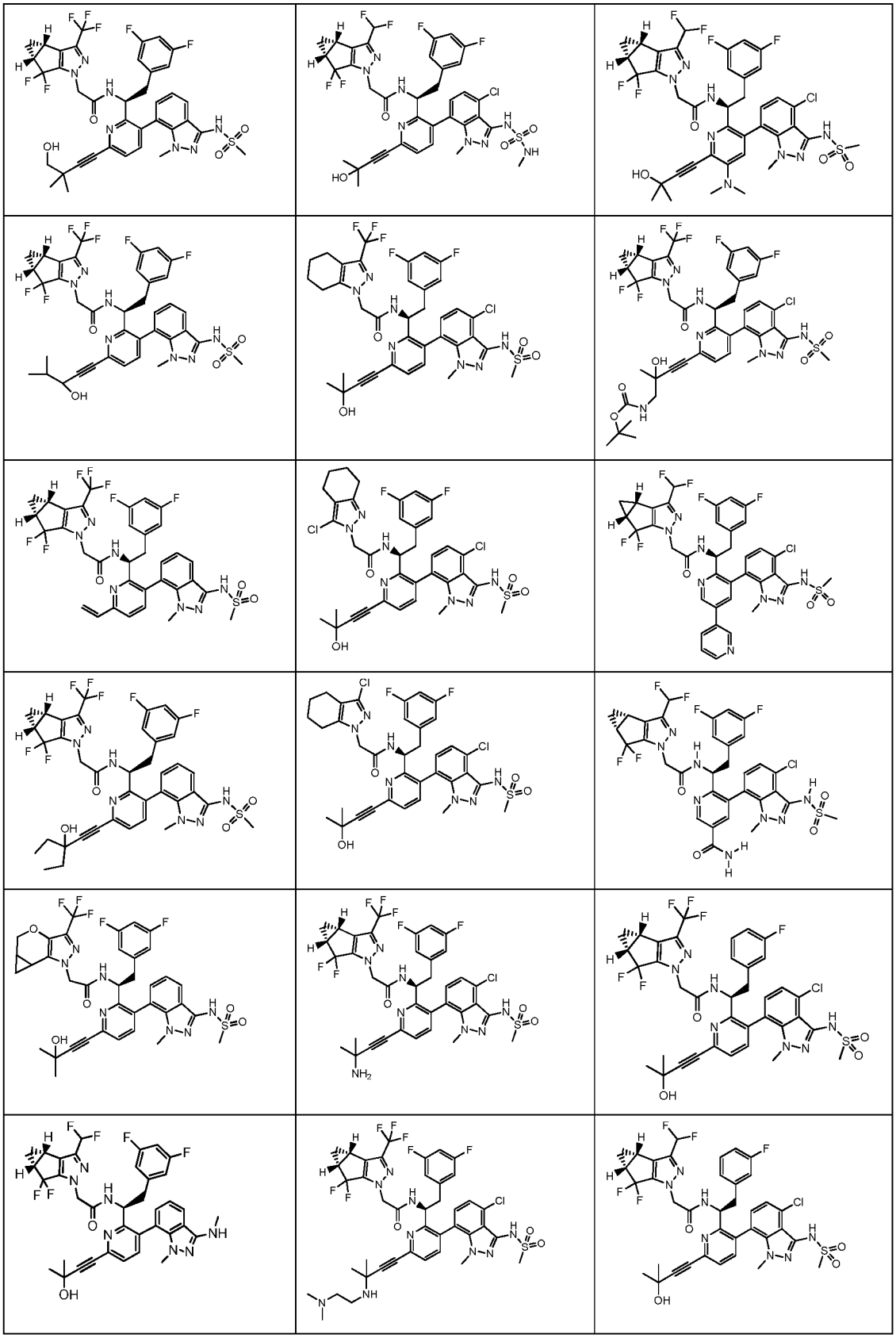


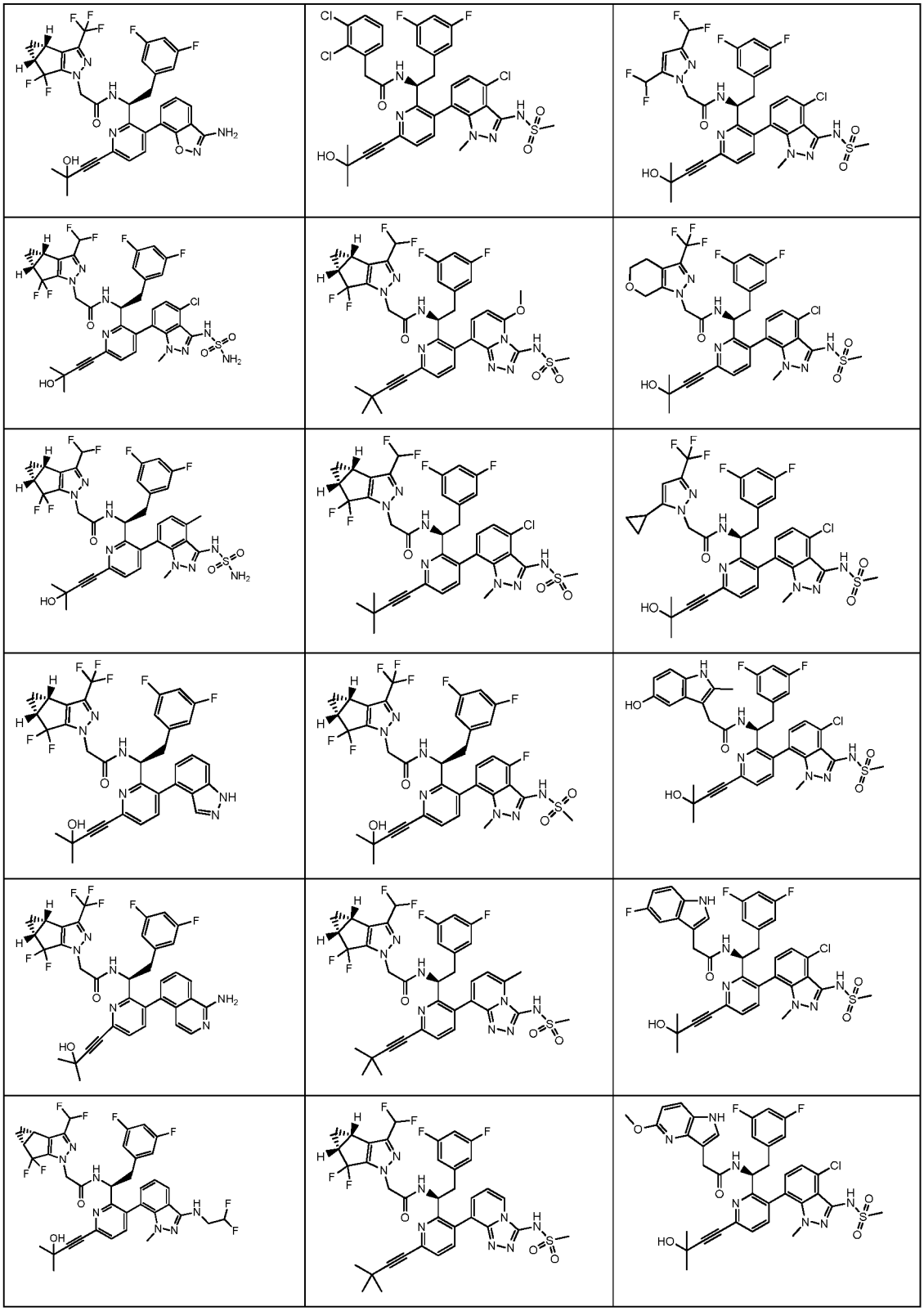


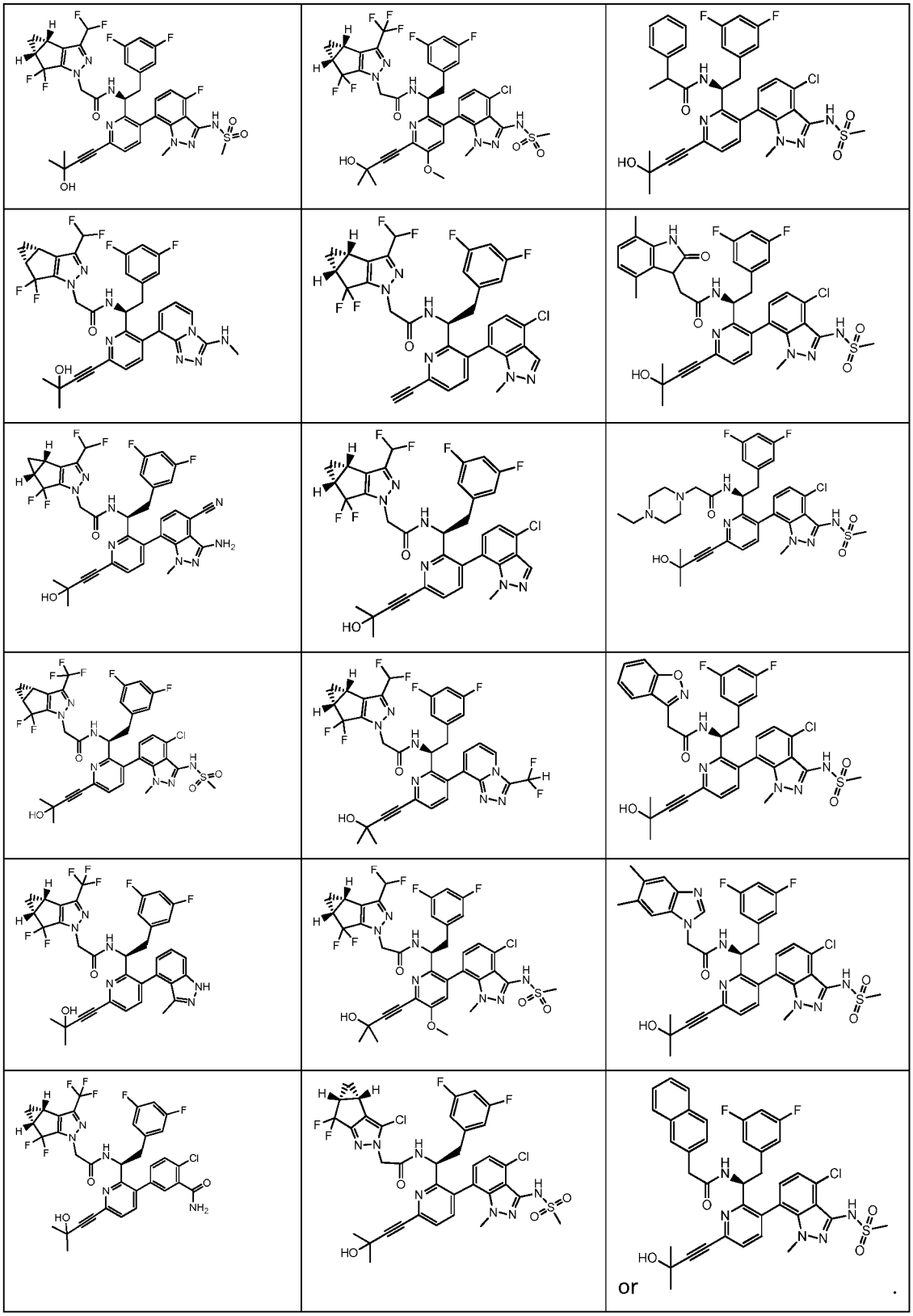






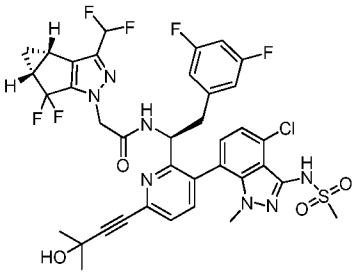






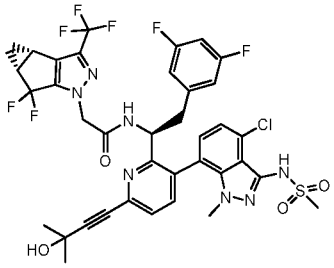
or .

[0346] In certain embodiments, a compound is:



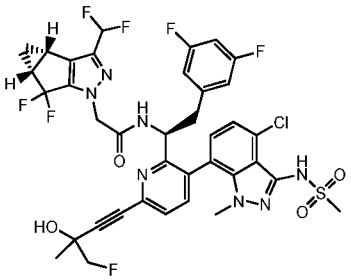
or a pharmaceutically acceptable salt thereof.

[0347] In certain embodiments, a compound is:



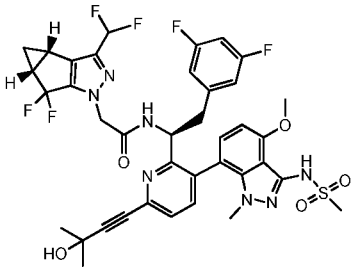
or a pharmaceutically acceptable salt thereof.

[0348] In certain embodiments, a compound is:



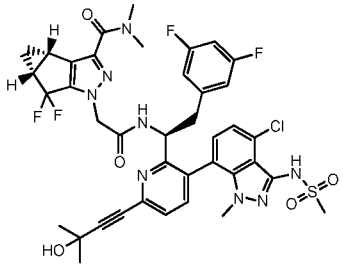
or a pharmaceutically acceptable salt thereof.

[0349] In certain embodiments, a compound is:



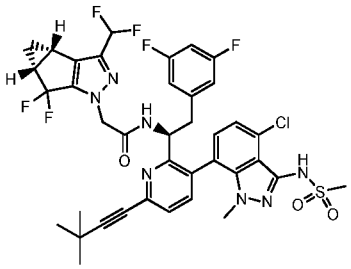
or a pharmaceutically acceptable salt thereof.

[0350] In certain embodiments, a compound is:



or a pharmaceutically acceptable salt thereof.

[0351] In certain embodiments, a compound is:

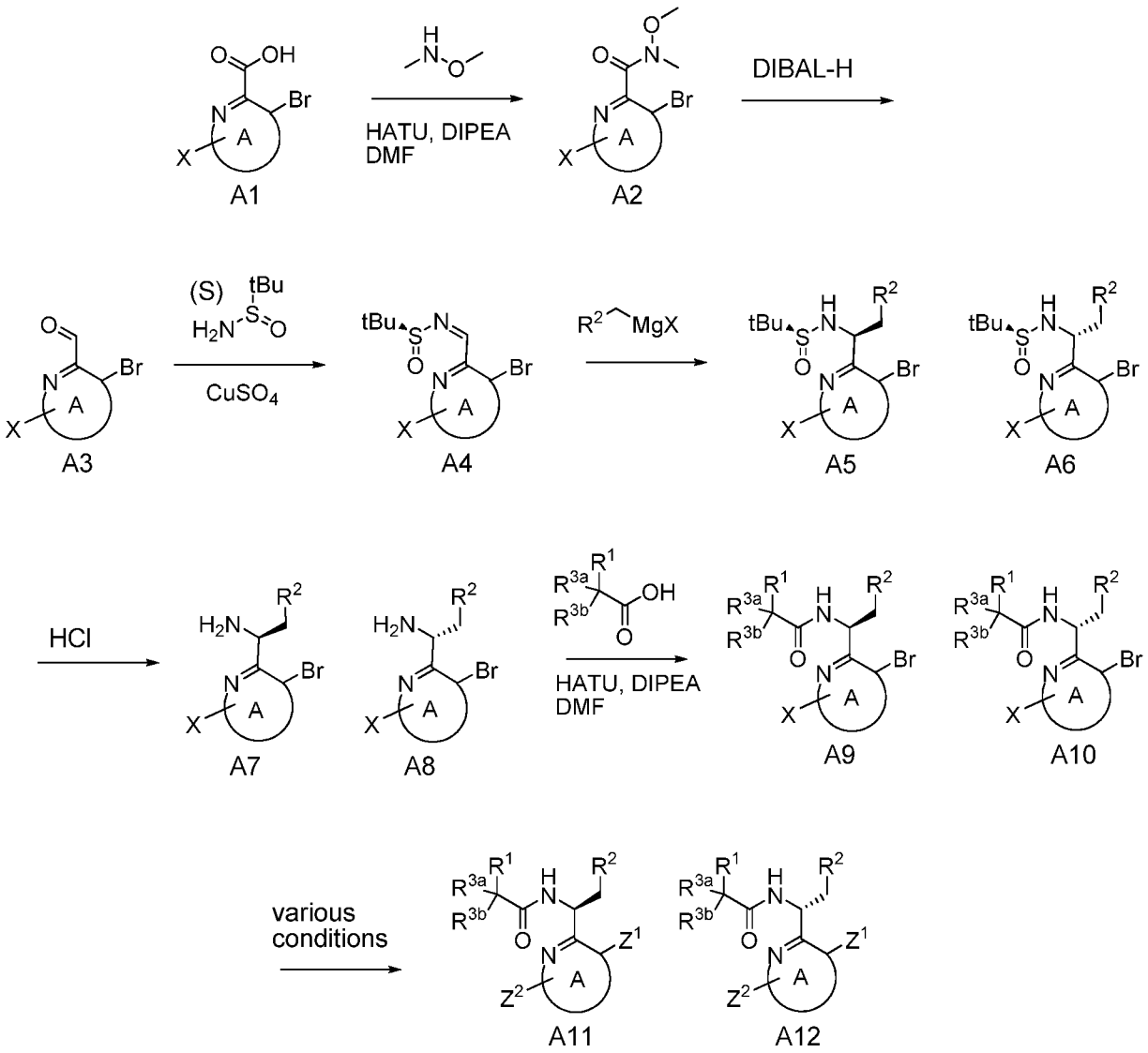


or a pharmaceutically acceptable salt thereof.

General Synthetic Procedures

[0352] The following schemes describe methods that are useful for preparing compounds of formula I. The following schemes similarly describe methods that are useful for preparing compounds of formula III.

Scheme 1

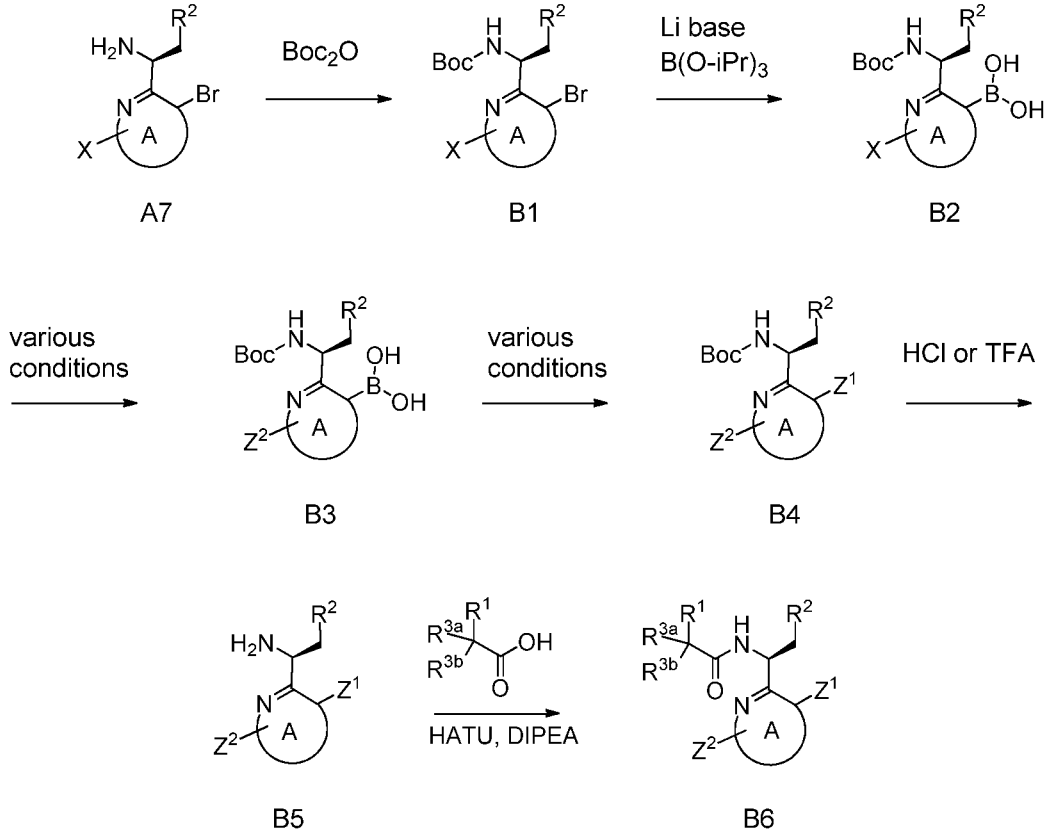


[0353] Scheme 1 describes a general stereoselective route which is used to prepare compounds of formula I. The scheme is also be used to prepare compounds of formula III. Heteroaryl acids of formula A1 (where X represents diversifiable chemical group such as NH_2, SH, or halogen that are suitably protected) are converted to the corresponding aldehydes then condensed with a chiral auxiliary to provide a stereoselective addition of a nucleophilic reagent. Depicted in Scheme 1 is the conversion of a heteroaryl acid A1 containing two diversifiable functional groups (e.g., X and Br) to the corresponding aldehyde. This is followed by the condensation of the aldehyde A3 with (S) tert-butane sulfinamide and the addition of a Grignard reagent to provide a mixture of A5 and A6 enriched in A5. This mixture is separated by column chromatography on silica gel to provide pure diastereomers. Removal of the auxiliary provides

amines A7 and A8 which are coupled to a variety of carboxylic acids to provide heteroaryl compounds of formula A9 and A10. Diversification of A9 and A10 is accomplished by a variety of methods including alkylation, acylation, cyanation, nucleophilic aromatic displacement, and metal catalyzed cross coupling reactions such as Suzuki couplings, Buchwald-Hartwig type couplings, and Sonogashira couplings.

[0354] Scheme 2 describes a general stereoselective route which can be used to prepare compounds of formulas I and III.

Scheme 2



[0355] Depicted in Scheme 2 is the protection of amine A7 to a compound of formula B1. This is followed by the conversion of the Br to the corresponding boronic acid. Diversification of the functional group X and boronic acid is accomplished by a variety of methods including alkylation, acylation, cyanation, nucleophilic aromatic displacement, and metal catalyzed cross coupling reactions such as Suzuki couplings, Buchwald-Hartwig type couplings, and Sonogashira couplings to provide compounds of formulas B3 and B4. Deprotection followed by amide formation with a variety of carboxylic acids provides compounds of formula I.

Combination Therapy

[0356] In one embodiment, the invention provides a method for treating an HIV infection, comprising administering to a patient in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents which are suitable for treating an HIV infection.

[0357] A compound as disclosed herein (e.g., a compound of any of formulas I and III or a pharmaceutically acceptable salt thereof) may be combined with one or more additional therapeutic agents in any dosage amount of the compound (e.g., from 50 mg to 300 mg of compound).

[0358] In one embodiment, a method for treating or preventing an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents.

[0359] In one embodiment, the invention provides pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with at least one additional therapeutic agent, and a pharmaceutically acceptable carrier. For example, the therapeutic agent used in combination with the compound disclosed herein can be any anti-HIV agent.

[0360] In one embodiment, combination pharmaceutical agents comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or more additional therapeutic agents are provided.

[0361] One embodiment provides pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with at least one additional therapeutic agent, and a pharmaceutically acceptable carrier. In one embodiment, the additional therapeutic agent may be an anti-HIV agent. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of HIV protease inhibiting compounds (HIV protease inhibitors), HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, entry inhibitors (e.g., CCR5 inhibitors, gp41 inhibitors (i.e., fusion inhibitors) and CD4 attachment inhibitors), CXCR4 inhibitors, gp120 inhibitors, G6PD and NADH-oxidase

inhibitors, capsid polymerization inhibitors or capsid disrupting compounds such as those disclosed in US 2013/0165489 (University of Pennsylvania), and WO 2013/006792 (Pharma Resources), pharmacokinetic enhancers, and other drug for treating HIV, and combinations thereof.

[0362] In further embodiments, the additional therapeutic agent is selected from one or more of:

(1) HIV protease inhibitors selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, PPL-100, DG35, and AG 1859;

(2) HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase selected from the group consisting of capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, TMC-120, rilpivirene, BILR 355 BS, VRX 840773, lersivirine (UK-453061), RDEA806, KM023 and MK-1439;

(3) HIV nucleoside inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, ±-FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), amdoxovir, KP-1461, GS-9131 (Gilead Sciences) and fosalvudine tidoxil (formerly HDP 99.0003);

(4) HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir disoproxil, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, tenofovir alafenamide, GS-7340 (Gilead Sciences), GS-9148 (Gilead Sciences), adefovir, adefovir dipivoxil, CMX-001 (Chimerix) or CMX-157 (Chimerix);

(5) HIV integrase inhibitors selected from the group consisting of curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, AR-177, L-870812, and L-870810,

raltegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048, BA 011, elvitegravir, dolutegravir and GSK-744;

(6) HIV non-catalytic site, or allosteric, integrase inhibitors (NCINI) including, but not limited to, BI-224436, CX0516, CX05045, CX14442, compounds disclosed in WO 2009/062285 (Boehringer Ingelheim), WO 2010/130034 (Boehringer Ingelheim), WO 2013/159064 (Gilead Sciences), WO 2012/145728 (Gilead Sciences), WO 2012/003497 (Gilead Sciences), WO 2012/003498 (Gilead Sciences) each of which is incorporated by reference in its entirety herein;

(7) gp41 inhibitors selected from the group consisting of enfuvirtide, sifuvirtide, albuvirtide, FB006M, and TRI-1144;

(8) the CXCR4 inhibitor AMD-070;

(9) the entry inhibitor SP01A;

(10) the gp120 inhibitor BMS-488043;

(11) the G6PD and NADH-oxidase inhibitor immunitin;

(12) CCR5 inhibitors selected from the group consisting of aplaviroc, vicriviroc, maraviroc, cenicriviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5mAb004;

(13) CD4 attachment inhibitors selected from the group consisting of ibalizumab (TMB-355) and BMS-068 (BMS-663068);

(14) pharmacokinetic enhancers selected from the group consisting of cobicistat, ritonavir, and SPI-452; and

(15) other drugs for treating HIV selected from the group consisting of BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevirimat), HRG214, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040).

[0363] In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with two, three, four or more additional therapeutic agents. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with two additional therapeutic agents. In other embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with three additional therapeutic agents. In further embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with four additional therapeutic agents. The two, three four or more additional therapeutic agents can be different therapeutic agents selected from the same

class of therapeutic agents, or they can be selected from different classes of therapeutic agents. In a specific embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleotide inhibitor of reverse transcriptase and an HIV non-nucleoside inhibitor of reverse transcriptase. In another specific embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleotide inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In a further embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In an additional embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and a pharmacokinetic enhancer.

[0364] In a specific embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with tenofovir, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir disoproxil, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide. In another specific embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir alafenamide. In a specific embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with emtricitibine, abacavir or lamivudine.

[0365] In a specific embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with one of: tenofovir, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir disoproxil, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and one of: emtricitibine, abacavir or lamivudine. In a specific embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with one of: tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide fumarate, or tenofovir alafenamide and one of: emtricitibine or abacavir.

[0366] In some embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 5-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. In some embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 5-

10; 5-15; 5-20; 5-25; 25-30; 20-30; 15-30; or 10-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. In some embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 10 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. In some embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. A compound as disclosed herein (e.g., a compound of any of formulas I and III or a pharmaceutically acceptable salt thereof) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 50 mg to 300 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[0367] In some embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 200-400 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil and 200 mg emtricitabine. In some embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 200-250; 200-300; 200-350; 250-350; 250-400; 350-400; 300-400; or 250-400 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil and 200 mg emtricitabine. In some embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 300 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil and 200 mg emtricitabine. A compound as disclosed herein (e.g., a compound of any of formulas I and III or a pharmaceutically acceptable salt thereof) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 50 mg to 300 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[0368] In some embodiments, one or more of the compounds disclosed herein are combined with one or more other active therapeutic agents in a unitary dosage form for simultaneous or sequential administration to a patient. In certain embodiments, a pharmaceutical composition including one or more of the compounds disclosed herein combined with one or more other active therapeutic agents is provided. In certain embodiments, the compounds disclosed herein are combined with one or more other active therapeutic agents in a solid dosage form. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

[0369] In some embodiments, one or more of the compounds disclosed herein are co-administered with one or more other active therapeutic agents. Co-administration of a compound disclosed herein with one or more other active therapeutic agents generally refers to simultaneous or sequential administration of a compound disclosed herein and one or more other active therapeutic agents, such that therapeutically effective amounts of disclosed herein and one or more other active therapeutic agents are both present in the body of the patient.

[0370] In yet another embodiment, the present application provides a method for treating an HIV infection comprising administering to a patient in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents such as those disclosed above.

Pharmaceutical Formulations

[0371] The compounds disclosed herein are formulated with conventional carriers (*e.g.*, inactive ingredient or excipient material) which will be selected in accord with ordinary practice. Tablets will contain excipients including glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the Handbook of Pharmaceutical Excipients (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. One embodiment provides the formulation as a solid dosage form including a solid oral dosage form. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

[0372] While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations (compositions). The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

[0373] The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such

methods include the step of bringing into association the active ingredient with inactive ingredients (e.g., a carrier, pharmaceutical excipients, etc.) which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0374] Formulations described herein that are suitable for oral administration may be presented as discrete units including but not limited to capsules, cachets or tablets each containing a predetermined amount of the active ingredient.

[0375] Pharmaceutical formulations disclosed herein comprise one or more compounds disclosed herein together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

[0376] The amount of active ingredient that is combined with the inactive ingredients to produce a dosage form will vary depending upon the host treated and the particular mode of administration. For example, in some embodiments, a dosage form for oral administration to humans contains approximately 1 to 1000 mg of active material formulated with an appropriate

and convenient amount of carrier material (*e.g.,* inactive ingredient or excipient material). In some embodiments, a dosage form (e.g., for oral administration to humans) contains: from 10 mg to 1000 mg or from 50 mg to 1000 mg or from 100 mg to 1000 mg or from 200 mg to 1000 mg or from 300 mg to 1000 mg or from 10 mg to 800 mg or from 10 mg to 600 mg or from 10 mg to 500 mg or from 10 mg to 400 mg or from 10 mg to 300 mg or from 50 mg to 800 mg or from 100 mg to 600 mg or from 150 mg to 500 mg or from 200 mg to 400 mg or from 50 mg to 500 mg or from 10 mg to 300 mg or from 50 mg to 300 mg or from 10 mg to 200 mg or from 50 mg to 200 mg or from 100 mg to 300 mg or from 100 mg to 200 mg or from 200 mg to 300 mg of active material (e.g., a compound of any of formulae I or III). In some embodiments, a dosage form for oral administration to humans contains at least any of 10, 25, 50, 100, 150, 200, 250 or 300 mg and no more than 500 or 800 or 1000 mg of active material (e.g., from at least 50 mg to no more than 500 mg). In some embodiments, a dosage form for oral administration to humans contains at least any of 10, 25, 50, 100, 150, 200, 250 or 300 mg or no more than 500 or 800 or 1000 mg of active material. In some embodiments, a dosage form for oral administration to humans contains any of 10, 25, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, or 1000 mg of active material. It is understood that a dosage form in an amount provided herein may be administered to a patient (e.g., a human in need thereof) in accordance with a dosing regimen provided herein, such as once, twice or thrice daily dosing. In one aspect, a dosing regimen provides for administration of at least 10 mg and no more that 1,000 mg of active material (e.g., a compound of any of formulas I or III) daily, and it is understood that the amount may be provided in any suitable dosage form and amount (e.g., 500 mg twice daily or 1,000 mg once daily would provide the same amount of 1,000 mg/day dosing). The invention embraces once daily dosing to an individual (e.g., a human in need thereof) of a dosage form of compound (e.g., a compound of any of formulas I or III) containing at least 50 mg and not more than 300 mg of compound. In certain embodiments, the carrier material varies from about 5 to about 95% of the total compositions (weight:weight).

[0377] It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

[0378] The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier.

[0379] Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

[0380] Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses), the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies.

Routes of Administration

[0381] One or more compounds disclosed herein (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds disclosed herein is that they are orally bioavailable and can be dosed orally.

Dosing Regimen

[0382] The compound, such as a compound of any of Formulas I and III, may be administered to an individual in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one month, at least about 2 months, at least about 3 months, at least about 6 months, or at least about 12 months or longer. In one variation, the compound is administered on a daily or intermittent schedule for the duration of the individual's life.

[0383] The dosage or dosing frequency of a compound of any of Formulas I and III may be adjusted over the course of the treatment, e.g., based on the judgment of the administering physician.

[0384] The compound may be administered to an individual (e.g., a human) in an effective amount. In one aspect, the compound is administered once daily. In one aspect, the compound is administered twice a day. In one aspect, the compound is administered three times daily. It is understood that the compound may be administered in any dosage amount provided herein, such as a dosage amount that would provide at least 10 mg/day dosing and no more than 1,000 mg/day dosing. Once daily oral dosing is embraced, such as by administering a dosage form containing from 50 mg to 300 mg of compound.

[0385] The antiviral properties of a compound of the invention may be determined using Test A described below.

Test A: Antiviral assay in MT4 Cells

[0386] For the antiviral assay, 40 µL of a concentration required to achieve a final effective 1X test concentration of 3-fold serially diluted compound in culture medium with 10% FBS was added to each well of a 384-well plate (10 concentrations) in quadruplicate. MT-4 cells were next mixed with HIV-IIIb at an m.o.i of 0.003 for 1 hour, after which time 35 µL of virus/cell mixture (2000 cells) was immediately added to each well containing 40 µL of diluted compound. The plates were then incubated at 37°C for 5 days. After 5 days of incubation, 25 µl of 2X concentrated CellTiter-Glo™ Reagent (catalog # G7571, Promega Biosciences, Inc., Madison, WI) was added to each well containing MT-4 cells. Cell lysis was carried out by incubating at room temperature for 10 min and then chemiluminescence was read. EC50 values were calculated as the compound concentration that caused a 50% decrease in luminescence signal, a measure of HIV-1 replication. Percent inhibition of virus-induced cell killing calculated from the dose response curve at 2 µM and 0.2 µM drug concentration is shown in the table below.

Test B: Cytotoxicity assay

[0387] Compound cytotoxicity and the corresponding CC50 values was determined using the same protocol as described in the antiviral assay (Test A) except that uninfected cells were used.

[0388] Compounds of the present invention demonstrate antiviral activity (Test A) as depicted in the table below. Shown below are the corresponding values for CC50 and percent inhibition of virus-induced cell killing in the presence of 2 µM and 0.2 µM drug concentration.

Compound	%inhibition at 2 µM	%inhibition at 0.2 µM	CC50 (nM)
1B	77	17	8569
2	90	79	14347
3D	82	82	4149
4H	74	8	22793
5G	58	3	>53192
6	73	5	>53192
7	92	8	5664
8C	86	6	21955
9B	95	92	14557

10B	85	1	>53192
11	66	3	>53192
12	58	1	>53192
13	0	--	>53192
14E	89	87	6824
15	94	93	10261
16C	65	23	3670
17	80	95	12556
18	90	96	6934
19G	93	97	19626
20	80	96	11162
21H	92	92	7628
22C	92	92	4949
23B	88	83	7619
24B	83	78	5921
25	89	89	9139
26	100	84	10014
27G	89	89	10412
28	84	71	12175
29B	81	80	15266
30	91	1	8582
31	89	89	8034
32	84	84	9177
33F	93	93	12867
34	78	78	8758
35D	91	28	14204
36C	92	88	3150
37F	90	90	6352
38	96	96	13516
39C	91	7	26475
40	87	87	8719
41	98	98	7631
42	100	100	11765
43	100	100	15419
44	94	94	6816
45G	92	92	10401
46	89	87	10490
47	100	100	21441
48	88	88	23969
49	87	87	23967
50	96	95	11736
51	95	95	11128

52	93	92	31753
53	92	92	8026
54	98	98	8076
55C	92	92	9559
56F	97	97	18961
57	93	93	7634
58G	95	95	8440
59B	94	94	22443
60	96	86	14337
61B	96	96	14309
62	100	100	5695
63	91	91	8888
64	98	98	7696
65	100	85	19301
66	97	97	6956
67I	94	94	21471
68G	96	96	9638
69	77	77	718
70	94	94	9976
71	87	87	9509
72	87	85	5865
73	86	86	4494
74D	99	99	6905
75	93	92	>40267
76F	98	98	22571
77E	97	96	11804
78	98	98	14418
79	100	100	4716
80	100	96	8579
81	100	100	12466
82	99	99	9698
83	94	94	9935
84	100	100	8734
85	96	96	7850
86	99	99	6471
87	96	95	6803
88	100	100	8488
89	95	95	7773
90D	97	97	7620
91E	100	100	9382

92	100	100	6244
93	92	92	4809
94	100	100	7577
95	93	93	6513
96	100	100	6998
97	100	100	7596
98	100	100	8410
99B	100	100	6366
100	99	99	5136
101	95	95	6526
102	100	100	5815
103	100	100	6792
104	100	100	7463
105E	74	--	31484
106E	96	95	12404
107B	95	95	5303
108C	94	94	>53076
109	97	97	29567
110E	98	15	>53192
111	90	89	9593
112D	97	97	13891
113D	97	--	1092
114G	100	100	14834
115C	91	84	9313
116A	93	62	10484
117F	100	93	27833
118	96	96	23924
119C	99	99	9242
120H	88	51	11699
121	98	46	9184
122	88	88	9072
123	90	90	7904
124	97	97	9145
125D	97	96	13628
126	92	92	15507
127	92	92	8762
128B	94	93	4181
129	82	54	12115
130	85	80	23158
131E	96	95	22533

132C	92	92	24161
133	90	90	16784
134	83	82	28027
135B	93	93	14242
136D	--	--	7427
137C	100	93	7881
138	83	61	33392
139B	94	94	15437
140M	98	98	20364
141D	100	100	19761
142	92	92	12621
143	98	98	11253
144	95	95	16236
145	99	99	8687
146I	--	--	33468
147	--	--	>53192
148B	83	83	23264
149	86	86	26728
150	87	87	28895
151	92	92	25316
152	89	89	11872
153	98	98	18649
154	97	97	12488
155I	99	99	26782
156E	78	78	25584
157G	87	87	10904
158G	71	71	26745
159	95	95	27427
160	100	100	20477
161	84	84	21843
162	81	81	22412
163	86	79	8853
164	97	96	40504
165	72	72	5456
166	92	92	24421
167	93	93	34110
168B	90	90	>53192
169	92	92	12421
170	88	88	16958
171D	--	--	>42470

172	--	--	61
173	92	92	>43678
174	85	85	>53192
175	95	95	>46082
176	100	100	17402
177D	100	100	>53192
178	100	95	13999
179	100	100	15481
180C	100	100	21252
181C	100	100	>53192
182L	100	100	9829
183F	84	84	12400
184	90	90	7694
185C	89	89	18160
186D	87	87	1517
187G	84	84	19776
188	92	92	26275
189	88	88	17249
190	98	98	13907
191	91	91	10142
192	98	95	28776
193	92	92	23055
194	99	84	21268
195	90	88	11235
196	92	76	10783
197	63	--	15373
198	98	64	23690
199	95	95	22472
200	90	89	12230

[0389] The data above represent an average over time of each assay for each compound. For certain compounds, multiple assays have been conducted over the life of the project. Thus, the data reported in the tables include the data reported in the priority document, as well as data from assays run in the intervening period. In the above table, percent inhibition values have been normalized to 100% where the calculation of percent inhibition would have resulted in a value greater than 100.

[0390] In one embodiment, the compounds demonstrate >10% inhibition at 2 μM. In one embodiment, the compounds demonstrate >30% inhibition at 2 μM. In one embodiment, the compounds demonstrate >50% inhibition at 2 μM. In one embodiment, the compounds

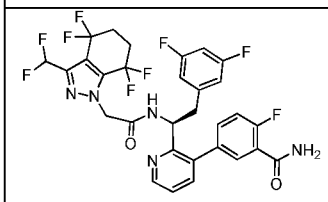
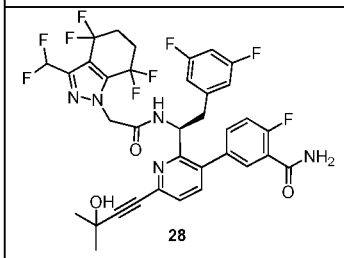
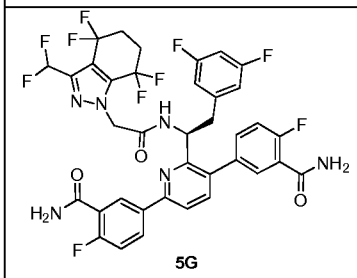
demonstrate >70% inhibition at 2 μM. In one embodiment, the compounds demonstrate >75% inhibition at 2 μM. In one embodiment, the compounds demonstrate >80% inhibition at 2 μM. In one embodiment, the compounds demonstrate >85% inhibition at 2 μM. In one embodiment, the compounds demonstrate >90% inhibition at 2 μM. In one embodiment, the compounds demonstrate >95% inhibition at 2 μM. It is to be understood that the compounds disclosed herein can be grouped according to their % inhibition as described above.

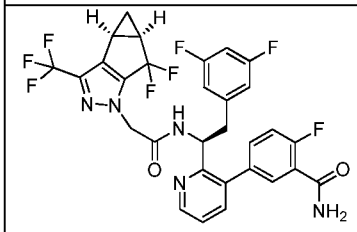
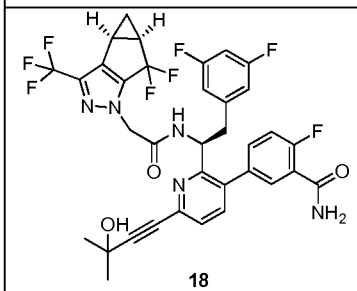
[0391] In one embodiment, the compounds demonstrate >10% inhibition at 0.2 μM. In one embodiment, the compounds demonstrate >30% inhibition at 0.2 μM. In one embodiment, the compounds demonstrate >50% inhibition at 0.2 μM. In one embodiment, the compounds demonstrate >70% inhibition at 0.2 μM. In one embodiment, the compounds demonstrate >75% inhibition at 0.2 μM. In one embodiment, the compounds demonstrate >80% inhibition at 0.2 μM. In one embodiment, the compounds demonstrate >85% inhibition at 0.2 μM. In one embodiment, the compounds demonstrate >90% inhibition at 0.2 μM. In one embodiment, the compounds demonstrate >95% inhibition at 0.2 μM. It is to be understood that the compounds disclosed herein can be grouped according to their % inhibition as described above.

[0392] In one variation, a compound is of any formulae provided herein, wherein the compound exhibits from 85%-100% inhibition of virus-induced cell killing at 2 μM. In one variation, a compound is of any formulae provided herein, wherein the compound exhibits from 85%-100% inhibition of virus-induced cell killing at 0.2 μM. In other embodiments, a compound is of any formulae provided herein wherein the compound exhibits from 50-100, 60-100, 70-100, 80-100, or 90-100% inhibition of virus-induced cell killing at 2 μM or at 0.2 μM.

[0393] It is understood that % inhibition may be evaluated by techniques known in the art. In a particular variation, a compound is of any formulae provided herein wherein the compound exhibits from 85%-110% inhibition of virus-induced cell killing at 2 μM or at 0.2 μM as measured by the method provided in the Test A and Test B sections discussed above.

[0394] Percent inhibition was also calculated for certain compounds as compared to previously published compounds (WO 2013/006738) and is shown below. The percent inhibition of virus-induced cell killing at 2 μM and 0.2 μM was measured by the method provided in the Test A and Test B sections discussed above.

Compound	Response at 2 μM	Response at 0.2 μM
 X1	94	21
 28	84	71
 5G	58	3

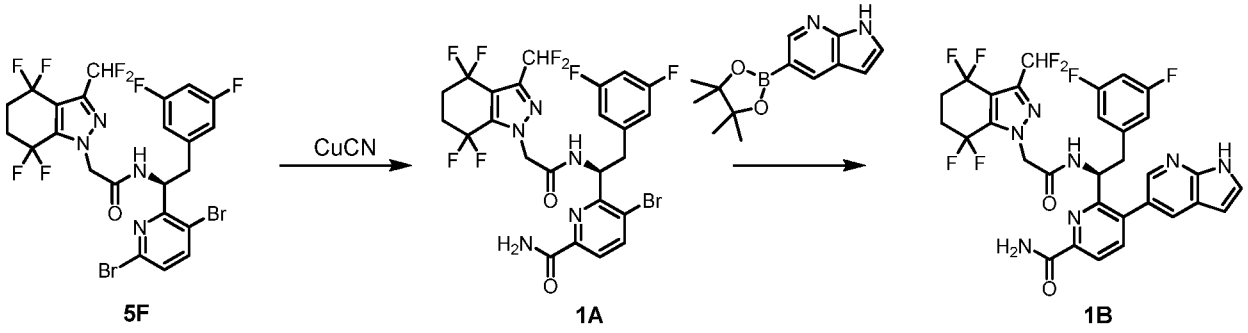
Compound	Response at 2 μM	Response at 0.2 μM
 X2	91	65
 18	90	96

[0395] The specific pharmacological responses observed may vary according to and depending on the particular active compound selected and whether there are present pharmaceutical carriers and/or pharmaceutically active compounds, as well as the type of

formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with practice of the present invention.

[0396] The Examples provided herein describe the synthesis of compounds disclosed herein as well as intermediates used to prepare the compounds. It is to be understood that individual steps described herein may be combined. It is also to be understood that separate batches of a compound may be combined and then carried forth in the next synthetic step.

Example 1.



5F **1A** **1B**

Synthesis of (S)-5-bromo-6-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)picolinamide (**1A**):

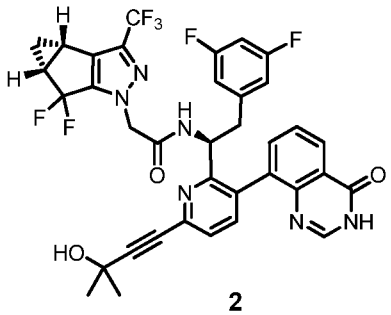
[0397] Compound **5F** (100 mg, 0.15 mmol) and CuCN (16 mg, 0.18 mmol) was dissolved in 0.3 mL of DMF. The reaction mixture was heated at 100 °C overnight. After cooled down to room temperature it was diluted with water and extracted with EtOAc. The organic phase was dried (Na_2SO_4), filtered and concentrated. The crude material was purified on reverse phase HPLC eluting with acetonitrile and water (with 0.1% TFA) to afford (S)-N-(1-(3-bromo-6-cyanopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide and the title product (**1A**). MS (*m/z*) 640.05 $[M+H]^+$.

Synthesis of (S)-6-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-5-(1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide (**1B**):

[0398] The title compound (**1B**) was prepared according to the method presented for the synthesis of compound **4H** of Example 4 utilizing 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine and **1A**. ^1H NMR (400 MHz, CD_3OD) δ 9.00 (d, J = 8.5 Hz, 1H), 8.12 (d, J = 7.9 Hz, 1H), 8.01 (s, 1H), 7.92 – 7.77 (m, 2H), 7.56 (d, J = 3.5 Hz, 1H), 6.97 – 6.53

(m, 3H), 6.26 (d, J = 6.1 Hz, 2H), 5.53 (m, 1H), 5.11 (s, 2H), 3.07 (m, 2H), 2.63 – 2.25 (m, 4H).MS (m/z) 678.08 $[M+H]^+$.

Example 2.

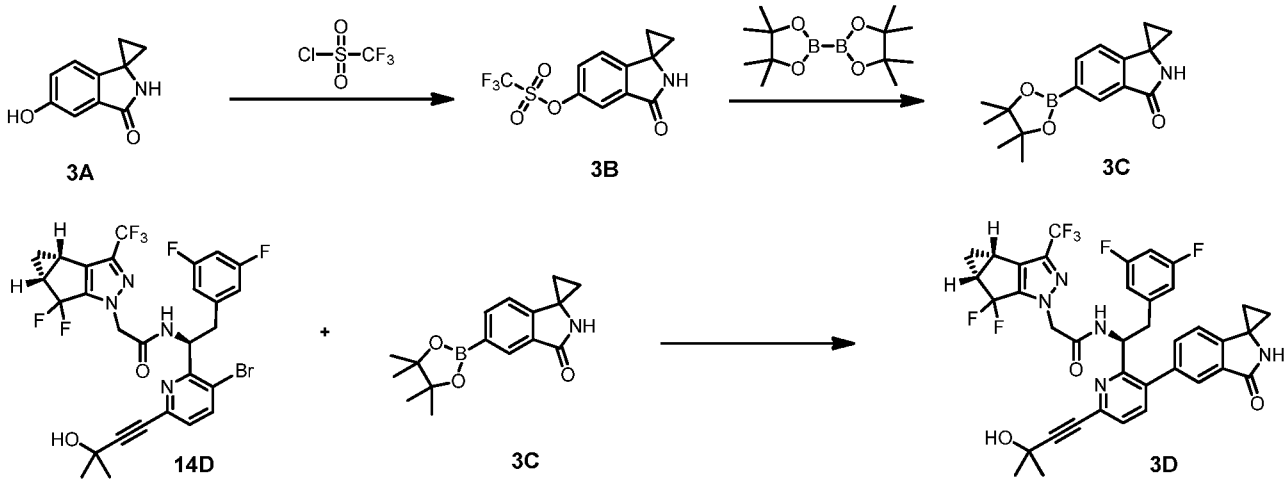


2

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(4-oxo-3,4-dihydroquinazolin-8-yl)pyridin-2-yl)ethyl)acetamide (**2**):

[0399] The title compound (**2**) was prepared according to the method presented for the synthesis of compound **4H** of Example 4 utilizing (4-oxo-3,4-dihydroquinazolin-8-yl)boronic acid and **14D**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (m, 1H), 7.82 (m, 1H), 7.75 (m, 1H), 7.50 (s, 1H), 7.44 (m, 2H), 6.86 (m, 1H), 6.61 (m, 2H), 6.32 (m, 1H), 6.15 (m, 2H), 5.21 (m, 1H), 4.76 (s, 2H), 3.11 (m, 2H), 2.92 (m, 2H), 2.48 (m, 4H), 1.62 (d, J = 6.6 Hz, 6H), 1.33 (m, 1H), 1.12 (m, 1H).MS (m/z) 725.14 $[M+H]^+$.

Example 3.



3A 3B 3C

14D 3C 3D

Synthesis of 3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl trifluoromethanesulfonate (**3B**):

[0400] The mixture of compound **3A** (1 g, 5.7 mmol, prepared according to the method presented in Tetrahedron Letters 50 (2009) 1267–1269), DCM (20 mL), and Et_3N (0.9 mL, 6.8

mmol) was cooled to 0 °C using an ice/water bath. Trifluoromethanesulfonyl chloride (0.91 mL, 8.5 mmol) was added dropwise via syringe. The mixture was then stirred for 1 h in ambient temperature. More Trifluoromethanesulfonyl chloride (0.8 mL) was added and the mixture was stirred at ambient temperature for another hour. Then diluted with DCM (150 mL) and washed with 1.0 N HCI (50 mL), saturated aqueous sodium bicarbonate (1 X 50 mL), and saturated aqueous sodium chloride (1 X 50 mL). The organic layer was dried over $MgSO_4$, filtered through Celite$^{(R)}$, and concentrated in vacuo to give the title product (**3B**). MS (*m/z*) 308.29 $[M+H]^+$.

Synthesis of 5'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[cyclopropane-1,1'-isoindolin]-3'-one (**3C**):

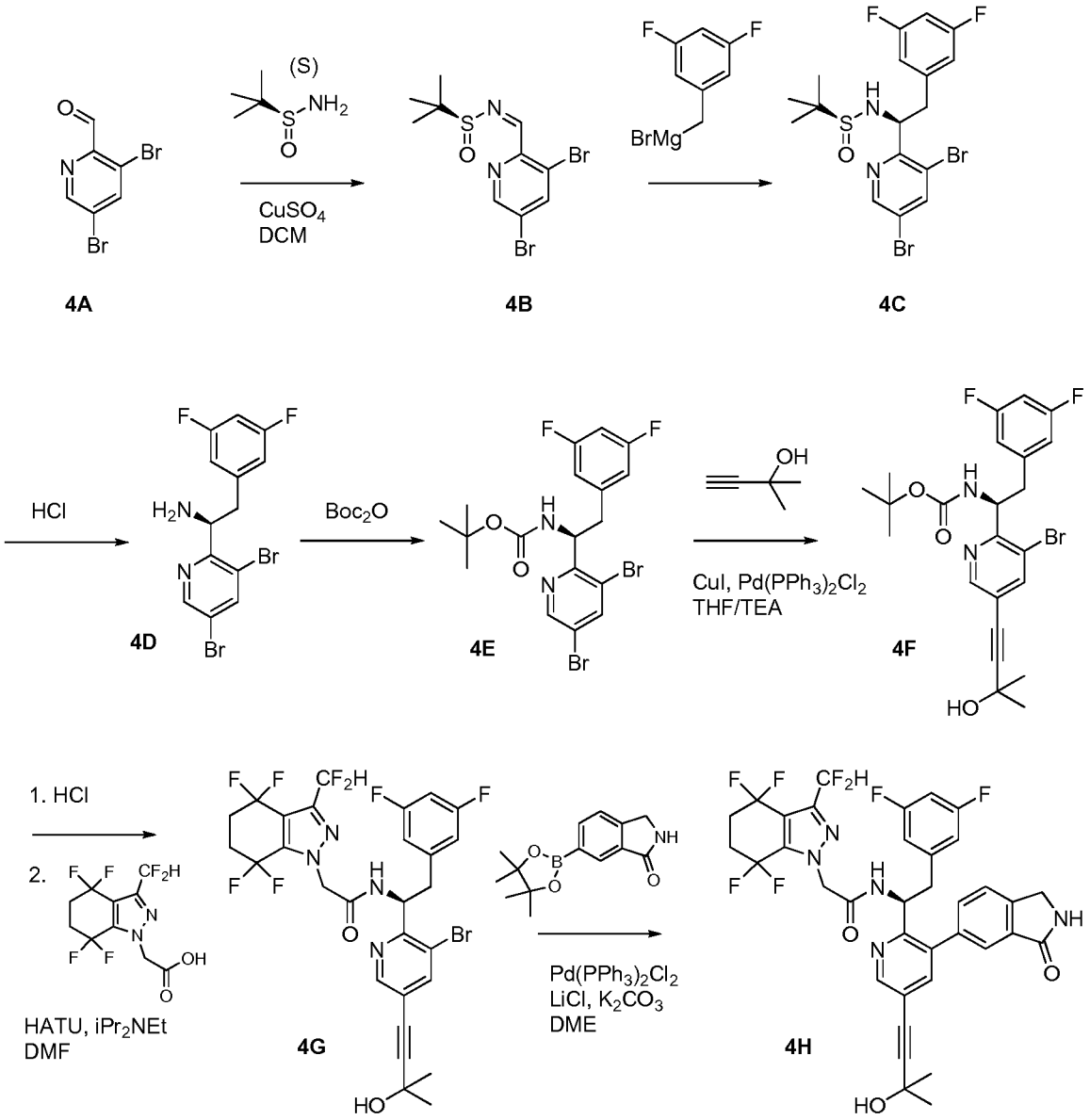
[0401] In a microwave tube were charged **3B** (200 mg, 0.65 mmol), bis(pinacolato)diboron (330 mg, 1.3 mmol) and potassium acetate (191 mg, 1.95 mmol), [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)(14 mg, 0.02 mmol) and 1,4-dioxane (8 mL) The mixture was heated up to 150 °C for 20 min in a Microwave Synthesizer. Upon completion the solution was diluted in EtOAc and the organic layer was washed with water and a saturated NaCl solution, dried over $MgSO_4$ and concentrated in vacuum to give the title compound as a dark brown solid. A half amount of the product was purified by silica gel chromatography eluting with EtOAc/hexanes to afford the title product. MS (*m/z*) 286.23 $[M+H]^+$.

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl)pyridin-2-yl)ethyl)acetamide (**3D**):

[0402] In a microwave tube were charged with **14D** (33 mg, 0.05 mmol), **3C** (21 mg, 0.075 mmol), LiCl (6 mg, 0.15 mmol), K_2CO_3 (21 mg, 0.15 mmol), $Pd(PPh_3)_2Cl_2$ (3 mg) and $Pd(dppf)Cl_2$ (3 mg). To the mixture was added 1 mL of DME and 0.2 mL of H_2O. The mixture was heated up to 165 °C for 12 min in a Microwave Synthesizer. After cooled down and filtered through a syringe filter, purified on reverse phase HPLC eluting with acetonitrile and water (with 0.1% TFA) to afford the title product. ^1H NMR (400 MHz, CD_3OD) δ 8.77 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.32 – 7.16 (m, 2H), 6.64 (t, J = 9.2 Hz, 1H), 6.24 (d, J = 6.5 Hz, 2H), 5.39 (t, J = 7.3 Hz, 1H), 4.86 (s, 2H), 3.08 – 2.92 (m, 2H), 2.58 – 2.31 (m, 2H), 1.62 (s, 6H), 1.60-1.33 (m, 5H), 1.12 (m, 1H).

MS (*m/z*) 738.15 $[M+H]^+$.

Example 4.



Synthesis of (S)-N-((3,5-dibromopyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (**4B**):

[0403] To 3,5-dibromopicolinaldehyde (1.9 g0, 7.17 mmol) in DCM (30 mL) was added (S)-2-methylpropane-2-sulfinamide (870 mg, 7.17 mmol) and $CuSO_4$ (2.29 g, 14.3 mmol). The reaction mixture was stirred for 15 h. Solids were filtered over celite. The solvents were removed in vacuo and the residue purified by column chromatography on silica to provide 2.6 g of the title compound. MS (*m/z*) 368.9 $[M+H]^+$.

Synthesis of (S)-N-((S)-1-(3,5-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (**4C**):

[0404] (S)-N-((3,5-dibromopyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (2.6 g, 7.1 mmol) was dissolved in THF (24 mL) and cooled to –78 °C. (3,5-difluorobenzyl)magnesium bromide (34 mL, 0.25 M in Et_2O) was added dropwise. The reaction was stirred at –78 °C for 3 hr then let warm to 0 °C and quenched. The reaction was partitioned between EtOAc and aq. NH_4Cl. The organics were separated, dried, and removed in vacuo. The residue purified by column chromatography on silica to provide the title compound. MS (*m/z*) 496.6 $[M+H]^+$.

Synthesis of (S)-1-(3,5-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethanamine (**4D**):

[0405] To (S)-N-((S)-1-(3,5-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (650 mg) dissolved in DCM (3 mL) was added 4N HCl in dioxanes (4 mL). The reaction was stirred for 2 hr at ambient temperature. Solvents were removed in vacuo and the crude desired product was used without further purification. MS (*m/z*) 393.0 $[M+H]^+$.

Synthesis of (S)-tert-butyl 1-(3,5-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (**4E**):

[0406] (S)-1-(3,5-Dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethanamine (780 mg, 1.84 mmol) was combined with di-tert-butyl dicarbonate (400 mg, 1.84 mmol) and TEA (515 μL, 3.7 mmol) in DCM (9 mL). The reaction was stirred for 2 hr at ambient temperature. The reaction was partitioned between EtOAc and H_2O. The organics were separated, dried, and removed in vacuo. The residue purified by column chromatography on silica to provide the title compound. MS (*m/z*) 492.9 $[M+H]^+$.

Synthesis of (S)-tert-butyl 1-(3-bromo-5-(3-hydroxy-3-methylbut-1-ynyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (**4F**):

[0407] To (S)-tert-butyl 1-(3,5-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (140 mg, 0.29 mmol) in THF (18 mL) was added 2-methylbut-3-yn-2-ol (42 μL, 0.43 mmol), TEA (0.9 mL), $Pd(PPh_3)_2Cl_2$ (30 mg) and CuI (16 mg). The reaction was stirred for 2 hr at ambient temperature and then partitioned between EtOAc and H_2O. The organics were separated, dried, and removed in vacuo. The residue purified by column chromatography on silica to provide the title compound as a mixture with **4E** which was used in the next step. MS (*m/z*) 496.7 $[M+H]^+$.

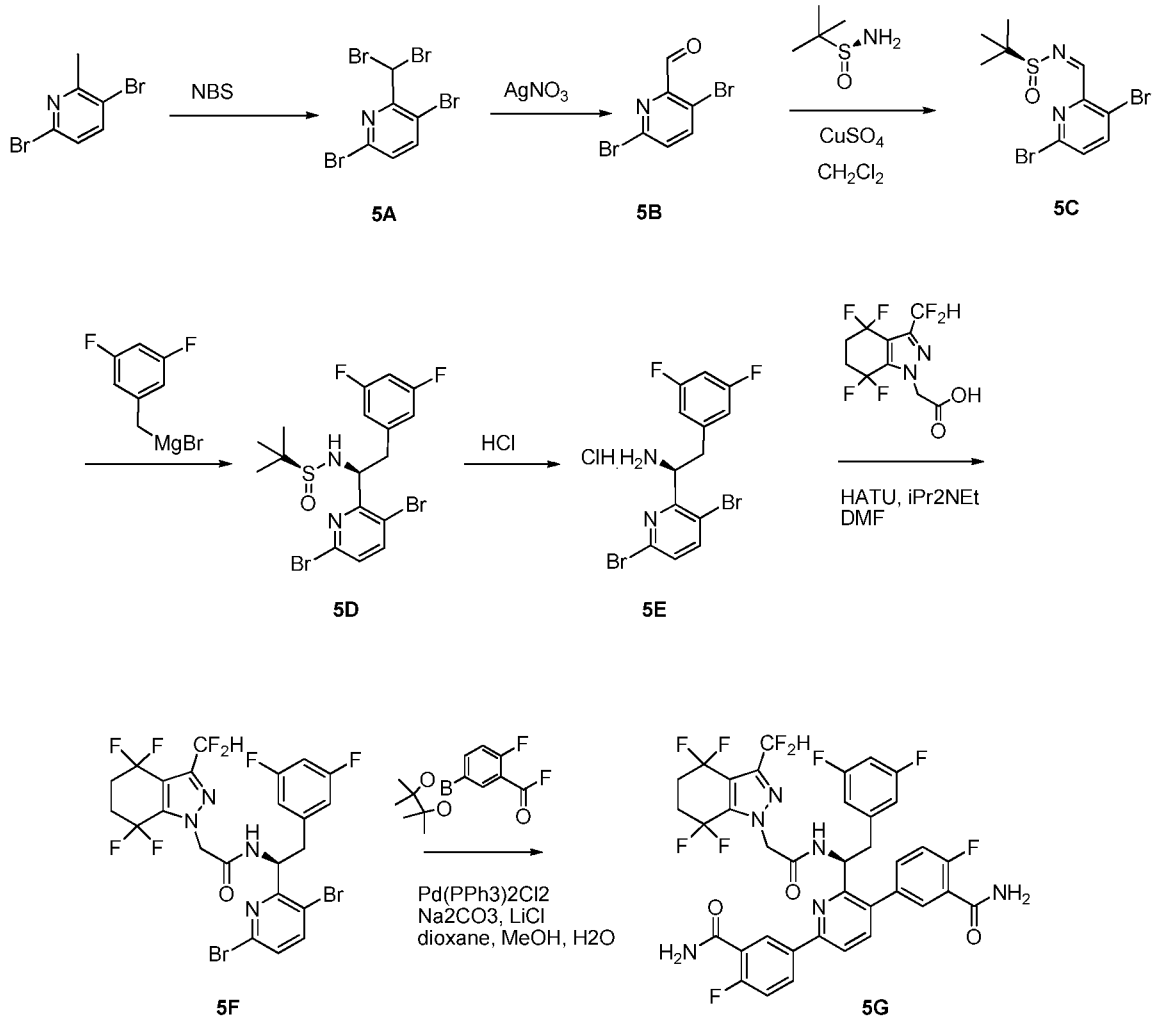
Synthesis of (S)-N-(1-(3-bromo-5-(3-hydroxy-3-methylbut-1-ynyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**4G**):

[0408] A mixture of (S)-tert-butyl 1-(3-bromo-5-(3-hydroxy-3-methylbut-1-ynyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate and (S)-tert-butyl 1-(3,5-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (105 mg) obtained from the previous step was dissolved in DCM (3 mL) and treated with 4N HCl in dioxanes (4 mL). The reaction was stirred for 2 hr then solvents removed in vacuo. The residue purified by column chromatography on silica to provide 18 mg of (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-bromopyridin-3-yl)-2-methylbut-3-yn-2-ol (MS (*m/z*) 395.0 $[M+H]^+$). To (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-bromopyridin-3-yl)-2-methylbut-3-yn-2-ol (18 mg, 0.046 mmol) in DMF (1 mL) was added 2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid (15 mg, 0.05 mmol), iPr_2NEt (17 μL, 0.1 mmol) and HATU (26 mg, 0.07 mmol). The reaction was stirred 30 min and then partitioned between EtOAc and H_2O. The organics were separated, dried, and removed in vacuo. The crude product was used directly in the next reaction. MS (*m/z*) 679.2$[M+H]^+$.

Synthesis of (S)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)-N-(2-(3,5-difluorophenyl)-1-(5-(3-hydroxy-3-methylbut-1-ynyl)-3-(3-oxoisoindolin-5-yl)pyridin-2-yl)ethyl)acetamide (**4H**):

[0409] To (S)-N-(1-(3-bromo-5-(3-hydroxy-3-methylbut-1-ynyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (16 mg, 0.02 mmol) in DME (0.7 mL) was added 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one (7 mg, 0.03 mmol), $Pd(PPh_3)_2Cl_2$ (2 mg), LiCl (1 mg), and aq 2M K_2CO_3 (30 μL). The reaction was heated in a microwave reactor to 150 °C for 20 min. The reaction was purified by RP HPLC to provide the desired product. ^1H NMR (400 MHz, Methanol-d_4) δ 8.69 (d, 1H), 7.62 – 7.49 (m, 2H), 7.43 (s, 1H), 7.28 (s, 1H), 6.98 – 6.58 (m, 4H), 6.26 (d, 2H), 5.34 (d, 2H), 5.18 (s, 1H), 5.05 (s, 2H), 4.48 (s, 2H), 3.02 (t, J = 7.5 Hz, 3H), 2.49 (s, 7H), 1.56 (s, 5H). MS (*m/z*) 732.1$[M+H]^+$.

Example 5.



Synthesis of 3,6-dibromo-2-(dibromomethyl)pyridine (**5A**):

[0410] To a solution of 3,6-dibromo-2-methylpyridine (5.2 g, 21 mmol) in CCl_4 (50 mL) was added N-bromosuccinimide (7.57 g, 42 mmol) and 2,2'-azobis(2-methylpropionitrile) (0.70 g, 4.3 mmol). The mixture was heated at 80 °C overnight and cooled to room temperature. The solid was removed by filtration and the filtrate was concentrated under reduced pressure. The product (**5A**) was obtained after flash chromatography eluding with 0-10 percent EtOAc in hexane (7.36 g). MS (m/z): 409.66 $[M+H]^+$

Synthesis of 3,6-dibromopicolinaldehyde (**5B**):

[0411] A solution of silver nitrate (7.6 g, 45 mmol) in water (24 mL) was added dropwise to a solution of **5A** (7.36 g, 18 mmol) in refluxing EtOH (90 mL). The mixture was stirred at 80 °C for 5 hours. After the mixture was cooled to room temperature, it was diluted with water (100 mL), extracted with EtOAc (3 times), dried over Na_2SO_4, filtered and concentrated under

reduced pressure. The crude product (**5B**, 4.6 G) was directly used for next step. MS (m/z): 265.96. $[M+H]^+$

Synthesis of (S,Z)-N-((3,6-dibromopyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (**5C**):

[0412] The title compound (**5C**) was prepared according to the method presented for the synthesis of compound **4B** of Example 4 utilizing **5B**. MS (*m/z*) 368.86 $[M+H]^+$

Synthesis of (S)-N-((S)-1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (**5D**):

[0413] The title compound (**5D**) was prepared according to the method presented for the synthesis of compound **4C** of Example 4 utilizing **5C**. MS (*m/z*) 496.99 $[M+H]^+$

Synthesis of (S)-1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethanamine hydrochloride(**5E**):

[0414] The title compound (**5E**) was prepared according to the method presented for the synthesis of compound **4D** of Example 4 utilizing **5D**. MS (*m/z*) 393.29 $[M+H]^+$

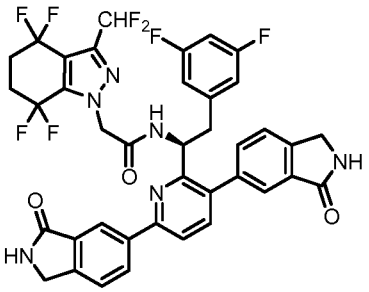
Synthesis of (S)-N-(1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**5F**):

[0415] The title compound (**5F**) was prepared according to the method presented for the synthesis of compound **10A** of Example 10 utilizing **5E**. MS (*m/z*) 676.96 $[M+H]^+$.

Synthesis of (S)-5,5'-(6-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridine-2,5-diyl)bis(2-fluorobenzamide) (**5G**):

[0416] In a microwave tube was charged with **5F** (100 mg, 0.15 mmol), (3-carbamoyl-4-fluorophenyl)boronic acid (81 mg, 0.45 mmol), LiCl (19 mg, 0.45 mmol), Na_2CO_3 (50 mg, 0.6 mmol) and 5 mg of $Pd(PPh_3)_2Cl_2$. To the mixture was added 1.4 mL of 1,4-dioxane / methanol / H_2O (5/1/1). The mixture was heated up to 170 °C for 15 min in a Microwave Synthesizer. After cooled down and filtered through a syringe filter, purified on reverse phase HPLC eluting with acetonitrile and water (with 0.1% TFA) to afford the title compound. ^1H NMR (400 MHz, CD_3OD) δ 8.90 (d, *J* = 8.6 Hz, 1H), 8.74 (dd, *J* = 7.2, 2.4 Hz, 1H), 8.51 – 8.30 (m, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.41 (m, 2H), 7.23 (dd, *J* = 10.7, 8.5 Hz, 1H), 7.02 – 6.49 (m, 2H), 6.35 (d, *J* = 6.2 Hz, 2H), 5.45 (m, 1H), 5.16 – 5.02 (m, 2H), 3.23 – 2.97 (m, 2H), 2.49 (m, 4H).MS (*m/z*) 793.19 $[M+H]^+$.

Example 6.

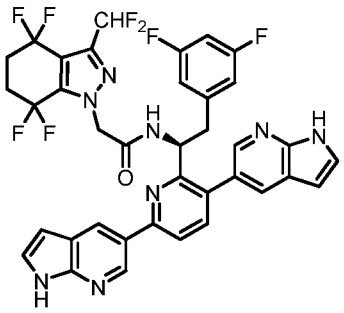


6

Synthesis of (S)-N-(1-(3,6-bis(3-oxoisoindolin-5-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**6**):

[0417] The title compound (**6**) was prepared according to the method presented for the synthesis of compound **5G** of Example 5 utilizing 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one and **5F**. 1H NMR (400 MHz, CD_3OD) δ 8.84 (d, *J* = 8.1 Hz, 1H), 8.72 (s, 1H), 8.49 (d, *J* = 7.9 Hz, 1H), 7.98 (d, *J* = 8.1 Hz, 2H), 7.72 (dd, *J* = 23.8, 8.0 Hz, 2H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.39 (s, 1H), 6.97 – 6.57 (m, 2H), 6.33 (m, 2H), 5.49 (m, 2H), 5.10 (s, 2H), 4.57 (s, 2H), 4.49 (s, 2H), 3.24 – 2.95 (m, 2H), 2.47 (m, 4H).MS (*m/z*) 781.02$[M+H]^+$.

Example 7.



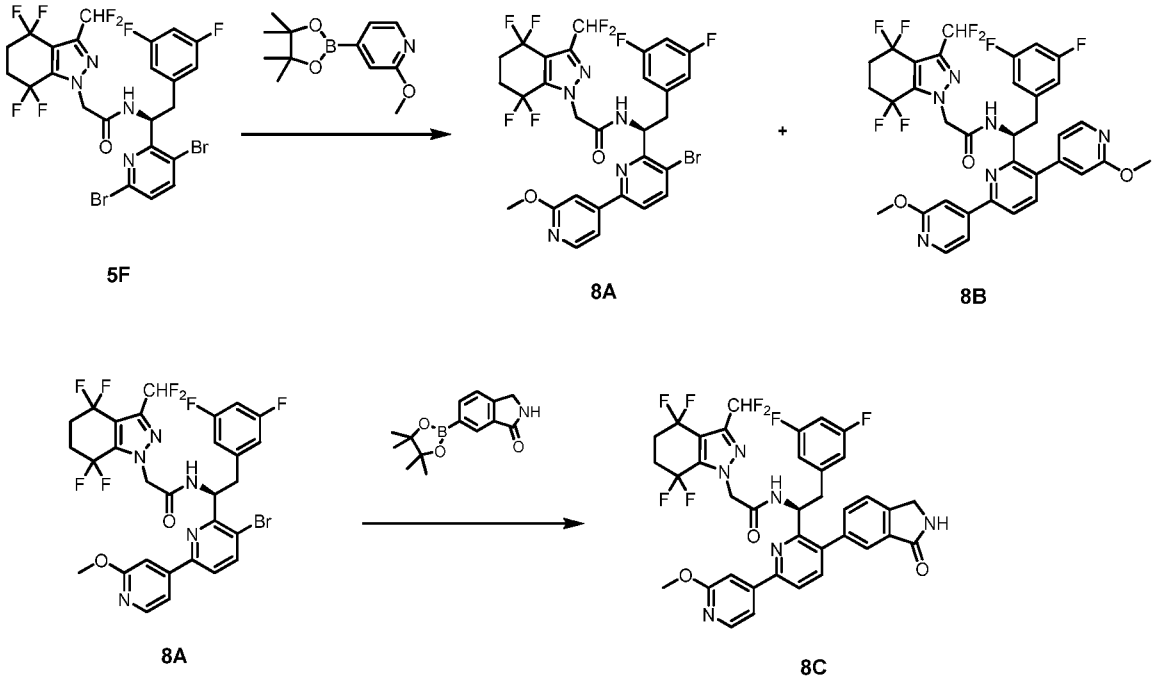
7

Synthesis of (S)-N-(1-(3,6-bis(1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**7**):

[0418] The title compound (**7**) was prepared according to the method presented for the synthesis of compound **5G** of Example 5 utilizing 6 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine and **5F**. ^1H NMR (400 MHz, CD_3OD) δ 9.23-9.17 (m, 2H), 9.04 (d, *J* = 8.1 Hz, 1H), 8.03 (m, 3H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.61 (dd, *J* = 7.3, 3.5 Hz, 2H), 6.93 –

6.52 (m, 4H), 6.34 (d, *J* = 6.2 Hz, 2H), 5.45 (m, 1H), 5.10 (m, 2H), 3.27 – 3.06 (m, 2H), 2.48 (m, 4H).MS (*m/z*) 751.22 $[M+H]^+$.

Example 8.



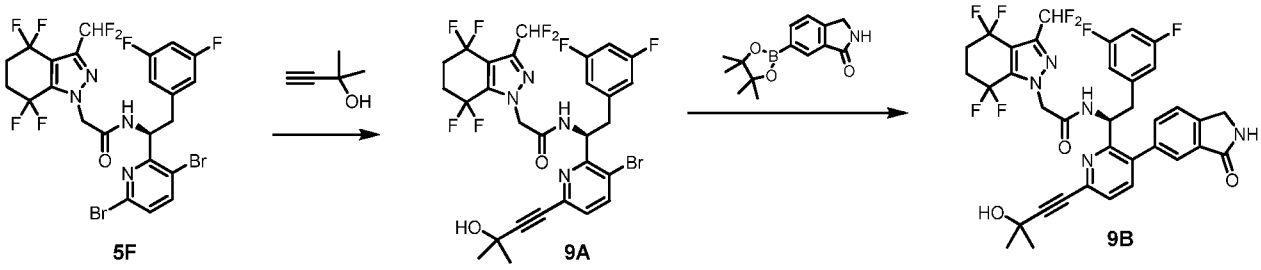
Synthesis of (S)-N-(1-(5-bromo-2'-methoxy-[2,4'-bipyridin]-6-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**8A**) and (S)-N-(1-(2',5'-di(methoxy-[2,4'-bipyridin]-6-yl))-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**8B**):

[0419] The title compounds (**8A and 8B**) were prepared according to the method presented for the synthesis of compound **5G** of Example 5 utilizing 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine(2 equiv.) and **5F**.

Synthesis of (S)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)-N-(2-(3,5-difluorophenyl)-1-(2'-methoxy-5-(3-oxoisoindolin-5-yl)-[2,4'-bipyridin]-6-yl)ethyl)acetamide (**8C**):

[0420] The title compound (**8C**) was prepared according to the method presented for the synthesis of compound **4H** of Example 4 utilizing **8A**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.85 (d, *J* = 8.1 Hz, 1H), 8.33 (d, *J* = 5.7 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 5.7 Hz, 1H), 7.82 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 6.3 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.38 (s, 1H), 6.91 – 6.44 (m, 2H), 6.29 (d, *J* = 6.3 Hz, 2H), 5.51 (dd, *J* = 14.8, 8.2 Hz, 1H), 5.18 – 4.98 (m, 2H), 4.50 (s, 2H), 4.09 (s, 3H), 3.12 (m, 2H), 2.49 (m, 4H).MS (m/z) 757.25 $[M+H]^+$.

Example 9.



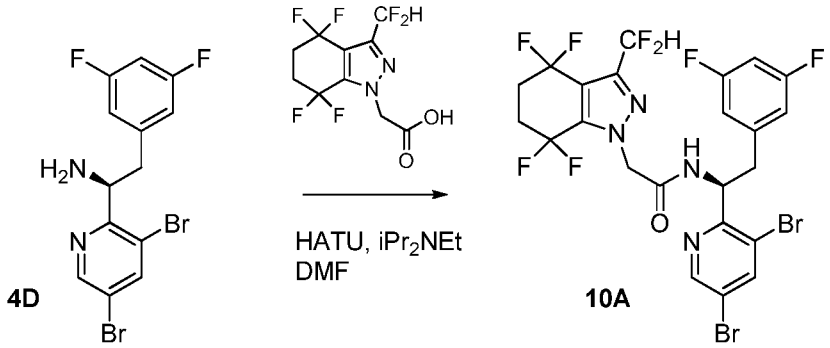
Synthesis of (S)-N-(1-(3-bromo-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**9A**):

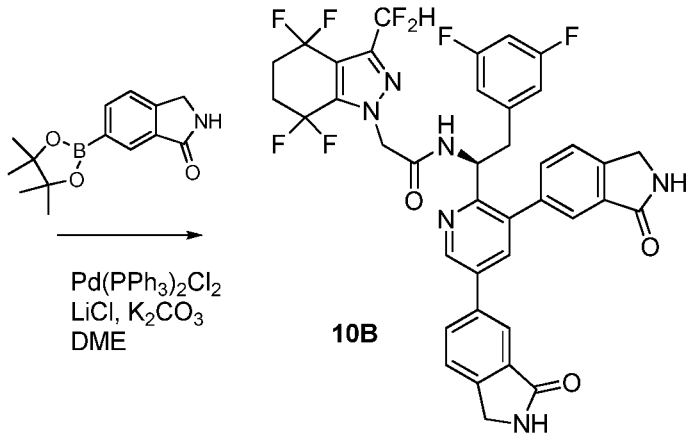
[0421] The title compound (**9A**) was prepared according to the method presented for the synthesis of compound **4F** of Example 4 utilizing 2-methylbut-3-yn-2-ol and **5F**. MS (m/z) 681.17 $[M+H]^+$.

Synthesis of (S)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)-N-(2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(3-oxoisoindolin-5-yl)pyridin-2-yl)ethyl)acetamide (**9B**):

[0422] The title compound (**9B**) was prepared according to the method presented for the synthesis of compound **4H** of Example 4 utilizing **9A**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.63 – 7.53 (m, 2H), 7.50 – 7.40 (m, 2H), 7.30 (s, 1H), 6.95 – 6.56 (m, 2H), 6.28 (d, J = 6.3 Hz, 2H), 5.39 (t, J = 7.4 Hz, 1H), 5.05 (s, 2H), 4.48 (s, 2H), 3.13 – 2.91 (m, 2H), 2.66 – 2.35 (m, 4H), 1.61 (s, 6H).MS (m/z) 732.23 $[M+H]^+$.

Example 10.





Synthesis of (S)-N-(1-(3,5-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**10A**):

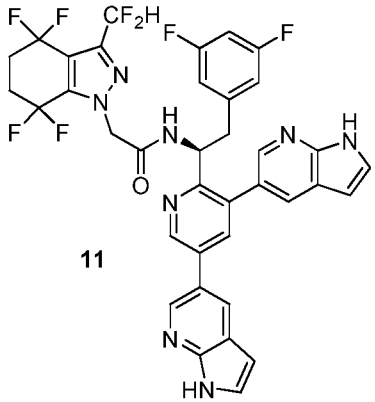
[0423] To (S)-1-(3,5-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethanamine (380 mg, 0.97 mmol) dissolved in DMF (10 mL) was added iPr_2NEt (350 μL, 2 mmol) and 2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid (293 mg, 0.97 mmol). HATU (442 mg, 1.16 mmol) was added and the reaction stirred for 30 min. The reaction was partitioned between EtOAc and H_2O. The organics were separated, dried, and removed in vacuo. The residue purified by column chromatography on silica to provide the title compound. MS (*m/z*) 677.1 $[M+H]^+$.

Synthesis of (S)-N-(1-(3,5-bis(3-oxoisoindolin-5-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**10B**):

[0424] To (S)-N-(1-(3,5-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (50 mg, 0.074 mmol) in DME (0.8 mL) and DMF (0.2 mL) was added 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one (48 mg, 0.19 mmol), $Pd(PPh_3)_2Cl_2$ (5 mg), LiCl (2 mg), and aq 2M K_2CO_3 (110 μL). The reaction was heated in a microwave reactor to 150 °C for 20 min. The reaction was purified by RP HPLC to provide the desired product. ^1H NMR (400 MHz,

Methanol-d_4) δ 9.02 (d, 1H), 8.11 (d, 1H), 7.97 (dd, 1.7 Hz, 1H), 7.89 (d, 1H), 7.72 (d, 1H), 7.67 – 7.48 (m, 3H), 7.42 (d, 1H), 6.70 – 6.61 (m, 2H), 6.37 – 6.30 (m, 2H), 5.44 (t, 1H), 5.07 (s, 2H), 4.51 (d, 4H), 3.18 – 3.01 (m, 3H), 2.50 (dd, 4H). MS (*m/z*) 798.1[M+H]$^+$.

Example 11.

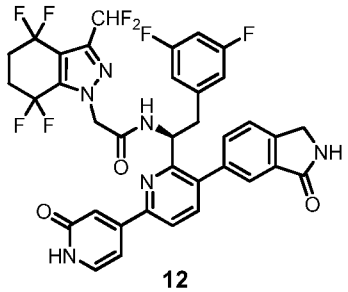


11

Synthesis of (S)-N-(1-(3,5-di(1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**11**):

[0425] The title compound was prepared according to the method presented for the synthesis of **10B** of Example 10 utilizing **10A** and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine. ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.10 (s, 1H), 8.62 (s, 1H), 8.56 (s, 1H), 8.14 (s, 1H), 8.05 – 7.94 (m, 2H), 7.58 (dd, 2H), 6.99 – 6.61 (m, 4H), 6.36 (d, 2H), 5.47 – 5.27 (m, 2H), 5.15 – 5.00 (m, 2H), 3.24 – 3.01 (m, 3H), 2.66 – 2.32 (m, 5H). MS (*m/z*) 751.1[M+H]$^+$.

Example 12.

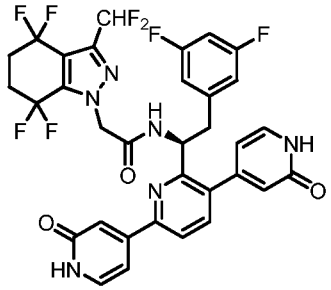


12

Synthesis of (S)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)-N-(2-(3,5-difluorophenyl)-1-(2'-oxo-5-(3-oxoisoindolin-5-yl)-1',2'-dihydro-[2,4'-bipyridin]-6-yl)ethyl)acetamide (**12**):

[0426] In a microwave tube were charged with (S)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)-N-(2-(3,5-difluorophenyl)-1-(2'-methoxy-5-(3-oxoisoindolin-5-yl)-[2,4'-bipyridin]-6-yl)ethyl)acetamide (**8C**, 5 mg), HCl in 1,4-dioxane (4N, 0.3 mL) and ethanol (0.3 mL). The mixture was heated up to 100 °C for 20 min in a Microwave Synthesizer. After cooled down, After cooled down, the solvent was removed and the residue was purified on reverse phase HPLC eluting with acetonitrile and water (with 0.1% TFA) to afford the title product. ^{1}H NMR (400 MHz, CD_3OD) δ 8.88 (m, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.60 (m, 2H), 7.53 (m, 1H), 7.43 (s, 1H), 7.37 (s, 1H), 7.27 (d, *J* = 6.8 Hz, 1H), 6.96 – 6.53 (m, 2H), 6.30 (d, *J* = 6.2 Hz, 2H), 5.49 (m, 1H), 5.09 (s, 2H), 4.49 (s, 2H), 3.12 (m, 2H), 2.48 (m, 4H). MS (*m/z*) 742.99 $[M+H]^+$.

Example 13.

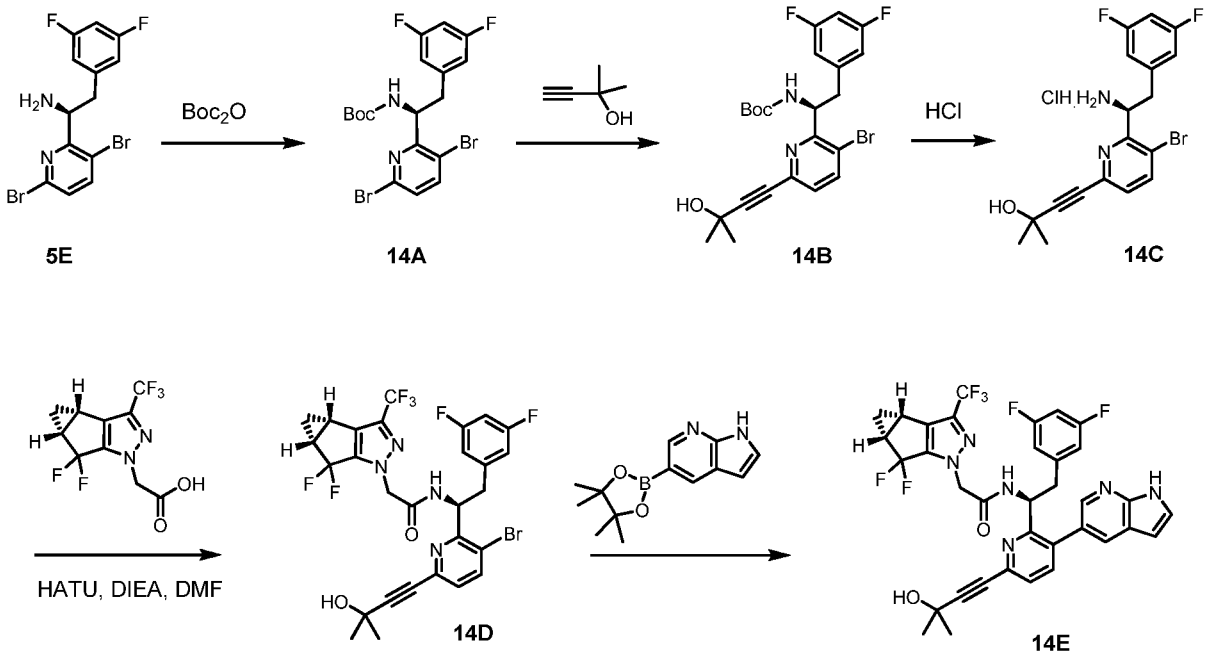


13

Synthesis of (S)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)-N-(2-(3,5-difluorophenyl)-1-(2,2"-dioxo-1,1",2,2"-tetrahydro-[4,2':5',4"-terpyridin]-6'-yl)ethyl)acetamide (**13**):

[0427] The title compound (**13**) was prepared according to the method presented for the synthesis of compound **12** of Example 12 utilizing **8B**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.95 (d, *J* = 7.8 Hz, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 6.8 Hz, 1H), 7.43 (d, *J* = 7.2 Hz, 1H), 7.25 (d, *J* = 6.9 Hz, 1H), 6.98 – 6.61 (m, 2H), 6.45 (d, *J* = 6.3 Hz, 2H), 6.33 (d, *J* = 6.6 Hz, 1H), 6.19 (s, 1H), 5.51 (m, 1H), 5.08 (m, 2H), 3.15 (m, 2H), 2.49 (m, 4H).MS (m/z) 705.00 $[M+H]^+$.

Example 14.



Synthesis of (S)-tert-butyl 1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate **(14A):**

[0428] The title compound was prepared according to the method presented for the synthesis of compound **4E** of Example 4 utilizing **5E**.

Synthesis of (S)-tert-butyl (1-(3-bromo-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**14B**):

[0429] The title compound (**14B**) was prepared according to the method presented for the synthesis of compound **4F** of Example 4 utilizing 2-methylbut-3-yn-2-ol and (S)-tert-butyl (1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate. MS (m/z) 496.90 $[M+H]^+$.

Synthesis of (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-bromopyridin-2-yl)-2-methylbut-3-yn-2-ol compound with 2-methylbut-3-yn-2-ol (1:1) hydrochloride (**14C**):

[0430] The title compound (**14C**) was prepared according to the method presented for the synthesis of compound **4G** of Example 4 utilizing **14B**. MS (m/z) 397.09 $[M+H]^+$.

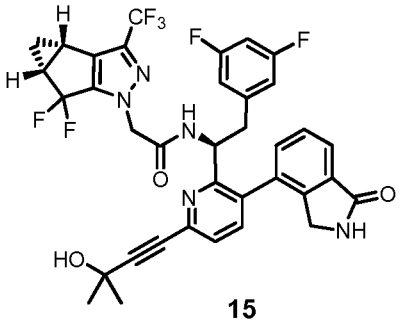
Synthesis of N-((S)-1-(3-bromo-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**14D**):

[0431] The title compound (**14D**) was prepared according to the method presented for the synthesis of compound **4G** of Example 4 utilizing 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid and **14C**. MS (m/z) 659.23 $[M+H]^+$.

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-oxoisoindolin-4-yl)pyridin-2-yl)ethyl)acetamide (**14E**):

[0432] The title compound (**14E**) was prepared according to the method presented for the synthesis of compound **4H** of Example 4 utilizing 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine and **14D.** ^{1}H NMR (400 MHz, CD_3OD) δ 8.92 (d, J = 8.7 Hz, 1H), 8.00 (s, 2H), 7.85 (s, 1H), 7.59 (m, 2H), 7.48 (d, J = 7.9 Hz, 1H), 6.77 – 6.56 (m, 2H), 6.28 (d, J = 6.3 Hz, 2H), 5.33 (m, 1H), 4.87 (s, 2H), 3.17 – 2.99 (m, 4H), 2.48 (m, 4H), 1.6 (s, 6H), 1.40 (m, 1H), 1.10 (m, 1H).MS (m/z) 697.28 $[M+H]^+$.

Example 15.

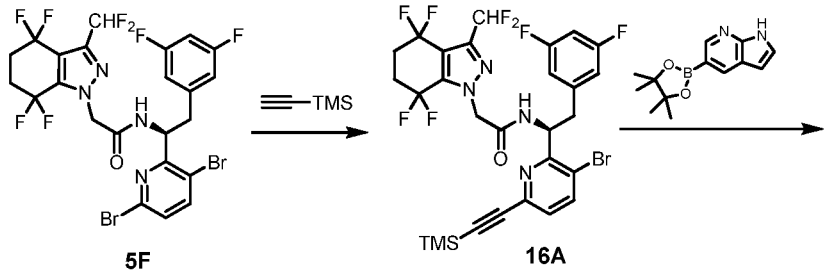


15

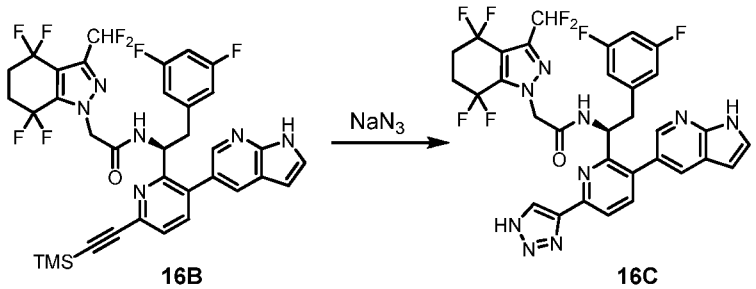
Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-oxoisoindolin-4-yl)pyridin-2-yl)ethyl)acetamide (**15**):

[0433] The title compound (**15**) was prepared according to the method presented for the synthesis of compound **4H** of Example 4 utilizing **14D** and 2,3-dihydro-1H-isoindol-1-one-4-boronic acid pinacol ester. ^{1}H NMR (400 MHz, CD_3OD) δ 7.82 (m, 1H), 7.53 (m, 4H), 6.78 (m, 1H), 6.30 (m, 2H), 5.35 (m, 1H), 4.83 (m, 2H), 4.17 (m, 2H), 3.16 – 3.04 (m, 1H), 2.98 (m, 1H), 2.48 (m, 2H), 1.53 (s, 6H),1.43 (m, 1H), 1.08 (m, 1H).MS (m/z) 712.18 $[M+H]^+$.

Example 16.



5F 16A



16B 16C

Synthesis of (S)-N-(1-(3-bromo-6-((trimethylsilyl)ethynyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**16A**):

[0434] The title compound (**16A**) was prepared according to the method presented for the synthesis of compound **4F** of Example 4 utilizing ethynyltrimethylsilane and **5F**. MS (m/z) 694.59 $[M+H]^+$.

Synthesis of (S)-N-(1-(3-(1H-pyrrolo[2,3-b]pyridin-5-yl)-6-((trimethylsilyl)ethynyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**16B**):

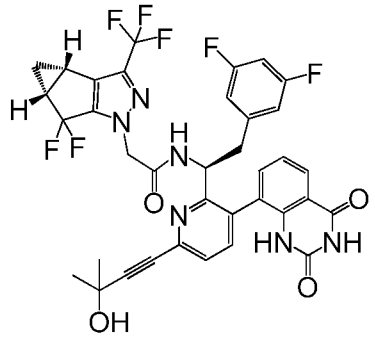
[0435] The title compound (**16B**) was prepared according to the method presented for the synthesis of compound **4H** of Example 4 utilizing 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine and **16A**. MS (m/z) 731.22 $[M+H]^+$.

Synthesis of (S)-N-(1-(3-(1H-pyrrolo[2,3-b]pyridin-5-yl)-6-(1H-1,2,3-triazol-4-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**16C**):

[0436] Compound **16B** (75 mg, 0.1 mmol), NaN_3 (13mg, 0.2 mmol) and NH_4Cl (5mg, 0.1 mmol) were dissolved in DMF (0.5 mL) and stirred at 100 °C for overnight. The reaction mixture was cooled down to room temperature and diluted with water and extracted with EtOAc. The organic phase was dried (Na_2SO_4), filtered and concentrated. The crude material was

purified on reverse phase HPLC eluting with acetonitrile and water (with 0.1% TFA) to afford the title product. ^{1}H NMR (400 MHz, CD_3OD) δ 9.01 (d, J = 7.7 Hz, 1H), 8.54 (s, 1H), 7.99 (m, 3H), 7.73 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 3.5 Hz, 1H), 6.97 – 6.55 (m, 3H), 6.31 (d, J = 6.3 Hz, 2H), 5.45 (m, 1H), 5.11 (s, 2H), 3.13 (m, 2H), 2.49 (m, 4H).MS (*m/z*) 702.02 $[M+H]^+$.

Example 17.

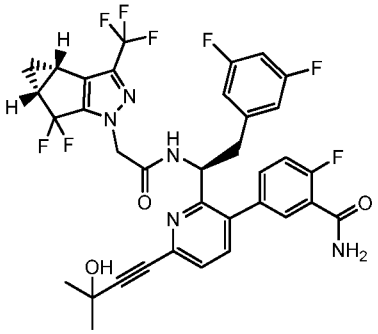


17

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(3-(2,4-dioxo-1,2,3,4-tetrahydroquinazolin-8-yl)-6-(3-hydroxy-3-methylbut-1-ynyl)pyridin-2-yl)ethyl)acetamide (**17**):

[0437] The title compound was prepared according to the method presented for the synthesis of compound **4F** of Example 4 utilizing 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazoline-2,4(1H,3H)-dione and **14D**. ^{1}H NMR (400 MHz, DMSO) δ 11.36 (d,1H), 10.12 (d, 1H), 8.87 (m, 1H), 7.98 (d, 1H), 7.75 – 6.70 (m, 7H), 6.47-6.57 (m, 2H), 4.74-4.50 (m, 2H), 3.01-2.90 (m, 2H), 2.48-2.60 (m, 2H), 1.49 (s, 6H), 1.45 – 1.24 (m, 1H), 0.96 (m, 1H). MS (*m/z*) 741.1 $[M+H]^+$.

Example 18.

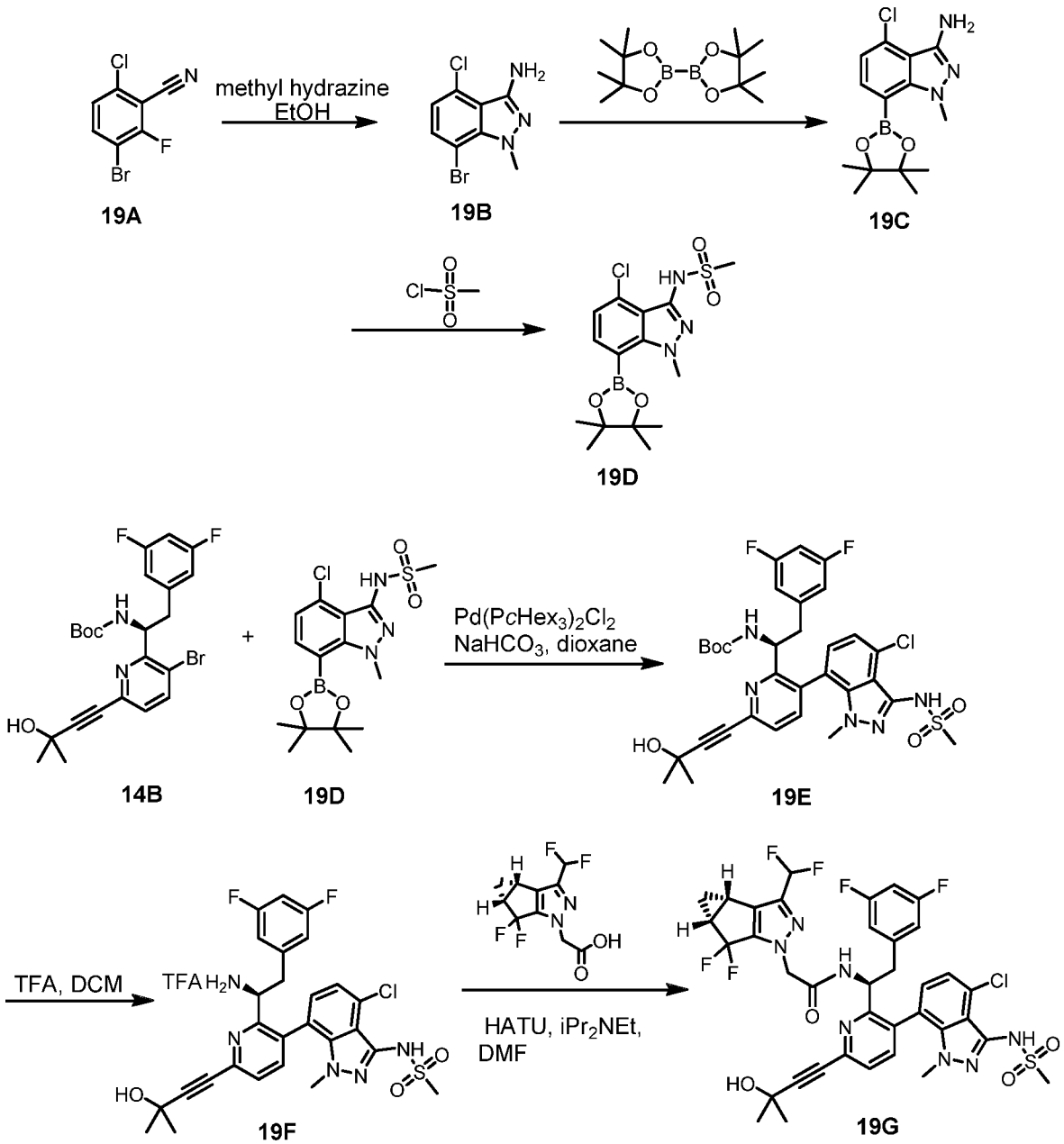


18

Synthesis of 5-(2-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-2-fluorobenzamide (**18**):

[0438] The title compound was prepared according to the method presented for the synthesis of compound **4F** of Example 4 utilizing (3-carbamoyl-4-fluorophenyl)boronic acid and **14D**. ^{1}H NMR (400 MHz, DMSO) δ 9.08 (d, 1H), 7.79 – 7.14 (m, 8H), 6.92 (m, 1H), 6.62 (d, 2H), 5.12 (m, 1H), 4.77-4.83 (m, 2H), 3.01 (m, 2H), 2.55 (m, 1H), 1.51 (s, 6H), 1.38 (m, 1H), 0.98 (m, 1H). MS (*m/z*) 718.2 $[M+H]^+$.

Example 19.



Synthesis of 7-bromo-4-chloro-1-methyl-1H-indazol-3-amine (**19B**):

[0439] To 3-bromo-6-chloro-2-fluorobenzonitrile (10 g, 42.7 mmol) in EtOH (100 mL) was added methylhydrazine (9 ml, 171 mmol). The reaction mixture was stirred for 4 hours at 110 °C. The reaction was allowed to slowly cool over 4 hours, then the solids were filtered off and used with no further purification to provide 7 g of the title compound (including minor amounts of the other regioisomer). MS (*m/z*) 262.0 $[M+H]^+$.

Synthesis of 4-chloro-1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-amine (**19C**):

[0440] To 7-bromo-4-chloro-1-methyl-1H-indazol-3-amine (3 g, 11.5 mmol) in dioxane (40 mL) and DMF (25 ml) was added bis (pinacolato) diborane (8.8 g, 34.6 mmol), potassium acetate (3.4 g, 34.6 mmol), and *trans*-dichlorobis(triphenylphosphine)palladium (II) (486.35 mg, 0.69 mmol). The reaction mixture was stirred for 3 hours at 130 °C. The reaction was cooled, diluted with EtOAc, and then the solids were filtered off over Celite and silica gel eluting with EtOAc. The mixture was concentrated and purified by flash column chromatography to provide 1.8 g of the title compound. MS (*m/z*) 308.3 $[M+H]^+$.

Synthesis of N-(4-chloro-1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-yl)methanesulfonamide (**19D**):

[0441] To 7-bromo-4-chloro-1-methyl-1H-indazol-3-amine (2.6 g, 8.5 mmol) in DCM (30 mL) was added N,N-Diisopropylethylamine (5.9 ml, 33.8 mmol) then the reaction was cooled in an ice bath and methansulfonyl chloride (2 ml, 25.4 mmol) was added. The reaction mixture was stirred for 20 minutes at 0 °C. The reaction was diluted with water and extracted 2X with DCM. The organic layer was dried over sodium sulfate and concentrated. The resulting mixture was taken up in EtOH (30 ml) and 8 ml of 10N NaOH was added. The reaction was followed by LC/MS and once done (10 minutes) the reaction was diluted with water and quenched with concentrated HCl to pH 2. The mixture was extracted 3X with DCM. The organic layer was dried over sodium sulfate and concentrated until solid starts to fall out. The mixture is then cooled in a brine/ice bath for 20 minutes and filtered to recover desired as two lots and used with no further purification to provide 2.1 g of the title compound. MS (*m/z*) 386.4 $[M+H]^+$.

Synthesis of (S)-tert-butyl 1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-ynyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (**19E**):

[0442] To N-(4-chloro-1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-yl)methanesulfonamide (39 mg, 0.1 mmol) in dioxane (5 mL) and DMF (0.3 ml) was added

14B (50 mg, 0.1 mmol), 1N sodium bicarbonate (0.9 ml, 0.9 mmol), and dichlorobis(tricyclohexylphosphine)palladium (II) (1.9 mg, 0.003 mmol). The reaction mixture was stirred for 4 hours at 140 °C. The reaction was cooled, diluted with EtOAc and brine. The mixture was extracted 2X with EtOAc, the organic layer was dried over sodium sulfate, was concentrated and purified by flash column chromatography to provide 30 mg of the title compound. MS (*m/z*) 674.7 $[M+H]^+$.

Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-ynyl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide TFA salt (**19F**):

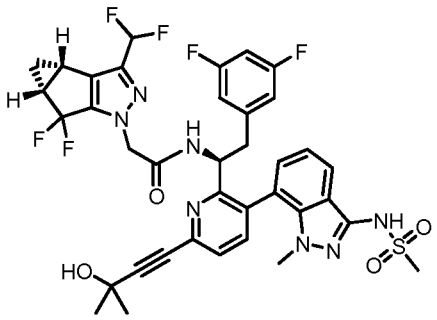
[0443] To (S)-tert-butyl 1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-ynyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (30 mg, 0.04 mmol) in DCM (4 mL) was added TFA (2 ml) . The reaction mixture was stirred for 0.5 hours at RT. The reaction was concentrated and used with no further purification to provide the title compound. MS (*m/z*) 574.4 $[M+H]^+$.

Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-ynyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**19G**):

[0444] The title compound (**19G**) was prepared according to the method presented for the synthesis of compound **4G** of Example 4 utilizing 2-((3bS,4aR)-5,5-difluoro-3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid and (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-ynyl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide to provide 20 mg of the title compound. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.69 (t, 1H), 7.69 (dd, 1H), 7.53 (dd, 1H), 7.17 (s, 1H), 7.06 (d, 1H), 6.88 – 6.52 (m, 2H), 6.44 – 6.33 (m, 2H), 5.28 (d, 1H), 5.02 – 4.92 (m, 1H), 4.78 – 4.64 (m, 2H), 3.33 (s, 3H), 3.24 (d, 3H), 3.19 – 3.08 (m, 2H), 3.05 – 2.92 (m, 2H), 2.44 (ddd, 2H), 1.64 (d, 6H), 1.38 (dt, 1H), 1.02 (s, 1H).

[0445] MS (m/z) 820.8 $[M+H]^+$.

Example 20.



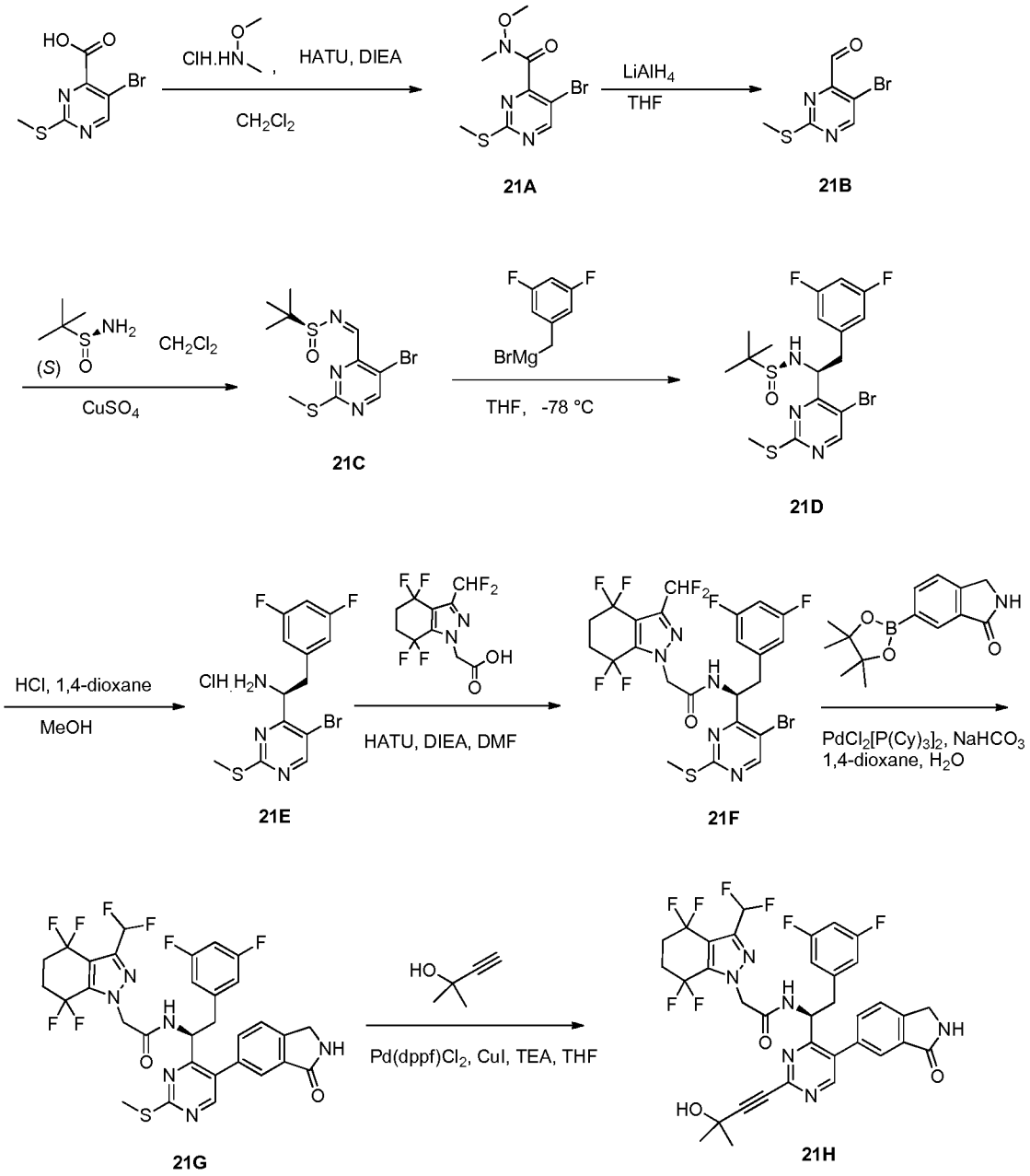
20

Synthesis of (S)-N-(1-(3-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-ynyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**20**):

[0446] The title compound was prepared according to the method presented for the synthesis of compound **19G** of utilizing N-(1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-yl)methanesulfonamide and compound **14B**.^{1}H NMR (400 MHz, Methanol-d_4) δ 8.69 (t, 1H), 7.88-7.80 (dd, 1H), 7.69 (dd, 1H), 7.53 (dd, 1H), 7.20 (s, 1H), 7.09 (d, 1H), 6.88 – 6.52 (m, 2H), 6.38 – 6.27 (m, 2H), 5.35 (m, 1H), 5.02 – 4.95 (m, 1H), 4.80 – 4.65 (m, 2H), 3.33 (s, 3H), 3.19 – 3.08 (m, 4H), 3.05 – 2.92 (m, 2H), 2.44 (m, 2H), 1.64 (d, 6H), 1.38 (m, 1H), 1.02 (m, 1H).

[0447] MS (m/z) 786.1 $[M+H]^+$.

Example 21.



Synthesis of 5-bromo-N-methoxy-N-methyl-2-(methylthio)pyrimidine-4-carboxamide (**21A**):

[0448] To a mixture of 5-bromo-2-(methylthio)pyrimidine-4-carboxylic acid (5 g, 20 mmol), N,O-dimethylhydroxylamine hydrochloride (2.9 g, 30 mmol) and HATU (9.1 g, 24 mmol) in 100 mL of CH_2Cl_2 at 0 °C was added N,N-diisopropylethylamine (17.4 mL, 100 mmol). The reaction mixture was allowed to stir at 0 °C for 30 min and then diluted with CH_2Cl_2. It was washed with water and half brine. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography to afford the title compound **21A**. MS (*m/z*) 292.16 $[M+H]^+$.

Synthesis of 5-bromo-2-(methylthio)pyrimidine-4-carbaldehyde (**21B**):

[0449] A solution of 5-bromo-N-methoxy-N-methyl-2-(methylthio)pyrimidine-4-carboxamide (**21A**, 8.2 g, 28 mmol) in THF (120 mL) was added dropwise to a suspension of lithium aluminum hydride (1.06 g, 28 mmol) and THF (120 mL) at -78 °C. The mixture was stirred for 10 minutes after addition finish. H_2O (1.06 mL), 15% aqueous NaOH solution (1.06 mL) and H_2O (3.18 mL) were successively added to the mixture at 0 °C very slowly. The resulting precipitate was filtered and washed with THF. The filtrate was concentrated in vacuo to afford crude of the title compound. MS (m/z): 233.14, $[M+H]^+$.

Synthesis of (S)-N-((5-bromo-2-(methylthio)pyrimidin-4-yl)methylene)-2-methylpropane-2-sulfinamide (**21C**):

[0450] Copper(II) sulfate (anhydrous, 8.9 g, 56 mmol) was added to a solution of 5-bromo-2-(methylthio)pyrimidine-4-carbaldehyde (**21B**, ~28 mmol) and (S)-2-methylpropane-2-sulfinamide (3.4 g, 28 mmol) in CH_2Cl_2 (100 mL). The suspension was stirred for 3 days at room temperature. The reaction was filtered and washed with CH_2Cl_2 (3x20 ml). The filtrate was concentrated. The crude product was purified by silica gel chromatography to yield the title compound **21C**. MS (*m/z*) 337.7 $[M+H]^+$

Synthesis of (S)-N-((S)-1-(5-bromo-2-(methylthio)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (**21D**):

[0451] To a solution of (S)-N-((5-bromo-2-(methylthio)pyrimidin-4-yl)methylene)-2-methylpropane-2-sulfinamide (**21C**, 2.97 g. 8.8 mmol) in THF (18 mL) cooled to-78 °C was drop wise added 3,5-Difluorobenzylmagnesium bromide (53 mL, 0.25 M in Ether,13.3 mmol). After stirring at -78 °C for 10 min, NH_4Cl (sat. aq.) (10 ml) was added to the reaction and warmed up to ambient temperature. Extracted with EtOAc and the organic layer was dried over Na_2SO_4(s).The solvent was removed and the residue was purified by silica gel chromatography to yield 1.44 g of the title compound **21D** MS (*m/z*) 465.87 $[M+H]^+$

Synthesis of (S)-1-(5-bromo-2-(methylthio)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethanamine hydrochloride (**21E**):

[0452] Compound **21D** (8 g, 17.23 mmol) was dissolved in 35 mL of methanol and cooled to 0 °C. To it was added 4N HCl/1,4-dioxane (10.7 mL). The reaction mixture was allowed to stir for 20 minutes and to it was added diethyl ether. The resulting precipitate was collected by vacuum filtration then dried to afford the title product **21E**. MS (m/z) 362.02 $[M+H]^+$.

Synthesis of (S)-N-(1-(5-bromo-2-(methylthio)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**21F**):

[0453] A mixture of 2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid (604 mg, 2 mmol), compound **21E** (793 mg, 2 mmol) and HATU (912 mg, 2.4 mmol) in 10 mL of DMF was cooled to 0 ℃. To it was drop wise added N,N-diisopropylethylamine (1.05 mL, 6 mmol). The reaction mixture was allowed to stir at 0 ℃ for 10 minutes then slowly poured it into ice water with stirring. The resulting precipitate was collected by vacuum filtration then dried to afford the title product **21F**. MS (*m/z*) 644.22 $[M+H]^+$.

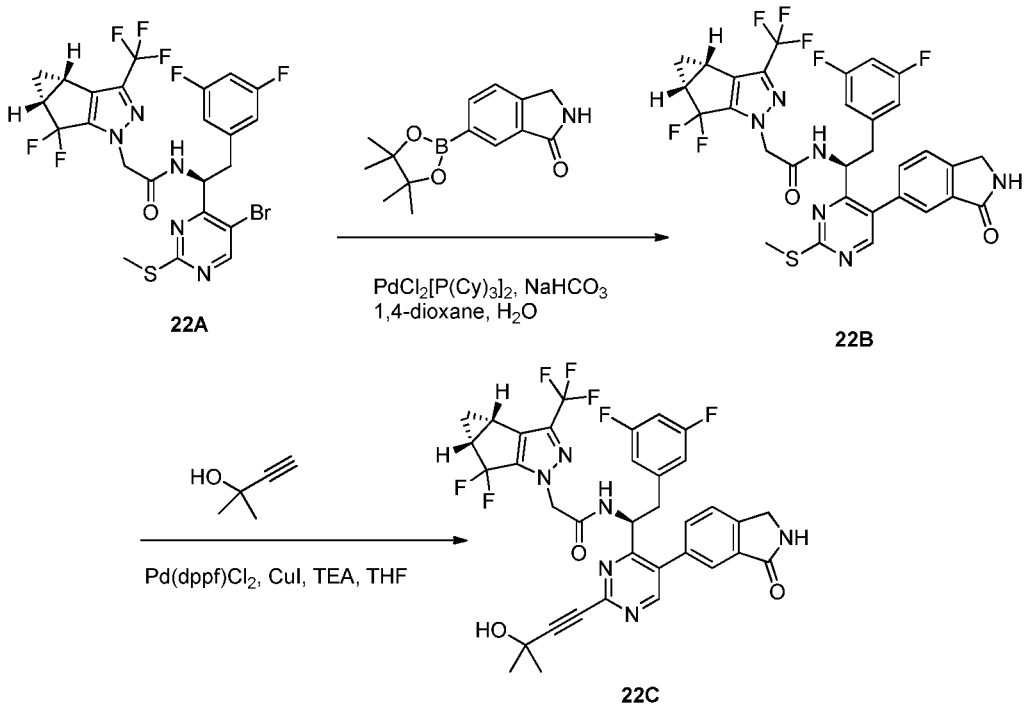
Synthesis of (S)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)-N-(2-(3,5-difluorophenyl)-1-(2-(methylthio)-5-(3-oxoisoindolin-5-yl)pyrimidin-4-yl)ethyl)acetamide (**21G**):

[0454] In a microwave tube were charged with compound **21F** (300 mg, 0.47 mmol), 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one (181 mg, 0.7 mmol) and $PdCl_2[P(Cy)_3]_2$ (17 mg, 0.023 mmol). To the mixture was added 10 mL of 1,4-dioxane and 1.4 mL of sodium bicarbonate aqueous solition (1M). The mixture was heated to 155 °C for 25 min in a microwave synthesizer. After cooled to room temperature, it was partitioned between EtOAc and water. The organic layer was separated and washed with brine, then dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography to afford the title compound **21G**. MS (*m/z*) 697.32 $[M+H]^+$).

Synthesis of (S)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)-N-(2-(3,5-difluorophenyl)-1-(2-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-(3-oxoisoindolin-5-yl)pyrimidin-4-yl)ethyl)acetamide (**21H**):

[0455] To the mixture of solid CuI (3.3 mg, 0.017 mmol), $Pd(dppf)Cl_2$ (7 mg, 0.009 mmol), 2-methylbut-3-yn-2-ol (22 mg, 0.26 mmol) and compound **21G** (60 mg, 0.086 mmol) were added THF (1 mL) and Et_3N (0.06 mL, 0.4 mmol). The reaction mixture was heated in a microwave at 160 °C for 20 min. After cooled to room temperature it was diluted with EtOAc. To it was added Si-Thiol (130 mg, 1.37 mmol/g) and the mixture was stirred at 40 °C for 1 hour. Then it was filtered and the filtrate was washed with 10% aqueous NH_4OH, water and brine. The organic layer was dried over $MgSO_4$, filtered, concentrated, and purified by reverse phase HPLC to afford the title compound (**21H**). ^1H NMR (400 MHz, Methanol-*d*4): δ 9.09 (d), 8.54 (s), 7.64 (dd), 7.58 (dd), 7.40 (d), 6.78 (t), 6.67 (tt), 6.43 – 6.20 (m), 5.40 (q), 4.50 (s), 3.05 (d), 2.50 (tdd), 1.62 (s). MS (*m/z*): 732.99 $[M+H]^+$.

Example 22.



22A 22B 22C

Synthesis of N-((S)-1-(5-bromo-2-(methylthio)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**22A**):

[0456] The title compound (**22A**) was prepared according to the method presented for the synthesis of compound **21F** of Example 21 utilizing 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid and compound **21E**. MS (*m/z*) 624.13 $[M+H]^+$.

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(2-(methylthio)-5-(3-oxoisoindolin-5-yl)pyrimidin-4-yl)ethyl)acetamide (**22B**):

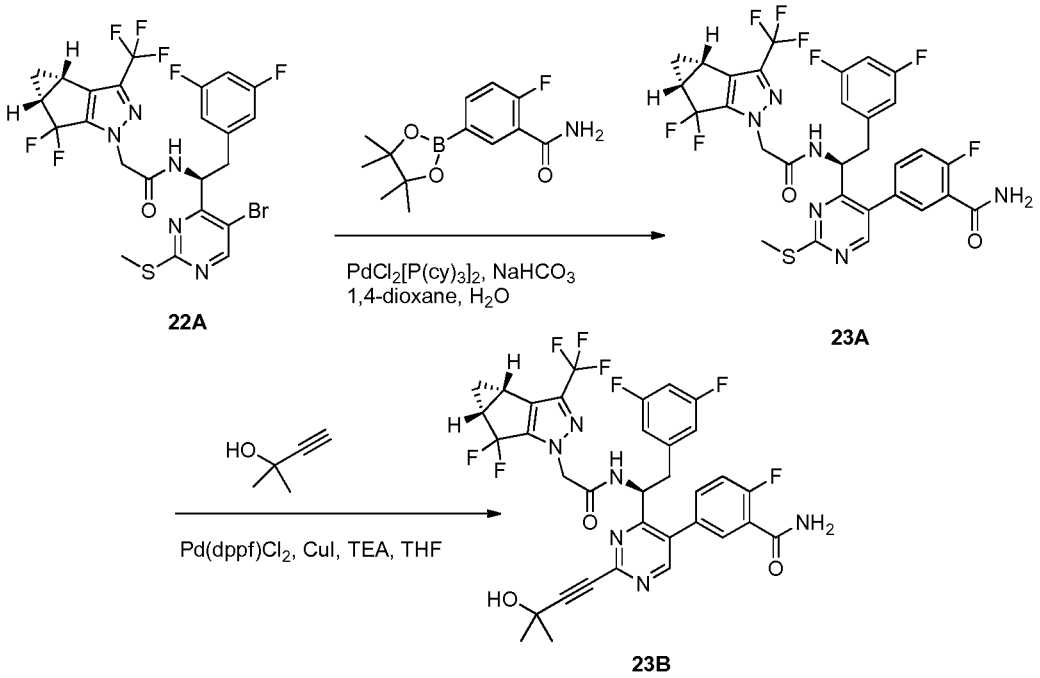
[0457] The title compound (**22B**) was prepared according to the method presented for the synthesis of compound **21G** of Example 21 utilizing compound **22A** and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one. MS (*m/z*) 677.05 $[M+H]^+$.

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(2-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-(3-oxoisoindolin-5-yl)pyrimidin-4-yl)ethyl)acetamide (**22C**):

[0458] The title compound (**22C**) was prepared according to the method presented for the synthesis of compound **21H** of Example 21 utilizing compound **22B** and 2-methylbut-3-yn-2-ol. ^{1}H NMR (400 MHz, Methanol-*d*4): δ 9.05 (d), 8.53 (s), 7.63 (dd), 7.58 (dd), 7.37 (d), 6.75 –

6.55 (m), 6.41 – 6.21 (m), 5.41 (q), 4.85 (s), 4.50 (s), 3.05 (dd), 2.48-2.45 (m), 1.62 (s), 1.38 (q), 1.18 – 0.97 (m, 1H). MS (*m/z*) 713.01 $[M+H]^+$.

Example 23.



22A 23A 23B

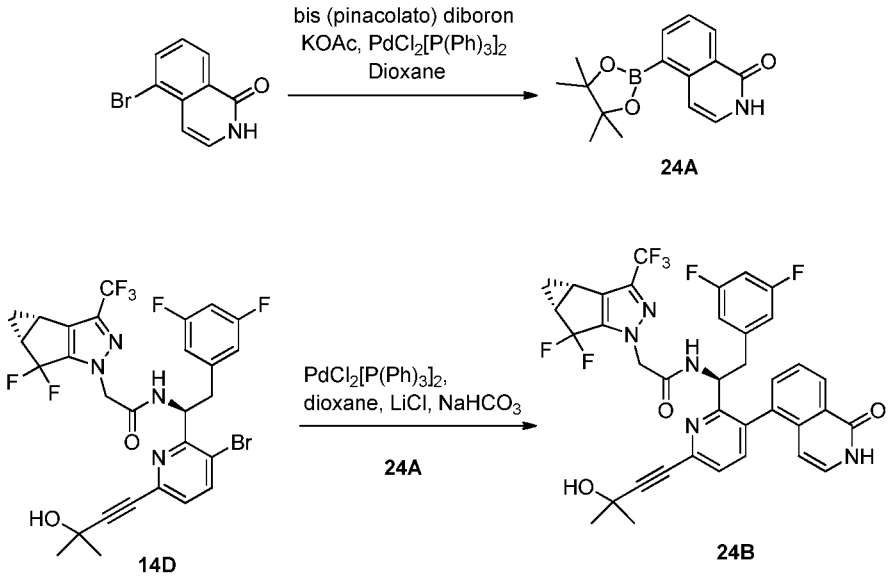
Synthesis of 5-(4-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-2-(methylthio)pyrimidin-5-yl)-2-fluorobenzamide (**23A**):

[0459] The title compound (**23A**) was prepared according to the method presented for the synthesis of compound **21G** of Example 21 utilizing compound **22A** and 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide. MS (*m/z*) 683.06 $[M+H]^+$.

Synthesis of 5-(4-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-2-(3-hydroxy-3-methylbut-1-yn-1-yl)pyrimidin-5-yl)-2-fluorobenzamide (**23B**):

[0460] The title compound (**23B**) was prepared according to the method presented for the synthesis of compound **21H** of Example 21 utilizing compound **23A** and 2-methylbut-3-yn-2-ol. ^{1}H NMR (400 MHz, Methanol-d_4): δ 9.09 (t), 8.51 (d), 7.46 (ddq), 7.27 (ddd), 6.69 (tt), 6.40 (h), 5.36 (q), 4.84 (s), 3.10 – 3.01 (m), 2.48-2.45 (m), 1.61 (s), 1.38 (q), 1.07 (dd). MS (*m/z*) 719.06 $[M+H]^+$.

Example 24.



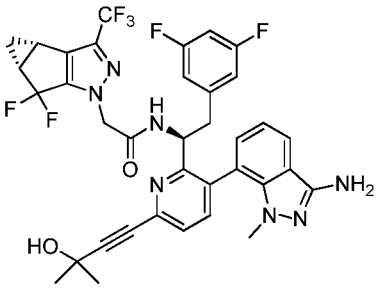
Synthesis of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (**24A**):

[0461] To 5-bromoisoquinolin-1(2H)-one (40 mg, 0.18 mmol) in dioxane (1 mL) was added bis(pinacolato)diboron (63 mg, 0.25 mmol), and $PdCl_2[P(Ph)_3]_2$ (6 mg, 0.01 mmol). The reaction mixture sealed and heated to 100 °C for 1h. The reaction was cooled to room temperature and telescoped to the next reaction. MS (*m/z*) 272.3 $[M+H]^+$.

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-oxo-1,2-dihydroisoquinolin-5-yl)pyridin-2-yl)ethyl)acetamide (**24B**):

[0462] To the reaction vial containing **24A** (0.18 mmol) was added **14D** (50 mg, 0.07 mmol), $PdCl_2[P(Ph)_3]_2$ (5 mg, 0.01 mmol), LiCl (11 mg, 0.22 mmol) and aq 1M $NaHCO_3$ (0.22 mL, 0.22 mmol). The reaction mixture was sealed and heated in a microwave reactor to 160 °C for 20 min. Upon cooling, the reaction mixture was diluted with EtOAc and washed with three portions of brine. The organic layer were dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by reverse phase HPLC to provide the title compound **24B** as a mixture of atropisomers. MS (*m/z*) 724.2 $[M+H]^+$. HPLC retention time 6.95 min and 7.09 min (2-98% acetonitrile: water with 0.1% trifluoroacetic acid, 8.5 min gradient on a Phenomonex Kinetex C18 column).

Example 25.

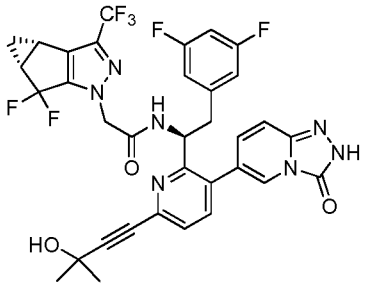


25

Synthesis of N-((S)-1-(3-(3-amino-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**25**):

[0463] The title compound (**25**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **33F** of Example 33 utilizing 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid and **37A**. ^{1}H NMR (400 MHz, cd_3od) δ 9.04-8.52 (m), 7.7-7.61 (m), 7.52 (dd), 7.17 (d), 7.04 (t), 7.00 – 6.90 (m), 6.77 – 6.66 (m), 6.60 (t), 6.48 9 (d), 6.40 – 6.25 (m), 5.32-5.25 (m), 5.11-5.04 (m), 4.80-4.79 (m), 3.22-3.06 (m), 2.96-2.85 (m), 2.52-2.46 (m), 1.64 (s), 1.43 – 1.39 (m), 1.14 – 1.07 (m). MS (*m/z*) 726.2 $[M+H]^+$.

Example 26.

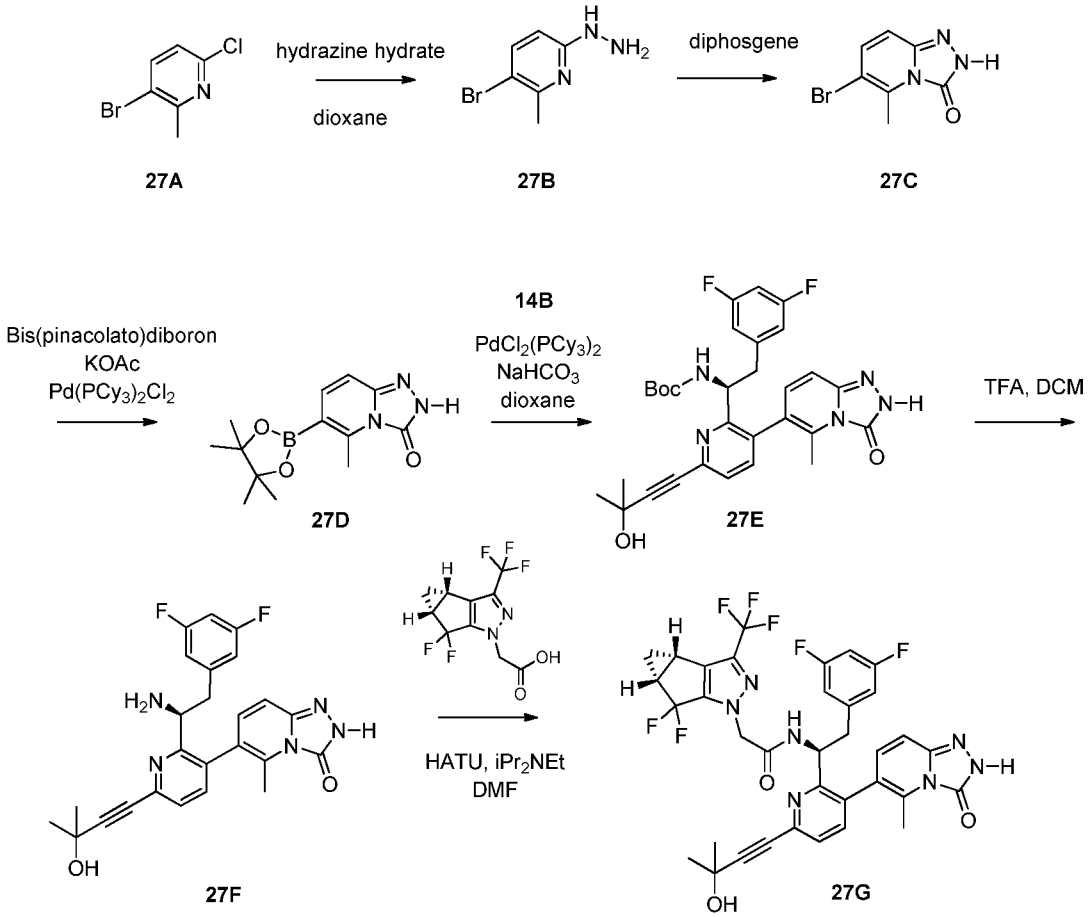


26

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-6-yl)pyridin-2-yl)ethyl)acetamide (**26**):

[0464] The title compound (**26**) was prepared according to the method presented for the synthesis of compound **24B** of Example 24 utilizing 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one MS (*m/z*) 714.1 $[M+H]^+$. HPLC retention time 6.58 min (2-98% acetonitrile: water with 0.1% trifluoroacetic acid, 8.5 min gradient on a Phenomonex Kinetex C18 column).

Example 27.



Synthesis of 3-bromo-6-hydrazinyl-2-methylpyridine (**27B**):

[0465] To 3-bromo-6-chloro-2-methylpyridine (1.53 g, 7.41 mmol) in dioxane (4.5 ml) was added hydrazine hydrate (1.8 ml, 37 mmol). The reaction was heated in a microwave reactor at 160 °C for 55 min. After cooling to ambient temperature, the reaction mixture was partitioned between EtOAc and saturated aqueous NaCl. The organics were separated and evaporated in vacuo. The product was used directly in the following step. MS (*m/z*) 202.0 $[M+H]^+$.

Synthesis of 6-bromo-5-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one (**27C**):

[0466] 3-bromo-6-hydrazinyl-2-methylpyridine (4.55 g, 22.52 mmol) was dissolved in DCE (35 ml) to which trichloromethyl chloroformate (2.72 ml, 22.52 mmol) was added. The reaction was stirred at ambient temperature for 1h. Hexanes (15 ml) was added and the solids filtered to provide the desired product. The eluent was reduced in a volume and a second crop of precipitate was isolated. The combined solids were used without further purification. MS (*m/z*) 228.0 $[M+H]^+$.

Synthesis of 5-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one (**27D**):

[0467] 6-bromo-5-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one (3.62 g, 15.87 mmol) was combined with bis(pinacolato)diboron (6.05 g, 23.81 mmol), KOAc (3.12 g, 31.75 mmol), and $PdCl_2(PCy_3)_2$ (0.23 g, 0.32 mmol) in dioxane (80 ml). Argon was bubbled into the reaction solution for 15 min. The reaction was then heated to 85 deg C for 15 h. Additional $PdCl_2(PCy_3)_2$ (250 mg) was added and the temperature was raised to 125 deg C. Heated for 15 h. After cooling to ambient temperature, the reaction was partitioned between EtOAc and water. The organics were separated, dried, and removed in vacuo. The residue was suspended in EtOAc (50 ml) and the resultant solids filtered to provide the title compound. MS (*m/z*) 276.2 $[M+H]^+$.

Synthesis of (S)-tert-butyl (2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(5-methyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-6-yl)pyridin-2-yl)ethyl)carbamate (**27E**):

[0468] In a microwave reaction vessel, **14B** (66 mg, 0.13 mmol) and 5-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one (55 mg, 0.2 mmol) were dissolved in dioxane (2 mL) and treated with aqueous 1M $NaHCO_3$ (0.4 mL) and $PdCl_2(PCy_3)_2$ (10 mg). The mixture was heated to 150 °C for 20 min. After cooling to ambient temperature, the reaction was partitioned between EtOAc and water. The organics were separated, dried, and removed in vacuo and the residue was purified by column chromatography on silica to provide the title compound as a mixture of atropisomers. MS (*m/z*) 563.8 $[M+H]^+$.

Synthesis of (S)-6-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-5-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one (**27F**):

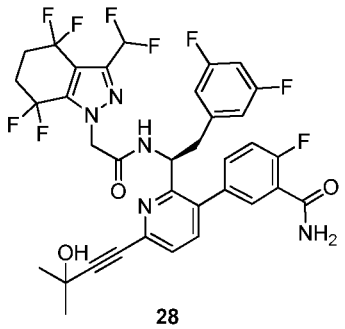
[0469] The title compound (**27F**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of **19F** in Example 19 utilizing **27E**. MS (*m/z*) 464.1 $[M+H]^+$.

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(5-methyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-6-yl)pyridin-2-yl)ethyl)acetamide (**27G**):

[0470] The title compound (**27G**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of **37E** in Example 37 utilizing **27F** and 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-

1-yl)acetic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.75 (dd), 7.44 – 7.54 (m), 6.83 – 6.92 (m), 6.68 –6.80 (m), 6.47 – 6.56 (dd), 5.98 (d), 5.16 – 5.24 (m), 3.13 – 3.26 (m), 3.03 – 3.08 (m), 2.45 – 2.51 (m), 2.37 (s), 2.11 (s), 1.36 –1.43 (m), 1.05 – 1.15 (m). MS (*m/z*) 728.0 $[M+H]^+$.

Example 28.

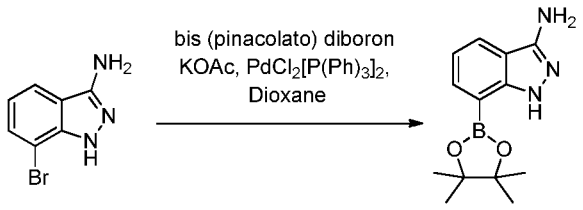


28

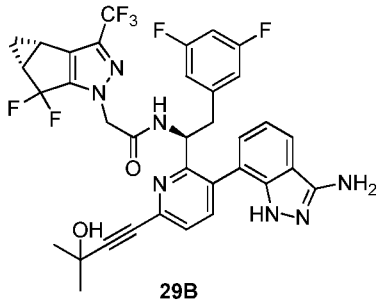
Synthesis of (S)-5-(2-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-2-fluorobenzamide (**28**):

[0471] The title compound (**28**) was prepared according to the method presented for the synthesis of compound **33F** of Example 33 utilizing (3-carbamoyl-4-fluorophenyl)boronic acid and 2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, cd_3od) δ 8.88 (d), 7.55 (d), 7.50 – 7.36 (m), 7.32 (s), 7.23 (dd), 6.94 (d), 6.82 (d), 6.72 – 6.62 (m), 6.40 – 6.31 (m), 5.40 – 5.32 (m), 5.22 (s), 5.06 (s), 4.36 – 4.29 (m), 3.75 – 3.57 (m), 3.14 – 2.98 (m), 2.66 – 2.42 (m), 1.62 (s). MS (*m/z*) 738.2 $[M+H]^+$.

Example 29.



29A



29B

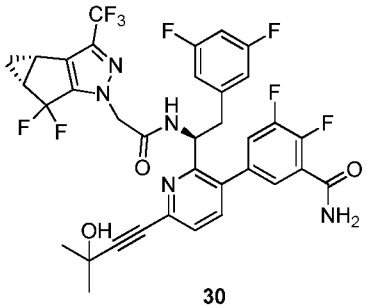
Synthesis of 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-amine (**29A**):

[0472] To 7-bromo-1H-indazol-3-amine (75 mg, 0.35 mmol) in dioxane (3 mL) was added bis(pinacolato)diboron (126 mg, 0.5 mmol), and $PdCl_2[P(Ph)_3]_2$ (12 mg, 0.01 mmol). The reaction mixture sealed and heated to 100 °C for 16h. The reaction was cooled to room temperature and telescoped to the next reaction. MS (*m/z*) 260.2 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(3-amino-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**29B**):

[0473] The title compound (**29**) was prepared according to the method presented for the synthesis of compound **24B** of Example 24 utilizing **29A**. MS (*m/z*) 712.4 $[M+H]^+$. PLC retention time 6.02 min (2-98% acetonitrile: water with 0.1% trifluoroacetic acid, 8.5 min gradient on a Phenomonex Kinetex C18 column).

Example 30.

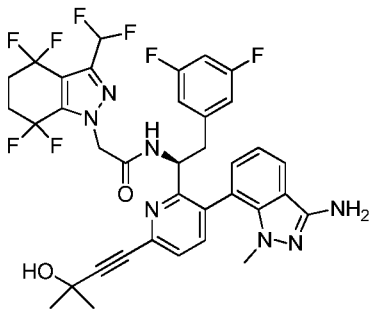


30

Synthesis of 5-(2-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-2,3-difluorobenzamide (**30**):

[0474] The title compound (**30**) was prepared according to the method presented for the synthesis of compound **33F** of Example 33 utilizing 5-bromo-2,3-difluorobenzamide and 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^1H NMR (400 MHz, cd_3od) δ 8.80 (d), 7.71- 7.65 (m), 7.60-7.50 (m), 7.49-7.40 (m), 7.25-7.18 (m), 7.17-7.10 (m), 6.79-6.65 (m), 6.43-6.31 (m), 5.33 (m, 1H), 5.03 (s), 4.33-4.30 (m), 3.20-3.00 (m), 2.59-2.45 (m), 1.65-1.55 (m), 1.49-1.37 (m), 1.15-1.04 (m). MS (*m/z*) 736.1 $[M+H]^+$.

Example 31.

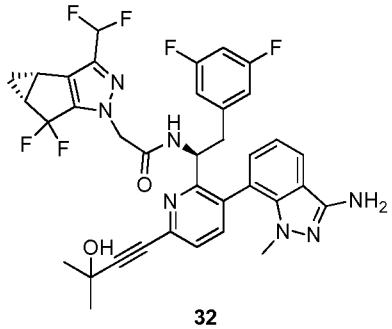


31

Synthesis of (S)-N-(1-(3-(3-amino-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**31**):

[0475] The title compound (**31**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **33F** of Example 33 utilizing **37A** and 2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, cd_3od) δ 8.85 (m), 7.87-7.85 (m), 7.70 (d), 7.54-7.46 (d), 7.33 (d), 7.25-7.15 (m), 6.81-6.71 (m), 6.40-6.32 (m), 5.35-5.24 (m), 5.03-4.98 (m), 3.19 (s), 3.08-2.95 (m), 2.61-2.40 (m), 1.64 (s). MS (*m/z*) 746.2 $[M+H]^+$.

Example 32.

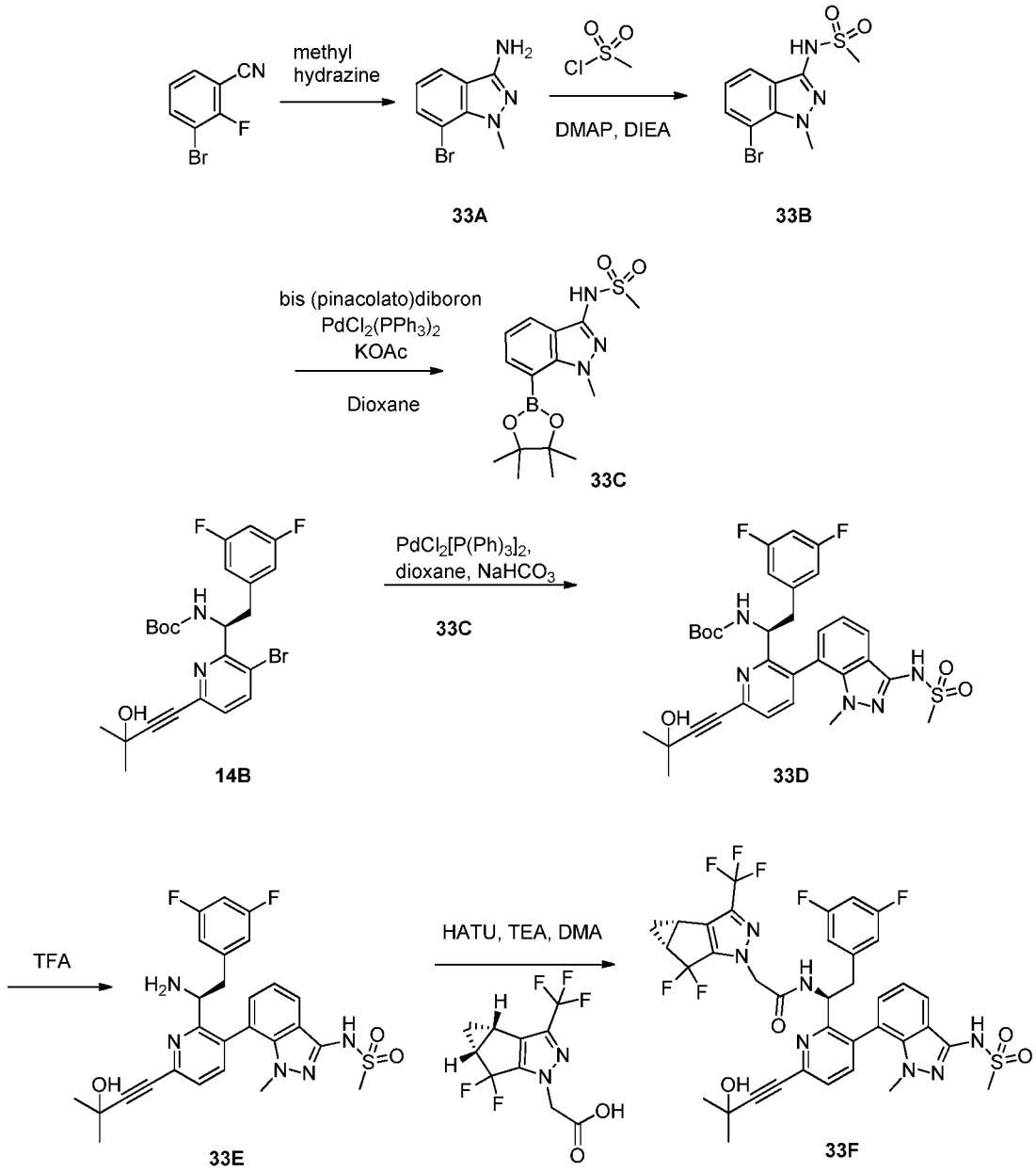


32

Synthesis of N-((S)-1-(3-(3-amino-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**32**):

[0476] The title compound (**32**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **33F** of Example 33 utilizing **37A**. ^{1}H NMR (400 MHz, cd_3od) δ 8.68 (d), 7.89 – 7.79 (m), 7.74 – 7.65 (m), 7.59 – 7.48 (m), 7.29 (d), 7.16 – 7.11 (m), 6.79 – 6.60 (m), 6.39 (d), 6.35 – 6.28 (m), 5.27 – 5.22 (m), 5.06 – 4.95 (m), 4.73 (d), 3.16 (s), 3.13 – 3.03 (m), 3.02 – 2.84 (m), 2.50 – 2.39 (m), 1.64 (s), 1.42 – 1.34 (m), 1.03 (s). MS (*m/z*) 708.2 $[M+H]^+$.

Example 33.



Synthesis of 7-bromo-1-methyl-1H-indazol-3-amine (**33A**):

[0477] In a microwave vial a solution of 3-bromo-2-fluorobenzonitrile (2g, 10 mmol) ethanol (10 mL) was treated with methylhydrazine (2.1 mL, 40 mmol), sealed, and heated to 120°C in a microwave reactor for 35 minutes. The reaction was concentrated in vacuo and the crude product dissolved with EtOAc (30mL) and washed with water (30 mL), then 2M NaCl (aq, 30 mL). The organics were dried with Na_2SO_4, filtered, and concentrated. Product was purified by silica chromatography to give the title compound. MS (*m/z*) 227.1 $[M+H]^+$.

Synthesis of N-(7-bromo-1-methyl-1H-indazol-3-yl)methanesulfonamide (**33B**):

[0478] To a stirred solution of **33A** (500 mg, 2.21 mmol), 4-Dimethylaminopyridine (13.5 mg, 0.11 mmol), and N,N-diisopropylethylamine (714.6 mg, 5.53 mmol) in DCM (20 ml) was added dropwise methanesulfonyl chloride (532.0 mg, 4.64 mmol) at 0°C. The reaction was warmed to RT and stirred for 2h. The reaction was washed with water, dried with Na_2SO_4, filtered, and concentrated. The crude product dissolved with EtOH (10mL) and treated with 8N NaOH (1.65 ml). The reaction mixture was heated at 60°C for 0.5h. The ethanol was removed under vacuum, pH to ~ 2 with 1.0 HCl then, extracted with EtOAc. The organics were dried with Na_2SO_4, filtered, and concentrated. The product was purified by silica chromatography to give the title compound. MS (*m/z*) 305.9 $[M+H]^+$.

Synthesis of N-(1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-yl)methanesulfonamide (**33C**):

[0479] To **33B** (1.2 g, 3.9 mmol) in dioxane (15 mL) was added bis(pinacolato)diboron (1.9 mg, 5.5 mmol), and $PdCl_2[P(Ph)_3]_2$ (138 mg, 0.19 mmol). The reaction mixture sealed and heated to 100 °C for 1h. The reaction was cooled to rt and filtered through Celite using ethyl acetate to rinse the pad. The collected organic phase was concentrated in vacuo and purified by silica gel chromatography to give the title compound. MS (*m/z*) 352.1 $[M+H]^+$.

Synthesis of (S)-tert-butyl (2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)carbamate (**33D**):

[0480] To **14B** (250 mg, 0.5 mmol) in dioxane (12 mL) was added N-(1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-yl)methanesulfonamide (**33C**, 253 mg, 0.72 mmol), $PdCl_2[P(Ph)_3]_2$ (35 mg, 0.05 mmol), and aq 1M $NaHCO_3$ (1.5 mL, 1.5 mmol). The reaction mixture sealed and heated in a microwave reactor to 150 °C for 20 min. Upon cooling, the reaction mixture was diluted with EtOAc and washed with three portions of brine. The organic layer were dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by silica gel column chromatography, eluting with 0-100% EtOAc in hexanes to give the title compound **33D** as a mixture of atropisomers.

Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)methanesulfonamide (**33E**):

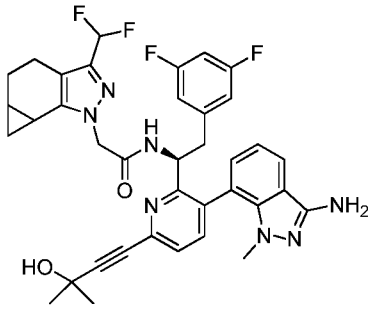
[0481] To a solution of **33D** (47 mg, 0.07 mmol) in DCM was added 4M HCl in dioxane (0.7 mL, 2.9 mmol). The reaction mixture was stirred at room temperature for 0.5 hours. Upon

complete removal of the Boc protecting group, the reaction was concentrated in vacuo to give the title compound **33E** as a mixture of atropisomers.

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)acetamide (**33F**):

[0482] To a solution of **33E** (70 mg) in DMA (3 mL) was added triethylamine (0.046 mL, 0.32 mmol), followed by 2-((3bS,4aR)-3-(trifluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (31 mg, 0.1 mmol) and HATU (46 mg, 0.12 mmol). After stirring for 30 minutes, the reaction mixture was filtered and purified by reverse phase HPLC to provide the product **33F** as a mixture of atropisomers. ^{1}H NMR (400 MHz, cd_3od) δ 7.83 (dd), 7.72-7.64 (m), 7.50-7.55 (m), 7.32-7.07 (m), 6.78-6.70 (m), 6.52-6.48 (m), 6.33-6.31 (m), 5.35-5.28 (m), 5.05-4.37 (m), 3.56 (s), 3.21-3.09 (m), 3.00 - 2.90 (m), 2.54-2.40 (m), 1.64 (s), 1.50 - 1.39 (m), 1.10 - 0.88 (m). MS (*m/z*) 804.1 $[M+H]^+$.

Example 34.

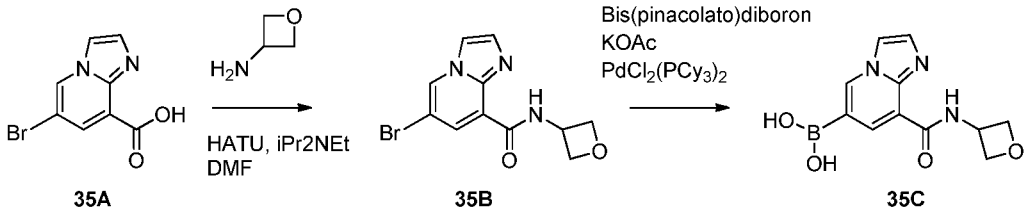


34

Synthesis of N-((S)-1-(3-(3-amino-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetamide (**34**):

[0483] The title compound (**34**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **33F** of Example 33 utilizing **37A** and 2-(3-(difluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetic acid (WO2013006738). ^{1}H NMR (400 MHz, cd_3od) δ 7.91 – 7.86 (m), 7.71 (dd), 7.54 (dd), 7.22 – 7.17 (m), 6.87 – 6.69 (m), 6.66 – 6.56 (m), 6.41 – 6.30 (m), 5.35-5.25 (m), 5.08 – 4.97 (m), 4.90 – 4.71 (m), 4.36 – 4.29 (m), 3.76 – 3.66 (m), 3.65 – 3.57 (m), 3.18 – 3.13 (m), 3.07 (dt), 3.01 – 2.90 (m), 2.75 – 2.64 (m), 2.21 – 2.04 (m), 1.76 – 1.61 (m), 1.10-1.03 (m), 1.00 – 0.90 (m), 0.75-0.70 (m), 0.69 – 0.62 (m). MS (*m/z*) 686.2 $[M+H]^+$.

Example 35.

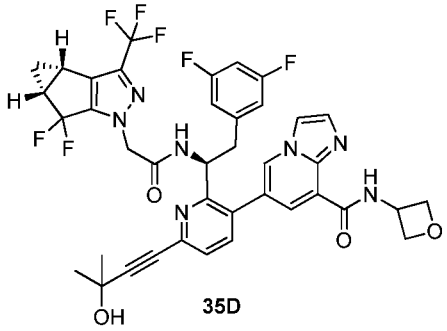


Synthesis of 6-bromo-N-(oxetan-3-yl)imidazo[1,2-a]pyridine-8-carboxamide (**35B**):

[0484] 6-bromoimidazo[1,2-a]pyridine-8-carboxylic acid hydrochloride (235 mg, 0.85 mmol) and HATU (386.16 mg, 1.02 mmol) were combined in DMF (4 ml) and treated with iPr_2NEt (0.37 ml, 2.12 mmol). 3-Oxetamine hydrochloride (92.31 mg, 0.85 mmol) was added and the reaction stirred at ambient temperature for 1 h. Water (2 ml) was added and a solid precipitated. The solids were collected by filtration to provide the desired product. MS (*m/z*) 296.0 $[M+H]^+$.

Synthesis of (8-(oxetan-3-ylcarbamoyl)imidazo[1,2-a]pyridin-6-yl)boronic acid (**35C**):

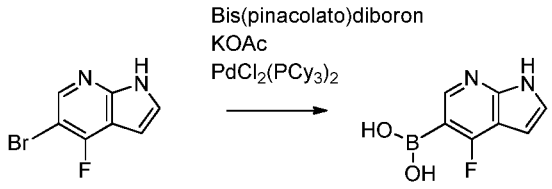
[0485] The title compound (**35C**) was prepared according to the method presented for the synthesis of **27D** in Example 27 utilizing **35B** wherein the boronic ester hydrolyzed and the corresponding boronic acid was isolated. MS (*m/z*) 262.1 $[M+H]^+$.



Synthesis of 6-(2-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-N-(oxetan-3-yl)imidazo[1,2-a]pyridine-8-carboxamide (**35D**):

[0486] The title compound (**35D**) was prepared according to the method presented for the synthesis of **27G** in Example 27 utilizing **14B** and **35C**. ^1H NMR (400 MHz, Methanol-d_4) δ 9.15 (d), 8.80 (d), 8.27 (d), 8.11 (d), 7.84 – 7.69 (m), 7.65 (dd), 7.53 (dd), 6.89 – 6.64 (m), 6.53 – 6.37 (m), 5.34 – 5.13 (m), 4.73 – 4.49 (m), 4.49 – 4.34 (m), 3.96 – 3.58 (m), 3.25 – 3.03 (m), 2.59 – 2.36 (m), 1.51 – 1.29 (m), 1.18 – 0.95 (m). MS (*m/z*) 796.2 $[M+H]^+$.

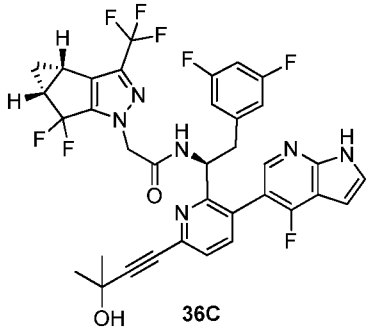
Example 36.



36A 36B

Synthesis of (4-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)boronic acid (**36B**):

[0487] In a microwave vessel, 5-bromo-4-fluoro-1H-pyrrolo[2,3-b]pyridine (100 mg, 0.47 mmol) was combined with bis(pinacolato)diboron (177 mg, 0.7 mmol), KOAc (91 mg, 0.93 mmol), and $PdCl_2(PCy_3)_2$ (34 mg) in dioxane (4.5 ml). Argon was bubbled into the reaction solution for 15 min. The reaction was heated in a microwave reactor at 155 °C for 15 min. After cooling to ambient temperature, the reaction was partitioned between EtOAc and water. The organics were separated, dried, and removed in vacuo to provide the title compound. MS (*m/z*) 181.1 $[M+H]^+$.

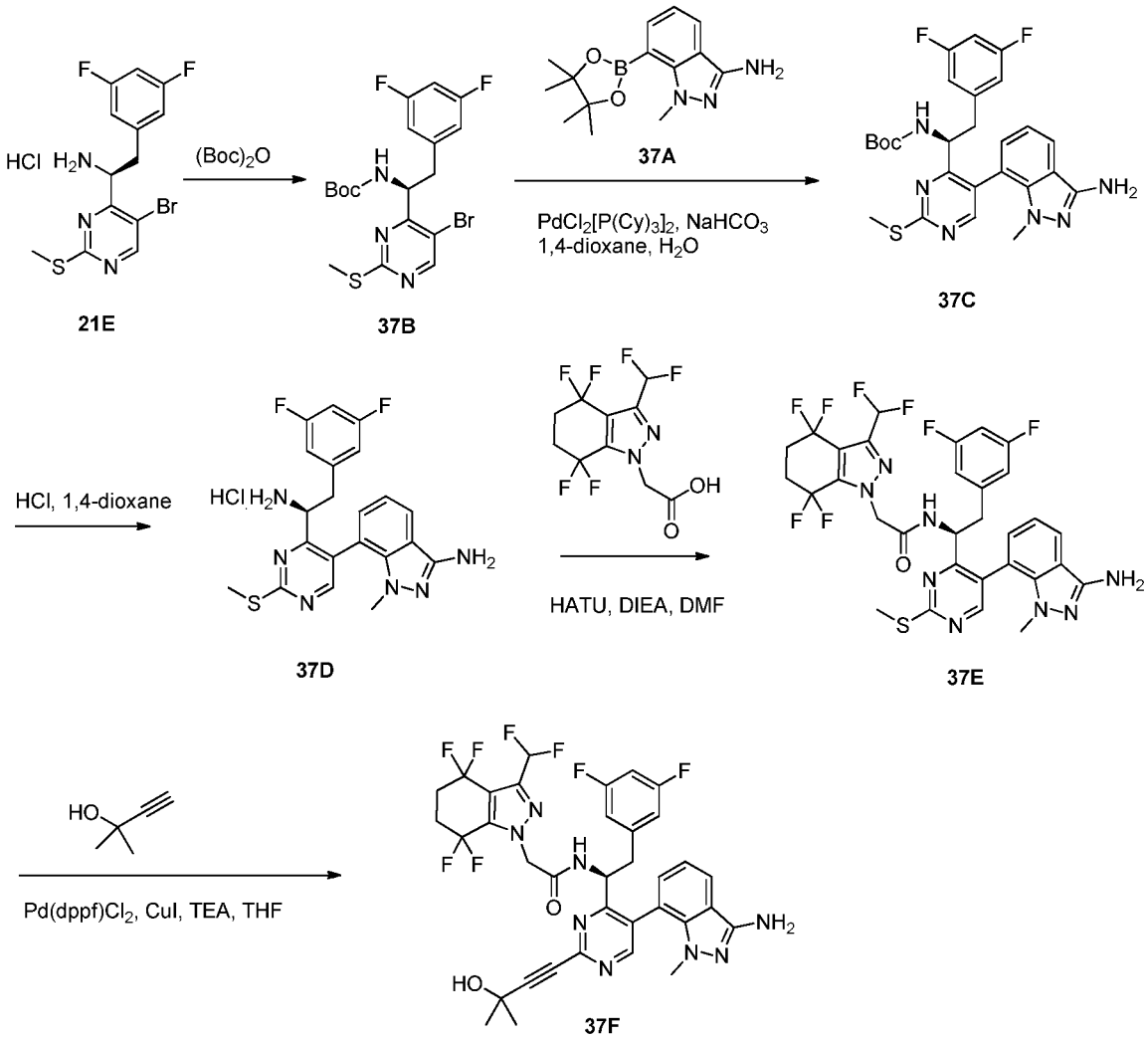


36C

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(3-(4-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)ethyl)acetamide (**36C**):

[0488] The title compound (**36C**) was prepared according to the method presented for the synthesis of **27G** in Example 27 utilizing **14B** and **36B**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.71 (s), 7.63 (s), 7.53 – 7.42 (m), 6.64 (s), 6.57 (s), 6.32 (s), 3.14 – 2.97 (m), 2.56 – 2.40 (m), 1.62 (s), 1.42 – 1.34 (m), 1.16 – 1.04 (m). MS (*m/z*) 715.1 $[M+H]^+$.

Example 37.



Synthesis of 1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-amine (**37A**):

[0489] The title compound (**37A**) was prepared according to the method presented for the synthesis of compound **39B** of Example 39 utilizing **33A**. MS (*m/z*) 274.2 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(5-bromo-2-(methylthio)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**37B**):

[0490] To compound **21E** (310 mg, 0.78 mmol) in dichloromethane (3 ml) was added triethylamine (217 μL, 1.56 mmol) and di-tert-butyldicarbonate (170 mg, 0.78 mmol). The mixture was stirred for one hour at ambient temperature then concentrated in vacuo.

[0491] The residue was purified by silica gel chromatography to afford the title compound (**37B**). MS (m/z) 459.86 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(5-(3-amino-1-methyl-1H-indazol-7-yl)-2-(methylthio)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**37C**):

[0492] The title compound (**37C**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **21G** of Example 21 utilizing compound **37B** and **37A**. MS (*m/z*) 526.81 $[M+H]^+$.

Synthesis of (S)-7-(4-(1-amino-2-(3,5-difluorophenyl)ethyl)-2-(methylthio)pyrimidin-5-yl)-1-methyl-1H-indazol-3-amine hydrochloride (**37D**):

[0493] Compound **37C** (78 mg, 0.15 mmol) was dissolved in 2 mL of 1,4-dioxane and cooled to 0 °C. To it was added 4N HCl/1,4-dioxane (2 mL). The reaction mixture was stirred at room temperature for 7 hours. The solvent was removed and dried to afford the title compound **37D** as a mixture of atropisomers. MS (m/z) 427.01 $[M+H]^+$.

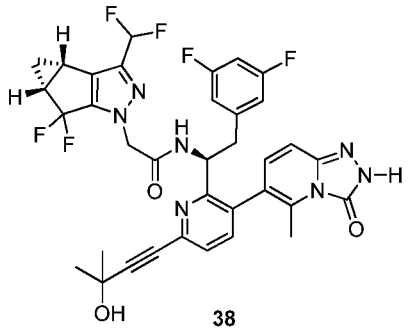
Synthesis of (S)-N-(1-(5-(3-amino-1-methyl-1H-indazol-7-yl)-2-(methylthio)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**37E**):

[0494] A mixture of 2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid (44 mg, 0.14 mmol), compound **37D** (69 mg, 0.15 mmol) and HATU (68 mg, 0.18 mmol) in 1.5 mL of DMF was cooled to 0 ℃. To it was added N,N-diisopropylethylamine (0.1 mL, 0.6 mmol). The reaction mixture was allowed to stir at 0 ℃ for 5 minutes then partitioned between EtOAc and 5% aqueous LiCl solution. The organic layer was separated, washed with brine and concentrated. The residue was purified by reverse phase HPLC) to afford the title product **37E** as a mixture of atropisomers. MS (*m/z*) 710.95 $[M+H]^+$.

Synthesis of (S)-N-(1-(5-(3-amino-1-methyl-1H-indazol-7-yl)-2-(3-hydroxy-3-methylbut-1-yn-1-yl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**37F**):

[0495] The title compound (**37F**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **21H** of Example 21 utilizing compound **37E** and 2-methylbut-3-yn-2-ol. ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.01 (d), 8.69 (d), 7.88 – 7.78 (m), 7.70 – 7.41 (m), 7.40 – 7.28 (m), 7.10 (dt), 6.96 – 6.52 (m), 6.35 (d), 5.41 – 5.23 (m), 5.15 – 5.05 (m), 5.04 – 4.91 (m), 3.45-3.47 (m), 3.20 (s), 3.13 – 2.83 (m), 2.62 – 2.35 (m), 1.62 (s). MS (*m/z*) 747.03 [M+H]+.

Example 38.

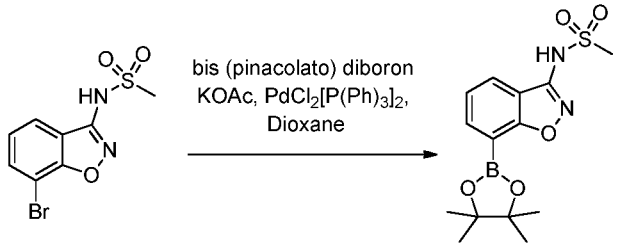


38

Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(5-methyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-6-yl)pyridin-2-yl)ethyl)acetamide (**38**):

[0496] The title compound (**38**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of **27G** in Example 27 utilizing **27F** and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. HPLC retention time 6.48 min and 6.58 min corresponding to each atropisomer (2-98% acetonitrile: water with 0.1% trifluoroacetic acid, 8.5 min gradient on a Phenomonex Kinetex C18 column 4.6 x 100 mm). MS (*m/z*) 710.1 $[M+H]^+$.

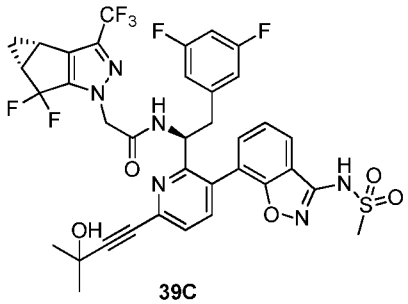
Example 39.



39A 39B

Synthesis of N-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]isoxazol-3-yl)methanesulfonamide (**39B**):

[0497] To **39A** (prepared similarly to **33B** of example 33 utilizing 7-bromobenzo[d]isoxazol-3-amine instead of 7-bromo-1-methyl-1H-indazol-3-amine) (87 mg, 0.3 mmol) in dioxane (3 mL) was added bis(pinacolato)diboron (107mg, 0.4 mmol), and $PdCl_2[P(Ph)_3]_2$ (21 mg, 0.03 mmol). The reaction mixture sealed and heated to 100 °C for 16h. The reaction was cooled to room temperature and telescoped to the next reaction. MS (*m/z*) 260.2 $[M+H]^+$.

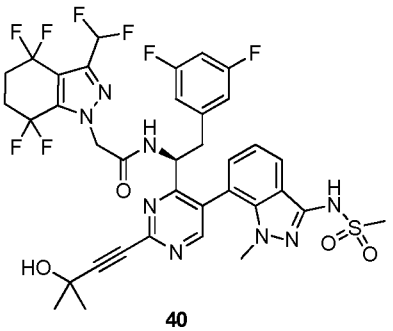


39C

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(3-(methylsulfonamido)benzo[d]isoxazol-7-yl)pyridin-2-yl)ethyl)acetamide (**39C**):

[0498] The title compound (**39C**) was prepared according to the method presented for the synthesis of compound **33F** of Example 33 utilizing **39B** and 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. MS (*m/z*) 791.1 $[M+H]^+$. HPLC retention time 7.25 min (2-98% acetonitrile: water with 0.1% trifluoroacetic acid, 8.5 min gradient on a Phenomonex Kinetex C18 column).

Example 40.

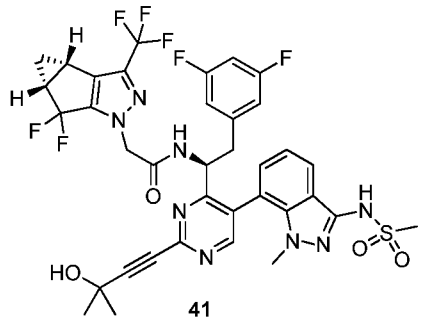


40

Synthesis of (S)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)-N-(2-(3,5-difluorophenyl)-1-(2-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyrimidin-4-yl)ethyl)acetamide (**40**):

[0499] The title compound (**40**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **37F** of Example 37 utilizing compound **37B** and N-(1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-yl)methanesulfonamide (compound **33C**). ^{1}H NMR (400 MHz, Methanol-d_4): δ 8.73 (d), 7.90 (ddd), 7.48-7.40 (m), 7.25 (dd), 7.18 (dd), 7.04 – 6.53 (m), 6.44 – 6.25 (m), 5.42-5.38 (m), 5.09 – 4.88 (m), 3.41 (s), 3.19 (s), 3.14-2.90 (m), 2.63 – 2.20 (m), 1.64 (d). MS (*m/z*) 824.90 $[M+H]^+$

Example 41

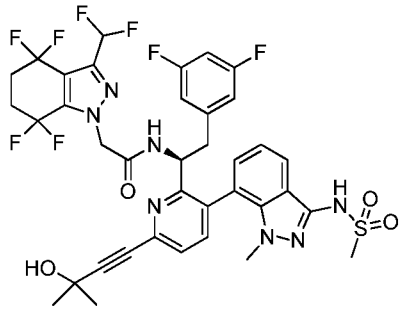


41

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(2-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyrimidin-4-yl)ethyl)acetamide (**41**):

[0500] The title compound (**41**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **23B** of Example 23 utilizing compound **22A** and N-(1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-yl)methanesulfonamide (**33C**). ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.12 – 8.90 (m), 8.73 (dd), 7.90 (dd), 7.42 (d), 7.24 (t), 7.17 (t), 6.87 – 6.68 (m), 6.61 (t), 6.37 (dd), 5.47-5.35 (m), 5.02 (q), 4.85 – 4.46 (m), 3.40 (d), 3.19 (d), 3.12 (dd), 3.07-2.83 (m), 2.62-2.33 (m) 1.64 (d), 1.48-1.31(m), 1.16-0.95 (m). MS (*m/z*) 804.85 $[M+H]^+$.

Example 42.



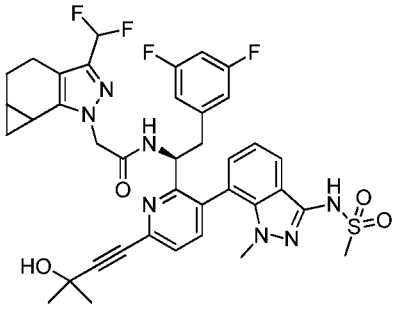
42

Synthesis of (S)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)-N-(2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)acetamide (**42**):

[0501] The title compound (**42**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **33F** of Example 33 utilizing 2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, cd_3od) δ 8.80 (d), 7.82 (d), 7.75 – 7.69 (m), 7.59 – 7.51 (m), 7.40-7.20 (m), 7.19-

7.05 (m), 6.80 (d), 6.60-6.52 (m), 6.30 (d), 5.08 – 4.97 (m), 4.90 – 4.71 (m), 3.34 (s), 3.25-3.00 (m), 2.90-2.75 (m), 2.76 – 2.64 (m), 2.25 – 2.00 (m, 5H), 1.64 (s). MS (*m/z*) 824.2 $[M+H]^+$.

Example 43.

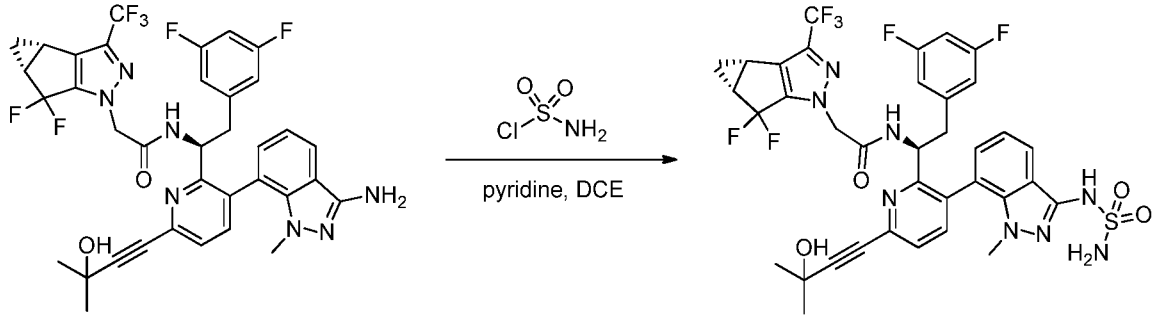


43

Synthesis of 2-(3-(difluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)acetamide (**43**):

[0502] The title compound (**43**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **33F** of Example 33 utilizing **20C** and 2-(3-(difluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetic acid. ^{1}H NMR (400 MHz, cd_3od) δ 7.80 (d), 7.45 (d), 7.51 (d), 7.25-7.20 (m, 1H), 6.80-6.52 (m), 6.45 (d), 5.35-5.25 (m), 5.08 – 4.97 (m), 4.90 – 4.71 (m), 3.34 (s), 3.25-3.02 (m), 2.98 – 2.64 (m,), 2.75-2.35 (m), 2.25 – 2.00 (m), 1.80 – 1.70 (m), 1.64 (d), 1.00 – 0.90 (m), 0.65 – 0.58 (m). MS (*m/z*) 764.2 $[M+H]^+$.

Example 44.

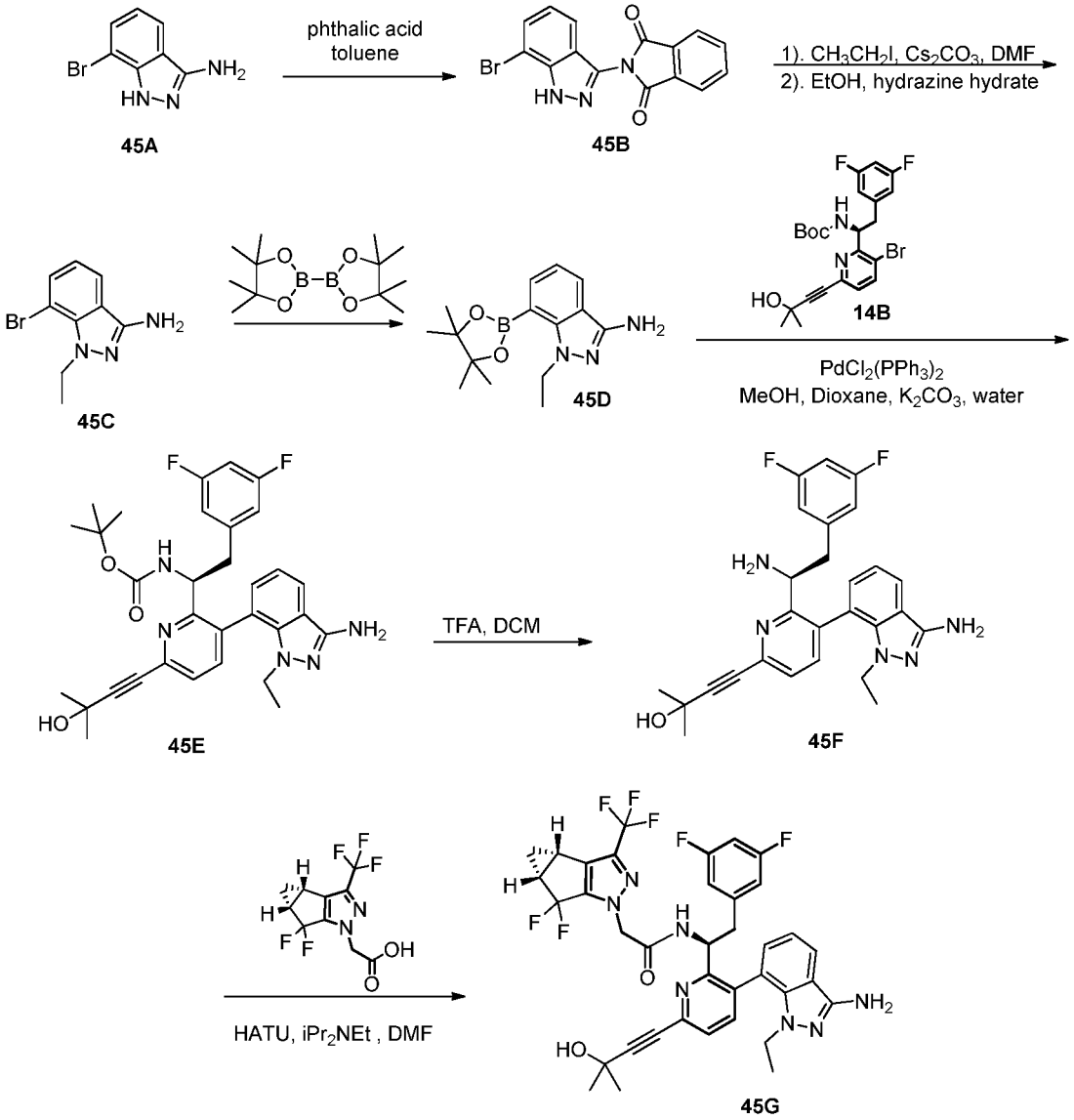


25 44

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-methyl-3-(sulfamoylamino)-1H-indazol-7-yl)pyridin-2-yl)ethyl)acetamide (**44**):

[0503] To a stirred solution of **25** (31 mg, 0.04 mmol) and pyridine (0.024 mL, 0.03 mmol) in dichloroethane (0.5 mL) was added a solution of sulfamoyl chloride (12 mg, 0.1 mmol) in dichloroethane (~0.2 mL). The reaction was heated at 60°C for 1h. Upon cooling, the reaction mixture was concentrated in vacuo, diluted with EtOAc and washed with water then 1 M HCl. The organic layer was dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by reverse phase HPLC to provide the title compound **44** as a mixture of atropisomers. ^{1}H NMR (400 MHz, cd_3od) δ 8.86 – 6.25 (m, 8H), 5.38 – 4.97 (m, 1H), 4.85 – 4.73 (m, 2H), 3.26 – 3.06 (m, 1H), 3.04 – 2.90 (m, 2H), 2.63 – 2.37 (m, 2H), 1.69 – 1.56 (m, 6H), 1.52 – 1.32 (m, 1H), 1.19 – 0.98 (m, 1H). MS (*m/z*) 805.1 $[M+H]^+$.

Example 45.



Synthesis of 2-(7-bromo-1H-indazol-3-yl)isoindoline-1,3-dione (**45B**):

[0504] To 7-bromo-1H-indazol-3-amine (**45A**, 1.2 g, 5.5 mmol) in toluene (30 mL) was added phthalic acid (990 mg, 6.0 mmol). The flask was fitted with a Dean-Stark trap and the reaction mixture was stirred for 12 hours at 180 °C. The reaction was allowed to cool, the solids were filtered off and used with no further purification to provide the title compound. MS (*m/z*) 343.1 $[M+H]^+$.

Synthesis of 7-bromo-1-ethyl-1H-indazol-3-amine (**45C**):

[0505] To **45B** (100 mg, 0.3 mmol) in DMF (2 mL) was added Cs_2CO_3 (95.2 mg, 0.3 mmol) and iodoethane (0.028 ml, 0.35 mmol). The reaction mixture was stirred for 10 minutes. The reaction mixture was diluted with EtOAc and brine, extracted 2X with EtOAc, organic layer dried over sodium sulfate, and concentrated. To the crude mixture was added EtOH (2 ml) and hydrazine hydrate (1 ml) the reaction mixture was stirred for 30 minutes. The mixture was concentrated and purified by flash column chromatography to provide the title compound. MS (*m/z*) 240.1 $[M+H]^+$.

Synthesis of 1-ethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-amine (**45D**):

[0506] To **45C** (80 mg, 0.3 mmol) in dioxane (5 mL) was added bis(pinacolato)diboron (84.6 mg, 0.3 mmol), potassium acetate (32.7 mg, 0.3 mmol), and $Pd(PCy_3)_2Cl_2$ (12.3 mg, 0.02 mmol). The reaction mixture was heated in the microwave for 30 minutes at 150 °C. The reaction was cooled and the solids were filtered off. The mixture was concentrated and purified by flash column chromatography to provide the title compound. MS (*m/z*) 288.2 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(3-(3-amino-1-ethyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**45E**):

[0507] To **45D** (40 mg, 0.1 mmol) in dioxane (4 mL) and MeOH (0.75 ml) was added **14B** (69 mg, 0.1 mmol), 2M K_2CO_3 (0.4 ml), LiCl (17.7 mg, 0.4 mmol) and $Pd(PPh_3)_2Cl_2$ (4.9 mg, 0.007 mmol). The reaction mixture was heated in the microwave for 30 minutes at 150 °C. The reaction was cooled, diluted with EtOAc and brine, and extracted 2X EtOAc. The organic layer was dried over sodium sulfate, concentrated and purified by flash column chromatography to provide the title compound as a mixture of atropisomers. MS (*m/z*) 576.0 $[M+H]^+$.

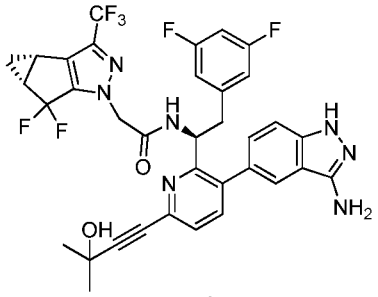
Synthesis of (S)-4-(5-(3-amino-1-ethyl-1H-indazol-7-yl)-6-(1-amino-2-(3,5-difluorophenyl)ethyl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (**45F**):

[0508] The title compound (**45F**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19F** of Example 19 utilizing **45E**. MS (m/z) 476.1 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(3-amino-1-ethyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**45G**):

[0509] The title compound (**45G**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **10A** of Example 10 utilizing **45F** and 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.67 (d), 7.87 – 7.75 (m), 7.71 (d), 7.59 – 7.50 (m), 7.26 – 7.19 (m), 7.18 – 7.12 (m), 7.12 – 7.04 (m), 6.76 – 6.63 (m), 6.60 (d), 6.47 – 6.41 (m), 6.27 (d), 5.11 – 5.01 (m), 4.81 (d), 4.72 (d), 3.67 – 3.55 (m), 3.51 – 3.43 (m), 3.39 – 3.24 (m), 3.15 – 3.10 (m), 3.09 – 2.84 (m), 2.56 – 2.40 (m), 1.64 (s), 1.45 – 1.33 (m), 1.31 – 1.25 (m), 1.14 – 1.03 (m), 0.87 (dt).MS (*m/z*) 740.2 $[M+H]^+$.

Example 46.

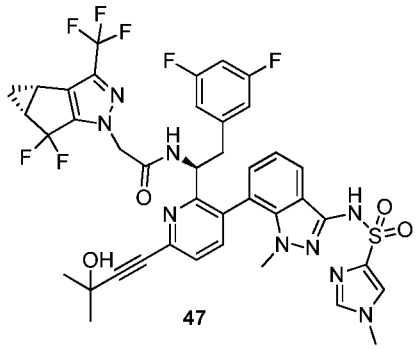


46

Synthesis of N-((S)-1-(3-(3-amino-1H-indazol-5-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**46**):

[0510] The title compound (**46**) was prepared according to the method presented for the synthesis of compound **33F** of Example 33 utilizing 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-amine and 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, cd_3od) δ 8.99 (d), 7.62 – 7.54 (m),7.51 – 7.40 (m), 7.33 (d), 6.72 – 6.62 (m), 6.29 – 6.22 (m), 5.53 – 5.43 (m,), 4.92 (d), 3.03 (d), 2.60 – 2.45 (m), 1.63 (s), 1.48 – 1.37 (m), 1.16 – 1.04 (m). MS (*m/z*) 712.1 $[M+H]^+$.

Example 47.

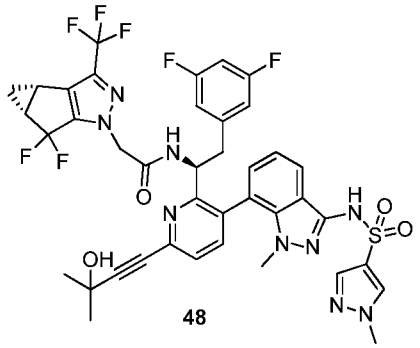


47

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-methyl-3-(1-methyl-1H-imidazole-4-sulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)acetamide (**47**):

[0511] To a solution of N-((S)-1-(3-(3-amino-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**25**, 10 mg, 0.014 mmol) in dichloromethane (0.2 mL) was added pyridine (6.6 μL, 0.083 mmol), followed by 1-methyl-1H-imidazole-4-sulfonyl chloride (3.7 mg, 0.021 mmol). After stirring for 1 h, the reaction mixture was concentrated and purified by reverse phase HPLC to provide the title product as a mixture of atropisomers. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.75 (dd), 7.71 – 7.63 (m), 7.57 – 7.48 (m), 7.30 (s), 7.14 – 7.03 (m), 6.79 – 6.70 (m), 6.66 – 6.55 (m), 6.38 – 6.26 (m), 5.25 (dd), 4.96 (dd), 4.87 – 4.72 (m), 3.67 (s), 3.46 (s), 3.27 (s), 3.25 – 3.18 (m), 3.09 – 3.02 (m), 3.00 – 2.87 (m), 2.58 – 2.43 (m), 1.64 (s), 1.64 (s), 1.50 – 1.37 (m), 1.16 – 1.06 (m). MS (*m/z*) 870.10 $[M+H]^+$.

Example 48.



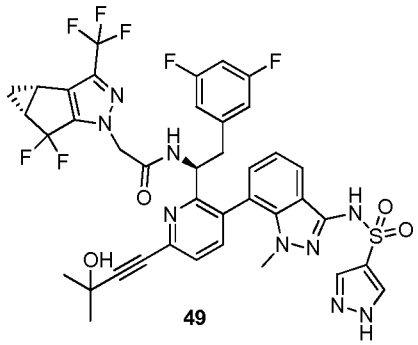
48

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-

3-methylbut-1-yn-1-yl)-3-(1-methyl-3-(1-methyl-1H-pyrazole-4-sulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)acetamide (**48**):

[0512] The title compound (**48**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound (**47**) of Example 47 utilizing 1-methyl-1H-pyrazole-4-sulfonyl chloride. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.95 (s), 7.77 – 7.66 (m), 7.61 (s), 7.57 – 7.48 (m), 7.24 – 7.18 (m), 7.17 – 7.10 (m), 7.07 (dd), 6.78 – 6.68 (m), 6.63 (dd), 6.60 – 6.50 (m), 6.40 – 6.26 (m), 5.26 (dd), 5.02 (dd), 4.88 – 4.71 (m), 3.83 (s), 3.60 (s), 3.29 (s), 3.27 – 3.21 (m), 3.09 – 3.01 (m), 3.00 – 2.87 (m), 2.58 – 2.39 (m), 1.64 (s), 1.49 – 1.36 (m), 1.16 – 1.04 (m). MS (*m/z*) 870.03 $[M+H]^+$.

Example 49.

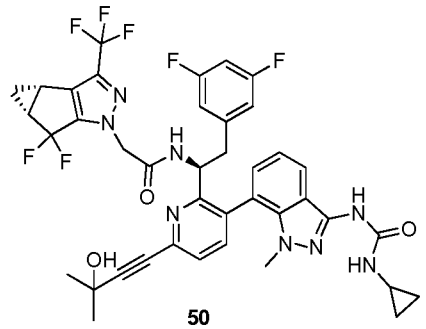


49

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-methyl-3-(1H-pyrazole-4-sulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)acetamide (**49**):

[0513] The title compound (**49**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound (**47**) of Example 47 utilizing 1H-pyrazole-4-sulfonyl chloride. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.74 (d), 8.60 (q), 7.91 (s), 7.83 (s), 7.76 – 7.63 (m), 7.57 – 7.47 (m), 7.21 (dd), 7.13 (dd), 7.03 (dd), 6.79 – 6.68 (m), 6.61 – 6.50 (m), 6.46 (dd), 6.38 – 6.25 (m), 5.34 – 5.22 (m), 5.05 – 4.94 (m), 4.87 – 4.78 (m), 3.28 (s), 3.26 – 3.16 (m), 3.15 – 3.07 (m), 3.00 – 2.90 (m), 2.58 – 2.43 (m), 1.64 (s), 1.64 – 1.64 (m), 1.49 – 1.37 (m), 1.17 – 1.07 (m). MS (*m/z*) 856.03 $[M+H]^+$.

Example 50.

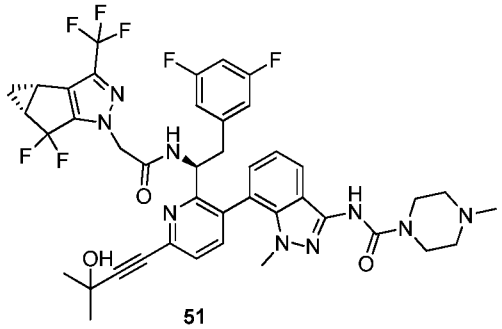


50

Synthesis of N-((S)-1-(3-(3-(3-cyclopropylureido)-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**50**):

[0514] To a solution of N-((S)-1-(3-(3-amino-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**25**, 10 mg, 0.014 mmol) and DIPEA (3.5 µL, 0.021 mmol) in dichloromethane (0.1 mL) was added triphosgene (4.5 mg, 0.015 mmol). After stirring for 1 minute cyclopropylamine (3.5 µL, 0.055 mmol) was added. After stirring for 15 minutes, the reaction mixture was concentrated and purified by reverse phase HPLC to provide the title product as a mixture of atropisomers. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.87 (m), 7.68 (dd), 7.53 (dd), 7.23 (dd), 7.13 (dd), 7.02 (dd), 6.77 – 6.68 (m), 6.63 – 6.54 (m), 6.49 (dd), 6.38 – 6.32 (m), 6.32 – 6.25 (m), 5.25 (dd), 5.01 (t), 4.79 (t), 3.26 (s), 3.25 – 3.19 (m), 3.14 – 3.04 (m), 3.00 – 2.89 (m), 2.73 – 2.64 (m), 2.56 – 2.41 (m), 1.64 (s), 1.64 (s), 1.49 – 1.36 (m), 1.17 – 1.04 (m), 0.81 – 0.71 (m), 0.61 – 0.51 (m). MS (*m/z*) 809.12 $[M+H]^+$.

Example 51.



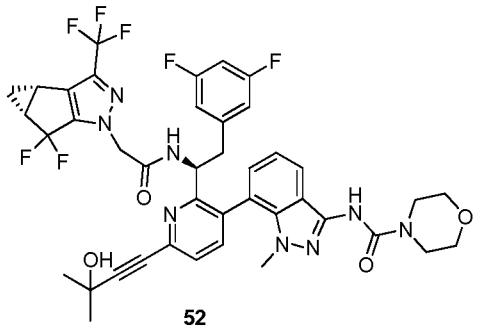
51

Synthesis of N-(7-(2-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-

hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)-4-methylpiperazine-1-carboxamide (**51**):

[0515] The title compound (**51**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound (**50**) of Example 50 utilizing 1-methylpiperazine. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.79 – 7.66 (m), 7.54 (dd), 7.23 (dd), 7.16 (dd), 7.09 (dd), 6.78 – 6.68 (m), 6.66 – 6.57 (m), 6.43 – 6.36 (m), 6.36 – 6.28 (m), 5.29 (dd), 5.02 (dd), 4.85 – 4.71 (m), 4.39 (s), 3.67 – 3.45 (m), 3.27 – 3.22 (m), 3.14 – 3.06 (m), 3.03 – 2.89 (m), 2.58 – 2.41 (m), 1.65 (s), 1.64 (s), 1.49 – 1.36 (m), 1.17 – 1.10 (m), 1.10 – 1.04 (m). MS (*m/z*) 852.11 $[M+H]^+$.

Example 52.

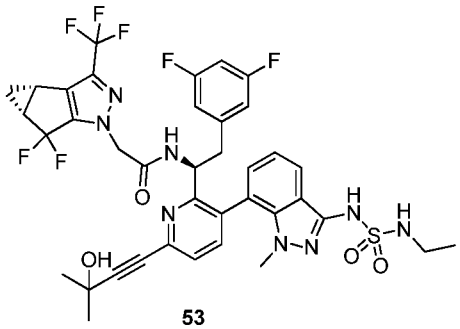


52

Synthesis of N-(7-(2-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)morpholine-4-carboxamide (**52**):

[0516] The title compound (**52**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound (**50**) of Example 50 utilizing morpholine. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.77 – 7.66 (m), 7.54 (dd), 7.22 (dd), 7.15 (dd), 7.08 (dd), 6.77 – 6.69 (m), 6.66 – 6.60 (m), 6.58 (dd), 6.42 – 6.36 (m), 6.36 – 6.29 (m), 5.32 (dd), 5.03 (dd), 4.85 – 4.79 (m), 4.79 – 4.71 (m), 3.74 (dd), 3.61 – 3.53 (m), 3.27 – 3.20 (m), 3.15 – 3.07 (m), 3.02 (s), 3.00 – 2.90 (m), 2.58 – 2.41 (m), 1.65 (s), 1.64 (s), 1.49 – 1.35 (m), 1.16 – 1.10 (m), 1.10 – 1.04 (m). MS (*m/z*) 839.13 $[M+H]^+$.

Example 53.

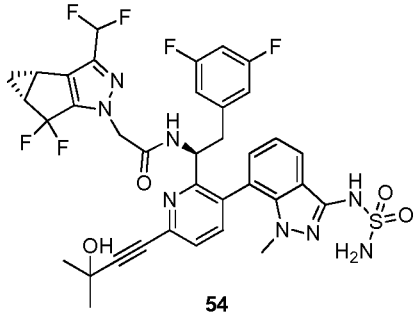


53

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(3-(3-((N-ethylsulfamoyl)amino)-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)ethyl)acetamide (**53**):

[0517] The title compound (**53**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound (**44**) of Example 44 utilizing ethyl sulfamoylchloride. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.84 – 8.74 (m), 7.95 – 7.85 (m), 7.69 (dd), 7.54 (dd), 7.23 (dd), 7.15 (dd), 7.09 (dd), 6.79 – 6.69 (m), 6.66 – 6.56 (m), 6.39 – 6.34 (m), 6.34 – 6.26 (m), 5.35 – 5.25 (m), 5.07 – 4.98 (m), 4.86 – 4.71 (m), 3.23 (m), 3.15 – 3.02 (m), 3.00 (s), 2.98 – 2.88 (m), 2.58 – 2.40 (m), 1.65 (s), 1.64 (s), 1.49 – 1.36 (m), 1.12 (t), 1.10 – 1.02 (m). MS (*m/z*) 833.14 $[M+H]^+$.

Example 54.



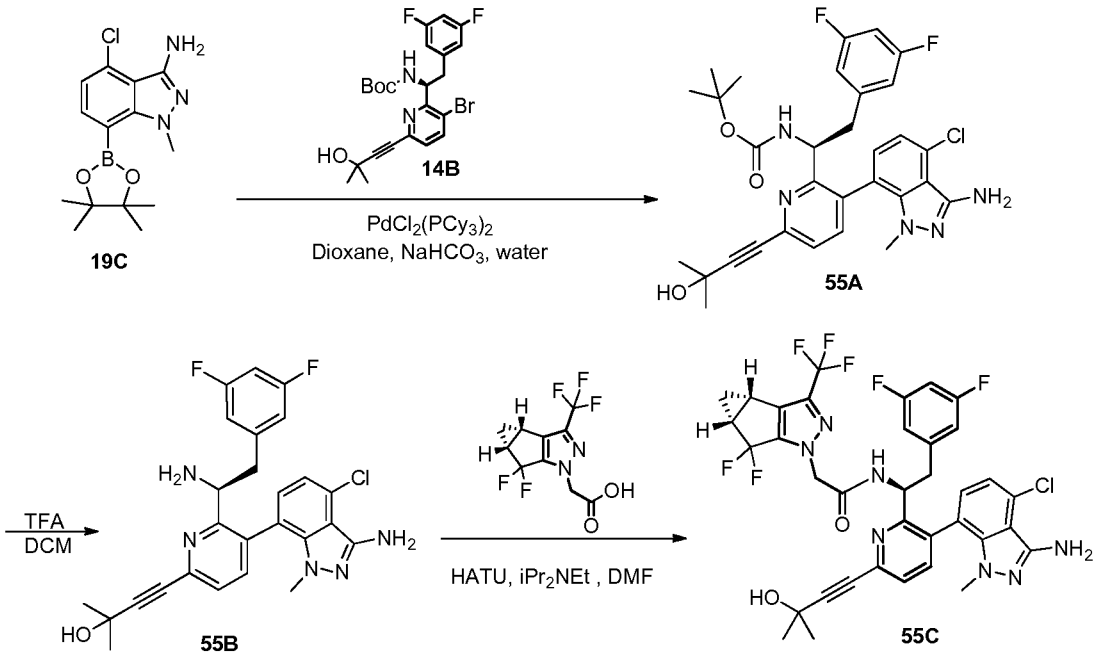
54

Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-methyl-3-(sulfamoylamino)-1H-indazol-7-yl)pyridin-2-yl)ethyl)acetamide (**54**):

[0518] The title compound (**54**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **44** of Example 44 utilizing and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, cd_3od) δ 8.75 (d), 8.01 – 7.93 (m), 7.72 – 7.63

(m), 7.53 (dd), 7.28 – 7.05 (m), 6.87 – 6.51 (m), 6.34 (m), 5.35-5.25 (m), 5.07 – 4.96 (m), 4.80 – 4.65 (m), 3.33 (s), 3.24 – 2.88 (m), 2.53 – 2.38 (m), 1.64 (d), 1.45 – 1.32 (m), 1.13 – 0.99 (m). MS (*m/z*) 787.1 $[M+H]^+$.

Example 55.



Synthesis of (S)-tert-butyl (1-(3-(3-amino-4-chloro-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**55A**):

[0519] To **19C** (1.5 g, 4.8 mmol) in dioxane (100 mL) was added **14B** (1.6 g, 3.2 mmol), 1N sodium bicarbonate (8.4 ml, 8.4 mmol), and $PdCl_2(PCy_3)_2$ (238 mg, 0.3 mmol). The reaction mixture was stirred for 30 minutes at 125 ^oC. The reaction was cooled, diluted with EtOAc and brine. The mixture was extracted 2X with EtOAc, the organic layer was dried over sodium sulfate, was concentrated and purified by flash column chromatography to provide the title compound as a mixture of atropisomers. MS (*m/z*) 596.7 $[M+H]^+$.

Synthesis of (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(3-amino-4-chloro-1-methyl-1H-indazol-7-yl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (**55B**):

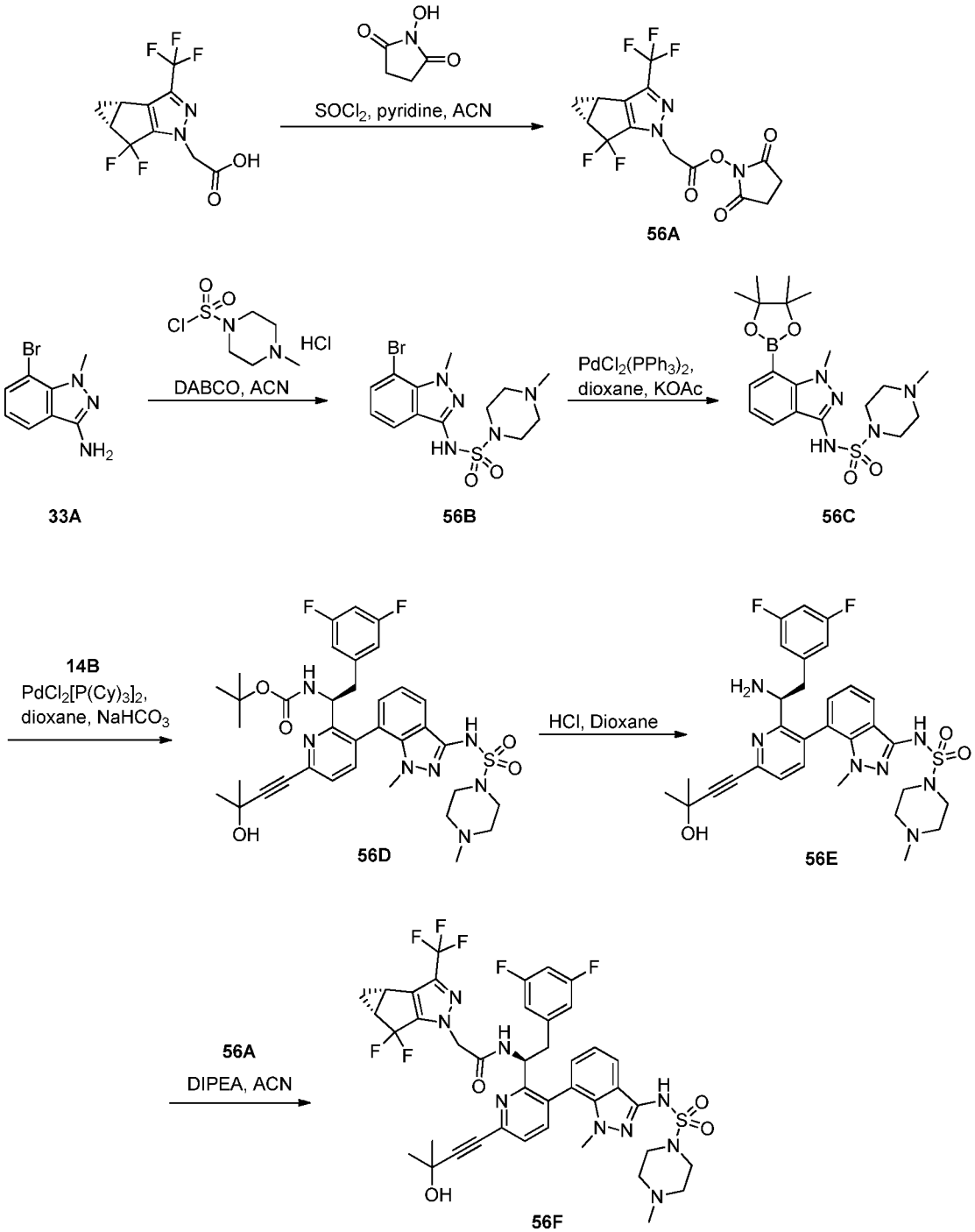
[0520] The title compound (**55B**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19F** of Example 19 utilizing **55A**. MS (m/z) 496.5 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(3-amino-4-chloro-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-

(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**55C**):

[0521] The title compound (**55C**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **10A** of Example 10 utilizing **55B** and 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.83 – 8.69 (m), 7.65 (d), 7.53 (d), 7.13 – 7.06 (m), 7.07 – 6.99 (m), 6.96 (d), 6.81 – 6.71 (m), 6.67 – 6.56 (m), 6.48 – 6.39 (m), 6.41 – 6.30 (m), 5.30 – 5.19 (m), 5.07 – 4.96 (m), 4.83 – 4.71 (m), 3.27 – 3.22 (m), 3.17 (s), 3.10 (s), 3.04 – 2.91 (m), 2.81 (s), 2.61 – 2.39 (m), 1.63 (s), 1.49 – 1.37 (m), 1.37 – 1.24 (m), 1.23 – 1.00 (m). MS (*m/z*) 760.3 $[M+H]^+$.

Example 56.



Synthesis of 2,5-dioxopyrrolidin-1-yl 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**56A**):

[0522] To a stirring solution of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (1.00 g, 3.54 mmol), N-hydroxysuccinimide (0.61 g, 5.32 mmol), and pyridine (0.968 mL, 12.1 mmol) was added dropwise at -5 ºC thionyl chloride (0.439 mL, 6.02 mmol). After stirring at -5 ºC for 20 min,

2.0M aqueous NaCl (10mL) was added and the product was extracted with two portions of ethyl acetate (12 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.88 – 5.63 (m, 4H), 2.77 – 2.55 (m, 2H), 1.56 – 1.31 (m, 2H), 1.12 – 0.98 (m, 2H).

Synthesis of N-(7-bromo-1-methyl-1H-indazol-3-yl)-4-methylpiperazine-1-sulfonamide (**56B**):

[0523] To a stirring solution of 7-bromo-1-methyl-1H-indazol-3-amine (**33A,** 250 mg, 1.11 mmol) and DABCO (310 mg, 2.77 mmol) in acetonitrile was added 4-methylpiperazine-1-sulfonyl chloride HCl (650 mg, 2.77 mmol). After stirring at 50 ºC for 3 h, the reaction was concentrated, diluted with water and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to give the title compound. MS (*m/z*) 387.97 $[M+H]^+$.

Synthesis of 4-methyl-N-(1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-yl)piperazine-1-sulfonamide (**56C**):

[0524] The title compound (**56C**) was prepared according to the method presented for the synthesis of compound (**19D)** of Example 19 utilizing N-(7-bromo-1-methyl-1H-indazol-3-yl)-4-methylpiperazine-1-sulfonamide (**56B**). MS (*m/z*) 436.18 $[M+H]^+$.

Synthesis of (S)-tert-butyl (2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-methyl-3-(4-methylpiperazine-1-sulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)carbamate (**56D**):

[0525] The title compound (**56D**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound (**19E)** of Example 19 utilizing 4-methyl-N-(1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-yl)piperazine-1-sulfonamide (**56C**).

Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)-4-methylpiperazine-1-sulfonamide (**56E**):

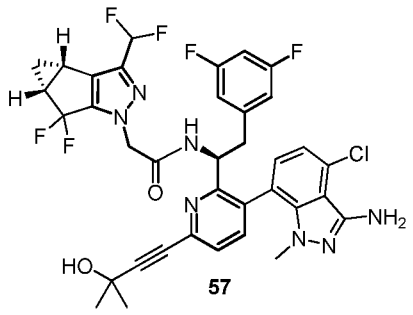
[0526] The title compound (**56E**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound (**14C**) of Example 14 utilizing (S)-tert-butyl (2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-methyl-3-(4-methylpiperazine-1-sulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)carbamate (**56D)**. The resulting crude product was basified to pH~8 with 1M aqueous $NaHCO_3$ and extracted with

ethyl acetate. The organic layer was dried over Na_2SO_4, filtered, concentrated *in vacuo*, and taken to the next step without further purification.

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-methyl-3-(4-methylpiperazine-1-sulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)acetamide (**56F**):

[0527] To a solution of crude (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)-4-methylpiperazine-1-sulfonamide (**56E**, 62.9 mg, 0.101 mmol assuming 100% purity) and DIPEA (17.5 µL, 0.101 mmol) in acetonitrile (2 mL) was 2,5-dioxopyrrolidin-1-yl 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**56A**, 38.3 mg, 0.101 mmol). After stirring for 1 h, the reaction mixture was filtered and purified by reverse phase HPLC to provide the title product as a mixture of atropisomers. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.01 (dd), 7.87 – 7.77 (m), 7.73 – 7.52 (m), 7.28 – 7.15 (m), 6.95 (dd), 6.76 – 6.61 (m), 6.46 – 6.41 (m), 6.19 – 6.11 (m), 5.24 (dd), 5.03 – 4.90 (m), 4.78 (d), 3.91 – 3.67 (m), 3.36 (s), 3.13 (dq), 3.00 (s), 2.94 – 2.87 (m), 2.75 (dd), 2.70 (s), 2.60 – 2.45 (m), 1.65 (s), 1.64 (s), 1.49 – 1.38 (m), 1.15 – 0.94 (m). MS (*m/z*) 888.35 $[M+H]^+$.

Example 57.



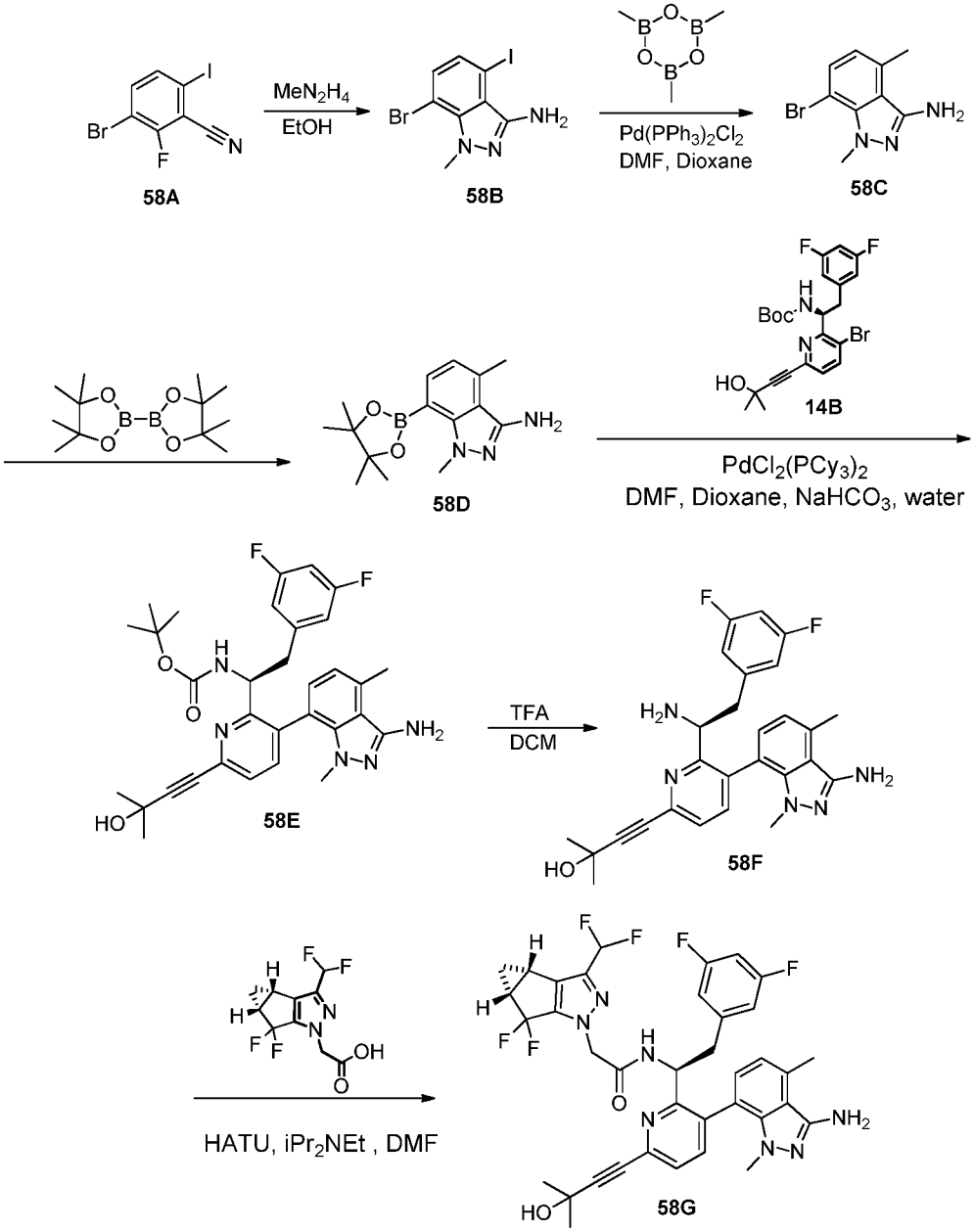
57

Synthesis of N-((S)-1-(3-(3-amino-4-chloro-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**57**):

[0528] The title compound (**57**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **10A** of Example 10 utilizing **55B** and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ

8.02 (s), 7.54 – 7.37 (m), 7.10 (d), 7.07 – 6.99 (m), 6.75 (d), 6.72 (t), 6.67 – 6.56 (m), 6.51 – 6.44 (m), 6.25 – 6.13 (m), 6.02 (d), 5.56 (q), 5.01 (td), 4.75 – 4.69 (m), 3.08 (s), 2.98 – 2.86 (m), 2.80 (s), 2.55 – 2.39 (m), 1.71 (s), 1.42 (q), 1.22 – 1.14 (m). MS (*m/z*) 742.8 $[M+H]^+$.

Example 58.



Synthesis of 7-bromo-4-iodo-1-methyl-1H-indazol-3-amine (**58B**):

[0529] The title compound (**58B**) was prepared according to the method presented for the synthesis of compound **19B** of Example 19 utilizing **58A**. MS (m/z) 352.4 $[M+H]^+$.

Synthesis of 7-bromo-1,4-dimethyl-1H-indazol-3-amine (**58C**):

[0530] To **58B** (3.0 g, 8.5 mmol) in dioxane (10 mL) and DMF (10 ml) was added Trimethylboroxine (4.8 ml, 34.1 mmol), 2M K_2CO_3 in water (8.5 ml), and $Pd(PPh_3)_2Cl_2$ (600 mg, 0.8 mmol). The reaction mixture was stirred for 5 hours at 160 °C. The reaction was cooled, diluted with EtOAc and brine. The mixture was extracted 2X with EtOAc, the organic layer was dried over sodium sulfate, concentrated and purified by flash column chromatography to provide the title compound. MS (*m/z*) 240.1 $[M+H]^+$.

Synthesis of 1,4-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-amine (**58D**):

[0531] The title compound (**58D**) was prepared according to the method presented for the synthesis of compound **19C** of Example 19 utilizing **58C**. MS (m/z) 288.2 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(3-(3-amino-1,4-dimethyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**58E**):

[0532] The title compound (**58E**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19E** of Example 19 utilizing **58D**. MS (*m/z*) 576.2 $[M+H]^+$.

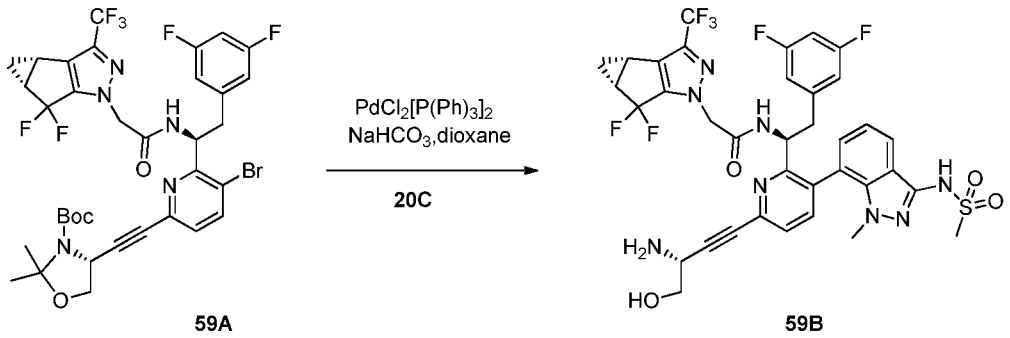
Synthesis of (S)-4-(5-(3-amino-1,4-dimethyl-1H-indazol-7-yl)-6-(1-amino-2-(3,5-difluorophenyl)ethyl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (**58F**):

[0533] The title compound (**58F**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19F** of Example 19 utilizing **58E**. MS (m/z) 476.1 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(3-amino-1,4-dimethyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**58G**):

[0534] The title compound (**58G**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **10A** of Example 10 utilizing **58F** and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^1H NMR (Methanol-d_4) δ: 8.68 – 8.57 (m), 7.69 – 7.45 (m), 7.06 (d), 6.85 (d), 6.80 (d), 6.76 – 6.66 (m), 6.66 – 6.53 (m), 6.45 (d), 6.38 (d), 6.31 (d), 5.26 (s), 5.08 – 4.98 (m), 4.73 (d), 3.27 – 3.19 (m), 3.16 (s), 3.06 (dd), 2.91 (dd), 2.84 (s), 2.74 – 2.66 (m), 2.53 – 2.38 (m), 1.64 (d), 1.43 – 1.24 (m), 1.12 – 0.98 (m). MS (*m/z*) 722.2 $[M+H]^+$.

Example 59.



59A 59B

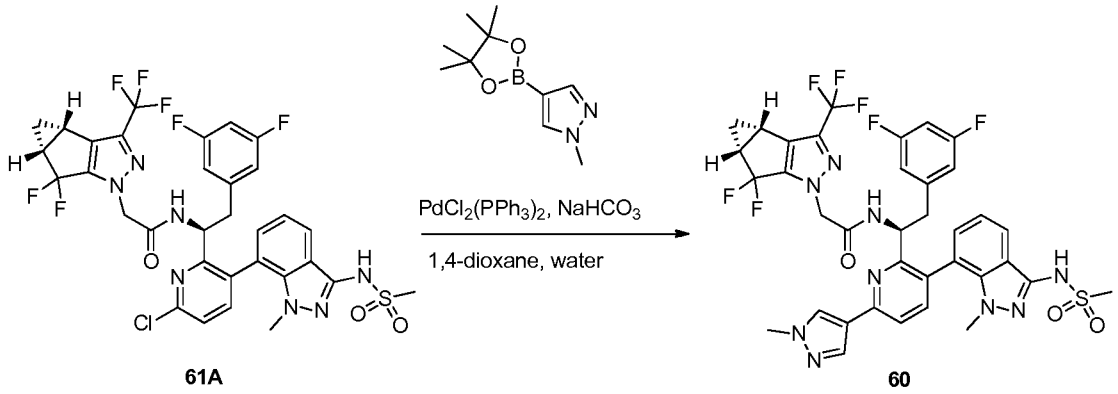
Synthesis of (R)-tert-butyl 4-((5-bromo-6-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-2-yl)ethynyl)-2,2-dimethyloxazolidine-3-carboxylate (**59A**):

[0535] The title compound was prepared similarly to compound **14D** in example 14 utilizing (R)-tert-butyl 4-ethynyl-2,2-dimethyloxazolidine-3-carboxylate instead of 2-methylbut-3-yn-2-ol. MS (*m/z*) 799 $[M-H]^-$.

Synthesis of N-((S)-1-(6-((R)-3-amino-4-hydroxybut-1-yn-1-yl)-3-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**59B**):

[0536] To a solution of **59A** (110 mg, 0.13 mmol) in dioxane (3 mL) was added **20C** (67 mg, 0.19 mmol), sodium bicarbonate (1M, 0.41 mL) followed by $PdCl_2[P(Ph)_3]_2$ (4.8 mg, 0.06 mmol). The reaction was sealed and heated in a microwave reactor for 20 min at 150°C. Upon cooling, the reaction mixture was first diluted with EtOAc and washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered and concentrated. The crude material purified by reverse phase HPLC. Fractions containing the product were pooled and treated with neat TFA to give the title compound **59B** as a mixture of atropisomers. ^1H NMR (400 MHz, cd_3od) δ 7.89 – 7.73 (m), 7.69 – 7.60 (m), 7.32-7.27 (m), 7.25-7.15 (m), 7.10 -7.07 (m), 6.80-6.70 (m), 6.69 –6.47 (m), 6.50 (d), 6.40 – 6.28 (m,), 5.32-5.25 (m), 5.05 – 4.96 (m), 4.80 – 4.72 (d), 4.52 – 4.44 (m), 4.09 – 3.98 (m), 3.94 – 3.84 (m), 3.21 – 3.08 (m), 3.05 – 2.89 (m), 2.59 – 2.37 (m), 1.46 – 1.35 (m), 1.11 (s), 1.04 (s). MS (*m/z*) 805.1 $[M+H]^+$.

Example 60.

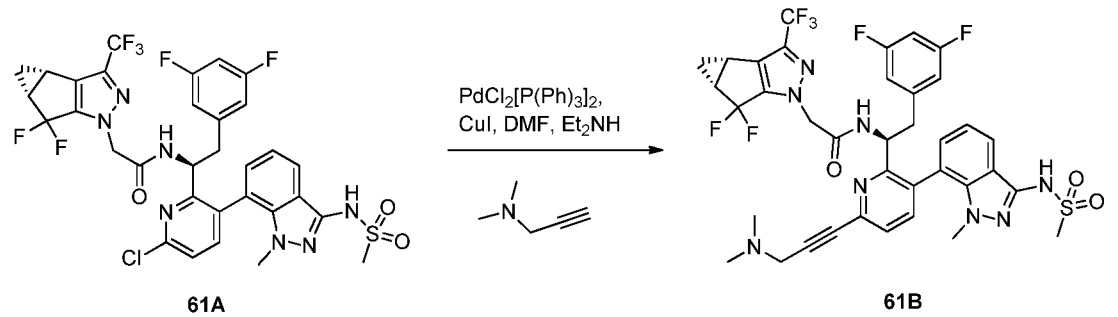


61A 60

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(1-methyl-1H-pyrazol-4-yl)-3-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)acetamide (**60**):

[0537] In a microwave tube were charged with compound **61A** (20 mg, 0.026 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (11 mg, 0.053 mmol) and $PdCl_2[PPh_3]_2$ (2 mg, 0.003 mmol). To the mixture was added 0.5 mL of 1,4-dioxane and 0.1 mL of sodium bicarbonate aqueous solution (1M). The mixture was heated to 120 °C for 4 minutes in a microwave synthesizer. After cooled to room temperature, it was partitioned between EtOAc and water. The organic layer was separated and washed with brine, then dried over $MgSO_4$, filtered and concentrated. The residue was purified by reverse phase HPLC to afford the title compound **60** as a mixture of atropisomers. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.43 – 8.29 (m), 8.28 – 8.09 (m), 7.91 – 7.72 (m), 7.76 – 7.58 (m), 7.15 – 7.00 (m), 6.82 – 6.68 (m), 6.53 (dd), 6.36 – 6.14 (m), 5.39 – 5.18 (m), 5.08 – 4.91 (m), 4.84 (d), 4.02 (d), 3.38 (s), 3.23 – 3.14 (m), 3.14 (s), 3.01 (d), 2.93 (dd), 2.63 – 2.30 (m), 1.50 – 1.26 (m), 1.17 – 0.79 (m). MS (*m/z*): 802.16 $[M+H]^+$

Example 61.



61A 61B

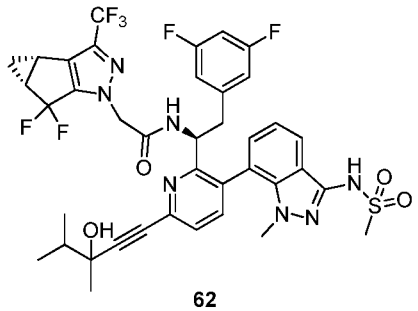
Synthesis of N-((S)-1-(6-chloro-3-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**61A**).

[0538] The title compound (**61A**) was prepared according to the method presented for the synthesis of compound **157F** of Example 157 utilizing N-(1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-yl)methanesulfonamide (**33C**) instead of **19D**. MS (m/z) 756.1 $[M+H]^+$.

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-(dimethylamino)prop-1-yn-1-yl)-3-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)acetamide (**61B**):

[0539] To the reaction vial containing **61A** (20 mg, 0.026 mmol) in DMF (0.2 mL) was added N,N-dimethylprop-2-yn-1-amine (11 mg, 0.13 mmol), $PdCl_2[P(Ph)_3]_2$ (1.87 mg, 0.003 mmol), and diethylamine (0.02 mL, 0.26 mmol). The reaction mixture was flushed with argon gas for 5 min then sealed and heated in a microwave reactor to 125°C for 15 min. Upon cooling, the reaction mixture was filtered and purified by reverse phase HPLC to provide the title product as a mixture of atropisomers. ^{1}H NMR δ 8.70 (m), 7.90 – 7.76 (m), 7.70 (d), 7.16 (m), 6.75 (tt), 6.57 (dd), 6.41 – 6.28 (m), 5.35-5.25 (m), 5.08 – 4.97 (m), 4.82 – 4.68 (m), 4.47 (d), 3.30 – 3.06 (m), 3.05 – 2.88 (m), 2.54 – 2.43 (m), 1.48 – 1.35 (m), 1.15-1.11 (m), 1.09 – 1.00 (m). MS (m/z) 803.2 $[M+H]^+$.

Example 62.

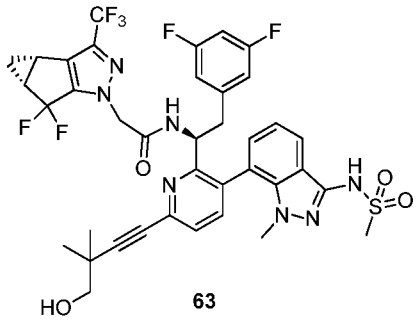


62

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((1S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3,4-dimethylpent-1-yn-1-yl)-3-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)acetamide (**62**):

[0540] The title compound (**62**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **61** of Example 61 utilizing 3,4-dimethylpent-1-yn-3-ol. ^{1}H NMR (400 MHz, cd_3od) δ 8.73 (m), 7.83-7.79 (m), 7.75-7.70 (m), 7.60-7.54 (m), 7.277.12 (m), 7.05 (t), 6.65 (t), 6.61 (t), 6.52 (t), 6.35-6.21 (m), 5.35-5.21 (m), 5.06 – 4.97 (m), 4.85 – 4.70 (m), 3.34 (s), 3.20 – 3.08 (m), 3.01 – 2.88 (m), 2.56 – 2.38 (m), 2.01 – 1.89 (m), 1.60 – 1.54 (d), 1.46 – 1.34 (m), 1.21 – 1.09 (m), 1.08 – 1.03 (m). MS (m/z) 832.1 $[M+H]^+$.

Example 63.

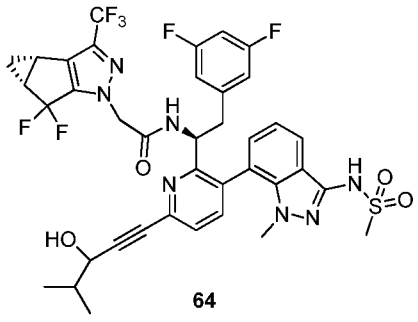


63

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(4-hydroxy-3,3-dimethylbut-1-yn-1-yl)-3-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)acetamide (**63**):

[0541] The title compound (**63**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **61** of Example 61 utilizing 2,2-dimethylbut-3-yn-1-ol. ^{1}H NMR (400 MHz, cd_3od) δ 8.65 (d), 7.83 (m), 7.66 (dd), 7.51 (dd), 7.08 (dd), 6.73 (tt), 6.50 (dt), 6.38 – 6.26 (m), 5.35-5.25 (m), 4.98 (t), 4.85 – 4.71 (m), 3.57 (s), 3.33 (s), 3.15 (d), 3.04 – 2.87 (m), 2.54 – 2.43 (m), 1.36 (s), 1.12 – 1.02 (m). MS (m/z) 818.2 $[M+H]^+$.

Example 64.



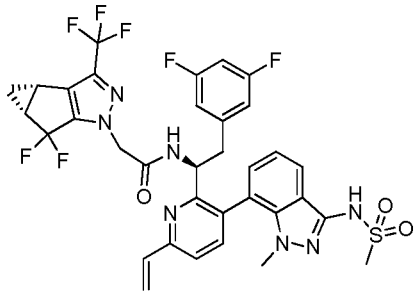
64

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((1S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-

4-methylpent-1-yn-1-yl)-3-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)acetamide (**64**):

[0542] The title compound (**64**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **61** of Example 61 utilizing 4-methylpent-1-yn-3-ol. ^{1}H NMR (400 MHz, cd_3od) δ 8.74 (d), 8.67 (d), 7.88 – 7.79 (m), 7.75 – 7.66 (m), 7.60 – 7.50 (m), 7.14 – 7.05 (m), 6.78 – 6.68 (m), 6.53 (ddt), 6.41 – 6.29 (m),5.31-5.25 (m), 5.06 – 4.95 (m), 4.78 (d), 4.45 – 4.38 (m), 3.34 (s), 3.15 (d), 3.03 – 2.88 (m), 2.55 – 2.43 (m), 2.06 – 1.91 (m), 1.39 (q), 1.18 – 1.10 (m), 1.07 (d). MS (m/z) 818.1 [M+H]+.

Example 65.



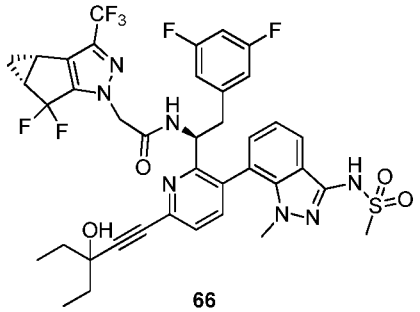
65

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(3-(1-methyl-3-(1-methyl-1H-imidazole-4-sulfonamido)-1H-indazol-7-yl)-6-vinylpyridin-2-yl)ethyl)acetamide (**65**):

[0543] Argon was bubbled through a solution of N-((S)-1-(6-chloro-3-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**61A**, 100 mg, 0.13 mmol), potassium vinyltrifluoroborate (35.4 mg, 0.26 mmol), dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (10.8 mg, 0.01 mmol), and triethylamine (0.06 ml, 0.43 mmol) in EtOH (2.6 ml) for 5 mins. The reaction was heated in a microwave reactor at 150 ºC for 20 mins. The product was solid loaded onto silica and purified by silica gel chromatography followed by re-purification by reverse phase HPLC to provide the title product as a mixture of atropisomers. ^{1}H NMR (400 MHz, Methanol-*d*4) δ 7.85 – 7.78 (m), 7.67 – 7.62 (m), 7.55 – 7.48 (m), 7.24 – 7.14 (m), 7.11 – 7.05 (m), 7.04 – 6.94 (m), 6.76 – 6.67 (m), 6.64 – 6.56 (m), 6.56 – 6.34 (m), 6.33 – 6.24 (m), 5.67 – 5.58 (m), 5.31 – 5.23 (m), 5.03 – 4.95 (m), 4.86 – 4.75 (m), 3.34 (s), 3.32 – 3.28 (m), 3.24 – 3.09

(m), 3.02 – 2.85 (m), 2.57 – 2.41 (m), 1.41 (m), 1.35 – 1.24 (m), 1.17 – 1.10 (m), 1.10 – 1.03 (m). MS (*m/z*) 748.15 $[M+H]^+$.

Example 66.

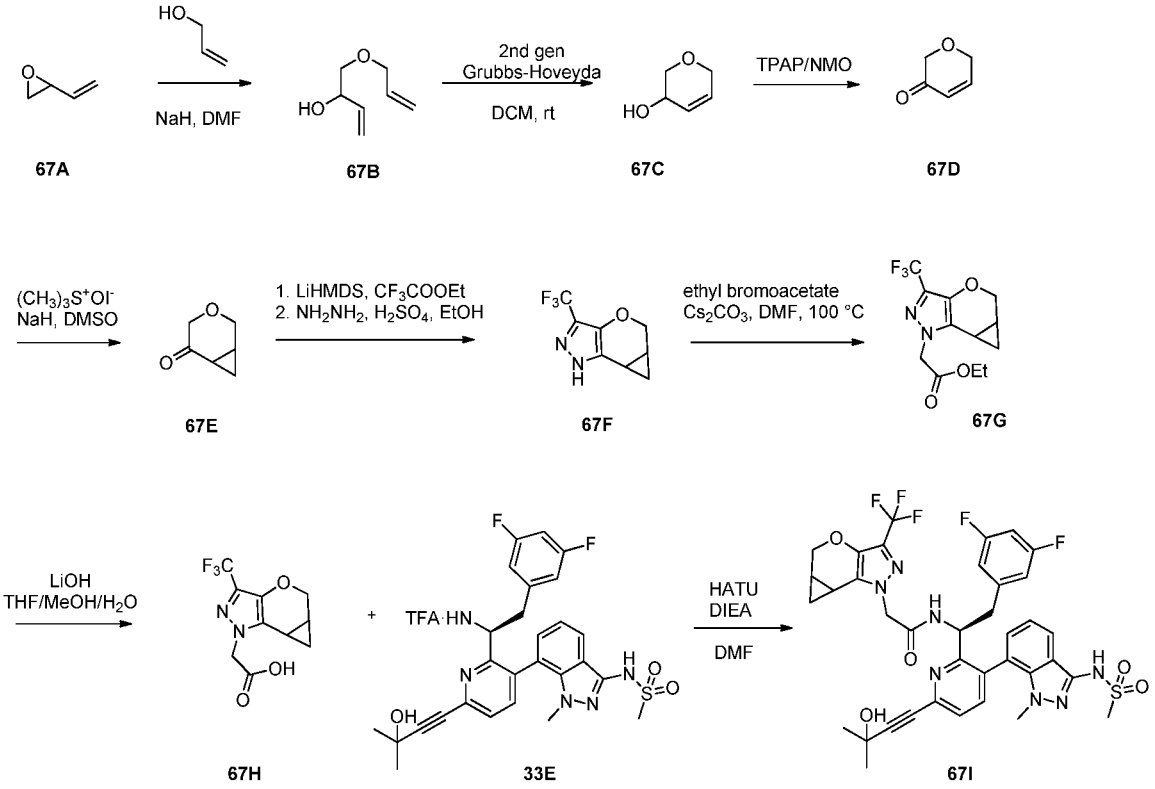


66

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-ethyl-3-hydroxypent-1-yn-1-yl)-3-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)acetamide (**66**):

[0544] The title compound (**66**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **61** of Example 61 utilizing 3-ethylpent-1-yn-3-ol. ^{1}H NMR (400 MHz, cd_3od) δ 7.83 (td), 7.74 – 7.65 (m), 7.54 (dd), 7.28 – 7.05 (m), 6.78 – 6.67 (m), 6.62 (s), 6.54 (dd), 6.35 (ddd), 5.00 (t), 5.32-5.25 (m), 4.84 – 4.70 (m), 3.34 (s), 3.15 (d), 3.03 – 2.88 (m), 2.55 – 2.42 (m), 1.93 – 1.73 (m), 1.41 (dq), 1.16 (td), 1.10 – 1.01 (m). MS (m/z) 832.1 $[M+H]^+$.

Example 67.



Synthesis of 1-(allyloxy)but-3-en-2-ol (**67B**):

[0545] The epoxide **67A** (3.5 g, 50 mmol) and allyl alcohol (5.8 g, 100 mmol) were dissolved in DMF (100 mL) in a pressure bottle. After cooled to 0 °C, NaH (60% suspension in mineral oil, 2.4 g) was added portionwise, stirred for 20 min under argon. The bottle was sealed and heated at 60 °C overnight. The reaction was cooled to 0 °C in an ice bath, quenched with 100 mL 2N HCl. The aqueous layer was extracted 3 times with ether (3X100 mL). The combined ether were washed with 5% LiCl and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column to yield the title compound **67B**. ^{1}H NMR (400 MHz, Chloroform-d) δ 6.00 – 5.74 (m, 2H), 5.45 – 5.08 (m, 4H), 4.31 (tdd, J = 7.0, 3.2, 1.5 Hz, 1H), 4.02 (dt, J = 5.7, 1.4 Hz, 2H), 3.49 (dd, J = 9.7, 3.4 Hz, 1H), 3.32 (dd, J = 9.7, 7.9 Hz, 1H), 2.56 (s, 1H).

Synthesis of 3,6-dihydro-2H-pyran-3-ol (**67C**):

[0546] The title compound (**67C**) was prepared according to reference: Angew. Chem. Intl. Ed. 2005, 44, 5306-5310. ^{1}H NMR data:1H NMR (400 MHz, Chloroform-d) δ 6.06 – 5.81 (m, 2H), 4.19 – 3.99 (m, 2H), 3.98 – 3.89 (m, 1H), 3.86 – 3.66 (m, 2H), 2.77 – 2.57 (m, 1H).

Synthesis of 2H-pyran-3(6H)-one (**67D**):

[0547] The title compound (**67D**) was prepared according to reference: Angew. Chem. Intl. Ed. 2005, 44, 5306-5310.

Synthesis of 3-oxabicyclo[4.1.0]heptan-5-one (**67E**):

[0548] To a suspension of NaH (60% in mineral oil, 0.19 g) in DMSO (20 mL) was added trimethylsulfonium iodide (1.75 g, 8 mmol) at room temperature. After stirring for 15 min, a solution of **67D** (0.6 g, 6 mmol) in DMSO (5 mL) was added. After stirring at room temperature for 5 min, the reaction mixture was diluted with ethyl acetate and washed with 5% LiCl aqueous solution. The organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to give the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 4.22 – 4.03 (m, 2H), 3.80 (s, 1H), 3.76 (d, J = 6.0 Hz, 1H), 1.95 (ddd, J = 9.8, 7.5, 4.7 Hz, 1H), 1.85 – 1.71 (m, 2H), 1.23 (ddd, J = 9.8, 7.1, 4.4 Hz, 1H).

Synthesis of 3-(trifluoromethyl)-5,5a,6,6a-tetrahydro-1H-cyclopropa[4,5]pyrano[3,2-c]pyrazole (**67F**):

[0549] A solution of compound **67E** (90 mg, 0.8 mmol) and ethyl trifluoroacetate (0.16 g, 1.2 mmol) in ether was cooled to -78 °C. LiHMDS (0.18 g, 1 mmol) was added in one portion. The resulting mixture was stirred at -78 °C for 2 h. The reaction was poured into 1 N HCl aqueous solution and the aqueous layer was extracted with ether. The organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo* to give the title compound which was used without further purification. MS (*m/z*) 209.06 $[M+H]^+$.

[0550] To a solution of crude from last step in ethanol (20 mL) was added concentrated sulfuric acid (0.5 mL) and hydrazine monohydrate (1 mL). The resulting mixture was heated at 90 °C for 5 min. Upon completion of the reaction, the volatiles were removed in vacuo to give the title compound which was used in the next step. MS (*m/z*) 205.18 $[M+H]^+$.

Synthesis of ethyl 2-(3-(trifluoromethyl)-5,5a,6,6a-tetrahydro-1H-cyclopropa[4,5]pyrano[3,2-c]pyrazol-1-yl)acetate (**67G**):

[0551] To a solution of compound **67F** (100 mg, 0.49 mmol) in DMF (2 mL) was added bromoethyl acetate (98 mg, 0.59 mmol) and cesium carbonate (160 mg, 0.5 mmol) at 0 °C. The reaction was heated at 50 °C overnight. Upon cooling, the mixture was purified by reverse phase HPLC to give the title compound. . MS (m/z) 291.19 $[M+H]^+$.

Synthesis of 2-(3-(trifluoromethyl)-5,5a,6,6a-tetrahydro-1H-cyclopropa[4,5]pyrano[3,2-c]pyrazol-1-yl)acetic acid (**67H**):

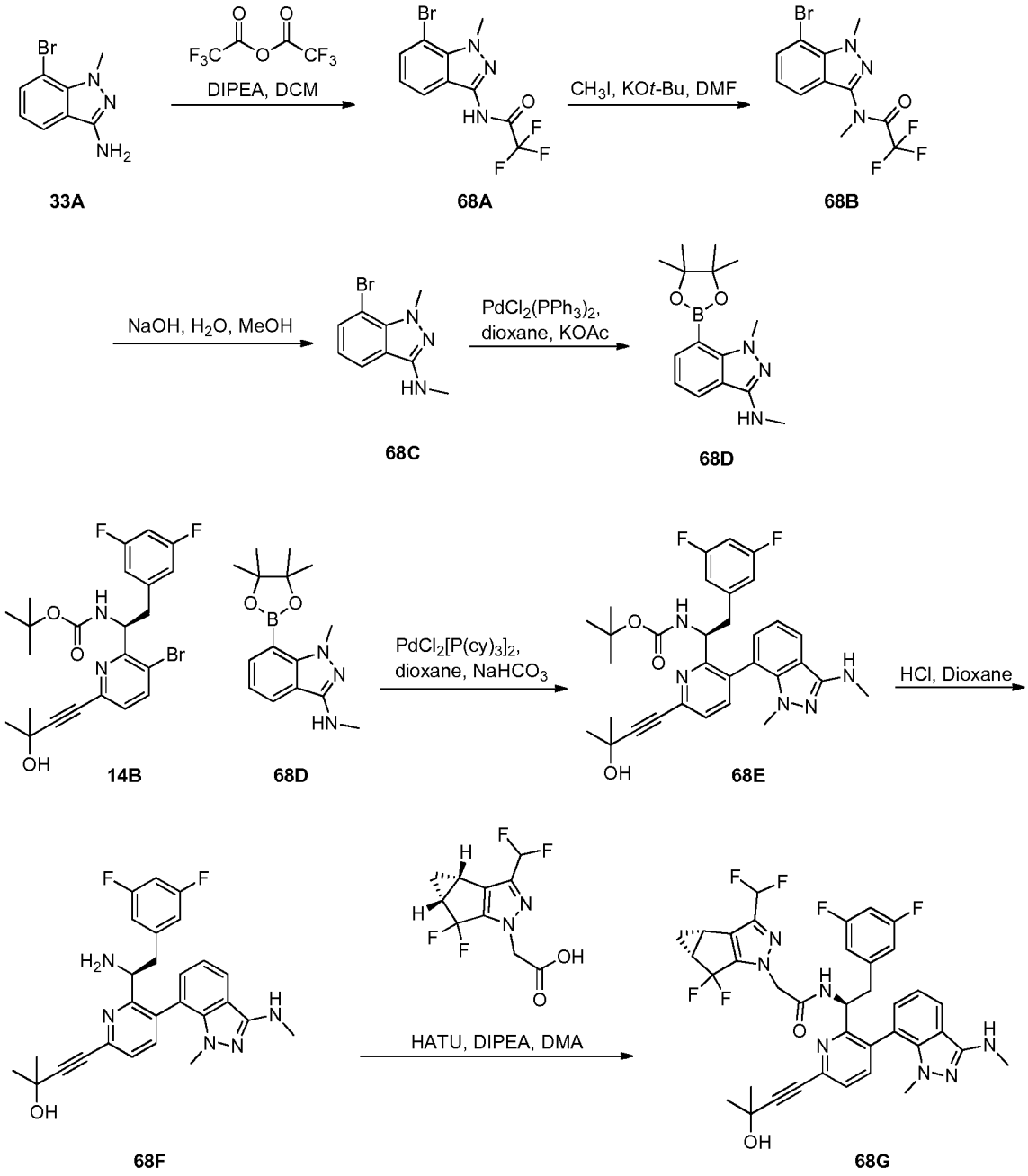
[0552] To a solution of compound **67G** (16 mg, 0.055 mmol) in a mixture of THF:water:MeOH (1 mL : 0.5 mL : 0.5 mL) was added solid LiOH monohydrate (7 mg, 0.165 mmol) at 0 °C. After stirring at room temperature for 10 min, the reaction mixture was poured

into EtOAc and the organic was washed with 2 N HCl. The organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo* to give the title compound which was used in the next step. MS (*m/z*) 263.04 $[M+H]^+$.

Synthesis of N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-5,5a,6,6a-tetrahydro-1H-cyclopropa[4,5]pyrano[3,2-c]pyrazol-1-yl)acetamide (**67I**):

[0553] The title compound (**67I**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **10A** of Example 10 utilizing 2-(3-(trifluoromethyl)-5,5a,6,6a-tetrahydro-1H-cyclopropa[4,5]pyrano[3,2-c]pyrazol-1-yl)acetic acid (**67H**) and compound **33E** . ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.93 – 7.78 (m), 7.75 – 7.65 (m), 7.61 – 7.45 (m), 7.39 – 6.98 (m), 6.73 (tq), 6.68 – 6.56 (m), 6.34 (tdd), 5.43 – 4.93 (m), 4.83 – 4.71 (m), 4.30 – 3.97 (m), 3.22 – 3.00 (m), 3.02 – 2.76 (m), 2.10 – 1.70 (m), 1.16 (dddd), 0.86 – 0.64 (m). MS (*m/z*) 784.34 $[M+H]^+$.

Example 68



Synthesis of N-(7-bromo-1-methyl-1H-indazol-3-yl)-2,2,2-trifluoroacetamide (**68A**):

[0554] To a solution of 7-bromo-1-methyl-1H-indazol-3-amine (**33A,** 500 mg, 2.21 mmol) and N,N-diisopropylethylamine (0.578 mL, 3.32 mmol) in dichloromethane (5 ml) was added dropwise at 0 ºC trifluoroacetic anhydride (697 mg, 3.32 mmol). The reaction was warmed to room temperature and stirred for 30 min. The reaction mixture was washed with water. The aqueous layer was back-extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica gel column

chromatography to give the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.51 (s, 1H), 7.87 (d, 1H), 7.60 (d, 1H), 7.01 (t, 1H), 4.37 (s, 3H).

Synthesis of N-(7-bromo-1-methyl-1H-indazol-3-yl)-2,2,2-trifluoro-N-methylacetamide (**68B**):

[0555] To a stirred solution of N-(7-bromo-1-methyl-1H-indazol-3-yl)-2,2,2-trifluoroacetamide (**68A**, 100 mg, 0.31 mmol) in DMF (0.6 ml) was added potassium t-butoxide (36.6 mg, 0.33 mmol). The reaction was sonicated until the solution became homogeneous and the reaction was stirred at room temperature for 30 mins. To the reaction was added iodomethane (29 µL, 0.47 mmol). After stirring for 1 h, the reaction was diluted with ethyl acetate and washed with water, followed by 0.5M aqueous NaCl. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was used in the next step without further purification.

Synthesis of 7-bromo-N,1-dimethyl-1H-indazol-3-amine (**68C**):

[0556] To a solution of N-(7-bromo-1-methyl-1H-indazol-3-yl)-2,2,2-trifluoro-N-methylacetamide (**68B**, 104 mg) in methanol (3 ml) was added 8M NaOH (46.6 µl). After stirring for 30 mins, the solution was concentrated, extracted with ethyl acetate (4 mL) and washed water (4 mL), followed by 2M aqueous NaCl (4 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was used in the next step without further purification. MS (*m/z*) 240.15 $[M+H]^+$.

Synthesis of N,1-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-amine (**68D**):

[0557] The title compound (**68D**) was prepared according to the method presented for the synthesis of compound **19C** of Example 19 utilizing 7-bromo-N,1-dimethyl-1H-indazol-3-amine (**68C**). MS (*m/z*) 288.22 $[M+H]^+$.

Synthesis of ((S)-tert-butyl (2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-methyl-3-(methylamino)-1H-indazol-7-yl)pyridin-2-yl)ethyl)carbamate (**68E**):

[0558] The title compound (**68E**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **55A** of Example 55 utilizing N,1-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-amine (**68D**). MS (*m/z*) 576.06 $[M+H]^+$.

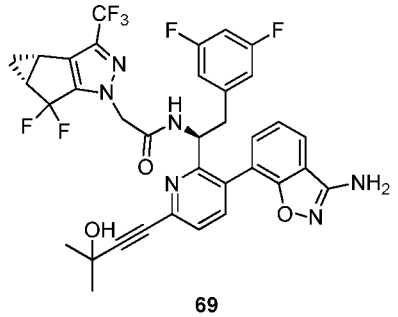
Synthesis of (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(1-methyl-3-(methylamino)-1H-indazol-7-yl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (**68F**):

[0559] The title compound (**68F**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **14C** of Example 14 utilizing ((S)-tert-butyl (2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-methyl-3-(methylamino)-1H-indazol-7-yl)pyridin-2-yl)ethyl)carbamate (**68E**). MS (*m/z*) 476.13 $[M+H]^+$.

Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-methyl-3-(methylamino)-1H-indazol-7-yl)pyridin-2-yl)ethyl)acetamide (**68G**):

[0560] The title compound (**68G**) was prepared according to the method presented for the synthesis of compound **33F** of Example 33 utilizing (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(1-methyl-3-(methylamino)-1H-indazol-7-yl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (**68F**) and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.90 – 7.86 (m), 7.86 – 7.80 (m), 7.71 (dd), 7.55 (dd), 7.34 (d), 7.22 – 7.12 (m), 6.84 – 6.77 (m), 6.77 – 6.70 (m), 6.70 – 6.67 (m), 6.66 – 6.62 (m), 6.56 (s), 6.54 (s), 6.47 – 6.41 (m), 6.36 – 6.29 (m), 5.22 (dd), 5.05 (t), 4.76 (d), 4.71 (s), 3.30 – 3.22 (m), 3.14 – 3.03 (m), 3.03 – 2.91 (m), 2.85 (s), 2.46 (ddt), 1.64 (s), 1.44 – 1.33 (m), 1.11 – 0.97 (m). MS (*m/z*) 722.18 $[M+H]^+$.

Example 69.



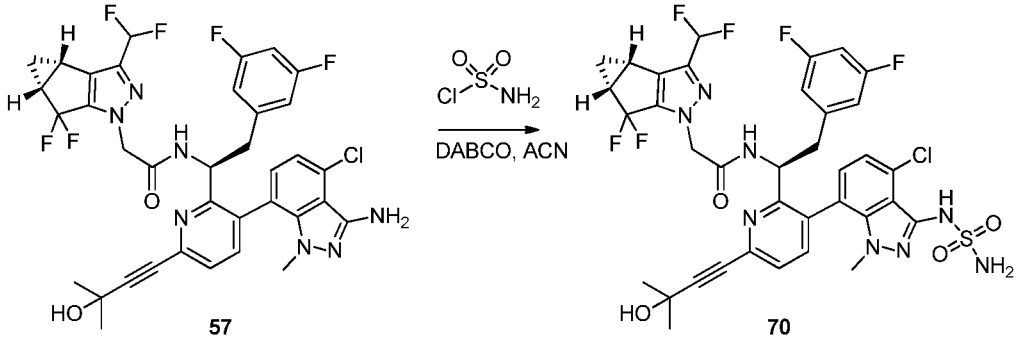
69

Synthesis of N-((S)-1-(3-(3-aminobenzo[d]isoxazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**69**):

[0561] The title compound (**69**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **33F** of Example 33 utilizing tert-butyl (7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]isoxazol-3-yl)carbamate and 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, cd_3od) δ 7.80

(dd), 7.69 (d), 7.54 – 7.40 (m), 7.33 (dt), 6.57 (ddd), 6.36 – 6.27 (m), 5.31 (t), 4.82 (s), 3.13 – 2.96 (m), 2.52 – 2.43 (m), 1.63 (s), 1.45 – 1.35 (m), 1.15 – 1.07 (m). MS (*m/z*) 713.3 $[M+H]^+$.

Example 70.

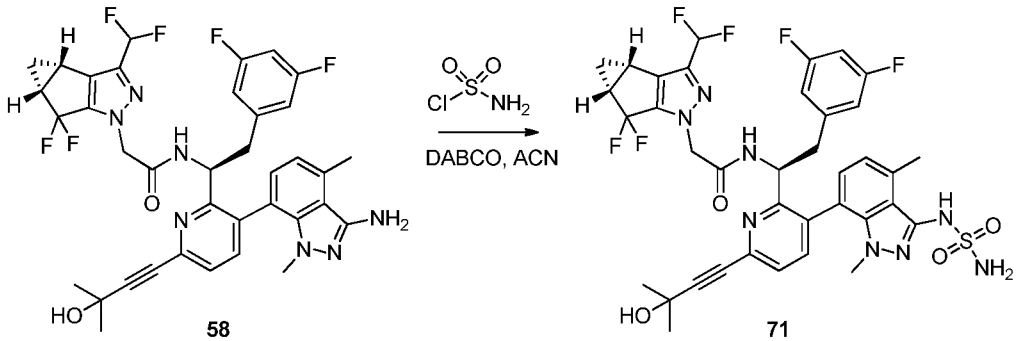


57 70

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(sulfamoylamino)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**70**):

[0562] Compound **57** (20 mg, 0.03 mmol) was dissolved in ACN (0.5 ml) and cooled in a salt-ice bath to −10 °C. The reaction solution was treated with DABCO (6 mg, 0.05 mmol) then a solution of sulfamoyl chloride (5 mg, 0.04 mmol) in ACN (0.2 ml) and let warm to ambient temperature. After 1 h, an additional aliquot of DABCO (2 eq) and sulfamoyl chloride (1.5 eq) were added. After another 1.5 hr, the reaction was diluted with KH_2PO_4 buffer and partitioned between brine and EtOAc. The organics were separated, dried, and removed in vacuo. The residue was purified by reverse phase HPLC to provide the title compound as a mixture of atropisomers. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.69 (d), 7.68 (dd), 7.53 (dd), 7.19 – 7.10 (m), 7.06 (d), 6.87 – 6.52 (m), 6.49 – 6.31 (m), 5.35 – 5.22 (m), 5.05 – 4.94 (m), 4.79 – 4.65 (m), 3.24 (dd), 3.12 (dd), 3.04 – 2.91 (m), 2.45 (ddt), 1.64 (d), 1.44 – 1.32 (m), 1.12 – 0.99 (m). MS (*m/z*) 820.9 $[M+H]^+$.

Example 71.

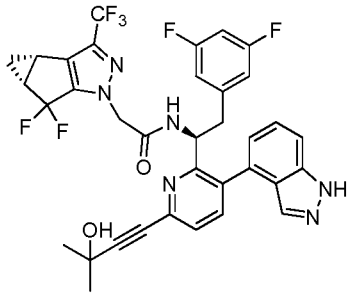


58 71

Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(3-(1,4-dimethyl-3-(sulfamoylamino)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)ethyl)acetamide (**71**):

[0563] The title compound (**71**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of **70** in Example 70 utilizing compound **58**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.71 – 8.54 (m), 7.73 – 7.60 (m), 7.57 – 7.45 (m), 7.08 (d), 7.00 – 6.89 (m), 6.89 – 6.77 (m), 6.77 – 6.64 (m), 6.66 – 6.56 (m), 6.54 (s), 6.44 (d), 6.41 – 6.33 (m), 6.33 – 6.25 (m), 5.40 – 5.29 (m), 5.08 – 4.94 (m), 4.75 – 4.67 (m), 3.12 – 2.86 (m), 2.86 – 2.74 (m), 2.54 – 2.35 (m), 1.44 – 1.29 (m), 1.12 – 0.98 (m). MS (*m/z*) 801.0 $[M+H]^+$.

Example 72.

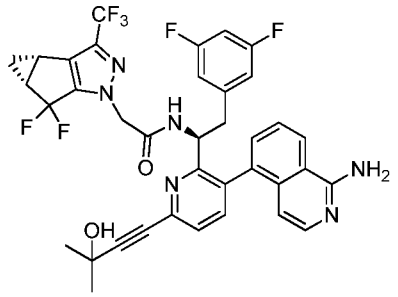


72

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1H-indazol-4-yl)pyridin-2-yl)ethyl)acetamide (**72**):

[0564] The title compound (**72**) was prepared according to the method presented for the synthesis of compound **33F** of Example 33 utilizing 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole and 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, cd_3od) δ 8.74 (d), 8.61 (m), 7.63 (dd), 7.56 – 7.46 (m), 7.39 (dd), 7.32 (dd), 6.99 (d), 6.72 (tt), 6.56 – 6.45 (m), 6.31 (d), 6.27 – 6.20 (m), 5.44 – 5.34 (m), 5.10 – 4.99 (m), 4.93 – 4.83 (m), 4.76 (s), 3.18 – 3.04 (m), 2.97 – 2.83 (m), 2.58 – 2.42 (m), 1.86 (s), 1.67 – 1.57 (m), 1.48 – 1.33 (m), 1.15 (s), 1.08 (s). MS (*m/z*) 697.2 $[M+H]^+$.

Example 73.

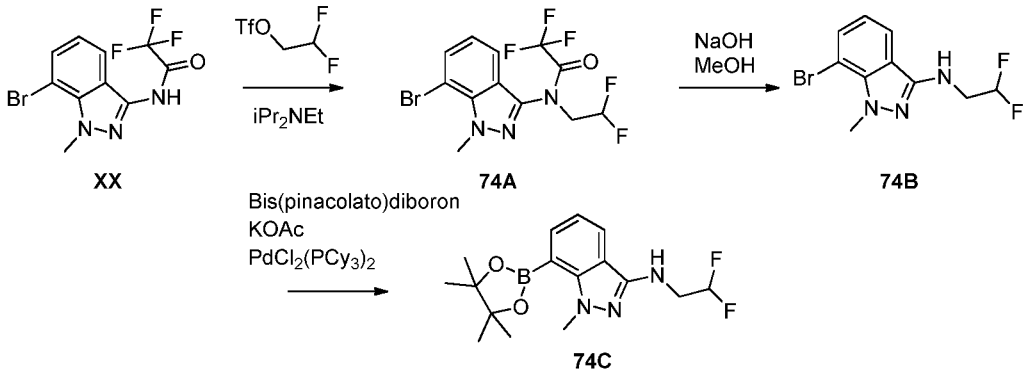


73

Synthesis of N-((S)-1-(3-(1-aminoisoquinolin-5-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**73**):

[0565] The title compound (**73**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **33F** of Example 33 utilizing 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1-amine and 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, cd_3od) δ 8.89 (d), 8.76 (d), 8.47 (d), 7.90 – 7.84 (m), 7.81 – 7.73 (m), 7.68 – 7.50 (m), 7.32 (dd), 7.07 (dd), 6.81 – 6.69 (m), 6.63 – 6.53 (m), 6.48 (dd), 6.35 – 6.25 (m), 6.05 (dd), 5.07 (td), 4.86 – 4.71 (m), 3.25 – 3.09 (m), 3.03 – 2.92 (m), 2.55 – 2.45 (m), 1.65 (s), 1.48 – 1.38 (m), 1.16 – 1.07 (m). MS (*m/z*) 723.3 $[M+H]^+$.

Example 74.



XX 74A 74B 74C

Synthesis of N-(7-bromo-1-methyl-1H-indazol-3-yl)-N-(2,2-difluoroethyl)-2,2,2-trifluoroacetamide (**74A**):

[0566] To N-(7-bromo-1-methyl-1H-indazol-3-yl)-2,2,2-trifluoroacetamide (150 mg, 0.47 mmol) in DCE (2 ml) was added iPr_2NEt (0.122 ml, 0.7 mmol) followed by 2,2-difluoroethyl trifluoromethanesulfonate (100 mg, 0.47 mmol). The reaction was stirred 15 h at ambient temperature. The reaction was partitioned between EtOAc and water. The organics were

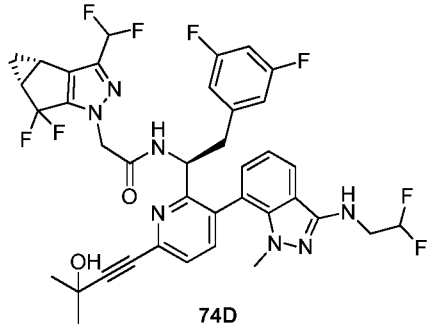
separated, dried, and removed in vacuo to provide the title compound which was used directly in the next reaction. MS (*m/z*) 387.9 $[M+H]^+$.

Synthesis of 7-bromo-N-(2,2-difluoroethyl)-1-methyl-1H-indazol-3-amine (**74B**):

[0567] N-(7-bromo-1-methyl-1H-indazol-3-yl)-N-(2,2-difluoroethyl)-2,2,2-trifluoroacetamide (0.18 g, 0.47 mmol) was dissolved in MeOH (2 ml) and treated with aqueous NaOH (1M, 3 ml). After 10 min, the reaction was neutralized and partitioned between EtOAc and 20% aqueous KH_2PO_4. The organics were separated, dried, and removed in vacuo to provide the title compound which was used directly in the next reaction. MS (*m/z*) 290.1 $[M+H]^+$.

Synthesis of N-(2,2-difluoroethyl)-1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-amine (**74C**):

[0568] The title compound (**74C**) was prepared according to the method presented for the synthesis of **27D** in Example 27 utilizing **74B**. MS (*m/z*) 338.1 $[M+H]^+$.



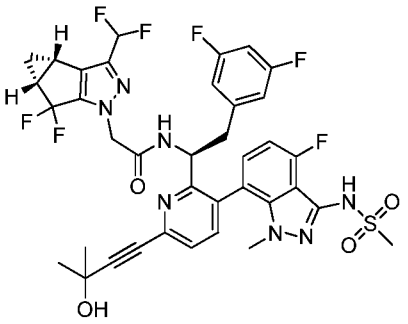
74D

Synthesis of N-((S)-1-(3-(3-((2,2-difluoroethyl)amino)-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**74D**):

[0569] The title compound (**36C**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of **27G** in Example 27 utilizing **14B** and **74C**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.75 (d), 7.67 (dd), 7.52 (dd), 7.18 (d), 7.04 (t), 6.95 (t), 6.85 – 6.49 (m), 6.39 – 6.26 (m), 6.26 – 6.20 (m), 6.12 – 6.04 (m), 5.99 – 5.91 (m), 5.32 – 5.22 (m), 5.05 (t), 4.74 (s), 3.79 – 3.56 (m), 3.23 – 3.11 (m), 3.07 (dd), 3.00 – 2.89 (m), 2.88 (s), 2.54 – 2.38 (m), 1.64 (s), 1.44 – 1.27 (m), 1.13 – 0.94 (m).

MS (*m/z*) 772.5 $[M+H]^+$.

Example 75.

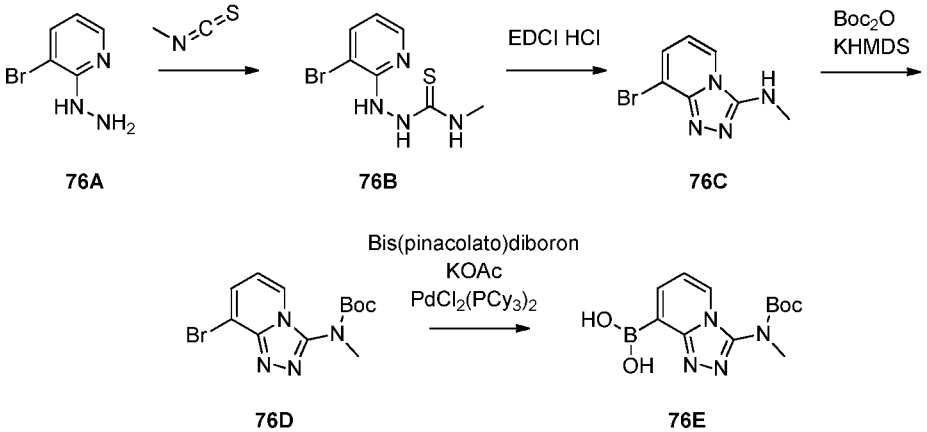


75

Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(3-(4-fluoro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)ethyl)acetamide (**75**):

[0570] The title compound (**75**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **132C** of Example 132 utilizing 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, cd_3od) δ 8.68 (dd), 7.72 – 7.65 (m), 7.54 (d), 7.51 (d), 7.21 (dd), 6.87 – 6.81 (m), 6.80 – 6.71 (m), 6.69 (s), 6.66 – 6.59 (m), 6.58 (s), 6.55 (s), 6.45 – 6.34 (m), 5.35 – 5.27 (m), 5.03 – 4.96 (m), 4.88 (s), 4.77 (s), 4.72 (d), 3.27 – 3.08 (m), 3.03 – 2.92 (m), 2.56 – 2.37 (m), 1.94 (s), 1.64 (d), 1.44 – 1.26 (m), 1.13 – 1.06 (m), 1.05 – 0.98 (m). MS (*m/z*) 804.1 $[M+H]^+$.

Example 76.



76A 76B 76C 76D 76E

Synthesis of 2-(3-bromopyridin-2-yl)-N-methylhydrazinecarbothioamide (**76B**):

[0571] 3-Bromo-2-hydrazinylpyridine (1500 mg, 7.98 mmol) was dissolved in DCM (50 ml) and treated with dropwise addition of methyl isothiocyanate (700 mg, 9.57 mmol) in DCM. The

reaction was heated to 45 °C and stirred for 2 hr. After cooling to ambient temperature, the solids were filtered to provide the title compound. MS (*m/z*) 261.0 $[M+H]^+$.

Synthesis of 8-bromo-N-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**76C**):

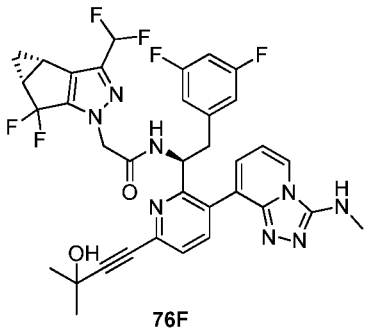
[0572] 2-(3-Bromopyridin-2-yl)-N-methylhydrazinecarbothioamide (1.6 g, 6.1 mmol) was treated with EDCI HCl (1.76 g, 9 mmol) in toluene and heated to 105 °C. After 1 hr, the hot toluene was decanted. To the residue was added H_2O (50 ml). The slurry was mixed thoroughly and heated to 100 °C for 15 min. After cooling to 0 °C, the resultant solids were filtered to provide the title compound. MS (*m/z*) 227.1 $[M+H]^+$.

Synthesis of tert-butyl (8-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)(methyl)carbamate (**76D**):

[0573] 8-bromo-N-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-amine (0.55 g, 2.42 mmol) was dissolved in DMF (10 ml) and treated with KHMDS (0.58 g, 2.91 mmol). Di-tert-butyl dicarbonate (0.79 g, 3.63 mmol) was then added. The reaction was stirred at ambient temperature for 2 d. The reaction was partitioned between EtOAc and water. The organics were separated, dried, and removed in vacuo and the residue was purified by column chromatography on silica to provide the title compound. MS (*m/z*) 326.9 $[M+H]^+$.

Synthesis of (3-((tert-butoxycarbonyl)(methyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)boronic acid (**76E**):

[0574] tert-Butyl (8-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)(methyl)carbamate (0.46 g, 1.41 mmol) was combined with bis (pinacolato) diboron (0.54 g), KOAc (0.41 g, 0 mol), and $PdCl_2(PCy_3)_2$ (0.05 g) in dioxane and DMF. Argon was bubbled into the reaction mixture for 10 min and then heated to 140 deg C for 2 h. The reaction was partitioned between EtOAc and water. The organics were separated, dried, and removed in vacuo to provide the title compound as a crude product contaminated with byproducts. The material was used directly in the following reaction. MS (*m/z*) 293.0 $[M+H]^+$.



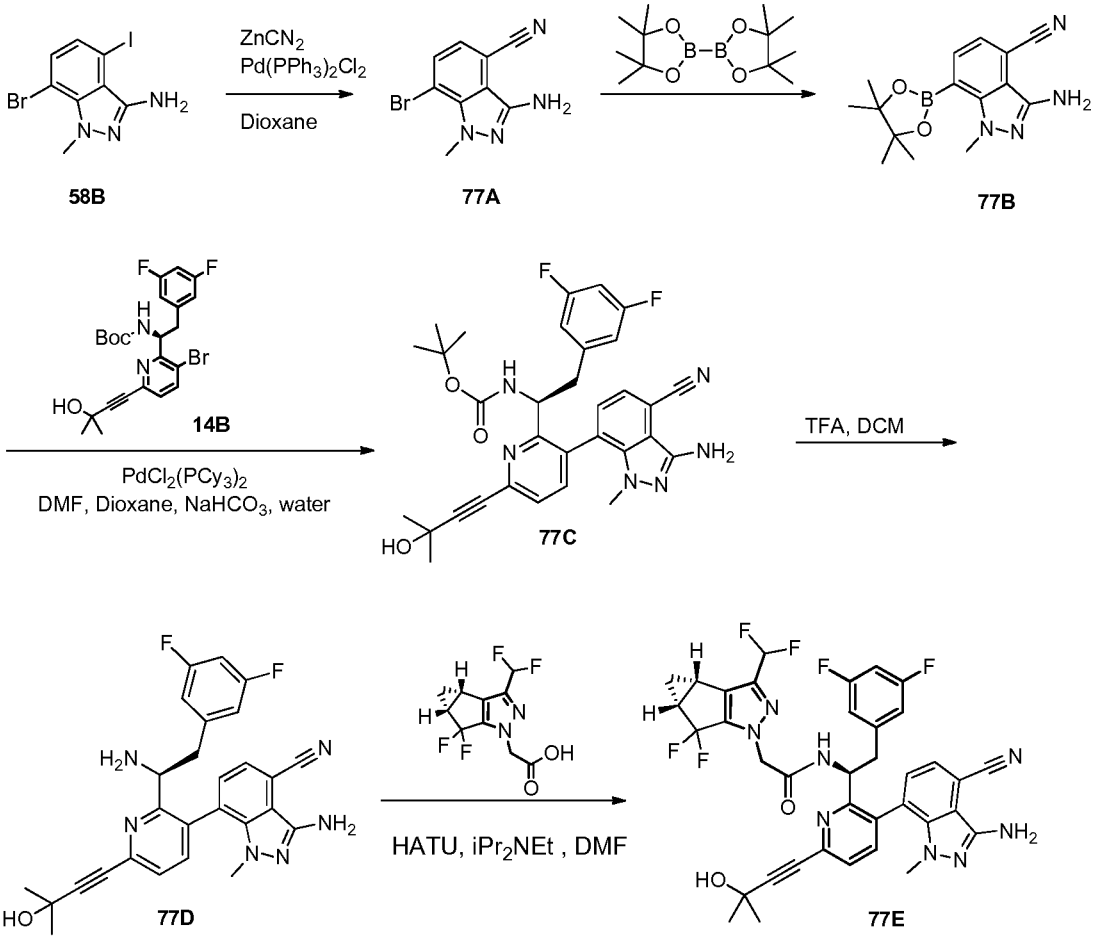
76F

Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-

3-methylbut-1-yn-1-yl)-3-(3-(methylamino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)pyridin-2-yl)ethyl)acetamide (**76F**):

[0575] The title compound (**76F**) was prepared according to the method presented for the synthesis of **27G** in Example 27 utilizing **14B** and **76E**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.88 (d), 8.22 (d), 7.75 (d), 7.56 (d), 7.37 (s), 7.18 (t), 6.67 (t), 6.70 – 6.59 (m), 6.55 – 6.44 (m), 5.31 – 5.17 (m), 4.69 (d), 3.23 – 3.08 (m), 2.55 – 2.39 (m), 1.63 (s), 1.46 – 1.25 (m), 1.08 – 1.00 (m). MS (*m/z*) 709.2 $[M+H]^+$.

Example 77.



Synthesis of 3-amino-7-bromo-1-methyl-1H-indazole-4-carbonitrile (**77A**):

[0576] To **58B** (3 g, 8.5 mmol) in dioxane (32 mL) and DMF (32 ml) was added zinc (6.7 g, 102.3 mmol) and $Pd(PPh_3)_2Cl_2$ (600 mg, 0.9 mmol). The reaction mixture was stirred at 160 °C and $ZnCN_2$ (500 mg, 4.3 mmol) was added to the reaction. After an hour another aliquot of $ZnCN_2$ (500 mg, 4.3 mmol) was added. The reaction was cooled, diluted with EtOAc and brine. The mixture was extracted 2X with EtOAc, the organic layer was dried over sodium sulfate, was

concentrated and purified by flash column chromatography to provide the title compound. MS (*m/z*) 251.1 $[M+H]^+$.

Synthesis of 3-amino-1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole-4-carbonitrile (**77B**):

[0577] The title compound (**77B**) was prepared according to the method presented for the synthesis of compound **19C** of Example 19 utilizing **77A**. MS (m/z) 299.3 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(3-(3-amino-4-cyano-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**77C**):

[0578] The title compound (**77C**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19E** of Example 19 utilizing **77B**. MS (*m/z*) 587.0 $[M+H]^+$.

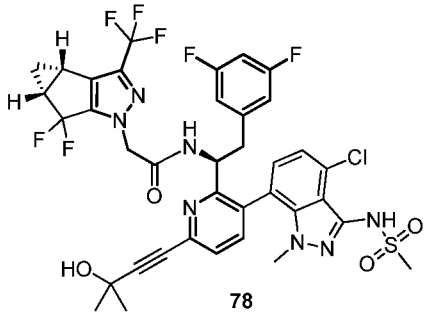
Synthesis of (S)-3-amino-7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazole-4-carbonitrile (**77D**):

[0579] The title compound (**77D**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19F** of Example 19 utilizing **77C**. MS (m/z) 487.2 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(3-amino-4-cyano-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**77E**):

[0580] The title compound (**77E**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **10A** of Example 10 utilizing **77D** and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (Chloroform-*d*) δ: 7.54 (t), 7.52 – 7.45 (m), 7.33 (d), 7.19 (t), 6.85 (t), 6.71 – 6.62 (m), 6.49 (d), 6.24 – 6.17 (m), 6.15 (d), 5.47 (d), 4.99 – 4.88 (m), 4.78 – 4.68 (m), 3.12 (s), 3.03 – 2.94 (m), 2.92 (s), 2.56 – 2.39 (m), 1.72 (s), 1.42 (q), 1.21 – 1.10 (m) MS (*m/z*) 733.3 $[M+H]^+$.

Example 78.

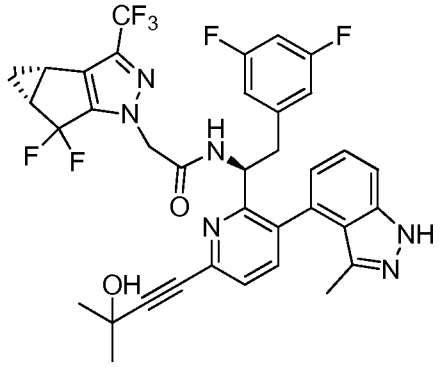


78

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**78**):

[0581] The title compound (**78**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19G** of Example 19 utilizing 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (Chloroform-*d*) δ: 7.60 – 7.46 (m), 7.32 – 7.24 (m), 7.24 – 7.15 (m), 6.92 (d), 6.71 – 6.62 (m), 6.48 (s), 6.27 – 6.17 (m), 6.08 (d), 5.55 (d), 4.98 (q), 4.79 (d), 4.73 (d), 3.56 (d), 3.40 (d), 3.27 (s), 3.07 – 2.91 (m), 2.66 – 2.40 (m), 1.71 (s), 1.44 (q), 1.28 – 1.15 (m). MS (*m/z*) 838.9 $[M+H]^+$.

Example 79.



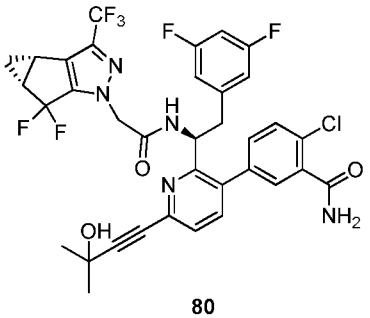
79

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(3-methyl-1H-indazol-4-yl)pyridin-2-yl)ethyl)acetamide (**79**):

[0582] The title compound (**79**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **20F** of Example 20 utilizing (3-carbamoyl-4-chlorophenyl)boronic acid and 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (400 MHz,

cd3od) δ 8.75 (d), 8.61 (d), 7.63 (dd), 7.56 – 7.46 (m), 7.39 (dd), 7.32 (dd), 6.99 (d), 6.72 (tt), 6.56 – 6.45 (m), 6.31 (d), 6.27 – 6.20 (m), 5.39 (dt), 5.10 – 4.99 (m), 4.76 (s), 3.18 – 3.04 (m), 2.97 – 2.83 (m), 2.58 – 2.42 (m), 1.86 (s), 1.64 (d), 1.60 (s), 1.48 – 1.33 (m), 1.18 – 1.11 (m), 1.11 – 1.03 (m). MS (*m/z*) 711.7 $[M+H]^+$.

Example 80.

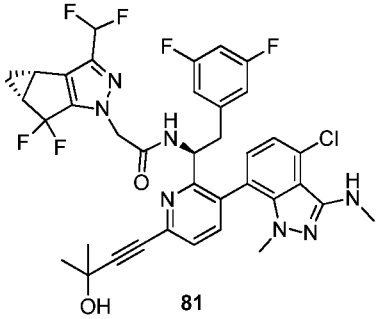


80

Synthesis of 2-chloro-5-(2-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)benzamide (**80**):

[0583] The title compound (**80**) was prepared according to the method presented for the synthesis of compound **33F** of Example 33 utilizing (3-carbamoyl-4-chlorophenyl)boronic acid and 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, cd_3od) δ 8.86 (d), 7.54 (d), 7.46 (dd), 7.17 (d), 7.07 – 6.99 (m), 6.70 (tt), 6.44 – 6.34 (m), 5.35 (dd), 4.84 (d), 3.19 – 3.00 (m), 2.57 – 2.42 (m), 1.62 (s), 1.46 – 1.36 (m), 1.15 – 1.06 (m). MS (*m/z*) 736.0 $[M+H]^+$.

Example 81.

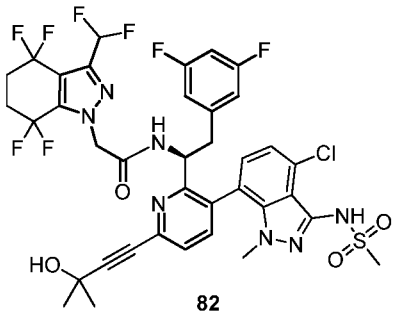


81

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylamino)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**81**):

[0584] The title compound (**81**) was prepared as a mixture of atropisomers according to the method presented in Example 68 utilizing 7-bromo-4-chloro-1-methyl-1H-indazol-3-amine (**19B**) in place of 7-bromo-1-methyl-1H-indazol-3-amine **(33A)**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.90 – 7.86 (m), 7.86 – 7.80 (m), 7.71 (dd), 7.55 (dd), 7.34 (d), 7.22 – 7.12 (m), 6.84 – 6.77 (m), 6.77 – 6.70 (m), 6.70 – 6.67 (m), 6.66 – 6.62 (m), 6.56 (s), 6.54 (s), 6.47 – 6.41 (m), 6.36 – 6.29 (m), 5.22 (dd), 5.05 (t), 4.76 (d), 4.71 (s), 3.30 – 3.22 (m), 3.14 – 3.03 (m), 3.03 – 2.91 (m), 2.85 (s), 2.46 (ddt), 1.64 (s), 1.44 – 1.33 (m), 1.11 – 0.97 (m). MS (*m/z*) 756.14 $[M+H]^+$.

Example 82.

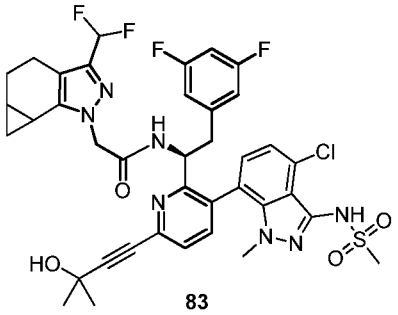


82

Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**82**):

[0585] The title compound (**82**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19G** of Example 19 utilizing 2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid. ^{1}H NMR (Chloroform-*d*) δ: 7.60 – 7.47 (m), 7.31 – 7.16 (m), 7.02 – 6.80 (m), 6.72 – 6.59 (m), 6.51 – 6.43 (m), 6.27 – 6.12 (m), 5.66 – 5.52 (m), 5.08 – 4.97 (m), 4.94 (d), 3.40 (s), 3.38 (s), 3.28 (t), 3.07 (s), 3.01 – 2.89 (m), 2.63 – 2.42 (m), 2.03 (s), 1.71 (s). MS (*m/z*) 858.8 $[M+H]^+$.

Example 83.

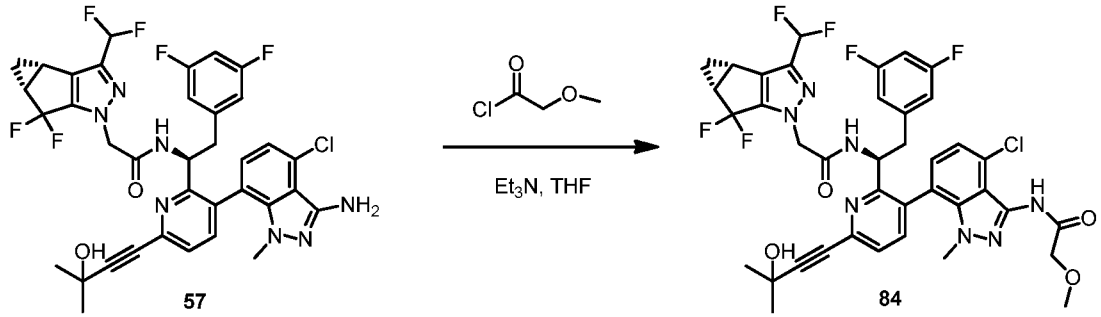


83

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetamide (**83**):

[0586] The title compound (**83**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19G** of Example 19 utilizing 2-(3-(difluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetic acid. ^{1}H NMR (Chloroform-*d*) δ: 7.55 - 7.43 (m), 7.38 (d), 7.29 (d), 7.18 (d), 6.96 (dd), 6.86 (d), 6.72 (d), 6.67 - 6.59 (m), 6.57 (d), 6.29 (d), 6.18 (td), 4.94 (dq), 4.84 - 4.79 (m), 4.76 (s), 3.39 (d), 3.30 (s), 3.24 (s), 3.07 (d), 3.01 - 2.89 (m), 2.89 - 2.74 (m), 2.63 - 2.47 (m), 2.29 - 2.08 (m), 1.82 - 1.62 (m), 1.71 (d), 1.05 (td), 0.96 (td), 0.74 (q), 0.65 (q). MS (*m/z*) 798.9 $[M+H]^+$.

Example 84.

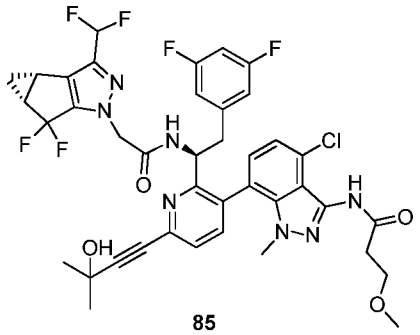


57 84

Synthesis of N-((S)-1-(3-(4-chloro-3-(2-methoxyacetamido)-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**84**):

[0587] To the reaction vial containing **57** (13 mg, 0.017 mmol) in THF (0.25 mL) was added 2-methoxyacetyl chloride (2 mg, 0.019 mmol), and triethylamine (0.004 mL, 0.026 mmol). The reaction mixture was stirred at room temperature until the majority of **57** was consumed. The reaction mixture was concentrated in vacuo and dissolved in methanol and treated with several drops of 2 M NaOH for 30 min. The reaction mixture was then acidified with TFA and purified by reverse phase HPLC to provide the title compound **84** as a mixture of atropisomers. ^{1}H NMR (400 MHz, cd_3od) δ 8.72-8.67 (m), 7.70 (dd), 7.54 (dd), 7.22 – 7.13 (m), 7.08 (d), 6.87 – 6.59 (m), 6.50 – 6.36 (m), 5.32-5.25 (m), 5.02 – 4.94 (m), 4.72 (dd), 4.14 (d), 3.56 (s), 3.34 (s), 3.15 (dd), 3.05 – 2.93 (m), 2.51 – 2.38 (m), 1.64 (d), 1.45 – 1.31 (m), 1.11-1.05 (m), 1.06 – 0.97 (m). MS (*m/z*) 815.2 $[M+H]^+$.

Example 85.

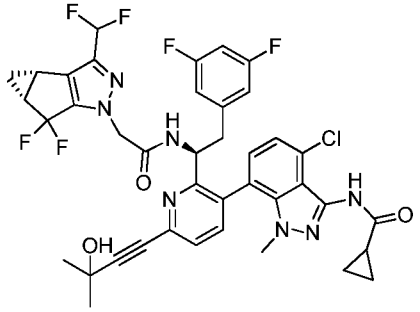


85

Synthesis of N-(4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)-3-methoxypropanamide (**85**):

[0588] The title compound (**85**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **84** of Example 84 utilizing 3-methoxypropanoyl chloride. ^{1}H NMR (400 MHz, cd_3od) δ 8.75-8.65 (m),7.69 (dd), 7.53 (dd), 7.21 – 7.12 (m), 7.07 (d), 6.87 – 6.52 (m), 6.47 – 6.35 (m),5.35-5.25 (m), 4.98 (t), 4.79 – 4.63 (m), 3.79 – 3.73 (m), 3.39 (s), 3.14 (dd), 3.05 – 2.93 (m), 2.76 – 2.68 (m), 2.51 – 2.39 (m), 1.64 (d), 1.45 – 1.32 (m), 1.11-1.05 (m), 1.06 – 0.97 (m). MS (*m/z*) 829.2 $[M+H]^+$.

Example 86.



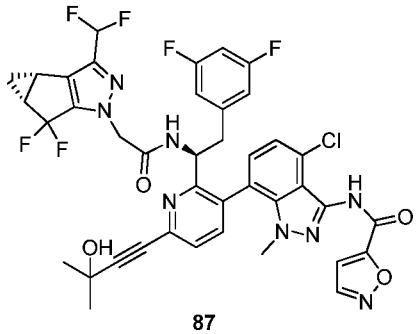
86

Synthesis of N-(4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)cyclopropanecarboxamide (**86**):

[0589] The title compound (**86**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **84** of Example 84 utilizing cyclopropanecarbonyl chloride. ^{1}H NMR (400 MHz, cd_3od) δ 8.75-8.52 (m),7.69 (dd), 7.53 (dd), 7.16 (d), 7.06 (d), 6.87 – 6.52 (m), 6.46 – 6.35 (m), 5.35-5.21 (m), 4.98 (t), 4.79 – 4.63 (m),

3.14 (dd), 3.00 (d), 2.53 – 2.39 (m), 1.90 (s), 1.64 (d), 1.45 – 1.32 (m), 1.06 – 0.96 (m), 0.90 (s). MS (*m/z*) 811.2 $[M+H]^+$.

Example 87.

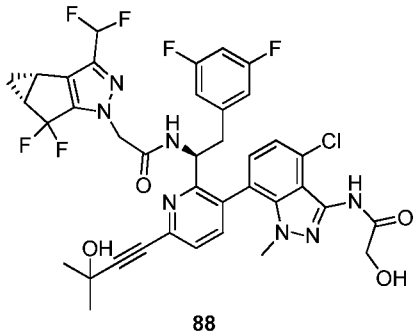


87

Synthesis of N-(4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)isoxazole-5-carboxamide (**87**):

[0590] The title compound (**87**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **84** of Example 84 utilizing isoxazole-5-carbonyl chloride. ^{1}H NMR (400 MHz, cd_3od) δ 8.71 (t), 8.60 (s), 7.72 (dd), 7.55 (dd), 7.24 – 7.07 (m), 6.87 – 6.61 (m), 6.60 – 6.37 (m), 5.35-5.25 (m), 5.00 (t), 4.79 – 4.64 (m), 3.37 (s), 3.21 – 3.12 (m), 3.08 – 2.95 (m), 2.52 – 2.39 (m), 1.92 (d), 1.64 (d), 1.42-132 (m), 1.08 (s), 1.02 (s). MS (*m/z*) 838.1 $[M+H]^+$.

Example 88.

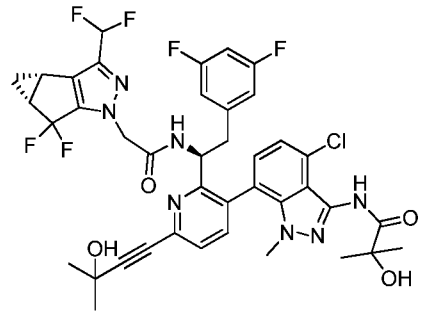


88

Synthesis of N-((S)-1-(3-(4-chloro-3-(2-hydroxyacetamido)-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**88**):

[0591] The title compound (**88**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **84** of Example 84 utilizing 2-chloro-2-oxoethyl acetate. ^{1}H NMR (400 MHz, cd_3od) δ 7.74 – 7.66 (m), 7.54 (dd), 7.23 – 7.13 (m), 7.08 (d), 6.87 – 6.58 (m), 6.50 – 6.35 (m), 5.25-5.31 (m), 4.99 (t), 4.76 (d), 4.68 (s), 4.21 (d), 3.34 (s), 3.30 – 3.11 (m), 3.04 – 2.94 (m), 2.51 – 2.38 (m), 1.64 (d), 1.45 – 1.33 (m), 1.11-1.05 (m), 1.06 – 0.97 (m). MS (*m/z*) 802.1 $[M+H]^+$.

Example 89.

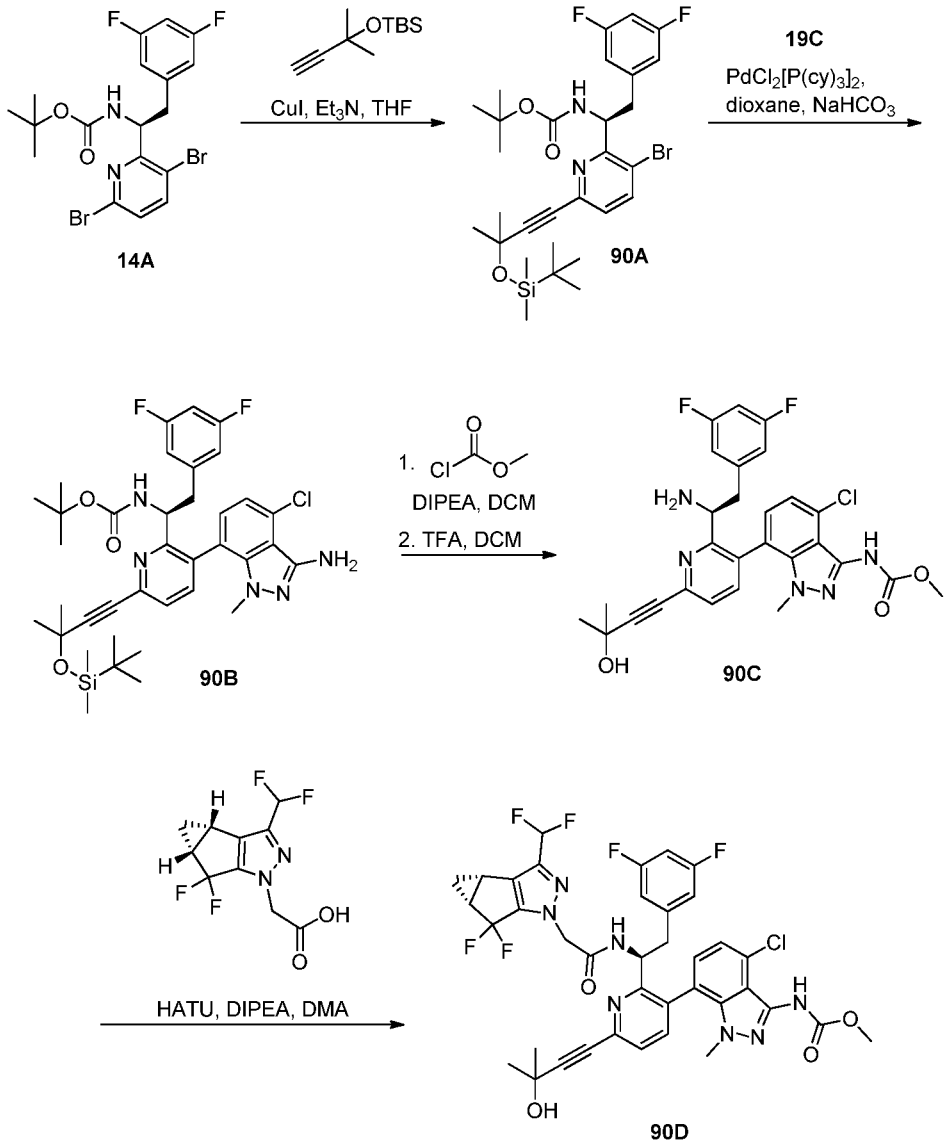


89

Synthesis of N-(4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)-2-hydroxy-2-methylpropanamide (**89**):

[0592] The title compound (**89**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **84** of Example 84 utilizing 1-chloro-2-methyl-1-oxopropan-2-yl acetate. ^{1}H NMR (400 MHz, cd_3od) δ 8.75-8.65 (m),7.70 (t), 7.54 (dd), 7.22 – 7.12 (m), 7.07 (d), 6.87 – 6.66 (m), 6.49 – 6.36 (m), 5.30-5.22 (m), 4.99 (t), 4.75 (d,), 4.67 (s), 3.35 (s), 3.28 – 3.12 (m), 3.04 – 2.93 (m), 2.49 – 2.38 (m), 1.64 (d), 1.51 (dd), 1.43 – 1.33 (m), 1.08 (s), 1.05 – 0.98 (m). MS (*m/z*) 829.2 $[M+H]^+$.

Example 90.



Synthesis of (S)-tert-butyl (1-(3-bromo-6-(3-((tert-butyldimethylsilyl)oxy)-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**90A**):

[0593] The title compound (**90A**) was prepared according to the method presented for the synthesis of compound (**14B**) of Example 14 utilizing tert-butyldimethyl((2-methylbut-3-yn-2-yl)oxy)silane. MS (*m/z*) 609.10 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(3-(3-amino-4-chloro-1-methyl-1H-indazol-7-yl)-6-(3-((tert-butyldimethylsilyl)oxy)-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**90B**).

[0594] The title compound (**90B**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound (**19E**) of Example 19 utilizing (S)-tert-butyl (1-(3-bromo-6-(3-((tert-butyldimethylsilyl)oxy)-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-

difluorophenyl)ethyl)carbamate (**90A**) and 4-chloro-1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-amine (**19C**). MS (*m/z*) 710.01 $[M+H]^+$.

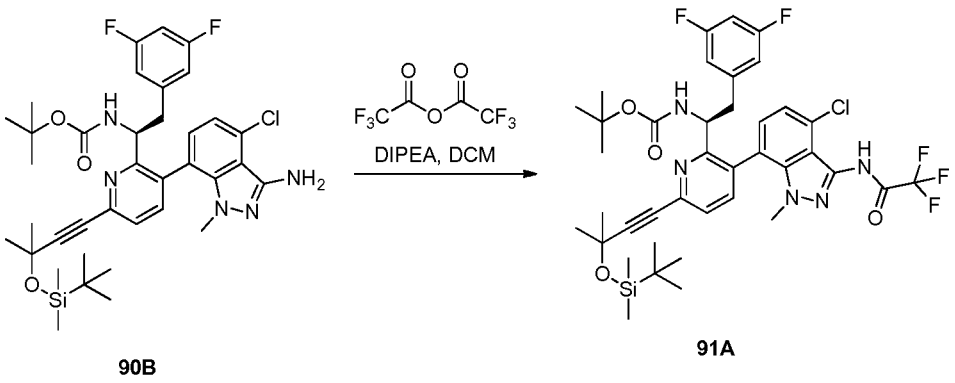
Synthesis of (S)-methyl (7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)carbamate (**90C**):

[0595] To a solution of (S)-tert-butyl (1-(3-(3-amino-4-chloro-1-methyl-1H-indazol-7-yl)-6-(3-((tert-butyldimethylsilyl)oxy)-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**90B**) (20 mg, 0.03 mmol) and DIPEA (0.08 µl, 0.06 mmol) in dichloromethane (0.5 ml) was added methyl chloroformate (3.27 µl, 0.04 mmol). After stirring overnight, trifluoroacetic acid (0.5 ml) was added and the reaction was stirred at room temperature for 1 hour. The reaction was concentrated, extracted with ethyl acetate, and basified with 2 M aqueous K_2CO_3. The organic layer was washed with 0.5 M NaCl and the organic layer was dried with Na_2SO_4, filtered, and concentrated. The crude product as a mixture of atropisomers was taken to the next step without further purification. MS (*m/z*) 554.13 $[M+H]^+$.

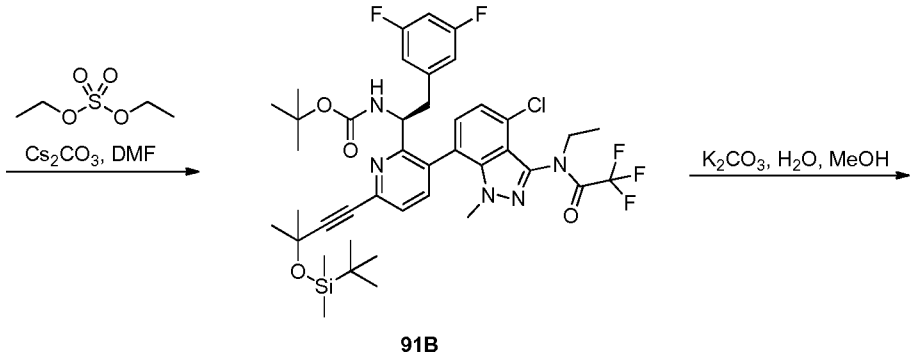
Synthesis of methyl (4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)carbamate (**90D**):

[0596] The title compound (**90D**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound (**33F**) of Example 33 utilizing (S)-methyl (7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)carbamate (**90C**) and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^1H NMR (400 MHz, Methanol-d_4) δ 8.72 (d), 8.66 (d), 7.74 – 7.63 (m), 7.59 – 7.48 (m), 7.20 – 7.14 (m), 7.07 (d), 6.87 – 6.53 (m), 6.46 – 6.33 (m), 5.35 – 5.26 (m), 5.05 – 4.95 (m), 4.80 – 4.64 (m), 3.75 (d), 3.33 (s), 3.28 – 3.07 (m), 2.99 (q), 2.53 – 2.39 (m), 1.64 (s), 1.50 – 1.28 (m), 1.09 (d), 1.06 – 0.99 (m). MS (*m/z*) 800.15 $[M+H]^+$.

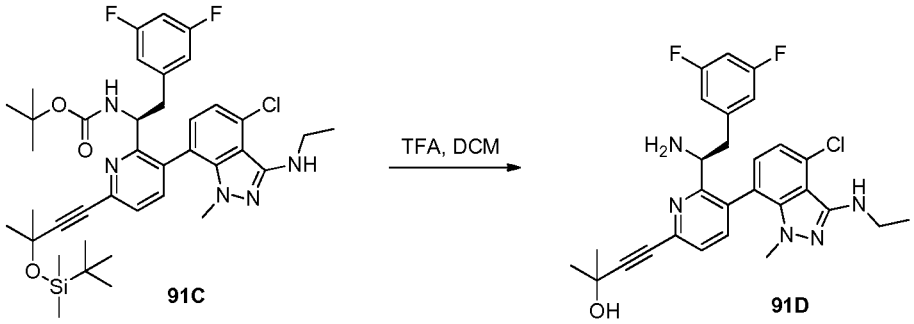
Example 91.



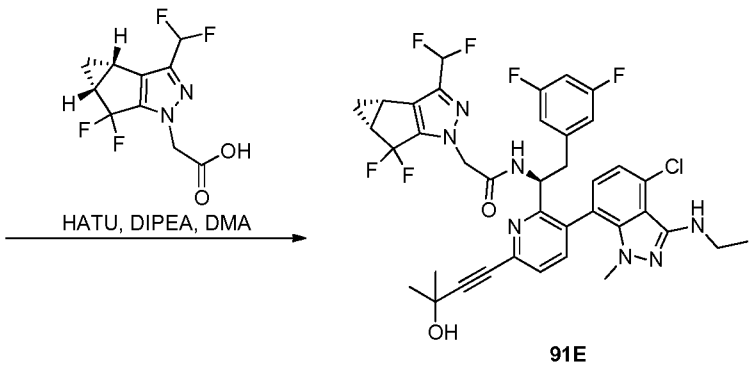
90B 91A



91B



91C 91D



91E

Synthesis of (S)-tert-butyl (1-(6-(3-((tert-butyldimethylsilyl)oxy)-3-methylbut-1-yn-1-yl)-3-(4-chloro-1-methyl-3-(2,2,2-trifluoroacetamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate **(91A)**.

[0597] To a solution of (S)-tert-butyl (1-(3-(3-amino-4-chloro-1-methyl-1H-indazol-7-yl)-6-(3-((tert-butyldimethylsilyl)oxy)-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**90B**) (93 mg, 0.13 mmol) in dichloromethane (0.5 ml) was added DIPEA (34.14 µl, 0.2 mmol), followed by trifluoroacetic anhydride (25.5 µl, 0.18 mmol). After stirring at room temperature for 1h, the product was extracted with dichloromethane and water. The organic layer was dried with Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica gel chromatography to provide the title compound. MS (*m/z*) 806.04 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(6-(3-((tert-butyldimethylsilyl)oxy)-3-methylbut-1-yn-1-yl)-3-(4-chloro-3-(N-ethyl-2,2,2-trifluoroacetamido)-1-methyl-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate **(91B).**

[0598] To a solution of (S)-tert-butyl (1-(6-(3-((tert-butyldimethylsilyl)oxy)-3-methylbut-1-yn-1-yl)-3-(4-chloro-1-methyl-3-(2,2,2-trifluoroacetamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**91A**) (20 mg, 0.02 mmol) in DMF (0.5 ml) was added cesium carbonate (20.2 mg, 0.06 mmol), followed by diethylsulfate (4.6 mg, 0.03 mmol). After stirring at room temperature overnight, the reaction mixture was extracted with ethyl acetate and water. The organic layer was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was taken to the next step without further purification.

Synthesis of (S)-tert-butyl (1-(6-(3-((tert-butyldimethylsilyl)oxy)-3-methylbut-1-yn-1-yl)-3-(4-chloro-3-(ethylamino)-1-methyl-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate **(91C).**

[0599] To a solution of (S)-tert-butyl (1-(6-(3-((tert-butyldimethylsilyl)oxy)-3-methylbut-1-yn-1-yl)-3-(4-chloro-3-(N-ethyl-2,2,2-trifluoroacetamido)-1-methyl-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (21 mg) (**91B**) in methanol (0.5mL) was added 2M aqueous K_2CO_3 (0.25mL). After stirring at room temperature for 2 h, the reaction mixture was concentrated *in vacuo*. The mixture was extracted with ethyl acetate and water. The organic layer was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was taken to the next step without further purification.

Synthesis of (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(4-chloro-3-(ethylamino)-1-methyl-1H-indazol-7-yl)pyridin-2-yl)-2-methylbut-3-yn-2-ol **(91D).**

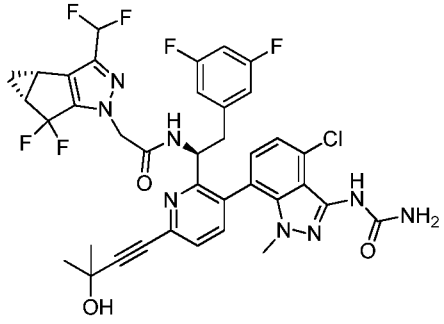
[0600] The title compound (**91D**) was prepared according to the method presented for the synthesis of compound (**90C**) of Example 90 utilizing (S)-tert-butyl (1-(6-(3-((tert-

butyldimethylsilyl)oxy)-3-methylbut-1-yn-1-yl)-3-(4-chloro-3-(ethylamino)-1-methyl-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**91C**). MS (*m/z*) 524.55 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(4-chloro-3-(ethylamino)-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide **(91E)**

[0601] The title compound (**91E**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound (**90D**) of Example 90 utilizing (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(4-chloro-3-(ethylamino)-1-methyl-1H-indazol-7-yl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (**91D**). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.73 – 7.60 (m), 7.58 – 7.48 (m), 7.12 (d), 7.04 (d), 6.93 (d), 6.85 – 6.79 (m), 6.78 – 6.71 (m), 6.71 – 6.66 (m), 6.67 – 6.58 (m), 6.58 – 6.53 (m), 6.49 – 6.32 (m), 6.32 – 6.28 (m), 5.26 – 5.20 (m), 5.04 (t), 4.80 – 4.67 (m), 4.10 (q), 3.42 – 3.28 (m), 3.27 – 3.17 (m), 3.17 – 3.05 (m), 3.05 – 2.91 (m), 2.82 (s), 2.53 – 2.40 (m), 2.01 (s), 1.64 (s), 1.41 – 1.21 (m), 0.96 – 0.82 (m). MS (*m/z*) 770.15 $[M+H]^+$.

Example 92.



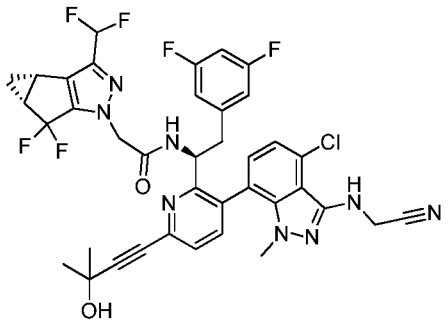
92

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-ureido-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide **(92)**.

[0602] To a solution of N-((S)-1-(3-(3-amino-4-chloro-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**57**) (30 mg, 0.04 mmol) in acetic acid (0.4 ml) was added a solution

of potassium cyanate (3.9 mg, 0.049 mmol) in water (0.05 ml). After stirring at 50 ºC for 2 h, the reaction was concentrated and purified by reverse phase HPLC to provide the title product as a mixture of atropisomers. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.72 (dd), 7.69 (dd), 7.54 (dd), 7.22 – 7.10 (m), 7.04 (d), 6.88 – 6.52 (m), 6.47 – 6.32 (m), 5.31 – 5.22 (m), 5.03 – 4.92 (m), 4.76 (s), 4.72 (d), 3.28 (s), 3.18 – 3.10 (m), 3.04 – 2.94 (m), 2.94 (s), 2.53 – 2.40 (m), 1.64 (s), 1.46 – 1.25 (m), 1.12 – 1.05 (m), 1.05 – 0.99 (m). MS (*m/z*) 785.15 $[M+H]^+$.

Example 93.

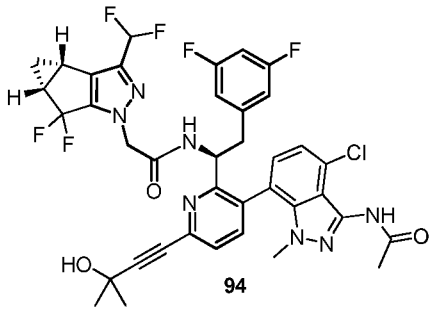


93

Synthesis of N-((S)-1-(3-(4-chloro-3-((cyanomethyl)amino)-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide **(93)**.

[0603] The title compound (**93**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound (**91D**) of Example 91 utilizing bromoacetonitrile in place of diethyl sulfate during the synthesis of compound (**91B**). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.69 (d), 8.63 – 8.55 (m), 7.67 (dd), 7.56 – 7.48 (m), 7.11 (d), 6.99 (d), 6.86 (dd), 6.78 – 6.72 (m), 6.70 (d), 6.67 – 6.60 (m), 6.57 (d), 6.45 – 6.31 (m), 5.35 – 5.28 (m), 5.08 – 5.00 (m), 4.77 (s), 4.73 (s), 4.35 – 4.23 (m), 3.20 (s), 3.12 (dd), 3.05 – 2.92 (m), 2.89 (s), 2.54 – 2.39 (m), 1.64 (s), 1.44 – 1.30 (m), 1.12 – 1.07 (m), 1.07 – 1.01 (m). MS (*m/z*) 828.18 $[M+H]^+$.

Example 94.

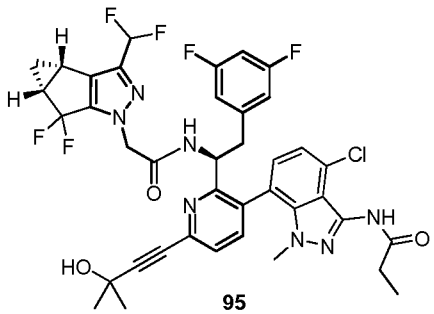


94

Synthesis of N-((S)-1-(3-(3-acetamido-4-chloro-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**94**):

[0604] The title compound (**94**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **84** of Example 84 utilizing acetyl chloride. ^{1}H NMR (Chloroform-*d*) δ: 7.63 – 7.57 (m), 7.54 – 7.48 (m), 7.25 – 7.22 (m), 6.97 (d), 6.70 (t), 6.70 – 6.63 (m), 6.48 (t), 6.24 (d), 6.19 (d), 6.15 (d), 5.63 – 5.55 (m), 4.99 (q), 4.76 (d), 4.70 (d), 3.29 (s), 3.09 – 2.94 (m), 2.55 – 2.40 (m), 2.30 (d), 1.72 (d), 1.41 (q), 1.21 – 1.12 (m). MS (*m/z*) 784.9 $[M+H]^+$.

Example 95.



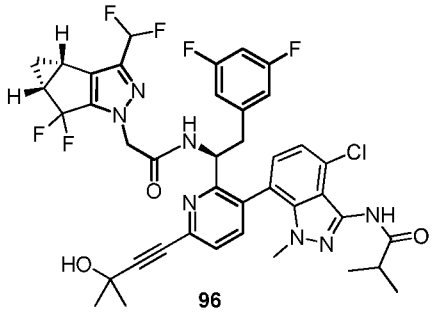
95

Synthesis of N-(4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)propionamide (**95**):

[0605] The title compound (**95**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **84** of Example 84 utilizing propionyl chloride. ^{1}H NMR (Chloroform-*d*) δ: 7.62 – 7.43 (m), 7.35 – 7.17 (m), 6.95 (d), 6.71 (t), 6.69 – 6.62 (m), 6.53 – 6.44 (m), 6.30 – 6.16 (m), 6.12 (d), 5.61 – 5.50 (m), 4.96 (q), 4.75 (d), 4.70 (d), 3.28 (s),

3.07 (s), 2.95 (d), 2.56 (qd), 2.61 – 2.36 (m), 1.71 (s), 1.41 (q), 1.36 – 1.21 (m), 1.20 – 1.08 (m). MS (*m/z*) 798.9 $[M+H]^+$.

Example 96.

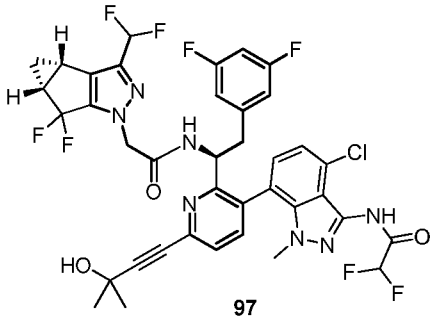


96

Synthesis of N-(4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)isobutyramide (**96**):

[0606] The title compound (**96**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **84** of Example 84 utilizing isobutyryl chloride. ^{1}H NMR (Chloroform-*d*) δ: 7.59 – 7.52 (m), 7.48 (dd), 7.31 – 7.23 (m), 7.22 (s), 6.94 (d), 6.70 (t), 6.69 – 6.61 (m), 6.48 (d), 6.22 (d), 6.18 (d), 6.11 (d), 5.56 (d), 4.96 (q), 4.75 (d), 4.69 (d), 3.28 (s), 3.15 (s), 3.09 (s), 2.96 (d), 2.72 (s), 2.55 – 2.40 (m), 1.71 (s), 1.41 (q), 1.33 (s), 1.21 – 1.13 (m). MS (*m/z*) 813.1 $[M+H]^+$.

Example 97.



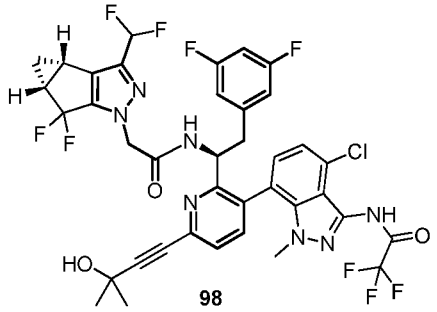
97

Synthesis of N-(4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)-2,2-difluoroacetamide (**97**):

[0607] The title compound (**97**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **84** of Example 84 utilizing 2,2-difluoroacetic

anhydride. ^{1}H NMR (Chloroform-*d*) δ: 8.80 (d), 7.63 – 7.55 (m), 7.54 – 7.46 (m), 7.43 – 7.30 (m), 7.30 – 7.23 (m), 6.99 (d), 6.71 (t), 6.70 – 6.63 (m), 6.53 – 6.46 (m), 6.25 (d), 6.19 (d), 6.17 – 6.11 (m), 6.04 – 5.95 (m), 5.65 – 5.53 (m), 4.98 (q), 4.79 – 4.73 (m), 4.69 (d), 3.33 (s), 3.12 (s), 3.07 – 2.94 (m), 2.60 – 2.34 (m), 1.71 (s), 1.41 (q), 1.26 (s), 1.23 – 1.12 (m)MS (*m/z*) 820.9 $[M+H]^+$.

Example 98.

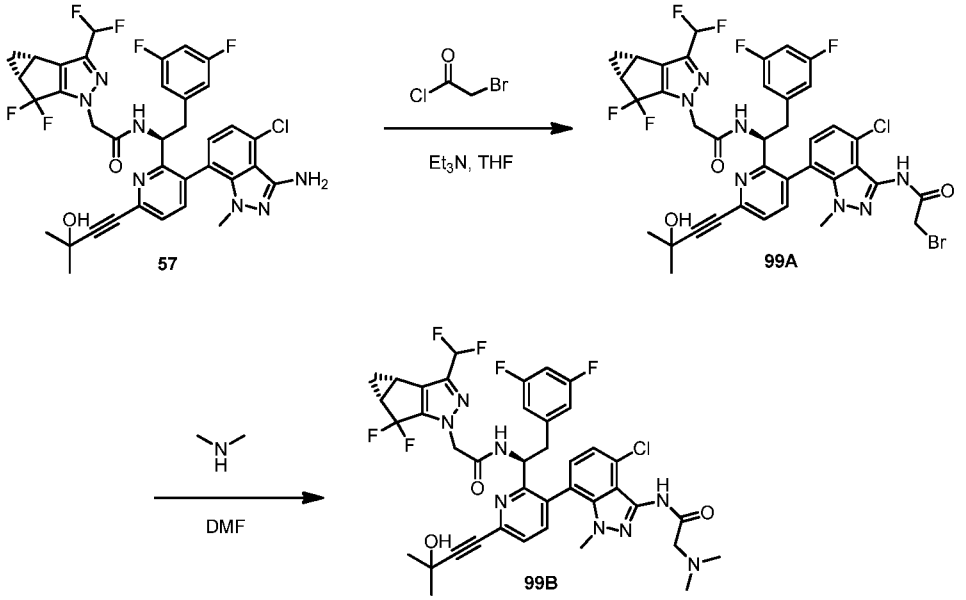


98

Synthesis N-(4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)-2,2,2-trifluoroacetamide (**98**):

[0608] The title compound (**98**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **84** of Example 84 utilizing 2,2,2-trifluoroacetic anhydride. ^{1}H NMR (Chloroform-*d*) δ: 8.77 – 8.72 (m), 8.69 – 8.63 (m), 7.56 – 7.43 (m), 7.31 – 7.19 (m), 7.18 – 7.06 (m), 7.01 – 6.95 (m), 6.71 (t), 6.70 – 6.61 (m), 6.52 – 6.45 (m), 6.24 – 6.16 (m), 6.11 (d), 5.60 – 5.52 (m), 4.93 (q), 4.75 (d), 4.69 (d), 3.32 (s), 3.10 (s), 3.01 – 2.91 (m), 2.57 – 2.38 (m), 2.23 – 2.02 (m), 1.72 (s), 1.47 – 1.37 (m), 1.25 (s), 1.22 – 1.12 (m). MS (*m/z*) 838.8 $[M+H]^+$.

Example 99.



57 99A 99B

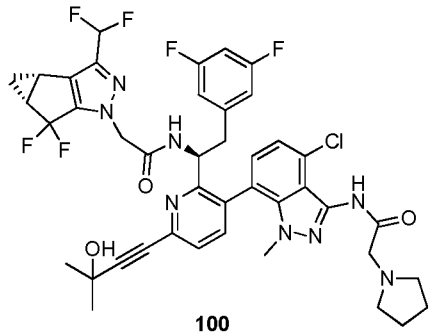
Synthesis of 2-bromo-N-(4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)acetamide (**99A**):

[0609] To the reaction vial containing **57** (32 mg, 0.043 mmol) in THF (0.25 mL) was added 2-bromoacetyl chloride (7 mg, 0.047 mmol), and triethylamine (0.009 mL, 0.06 mmol). The reaction mixture was stirred at room temperature until the majority of **57** was consumed. The reaction mixture was concentrated in vacuo and telescoped to the next reaction. MS (*m/z*) 862.1 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(4-chloro-3-(2-(dimethylamino)acetamido)-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**99B**):

[0610] The crude **99A** material was dissolved in DMF (0.1 mL) and treated with excess dimethylamine at room temperature for 30 min. The reaction mixture was then acidified with TFA and purified by reverse phase HPLC to provide the title compound **99B** as a mixture of atropisomers. ^{1}H NMR (400 MHz, cd_3od) δ 8.90 – 8.69 (m, 1H), 7.73 – 7.65 (m, 1H), 7.59 – 7.49 (m, 1H), 7.23 – 7.06 (m, 1H), 6.89 – 6.59 (m, 2H), 6.53 – 6.29 (m, 3H), 5.03-4.93 (m, 1H), 4.80 – 4.68 (m, 2H), 4.28 (s, 2H), 3.38 –2.96 (m, 9H), 2.91-2.73 (m, 2H), 2.61 – 2.33 (m, 2H), 1.64 (s, 6H), 1.43 – 1.28 (m, 1H), 1.15 – 0.98 (m, 1H). MS (*m/z*) 829.2 $[M+H]^+$.

Example 100.

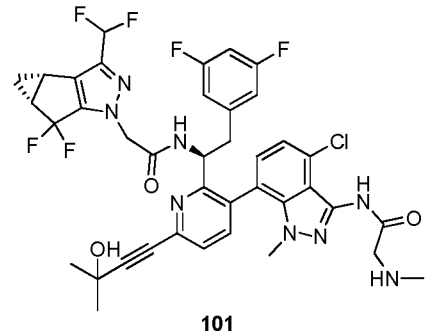


100

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(2-(pyrrolidin-1-yl)acetamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**100**):

[0611] The title compound (**100**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **99B** of Example 99 utilizing pyrrolidine. ^{1}H NMR (400 MHz, cd_3od) δ 8.87 – 8.69 (m), 7.73-7.68 (m), 7.59-7.49 (m), 7.20 (s,), 7.10 (s), 6.90 – 6.69 (m), 6.45 – 6.32 (m), 5.30-5.25 (m), 5.03-4.98 (m), 4.79 – 4.63 (m), 4.37 (s), 3.82-3.64 (m), 3.35 (s), 3.24 – 3.19 (m), 3.01 (s), 2.51-2.43 (m, 2H), 2.30-2.13(m), 1.64 (d), 1.42-1.25 (m), 1.10 (s), 1.00 (s). MS (*m/z*) 854.4 $[M+H]^+$.

Example 101.



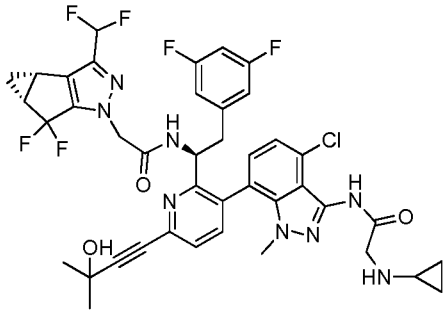
101

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(2-(methylamino)acetamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**101**):

[0612] The title compound (**101**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **99B** of Example 99 utilizing methylamine. ^{1}H NMR (400 MHz, cd_3od) δ 8.85-8.65 (m), 7.79-7.62 (m), 7.60-7.50 (m), 7.21- 7.15 (m), 7.13-7.09 (m), 6.91-6.50 (m), 6.45-6.23 (m), 5.32-5.21 (m), 5.00-4.98 (m), 4.82- 4.68 (m), 4.20-4.15

(s), 4.14-4.08 (s), 3.35 (s), 3.13 – 3.08 (m), 3.03 – 2.98 (m), 2.81 (s), 2.48-2.43 (m), 1.64 (d), 1.50-1.29 (m), 1.12-1.05 (m), 1.03-0.98 (m). MS (*m/z*) 814.2 $[M+H]^+$.

Example 102.

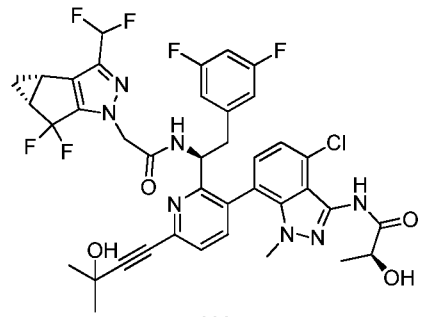


102

Synthesis of N-((S)-1-(3-(4-chloro-3-(2-(cyclopropylamino)acetamido)-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**102**):

[0613] The title compound (**102**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **99B** of Example 99 utilizing cyclopropylamine. ^{1}H NMR (400 MHz, cd_3od) δ 8.74 – 8.69 (m), 7.74 – 7.65 (m), 7.59 – 7.49 (m), 7.19 (s), 7.12 (s) 6.91 – 6.53 (m), 6.38 (m),5.35-5.20 (m), 5.01-4.94 (m), 4.79 – 4.64 (m), 4.21 (s), 3.35 (s), 3.03 – 2.98 (m), 2.91 – 2.86 (m), 2.53 – 2.38 (m), 1.64 (s), 1.45 – 1.36 (m), 1.11 – 0.70 (m). MS (*m/z*) 840.2 $[M+H]^+$.

Example 103.

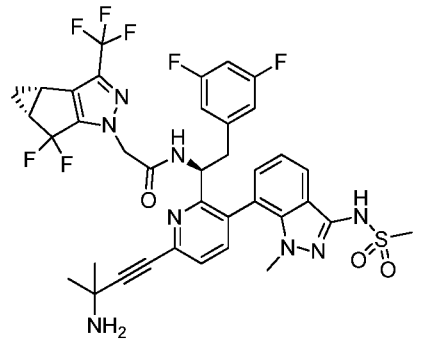


103

Synthesis of (S)-N-(4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)-2-hydroxypropanamide (**103**):

[0614] The title compound (**103**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **84** of Example 84 utilizing (S)-1-chloro-1-oxopropan-2-yl acetate. ^{1}H NMR (400 MHz, cd_3od) δ 8.72-8.64 (m), 7.70 (dd), 7.54 (dd), 7.22 – 7.12 (m), 7.07 (d), 6.87 – 6.66 (m), 6.50 – 6.36 (m), 5.30-5.25 9 (m), 4.99 (t), 4.75 (d), 4.68 (s), 4.38 – 4.28 (m), 3.33 (s), 3.26 – 3.12 (m)), 3.04 – 2.93 (m), 2.52 – 2.38 (m), 1.64 (d), 1.50 (dd), 1.43 – 1.31 (m), 1.10-1.05 (m), 1.04 – 0.98 (m). MS (*m/z*) 815.2 $[M+H]^+$.

Example 104.

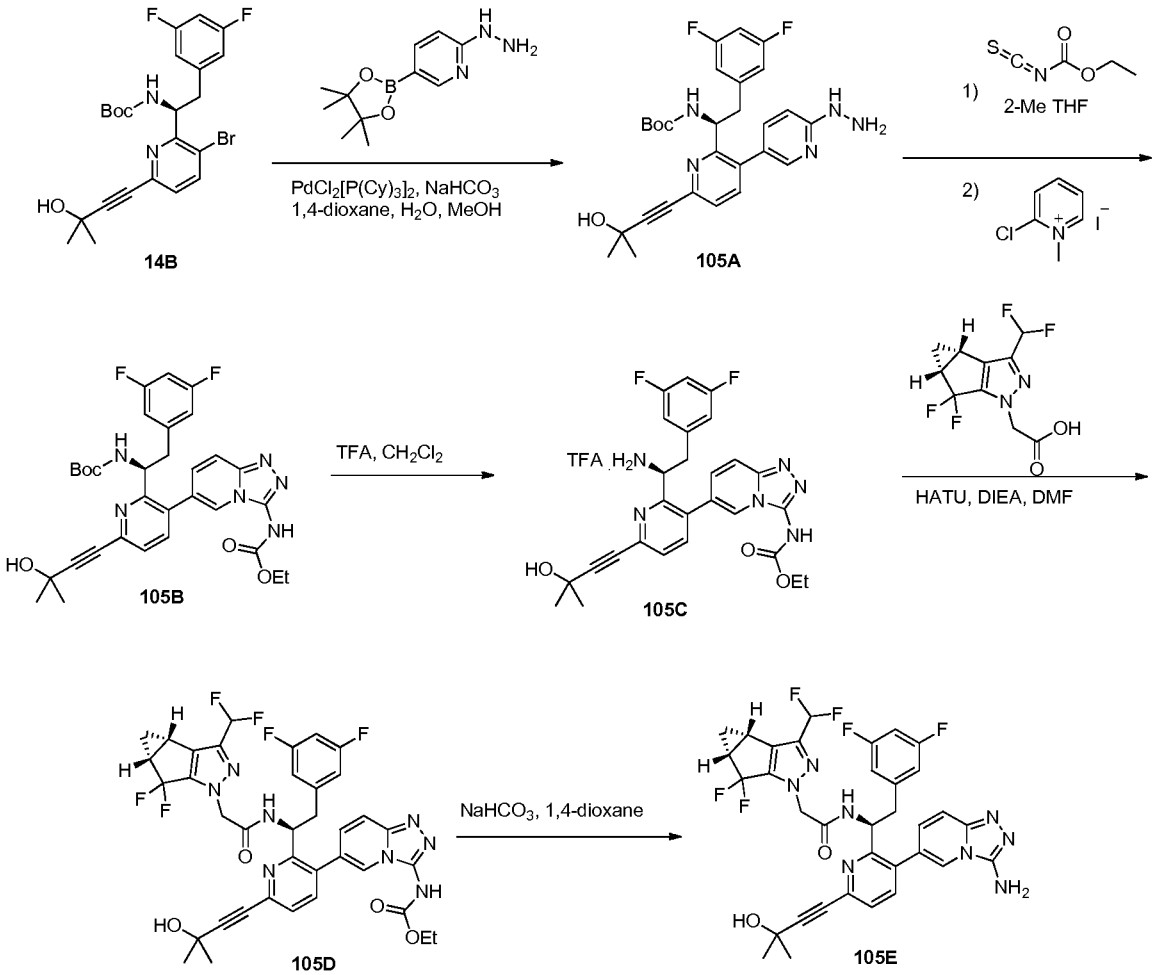


104

Synthesis of N-((S)-1-(6-(3-amino-3-methylbut-1-yn-1-yl)-3-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide **(104).**

[0615] The title compound (**104**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound (**61**) of Example 61 utilizing 2-methylbut-3-yn-2-amine. ^{1}H NMR (400 MHz, Methanol-*d*4) δ 8.71 (d), 7.89 – 7.81 (m), 7.78 (t), 7.63 (dd), 7.27 (dd), 7.20 (dd), 7.10 (dd), 6.79 – 6.71 (m), 6.68 – 6.58 (m), 6.52 (dd), 6.40 – 6.27 (m), 5.33 – 5.24 (m), 5.02 (q), 4.80 – 4.68 (m), 3.32 (s), 3.28 – 3.20 (m), 3.18 (s), 3.16 – 3.10 (m), 3.04 – 2.91 (m), 2.58 – 2.40 (m), 1.83 (s), 1.47 – 1.36 (m), 1.15 – 1.10 (m), 1.08 – 1.02 (m). MS (*m/z*) 803.13 $[M+H]^+$.

Example 105.



Synthesis of (S)-tert-butyl (2-(3,5-difluorophenyl)-1-(6'-hydrazinyl-6-(3-hydroxy-3-methylbut-1-yn-1-yl)-[3,3'-bipyridin]-2-yl)ethyl)carbamate (**105A**):

[0616] In a microwave tube were charged with compound **14B** (50 mg, 0.1 mmol), 2-hydrazinyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (36 mg, 0.15 mmol), potassium carbonate (42 mg, 0.3 mmol) and dichlorobis(tricyclohexylphosphine)palladium(II) (4 mg, 0.005 mmol). To the mixture was added was added 1,4-dioxane (2 mL), water (0.5 mL) and MeOH (0.3 mL). The mixture was heated to 150 °C for 10 minutes in a microwave synthesizer. After cooling to room temperature, the reaction was partitioned between EtOAc and water. The organic layer was separated and washed with brine, then dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography to afford the title compound **105A**. MS (m/z): 524.10 $[M+H]^+$;

Synthesis of Boc-(S)-ethyl (6-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)carbamate (**105B**):

[0617] To a reaction mixture of compound **105A** (28 mg, 0.053 mmol) in 0.5 mL 2-methyltetrahydrofuran was added ethoxycarbonyl isothiocyanate (7 mg, 0.053 mmol) and the reaction was allowed to stir at room temperature for 1 min. The solvent was removed in vacuo. The residue was dissolved in 0.5 mL of methylene chloride and to it was added 2-chloro-1-methylpyridinium iodide (12 mg, 0.046 mmol) followed by triethylamine (0.08 mL, 0.057 mmol). The reaction mixture was stirred at room temperature for 1 min. The solvent was removed in vacuo and the residue was purified by silica gel chromatography to afford the title compound **105B**. MS (m/z): 621.07 $[M+H]^+$.

Synthesis of (S)-ethyl (6-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)carbamate (**105C**):

[0618] Compound **105B** (14 mg, 0.023 mmol) was dissolved in 1 mL of methylene chloride and to it was added 0.15 mL of TFA. The reaction mixture was stirred at room temperature for 40 minutes. The solvent was removed to afford the title compound **105C** as a TFA salt. MS (*m/z*): 521.09 $[M+H]^+$.

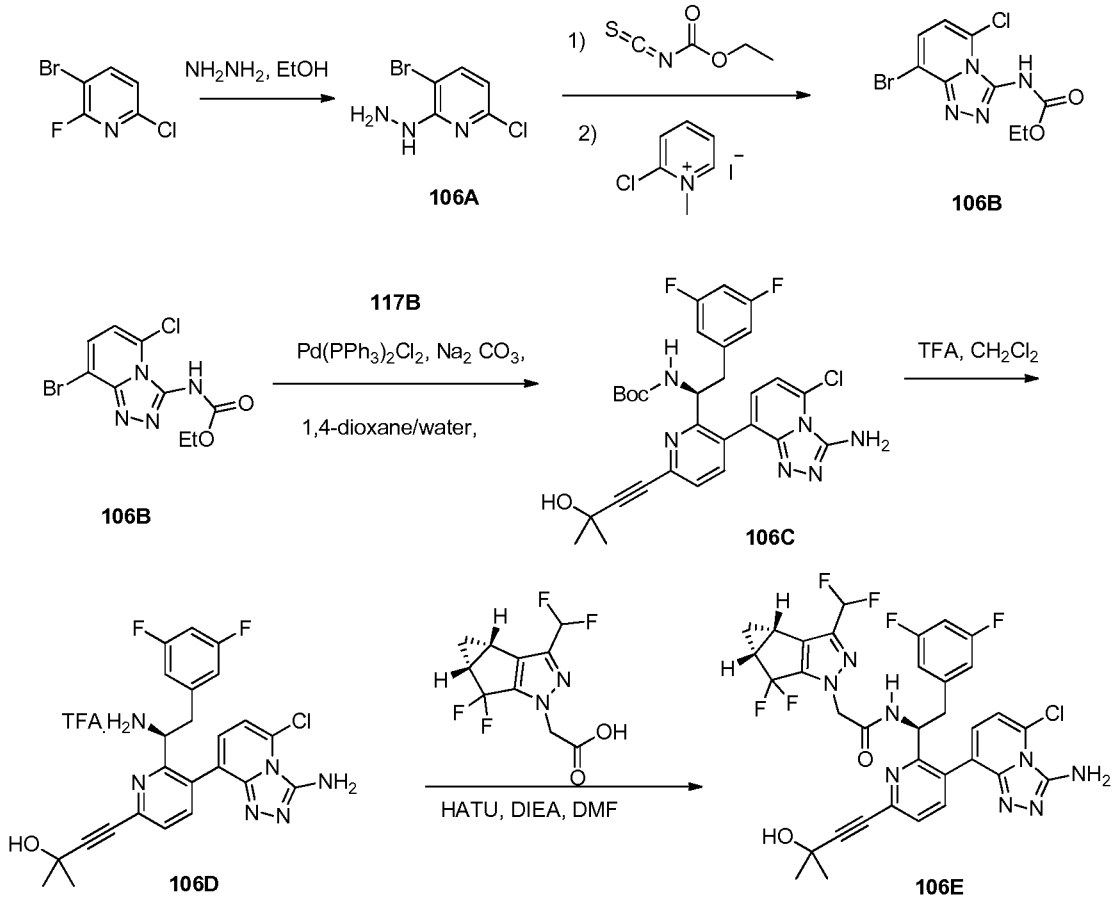
Synthesis of ethyl (6-(2-((S)-1-(2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)carbamate (**105D**):

[0619] The title compound (**105D**) was prepared according to the method presented for the synthesis of compound **37E** of Example 37 utilizing 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid and compound **105C**. MS (*m/z*) 767.18 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(3-amino-[1,2,4]triazolo[4,3-a]pyridin-6-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**105E**):

[0620] Compound **105D** (15.3 mg, 0.05 mmol) was dissolved in 2 mL of 1,4-dioxane and to it was added 0.5 mL of 1M sodium bicarbonate aqueous solution. The reaction mixture was heated in microwave for 1 hour at 140 °C. The solvent was removed and the residue was purified by RP-HPLC to afford the title compound **105E**. ^{1}H NMR (400 MHz, Methanol-d_4): δ 8.08 (s), 7.81 – 7.60 (m), 7.57 – 7.38 (m), 6.77 – 6.70 (m), 6.61 (t), 6.52 – 6.35 (m), 5.36 (t), 4.81 (d), 3.15 (d), 2.59 – 2.27 (m), 1.63 (s), 1.48 – 1.20 (m), 1.10 – 0.78 (m). MS (*m/z*): 695.30 $[M+H]^+$.

Example 106.



Synthesis of 3-bromo-6-chloro-2-hydrazinylpyridine (**106A**):

[0621] To a mixture of 3-bromo-6-chloro-2-fluoropyridine (6 g, 28.5 mmol) in 200 mL ethanol was added 14 mL of hydrazine monohydrate . The reaction mixture was stir at room temperature for overnight and then removed most of the solvent. The precipitate was collected by vacuum filtration to afford the title compound **106A**. MS (*m/z*): 223.97 $[M+H]^+$.

Synthesis of ethyl (8-bromo-5-chloro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)carbamate (**106B**):

[0622] The title compound (**106B**) was prepared according to the method presented for the synthesis of compound **105B** of Example 105 utilizing compound **106A**. MS (*m/z*) 321.01 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(3-(3-amino-5-chloro-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**106C**):

[0623] In a microwave tube were charged with compound **117B** (48 mg, 0.1 mmol), compound **106B** (40 mg, 0.13 mmol), sodium carbonate (33 mg, 0.03 mmol) and $PdCl_2[PPh_3]_2$ (8 mg, 0.01 mmol). To the mixture was added 2.5 mL of 1,4-dioxane and 0.5 mL of water. The mixture was heated to 170 °C for 20 minutes in a microwave synthesizer. After cooling to room

temperature, the reaction was partitioned between EtOAc and water. The organic layer was separated and washed with brine, then dried over $MgSO_4$, filtered and concentrated. The residue was purified by reverse phase HPLC to afford the title compound **106C**. MS (*m/z*): 583.01 $[M+H]^+$

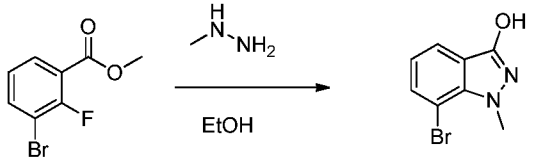
Synthesis of (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(3-amino-5-chloro-[1,2,4]triazolo[4,3-a]pyridin-8-yl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (**106D**):

[0624] The title compound (**106D**) was prepared according to the method presented for the synthesis of compound **105C** of Example 105 utilizing compound **106C**. MS (*m/z*) 483.28 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(3-amino-5-chloro-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**106E**):

[0625] The title compound (**106E**) was prepared according to the method presented for the synthesis of compound **37E** of Example 37 utilizing 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid and compound **106D** . ^1H NMR (400 MHz, Methanol-d_4): δ 8.79 (d), 7.71 (d), 7.52 (d), 7.04 (d), 6.69 – 6.63 (m), 6.68 (t), 6.59 – 6.36 (m), 5.41 – 5.12 (m), 4.75 – 4.48 (m), 3.25 – 2.97 (m), 2.55 – 2.35 (m), 1.62 (s), 1.38 (q), 1.12 – 0.96 (m). MS (*m/z*): 729.24 $[M+H]^+$.

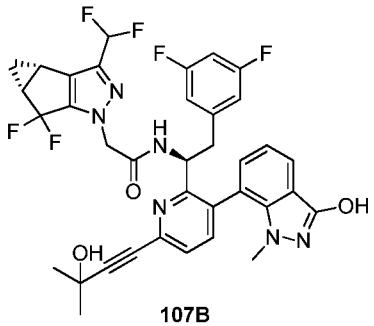
Example 107.



107A

Synthesis of 7-bromo-1-methyl-1H-indazol-3-ol (**107A**):

[0626] To the reaction vial containing methyl 3-bromo-2-fluorobenzoate (1 g, 4.5 mmol) in ethanol (5 mL) was added methylhydrazine (0.29 mL, 6 mmol). The reaction mixture was sealed and heated to 125°C overnight. Upon cooling, the reaction mixture was treated with water and the resulting solid was collected by filtration to give the title product **107A**. MS (*m/z*) 229.1 $[M+2H]^+$.

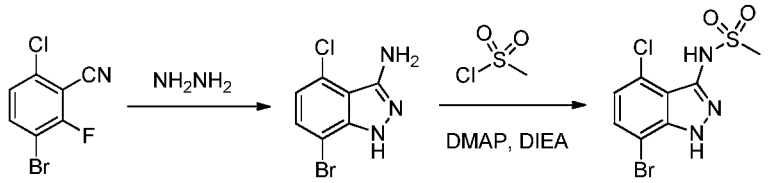


107B

Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-methyl-3-oxo-2,3-dihydro-1H-indazol-7-yl)pyridin-2-yl)ethyl)acetamide (**107B**):

[0627] The title compound (**107B**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **117F** of Example 117 utilizing **107A** and **117B**. ^{1}H NMR (400 MHz, cd_3od) δ 8.61 (d), 7.79 – 7.63 (m), 7.52 (dd), 7.28 – 7.21 (m), 7.12 (t), 7.02 (t), 6.76 – 6.67 (m), 6.66 – 6.54 (m), 6.40 (d), 6.34 – 6.27 (m), 5.26 (t), 5.17 – 5.07 (m), 4.83 – 4.74 (m), 3.24 (dd), 3.12 – 2.88 (m), 2.75 (s), 2.55 – 2.42 (m), 1.64 (s), 1.45 – 1.35 (m), 1.14 – 1.06 (m). MS (*m/z*) 727.1 $[M+H]^+$.

Example 108.



108A 108B

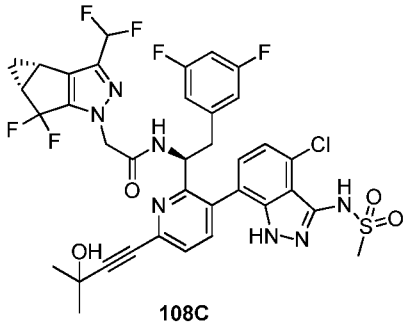
Synthesis of 7-bromo-4-chloro-1H-indazol-3-amine (**108A**):

[0628] In a microwave vial a solution of 3-bromo-2-fluorobenzonitrile (1g, 4.26 mmol) ethanol (5 mL) was treated with hydrazine (0.85 mL, 17 mmol), sealed, and heated to 120 °C in a microwave reactor for 35 minutes. The reaction was concentrated in vacuo and the crude product dissolved with EtOAc (30mL) and washed with water (30 mL), then 2M NaCl (aq, 30 mL). The organics were dried with Na_2SO_4, filtered, and concentrated. Product was purified by silica chromatography to give the title compound. MS (*m/z*) 247.1 $[M+H]^+$.

Synthesis of N-(7-bromo-4-chloro-1H-indazol-3-yl)methanesulfonamide (**108B**):

[0629] To a stirred solution of **108A** (161 mg, 0.65 mmol), 4-dimethylaminopyridine (4 mg, 0.03 mmol), and N,N-diisopropylethylamine (0.28 mL, 1.6 mmol) in DCM (5 ml) at, 0°C was

added drop wise methanesulfonyl chloride (156 mg, 1.3 mmol). The ice bath was removed immediately after the addition and the reaction was warmed to room temperature and stirred for 2h. The reaction was washed with water, dried with Na_2SO_4, filtered, and concentrated. The crude product dissolved with EtOH (10mL) and treated with 8N NaOH (3.3 ml). The reaction mixture was heated at 60°C for 0.5h. The ethanol was removed under vacuum, pH to ~ 2 with 1.0 HCl then, extracted with EtOAc. The organics were dried with Na_2SO_4, filtered, and concentrated. The product was purified by silica chromatography to give the title compound. MS (*m/z*) 325.9 $[M+H]^+$.

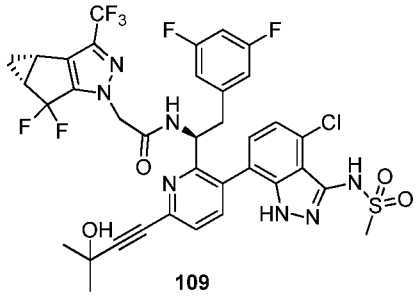


108C

Synthesis of N-((S)-1-(3-(4-chloro-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**108C**):

[0630] The title compound (**108C**) was prepared according to the method presented for the synthesis of compound **117F** of Example 117 utilizing **108B** and **117B**. MS (*m/z*) 807.1 $[M+H]^+$. HPLC retention time 6.96 min (2-98% acetonitrile: water with 0.1% trifluoroacetic acid, 8.5 min gradient on a Phenomonex Kinetex C18 column).

Example 109.



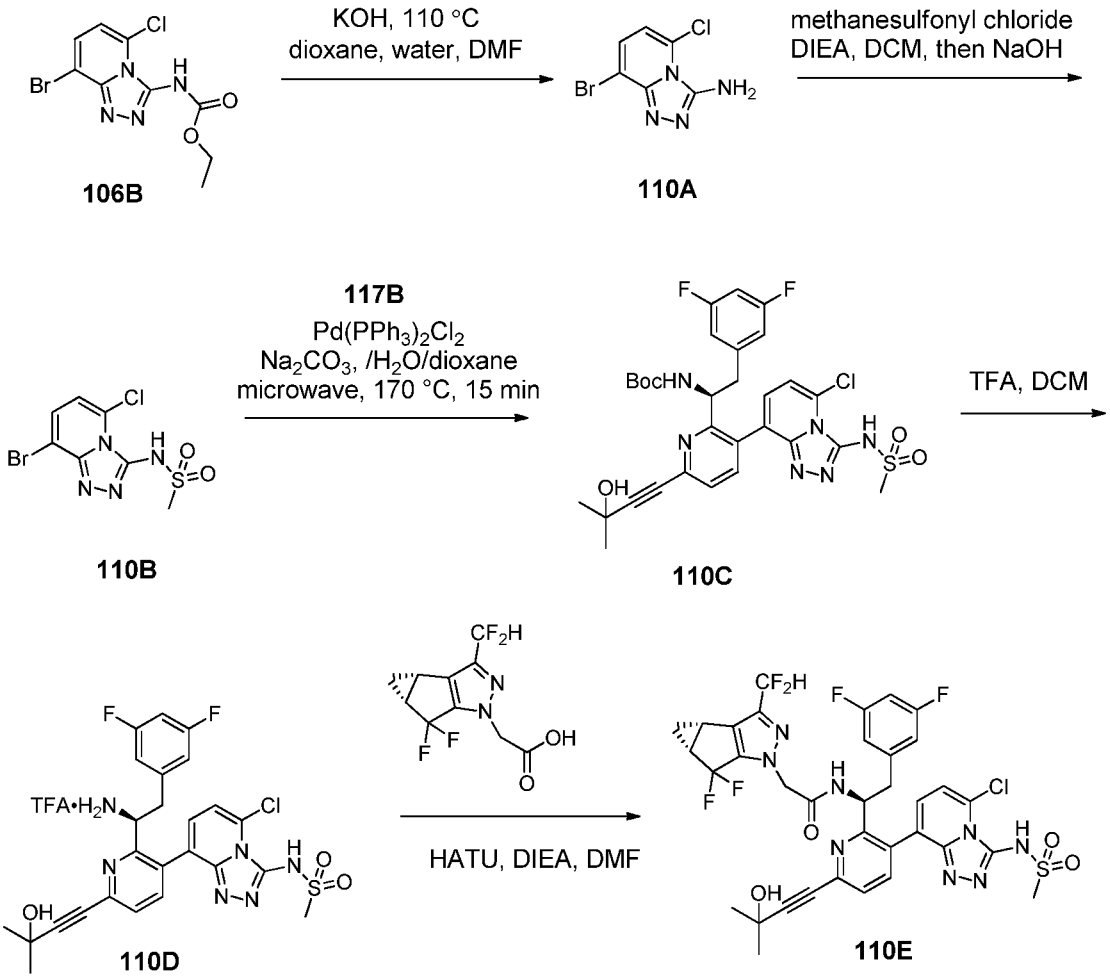
109

Synthesis of N-((S)-1-(3-(4-chloro-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-

(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**109**):

[0631] The title compound (**109**) was prepared according to the method presented for the synthesis of compound **117F** of Example 117 utilizing **108B** , **117B** and 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. MS (*m/z*) 824.2 $[M+H]^+$. HPLC retention time 7.16 min (2-98% acetonitrile: water with 0.1% trifluoroacetic acid, 8.5 min gradient on a Phenomonex Kinetex C18 column).

Example 110.



Synthesis of 8-bromo-5-chloro-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**110A**):

[0632] To a solution of compound **106B** (2.1 g, 6.6 mmol) in a mixture of dioxane (90 mL), water (15 mL) and DMF (9 mL) was added KOH (0.37 g, 6.6 mmol). The mixture was heated at 110 °C overnight. After removing volatiles in vacuo, the residue was purified by silica gel column to yield the title compound **110A**. MS (*m/z*) 248.95 $[M+H]^+$.

Synthesis of N-(8-bromo-5-chloro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methanesulfonamide (**110B**):

[0633] To a solution of compound **110A** (80 mg, 0.3 mmol) in DCM (5 mL) was added DIEA (0.42g, 3 mmol) and methanesulfonyl chloride (0.19 g, 2 mmol). After stirred at room temperature for 5 min, the volatiles was removed in vacuo. The residue was dissolved in a mixture of THF (2 mL), MeOH (2 mL) and 2 N NaOH (2 mL) and stirred for 15 min. After removing volatiles, the residue was purified by reverse phase HPLC to yield the title compound. MS (*m/z*) 326.82 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(3-(5-chloro-3-(methylsulfonamido)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**110C**):

[0634] The title compound (**110C**) was prepared according to the method presented for the synthesis of compound **117D** of Example 117 utilizing compound **110B** and **117B** . MS (*m/z*) 661.02 $[M+H]^+$.

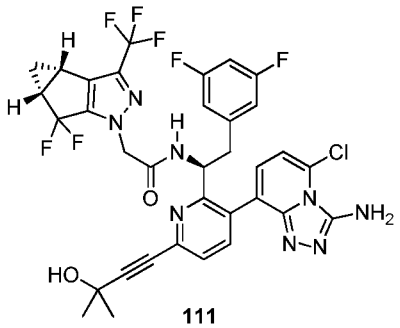
Synthesis of (S)-N-(8-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-5-chloro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methanesulfonamide TFA salt (**110D**):

[0635] The title compound (**110D**) was prepared according to the method presented for the synthesis of compound **19F** of Example 19 utilizing compound **110C**. MS (*m/z*) 561.00 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(5-chloro-3-(methylsulfonamido)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**110E**):

[0636] The title compound (**110E**) was prepared according to the method presented for the synthesis of compound **10A** of Example 10 utilizing compound **110D** and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. HPLC retention time 6.63 min (2-98% acetonitrile: water with 0.1% trifluoroacetic acid, 8.5 min gradient on a Phenomonex Kinetex C18 column 4.6 x 100 mm). MS (*m/z*) 807.16 $[M+H]^+$.

Example 111.

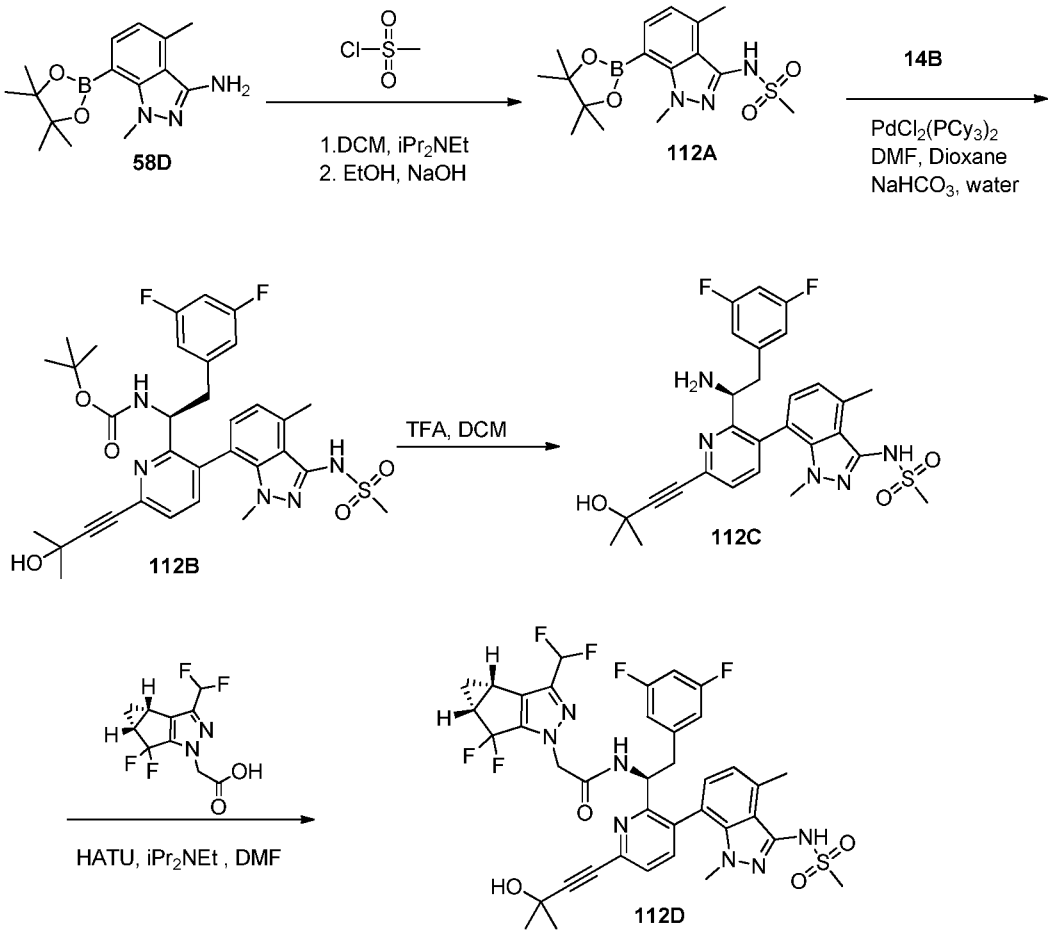


111

Synthesis of N-((S)-1-(3-(3-amino-5-chloro-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**111**):

[0637] The title compound (**111**) was prepared according to the method presented for the synthesis of compound **106E** of Example 106 utilizing 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid and **106D**. ^{1}H NMR (400 MHz, Methanol-d_4): δ 8.83 (d), 7.72 (d), 7.51 (d), 6.98 (d), 6.64 (t), 6.58 – 6.44 (m), 5.41 – 5.18 (m), 4.74 (s), 3.27 – 2.96 (m), 2.67 – 2.18 (m), 1.62 (s), 1.40 (q), 1.17 – 0.99 (m). MS (*m/z*): 747.30 $[M+H]^+$

Example 112.



Synthesis of N-(1,4-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-yl)methanesulfonamide (**112A**):

[0638] The title compound (**112A**) was prepared according to the method presented for the synthesis of compound **19D** of Example 19 utilizing **58D**. MS (m/z) 366.1 $[M+H]^+$.

Synthesis of (S)-tert-butyl (2-(3,5-difluorophenyl)-1-(3-(1,4-dimethyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)ethyl)carbamate (**112B**):

[0639] The title compound (**112B**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19E** of Example 19 utilizing **112A**. MS (*m/z*) 654.4 $[M+H]^+$.

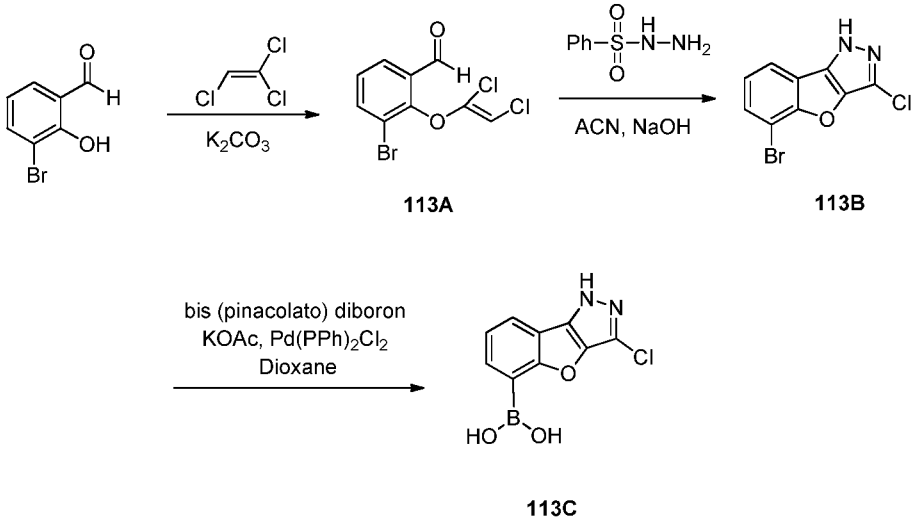
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1,4-dimethyl-1H-indazol-3-yl)methanesulfonamide (**112C**):

[0640] The title compound (**112C**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19F** of Example 19 utilizing **112B**. MS (m/z) 554.2$[M+H]^+$.

Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(3-(1,4-dimethyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)ethyl)acetamide (**112D**):

[0641] The title compound (**112D**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **10A** of Example 10 utilizing **112C** and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (Chloroform-*d*) δ: 8.16 – 8.10 (m), 8.00 (d), 7.76 (d), 7.58 (d), 7.38 (d), 7.06 (dd), 6.86 (dd), 6.67 (t), 6.64 (dt), 6.51 – 6.41 (m), 6.38 (d), 6.24 (dd), 6.13 (dd), 5.62 (q), 5.06 (q), 4.78 (d), 4.69 (s), 3.35 (s), 3.32 (s), 3.29 (s), 3.11 (s), 3.10 – 2.91 (m), 2.87 – 2.78 (m), 2.55 – 2.34 (m), 1.71 (s), 1.45 – 1.34 (m), 1.20 – 1.07 (m) MS (*m/z*) 800.6 $[M+H]^+$.

Example 113.



Synthesis of (Z)-3-bromo-2-((1,2-dichlorovinyl)oxy)benzaldehyde (**113A**):

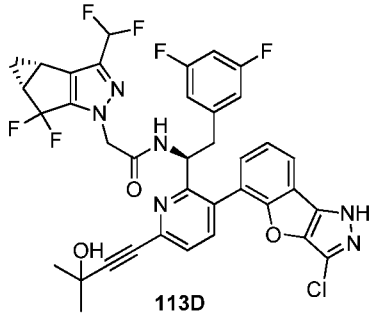
[0642] Trichloroethylene (2.68 mL, 30 mmol) was added drop wise over a period of 30 min to a solution of 3-bromo-2-hydroxybenzaldehyde (2 g, 9.9 mmol) suspended with K_2CO_3 (4.1 g, 30 mmol) in DMF (8 mL) at 60 °C under N_2. The reaction was stirred for 15 h then cooled to room temperature and partitioned between 150 mL of ethylacetate and 100 mL of water. The organic phase was washed with brine 100 mL, dried over sodium sulfate, filtered and concentrated. The crude material was purified by silica gel to give the title compound.

Synthesis of 5-bromo-3-chloro-1H-benzofuro[3,2-c]pyrazolebenzaldehyde (**113B**):

[0643] Benzenesulfonylhydrazide (0.57 g, 3.3 mmol) was added all at once to a solution of the **113A** (0.9 g, 3.0 mmol) in acetonitrile (13 mL) at room temperature. After stirring for 2 h, aqueous 2 M NaOH (3 mL, 6 mmol) was added drop wise over 10 min. The solution was heated to 50 °C and stirred for 1 h. After cooling to room temperature, the solvents were removed under vacuum. The residue was partitioned between 20 mL EtOAc and 15 mL H_2O. The organic layer was dried over $MgSO_4$, filtered and solvent removed under vacuum yielding the title compound **113B**.

Synthesis of (3-chloro-1H-benzofuro[3,2-c]pyrazol-5-yl)boronic acid (**113C**):

[0644] To **113B** (200 mg, 0.73 mmol) in dioxane (5 mL) was added bis(pinacolato)diboron (262 mg, 1 mmol), potassium acetate (0.144 g, 1 mmol), and $Pd(PPh_3)_2Cl_2$ (26 mg, 0.03 mmol). The reaction mixture sealed and heated to 100 °C for 1h. The reaction was cooled to room temperature and telescoped to the next reaction. MS (*m/z*) 237.1 $[M+H]^+$.

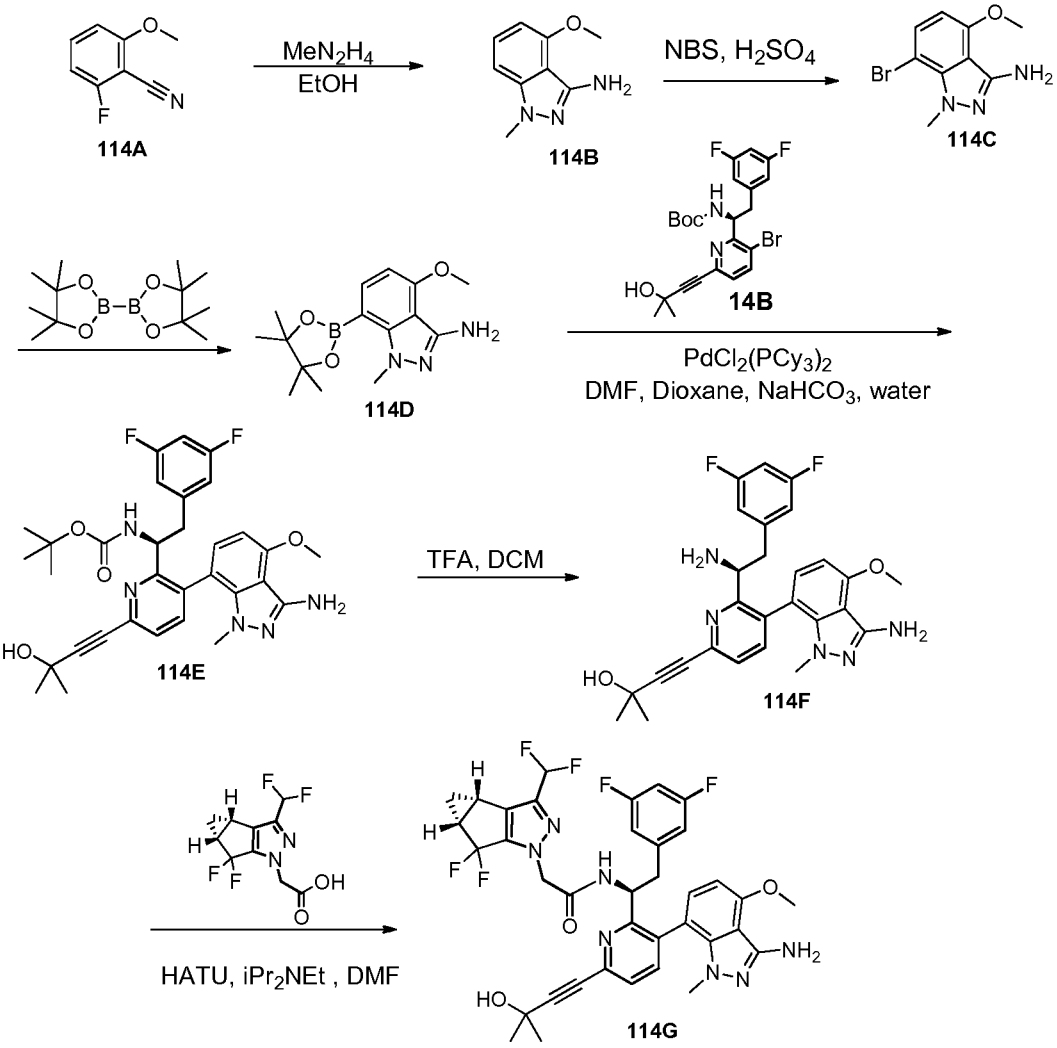


113D

Synthesis of N-((S)-1-(3-(3-chloro-1H-benzofuro[3,2-c]pyrazol-5-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**113D**):

[0645] The title compound (**113D**) was prepared according to the method presented for the synthesis of compound **33F** of Example 33 utilizing **113C** and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^1H NMR (400 MHz, cd_3od) δ 8.88 – 8.60 (m, 1H), 7.80 (d), 7.70 (d), 7.51 (d), 7.35 (t), 6.44 – 6.17 (m), 5.50 – 5.27 (m), 4.80 – 4.74 (m), 3.12 – 2.72 (m), 2.55-2.48 (m), 1.64 (s), 1.45 – 1.35 (m), 1.14 – 1.06 (m). MS (*m/z*) 772.2 $[M+H]^+$.

Example 114.



Synthesis of 4-methoxy-1-methyl-1H-indazol-3-amine (**114B**):

[0646] The title compound (**114B**) was prepared according to the method presented for the synthesis of compound **19B** of Example 19 utilizing **114A**. MS (m/z) 178.1 $[M+H]^+$.

Synthesis of 7-bromo-4-methoxy-1-methyl-1H-indazol-3-amine (**114C**):

[0647] A flask was charged with **114B** (3.7 g, 20.9 mmol) and H_2SO_4 (35 mL) and cooled to 0 ^oC in an ice bath. Then NBS (1.9 g, 10 mmol) was added. The reaction mixture was allowed to warm to room temperature and diluted with ice water and filtered to remove solids. The mother liquor was basified with saturated $NaHCO_3$ and extracted 2X EtOAc. The organic layer was dried over sodium sulfate, concentrated, and purified by flash column chromatography to provide the title compound. MS (*m/z*) 256.2 $[M+H]^+$.

Synthesis of 4-methoxy-1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-amine (**114D**):

[0648] The title compound (**114D**) was prepared according to the method presented for the synthesis of compound **19C** of Example 19 utilizing **114C**. MS (m/z 304.2 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(3-(3-amino-4-methoxy-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**114E**):

[0649] The title compound (**114E**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19E** of Example 19 utilizing **114D**. MS (*m/z* 592.1 $[M+H]^+$.

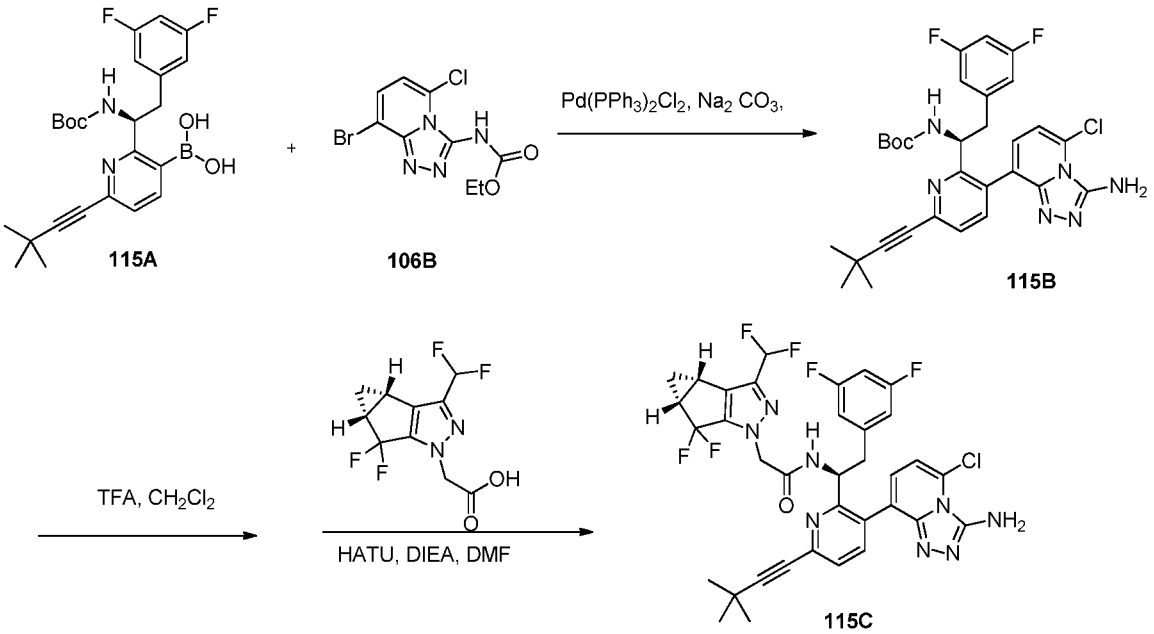
Synthesis of (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(3-amino-4-methoxy-1-methyl-1H-indazol-7-yl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (**114F**):

[0650] The title compound (**114F**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19F** of Example 19 utilizing **114E**. MS (m/z) 492.2 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(3-amino-4-methoxy-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**114G**):

[0651] The title compound (**114G**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **10A** of Example 10 utilizing **114F** and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (Methanol-d_4) δ: 8.72 – 8.62 (m), 7.66 (dd), 7.51 (dd), 7.19 (d), 6.87 – 6.65 (m), 6.65 – 6.51 (m), 6.44 (d), 6.40 – 6.30 (m), 5.34 – 5.26 (m), 5.11 – 4.99 (m), 4.79 – 4.71 (m), 4.02 (d), 3.28 – 3.22 (m), 3.14 (d), 3.07 (dd), 3.02 – 2.90 (m), 2.83 (s), 2.53 – 2.35 (m), 1.63 (d), 1.38 (q), 1.11 – 0.99 (m). MS (*m/z*) 738.6 $[M+H]^+$.

Example 115.



Synthesis of (S)-(2-(1-((tert-butoxycarbonyl)amino)-2-(3,5-difluorophenyl)ethyl)-6-(3,3-dimethylbut-1-yn-1-yl)pyridin-3-yl)boronic acid (**115A**):

[0652] The title compound (**115A**) was prepared according to the method presented for the synthesis of compound **117B** of Example 117 utilizing (S)-(6-bromo-2-(1-((tert-butoxycarbonyl)amino)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)boronic acid (**117A**) and 3,3-dimethylbut-1-yne. MS (*m/z*): 459.22 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(3-(3-amino-5-chloro-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-6-(3,3-dimethylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**115B**):

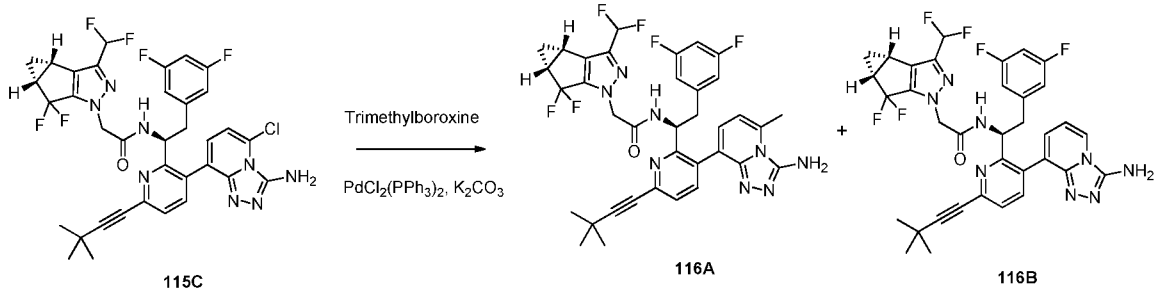
[0653] The title compound (**115B**) was prepared according to the method presented for the synthesis of compound **106C** of Example 106 utilizing compound **115A** and compound **106B**. MS (*m/z*): 581.14 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(3-amino-5-chloro-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-6-(3,3-dimethylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**115C**):

[0654] The title compound (**115C**) was prepared according to the method presented for the synthesis of compound **37E** of Example 37 utilizing 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid and compound **115B**. ^{1}H NMR (400 MHz, Methanol-d_4): δ 8.74 (d), 7.68 (d), 7.45 (d), 7.03 (d),

6.69-6.62 (m), 6.65 (t), 6.59-6.45 (m), 5.36-5.14 (m), 4.69 (s), 3.23-3.05 (m), 2.59-2.22 (m), 1.39 (s), 1.41-1.28 (m), 1.13 – 0.83 (m). MS (*m/z*): 727.41 $[M+H]^+$.

Example 116.



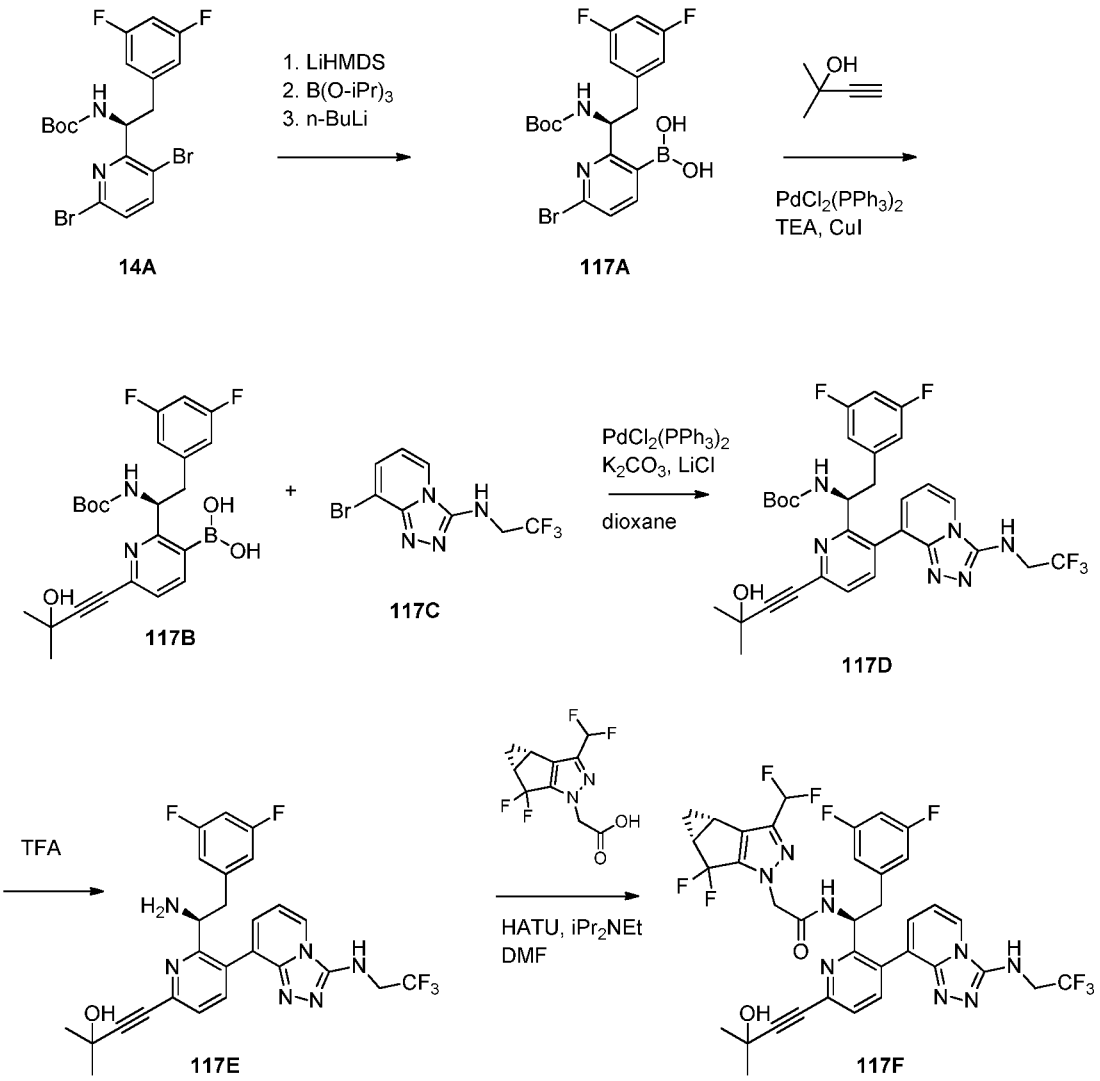
115C 116A 116B

Synthesis of N-((S)-1-(3-(3-amino-5-methyl-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-6-(3,3-dimethylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**116A**):

[0655] In a microwave tube were charged with compound **115C** (15mg, 0.02 mmol), trimethylboroxine (9 μL, 0.06 mmol), potassium carbonate (8.5 mg, 0.06 mmol) and $PdCl_2[PPh_3]_2$ (1.5 mg, 0.002 mmol). To the mixture was added 1 mL of 1,4-dioxane and 0.1 mL of water. The mixture was heated to 160 °C for 20 minutes in a microwave synthesizer. After cooled to room temperature, it was partitioned between EtOAc and water. The organic layer was separated and washed with brine, then dried over $MgSO_4$, filtered and concentrated. The residue was purified by reverse phase HPLC to afford the title compound **116A**. ^1H NMR (400 MHz, Methanol-d_4) δ 8.82 (d), 7.67 (d), 7.47 (d), 6.87 (dd), 6.72-6.65 (m), 6.68 (t), 6.58 – 6.45 (m), 5.26-5.11 (m), 4.70 (s), 3.25-3.05 (m), 2.99 (d), 2.58-2.32 (m), 1.39 (s), 1.39-1.37 (m), 1.14-0.88 (m). MS (*m/z*) 707.30 $[M+H]^+$.

[0656] Compound **116B** was obtained as a side product. MS (*m/z*): 693.23 $[M+H]^+$.

Example 117.



Synthesis of (S)-(6-bromo-2-(1-((tert-butoxycarbonyl)amino)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)boronic acid (**117A**):

[0657] To a solution (S)-tert-butyl (1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**14A**) (6.2 g, 12.6 mmol) in 2-methyltetrahydrofuran (25 ml) was added dropwise 1M LiHMDS in THF (12.6 ml) at 0 °C. After stirring at room temperature for 20 minutes, the reaction was concentrated *in vacuo*, dissolved in toluene (30 mL), concentrated *in vacuo*, and re-dissolved in 2-MeTHF (25 ml). To the resulting solution was added triisopropyl borate (7.11 ml, 37.8 mmol) at -78 °C followed by the dropwise addition of 1M n-butyllithium in hexanes (20 ml) over 15 minutes. After stirring for 5 minutes, the reactions were gradually warmed to 0 °C, and quenched with 4M aqueous NH_4Cl (75mL). Additional 2-MeTHF (25 mL) was added and the organic layer was dried with Na_2SO_4,

filtered, and concentrated *in vacuo*. The crude product was taken to the next step without further purification. MS (*m/z*) 456.87 $[M+H]^+$.

Synthesis of (S)-(2-(1-((tert-butoxycarbonyl)amino)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)boronic acid (**117B**):

[0658] A solution of (S)-(6-bromo-2-(1-((tert-butoxycarbonyl)amino)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)boronic acid (**117A**) (5.76 g, 12.6 mmol), 2-methyl-3-butyn-2-ol (2.44 ml, 25.2 mmol), and triethylamine (7.0 ml, 50.4 mmol) in tetrahydrofuran (21 ml) was degassed with argon. To the reaction was added CuI (72 mg, 0.38 mmol) and $PdCl_2(PPh_3)_2$ (2.65 g, 0.38 mmol) and the resulting mixture was stirred at room temperature for 1h. The reaction was concentrated *in vacuo* and extracted with ethyl acetate and water. The organic layer was dried with Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica chromatography to give the title compound. MS (*m/z*) 460.11 $[M+H]^+$.

Synthesis of 8-bromo-N-(2,2,2-trifluoroethyl)-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**117C**):

[0659] The title compound (**117C**) was prepared according to the method presented for the synthesis of **76C** in Example 76 utilizing 3-bromo-2-hydrazinylpyridine and 1,1,1-trifluoro-2-isothiocyanatoethane. MS (*m/z*) 295.0 $[M+H]^+$.

Synthesis of (S)-tert-butyl (2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(3-((2,2,2-trifluoroethyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)pyridin-2-yl)ethyl)carbamate (**117D**):

[0660] In a microwave vial, (S)-(2-(1-((tert-butoxycarbonyl)amino)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)boronic acid (**117B**, 30 mg, 0.07 mmol) was combined with 8-bromo-N-(2,2,2-trifluoroethyl)-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**117C**, 19 mg, 0.07 mmol), $PdCl_2(PPh_3)_2$ (2 mg, 5 mol%), K_2CO_3 (65 ml of 2 M aqueous solution), and LiCl (1 mg) in dioxane (1 ml). Argon was bubbled into the reaction solution for 5 min. The reaction was heated in a microwave reactor at 155 °C for 15 min. After cooling to ambient temperature, the reaction was partitioned between EtOAc and water. The organics were separated, dried, and removed in vacuo and the residue was purified by column chromatography on silica to provide the title compound (**117D**). MS (*m/z*) 631.0 $[M+H]^+$.

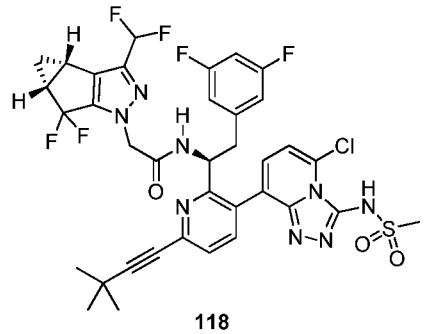
Synthesis of (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(3-((2,2,2-trifluoroethyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (**117E**):

[0661] The title compound (**117E**) was prepared according to the method presented for the synthesis of compound **19F** of Example 19 utilizing compound **117D**.

Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(3-((2,2,2-trifluoroethyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)pyridin-2-yl)ethyl)acetamide (**117F**):

[0662] The title compound (**117F**) was prepared according to the method presented for the synthesis of compound **37E** of Example 37 utilizing compound **117E**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.85 (d), 8.34 (d), 7.76 (d), 7.56 (d), 7.38 (s), 7.23 (t), 6.67 (t), 6.66 – 6.58 (m), 6.51 – 6.45 (m), 5.30 – 5.12 (m), 4.69 (s), 4.33 – 4.18 (m), 3.27 – 3.04 (m), 2.53 – 2.36 (m), 2.00 (d), 1.43 – 1.26 (m), 1.03 (s). MS (*m/z*) 777.1 $[M+H]^+$.

Example 118.

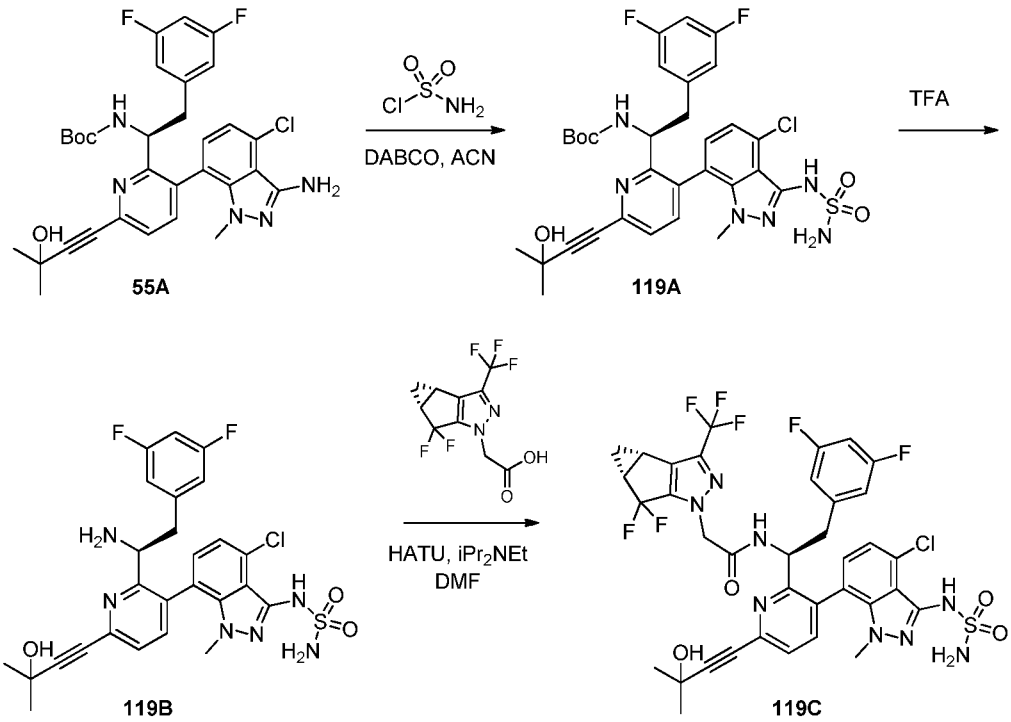


118

Synthesis of N-((S)-1-(3-(5-chloro-3-(methylsulfonamido)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-6-(3,3-dimethylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**118**):

[0663] The title compound (**118**) was prepared according to the method presented for the synthesis of compound **19D** of Example 19 utilizing compound **115C**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.67 (d), 7.69 (d), 7.42 (d), 7.09 – 6.97 (m), 6.89 (d), 6.70 (t), 6.63 (t), 6.53 – 6.41 (m), 5.37-5.19 (m), 4.72 (s), 3.22 – 3.00 (m), 3.11 (s), 2.56 – 2.35 (m), 1.39 (s), 1.39 – 1.33 (m), 1.13 – 0.91 (m).. MS (*m/z*): 805.78 $[M+H]^+$.

Example 119.



Synthesis of (S)-tert-butyl (1-(3-(4-chloro-1-methyl-3-(sulfamoylamino)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**119A**):

[0664] The title compound (**119A**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of **70** in Example 70 utilizing **55**A. MS (*m/z*) 675.0 $[M+H]^+$.

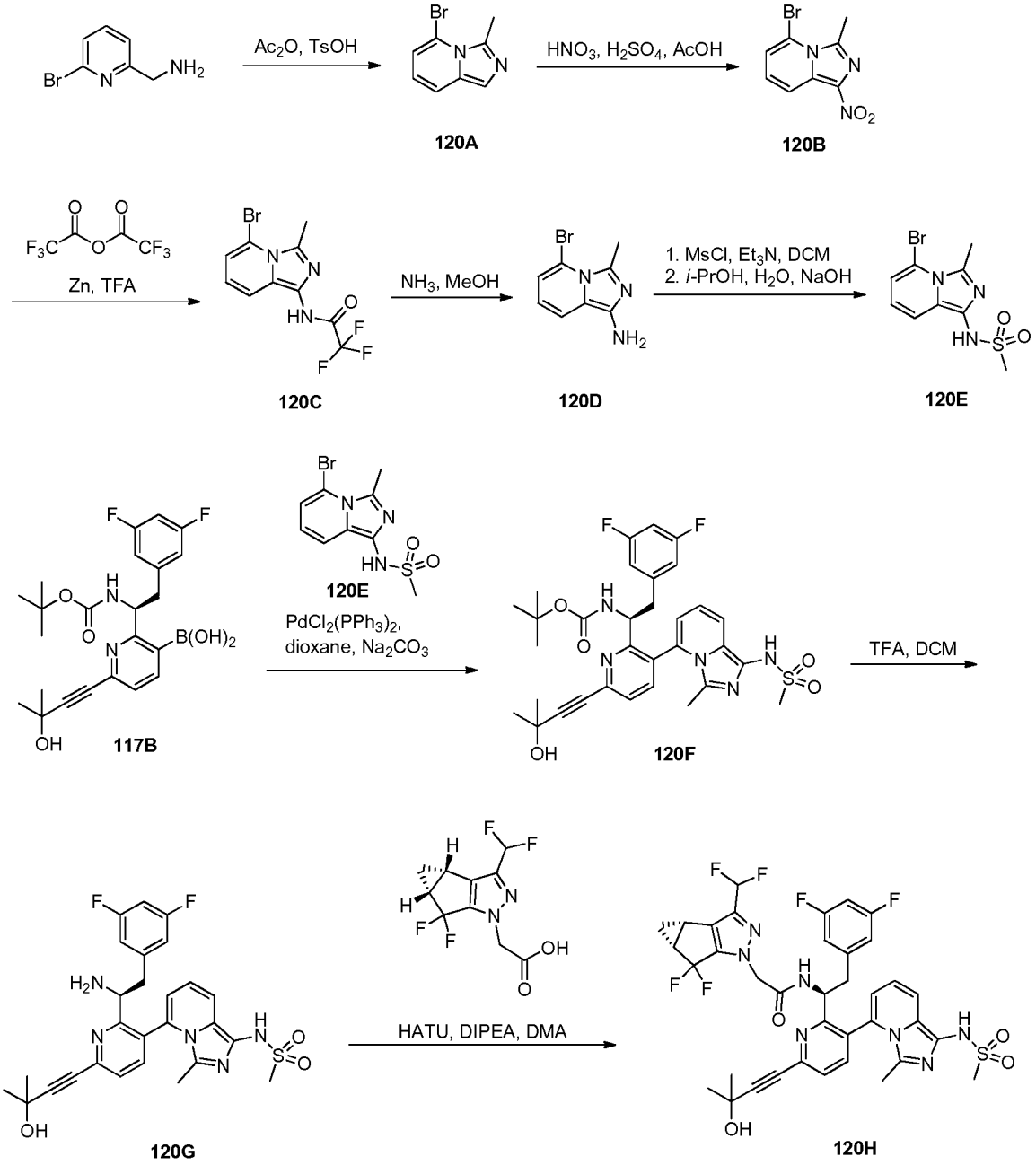
Synthesis of **119B**:

[0665] The title compound (**119B**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of **19F** in Example 19 utilizing **119**A. MS (*m/z*) 575.2 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(sulfamoylamino)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**119C**):

[0666] The title compound (**119C**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of **10A** in Example 10 utilizing **119B** and 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.76 (d), 7.68 (dd), 7.53 (dd), 7.14 (q), 7.05 (d), 6.82 – 6.69 (m), 6.69 – 6.57 (m), 6.46 – 6.40 (m), 6.40 – 6.30 (m), 5.33 – 5.21 (m), 5.05 – 4.92 (m), 4.81 – 4.76 (m), 3.52 – 3.43 (m), 3.29 – 3.20 (m), 3.12 (dd), 3.06 – 2.92 (m), 2.60 – 2.40 (m), 1.49 – 1.31 (m), 1.25 (dd), 1.17 – 1.03 (m). MS (*m/z*): 839.8 $[M+H]^+$.

Example 120.



Synthesis of 5-bromo-3-methylimidazo[1,5-a]pyridine (**120A**):

[0667] 6-(Bromopyridin-2-yl)methylamine (4.0 g, 21.4 mmol) was added dropwise to acetic anhydride (10 ml) at 0 °C. The reaction was warmed to room temperature and to the reaction was added *p*-toluenesulfonic acid (4.07 g, 20.4 mmol). The reaction was heated in a microwave reactor at 140°C for 25 minutes. The reaction was concentrated *in vacuo*, the crude product was taken up in water, pH adjusted to ~9 with 1N aqueous NaOH, and extracted with twice with

ethyl acetate. The organic layers were dried with Na_2SO_4, filtered, concentrated *in vacuo,* and purified by silica gel chromatography to give the title compound. MS (*m/z*) 213.06 $[M+H]^+$.

Synthesis of 5-bromo-3-methyl-1-nitroimidazo[1,5-a]pyridine (**120B**):

[0668] To 5-bromo-3-methylimidazo[1,5-a]pyridine (**120A**) (3.0 g, 14.2 mmol) in acetic acid (15 ml) was added dropwise a solution of 70% HNO_3 (0.82 ml) and conc. H_2SO_4 (0.82 ml) in acetic acid (8 ml). An exotherm was produced during the reaction. After stirring at room temperature for 45 mins, the resulting solution was added to stirring mixture of ice and brine (150 mL). To the chilled solution was added 8M aqueous NaOH (4.3mL). The yellow precipitate was filtered and washed with water. The crude product was taken to the next step without further purification. MS (*m/z*) 255.95 $[M+H]^+$.

Synthesis of N-(5-bromo-3-methylimidazo[1,5-a]pyridin-1-yl)-2,2,2-trifluoroacetamide (**120C**):

[0669] To a solution of 5-bromo-3-methyl-1-nitroimidazo[1,5-a]pyridine (**120B**) (0.30 g, 1.17 mmol) and trifluoroacetic acid anhydride (0.5 ml, 3.51 mmol) in trifluoroacetic acid (4.2 ml) was added in portions zinc dust (0.15 g, 2.34 mmol). The reaction produces a strong exotherm. Upon completion, the reaction was concentrated *in vacuo,* and extracted with EtOAc and saturated aqueous $NaHCO_3$. The organic layer was dried with Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica gel chromatography eluting with ethyl acetate and hexanes to give the title compound. MS (*m/z*) 322.018 $[M+H]^+$.

Synthesis of 5-bromo-3-methylimidazo[1,5-a]pyridin-1-amine (**120D**):

[0670] A solution of N-(5-bromo-3-methylimidazo[1,5-a]pyridin-1-yl)-2,2,2-trifluoroacetamide (**120C**) (50 mg, 0.16 mmol) in 7N ammonia in methanol (1 ml) was heated in a microwave reactor at 70 °C for 30 minutes. The reaction was concentrated *in vacuo.* The resulting crude mixture was suspended in EtOAc, concentrated *in vacuo,* and dried under vacuum. The crude product was taken to the next step without further purification. MS (*m/z*) 228.12 $[M+H]^+$.

Synthesis of N-(5-bromo-3-methylimidazo[1,5-a]pyridin-1-yl)methanesulfonamide (**120E**):

[0671] To a solution of 5-bromo-3-methylimidazo[1,5-a]pyridin-1-amine **(120D)** (35 mg) and triethylamine (48 ul, 0.34 mmol) in dichloromethane (0.5 ml) was added methanesulfonyl chloride (24 µl, 0.31 mmol). After stirring at room temperature for 30 minutes, 2M methylamine in THF (0.250mL) was added, and the reaction was concentrated *in vacuo.* The crude product was dissolved in 2-propanol (2.0 mL) and to the reaction was added 1.0M aqueous NaOH (2.0 mL). After stirring at room temperature for 1.5 h, the reaction was acidified with

AcOH (180 uL), and the resulting mixture was concentrated *in vacuo*. The mixture was extracted with ethyl acetate and water. The organic layers were dried with Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica gel chromatography to give the title compound. MS (*m/z*) 305.88 $[M+H]^+$.

Synthesis of (S)-tert-butyl (2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(3-methyl-1-(methylsulfonamido)imidazo[1,5-a]pyridin-5-yl)pyridin-2-yl)ethyl)carbamate (**120F**):

[0672] A solution of N-(5-bromo-3-methylimidazo[1,5-a]pyridin-1-yl)methanesulfonamide (**120E**) (50 mg, 0.16 mmol), (S)-(2-(1-((tert-butoxycarbonyl)amino)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)boronic acid (**117B**) (90.8 mg, 0.20 µmol) , and dichlorobis(triphenylphosphine)palladium(II) (11.5 mg, 0.016 mmol) in dioxane (1.2 ml) was purged with argon. To the reaction was added 1M aqueous Na_2CO_3 (0.4 ml), solution was purged with argon, and heated in a microwave reactor for 30 mins at 120 °C. To the resulting solution was added 5% AcOH in brine (10 mL) and was extracted twice with EtOAc. The organic layers were dried with Na_2SO_4, filtered, concentrated *in vacuo,* and purified by silica gel chromatography to give the title compound as a mixture of atropisomers. MS (*m/z*) 639.94 $[M+H]^+$.

Synthesis of (S)-N-(5-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-3-methylimidazo[1,5-a]pyridin-1-yl)methanesulfonamide (**120G**):

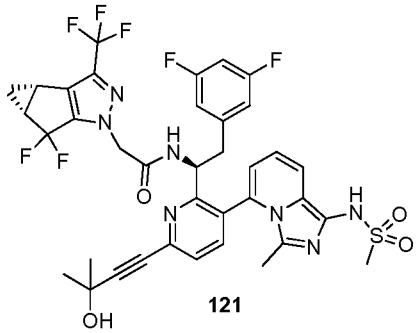
[0673] (S)-tert-butyl (2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(3-methyl-1-(methylsulfonamido)imidazo[1,5-a]pyridin-5-yl)pyridin-2-yl)ethyl)carbamate (**120F**) (75 mg ,0.12 mmol) was dissolved in DCM (1.0 mL) and TFA (0.5 mL) and stirred at room temperature for 30 mins. The resulting solution was concentrated *in vacuo* and extracted with ethyl acetate and saturated aqueous $NaHCO_3$ followed by water. The organic layer was dried with Na_2SO_4, filtered, and concentrated *in vacuo.* The crude product as a mixture of atropisomers was taken to the next step without further purification. MS (*m/z*) 540.12 $[M+H]^+$.

Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(3-methyl-1-(methylsulfonamido)imidazo[1,5-a]pyridin-5-yl)pyridin-2-yl)ethyl)acetamide (**120H**):

[0674] The title compound (**120H**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound (**33F**) of Example 33 utilizing (S)-N-(5-(2-(1-

amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-3-methylimidazo[1,5-a]pyridin-1-yl)methanesulfonamide (**120G**). ^{1}H NMR (400 MHz, Methanol-*d*4) δ 8.88 – 8.81 (m), 8.75 (d), 7.84 (dd), 7.70 – 7.53 (m), 6.90 (dd), 6.83 – 6.74 (m), 6.73 – 6.65 (m), 6.58 (dd), 6.54 – 6.46 (m), 5.99 (dd), 5.31 – 5.22 (m), 5.01 – 4.92 (m), 4.74 – 4.61 (m), 3.41 – 3.28 (m), 3.24 – 3.12 (m), 3.10 – 2.99 (m), 2.53 – 2.39 (m), 1.87 (s), 1.65 (s), 1.64 (s), 1.43 – 1.33 (m), 1.11 – 1.04 (m), 1.05 – 0.97 (m). MS (*m/z*) 786.13 $[M+H]^+$.

Example 121.

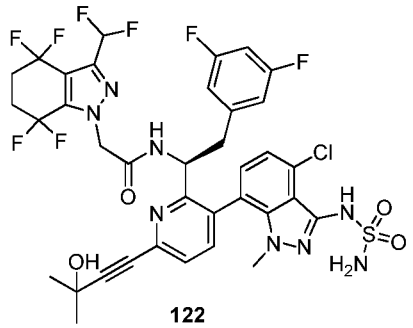


121

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(3-methyl-1-(methylsulfonamido)imidazo[1,5-a]pyridin-5-yl)pyridin-2-yl)ethyl)acetamide (**121**):

[0675] The title compound (**121**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound (**33F**) of Example 33 utilizing (S)-N-(5-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-3-methylimidazo[1,5-a]pyridin-1-yl)methanesulfonamide (**120G**) and 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.97 (d), 8.83 (d), 7.84 (dd), 7.70 (dd), 7.65 – 7.52 (m), 6.96 – 6.86 (m), 6.84 – 6.74 (m), 6.70 – 6.62 (m), 6.62 – 6.55 (m), 6.54 – 6.43 (m), 5.99 (dd), 5.32 – 5.22 (m), 5.01 – 4.89 (m), 4.81 – 4.66 (m), 3.51 – 3.36 (m), 3.26 – 3.15 (m), 3.14 – 2.97 (m), 2.55 – 2.43 (m), 1.88 (s), 1.65 (s), 1.64 (s), 1.46 (s), 1.45 – 1.36 (m), 1.13 (s), 1.09 – 1.04 (m). MS (*m/z*) 804.15 $[M+H]^+$.

Example 122.

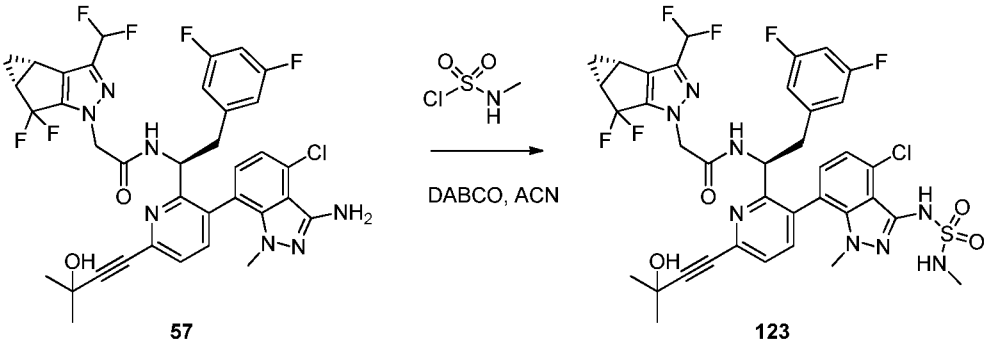


122

Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(sulfamoylamino)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**122**):

[0676] The title compound (**122**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of **10A** in Example 10 utilizing **119B** and 2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.91 – 8.81 (m), 7.69 (dd), 7.53 (dd), 7.22 – 7.12 (m), 7.06 (d), 6.98 – 6.59 (m), 6.50 – 6.32 (m), 5.36 – 5.24 (m), 4.99 (d), 3.34 (s), 3.24 (dd), 3.14 (dd), 3.02 (s), 2.97 (dd), 2.66 – 2.38 (m), 1.63 (s). MS (*m/z*): 859.3 $[M+H]^+$.

Example 123.



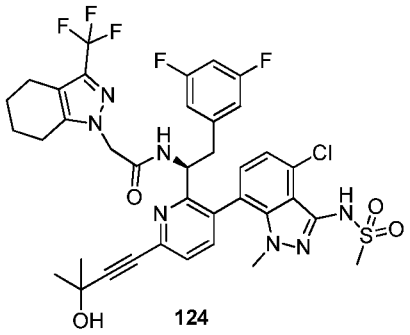
57 123

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-((N-methylsulfamoyl)amino)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**123**):

[0677] The title compound (**123**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of **70** in Example 70 utilizing **57** and methylsulfamoyl chloride. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.75 – 8.67 (m), 7.68 (d), 7.57 – 7.51 (m), 7.15 (d), 7.06 (d), 6.86 – 6.52 (m), 6.48 – 6.29 (m), 5.33 – 5.23 (m), 4.96 (q), 4.80 – 4.64 (m), 3.21 –

3.05 (m), 3.05 – 2.89 (m), 2.78 (s), 2.72 (s), 2.55 – 2.39 (m), 1.64 (s), 1.48 – 1.28 (m), 1.11 – 0.95 (m). MS (*m/z*) 835.8 $[M+H]^+$.

Example 124.

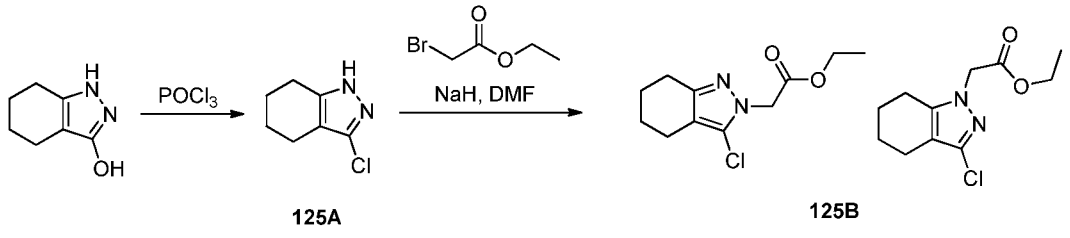


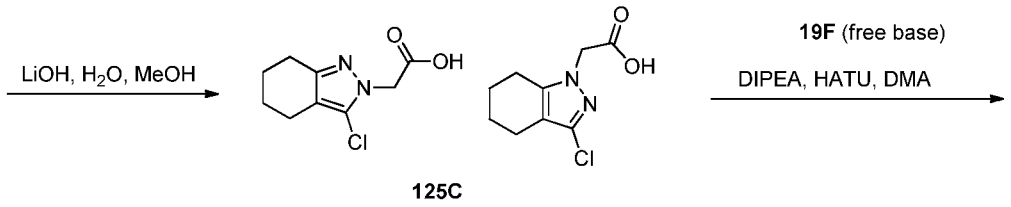
124

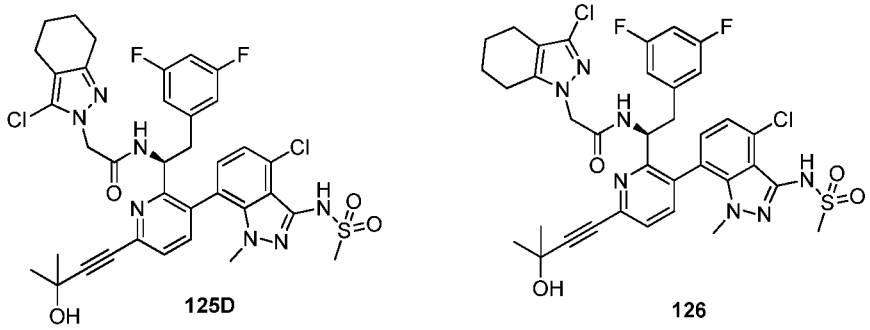
Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**124**):

[0678] The title compound (**124**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **10A** of Example 10 utilizing (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**19F**) and 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, Methanol-d_4) 8.68 (t), 7.71 (dd), 7.54 (dd), 7.25 – 7.14 (m), 7.11 (d), 6.80 – 6.73 (m), 6.69 – 6.60 (m), 6.53 (dd), 6.46 – 6.36 (m), 5.29 – 5.22 (m), 5.04 – 4.96 (m), 4.91 – 4.75 (m), 4.72 (d), 4.67 (d), 4.17 (s), 3.58 (s), 3.33 (s), 3.26 (s), 3.23 (s), 3.15 (dd), 3.04 (s), 3.02 – 2.94 (m), 2.65 – 2.43 (m), 2.40 – 2.28 (m), 1.85 – 1.69 (m), 1.64 (s), 1.64 (s). MS (*m/z*) 804.18 $[M+H]^+$.

Examples 125 and 126.







Synthesis of 3-chloro-4,5,6,7-tetrahydro-1H-indazole **(125A)**:

[0679] A solution of 4,5,6,7-tetrahydro-1H-indazol-3-ol (0.41 g, 3.0 mmol) in trichlorophosphate (1.5 ml) was heated in a microwave reactor under argon at 225 °C for 15 minutes. The reaction was concentrated *in vacuo* and carefully quenched with 1.0N aqueous NaOH at 0°C and extracted with dichloromethane. The organic layer was dried with Na_2SO_4, filtered, concentrated *in* vacuo and purified by silica gel chromatography to give the title compound. MS (*m/z*) 157.14 $[M+H]^+$.

Synthesis of a 1:5 mixture of ethyl 2-(3-chloro-4,5,6,7-tetrahydro-2H-indazol-2-yl)acetate and ethyl 2-(3-chloro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate **(125B)**:

[0680] To a solution of 3-chloro-4,5,6,7-tetrahydro-1H-indazole (**125A**) in DMF (1.6 ml) was added portionwise NaH (60% w/ mineral oil) (74.9 mg, 1.95 mmol). After stirring at room temperature for 15 mins, ethyl bromoacetate (0.22 ml, 1.95 mmol) was added dropwise at 0°C. The reaction was warmed to room temperature and stirred for 2 h. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with water. The organic layer was dried with Na_2SO_4, filtered, concentrated *in vacuo* and purified by

silica gel chromatography to give the title compounds as a 1:5 mixture of ethyl 2-(3-chloro-4,5,6,7-tetrahydro-2H-indazol-2-yl)acetate and ethyl 2-(3-chloro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate **(125B)**. MS (*m/z*)243.11 $[M+H]^+$.

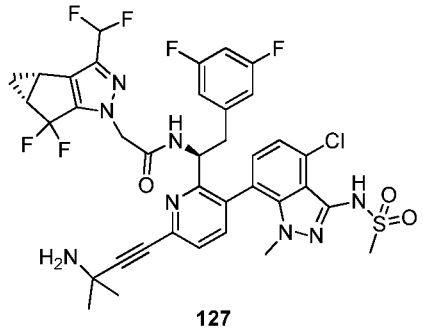
Synthesis of a 1:5 mixture of 2-(3-chloro-4,5,6,7-tetrahydro-2H-indazol-2-yl)acetic acid and 2-(3-chloro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid **(125C)**:

[0681] To a 1:5 mixture of ethyl 2-(3-chloro-4,5,6,7-tetrahydro-2H-indazol-2-yl)acetate and ethyl 2-(3-chloro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (**125B**) (15 mg, 61.8 μmol) in methanol (250 μl) was added 2M aqueous LiOH (62 μl). The reaction was heated at 50°C for 1.5 h. The mixture was concentrated *in vacuo*, extracted with 2-methyltetrahydrofuran (2 mL) and 0.1N HCl (1.3 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was taken to the next step without further purification. MS (*m/z*) 215.14 $[M+H]^+$.

Syntheses of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-chloro-4,5,6,7-tetrahydro-2H-indazol-2-yl)acetamide **(125D)** and of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-chloro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide **(126)**.

[0682] The title compounds (**125D and 126**) were both prepared as mixtures of atropisomers according to the method presented for the synthesis of compound **33F** of Example 33 utilizing the free base form of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**19F**) and 1:5 mixture of 2-(3-chloro-4,5,6,7-tetrahydro-2H-indazol-2-yl)acetic acid and 2-(3-chloro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid **(125C)**. The regioisomers were separated by reverse phase HPLC to provide the title products. **(125D):** ^{1}H NMR (400 MHz, Methanol-*d*4) δ 8.56 – 8.45 (m), 7.70 (dd), 7.53 (dd), 7.27 – 7.14 (m), 7.10 (d), 6.79 – 6.71 (m), 6.66 – 6.59 (m), 6.53 – 6.47 (m), 6.44 – 6.33 (m), 5.32 – 5.22 (m), 5.05 – 4.92 (m), 4.71 (d), 4.67 (s), 3.36 (s), 3.25 (s), 3.23 (s), 3.21 – 3.16 (m), 3.16 – 3.07 (m), 3.03 (s), 3.01 – 2.90 (m), 2.64 – 2.53 (m), 2.44 – 2.30 (m), 1.76 (dd), 1.64 (s), 1.64 (s). MS (*m/z*) 770.24 $[M+H]^+$. **(126):** ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.71 (dd), 7.53 (dd), 7.27 – 7.14 (m), 7.11 (d), 6.82 – 6.7 (m), 6.68 – 6.60 (m), 6.54 (d), 6.47 – 6.34 (m), 5.26 (dd), 5.00 (t), 4.60 (s), 4.55 (s), 3.34 (s), 3.26 (s), 3.23 (s), 3.25 – 3.19 (m), 3.17 – 3.10 (m), 3.03 (s), 3.02 – 2.92 (m), 2.47 – 2.27 (m), 1.85 – 1.67 (m), 1.64 (s), 1.64 (s). MS (*m/z*) 770.24 $[M+H]^+$.

Example 127.

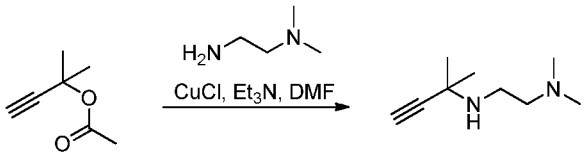


127

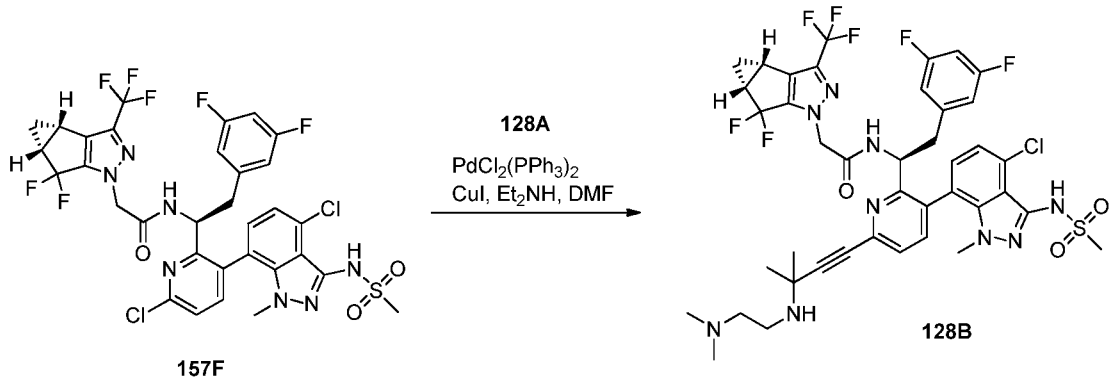
Synthesis of N-((S)-1-(6-(3-amino-3-methylbut-1-yn-1-yl)-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**127**):

[0683] The title compound (**127**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **142** of Example 142 utilizing 2-methylbut-3-yn-2-amine. ^{1}H NMR (400 MHz, cd_3od) δ 8.79 (t), 7.79 (d), 7.76 (d), 7.64 (d), 7.61 (d), 7.22 – 7.15 (m), 7.08 (d), 6.82 – 6.75 (m), 6.70 – 6.63 (m), 6.45 – 6.40 (m), 6.40 – 6.35 (m), 5.30 – 5.21 (m), 5.04 – 4.95 (m), 4.78 (s), 4.75 (d), 3.32 (s), 3.26 (s), 3.23 (s), 3.20 – 3.13 (m), 3.06 – 2.95 (m), 2.94 (s), 2.50 (ddt), 1.82 (s), 1.82 (s), 1.48 – 1.28 (m), 1.14 (dd), 1.09 – 1.00 (m). MS (*m/z*) 838.3 $[M+H]^+$.

Example 128.



128A



157F

128B

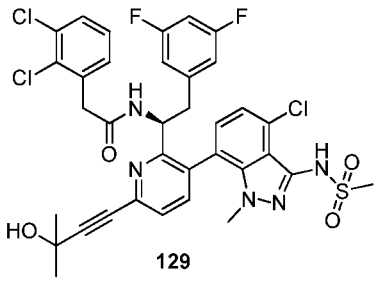
Synthesis of N1,N1-dimethyl-N2-(2-methylbut-3-yn-2-yl)ethane-1,2-diamine (**128A**):

[0684] Argon was bubbled through a solution of 2-methylbut-3-yn-2-yl acetate (15.96 mg, 126.5 µmol), copper chloride (0.75 mg, 7.59 µmol), triethylamine (17.63 µl, 126.5 µmol), and N,N-dimethylethylenediamine (20.73 µl, 189.74 µmol) in DMF (0.2 ml). The reaction was heated in a microwave reactor at 110 °C for 5 min. The reaction was cooled to room temperature and telescoped to the next reaction.

Synthesis of N-((S)-1-(6-(3-amino-3-methylbut-1-yn-1-yl)-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**128B**):

[0685] Into the reaction was added **157F** (20 mg, 25.3 µmol) in DMF (0.2 mL), CuI (1 mg, 5.06 µmol), and $PdCl_2(PPh_3)_2$ (3.55 mg, 5.06 µmol). Argon was bubbled through the reaction and diethylamine (39 µl, 379 µmol) was added. The reaction was heated in a microwave reactor for 15 mins at 125 °C. The excess amines were removed under vacuum and the product was purified by reverse phase HPLC the title product **128B** as a mixture of atropisomers. ^{1}H NMR (400 MHz, cd_3od) δ 8.76 (t), 7.76 (d), 7.73 (d), 7.64 (d), 7.61 (d), 7.21 – 7.16 (m), 7.07 (d), 6.82 – 6.74 (m), 6.69 – 6.62 (m), 6.45 – 6.40 (m), 6.37 (ddd), 5.30 – 5.24 (m), 4.99 (dd), 4.78 (s), 4.76 (d), 3.60 – 3.48 (m), 3.32 (s), 3.26 (s), 3.23 (s), 3.18 – 3.11 (m), 3.01 (s), 2.97 (s), 2.58 – 2.42 (m), 1.77 (s), 1.48 – 1.37 (m), 1.13 (tt), 1.10 – 1.03 (m). MS (*m/z*) 908.3 $[M+H]^+$.

Example 129.



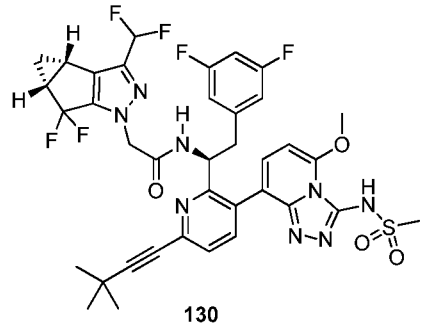
129

Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(2,3-dichlorophenyl)acetamide (**129**):

[0686] The title compound (**129**) was prepared as a mixture of atropisomers according to the method presented in the synthesis of **10A** in Example 10 utilizing **19F** and 2-(2,3-dichlorophenyl)acetic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.70 (dd), 7.53 (dd), 7.44 (dd), 7.39 (dd), 7.28 – 7.05 (m), 6.80 – 6.69 (m), 6.68 – 6.61 (m), 6.60 (d), 6.48 – 6.36 (m), 5.35 –

5.20 (m), 5.06 – 4.92 (m), 3.67 (s), 3.62 (s), 3.22 (s), 3.20 – 3.11 (m), 3.07 (s), 3.00 (dd), 1.64 (s). MS (*m/z*) 762.3 $[M+H]^+$.

Example 130.

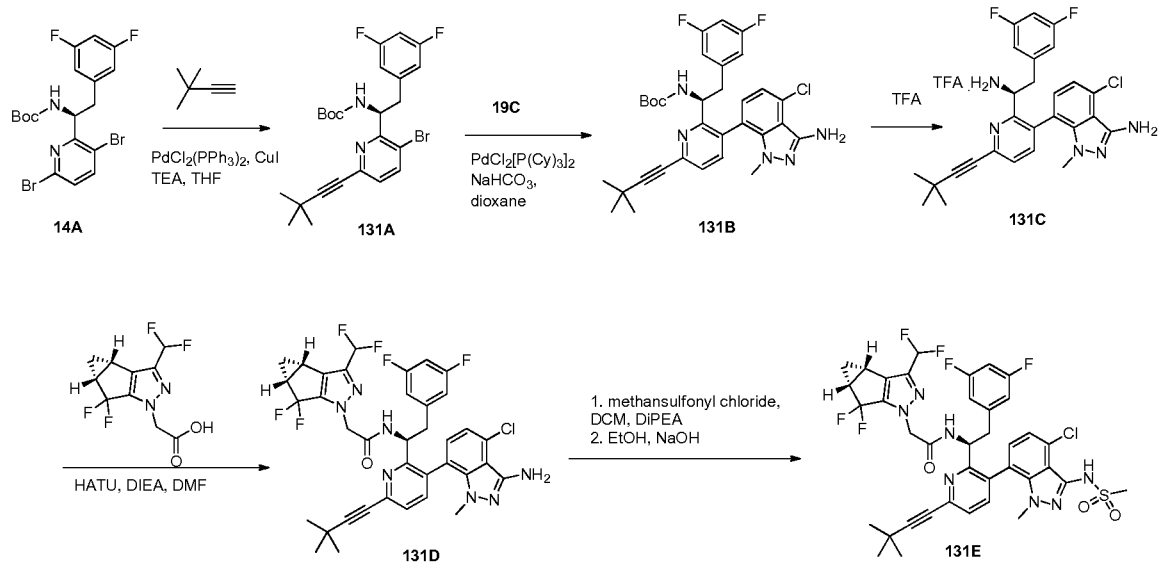


130

Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3,3-dimethylbut-1-yn-1-yl)-3-(5-methoxy-3-(methylsulfonamido)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)pyridin-2-yl)ethyl)acetamide (**130**):

[0687] To compound **115C** (15 mg, 0.2 mmol) dissolved in 0.5 mL of methylene chloride was added triethylamine (37 µL, 0.2 mmol) followed by methanesulfonyl chloride (8 µL, 0.1 mmol). The reaction mixture was allowed to stir at room temperature for 30 minutes. The reaction was diluted with methylene chloride and water. The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The residue was dissolved in 1 mL of methanol and to it was added 0.1 mL of 15 % NaOH aqueous solution. The mixture was stirred at 40 °C for overnight then 60 °C for 7 hours. The solvent was removed and the residue was purified by RP-HPLC to afford the title compound **130**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.68 (d), 7.43 (d), 7.22 – 7.11 (m), 6.70 (t), 6.63 (t), 6.53 – 6.43 (m), 6.27 (d), 5.28 (t), 4.71 (s), 4.12 (s), 3.26 – 2.89 (m), 3.18 (s), 2.52 – 2.40 (m), 1.40 – 1.31 (m), 1.39 (s), 1.09 – 1.00 (m). MS (*m/z*): 801.65 $[M+H]^+$.

Example 131.



Synthesis of (S)-tert-butyl (1-(3-bromo-6-(3,3-dimethylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**131A**):

[0688] The title compound (**131A**) was prepared according to the method presented for the synthesis of compound **4F** of Example 4 utilizing compound **14A** and 3,3-dimethylbut-1-yne. MS (*m/z*) 494.92 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(3-(3-amino-4-chloro-1-methyl-1H-indazol-7-yl)-6-(3,3-dimethylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**131B**):

[0689] The title compound (**131B**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19E** of Example 19 utilizing compound **131A** and compound **19C**. MS (*m/z*) 594.44 $[M+H]^+$.

Synthesis of (S)-7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3,3-dimethylbut-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-amine (**131C**):

[0690] The title compound (**131C**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **105C** of Example 105 utilizing compound **131B**. MS (*m/z*) 494.26 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(3-amino-4-chloro-1-methyl-1H-indazol-7-yl)-6-(3,3-dimethylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**131D**):

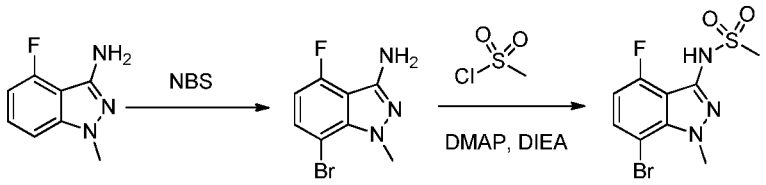
[0691] The title compound **131D** was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **37E** of Example 37 utilizing 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-

cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid and compound **131C**. MS (*m/z*) 740.35 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3,3-dimethylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**131E**):

[0692] The title compound (**131E**) was prepared according to the method presented for the synthesis of compound **19D** of Example 19 utilizing compound **131D**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.67 – 7.63 (m), 7.49 – 7.44 (m), 7.17 (d), 7.06 (d), 6.90 – 6.47 (m), 6.79 (t), 6.47 – 6.20 (m), 5.33-5.23 (m), 4.95 (t), 4.79 – 4.49 (m), 3.33 (s), 3.24 (d), 3.13 (dd), 3.05 – 2.83 (m), 3.00 (s), 2.58 – 2.14 (m), 1.43-1.31 (m), 1.41 (s), 1.13 – 0.93 (m). MS (m/z): 818.15 $[M+H]^+$.

Example 132.



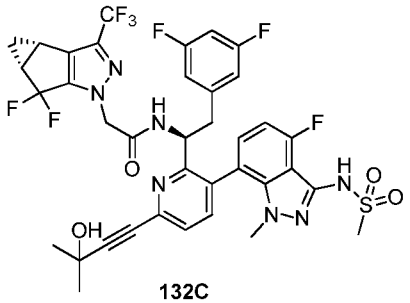
132A **132B**

Synthesis of 7-bromo-4-fluoro-1-methyl-1H-indazol-3-amine (**132A**):

[0693] A solution of 4-fluoro-1-methyl-1H-indazol-3-amine (4.3 g, 26 mmol) in concentrated sulfuric acid (26 ml) was cooled to 0 °C then treated in three portions with N-bromosuccinimide (4.64 g, 26 mmol). The reaction was allowed to slowly reach room temperature and stirred for 15 h. The reaction was carefully quenched with water, filtered, and the filtrate was neutralized. The neutralized solution was then extracted with ethyl acetate, dried over sodium sulfate, filtered and concentrated. The crude material was purified by silica gel chromatography to give the title compound. MS (*m/z*) 246.1$[M+H]^+$.

Synthesis of N-(7-bromo-4-fluoro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**132B**):

[0694] The title compound was prepared similarly to **108B** of Example 108 starting from **132A**. MS (*m/z*) 320.3 $[M-H]^-$.

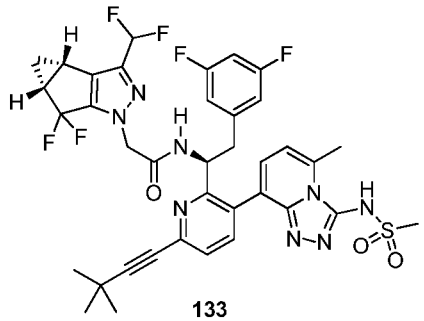


132C

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(3-(4-fluoro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)ethyl)acetamide (**132C**):

[0695] The title compound (**132C**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **117F** of Example 117 utilizing **132B** , **117B** and 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, cd_3od) δ 8.80 – 8.75 (m), 7.70 (d), 7.65 – 7.59 (m), 7.52 (d), 7.35 – 7.30 (m), 7.22 – 7.17 (m), 7.11 – 7.06 (m), 6.75 – 6.70 (m), 6.49 – 6.44 (m), 6.23 – 6.16 (m), 5.52 – 5.47 (m),5.00-4.95 (m), 4.86 (d), 3.26 (t), 3.02 – 2.97 (m), 2.52 – 2.47 (m), 1.63 (s), 1.45 – 1.36 (m), 1.33 – 1.27 (m), 1.15 – 1.10 (m). MS (*m/z*) 822.1 $[M+H]^+$.

Example 133.



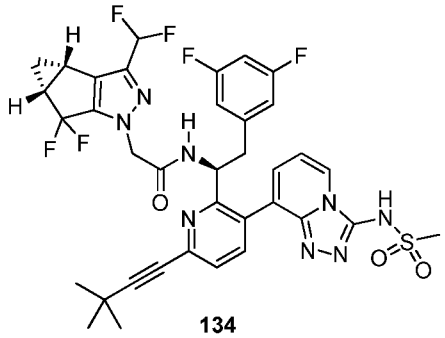
133

Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3,3-dimethylbut-1-yn-1-yl)-3-(5-methyl-3-(methylsulfonamido)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)pyridin-2-yl)ethyl)acetamide (**133**):

[0696] The title compound (**133**) was prepared according to the method presented for the synthesis of compound **19D** of Example 19 utilizing compound **116A**. ^{1}H NMR (400 MHz, Methanol-d_4): δ 7.66 (d), 7.41 (dd), 7.02 – 6.90 (m), 6.71 (t), 6.63 (t), 6.56 – 6.37 (m), 5.41-5.23

(m), 4.74 (d), 3.23 – 2.75 (m), 3.06 (s), 2.92 (s), 2.46 (ddd), 1.45 – 1.32 (m), 1.39 (s), 1.11 – 1.01 (m). MS (*m/z*): 785.31 $[M+H]^+$.

Example 134.

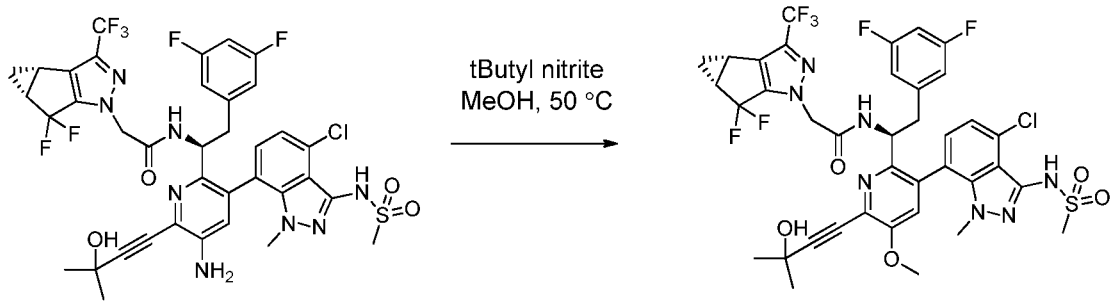


134

Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3,3-dimethylbut-1-yn-1-yl)-3-(3-(methylsulfonamido)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)pyridin-2-yl)ethyl)acetamide (**134**):

[0697] The title compound (**134**) was prepared according to the method presented for the synthesis of compound **19D** of Example 19 utilizing compound **116B.** ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.69 (d), 8.04 (dd), 7.71 (d), 7.43 (d), 7.21-7.12 (m), 6.91 (t), 6.70 (t), 6.62 (t), 6.50-6.41 (m), 5.41-5.26 (m), 4.74 (s), 3.25 – 3.10 (m), 3.06 (s), 2.55 – 2.36 (m), 1.43-1.21 (m), 1.40 (s), 1.14-0.96 (m). MS (*m/z*): 771.12 $[M+H]^+$.

Example 135.



135A **135B**

Synthesis of N-((S)-1-(5-amino-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**135A**):

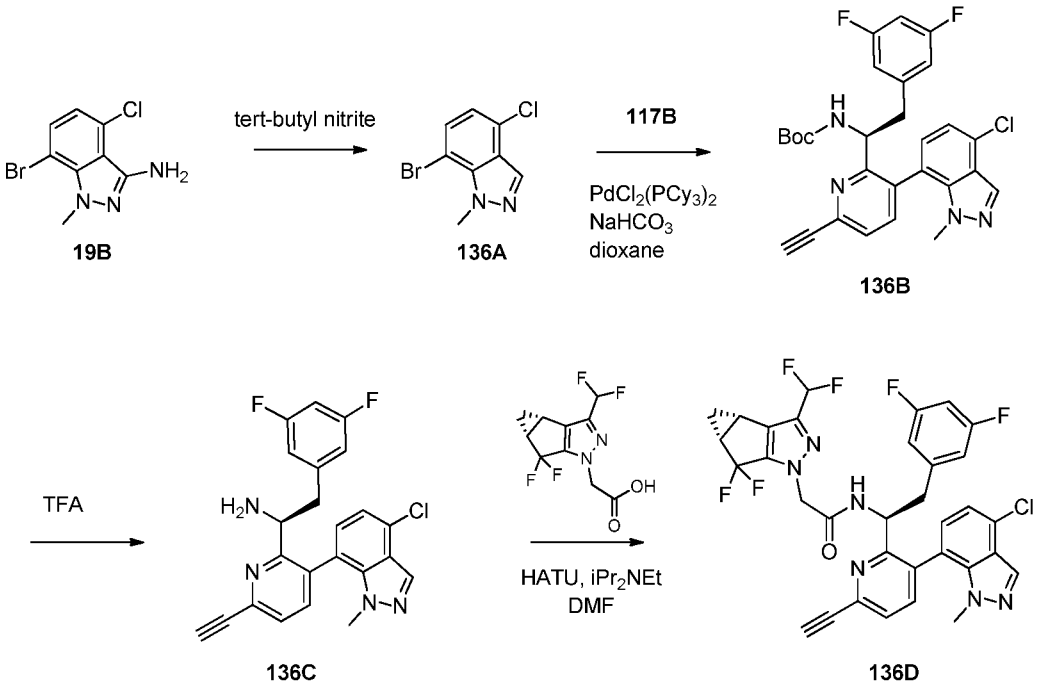
[0698] The title compound (**135A**) may be prepared analogously to the method presented for the synthesis of compound **139A** of Example 139 utilizing 2-((3bS,4aR)-5,5-difluoro-3-

(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid and compound **182H.** MS (m/z): 853.26 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methoxypyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**135B**):

[0699] To a solution of compound **135A** (25 mg, 0.029 mmol) in MeOH (1 mL) was added t-butyl nitrite (15 mg, 0.15 mmol). The resulting solution was heated at 50 °C for 2 h. The volatiles were removed in vacuo and residue was purified by reverse phase HPLC to yield the title compound as a mixture of atropisomers. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.73 (dd), 7.69 (dd), 7.53 (dd), 7.34 (d), 7.22 – 7.10 (m), 7.05 (dd), 6.76 (t), 6.52 – 6.23 (m), 4.82 – 4.67 (m), 3.87 (d), 3.37 (s), 3.24 (d), 3.17 – 3.04 (m), 2.97 (q), 2.49 (s), 1.71 – 1.55 (m), 1.49 – 1.31 (m), 1.07 (s).MS (*m/z*) 868.24 $[M+H]^+$.

Examples 136.



Synthesis of 7-bromo-4-chloro-1-methyl-1H-indazole (**136A**):

[0700] Compound **19B** (150 mg, 0.58 mmol) was dissolved in Me-THF and treated with tert-butyl nitrite (0.21 ml, 1.73 mmol). The reaction was heated to 75 ° C for 2 h. The reaction was diluted with EtOAc and saturated aqueous NaCl. The organics were separated, dried, and removed in vacuo and the residue was purified by column chromatography on silica to provide the title compound (**136A**). MS (*m/z*) 247.0 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(3-(4-chloro-1-methyl-1H-indazol-7-yl)-6-ethynylpyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**136B**):

[0701] In a microwave vial, (S)-(2-(1-((tert-butoxycarbonyl)amino)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)boronic acid (**117B**, 35 mg, 0.08 mmol) was combined with 7-bromo-4-chloro-1-methyl-1H-indazole (**136A**, 19 mg, 0.08 mmol), $PdCl_2(PCy_3)_2$ (6 mg), and $NaHCO_3$ (228 µl of 1 M aqueous solution) in dioxane (1 ml). Argon was bubbled into the reaction solution for 5 min. The reaction was heated in a microwave reactor at 155 °C for 15 min. After cooling to ambient temperature, the reaction was partitioned between EtOAc and water. The organics were separated, dried, and removed in vacuo and the residue was purified by column chromatography on silica to provide the title compound (**136B**). MS (*m/z*) 523.2 $[M+H]^+$.

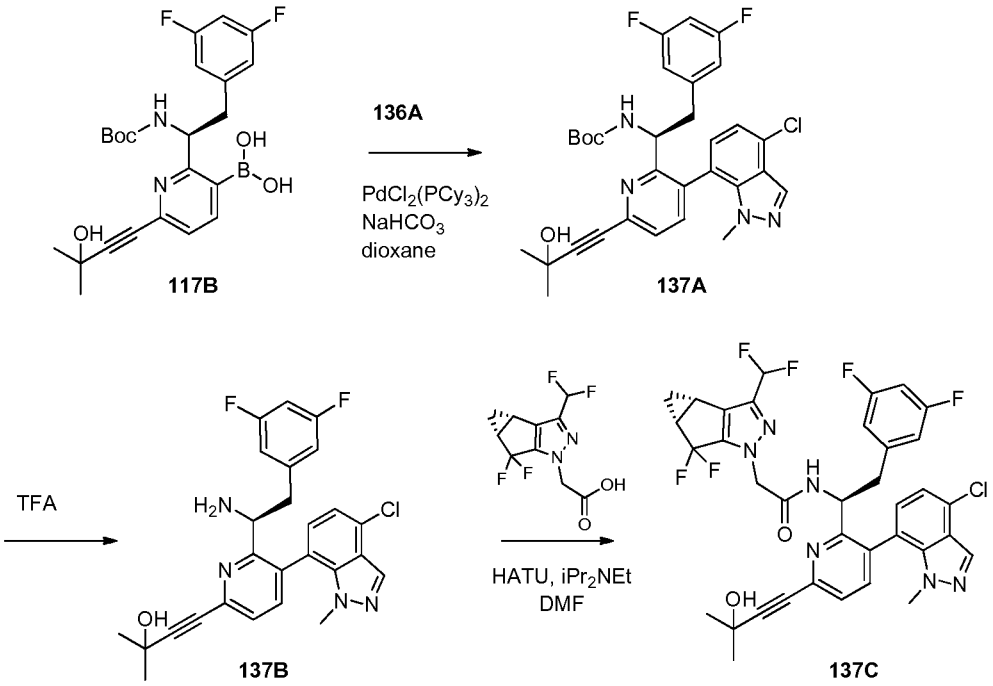
Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-1H-indazol-7-yl)-6-ethynylpyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**136C**):

[0702] The title compound (**136C**) was prepared according to the method presented for the synthesis of compound **19F** of Example 19 utilizing compound **136B.** MS (*m/z*): 423.1 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-1H-indazol-7-yl)-6-ethynylpyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**136D**):

[0703] The title compound (**136D**) was prepared according to the method presented for the synthesis of compound **10A** of Example 10 utilizing compound **136C** and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid**.** ^1H NMR (400 MHz, DMSO-d_6) δ 8.89 (d), 8.23 (s), 7.87 (t), 7.66 (dd), 7.43 (d), 7.29 (d), 7.07 – 6.99 (m), 6.98 – 6.96 (m), 6.94 (t), 5.25 – 5.11 (m), 4.90 – 4.62 (m), 3.27 – 2.97 (m), 2.61 – 2.49 (m), 1.44 – 1.30 (m), 0.95 – 0.84 (m). MS (*m/z*): 669.1 $[M+H]^+$.

Example 137.



Synthesis of (S)-tert-butyl (1-(3-(4-chloro-1-methyl-1H-indazol-7-yl)-6-ethynylpyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**137A**):

[0704] In a microwave vial, (S)-(2-(1-((tert-butoxycarbonyl)amino)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)boronic acid (**117B**, 35 mg, 0.08 mmol) was combined with 7-bromo-4-chloro-1-methyl-1H-indazole (**136A**, 19 mg, 0.08 mmol), $PdCl_2(PPh_3)_2$ (5 mg), and K_2CO_3 (95 µl of 2 M aqueous solution) in dioxane (1 ml). Argon was bubbled into the reaction solution for 5 min. The reaction was heated in a microwave reactor at 115 °C for 15 min. After cooling to ambient temperature, the reaction was partitioned between EtOAc and water. The organics were separated, dried, and removed in vacuo and the residue was purified by column chromatography on silica to provide the title compound as a mixture of atropisomers. MS (*m/z*) 581.0 $[M+H]^+$.

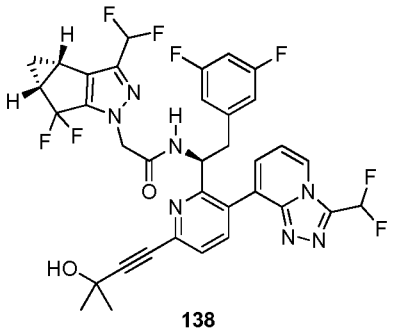
Synthesis of (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(4-chloro-1-methyl-1H-indazol-7-yl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (**137B**):

[0705] The title compound (**137B**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19F** of Example 19 utilizing compound **137A.** MS (*m/z*): 481.1 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**137C**):

[0706] The title compound (**137C**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **10A** of Example 10 utilizing compound **137B** and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid**.** ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.75 – 8.70 (m), 8.70 – 8.62 (m), 8.10 – 8.05 (m), 7.69 (dd), 7.53 (dd), 7.18 (s), 7.08 (d), 6.89 – 6.52 (m), 6.42 (d), 6.39 – 6.30 (m), 5.31 – 5.20 (m), 5.04 – 4.91 (m), 4.70 (d), 3.48 (t), 3.40 (s), 3.19 – 3.07 (m), 3.04 (s), 2.96 (dd), 2.54 – 2.38 (m), 1.64 (d), 1.44 – 1.27 (m), 1.14 – 0.96 (m). MS (*m/z*): 727.1 $[M+H]^+$.

Example 138.



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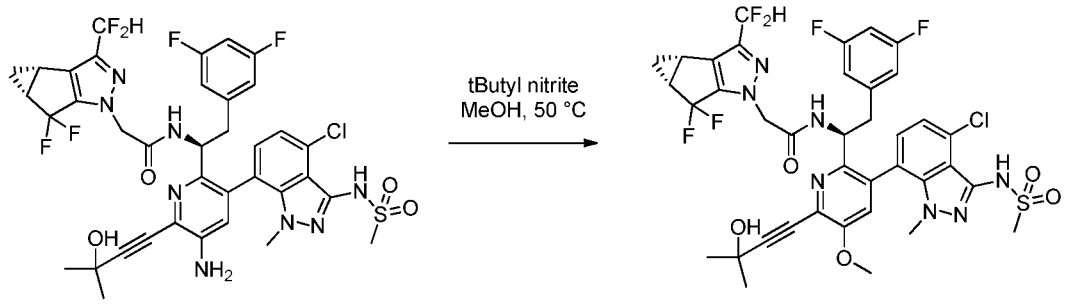
Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-1-(3-(3-(difluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)acetamide (**138**):

[0707] The title compound (**138**) was prepared according to the method presented for the synthesis of compound **106E** of Example 106 utilizing compound **117B** and 8-bromo-5-chloro-3-(difluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.61 (dd), 7.78 (dd), 7.55 (d), 7.48 (t), 7.46 – 7.37 (m), 7.33 – 7.18 (m), 6.83 – 6.74 (m), 6.67 (t), 6.62 – 6.47 (m), 6.46 – 6.35 (m), 5.38 – 5.03 (m), 4.75 – 4.57 (m), 3.26 – 3.17 (m), 3.17 – 2.98 (m), 2.44 (ddd), 1.61 (d), 1.42-1.30 (m), 1.06 – 0.96 (m, 1H). MS (*m/z*): 730.22 $[M+H]^+$.

Example 139.



139A 139B

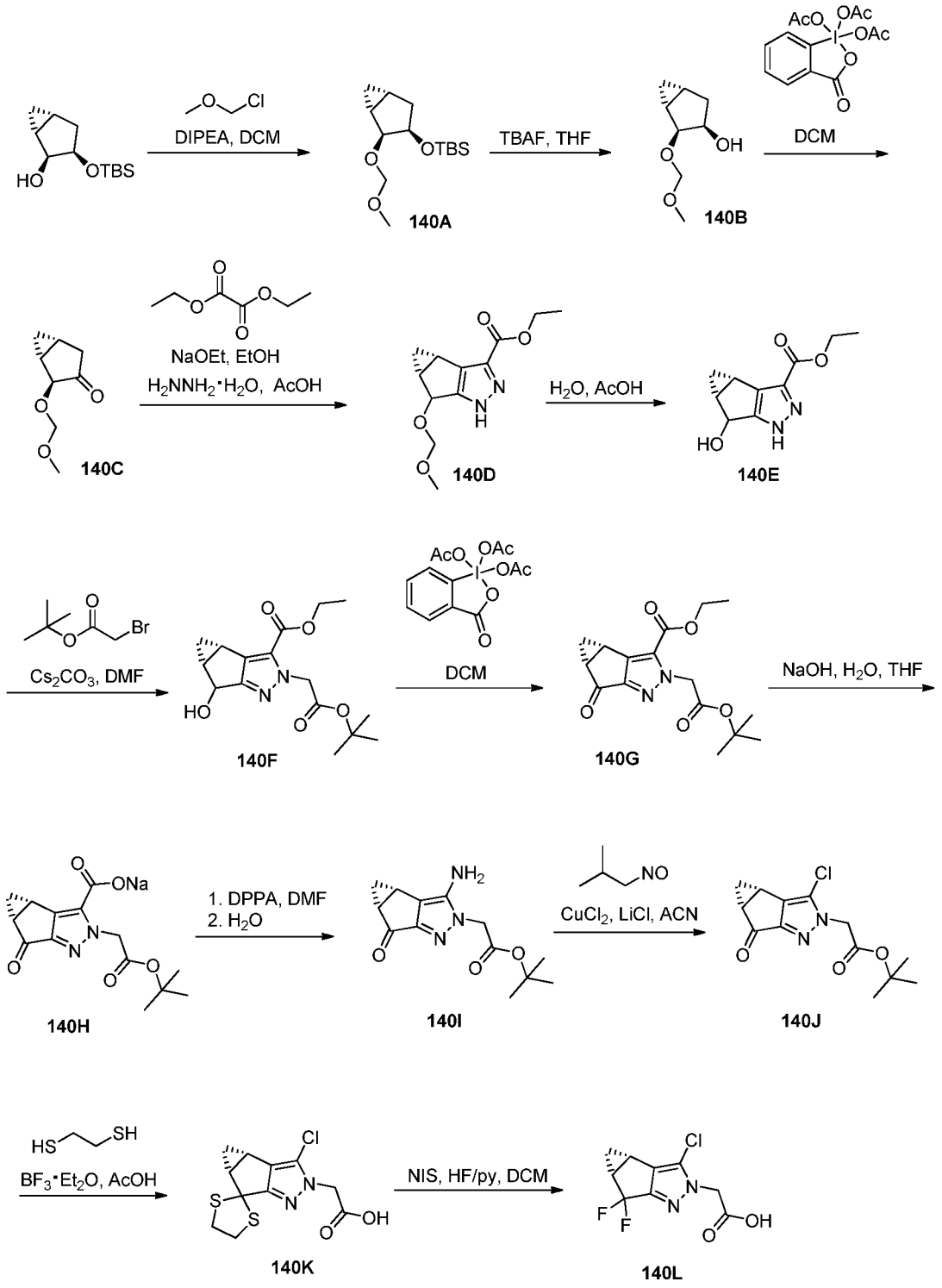
Synthesis of N-((S)-1-(5-amino-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**139A**):

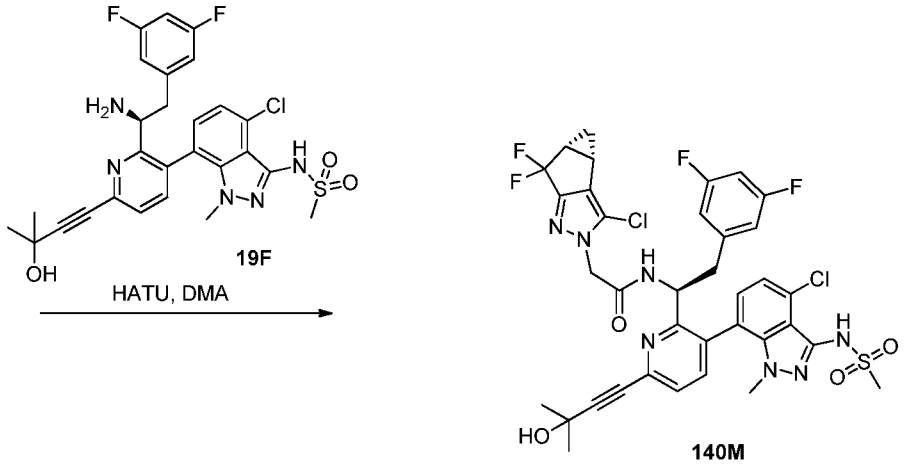
[0708] The title compound (**139A**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19G** of Example 19 utilizing compound **182H.** MS (m/z): 835.67 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methoxypyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**139B**):

[0709] The title compound (**139B**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **135A** of Example 135 utilizing compound **139A**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.62 (t), 7.75 – 7.47 (m), 7.34 (d), 7.21 – 6.96 (m), 6.90 – 6.64 (m), 6.53 – 6.21 (m), 4.78 – 4.60 (m), 3.86 (d), 3.36 (s), 3.24 (d), 3.15 – 3.07 (m), 3.01 – 2.90 (m), 2.61 – 2.35 (m), 1.64 (d), 1.37 (q), 1.28 (d), 1.03 (d).MS (*m/z*) 850.52 $[M+H]^+$.

Example 140.





Synthesis of tert-butyl(((1R,2S,3R,5R)-2-(methoxymethoxy)bicyclo[3.1.0]hexan-3-yl)oxy)dimethylsilane (**140A**):

[0710] To a solution of (1R,2S,3R,5R)-3-((tert-butyldimethylsilyl)oxy)bicyclo[3.1.0]hexan-2-ol (10.4 g, 45.6 mmol, synthesis previous reported in JACS, 2007, 129, 4456-4462), DIPEA (31.7 ml, 182.4 mmol), and DMAP (556 mg, 4.56 mmol) in dichloromethane (90 mL) was added chloromethyl methyl ether (14.6 ml, 182.4 mmol) at 0°C. The mixture was warmed to room temperature and stirred overnight. The resulting solution was concentrated *in vacuo* and extracted twice with EtOAc and water. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was taken to next step without further purification. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.09 – 3.99 (m, 1H), 2.50 – 2.38 (m, 1H), 2.05 – 1.96 (m, 2H), 1.84 – 1.76 (m, 1H), 1.57 (s, 1H), 1.31 – 1.14 (m, 2H), 1.06 – 0.99 (m, 1H), 0.95 – 0.81 (m, 10H), 0.07 (dd, 6H).

Synthesis of (1R,2S,3R,5R)-2-(methoxymethoxy)bicyclo[3.1.0]hexan-3-ol (**140B**):

[0711] To a crude solution of tert-butyl(((1R,2S,3R,5R)-2-(methoxymethoxy)bicyclo[3.1.0]hexan-3-yl)oxy)dimethylsilane (**140A**) (12.4g) in THF (100 ml) was added 1M tetrabutylammonium fluoride in THF (64 mL). After stirring at room temperature for 2h, the mixture was partially concentrated *in vacuo*, and extracted twice with EtOAc and water. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting mixture was slurried in 25% EtOAc and hexanes, solids filtered, and the filtrate was purified by silica gel chromatography to give the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.85 – 4.73 (m, 2H), 4.01 – 3.92 (m, 1H), 3.87 – 3.74 (m, 1H), 3.47 – 3.41 (m, 3H), 2.16 – 2.06 (m, 1H), 1.73 – 1.61 (m, 1H), 1.52 – 1.35 (m, 2H), 0.53 – 0.42 (m, 1H), 0.19 – 0.11 (m, 1H).

Synthesis of (1R,2S,5R)-2-(methoxymethoxy)bicyclo[3.1.0]hexan-3-one (**140C**):

[0712] To a mixture of (1R,2S,3R,5R)-2-(methoxymethoxy)bicyclo[3.1.0]hexan-3-ol (**140B**) (5.8 g, 36.7 mmol) and $NaHCO_3$ (4.62 g, 55.1 mmol) in dichloromethane (75 ml) was added in portions Dess-Martin periodinane (17.1 g, 40.37 mmol) at -15°C. The mixture was slowly warmed to room temperature and stirred for 1 h. Upon completion, the reaction was cooled to 0 °C and 1M aqueous $NaHCO_3$ (150 ml) was added. The solution was stirred until evolution of gas ceased, and the organic layer was separated. The aqueous layer was back extracted twice with dichloromethane, the organic layers were combined, dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting mixture was slurried in 25% Et_2O and hexanes, solids filtered, and the filtrate was concentrated *in vacuo* then, purified by silica gel chromatography to give the title compound. ^1H NMR (400 MHz, Chloroform-*d*) δ 4.89 – 4.62 (m, 2H), 3.66 (s, 1H), 3.45 – 3.35 (m, 3H), 2.81 – 2.69 (m, 1H), 2.19 – 2.08 (m, 1H), 1.73 – 1.54 (m, 2H), 1.03 – 0.92 (m, 1H), -0.00 – -0.11 (m, 1H).

Synthesis of (3bS,4aR)-ethyl 5-(methoxymethoxy)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylate (**140D**):

[0713] To a solution of (1R,2S,5R)-2-(methoxymethoxy)bicyclo[3.1.0]hexan-3-one (**140C**) (4.4 g, 28.2 mmol) in ethanol (28 ml) was added a solution of 21% NaOEt in EtOH (11.0 ml, 29.6 mmol) at 0 °C. After stirring at room temperature for 5 minutes, diethyl oxalate (4.02 ml, 29.6 mmol) was added, and the reaction was stirred at 70°C for 45 minutes. Upon completion, the mixture was concentrated *in vacuo*, dissolved in acetic acid (15 ml) and water (2 ml), and hydrazine hydrate (2.82 g, 56.4 mmol) was slowly added at 0°C. The reaction was heated in a microwave reactor at 120°C for 10 minutes. The mixture was concentrated *in vacuo* and extracted with twice with 2-methyltetrahydrofuran and water. The organic layers were combined and washed with water. The organic layer was dried with Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to give the title compound. MS (*m/z*) 252.84 $[M+H]^+$.

Synthesis of (3bS,4aR)-ethyl 5-hydroxy-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylate (**140E**):

[0714] A solution of (3bS,4aR)-ethyl 5-(methoxymethoxy)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylate (**140D**) (1.2 g, 4.76 mmol) in 1:1 AcOH:H_2O (5 ml) was heated in a microwave reactor at 130 °C for 10 minutes. The resulting mixture was concentrated *in vacuo* and extracted with three times with EtOAc and water. The

combined organic layers were dried with Na_2SO_4, filtered, concentrated *in vacuo*, and partially purified by silica gel chromatography eluting with ethyl acetate and hexanes. MS (*m/z*) 208.98 $[M+H]^+$.

Synthesis of (3bS,4aR)-ethyl 2-(2-(tert-butoxy)-2-oxoethyl)-5-hydroxy-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylate (**140F**):

[0715] To a solution of (3bS,4aR)-ethyl 5-hydroxy-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylate (**140E**) (990 mg) in DMF (10 ml) was added cesium carbonate (2.32 g, 7.14 mmol) followed by tert-butyl bromoacetate (0.70 ml, 4.76 mmol). After heating the reaction at 45°C for 1 h, the resulting mixture was extracted with EtOAc and water. The organic layer was dried with Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica gel chromatography to give the title compound. MS (*m/z*) 322.83 $[M+H]^+$.

Synthesis of (3bS,4aR)-ethyl 2-(2-(tert-butoxy)-2-oxoethyl)-5-oxo-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylate (**140G**):

[0716] To a solution of (3bS,4aR)-ethyl 2-(2-(tert-butoxy)-2-oxoethyl)-5-hydroxy-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylate (**140F**) (0.27 g, 0.83 mmol) in DCM (10 ml) was added Dess Martin periodinane (0.34 g, 0.91 mmol). After stirring at room temperature for 3 h, mixture was solid loaded onto silica gel and purified by silica gel chromatography to give the title compound. MS (*m/z*) 320.74 $[M+H]^+$.

Synthesis of sodium (3bS,4aR)-2-(2-(tert-butoxy)-2-oxoethyl)-5-oxo-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylate (**140H**):

[0717] To a solution of (3bS,4aR)-ethyl 2-(2-(tert-butoxy)-2-oxoethyl)-5-oxo-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylate (**140G**) (0.22 g, 0.69 mmol) in THF (2 ml) was added 0.25M aqueous NaOH (1.87 ml). The reaction was heated at 60 °C for 1.5 h. Upon completion, the reaction was concentrated *in vacuo*, and dried under vacuum. The crude product was taken to next step without further purification. MS (*m/z*) 291.04 $[M-H]^-$.

Synthesis of tert-butyl 2-((3bS,4aR)-3-amino-5-oxo-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-2-yl)acetate (**140I**):

[0718] The title compound (**140I**) was prepared according to the method presented for the synthesis of compound (**148B**) of Example 148 utilizing sodium (3bS,4aR)-2-(2-(tert-butoxy)-2-oxoethyl)-5-oxo-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylate (**140H**). MS (*m/z*) 263.86 $[M+H]^+$.

Synthesis of tert-butyl 2-((3bS,4aR)-3-chloro-5-oxo-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-2-yl)acetate (**140J**):

[0719] The title compound (**140J**) was prepared according to the method presented for the synthesis of compound (**149**) of Example 149 utilizing tert-butyl 2-((3bS,4aR)-3-amino-5-oxo-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-2-yl)acetate (**140I**). MS (*m/z*) 282.73 $[M+H]^+$.

Synthesis of 2-((3bS,4aR)-3-chloro-4,4a-dihydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-[1,3]dithiolane]-2(3bH)-yl)acetic acid (**140K**):

[0720] To a solution of tert-butyl 2-((3bS,4aR)-3-chloro-5-oxo-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-2-yl)acetate (**140J**) (19 mg, 0.07 mmol), 1,2-ethanedithiol (11.3 µl, 0.13 mmol), and acetic acid (19.2 µl, 0.34 mmol) in dichloromethane (400 µl) was added boron trifluoride diethyl etherate (20.7 µl, 0.17 mmol). After stirring at room temperature for 2 h, the mixture was dry loaded onto silica and purified by silica gel chromatography to give the title compound as a partially purified product. MS (*m/z*) 302.93 $[M+H]^+$.

Synthesis of 2-((3bS,4aR)-3-chloro-5,5-difluoro-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-2-yl)acetic acid (**140L**):

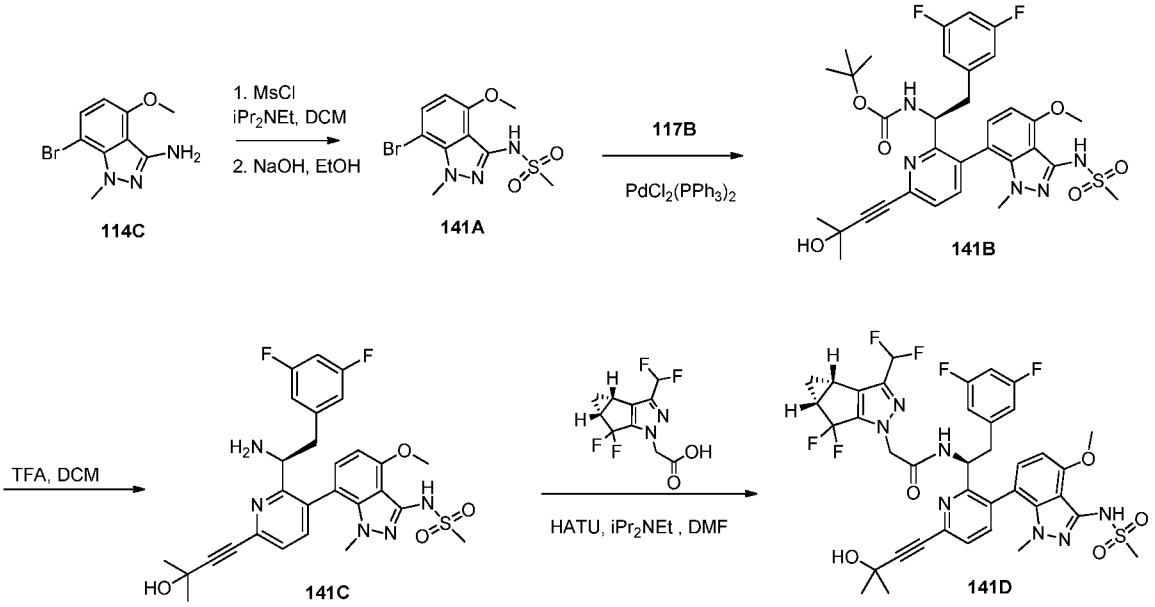
[0721] To a solution of N-iodosuccinimide (27.9 mg, 0.12 mmol) in dichloromethane (0.10 ml) was added dropwise 70% HF in pyridine (0.10 ml) at -78°C. After stirring for 15 minutes, a suspension of **140K** (15 mg, 0.05 mmol) in dichloromethane (0.10 ml) was added and the reaction was gradually warmed to 0 °C over 1 h. The mixture was extracted with 2-methyltetrahydrofuran and water. The organic layer was washed with brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified by preparative TLC eluting to give the title compound. MS (*m/z*) 249.05 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-chloro-5,5-difluoro-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-2-yl)acetamide (**140M**):

[0722] The title compound (**140M**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound (**33F**) of Example 33 utilizing **19F** and 2-((3bS,4aR)-3-chloro-5,5-difluoro-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-2-yl)acetic acid (**140L**). ^1H NMR (400 MHz, Methanol-d_4) δ 8.75 (t), 7.71 (dd), 7.54

(dd), 7.27 – 7.15 (m), 7.10 (d), 6.81 – 6.72 (m), 6.69 – 6.59 (m), 6.50 (d), 6.46 – 6.36 (m), 5.30 – 5.21 (m), 5.05 – 4.95 (m), 4.81 (s), 4.77 (s), 3.35 (s), 3.26 (s), 3.28 – 3.21 (m), 3.23 (s), 3.19 – 3.12 (m), 3.03 (s), 3.04 – 2.97 (m), 2.45 – 2.32 (m), 1.94 (s), 1.64 (s), 1.64 (s), 1.42 – 1.25 (m), 1.01 – 0.96 (m), 0.96 – 0.92 (m). MS (*m/z*) 804.14[M+H]$^+$.

Example 141.



Synthesis of N-(7-bromo-4-methoxy-1-methyl-1H-indazol-3-yl)methanesulfonamide (**141A**):

[0723] The title compound (**141A**) was prepared according to the method presented for the synthesis of compound **19D** of Example 19 utilizing **114C**. MS (m/z) 334.1 [M+H]$^+$.

Synthesis of (S)-tert-butyl (2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(4-methoxy-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)carbamate (**141B**):

[0724] In a microwave vial, (**117B**, 30 mg, 0.07 mmol) was combined with (**141A**, 65 mg, 0.2 mmol), $PdCl_2(PPh_3)_2$ (5 mg, 0.007 mmol), and K_2CO_3 (0.2 ml of 2 M aqueous solution) in dioxane (1.5 ml) and DMF (0.1 ml). Nitrogen was bubbled into the reaction solution for 5 min. The reaction was heated in a microwave reactor at 120 °C for 15 min. After cooling to ambient temperature, the reaction was partitioned between EtOAc and brine. The organics were separated, dried, and removed in vacuo and the residue was purified by column chromatography on silica to provide the title compound as a mixture of atropisomers. MS (m/z) 670.3 [M+H]$^+$.

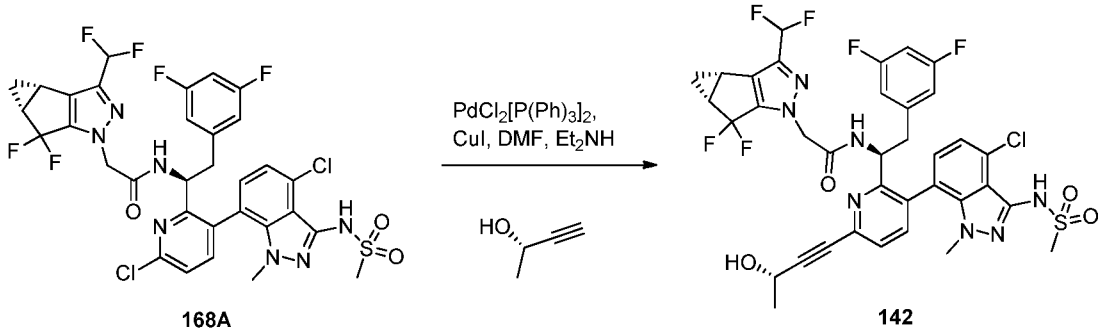
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-methoxy-1-methyl-1H-indazol-3-yl)methanesulfonamide (**141C**):

[0725] The title compound (**141C**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19F** of Example 19 utilizing **141B**. MS (m/z) 570.1 $[M+H]^+$.

Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(4-methoxy-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)acetamide (**141D**):

[0726] The title compound (**141D**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **10A** of Example 10 utilizing **141C** and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (Chloroform-*d*) δ: 7.91 – 7.84 (m), 7.64 (dd), 7.54 – 7.42 (m), 7.34 – 7.28 (m), 6.70 (t), 6.68 – 6.61 (m), 6.55 – 6.53 (m), 6.52 – 6.44 (m), 6.30 – 6.24 (m), 6.24 – 6.15 (m), 5.74 – 5.66 (m), 5.12 – 5.01 (m), 4.78 (d), 4.71 (d), 4.03 (s), 3.99 (s), 3.39 (d), 3.25 (s), 3.07 (s), 3.06 – 2.91 (m), 2.81 – 2.54 (m), 2.54 – 2.36 (m), 1.71 (s), 1.41 (dd), 1.30 – 1.22 (m), 1.22 – 1.10 (m). MS (*m/z*) 816.5 $[M+H]^+$.

Example 142.



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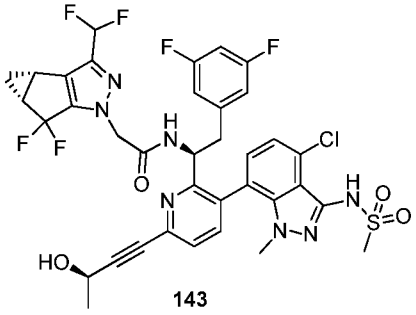
Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-((S)-3-hydroxybut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**142**):

[0727] To the reaction vial containing **168A** (20 mg, 0.027 mmol) in DMF (1 mL) was added (S)-but-3-yn-2-ol (0.012 mL, 0.13 mmol), $PdCl_2[P(Ph)_3]_2$ (1.9 mg, 0.003 mmol), and diethylamine (0.02 mL, 0.27 mmol). The reaction mixture was flushed with argon gas for 5 min then sealed and heated in a microwave reactor to 125°C for 20 min. Upon cooling, the reaction mixture was filtered and purified by reverse phase HPLC, to provide the title compound **142** as a mixture of atropisomers. ^{1}H NMR (400 MHz, cd_3od) 1H NMR (400 MHz, cd3od) δ 8.62 (dd),

7.70 (dd), 7.54 (dd), 7.16 (s), 7.07 (d), 6.88 – 6.52 (m), 6.44 – 6.33 (m),5.31-5.23 (m), 5.02 – 4.92 (m), 4.82 – 4.64 (m), 3.33 (s), 3.24 (d), 3.18 – 3.08 (m), 3.04 – 2.91 (m), 2.53 – 2.39 (m), 1.57 (dd), 1.42 – 1.32 (m), 1.11 –1.08 (m), 1.07- 0.99 (m). MS (*m/z*) 806.1 $[M+H]^+$.

Example 143.

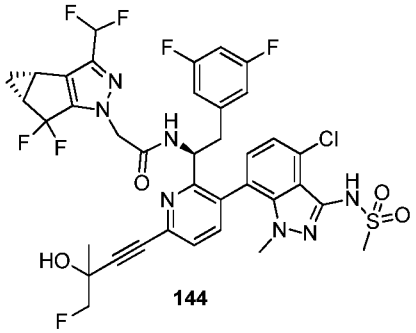


143

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-((R)-3-hydroxybut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**143**):

[0728] The title compound (**143**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **142** of Example 142 utilizing (R)-but-3-yn-2-ol. ^{1}H NMR (400 MHz, cd_3od) δ 8.63 (dd), 7.70 (dd), 7.54 (dd), 7.16 (s), 7.06 (d), 6.88 – 6.52 (m), 6.44 – 6.33 (m),5.30-5.25 (m), 5.02 – 4.92 (m), 4.83 – 4.64 (m), 3.33 (s), 3.24 (d), 3.18 – 3.08 (m), 3.04 – 2.91 (m), 2.50 – 2.39 (m), 1.57 (dd), 1.38 (m), 1.05 (s), 1.03 (s). MS (*m/z*) 806.1 $[M+H]^+$.

Example 144.

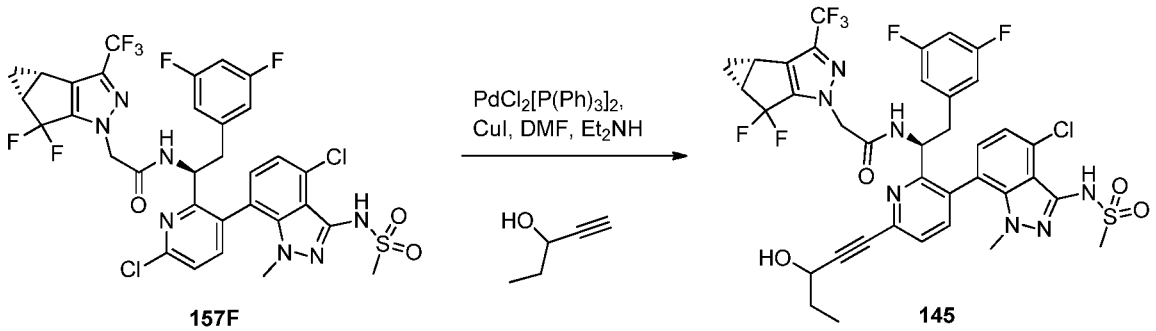


144

Synthesis of N-((1S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(4-fluoro-3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**144**):

[0729] The title compound (**144**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **142** of Example 142 utilizing 1-fluoro-2-methylbut-3-yn-2-ol. ^{1}H NMR (400 MHz, cd_3od) δ 8.69 (t), 7.71 (dd), 7.56 (dd), 7.17 (s), 7.07 (d), 6.87 – 6.52 (m), 6.44 – 6.34 (m), 5.33 – 5.23 (m), 5.03 – 4.94 (m), 4.78 – 4.63 (m), 4.50 (d), 4.38 (d), 3.24 (d), 3.19 – 3.08 (m), 3.05 – 2.92 (m), 2.44 (ddd), 1.63 (dd), 1.39 (dd), 1.08 (s), 1.02 (s). MS (*m/z*) 839.1 $[M+H]^+$.

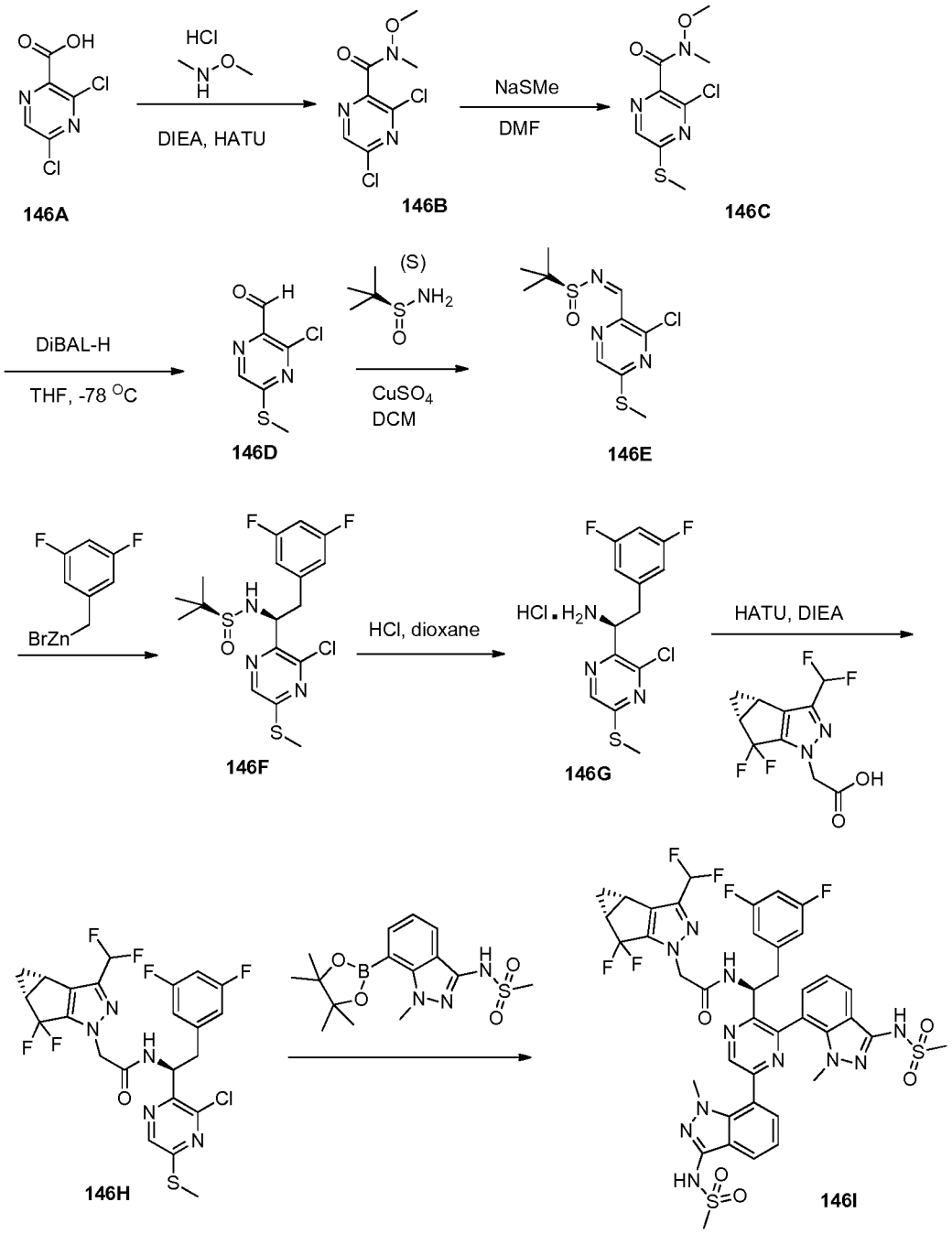
Example 145.



Synthesis of N-((1S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxypent-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**145**):

[0730] To the reaction vial containing **157F** (20 mg, 0.025 mmol) in DMF (1 mL) was added pent-1-yn-3-ol (0.011 g, 0.13 mmol), $Pd(PPh_3)_2Cl_2$ (1.7 mg, 0.003 mmol), and diethylamine (0.02 mL, 0.25 mmol). The reaction mixture was flushed with argon gas for 5 min then sealed and heated in a microwave reactor to 125°C for 20 min. Upon cooling, the reaction mixture was filtered and purified by reverse phase HPLC the title compound **145** as a mixture of atropisomers. ^{1}H NMR (400 MHz, cd_3od) δ 8.72 (dd), 7.70 (dd), 7.54 (dd), 7.16 (d), 7.06 (d), 6.81 – 6.71 (m), 6.66-6.59 (m), 6.46 – 6.34 (m), 5.35-5.20 (m), 5.03 – 4.93 (m), 4.81 – 4.70 (m), 4.61 – 4.52 (m), 3.34 (s), 3.24 (d), 3.20 – 3.11 (m), 3.05 – 2.93 (m), 2.52 – 2.43 (m), 1.96 – 1.79 (m), 1.41 (dt), 1.13 (td). MS (*m/z*) 840.0 $[M+H]^+$.

Example 146.



Synthesis of 3,5-dichloro-N-methoxy-N-methylpyrazine-2-carboxamide (**146B**):

[0731] To a solution of **146A** (10 g, 51.82 mmol) and HATU (21.67 g, 57 mmol) in DMF (50 mL), DIEA (19.86 mL, 114 mmol) was added to the solution. After 30 minutes, N,O-dimethylhydroxyamine hydrochloride (6.09 g, 62.18 mmol) was added to the solution. The mixture was stirred for overnight. 300 mL of water was added and extracted with EtOAc three times (100 mL). The crude product was purified by flash column to provide the desired product. MS (*m/z*) 236 $[M+H]^+$.

Synthesis of 3-chloro-N-methoxy-N-methyl-5-(methylthio)pyrazine-2-carboxamide (**146C**):

[0732] To a solution of **146B** (2g, 8.47 mmol) in DMF (10 mL), 1 eq. of sodium methanethiolate was added to the solution. After 5 hours, 0.5 eq. of sodium methanethiolate was added to the suspension. The reaction was stirred overnight then diluted with EtOAc and washed with $NaHCO_3$(aq) and brine. The organic layer was concentrated and purified by flash column to provide the title compound. MS (m/z) 248 $[M+H]^+$.

Synthesis of 3-chloro-5-(methylthio)pyrazine-2-carbaldehyde (**146D**):

[0733] To a solution of **146C** (750 mg, 3.03 mmol) in THF at -78 °C, DIBAL-H (3.33 mL, 3.33 mmol) in toluene was added to the solution slowly. Then, it was stirred for 2 hours at -78 °C. 4 mL of 1 N HCl(aq) was added to the solution and warmed to 0 °C. The mixture was stirred for 20 minutes at 0 °C then extracted with EtOAc twice. The organic layer was dried and concentrated and used without further purification. MS (m/z) 189 $[M+H]^+$.

Synthesis of (S,Z)-N-((3-chloro-5-(methylthio)pyrazin-2-yl)methylene)-2-methylpropane-2-sulfinamide (**146E**):

[0734] The title compound (**146E**) was prepared according to the method presented for the synthesis of compound **21C** of Example 21 utilizing **146D**. MS (m/z) 292 $[M+H]^+$.

Synthesis of (S)-N-((S)-1-(3-chloro-5-(methylthio)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (**146F**):

[0735] The title compound (**146F**) was prepared according to the method presented for the synthesis of compound **182D** of Example 182 utilizing **146E**. MS (m/z) 420 $[M+H]^+$.

Synthesis of (S)-1-(3-chloro-5-(methylthio)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethanamine hydrochloride (**146G**):

[0736] The title compound (**146G**) was prepared according to the method presented for the synthesis of compound **21E** of Example 21 utilizing **146F**. MS (m/z) 316 $[M+H]^+$.

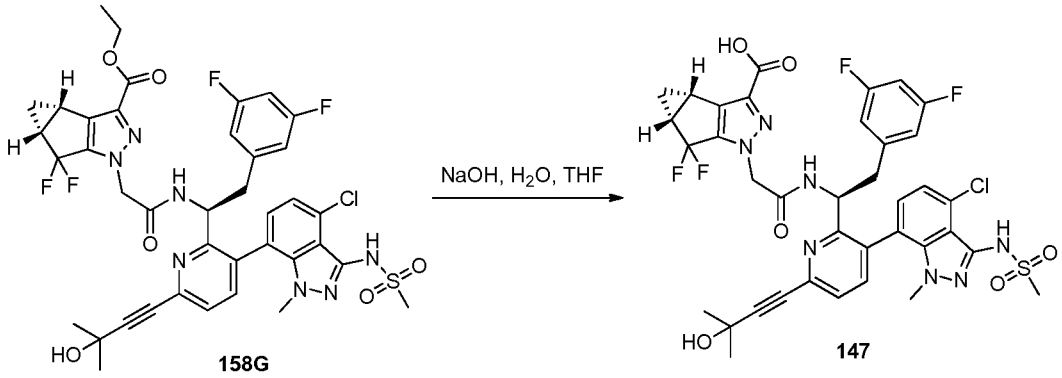
Synthesis of N-((S)-1-(3-chloro-5-(methylthio)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**146H**):

[0737] The title compound (**146H**) was prepared according to the method presented for the synthesis of compound **10A** of Example 10 utilizing **146G** and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. MS (*m/z*) 562 $[M+H]^+$.

Synthesis of N-((S)-1-(3,5-bis(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**146I**):

[0738] The title compound (**146I**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19E** of Example 19 utilizing **33B** and **146H**. ^{1}H NMR (400 MHz, Methanol-d4) δ 9.15 (d), 8.91 (s), 7.93 (t), 7.63 (d), 7.35-7.25 (m), 7.23-7.1 (m), 6.85-6.75 (m), 6.74-6.6 (m), 6.6-6.50 (m), 6.4-6.32 (m), 5.75-5.6 (m), 5.10-5.25 (m), 4.71 (s), 3.65 (s), 3.56 (s), 3.10-3.25 (m), 2.92 (s), 2.60-2.40 (m), 1.45-1.30 (m), 1.1-0.80 (m). MS (*m/z*) 928 $[M+H]^+$.

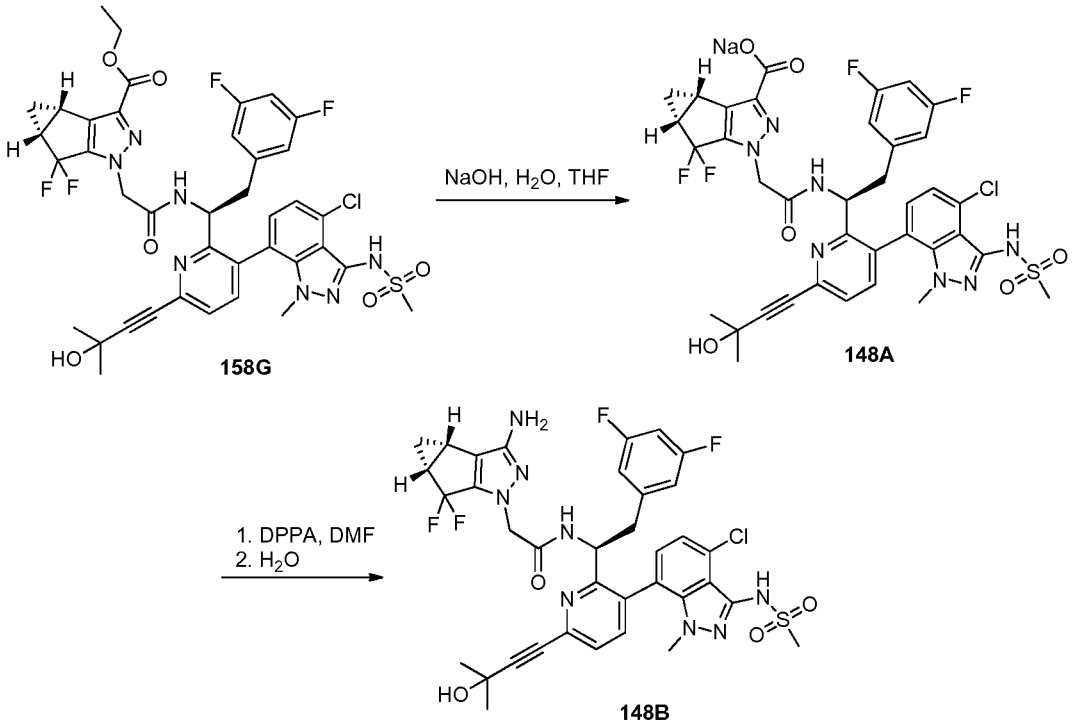
Example 147.



Synthesis of (3bS,4aR)-1-(2-(((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)amino)-2-oxoethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylic acid (**147**):

[0739] A solution of **158G** (0.41 g, 0.49 mmol) in THF (0.5 ml) was treated with 1M NaOH (2 ml). The reaction was stirred at room temperature for 1.5 h. The solution was acidified to ~ pH=4 with AcOH and extracted with 2-MeTHF (2 x 5 mL) and water (5 mL). The organics were dried with Na_2SO_4, filtered, and concentrated. The crude material was purified by reverse phase HPLC to provide the product **147** as a mixture of atropisomers. ^{1}H NMR (400 MHz, cd_3od) δ , 8.69 (d), 7.69 (d), 7.53 (dd), 7.19 (d), 7.06 (d), 6.81 – 6.71 (m), 6.63 (t), 6.46 – 6.35 (m), 5.32 – 5.23 (m), 5.03 – 4.93 (m), 4.85 – 4.80 (m), 4.72 (s), 3.36 (s), 3.26 (s), 3.23 (s), 3.22 – 3.09 (m), 3.05 – 2.92 (m), 2.63 – 2.51 (m), 2.50 – 2.39 (m), 1.65 (s), 1.64 (s), 1.49 – 1.35 (m), 1.15 – 1.07 (m), 1.08 – 0.97 (m). MS (*m/z*) 814.1 $[M+H]^+$.

Example 148.



Synthesis of sodium (3bS,4aR)-1-(2-(((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)amino)-2-oxoethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylate (**148A**):

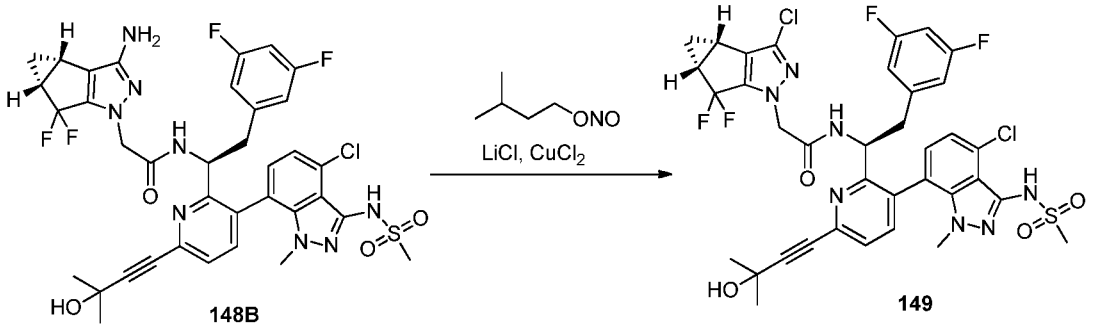
[0740] To a solution of **158G** (0.22 g, 0.26 mmol) in THF (0.65 ml) was added 1M NaOH (0.65 ml). The reaction was stirred at room temperature for 1.5 h. The solution was acidified to ~ pH=4 with AcOH and extracted with with 2-MeTHF (2 x 5 mL) and brine (5 mL). The organic layer was washed with $NaHCO_3$ (10mL). The organics were dried with Na_2SO_4, filtered, and concentrated. The product was taken to the next step without further purification. MS (*m/z*) 814.1 $[M+H]^+$.

Synthesis of 2-((3bS,4aR)-3-amino-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)acetamide (**148B**):

[0741] To a solution of **148A** (110 mg, 0.13 mmol) in DMF (1.0 ml) was added diphenyl phosphoryl azide (28.35 µl, 0.13 mmol). The reaction was stirred at room temperature for 45 min. The solution was cooled to 0 °C and water (0.75 mL) was added dropwise. The resulting solution was sealed and heated in microwave reactor at 130 °C for 15 min. The crude material treated with TFA (20 µl) and purified by prep HPLC to provide the product **148B** as a mixture of

atropisomers. ^{1}H NMR (400 MHz, cd$_3$o*d*) δ 8.72 – 8.59 (m), 7.75 – 7.65 (m), 7.53 (dd), 7.22 – 7.15 (m), 7.09 (d), 6.83 – 6.72 (m), 6.67 – 6.60 (m), 6.46 – 6.33 (m), 5.28 (dd), 4.96 (t), 4.90 – 4.70 (m), 4.69 – 4.52 (m), 3.35 (s), 3.26 (s), 3.25 – 3.22 (m), 3.20 (s), 3.17 – 3.10 (m), 3.04 – 2.91 (m), 2.51 – 2.33 (m), 1.65 (s), 1.47 – 1.31 (m), 1.15 – 1.06 (m), 1.03 (m). MS (*m/z*) 785.2 $[M+H]^+$.

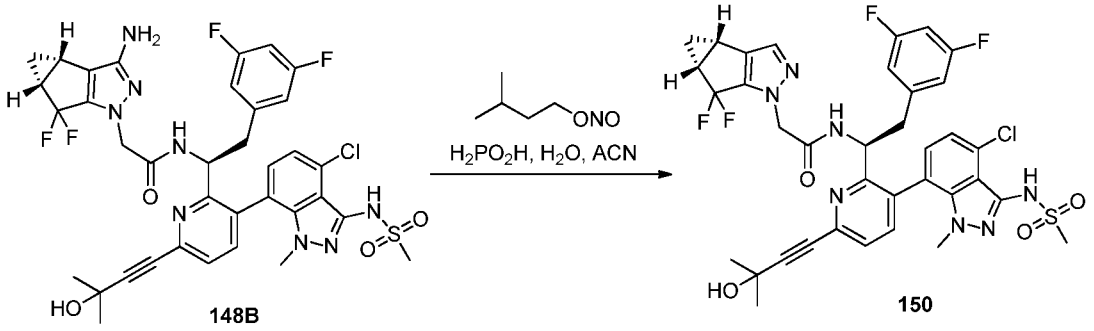
Example 149.



Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-chloro-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**149**):

[0742] A solution of **148B** (19.1 mg, 0.02 mmol), ground lithium chloride (5.16 mg, 0.12 mmol), and cupric chloride (6.54 mg, 0.05 mmol) in ACN (1 ml) was sonicated for 5 min. Isoamyl nitrite (6.51 µl, 0.05 mmol) was added and the reaction was sonicated for an additional 5 min then stirred for 45 min. The crude material was purified by prep HPLC to provide the desired product **149** as a mixture of atropisomers. ^{1}H NMR (400 MHz, cd$_3$o*d*) δ 8.67 (d), 8.62 (d), 7.69 (dd), 7.53 (dd), 7.19 (s), 7.07 (d), 6.82 – 6.72 (m), 6.68 – 6.58 (m), 6.47 – 6.32 (m), 5.27 (m), 5.03 – 4.92 (m), 4.69 – 4.67 (m), 4.64 (d), 3.34 (s), 3.26 (s), 3.24 (s), 3.18 – 3.08 (m), 3.05 – 2.92 (m), 2.53 – 2.30 (m), 1.64 (s), 1.45 – 1.27 (m), 1.13 – 1.07 (m), 1.08 – 1.01 (m). MS (*m/z*) 804.1 $[M+H]^+$.

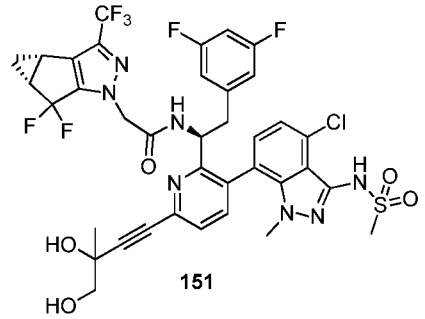
Example 150.



Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**150**):

[0743] To a solution of **148B** (10 mg, 0.01 mmol) in ACN (0.2 ml) and 50% hypophosphorus acid in water (50 µl) was added isoamyl nitrite (3.41 µl, 0.03 mmol). The reaction mixture was stirred at room temperature for 30 min. The crude material was purified by prep HPLC to provide the title product **150** as a mixture of atropisomers. ^{1}H NMR (400 MHz, cd_3od) δ 8.48 (d), 8.41 (d), 7.74 – 7.63 (m), 7.54 (d), 7.51 (d), 7.34 (s), 7.31 (s), 7.17 (s), 7.07 (d), 6.81 – 6.72 (m), 6.66 – 6.58 (m), 6.45 – 6.33 (m), 5.34 – 5.26 (m), 5.02 – 4.93 (m), 4.74 (d), 4.69 (d), 3.33 (s), 3.26 (s), 3.24 (s), 3.14 – 3.06 (m), 3.03 – 2.91 (m), 2.46 – 2.33 (m), 1.65 (s), 1.39 – 1.28 (m), 1.03 (s), 1.00 – 0.93 (m). MS (*m/z*) 770.1 $[M+H]^+$.

Example 151.

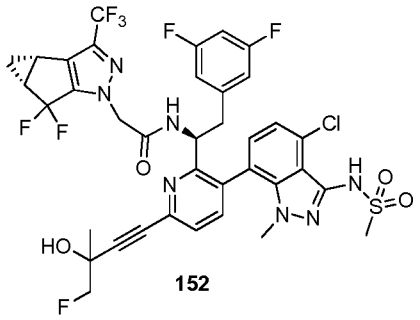


151

Synthesis of N-((1S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3,4-dihydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**151**):

[0744] The title compound (**151**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **145** of Example 145 utilizing 2-methylbut-3-yne-1,2-diol. ^{1}H NMR (400 MHz, cd_3od) δ 8.78 (d), 7.70 (dd), 7.62 – 7.52 (m), 7.16 (s), 7.05 (d), 6.81 – 6.72 (m), 6.65-6.60 (m), 6.44 – 6.30 (m), 5.28 (d), 4.97 (d), 4.84 – 4.70 (m), 3.66 (d), 3.33 (s), 3.24 (d), 3.14 (dd), 3.07 – 2.92 (m), 2.86 (s), 2.53 – 2.42 (m), 1.59 (d), 1.47 – 1.36 (m), 1.29 (t), 1.19-1.10 (m), 1.09 – 1.04 (m). MS (*m/z*) 854.1 $[M+H]^+$.

Example 152.

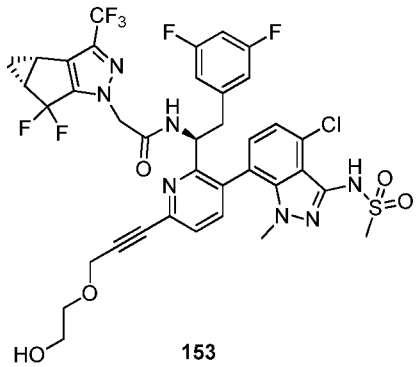


152

Synthesis of N-((1S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(4-fluoro-3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**152**):

[0745] The title compound (**152**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **145** of Example 145 utilizing 1-fluoro-2-methylbut-3-yn-2-ol. ^{1}H NMR (400 MHz, cd_3od) δ 7.71 (dd), 7.64 – 7.51 (m), 7.22 – 7.12 (m), 7.06 (d), 6.81 – 6.71 (m),6.68-6.58 (m), 6.44 – 6.33 (m), 5.30-5.21 (m), 4.98 (t), 4.85 – 4.70 (m), 4.50 (d), 4.38 (d), 3.24 (d), 3.20 – 3.11 (m), 3.06 – 2.93 (m), 2.56 – 2.43 (m), 1.62 (s), 1.47 – 1.27 (m),1.16-1.10 (m), 1.09-1.04 (s). MS (*m/z*) 858.0 $[M+H]^+$.

Example 153.



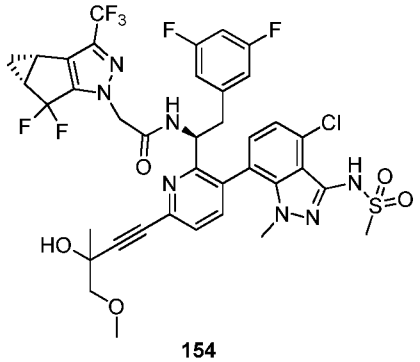
153

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-(2-hydroxyethoxy)prop-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**153**):

[0746] The title compound (**153**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **145** of Example 145 utilizing 2-(prop-2-yn-1-yloxy)ethanol. ^{1}H NMR (400 MHz, cd_3od) δ 8.67 (d), 7.71 (dd), 7.62 – 7.52 (m), 7.17 (d), 7.07 (d), 6.81 – 6.71 (m), 6.68 – 6.60 (m), 6.45 – 6.34 (m), 5.29 – 5.24 (m), 4.98 (q), 4.84 – 4.70 (m),

4.54 (d), 3.86 – 3.80 (m), 3.80 – 3.66 (m), 3.36 – 3.31 (m), 3.28 – 3.09 (m), 2.98 (d), 2.52 – 2.44 (m), 1.40 (q), 1.16 – 1.11 (m), 1.10 – 1.05 (m). MS (*m/z*) 854.2 $[M+H]^+$.

Example 154.



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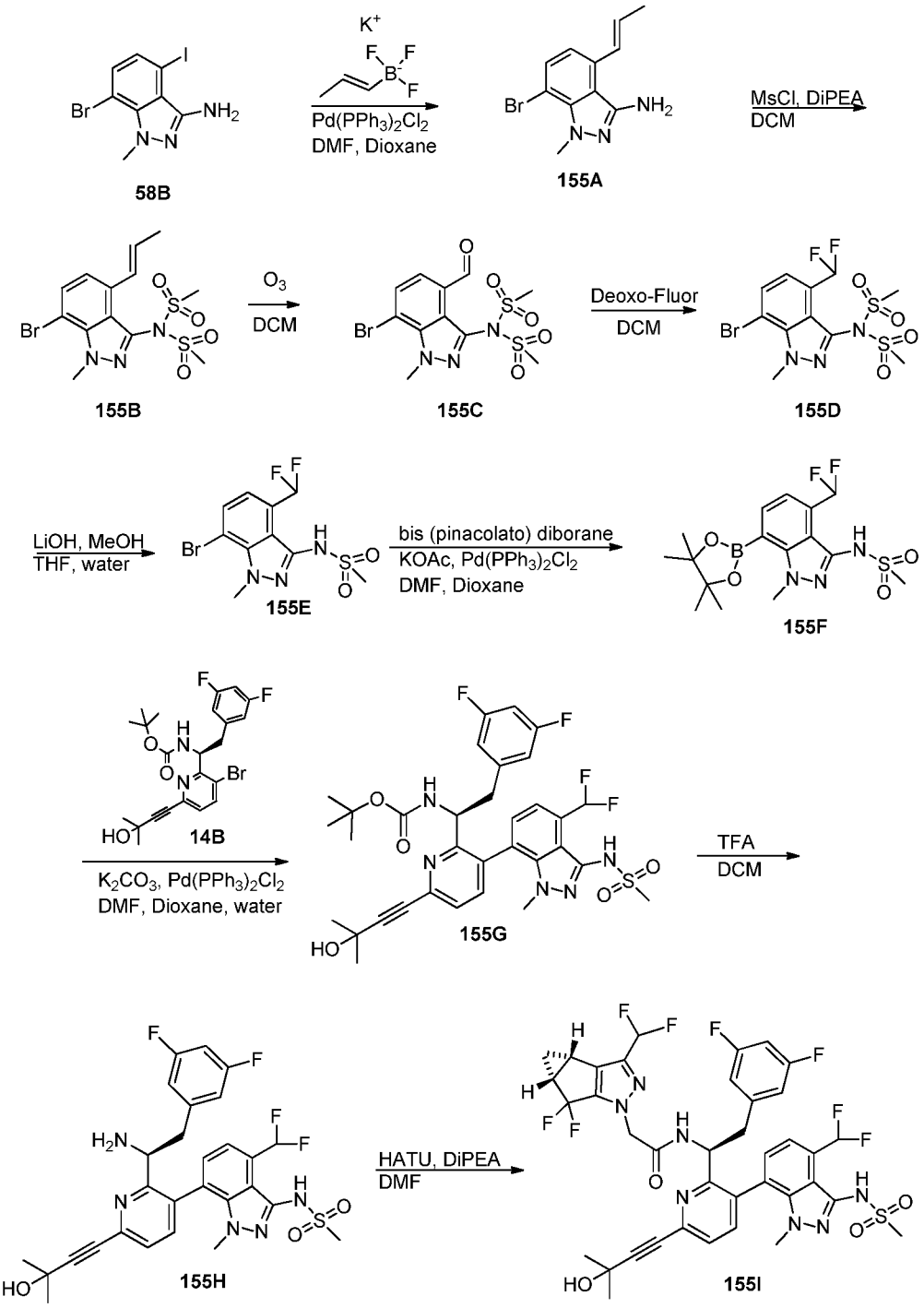
Synthesis of N-((1S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-4-methoxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**154**):

[0747] The title compound (**154**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **145** of Example 145 utilizing 1-methoxy-2-methylbut-3-yn-2-ol. ^{1}H NMR (400 MHz, cd_3od) δ 8.67 (d), 7.71 (dd), 7.62 – 7.52 (m), 7.17 (d), 7.07 (d), 6.81 – 6.71 (m), 6.64 (d), 6.45 – 6.34 (m), 5.26 (s), 4.98 (q), 4.84 – 4.70 (m), 4.62 (s), 4.54 (d), 3.86 – 3.80 (m), 3.80 – 3.66 (m), 3.34 (s), 3.28 – 3.09 (m), 2.98 (d), 2.48 (dd), 1.40 (q), 1.14 (m), 1.07 (m).MS (*m/z*) 869.1 $[M+H]^+$.

Example 155.



Synthesis of (E)-7-bromo-1-methyl-4-(prop-1-en-1-yl)-1H-indazol-3-amine (**155A**):

[0748] To **58B** (7.4 g, 21.0 mmol) in dioxane (40 mL) and DMF (40 ml) was added potassium trifluoro(prop-1-en-1-yl)borate (3.7 g, 25.2 mmol), 2M K_2CO_3 in water (21.0 ml), and $Pd(PPh_3)_2Cl_2$ (740.0 mg, 1.1 mmol). The reaction mixture was stirred for 2 hours at 100 °C. The reaction was cooled, diluted with EtOAc and brine. The mixture was extracted 2X with EtOAc,

the organic layer was dried over sodium sulfate, was concentrated and purified by flash column chromatography to provide the title compound. MS (*m/z*) 266.3 $[M+H]^+$.

Synthesis of (E)-N-(7-bromo-1-methyl-4-(prop-1-en-1-yl)-1H-indazol-3-yl)-N-(methylsulfonyl)methanesulfonamide (**155B**):

[0749] To **155A** (3.7 g, 13.9 mmol) in DCM (100 mL) was added N,N-diisopropylethylamine (9.7 ml, 55.6 mmol) then the reaction was cooled in an ice bath and methanesulfonyl chloride (3.2 ml, 41.7 mmol) was added. The reaction mixture was stirred for 30 minutes at 0 °C. The reaction was diluted with water and extracted 2X with DCM. The organic layer was dried over sodium sulfate and concentrated. The mixture was purified by flash column chromatography to provide the title compound. MS (*m/z*) 421.9 $[M+H]^+$.

Synthesis of N-(7-bromo-4-formyl-1-methyl-1H-indazol-3-yl)-N-(methylsulfonyl)methanesulfonamide (**155C**):

[0750] A round bottom is charged with **155B** (2.7 g, 6.4 mmol) and DCM (100 mL). The mixture was cooled to -78 °C and ozone was bubbled into the reaction. Once the conversion was complete, DMS was added to quench the reaction under stirring for 30 minutes. To the stirring mixture a saturated sodium thiosulfate solution was added and the mixture was allowed to warm to room temperature and stirred another 30 minutes. The layers were separated and the water layer was extracted again with DCM. The combined organic layers were dried over sodium sulfate and concentrated. The residue was dissolved in DCM and followed by the addition of hexane. The mixture was filtered to provide the title compound. MS (*m/z*) 410.0 $[M+H]^+$.

Synthesis of N-(7-bromo-4-(difluoromethyl)-1-methyl-1H-indazol-3-yl)-N-(methylsulfonyl)methanesulfonamide (**155D**):

[0751] A teflon flask was charged with **155C** (650 mg, 1.6 mmol) and DCM (100 mL). The mixture was cooled to 0 °C and Deoxo-Fluor (0.4 ml, 2.4 mmol) was added into the reaction and then the mixture was allowed to warm to room temperature. The mixture is stirred for 8 hours and checked. Another equivalent of Deoxo-Fluor was added and the mixture was stirred overnight. The mixture is diluted with water and extracted 2X with DCM. The organic layers are dried over sodium sulfate and concentrated. The residue was dissolved in DCM followed by the addition of hexane. The mixture was filtered to provide the title compound. MS (*m/z*) 431.9 $[M+H]^+$.

Synthesis of N-(7-bromo-4-(difluoromethyl)-1-methyl-1H-indazol-3-yl)methanesulfonamide (**155E**):

[0752] To **155D** (5.9 g, 13.7 mmol), THF (50 ml) and MeOH (20 ml) was added a saturated solution of LiOH (10 ml) and water (10 ml). The mixture was stirred for 10 minutes, then diluted with water and extracted 2X EtOAc. The organic layers were dried over sodium sulfate and concentrated. The residue was dissolved in DCM followed by the addition of hexane. The mixture was filtered to provide the title compound. MS (*m/z*) 354.6 $[M+H]^+$.

Synthesis of N-(4-(difluoromethyl)-1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-yl)methanesulfonamide (**155F**):

[0753] The title compound (**155F**) was prepared according to the method presented for the synthesis of compound **19C** of Example 19 utilizing **155E**. MS (m/z) 402.3 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(3-(4-(difluoromethyl)-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**155G**):

[0754] To **14B** (100 mg, 0.2 mmol) in dioxane (8 mL) and DMF (2 ml) was added 2N K_2CO_3 (0.2 ml), and $Pd(PPh_3)_2Cl_2$ (7.1 mg, 0.01 mmol). The reaction mixture was stirred at 110 ^oC, then **155F** (170 mg, 0.4 mml) dissolved in dioxane (4 ml) and DMF (2 ml) was slower added into the reaction by syringe. The reaction was cooled after 8 hours, diluted with EtOAc and brine. The mixture was extracted 2X with EtOAc, the organic layer was dried over sodium sulfate, was concentrated and purified by flash column chromatography to provide the title compound as a mixture of atropisomers. MS (*m/z*) 689.8 $[M+H]^+$.

Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-(difluoromethyl)-1-methyl-1H-indazol-3-yl)methanesulfonamide (**155H**):

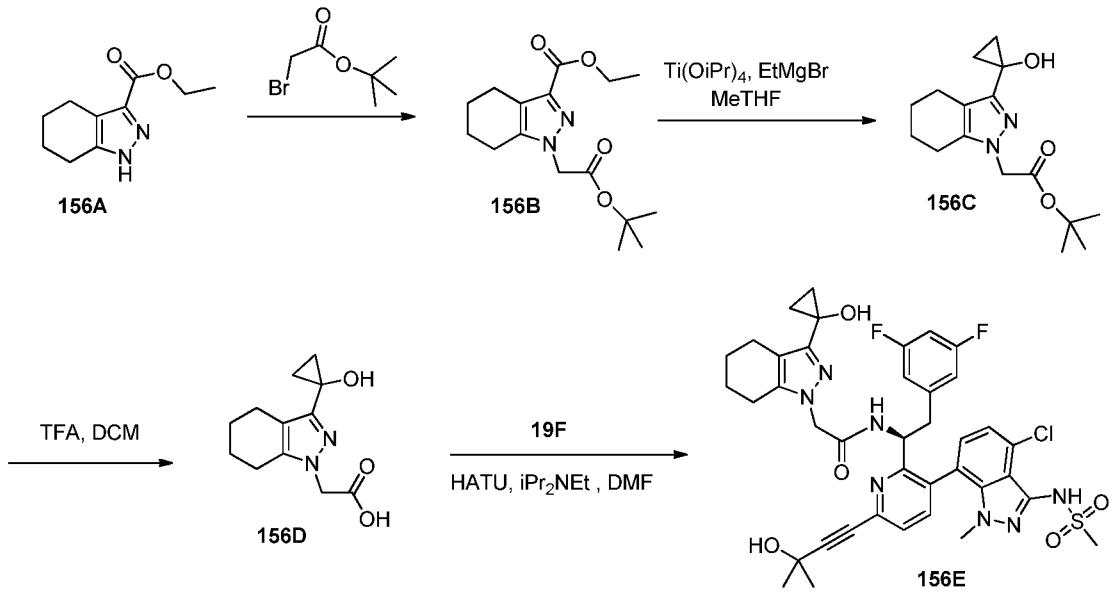
[0755] The title compound (**155H**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19F** of Example 19 utilizing **155G**. MS (m/z) 590.1 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(4-(difluoromethyl)-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**155I**):

[0756] The title compound (**155I**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **10A** of Example 10 utilizing **155H** and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^1H NMR (Chloroform-*d*) δ: 7.60 (dd),

7.53 (dd), 7.49 – 7.38 (m), 7.30 – 7.19 (m), 7.14 (s), 6.83 – 6.78 (m), 6.70 (t), 6.69 – 6.62 (m), 6.34 (d), 6.25 – 6.14 (m), 4.95 (q), 4.75 – 4.69 (m), 3.59 – 3.42 (m), 3.35 (s), 3.01 – 2.88 (m), 2.56 – 2.36 (m), 1.72 (s), 1.46 – 1.37 (m), 1.19 – 1.09 (m). MS (*m/z*) 836.2 $[M+H]^+$.

Example 156.



Synthesis of ethyl 1-(2-(tert-butoxy)-2-oxoethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (**156B**):

[0757] To **156A** (2 g, 10.3 mmol) in MeTHF (100 mL) and DMF (5 ml) was added Cs_2CO_3 (4.0 g, 12.3 mmol) and tert-butyl 2-bromoacetate (2.3 ml, 15.5 mmol). The reaction mixture was stirred for 4 hours. Solids were filtered, the eluent was concentrated and purified by flash column chromatography to provide the title compound. MS (*m/z*) 309.6 $[M+H]^+$.

Synthesis of tert-butyl 2-(3-(1-hydroxycyclopropyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (**156C**):

[0758] To **156B** (300 mg, 1.0 mmol) in MeTHF (20 mL) was added titanium (iv) isopropoxide (2.9 ml, 9.73mmol). To the stirring mixture 3M EtMgBr (3.2 ml) was slowly added. The reaction mixture was stirred for 1 hour. The reaction was diluted with EtOAc and brine. The mixture was extracted 2X with EtOAc, the organic layer was dried over sodium sulfate, was concentrated and purified by flash column chromatography to provide the title compound. MS (*m/z*) 293.0 $[M+H]^+$.

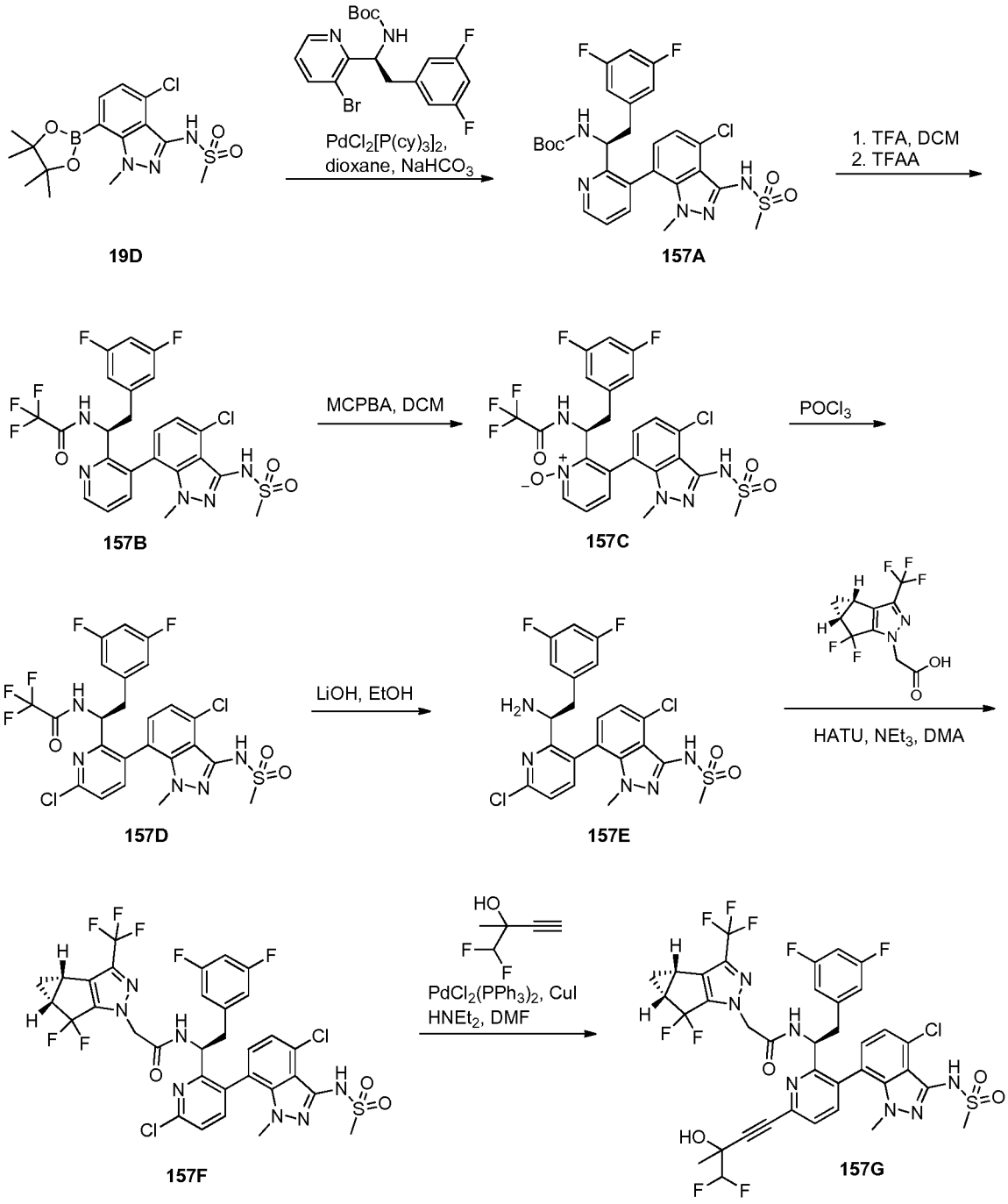
Synthesis of 2-(3-(1-hydroxycyclopropyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid (**156D**):

[0759] To **156C** (20 mg, 0.07 mmol) in DCM (2 mL) was added TFA (0.5 ml). The reaction mixture was stirred for 0.5 hours at RT. The reaction was concentrated and then diluted with 1 N HCl and extracted 2X with DCM. The water layer was lyophilized to provide the title compound. MS (*m/z*) 237.1 $[M+H]^+$.

Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(1-hydroxycyclopropyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**156E**):

[0760] The title compound (**156E**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **10A** of Example 10 utilizing **156D** and **19F**. ^1H NMR (Methanol-d_4) δ: 7.76 – 7.68 (m), 7.53 (dd), 7.25 – 7.14 (m), 6.64 (tt), 6.39 (dd), 5.27 (dd), 4.64 (d), 3.28 – 3.21 (m), 3.21 – 3.10 (m), 3.04 (s), 2.98 (dd), 2.67 – 2.55 (m), 2.47 – 2.37 (m), 1.86 – 1.69 (m), 1.64 (s), 1.10 – 0.97 (m). MS (*m/z*) 792.3 $[M+H]^+$.

Example 157.



Synthesis of (S)-tert-butyl (1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**157A**):

[0761] (S)-tert-butyl (1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (1.0 g, 2.42 mmol), N-(4-chloro-1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-yl)methanesulfonamide (**19D**, 1.12 g, 2.90 mmol), and $PdCl_2[P(cy)_3]_2$ (89.0 mg, 0.121 mmol) were suspended in 1,4-dioxane (12 mL) and 1.0 M aqueous $NaHCO_3$ (4 mL). The reaction mixture was degassed by bubbling argon for 5 minutes then sealed and heated at 150 ºC for 15

minutes in a microwave reactor. Upon cooling, the reaction mixture was diluted with water and extracted with three portions of EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to give the title compound **157A**. MS (*m/z*) 591.72 $[M+H]^+$.

Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2,2,2-trifluoroacetamide (**157B**):

[0762] To (S)-tert-butyl (1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**157A**, 3.39 g, 5.73 mmol) in DCM (5 mL) was added trifluoroacetic acid (5 mL). The reaction mixture was stirred at room temperature for 2.5 hours. Upon complete removal of the Boc protecting group, trifluoroacetic anhydride (2.02 mL, 14.31 mmol) was added. The reaction mixture was stirred at room temperature for 30 minutes. Upon completion, the reaction mixture was filtered through celite, concentrated *in vacuo*, taken in EtOAc, and carefully neutralized with 1M aqueous $NaHCO_3$ until the aqueous layer was at pH 10. The organic layer was collected and the aqueous layer extracted once more with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to give the title compound **157B**. MS (*m/z*) 588.14 $[M+H]^+$.

Synthesis of (S)-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-2-(2-(3,5-difluorophenyl)-1-(2,2,2-trifluoroacetamido)ethyl)pyridine 1-oxide (**157C**):

[0763] To a solution of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2,2,2-trifluoroacetamide (**157B**, 8.0 g, 13.61 mmol) in DCM (70 mL) was added MCPBA (3.659 g, 16.33 mmol) in 4 portions over a 15 minute period. The reaction mixture was stirred at room temperature for 16 hours. Upon completion, the reaction was quenched with 1M aqueous $NaHSO_3$ and saturated aqueous $NaHCO_3$. The organic layer was collected and the aqueous layer was extracted an additional time with DCM. The combined organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to give the title compound **157C**. MS (*m/z*) 604.10 $[M+H]^+$.

Synthesis of (S)-N-(1-(6-chloro-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2,2,2-trifluoroacetamide (**157D**):

[0764] (S)-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-2-(2-(3,5-difluorophenyl)-1-(2,2,2-trifluoroacetamido)ethyl)pyridine 1-oxide (**157C**, 1.0 g, 1.66 mmol)

was taken in $POCl_3$ (2.32 mL, 24.84 mmol). The reaction mixture was heated at 115 °C for 2 hours. Upon cooling, the reaction was concentrated *in vacuo*, taken in DCM, and vigorously stirred with saturated aqueous $NaHCO_3$ for 1 hour. The organic layer was collected, and the aqueous layer was extracted an additional time with DCM. The combined organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to give the title compound **157D**. MS (*m/z*) 622.13 $[M+H]^+$.

Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-chloropyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**157E**):

[0765] To a solution of (S)-N-(1-(6-chloro-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2,2,2-trifluoroacetamide (**157D**, 870 mg, 1.40 mmol) in EtOH (16 mL) was added 2M aqueous LiOH (7.0 mL, 13.98 mmol). The reaction was heated at 130 °C for 10 minutes. Upon cooling, the reaction mixture was acidified with 2N aqueous HCl until at pH 5. The reaction mixture was then concentrated *in vacuo* and taken in EtOAc. To the solution was added saturated aqueous $NaHCO_3$ until the aqueous layer was at pH 10. The organic layer was collected, and the aqueous layer was extracted an additional time with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo*, and used without further purification. MS (*m/z*) 526.06 $[M+H]^+$.

Synthesis of N-((S)-1-(6-chloro-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**157F**):

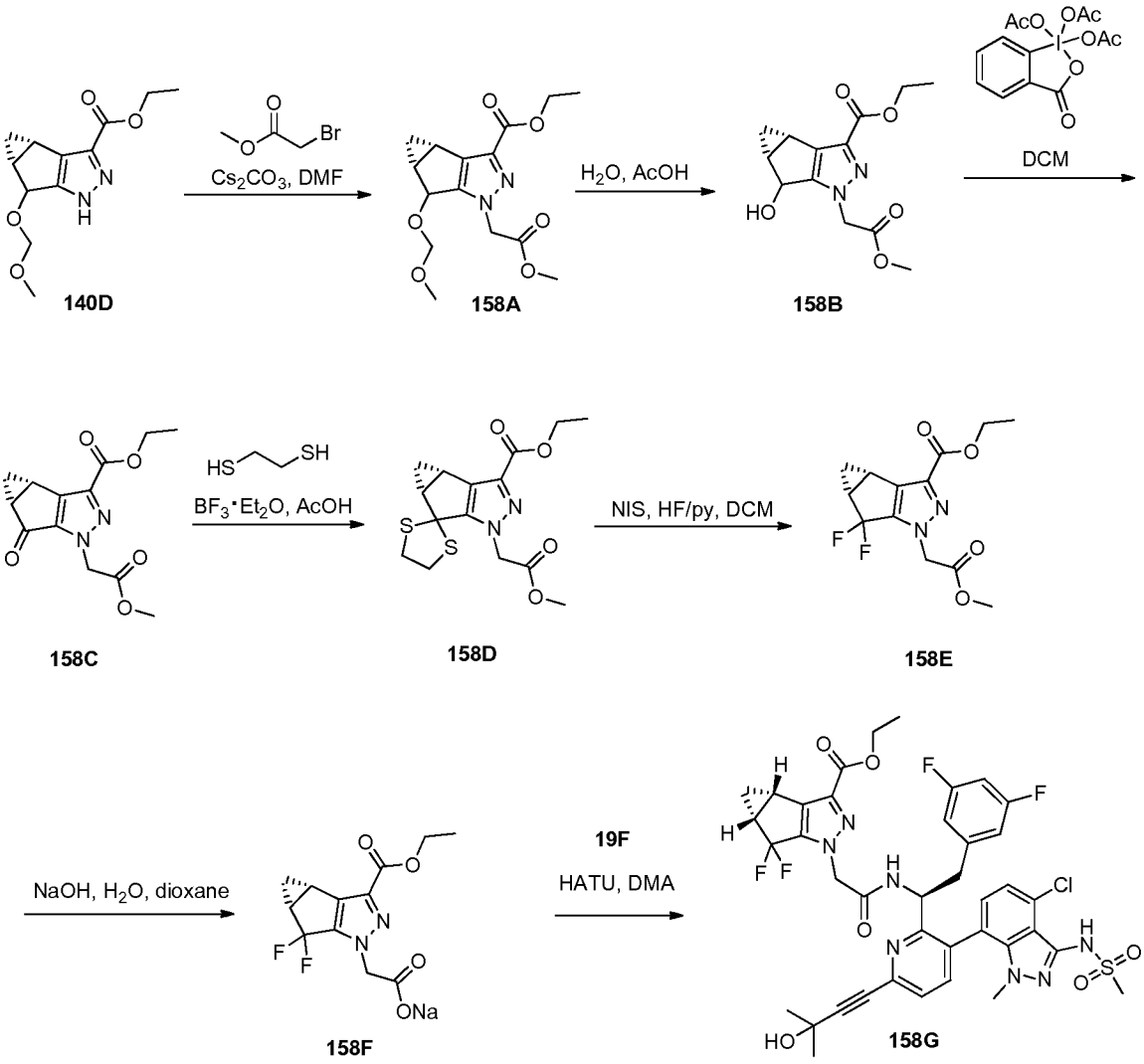
[0766] To a solution of crude (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-chloropyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**157E**, 400 mg, 0.76 mmol) in DMA (6 mL) was added NEt_3 (0.32 mL, 2.28 mmol), 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (160.6 mg, 0.61 mmol), then HATU (173.4 mg, 0.46 mmol). The reaction mixture was stirred at room temperature for 15 minutes, then additional HATU (86.7 mg, 0.23 mmol) was added. The reaction mixture was stirred at room temperature for an additional 15 minutes. Upon completion, the reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography to give the title compound **157F**. MS (*m/z*) 790.12 $[M+H]^+$.

Synthesis of N-((1S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(4,4-difluoro-3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-

((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**157G**):

[0767] N-((S)-1-(6-chloro-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**157F**, 20 mg, 0.025 mmol), 1,1-difluoro-2-methylbut-3-yn-2-ol (15.2 mg, 0.126 mmol), $PdCl_2(PPh_3)_2$ (1.8 mg, 0.003 mmol), and CuI (0.5 mg, 0.003 mmol) were taken in DMF (0.25 mL). To the reaction mixture was added diethylamine (26 μL, 0.253 mmol), and the reaction mixture was degassed by bubbling argon for 5 minutes then sealed and heated at 125 ºC for 30 minutes in a microwave reactor. Upon cooling, the reaction mixture was filtered and purified by reverse phase HPLC to give the title compound **157G** as a mixture of atropisomers. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.88 – 8.78 (m), 7.74 (dd), 7.60 (dd), 7.24 – 7.13 (m), 7.10 – 7.05 (m), 6.77 (t), 6.64 (t), 6.46 – 6.33 (m), 5.82 (t), 5.35 – 5.23 (m), 5.00 (q), 4.82 (s), 4.79 (s), 4.76 (s), 3.34 (s), 3.26 (s), 3.23 (s), 3.20 – 3.10 (m), 3.07 – 2.93 (m), 2.58 – 2.37 (m), 1.63 (s), 1.50 – 1.34 (m), 1.18 – 1.11 (m), 1.10 – 1.01 (m). MS (*m/z*) 874.07 $[M+H]^+$.

Example 158.



Synthesis of (3bS,4aR)-ethyl 1-(2-methoxy-2-oxoethyl)-5-(methoxymethoxy)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylate (**158A**):

[0768] To a solution of (3bS,4aR)-ethyl 5-(methoxymethoxy)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylate (**140D**) (3.3 g, 13.1 mmol) in DMF (12 ml) was added portionwise potassium t-butoxide (1.61 g, 14.39 mmol) at 0 °C. To the reaction was added 2-methyltetrahydrofuran (12 ml) followed by a dropwise addition of methyl bromoacetate (1.36 ml, 14.4 mmol). After gradually warming to room temperature and stirring for 1 h, the reaction was extracted with EtOAc and water. The organic layer was washed with water. The organics layer was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was taken to next step without further purification. MS (*m/z*) 324.96 $[M+H]^+$.

Synthesis of (3bS,4aR)-ethyl 5-hydroxy-1-(2-methoxy-2-oxoethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylate (**158B**):

[0769] To a solution of (3bS,4aR)-ethyl 1-(2-methoxy-2-oxoethyl)-5-(methoxymethoxy)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylate (**158A**) (4.2 g) in acetic acid (15 ml) was added water (30 ml). After stirring at reflux for 2h, the reaction was concentrated *in vacuo*. The resulting mixture was diluted with dioxane (40 ml) and concentrated *in vacuo*. The crude product was dissolved in dichloromethane (20 ml), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was taken to next step without further purification. MS (*m/z*) 281.02 $[M+H]^+$.

Synthesis of (3bS,4aR)-ethyl 1-(2-methoxy-2-oxoethyl)-5-oxo-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylate (**158C**):

[0770] To a solution of **156B** (3.63 g, 12.95 mmol) in DCM (30 mL) was added Dess– Martin periodinane (4.87 g, 12.95 mmol). The reaction was stirred at room temperature overnight. The reaction mixture was filtered through celite, solid loaded onto silica and purified by silica gel chromatography to give the title compound. MS (*m/z*) 278.9 $[M+H]^+$.

Synthesis of (3bS,4aR)-ethyl 1-(2-methoxy-2-oxoethyl)-1,3b,4,4a-tetrahydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-[1,3]dithiolane]-3-carboxylate (**158D**):

[0771] To a solution of **158C** (0.69 g, 2.61 mmol), 1,2-ethanedithiol (0.44 ml, 5.22 mmol), acetic acid (0.75 ml, 13.06 mmol) in DCM (10 ml) was added boron trifluoride diethyl etherate (0.81 ml, 6.53 mmol). The reaction was stirred at room temperature for 2 days. The reaction mixture was concentrated, solid loaded onto silica and purified by silica chromatography to give the title compound **158D**. MS (*m/z*) 354.9 $[M+H]^+$.

Synthesis of (3bS,4aR)-ethyl 5,5-difluoro-1-(2-methoxy-2-oxoethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylate (**158E**):

[0772] To suspension of N-iodosuccinimide, 98% (1.35 g, 6.0 mmol) in DCM (5 ml) was added dropwise 70% HF in pyridine (5 ml) at -78 °C. After stirring for 15 min **158D** (0.85 g, 2.39 mmol) in DCM (5 ml) was added and the reaction was slowly warmed to - 30 °C and stirred at that temperature for 1h. The resulting solution was carefully poured onto ice containing 1.0 N $NaHCO_3$. The product was extracted with ethyl acetate, washed with $NaHSO_3$, brine and water. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude material was purified by silica chromatography to give the title compound **158E**. MS (*m/z*) 300.9 $[M+H]^+$.

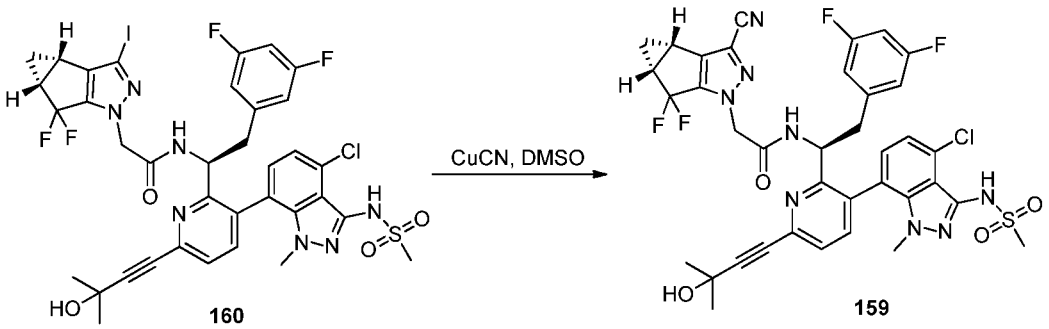
Synthesis of sodium 2-((3bS,4aR)-3-(ethoxycarbonyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**158F**):

[0773] To a solution of **158E** (0.16 g, 532.87 µmol) in dioxane (3 ml) was added dropwise 1M NaOH (0.55 ml). The reaction was stirred at room temperature for 0.5 h. An additional 0.500 mL of 1M NaOH was added and stirred for an additional 0.5 h. The reaction was concentrated, diluted with DMA (3mL) and concentrated until dryness. The crude product was taken to next step without further purification. MS (*m/z*) 286.9 $[M+H]^+$.

Synthesis of (3bS,4aR)-ethyl 1-(2-(((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)amino)-2-oxoethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylate (**158G**):

[0774] To a solution of **19F** (305.45 mg, 532.1 µmol) and **158F** (164 mg, 532.1 µmol) in DMA (2 mL) was added HATU (212.31 mg, 558.7 µmol). The reaction was stirred at room temperature for 0.5 h. The reaction was diluted with 0.1 M NaCl (10mL) and extracted with ethyl acetate (2x10mL). The combined organic layers was washed with water (20 mL), dried with Na_2SO_4, filtered, and concentrated. The crude material was purified by silica chromatography to give the title compound **158G** as a mixture of atropisomers. ^{1}H NMR (400 MHz, cd_3od) δ 8.77 (d), 8.75 – 8.68 (m), 8.43 (dd), 7.70 (t), 7.57 – 7.48 (m), 7.22 – 7.15 (m), 7.06 (d), 6.81 – 6.72 (m), 6.68 – 6.59 (m), 6.41 (dd), 5.30 – 5.19 (m), 4.99 (q), 4.82 (d), 4.73 (s), 4.42 – 4.31 (m), 3.36 (s), 3.34 – 3.27 (m), 3.25 (s), 3.22 (s), 3.17 (dd), 3.04 – 2.97 (m), 2.96 (s), 2.63 – 2.39 (m), 1.65 (s), 1.64 (s), 1.49 – 1.32 (m), 1.14 – 1.07 (m), 1.07 – 0.99 (m). MS (*m/z*) 842.2 $[M+H]^+$.

Example 159.

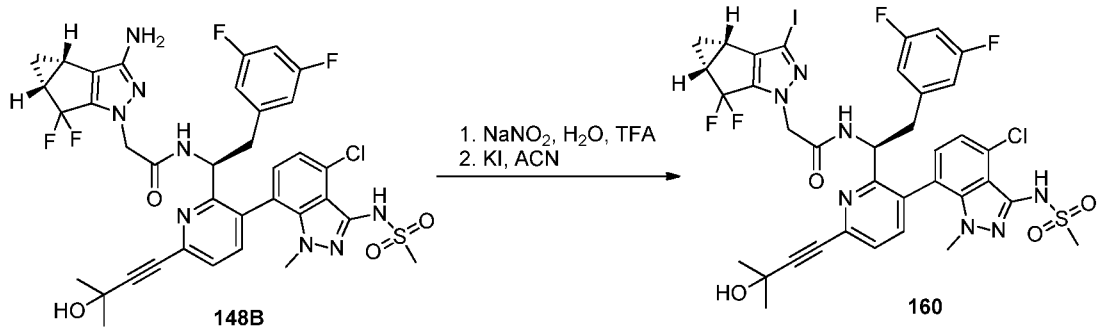


Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-

cyano-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**159**):

[0775] To a solution of **160** (11 mg, 12.2 μmol) in DMSO (0.2 ml) was added cuprous cyanide (2.7 mg, 30.7 μmol). The reaction mixture sealed and heated to 180 °C for 0.5 h. The reaction was cooled rt, diluted with ethyl acetate, and washed with water. The organic phase was then dried with Na_2SO_4, filtered and concentrated. The crude material was purified by prep HPLC to provide the product **159** as a mixture of atropisomers. ^{1}H NMR (400 MHz, cd_3od) δ 8.87 – 8.78 (m), 7.73 – 7.66 (m), 7.58 – 7.48 (m), 7.18 (s), 7.07 (d), 6.81 – 6.71 (m), 6.68 – 6.58 (m), 6.48 – 6.32 (m), 5.32 – 5.20 (m), 5.03 – 4.91 (m), 4.80 (d), 3.34 (s), 3.25 (s), 3.24 (s), 3.15 (dd), 3.06 – 2.93 (m), 2.63 – 2.47 (m), 1.64 (s), 1.45 (dd), 1.19 – 1.14 (m), 1.11 – 1.06 (m). MS (*m/z*) 795.1 $[M+H]^+$.

Example 160.



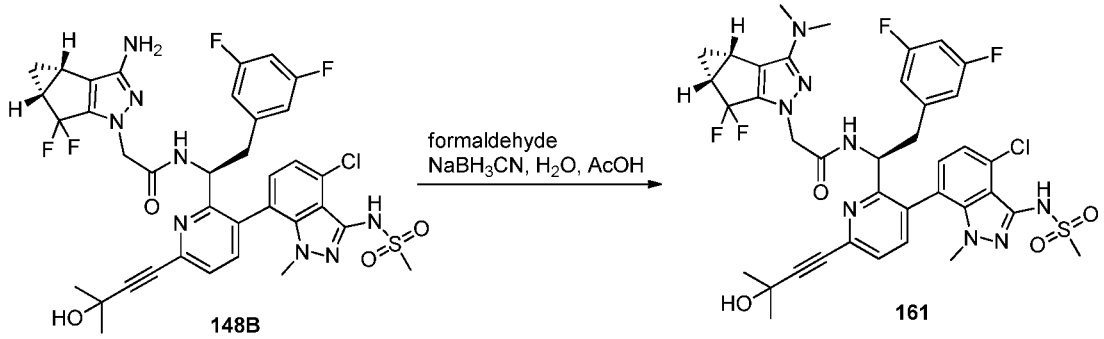
148B 160

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-iodo-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**160**):

[0776] To a solution of **148B** (75 mg, 95.5μmol) in trifluoroacetic acid (0.5 ml) and water (0.2 mL was added sodium nitrite (1M in water, 0.3 mL) followed by stirring for 15 min at room temperature. The reaction mixture was then treated with potassium iodide (238 mg, 1.4 mmol), acetonitrile (0.8 mL) and stirred for an additional 1.5 h. The reaction was basified with 1M $NaHCO_3$, quenched with 1M $NaHSO_3$, and extracted with ethyl acetate (20 mL). The organic phase was then dried with Na_2SO_4, filtered and concentrated. The crude material was purified by prep HPLC to provide the product **160** as a mixture of atropisomers. ^{1}H NMR (400 MHz, cd_3od) δ7.75 – 7.63 (m), 7.58 – 7.48 (m), 7.18 (s), 7.12 – 7.02 (m), 6.82 – 6.72 (m), 6.68 – 6.58 (m), 6.46 – 6.32 (m), 5.32 – 5.22 (m), 4.96 (t), 4.76 – 4.56 (m), 3.34 (s), 3.30 – 3.22 (m), 3.26

(s), 3.25 (s), 3.20 – 3.06 (m), 3.04 – 2.91 (m), 2.51 – 2.35 (m), 2.30 – 2.16 (m), 2.03 (), 1.65 (s), 1.42 – 1.27 (m), 1.10 – 1.04 (m), 1.04 – 0.99 (m). MS (*m/z*) 896.0 $[M+H]^+$.

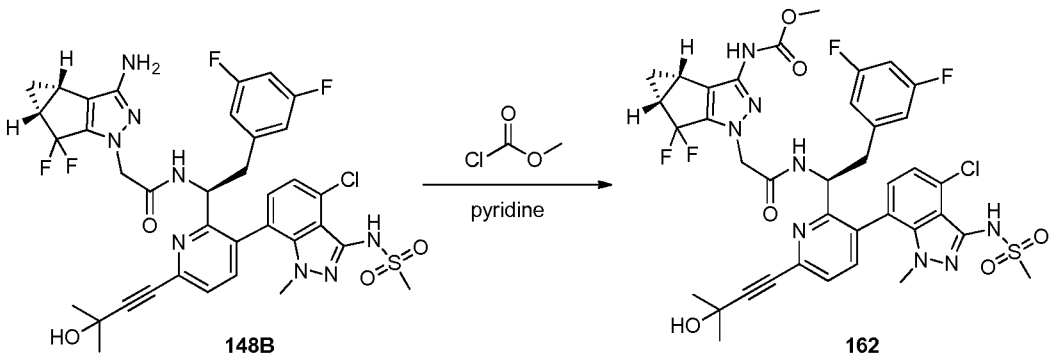
Example 161.



Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(dimethylamino)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**161**):

[0777] To a solution of **148B** (10 mg, 12.7 µmol) in acetic acid (0.1 ml) and formaldehyde (35% in water, 6.7 µl, 63.6 µmol) was added sodium cyanoborohydride (1.7 mg, 26.7 µmol) followed by stirring for 16 h at rt. The reaction mixture was diluted with ACN and purified by prep HPLC to provide the product **161** as a mixture of atropisomers. ^{1}H NMR (400 MHz, cd_3od) δ 7.74 – 7.64 (m), 7.58 – 7.48 (m), 7.16 (q), 7.07 (d), 6.82 – 6.72 (m), 6.68 – 6.56 (m), 6.45 – 6.30 (m), 5.28 (dd), 4.95 (t), 4.51 (d), 4.47 (d), 3.33 (s), 3.26 (s), 3.25 (s), 3.27 – 3.18 (m), 3.09 (dd), 2.98 (s), 2.92 (s), 2.92 (s), 2.49 – 2.40 (m), 2.40 – 2.28 (m), 1.65 (s), 1.41 – 1.29 (m), 1.09 – 0.98 (m). MS (*m/z*) 813.2 $[M+H]^+$.

Example 162.

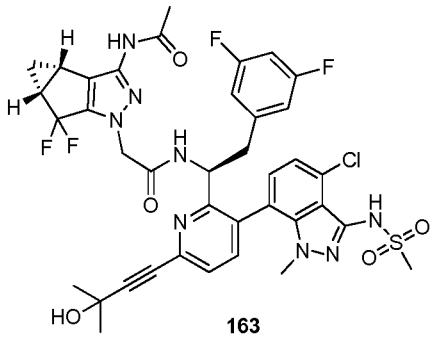


Synthesis of methyl ((3bS,4aR)-1-(2-(((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-

difluorophenyl)ethyl)amino)-2-oxoethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-3-yl)carbamate (**162**):

[0778] To a solution of **148B** (6 mg, 7.64 μmol) in DCM (0.1 ml) was added pyridine (3.08 μl, 38.21 μmol) followed by methylchloroformate (0.7 mg, 7.18 μmol) then stirred for 30 min at rt. The reaction was concentrated and the product was purified by prep HPLC to provide the product **162** as a mixture of atropisomers. ^{1}H NMR (400 MHz, cd_3od) δ 7.72 – 7.65 (m), 7.54 (d), 7.51 (d), 7.17 (s), 7.06 (d), 6.81 – 6.73 (m), 6.67 – 6.59 (m), 6.44 – 6.33 (m), 5.27 (dd), 4.96 (t), 4.59 (d), 4.54 (d), 3.76 (s), 3.75 (s), 3.34 (s), 3.26 (s), 3.23 (s), 3.15 – 3.07 (m), 3.04 – 2.91 (m), 2.61 (s), 2.37 – 2.22 (m), 1.64 (s), 1.37 – 1.25 (m), 1.06 – 0.99 (m), 0.99 – 0.93 (m). MS (*m/z*) 843.2 $[M+H]^+$.

Example 163.

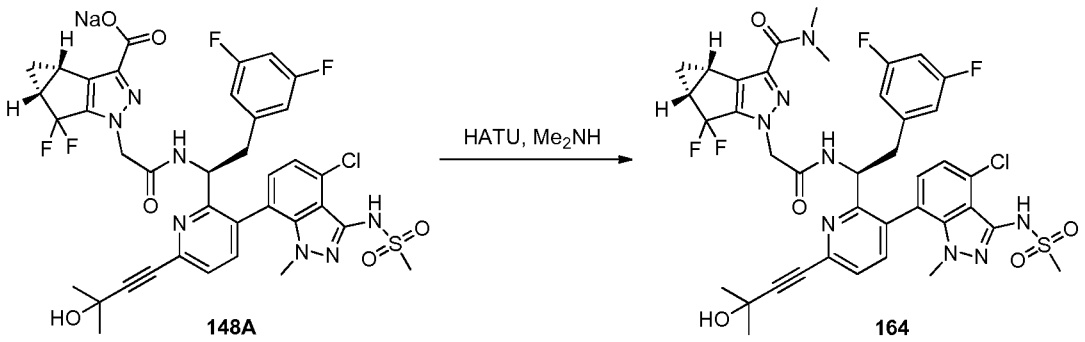


163

Synthesis of 2-((3bS,4aR)-3-acetamido-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)acetamide (**163**):

[0779] The title compound (**163**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **162** of Example 162 utilizing acetyl chloride. ^{1}H NMR (400 MHz, cd_3od) δ 7.69 (t), 7.54 (d), 7.51 (d), 6.80 – 6.74 (m), 6.67 – 6.60 (m), 6.44 – 6.33 (m), 5.27 (dd), 4.96 (t), 4.61 (s), 4.56 (d), 3.34 (s), 3.26 (s), 3.23 (s), 3.16 – 3.07 (m), 3.02 – 2.92 (m), 2.68 – 2.56 (m), 2.34 – 2.23 (m), 2.12 (s), 2.11 (s), 1.64 (s), 1.36 – 1.25 (m), 1.03 – 0.98 (m), 0.98 – 0.92 (m). MS (*m/z*) 827.1 $[M+H]^+$.

Example 164.

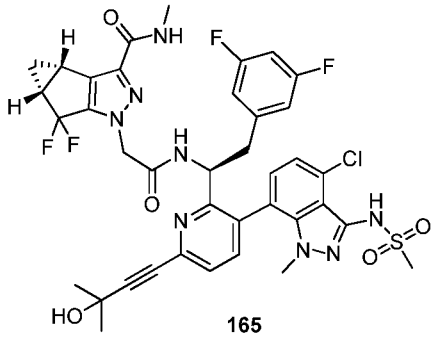


148A 164

Synthesis of (3bS,4aR)-1-(2-(((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)amino)-2-oxoethyl)-5,5-difluoro-N,N-dimethyl-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxamide (**164**):

[0780] To a solution of **148A** (6 mg, 7.18 µmol) in DMA (100 µl) was added a solution of HATU (2.73 mg, 7.18 µmol) in DMA (50 µl) followed by dimethylamine (2M in THF, 50 µl, 0.1 mmol), then stirred for 16 h at rt. The reaction mixture was concentrated, filtered, and purified by reverse phase HPLC to provide the product **164** as a mixture of atropisomers. ^{1}H NMR (400 MHz, cd_3od) δ 8.64 (d), 8.59 (d), 7.76 – 7.65 (m), 7.54 (d), 7.51 (d), 7.16 (s), 7.08 (d), 6.80 – 6.72 (m), 6.66 – 6.60 (m), 6.44 (d), 6.42 – 6.34 (m), 5.28 (dd), 4.98 (t), 4.78 (s), 4.73 (d), 3.34 (s), 3.33 (s), 3.28 (s), 3.25 (s), 3.23 (s), 3.15 – 3.07 (m), 3.09 (s), 3.07 (s), 3.03 – 2.92 (m), 2.57 – 2.38 (m), 1.66 – 1.61 (m), 1.43 – 1.26 (m), 1.13 – 1.07 (m), 1.03 (dt). MS (*m/z*) 841.1 $[M+H]^+$.

Example 165.

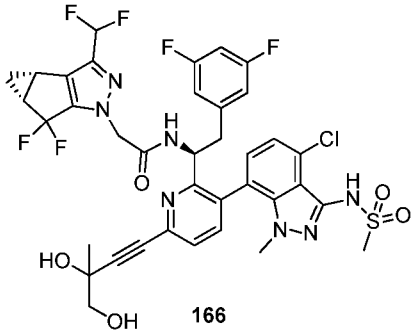


165

Synthesis of (3bS,4aR)-1-(2-(((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)amino)-2-oxoethyl)-5,5-difluoro-N-methyl-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxamide (**165**):

[0781] The title compound (**165**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **164** of Example 164 utilizing methylamine. ^{1}H NMR (400 MHz, cd$_3$o*d*) δ 8.65-8.60 (m), 7.18-7.07 (m), 6.79-6.61 (m), 7.73 – 7.65 (m), 7.54 (d), 7.51 (d), 7.17 (s), 7.08 (d), 6.81 – 6.71 (m), 6.65 – 6.57 (m), 6.45 (d), 6.42 – 6.34 (m), 5.29 (dd), 4.97 (t), 4.78 (s), 4.72 (d), 3.34 (s), 3.25 (s), 3.21 (s), 3.24 – 3.11 (m), 3.02 – 2.93 (m), 2.88 (s), 2.87 (s), 2.69 – 2.52 (m), 2.51 – 2.36 (m), 1.64 (s), 1.45 – 1.24 (m), 1.10 – 1.02 (m), 1.02 – 0.95 (m). MS (*m/z*) 827.2 [M+H]$^+$.

Example 166.

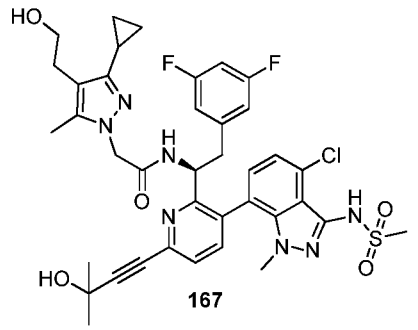


166

Synthesis of N-((1S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3,4-dihydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**166**):

[0782] The title compound (**166**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **142** of Example 142 utilizing 2-methylbut-3-yne-1,2-diol. ^{1}H NMR (400 MHz, cd$_3$od) 1H NMR (400 MHz, Methanol-d4) δ 8.68 (d), 7.70 (dd), 7.62 – 7.52 (m), 7.17 (s), 7.06 (d), 6.88 – 6.66 (m), 6.65 – 6.52 (m), 6.44 – 6.32 (m), 5.00 – 4.93 (m), 4.78 – 4.64 (m), 3.67 (s), 3.24 (d), 3.02 – 2.92 (m), 2.49 – 2.42 (m), 1.59 (s), 1.40 – 1.34 (m), 1.12-1.07 (m), 1.05-0.98 (s). MS (*m/z*) 837.9 [M+H]$^+$.

Example 167.

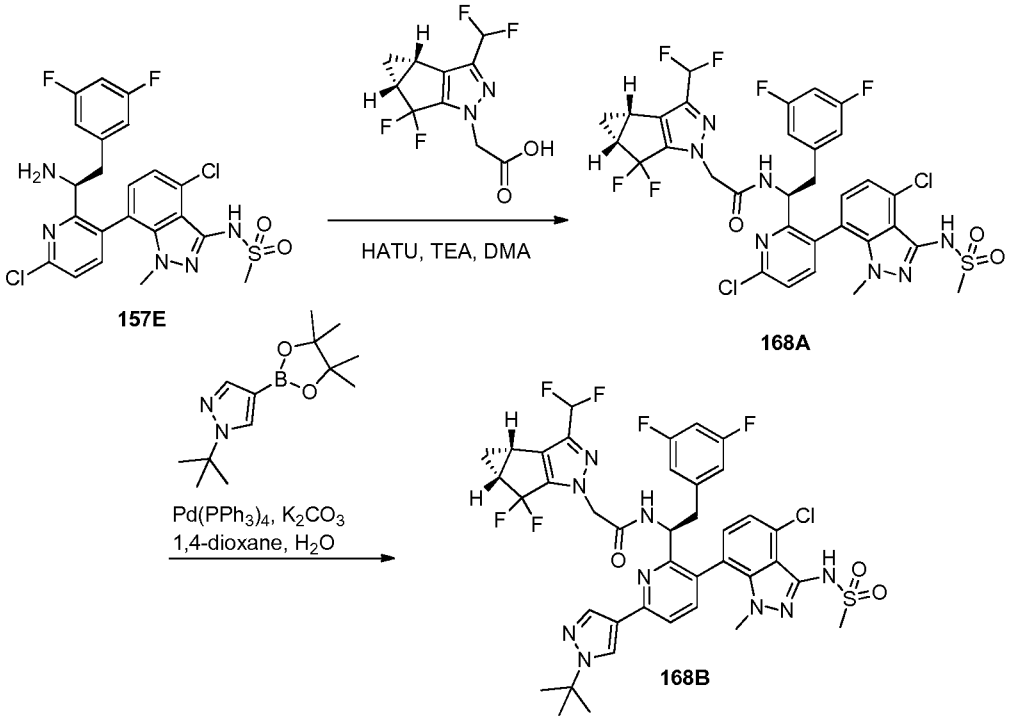


167

Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1H-pyrazol-1-yl)acetamide (**167**):

[0783] The title compound (**167**) was prepared as a mixture of atropisomers according to the method presented in the synthesis of **10A** in Example 10 utilizing **19F** and 2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1H-pyrazol-1-yl)acetic acid (prepared as described in US2012045761). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.71 (dd), 7.53 (dd), 7.27 – 7.15 (m), 7.12 (d), 6.80 – 6.70 (m), 6.69 – 6.58 (m), 6.55 (d), 6.44 – 6.29 (m), 5.33 – 5.22 (m), 5.03 – 4.93 (m), 4.73 – 4.52 (m), 3.69 – 3.53 (m), 3.32 (s), 3.27 – 3.21 (m), 3.17 – 3.08 (m), 3.05 (s), 2.99 – 2.85 (m), 2.76 – 2.60 (m), 2.11 (s), 2.01 (s), 1.88 – 1.78 (m), 1.64 (s), 0.93 – 0.86 (m), 0.79 – 0.70 (m). MS (*m/z*) 780.8 [M+H]$^+$.

Example 168.



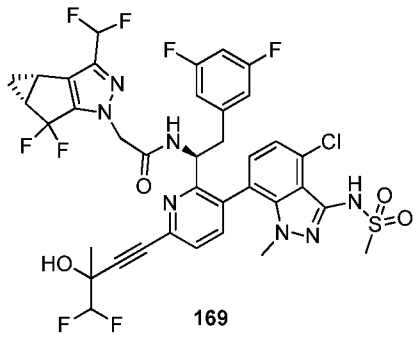
Synthesis of N-((S)-1-(6-chloro-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**168A**):

[0784] The title compound (**168A**) was prepared according to the method presented for the synthesis of compound **157F** of Example 157 utilizing 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. MS (*m/z*) 772.03 [M+H]$^+$.

Synthesis of N-((S)-1-(6-(1-(tert-butyl)-1H-pyrazol-4-yl)-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**168B**):

[0785] N-((S)-1-(6-chloro-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**168A**, 20 mg, 0.026 mmol), 1-*t*-Butylpyrazole-4-boronic acid, pinacol ester (7.77 mg, 0.031 mmol), $Pd(PPh_3)_4$ (1.50 mg, 0.001 mmol), and K_2CO_3 (10.7 mg, 0.078 mmol) were suspended in 1,4-dioxane (0.2 mL). To the suspension was added water (0.05 mL). The resulting reaction mixture was degassed by bubbling argon for 60 seconds then sealed and heated thermally at 110 °C for 3.5 hours. Upon completion, the reaction mixture was filtered, concentrated *in vacuo*, taken in DMF, and purified by reverse phase HPLC to give the title compound **168B** as a mixture of atropisomers. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.51 (s), 8.50 (s), 8.25 (s), 8.22 (d), 7.70 (t), 7.68 – 7.60 (m), 7.17 (s), 7.08 (s), 7.06 (s), 6.87 – 6.51 (m), 6.46 – 6.33 (m), 5.34 – 5.24 (m), 4.98 (dd), 4.81 (s), 4.79 (s), 4.77 (s), 3.38 (s), 3.26 (s), 3.24 (s), 3.22 – 3.17 (m), 3.04 (s), 2.98 (dd), 2.53 – 2.36 (m), 1.70 (s), 1.46 – 1.27 (m), 1.08 (m), 1.00 (m). MS (*m/z*) 860.21 $[M+H]^+$.

Example 169.



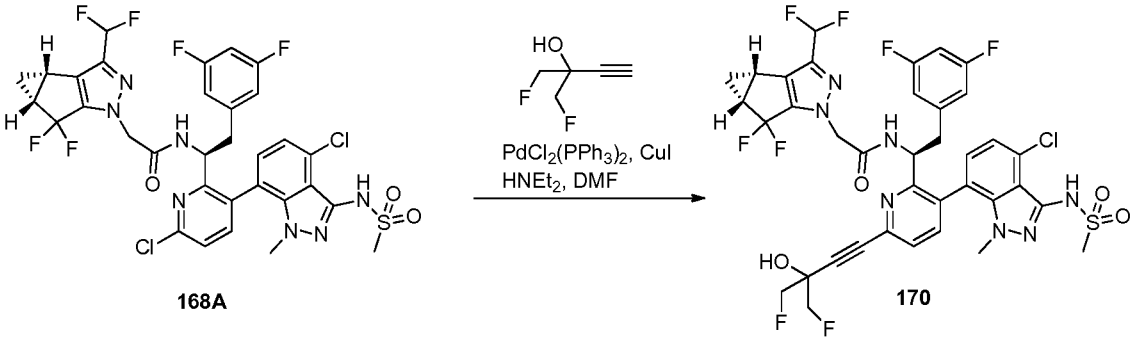
169

Synthesis of N-((1S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(4,4-difluoro-3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**169**):

[0786] The title compound (**169**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **142** of Example 142 utilizing 1,1-difluoro-2-methylbut-3-yn-2-ol. ^{1}H NMR (400 MHz, cd_3od) δ 8.73 (t), 7.77 – 7.68 (d), 7.64-7.59 (m), 7.22 – 7.13 (m), 7.07 (dd), 6.87 – 6.51 (m), 6.46 – 6.34 (m), 5.82 (t), 5.37-5.21 (m), 5.04 – 4.93 (m),

4.78 – 4.63 (m), 3.24 (d), 3.05 – 2.93 (m), 2.45 (m), 1.63 (s), 1.47 – 1.32 (m), 1.08 (s), 1.01 (s). MS (*m/z*) 857.1 $[M+H]^+$.

Example 170.

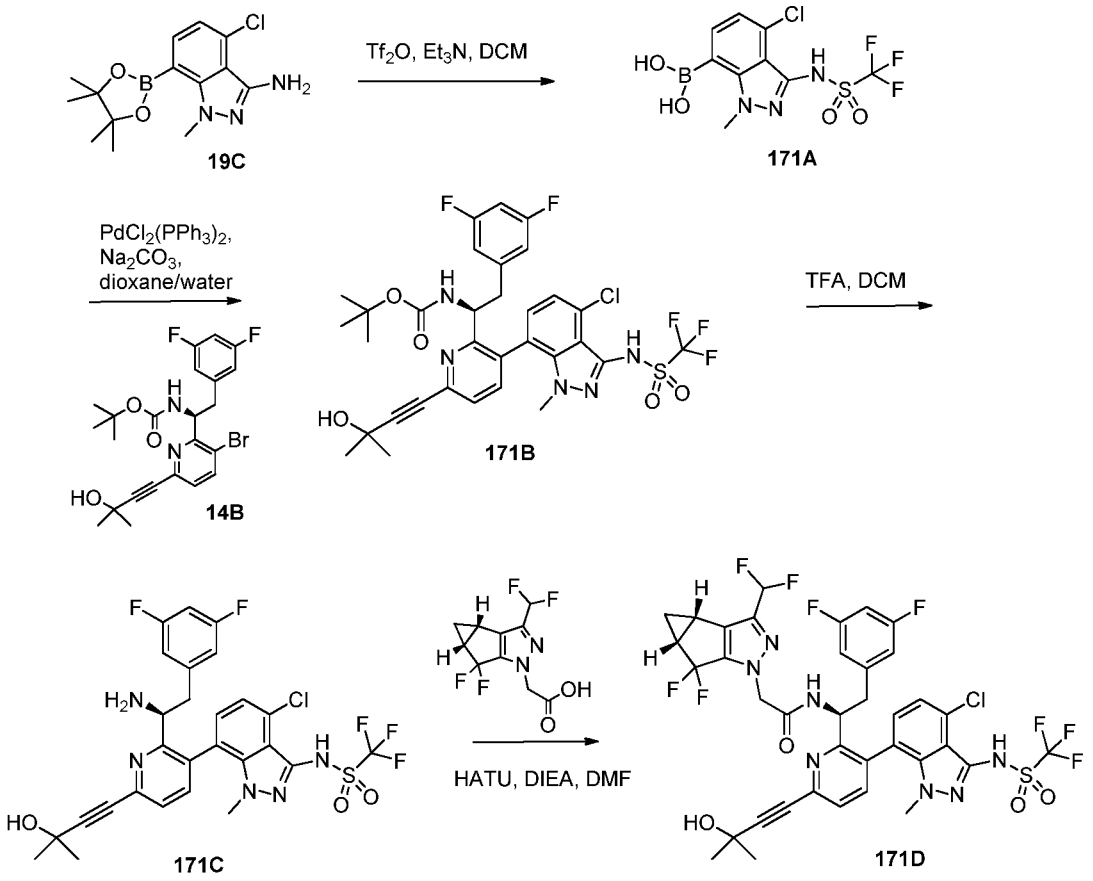


168A 170

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(4-fluoro-3-(fluoromethyl)-3-hydroxybut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**170**):

[0787] N-((S)-1-(6-chloro-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**168A**, 20 mg, 0.025 mmol), 1-fluoro-2-(fluoromethyl)but-3-yn-2-ol (15.5 mg, 0.129 mmol), $PdCl_2(PPh_3)_2$ (1.8 mg, 0.003 mmol), and CuI (0.5 mg, 0.003 mmol) were suspended in DMF (0.25 mL). To the reaction mixture was added diethylamine (27 µL, 0.259 mmol), and the reaction mixture was degassed by bubbling argon for 5 minutes then sealed and heated at 125 ºC for 30 minutes in a microwave reactor. Upon cooling, the reaction mixture was filtered and purified by reverse phase HPLC. Fractions containing the product were pooled and lyophilized to give the title compound **170** as a mixture of atropisomers. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.72 (t), 7.74 (dd), 7.61 (dd), 7.22 – 7.14 (m), 7.09 (s), 7.07 (s), 6.87 – 6.53 (m), 6.46 – 6.35 (m), 5.35 – 5.26 (m), 4.99 (q), 4.76 (s), 4.72 (s), 4.70 (s), 4.66 (d), 4.54 (d), 3.33 (s), 3.26 (s), 3.23 (s), 3.18 – 3.09 (m), 3.05 – 2.91 (m), 2.54 – 2.37 (m), 1.45 – 1.33 (m), 1.09 (s), 1.02 (s). MS (*m/z*) 856.09 $[M+H]^+$.

Example 171.



Synthesis of (4-chloro-1-methyl-3-(trifluoromethylsulfonamido)-1H-indazol-7-yl)boronic acid (**171A**):

[0788] 4-chloro-1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-amine (**19C**) (0.20 g, 0.65 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (0.36 mL, 2.6 mmol). The mixture was cooled to 0 ºC and triflic anhydride (0.55 g, 1.95 mmol) was added dropwise. After stirring for 30 minutes the reaction was quenched with water (10 mL) and extracted with dichloromethane (3 x 20 mL). The combined extracts were washed with brine and evaporated under vacuum. The residue was dissolved in ethanol (10 mL) and cooled to 0 ºC. 50% aqueous KOH solution (0.2 mL) was added dropwise and stirring was continued for 30 minutes. The mixture was acidified with 1N aqueous HCl. The formed precipitate was filtered and dried to give the title compound. MS (*m/z*) 358.0 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(3-(4-chloro-1-methyl-3-(trifluoromethylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**171B**):

[0789] (4-chloro-1-methyl-3-(trifluoromethylsulfonamido)-1H-indazol-7-yl)boronic acid (**171A**, 26 mg, 0.073 mmol), (S)-tert-butyl (1-(3-bromo-6-(3-hydroxy-3-methylbut-1-yn-1-

yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**14B**, 36 mg, 0.073 mmol), and $PdCl_2(PPh_3)_2$ (5.1 mg, 0.007 mmol) were suspended in 1,4-dioxane (1 mL) and 1.0 M aqueous $NaHCO_3$ (1 mL). The reaction mixture was heated at 150 °C for 15 minutes in a microwave reactor. After cooling, the reaction mixture was diluted with EtOAc (50 mL), washed with water and brine, concentrated *in vacuo*, and purified by silica gel column chromatography, eluting with 20-100% EtOAc in hexanes to give the title compound. MS (*m/z*) 728.3 $[M+H]^+$.

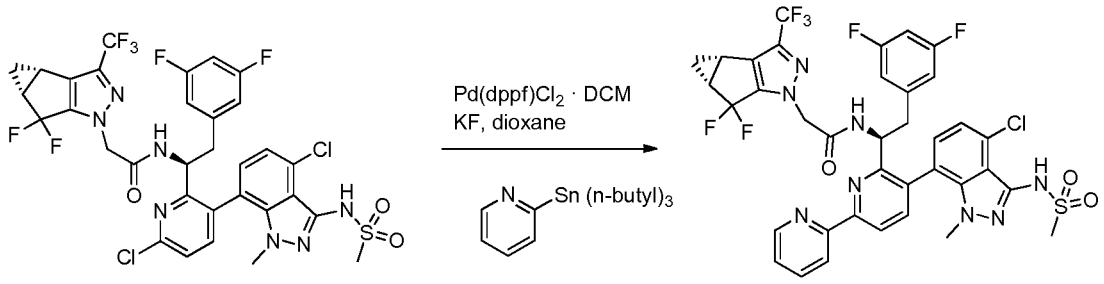
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)-1,1,1-trifluoromethanesulfonamide (**171C**):

[0790] To a solution of (S)-tert-butyl (1-(3-(4-chloro-1-methyl-3-(trifluoromethylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**171B**, 43 mg, 0.059 mmol) in DCM (1 mL) was added trifluoroacetic acid (1 mL). The reaction mixture was stirred at room temperature for 3 hours and then concentrated *in vacuo* and azeotroped once with toluene (20 mL) to give the title compound. MS (*m/z*) 628.2 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(trifluoromethylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**171D**):

[0791] To a solution of crude (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-((2-hydroxyethyl)(methyl)amino)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**171C**, 44 mg, 0.059 mmol) in DMF (1 mL) was added 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (15.6 mg, 0.059 mmol), and HATU (27 mg, 0.071 mmol) followed by diisopropylethylamine (31 µL, 0.177 mmol). After stirring for two hours at ambient temperature, the reaction mixture was filtered and purified by reverse phase HPLC to provide the title compound as a mixture of atropisomers. ^1H NMR (400 MHz, DMSO-d_6) δ 9.11 (d), 8.95 (d), 7.87 (d), 7.83 (d), 7.51 (d), 7.26 (d), 7.19 (s), 7.12 – 6.74 (m), 6.62 – 6.56 (m), 6.49 – 6.35 (m), 4.95 (q), 4.79 – 4.54 (m), 3.26 (s), 3.06 (s), 3.31 – 2.92 (m), 2.58 – 2.38 (m), 1.52 (s), 1.42 – 1.30 (m), 0.95 – 0.78 (m). MS (*m/z*) 874.2 $[M+H]^+$.

Example 172.

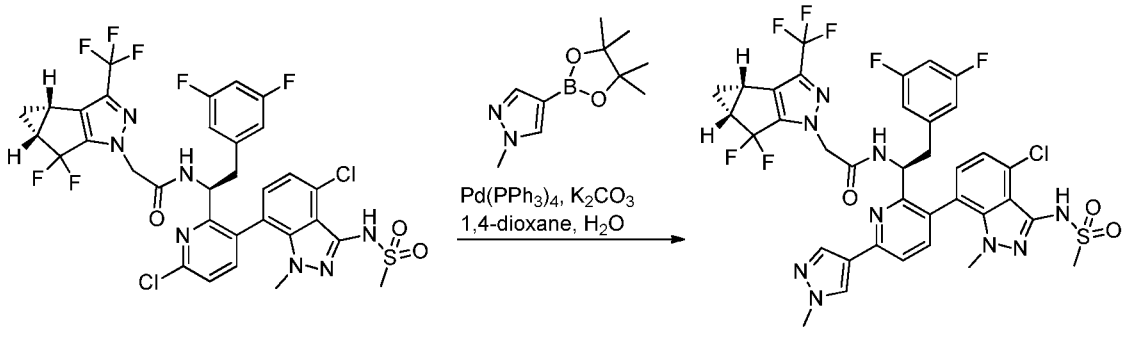


157F 172

Synthesis of N-((S)-1-(5-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-[2,2'-bipyridin]-6-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**172**):

[0792] To the reaction vial containing **157F** (20 mg, 0.025 mmol) in dioxane (0.25 mL) was added 2-(tributylstannyl)pyridine (0.01 mL, 0.027 mmol), Pd(dppf)Cl_2·DCM (1.2 mg, 0.001 mmol), and KF (4 mg, 0.75 mmol). The reaction mixture was flushed with argon gas for 5 min then sealed and heated in a microwave reactor to 135°C for 30 min. Upon cooling, the reaction mixture was filtered and purified by reverse phase HPLC to provide the title compound **172** as a mixture of atropisomers. ^{1}H NMR (400 MHz, cd_3od) δ 9.90-9.8 (m), 8.80-8.76 (m), 8.74 – 8.70 (m,), 8.52-8.45 (m), 7.98 – 7.88 (m, 1H), 7.30 – 7.04 (m,), 6.82 – 6.71 (m), 6.51 – 6.34 (m), 5.45-5.35 (m), 5.14 – 5.05 (m), 4.98 – 4.86 (m), 3.35 (s), 3.21 – 3.00 (m), 2.60 – 2.38 (m), 1.42 – 1.22 (m), 1.19 – 1.09 (m,), 1.06-1.00 (m). MS (*m/z*) 833.2 $[M+H]^+$.

Example 173.



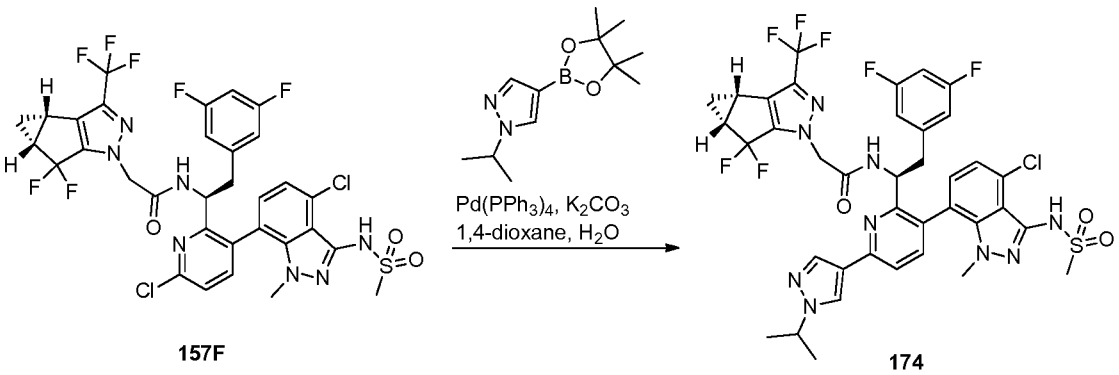
157F 173

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**173**):

[0793] N-((S)-1-(6-chloro-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-

3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**157F**, 20 mg, 0.025 mmol), 1-methylpyrazole-4-boronic acid (3.8 mg, 0.030 mmol), $Pd(PPh_3)_4$ (1.5 mg, 0.001 mmol), and K_2CO_3 (10.5 mg, 0.076 mmol) were suspended in 1,4-dioxane (0.2 mL). To the suspension was added water (0.05 mL). The resulting reaction mixture was degassed by bubbling argon for 60 seconds then sealed and heated thermally at 110 ºC for 2 hours. Upon completion, the reaction mixture was filtered, concentrated *in vacuo*, taken in DMF, and purified by reverse phase HPLC to give the title compound **173** as a mixture of atropisomers. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.39 (s), 8.35 (s), 8.23 (s), 8.20 (s), 7.71 – 7.60 (m), 7.15 (s), 7.06 (d), 6.76 (tt), 6.63 (tt), 6.49 – 6.41 (m), 6.41 – 6.34 (m), 5.24 (dd), 4.99 (dd), 4.03 (s), 4.02 (s), 3.46 – 3.41 (m), 3.39 (s), 3.26 (s), 3.24 (s), 3.23 – 3.17 (m), 3.07 – 2.95 (m), 2.59 – 2.38 (m), 1.49 – 1.34 (m), 1.17 – 1.11 (m), 1.09 – 1.03 (m). MS (*m/z*) 836.16 $[M+H]^+$.

Example 174.

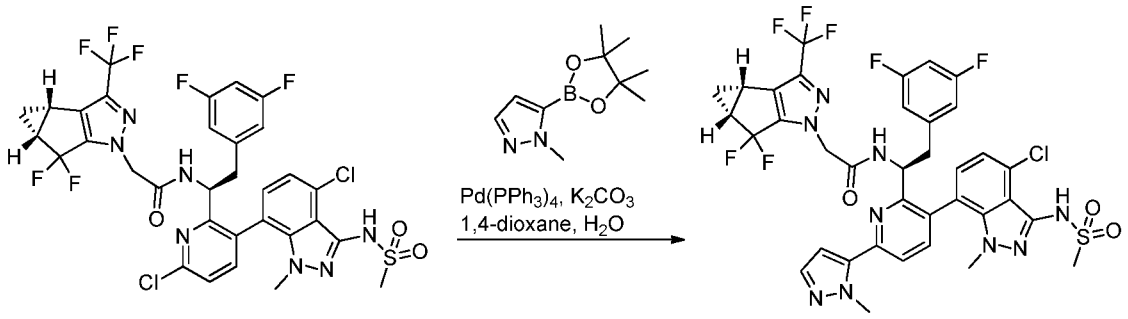


157F **174**

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(1-isopropyl-1H-pyrazol-4-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**174**):

[0794] The title compound (**174**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **173** of Example 173 utilizing 1-isopropylpyrazole-4-boronic acid, pinacol ester. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.46 (s), 8.44 (s), 8.24 (s), 8.22 (s), 7.72 – 7.60 (m), 7.16 (s), 7.06 (d), 6.76 (tt), 6.68 – 6.57 (m), 6.49 – 6.42 (m), 6.41 – 6.33 (m), 5.26 (dd), 4.99 (dd), 4.86 (s), 4.70 – 4.58 (m), 3.47 – 3.40 (m), 3.39 (s), 3.37 – 3.34 (m), 3.26 (s), 3.24 (s), 3.23 – 3.16 (m), 3.09 – 2.93 (m), 2.59 – 2.37 (m), 1.61 (d), 1.49 – 1.34 (m), 1.17 – 1.11 (m), 1.09 – 1.02 (m). MS (*m/z*) 864.20 $[M+H]^+$.

Example 175.

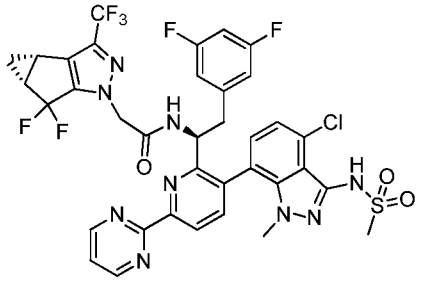


157F 175

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(1-methyl-1H-pyrazol-5-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**175**):

[0795] The title compound (**175**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **173** of Example 173 utilizing 1-methyl-1*H*-pyrazole-5-boronic acid pinacol ester. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.87 – 7.78 (m), 7.59 (d), 7.31 (d), 7.20 (d), 7.11 (d), 6.90 (d), 6.88 (d), 6.79 (tt), 6.63 (tt), 6.55 – 6.51 (m), 6.47 – 6.37 (m), 5.40 (dd), 5.07 (dd), 4.78 (s), 4.77 (s), 4.43 (s), 4.34 (s), 3.39 (s), 3.25 (s), 3.24 – 3.21 (m), 3.15 – 3.12 (m), 3.11 – 3.02 (m), 2.59 – 2.35 (m), 1.47 – 1.33 (m), 1.15 – 1.08 (m), 1.06 – 0.98 (m). MS (*m/z*) 836.15 $[M+H]^+$.

Example 176.



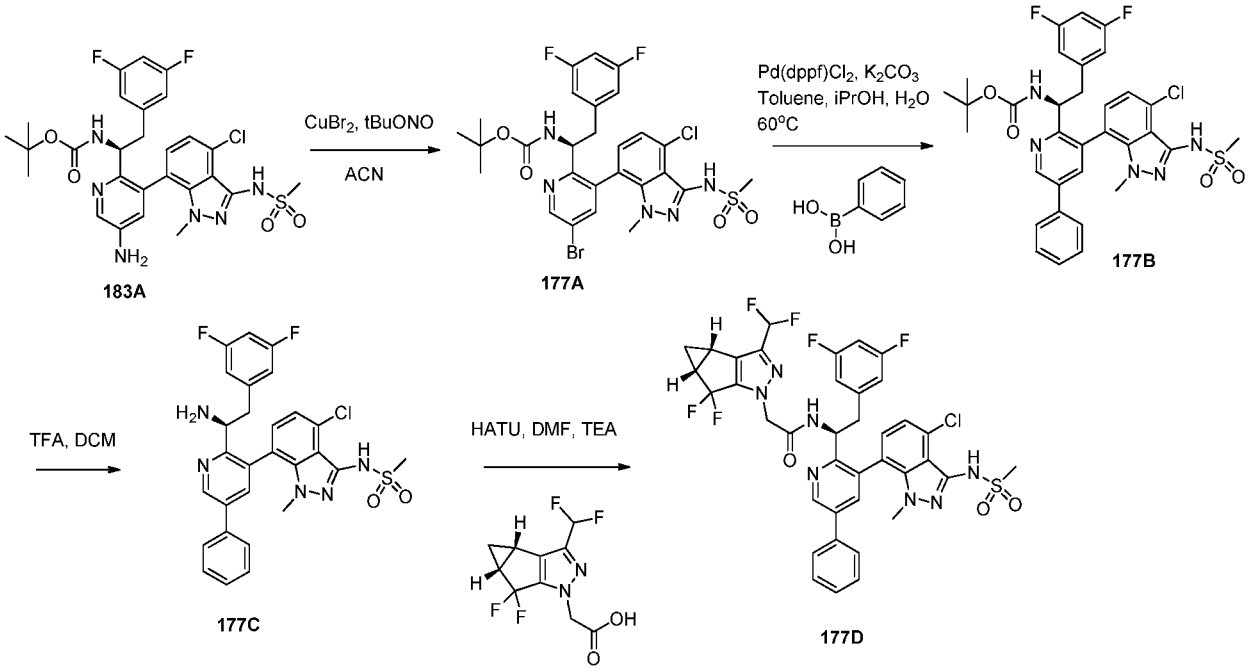
176

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(pyrimidin-2-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**176**):

[0796] The title compound (**176**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **172** of Example 172 utilizing 2-(tributylstannyl)pyrimidine. ^{1}H NMR (400 MHz, cd_3od) δ 9.90 – 9.86 (m), 9.84-9.80 (m), 8.80-

8.75 (m, 1H), 8.74 (d), 8.47 (d),7.92 (t), 7.25 – 7.12 (m), 6.80 – 6.50 (m), 6.45-6.40 (m), 5.45-5.38 (m), 5.15-5.05 (m), 4.90 – 4.81 (m), 3.37 (s), 3.18-3.04 (m), 2.50-2.39 (m), 1.44 – 1.25 (m), 1.15-1.09 (m), 1.08 – 0.97 (m). MS (*m/z*) 835.1 $[M+H]^+$.

Example 177.



Synthesis of (S)-tert-butyl (1-(5-bromo-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**177A**):

[0797] Compound **183A** (0.500g, 0.82mmol) was added to a stirred suspension of t-BuONO (0.15mL, 1.24mmol) and $CuBr_2$ (0.276g, 1.24mmol) in acetonitrile with ice bath, the suspension was allowed to warm up to room temperature and stirred overnight. Aqueous ammonium chloride was added. The mixture was extracted with EtOAc. The organic layer was dried with $MgSO_4$, concentrated and purified by silica gel column to afford the title compound as mixture of atropisomers (**177A**). MS (m/z) 670 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-5-phenylpyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**177B**):

[0798] Compound **177A** (31.3mg, 0.047mmol), phenylbronic acid (6.3mg, 0.051mmol), K_2CO_3 (39mg, 0.28mmol) and $Pd(dppf)Cl_2$ (14mg, 0.019mmol) were mixed together. Toluene (1mL), iPrOH (0.5mL) and water (1mL) were added. The vial was capped tight, stirred at 60 °C for 30 minutes. The reaction mixture was diluted with EtOAc, washed with brine, dried with

$MgSO_4$ and concentrated. The crude was purified by silica gel column to afford the title compound as mixture of atropisomers (**177B**). MS (m/z) 668 $[M+H]^+$.

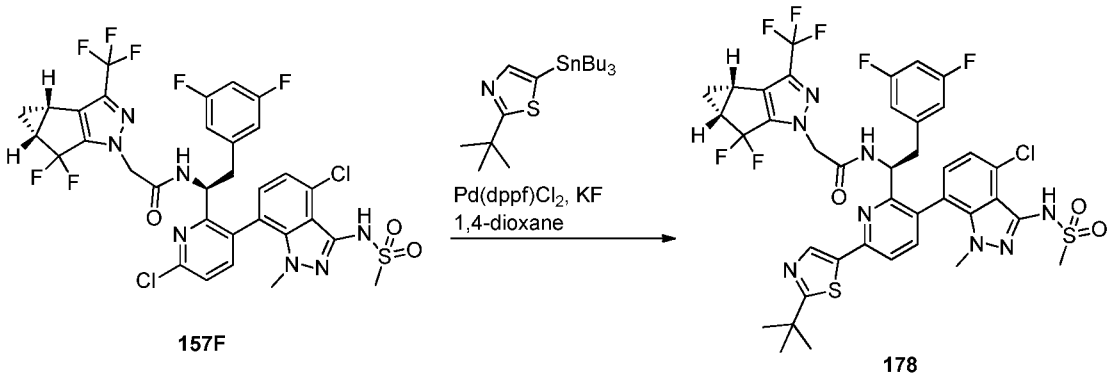
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-phenylpyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**177C**):

[0799] Compound **177B** (21.7mg, 0.032mmol) was dissolved in DCM (1mL). TFA (0.5mL) was added. The resultant solution was stirred at ambient temperature for 2 hours. The reaction was concentrated to afford title compound as mixture of atropisomers (**177C**). MS (m/z) 568 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-5-phenylpyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**177D**):

[0800] Compound **177C** (18.4mg, 0.032mmol) and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (8.6mg, 0.032mmol) were dissolved in DMF (1mL). TEA (23uL, 0.162mmol) and HATU (18.5mg, 0.049mmol) were added. Upon completion, a few drops of 1M HCl were added. The reaction was purified by HPLC to afford the title compound as mixture of atropisomers (**177D**). ^1H NMR (400 MHz, Acetonitrile-d3) δ 9.04 (dd), 7.99 (dd), 7.82 – 7.73 (m), 7.69 (d), 7.59 – 7.43 (m), 7.34 (d), 7.29 – 7.18 (m), 7.15 (d), 6.90 (d), 6.85 – 6.73 (m), 6.69 – 6.58 (m), 6.49 – 6.36 (m), 5.30 (q), 4.96 (q), 4.69 (d), 3.33 (s), 3.28 (s), 3.27 (s), 3.20 – 2.91 (m), 2.58 – 2.40 (m), 1.40 (q), 1.09 – 0.97 (m). MS (m/z) 814 $[M+H]^+$.

Example 178.

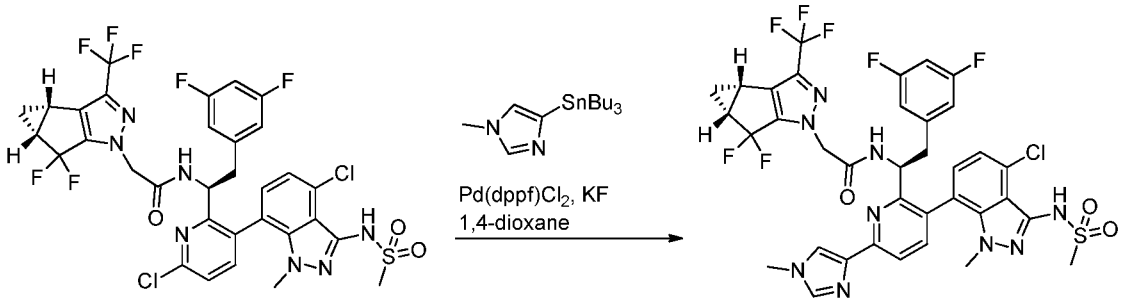


157F **178**

Synthesis of N-((S)-1-(6-(2-(tert-butyl)thiazol-5-yl)-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**178**):

[0801] N-((S)-1-(6-chloro-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**157F**, 20 mg, 0.025 mmol), 2-(tert-butyl)-5-(tributylstannyl)thiazole (12.03 mg, 0.028 mmol), $Pd(dppf)Cl_2$ (1.1 mg, 0.001 mmol), and KF (4.4 mg, 0.076 mmol) were suspended in 1,4-dioxane (0.25 mL). The resulting reaction mixture was degassed by bubbling argon for 60 seconds then sealed and heated at 130 °C for 30 minutes in a microwave reactor. Upon cooling, the reaction mixture was filtered, concentrated *in vacuo*, taken in DMF, and purified by reverse phase HPLC to give the title compound **178** as a mixture of atropisomers. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.40 (s), 7.91 (dd), 7.76 (d), 7.74 (d), 7.20 – 7.13 (m), 7.08 (d), 6.77 (tt), 6.65 (tt), 6.55 – 6.47 (m), 6.45 – 6.38 (m), 5.20 (dd), 5.02 (dd), 4.80 (s), 3.41 (s), 3.26 (s), 3.25 (s), 3.09 – 2.98 (m), 2.95 (s), 2.60 – 2.39 (m), 1.71 (s), 1.70 (s), 1.69 (s), 1.48 – 1.34 (m), 1.17 – 1.11 (m), 1.09 – 1.03 (m). MS (*m/z*) 897.04 $[M+H]^+$.

Example 179.

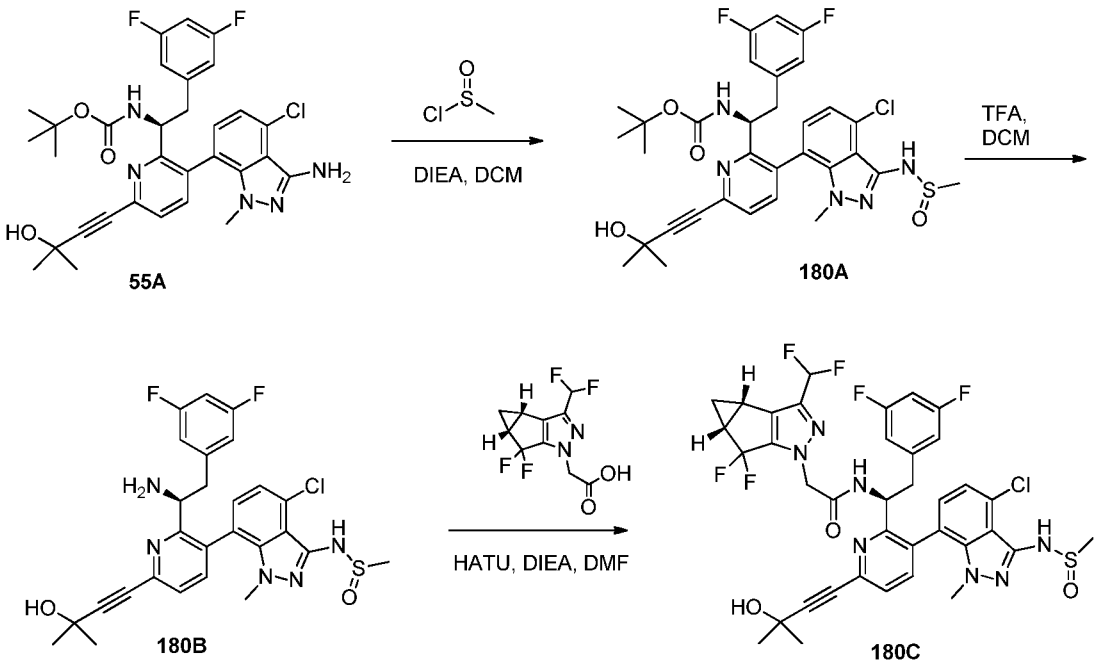


157F **179**

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(1-methyl-1H-imidazol-4-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**179**):

[0802] The title compound (**179**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **178** of Example 178 utilizing 1-methyl-4-(tributylstannyl)-1*H*-imidazole. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.89 (s), 8.84 (s), 8.29 (s), 8.25 (s), 7.94 – 7.82 (m), 7.19 (s), 7.07 (d), 6.78 (tt), 6.64 (tt), 6.48 – 6.41 (m), 6.37 (dd), 5.35 (dd), 5.05 (dd), 4.81 (s), 4.77 (s), 4.05 (s), 4.04 (s), 3.36 (s), 3.27 (s), 3.25 (s), 3.23 – 3.18 (m), 3.12 – 2.98 (m), 2.59 – 2.41 (m), 1.48 – 1.37 (m), 1.33 – 1.26 (m), 1.16 – 1.10 (m), 1.09 – 1.03 (m). MS (*m/z*) 836.15 $[M+H]^+$.

Example 180.



Synthesis of tert-butyl ((1S)-1-(3-(4-chloro-1-methyl-3-(methylsulfinamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**180A**):

[0803] (S)-tert-butyl (1-(3-(3-amino-4-chloro-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**55A**, 61 mg, 0.102 mmol) was dissolved in dichloromethane (2 mL) and diisopropylethylamine (0.071 mL, 0.409 mmol). The mixture was cooled to 0 ºC and methanesulfinyl chloride (30.3 mg, 0.307 mmol) was added dropwise. After stirring at ambient temperature overnight the reaction mixture was diluted with ethyl acetate (50 mL), washed with water and brine and evaporated under vacuum. Purification on silica gel gave the title compound. MS (*m/z*) 658.3 $[M+H]^+$.

Synthesis of N-(7-(2-((S)-1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfinamide (**180B**):

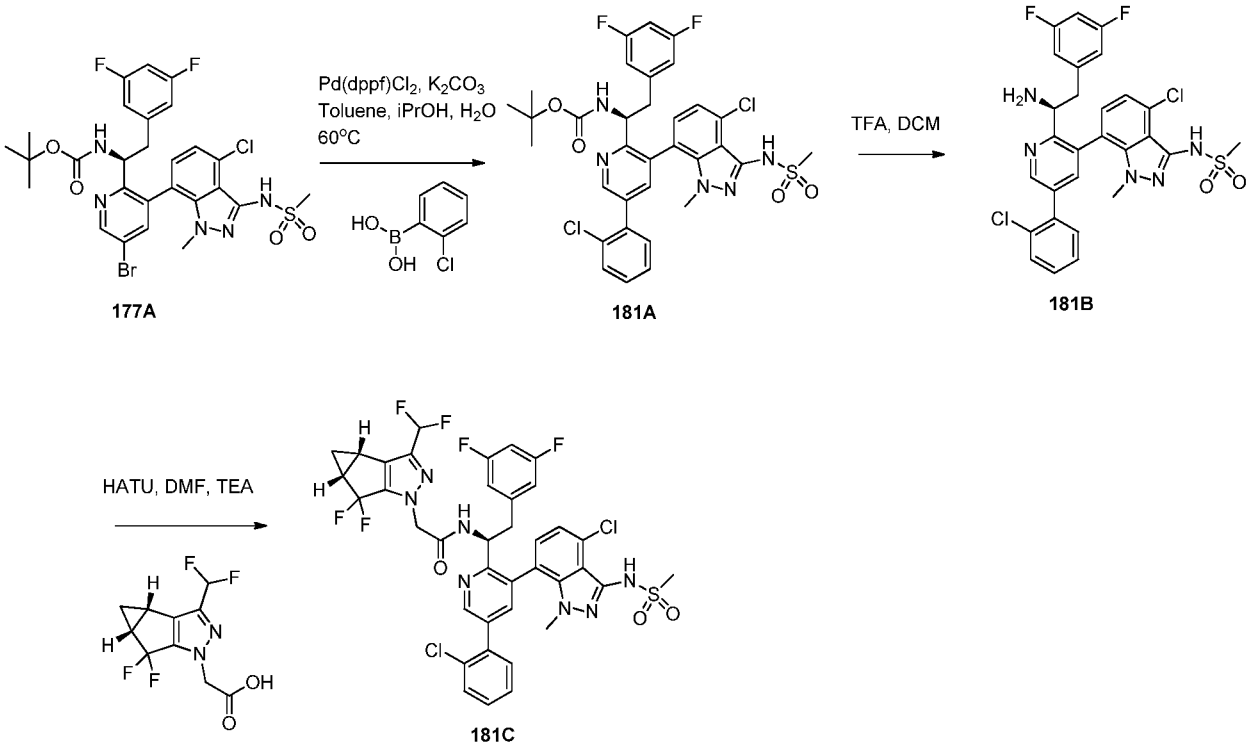
[0804] To a solution of tert-butyl ((1S)-1-(3-(4-chloro-1-methyl-3-(methylsulfinamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**180A**, 50 mg, 0.076 mmol) in DCM (1 mL) was added trifluoroacetic acid (1 mL). The reaction mixture was stirred at room temperature for 3 hours and then concentrated *in vacuo* and azeotroped once with toluene (20 mL) to give the title compound. MS (*m/z*) 558.2 $[M+H]^+$.

Synthesis of N-((1S)-1-(3-(4-chloro-1-methyl-3-(methylsulfinamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-

(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**180C**):

[0805] To a solution of crude N-(7-(2-((S)-1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfinamide (**180B**, 52 mg, 0.076 mmol) in DMF (1 mL) was added 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (20 mg, 0.076 mmol), and HATU (34.7 mg, 0.091 mmol) followed by diisopropylethylamine (66 µL, 0.38 mmol). After stirring for two hours at ambient temperature, the reaction mixture was filtered and purified by reverse phase HPLC to provide the title compound as a mixture of diastereomers and atropisomers. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 – 8.60 (m), 7.85 – 7.70 (m), 7.55 (d), 7.05 – 6.70 (m), 6.56 – 6.28 (m), 4.93 – 4.49 (m), 3.30 – 2.59 (m), 2.96 (s), 2.65 (s), 2.48 – 2.30 (m), 1.72 – 1.66 (m), 1.42 – 1.30 (m), 0.95 – 0.78 (m). MS (*m/z*) 804.2 $[M+H]^+$.

Example 181.



Synthesis of (S)-tert-butyl (1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-5-(2-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**181A**):

[0806] The title compound as mixture of atropisomers (**181A**) was prepared according to the method presented for the synthesis of compound **177B** of Example 177 utilizing compound **177A** and 2-chlorophenylbronic acid. MS (m/z) 702 $[M+H]^+$.

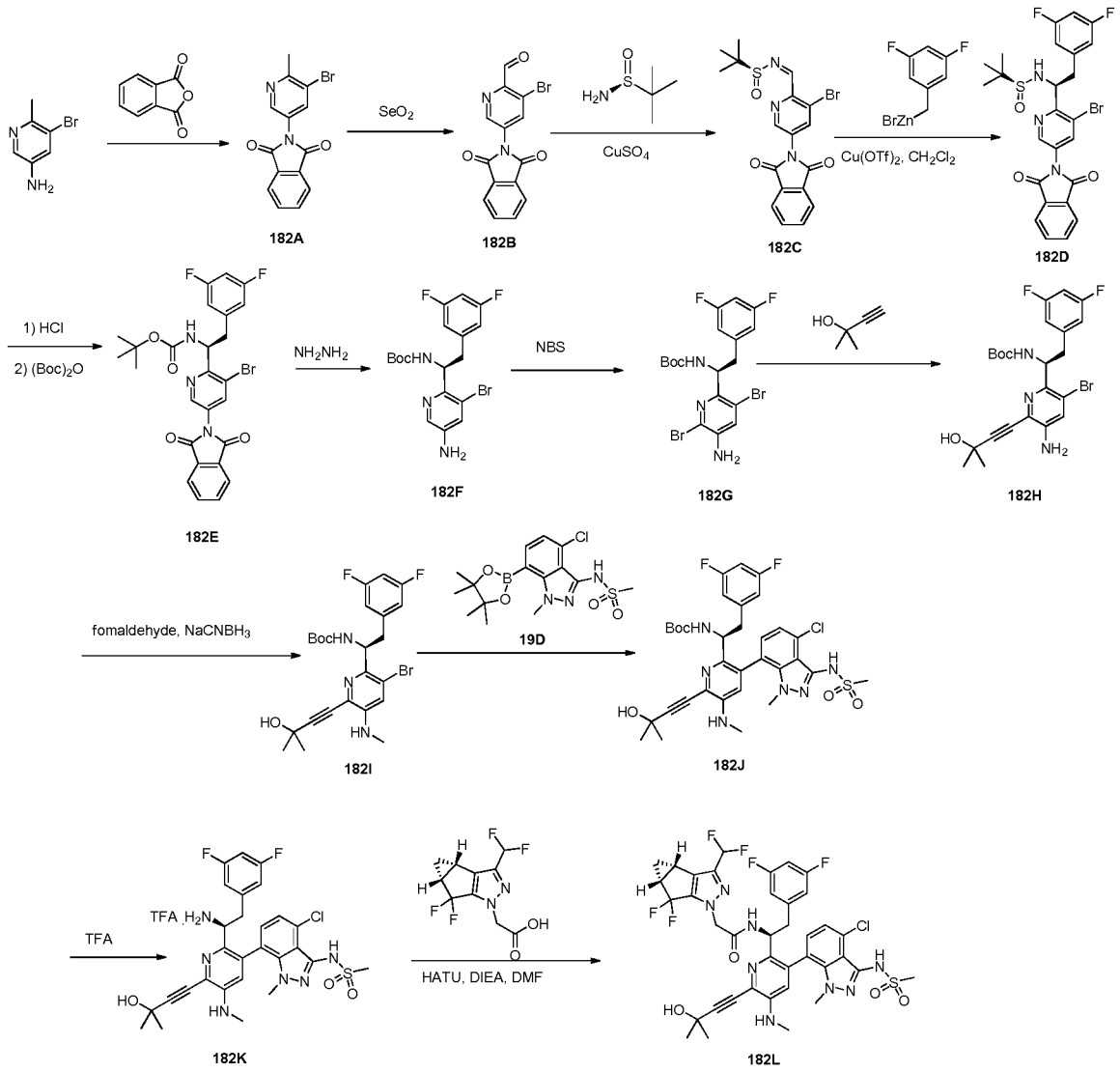
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(2-chlorophenyl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**181A**):

[0807] The title compound as mixture of atropisomers (**181B**) was prepared according to the method presented for the synthesis of compound **177C** of Example 177 utilizing compound **181A**. MS (m/z) 602 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-5-(2-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**181C**):

[0808] The title compound as mixture of atropisomers (**181C**) was prepared according to the method presented for the synthesis of compound **177D** of Example 177 utilizing compound **181B** and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.82 (s), 9.75 (s), 9.07 (d), 8.94 (d), 8.87 (dd), 7.97(d), 7.90 (d), 7.69 – 7.39 (m), 7.23 – 6.74 (m), 6.54 (d), 6.44 (d), 5.03 (q), 4.90 – 4.53 (m), 3.32 (s), 3.23 – 2.89 (m), 2.60 – 2.37 (m), 1.47 – 1.30 (m), 0.83 (s). MS (m/z) 848 $[M+H]^+$.

Example 182.



Synthesis of 2-(5-bromo-6-methylpyridin-3-yl)isoindoline-1,3-dione (**182A**):

[0809] A mixture of phthalic anhydride (3.7 g, 25 mmol), 5-bromo-6-methylpyridin-3-amine (3.9 g, 20.85 mmol) and sodium acetate (1.5 g, 25 mmol) in glacial acetic acid (44 ml) was refluxed for overnight. After cooling down to room temperature, the precipitate was collected by vacuum filtration and washed with water. Then it was dried under high vacuum to afford the title compound **182A**. MS (*m/z*) 318.91 $[M+H]^+$.

Synthesis of 3-bromo-5-(1,3-dioxoisoindolin-2-yl)picolinaldehyde (**182B**):

[0810] To a microwave tube was charged with compound **182A** (1.5 g, 4.73 mmol) and selenium dioxide (682 mg, 6.15 mmol). To it was added 14 mL of 1,2-dimethoxyethane and the microwave tube was sealed. The reaction mixture was heated in a 130 °C heating bath for 20 hours. The reaction mixture was cooled down and the solids filtered off. The filtrate was

concentrated to afford the title compound **182B**. ^{1}H NMR (400 MHz, DMSO) δ 10.04 (s, 1H), 8.95 (d, J = 1.9 Hz, 1H), 8.41 (d, J = 1.7 Hz, 1H), 8.07 – 7.84 (m, 4H).

Synthesis of (S,Z)-N-((3-bromo-5-(1,3-dioxoisoindolin-2-yl)pyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (**182C**):

[0811] Copper(II) sulfate (anhydrous, 5.8 g, 36.2 mmol) was added to a solution of 3-bromo-5-(1,3-dioxoisoindolin-2-yl)picolinaldehyde (**182B**, 6 g, 18 mmol) and (S)-2-methylpropane-2-sulfinamide (2.2 g, 18 mmol) in CH_2Cl_2 (60 mL). The reaction mixture was stirred at ambient temperature for 2 hours and then filtered and washed with CH_2Cl_2. The filtrate was concentrated and the residue was purified by silica gel chromatography eluting with EtOAc and methylene chloride to yield the title compound **182C**. MS (*m/z*) 433.87 $[M+H]^+$.

Synthesis of (S)-N-((S)-1-(3-bromo-5-(1,3-dioxoisoindolin-2-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (**182D**):

[0812] To a solution of compound (**182C**, 3.7 g, 8.5 mmol) and $Cu(OTf)_2$ (154 mg, 0.4 mmol) in methylene chloride (30 ml) at 0 °C was added (3,5-difluorobenzyl)zinc bromide (0.5 M in THF, 25.5 ml, 12.8 mmol) dropwise. The reaction stirred at room temperature for one hour. Ammonium chloride (aq, 100 ml) was added to the reaction and the mixture was extracted with methylene chloride (2x100ml). The organic layer was dried over Na_2SO_4, filtered and concentrated. The reaction mixture was purified by silica gel chromatography then by reverse phase HPLC to afford the title compound **182D**. MS (m/z) 563.83 $[M+H]^+$.

Synthesis of (S)-tert-butyl 1-(3-bromo-5-(1,3-dioxoisoindolin-2-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (**182E**):

[0813] Compound **182D** (2.6 g, 4.6 mmol) was dissolved in 40 mL of methanol and cooled to 0 °C. To it was added 4N HCl/1,4-dioxane (4.6 ml). The reaction mixture was allowed to stir at room temperature for 10 minutes and concentrated to afford product (S)-2-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-bromopyridin-3-yl)isoindoline-1,3-dione hydrochloride. To the mixture of the above HCl salt (~4.6 mmol) and Di-tert-Butyl dicarbonate (1 g, 4.6 mmol) in 50 mL of CH_2Cl_2 was added triethylamine (1.28 mL, 9.2 mmol) at 0 °C. The reaction mixture was stirred for overnight and concentrated in vacuo. The residue was partitioned between EtOAc and water. The organic layer was washed with brine, dried over MgSO4, filtered and concentrated. Then it was purified on silica gel chromatography to yield the title compound **182E**. MS (m/z) 559.71 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(5-amino-3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**182F**):

[0814] To a mixture of compound **182E** (1.5 g, 2.7 mmol) in 27 ml of ethanol, 0.9 ml of hydrazine monohydrate was added and stirred at room temperature for 2 hours. More ethanol was added to the reaction mixture. The precipitate was filtered off and the filtrate was concentrated. The residue was diluted with ethyl acetate, and washed with water and then with a saturated sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give the title compound **182F**. MS (m/z) 427.83 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(5-amino-3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**182G**):

[0815] A solution of compound **182F** (960 mg, 2.24 mmol) in 20 mL of acetonitrile was cooled to 0° C and treated with *N*-Bromosuccinimide (399 mg, 2.24 mmol) as a solution in 20 mL of acetonitrile. The reaction mixture was partitioned with EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated and washed with brine, then dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography to afford the title compound **182G**. MS (m/z): 507.52 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(5-amino-3-bromo-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**182H**):

[0816] The title compound (**182H**) was prepared according to the method presented for the synthesis of compound **4F** of Example 4 utilizing compound **182G**. MS (*m/z*) 511.87 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(3-bromo-6-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-(methylamino)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**182I**):

[0817] Compound **182H** (200 mg, 0.39 mmol) was dissolved in 2 mL of acetonitrile, to it was added formaldehyde (0.1 mL, 37 % in H_2O) and acetic acid (0.2 mL, 4 mmol) followed by slow addition of sodium cyanoborohydride solution (1.2 mL, 1M in THF). The reaction mixture was allowed to stir at room temperature for 3 hours and quenched by adding aqueous sodium bicarbonate. It was extracted with ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by RP-HPLC to afford the title compound **182I**. MS (*m/z*): 525.99 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-(methylamino)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**182J**):

[0818] The title compound (**182J**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19E** of Example 19 utilizing compound **182I** and compound **19D**. MS (*m/z*) 703.35 $[M+H]^+$.

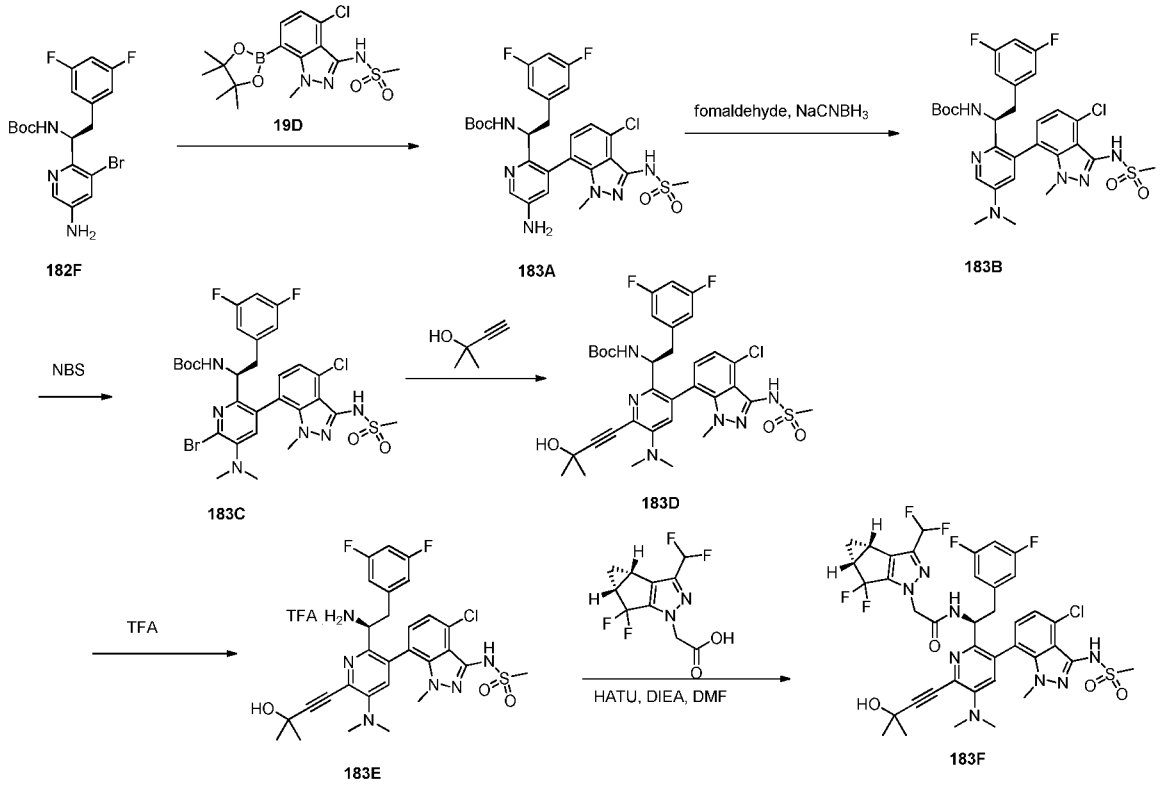
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-(methylamino)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**182K**):

[0819] The title compound (**182K**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **105C** of Example 105 utilizing compound **182J**. MS (*m/z*) 603.17 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-(methylamino)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**182L**):

[0820] The title compound (**182L**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **37E** of Example 37 utilizing 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid and compound **182K**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.00 (d), 6.82 (d), 6.76 (tt), 6.70 (t), 6.43 – 6.30 (m), 6.24 (d), 4.78 – 4.56 (m), 3.39 (s), 3.22 (s), 3.16-2.99 (m), 2.98 – 2.88 (m), 2.84 (s), 2.52-2.31 (m), 1.66 (d), 1.49 – 1.21 (m), 1.12 – 0.86 (m). MS (*m/z*) 849.90 $[M+H]^+$.

Example 183.



Synthesis of (S)-tert-butyl (1-(5-amino-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**183A**):

[0821] The title compound (**183A**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19E** of Example 19 utilizing compound **182F** and compound **19D**. MS (*m/z*) 606.88 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-5-(dimethylamino)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**183B**):

[0822] The title compound (**183B**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **182I** of Example 182 utilizing compound **183A.** MS (*m/z*) 635.48 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(6-bromo-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-5-(dimethylamino)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**183C**):

[0823] The title compound (**183C**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **182G** of Example 182 utilizing compound **183B.** MS (*m/z*) 714.81 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-5-(dimethylamino)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**183D**):

[0824] The title compound (**183D**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **4F** of Example 4 utilizing compound **183C**. MS (*m/z*) 717.62 $[M+H]^+$.

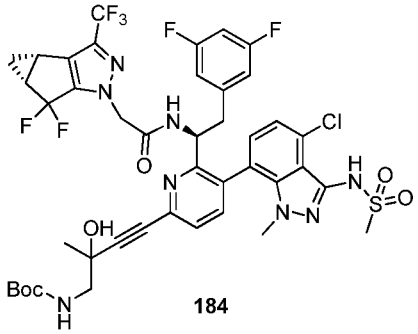
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(dimethylamino)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**183E**):

[0825] The title compound (**183E**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **105C** of Example 105 utilizing compound **183D**. MS (*m/z*) 617.09 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-5-(dimethylamino)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**183F**):

[0826] The title compound (**183F**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **37E** of Example 37 utilizing 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid and compound **183E** . ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.26 – 7.10 (m), 7.03 (d), 6.76 (t), 6.69 (t), 6.60 (t), 6.52 – 6.33 (m), 6.32 (d), 4.85 – 4.78 (m), 4.78 – 4.60 (m), 3.37 (s), 3.23 (d), 3.10 (dd), 2.99 (d), 2.98 – 2.74 (m), 2.45 (ddd), 1.66 (s), 1.48 – 1.30 (m), 1.17 – 0.92 (m).). MS(*m/z*): 863.19 $[M+H]^+$.

Example 184.



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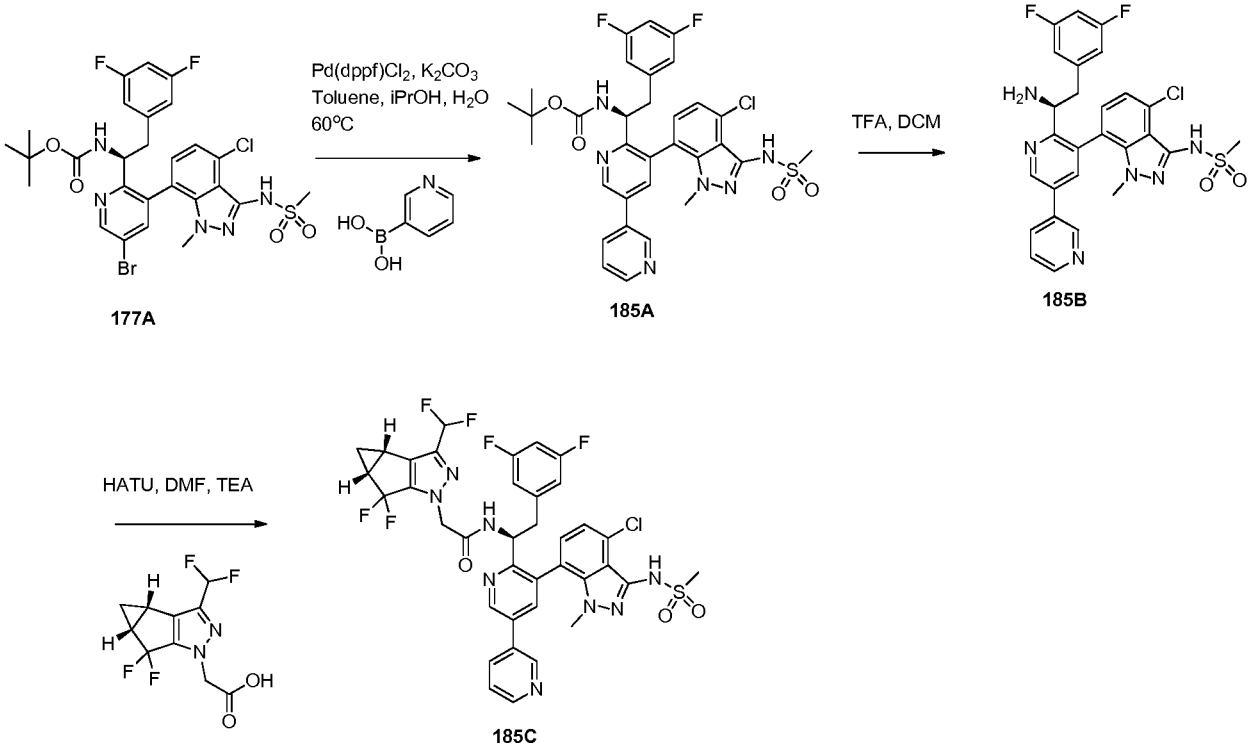
Synthesis of tert-butyl (4-(5-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-2-yl)-2-hydroxy-2-methylbut-3-yn-1-yl)carbamate (**184**):

[0827] The title compound (**184**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **145** of Example 145 utilizing tert-butyl (2-hydroxy-2-methylbut-3-yn-1-yl)carbamate. MS (*m/z*) 953.9 $[M+H]^+$. HPLC retention time 7.54 min and 7.69 min (2-98% acetonitrile: water with 0.1% trifluoroacetic acid, 8.5 min gradient on a Phenomonex Kinetex C18 column).

Example 185.



Synthesis of (S)-tert-butyl (1-(5-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-[3,3'-bipyridin]-6-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**185A**):

[0828] The title compound as mixture of atropisomers (**185A**) was prepared according to the method presented for the synthesis of compound **177B** of Example 177 utilizing compound **177A** and 3-pyridinebronic acid. MS (m/z) 669 $[M+H]^+$.

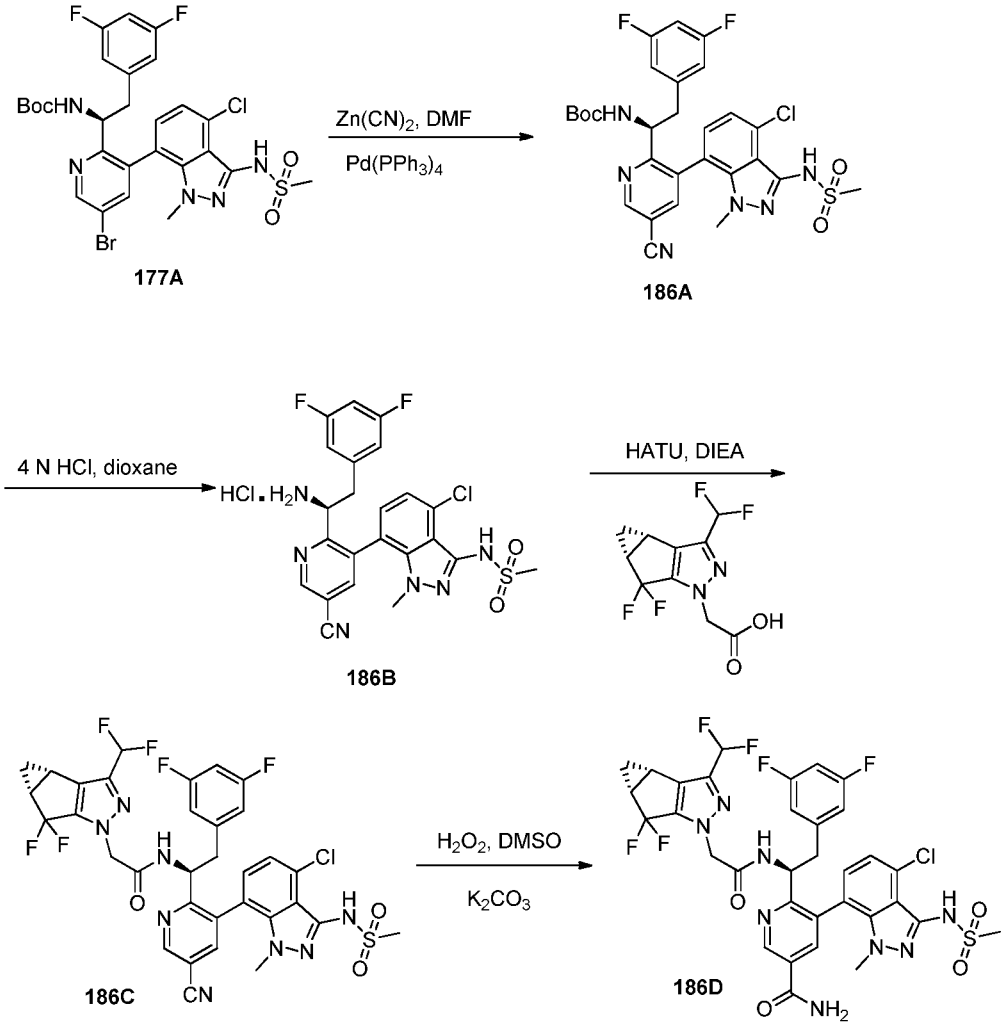
Synthesis of (S)-N-(7-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-[3,3'-bipyridin]-5-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**185B**):

[0829] The title compound as mixture of atropisomers (**185B**) was prepared according to the method presented for the synthesis of compound **177C** of Example 177 utilizing compound **185A**. MS (m/z) 569 $[M+H]^+$.

Synthesis of N-((S)-1-(5-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-[3,3'-bipyridin]-6-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**185C**):

[0830] The title compound as mixture of atropisomers (**185C**) was prepared according to the method presented for the synthesis of compound **177D** of Example 177 utilizing compound **185B**. ^{1}H NMR (400 MHz, Acetonitrile-d3) δ 9.07 (t), 8.96 (dd), 8.66 (dd), 8.15 – 8.06 (m), 8.03 (dd), 7.56 – 7.44 (m), 7.35 (d), 7.28 (d), 7.22 (d), 7.16 (dd), 6.93 – 6.87 (m), 6.86 – 6.72 (m), 6.69 – 6.57 (m), 6.48 – 6.34 (m), 5.37 – 5.29 (q), 4.98 (q), 4.78 – 4.59 (m), 3.36 – 2.91 (m), 2.49 (dtd), 1.41 (p), 1.05 (t). MS (m/z) 815 $[M+H]^+$.

Example 186.



Synthesis of (S)-tert-butyl (1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-5-cyanopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**186A**):

[0831] To a suspension of **177A** (140 mg, 0.21 mmol) in anhydrous/degassed DMF (1.5 ml) was treated with $Zn(CN)_2$ (14.7 mg, 0.125 mmol), and tetrakis(triphenylphosphine)palladium(0) (24.1 mg, 0.021 mmol). The mixture was heated at 90°C for 16 hours under a nitrogen atmosphere. The reaction mixture was allowed to cool to ambient temperature and poured into EtOAc (50 ml). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified on flash column to provide the title compound as a mixture of atropisomers. MS (m/z) 617 $[M+H]^+$.

Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-cyanopyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide hydrochloride (**186B**):

[0832] The title compound (**186B**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **21E** of Example 21 utilizing **186A**. MS (m/z) 517 $[M+H]^+$.

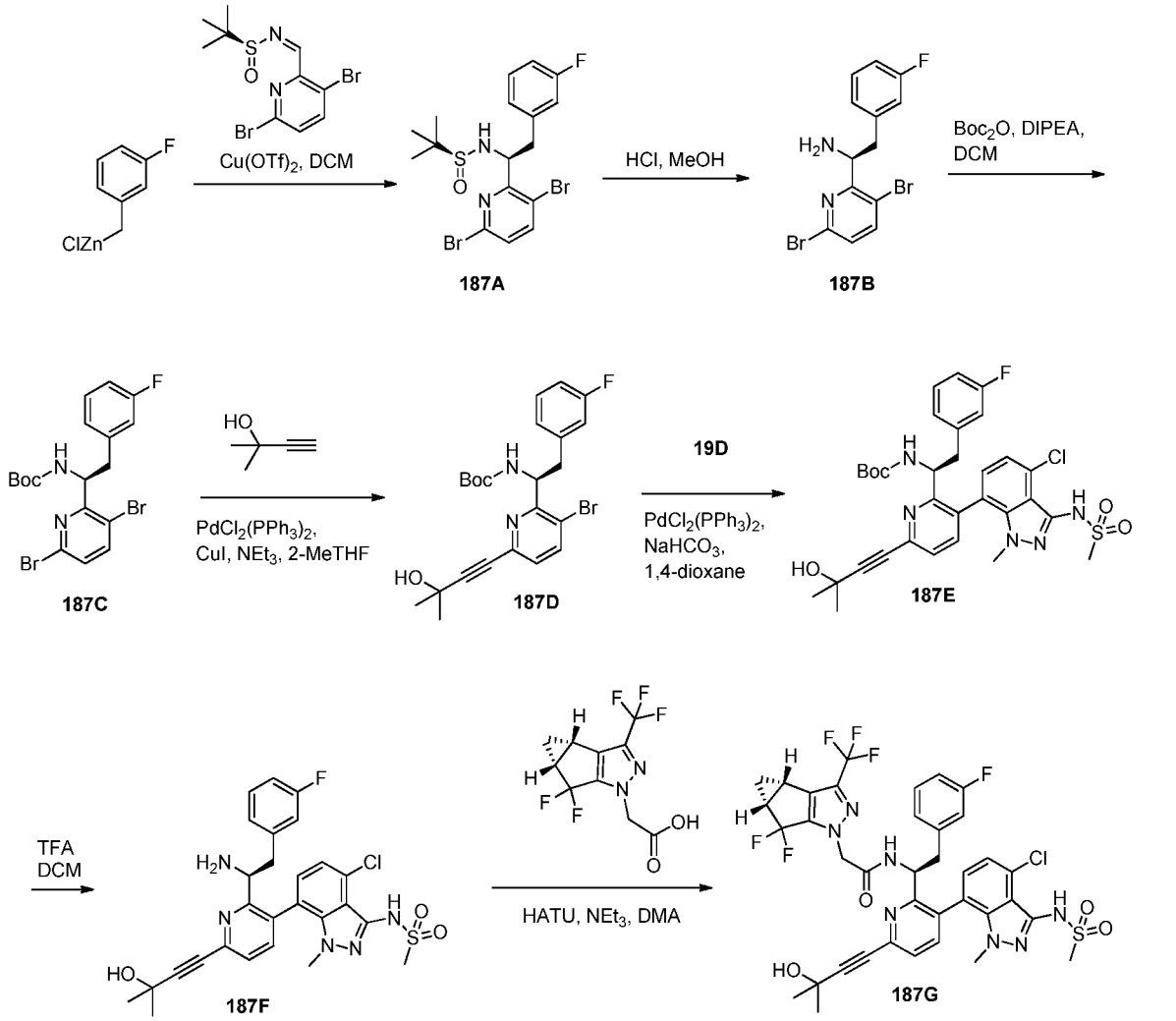
Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-5-cyanopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**186C**):

[0833] The title compound (**186C**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **10A** of Example 10 utilizing **186B** and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. MS (*m/z*) 763 $[M+H]^+$.

Synthesis of 5-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-((S)-1-(2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)nicotinamide (**186D**):

[0834] To a suspension of **186C** (21 mg, 0.028 mmol) and K_2CO_3(38 mg, 0.28 mmol) in DMSO, H_2O_2 (30 wt. % in H_2O, 0.028 mL, 0.28 mmol) was added to the suspension slowly. After 10 minutes, the mixture was filtered and purified by reverse phase HPLC to provide the title compound as a mixture of atropisomers. ^1H NMR (400 MHz, Methanol-d4) 1H NMR (400 MHz, Methanol-d4) δ 9.26 (t), 8.73 (t), 8.14 (dd), 7.31 – 7.14 (m), 7.09 (d), 6.77 (tt),6.72 (t), 6.68 – 6.59 (m), 6.49 – 6.30 (m), 5.35-5.25 (m), 5.08 – 5.00 (m), 4.78 – 4.68 (m), 3.25 (d), 3.18 – 3.09 (m), 3.05 – 2.93 (m), 2.65 (s), 2.44 (ddd), 1.39 (dq), 1.01 (h). MS (m/z) 781 $[M+H]^+$.

Example 187.



Synthesis of (S)-N-((S)-1-(3,6-dibromopyridin-2-yl)-2-(3-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (**187A**):

[0835] To a solution of (S,Z)-N-((3,6-dibromopyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (1.0 g, 2.717 mmol) and $Cu(OTf)_2$ (49.1 mg, 0.136 mmol) in DCM (10 mL) was added 3-fluorobenzyl zinc chloride (0.5M in THF, 7.6 mL, 3.803 mmol) dropwise over 7 mintues at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, then quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The organic layer was collected, and the aqueous layer was extracted an additional time with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by silica gel column chromatography to provide the title compound **187A**. MS (*m/z*) 476.93, 478.84, 480.79 $[M+H]^+$.

Synthesis of (S)-1-(3,6-dibromopyridin-2-yl)-2-(3-fluorophenyl)ethanamine (**187B**):

[0836] To a solution of (S)-N-((S)-1-(3,6-dibromopyridin-2-yl)-2-(3-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (**187A**, 714.2 mg, 1.493 mmol) in MeOH (3.7 mL) was added HCl

(4M in 1,4-dioxane, 3.7 mL, 14.93 mmol). The reaction mixture was stirred at room temperature for 30 minutes. Upon completion, the reaction mixture was concentrated *in vacuo* to provide the title compound **187B**, which was used without purification. MS (*m/z*) 373.08, 374.92, 376.86 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(3,6-dibromopyridin-2-yl)-2-(3-fluorophenyl)ethyl)carbamate (**187C**):

[0837] To a solution of (S)-1-(3,6-dibromopyridin-2-yl)-2-(3-fluorophenyl)ethanamine (**187B**, 558.62 mg, 1.493 mmol) in DCM was added DIPEA (0.52 mL, 2.987 mmol). The reaction mixture was cooled to 0 °C, then Boc_2O (358.6 mg, 1.643 mmol) was added. The reaction mixture was warmed to room temperature and stirred at room temperature for 2.5 hours. Upon completion, the reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography to provide the title compound **187C**. MS (*m/z*) 472.71, 474.68, 476.68 $[M+H]^+$.

Synthesis of (S)-tert-butyl (1-(3-bromo-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3-fluorophenyl)ethyl)carbamate (**187D**):

[0838] A solution of (S)-tert-butyl (1-(3,6-dibromopyridin-2-yl)-2-(3-fluorophenyl)ethyl)carbamate (**187C**, 200.0 mg, 0.422 mmol) in 2-MeTHF was degassed by bubbling argon for 60 seconds. To the degassed solution were added NEt_3 (0.18 mL, 1.268 mmol) and 2-methyl-3-butyn-2-ol (62 µL, 0.633 mmol) followed by CuI (2.4 mg, 0.013 mmol) and $PdCl_2(PPh_3)_2$ (8.9 mg, 0.013 mmol). The reaction mixture was stirred at room temperature for 30 minutes. Upon completion, the reaction mixture was diluted with water and extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to provide the title compound **187D**. MS (*m/z*) 476.91, 478.83 $[M+H]^+$.

Synthesis (S)-tert-butyl (1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3-fluorophenyl)ethyl)carbamate (**187E**):

[0839] (S)-tert-butyl (1-(3-bromo-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3-fluorophenyl)ethyl)carbamate (**187D**, 189.7 mg, 0.397 mmol), N-(4-chloro-1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-yl)methanesulfonamide (**19D**, 214.6 mg, 0.556 mmol), and $PdCl_2(PPh_3)_2$ (27.9 mg, 0.04 mmmol) were taken in 1,4-dioxane (10 mL) and $NaHCO_3$ (1 M in water, 1.19 mL, 1.19 mmol). The resulting solution was degassed by bubbling argon for 5 minutes, then the reaction flask was sealed and the reaction heated at 150 °C for 20 minutes in a microwave reactor. Upon cooling, the reaction mixture was filtered, concentrated

in vacuo, and purified by silica gel column chromatography to provide the title compound **187E** as a mixture of atropisomers. MS (*m/z*) 655.92 $[M+H]^+$.

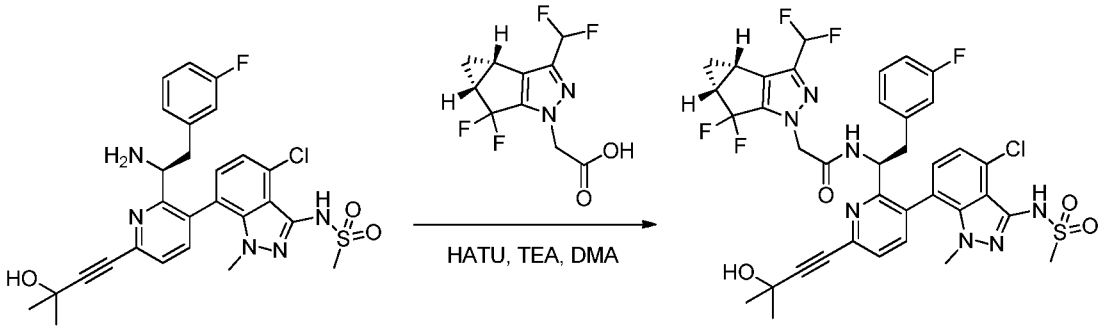
Synthesis of (S)-N-(7-(2-(1-amino-2-(3-fluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**187F**):

[0840] To a solution of (S)-tert-butyl (1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3-fluorophenyl)ethyl)carbamate (**187E**, 257.3 mg, 0.392 mmol) in DCM (4 mL) was added TFA (4 mL). The reaction mixture was stirred at room temperature for 1 hour 15 minutes. Upon completion, the reaction mixture was concentrated *in vacuo* to provide the title compound **187F** as a mixture of atropisomers which was used without further purification. MS (*m/z*) 556.15 $[M+H]^+$.

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3-fluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**187G**):

[0841] To a solution of (S)-N-(7-(2-(1-amino-2-(3-fluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**187F**, 218.0 mg, 0.392 mmol) in DMA (3 mL) was added NEt_3 (0.16 mL, 1.176 mmol), 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (77.5 mg, 0.274 mmol), then HATU (104.4 mg, 0.274 mmol) at room temperature. The reaction mixture was stirred at room temperature for 15 minutes. Upon completion, the reaction mixture was filtered and purified by reverse phase HPLC. Fractions containing the product were pooled and lyophilized to give the title compound **187G** as a mixture of atropisomers. ^1H NMR (400 MHz, Methanol-d_4) δ 8.80 – 8.70 (m), 7.65 (dd), 7.51 (dd), 7.22 – 7.11 (m), 6.99 (d), 6.96 – 6.89 (m), 6.77 (t), 6.60 – 6.46 (m), 6.15 – 6.07 (m), 5.37 – 5.25 (m), 5.02 – 4.93 (m), 4.84 (s), 4.80 (s), 4.78 (s), 4.74 (s), 3.26 (s), 3.23 (s), 3.21 – 3.11 (m), 3.04 – 2.94 (m), 2.82 (s), 2.61 – 2.39 (m), 1.65 (s), 1.50 – 1.35 (m), 1.19 – 1.12 (m), 1.11 – 1.02 (m). MS (*m/z*) 820.12 $[M+H]^+$.

Example 188.

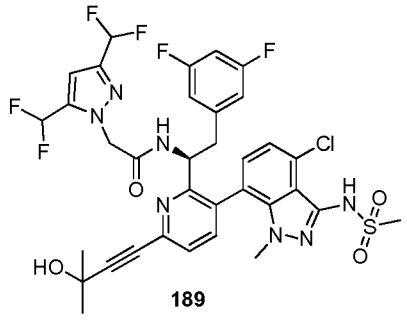


187F 188

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3-fluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**188**):

[0842] The title compound (**188**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **187G** of Example 187 utilizing 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.72 – 8.62 (m), 7.65 (dd), 7.57 – 7.44 (m), 7.33 (dd), 7.22 – 7.11 (m), 6.99 (d), 6.98 – 6.65 (m), 6.61 – 6.46 (m), 6.14 (d), 6.13 (d), 5.31 (dd), 4.96 (dd), 4.79 (s), 4.74 (s), 4.72 (s), 4.68 (s), 3.26 (s), 3.22 (s), 3.20 – 3.11 (m), 3.04 – 2.92 (m), 2.83 (s), 2.55 – 2.39 (m), 1.65 (s), 1.45 – 1.32 (m), 1.15 – 1.07 (m), 1.07 – 0.98 (m). MS (*m/z*) 802.15 $[M+H]^+$.

Example 189.



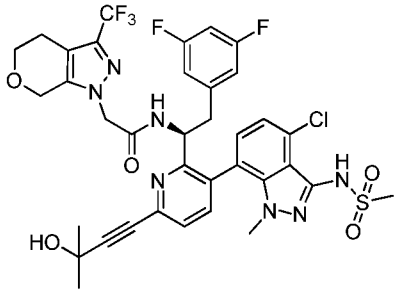
189

Synthesis of (S)-2-(3,5-bis(difluoromethyl)-1H-pyrazol-1-yl)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)acetamide (**189**):

[0843] The title compound (**189**) was prepared as a mixture of atropisomers according to the method presented in the synthesis of **10A** in Example 10 utilizing **19F** and 2-(3,5-bis(difluoromethyl)-1H-pyrazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.70 (dd),

7.53 (dd), 7.18 (q), 7.07 (d), 7.01 – 6.56 (m), 6.42 (d), 6.40 – 6.31 (m), 5.26 (dd), 5.04 – 4.86 (m), 3.25 (s), 3.21 (s), 3.15 (dd), 3.04 – 2.93 (m), 1.64 (s). MS (*m/z*) 783.1 $[M+H]^+$.

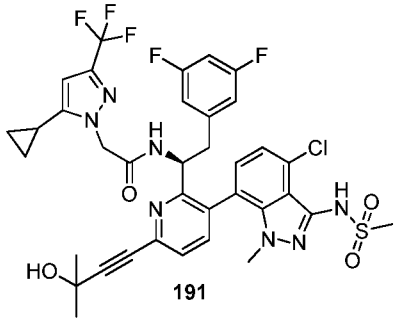
Example 190.



Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(trifluoromethyl)-4,5-dihydropyrano[3,4-c]pyrazol-1(7H)-yl)acetamide (**190**):

[0844] The title compound (**190**) was prepared as a mixture of atropisomers according to the method presented in the synthesis of **10A** in Example 10 utilizing **19F** and 2-(3-(trifluoromethyl)-4,5-dihydropyrano[3,4-c]pyrazol-1(7H)-yl)acetic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.71 (dd), 7.53 (dd), 7.17 (q), 7.09 (d), 6.82 – 6.69 (m), 6.68 – 6.59 (m), 6.42 (dd), 5.28 – 5.19 (m), 5.01 – 4.92 (m), 4.69 (t), 4.52 (s), 3.92 – 3.78 (m), 3.25 (d), 3.20 – 3.09 (m), 3.01 (s), 2.96 (dd), 2.73 – 2.59 (m), 1.64 (s). MS (*m/z*) 807.0 $[M+H]^+$.

Example 191.



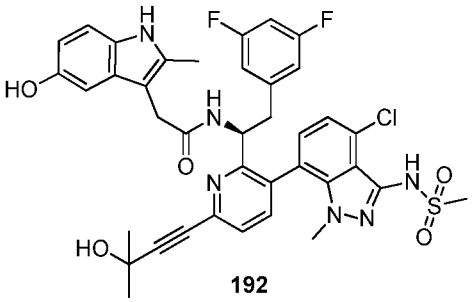
191

Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (**191**):

[0845] The title compound (**191**) was prepared as a mixture of atropisomers according to the method presented in the synthesis of **10A** in Example 10 utilizing **19F** and 2-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.71 (dd), 7.53 (dd), 7.27 (d), 7.17 (d), 7.10 (d), 6.80 – 6.72 (m), 6.67 – 6.58 (m), 6.52 (d), 6.45 – 6.33 (m), 6.24 (s), 6.19 (s), 5.37 – 5.22 (m), 5.05 – 4.95 (m), 4.90 (d), 3.23 (d), 3.21 – 3.08 (m), 3.05 (s),

3.03 – 2.93 (m), 1.64 (s), 1.59 – 1.47 (m), 1.04 – 0.90 (m), 0.69 – 0.55 (m). MS (*m/z*) 791.0 $[M+H]^+$.

Example 192.

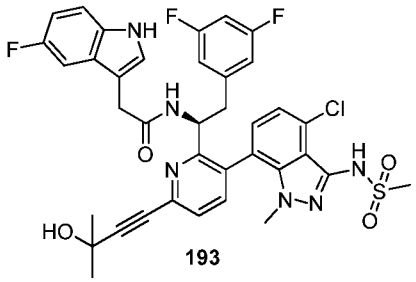


192

Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-hydroxy-2-methyl-1H-indol-3-yl)acetamide (**192**):

[0846] The title compound (**192**) was prepared as a mixture of atropisomers according to the method presented in the synthesis of **10A** in Example 10 utilizing **19F** and 2-(5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.63 (dd), 7.46 (dd), 7.13 – 7.03 (m), 7.03 – 6.92 (m), 6.74 – 6.54 (m), 6.46 (d), 6.35 (d), 6.26 (d), 5.29 – 5.18 (m), 5.04 – 4.89 (m), 3.47 (d), 3.43 (s), 3.22 (d), 3.18 – 3.08 (m), 2.97 (s), 2.95 – 2.75 (m), 2.31 (s), 2.28 (s), 1.65 (s). MS (*m/z*) 761.5 $[M+H]^+$.

Example 193.



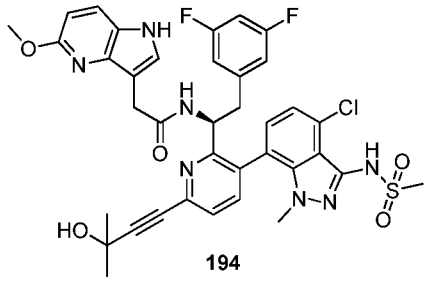
193

Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**193**):

[0847] The title compound (**193**) was prepared as a mixture of atropisomers according to the method presented in the synthesis of **10A** in Example 10 utilizing **19F** and 2-(5-fluoro-1H-indol-3-yl)acetic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.63 (d), 7.53 – 7.43 (m), 7.34 – 7.24 (m), 7.18 – 7.06 (m), 7.02 (dd), 6.91 – 6.77 (m), 6.74 – 6.64 (m), 6.64 – 6.56 (m), 6.49 (d), 6.43 –

6.30 (m), 5.26 – 5.16 (m), 5.05 – 4.95 (m), 3.64 – 3.39 (m), 3.24 (s), 3.23 (s), 3.14 – 2.80 (m), 1.64 (s). MS (*m/z*) 749.5 $[M+H]^+$.

Example 194.

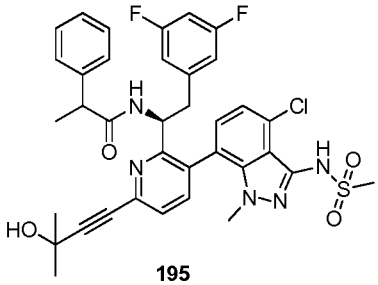


194

Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-methoxy-1H-pyrrolo[3,2-b]pyridin-3-yl)acetamide (**194**):

[0848] The title compound (**194**) was prepared as a mixture of atropisomers according to the method presented in the synthesis of **10A** in Example 10 utilizing **19F** and 2-(5-methoxy-1H-pyrrolo[3,2-b]pyridin-3-yl)acetic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.32 – 8.20 (m), 7.77 – 7.59 (m), 7.56 – 7.49 (m), 7.17 (dd), 7.09 – 6.97 (m), 6.94 (d), 6.72 (d), 6.57 – 6.48 (m), 6.38 (d), 6.29 (d), 5.29 – 5.17 (m), 5.12 – 5.00 (m), 4.18 – 4.14 (m), 4.03 (d), 3.69 – 3.45 (m), 3.29 – 3.18 (m), 3.20 – 3.03 (m), 3.03 – 2.90 (m), 1.65 (s). MS (*m/z*) 762.3 $[M+H]^+$.

Example 195.



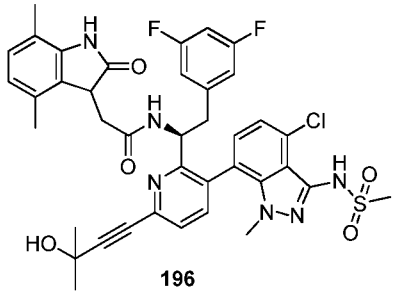
195

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-phenylpropanamide (**195**):

[0849] The title compound (**195**) was prepared as a mixture of atropisomers according to the method presented in the synthesis of **10A** in Example 10 utilizing **19F** and 2-phenylpropanoic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.71 (dd), 7.63 – 7.42 (m), 7.37 – 7.05 (m), 6.81 – 6.72 (m), 6.69 (d), 6.67 – 6.52 (m), 6.49 (d), 6.47 – 6.39 (m), 6.35 – 6.24 (m), 5.28 – 5.22 (m),

5.08 – 5.00 (m), 5.00 – 4.95 (m), 3.72 – 3.49 (m), 3.39 (s), 3.29 – 3.22 (m), 3.18 – 2.95 (m), 2.91 (s), 2.88 – 2.84 (m), 2.81 (s), 1.64 (s), 1.35 (dd), 1.32 – 1.19 (m). MS (*m/z*) 706.8 $[M+H]^+$.

Example 196.

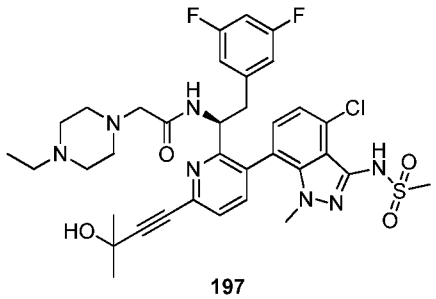


196

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(4,7-dimethyl-2-oxoindolin-3-yl)acetamide (**196**) :

[0850] The title compound (**196**) was prepared as a mixture of atropisomers according to the method presented in the synthesis of **10A** in Example 10 utilizing **19F** and 2-(4,7-dimethyl-2-oxoindolin-3-yl)acetic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.69 – 7.61 (m), 7.61 – 7.41 (m), 7.16 (d), 7.12 – 7.06 (m), 7.03 (d), 6.89 – 6.76 (m), 6.76 – 6.68 (m), 6.67 (d), 6.64 – 6.54 (m), 6.49 (d), 6.43 – 6.36 (m), 6.34 (d), 5.18 (s), 5.14 – 5.06 (m), 4.83 – 4.75 (m), 3.67 – 3.57 (m), 3.57 – 3.43 (m), 3.36 (s), 3.25 (dd), 3.21 – 3.11 (m), 3.10 – 2.97 (m), 2.97 – 2.68 (m), 2.35 – 2.06 (m), 1.71 – 1.59 (m). MS (*m/z*) 776.1 $[M+H]^+$.

Example 197.



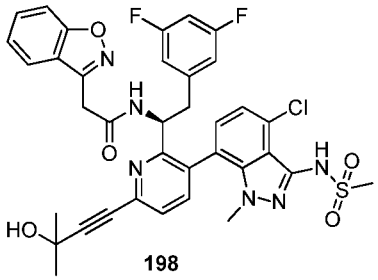
197

Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(4-ethylpiperazin-1-yl)acetamide (**197**):

[0851] The title compound (**197**) was prepared as a mixture of atropisomers according to the method presented in the synthesis of **10A** in Example 10 utilizing **19F** and 2-(4-ethylpiperazin-1-yl)acetic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.75 (dd), 7.54 (dd), 7.35 (d), 7.27 (d),

7.20 (d), 6.82 (d), 6.80 – 6.73 (m), 6.69 – 6.62 (m), 6.50 – 6.37 (m), 5.47 – 5.39 (m), 5.07 (dd), 3.40 (s), 3.27 (s), 3.23 – 2.87 (m), 1.63 (s), 1.35 (td). MS (*m/z*) 729.0 $[M+H]^+$.

Example 198.

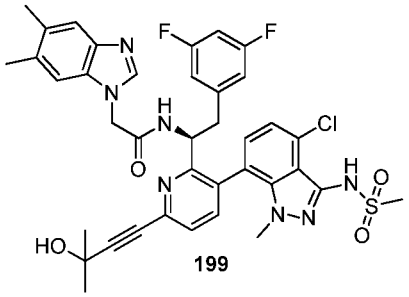


198

Synthesis of (S)-2-(benzo[d]isoxazol-3-yl)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)acetamide (**198**):

[0852] The title compound (**198**) was prepared as a mixture of atropisomers according to the method presented in the synthesis of **10A** in Example 10 utilizing **19F** and 2-(benzo[d]isoxazol-3-yl)acetic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.72 – 7.63 (m), 7.60 (d), 7.59 – 7.49 (m), 7.37 – 7.30 (m), 7.31 – 7.24 (m), 7.16 (d), 7.11 (d), 7.00 (d), 6.74 – 6.66 (m), 6.58 (d), 6.47 – 6.38 (m), 5.30 – 5.22 (m), 5.07 – 4.95 (m), 3.93 – 3.76 (m), 3.24 (s), 3.21 – 3.10 (m), 3.08 – 2.93 (m), 1.65 (s). MS (*m/z*) 733.2 $[M+H]^+$.

Example 199.



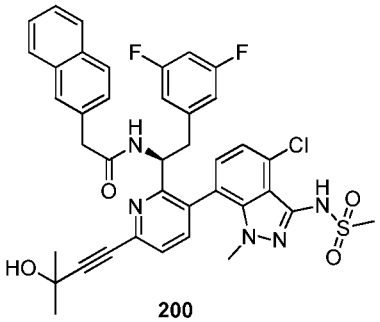
199

Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetamide (**199**):

[0853] The title compound (**199**) was prepared as a mixture of atropisomers according to the method presented in the synthesis of **10A** in Example 10 utilizing **19F** and 2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.19 (s), 9.07 (s), 7.74 (dd), 7.63 – 7.50 (m), 7.49 – 7.33 (m), 7.27 (s), 7.24 – 6.99 (m), 6.74 – 6.56 (m), 6.47 – 6.34

(m), 5.38 – 5.29 (m), 5.22 – 4.91 (m), 4.03 (s), 3.25 (d), 3.23 – 3.19 (m), 3.14 (s), 3.09 – 2.95 (m), 2.52 – 2.38 (m), 1.65 (s). MS (*m/z*) 761.1 $[M+H]^+$.

Example 200.



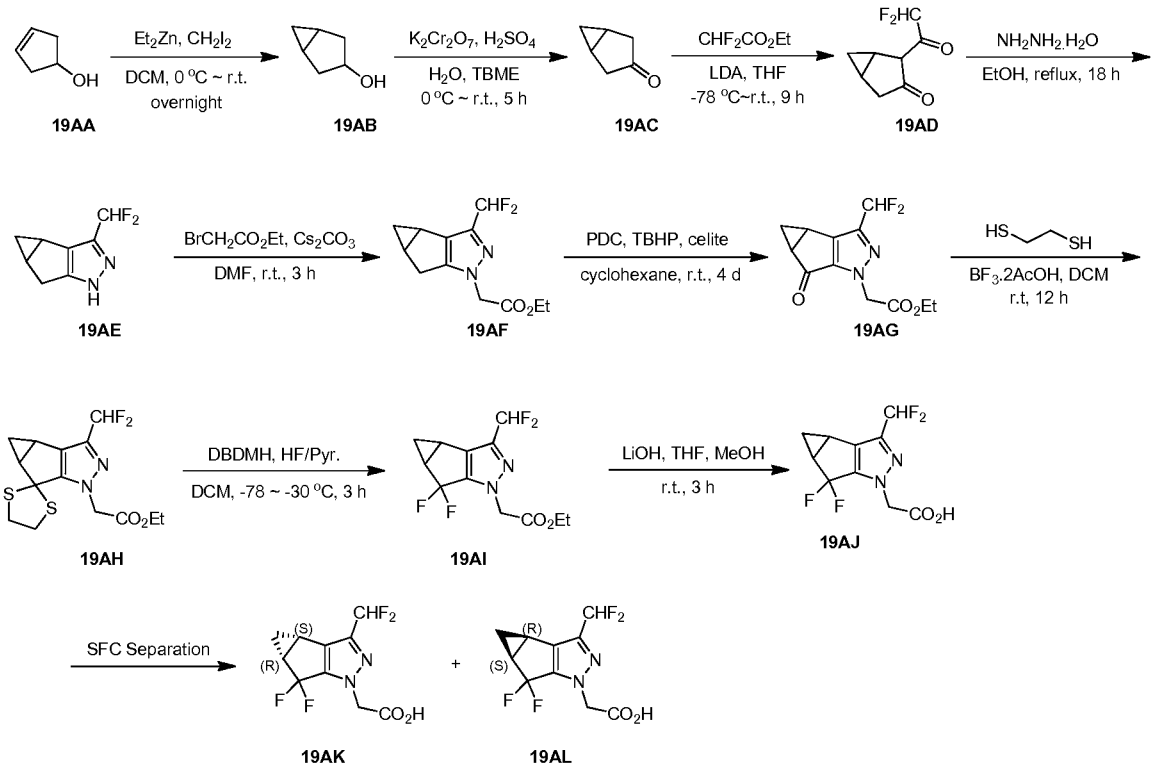
200

Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(naphthalen-2-yl)acetamide (**200**):

[0854] The title compound (**200**) was prepared as a mixture of atropisomers according to the method presented in the synthesis of **10A** in Example 10 utilizing **19F** and 2-(naphthalen-2-yl)acetic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.86 – 7.69 (m), 7.69 – 7.62 (m), 7.59 (s), 7.55 – 7.49 (m), 7.50 – 7.37 (m), 7.34 (d), 7.25 – 7.19 (m), 7.10 (dd), 6.99 (d), 6.84 (d), 6.71 – 6.62 (m), 6.60 – 6.57 (m), 6.55 (dd), 6.47 – 6.34 (m), 5.24 – 5.16 (m), 5.02 (t), 3.64 – 3.44 (m), 3.24 (s), 3.20 (s), 3.18 – 3.11 (m), 3.10 (d), 3.03 – 2.93 (m), 1.64 (s). MS (*m/z*) 742.8 $[M+H]^+$.

Example 201.

Large scale preparation of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-ynyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**19G**).



Synthesis of bicyclo[3.1.0]hexan-3-ol (**19AB**):

[0855] Et_2Zn (1M in hexane, 2.37 L, 2.37 mol) was added drop-wise to a solution of compound **19AA** (100 g, 1.19 mol) in DCM (800 ml) under N_2 at 0-5 °C. The mixture was stirred at 0-5 °C for 30 min, then CH_2I_2 (636 g, 2.37 mol) in DCM (200 ml) was added drop-wise in 1 h at 0-5 °C. The resulting mixture was stirred at room temperature overnight. The mixture was added slowly to ice-cold aq. NH_4Cl (1.5 L). The mixture was filtered. The aqueous phase was extracted with DCM (2L x 3). The combined organic layer was dried over $MgSO_4$, concentrated in vacuo to give crude residue, which was purified by distillation (20 mmHg, 80 °C-82 °C) to give compound **19AB**. ^1H NMR: (400 MHz, $CDCl_3$) δ 4.35 (t, J = 6.4 Hz, 1H), 2.10-2.06 (m, 2H), 1.70 (d, J = 14.0 Hz, 2H), 1.65 (s, 1H), 1.27-1.24 (m, 2H), 0.52-0.47 (m, 2H).

Synthesis of bicyclo[3.1.0]hexan-3-one (**19AC**):

[0856] To a solution of $K_2Cr_2O_7$ (240 g, 0.82 mol) in H_2O (2 L), H_2SO_4 (240 g, 2.45 mol) was added drop-wise at room temperature. The mixture was stirred at room temperature for 1 h. The system was cooled to 0 °C, compound **19AB** (100 g, 1.02 mol) in TBME (2 L) was added drop-wise. The reaction mixture was stirred at room temperature for 4 h. The organic layer was separated. The aqueous layer was extracted with TBME (1 L x 3). The combined organic layer was dried over $MgSO_4$, filtered, concentrated in vacuo to give the crude product, which was purified by distillation (20 mmHg, 60 °C-62 °C) to give compound **19AC**. ^1H NMR (400 MHz,

$CDCl_3$) δ 2.57-2.52 (m, 2H), 2.13-2.08 (m, 2H), 1.50-1.47 (m, 2H), 0.88-0.85 (m, 1H), 0.08--0.01(m, 1H).

Synthesis of 2-(2,2-difluoroacetyl)bicyclo[3.1.0]hexan-3-one (**19AD**):

[0857] To the solution of compound **19AC** (100 g, 1.04 mol) in THF (1 L), LDA (700 ml, 1.05 mol, 1.5M in THF) was added drop-wise under N_2 over a period of 2 h. The resulting mixture was stirred 1 h at -78 °C. Ethyl difluoroacetate (142 g, 1.14 mol) in THF (500 ml) was added drop-wise over a period of 1 h and the reaction was stirred 1 h at -78 °C. The reaction was warmed to room temperature and stirred for 4 h. The reaction was quenched by aqueous 1N HCl (1.5 L) and then partitioned between EA (1.0 L) and aqueous citric acid (300 ml). The organic layer was separated and washed with brine. Solvents were removed in vacuo to give compound **19AD** which was used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (t, J = 53.6 Hz, 1H), 2.78-2.73 (m, 1H), 2.44-2.39 (m, 1H), 2.25-2.24 (m, 1H), 1.70-1.69 (m, 1H), 1.22-1.14 (m, 1H), 0.31-0.27 (m, 1H).

Synthesis of 3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole (**19AE**):

[0858] $N_2H_4{\cdot}H_2O$ (104 g, 2.08 mol) was added drop-wise in 30 min to the solution of compound **19AD** (380 g, 2.08 mol) in EtOH (4 L) at room temperature The mixture was stirred at reflux overnight. The mixture was concentrated in vacuo then purified by silica gel column chromatography (PE: EA= 10:1- 5:1) to give compound **19AE**. MS (m/z): 171.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (t, J = 55.6 Hz, 1H), 2.99-2.94 (m, 1H), 2.82-2.78 (m, 1H), 2.13-2.07 (m, 2H), 1.14-1.08 (m, 1H), 0.30-0.27 (m, 1H).

Synthesis of ethyl 2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**19AF**):

[0859] To a solution of compound **19AE** (201 g, 1.18 mol) in DMF (2 L), ethyl bromoacetate (207 g, 1.24 mol) and Cs_2CO_3 (404 g, 1.24 mol) were added in one portion at room temperature. The mixture was stirred at room temperature for 3 h. The mixture was poured into H_2O (4 L) and then extracted with EA (2 L x 3). The combined organic phase was washed with brine (2 L x 3), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (PE: EA= 20:1- 8:1) to obtain a mixture of N1 and N2 alkylation isomers. An additional purification from PE/EA (10/1) provided compound **19AF**. MS (m/z): 257.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (t, J = 55.2 Hz, 1H), 4.70 (dd, J = 17.2, 11.2

Hz, 2H), 4.23 (q, J = 7.2 Hz, 2H), 2.91 (dd, J = 16.0, 6.0 Hz, 1H), 2.72 (d, J = 16.4 Hz, 1H), 2.17-2.09 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.10-1.07 (m, 1H), 0.33-0.30 (m, 1H).

Synthesis of ethyl 2-(3-(difluoromethyl)-5-oxo-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**19AG**):

[0860] Compound **19AF** (102 g, 0.39 mol) and celite 545 (390 g) were added to cyclohexane (3.5 L) and the mixture was stirred at 10 °C. PDC (599 g, 1.59 mol) was added in one portion followed by TBHP (289 ml, 1.59 mol) drop-wise in 30 min at 10 °C. The reaction was slowly warmed to room temperature and stirred for 4 days. The reaction was filtered through celite and filter cake was washed with EtOAc (600 ml). The combined organic layer was stirred with saturated aqueous $Na_2S_2O_3$ (1000 ml) for 1 h. The organic layer was separated and treated with half saturated $FeSO_4$ (300 ml), washed with brine and dried over Na_2SO_4. Solvents were removed in vacuo to give crude product, which was additionally purified from PE (300 ml) to give compound **19AG**. MS (m/z): 271.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 6.67 (t, J = 54.8 Hz, 1H), 4.94 (s, 2H), 4.23 (q, J = 7.2 Hz, 2H), 2.79-2.78 (m, 1H), 2.59-2.56 (m, 1H), 1.70-1.65 (m, 2H), 1.28 (t, J = 6.8 Hz, 3H).

Synthesis of ethyl 2-(3-(difluoromethyl)-4,4a-dihydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-[1,3]dithiolane]-1(3bH)-yl)acetate (**19AH**):

[0861] To compound **19AG** (148.5 g, 0.55 mol) in DCM (2.0 L) was added ethane-1,2-dithiol (88.0 g, 0.94 mol) in one portion and the solution was stirred at room temperature. BF_3.2AcOH (175.8 g, 0.94 mol) was added to above solution. The reaction was stirred at room temperature for 12 h. The system was cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$ (1000 ml). The organic layer was separated, washed with brine (500 ml) and dried over Na_2SO_4. Solvents were removed in vacuo and the residue was purified by silica gel column chromatography (PE: EtOAc =30:1- 10:1) to provide compound **19AH**. MS (m/z): 347.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 6.61 (t, J = 55.0 Hz, 1H), 4.90 (dd, J = 17.2, 10.8 Hz, 2H), 4.21 (q, J = 4.8 Hz, 2H), 3.51-3.45 (m, 4H), 2.60-2.58 (m, 1H), 2.43-2.42 (m, 1H), 1.29-1.23 (m, 4H), 0.63-0.61 (m, 1H).

Synthesis of ethyl 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**19AI**):

[0862] A solution of DBDMH (99 g, 0.35 mol) in dry DCM (120 mL) was cooled to -78 °C in a teflon bottle. HF/Py (120 mL) was added drop-wise over a period of 30 min. The reaction was stirred at -78 °C for 30 min. Then a solution of compound **19AH** (40 g, 0.12 mol) in dry

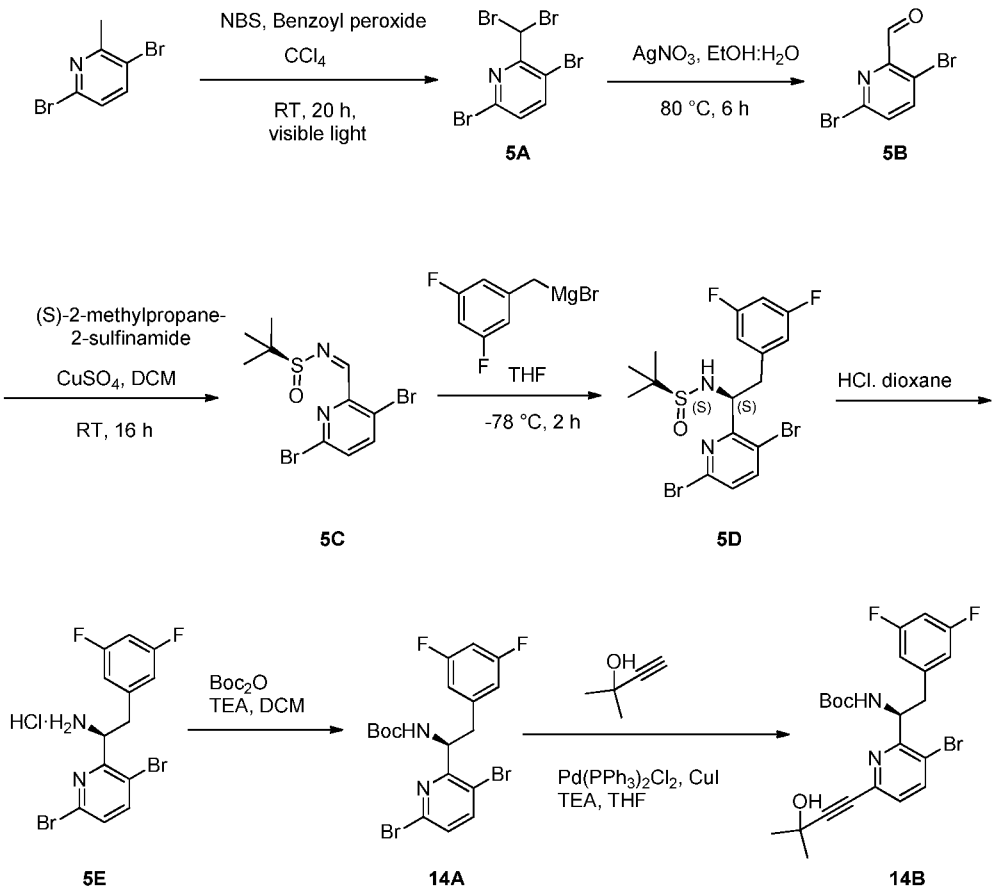
DCM (80 mL) was added drop-wise over a period of 15 min at -78 °C. The resulting mixture was stirred for 30 min at this temperature, then slowly warm to -30 °C and stirred for 1.5 h. The reaction mixture was slowly poured into aq. $NaHCO_3$ (500 mL) and extracted with EA (500 mLx3). The combined organic layer was washed with 10% aq. $Na_2S_2O_3$ (500 mL), brine (500 mL) and dried over Na_2SO_4. Solvents were removed in vacuo to afford the crude product, which was further purified by column chromatography (PE: EA =80: 1 to 50: 1) to give compound **19AI**. MS (m/z): 293.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 6.63 (t, J = 54.8 Hz, 1H), 4.83 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 2.48-2.45 (m, 2H), 1.38-1.36 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.13-1.12 (m, 1H).

Synthesis of 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (**19AJ**):

[0863] To a solution of compound **19AI** (50 g, 171 mmol) in THF (87.5 mL) and MeOH (350 mL) was added the solution of LiOH (6.2 g, 257 mmol) in H_2O (350 mL). The mixture was stirred at 20 °C for 3 h. The mixture was concentrated to remove most of THF and MeOH, the aqueous was acidified by 1N HCl to adjust pH to 2-3, then extracted with EA (600 mLx2). The organic phase was separated and combined, dried over Na_2SO_4, filtered and concentrated in vacuum to give compound **19AJ**.

2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (**19AK**) and 2-((3bR,4aS)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (**19AL**):

[0864] Compound **19AJ** was separated by SFC (ChiralPak IC-10 u, 300×50mm I.D., mobile phase: CO_2 / isopropanol (0.1% $NH_3.H_2O$), 35% gradient, 200 mL / min flow rate, 38 °C column temperature, detection at 220 nm) to give compound **19AK** (79.3 g) and **19AL** (80.8 g). **19AK:** MS (m/z): 265.0 $[M+H]^+$; ^1H NMR: (400 MHz, DMSO-d_6) δ 13.43 (br, 1H), 7.04 (t, J = 54.0 Hz, 1H), 4.99-4.87 (m, 2H), 2.62-2.57 (m, 2H), 1.46-1.41 (m, 1H), 0.96 (s, 1H). **19AL:** MS (m/z): 265.0 $[M+H]^+$; ^1H NMR: (400 MHz, DMSO-d_6) δ 13.42 (br, 1H), 7.04 (t, J = 54.0 Hz, 1H), 4.99-4.88 (m, 2H), 2.63-2.51 (m, 2H), 1.46-1.41 (m, 1H), 0.97 (s, 1H).



Synthesis of 3,6-dibromo-2-(dibromomethyl)pyridine (**5A**):

[0865] To a stirred solution of 3,6-dibromo-2-methylpyridine (200.0 g, 797.06 mmol) in CCl_4 (4000 mL), benzoyl peroxide (192.89 g, 797.06 mmol) followed by NBS (565.0 g, 3188.0 mmol) was added at room temperature. After addition was completed, the resulting reaction mixture was stirred in presence of white light 400 watt bulb at room temperature for 20 h. The reaction mixture was stirred at room temperature for 20 h. The reaction mixture was filtered and washed with CCl_4 (2 x 800 mL). The filtrate was evaporated under reduced pressure which was further purified by column chromatography on silica gel using 0- 5% EA in hexane as an eluent to afford compound **5A**. MS (m/z): 409.66 $[M+H]^+$.

Synthesis of 3,6-dibromopicolinaldehyde (**5B**):

[0866] To a solution of compound **5A** (100.0 g, 244.67 mmol) in EtOH (1000 mL) at 80 °C, aqueous silver nitrate (103.9 g, 611.6 mmol, in 300 mL water) was added drop-wise, in 1 h at same temperature. After addition was completed, the resulting reaction mixture was stirred to reflux for another 5 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was evaporated under reduced pressure and the resultant crude was diluted with water (1000 mL). The aqueous layer was extracted with ethyl acetate (3 x 400 mL). The combined

organic layers were washed with water (2 x 400 mL), dried over sodium sulfate and distilled off under reduced pressure gave compound **5B**. MS (m/z): 265.96. $[M+H]^+$

Synthesis of (S,Z)-N-((3,6-dibromopyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (**5C**):

[0867] To a stirred solution of compound **5B** (68.0 g, 256.7 mmol) in DCM (1400 mL), copper (II) sulfate anhydrous (102.3 g, 641.75 mmol) was added followed by (S)-2-methylpropane-2-sulfinamide (37.3 g, 308.0 mmol) at room temperature. The resulting suspension was stirred at room temperature for 16 h. The reaction mixture was filtered and washed with DCM (100 mL). The eluent was evaporated under reduced pressure. The resultant crude compound was recrystallized from diethyl ether (300 mL) to provide compound **5C**. MS (*m/z*) 368.86 $[M+H]^+$

Synthesis of (S)-N-((S)-1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (**5D**):

[0868] To a stirred solution of compound **5C** (20.0 g, 54.33 mmol) in dry THF (300 mL), at -78 °C a solution of 3,5-difluorobenzylmagnesium bromide (260.8 mL, 0.2M in ether, 65.20 mmol) was added drop-wise in 1 h at -78 °C. After addition was completed, the resulting reaction mixture was stirred at -78 °C for 1h. The reaction mixture was quenched with aqueous NH_4Cl (200 mL) at same temperature. Organic layer was separated and aqueous layer was extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with water (2 x 200 mL) and brine, dried over Na_2SO_4. The solvent was distilled off under reduced pressure and the resultant crude compound was purified by column chromatography on silica-gel using 0-18% EA in hexane as an eluent to provide compound **5D**. MS (*m/z*) 496.99 $[M+H]^+$

Synthesis of (S)-1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethanamine hydrochloride(**5E**):

[0869] To a solution of compound **5D** (53 g, 107 mmol) in methanol (100 mL) was slowly added 4 N HCl in dioxane (30 mL) at room temperature. Upon completion of the reaction, the volatiles were removed in vacuo. The resulting solid was suspended in ether (200 mL) and collected by filtration to provide compound **5E**. MS (*m/z*) 393.17 $[M+H]^+$

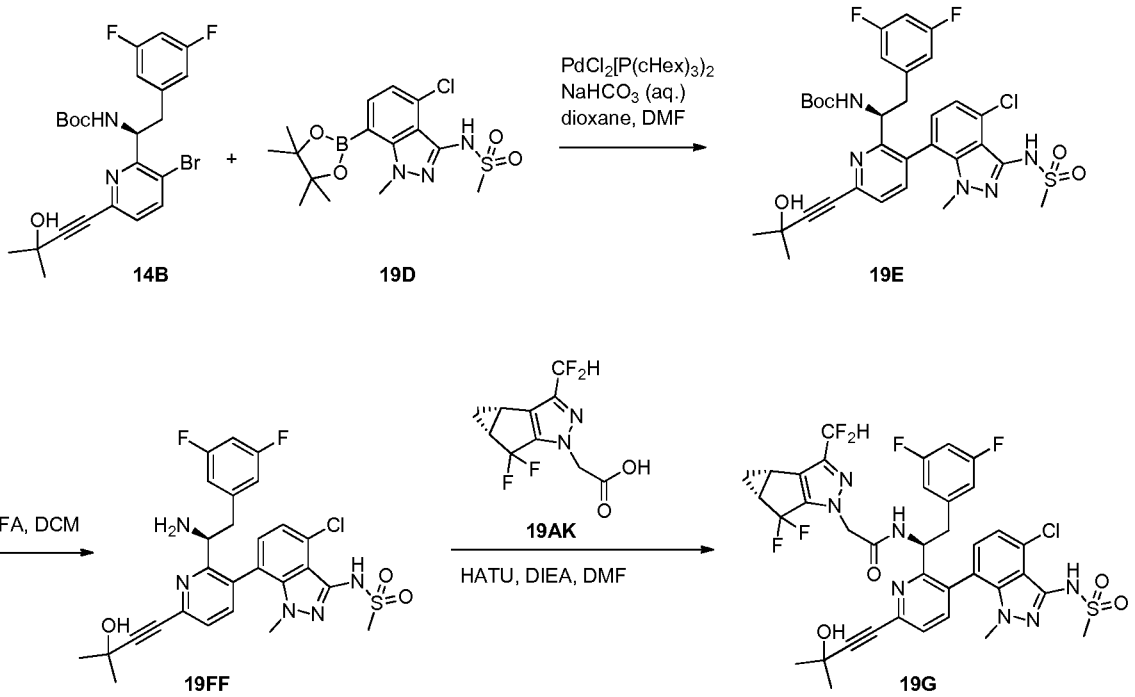
Synthesis of (S)-tert-butyl 1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (**14A**):

[0870] To a suspension of compound **5E** (5 g, 11.7 mmol) in DCM (50 mL) was added di-tert-butyl dicarbonate (3.1 g, 14 mmol) and triethylamine (2.4 g, 23 mmol) at room temperature.

Upon completion of the reaction, the volatiles were removed in vacuo. The resulting residue was dissolved in EtOAc and washed with saturated aqueous ammonium chloride and brine. The organic layer was dried over sodium sulfate. The solvent was distilled off under reduced pressure and the resultant crude compound was purified by column chromatography on silica-gel using ethyl acetate in hexane as an eluent to provide compound **14A**. MS (*m/z*) 492.96 $[M+H]^+$

Synthesis of (S)-tert-butyl (1-(3-bromo-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**14B**):

[0871] A solution of compound **14A** (570 mg, 1.16 mmol), 3-methyl butynol (179 µL, 1.74 mmol), CuI (6 mg, 0.03 mmol), $Pd(PPh_3)_2Cl_2$ (20 mg, 0.03 mmol) and triethylamine (0.5 mL) in THF (2 mL) was degassed with argon for 15 min. The resulting solution was then heated at 35 ^oC for 2 h. Upon completion of the reaction, the mixture was filtered through a pad of celite and washed with ethyl acetate. The combined organic layers were washed with aqueous NH_4Cl, water and brine, dried over Na_2SO_4. The solvent was distilled off under reduced pressure and the resultant crude compound was purified by column chromatography on silica-gel using ethyl acetate in hexane as an eluent to provide compound **14B**. MS (*m/z*) 496.90 $[M+H]^+$



Synthesis of (S)-tert-butyl 1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-ynyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (**19E**):

[0872] To a flask of **14B** (4000 mg, 8.075 mmol) in dioxane (150 mL) and DMF (75 ml) was added N-(4-chloro-1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-

yl)methanesulfonamide (3114 mg, 8.075 mmol), 1N sodium bicarbonate (20.2 ml, 20.2 mmol), and dichlorobis(tricyclohexylphosphine)palladium(II) (715.3 mg, 0.97 mmol). The reaction mixture was degased by N_2 for 30 minutes and then moved to oil bath at 150 °C for 45 minutes. The reaction was cooled to room temperature and filtered. The filtrate was concentrated and dissolved in EtOAc (300 mL) and washed with brine twice. The organic layer was dried over sodium sulfate, concentrated and purified by column chromatography on silica-gel using 50-90% EtOAc in hexane as an eluent to provide **19E**. MS (*m/z*) 674.7 $[M+H]^+$.

Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-ynyl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide TFA salt (**19FF**):

[0873] To a flask of **19E** (1g, 1.48 mmol), 10 mL of 40% of TFA in dichloromethane was added to the flask. The mixture was neutralized by $NaHCO_3$ (aq) and extracted with EtOAc (200 mL twice). The organic layer was concentrated and dried to provide 0.85 g of the desired product **19FF** that was used without further purification. MS (*m/z*) 574.4 $[M+H]^+$.

Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-ynyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**19G**):

[0874] To a flask of **19FF** (850 mg, 1.48 mmol) and DIEA (0.5 mL, 2.96 mmol) in 20 mL DMF, **19AK** (350 mg, 1.33 mmol) and HATU (507 mg, 1.33 mmol) in 10 mL of DMF was added to the mixture slowly at 0 °C. The mixture was diluted with EtOAc (300 mL) and washed with $NaHCO_3$. The organic layer was concentrated and purify by column chromatography on silica-gel using 50-80% EtOAc in hexane as an eluent to provide **19G**. MS (m/z) 820.8 $[M+H]^+$.

Example 202

[0875] The following illustrate representative pharmaceutical dosage forms, containing a compound of formula I ('Compound X'), for therapeutic or prophylactic use in humans.

(i) Tablet 1	mg/tablet
Compound X=	100.0
Lactose	77.5
Povidone	15.0
Croscarmellose sodium	12.0
Microcrystalline cellulose	92.5
Magnesium stearate	3.0
	300.0

(ii) Tablet 2	mg/tablet
Compound X=	20.0
Microcrystalline cellulose	410.0
Starch	50.0
Sodium starch glycolate	15.0
Magnesium stearate	5.0
	500.0

(iii) Capsule	mg/capsule
Compound X=	10.0
Colloidal silicon dioxide	1.5
Lactose	465.5
Pregelatinized starch	120.0
Magnesium stearate	3.0
	600.0

(iv) Injection 1 (1 mg/ml)	mg/ml
Compound X= (free acid form)	1.0
Dibasic sodium phosphate	12.0
Monobasic sodium phosphate	0.7
Sodium chloride	4.5
1.0 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

(v) Injection 2 (10 mg/ml)	mg/ml
Compound X= (free acid form)	10.0
Monobasic sodium phosphate	0.3
Dibasic sodium phosphate	1.1
Polyethylene glycol 400	200.0
1.0 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

(vi) Aerosol	mg/can
Compound X=	20.0
Oleic acid	10.0
Trichloromonofluoromethane	5,000.0
Dichlorodifluoromethane	10,000.0
Dichlorotetrafluoroethane	5,000.0

[0876] The above formulations may be obtained by conventional procedures well known in the pharmaceutical art.

[0877] All references, including publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques.

However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

[0878] The use of the terms "a" and "an" and "the" and similar references in the context of this disclosure (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., such as, preferred, preferably) provided herein, is intended merely to further illustrate the content of the disclosure and does not pose a limitation on the scope of the claims. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the present disclosure.

[0879] Alternative embodiments of the claimed disclosure are described herein, including the best mode known to the inventors for practicing the claimed invention. Of these, variations of the disclosed embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing disclosure. The inventors expect skilled artisans to employ such variations as appropriate (e.g., altering or combining features or embodiments), and the inventors intend for the invention to be practiced otherwise than as specifically described herein.

[0880] Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

[0881] The use of individual numerical values is stated as approximations as though the values were preceded by the word "about" or "approximately." Similarly, the numerical values in the various ranges specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about" or "approximately." In this manner, variations above and below the stated ranges can be used to achieve substantially the same results as values within the ranges. As used herein, the terms "about" and "approximately" when referring to a numerical value shall have their plain and ordinary meanings to a person of ordinary skill in the art to which the disclosed subject matter is most closely related or the art relevant to the range or element at issue. The amount of broadening from the strict numerical boundary depends upon many factors. For example, some of the factors which may be considered include the criticality

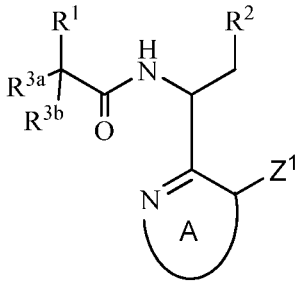
of the element and/or the effect a given amount of variation will have on the performance of the claimed subject matter, as well as other considerations known to those of skill in the art. As used herein, the use of differing amounts of significant digits for different numerical values is not meant to limit how the use of the words "about" or "approximately" will serve to broaden a particular numerical value or range. Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values plus the broadening of the range afforded by the use of the term "about" or "approximately." Thus, recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. In one aspect, about a value includes and intends that value *per se*. For example, about x includes and intends x *per se*.

[0882] It is to be understood that any ranges, ratios and ranges of ratios that can be formed by, or derived from, any of the data disclosed herein represent further embodiments of the present disclosure and are included as part of the disclosure as though they were explicitly set forth. This includes ranges that can be formed that do or do not include a finite upper and/or lower boundary. Accordingly, a person of ordinary skill in the art most closely related to a particular range, ratio or range of ratios will appreciate that such values are unambiguously derivable from the data presented herein.

Embodiments

[0883] Provided below are certain embodiments.

Embodiment I-1. A compound of formula I:



I

wherein:

A is a 6-membered monocyclic-heteroaryl with one or two nitrogen atoms, wherein the 6-membered monocyclic-heteroaryl is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with one or more (e.g., 1 or 2) Z^3 groups;

R^1 is 6-12 membered aryl, 5-12 membered heteroaryl or 3-12 membered heterocycle, wherein any 6-12 membered aryl, 5-12 membered heteroaryl or 3-12 membered heterocycle of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups;

R^2 is phenyl, 5-membered monocyclic-heteroaryl, 6-membered monocyclic-heteroaryl or $(C_3$-$C_7)$carbocycle, wherein any phenyl, 5-membered monocyclic-heteroaryl, 6-membered monocyclic-heteroaryl or $(C_3$-$C_7)$carbocycle of R^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^5 groups;

each R^{3a} and R^{3b} is independently selected from H, halogen, $(C_1$-$C_3)$alkyl and $(C_1$-$C_3)$haloalkyl, or R^{3a} is selected from H, $(C_1$-$C_3)$alkyl and $(C_1$-$C_3)$haloalkyl and R^{3b} is selected from -OH and -CN;

Z^1 is selected from 6-12 membered aryl, 5-14 membered heteroaryl and 3-14 membered heterocycle, wherein any 6-12 membered aryl, 5-14 membered heteroaryl and 3-14 membered heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b};

each Z^{1a} is independently selected from $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, $-OR^{n1}$, $-OC(O)R^{p1}$, $-OC(O)NR^{q1}R^{r1}$, $-SR^{n1}$, $-S(O)R^{p1}$, $-S(O)_2OH$, $-S(O)_2R^{p1}$, $-S(O)_2NR^{q1}R^{r1}$, $-NR^{q1}R^{r1}$, $-NR^{n1}COR^{p1}$, $-NR^{n1}CO_2R^{p1}$, $-NR^{n1}CONR^{q1}R^{r1}$, $-NR^{n1}S(O)_2R^{p1}$, $-NR^{n1}S(O)_2OR^{p1}$, $-NR^{n1}S(O)_2NR^{q1}R^{r1}$, NO_2, $-C(O)R^{n1}$, $-C(O)OR^{n1}$, $-C(O)NR^{q1}R^{r1}$ and $-S(O)_2NR^{n1}COR^{p1}$, wherein any $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{1a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups;

each Z^{1b} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl, wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of Z^{1b} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

each Z^{1c} is independently selected from $(C_3$-$C_7)$carbocycle, phenyl, 5-6 membered monocyclic-heteroaryl, 3-7 membered heterocycle, halogen, -CN, $-OR^{n2}$, $-OC(O)R^{p2}$, $-OC(O)NR^{q2}R^{r2}$, $-SR^{n2}$, $-S(O)R^{p2}$, $-S(O)_2OH$, $-S(O)_2R^{p2}$, $-S(O)_2NR^{q2}R^{r2}$, $-NR^{q2}R^{r2}$, $-NR^{n2}COR^{p2}$, $-NR^{n2}CO_2R^{p2}$, $-NR^{n2}CONR^{q2}R^{r2}$, $-NR^{n2}S(O)_2R^{p2}$, $-NR^{n2}S(O)_2OR^{p2}$, $-NR^{n2}S(O_2NR^{q2}R^{r2}$, NO_2, $-C(O)R^{n2}$, $-C(O)OR^{n2}$, $-C(O)NR^{q2}R^{r2}$, halophenyl, 5-6 membered haloheteroaryl, 3-7 membered haloheterocycle and $(C_1$-$C_8)$heteroalkyl;

each Z^{1d} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl and $(C_1$-$C_8)$haloalkyl;

each R^{n1} is independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R^{n1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of R^{n1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

each R^{p1} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R^{p1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of R^{p1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

R^{q1} and R^{r1} are each independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R^{q1} or R^{r1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of R^{q1} or R^{r1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups, or R^{q1} and R^{r1} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or 7-membered heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups;

each R^{n2} is independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, $(C_1$-$C_8)$haloalkyl and $(C_1$-$C_8)$heteroalkyl;

each R^{p2} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, $(C_1$-$C_8)$haloalkyl and $(C_1$-$C_8)$heteroalkyl;

R^{q2} and R^{r2} are each independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered

haloheterocycle, $(C_1$-$C_8)$haloalkyl and $(C_1$-$C_8)$heteroalkyl, or R^{q2} and R^{r2} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

Z^2 is selected from $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, $-C(O)R^{n3}$ and $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl and 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with one or more (e.g.,1, 2, 3, 4, or 5) Z^{2c} groups;

each Z^{2a} is independently selected from $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, $-CN$, $-OR^{n4}$, $-OC(O)R^{p4}$, $-OC(O)NR^{q4}R^{r4}$, $-SR^{n4}$, $-S(O)R^{p4}$, $-S(O)_2OH$, $-S(O)_2R^{p4}$, $-S(O)_2NR^{q4}R^{r4}$, $-NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}CONR^{q4}R^{r4}$, $-NR^{n4}S(O)_2R^{p4}$, $-NR^{n4}S(O)_2OR^{p4}$, $-NR^{n4}S(O)_2NR^{q4}R^{r4}$, NO_2, $-C(O)R^{n4}$, $-C(O)OR^{n4}$ and $-C(O)NR^{q4}R^{r4}$, wherein any $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{2a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups;

each Z^{2b} is independently selected from $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$heteroalkyl and $(C_1$-$C_4)$haloalkyl;

each Z^{2c} is independently selected from halogen, $-CN$, $-OR^{n4}$, $-OC(O)R^{p4}$, $-OC(O)NR^{q4}R^{r4}$, $-SR^{n4}$, $-S(O)R^{p4}$, $-S(O)_2OH$, $-S(O)_2R^{p4}$, $-S(O)_2NR^{q4}R^{r4}$, $-NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}CONR^{q4}R^{r4}$, $-NR^{n4}S(O)_2R^{p4}$, $-NR^{n4}S(O)_2OR^{p4}$, $-NR^{n4}S(O)_2NR^{q4}R^{r4}$, NO_2, $-C(O)R^{n4}$, $-C(O)OR^{n4}$ and $-C(O)NR^{q4}R^{r4}$;

each R^{n3} is independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl, wherein any $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl of R^{n3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl and $(C_2$-$C_4)$alkynyl of R^{n3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups;

R^{q3} and R^{r3} are each independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl, wherein any $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl of R^{q3} or R^{r3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_1$-$C_4)$alkyl and $(C_2$-$C_4)$alkenyl of R^{q3} or R^{r3} is

optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups, or R^{q3} and R^{r3} together with the nitrogen to which they are attached form a heterocycle or heteroaryl, wherein the heterocycle or heteroaryl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups;

each R^{n4} is independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_4)$haloalkyl and $(C_1$-$C_4)$heteroalkyl;

each R^{p4} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_2$-$C_4)$alkynyl, $(C_1$-$C_4)$haloalkyl and $(C_1$-$C_4)$heteroalkyl;

R^{q4} and R^{r4} are each independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_2$-$C_4)$alkynyl, $(C_1$-$C_4)$haloalkyl and $(C_1$-$C_4)$heteroalkyl;

each Z^3 is independently selected from halogen, $(C_1$-$C_4)$alkyl, -OH, -CN, $(C_1$-$C_4)$heteroalkyl and $(C_1$-$C_4)$haloalkyl;

each Z^4 is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, halogen, -CN, $-OR^{n5}$, $-OC(O)R^{p5}$, $-OC(O)NR^{q5}R^{r5}$, $-SR^{n5}$, $-S(O)R^{p5}$, $-S(O)_2OH$, $-S(O)_2R^{p5}$, $-S(O)_2NR^{q5}R^{r5}$, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-NR^{n5}CONR^{q5}R^{r5}$, $-NR^{n5}S(O)_2R^{p5}$, $-NR^{n5}S(O)_2OR^{p5}$, $-NR^{n5}S(O)_2NR^{q5}R^{r5}$, NO_2, $-C(O)R^{n5}$, $-C(O)OR^{n5}$ and $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3$-$C_7)$carbocycle, of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} or Z^{4b} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} groups;

each Z^{4a} is independently selected from halogen, $-OR^{n6}$, $-OC(O)R^{p6}$, $-OC(O)NR^{q6}R^{r6}$, $-SR^{n6}$, $-S(O)R^{p6}$, $-S(O)_2OH$, $-S(O)_2R^{p6}$, $-S(O)_2NR^{q6}R^{r6}$, $-NR^{q6}R^{r6}$, $-NR^{n6}COR^{p6}$, $-NR^{n6}CO_2R^{p6}$, $-NR^{n6}CONR^{q6}R^{r6}$, $-NR^{n6}S(O)_2R^{p6}$, $-NR^{n6}S(O)_2OR^{p6}$, $-NR^{n6}S(O)_2NR^{q6}R^{r6}$, NO_2, $-C(O)R^{n6}$, $-C(O)OR^{n6}$ and $-C(O)NR^{q6}R^{r6}$;

each Z^{4b} is independently selected from $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl $(C_2$-$C_4)$alkynyl and $(C_1$-$C_4)$haloalkyl;

each R^{n5} is independently selected from H, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, $(C_1$-$C_4)$heteroalkyl, $(C_2$-$C_4)$alkenyl and $(C_2$-$C_4)$alkynyl;

each R^{p5} is independently selected from $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, $(C_1$-$C_4)$heteroalkyl, $(C_2$-$C_4)$alkenyl and $(C_2$-$C_4)$alkynyl;

R^{q5} and R^{r5} are each independently selected from H, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, $(C_1$-$C_4)$heteroalkyl, $(C_2$-$C_4)$alkenyl and $(C_2$-$C_4)$alkynyl;

each R^{n6} is independently selected from H, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, $(C_1$-$C_4)$heteroalkyl, $(C_2$-$C_4)$alkenyl and $(C_2$-$C_4)$alkynyl;

each R^{p6} is independently selected from $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, $(C_1$-$C_4)$heteroalkyl, $(C_2$-$C_4)$alkenyl and $(C_2$-$C_4)$alkynyl;

R^{q6} and R^{r6} are each independently selected from H, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, $(C_1$-$C_4)$heteroalkyl, $(C_2$-$C_4)$alkenyl and $(C_2$-$C_4)$alkynyl;

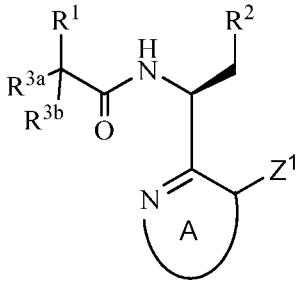
each Z^5 is independently selected from $(C_1$-$C_6)$alkyl, halogen, -CN and $-OR^{n7}$,

wherein any $(C_1$-$C_6)$alkyl of Z^5 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen; and

each R^{n7} is independently selected from H, $(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$haloalkyl and $(C_3$-$C_7)$carbocycle;

or a pharmaceutically acceptable salt thereof.

Embodiment I-2. The compound of Embodiment I-1 which is a compound of formula Ia:



Ia

or a pharmaceutically acceptable salt thereof.

Embodiment I-3. The compound of Embodiment I-1 or Embodiment I-I-2 wherein R^{3a} and R^{3b} are each H.

Embodiment I-4. The compound of any one of Embodiments I-1 to I-3 wherein R^2 is phenyl or a 5-membered monocyclic-heteroaryl, wherein any phenyl or 5-membered monocyclic-heteroaryl of R^2 is optionally substituted with one or more Z^5 groups.

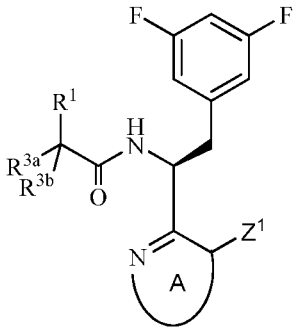
Embodiment I-5. The compound of any one of Embodiments I-1 to I-3 wherein R^2 is phenyl optionally substituted with one or more Z^5 groups.

Embodiment I-6. The compound of any one of Embodiments I-1 to I-5 wherein each Z^5 is halogen.

Embodiment I-7. The compound of any one of Embodiments I-1 to I-5 wherein each Z^5 is fluoro.

Embodiment I-8. The compound of Embodiment I-1 or Embodiment I-2 wherein R^2 is 3,5-difluorophenyl.

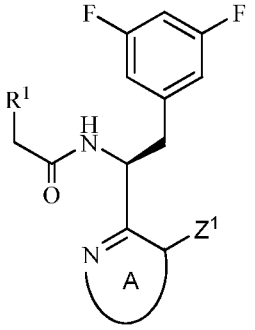
Embodiment I-9. The compound of Embodiment I-1 which is a compound of formula Ig:



Ig

or a pharmaceutically acceptable salt thereof.

Embodiment I-10. The compound of Embodiment I-1 which is a compound of formula Ie:



Ie

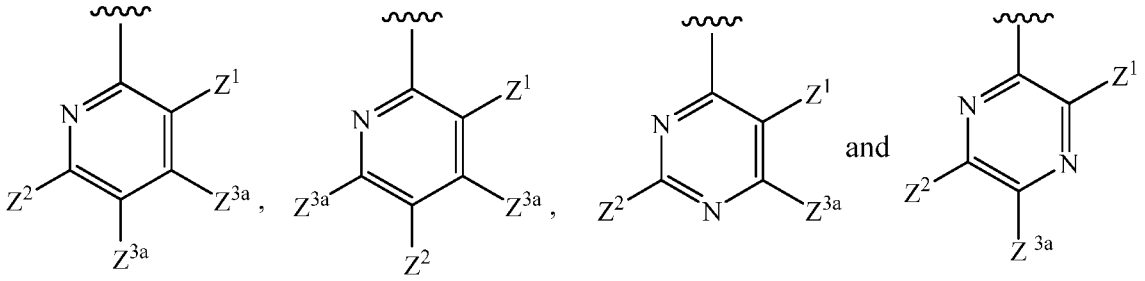
or a pharmaceutically acceptable salt thereof.

Embodiment I-11. The compound of any one of Embodiments I-1 to I-10 wherein A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein any pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl of A is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with one or more Z^3 groups.

Embodiment I-12. The compound of any one of Embodiments I-1 to I-10 wherein A is pyridinyl, wherein any pyridinyl of A is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with one or more Z^3 groups.

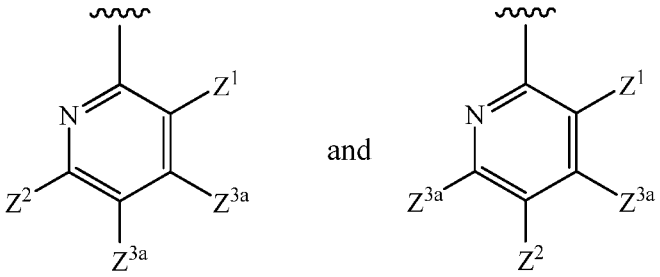
Embodiment I-13. The compound of any one of Embodiments I-1 to I-12 wherein A is substituted with one Z^1 group at the position shown and one Z^2 group.

Embodiment I-14. The compound of any one of Embodiments I-1 to I-10 wherein A-Z^1 is selected from:



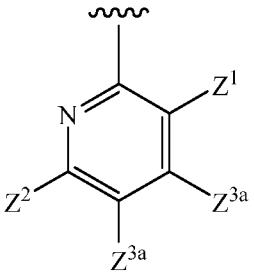
wherein each Z^{3a} is independently selected from H and Z^3.

Embodiment I-15. The compound of any one of Embodiments I-1 to I-10 wherein A-Z^1 is selected from:



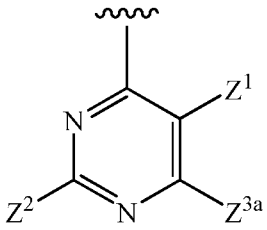
wherein each Z^{3a} is independently selected from H and Z^3.

Embodiment I-16. The compound of any one of Embodiments I-1 to I-10 wherein A-Z^1 is:



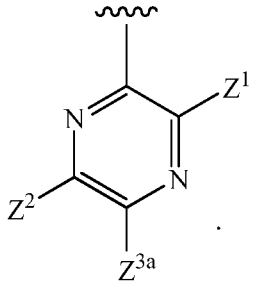
wherein each Z^{3a} is independently selected from H and Z^3.

Embodiment I-17. The compound of any one of Embodiments I-1 to I-10 wherein A-Z^1 is:



wherein Z^{3a} is selected from H and Z^3.

Embodiment I-18. The compound of any one of Embodiments I-1 to I-10 wherein A-Z^1 is:



wherein Z^{3a} is selected from H and Z^3.

Embodiment I-19. The compound of any one of Embodiments I-14 to I-18 wherein each Z^{3a} is H.

Embodiment I-20. The compound of any one of Embodiments I-1 to I-19 wherein Z^1 is selected from phenyl, 5-14 membered heteroaryl and 3-14 membered heterocycle, wherein any phenyl, 5-14 membered heteroaryl and 3-14 membered heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups.

Embodiment I-21. The compound of any one of Embodiments I-1 to I-19 wherein Z^1 is selected from phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups.

Embodiment I-22. The compound of any one of Embodiments I-1 to I-19 wherein Z^1 is selected from phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle, wherein the 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-

heterocycle and 9-12 membered tricyclic-heterocycle have 1-11 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups.

Embodiment I-23. The compound of any one of Embodiments I-1 to I-19 wherein Z^1 is selected from 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle,wherein any from 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups.

Embodiment I-24. The compound of any one of Embodiments I-1 to I-19 wherein Z^1 is selected from 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle, wherein the 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle have 3-9 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups.

Embodiment I-25. The compound of any one of Embodiments I-1 to I-19 wherein Z^1 is selected from phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 4-oxo-3,4-dihydroquinazolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, 1H-2-oxo-pyridinyl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolinyl, wherein any phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 4-oxo-3,4-dihydroquinazolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, 1H-2-oxo-pyridinyl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolinyl of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups.

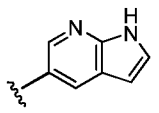
Embodiment I-26. The compound of any one of Embodiments I-1 to I-19 wherein Z^1 is selected from phenyl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1-oxoisoindolin-5-yl, 1-oxoisoindolin-4-yl, 4-oxo-3,4-dihydroquinazolin-8-yl, 3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl, 1H-2-oxo-pyridin-4-yl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolin-8-yl, wherein any phenyl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1-oxoisoindolin-5-yl, 1-oxoisoindolin-4-yl, 4-oxo-3,4-dihydroquinazolin-8-yl, 3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl, 1H-2-oxo-pyridin-4-yl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolin-8-yl of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups.

Embodiment I-27. The compound of any one of Embodiments I-1 to I-26 wherein each Z^{1a} is independently selected from halogen, $-OR^{n1}$, $NR^{q1}R^{r1}$, and $-C(O)NR^{q1}R^{r1}$.

Embodiment I-28. The compound of any one of Embodiments I-1 to I-26 wherein each Z^{1a} is independently selected from halogen and $-C(O)NR^{q1}R^{r1}$.

Embodiment I-29. The compound of any one of Embodiments I-1 to I-26 wherein R^{n1}, R^{q1} and R^{r1} are each H.

Embodiment I-30. The compound of any one of Embodiments I-1 to I-19 wherein Z^1 is selected from: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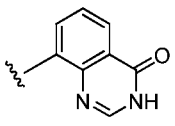
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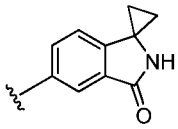
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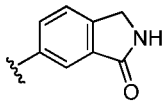
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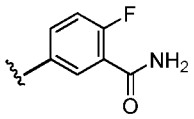
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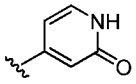
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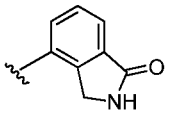
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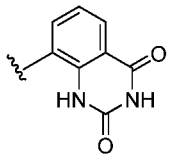
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Embodiment I-31. The compound of any one of Embodiments I-1 to I-30 wherein Z^2 is selected from $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle and $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl and 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with one or more Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with one or more Z^{2c} groups.

Embodiment I-32. The compound of any one of Embodiments I-1 to I-30 wherein Z^2 is selected from $(C_2$-$C_8)$alkynyl, phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heterocycle and $-C(O)NR^{q3}R^{r3}$, wherein any phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl and 8-10 membered C-linked-bicyclic-heterocycle of Z^2 is optionally substituted with one or more Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with one or more Z^{2c} groups.

Embodiment I-33. The compound of any one of Embodiments I-1 to I-30 wherein Z^2 is selected from $(C_2$-$C_8)$alkynyl, phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heterocycle and $-C(O)NR^{q3}R^{r3}$, wherein the 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl and 8-10 membered C-linked-bicyclic-heterocycle have 1-9 carbon atoms and 1-4 heteroatoms in the ring system, and wherein any phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered and C-linked-bicyclic-heterocycle of Z^2 is optionally substituted with one or more Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with one or more Z^{2c} groups.

Embodiment I-34. The compound of any one of Embodiments I-1 to I-30 wherein Z^2 is selected from 4-methylpentynyl, phenyl, pyridinyl, 1H-2-oxo-pyridinyl, triazolyl, 1-oxoisoindolinyl, 1H-pyrrolo[2,3-b]pyridinyl and $-C(O)NR^{q3}R^{r3}$, wherein any phenyl, pyridinyl, 2-oxopyridinyl, triazolyl, 1-oxoisoindolinyl and 1H-pyrrolo[2,3-b]pyridinyl of Z^2 is optionally substituted with one or more Z^{2b} or Z^{2c} groups, and wherein any 4-methylpentynyl of Z^2 is optionally substituted with one or more Z^{2c} groups.

Embodiment I-35. The compound of any one of Embodiments I-1 to I-30 wherein Z^2 is selected from 4-methylpentyn-1-yl, phenyl, pyridin-4-yl, 1H-2-oxo-pyridin-2-yl, triazol-4-yl, 1-oxoisoindolin-6-yl, 1H-pyrrolo[2,3-b]pyridine-5-yl and $-C(O)NR^{q3}R^{r3}$, wherein any phenyl, pyridin-4-yl, 2-hydroxypyridin-2-yl, triazol-4-yl, 1-oxoisoindolin-6-yl and 1H-pyrrolo[2,3-b]pyridine-5-yl of Z^2 is optionally substituted with one or more Z^{2b} or Z^{2c} groups, and wherein any 4-methylpentyn-1-yl of Z^2 is optionally substituted with one or more Z^{2c} groups.

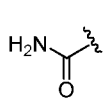
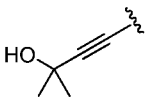
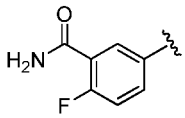
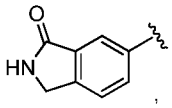
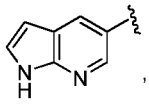
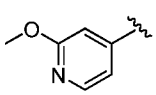
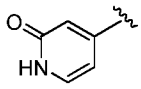
Embodiment I-36. The compound of any one of Embodiments I-1 to I-35 wherein Z^2 is optionally substituted with one or more Z^{2c} groups.

Embodiment I-37. The compound of any one of Embodiments I-1 to I-36 wherein R^{q3} and R^{r3} are each H.

Embodiment I-38. The compound of any one of Embodiments I-1 to I-37 wherein each Z^{2c} is independently selected from halogen, $-OR^{n4}$ and $-C(O)NR^{q4}R^{r4}$.

Embodiment I-39. The compound of any one of Embodiments I-1 to I-38 wherein R^{n4} is H or methyl, and R^{q4} and R^{r4} are each H.

Embodiment I-40. The compound of any one of Embodiments I-1 to I-30 wherein Z^2 is selected from: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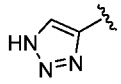
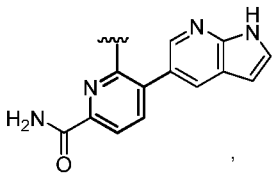
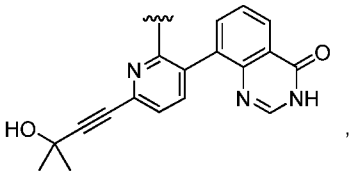
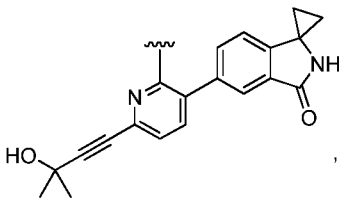
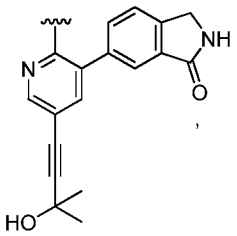
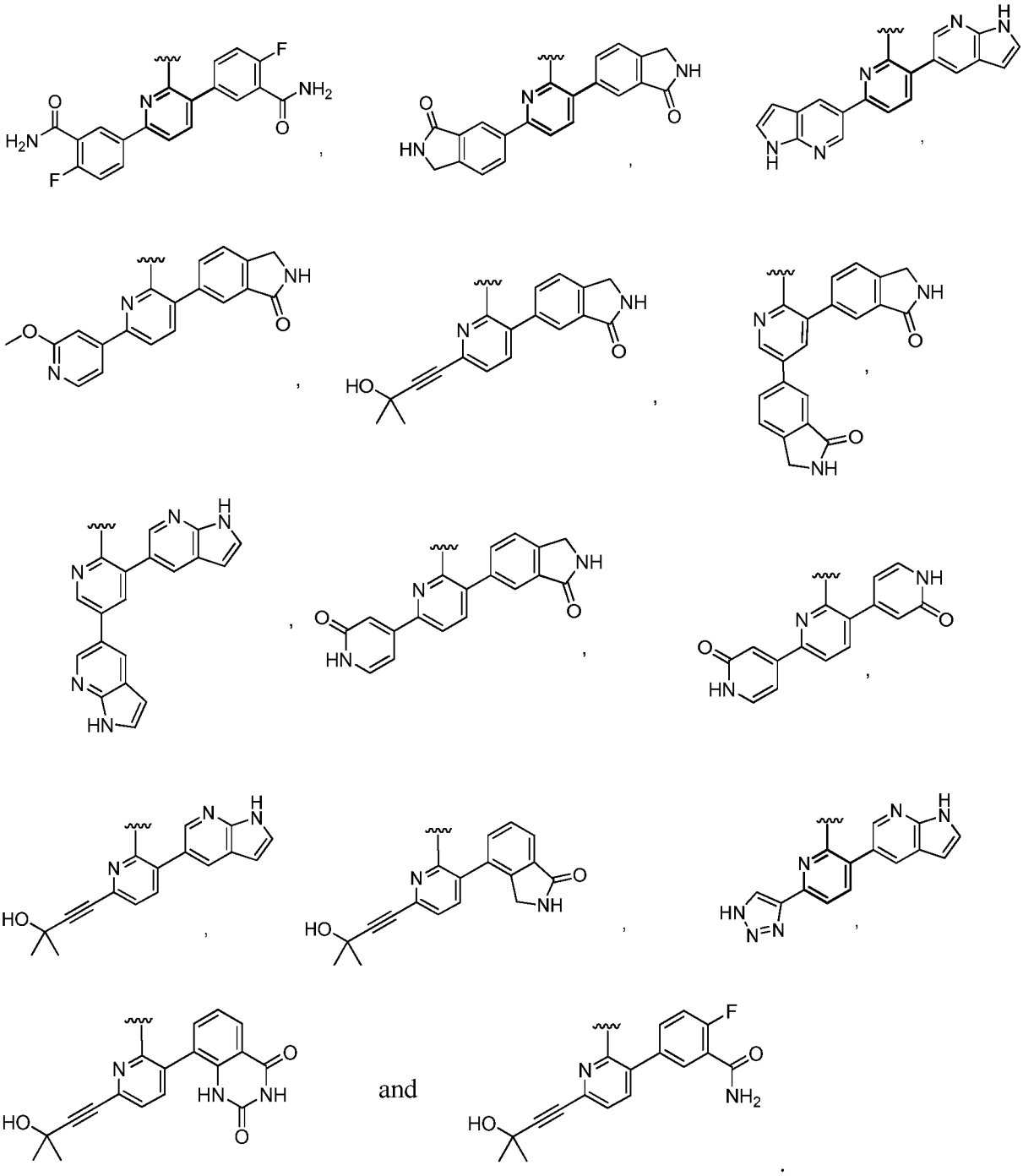


Embodiment I-41. The compound of any one of Embodiments I-1 to I-10 wherein A-Z^1 is selected from:



and

Embodiment I-42. The compound of any one of Embodiments I-1 to I-41 wherein R^1 is a 5-12 membered heteroaryl, wherein any 5-12 membered heteroaryl of R^1 is optionally substituted with one or more Z^4 groups.

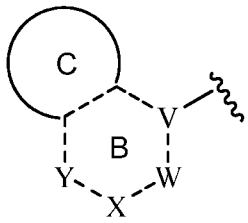
Embodiment I-43. The compound of any one of Embodiments I-1 to I-41 wherein R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein any 8-12

membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with one or more Z^4 groups.

Embodiment I-44. The compound of any one of Embodiments I-1 to I-41 wherein R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein the 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl have 4-10 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with one or more Z^4 groups.

Embodiment I-45. The compound of any one of Embodiments I-1 to I-41 wherein R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein the 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl contains at least one partially unsaturated ring, and wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

Embodiment I-46. The compound of any one of Embodiments I-1 to I-41 wherein R^1 has the following formula IIb:



IIb

wherein:

C together with the two carbon atoms of ring B to which it is attached forms a 3-7 membered monocyclic-carbocycle, 5-8 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-8 membered bicyclic heterocycle, wherein any 3-7 membered monocyclic-carbocycle, 5-8 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-8 membered bicyclic heterocycle of C is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^4 groups; and

B is a 5 or 6 membered monocyclic-heteroaryl having 1, 2 or 3 nitrogen atoms;

V is C or N;

W is CZ^{4c}, NZ^{4c} or N;

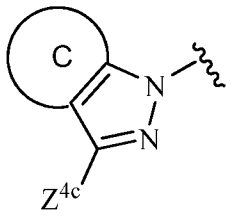
X is CZ^{4c}, NZ^{4c} or N;

Y is CZ^{4c}, N or absent;

the dashed bonds are selected from single bonds and double bonds, wherein the dashed bonds, V, W, X and Y are selected so that the 5 or 6 membered monocyclic-heteroaryl B is aromatic; and

each Z^{4c} is independently selected from H or Z^4.

Embodiment I-47. The compound of any one of Embodiments I-1 to I-41 wherein R^1 has the following formula IId:



IId

wherein:

C together with the two carbon atoms to which it is attached forms a 3-7 membered monocyclic-carbocycle, 5-9 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-9 membered bicyclic heterocycle, wherein any 3-7 membered monocyclic-carbocycle, 5-9 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-9 membered bicyclic heterocycle of C is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^4 groups; and

each Z^{4c} is independently selected from H or Z^4.

Embodiment I-48. The compound of any one of Embodiments I-1 to I-41 wherein R^1 is selected from 3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazolyl and 4,5,6,7-tetrahydro-indazolyl, wherein any 3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazolyl and 4,5,6,7-tetrahydro-indazolyl of R^1 is optionally substituted with one or more Z^4 groups.

Embodiment I-49. The compound of any one of Embodiments I-1 to I-41 wherein R^1 is selected from 3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl and 4,5,6,7-tetrahydro-indazol-1-yl, wherein any 3b,4,4a,5-tetrahydro-1H-

cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl and 4,5,6,7-tetrahydro-indazol-1-yl of R^1 is optionally substituted with one or more Z^4 groups.

Embodiment I-50. The compound of any one of Embodiments I-1 to I-49 wherein each Z^4 is independently selected from $(C_1$-$C_6)$alkyl and halogen, wherein any $(C_1$-$C_6)$alkyl of Z^4 is optionally substituted with one or more halogen.

Embodiment I-51. The compound of any one of Embodiments I-1 to I-49 wherein each Z^4 is independently selected from fluoro, trifluoromethyl and difluoromethyl.

Embodiment I-52. The compound of any one of Embodiments I-1 to I-41 wherein R^1 is selected from:

and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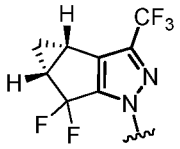
Embodiment I-53. The compound of any one of Embodiments I-1 to I-41 wherein R^1 is selected from:



and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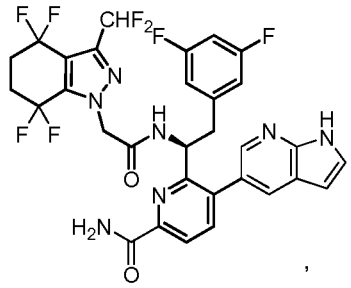
Embodiment I-54. The compound of Embodiment I-1 selected from:



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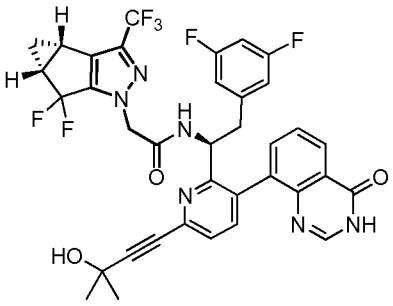

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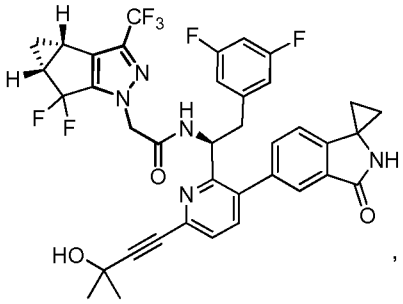

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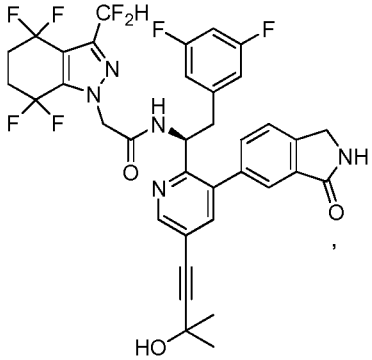

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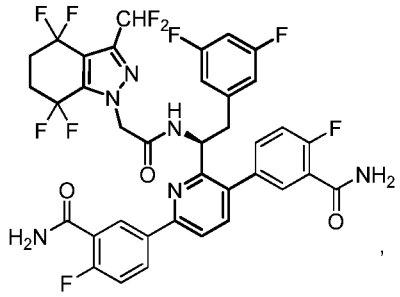

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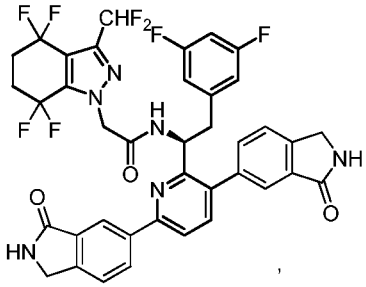

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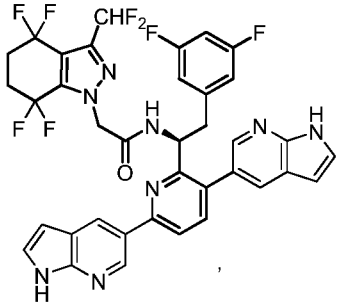

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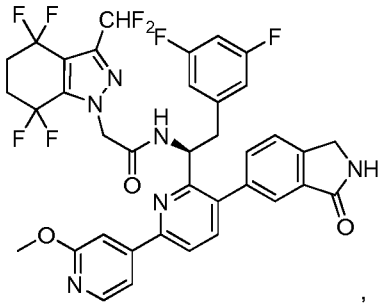
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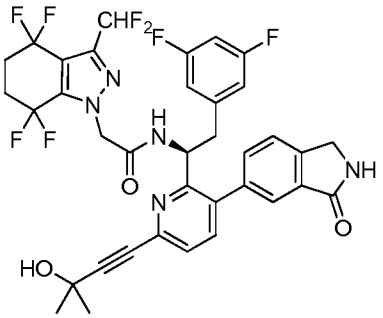
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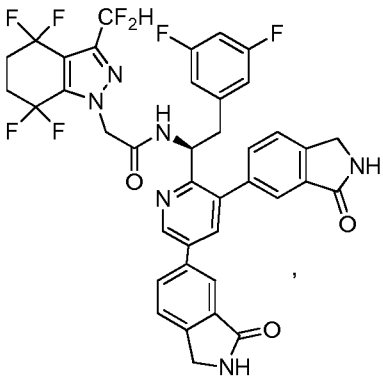
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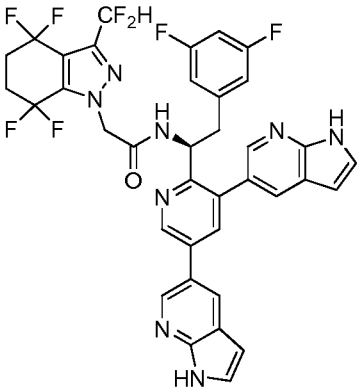
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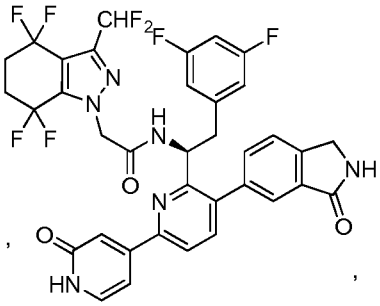
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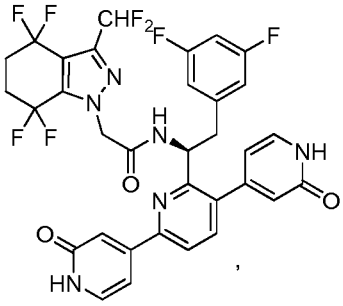
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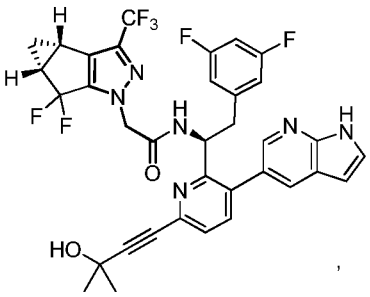
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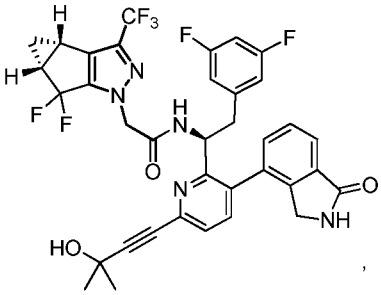
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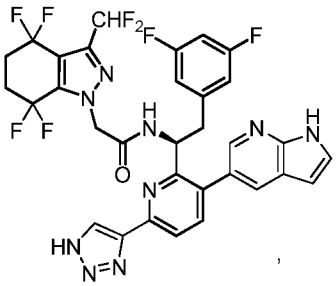
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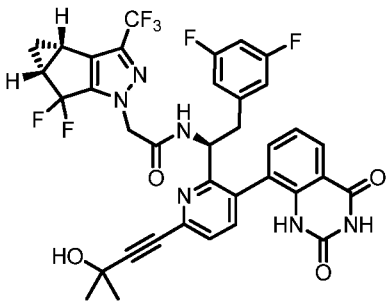
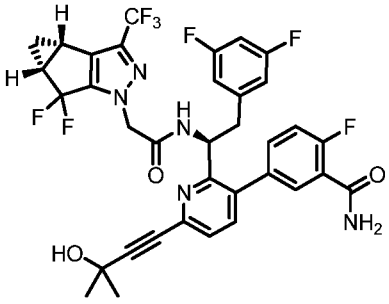

and


and pharmaceutically acceptable salts thereof.

Embodiment I-55. A pharmaceutical composition comprising a compound of formula I as described in any one of Embodiments I-1 to I-54, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Embodiment I-56. A method for treating a *Retroviridae* virus infection in a mammal comprising administering a therapeutically effective amount of a compound of any one of Embodiments I-1 to I-54, or a pharmaceutically acceptable salt thereof, to the mammal.

Embodiment I-57. The method of claim 56 wherein the *Retroviridae* virus infection is an HIV virus infection.

Embodiment I-58. A method for treating an HIV infection in a mammal comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of formula I as described in any one of Embodiments I-1 to I-54, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and other drugs for treating HIV, and combinations thereof.

Embodiment I-59. A compound of formula I as described in any of Embodiments I-1 to I-54, or a pharmaceutically acceptable salt thereof for use in medical therapy.

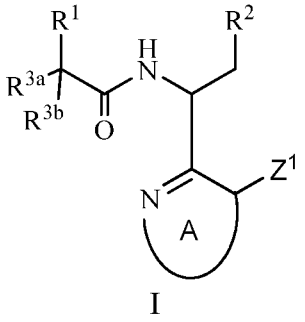
Embodiment I-60. A compound of formula I as described in any one of Embodiments I-1 to I-54 or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of a *Retroviridae* virus infection or an HIV virus infection.

Embodiment I-61. The use of a compound as described in any one of Embodiments I-1 to I-54 or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a *Retroviridae* virus infection or an HIV virus infection in a mammal.

Embodiment I-62. A compound or method as described herein.

[0884] Also provided below are certain embodiments.

Embodiment II-1. A compound of formula I:



I

wherein:

A is a 6-membered monocyclic-heteroaryl with one or two nitrogen atoms, wherein the 6-membered monocyclic-heteroaryl is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with one or more (e.g., 1 or 2) Z^3 groups;

R^1 is 6-12 membered aryl, 5-12 membered heteroaryl or 3-12 membered heterocycle, wherein any 6-12 membered aryl, 5-12 membered heteroaryl or 3-12 membered heterocycle of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups;

R^2 is phenyl, 5-membered monocyclic-heteroaryl, 6-membered monocyclic-heteroaryl or $(C_3$-$C_7)$carbocycle, wherein any phenyl, 5-membered monocyclic-heteroaryl, 6-membered monocyclic-heteroaryl or $(C_3$-$C_7)$carbocycle of R^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^5 groups;

each R^{3a} and R^{3b} is independently selected from H, halogen, $(C_1$-$C_3)$alkyl and $(C_1$-$C_3)$haloalkyl, or R^{3a} is selected from H, $(C_1$-$C_3)$alkyl and $(C_1$-$C_3)$haloalkyl and R^{3b} is selected from -OH and -CN;

Z^1 is selected from 6-12 membered aryl, 5-14 membered heteroaryl and 3-14 membered heterocycle, wherein any 6-12 membered aryl, 5-14 membered heteroaryl and 3-14 membered heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b};

each Z^{1a} is independently selected from $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, $-OR^{n1}$, $-OC(O)R^{p1}$, $-OC(O)NR^{q1}R^{r1}$, $-SR^{n1}$, $-S(O)R^{p1}$, $-S(O)_2OH$, $-S(O)_2R^{p1}$, $-S(O)_2NR^{q1}R^{r1}$, $-NR^{q1}R^{r1}$, $-NR^{n1}COR^{p1}$, $-NR^{n1}CO_2R^{p1}$, $-NR^{n1}CONR^{q1}R^{r1}$, $-NR^{n1}S(O)_2R^{p1}$, $-NR^{n1}S(O)_2OR^{p1}$, $-NR^{n1}S(O)_2NR^{q1}R^{r1}$, NO_2, $-C(O)R^{n1}$, $-C(O)OR^{n1}$, $-C(O)NR^{q1}R^{r1}$ and $-S(O)_2NR^{n1}COR^{p1}$, wherein any $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{1a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups;

each Z^{1b} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl, wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of Z^{1b} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

each Z^{1c} is independently selected from $(C_3$-$C_7)$carbocycle, phenyl, 5-6 membered monocyclic-heteroaryl, 3-7 membered heterocycle, halogen, -CN, $-OR^{n2}$, $-OC(O)R^{p2}$, $-OC(O)NR^{q2}R^{r2}$, $-SR^{n2}$, $-S(O)R^{p2}$, $-S(O)_2OH$, $-S(O)_2R^{p2}$, $-S(O)_2NR^{q2}R^{r2}$, $-NR^{q2}R^{r2}$, $-NR^{n2}COR^{p2}$, $-NR^{n2}CO_2R^{p2}$, $-NR^{n2}CONR^{q2}R^{r2}$, $-NR^{n2}S(O)_2R^{p2}$, $-NR^{n2}S(O)_2OR^{p2}$, $-NR^{n2}S(O_2NR^{q2}R^{r2}$, NO_2, $-C(O)R^{n2}$, $-C(O)OR^{n2}$, $-C(O)NR^{q2}R^{r2}$, halophenyl, 5-6 membered haloheteroaryl, 3-7 membered haloheterocycle and $(C_1$-$C_8)$heteroalkyl;

each Z^{1d} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl and $(C_1$-$C_8)$haloalkyl;

each R^{n1} is independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R^{n1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of R^{n1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

each R^{p1} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R^{p1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of R^{p1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

R^{q1} and R^{r1} are each independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R^{q1} or R^{r1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of R^{q1} or R^{r1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups, or R^{q1} and R^{r1} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or 7-membered heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups;

each R^{n2} is independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, $(C_1$-$C_8)$haloalkyl and $(C_1$-$C_8)$heteroalkyl;

each R^{p2} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, $(C_1$-$C_8)$haloalkyl and $(C_1$-$C_8)$heteroalkyl;

R^{q2} and R^{r2} are each independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, $(C_1$-$C_8)$haloalkyl and $(C_1$-$C_8)$heteroalkyl, or R^{q2} and R^{r2} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

Z^2 is selected from $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, $-C(O)R^{n3}$ and $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl and 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with one or more (e.g.,1, 2, 3, 4, or 5) Z^{2c} groups;

each Z^{2a} is independently selected from $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, $-CN$, $-OR^{n4}$, $-OC(O)R^{p4}$, $-OC(O)NR^{q4}R^{r4}$, $-SR^{n4}$, $-S(O)R^{p4}$, $-S(O)_2OH$, $-S(O)_2R^{p4}$, $-S(O)_2NR^{q4}R^{r4}$, $-NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}CONR^{q4}R^{r4}$, $-NR^{n4}S(O)_2R^{p4}$, $-NR^{n4}S(O)_2OR^{p4}$, $-NR^{n4}S(O)_2NR^{q4}R^{r4}$, NO_2, $-C(O)R^{n4}$, $-C(O)OR^{n4}$ and $-C(O)NR^{q4}R^{r4}$, wherein any $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{2a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups;

each Z^{2b} is independently selected from $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$heteroalkyl and $(C_1$-$C_4)$haloalkyl;

each Z^{2c} is independently selected from halogen, $-CN$, $-OR^{n4}$, $-OC(O)R^{p4}$, $-OC(O)NR^{q4}R^{r4}$, $-SR^{n4}$, $-S(O)R^{p4}$, $-S(O)_2OH$, $-S(O)_2R^{p4}$, $-S(O)_2NR^{q4}R^{r4}$, $-NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}CONR^{q4}R^{r4}$, $-NR^{n4}S(O)_2R^{p4}$, $-NR^{n4}S(O)_2OR^{p4}$, $-NR^{n4}S(O)_2NR^{q4}R^{r4}$, NO_2, $-C(O)R^{n4}$, $-C(O)OR^{n4}$ and $-C(O)NR^{q4}R^{r4}$;

each R^{n3} is independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl, wherein any $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl of R^{n3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl and $(C_2$-$C_4)$alkynyl of R^{n3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups;

R^{q3} and R^{r3} are each independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl, wherein any $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl of R^{q3} or R^{r3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_1$-$C_4)$alkyl and $(C_2$-$C_4)$alkenyl of R^{q3} or R^{r3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups, or R^{q3} and R^{r3} together with the nitrogen to which they are attached form a heterocycle or heteroaryl, wherein the heterocycle or heteroaryl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups;

each R^{n4} is independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_4)$haloalkyl and $(C_1$-$C_4)$heteroalkyl;

each R^{p4} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_2$-$C_4)$alkynyl, $(C_1$-$C_4)$haloalkyl and $(C_1$-$C_4)$heteroalkyl;

R^{q4} and R^{r4} are each independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_2$-$C_4)$alkynyl, $(C_1$-$C_4)$haloalkyl and $(C_1$-$C_4)$heteroalkyl;

each Z^3 is independently selected from halogen, $(C_1$-$C_4)$alkyl, -OH, -CN, $(C_1$-$C_4)$heteroalkyl and $(C_1$-$C_4)$haloalkyl;

each Z^4 is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, halogen, -CN, $-OR^{n5}$, $-OC(O)R^{p5}$, $-OC(O)NR^{q5}R^{r5}$, $-SR^{n5}$, $-S(O)R^{p5}$, $-S(O)_2OH$, $-S(O)_2R^{p5}$, $-S(O)_2NR^{q5}R^{r5}$, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-NR^{n5}CONR^{q5}R^{r5}$, $-NR^{n5}S(O)_2R^{p5}$, $-NR^{n5}S(O)_2OR^{p5}$, $-NR^{n5}S(O)_2NR^{q5}R^{r5}$, NO_2, $-C(O)R^{n5}$, $-C(O)OR^{n5}$ and $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3$-$C_7)$carbocycle, of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} or Z^{4b} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} groups;

each Z^{4a} is independently selected from halogen, -CN, $-OR^{n6}$, $-OC(O)R^{p6}$, $-OC(O)NR^{q6}R^{r6}$, $-SR^{n6}$, $-S(O)R^{p6}$, $-S(O)_2OH$, $-S(O)_2R^{p6}$, $-S(O)_2NR^{q6}R^{r6}$, $-NR^{q6}R^{r6}$, $-NR^{n6}COR^{p6}$,

$-NR^{n6}CO_2R^{p6}$, $-NR^{n6}CONR^{q6}R^{r6}$, $-NR^{n6}S(O)_2R^{p6}$, $-NR^{n6}S(O)_2OR^{p6}$, $-NR^{n6}S(O)_2NR^{q6}R^{r6}$, NO_2, $-C(O)R^{n6}$, $-C(O)OR^{n6}$ and $-C(O)NR^{q6}R^{r6}$;

each Z^{4b} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl $(C_2\text{-}C_4)$alkynyl and $(C_1\text{-}C_4)$haloalkyl;

each R^{n5} is independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

each R^{p5} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

R^{q5} and R^{r5} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

each R^{n6} is independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

each R^{p6} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

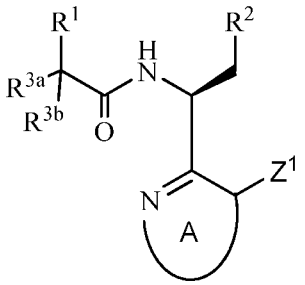
R^{q6} and R^{r6} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

each Z^5 is independently selected from $(C_1\text{-}C_6)$alkyl, halogen, -CN and $-OR^{n7}$, wherein any $(C_1\text{-}C_6)$alkyl of Z^5 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen; and

each R^{n7} is independently selected from H, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$haloalkyl and $(C_3\text{-}C_7)$carbocycle;

or a pharmaceutically acceptable salt thereof.

Embodiment II-2. The compound of Embodiment II-1 which is a compound of formula Ia:



Ia

or a pharmaceutically acceptable salt thereof.

Embodiment II-3. The compound of Embodiment II-1 or Embodiment II-2 wherein R^{3a} and R^{3b} are each H.

Embodiment II-4. The compound of any one of Embodiments II-1-3 wherein R^2 is phenyl or a 5-membered monocyclic-heteroaryl, wherein any phenyl or 5-membered monocyclic-heteroaryl of R^2 is optionally substituted with one or more Z^5 groups.

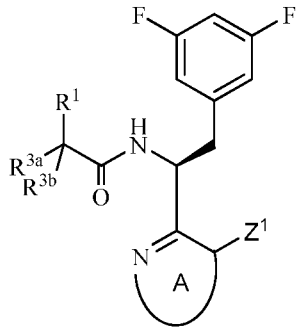
Embodiment II-5. The compound of any one of Embodiments II-1 to II-3 wherein R^2 is phenyl optionally substituted with one or more Z^5 groups.

Embodiment II-6. The compound of any one of Embodiments II-1 to II-5 wherein each Z^5 is halogen.

Embodiment II-7. The compound of any one of Embodiments II-1 to II-5 wherein each Z^5 is fluoro.

Embodiment II-8. The compound of Embodiment II-1 or Embodiment II-2 wherein R^2 is 3,5-difluorophenyl.

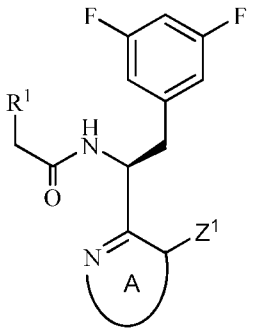
Embodiment II-9. The compound of Embodiment II-1 which is a compound of formula Ig:



Ig

or a pharmaceutically acceptable salt thereof.

Embodiment II-10. The compound of Embodiment II-1 which is a compound of formula Ie:



Ie

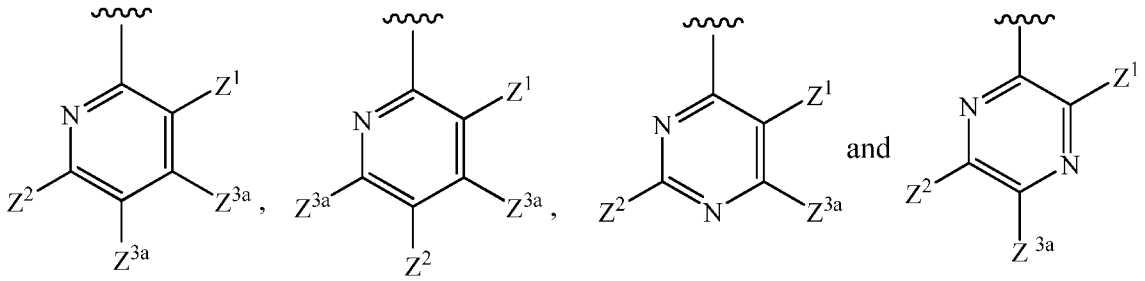
or a pharmaceutically acceptable salt thereof.

Embodiment II-11. The compound of any one of Embodiments II-1 to II-10 wherein A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein any pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl of A is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with one or more Z^3 groups.

Embodiment II-12. The compound of any one of Embodiments II-1 to II-10 wherein A is pyridinyl, wherein any pyridinyl of A is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with one or more Z^3 groups.

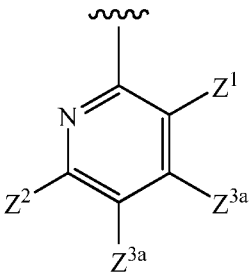
Embodiment II-13. The compound of any one of Embodiments II-1 to II-12 wherein A is substituted with one Z^1 group at the position shown and one Z^2 group.

Embodiment II-14. The compound of any one of Embodiments II-1 to II-10 wherein A-Z^1 is selected from:

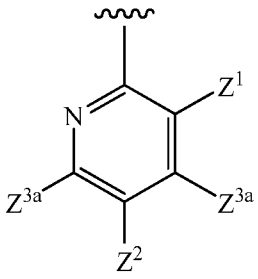


wherein each Z^{3a} is independently selected from H and Z^3.

Embodiment II-15. The compound of any one of Embodiments II-1 to II-10 wherein A-Z^1 is selected from:

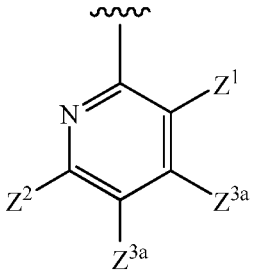


and



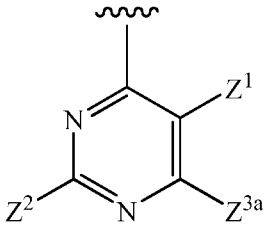
wherein each Z^{3a} is independently selected from H and Z^3.

Embodiment II-16. The compound of any one of Embodiments II-1 to II-10 wherein A-Z^1 is:



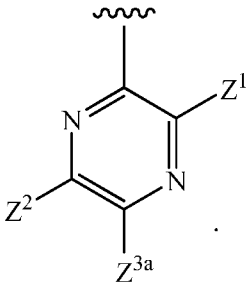
wherein each Z^{3a} is independently selected from H and Z^3.

Embodiment II-17. The compound of any one of Embodiments II-1 to II-10 wherein A-Z^1 is:



wherein Z^{3a} is selected from H and Z^3.

Embodiment II-18. The compound of any one of Embodiments II-1 to II-10 wherein A-Z^1 is:



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wherein Z^{3a} is selected from H and Z^3.

Embodiment II-19. The compound of any one of Embodiments II-14 to II-18 wherein each Z^{3a} is H.

Embodiment II-20. The compound of any one of Embodiments II-1 to II-19 wherein Z^1 is selected from phenyl, 5-14 membered heteroaryl and 3-14 membered heterocycle, wherein any phenyl, 5-14 membered heteroaryl and 3-14 membered heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups.

Embodiment II-21. The compound of any one of Embodiments II-1 to II-19 wherein Z^1 is selected from phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups.

Embodiment II-22. The compound of any one of Embodiments II-1 to II-19 wherein Z^1 is selected from phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle, wherein the 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle have 1-11 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle and 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups.

Embodiment II-23. The compound of any one of Embodiments II-1 to II-19 wherein Z^1 is selected from 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle ,wherein any from 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups.

Embodiment II-24. The compound of any one of Embodiments II-1 to II-19 wherein Z^1 is selected from 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle, wherein the 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle have 3-9 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any 8-10 membered

bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups.

Embodiment II-25. The compound of any one of Embodiments II-1 to II-19 wherein Z^1 is selected from phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 4-oxo-3,4-dihydroquinazolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, 1H-2-oxo-pyridinyl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolinyl, wherein any phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 4-oxo-3,4-dihydroquinazolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, 1H-2-oxo-pyridinyl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolinyl of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups.

Embodiment II-26. The compound of any one of Embodiments II-1 to II-19 wherein Z^1 is selected from phenyl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1-oxoisoindolin-5-yl, 1-oxoisoindolin-4-yl, 4-oxo-3,4-dihydroquinazolin-8-yl, 3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl, 1H-2-oxo-pyridin-4-yl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolin-8-yl, wherein any phenyl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1-oxoisoindolin-5-yl, 1-oxoisoindolin-4-yl, 4-oxo-3,4-dihydroquinazolin-8-yl, 3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl, 1H-2-oxo-pyridin-4-yl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolin-8-yl of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups.

Embodiment II-27. The compound of any one of Embodiments II-1 to II-19 wherein Z^1 is 1H-indazol-7-yl, wherein Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups.

Embodiment II-28. The compound of any one of Embodiments II-1 to II-27 wherein each Z^{1a} is independently selected from halogen, $-OR^{n1}$, $NR^{q1}R^{r1}$, and $-C(O)NR^{q1}R^{r1}$.

Embodiment II-29. The compound of any one of Embodiments II-1 to II-27 wherein each Z^{1a} is independently selected from halogen and $-NR^{n1}S(O)_2R^{p1}$.

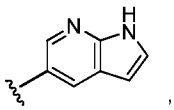
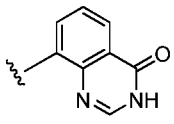
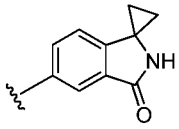
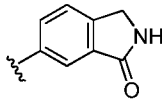
Embodiment II-30. The compound of any one of Embodiments II-1 to II-27 wherein each Z^{1b} is independently selected from $(C_1\text{-}C_8)$alkyl.

Embodiment II-31. The compound of any one of Embodiments II-1 to II-27 wherein each Z^{1a} is independently selected from halogen and $-NR^{n1}S(O)_2R^{p1}$ and each Z^{1b} is independently selected from $(C_1\text{-}C_8)$alkyl.

Embodiment II-32. The compound of any one of Embodiments II-1 to II-27 wherein each Z^{1a} is independently selected from halogen and $-C(O)NR^{q1}R^{r1}$.

Embodiment II-33. The compound of any one of Embodiments II-1 to II-27 wherein R^{n1}, R^{q1} and R^{r1} are each H.

Embodiment II-34. The compound of any one of Embodiments II-1 to II-19 wherein Z^1 is selected from:


,

,

,

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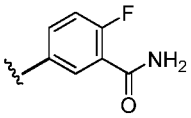
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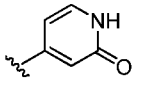
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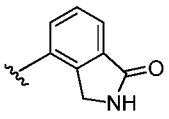
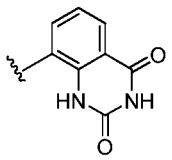

and

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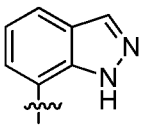
Embodiment II-35. The compound of any one of Embodiments II-1 to II-19 wherein Z^1 is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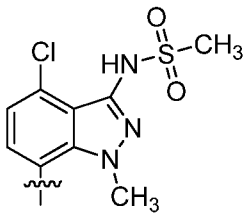
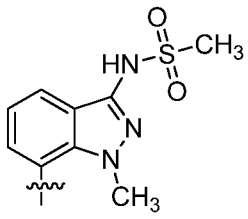
Embodiment II-36. The compound of any one of Embodiments II-1 to II-19 wherein Z^1 is selected from


and

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Embodiment II-37. The compound of any one of Embodiments II-1 to II-36 wherein Z^2 is selected from $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle and $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl and 3-12 membered C-linked-heterocycle of Z^2 is optionally

substituted with one or more Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with one or more Z^{2c} groups.

Embodiment II-38. The compound of any one of Embodiments II-1 to II-36 wherein Z^2 is selected from $(C_2$-$C_8)$alkynyl, phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heterocycle and -C(O)$NR^{q3}R^{r3}$, wherein any phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl and 8-10 membered C-linked-bicyclic-heterocycle of Z^2 is optionally substituted with one or more Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with one or more Z^{2c} groups.

Embodiment II-39. The compound of any one of Embodiments II-1 to II-36 wherein Z^2 is selected from $(C_2$-$C_8)$alkynyl, phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heterocycle and -C(O)$NR^{q3}R^{r3}$, wherein the 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl and 8-10 membered C-linked-bicyclic-heterocycle have 1-9 carbon atoms and 1-4 heteroatoms in the ring system, and wherein any phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered and C-linked-bicyclic-heterocycle of Z^2 is optionally substituted with one or more Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with one or more Z^{2c} groups.

Embodiment II-40. The compound of any one of Embodiments II-1 to II-36 wherein Z^2 is selected from 4-methylpentynyl, phenyl, pyridinyl, 1H-2-oxo-pyridinyl, triazolyl, 1-oxoisoindolinyl, 1H-pyrrolo[2,3-b]pyridinyl and -C(O)$NR^{q3}R^{r3}$, wherein any phenyl, pyridinyl, 2-oxopyridinyl, triazolyl, 1-oxoisoindolinyl and 1H-pyrrolo[2,3-b]pyridinyl of Z^2 is optionally substituted with one or more Z^{2b} or Z^{2c} groups, and wherein any 4-methylpentynyl of Z^2 is optionally substituted with one or more Z^{2c} groups.

Embodiment II-41. The compound of any one of Embodiments II-1 to II-36 wherein Z^2 is selected from 4-methylpentyn-1-yl, phenyl, pyridin-4-yl, 1H-2-oxo-pyridin-2-yl, triazol-4-yl, 1-oxoisoindolin-6-yl, 1H-pyrrolo[2,3-b]pyridine-5-yl and -C(O)$NR^{q3}R^{r3}$, wherein any phenyl, pyridin-4-yl, 2-hydroxypyridin-2-yl, triazol-4-yl, 1-oxoisoindolin-6-yl and 1H-pyrrolo[2,3-b]pyridine-5-yl of Z^2 is optionally substituted with one or more Z^{2b} or Z^{2c} groups, and wherein any 4-methylpentyn-1-yl of Z^2 is optionally substituted with one or more Z^{2c} groups.

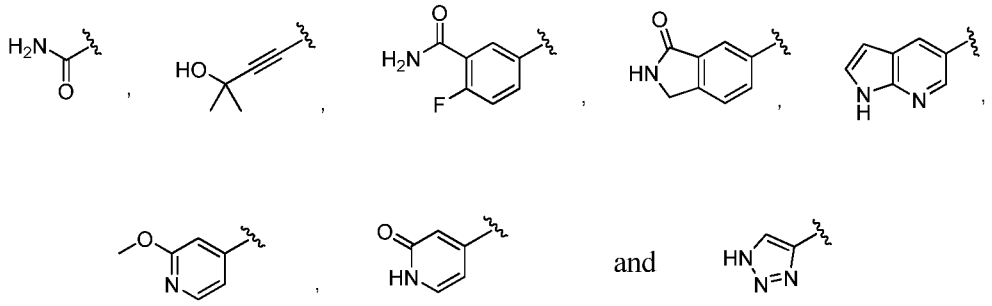
Embodiment II-42. The compound of any one of Embodiments II-1 to II-41 wherein Z^2 is optionally substituted with one or more Z^{2c} groups.

Embodiment II-43. The compound of any one of Embodiments II-1 to II-42 wherein R^{q3} and R^{r3} are each H.

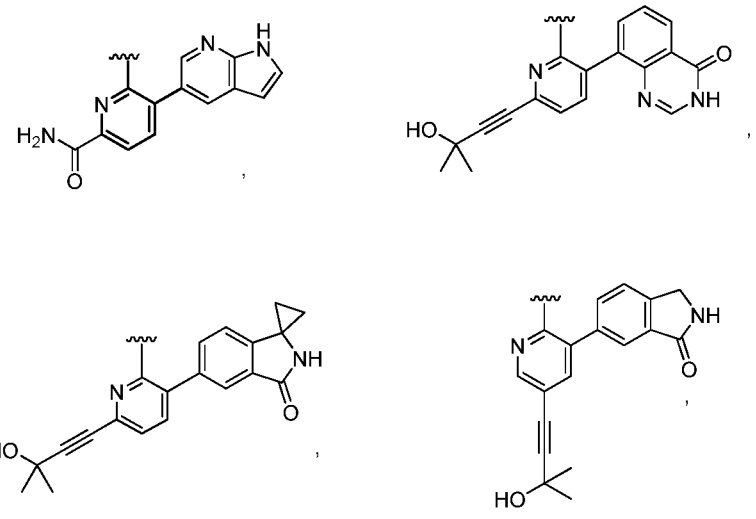
Embodiment II-44. The compound of any one of Embodiments II-1 to II-43 wherein each Z^{2c} is independently selected from halogen, $-OR^{n4}$ and $-C(O)NR^{q4}R^{r4}$.

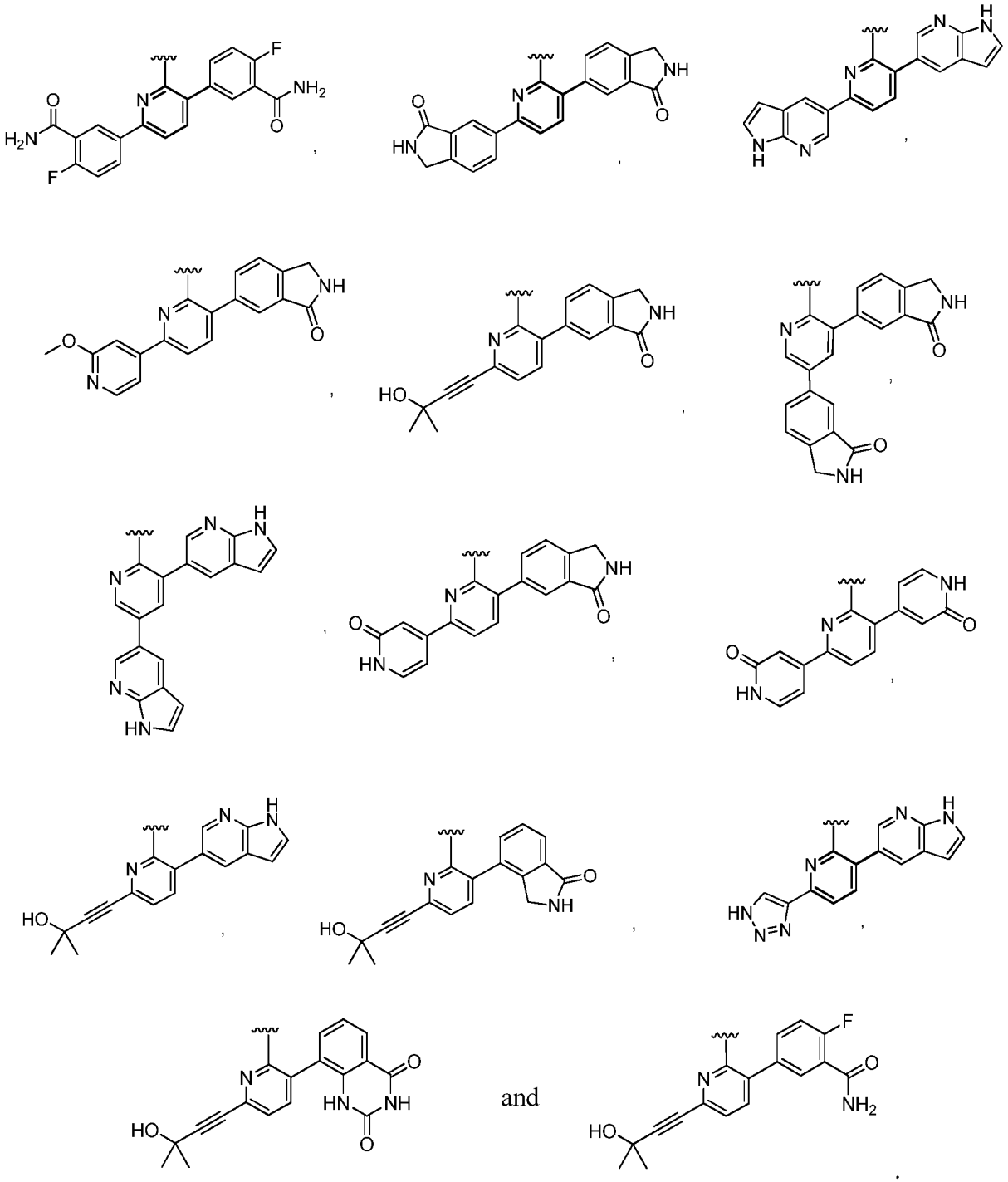
Embodiment II-45. The compound of any one of Embodiments II-1 to II-44 wherein R^{n4} is H or methyl, and R^{q4} and R^{r4} are each H.

Embodiment II-46. The compound of any one of Embodiments II-1 to II-36 wherein Z^2 is selected from:



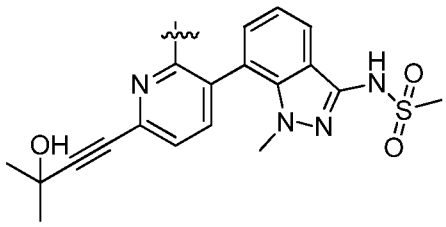
Embodiment II-47. The compound of any one of Embodiments II-1 to II-10 wherein A-Z^1 is selected from:



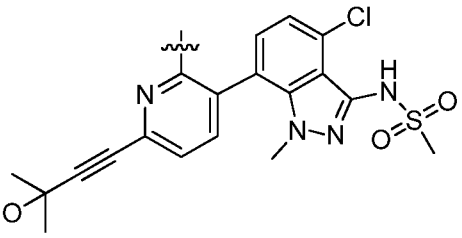


and

Embodiment II-48. The compound of any one of Embodiments II-1 to II-10 wherein A-Z^1 is selected from:



and.



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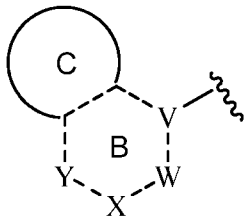
Embodiment II-49. The compound of any one of Embodiments II-1 to II-48 wherein R^1 is a 5-12 membered heteroaryl, wherein any 5-12 membered heteroaryl of R^1 is optionally substituted with one or more Z^4 groups.

Embodiment II-50. The compound of any one of Embodiments II-1 to II-48 wherein R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with one or more Z^4 groups.

Embodiment II-51. The compound of any one of Embodiments II-1 to II-48 wherein R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein the 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl have 4-10 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with one or more Z^4 groups.

Embodiment II-52. The compound of any one of Embodiments II-1 to II-48 wherein R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein the 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl contains at least one partially unsaturated ring, and wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

Embodiment II-53. The compound of any one of Embodiments II-1 to II-48 wherein R^1 has the following formula IIb:



IIb

wherein:

C together with the two carbon atoms of ring B to which it is attached forms a 3-7 membered monocyclic-carbocycle, 5-8 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-8 membered bicyclic heterocycle, wherein any 3-7 membered monocyclic-carbocycle, 5-8 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-8 membered bicyclic heterocycle of C is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^4 groups; and

B is a 5 or 6 membered monocyclic-heteroaryl having 1, 2 or 3 nitrogen atoms;

V is C or N;

W is CZ^{4c}, NZ^{4c} or N;

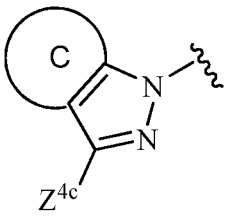
X is CZ^{4c}, NZ^{4c} or N;

Y is CZ^{4c}, N or absent;

the dashed bonds are selected from single bonds and double bonds, wherein the dashed bonds, V, W, X and Y are selected so that the 5 or 6 membered monocyclic-heteroaryl B is aromatic; and

each Z^{4c} is independently selected from H or Z^4.

Embodiment II-54. The compound of any one of Embodiments II-1 to II-48 wherein R^1 has the following formula IId:



IId

wherein:

C together with the two carbon atoms to which it is attached forms a 3-7 membered monocyclic-carbocycle, 5-9 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-9 membered bicyclic heterocycle, wherein any 3-7 membered monocyclic-carbocycle, 5-9 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-9 membered bicyclic heterocycle of C is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^4 groups; and

each Z^{4c} is independently selected from H or Z^4.

Embodiment II-55. The compound of any one of Embodiments II-1 to II-48 wherein R^1 is selected from 3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazolyl and 4,5,6,7-tetrahydro-indazolyl, wherein any 3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazolyl and 4,5,6,7-tetrahydro-indazolyl of R^1 is optionally substituted with one or more Z^4 groups.

Embodiment 56. The compound of any one of Embodiments II-1 to II-48 wherein R^1 is selected from 3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl and 4,5,6,7-tetrahydro-indazol-1-yl, wherein any 3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl and 4,5,6,7-tetrahydro-indazol-1-yl of R^1 is optionally substituted with one or more Z^4 groups.

Embodiment II-57. The compound of any one of Embodiments II-1 to II-56 wherein each Z^4 is independently selected from $(C_1$-$C_6)$alkyl and halogen, wherein any $(C_1$-$C_6)$alkyl of Z^4 is optionally substituted with one or more halogen.

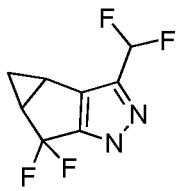
Embodiment II-58. The compound of any one of Embodiments II-1 to II-56 wherein each Z^4 is independently selected from fluoro, trifluoromethyl and difluoromethyl.

Embodiment II-59. The compound of any one of Embodiments II-1 to II-48 wherein R^1 is selected from:

and

.

Embodiment II-60. The compound of any one of Embodiments II-1 to II-48 wherein R^1 is



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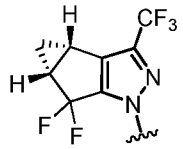
Embodiment II-61. The compound of any one of Embodiments II-1 to II-48 wherein R^1 is selected from: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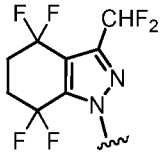
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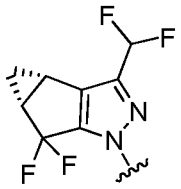
Embodiment II-62. The compound of any one of Embodiments II-1 to II-48 wherein R^1 is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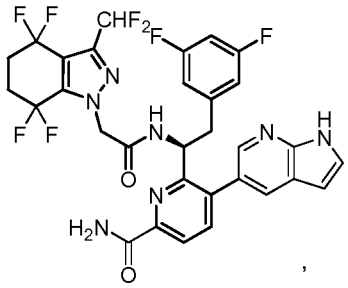
Embodiment II-63. The compound of Embodiment II-1 selected from: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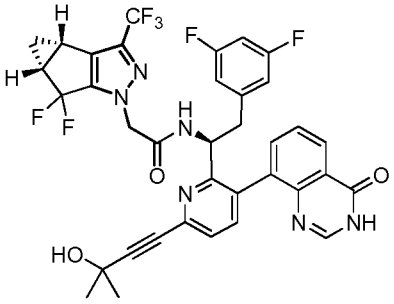
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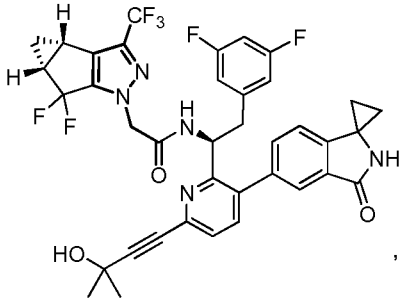
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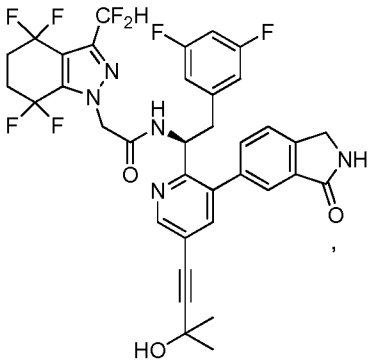
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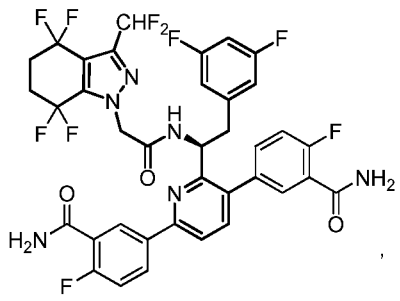

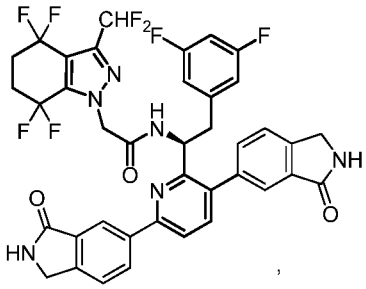

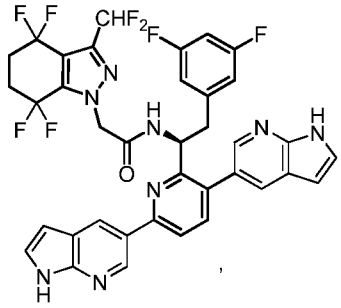

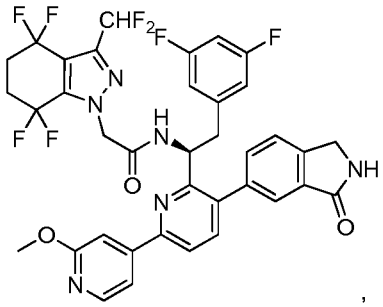

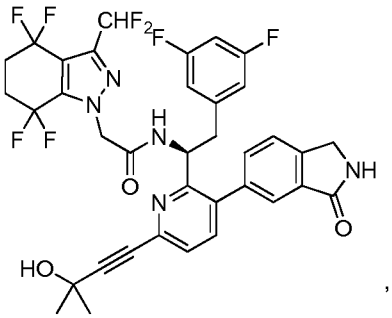

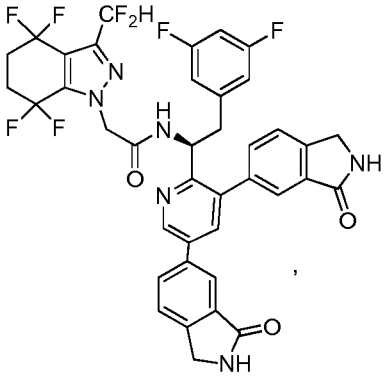

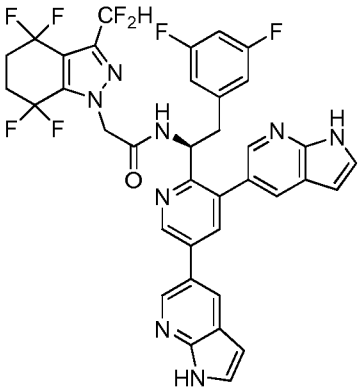

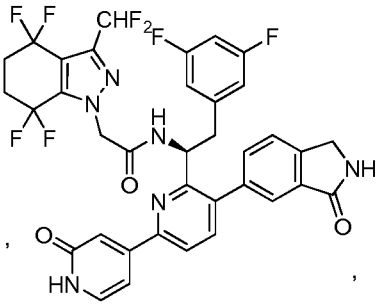

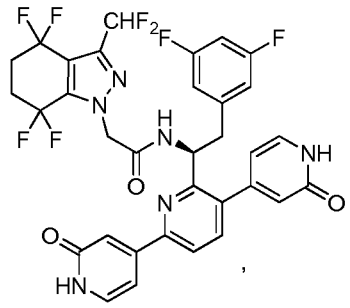

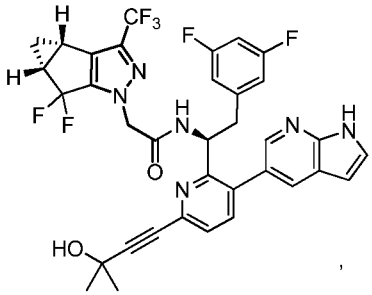

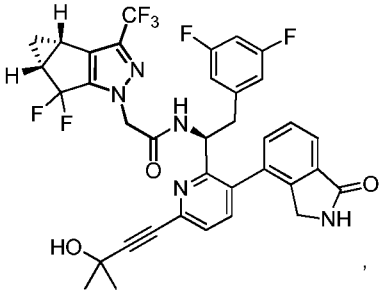

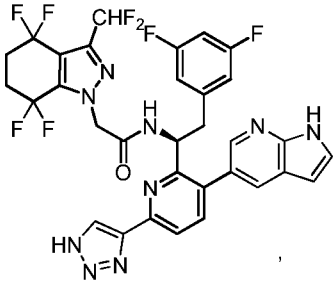

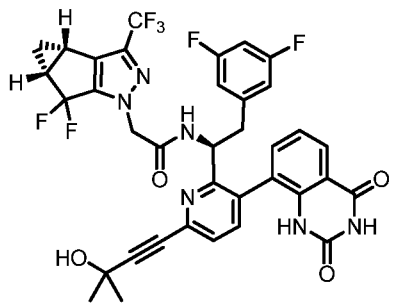
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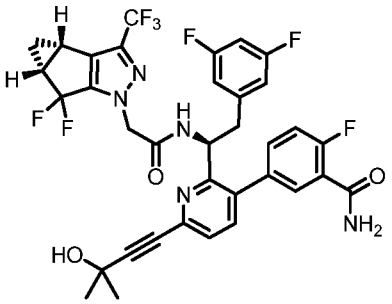
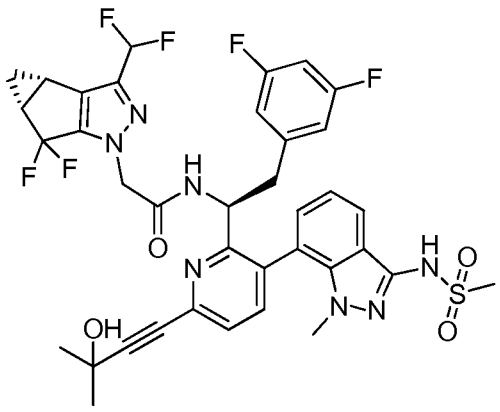
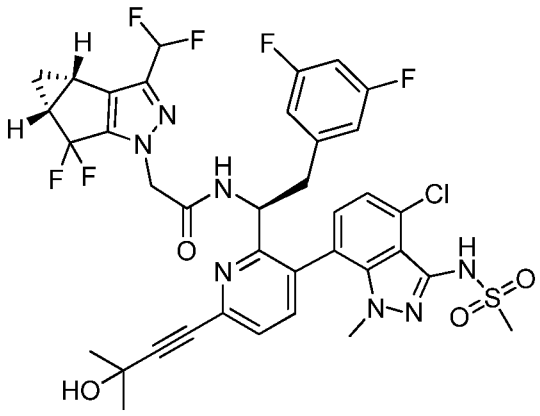


and pharmaceutically acceptable salts thereof.

Embodiment II-64. The compound of Embodiment II-1 selected from:


and.


and pharmaceutically acceptable salts thereof.

Embodiment II-65. A pharmaceutical composition comprising a compound of formula I as described in any one of Embodiments II-1 to II-64, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Embodiment II-66. A method for treating a *Retroviridae* virus infection in a mammal comprising administering a therapeutically effective amount of a compound of any one of Embodiments II-1 to II-64, or a pharmaceutically acceptable salt thereof, to the mammal.

Embodiment II-67. The method of Embodiment II-66 wherein the *Retroviridae* virus infection is an HIV virus infection.

Embodiment II-68. A method for treating an HIV infection in a mammal comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of formula I as described in any one of Embodiments II-1 to II-64, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more

additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and other drugs for treating HIV, and combinations thereof.

Embodiment II-69. A compound of formula I as described in any of Embodiments II-1 to II-44, or a pharmaceutically acceptable salt thereof for use in medical therapy.

Embodiment II-70. A compound of formula I as described in any one of Embodiments II-1 to II-44 or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of a *Retroviridae* virus infection or an HIV virus infection.

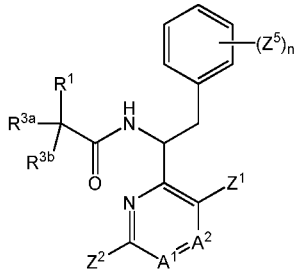
Embodiment II-71. The use of a compound as described in any one of Embodiments II-1 to II-44 or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a *Retroviridae* virus infection or an HIV virus infection in a mammal.

Embodiment II-72. A compound or method as described herein.

CLAIMS

What is claimed is:

1. A compound of formula IIId:



IIId

wherein

A^1 is CH, C-Z^3, or nitrogen;

A^2 is CH or nitrogen;

R^1 is 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle, wherein any 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle of R^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, wherein the Z^4 groups are the same or different;

each R^{3a} and R^{3b} is independently H or (C_1-C_3)alkyl;

Z^1 is 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle, wherein any 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b}, wherein the Z^{1a} and Z^{1b} groups are the same or different;

each Z^{1a} is independently (C_3-C_7)carbocycle, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, -OR^{n1}, -$OC(O)R^{p1}$, -$OC(O)NR^{q1}R^{r1}$, -SR^{n1}, -$S(O)R^{p1}$, -$S(O)_2OH$, -$S(O)_2R^{p1}$, -$S(O)_2NR^{q1}R^{r1}$, -$NR^{q1}R^{r1}$, -$NR^{n1}COR^{p1}$, -$NR^{n1}CO_2R^{p1}$, -$NR^{n1}CONR^{q1}R^{r1}$, -$NR^{n1}S(O)_2R^{p1}$, -$NR^{n1}S(O)_2OR^{p1}$, -$NR^{n1}S(O)_2NR^{q1}R^{r1}$, -$C(O)R^{n1}$, -$C(O)OR^{n1}$, -$C(O)NR^{q1}R^{r1}$ and -$S(O)_2NR^{n1}COR^{p1}$, wherein any (C_3-C_7)carbocycle, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{1a} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different;

each Z^{1b} is independently (C_1-C_8)alkyl optionally substituted with 1, 2, 3, 4 or 5 halogen, which are the same or different;

each Z^{1c} is independently halogen, -CN, -OH, -NH_2, -$C(O)NR^{q2}R^{r2}$, or (C_1-C_8)heteroalkyl;

each Z^{1d} is independently $(C_1\text{-}C_8)$alkyl or $(C_1\text{-}C_8)$haloalkyl;

each R^{n1} is independently H, $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{n1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any $(C_1\text{-}C_8)$alkyl of R^{n1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different;

each R^{p1} is independently $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any $(C_1\text{-}C_8)$alkyl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different;

each R^{q1} and R^{r1} is independently H, $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any $(C_3\text{-}C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any $(C_1\text{-}C_8)$alkyl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different, or R^{q1} and R^{r1} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or 7-membered heterocycle is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different;

each R^{q2} and R^{r2} is independently H, $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_7)$carbocycle, or R^{q2} and R^{r2} together with the nitrogen to which they are attached form a 5, 6, or 7-membered heterocycle;

Z^2 is $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, $-C(O)R^{n3}$, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, wherein the Z^{2b} and Z^{2c} groups are the same or different, and wherein any $(C_2\text{-}C_8)$alkenyl or $(C_2\text{-}C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4, or 5 Z^{2c} groups, wherein the Z^{2c} groups are the same or different;

each R^{n3} is independently H or $(C_1\text{-}C_4)$alkyl;

each R^{q3} and R^{r3} is independently H or $(C_1\text{-}C_4)$alkyl;

each Z^{2b} is independently oxo, (C_1-C_4)alkyl, (C_1-C_4)heteroalkyl or (C_1-C_4)haloalkyl;

each Z^{2c} is independently oxo, halogen, -CN, -OR^{n4}, -$OC(O)R^{p4}$, -$OC(O)NR^{q4}R^{r4}$, -SR^{n4}, -$S(O)R^{p4}$, -$S(O)_2OH$, -$S(O)_2R^{p4}$, -$S(O)_2NR^{q4}R^{r4}$, -$NR^{q4}R^{r4}$, -$NR^{n4}COR^{p4}$, -$NR^{n4}CO_2R^{p4}$, -$NR^{n4}CONR^{q4}R^{r4}$, -$NR^{n4}S(O)_2R^{p4}$, -$NR^{n4}S(O)_2OR^{p4}$, -$NR^{n4}S(O)_2NR^{q4}R^{r4}$, -$NO_2$, -$C(O)R^{n4}$, -$C(O)OR^{n4}$, or -$C(O)NR^{q4}R^{r4}$;

each R^{n4} is independently H, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, or (C_1-C_4)heteroalkyl;

each R^{p4} is independently (C_1-C_8)alkyl, (C_1-C_4)haloalkyl, or (C_1-C_4)heteroalkyl;

each R^{q4} and R^{r4} is independently H, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, or (C_1-C_4)heteroalkyl;

each Z^3 is independently a (C_1-C_4)heteroalkyl;

each Z^4 is independently oxo, (C_1-C_8)alkyl, (C_3-C_7)carbocycle, halogen, -CN, -OR^{n5}, -$NR^{q5}R^{r5}$, -$NR^{n5}COR^{p5}$, -$NR^{n5}CO_2R^{p5}$, -$C(O)R^{n5}$, -$C(O)OR^{n5}$, or -$C(O)NR^{q5}R^{r5}$, wherein any (C_3-C_7)carbocycle or (C_1-C_8)alkyl of Z^4 is optionally substituted with 1, 2, 3, 4 or 5 Z^{4a} groups, wherein the Z^{4a} groups are the same or different;

each Z^{4a} is independently halogen, -CN, or -OR^{n6};

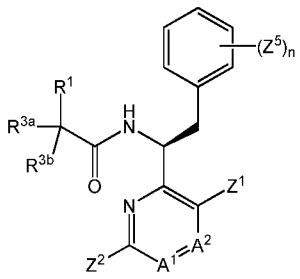
each R^{n5}, R^{p5}, R^{q5}, R^{r5}, and R^{n6} is independently H or (C_1-C_4)alkyl;

each Z^5 is independently halogen, which may be same or different; and

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof.

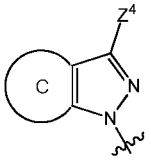
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, which is a compound of formula IIIe:



IIIe

or a pharmaceutically acceptable salt thereof.

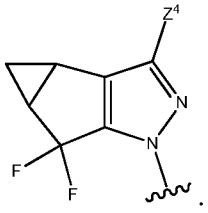
3. The compound of any one of claims 1-2, or a pharmaceutically acceptable salt thereof, wherein R^1 is



wherein

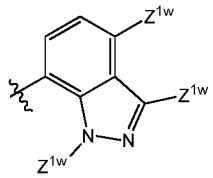
C together with the two carbon atoms to which it is attached forms a 3-7 membered monocyclic-carbocycle or 5-9 membered bicyclic-carbocycle, wherein any 3-7 membered monocyclic-carbocycle or 5-9 membered bicyclic-carbocycle of C is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, wherein the Z^4 groups are the same or different.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof,

wherein R^1 is 

.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein Z^1 is



wherein each Z^{1w} is independently Z^{1a}, Z^{1b}, or H.

6. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein:

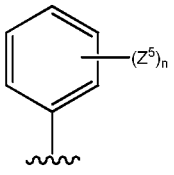
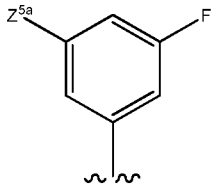
each Z^{1a} is independently halogen, -CN, -OR^{n1}, -$NR^{n1}S(O)_2R^{p1}$, -$NR^{n1}S(O)_2NR^{q1}R^{r1}$, -$NR^{q1}R^{r1}$, -$NR^{n1}COR^{p1}$, -$NR^{n1}CONR^{q1}R^{r1}$, or -$NR^{n1}CO_2R^{p1}$;

each Z^{1b} is independently (C_1-C_8alkyl), wherein the (C_1-C_8alkyl) is optionally substituted with 1, 2, or 3 halogen, which are the same or different; and

at least one of Z^{1w} is Z^{1a} or Z^{1b}.

7. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein at least two of Z^{1w} are independently Z^{1a}.

8. The compound of claim 6 or 7, or a pharmaceutically acceptable salt thereof, wherein each Z^{1a} is independently halogen, $-NR^{n1}S(O)_2R^{p1}$, or $-NR^{n1}S(O)_2NR^{q1}R^{r1}$.

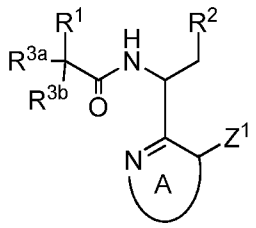
9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein the moiety  is  wherein Z^{5a} is H or halogen.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein A^1 is CH.

11. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein A^1 is C-Z^3.

12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein A^2 is CH.

13. A compound of formula III:



III

wherein

A is a 6-membered monocyclic-heteroaryl with one or two nitrogen atoms, wherein the 6-membered monocyclic-heteroaryl is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with 1 or 2 Z^3 groups, wherein the Z^3 groups are the same or different;

R^1 is 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle, wherein any 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle of R^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, wherein the Z^4 groups are the same or different;

R^2 is phenyl optionally substituted with 1, 2, 3, 4 or 5 halogen, which are the same or different;

each R^{3a} and R^{3b} is independently H or $(C_1$-$C_3)$alkyl;

Z^1 is 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle, wherein any 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b}, wherein the Z^{1a} and Z^{1b} groups are the same or different;

each Z^{1a} is independently $(C_3$-$C_7)$carbocycle, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, -OR^{n1}, -$OC(O)R^{p1}$, -$OC(O)NR^{q1}R^{r1}$, -SR^{n1}, -$S(O)R^{p1}$, -$S(O)_2OH$, -$S(O)_2R^{p1}$, -$S(O)_2NR^{q1}R^{r1}$, -$NR^{q1}R^{r1}$, -$NR^{n1}COR^{p1}$, -$NR^{n1}CO_2R^{p1}$, -$NR^{n1}CONR^{q1}R^{r1}$, -$NR^{n1}S(O)_2R^{p1}$, -$NR^{n1}S(O)_2OR^{p1}$, -$NR^{n1}S(O)_2NR^{q1}R^{r1}$, -$C(O)R^{n1}$, -$C(O)OR^{n1}$, -$C(O)NR^{q1}R^{r1}$ and -$S(O)_2NR^{n1}COR^{p1}$, wherein any $(C_3$-$C_7)$carbocycle, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{1a} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different;

each Z^{1b} is independently $(C_1$-$C_8)$alkyl optionally substituted with 1, 2, 3, 4 or 5 halogen, which are the same or different;

each Z^{1c} is independently halogen, -CN, -OH, -NH_2, -$C(O)NR^{q2}R^{r2}$, or $(C_1$-$C_8)$heteroalkyl;

each Z^{1d} is independently $(C_1$-$C_8)$alkyl or $(C_1$-$C_8)$haloalkyl;

each R^{n1} is independently H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{n1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any $(C_1$-$C_8)$alkyl of R^{n1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different;

each R^{p1} is independently $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{p1} is optionally substituted with 1, 2, 3,

4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any (C_1-C_8)alkyl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different;

each R^{q1} and R^{r1} is independently H, (C_1-C_8)alkyl, (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any (C_1-C_8)alkyl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different, or R^{q1} and R^{r1} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or 7-membered heterocycle is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different;

each R^{q2} and R^{r2} is independently H, (C_1-C_8)alkyl, (C_3-C_7)carbocycle, or R^{q2} and R^{r2} together with the nitrogen to which they are attached form a 5, 6, or 7-membered heterocycle;

Z^2 is (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, -C(O)R^{n3}, or -C(O)N$R^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, wherein the Z^{2b} and Z^{2c} groups are the same or different, and wherein any (C_2-C_8)alkenyl or (C_2-C_8)alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4, or 5 Z^{2c} groups, wherein the Z^{2c} groups are the same or different;

each R^{n3} is independently H or (C_1-C_4)alkyl;

each R^{q3} and R^{r3} is independently H or (C_1-C_4)alkyl;

each Z^{2b} is independently oxo, (C_1-C_4)alkyl, (C_1-C_4)heteroalkyl, or (C_1-C_4)haloalkyl;

each Z^{2c} is independently oxo, halogen, -CN, -OR^{n4}, -OC(O)R^{p4}, -OC(O)N$R^{q4}R^{r4}$, -SR^{n4}, -S(O)R^{p4}, -S(O)$_2$OH, -S(O)$_2R^{p4}$, -S(O)$_2$N$R^{q4}R^{r4}$, -N$R^{q4}R^{r4}$, -NR^{n4}COR^{p4}, -NR^{n4}CO$_2R^{p4}$, -NR^{n4}CON$R^{q4}R^{r4}$, -NR^{n4}S(O)$_2R^{p4}$, -NR^{n4}S(O)$_2$OR^{p4}, -NR^{n4}S(O)$_2$N$R^{q4}R^{r4}$, -NO_2, -C(O)R^{n4}, -C(O)OR^{n4}, or -C(O)N$R^{q4}R^{r4}$;

each R^{n4} is independently H, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, or (C_1-C_4)heteroalkyl;

each R^{p4} is independently (C_1-C_8)alkyl, (C_1-C_4)haloalkyl, or (C_1-C_4)heteroalkyl;

each R^{q4} and R^{r4} is independently H, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, or (C_1-C_4)heteroalkyl;

each Z^3 is independently a (C_1-C_4)heteroalkyl or halogen;

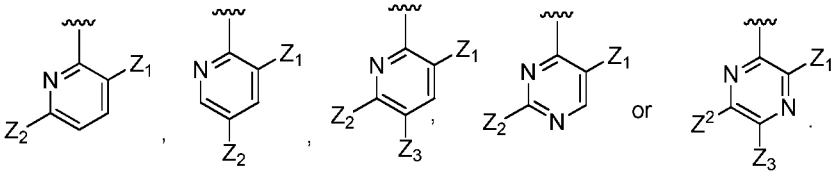
each Z^4 is independently oxo, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, halogen, -CN, $-OR^{n5}$, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-C(O)R^{n5}$, $-C(O)OR^{n5}$, or $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3$-$C_7)$carbocycle or $(C_1$-$C_8)$alkyl of Z^4 is optionally substituted with 1, 2, 3, 4 or 5 Z^{4a} groups, wherein the Z^{4a} groups are the same or different;

each Z^{4a} is independently halogen, -CN, or $-OR^{n6}$; and

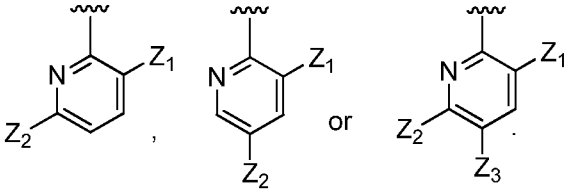
each R^{n5}, R^{p5}, R^{q5}, R^{r5}, and R^{n6} is independently H or $(C_1$-$C_4)$alkyl;

or a pharmaceutically acceptable salt thereof.

14. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein A is:



15. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein A is:



16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein each Z^3, where present, is independently methoxy, dimethylamino, or methylamino.

17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^{3a} and R^{3b} are each H.

18. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is methyl and R^{3b} is H.

19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein Z^2 is $(C_2$-$C_8)$alkynyl, phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heterocycle, or $-C(O)NR^{q3}R^{r3}$, wherein any phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10

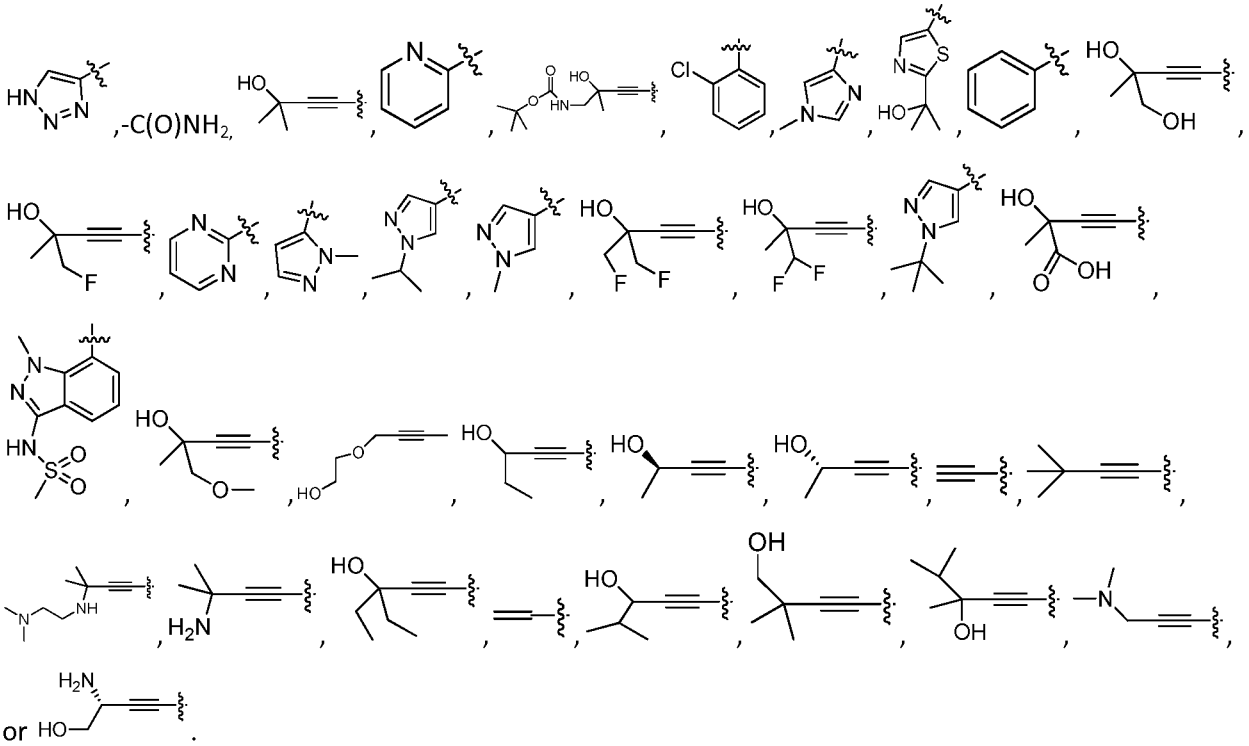
membered C-linked-bicyclic-heteroaryl, or 8-10 membered C-linked-bicyclic-heterocycle of Z^2 is optionally substituted with 1, 2, or 3 Z^{2b} or Z^{2c} groups, and wherein any $(C_2\text{-}C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, or 3 Z^{2c} groups.

20. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein Z^2 is $(C_2\text{-}C_8)$alkynyl, optionally substituted with 1, 2, or 3 Z^{2c} groups.

21. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein each Z^{2c} is independently halogen, $-OR^{n4}$, $NR^{q4}R^{r4}$, $-NR^{n4}CO_2R^{p4}$, $-C(O)OR^{n4}$, or $-C(O)NR^{q4}R^{r4}$.

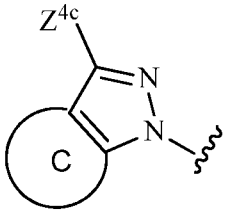
22. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein each Z^{2c} is independently halogen or $-OR^{n4}$.

23. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein Z^2 optionally substituted with 1, 2, 3, 4, or 5 Z^{2b} or Z^{2c} groups is



24. The compound of any one of claims 1-2 and 5-23, or a pharmaceutically acceptable salt thereof, wherein R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups.

25. The compound of any one of claims 1-2 and 5-23, or a pharmaceutically acceptable salt thereof, wherein R^1 has the following formula IId:



IId

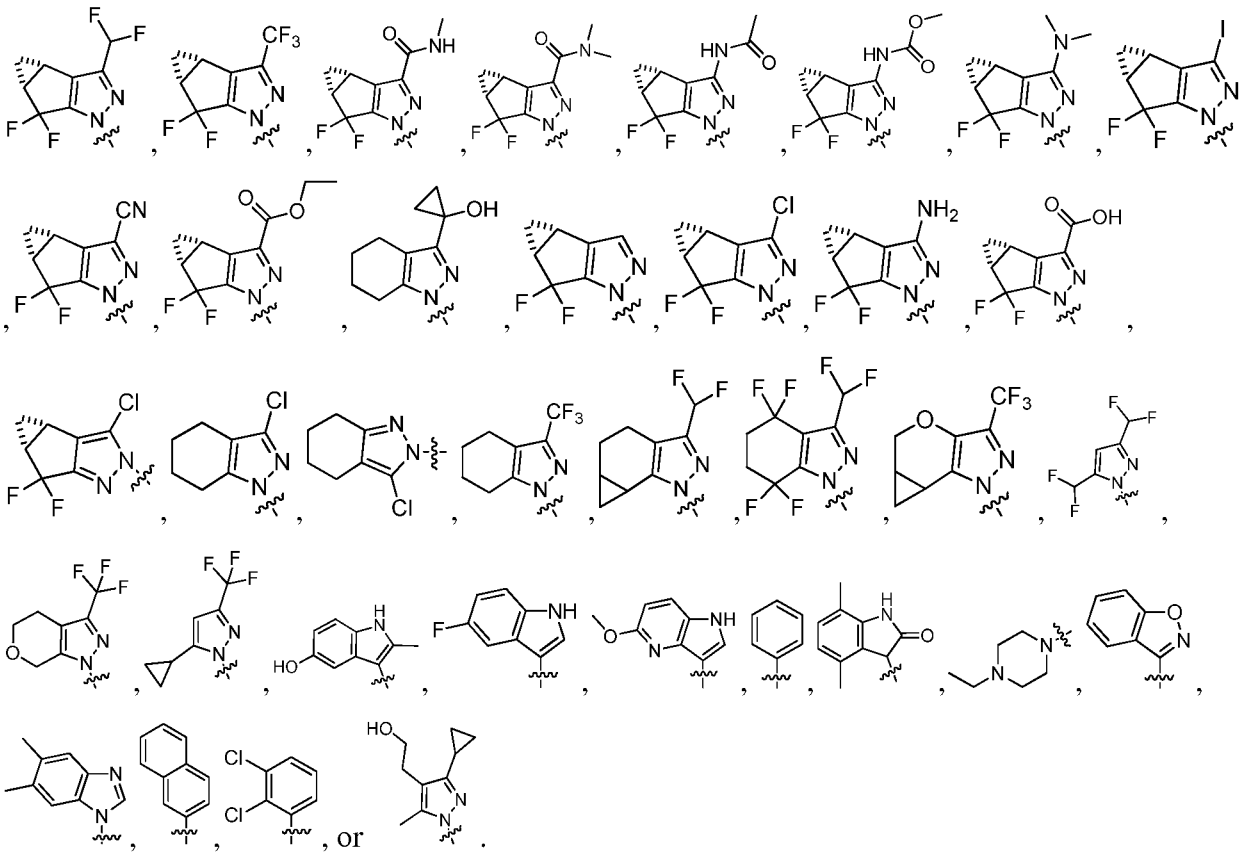
wherein:

C together with the two carbon atoms to which it is attached forms a 3-7 membered monocyclic-carbocycle, 5-9 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle, or 5-9 membered bicyclic heterocycle, wherein any 3-7 membered monocyclic-carbocycle, 5-9 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-9 membered bicyclic heterocycle of C is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, wherein the Z^4 groups are the same or different; and

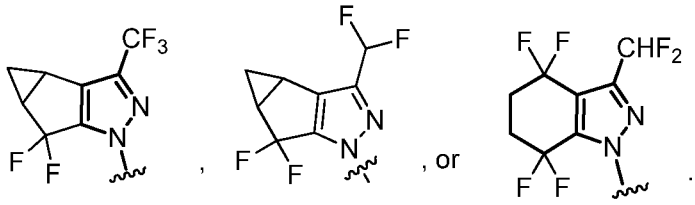
each Z^{4c} is independently selected from H or Z^4, wherein the Z^4 groups are the same or different.

26. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein each Z^4 is independently $(C_1\text{-}C_4)$alkyl or halogen, wherein any $(C_1\text{-}C_4)$alkyl of Z^4 is optionally substituted with 1, 2, 3, 4 or 5 halogen.

27. The compound of any one of claims 1-2 and 5-23, or a pharmaceutically acceptable salt thereof, wherein R^1 optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups is



28. The compound of any one of claims 1-2 and 5-23, or a pharmaceutically acceptable salt thereof, wherein R^1 optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups is



29. The compound of any one of claims 1-4 and 9-28, or a pharmaceutically acceptable salt thereof, wherein Z^1 is phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle, wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^{1a} or Z^{1b} groups.

30. The compound of any one of claims 1-4 and 9-28, or a pharmaceutically acceptable salt thereof, wherein Z^1 is 8-10 membered bicyclic-heteroaryl or 8-10 membered bicyclic-

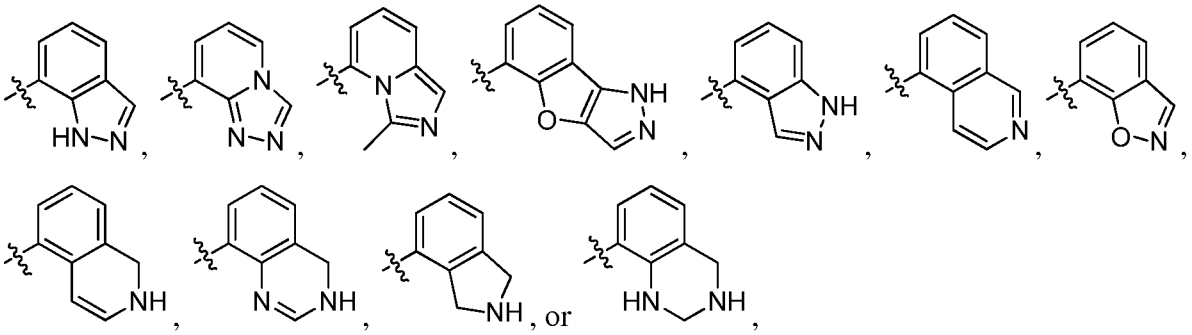
heterocycle, wherein any 8-10 membered bicyclic-heteroaryl or 8-10 membered bicyclic-heterocycle has 3-9 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any 8-10 membered bicyclic-heteroaryl or 8-10 membered bicyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^{1a} or Z^{1b} groups.

31. The compound of any one of claims 1-5 and 9-30, or a pharmaceutically acceptable salt thereof, wherein each Z^{1a} is independently oxo, $(C_3$-$C_7)$carbocycle, halogen, -CN, -O-$(C_1$-$C_8)$alkyl, $-NR^{q1}R^{r1}$, $-NR^{n1}COR^{p1}$, $-NR^{n1}CO_2R^{p1}$, $-NR^{n1}CONR^{q1}R^{r1}$, $-NR^{n1}S(O)_2R^{p1}$, $-NR^{n1}S(O)_2NR^{q1}R^{r1}$, or $-C(O)NR^{q1}R^{r1}$.

32. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein each Z^{1b} is independently methyl or difluoromethyl.

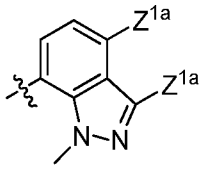
33. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt thereof, wherein Z^1 is substituted with 2 Z^{1a} groups, wherein each Z^{1a} is independently $-NR^{n1}S(O)_2R^{p1}$, $-NR^{n1}S(O)_2NR^{q1}R^{r1}$, or halogen.

34. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein Z^1 is

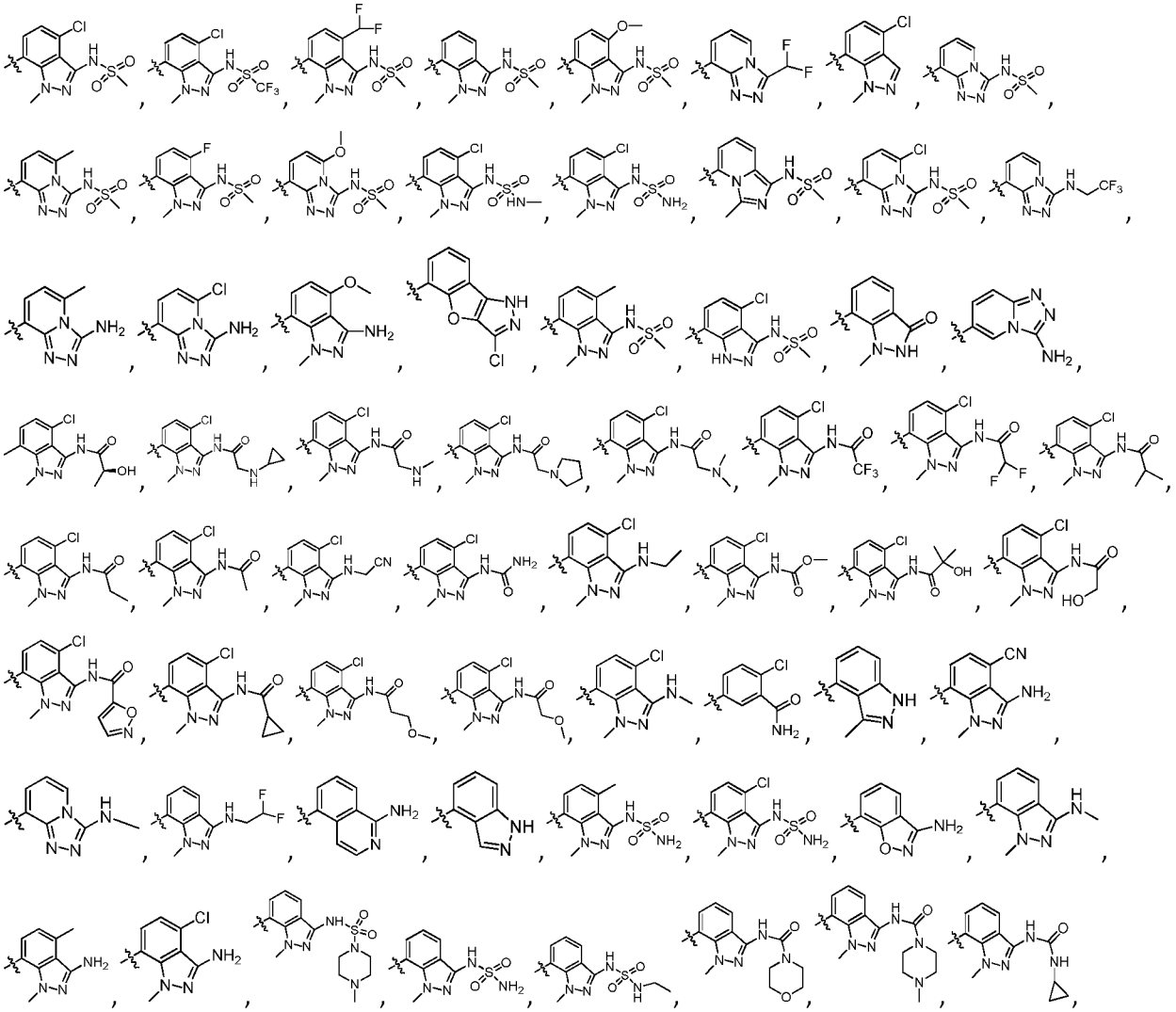


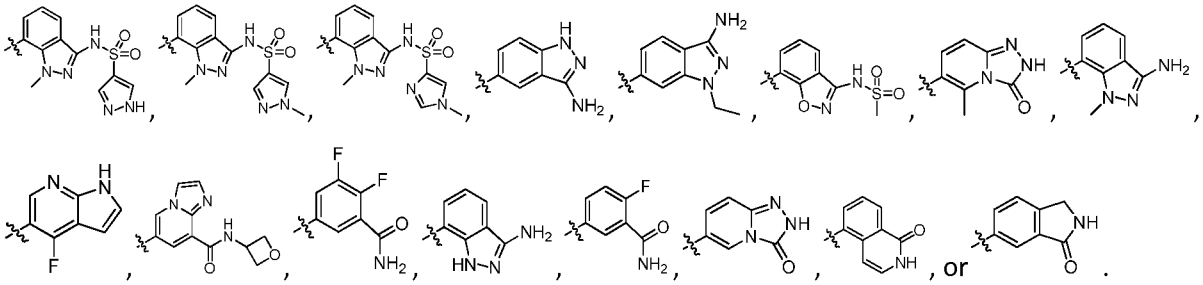
optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b}.

35. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof,

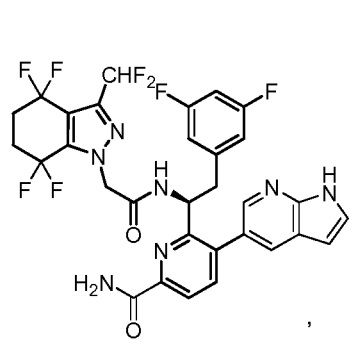
wherein Z^1 is  , wherein each Z^{1a} is independently halogen, $-NR^{n1}S(O)_2R^{p1}$ or $-NR^{n1}S(O)_2NR^{q1}R^{r1}$.

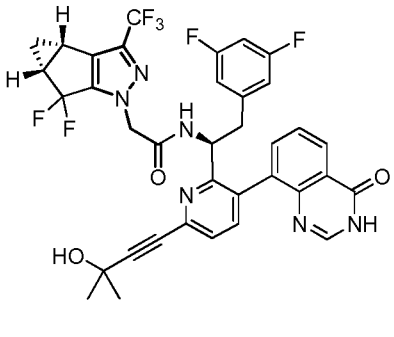
36. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein Z^1 optionally substituted with 1, 2, 3, 4, or 5 Z^{1a} or Z^{1b} groups is

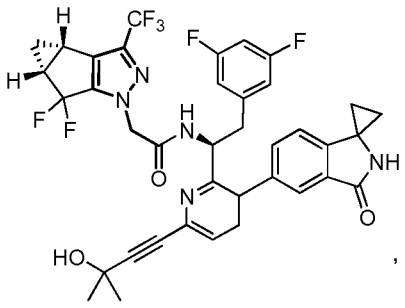


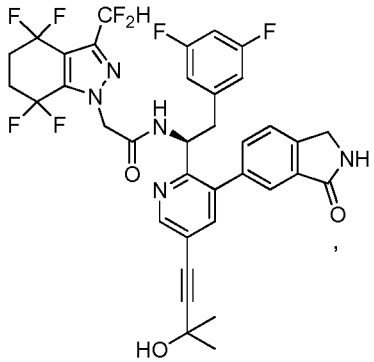


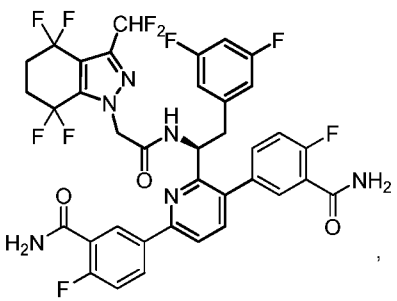
37. A compound or a pharmaceutically acceptable salt thereof, which is

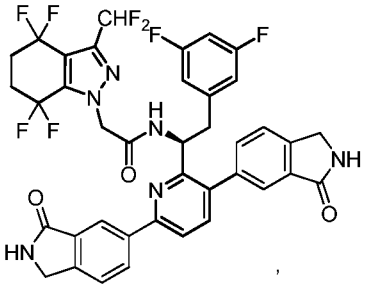


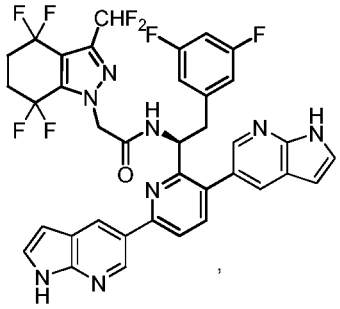


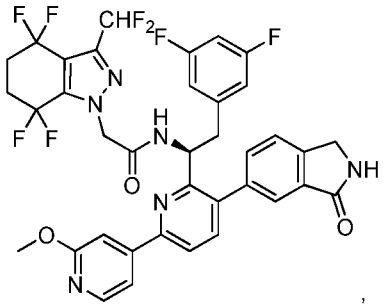


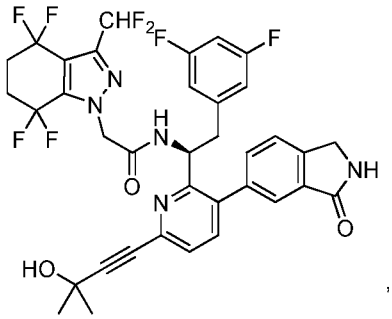


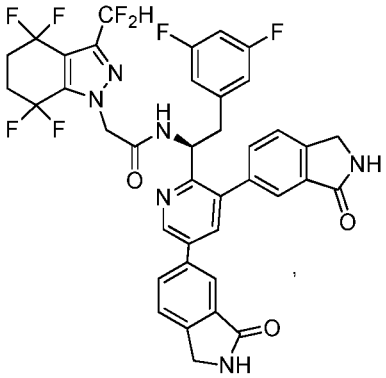


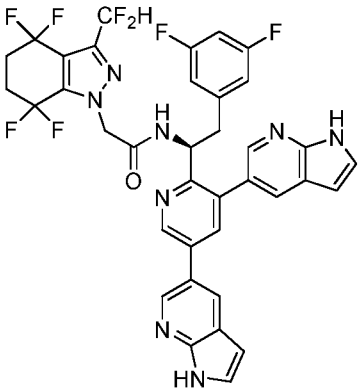


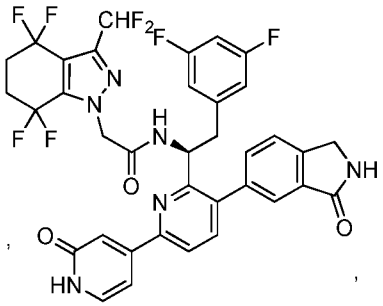


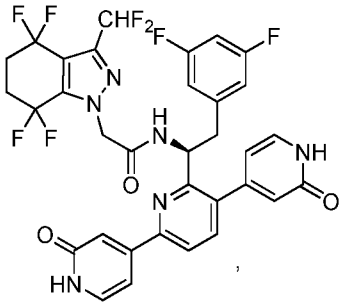


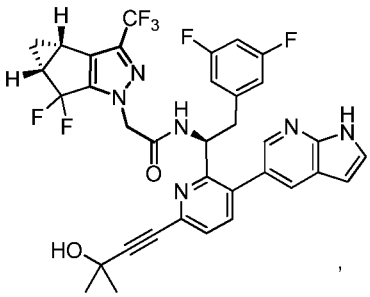


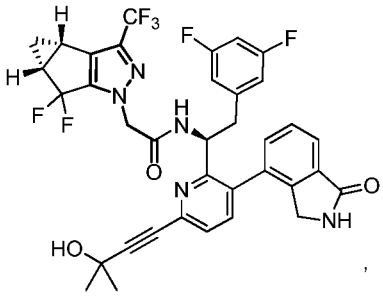


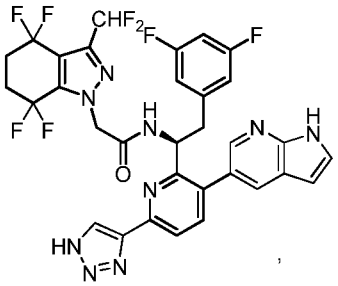


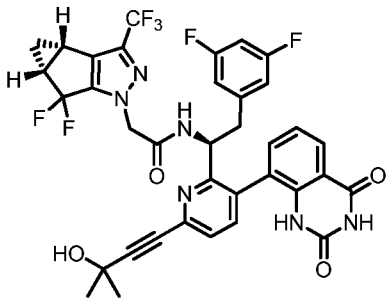


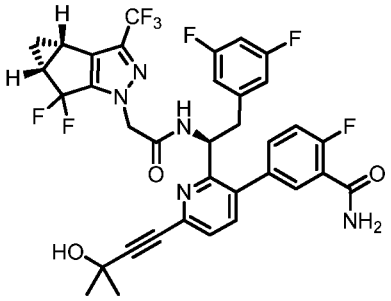


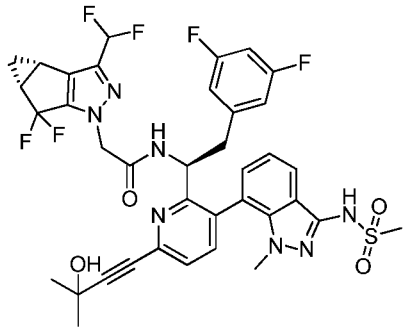


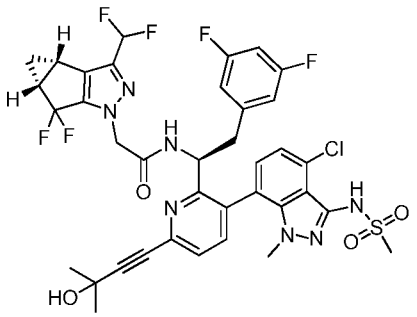


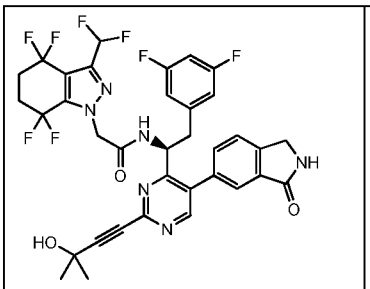


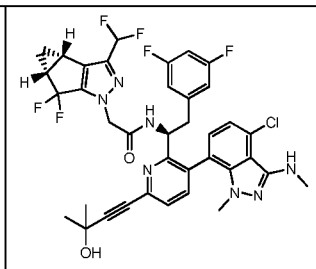


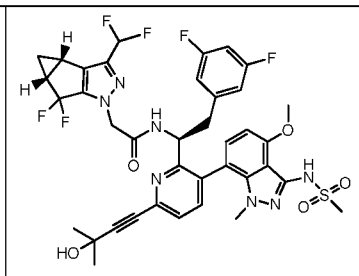


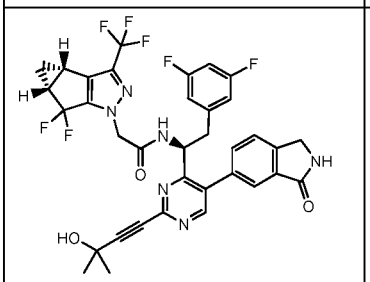


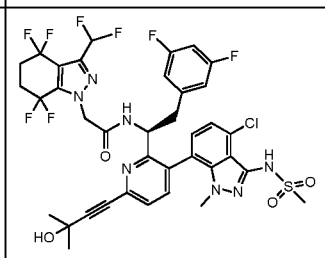


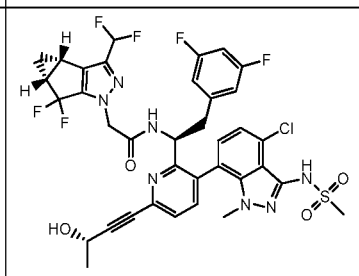


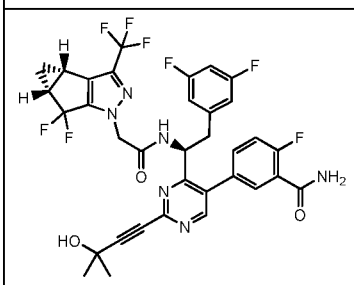


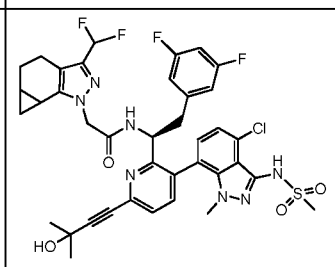


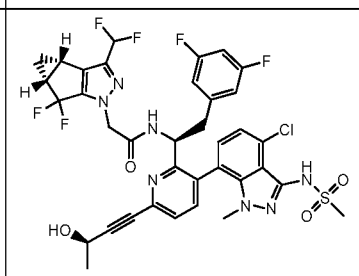


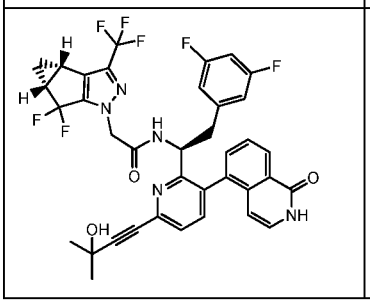


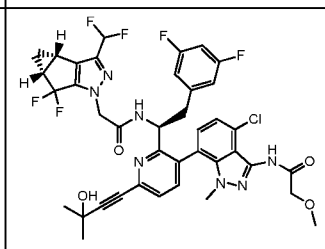


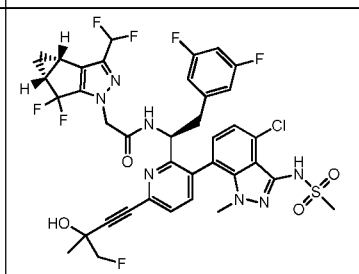


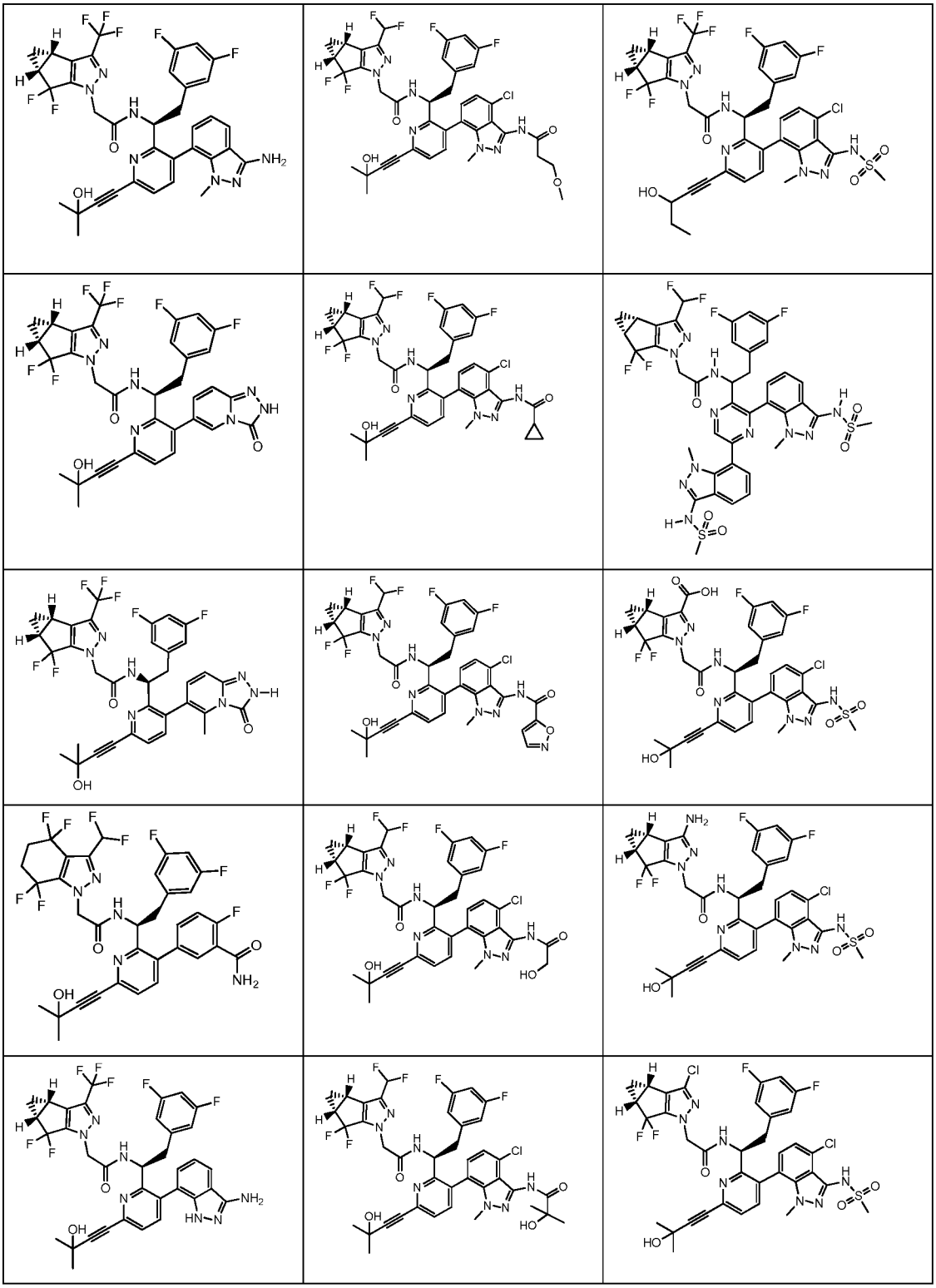


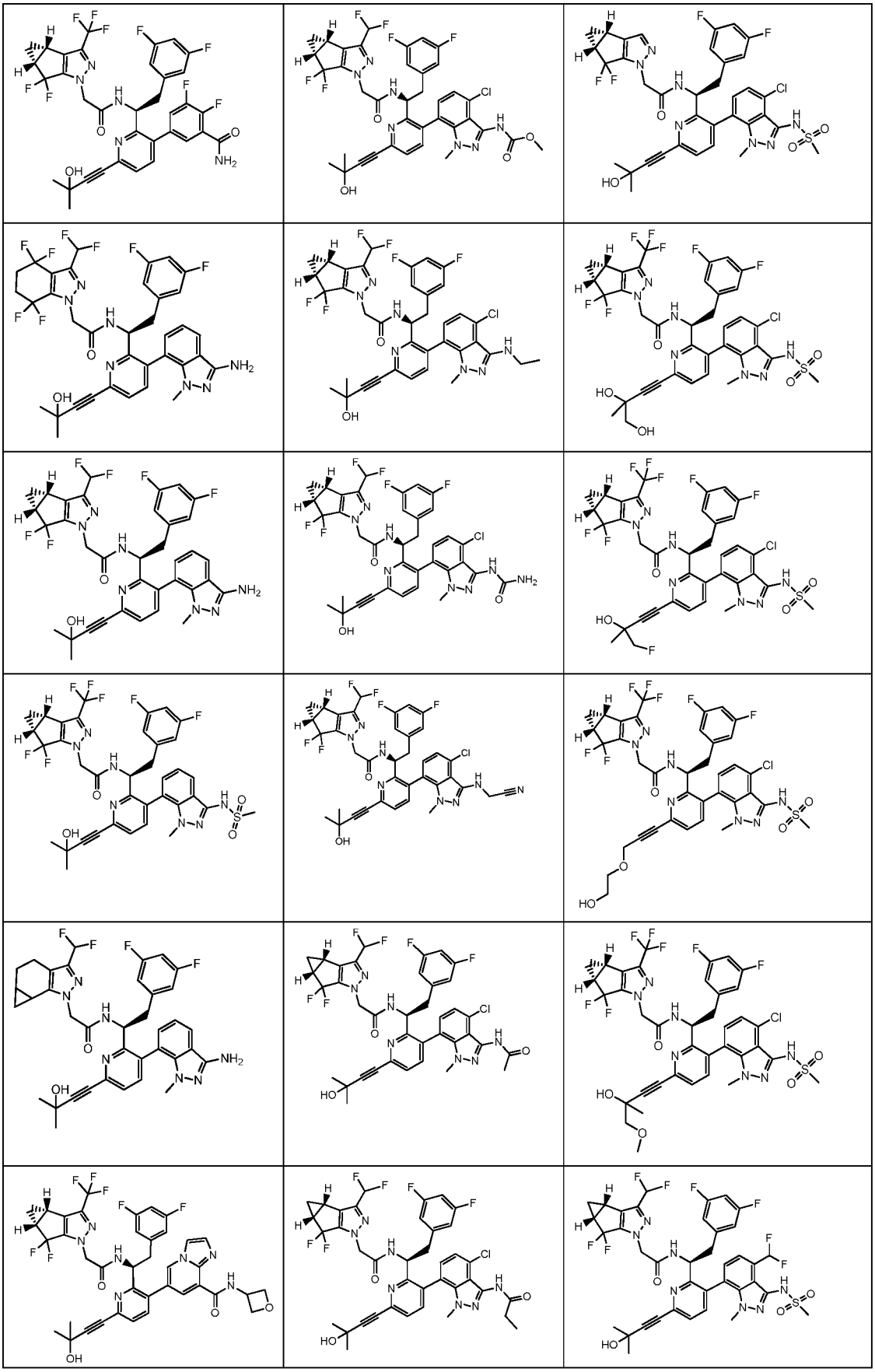


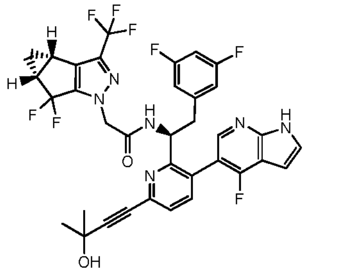
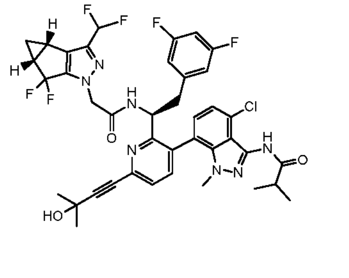
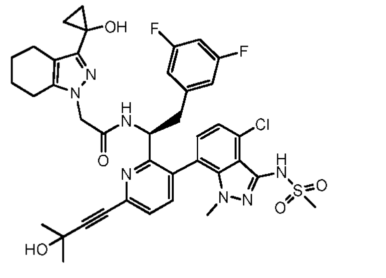
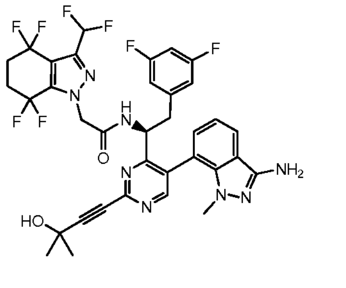
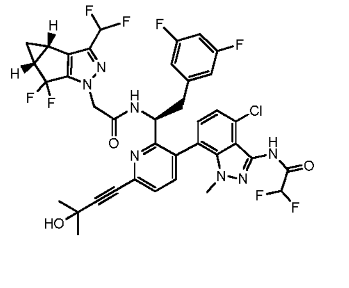
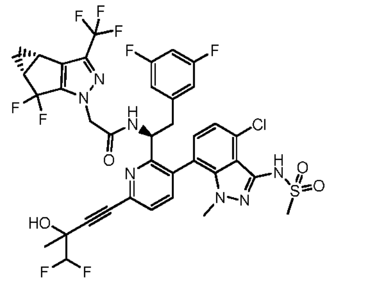
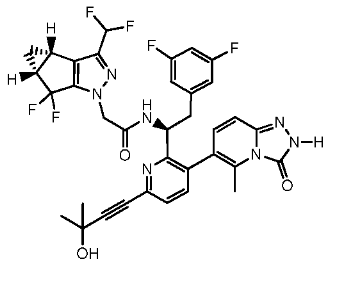
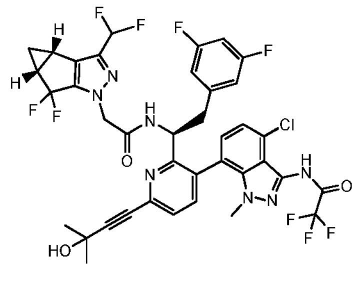
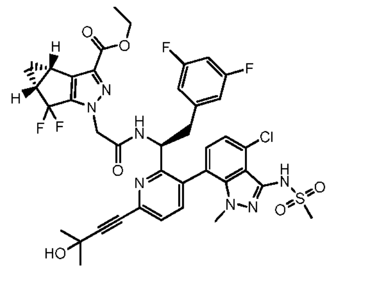
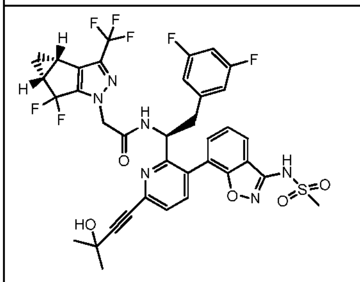
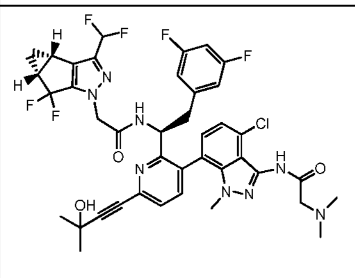
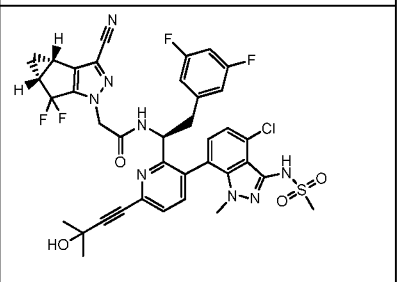
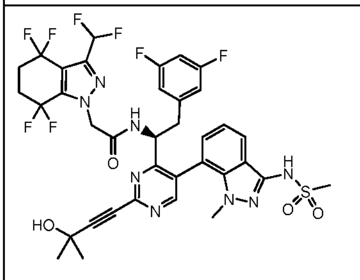
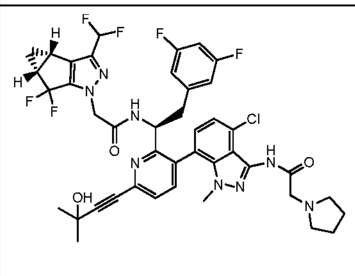
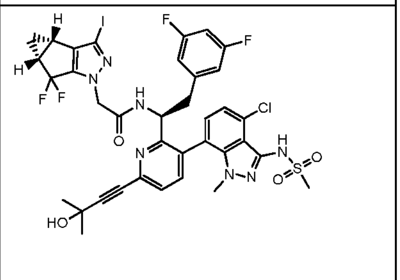
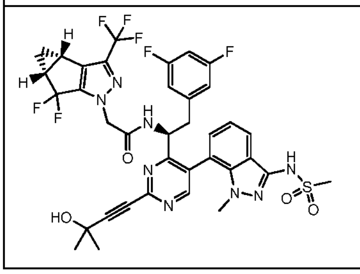
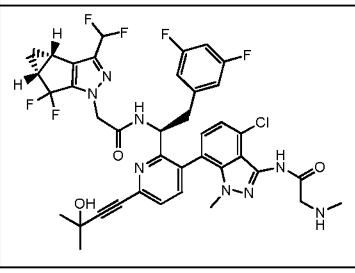
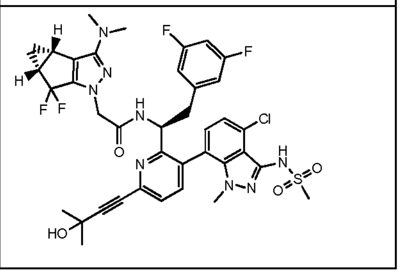


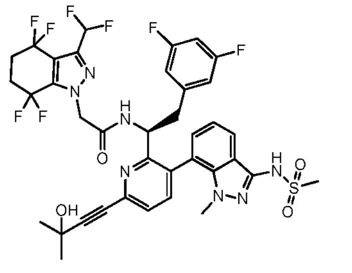
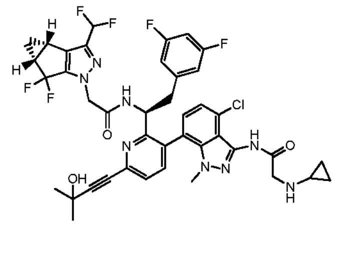
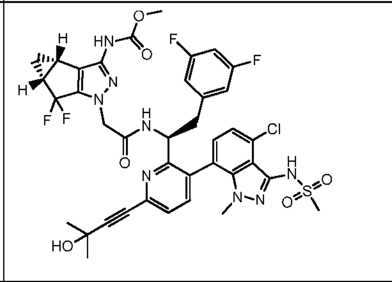
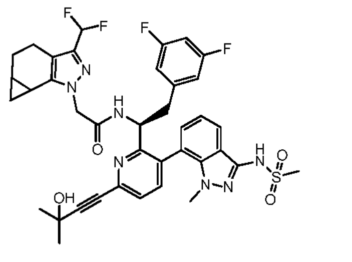
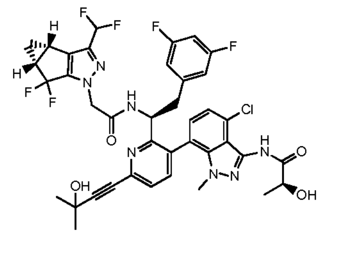
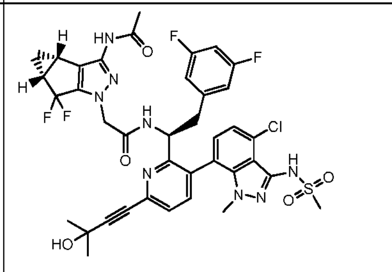
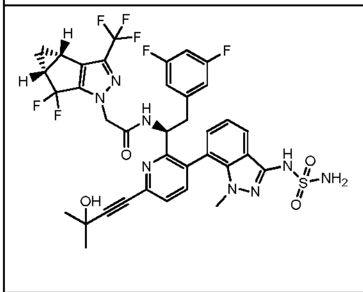
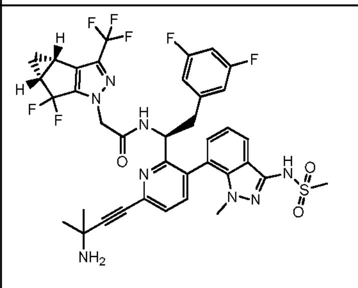
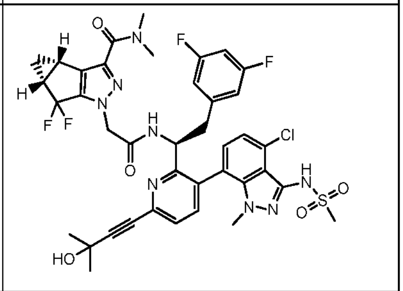
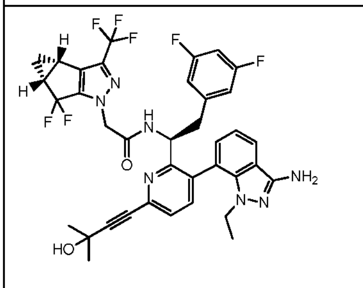
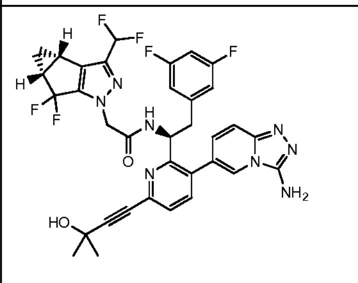
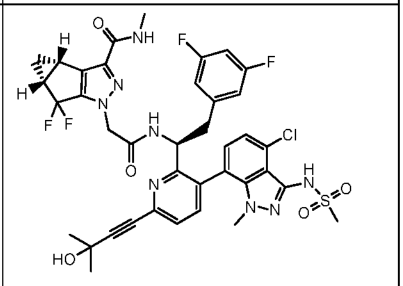
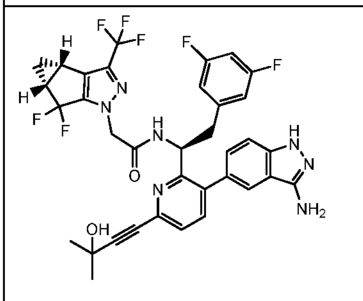
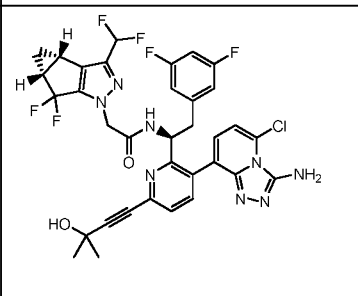
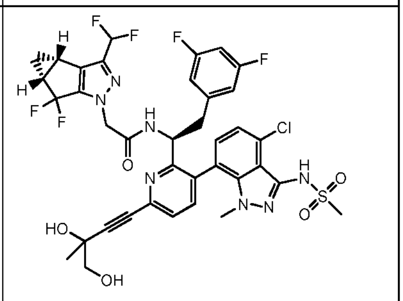
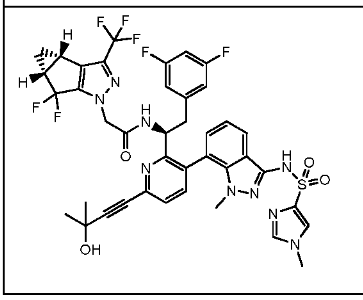
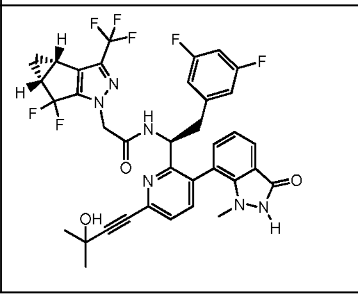
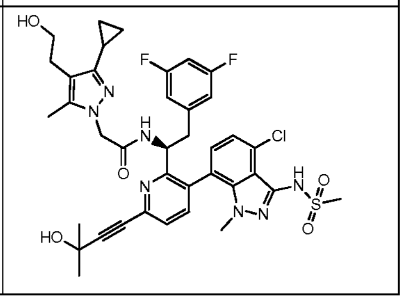


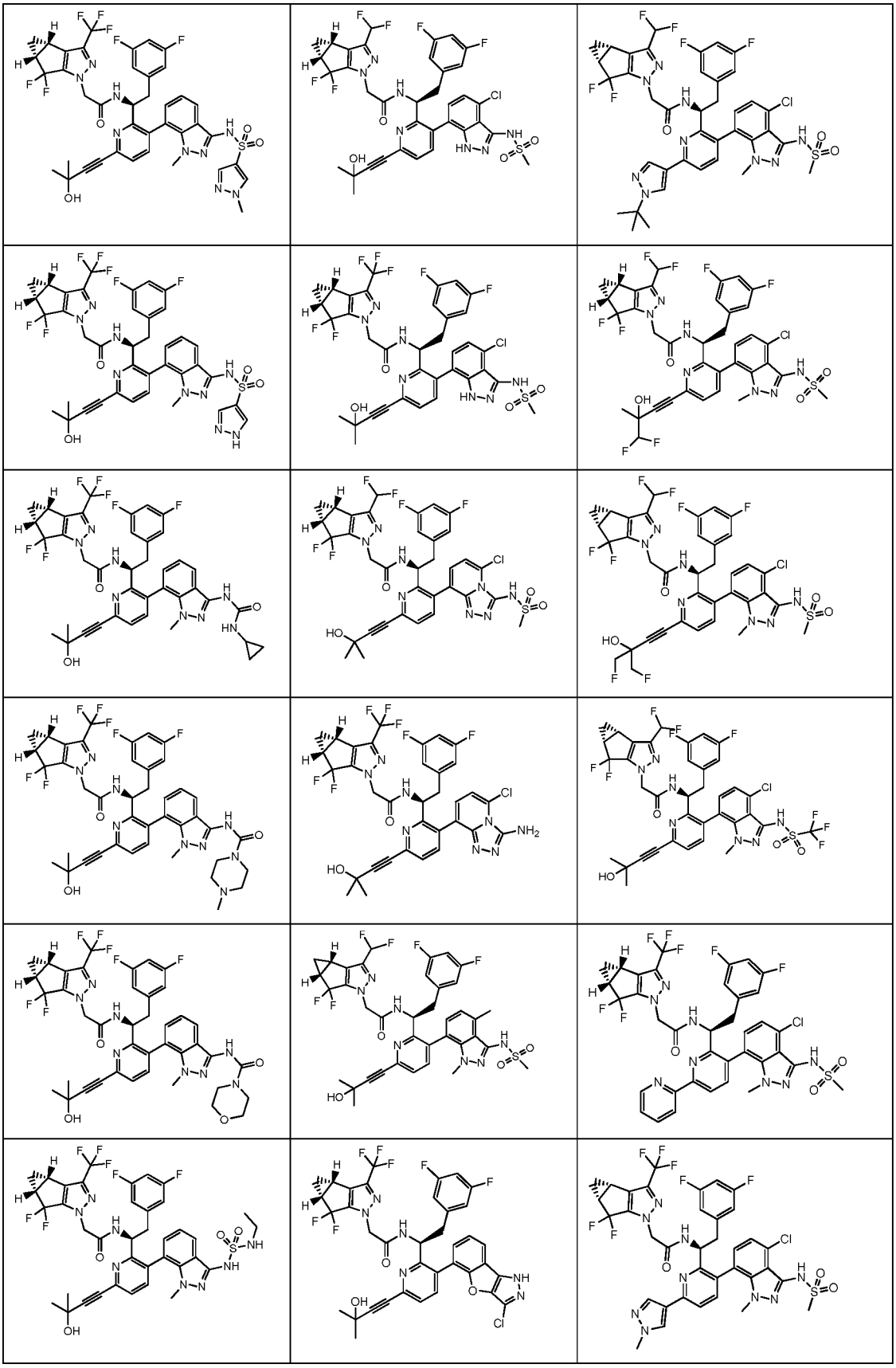


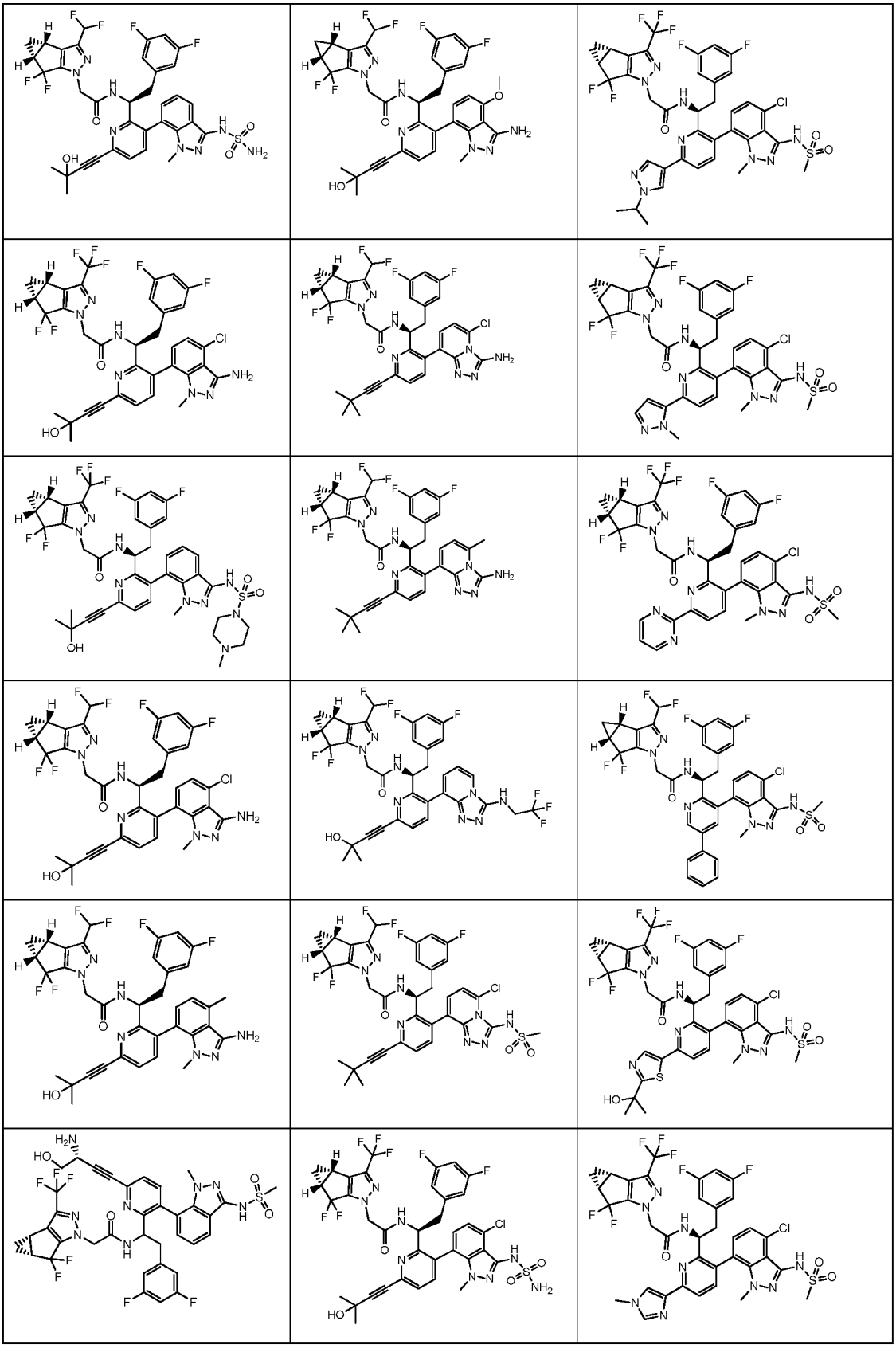


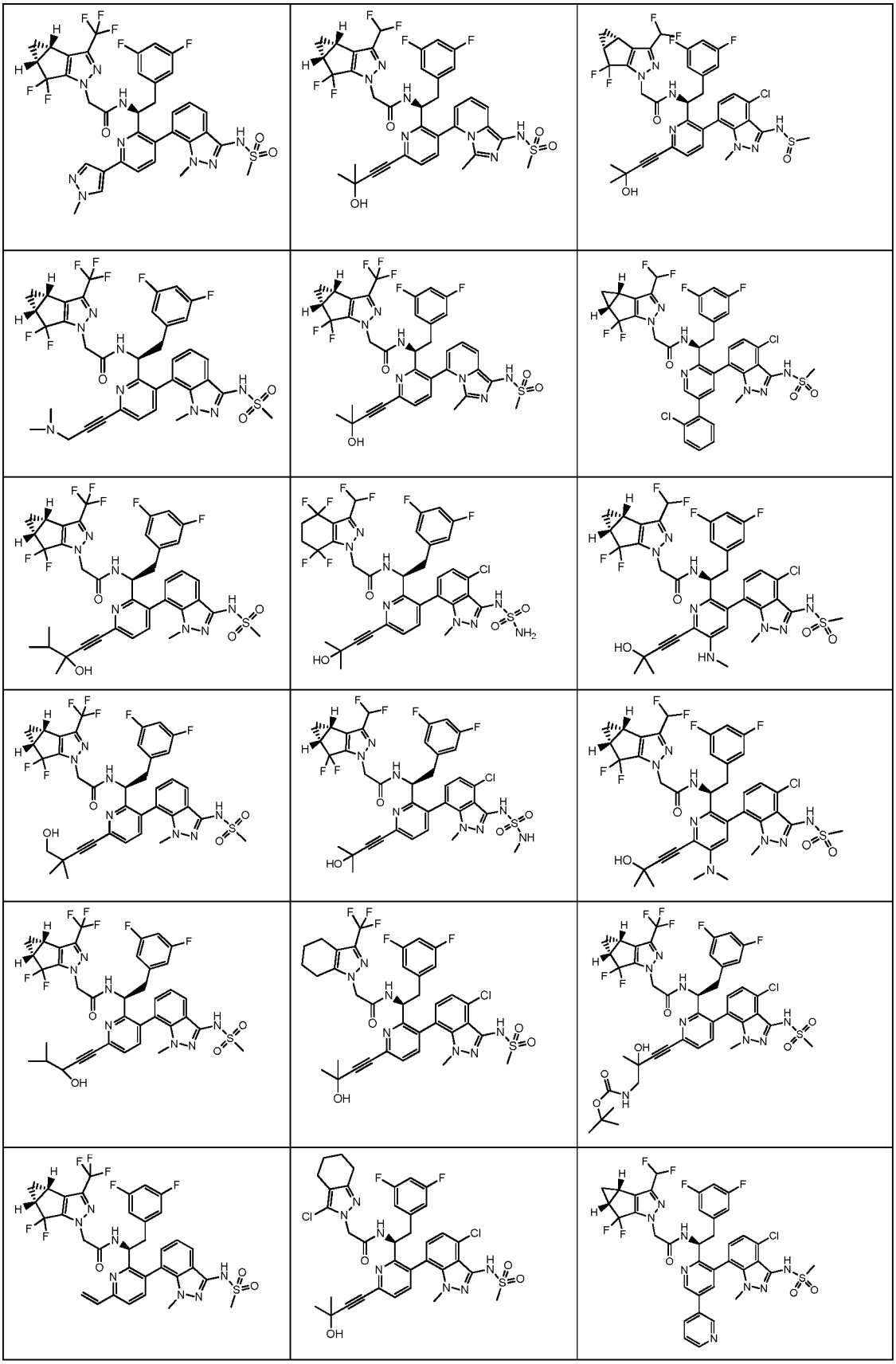


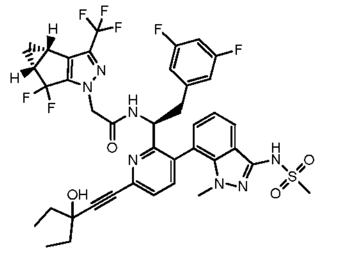
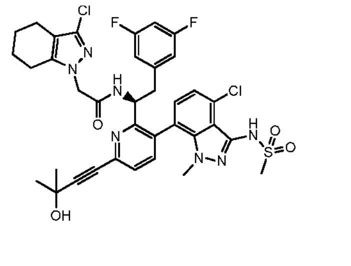
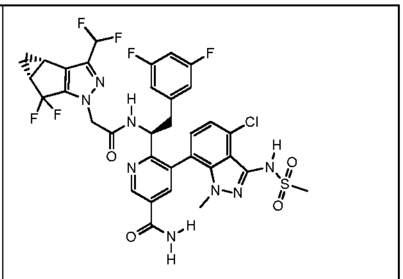
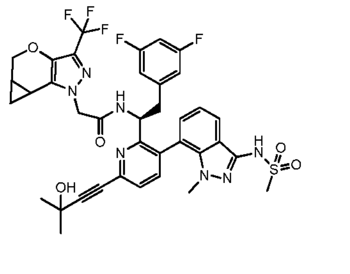
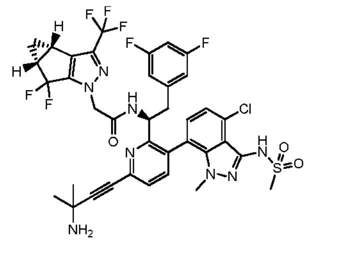
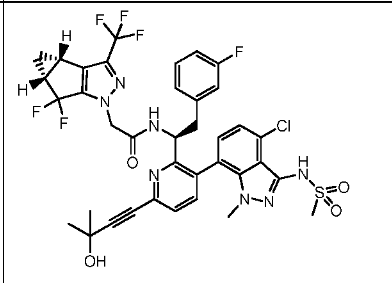
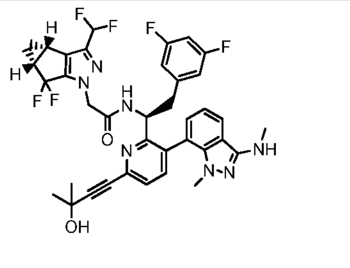
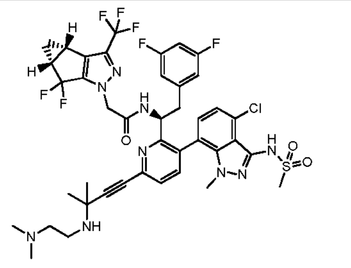
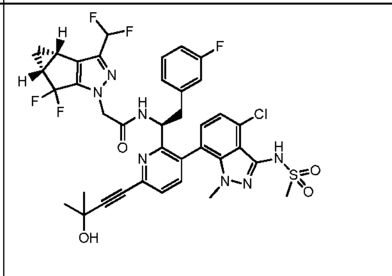
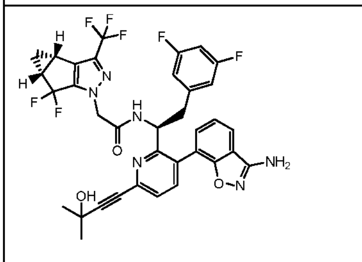
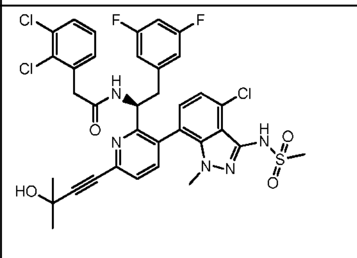
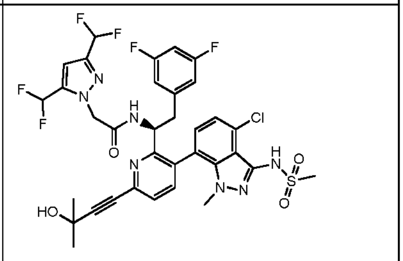
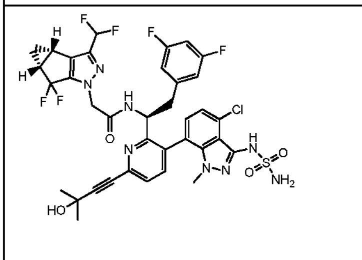
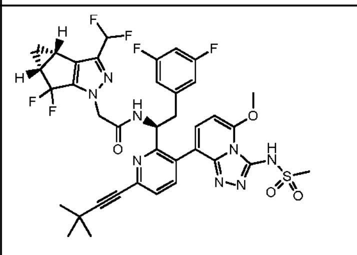
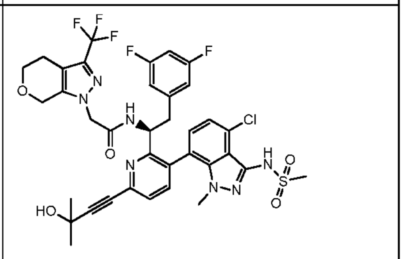
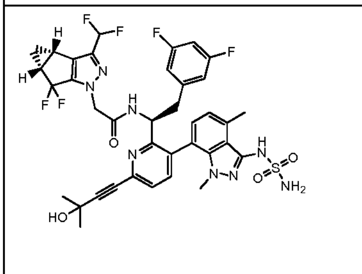
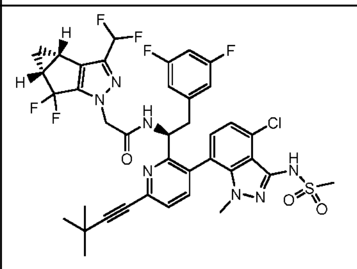
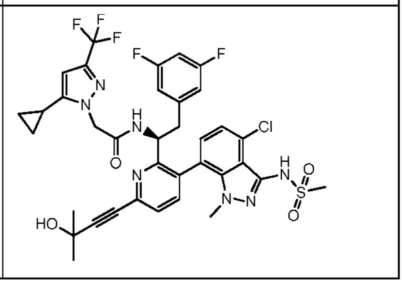
		
		
		
		
		
		

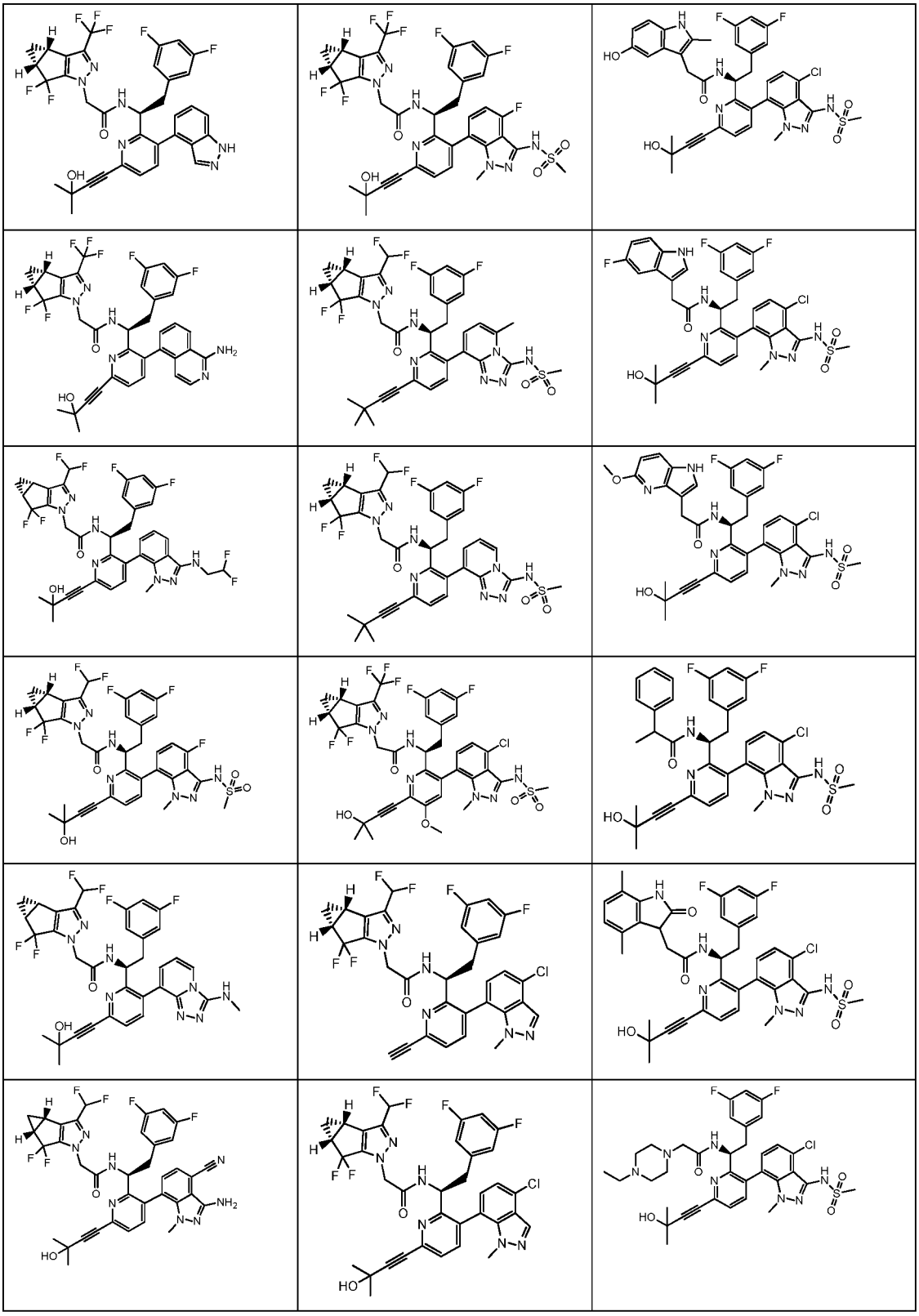
		
		
		
		
		
		

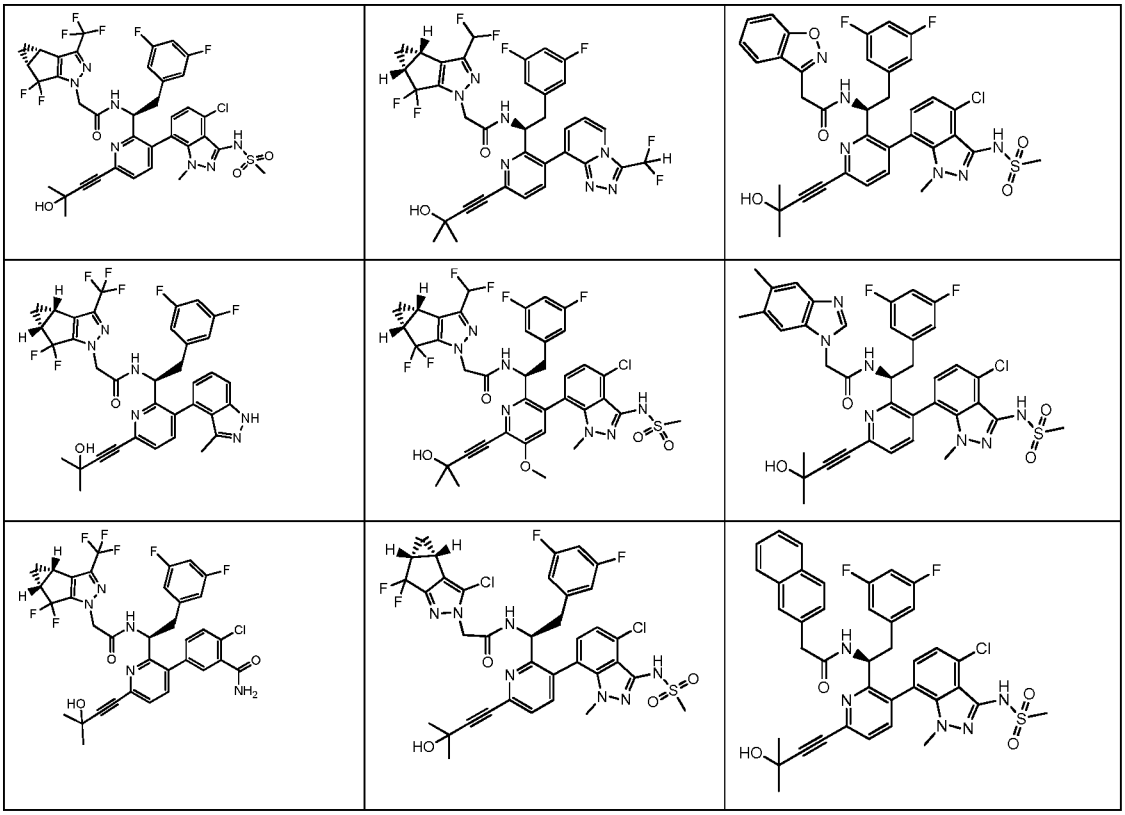










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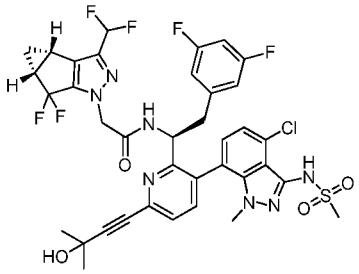
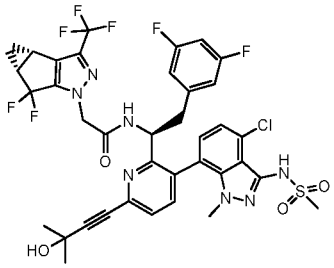


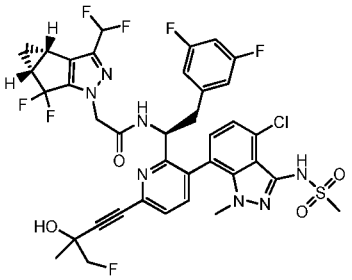
or a pharmaceutically acceptable salt thereof.

39. A compound of formula:



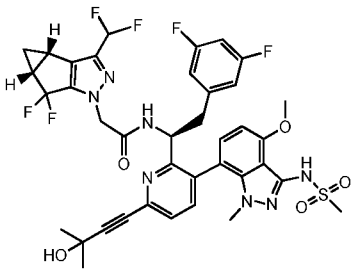
or a pharmaceutically acceptable salt thereof.

40. A compound of formula:



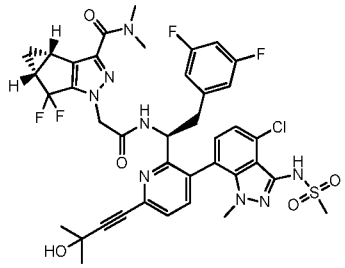
or a pharmaceutically acceptable salt thereof.

41. A compound of formula:



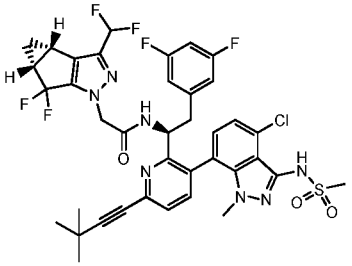
or a pharmaceutically acceptable salt thereof.

42. A compound of formula:



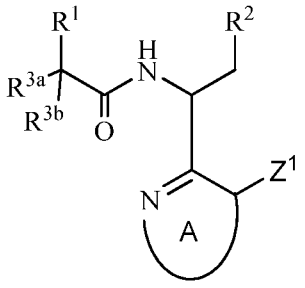
or a pharmaceutically acceptable salt thereof.

43. A compound of formula:



or a pharmaceutically acceptable salt thereof.

44. A compound of formula I:



I

wherein:

A is a 6-membered monocyclic-heteroaryl with one or two nitrogen atoms, wherein the 6-membered monocyclic-heteroaryl is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with one or more (e.g., 1 or 2) Z^3 groups;

R^1 is 6-12 membered aryl, 5-12 membered heteroaryl or 3-12 membered heterocycle, wherein any 6-12 membered aryl, 5-12 membered heteroaryl or 3-12 membered heterocycle of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups;

R^2 is phenyl, 5-membered monocyclic-heteroaryl, 6-membered monocyclic-heteroaryl or $(C_3$-$C_7)$carbocycle, wherein any phenyl, 5-membered monocyclic-heteroaryl, 6-membered monocyclic-heteroaryl or $(C_3$-$C_7)$carbocycle of R^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^5 groups;

each R^{3a} and R^{3b} is independently selected from H, halogen, $(C_1$-$C_3)$alkyl and $(C_1$-$C_3)$haloalkyl, or R^{3a} is selected from H, $(C_1$-$C_3)$alkyl and $(C_1$-$C_3)$haloalkyl and R^{3b} is selected from -OH and -CN;

Z^1 is selected from 6-12 membered aryl, 5-14 membered heteroaryl and 3-14 membered heterocycle, wherein any 6-12 membered aryl, 5-14 membered heteroaryl and 3-14 membered heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b};

each Z^{1a} is independently selected from $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, $-OR^{n1}$, $-OC(O)R^{p1}$, $-OC(O)NR^{q1}R^{r1}$, $-SR^{n1}$, $-S(O)R^{p1}$, $-S(O)_2OH$, $-S(O)_2R^{p1}$, $-S(O)_2NR^{q1}R^{r1}$, $-NR^{q1}R^{r1}$, $-NR^{n1}COR^{p1}$, $-NR^{n1}CO_2R^{p1}$, $-NR^{n1}CONR^{q1}R^{r1}$, $-NR^{n1}S(O)_2R^{p1}$, $-NR^{n1}S(O)_2OR^{p1}$, $-NR^{n1}S(O)_2NR^{q1}R^{r1}$, NO_2, $-C(O)R^{n1}$, $-C(O)OR^{n1}$, $-C(O)NR^{q1}R^{r1}$ and $-S(O)_2NR^{n1}COR^{p1}$, wherein any $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{1a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups;

each Z^{1b} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl, wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of Z^{1b} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

each Z^{1c} is independently selected from $(C_3$-$C_7)$carbocycle, phenyl, 5-6 membered monocyclic-heteroaryl, 3-7 membered heterocycle, halogen, -CN, $-OR^{n2}$, $-OC(O)R^{p2}$, $-OC(O)NR^{q2}R^{r2}$, $-SR^{n2}$, $-S(O)R^{p2}$, $-S(O)_2OH$, $-S(O)_2R^{p2}$, $-S(O)_2NR^{q2}R^{r2}$, $-NR^{q2}R^{r2}$, $-NR^{n2}COR^{p2}$, $-NR^{n2}CO_2R^{p2}$, $-NR^{n2}CONR^{q2}R^{r2}$, $-NR^{n2}S(O)_2R^{p2}$, $-NR^{n2}S(O)_2OR^{p2}$, $-NR^{n2}S(O_2NR^{q2}R^{r2}$, NO_2, $-C(O)R^{n2}$, $-C(O)OR^{n2}$, $-C(O)NR^{q2}R^{r2}$, halophenyl, 5-6 membered haloheteroaryl, 3-7 membered haloheterocycle and $(C_1$-$C_8)$heteroalkyl;

each Z^{1d} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl and $(C_1$-$C_8)$haloalkyl;

each R^{n1} is independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R^{n1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of R^{n1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

each R^{p1} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R^{p1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of R^{p1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

R^{q1} and R^{r1} are each independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R^{q1} or R^{r1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of R^{q1} or R^{r1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups, or R^{q1} and R^{r1} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or 7-membered heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups;

each R^{n2} is independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, $(C_1$-$C_8)$haloalkyl and $(C_1$-$C_8)$heteroalkyl;

each R^{p2} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, $(C_1$-$C_8)$haloalkyl and $(C_1$-$C_8)$heteroalkyl;

R^{q2} and R^{r2} are each independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, $(C_1$-$C_8)$haloalkyl and $(C_1$-$C_8)$heteroalkyl, or R^{q2} and R^{r2} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

Z^2 is selected from $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, $-C(O)R^{n3}$ and $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl and 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with one or more (e.g.,1, 2, 3, 4, or 5) Z^{2c} groups;

each Z^{2a} is independently selected from $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, $-CN$, $-OR^{n4}$, $-OC(O)R^{p4}$, $-OC(O)NR^{q4}R^{r4}$, $-SR^{n4}$, $-S(O)R^{p4}$, $-S(O)_2OH$, $-S(O)_2R^{p4}$, $-S(O)_2NR^{q4}R^{r4}$, $-NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}CONR^{q4}R^{r4}$, $-NR^{n4}S(O)_2R^{p4}$, $-NR^{n4}S(O)_2OR^{p4}$, $-NR^{n4}S(O)_2NR^{q4}R^{r4}$, NO_2, $-C(O)R^{n4}$, $-C(O)OR^{n4}$ and $-C(O)NR^{q4}R^{r4}$, wherein any $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{2a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups;

each Z^{2b} is independently selected from $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$heteroalkyl and $(C_1$-$C_4)$haloalkyl;

each Z^{2c} is independently selected from halogen, $-CN$, $-OR^{n4}$, $-OC(O)R^{p4}$, $-OC(O)NR^{q4}R^{r4}$, $-SR^{n4}$, $-S(O)R^{p4}$, $-S(O)_2OH$, $-S(O)_2R^{p4}$, $-S(O)_2NR^{q4}R^{r4}$, $-NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}CONR^{q4}R^{r4}$, $-NR^{n4}S(O)_2R^{p4}$, $-NR^{n4}S(O)_2OR^{p4}$, $-NR^{n4}S(O)_2NR^{q4}R^{r4}$, NO_2, $-C(O)R^{n4}$, $-C(O)OR^{n4}$ and $-C(O)NR^{q4}R^{r4}$;

each R^{n3} is independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl, wherein any $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl of R^{n3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl and $(C_2$-$C_4)$alkynyl of R^{n3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups;

R^{q3} and R^{r3} are each independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl, wherein any $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl of R^{q3} or R^{r3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_1$-$C_4)$alkyl and $(C_2$-$C_4)$alkenyl of R^{q3} or R^{r3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups, or R^{q3} and R^{r3} together with the nitrogen to which they are attached form a heterocycle or heteroaryl, wherein the heterocycle or heteroaryl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups;

each R^{n4} is independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_4)$haloalkyl and $(C_1$-$C_4)$heteroalkyl;

each R^{p4} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_2$-$C_4)$alkynyl, $(C_1$-$C_4)$haloalkyl and $(C_1$-$C_4)$heteroalkyl;

R^{q4} and R^{r4} are each independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_2$-$C_4)$alkynyl, $(C_1$-$C_4)$haloalkyl and $(C_1$-$C_4)$heteroalkyl;

each Z^3 is independently selected from halogen, $(C_1$-$C_4)$alkyl, -OH, -CN, $(C_1$-$C_4)$heteroalkyl and $(C_1$-$C_4)$haloalkyl;

each Z^4 is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, halogen, -CN, $-OR^{n5}$, $-OC(O)R^{p5}$, $-OC(O)NR^{q5}R^{r5}$, $-SR^{n5}$, $-S(O)R^{p5}$, $-S(O)_2OH$, $-S(O)_2R^{p5}$, $-S(O)_2NR^{q5}R^{r5}$, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-NR^{n5}CONR^{q5}R^{r5}$, $-NR^{n5}S(O)_2R^{p5}$, $-NR^{n5}S(O)_2OR^{p5}$, $-NR^{n5}S(O)_2NR^{q5}R^{r5}$, NO_2, $-C(O)R^{n5}$, $-C(O)OR^{n5}$ and $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3$-$C_7)$carbocycle, of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} or Z^{4b} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} groups;

each Z^{4a} is independently selected from halogen, -CN, $-OR^{n6}$, $-OC(O)R^{p6}$, $-OC(O)NR^{q6}R^{r6}$, $-SR^{n6}$, $-S(O)R^{p6}$, $-S(O)_2OH$, $-S(O)_2R^{p6}$, $-S(O)_2NR^{q6}R^{r6}$, $-NR^{q6}R^{r6}$, $-NR^{n6}COR^{p6}$,

$-NR^{n6}CO_2R^{p6}$, $-NR^{n6}CONR^{q6}R^{r6}$, $-NR^{n6}S(O)_2R^{p6}$, $-NR^{n6}S(O)_2OR^{p6}$, $-NR^{n6}S(O)_2NR^{q6}R^{r6}$, NO_2, $-C(O)R^{n6}$, $-C(O)OR^{n6}$ and $-C(O)NR^{q6}R^{r6}$;

each Z^{4b} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl $(C_2\text{-}C_4)$alkynyl and $(C_1\text{-}C_4)$haloalkyl;

each R^{n5} is independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

each R^{p5} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

R^{q5} and R^{r5} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

each R^{n6} is independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

each R^{p6} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

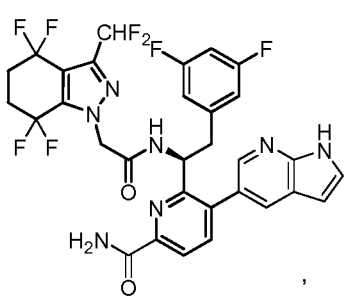
R^{q6} and R^{r6} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

each Z^5 is independently selected from $(C_1\text{-}C_6)$alkyl, halogen, -CN and $-OR^{n7}$, wherein any $(C_1\text{-}C_6)$alkyl of Z^5 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen; and

each R^{n7} is independently selected from H, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$haloalkyl and $(C_3\text{-}C_7)$carbocycle;

or a pharmaceutically acceptable salt thereof.

45. The compound of Claim 44, or a pharmaceutically acceptable salt thereof, which is:



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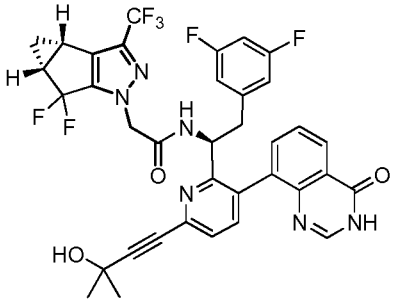

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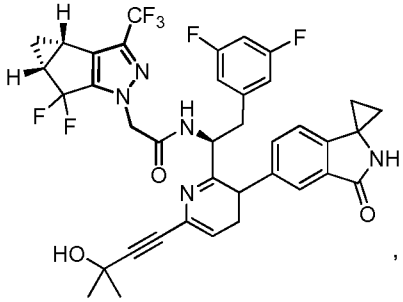

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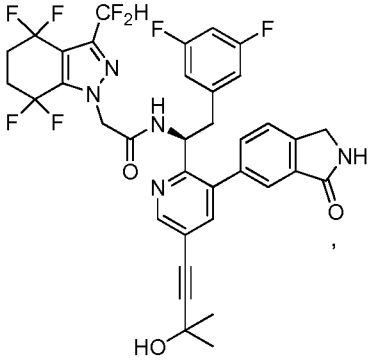

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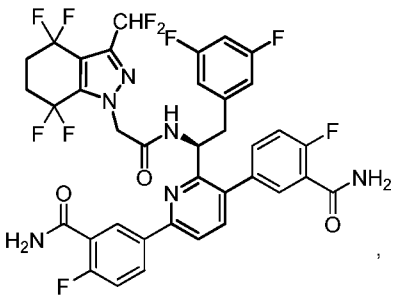

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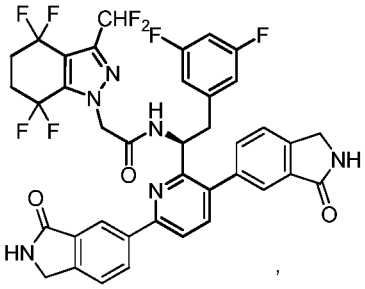

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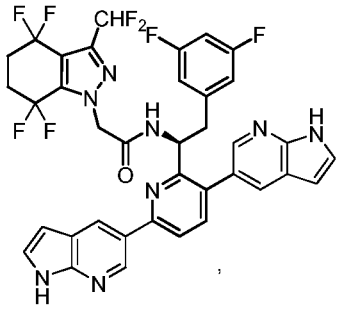

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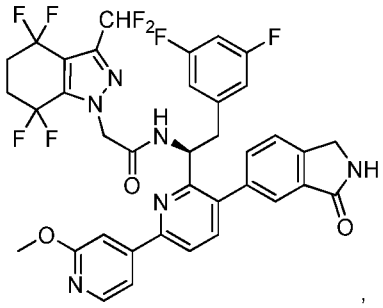
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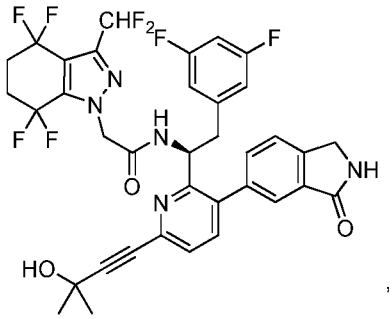
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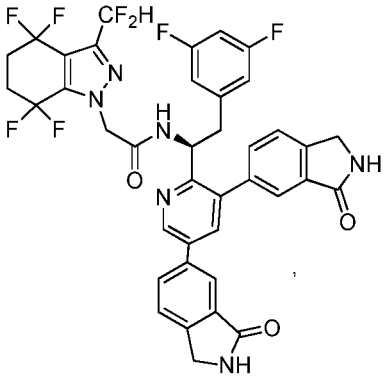
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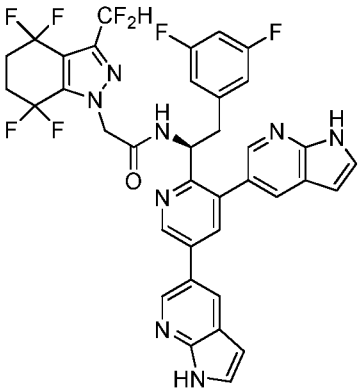
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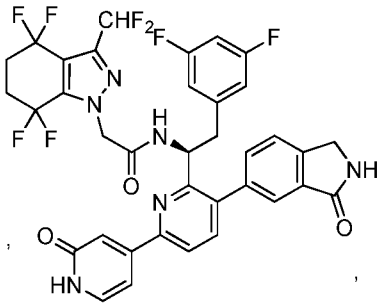
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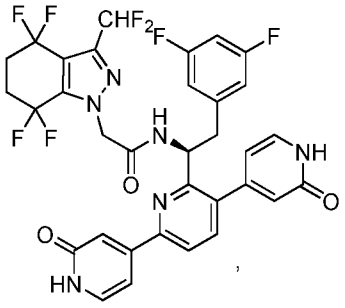
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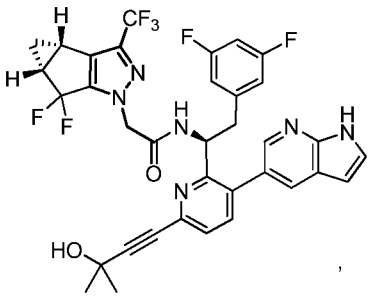
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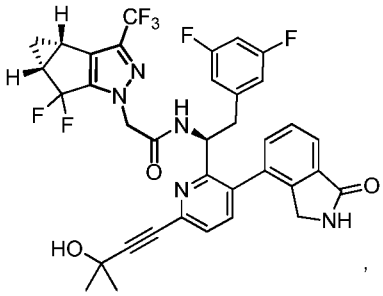
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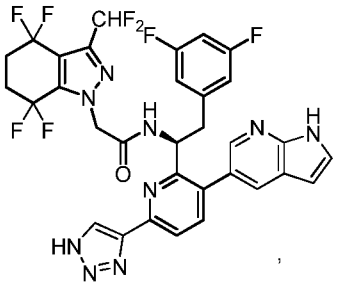
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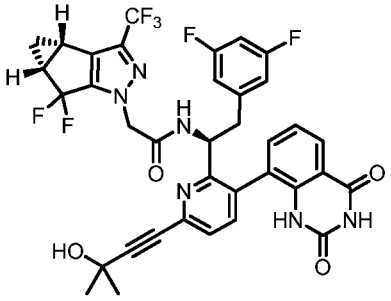
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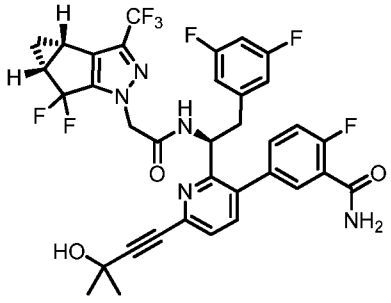
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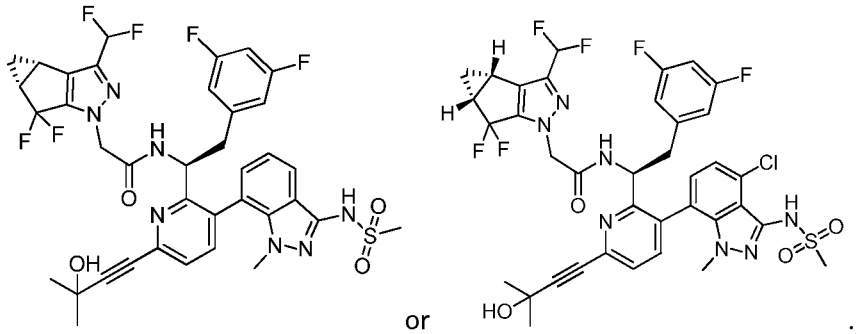
46. The compound of Claim 44, or a pharmaceutically acceptable salt thereof, which is:



or

.

47. A pharmaceutical composition comprising a compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

48. A pharmaceutical composition comprising a compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, and an additional therapeutic agent, wherein the additional therapeutic agent is an HIV protease inhibiting compound, an HIV non-nucleoside inhibitor of reverse transcriptase, an HIV nucleoside inhibitor of reverse transcriptase, an HIV nucleotide inhibitor of reverse transcriptase, an HIV integrase inhibitor, a gp41 inhibitor, a CXCR4 inhibitor, a gp120 inhibitor, a CCR5 inhibitor, a capsid polymerization inhibitor, or a non-catalytic site site HIV integrase inhibitor and combinations thereof.

49. A method for treating a HIV infection in a patient in need thereof comprising administering a therapeutically effective amount of a compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, to the patient.

50. A method for treating an HIV infection in a patient in need thereof comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of an additional therapeutic agent, wherein the additional therapeutic agent is an HIV protease inhibiting compound, an HIV non-nucleoside inhibitor of reverse transcriptase, an HIV nucleoside inhibitor of reverse transcriptase, an HIV nucleotide inhibitor of reverse transcriptase, an HIV integrase inhibitor, a gp41 inhibitor, a CXCR4 inhibitor, a gp120 inhibitor, a CCR5 inhibitor, a capsid polymerization inhibitor, or a non-catalytic site HIV integrase site inhibitor and combinations thereof.

51. A compound of any of claims 1-46, or a pharmaceutically acceptable salt thereof, for use in medical therapy.

52. A compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of an HIV virus infection.

53. The use of a compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating an HIV virus infection in a mammal.

54. A compound or method as described herein.

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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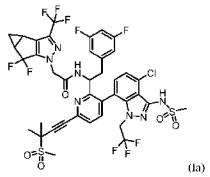
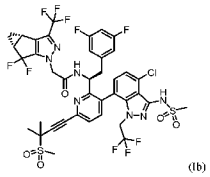
(54) Title: THERAPEUTIC COMPOUNDS USEFUL FOR THE PROPHYLACTIC OR THERAPEUTIC TREATMENT OF AN HIV VIRUS INFECTION


(Ia)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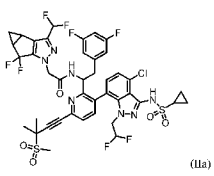
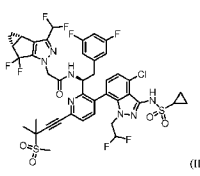

(IIa)


(IIb)

(57) Abstract: The present disclosure relates to a compound of formula (Ia), (Ib), (IIa), and (IIb): (Ia) (Ib) (IIa) (IIb) which are useful in the treatment of a Retroviridae viral infection including an infection caused by the HIV virus.

WO 2018/035359 A1

[Continued on next page]

UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

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THERAPEUTIC COMPOUNDS USEFUL FOR THE PROPHYLACTIC OR THERAPEUTIC TREATMENT OF AN HIV VIRUS INFECTION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit to U.S. Provisional Application Serial No. 62/377,312, filed on August 19, 2016 and to U.S. Provisional Application Serial No. 62/457,555, filed February 10, 2017, the disclosures of which are incorporated by reference in their entireties

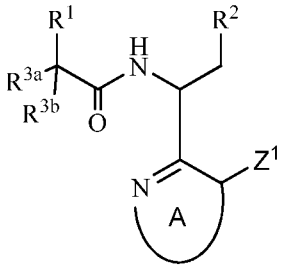
FIELD

[0002] The present disclosure relates to novel compounds for use in the treatment of a *Retroviridae* viral infection including an infection caused by the HIV virus. The present disclosure also relates to intermediates for its preparation and to pharmaceutical compositions containing said novel compound.

BACKGROUND

[0003] Positive-single stranded RNA viruses comprising the *Retroviridae* family include those of the subfamily *Orthoretrovirinae* and genera *Alpharetrovirus*, *Betaretrovirus*, *Gammaretrovirus*, *Deltaretrovirus*, *Epsilonretrovirus*, *Lentivirus*, and *Spumavirus* which cause many human and animal diseases. Among the *Lentivirus*, HIV-1 infection in humans leads to depletion of T helper cells and immune dysfunction, producing immunodeficiency and vulnerability to opportunistic infections. Treating HIV-1 infections with highly active antiretroviral therapies (HAART) has proven to be effective at reducing viral load and significantly delaying disease progression (Hammer, S.M., et al.; *JAMA* 2008, 300: 555-570). However, these treatments could lead to the emergence of HIV strains that are resistant to current therapies (Taiwo, B., *International Journal of Infectious Diseases* 2009, 13:552-559; Smith, R. J., et al., *Science* 2010, 327:697-701). Therefore, there is a pressing need to discover new antiretroviral agents that are active against emerging drug-resistant HIV variants.

[0004] U.S. Patent Publication No. 2014/0296266A1, published October 2, 2014, discloses compounds useful for treating a *Retroviridae* viral infection including an infection caused by the HIV virus. U.S. Patent Publication 2014/0296266A1 relates to, among other things, compounds of Formula I:



I

wherein:

A is a 6-membered monocyclic-heteroaryl with one or two nitrogen atoms, wherein the 6-membered monocyclic-heteroaryl is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with one or more (e.g., 1 or 2) Z^3 groups;

R^1 is 6-12 membered aryl, 5-12 membered heteroaryl or 3-12 membered heterocycle, wherein any 6-12 membered aryl, 5-12 membered heteroaryl or 3-12 membered heterocycle of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups;

R^2 is phenyl, 5-membered monocyclic-heteroaryl, 6-membered monocyclic-heteroaryl or $(C_3$-$C_7)$carbocycle, wherein any phenyl, 5-membered monocyclic-heteroaryl, 6-membered monocyclic-heteroaryl or $(C_3$-$C_7)$carbocycle of R^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^5 groups;

each R^{3a} and R^{3b} is independently selected from H, halogen, $(C_1$-$C_3)$alkyl and $(C_1$-$C_3)$haloalkyl, or R^{3a} is selected from H, $(C_1$-$C_3)$alkyl and $(C_1$-$C_3)$haloalkyl and R^{3b} is selected from -OH and -CN;

Z^1 is selected from 6-12 membered aryl, 5-14 membered heteroaryl and 3-14 membered heterocycle, wherein any 6-12 membered aryl, 5-14 membered heteroaryl and 3-14 membered heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b};

each Z^{1a} is independently selected from $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, $-OR^{n1}$, $-OC(O)R^{p1}$, $-OC(O)NR^{q1}R^{r1}$, $-SR^{n1}$, $-S(O)R^{p1}$, $-S(O)_2OH$, $-S(O)_2R^{p1}$, $-S(O)_2NR^{q1}R^{r1}$, $-NR^{q1}R^{r1}$, $-NR^{n1}COR^{p1}$, $-NR^{n1}CO_2R^{p1}$, $-NR^{n1}CONR^{q1}R^{r1}$, $-NR^{n1}S(O)_2R^{p1}$, $-NR^{n1}S(O)_2OR^{p1}$, $-NR^{n1}S(O)_2NR^{q1}R^{r1}$, NO_2, $-C(O)R^{n1}$, $-C(O)OR^{n1}$, $-C(O)NR^{q1}R^{r1}$ and $-S(O)_2NR^{n1}COR^{p1}$, wherein any $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{1a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups;

each Z^{1b} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl, wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of Z^{1b} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

each Z^{1c} is independently selected from $(C_3$-$C_7)$carbocycle, phenyl, 5-6 membered monocyclic-heteroaryl, 3-7 membered heterocycle, halogen, -CN, $-OR^{n2}$, $-OC(O)R^{p2}$, $-OC(O)NR^{q2}R^{r2}$, $-SR^{n2}$, $-S(O)R^{p2}$, $-S(O)_2OH$, $-S(O)_2R^{p2}$, $-S(O)_2NR^{q2}R^{r2}$, $-NR^{q2}R^{r2}$, $-NR^{n2}COR^{p2}$, $-NR^{n2}CO_2R^{p2}$, $-NR^{n2}CONR^{q2}R^{r2}$, $-NR^{n2}S(O)_2R^{p2}$, $-NR^{n2}S(O)_2OR^{p2}$, $-NR^{n2}S(O_2NR^{q2}R^{r2}$, NO_2, $-C(O)R^{n2}$, $-C(O)OR^{n2}$, $-C(O)NR^{q2}R^{r2}$, halophenyl, 5-6 membered haloheteroaryl, 3-7 membered haloheterocycle and $(C_1$-$C_8)$heteroalkyl;

each Z^{1d} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl and $(C_1$-$C_8)$haloalkyl;

each R^{n1} is independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R^{n1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of R^{n1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

each R^{p1} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R^{p1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of R^{p1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

R^{q1} and R^{r1} are each independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R^{q1} or R^{r1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of R^{q1} or R^{r1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups, or R^{q1} and R^{r1} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or 7-membered heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups;

each R^{n2} is independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, $(C_1$-$C_8)$haloalkyl and $(C_1$-$C_8)$heteroalkyl;

each R^{p2} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, $(C_1$-$C_8)$haloalkyl and $(C_1$-$C_8)$heteroalkyl;

R^{q2} and R^{r2} are each independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, $(C_1$-$C_8)$haloalkyl and $(C_1$-$C_8)$heteroalkyl, or R^{q2} and R^{r2} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

Z^2 is selected from $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, $-C(O)R^{n3}$ and $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl and 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) Z^{2c} groups;

each Z^{2a} is independently selected from $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, $-CN$, $-OR^{n4}$, $-OC(O)R^{p4}$, $-OC(O)NR^{q4}R^{r4}$, $-SR^{n4}$, $-S(O)R^{p4}$, $-S(O)_2OH$, $-S(O)_2R^{p4}$, $-S(O)_2NR^{q4}R^{r4}$, $-NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}CONR^{q4}R^{r4}$, $-NR^{n4}S(O)_2R^{p4}$, $-NR^{n4}S(O)_2OR^{p4}$, $-NR^{n4}S(O)_2NR^{q4}R^{r4}$, NO_2, $-C(O)R^{n4}$, $-C(O)OR^{n4}$ and $-C(O)NR^{q4}R^{r4}$, wherein any $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{2a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups;

each Z^{2b} is independently selected from $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$heteroalkyl and $(C_1$-$C_4)$haloalkyl;

each Z^{2c} is independently selected from halogen, $-CN$, $-OR^{n4}$, $-OC(O)R^{p4}$, $-OC(O)NR^{q4}R^{r4}$, $-SR^{n4}$, $-S(O)R^{p4}$, $-S(O)_2OH$, $-S(O)_2R^{p4}$, $-S(O)_2NR^{q4}R^{r4}$, $-NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}CONR^{q4}R^{r4}$, $-NR^{n4}S(O)_2R^{p4}$, $-NR^{n4}S(O)_2OR^{p4}$, $-NR^{n4}S(O)_2NR^{q4}R^{r4}$, NO_2, $-C(O)R^{n4}$, $-C(O)OR^{n4}$ and $-C(O)NR^{q4}R^{r4}$;

each R^{n3} is independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl, wherein any $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl of R^{n3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl and $(C_2$-$C_4)$alkynyl of R^{n3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups;

R^{q3} and R^{r3} are each independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl, wherein any $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl of R^{q3} or R^{r3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_1$-$C_4)$alkyl and $(C_2$-$C_4)$alkenyl of R^{q3} or R^{r3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups, or R^{q3} and R^{r3} together with the nitrogen to which they are attached form a heterocycle or heteroaryl, wherein the heterocycle or heteroaryl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups;

each R^{n4} is independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_4)$haloalkyl and $(C_1$-$C_4)$heteroalkyl;

each R^{p4} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_2$-$C_4)$alkynyl, $(C_1$-$C_4)$haloalkyl and $(C_1$-$C_4)$heteroalkyl;

R^{q4} and R^{r4} are each independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_2$-$C_4)$alkynyl, $(C_1$-$C_4)$haloalkyl and $(C_1$-$C_4)$heteroalkyl;

each Z^3 is independently selected from halogen, $(C_1$-$C_4)$alkyl, -OH, -CN, $(C_1$-$C_4)$heteroalkyl and $(C_1$-$C_4)$haloalkyl;

each Z^4 is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, halogen, -CN, $-OR^{n5}$, $-OC(O)R^{p5}$, $-OC(O)NR^{q5}R^{r5}$, $-SR^{n5}$, $-S(O)R^{p5}$, $-S(O)_2OH$, $-S(O)_2R^{p5}$, $-S(O)_2NR^{q5}R^{r5}$, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-NR^{n5}CONR^{q5}R^{r5}$, $-NR^{n5}S(O)_2R^{p5}$, $-NR^{n5}S(O)_2OR^{p5}$, $-NR^{n5}S(O)_2NR^{q5}R^{r5}$, NO_2, $-C(O)R^{n5}$, $-C(O)OR^{n5}$ and $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3$-$C_7)$carbocycle, of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} or Z^{4b} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} groups;

each Z^{4a} is independently selected from halogen, -CN, $-OR^{n6}$, $-OC(O)R^{p6}$, $-OC(O)NR^{q6}R^{r6}$, $-SR^{n6}$, $-S(O)R^{p6}$, $-S(O)_2OH$, $-S(O)_2R^{p6}$, $-S(O)_2NR^{q6}R^{r6}$, $-NR^{q6}R^{r6}$,

$-NR^{n6}COR^{p6}$, $-NR^{n6}CO_2R^{p6}$, $-NR^{n6}CONR^{q6}R^{r6}$, $-NR^{n6}S(O)_2R^{p6}$, $-NR^{n6}S(O)_2OR^{p6}$, $-NR^{n6}S(O)_2NR^{q6}R^{r6}$, NO_2, $-C(O)R^{n6}$, $-C(O)OR^{n6}$ and $-C(O)NR^{q6}R^{r6}$;

each Z^{4b} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl $(C_2\text{-}C_4)$alkynyl and $(C_1\text{-}C_4)$haloalkyl;

each R^{n5} is independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

each R^{p5} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

R^{q5} and R^{r5} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

each R^{n6} is independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

each R^{p6} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

R^{q6} and R^{r6} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

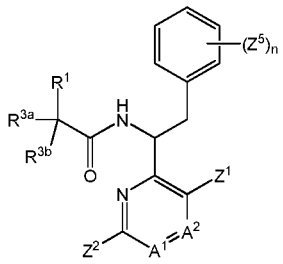
each Z^5 is independently selected from $(C_1\text{-}C_6)$alkyl, halogen, -CN and $-OR^{n7}$,

wherein any $(C_1\text{-}C_6)$alkyl of Z^5 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen; and

each R^{n7} is independently selected from H, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$haloalkyl and $(C_3\text{-}C_7)$carbocycle;

or a pharmaceutically acceptable salt thereof.

[0005] U.S. Patent Publication No. 2014/0303164A1, published October 9, 2014, discloses compounds useful for treating a *Retroviridae* viral infection including an infection caused by the HIV virus. U.S. Patent Publication 2014/0303164A1 relates to, among other things, compounds of Formula IIId:



IIId

wherein

A^1 is CH, C-Z^3, or nitrogen;

A^2 is CH or nitrogen;

R^1 is 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle, wherein any 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle of R^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, wherein the Z^4 groups are the same or different;

each R^{3a} and R^{3b} is independently H or $(C_1$-$C_3)$alkyl;

Z^1 is 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle, wherein any 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b}, wherein the Z^{1a} and Z^{1b} groups are the same or different;

each Z^{1a} is independently $(C_3$-$C_7)$carbocycle, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, -OR^{n1}, -$OC(O)R^{p1}$, -$OC(O)NR^{q1}R^{r1}$, -SR^{n1}, -$S(O)R^{p1}$, -$S(O)_2OH$, -$S(O)_2R^{p1}$, -$S(O)_2NR^{q1}R^{r1}$, -$NR^{q1}R^{r1}$, -$NR^{n1}COR^{p1}$, -$NR^{n1}CO_2R^{p1}$, -$NR^{n1}CONR^{q1}R^{r1}$, -$NR^{n1}S(O)_2R^{p1}$, -$NR^{n1}S(O)_2OR^{p1}$, -$NR^{n1}S(O)_2NR^{q1}R^{r1}$, -$C(O)R^{n1}$, -$C(O)OR^{n1}$, -$C(O)NR^{q1}R^{r1}$ and -$S(O)_2NR^{n1}COR^{p1}$, wherein any $(C_3$-$C_7)$carbocycle, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{1a} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different;

each Z^{1b} is independently $(C_1$-$C_8)$alkyl optionally substituted with 1, 2, 3, 4 or 5 halogen, which are the same or different;

each Z^{1c} is independently halogen, -CN, -OH, -NH_2, -$C(O)NR^{q2}R^{r2}$, or $(C_1$-$C_8)$heteroalkyl;

each Z^{1d} is independently $(C_1$-$C_8)$alkyl or $(C_1$-$C_8)$haloalkyl;

each R^{n1} is independently H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{n1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any $(C_1$-$C_8)$alkyl of R^{n1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different;

each R^{p1} is independently $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same

or different, and wherein any $(C_1$-$C_8)$alkyl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different;

each R^{q1} and R^{r1} is independently H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any $(C_1$-$C_8)$alkyl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different, or R^{q1} and R^{r1} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or 7-membered heterocycle is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different;

each R^{q2} and R^{r2} is independently H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, or R^{q2} and R^{r2} together with the nitrogen to which they are attached form a 5, 6, or 7-membered heterocycle;

Z^2 is $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, $-C(O)R^{n3}$, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, wherein the Z^{2b} and Z^{2c} groups are the same or different, and wherein any $(C_2$-$C_8)$alkenyl or $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4, or 5 Z^{2c} groups, wherein the Z^{2c} groups are the same or different;

each R^{n3} is independently H or $(C_1$-$C_4)$alkyl;

each R^{q3} and R^{r3} is independently H or $(C_1$-$C_4)$alkyl;

each Z^{2b} is independently oxo, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$heteroalkyl or $(C_1$-$C_4)$haloalkyl;

each Z^{2c} is independently oxo, halogen, -CN, $-OR^{n4}$, $-OC(O)R^{p4}$, $-OC(O)NR^{q4}R^{r4}$, $-SR^{n4}$, $-S(O)R^{p4}$, $-S(O)_2OH$, $-S(O)_2R^{p4}$, $-S(O)_2NR^{q4}R^{r4}$, $-NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}CONR^{q4}R^{r4}$, $-NR^{n4}S(O)_2R^{p4}$, $-NR^{n4}S(O)_2OR^{p4}$, $-NR^{n4}S(O)_2NR^{q4}R^{r4}$, $-NO_2$, $-C(O)R^{n4}$, $-C(O)OR^{n4}$, or $-C(O)NR^{q4}R^{r4}$;

each R^{n4} is independently H, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, or $(C_1$-$C_4)$heteroalkyl;

each R^{p4} is independently $(C_1$-$C_8)$alkyl, $(C_1$-$C_4)$haloalkyl, or $(C_1$-$C_4)$heteroalkyl;

each R^{q4} and R^{r4} is independently H, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, or $(C_1$-$C_4)$heteroalkyl;

each Z^3 is independently a $(C_1$-$C_4)$heteroalkyl;

each Z^4 is independently oxo, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, halogen, -CN, $-OR^{n5}$, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-C(O)R^{n5}$, $-C(O)OR^{n5}$, or $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3$-$C_7)$carbocycle or $(C_1$-$C_8)$alkyl of Z^4 is optionally substituted with 1, 2, 3, 4 or 5 Z^{4a} groups, wherein the Z^{4a} groups are the same or different;

each Z^{4a} is independently halogen, -CN, or $-OR^{n6}$;

each R^{n5}, R^{p5}, R^{q5}, R^{r5}, and R^{n6} is independently H or $(C_1$-$C_4)$alkyl;

each Z^5 is independently halogen, which may be same or different; and

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof.

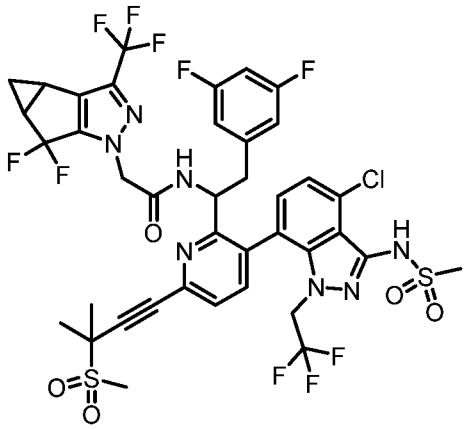
[0006] The above disclosures notwithstanding, there is a need for compounds that are potent and stable and exhibit improved pharmacokinetic and/or pharmacodynamic profiles for the treatment of a *Retroviridae* viral infection including an infection caused by the HIV virus.

[0007] Also of interest in the area of HIV therapies and treatments is extending the pharmacokinetic property of regimens provided to patients. While current regimens for treating HIV have progressed enough that patients no longer have to take multiple pills multiple times a day, patients today still are required to take a pill every day for the foreseeable span of their life. Thus, it would be beneficial to have HIV therapies that require patients take medication less than once a day (e.g. once every couple of days, once a week, once every other week, once a month, and so forth).

[0008] Provided herein are novel compounds exhibiting improved potency, improved metabolic stability, and improved pharmacokinetic and/or pharmacodynamic profiles.

SUMMARY

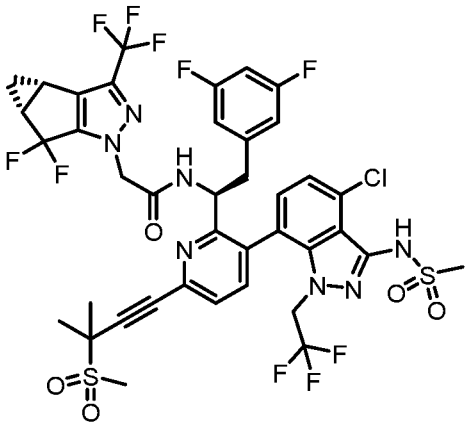
[0009] In some embodiments, the current disclosure relates to a compound of formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof.

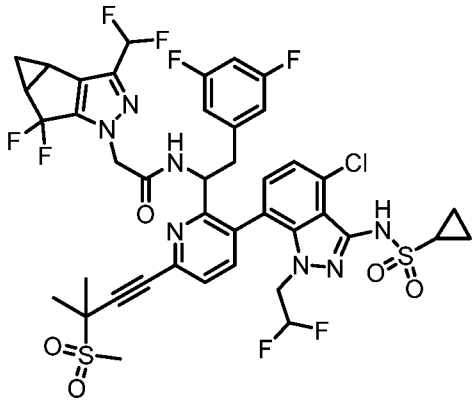
[0010] In some embodiments, the current disclosure relates to a compound of formula (Ib):



(Ib)

or a pharmaceutically acceptable salt thereof.

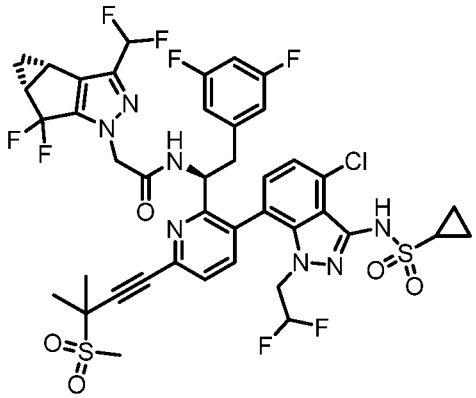
[0011] In some embodiments, the current disclosure relates to a compound of formula (IIa):



(IIa)

or a pharmaceutically acceptable salt thereof.

[0012] In some embodiments, the current disclosure relates to a compound of formula (IIb):



(IIb)

or a pharmaceutically acceptable salt thereof.

[0013] In one embodiment, the current disclosure relates to the use of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in the treatment of a disease in a subject in need thereof.

[0014] In one embodiment, the current disclosure relates to the use of a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, in the treatment of a disease in a subject in need thereof.

[0015] In certain embodiments, the current disclosure relates to a pharmaceutical composition comprising a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition is an injectable form. In certain embodiments, the pharmaceutical composition is suitable for oral administration.

[0016] In some embodiments, the current disclosure relates to a pharmaceutical composition comprising a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition is a parenteral (e.g., injectable) form. In certain embodiments, the pharmaceutical composition is suitable for oral administration.

[0017] In certain embodiments, the current disclosure relates to an article of manufacture comprising a unit dosage of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof.

[0018] In some embodiments, the current disclosure relates to an article of manufacture comprising a unit dosage of a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof.

[0019] In certain embodiments, the current disclosure relates to a method for treating or preventing an HIV infection in a subject in need thereof, comprising administering to the subject a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof.

[0020] In some embodiments, the current disclosure relates to a method for treating or preventing an HIV infection in a subject in need thereof, comprising administering to the subject a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof.

[0021] In certain embodiments, the current disclosure relates to a method for preventing an HIV infection in a subject, comprising administering to the subject a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof. In certain embodiments, the subject is at risk of contracting the HIV virus, such as a subject who has one or more risk factors known to be associated with contracting the HIV virus.

[0022] In certain embodiments, the current disclosure relates to a method for preventing an HIV infection in a subject, comprising administering to the subject a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof. In certain embodiments, the subject is at risk of contracting the HIV virus, such as a subject who has one or more risk factors known to be associated with contracting the HIV virus.

[0023] In certain embodiments, the current disclosure relates to a method for treating or preventing an HIV infection in a subject in need thereof, comprising administering to the subject a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents.

[0024] In certain embodiments, the current disclosure relates to a method for treating or preventing an HIV infection in a subject in need thereof, comprising administering to the subject a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents.

[0025] In certain embodiments, the current disclosure relates to a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof for use in medical therapy.

[0026] In certain embodiments, the current disclosure relates to a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof for use in medical therapy.

[0027] In certain embodiments, the current disclosure relates to a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for use in treating or preventing an HIV infection in a subject.

[0028] In certain embodiments, the current disclosure relates to a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for use in treating or preventing an HIV infection in a subject.

[0029] In certain embodiments, the current disclosure relates to the use of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating or preventing an HIV infection in a subject.

[0030] In certain embodiments, the current disclosure relates to the use of a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating or preventing an HIV infection in a subject.

[0031] In another embodiment, the current disclosure relates to intermediates useful for the synthesis of the compound of formula (Ia) or (Ib).

[0032] In another embodiment, the current disclosure relates to intermediates useful for the synthesis of the compound of formula (Ia), (Ib), (IIa), and/or (IIb).

[0033] In some embodiments, the pharmaceutically acceptable salt of the compound of formula (Ia), (Ib), (IIa), and/or (IIb) is the sodium salt.

[0034] Additional embodiments of the current disclosure are disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0035] FIG. 1 shows ^{1}H NMR of (400 MHz, Methanol-d_4) of *N*-((*S*)-1-(3-(4-chloro-3-(methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1*H*-indazol-7-yl)-6-(3-methyl-3-

(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3b*S*,4a*R*)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1*H*-cyclopropa[3,4]cyclopenta[1,2-*c*]pyrazol-1-yl)acetamide.

[0036] FIG. 2 shows ^{1}H NMR of (400 MHz, Methanol-d_4) N-((S)-1-(3-(4-chloro-3-(cyclopropanesulfonamido)-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide.

[0037] FIG. 3 shows the plasma concentration (nM) of Compound 38 after a single subcutaneous (SC) dose in rats.

[0038] FIG. 4 shows a plot of plasma concentration over time of 200mg/mL of Formula Ib in 2% poloxamer 188 in saline when subcutaneously dosed in dogs at 6mg/kg.

[0039] FIG. 5 shows a plot of plasma concentration over time of 100mg/mL of Formula Ib in 2% poloxamer 188 in saline when subcutaneously dosed in dogs at 6mg/kg.

[0040] FIG. 6 shows a plot of plasma concentration over time of 200mg/mL of Formula Ib, sodium salt in 2% poloxamer 188 in saline when subcutaneously dosed in dogs at 6mg/kg.

[0041] FIG. 7 shows a plot of plasma concentration over time of 100mg/mL of Formula Ib, free acid form in NMP when subcutaneously dosed in dogs at 6 mg/kg.

[0042] FIG. 8 shows a plot of plasma concentration over time of 200mg/mL of Formula Ib, free acid form in NMP when subcutaneously dosed in dogs at 6mg/kg.

[0043] FIG. 9 shows a plot of plasma concentration over time of 200mg/mL of Formula Ib, sodium salt in NMP when subcutaneously dosed in subjects at 6mg/kg.

[0044] FIG. 10 shows a plot of plasma concentration over time of 200mg/mL of Formula Ib in 10% ethanol, 12% water, and 78% PEG 200 when dosed subcutaneously in subjects at 6mg/kg.

[0045] FIG. 11 shows a plot of plasma concentration over time of 200mg/mL of Formula Ib, *in situ* salt, in 10% ethanol, 12% water, and 77% PEG 200 when dosed subcutaneously in subjects at 6mg/kg.

[0046] FIG. 12 shows a plot of plasma concentration over time of 200mg/mL of Formula Ib in 10% ethanol, 13% water, and 77% glycofurol, with 1.2 mol-eq. NaOH to form *in situ* Na salt when dosed in subjects at 6mg/kg.

[0047] FIG. 13 shows a plot of plasma concentration over time of a fixed 7.5mg oral dose of Formula Ib in 10% ethanol, 20% Vitamin E TPGS, 70% MIGLYOL 812 in dogs.

DETAILED DESCRIPTION

[0048] The description below is made with the understanding that the present disclosure is to be considered as an exemplification of the claimed subject matter, and is not intended to limit the appended claims to the specific embodiments illustrated. The headings used throughout this disclosure are provided for convenience and are not to be construed to limit the claims in any way. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

[0049] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art.

[0050] When trade names are used herein, it is intended to independently include the tradename product and the active pharmaceutical ingredient(s) of the tradename product.

[0051] As used herein and in the appended claims, the singular forms "a" and "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, *e.g.*, reference to "the compound" includes a plurality of such compounds and reference to "the assay" includes reference to one or more assays, and so forth.

[0052] As used herein, the term "C_{max}" refers to the maximum observed plasma/serum concentration of drug.

[0053] "Pharmaceutically acceptable" refers to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

[0054] "Pharmaceutically acceptable excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

[0055] "Pharmaceutically acceptable salt" refers to a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, lactic acid, maleic acid,

malonic acid, mandelic acid, methanesulfonic acid, 2-naphthalenesulfonic acid, oleic acid, palmitic acid, propionic acid, stearic acid, succinic acid, tartaric acid, p-toluenesulfonic acid, trimethylacetic acid, and the like, and salts formed when an acidic proton present in the parent compound is replaced by either a metal ion, *e.g.*, an alkali metal ion (*e.g.* a sodium or potassium), an alkaline earth ion (*e.g.* calcium or magnesium), or an aluminum ion; or coordinates with an organic base such as diethanolamine, triethanolamine, *N*-methylglucamine and the like. Also included in this definition are ammonium and substituted or quaternized ammonium salts. Representative non-limiting lists of pharmaceutically acceptable salts can be found in S.M. Berge et al., J. Pharma Sci., 66(1), 1-19 (1977), and Remington: The Science and Practice of Pharmacy, R. Hendrickson, ed., 21st edition, Lippincott, Williams & Wilkins, Philadelphia, PA, (2005), at p. 732, Table 38-5, both of which are hereby incorporated by reference herein.

[0056] "Subject" and "subjects" refers to humans, domestic animals (*e.g.*, dogs and cats), farm animals (*e.g.*, cattle, horses, sheep, goats and pigs), laboratory animals (*e.g.*, mice, rats, hamsters, guinea pigs, pigs, rabbits, dogs, and monkeys), and the like.

[0057] As used herein, "treatment" or "treating" is an approach for obtaining beneficial or desired results. For purposes of the present disclosure, beneficial or desired results include, but are not limited to, alleviation of a symptom and/or diminishment of the extent of a symptom and/or preventing a worsening of a symptom associated with a disease or condition. In one embodiment, "treatment" or "treating" includes one or more of the following: a) inhibiting the disease or condition (*e.g.*, decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); b) slowing or arresting the development of one or more symptoms associated with the disease or condition (*e.g.*, stabilizing the disease or condition, delaying the worsening or progression of the disease or condition); and/or c) relieving the disease or condition, e.g., causing the regression of clinical symptoms, ameliorating the disease state, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival.

[0058] As used herein, "delaying" development of a disease or condition means to defer, hinder, slow, retard, stabilize and/or postpone development of the disease or condition. This delay can be of varying lengths of time, depending on the history of the disease and/or subject being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the subject does not develop the disease or condition. For example, a method that "delays" development of AIDS is a method that

reduces the probability of disease development in a given time frame and/or reduces extent of the disease in a given time frame, when compared to not using the method. Such comparisons may be based on clinical studies, using a statistically significant number of subjects. For example, the development of AIDS can be detected using known methods, such as confirming a subject's HIV^+ status and assessing the subject's T-cell count or other indication of AIDS development, such as extreme fatigue, weight loss, persistent diarrhea, high fever, swollen lymph nodes in the neck, armpits or groin, or presence of an opportunistic condition that is known to be associated with AIDS (*e.g.*, a condition that is generally not present in subjects with functioning immune systems but does occur in AIDS patients). Development may also refer to disease progression that may be initially undetectable and includes occurrence, recurrence and onset.

[0059] As used herein, "prevention" or "preventing" refers to a regimen that protects against the onset of the disease or disorder such that the clinical symptoms of the disease do not develop. Thus, "prevention" relates to administration of a therapy (e.g., administration of a therapeutic substance) to a subject before signs of the disease are detectable in the subject (e.g., administration of a therapeutic substance to a subject in the absence of detectable infectious agent (e.g., virus) in the subject). The subject may be an individual at risk of developing the disease or disorder, such as an individual who has one or more risk factors known to be associated with development or onset of the disease or disorder. Thus, the term "preventing HIV infection" refers to administering to a subject who does not have a detectable HIV infection an anti-HIV therapeutic substance. It is understood that the subject for anti-HIV preventative therapy may be an individual at risk of contracting the HIV virus. Further, it is understood that prevention may not result in complete protection against onset of the disease or disorder. In some instances, prevention includes reducing the risk of developing the disease or disorder. The reduction of the risk may not result in complete elimination of the risk of developing the disease or disorder.

[0060] As used herein, an "at risk" individual is an individual who is at risk of developing a condition to be treated. An individual "at risk" may or may not have detectable disease or condition, and may or may not have displayed detectable disease prior to the treatment of methods described herein. "At risk" denotes that an individual has one or more so-called risk factors, which are measurable parameters that correlate with development of a disease or condition and are known in the art. An individual having one or more of these risk

factors has a higher probability of developing the disease or condition than an individual without these risk factor(s). For example, individuals at risk for AIDS are those having HIV.

[0061] As used herein, the term "therapeutically effective amount" or "effective amount" refers to an amount that is effective to elicit the desired biological or medical response, including the amount of a compound that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease or to an amount that is effective to protect against the contracting or onset of a disease. The effective amount will vary depending on the compound, the disease, and its severity and the age, weight, etc., of the subject to be treated. The effective amount can include a range of amounts. As is understood in the art, an effective amount may be in one or more doses, *i.e.*, a single dose or multiple doses may be required to achieve the desired treatment outcome. An effective amount may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable or beneficial result may be or is achieved. Suitable doses of any co-administered compounds may optionally be lowered due to the combined action (*e.g.*, additive or synergistic effects) of the compounds.

[0062] "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. A mixture of enantiomers at a ratio other than 1:1 is a "scalemic" mixture.

[0063] "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other.

[0064] The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and/or hindered rotation about a bond axis and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present disclosure is meant to include all such possible isomers, including racemic mixtures, scalemic mixtures, diastereomeric mixtures, optically pure forms and intermediate mixtures. Optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques.

[0065] Except as expressly defined otherwise, the present disclosure includes all tautomers of compounds detailed herein, even if only one tautomer is expressly represented (*e.g.*, both tautomeric forms are intended and described by the presentation of one tautomeric form where a pair of two tautomers may exist). For example, if reference is made to a compound containing an amide (*e.g.*, by structure or chemical name), it is understood that the corresponding imidic acid tautomer is included by this disclosure and described the same as if the amide were expressly recited either alone or together with the imidic acid. Where more than two tautomers may exist, the present disclosure includes all such tautomers even if only a single tautomeric form is depicted by chemical name and/or structure.

[0066] The present disclosure also provides for prodrugs of the compound of Formula (Ia) or (Ib). A "prodrug" is defined in the pharmaceutical field as a biologically inactive derivative of a drug that upon administration to the human body is converted to the biologically active parent drug according to some chemical or enzymatic pathway.

[0067] Additionally, in some embodiments, the present disclosure also provides for prodrugs of the compound of Formula (Ia), (Ib), (IIa), and/or (IIb).

[0068] It is understood by one skilled in the art that this disclosure also includes any compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)) that may be enriched at any or all atoms above naturally occurring isotopic ratios with one or more isotopes such as, but not limited to, deuterium (^{2}H or D).

[0069] Disclosed are also compounds in which from 1 to n hydrogen atoms attached to a carbon atom may be replaced by a deuterium atom or D, in which n is the number of hydrogen atoms in the molecule. As known in the art, the deuterium atom is a non-radioactive isotope of the hydrogen atom. Such compounds may increase resistance to metabolism, and thus may be useful for increasing the half-life of the compounds when administered to a mammal. *See, e.g.*, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism", Trends Pharmacol. Sci., 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogen atoms have been replaced by deuterium.

[0070] Examples of isotopes that can be incorporated into the disclosed compounds also include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate

receptor occupancy. Isotopically-labeled compounds of Formula (Ia) or (Ib), can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0071] Additionally, in some embodiments, isotopically-labeled compounds of Formula (Ia), (Ib), (IIa), and/or (IIb), can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0072] Compounds described herein may have chiral centers and/or geometric isomeric centers (E- and Z- isomers), and it is to be understood that all such optical, enantiomeric, diastereoisomeric and geometric isomers are encompassed. Where compounds are represented in their chiral form, it is understood that the embodiment encompasses, but is not limited to, the specific diastereomerically or enantiomerically enriched form. Where chirality is not specified but is present, it is understood that the embodiment is directed to either the specific diastereomerically or enantiomerically enriched form; or a racemic or scalemic mixture of such compound(s). As used herein, "scalemic mixture" is a mixture of stereoisomers at a ratio other than 1:1.

[0073] Also provided are also pharmaceutically acceptable hydrates, solvates, tautomeric forms, polymorphs, and prodrugs of the compounds described herein.

[0074] In a preferred embodiment, the current disclosure relates to the use of the compound of formula (Ia) or (Ib) in treating a *Retroviridae* viral infection including an infection caused by the HIV virus comprising administering a therapeutically effective amount to a subject in need thereof.

[0075] In a preferred embodiment, the current disclosure relates to the use of the compound of formula (Ia), (Ib), (IIa), and/or (IIb) in treating a *Retroviridae* viral infection including an infection caused by the HIV virus comprising administering a therapeutically effective amount to a subject in need thereof.

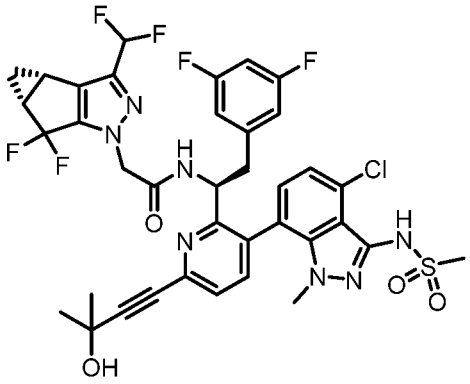
[0076] It is a desirable goal to discover a compound or a pharmaceutically acceptable salt thereof having a low EC_{50}. The EC_{50} value refers to the concentration of a compound in an assay that achieves 50% of the maximum efficacy. A compound with a lower EC_{50} achieves similar efficacy with lower compound concentration relative to a compound with a higher EC_{50}. Thus, a lower EC_{50} is generally preferred for drug development.

[0077] It is a desirable goal to discover a compound or a pharmaceutically acceptable salt thereof that has good physical and/or chemical stability. An increase in overall stability of a compound can provide an increase in circulation time in the body. With less degradation, a stable compound can be administered in lower doses and still maintain efficacy. Also, with less degradation, there is less concern about by-products from degradation of a compound.

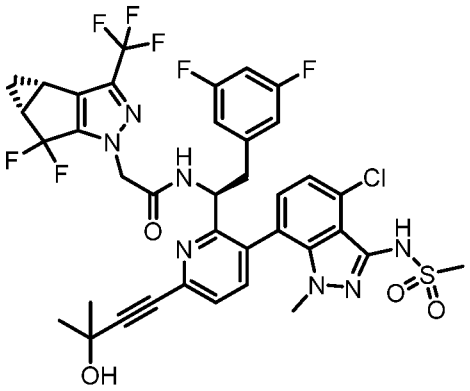
[0078] It is a desirable goal to discover a compound or a pharmaceutically acceptable salt thereof that has improved pharmacokinetic and/or pharmacodynamic profiles and long half-life. It is advantageous for a drug to have a moderate or low clearance and a long half-life, as this can lead to a good bioavailability and high exposure in systemic exposure. Reducing the clearance and increasing half-life time of a compound could reduce the daily dose required for efficacy and therefore give a better efficacy and safety profile. Thus, improved pharmacokinetic and/or pharmacodynamic profiles and long half-life can provide for better patient compliance.

[0079] It is a desirable goal to discover a compound or a pharmaceutically acceptable salt thereof that has good pharmacokinetic profile from a slow release injectable formulation. It is advantageous for a drug to have a low EC_{50} and long acting pharmacokinetics, as this can lead to low frequency of administration. Reducing the frequency of administration can provide for better patient compliance. Reducing the frequency of administration can be desirable for patients with difficult or limited access to health care.

[0080] Advantageously, discovered is a compound of formula (Ia) and (Ib) herein that provides advantages compared to structurally close compounds (herein designated as compounds A and B) disclosed in U.S. Patent Publication Nos. 2014/0296266A1 and 2014/0303164A1:

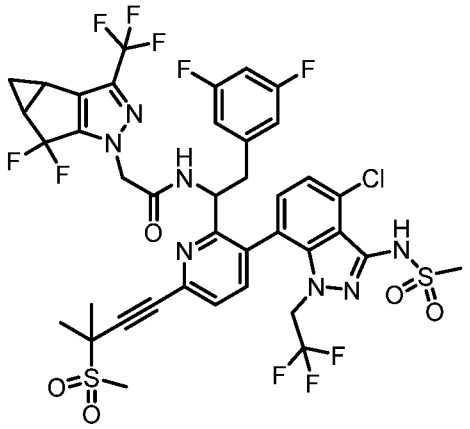


Compound A



Compound B

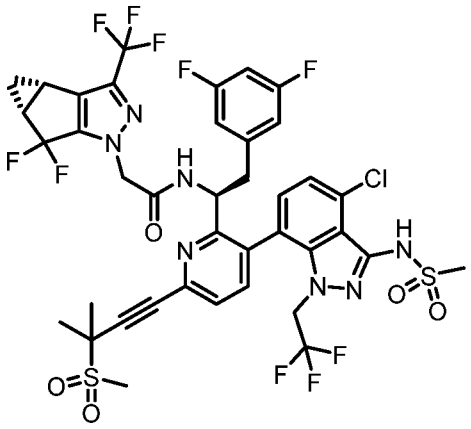
[0081] Therefore, the present disclosure includes but is not limited to the provision of a compound of formula (Ia)



(Ia)

or pharmaceutically acceptable salt thereof, and methods of using the compound of formula (Ia) for the treatment of a *Retroviridae* viral infection including an infection caused by the HIV virus.

[0082] Therefore, the present disclosure includes but is not limited to the provision of a compound of formula (Ib)

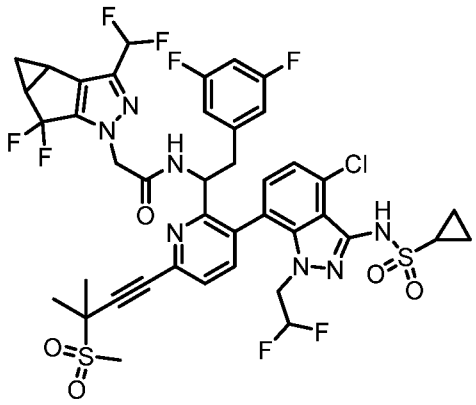


(Ib)

or pharmaceutically acceptable salt thereof, and methods of using the compound of formula (Ib) for the treatment of a *Retroviridae* viral infection including an infection caused by the HIV virus.

[0083] Also disclosed herein is a compound of formula (IIa) and (IIb), which provides advantages compared to Compounds A and B (shown above).

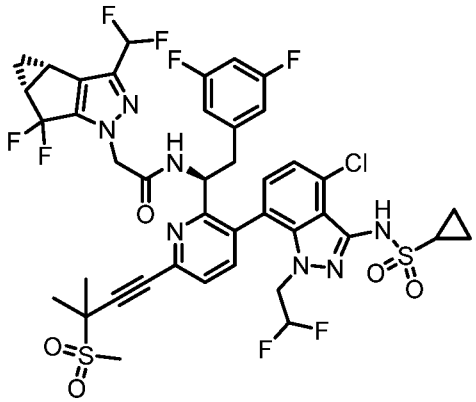
[0084] Therefore, the present disclosure includes but is not limited to the provision of a compound of formula (IIa)



(IIa)

or pharmaceutically acceptable salt thereof, and methods of using the compound of formula (IIa) for the treatment of a *Retroviridae* viral infection including an infection caused by the HIV virus.

[0085] Therefore, the present disclosure includes but is not limited to the provision of a compound of formula (IIb)



(IIb)

or pharmaceutically acceptable salt thereof, and methods of using the compound of formula (IIb) for the treatment of a *Retroviridae* viral infection including an infection caused by the HIV virus.

[0086] In some embodiments, the compounds disclosed herein (e.g., a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or pharmaceutically acceptable salt thereof) are used for preventing an HIV infection in a subject. In some embodiments, the compounds disclosed herein are used for preventing an HIV infection in a subject at risk for infection. In some embodiments, the compounds disclosed herein are used for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1.

[0087] It is believed that the compounds disclosed herein (e.g., a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof) are active against major HIV-1 mutants selected by clinical Protease Inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), and Integrase inhibitors (INSTIs).

Combination Therapy

[0088] In certain embodiments, a method for treating or preventing an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein (e.g., a compound of formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents. In one embodiment, a method for treating an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound

disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents.

[0089] In some embodiments, a method for treating or preventing an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein (e.g., a compound of formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents. In one embodiment, a method for treating an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein (e.g., a compound of formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents.

[0090] In one embodiment, pharmaceutical compositions comprising a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, in combination with one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents, and a pharmaceutically acceptable excipient are provided.

[0091] In some embodiments, pharmaceutical compositions comprising a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, in combination with one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents, and a pharmaceutically acceptable excipient are provided.

[0092] In certain embodiments, the present disclosure provides a method for treating an HIV infection, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents which are suitable for treating an HIV infection.

[0093] In certain embodiments, the present disclosure provides a method for treating an HIV infection, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents which are suitable for treating an HIV infection.

[0094] In certain embodiments, the present disclosure provides a method for treating an HIV infection, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof.

[0095] In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with one, two, three, four, or more additional therapeutic agents. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with one additional therapeutic agent. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with two additional therapeutic agents. In other embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with three additional therapeutic agents. In further embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with four additional therapeutic agents. The one, two, three, four, or more additional therapeutic agents can be different therapeutic agents selected from the same class of therapeutic agents, and/or they can be selected from different classes of therapeutic agents.

[0096] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with one, two, three, four, or more additional therapeutic agents. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with one additional therapeutic agent. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with two additional therapeutic agents. In other embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt

thereof, is combined with three additional therapeutic agents. In further embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with four additional therapeutic agents. The one, two, three, four, or more additional therapeutic agents can be different therapeutic agents selected from the same class of therapeutic agents, and/or they can be selected from different classes of therapeutic agents.

Administration of HIV Combination Therapy

[0097] In certain embodiments, a compound disclosed herein (e.g., a compound of formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is administered with one or more additional therapeutic agents. Co-administration of a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, with one or more additional therapeutic agents generally refers to simultaneous or sequential administration of a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)) and one or more additional therapeutic agents, such that therapeutically effective amounts of the compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, and the one or more additional therapeutic agents are both present in the body of the subject. When administered sequentially, the combination may be administered in two or more administrations.

[0098] In some embodiments, a compound disclosed herein (e.g., a compound of formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is administered with one or more additional therapeutic agents. Co-administration of a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, with one or more additional therapeutic agents generally refers to simultaneous or sequential administration of a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)) and one or more additional therapeutic agents, such that therapeutically effective amounts of the compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, and the one or more additional therapeutic agents are both present in the body of the subject. When administered sequentially, the combination may be administered in two or more administrations.

[0099] Co-administration includes administration of unit dosages of the compounds disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or pharmaceutically acceptable

salts thereof, before or after administration of unit dosages of one or more additional therapeutic agents. For example, the compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, may be administered within seconds, minutes, or hours of the administration of the one or more additional therapeutic agents. In some embodiments, a unit dose of a compound disclosed herein (e.g., a compound of formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents. Alternatively, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)) within seconds or minutes. In other embodiments, a unit dose of a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)) is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In yet other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)).

[00100] In some embodiments, co-administration includes administration of unit dosages of the compounds disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or pharmaceutically acceptable salts thereof, before or after administration of unit dosages of one or more additional therapeutic agents. For example, the compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, may be administered within seconds, minutes, or hours of the administration of the one or more additional therapeutic agents. In some embodiments, a unit dose of a compound disclosed herein (e.g., a compound of formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents. Alternatively, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)) within seconds or minutes. In other embodiments, a unit dose of a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)) is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In yet other embodiments, a unit dose of one or more additional therapeutic agents is administered first,

followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)).

[00101] For the avoidance of doubt, co-administration of a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, with one or more additional therapeutic agents, may refer to co-administration with one or more of the thereapeutic agents described herein, e.g. for example those agents listed in paragraphs [00111] to [00162].

[00102] In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with one or more additional therapeutic agents in a unitary dosage form for simultaneous administration to a subject. In certain embodiments, such a unitary dosage form can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. In certain embodiments, the compounds disclosed can be dosed parenterally. In certain embodiments, the unitary dosage form can be dosed intravenous, subcutaneous, or intramuscular. In certain embodiments, the unitary dosage form is orally bioavailable and can be dosed orally. In certain embodiments, the unitary dosage form can be a solid dosage form for oral administration.

[00103] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with one or more additional therapeutic agents in a unitary dosage form for simultaneous administration to a subject. In certain embodiments, such a unitary dosage form can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. In certain embodiments, the compounds disclosed can be dosed parenterally. In certain embodiments, the unitary dosage form can be dosed intravenous, subcutaneous, or intramuscular. In certain embodiments, the unitary dosage form is orally bioavailable and can be dosed orally. In certain embodiments, the unitary dosage form can be a solid dosage form for oral administration.

[00104] The compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof), in combination with one or more additional

therapeutic agents can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. In certain embodiments, the compounds disclosed can be dosed parenterally. In certain embodiments, the compounds disclosed can be dosed intravenous, subcutaneous, or intramuscular. In certain embodiments, the compounds disclosed are orally bioavailable and can be dosed orally.

[00105] The compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof), in combination with one or more additional therapeutic agents can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. In certain embodiments, the compounds disclosed can be dosed parenterally. In certain embodiments, the compounds disclosed can be dosed intravenous, subcutaneous, or intramuscular. In certain embodiments, the compounds disclosed are orally bioavailable and can be dosed orally.

[00106] In certain embodiments, a compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, is formulated as a tablet, which may optionally contain one or more other compounds useful for treating HIV. In certain embodiments, the tablet can one or more other compounds useful for treating HIV, such as HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, pharmacokinetic enhancers, and combinations thereof.

[00107] In certain embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, is formulated as a tablet, which may optionally contain one or more other compounds useful for treating HIV. In certain embodiments, the tablet can one or more other compounds useful for treating HIV, such as HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, pharmacokinetic enhancers, and combinations thereof.

[00108] In certain embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, is formulated as a solution formulation, which may optionally contain one or more other compounds useful for treating HIV. In certain embodiments, the tablet can one or more other compounds useful for treating HIV, such as HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, pharmacokinetic enhancers, and combinations thereof.

[00109] In certain embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, is formulated as a suspension, which may optionally contain one or more other compounds useful for treating HIV. In certain embodiments, the tablet can one or more other compounds useful for treating HIV, such as HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, pharmacokinetic enhancers, and combinations thereof.

[00110] In certain embodiments, such tablets are suitable for once daily dosing.

HIV Combination Therapy

[00111] In the above embodiments, the additional therapeutic agent may be an anti-HIV agent selected from the group consisting of combination drugs for treating HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing

factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, HIV vaccines, and combinations thereof.

[00112] In some embodiments, the additional therapeutic agent is selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV reverse transcriptase inhibitors, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry (fusion) inhibitors, HIV maturation inhibitors, latency reversing agents, capsid inhibitors, immune-based therapies, PI3K inhibitors, HIV antibodies, and bispecific antibodies, and "antibody-like" therapeutic proteins, and combinations thereof.

HIV Combination Drugs

[00113] Examples of combination drugs include ATRIPLA® (efavirenz, tenofovir disoproxil fumarate, and emtricitabine); COMPLERA® (EVIPLERA®; rilpivirine, tenofovir disoproxil fumarate, and emtricitabine); STRIBILD® (elvitegravir, cobicistat, tenofovir disoproxil fumarate, and emtricitabine); TRUVADA® (tenofovir disoproxil fumarate and emtricitabine; TDF+FTC); DESCOVY® (tenofovir alafenamide and emtricitabine); ODEFSEY® (tenofovir alafenamide, emtricitabine, and rilpivirine); GENVOYA® (tenofovir alafenamide, emtricitabine, cobicistat, and elvitegravir); darunavir, tenofovir alafenamide hemifumarate, emtricitabine, and cobicistat; efavirenz, lamivudine, and tenofovir disoproxil fumarate; lamivudine and tenofovir disoproxil fumarate; tenofovir and lamivudine; tenofovir alafenamide and emtricitabine; tenofovir alafenamide hemifumarate and emtricitabine; tenofovir alafenamide hemifumarate, emtricitabine, and rilpivirine; tenofovir alafenamide hemifumarate, emtricitabine, cobicistat, and elvitegravir; COMBIVIR® (zidovudine and lamivudine; AZT+3TC); EPZICOM® (LIVEXA®; abacavir sulfate and lamivudine; ABC+3TC); KALETRA® (ALUVIA®; lopinavir and ritonavir); TRIUMEQ® (dolutegravir, abacavir, and lamivudine); TRIZIVIR® (abacavir sulfate, zidovudine, and lamivudine; ABC+AZT+3TC); atazanavir and cobicistat; atazanavir sulfate and cobicistat; atazanavir

sulfate and ritonavir; darunavir and cobicistat; dolutegravir and rilpivirine; dolutegravir and rilpivirine hydrochloride; cabotegravir and rilpivirine; cabotegravir and rilpivirine hydrochloride; dolutegravir, abacavir sulfate, and lamivudine; lamivudine, nevirapine, and zidovudine; raltegravir and lamivudine; doravirine, lamivudine, and tenofovir disoproxil fumarate; doravirine, lamivudine, and tenofovir disoproxil; dolutegravir + lamivudine; lamivudine + abacavir + zidovudine; lamivudine + abacavir; lamivudine + tenofovir disoproxil fumarate; lamivudine + zidovudine + nevirapine; lopinavir + ritonavir; lopinavir + ritonavir + abacavir + lamivudine; lopinavir + ritonavir + zidovudine + lamivudine; tenofovir + lamivudine; and tenofovir disoproxil fumarate + emtricitabine + rilpivirine hydrochloride; lopinavir , ritonavir, zidovudine and lamivudine; Vacc-4x and romidepsin; and APH-0812.

Other HIV Drugs

[00114] Examples of other drugs for treating HIV include acemannan, alisporivir, BanLec, deferiprone, Gamimune, metenkefalin, naltrexone, Prolastin, REP 9, RPI-MN, VSSP, H1viral, SB-728-T, 1,5-dicaffeoylquinic acid, rHIV7-shl-TAR-CCR5RZ, AAV-eCD4-Ig gene therapy, MazF gene therapy, BlockAide, ABX-464, AG-1105, APH-0812, BIT-225, CYT-107, HGTV-43, HPH-116, HS-10234, IMO-3100, IND-02, MK-1376, MK-8507, MK-8591, NOV-205, PA-1050040 (PA-040), PGN-007, SCY-635, SB-9200, SCB-719, TR-452, TEV-90110, TEV-90112, TEV-90111, TEV-90113, RN-18, Immuglo, and VIR-576.

HIV Protease Inhibitors

[00115] Examples of HIV protease inhibitors include amprenavir, atazanavir, brecanavir, darunavir, fosamprenavir, fosamprenavir calcium, indinavir, indinavir sulfate, lopinavir, nelfinavir, nelfinavir mesylate, ritonavir, saquinavir, saquinavir mesylate, tipranavir, DG-17, TMB-657 (PPL-100), T-169, BL-008, and TMC-310911.

HIV Reverse Transcriptase Inhibitors

[00116] Examples of HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase include dapivirine, delavirdine, delavirdine mesylate, doravirine, efavirenz, etravirine, lentinan, nevirapine, rilpivirine, AIC-292, KM-023, and VM-1500. Further

examples of non-nucleoside reverse transcriptase inhibitors are disclosed in U.S. Patent Publication No. US2016/0250215.

[00117] Examples of HIV nucleoside or nucleotide inhibitors of reverse transcriptase include adefovir, adefovir dipivoxil, azvudine, emtricitabine, tenofovir, tenofovir alafenamide, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, VIDEX® and VIDEX EC® (didanosine, ddl), abacavir, abacavir sulfate, alovudine, apricitabine, censavudine, didanosine, elvucitabine, festinavir, fosalvudine tidoxil, CMX-157, dapivirine, doravirine, etravirine, OCR-5753, tenofovir disoproxil orotate, fozivudine tidoxil, lamivudine, phosphazid, stavudine, zalcitabine, zidovudine, GS-9131, GS-9148, and KP-1461.

[00118] In some embodiments, examples of HIV nucleoside or nucleotide inhibitors of reverse transcriptase include adefovir, adefovir dipivoxil, azvudine, emtricitabine, tenofovir, tenofovir alafenamide, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, VIDEX® and VIDEX EC® (didanosine, ddl), abacavir, abacavir sulfate, alovudine, apricitabine, censavudine, didanosine, elvucitabine, festinavir, fosalvudine tidoxil, CMX-157, dapivirine, doravirine, etravirine, OCR-5753, tenofovir disoproxil orotate, fozivudine tidoxil, lamivudine, phosphazid, stavudine, zalcitabine, zidovudine, GS-9131, GS-9148, KP-1461, and 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA).

HIV Integrase Inhibitors

[00119] Examples of HIV integrase inhibitors include elvitegravir, curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, raltegravir, dolutegravir, JTK-351, bictegravir, AVX-15567, diketo quinolin-4-1 derivatives, integrase-LEDGF inhibitor, ledgins, M-522, M-532, NSC-310217, NSC-371056, NSC-48240, NSC-642710, NSC-699171, NSC-699172, NSC-699173, NSC-699174, stilbenedisulfonic acid, T-169 and cabotegravir.

[00120] Examples of HIV non-catalytic site, or allosteric, integrase inhibitors (NCINI) include CX-05045, CX-05168, and CX-14442.

HIV Entry Inhibitors

[00121] Examples of HIV entry (fusion) inhibitors include cenicriviroc, CCR5 inhibitors, gp41 inhibitors, CD4 attachment inhibitors, gp120 inhibitors, and CXCR4 inhibitors.

[00122] Examples of CCR5 inhibitors include aplaviroc, vicriviroc, maraviroc, cenicriviroc, PRO-140, adaptavir (RAP-101), nifeviroc (TD-0232), anti-GP120/CD4 or CCR5 bispecific antibodies, B-07, MB-66, polypeptide C25P, TD-0680, and vMIP (Haimipu).

[00123] Examples of gp41 inhibitors include albuvirtide, enfuvirtide, BMS-986197, enfuvirtide biobetter, enfuvirtide biosimilar, HIV-1 fusion inhibitors (P26-Bapc), ITV-1, ITV-2, ITV-3, ITV-4, PIE-12 trimer and sifuvirtide.

[00124] Examples of CD4 attachment inhibitors include ibalizumab and CADA analogs

[00125] Examples of gp120 inhibitors include Radha-108 (receptol) 3B3-PE38, BanLec, bentonite-based nanomedicine, fostemsavir tromethamine, IQP-0831, and BMS-663068

[00126] Examples of CXCR4 inhibitors include plerixafor, ALT-1188, N15 peptide, and vMIP (Haimipu).

HIV Maturation Inhibitors

[00127] Examples of HIV maturation inhibitors include BMS-955176 and GSK-2838232.

Latency Reversing Agents

[00128] Examples of latency reversing agents include histone deacetylase (HDAC) inhibitors, proteasome inhibitors such as velcade, protein kinase C (PKC) activators, BET-bromodomain 4 (BRD4) inhibitors, ionomycin, PMA, SAHA (suberanilohydroxamic acid, or suberoyl, anilide, and hydroxamic acid), IL-15, JQ1, disulfram, amphotericin B, and ubiquitin inhibitors such as largazole analogs, and GSK-343.

[00129] Examples of HDAC inhibitors include romidepsin, vorinostat, and panobinostat.

[00130] Examples of PKC activators include indolactam, prostratin, ingenol B, and DAG-lactones.

Capsid Inhibitors

[00131] Examples of capsid inhibitors include capsid polymerization inhibitors or capsid disrupting compounds, HIV nucleocapsid p7 (NCp7) inhibitors such as azodicarbonamide, HIV p24 capsid protein inhibitors, AVI-621, AVI-101, AVI-201, AVI-301, and AVI-CAN1-15 series;

Immune-based Therapies

[00132] Examples of immune-based therapies include toll-like receptors modulators such as tlr1, tlr2, tlr3, tlr4, tlr5, tlr6, tlr7, tlr8, tlr9, tlr10, tlr11, tlr12, and tlr13; programmed cell death protein 1 (Pd-1) modulators; programmed death-ligand 1 (Pd-L1) modulators; IL-15 agonists; DermaVir; interleukin-7; plaquenil (hydroxychloroquine); proleukin (aldesleukin, IL-2); interferon alfa; interferon alfa-2b; interferon alfa-n3; pegylated interferon alfa; interferon gamma; hydroxyurea; mycophenolate mofetil (MPA) and its ester derivative mycophenolate mofetil (MMF); ribavirin; rintatolimod, polymer polyethyleneimine (PEI); gepon; rintatolimod; IL-12; WF-10; VGV-1; MOR-22; BMS-936559; CYT-107, interleukin-15/Fc fusion protein, normferon, peginterferon alfa-2a, peginterferon alfa-2b, recombinant interleukin-15, RPI-MN, GS-9620, and IR-103.

Phosphatidylinositol 3-kinase (PI3K) Inhibitors

[00133] Examples of PI3K inhibitors include idelalisib, alpelisib, buparlisib, CAI orotate, copanlisib, duvelisib, gedatolisib, neratinib, panulisib, perifosine, pictilisib, pilaralisib, puquitinib mesylate, rigosertib, rigosertib sodium, sonolisib, taselisib, AMG-319, AZD-8186, BAY-1082439, CLR-1401, CLR-457, CUDC-907, DS-7423, EN-3342, GSK-2126458, GSK-2269577, GSK-2636771, INCB-040093, LY-3023414, MLN-1117, PQR-309, RG-7666, RP-6530, RV-1729, SAR-245409, SAR-260301, SF-1126, TGR-1202, UCB-5857, VS-5584, XL-765, and ZSTK-474.

HIV Antibodies, Bispecific Antibodies, and "Antibody-like" Therapeutic Proteins

[00134] Examples of HIV antibodies, bispecific antibodies, and "antibody-like" therapeutic proteins include DARTs®, DUOBODIES®, BITES®, XmAbs®, TandAbs®, Fab derivatives, bnABs (broadly neutralizing HIV-1 antibodies), BMS-936559, TMB-360, and

those targeting HIV gp120 or gp41, antibody-Recruiting Molecules targeting HIV, anti-CD63 monoclonal antibodies , anti-GB virus C antibodies, anti-GP120/CD4, CCR5 bispecific antibodies, anti-nef single domain antibodies, anti-Rev antibody, camelid derived anti-CD18 antibodies, camelid-derived anti-ICAM-1 antibodies, DCVax-001, gp140 targeted antibodies, gp41-based HIV therapeutic antibodies, human recombinant mAbs (PGT-121), ibalizumab, Immuglo, MB-66

[00135] Examples of those targeting HIV in such a manner include bavituximab, UB-421, C2F5, C2G12, C4E10, C2F5+C2G12+C4E10, 3-BNC-117, PGT145, PGT121, MDX010 (ipilimumab), VRC01, A32, 7B2, 10E8, VRC-07-523, VRC-HIVMAB080-00-AB, MGD-014 and VRC07.

Pharmacokinetic Enhancers

[00136] Examples of pharmacokinetic enhancers include cobicistat and ritonavir.

Additional Therapeutic Agents

[00137] Examples of additional therapeutic agents include the compounds disclosed in WO 2004/096286 (Gilead Sciences), WO 2006/015261 (Gilead Sciences), WO 2006/110157 (Gilead Sciences), WO 2012/003497 (Gilead Sciences), WO 2012/003498 (Gilead Sciences), WO 2012/145728 (Gilead Sciences), WO 2013/006738 (Gilead Sciences), WO 2013/159064 (Gilead Sciences), WO 2014/100323 (Gilead Sciences), US 2013/0165489 (University of Pennsylvania), US 2014/0221378 (Japan Tobacco), US 2014/0221380 (Japan Tobacco), WO 2009/062285 (Boehringer Ingelheim), WO 2010/130034 (Boehringer Ingelheim), WO 2013/006792 (Pharma Resources), US 20140221356 (Gilead Sciences), US 20100143301 (Gilead Sciences) and WO 2013/091096 (Boehringer Ingelheim).

HIV Vaccines

[00138] Examples of HIV vaccines include peptide vaccines, recombinant subunit protein vaccines, live vector vaccines, DNA vaccines, CD4-derived peptide vaccines, vaccine combinations, rgp120 (AIDSVAX), ALVAC HIV (vCP1521)/AIDSVAX B/E (gp120) (RV144), monomeric gp120 HIV-1 subtype C vaccine, Remune, ITV-1, Contre Vir, Ad5-ENVA-48, DCVax-001 (CDX-2401), Vacc-4x, Vacc-C5, VAC-3S, multiclade DNA recombinant adenovirus-5 (rAd5), Pennvax-G, Pennvax-GP, HIV-TriMix-mRNA vaccine,

HIV-LAMP-vax, Ad35, Ad35-GRIN, NAcGM3/VSSP ISA-51, poly-ICLC adjuvanted vaccines, TatImmune, GTU-multiHIV (FIT-06), gp140[delta]V2.TV1+MF-59, rVSVIN HIV-1 gag vaccine, SeV-Gag vaccine, AT-20, DNK-4, ad35-Grin/ENV, TBC-M4, HIVAX, HIVAX-2, NYVAC-HIV-PT1, NYVAC-HIV-PT4, DNA-HIV-PT123, rAAV1-PG9DP, GOVX-B11, GOVX-B21, TVI-HIV-1, Ad-4 (Ad4-env Clade C+Ad4-mGag), EN41-UGR7C, EN41-FPA2, PreVaxTat, AE-H, MYM-V101, CombiHIVvac, ADVAX, MYM-V201, MVA-CMDR, DNA-Ad5 gag/pol/nef/nev (HVTN505), MVATG-17401, ETV-01, CDX-1401, rcAD26.MOS1.HIV-Env, Ad26.Mod.HIV vaccine, AGS-004, AVX-101, AVX-201, PEP-6409, SAV-001, ThV-01, TL-01, TUTI-16, VGX-3300, IHV-001, and virus-like particle vaccines such as pseudovirion vaccine, CombiVICHvac, LFn-p24 B/C fusion vaccine, GTU-based DNA vaccine, HIV gag/pol/nef/env DNA vaccine, anti-TAT HIV vaccine, conjugate polypeptides vaccine, dendritic-cell vaccines, gag-based DNA vaccine, GI-2010, gp41 HIV-1 vaccine, HIV vaccine (PIKA adjuvant), I i-key/MHC class II epitope hybrid peptide vaccines, ITV-2, ITV-3, ITV-4, LIPO-5, multiclade Env vaccine, MVA vaccine, Pennvax-GP, pp71-deficient HCMV vector HIV gag vaccine, recombinant peptide vaccine (HIV infection), NCI, rgp160 HIV vaccine, RNActive HIV vaccine, SCB-703, Tat Oyi vaccine, TBC-M4, therapeutic HIV vaccine, UBI HIV gp120, Vacc-4x + romidepsin, variant gp120 polypeptide vaccine, rAd5 gag-pol env A/B/C vaccine.

HIV Combination Therapy

[00139] In a particular embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with one, two, three, four or more additional therapeutic agents selected from ATRIPLA® (efavirenz, tenofovir disoproxil fumarate, and emtricitabine); COMPLERA® (EVIPLERA®; rilpivirine, tenofovir disoproxil fumarate, and emtricitabine); STRIBILD® (elvitegravir, cobicistat, tenofovir disoproxil fumarate, and emtricitabine); TRUVADA® (tenofovir disoproxil fumarate and emtricitabine; TDF +FTC); DESCOVY® (tenofovir alafenamide and emtricitabine); ODEFSEY® (tenofovir alafenamide, emtricitabine, and rilpivirine); GENVOYA® (tenofovir alafenamide, emtricitabine, cobicistat, and elvitegravir); adefovir; adefovir dipivoxil; cobicistat; emtricitabine; tenofovir; tenofovir disoproxil; tenofovir disoproxil fumarate; tenofovir alafenamide; tenofovir alafenamide hemifumarate; TRIUMEQ® (dolutegravir, abacavir, and lamivudine); dolutegravir, abacavir sulfate, and lamivudine; raltegravir; raltegravir and lamivudine; maraviroc; enfuvirtide; ALUVIA®

(KALETRA®; lopinavir and ritonavir); COMBIVIR® (zidovudine and lamivudine; AZT+3TC); EPZICOM® (LIVEXA®; abacavir sulfate and lamivudine; ABC+3TC); TRIZIVIR® (abacavir sulfate, zidovudine, and lamivudine; ABC+AZT+3TC); rilpivirine; rilpivirine hydrochloride; atazanavir sulfate and cobicistat; atazanavir and cobicistat; darunavir and cobicistat; atazanavir; atazanavir sulfate; dolutegravir; elvitegravir; ritonavir; atazanavir sulfate and ritonavir; darunavir; lamivudine; prolastin; fosamprenavir; fosamprenavir calcium efavirenz; etravirine; nelfinavir; nelfinavir mesylate; interferon; didanosine; stavudine; indinavir; indinavir sulfate; tenofovir and lamivudine; zidovudine; nevirapine; saquinavir; saquinavir mesylate; aldesleukin; zalcitabine; tipranavir; amprenavir; delavirdine; delavirdine mesylate; Radha-108 (receptol); lamivudine and tenofovir disoproxil fumarate; efavirenz, lamivudine, and tenofovir disoproxil fumarate; phosphazid; lamivudine, nevirapine, and zidovudine; abacavir; and abacavir sulfate.

[00140] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with one, two, three, four or more additional therapeutic agents selected from ATRIPLA® (efavirenz, tenofovir disoproxil fumarate, and emtricitabine); COMPLERA® (EVIPLERA®; rilpivirine, tenofovir disoproxil fumarate, and emtricitabine); STRIBILD® (elvitegravir, cobicistat, tenofovir disoproxil fumarate, and emtricitabine); TRUVADA® (tenofovir disoproxil fumarate and emtricitabine; TDF +FTC); DESCOVY® (tenofovir alafenamide and emtricitabine); ODEFSEY® (tenofovir alafenamide, emtricitabine, and rilpivirine); GENVOYA® (tenofovir alafenamide, emtricitabine, cobicistat, and elvitegravir); adefovir; adefovir dipivoxil; cobicistat; emtricitabine; tenofovir; tenofovir disoproxil; tenofovir disoproxil fumarate; tenofovir alafenamide; tenofovir alafenamide hemifumarate; TRIUMEQ® (dolutegravir, abacavir, and lamivudine); dolutegravir, abacavir sulfate, and lamivudine; raltegravir; raltegravir and lamivudine; maraviroc; enfuvirtide; ALUVIA® (KALETRA®; lopinavir and ritonavir); COMBIVIR® (zidovudine and lamivudine; AZT+3TC); EPZICOM® (LIVEXA®; abacavir sulfate and lamivudine; ABC+3TC); TRIZIVIR® (abacavir sulfate, zidovudine, and lamivudine; ABC+AZT+3TC); rilpivirine; rilpivirine hydrochloride; atazanavir sulfate and cobicistat; atazanavir and cobicistat; darunavir and cobicistat; atazanavir; atazanavir sulfate; dolutegravir; elvitegravir; ritonavir; atazanavir sulfate and ritonavir; darunavir; lamivudine; prolastin; fosamprenavir; fosamprenavir calcium efavirenz; etravirine; nelfinavir; nelfinavir mesylate; interferon; didanosine; stavudine; indinavir; indinavir sulfate; tenofovir and lamivudine; zidovudine;

nevirapine; saquinavir; saquinavir mesylate; aldesleukin; zalcitabine; tipranavir; amprenavir; delavirdine; delavirdine mesylate; Radha-108 (receptol); lamivudine and tenofovir disoproxil fumarate; efavirenz, lamivudine, and tenofovir disoproxil fumarate; phosphazid; lamivudine, nevirapine, and zidovudine; abacavir; abacavir sulfate; 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA); and Bictegravir, or a pharmaceutically acceptable salt thereof.

[00141] It will be appreciated by one of skill in the art that the additional therapeutic agents listed above may be included in more than one of the classes listed above. The particular classes are not intended to limit the functionality of those compounds listed in those classes.

[00142] In a specific embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with one or two HIV nucleoside or nucleotide inhibitors of reverse transcriptase. In a specific embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase and an HIV non-nucleoside inhibitor of reverse transcriptase. In another specific embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In an additional embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and a pharmacokinetic enhancer. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with at least one HIV nucleoside inhibitor of reverse transcriptase, an integrase inhibitor, and a pharmacokinetic enhancer. In another embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with two HIV nucleoside or nucleotide inhibitors of reverse transcriptase.

[00143] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with one or two HIV nucleoside or nucleotide inhibitors of reverse transcriptase. In a specific embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with an HIV

nucleoside or nucleotide inhibitor of reverse transcriptase and an HIV non-nucleoside inhibitor of reverse transcriptase. In another specific embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In an additional embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and a pharmacokinetic enhancer. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with at least one HIV nucleoside inhibitor of reverse transcriptase, an integrase inhibitor, and a pharmacokinetic enhancer. In another embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with two HIV nucleoside or nucleotide inhibitors of reverse transcriptase.

[00144] In a particular embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, tenofovir alafenamide fumarate or tenofovir alafenamide hemifumarate.

[00145] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, bictegravir (or a pharmaceutically acceptable salt thereof), or 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA).

[00146] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with a HIV integrase inhibitor.

[00147] In a particular embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, tenofovir alafenamide fumarate or tenofovir alafenamide hemifumarate.

[00148] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, bictegravir (or a pharmaceutically acceptable salt thereof), or 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA).

[00149] In a particular embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, tenofovir alafenamide fumarate and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent selected from the group consisting of emtricitabine and lamivudine.

[00150] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, tenofovir alafenamide fumarate and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent selected from the group consisting of emtricitabine and lamivudine.

[00151] In a particular embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine. In a particular embodiment, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of tenofovir alafenamide fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine. In a particular embodiment, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of tenofovir disoproxil fumarate, tenofovir disoproxil, and tenofovir disoproxil hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine. In some embodiments, the compound of formula (Ia) or

(Ib), or a pharmaceutically acceptable salt thereof, and the first and second additional therapeutic agents as disclosed above are administered simultaneously. Optionally, the compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, and the first and second additional therapeutic agents as disclosed above are combined in a unitary dosage form for simultaneous administration to a subject. In other embodiments, the compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, and the first and second additional therapeutic agents as disclosed above are administered sequentially.

[00152] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine. In a particular embodiment, a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of tenofovir alafenamide fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine. In a particular embodiment, a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of tenofovir disoproxil fumarate, tenofovir disoproxil, and tenofovir disoproxil hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine. In some embodiments, the compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, and the first and second additional therapeutic agents as disclosed above are administered simultaneously. Optionally, the compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, and the first and second additional therapeutic agents as disclosed above are combined in a unitary dosage form for simultaneous administration to a subject. In other embodiments, the compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, and the first and second additional therapeutic agents as disclosed above are administered sequentially.

[00153] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with bictegravir or a pharmaceutically acceptable salt thereof.

[00154] A compound as disclosed herein (e.g., any compound of formula (Ia) or (Ib)) may be combined with one or more additional therapeutic agents in any dosage amount of the compound of formula (Ia) or (Ib) (e.g., from 1 mg to 1000 mg of compound).

[00155] In some embodiments, a compound as disclosed herein (e.g., any compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof) may be combined with one or more additional therapeutic agents in any dosage amount of the compound of Formula (Ia), (Ib), (IIa), and/or (IIb) (e.g., from 1 mg to 1000 mg of compound).

[00156] In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with 5-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with 5-10, 5-15, 5-20, 5-25, 25-30, 20-30, 15-30, or 10-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with 10 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. A compound as disclosed herein (e.g., a compound of Formula (Ia) or (Ib)) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 1 mg to 1000 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[00157] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with 5-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with 5-10, 5-15, 5-20, 5-25, 25-30, 20-30, 15-30, or 10-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. In certain embodiments, a compound disclosed

herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with 10 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. A compound as disclosed herein (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 1 mg to 1000 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[00158] In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with 200-400 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with 200-250, 200-300, 200-350, 250-350, 250-400, 350-400, 300-400, or 250-400 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with 300 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and 200 mg emtricitabine. A compound as disclosed herein (e.g., a compound of Formula (Ia) or (Ib)) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 1 mg to 1000 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[00159] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with 200-400 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with 200-250, 200-300, 200-350, 250-350, 250-400, 350-400, 300-400, or 250-400 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a

pharmaceutically acceptable salt thereof, is combined with 300 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and 200 mg emtricitabine. A compound as disclosed herein (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 1 mg to 1000 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[00160] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with 20-80 mg of bictegravir or a pharmaceutically acceptable salt thereof. A compound as disclosed herein (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 1 mg to 1000 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[00161] In one embodiment, kits comprising a compound disclosed herein (e.g., a compound of formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents are provided.

[00162] In some embodiments, kits comprising a compound disclosed herein (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents are provided.

Pharmaceutical Compositions

[00163] Pharmaceutical compositions disclosed herein comprise a compound disclosed herein (e.g., a compound of formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable excipients and optionally other therapeutic agents. Pharmaceutical compositions containing the active ingredient may be in any form suitable for the intended method of administration.

[00164] In some embodiments, pharmaceutical compositions disclosed herein comprise a compound disclosed herein (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable excipients and optionally other therapeutic agents. Pharmaceutical compositions

containing the active ingredient may be in any form suitable for the intended method of administration.

[00165] Pharmaceutical compositions comprising the compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, may be prepared with conventional carriers (*e.g.,* inactive ingredient or excipient material) which may be selected in accord with ordinary practice. Tablets may contain excipients including glidants, fillers, binders and the like. Aqueous compositions may be prepared in sterile form, and when intended for delivery by other than oral administration generally may be isotonic. All compositions may optionally contain excipients such as those set forth in the Rowe et al, Handbook of Pharmaceutical Excipients, 5th edition, American Pharmacists Association, 1986. Excipients can include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like.

[00166] In some embodiments, pharmaceutical compositions comprising the compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, may be prepared with conventional carriers (*e.g.,* inactive ingredient or excipient material) which may be selected in accord with ordinary practice. Tablets may contain excipients including glidants, fillers, binders and the like. Aqueous compositions may be prepared in sterile form, and when intended for delivery by other than oral administration generally may be isotonic. All compositions may optionally contain excipients such as those set forth in the Rowe et al, Handbook of Pharmaceutical Excipients, 5th edition, American Pharmacists Association, 1986. For example, excipients can include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like.

[00167] While it is possible for the active ingredient to be administered alone, it may be preferable to present the active ingredient as pharmaceutical compositions. The compositions, both for veterinary and for human use, comprise at least the compound of formula (Ia) or (Ib), together with one or more acceptable carriers and optionally other therapeutic ingredients. In one embodiment, the pharmaceutical composition comprises a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable excipient and a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional

therapeutic agents as defined hereinbefore. In one embodiment, the pharmaceutical composition comprises a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable excipient and one other therapeutic ingredient. The carrier(s) are "acceptable" in the sense of being compatible with the other ingredients of the composition and physiologically innocuous to the recipient thereof.

[00168] In some embodiments, even though it is possible for the active ingredient to be administered alone, it may be preferable to present the active ingredient as pharmaceutical compositions. The compositions, both for veterinary and for human use, comprise at least the compound of Formula (Ia), (Ib), (IIa), and/or (IIb), together with one or more acceptable carriers and optionally other therapeutic ingredients. In some embodiments, the pharmaceutical composition comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable excipient and a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents as defined hereinbefore. In some embodiments, the pharmaceutical composition comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable excipient and one other therapeutic ingredient. The carrier(s) are "acceptable" in the sense of being compatible with the other ingredients of the composition and physiologically innocuous to the recipient thereof.

[00169] The compositions include those suitable for various administration routes. The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient (*e.g.*, a compound of formula (Ia) or (Ib) or a pharmaceutical salt thereof) with one or more inactive ingredients (*e.g.*, a carrier, pharmaceutical excipient, etc.). The compositions may be prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product. Techniques and formulations generally are found in Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Wiliams and Wilkins, Philadelphia, Pa., 2006.

[00170] In some embodiments, the compositions include those suitable for various administration routes. The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient (*e.g.*, a compound

of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutical salt thereof) with one or more inactive ingredients (*e.g.*, a carrier, pharmaceutical excipient, etc.). The compositions may be prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product. Techniques and formulations generally are found in Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Wiliams and Wilkins, Philadelphia, Pa., 2006.

[00171] Compositions described herein that are suitable for oral administration may be presented as discrete units (a unit dosage form) including but not limited to capsules, cachets or tablets each containing a predetermined amount of the active ingredient.

[00172] When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

[00173] In some embodiments, disclosed herein are oral dosage forms (e.g., tablets), which may be prepared from hot melt extrusion or spray-drying dispersion (SDD) technologies.

[00174] In some embodiments, disclosed herein are hard capsules filled with powder, beads, or granules containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of hard or soft capsules. These excipients may be, for example, inert diluents, such as calcium or sodium

carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc.

[00175] In some embodiments, disclosed herein are hard or soft capsules filled with liquid or semi-solid mixtures containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of hard or soft capsules. These excipients may be, for example, solubilizing oils such as maize oil, sesame oil, or corn oil; medium chain triglycerides and related esters, such as, derivitized palm kernel oil or coconut oil; self-emulsifying lipid systems (SEDDS or SMEDDS), such as caprylic triglyceride or propylene glycol monocaprylate; viscosity modifiers, such as, cetyl alcohol, steryl alcohol, glycerol stearate; and solubilizing agents and surfactants, such as polyethylene glycol, propylene glycol, glycerin, ethanol, polyethoxylated castor oil, poloxamers, or polysorbates.

[00176] The pharmaceutical compositions of the present disclosure may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

[00177] In some embodiments, the sterile injectable preparation disclosed herein may also be a sterile injectable solution or suspension prepared from a reconstituted lyophilized powder in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland

fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

[00178] Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. In certain embodiments the suspension is a microsuspension. In certain embodiments the suspension is a nanosuspension.

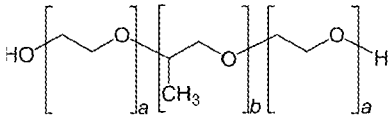
[00179] In some embodiments, formulations suitable for parenteral administration (e.g., intramuscular (IM) and subcutaneous (SC) administration) will include one or more excipients. Excipients should be compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof. Examples of suitable excipients are well known to the person skilled in the art of parenteral formulation and may be found e.g., in Handbook of Pharmaceutical Excipients (eds. Rowe, Sheskey & Quinn), 6th edition 2009.

[00180] Examples of solubilizing excipients in a parenteral formulation (e.g., an SC or IM formulation) include, but are not limited to, polysorbates (such as polysorbate 20 or 80) and poloxamers (such as poloxamer 338, 188, or 207). In some embodiments, disclosed herein is a parenteral administration (e.g., an SC or IM formulation) that comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutical salt thereof, and a poloxamer, in particular poloxamer 338. In some embodiments, the amount of poloxamer (e.g., poloxamer 388) in a parenteral administration disclosed herein is less than about 5%, such as less than about 3%, about 2%, about 1%, or about 0.5%.

[00181] Examples of solubilizing excipients in a parenteral formulation (e.g., an SC or IM formulation) include, but are not limited to, polysorbates (such as polysorbate 20 or 80) , poloxamers (such as poloxamer 338, 188, or 207). In some embodiments, disclosed herein is a parenteral administration (e.g., an SC or IM formulation) that comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutical salt thereof, and a poloxamer.

[00182] In certain embodiments, excipients include N-methyl-2- pyrrolidone (NMP), dimethyl sulfoxide, polyethylene glycol and/or tetraglycol/glycofurol.

[00183] In general, poloxamers are synthetic non-ionic triblock of linear copolymers having a central hydrophobic chain of polyoxypropylene adjacent to two hydrophilic polypropylene oxide, in certain instances in a 4:2:4 weight ratio. Accordingly, in certain embodiments, the compositions disclosed herein include a compound of Formula (Ia), (Ib),

(IIa), and/or (IIb), or a pharmaceutical salt thereof, and a block copolymer comprised of one polyoxypropylene segment and two hydrophilic polypropylene oxide segments. In certain embodiments, the ratio of the polyoxypropylene segment to the two hydrophilic polypropylene oxide segments is 4:2:4 (hydrophilic polypropylene oxide: polyoxypropylene: hydrophilic polypropylene oxide). Poloxamers are generally understood to have th following structure: 

, where a and b are integers (e.g. a is 2-130 and b is 15-67). Poloxamer 188, for example, is understood to range in molecular weight from about 7680 to about 9510 Daltons (where a is about 80 and b is about 27). International Journal of PharmTech Research, Vol.1, No.2, pp 299-303, April-June 2009. In some instances, poloxamer 188 has an average molecular weight of about 8400 Daltons. Similarly, poloxamer 338 has a molecular weight in the range of from about 12700 to about 17400 Da (where a is about 141 and b is about 44).

[00184] Examples of excipients in a parenteral formulation (e.g. an SC or an IM formulation) may also include polyethylene glycol. In general, polyethylene glycol (PEG) is a polyether having a general formula $H-(O-CH_2-CH_2)_n-OH$. In certain embodiments the PEG may be "capped" by an alkyl group. In those embodiments, the capped PEG is of the formula alkyl-($O-CH_2-CH_2)_n-O$-alkyl (e.g. $CH_3-(O-CH_2-CH_2)_n-OCH_3$. The pharmaceutical compositions of the present disclosure may include PEG having an average molecular weight of approximately 100 to approximately 1000. In some embodiments, the average molecular weight of PEG within the pharmaceutical composition is approximately 100 to approximately 800. In some embodiments, the average molecular weight of PEG within the pharmaceutical composition is approximately 200 to approximately 600. In some embodiments, the average molecular weight of PEG within the pharmaceutical composition is approximately 400. In some embodiments, the average molecular weight of PEG within the pharmaceutical composition is approximately 300. In some embodiments, the average molecular weight of PEG within the pharmaceutical composition is approximately 200. In some embodiments of the pharmaceutical composition, different molecular weight PEG may be combined to obtain a desired property or properties (e.g. viscosity). Specific examples of PEG include but are not limited to PEG 100, PEG 200, PEG 300, PEG 400, PEG 500, PEG 600, and so forth. PEG 100, for example, refers to a polyethylene glycol with an average molecular weight of about 100.

[00185] In some embodiments, the parenteral formulation (e.g., an SC or IM formulation) disclosed herein is an aqueous suspension. In some embodiments, the parenteral formulation (e.g., an SC or IM formulation) disclosed herein is an aqueous suspension that comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutical salt thereof, and saline. In some embodiments, the parenteral formulation (e.g., an SC or IM formulation) disclosed herein is an aqueous suspension that comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, saline, and a poloxamer (such as poloxamer 338, 188, or 207).

[00186] In some embodiments, the parenteral formulation (e.g., an SC or IM formulation) disclosed herein is an aqueous suspension. In some embodiments, the parenteral formulation (e.g., an SC or IM formulation) disclosed herein is an aqueous suspension that comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutical salt thereof, and saline. In some embodiments, the parenteral formulation (e.g., an SC or IM formulation) disclosed herein is an aqueous suspension that comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, saline, and a suspending agent. In some embodiments, the parenteral formulation (e.g., an SC or IM formulation) disclosed herein is an aqueous suspension that comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, saline, and poloxamer (such as poloxamer 338, 188, or 207).

[00187] In some embodiments, a suspension comprising a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutical salt thereof, in a poloxamer and saline is provided. In some embodiments, the concentration of poloxamer in saline is from about 0.1 to about 20%. In some embodiments, the concentration of poloxamer in saline is from about 0.1 to about 10%. In some in embodiments, the concentration of poloxamer in saline is about 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 2,%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, or about 10%. In certain embodiments, the concentration of poloxamer in saline is about 2%. In certain embodiments, the poloxamer is poloxamer 188. In certain embodiments, the compound is a compound of Formula (Ib) or a pharmaceutically acceptable salt therof. In certain embodiments, the compound is a compound of Formula (Ib). In certain embodiments, the compound is a sodium salt of the compound of Formula (Ib).

[00188] In some embodiments, a suspension comprising a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutical salt thereof, in a poloxamer and mannitol is provided. In some embodiments, the concentration of poloxamer in mannitol is from about 0.1 to about

20%. In some embodiments, the concentration of poloxamer in mannitol is from about 0.1 to about 10%. In some in embodiments, the concentration of poloxamer in mannitol is about 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 2,%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, or about 10%. In certain embodiments, the concentration of poloxamer in mannitol is about 2%. In certain embodiments, the poloxamer is poloxamer 188. In certain embodiments, the compound is a compound of Formula (Ib) or a pharmaceutically acceptable salt therof. In certain embodiments, the compound is a compound of Formula (Ib). In certain embodiments, the compound is a sodium salt of the compound of Formula (Ib).

[00189] In certain embodiments, the composition is disclosed as a solid dosage form, including a solid injectable dosage form, such as a solid depot form.

[00190] In certain embodiments, the active ingredient (e.g. a compound of Formula Ib) is present as a free acid. In certain embodiments, the active ingredient (e.g. a compound of Formula Ib) is present as a sodium salt.

[00191] In certain embodiments the pharmaceutical composition disclosed herein is a parenteral formulation. In certain embodiments, the formulation is administered subcutaneously to a subject in need thereof. In certain embodiments, the formulation is administered intramuscularly to a subject in need thereof.

[00192] In certain embodiments, the parenteral formulation comprises N-methyl-2-pyrrolidone. In certain embodiments, the parenteral formulation consists essentially of N-methyl-2-pyrrolidone. In certain embodiments, the parenteral formulation comprises dimethyl sulfoxide.

[00193] In certain embodiments, the parenteral formulation comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutical salt thereof and water. In certain embodiments, the parenteral formulation comprises a compound of Formula (Ib) or a pharmaceutical salt thereof and water. In certain embodiments, the parenteral formulation further comprises an alcohol. In certain embodiments, the alcohol is ethanol. In certain embodiments, the parenteral formulation further comprises polyethylene glycol. In certain embodiments, the polyethylene glycol has an average molecular weight of about 200 g/mol. (polyethylene glycol 200). In certain embodiments, the parenteral formulation further comprises an inorganic base. In certain embodiments, the inorganic base is sodium hydroxide. In certain embodiments, the the inorganic base a sodium ethoxide. In certain embodiments the formulation comprises from about 0.1 molar equivalents to about 1.5 molar equivalents of the inorganic base (e.g. NaOH or NaOEt). In certain embodiments, the

formulation comprises from about 0.5 molar equivalents to about 1.5 molar equivalents of the inorganic base (e.g. NaOH or NaOEt). In certain embodiments the formulation comprises from about 1.0 molar equivalents to about 1.2 molar equivalents of the inorganic base (e.g. NaOH or NaOEt). In certain embodiments the formulation comprises about 1.2 molar equivalents inorganic base (e.g. NaOH or NaOEt).

[00194] In certain embodiments, the parenteral formulation consists essentially of a compound of Formula (Ib) or a pharmaceutical salt thereof, water, ethanol, and polyethylene glycol 200.

[00195] In certain embodiments, the parenteral formulation consists essentially of a compound of Formula (Ib) or a pharmaceutical salt thereof, water, ethanol, polyethylene glycol 200 (polyethylene glycole with an average molecular weight of 200 g/mol.), and NaOH. In certain embodiments, the parenteral formulation consists essentially of a compound of Formula (Ib) or a pharmaceutical salt thereof, water, ethanol, polyethylene glycol 200, and NaOEt. In certain embodiments,the formulation comprises from about 0.1 molar equivalents to about 1.5 molar equivalents of NaOH or NaOEt. In certain embodiments, the formulation comprises from about 0.5 molar equivalents to about 1.5 molar equivalents of NaOH or NaOEt. In certain embodiments the formulation comprises from about 1.0 molar equivalents to about 1.2 molar equivalents of NaOH or NaOEt. In certain embodiments the formulation comprises about 1.2 molar equivalents of NaOH or NaOEt.

[00196] In certain embodiments, the parenteral formulation is a solution formulation comprises a mixture of ethanol, water, and polyethylene glycol. In certain embodiments, the parenteral formulation is a solution formulation comprising a mixture of ethanol, water, and PEG 200. In certain embodiments, the solution formulation comprises about 5%-20% ethanol, about 5% to 20% water, and about 60% to 90% PEG 200. In certain embodiments, the solution formulation comprises about 10%-15% ethanol, about 10% to 15% water, and about 70% to 80% PEG 200. In certain embodiments, the solution formulation comprises about 10% ethanol, about 12% water, and about 78% PEG 200. In certain embodiments, the solution formulation further comprises an inorganic base. In certain embodiments, the solution formulation further comprises sodium hydroxide or sodium ethoxide. In certain embodiments, the solution formulation further comprises sodium hydroxide. In certain embodiments the formulation comprises from about 0.1 molar equivalents to about 1.5 molar equivalents of the inorganic base (e.g. NaOH or NaOEt). In certain embodiments, the formulation comprises from about 0.5 molar equivalents to about 1.5 molar equivalents of the

inorganic base (e.g. NaOH or NaOEt). In certain embodiments the formulation comprises from about 1.0 molar equivalents to about 1.2 molar equivalents of the inorganic base (e.g. NaOH or NaOEt). In certain embodiments the formulation comprises about 1.2 molar equivalents inorganic base (e.g. NaOH or NaOEt).

[00197] In some embodiments, solution formulations containing 200 mg/mL of Formula Ib with about 0.1 to about 1.5 equivalents of NaOH in about 10% ethanol, about 12% water, and about 77% PEG are provided.

[00198] In certain embodiments, an oral formulation of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), comprising at least one excipient is provided. Excipients can include ethanol, medium chain triglycerides (e.g. MIGLYOL 810, MIGLYOL 821, MIGLYOL 840, and so forth), Vitamin E TPGS, glycerin, and/or pharmaceutically acceptable oils (e.g. sesame oil, castor oil, safflower oil, vegetable oil, soybean oil, and so forth). Oral formulations disclosed herein can include any combination of one or more suitable excipients. Excipients taken together can be present in >65% by weight of the total oral formulation, >70% by weight of the total oral formulation, >80% by weight of the total oral formulation, >90% by weight of the total oral formulation, or >95% by weight of the total oral formulation.

[00199] In some embodiments, an oral formulation of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), is provided. In certain embodiments the oral formulation comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), about 5% to about 20% ethanol, about 10% to about 30% Vitamin E TPGS, and about 50% to about 85% MIGLYOL 812. In some embodiments, the oral formulation comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), about 8% to about 15% ethanol, about 15% to about 25% Vitamin E TPGS, and about 60% to about 77% MIGLYOL 812. In certain embodiments the oral formulation comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), in about 10% ethanol, about 20% Vitamin E TPGS, and about 70% MIGLYOL 812. In certain embodments, the oral formulation is prepared in hard gelatin capsules.

[00200] The amount of active ingredient that may be combined with the inactive ingredients to produce a dosage form may vary depending upon the intended treatment subject and the particular mode of administration. For example, in some embodiments, a dosage form for oral administration to humans may contain approximately 1 to 1000 mg of active material formulated with an appropriate and convenient amount of carrier material

(*e.g.*, inactive ingredient or excipient material). In certain embodiments, the carrier material varies from about 5 to about 95% of the total compositions (weight: weight).

[00201] It should be understood that in addition to the ingredients particularly mentioned above the compositions of these embodiments may include other agents conventional in the art having regard to the type of composition in question, for example those suitable for oral administration may include flavoring agents.

[00202] In certain embodiments, a composition comprising an active ingredient disclosed herein (*e.g.*, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof) in one variation does not contain an agent that affects the rate at which the active ingredient is metabolized. Thus, it is understood that compositions comprising a compound of formula (Ia) or (Ib) in certain embodiments do not comprise an agent that would affect (*e.g.*, slow, hinder or retard) the metabolism of a compound of formula (Ia) or (Ib) or any other active ingredient administered separately, sequentially or simultaneously with a compound of formula (Ia) or (Ib). It is also understood that any of the methods, kits, articles of manufacture and the like detailed herein in certain embodiments do not comprise an agent that would affect (*e.g.*, slow, hinder or retard) the metabolism of a compound of formula (Ia) or (Ib) or any other active ingredient administered separately, sequentially or simultaneously with a compound of any one of formula (Ia) or (Ib).

[00203] In some embodiments, a composition comprising an active ingredient disclosed herein (*e.g.*, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof) in one variation does not contain an agent that affects the rate at which the active ingredient is metabolized. Thus, it is understood that compositions comprising a compound of Formula (Ia), (Ib), (IIa), and/or (IIb) in certain embodiments do not comprise an agent that would affect (*e.g.*, slow, hinder or retard) the metabolism of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb) or any other active ingredient administered separately, sequentially or simultaneously with a compound of Formula (Ia), (Ib), (IIa), and/or (IIb). It is also understood that any of the methods, kits, articles of manufacture and the like detailed herein in certain embodiments do not comprise an agent that would affect (*e.g.*, slow, hinder or retard) the metabolism of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb) or any other active ingredient administered separately, sequentially or simultaneously with a compound of any one of Formula (Ia), (Ib), (IIa), and/or (IIb).

Methods of Use

[00204] In certain embodiments, a method for treating or preventing an HIV infection in a subject (*e.g.*, a human), comprising administering a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, to the subject is disclosed.

In some embodiments, a method for treating or preventing an HIV infection in a subject (*e.g.*, a human), comprising administering a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, to the subject is disclosed.

In certain embodiments, a method for inhibiting the replication of the HIV virus, treating AIDS or delaying the onset of AIDS in a subject (*e.g.*, a human), comprising administering a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, to the subject is disclosed.

[00205] In some embodiments, a method for inhibiting the replication of the HIV virus, treating AIDS or delaying the onset of AIDS in a subject (*e.g.*, a human), comprising administering a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, to the subject is disclosed.

In certain embodiments, a method for preventing an HIV infection in a subject (*e.g.*, a human), comprising administering a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, to the subject is disclosed. In certain embodiments, the subject is at risk of contracting the HIV virus, such as a subject who has one or more risk factors known to be associated with contracting the HIV virus.

[00206] In some embodiments, a method for preventing an HIV infection in a subject (*e.g.*, a human), comprising administering a therapeutically effective amount of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, to the subject is disclosed. In certain embodiments, the subject is at risk of contracting the HIV virus, such as a subject who has one or more risk factors known to be associated with contracting the HIV virus.

[00207] In certain embodiments, a method for treating an HIV infection in a subject (*e.g.*, a human), comprising administering a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, to the subject is disclosed.

In some embodiments, a method for treating an HIV infection in a subject (*e.g.*, a human), comprising administering a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, to the subject is disclosed.

[00208] In certain embodiments, a method for treating an HIV infection in a subject (*e.g.*, a human), comprising administering to the subject in need thereof a therapeutically effective amount of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, and combinations thereof is disclosed. In certain embodiments, a method for treating an HIV infection in a subject (*e.g.*, a human), comprising administering to the subject in need thereof a therapeutically effective amount of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase

PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof is disclosed.

[00209] In some embodiments, a method for treating an HIV infection in a subject (*e.g.*, a human), comprising administering to the subject in need thereof a therapeutically effective amount of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, and combinations thereof is disclosed. In certain embodiments, a method for treating an HIV infection in a subject (*e.g.*, a human), comprising administering to the subject in need thereof a therapeutically effective amount of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1

modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof is disclosed.
In certain embodiments, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof for use in medical therapy of an HIV infection (*e.g.* HIV-1 or the replication of the HIV virus (*e.g.* HIV-1) or AIDS or delaying the onset of AIDS in a subject (*e.g.*, a human)) is disclosed.

[00210] In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof for use in medical therapy of an HIV infection (*e.g.* HIV-1 or the replication of the HIV virus (*e.g.* HIV-1) or AIDS or delaying the onset of AIDS in a subject (*e.g.*, a human)) is disclosed.
In certain embodiments, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof for use in the manufacture of a medicament for treating an HIV infection or the replication of the HIV virus or AIDS or delaying the onset of AIDS in a subject (*e.g.*, a human) is disclosed. One embodiment relates to a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of an HIV infection or AIDS or for use in the therapeutic treatment or delaying the onset of AIDS.

[00211] In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof for use in the manufacture of a medicament for treating an HIV infection or the replication of the HIV virus or AIDS or delaying the onset of AIDS in a subject (*e.g.*, a human) is disclosed. One embodiment relates to a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of an HIV infection or AIDS or for use in the therapeutic treatment or delaying the onset of AIDS.
In certain embodiments, the use of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for an HIV infection in a subject (*e.g.*, a human) is disclosed. In certain embodiments, a compound of any of formula (Ia) or

(Ib), or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of an HIV infection is disclosed.

[00212] In some embodiments, the use of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for an HIV infection in a subject (*e.g.*, a human) is disclosed. In certain embodiments, a compound of any of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of an HIV infection is disclosed.

[00213] In certain embodiments, in the methods of use, the administration is to a subject (*e.g.*, a human) in need of the treatment. In certain embodiments, in the methods of use, the administration is to a subject (*e.g.*, a human) who is at risk of developing AIDS.

Disclosed herein is a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for use in therapy. In one embodiment, the compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, is for use in a method of treating an HIV infection or the replication of the HIV virus or AIDS or delaying the onset of AIDS in a subject (*e.g.*, a human).

[00214] In some embodiments, disclosed herein is a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for use in therapy. In some embodiments, the compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, is for use in a method of treating an HIV infection or the replication of the HIV virus or AIDS or delaying the onset of AIDS in a subject (*e.g.*, a human).

Also disclosed herein is a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for use in a method of treating or preventing HIV infection in a subject in need thereof. In certain embodiments, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for use in a method of treating HIV infection in a subject in need thereof is provided. In certain embodiments, the subject in need thereof is a human who has been infected with HIV. In certain embodiments, the subject in need thereof is a human who has been infected with HIV but who has not developed AIDS. In certain embodiments, the subject in need thereof is a subject at risk for developing AIDS. In certain embodiments, the subject in need thereof is a human who has been infected with HIV and who has developed AIDS.

[00215] In some embodiments, disclosed herein is a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for use in a method of treating or

preventing HIV infection in a subject in need thereof. In certain embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for use in a method of treating HIV infection in a subject in need thereof is provided. In certain embodiments, the subject in need thereof is a human who has been infected with HIV. In certain embodiments, the subject in need thereof is a human who has been infected with HIV but who has not developed AIDS. In certain embodiments, the subject in need thereof is a subject at risk for developing AIDS. In certain embodiments, the subject in need thereof is a human who has been infected with HIV and who has developed AIDS.

[00216] In one embodiment, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in combination with one or more (e.g. one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents as described herein for use in a method of treating or preventing HIV infection in a subject in need thereof is provided. In one embodiment, said additional therapeutic agents are selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof. In one

embodiment, said additional therapeutic agents are selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, and combinations thereof.

[00217] In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, in combination with one or more (e.g. one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents as described herein for use in a method of treating or preventing HIV infection in a subject in need thereof is provided. In one embodiment, said additional therapeutic agents are selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof. In one embodiment, said additional therapeutic agents are selected

from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, and combinations thereof.

In one embodiment, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in combination with a first additional therapeutic agent selected from the group consisting of tenofovir alafenamide fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine, is provided for use in a method of treating or preventing HIV infection in a subject in need thereof. In a particular embodiment, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in combination with a first additional therapeutic agent selected from the group consisting of tenofovir disoproxil fumarate, tenofovir disoproxil, and tenofovir disoproxil hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine, is provided for use in a method of treating or preventing HIV infection in a subject in need thereof.

[00218] In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, in combination with a first additional therapeutic agent selected from the group consisting of tenofovir alafenamide fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine, is provided for use in a method of treating or preventing HIV infection in a subject in need thereof. In a particular embodiment, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, in combination with a first additional therapeutic agent selected from the group consisting of tenofovir disoproxil fumarate, tenofovir disoproxil, and tenofovir disoproxil hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine, is provided for use in a method of treating or preventing HIV infection in a subject in need thereof.

[00219] In a particular embodiment, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, are provided for use to prevent HIV infection from taking hold if the individual is exposed to the virus and/or to keep the virus from establishing

a permanent infection and/or to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectable levels in the blood, for example for pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP). Accordingly, in certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) are provided. For example, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof. In certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in combination with one or more additional therapeutic agents. In certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration of a pharmaceutical composition comprising a therapeutically effective amount of the compound of formula (Ia) or (Ib), or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[00220] In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, are provided for use to prevent HIV infection from taking hold if the individual is exposed to the virus and/or to keep the virus from establishing a permanent infection and/or to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectable levels in the blood, for example for pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP). Accordingly, in certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) are provided. For example, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof. In certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, in combination with one or more additional therapeutic agents. In certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration of a pharmaceutical composition comprising a therapeutically effective amount of the compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[00221] In certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration of a compound of formula (Ia) or (Ib), or a

pharmaceutically acceptable salt thereof, in combination with safer sex practices. In certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration to an individual at risk of acquiring HIV. Examples of individuals at high risk for acquiring HIV include, without limitation, an individual who is at risk of sexual transmission of HIV.

[00222] In some embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, in combination with safer sex practices. In certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration to an individual at risk of acquiring HIV. Examples of individuals at high risk for acquiring HIV include, without limitation, an individual who is at risk of sexual transmission of HIV.

[00223] In certain embodiments, the reduction in risk of acquiring HIV is at least about 40%, 50%, 60%, 70%, 80%, 90%, or 95%. In certain embodiments, the reduction in risk of acquiring HIV is at least about 75%. In certain embodiments, the reduction in risk of acquiring HIV is about 80%, 85%, or 90%.

[00224] In another embodiment, the use of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of an HIV infection in a human being having or at risk of having the infection is disclosed.

[00225] In some embodiments, the use of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of an HIV infection in a human being having or at risk of having the infection is disclosed.

[00226] Also disclosed herein is a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for use in the therapeutic treatment or delaying the onset of AIDS.

[00227] In some embodiments, disclosed herein is a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for use in the therapeutic treatment or delaying the onset of AIDS.

[00228] Also disclosed herein is a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of an HIV infection.

[00229] In some embodiments, disclosed herein is a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of an HIV infection.

[00230] In certain embodiments, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof can be used as a research tool (e.g. to study the inhibition of HIV reverse transcriptase in a subject or *in vitro*).

[00231] In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof can be used as a research tool (e.g., to study the inhibition of HIV reverse transcriptase in a subject or *in vitro*).

Routes of Administration

[00232] The compound of the formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, (also referred to herein as the active ingredient) can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with, for example, the condition of the recipient. In certain embodiments, the compounds disclosed can be dosed parenterally. In certain embodiments, the compounds disclosed can be dosed intravenous, subcutaneous, or intramuscular. In certain embodiments, the compounds disclosed are orally bioavailable and can be dosed orally.

[00233] In some embodiments, the compound of the Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, (also referred to herein as the active ingredient) can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with, for example, the condition of the recipient. In certain embodiments, the compounds disclosed can be dosed parenterally. In certain embodiments, the compounds disclosed can be dosed intravenous, subcutaneous, or intramuscular. In certain embodiments, the compounds disclosed are orally bioavailable and can be dosed orally.

[00234] In some embodiments, the compound of the Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, may be administered with a syringe suitable for

administration of the compound. In some embodiments, the syringe is disposable. In some embodiments, the syringe is reusable. In some embodiments, the syringe is pre-filled with the compound of the Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof.

[00235] In some embodiments, the compound of the Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, may be administered with an auto-injector comprising a syringe. In some embodiments, the syringe is disposable. In some embodiments, the syringe is reusable. In some embodiments, the syringe is pre-filled with the compound of the Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof.

Dosing Regimen

[00236] The compound, such as a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, may be administered to a subject in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one day, at least about one week, at least about one month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 6 months, or at least about 12 months or longer. In one variation, the compound is administered on a daily or intermittent schedule. In one variation, the compound is administered on a monthly schedule. In one variation, the compound is administered every two months. In one variation, the compound is administered every three months. In one variation, the compound is administered every four months. In one variation, the compound is administered every five months. In one variation, the compound is administered every 6 months.

[00237] In some embodiments, the compound, such as a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, may be administered to a subject in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one day, at least about one week, at least about one month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 6 months, or at least about 12 months or longer. In some embodiments, the compound is administered on a daily or intermittent schedule. In some embodiments, the compound is administered on a monthly schedule. In some embodiments, the compound is administered every two months. In some embodiments, the compound is administered every three months. In some embodiments, the compound is administered every four months. I In some

embodiments, the compound is administered every five months. In some embodiments, the compound is administered every 6 months.

[00238] In some embodiments, the compound, such as a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, may be administered to a subject at least about one month, at least about 4 months, or at least about 6 months. In some embodiments, the compound (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof), may be subcutaneously administered to a subject at least about one month. In some embodiments, the compound (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof), may be subcutaneously or intramuscularly administered to a subject at least about 4 months, or at least about 6 months. In some embodiments, the compound (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof), may be subcutaneously administered to a subject at least about one month. In some embodiments, the compound (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof), may be subcutaneously or intramuscularly administered to a subject at least about every 3 months.

[00239] The dosage or dosing frequency of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, may be adjusted over the course of the treatment, based on the judgment of the administering physician.

[00240] In some embodiments, the dosage or dosing frequency of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, may be adjusted over the course of the treatment, based on the judgment of the administering physician.

[00241] The compound may be administered to a subject (*e.g.*, a human) in an effective amount. In certain embodiments, the compound is administered once daily.

In some embodiments, the compound may be administered to a subject (*e.g.*, a human) in an therapeutically effective amount. In some embodiments, the compound is administered once daily. In some embodiments, the compound is administered monthly. In some embodiments, the compound is administered every three months. In some embodiments, the compound is administered every four months. In some embodiments, the compound is administered every six months.

[00242] A compound as disclosed herein (e.g., a compound of formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, may be administered in a dosage amount that is effective. For example, the dosage amount can be from 1 mg to 1000 mg of compound. In

certain embodiments, the dosage amount is about 10, 20, 30, 40, 50, 60, 70, 80, 90, 95, 100, 105, 110, 120, 130, 140, or 150 mg of compound. In certain embodiments the dosage amount is about 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, or 1000 mg.

[00243] In some embodiments, a compound as disclosed herein (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, may be administered in a dosage amount that is effective. For example, the dosage amount can be from 1 mg to 1000 mg of compound. In certain embodiments, the dosage amount is about 1, 10, 20, 30, 40, 50, 60, 70, 80, 90, 95, 100, 105, 110, 120, 130, 140, or 150 mg of compound. In certain embodiments the dosage amount is about 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, or 1000 mg.

[00244] In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is administered in a once daily dose. In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 1 mg.

[00245] In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is administered monthly. In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 100 mg.

[00246] In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is administered every 6 months. In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is administered every 6 months at a dose of about 600 mg.

Kits and Articles of Manufacture

[00247] The present disclosure relates to a kit comprising a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof. In one embodiment, the kit may comprise one or more additional therapeutic agents as described hereinbefore. The kit may further comprise instructions for use, *e.g.*, for use in inhibiting an HIV reverse transcriptase, such as for use in treating an HIV infection or AIDS or as a research tool. The instructions for use are generally written instructions, although electronic storage media (*e.g.*, magnetic diskette or optical disk) containing instructions are also acceptable.

[00248] In some embodiments, the present disclosure relates to a kit comprising a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof. In one embodiment, the kit may comprise one or more additional therapeutic agents as described hereinbefore. The kit may further comprise instructions for use, *e.g.*, for use in inhibiting an HIV reverse transcriptase, such as for use in treating an HIV infection or AIDS or as a research tool. The instructions for use are generally written instructions, although electronic storage media (*e.g.*, magnetic diskette or optical disk) containing instructions are also acceptable.

[00249] The present disclosure also relates to a pharmaceutical kit comprising one or more containers comprising a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice reflects approval by the agency for the manufacture, use or sale for human administration. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit. The kits may be in unit dosage forms, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. Kits may also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (*e.g.*, hospital pharmacies and compounding pharmacies).

[00250] In some embodiments, the present disclosure also relates to a pharmaceutical kit comprising one or more containers comprising a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice reflects approval by the agency for the manufacture, use or sale for human administration. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit. The kits may be in unit dosage forms, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. Kits may also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (*e.g.*, hospital pharmacies and compounding pharmacies).

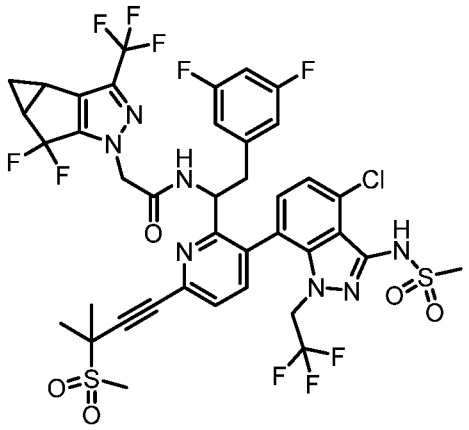
[00251] Also disclosed are articles of manufacture comprising a unit dosage of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in suitable

packaging for use in the methods described herein. Suitable packaging is known in the art and includes, for example, vials, vessels, ampules, bottles, jars, flexible packaging and the like. An article of manufacture may further be sterilized and/or sealed.

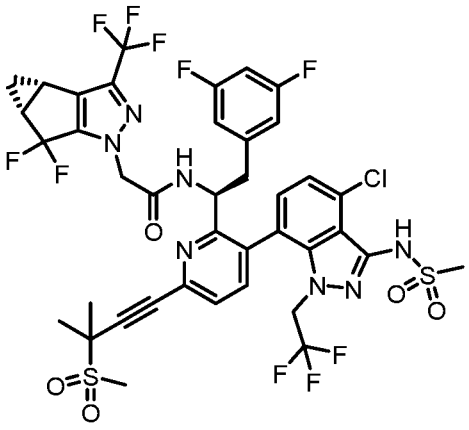
In some embodiments, disclosed herein are articles of manufacture comprising a unit dosage of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, in suitable packaging for use in the methods described herein. Suitable packaging is known in the art and includes, for example, vials, vessels, ampules, bottles, jars, flexible packaging and the like. An article of manufacture may further be sterilized and/or sealed.

Nomenclature

[00252] The name of the compound of formula (Ia) and (Ib) of the current disclosure as generated using ChemBioDraw Ultra 11.

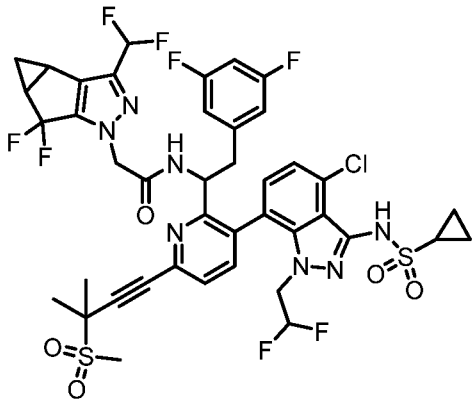


is N-(1-(3-(4-chloro-3-(methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide.

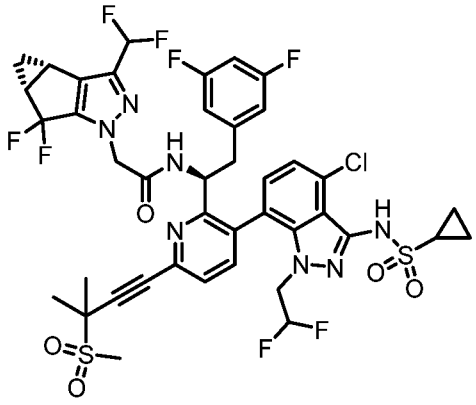


is N-((S)-1-(3-(4-chloro-3-(methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide.

[00253] The name of the compound of formula (IIa) and (IIb) of the current disclosure as generated using ChemBioDraw Ultra 14.



is N-(1-(3-(4-chloro-3-(cyclopropanesulfonamido)-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide.



is N-((S)-1-(3-(4-chloro-3-(cyclopropanesulfonamido)-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide.

Synthesis of the Compound of Formula (Ia), (Ib), (IIa), and (IIb)

[00254] The present disclosure is also directed to processes and intermediates useful for preparing the subject compound or pharmaceutically acceptable salts thereof.

[00255] Except as otherwise noted, the methods and techniques of the present disclosure are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. See, *e.g.*, Loudon, Organic Chemistry, 5th edition, New York: Oxford University Press, 2009; Smith, March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 7th edition, Wiley-Interscience, 2013.

[00256] In certain instances, the processes disclosed herein involve a step of forming a salt of a compound of the present disclosure.

[00257] In certain instances, the intermediates useful in preparing a compound of formula (Ia) or (Ib) of the present disclosure are provided. For example, those intermediates include any one of or a combination of Compounds 1 to 23 or a salt thereof. In certain embodiments, the intermediates are selected from Compound 8a, 12, 14, 19, 20, 21, 22, 23, and/or 23b, combinations thereof, or salts thereof.

[00258] In some embodiments, the intermediates useful in preparing a compound of formula (IIa) or (IIb) of the present disclosure are provided. For example, those intermediates include any one of or a combination of Compounds 1, 10, 20 and 25-37 or a salt thereof. In some embodiments, the intermediates are selected from Compound 20, 32, 34, 35, 36, and/or 37, combinations thereof, or salts thereof.

[00259] Compounds as described herein can be purified by any of the means known in the art, including chromatographic means, such as high performance liquid chromatography (HPLC), preparative thin layer chromatography, flash column chromatography, supercritical fluid chromatography (SFC), and ion exchange chromatography. Any suitable stationary phase can be used, including normal and reversed phases as well as ionic resins. Most typically the disclosed compounds are purified via silica gel and/or alumina chromatography. See, *e.g.*, Introduction to Modern Liquid Chromatography, 2nd ed., ed. L. R. Snyder and J. J. Kirkland, John Wiley and Sons, 1979; and Thin Layer Chromatography, E. Stahl (ed.), Springer-Verlag, New York, 1969.

[00260] During any of the processes for preparation of the subject compounds, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules

concerned. This may be achieved by means of conventional protecting groups as described in standard works, such as T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis," 4th ed., Wiley, New York 2006. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

[00261] Exemplary chemical entities useful in methods of the embodiments will now be described by reference to illustrative synthetic schemes for their general preparation herein and the specific examples that follow. One of skill in the art will recognize that the transformations shown in the schemes below may be performed in any order that is compatible with the functionality of the particular pendant groups. Each of the reactions depicted in the general schemes is preferably run at a temperature from about 0 °C to the reflux temperature of the organic solvent used.

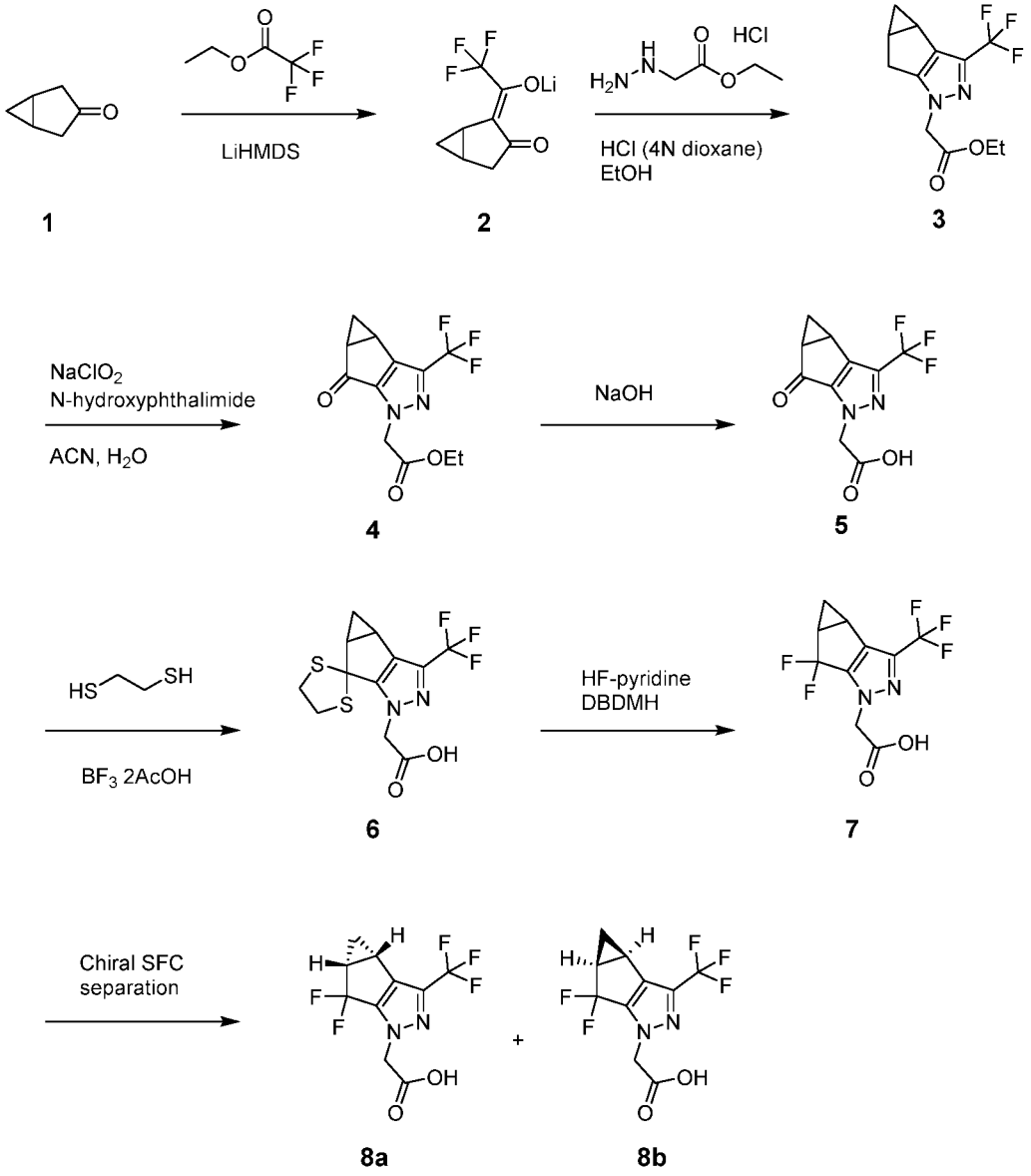
[00262] The compounds disclosed herein may display atropisomerism resulting from steric hindrance affecting the axial rotation rate around a single bond. The resultant conformational isomers may each be observed as distinct entities by characterization techniques such as NMR and HPLC. The compounds disclosed herein may exist as a mixture of atropisomers. However, the detection of atropisomers is dependent on factors such as temperature, solvent, conditions of purification, and timescale of spectroscopic technique. The interconversion rate at room temperature has a half-life of minutes to hours, hours to days, or days to years. The ratio of atropisomers at equilibrium may not be unity. Characterization data presented herein may not represent the equilibrium state depending on the conditions of isolation and characterization which may include but not limited to handling, solvents used, and temperature.

[00263] Representative syntheses of compounds of the present disclosure are described in schemes below, and the particular examples that follow. The following examples are merely illustrative, and not intended to limit this disclosure in any way.

Preparation of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (8a) and 2-((3bR,4aS)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (8b):

Example 1

Preparation of Compounds 8a and 8b



Synthesis of lithium 2,2,2-trifluoro-1-(3-oxobicyclo[3.1.0]hexan-2-ylidene)ethan-1-olate (**2**):
A reactor was charged with bicyclo[3.1.0]hexan-3-one (95.6 g, 0.99 mol) and ethyl 2,2,2-trifluoroacetate (113.2 mL, 0.95 mol) and THF (50 mL). The reaction mixture was cooled to 0 °C. LiHMDS (Lithium bis(trimethylsilyl)amide) (1L of 1.0M solution in THF, 1 mol) was added via an addition funnel at a rate to maintain internal temperature at ≤ 1 °C. After the addition was complete, hexanes (235 mL) was added in a steady stream via an addition funnel and stirred for 15 min. The resultant solids were collected by filtration, washed with hexanes (3 x 400 mL), and dried to provide the title compound.

Synthesis of ethyl 2-(3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**3**):
A reactor was charged with lithium 2,2,2-trifluoro-1-(3-oxobicyclo[3.1.0]hexan-2-ylidene)ethan-1-olate (177.2 g, 0.89 mol) and EtOH (ethanol) (779 mL). The temperature was brought to and maintained at 0 °C. HCl in dioxane (4.0 N, 443 mL) was added via an addition funnel followed by the addition of solid ethyl hydrazinoacetate HCl salt (138.4 g, 0.90 mol). The reaction temperature was adjusted to 35 °C. After 1 h, the reaction volume was reduced by ~40% by distillation at reduced pressure. Water (1.3 L) was added with vigorous agitation and temperature adjusted to 15 °C. The resultant solids were collected by filtration, washed with water (3 x 500 mL), hexanes (3 x 400 mL), and dried to provide the title compound. MS (*m/z*) 275.1 $[M+H]^+$.

Synthesis of ethyl 2-(5-oxo-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**4**):
A reactor was charged with ethyl 2-(3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (291.2 g, 1.06 mol), acetonitrile (1.65 L) and water (825 mL) to which N-hydroxyphthalimide (17.4 g, 0.103 mol) and $NaClO_2$ (41.0 g, 0.45 mol, ~20% of total amount to be added) were added. The reaction mixture was heated to 50 °C and the remaining $NaClO_2$ (163.0 g, 1.80 mol) was added in five portions over 2 h. After consumption of starting material, the temperature was adjusted to 20 °C and aqueous sodium bisulfite (40% w/w, 350 mL) was added via an addition funnel. Ethyl acetate (1.75 L) was added and the layers were separated. The aqueous layer was back extracted with EtOAc (ethyl acetate) (500 mL). The organic layers were combined and washed with saturated aqueous $NaHCO_3$ (500 mL) and 1:1 water/ brine (500 mL). The

organic layer was concentrated under reduced pressure and co-evaporated with IPAc (isopropyl acetate) (300 mL). The crude solid was crystallized from a mixture of IPAc /heptane. The resultant solids were collected by filtration, washed with heptane, and dried to provide the title compound. MS (*m/z*) 289.0 $[M+H]^+$.

Synthesis of 2-(5-oxo-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (**5**):
To a solution of ethyl 2-(5-oxo-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (80.40 g, 278.95 mmol) in 2-MeTHF (2-methyltetrahydrofuran) (167 mL) was added 2M aqueous sodium hydroxide (167 mL). After 25 minutes of stirring at room temperature, the reaction mixture was diluted with 2-MeTHF and was slowly acidified by the dropwise addition of concentrated HCl. The organic layer was isolated and the aqueous layer was extracted with an additional portion of 2-MeTHF. The combined organic layers were washed with saturated aqueous sodium chloride, then dried over sodium sulfate, filtered, and concentrated. The resulting oil was taken in ethyl acetate. Hexanes was added with vigorous stirring until solid formation was observed. The solid was isolated by filtration and dried to provide the title compound. MS (*m/z*) 259.00 $[M-H]^-$.

Synthesis of 2-(3-(trifluoromethyl)-4,4a-dihydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-[1,3]dithiolane]-1(3bH)-yl)acetic acid (**6**):
To a solution of 2-(5-oxo-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (3.0 g, 11.5 mmol) in DCM (dichloromethane) (25 mL) was added 1,2-ethanedithiol (1.07 mL, 12.68 mmol) followed by boron trifluoride-acetic acid complex (4.0 mL, 28.8 mmol). The reaction mixture was stirred at room temperature overnight. To the reaction mixture was added water (60 mL) and 2-MeTHF (60 mL). The organic layer was isolated, dried over sodium sulfate, filtered, and concentrated. The crude was dissolved in ethyl acetate (2 mL) and the solution diluted with hexanes (12 mL) with vigorous stirring to provide a solid. The solid was isolated by filtration and dried to provide the title compound. MS (*m/z*) 337.12 $[M+H]^+$.

Synthesis of 2-(5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (**7**):

To a suspension of 1,3-dibromo-5,5-dimethylhydantoin (12.75 g, 44.6 mmol) in DCM (35 mL) was added pyridine hydrofluoride (5.0 mL) at 0 °C. The suspension was stirred at 0 °C for 10 minutes. To the suspension was added a solution of 2-(3-(trifluoromethyl)-4,4a-dihydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-[1,3]dithiolane]-1(3bH)-yl)acetic acid (5.00 g, 14.9 mmol) dropwise. After addition was complete, the reaction mixture was stirred at 0 °C for an additional 15 minutes. The reaction mixture was poured into saturated aqueous sodium bicarbonate solution (300 mL) with vigorous stirring. The organic layer was removed and the aqueous layer was acidified to pH ~1 with concentrated HCl. The aqueous phase was extracted with three portions of MTBE (methyl *tert*-butyl ether). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The resulting solid was taken in MTBE (16 mL) and filtered to remove any resulting solid. The solution was then extracted with 2N NaOH (16 mL). The aqueous layer was diluted with water (16 mL) with vigorous stirred and stirred at room temperature for 15 minutes. The resulting solid was removed by filtration. The aqueous layer was acidified by slow, dropwise addition of concentrated HCl to pH ~1 with vigorous stirring to provide a solid precipitate. The solid was isolated by filtration to provide the title compound. MS (*m/z*) 281.12 $[M+H]^+$.

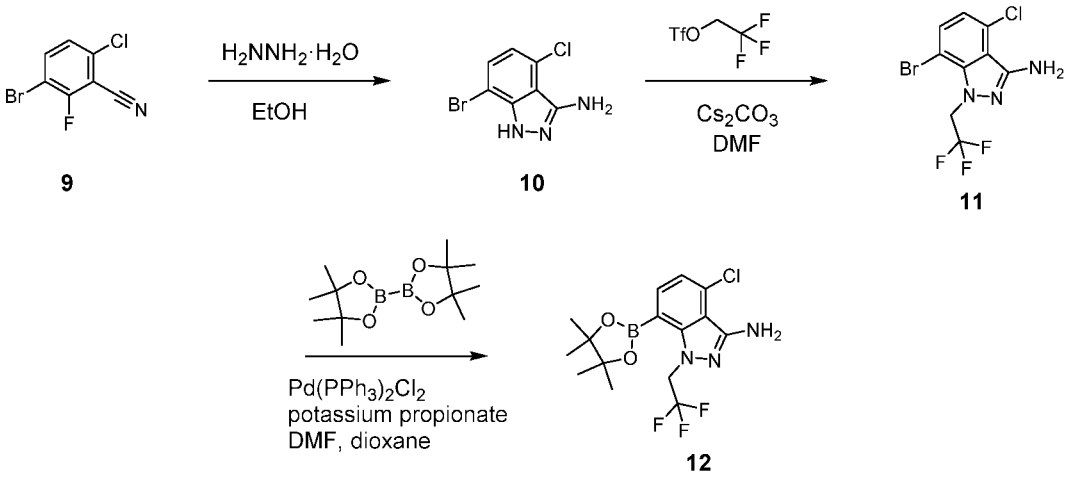
Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (**8a**) and 2-((3bR,4aS)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (**8b**):

2-(5,5-Difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid was separated to its constituent enantiomers, the title compounds, by chiral SFC under the following conditions: Instrument: Thar 350 preparative SFC; Column: ChiralPak IC-10 u, 300×50mmI.D; Mobile phase: 35% Isopropanol(0.1% $NH_3 \cdot H_2O$) and CO_2; Flow rate: 200 mL / min; Column temperature: 38 °C; UV detection: 220 nm; Sample preparation: Compound was dissolved in isopropanol to ~ 45 mg/mL; Injection: 6.5 mL per injection. Analytical SFC [mobile phase: A for CO_2 and B for Isopropanol (0.05% DEA); Gradient: B 20%; A; Flow rate: 2.35 mL/min; Column: Chiralpak IC-3, 150×4.6 mm, 3um; Wavelength: 254 nm] **8a:** t= 3.39 min, **8b:** t= 2.17 min.

Compound **8a** - ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.93 (s, 2H), 2.52 – 2.43 (m, 2H), 1.44 – 1.38 (m, 1H), 1.15 (m, 1H).

Example 2

Preparation of Compound 12



Synthesis of 7-bromo-4-chloro-1H-indazol-3-amine (**10**):

To 3-bromo-6-chloro-2-fluorobenzonitrile (13.9 g, 59.3 mmol) in EtOH (ethanol) (60 mL) was added hydrazine monohydrate (5.77 mL). The reaction mixture was heated to 80 °C for 3 h. After cooling to ambient temperature, EtOH (20 mL) was added to allow for stirring. The solids were isolated by filtration, washed with cold EtOH, and dried to provide the title compound. MS (*m/z*) 247.9 $[M+H]^+$.

Synthesis of 7-bromo-4-chloro-1-(2,2,2-trifluoroethyl)-1H-indazol-3-amine (**11**):

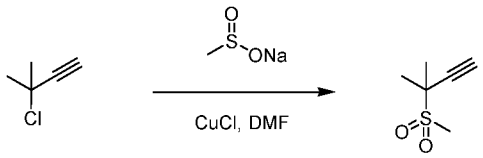
A reactor was charged with 7-bromo-4-chloro-1H-indazol-3-amine (397.2 g, 1.6 mol) and Cs_2CO_3 (1052 g, 3.2 mol) then diluted with DMF (dimethylformamide) (4000 mL). To this was slowly added 2,2,2-trifluoroethyl trifluoromethanesulfonate (463.2 g, 1.9 mol) via addition funnel. Upon completion of the addition, the reaction mixture was allowed to stir for 1 hour, at which time, H_2O (16 L) was added slowly. Upon completion of the addition, the mixture was allowed to stir for 12 hours at 15 °C. The slurry was filtered and the collected solids were suspended in DMF (800 mL). To this was added H_2O (4800 mL) and the resulting solids were collected by filtration and dried to provide the title compound. MS (*m/z*) 330.1 $[M+H]^+$.

Synthesis of 4-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)-1H-indazol-3-amine (**12**):

A reaction vessel was charged with 7-bromo-4-chloro-1-(2,2,2-trifluoroethyl)-1H-indazol-3-amine (15.00 g, 45.66 mmol), bis(pinacolato)diboron (17.39 g, 68.49 mmol), potassium propionate (15.36 g, 136.98 mmol), dioxane (90 mL) and DMF (dimethylformamide) (30 mL). Bis(triphenylphosphine)palladium(II) dichloride (0.64g, 0.91 mmol) was added and the reaction solution degassed by bubbling argon for 2 min. The reaction mixture was heated to 105 °C for 4 hrs. After cooling to ambient temperature, the reaction mixture was filtered through a pad of Celite and silica gel washing with EtOAc. The filtrate was washed with 5% LiCl solution and brine. The organic layers were separated, dried, and concentrated under reduced pressure. The residue was treated with IPAc/heptane (1/10) at 60 °C then cooled to ambient temperature and stirred for 15 h. The solids were collected by filtration and dried to afford the title compound. MS (*m/z*) 376.7 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 (d, 1H), 7.06 (d, 1H), 5.55 (s, 2H), 5.45 (q, 2H), 1.32 (s, 12H).

Example 3

Preparation of Compound 14



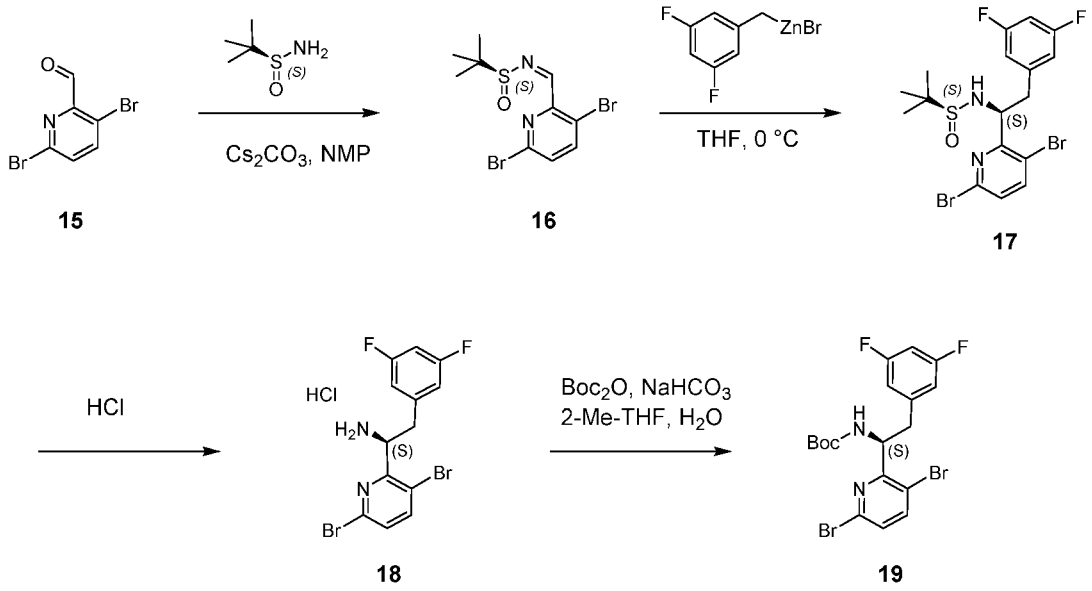
13 **14**

Synthesis of 3-methyl-3-(methylsulfonyl)but-1-yne (**14**):

To a stirred suspension of sodium methanesulfinate (18.47 g, 175.5 mmol) and copper(I) chloride (1.45 g, 14.6 mmol) in DMF (dimethylformamide) (50 mL) was added 3-chloro-3-methylbut-1-yne (15.00 g, 146.3 mmol, 16.4 mL) dropwise. The resulting reaction mixture was heated to 40 °C and stirred for 16 h. The reaction mixture was cooled to room temperature and diluted with EtOAc. The solution was washed with water and brine. The organic layer was collected and dried over sodium sulfate, then filtered. The solution was concentrated under vacuum and purified by silica gel chromatography to provide the title compound. Mp: 114.8–115.5 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.04 (s, 3H), 2.58 (s, 1H), 1.67 (s, 6H).

Example 4

Preparation of Compound 19



15 16 17 18 19

Synthesis of (S)-N-((3,6-dibromopyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (**16**):

3,6-Dibromopicolinaldehyde (76.0g, 0.287 mol) and (S)-2-methylpropane-2-sulfinamide (36.51g, 0.301 mol) were combined in NMP (*N*-methyl-2-pyrrolidone) (200 mL). To the reaction mixture was added Cs_2CO_3 (41.94g, 0.316 mol) as a solid in one portion. The reaction mixture was stirred 2h then cooled to 5 °C. Water (1.3 L) was added to the reaction

mixture. The resulting suspension was stirred for 1h, solids isolated by filtration, washed with water (5x100mL) and dried to provide the title compound. MS (*m/z*) 368.9 $[M+H]^+$.

Synthesis of (S)-N-((S)-1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (**17**):

A reaction vessel was charged with (S)-N-((3,6-dibromopyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (65.5 g, 177.95 mmol) followed by DMF (dimethylformamide) (260 mL). The mixture was stirred for 5 min until homogeneous and the solution was cooled to 8 °C. To the reaction mixture was added (3,5-difluorobenzyl)zinc bromide (0.5 M in THF (tetrahydrofuran), 516.04 mL) dropwise over 90 mins. The mixture was stirred for an additional 2.5h. To the reaction mixture, 5% AcOH (acetic acid) in water (640 mL) was added over 10 mins followed by CPME (cyclopentyl methyl ether) (320 mL) in one portion. The mixture was stirred for 5 mins, warmed to room temperature, and the layers were separated. The organic layer was washed with 5% AcOH (320 mL) then treated with 0.5M NaOH (330 mL) and washed with brine. The organic layer was collected, dried with Na_2SO_4, and filtered. To the crude mixture was added MeOH (methanol) (33 mL). To the stirring mixture was added dropwise 3M HCl in CPME (128 mL) over 15 mins. After stirring for 1h, the precipitate was removed by filtration. The filtrate was diluted with hexane (300 mL) and the product was extracted with water (450 mL). The aqueous layer was basified with 8M NaOH and extracted with CPME (375 mL). The organic layer was washed with brine, dried over Na_2SO_4 and filtered to provide the title compound in solution which was used directly in the next reaction. MS (*m/z*) 497.0 $[M+H]^+$.

Synthesis of (S)-1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethan-1-amine (**18**):

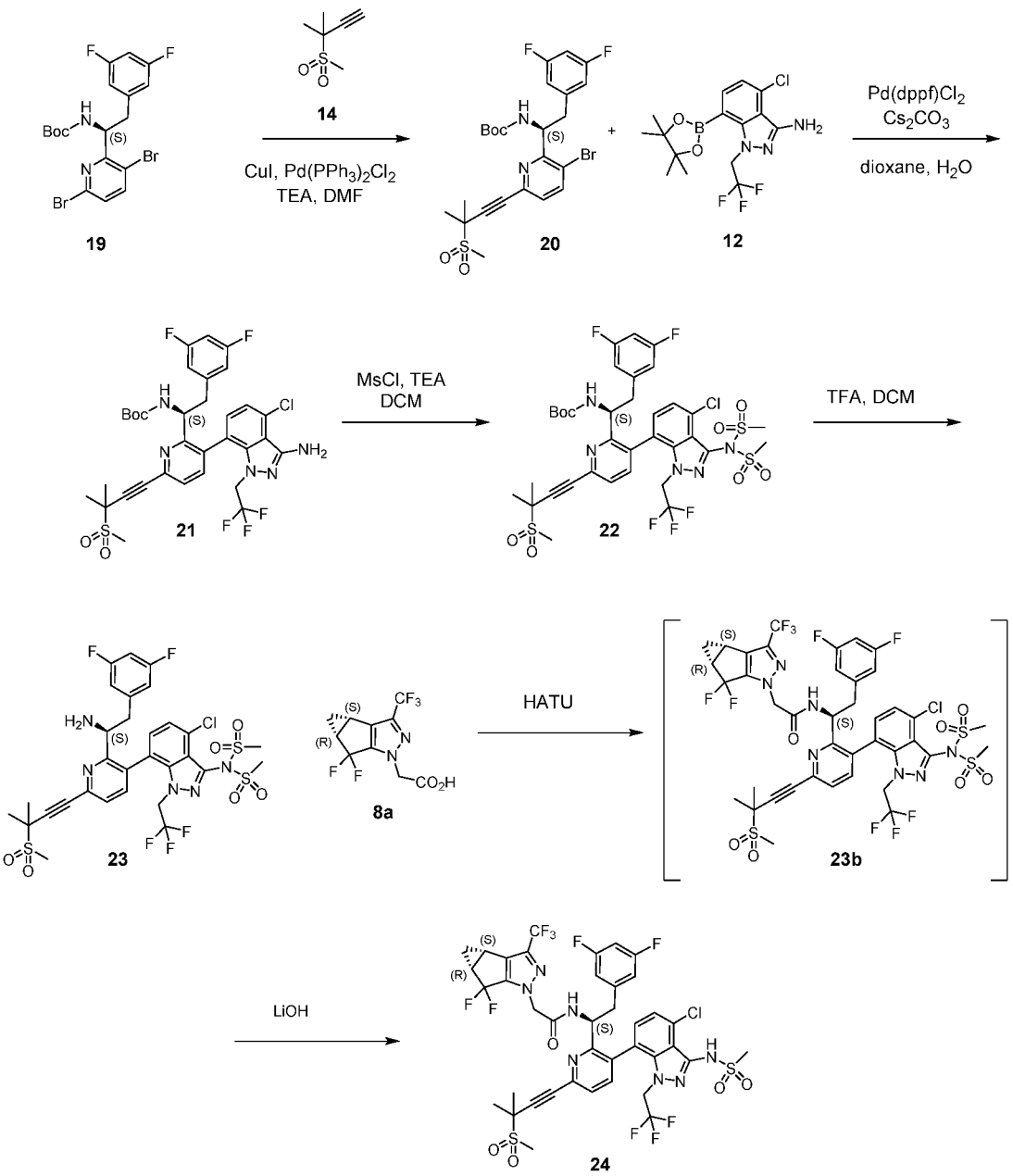
The resulting solution of (S)-N-((S)-1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide was diluted with CPME to a volume of 700 mL to which acetonitrile (350 mL) was added. To the stirring mixture, concentrated HCl (37%, 16.4 mL) was added dropwise over 10 mins at room temperature. The thick slurry was vigorously stirred for 4h. The solids were filtered and washed with 2:1 CPME (cyclopropyl methyl ether):ACN to provide the title compound. MS (*m/z*) 393.3 $[M+H]^+$.

Synthesis of tert-butyl (S)-(1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**19**):

A reaction vessel was charged with 2-MeTHF (190 mL), water (190 mL) and (S)-1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethan-1-amine (46.9 g, 0.11 mol) followed by portionwise addition of $NaHCO_3$ (30.34 g, 0.36 mol). The reaction mixture was cooled to 5 °C and di-tert-butyl dicarbonate (27.47 g, 0.13 mol) was added. The reaction mixture was stirred at 0 °C for 2h and ambient temperature for 2h. The reaction mixture was diluted with water and extracted with MTBE (methyl *tert*-butyl ether). The organic layers were washed with brine, dried and concentrated. Crude compound was purified by column chromatography on silica to provide the title compound. MS (*m/z*) 492.8 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 7.85 (d, 1H), 7.42 (d, 1H), 6.90 – 6.72 (m, 3H), 5.33 (dd, 1H), 3.10 (dd, 1H), 2.92 (dd, 1H), 1.36 (s, 9H).

Example 5

Preparation of Formula (Ib) (Compound 24)



Synthesis of tert-butyl (S)-(1-(3-bromo-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate **(20)**

A reactor was charged with tert-butyl (*S*)-(1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (50.00 g, 101.8 mmol), 3-methyl-3-methylsulfonyl-but-1-yne (17.86 g, 122.2 mmol), DMF (dimethylformamide) (90 mL) and Et_3N (trimethylamine) (42.5

mL, 305.4 mmol). The reaction mixture was heated to 50 °C. Bis(triphenylphosphine)palladium(II) dichloride (2.14 g, 3.1 mmol) and copper(I) iodide (0.58 g, 3.1 mmol) were added. After 30 min, the reaction mixture was diluted with MeCN (acetonitrile) (200 mL) and then 7% aq. NH_4Cl (200 mL) was added dropwise. A slurry was formed and adjusted to ambient temperature. After 3h, the solids were collected by filtration. The cake was washed with MeCN/water (1:1, 75 mL) twice and MTBE (methyl *tert*-butyl ether) (75 mL). The solid was dried to provide the title compound. MS (*m/z*) 556 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.84 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.15 (m, 1H), 6.70 – 6.55 (m, 2H), 5.79 (d, *J* = 9.0 Hz, 1H), 5.57 – 5.45 (m, 1H), 3.21 – 3.05 (m, 4H), 2.99 – 2.88 (m, 1H), 1.80 (s, 6H), 1.40* (s, 7H), 1.30* (s, 2H). *denotes presence of atropisomers in 4.6:1 ratio.

Synthesis of tert-butyl (S)-(1-(3-(3-amino-4-chloro-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**21**):

tert-Butyl (S)-(1-(3-bromo-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (1000.0 mg, 1.79 mmol), 4-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)-1H-indazol-3-amine (808.5 mg, 2.15 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (65.6 mg, 0.09 mmol), and cesium carbonate (876.7 mg, 2.69 mmol) were charged in a round bottom flask and placed under argon. Dioxane (10 mL) and water (2 mL) were added, and the suspension was degassed by bubbling argon for 60 seconds. After degassing, the reaction flask was fitted with a reflux condenser and heated to 80 °C overnight. The reaction mixture was cooled to room temperature, and the aqueous layer was removed. The organic layer was concentrated under vacuum, and the resulting residue was purified by silica gel column chromatography to provide the title compound. MS (*m/z*) 726.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.69 – 7.55 (m), 7.55 – 7.42 (m), 7.16 – 7.06 (m), 7.07 – 6.96 (m), 6.89 (d), 6.60 (tt), 6.44 (dd), 6.20 (d), 6.16 (d), 6.08 (s), 5.69 – 5.53 (m), 5.29 (s), 5.26 (d), 4.95 – 4.85 (m), 4.64 (q), 4.59 – 4.46 (m), 4.36 – 4.19 (m), 3.94 – 3.76 (m), 3.64 – 3.54 (m), 3.18 (s), 3.17 (s), 3.01 – 2.84 (m), 2.78 – 2.68 (m), 1.86 – 1.82 (m), 1.38 (s), 1.34 (s), 1.26 (s), 1.23 (s), 1.15 (s).

Synthesis of tert-butyl (S)-(1-(3-(4-chloro-3-(N-(methylsulfonyl)methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**22**):

tert-Butyl (S)-(1-(3-(3-amino-4-chloro-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (37.89 g, 52.18 mmol) was dissolved in methylene chloride (380 mL) with stirring at ambient temperature. To it was added triethylamine (21.82 mL, 156.54 mmol) followed by slow addition of methanesulfonyl chloride (8.08 mL, 104.36 mmol). When the reaction was complete, water (200 mL) was added and stirred for 0.5 hours. The organic layer was separated and the aqueous layer was extracted with methylene chloride once. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated to a small volume. Hexanes was added. The liquid suspension was decanted. The remaining solid was dried under reduced pressure to afford the title compound. MS (*m/z*): 882.69 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 7.87 (d), 7.83 (d), 7.76 (s), 7.74 (s), 7.69 (s), 7.67 (s), 7.65 (s), 7.52 – 7.47 (m), 7.46 (s), 7.37 (d), 7.33 (d), 7.11 – 7.03 (m), 4.79 – 4.55 (m), 4.51 (t), 4.36 (dt), 4.20 – 4.05 (m), 3.64 (s), 3.62 (s), 3.60 (s), 3.59 (s), 3.23 (s), 3.04 (d), 3.01 (d), 2.95 – 2.83 (m), 1.81 (s), 1.34 (s), 1.29 (s), 0.98 (s).

Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-(2,2,2-trifluoroethyl)-1H-indazol-3-yl)-N-(methylsulfonyl)methanesulfonamide (**23**):

To tert-butyl (S)-(1-(3-(4-chloro-3-(N-(methylsulfonyl)methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (39 g, 44 mmol) dissolved in methylene chloride (120 mL) was added trifluoroacetic acid (80 mL). The reaction mixture was stirred at ambient temperature for 50 minutes. The reaction mixture was diluted with methylene chloride and slowly poured into ice cold saturated aqueous $NaHCO_3$. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, filtered and concentrated to dryness to afford the title compound. MS (*m/z*): 782.84 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.61 (d), 7.54 – 7.44 (m), 7.40 (d), 7.33 (d), 7.20 (d), 6.66 – 6.57 (m), 6.44 (d), 6.33 (d), 6.17 (d), 4.64 (s), 3.68 (s), 3.64 (s), 3.61 (s), 3.55 (s), 3.19 (s), 3.05 (dd), 2.85 – 2.72 (m), 1.86 (s), 1.62 (s).

Synthesis of N-((S)-1-(3-(4-chloro-3-(methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**24**):

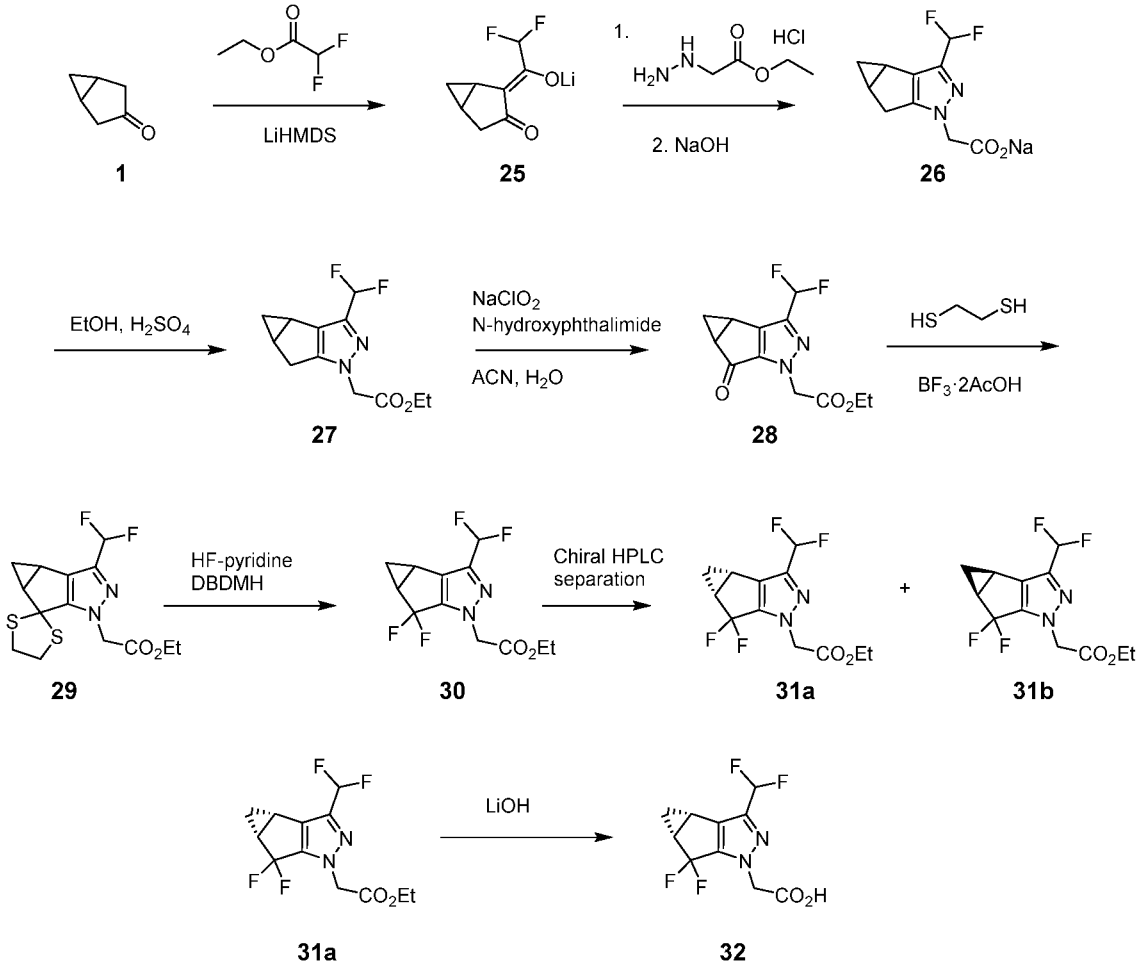
(S)-N-(7-(2-(1-Amino-2-(3,5-difluorophenyl)ethyl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-(2,2,2-trifluoroethyl)-1H-indazol-3-yl)-N-(methylsulfonyl)methanesulfonamide (1757 mg, 2.25 mmol), 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (666 mg, 2.36 mmol), and HATU (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (854 mg, 2.25 mmol) were charged in a round bottom flask and dissolved in DMF (dimethylformamide) (10.0 mL). To the solution was added N,N-diisopropylethylamine (0.80 mL, 4.49 mmol) at a rapid dropwise rate. After addition was complete, the reaction mixture was stirred at room temperature for 15 minutes to provide the intermediate **23b** which was not isolated (MS (*m/z*) 1046.65 $[M+H]^+$). To the solution was added 2N aq. sodium hydroxide solution (5.0 mL). The mixture was stirred at room temperature for 30 minutes. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was collected and washed with two portions of 5% lithium chloride solution followed by brine. The organic layer was isolated, dried over sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography to yield the title compound as an amorphous solid. MS (*m/z*) 968.24 $[M+H]^+$. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.87 – 7.57 (m), 7.33 – 7.09 (m), 6.80 – 6.70 (m), 6.54 (d), 6.47 (d), 6.37 – 6.19 (m), 5.02-4.94(m), 4.90 – 4.70 (m), 4.70 – 4.51 (m), 3.94 (dq), 3.32-3.28 (m), 3.23 (d), 3.07 (dd, J = 13.1, 7.6 Hz), 2.93 (dd), 2.68 – 2.35 (m), 1.81 (s), 1.41 (q), 1.12 – 1.00 (m). ^{19}F NMR (377 MHz, Methanol-d_4) δ –63.65 , –71.78 (t), –72.35 (t), –82.75 (dd), –105.70 (ddd), –111.73 – –113.10 (m).

To more fully characterize **23b**, that compound was isolated. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (d), 8.99 (d), 7.96 (d), 7.83 (d), 7.80 (d), 7.76 (d), 7.45 (d), 7.41 (d), 7.31 (d), 7.02 (tt), 6.92 (m), 6.91 (d), 6.48 (m), 4.92 (m) 4.88 (d), 4.79 (d), 4.73 (d), 4.71 (m), 4.69 (m), 4.62 (m), 4.60 (m), 4.38 (dq), 4.12 (dq), 3.68 (s), 3.66 (s), 3.63 (s), 3.58 (s), 3.26 (s), 3.12 (dd), 3.05 (dd), 2.97 (dd), 2.78 (dd), 2.59 (m), 2.53 (m), 1.75 (s), 1.39 (m), 0.98 (m).

Preparation of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (32)

Example 6

Preparation Compound 32



Synthesis of lithium 2,2-difluoro-1-(3-oxobicyclo[3.1.0]hexan-2-ylidene)ethan-1-olate (**25**):

The title compound was prepared according to the method presented for the synthesis of compound **2** utilizing ethyl 2,2-difluoroacetate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (t, J = 53.6 Hz, 1H), 2.78-2.73 (m, 1H), 2.44-2.39 (m, 1H), 2.25-2.24 (m, 1H), 1.70-1.69 (m, 1H), 1.22-1.14 (m, 1H), 0.31-0.27 (m, 1H).

Synthesis of sodium 2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**26**):

Me-THF (1.32L) was added in to 4L reactor followed by lithium 2,2-difluoro-1-(3-oxobicyclo[3.1.0]hexan-2-ylidene)ethan-1-olate (247g, 1.32mol). HCl (4N in dioxane) (0.685L, 2.74mol) was slowly added to the mixture maintaining an internal temperature around 20 °C. Following addition of ethyl hydrazinoacetate hydrochloride (212.05g, 1.372 mol), the resulting mixture was stirred at 20 °C for 4 hours. The reaction mixture was heated to 50 °C for overnight. 10N aqueous NaOH (0.548 L, 5.48 mol) was slowly added to the reaction mixture and the internal temperature was maintained at 20 °C. After addition, 300ml MeTHF was added, and the resultant suspension was stirred at 20°C for 3 hours. The suspension was drained and filtered. The filter cake was washed with hexane (1 L) and dried in vacuum oven at 56°C to obtain the title compound which was used directly in the next step. MS (m/z) 229.1 $[M–Na+H]^+$.

Synthesis of ethyl 2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**27**):

Ethyl 2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate from the previous step was charged in 4 L reactor and followed by the addition of EtOH (3.5 L) and concentrated H_2SO_4 (152 ml. 2.74 mol). The resulting mixture was stirred under reflux for 2 hours. EtOH was reduced under vacuo to 150ml. H_2O (500ml) was added slowly. Solids were collected and washed with H_2O and $NaHCO_3$, and followed by hexane (500ml). Solid was dried under oven at 45 °C to obtain the title compound. MS (m/z) 257.1 $[M+H]^+$.

Synthesis of ethyl 2-(3-(difluoromethyl)-5-oxo-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**28**):

The title compound was prepared according to the method presented for the synthesis of compound **4** utilizing ethyl 2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate. MS (m/z) 271.1 $[M+H]^+$.

Synthesis of ethyl 2-(3-(difluoromethyl)-4,4a-dihydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-[1,3]dithiolane]-1(3bH)-yl)acetate (**29**):

To ethyl 2-(3-(difluoromethyl)-5-oxo-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (148.5 g, 0.55 mol) in DCM (2.0 L) was added ethane-1,2-dithiol (88.0 g, 0.94 mol) in one portion followed by BF_3•2AcOH (175.8 g, 0.94 mol). The reaction was stirred at room temperature for 12 h. The system was cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$ (1000 ml). The organic layer was separated, washed with brine (500 ml) and dried over Na_2SO_4. Solvents were removed in vacuo and the residue was purified by silica gel column chromatography to provide the title compound. MS (m/z): 347.1 $[M+H]^+$.

Synthesis of ethyl 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**30**):

A solution of DBDMH (99 g, 0.35 mol) in DCM (120 mL) was cooled to –8 °C in a teflon bottle. HF/Py (120 mL) was added drop-wise over a period of 30 min. The reaction was stirred at –78 °C for 30 min. A solution of ethyl 2-(3-(difluoromethyl)-4,4a-dihydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-[1,3]dithiolane]-1(3bH)-yl)acetate (40 g, 0.12 mol) in DCM (80 mL) was added drop-wise over a period of 15 min at –78 °C. The resulting mixture was stirred for 30 min then slowly warm to –30 °C and stirred for 1.5 h. The reaction mixture was slowly poured into aq. $NaHCO_3$ (500 mL) and extracted with EA (500 mLx3). The combined organic layer was washed with 10% aq. $Na_2S_2O_3$ (500 mL), brine (500 mL) and dried over Na_2SO_4. Solvents were removed in vacuo to afford the crude product, which was further purified by column chromatography to provide the title compound. MS (m/z): 293.2 $[M+H]^+$.

Separation of ethyl 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**31a**) and ethyl 2-((3bR,4aS)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**31b**):

Ethyl 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate was separated to its constituent enantiomers, the title compounds, by chiral HPLC under the following conditions: Column: ChiralPak AD; Mobile phase: Hex/3C EtOH = 95/5; Room temperature; UV detection: 250

nm. Analytical HPLC [mobile phase: Hex/3C EtOH = 95/5; Flow rate: 0.75 mL/min; Column: Chiralpak AD-H, 150×4.6 mm, 5um; Wavelength: 220 nm] **31a:** t= 5.30 min, **31b:** t= 7.00 min.

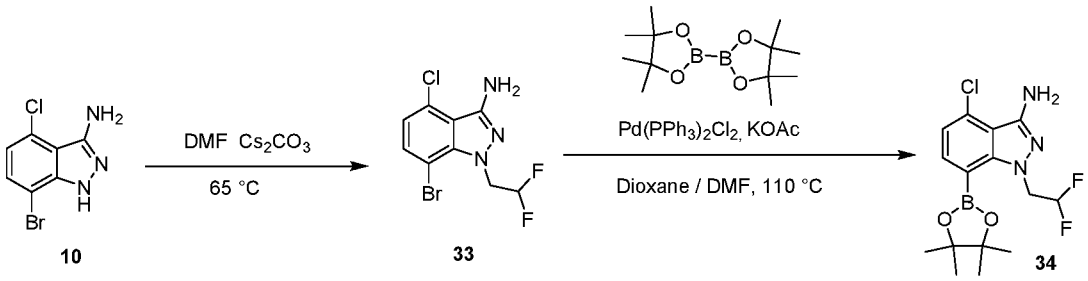
Compound **31a** - ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.63 (t, J = 54.8 Hz, 1H), 4.83 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 2.48-2.45 (m, 2H), 1.38-1.36 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.13-1.12 (m, 1H).

Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (**32**):

To a solution of ethyl 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (26 g, 89.0 mmol) in THF (180 mL), MeOH (90 mL) and water (90 mL) was added LiOH (5.13 g, 213.5 mmol). The mixture was stirred for 4 h. The mixture was concentrated to remove most of THF and MeOH, the aqueous was acidified by 1N HCl to adjust pH to 2-3, then extracted with EA (600 mLx2). The organic phase was separated and combined, dried over Na_2SO_4, filtered and concentrated in vacuum to provide the title compound. MS (m/z) 265.0 $[M+H]^+$.

Example 7

Preparation of Compound 34



Synthesis of 7-bromo-4-chloro-1-(2,2-difluoroethyl)-1H-indazol-3-amine (**33**):

To a 2000-mL 4-necked round-bottom flask was placed 7-bromo-4-chloro-1H-indazol-3-amine (130 g, 527.40 mmol, 1.00 equiv), N,N-dimethylformamide (1300 mL), Cs_2CO_3 (260 g, 797.99 mmol, 1.50 equiv) with stirring for 20 min, followed by the addition of 1,1-difluoro-2-iodoethane (122 g, 635.59 mmol, 1.20 equiv). The resulting mixture was stirred overnight at 65°C, then cooled to room temperature, quenched by the addition of 3 L of water/ice, extracted with 3x1.5 L of ethyl acetate. The combined organic layer was washed

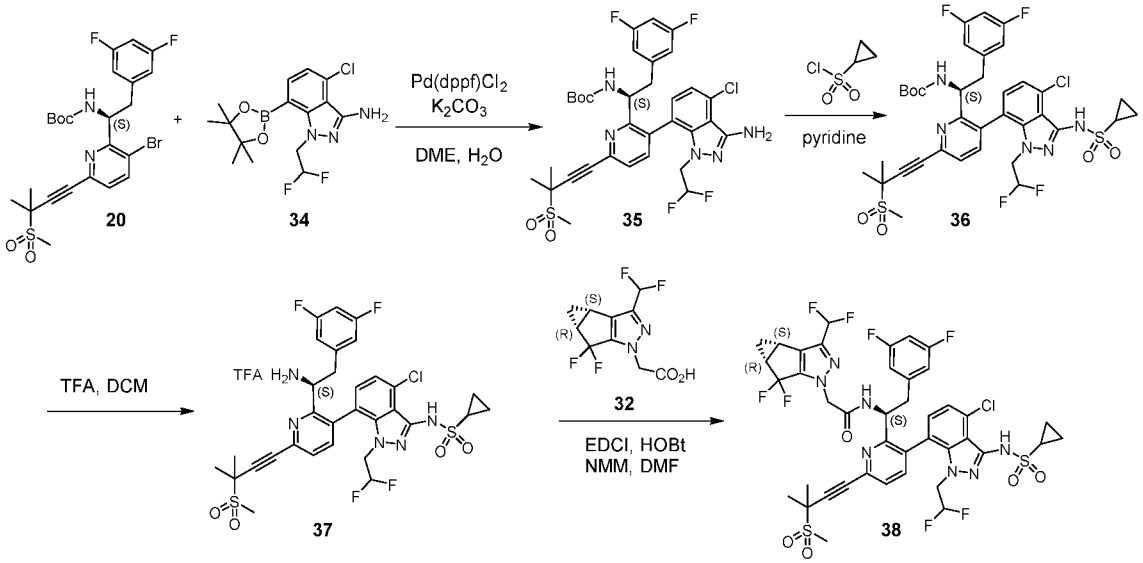
with 1x1.5 L of H_2O, 1x1.5 L of brine, dried over anhydrous sodium sulfate, concentrated under vacuum, and recrystallized from ethanol to afford the title compound. MS (m/z) 312.1 $[M+H]^+$.

Synthesis of 4-chloro-1-(2,2-difluoroethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-amine (**34**):

To a 3000-mL 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 7-bromo-4-chloro-1-(2,2-difluoroethyl)-1H-indazol-3-amine (80 g, 257.63 mmol, 1.00 equiv), 1,4-dioxane (800 mL), N,N-dimethylformamide (800 mL), KOAc (76 g, 774.40 mmol, 3.00 equiv), 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (197 g, 775.78 mmol, 3.00 equiv) and $Pd(PPh_3)_2Cl_2$ (8 g, 11.40 mmol, 0.04 equiv). The mixture was stirred for 4 h at 110°C, then cooled to room temperature, quenched by the addition of 5 L of water/ice, extracted with 2x2 L of ethyl acetate. The combined organic layer was washed with 1x1 L of H_2O, 1x1 L of brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column eluted with ethyl acetate/petroleum ether (1:10) to afford the title compound. MS (*m/z*): 358 $[M+H]^+$. ^{1}H-NMR: (DMSO-d6, 300MHz, ppm): δ7.63-7.66 (1H, d), 7.00-7.03 (1H, d), 6.06-6.43 (1H, t), 5.46 (2H, s), 4.90-5.01 (2H, t), 1.34 (12H, s).

Example 8

Preparation of Formula (IIb) (Compound 38)



Synthesis of tert-butyl (S)-(1-(3-(3-amino-4-chloro-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**35**):

tert-Butyl (S)-(1-(3-bromo-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (300 mg, 0.53 mmol), 4-chloro-1-(2,2-difluoroethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-amine (250 mg, 0.7 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (14 mg, 0.016 mmol), and potassium carbonate (186 mg, 1.35 mmol) were charged in a microwave tube and placed under argon. Dimethoxyethane (2.5 mL) and water (0.3 mL) were added, and the reaction mixture was heated to 130 °C in a microwave reactor (Biotage® Initiator+) for 7 minutes. The reaction mixture was cooled to room temperature, and partitioned between EtOAc and 0.1 N HCl. The aqueous layer was removed and the organic layer was concentrated under vacuum. The resulting residue was purified by silica gel column chromatography to provide the title compound. MS (m/z) 708.20 $[M+H]^+$). ^{1}H NMR (400 MHz, Methanol-d4) δ 7.91 – 7.50 (m), 7.28 – 6.89 (m), 6.88 – 6.65 (m), 6.56 (dd), 6.46 – 6.17 (m), 6.08 – 5.60 (m), 4.76 – 4.47 (m), 4.04 – 3.73 (m), 3.73 – 3.41 (m), 3.22 (s), 3.17 – 2.69 (m), 1.80 (s), 1.29 (d), 0.98 (d).

Synthesis of tert-butyl (S)-(1-(3-(4-chloro-3-(cyclopropanesulfonamido)-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**36**):

tert-Butyl (S)-(1-(3-(3-amino-4-chloro-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (700 mg, 0.99 mmol) and 4-dimethylaminopyridine (24 mg, 0.2 mmol) were dissolved in pyridine (2 mL) with stirring at ambient temperature. To it was added cyclopropane-1-sulfonyl chloride (222 μL, 2.2 mmol). The reaction mixture was stirred at 70 °C until the reaction was complete. Water was added and stirred for 1 hour, and the resulting precipitate was collected by vacuum filtration then dissolved in methylene chloride, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica chromatography to afford the title compound. MS (m/z): 812.44 $[M+H]^+$. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.93 – 7.58 (m), 7.50 – 7.15 (m), 7.00 (dd), 6.82 – 6.51 (m), 6.47 – 6.29 (m), 6.18 – 5.65 (m), 4.77 – 4.43 (m), 4.31 – 4.08 (m), 3.99 – 3.63 (m), 3.22 (s), 3.18 – 2.71 (m), 1.80 (s), 1.28 (s), 1.20 – 0.76 (m).

Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-(2,2-difluoroethyl)-1H-indazol-3-yl)cyclopropanesulfonamide (**37**):

To a solution of tert-butyl (S)-(1-(3-(4-chloro-3-(cyclopropanesulfonamido)-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (705 mg, 0.87 mmol) in methylene chloride (5 mL) was added trifluoroacetic acid (3 mL). The reaction mixture was stirred for 1 hour then slowly poured into a saturated sodium bicarbonate solution. It was extracted with EtOAc. Organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and concentrated to afford the title compound. MS (m/z): 712.34 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d4) δ 7.93 - 7.58 (m), 7.50 - 7.15 (m), 7.00 (dd), 6.82 - 6.51 (m), 6.47 - 6.29 (m), 6.18 - 5.65 (m), 4.77 - 4.43 (m), 4.31 - 4.08 (m), 3.99 - 3.63 (m), 3.22 (d), 3.18 - 2.71 (m), 1.80 (d), 1.28 (s), 1.20 - 0.76 (m).

Synthesis of N-((S)-1-(3-(4-chloro-3-(cyclopropanesulfonamido)-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**38**):

(S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-(2,2-difluoroethyl)-1H-indazol-3-yl)cyclopropanesulfonamide (514 mg, 0.72 mmol), 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (191 mg, 0.72 mmol), 1-hydroxybenzotriazole (49 mg, 0.36 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (180 mg, 0.94 mmol) were charged in a round bottom flask and dissolved in DMF (10 mL). n-Methylmorpholine (0.20 mL, 1.8 mmol) was added. The reaction mixture was stirred at ambient temperature for 30 minutes. Water was added and stirred for 1 hour. The resulting precipitate was collected by vacuum filtration then dissolved in methylene chloride, dried over $MgSO_4$, filtered and concentrated. The residue was purified by RP-HPLC to yield the title compound as a TFA salt. MS (m/z) 958.88 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d4) δ 7.90 – 7.56 (m), 7.30 – 7.07 (m), 6.91 – 6.54 (m), 6.54 – 6.39 (m), 6.37 – 6.21 (m), 6.16 – 5.70 (m), 4.85 – 4.57 (m), 4.34 – 4.12 (m), 3.87 – 3.41 (m), 3.23 (s), 3.17 – 3.02 (m), 3.00 – 2.77 (m), 2.57 – 2.37 (m), 1.81 (s), 1.50 – 0.84 (m).

Biological Examples

Example A

Test A: Antiviral assay in MT4 Cells

For the antiviral assay, 0.4 µL of 189X test concentration of 3-fold serially diluted compound in DMSO was added to 40 µL of cell growth medium (RPMI 1640, 10% FBS, 1% Penicillin-Streptomycin, 1% L-Glutamine, 1% HEPES) in each well of 384-well plate (10 concentrations) in quadruplicate.

1 mL Aliquots of MT4 cells were pre-infected for 3 hours at 37°C with 25 µL of cell growth medium (mock-infected) or a fresh 1:250 dilution of an HIV-IIIb concentrated ABI stock (0.004 m.o.i.). Infected and uninfected cells were diluted in cell growth media and 35 µL (2000 cells) was added to each well of the assay plates.

Assay plates were then maintained in a humidified, 5% CO_2 incubator at 37°C. After 5 days of incubation, 25 µl of 2X concentrated CellTiter-Glo™ Reagent (catalog # G7573, Promega Biosciences, Inc., Madison, WI) was added to each well of the assay plate. Cell lysis was carried out by incubating at room temperature for 10 minutes and then chemiluminescence was read using an Envision plate reader (PerkinElmer). EC_{50} values were calculated as the compound concentration that caused a 50% decrease in luminescence signal, a measure of HIV-1 replication.

Example B

Test B: Cytotoxicity assay

Compound cytotoxicity and the corresponding CC_{50} values was determined using the same protocol as described in the antiviral assay (Test A) except that uninfected cells were used.

The compound of the present disclosure demonstrates antiviral activity (Test A) as depicted in the table below in comparison to Compound A and Compound B.

Compound	EC_{50} (nM)	CC_{50} (nM)
Compound 24	0.185	30068
Compound 38	0.399	55218
Compound A	1.715	21839

Compound B	2.991	14491

Example C

Test C. Pharmacokinetic Analysis Following Intravenous Administration to Sprague-Dawley Rats and Beagle Dogs and Cynomologous Monkeys

Test article and formulation

Compound 24 and 38 IV administration was formulated in 5% ethanol, 20% PG, 45% PEG 300, 30% pH 2 (0.01N HCl) water at 0.5 mg/mL. Compound A and Compound B intravenous infusion doses were formulated in a sterile solution of 5% ethanol, 45% PEG 400 and 50% water (pH 2.0) at 0.5 mg/mL. All IV formulations were in solution.

Animals Used

Each rat IV dosing group consisted of 3 male SD rats. At dosing, the animals generally weighed between 0.317 and 0.355 kg. The animals were fasted overnight prior to dose administration and up to 4 hr after dosing. Each dog IV dosing group consisted of 3 male, naïve beagle dogs. At dosing, the animals weighed ~ 10-12 kg. The animals were fasted overnight prior to dose administration and up to 2 hr after dosing.

Each cynomolgus (cyno) monkey IV dosing group consisted of 3 male, naïve cyno monkeys At dosing, the animals weighed ~3.2-4 kg. The animals were fasted overnight prior to dose administration and up to 2 hr after dosing.

Dosing

For the IV infusion group, the test compound was administered by intravenous infusion over 30 minutes. The rate of infusion was adjusted according to the body weight of each animal to deliver a dose of 1 mg/kg at 2 mL/kg.

Sample collection

Serial venous blood samples (approximately 0.4 mL each for rat and 1.0 mL for dog) were taken at specified time points after dosing from each animal. The blood samples were collected into Vacutainer™ tubes (Becton-Disckinson Corp, New Jersey, USA) containing EDTA as the anti-coagulant and were immediately placed on wet ice pending centrifugation for plasma. Centrifugation began within 1 hour of collection. All samples were placed into 96-well tubes and maintained on dry ice prior to storage at approximately -70°C.

Determination of the concentrations of the Compound of Formula (I) in plasma

An LC/MS/MS method was used to measure the concentration of test compounds in plasma.

Calculations

Non-compartmental pharmacokinetic analysis was performed on the plasma concentration-time data. A summary of pharmacokinetic parameters are shown in the tables below.

Compound	Rat CL (L/h/kg)	Rat V_{ss} (L/kg)	Rat $t_{1/2}$ (h)	Dog CL (L/h/kg)	Dog V_{ss} (L/kg)	Dog $t_{1/2}$ (h)	Cyno CL (L/h/kg)	Cyno Vss (L/kg)	Cyno $t_{1/2}$ (h)
Compound 24	0.05	1.8	28	0.07	1.6	22	0.24	2.7	12
Compound 38	0.08	1.8	19	0.33	1.77	7	0.21	2.1	9.5
Compound A	0.50	1.0	2	0.25	0.8	4	0.45	1.18	2.3
Compound B	0.43	1.4	3	0.28	1.3	6	0.42	1.59	3.4
CL: observed clearance; Vss: volume of distribution at steady state; $t_{1/2}$: terminal half-life									

Compound	Rat C_{max}	Rat AUC_{inf} (μM·h)	Dog C_{max}	Dog AUC_{inf} (μM·h)	Cyno C_{max}	Cyno AUC_{inf} (μM·h)
Compound 24	1.8	19	2.2	14.8	1.3	4.5
Compound 38	2.4	13	1.6	3.3	1.3	4.9
Compound A	1.4	2.7	2.1	5	1.8	2.6
Compound B	1.1	2.7	1.4	4.3	1.4	2.9
AUC_{inf}: Area Under the Curve from t = 0 to infinity; C_{max}: Maximum plasma concentration						

Example D

Test D. Metabolic Stability in Cultured Human Liver Hepatocytes

Radiolabelled test compounds, wherein tritium was introduced into the structure in place of one or more hydrogens, were prepared according to known methods in the art.

The radiolabelled compounds were incubated in pooled cryopreserved hepatocytes at a substrate concentration of 0.25 μM and radioactivity concentration of 10 uCi/mL. The final hepatocyte concentration was 1 million cells/mL. The hepatocyte/compound reaction mixture was dissolved in InVitroGRO™ KHB buffer (catalog # Z99074, BioreclamationIVT, Inc., Baltimore, MD) at pH 7.4. The incubations were performed in duplicate. A cell free control and a positive control were included in the incubations. The incubations were carried out with gentle shaking in a 37°C incubator under a humid atmosphere of 95% air/5% CO_2 (v/v). Aliquots (100 mL) were removed after 0, 1, 3, and 6 hours and added to 200 mL quenching solution that comprised 0.1% (v/v) TFA in 5% water/95% acetonitrile (v/v). The samples were placed on a shaker for 10 min, followed by centrifugation at 3000 g for 30 min. The samples of the supernatant were analyzed on a Dionex HPLC/PerkinElmer Flow Scintillation Analyzer as described below.

Liquid Chromatography–Radiochromatography

Quantification was done by comparison of radiolabeled metabolites and parent peaks measured on a Radiomatic 625TR Flow Scintillation Analyzer coupled to a Dionex/Chromeleon chromatography system. The column was a Phenomenex Synergi fusion RP (150 x 4.6 mm, 4 mm) maintained at 32 degrees Celsius. Mobile Phase A consisted of 0.1% (v/v) TFA in 99% water/1% acetonitrile (v/v). Mobile Phase B consisted of 0.1% (v/v) TFA in 5% water/95% acetonitrile (v/v). The flow rate was 1 mL/min using a sample injection volume of 100 mL. Gradient was as following: Mobile phase B was linearly increased from to 75% over 47 min, maintained at 75% for 3 min, changed back to 2%, maintained at 2% for 10 min.

Metabolic stability was determined by measuring the change in relative abundance of metabolites and parent over time and calculating from it the rate of disappearance of the parent compound. The stability data was utilized to calculate predicted human hepatic clearance values according to methods known in the art. The predicted human hepatic clearance values are shown in the table below.

	Predicted Human Hepatic Clearance (L/hr/kg)
Compound 24	0.01

Compound 38	0.02
Compound A	0.09
Compound B	0.04

The following can be deduced from the above comparative data:

Compound 24 is more potent in an HIV antiviral assay relative to compounds A and B (about 9 and about 16 times more potent, respectively). Compound 24 has a longer *in vivo* terminal half-life in rat relative to compounds A and B (about 14 and about 9 times longer, respectively). Compound 24 has a lower *in vivo* clearance in rat relative to compounds A and B (about 10 and about 8.6 times lower, respectively). Compound 24 has a longer *in vivo* terminal half-life in dog relative to compounds A and B (about 5 and about 4 times longer, respectively). Compound 24 has a lower *in vivo* clearance in dog relative to compounds A and B (about 3 and about 4 times lower, respectively). Compound 24 is more stable in human hepatocytes with a lower predicted hepatic clearance relative to compounds A and B (about 9 and about 4 times more stable, respectively).

The above data demonstrate that compound 24, has improved antiviral potency and an improved pharmacokinetic profile (which is demonstrated by longer half-life in rat and dog and lower predicted human clearance) when compared to compounds A and B.

Additionally, compound 38 is more potent in an HIV antiviral assay relative to compounds A and B (about 4 and about 8 times more potent, respectively). Compound 38 has a longer *in vivo* terminal half-life in rat relative to compounds A and B (about 9.5 and about 6.3 times longer, respectively). Compound 38 has a lower *in vivo* clearance in rat relative to compounds A and B (about 6.3 and about 5.4 times lower, respectively). Compound 38 has a similar *in vivo* clearance and terminal half-life in dog compared to compounds A and B. Compound 38 is more stable in human hepatocytes with a lower predicted hepatic clearance relative to compounds A and B (about 4.5 and about 2 times more stable, respectively).

The above data demonstrate that compound 38, has improved antiviral potency and an improved pharmacokinetic profile (which is demonstrated by longer half-life in rat and dog and lower predicted human clearance) when compared to compounds A and B.

The specific pharmacological responses observed may vary according to and depending on the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with practice of the present disclosure.

The Examples disclosed herein describe the synthesis of compounds disclosed herein as well as intermediates used to prepare the compounds. It is to be understood that individual steps described herein may be combined. It is also to be understood that separate batches of a compound may be combined and then carried forth in the next synthetic step.

Formulation Example

Compound 38 (about 30 mg/kg) was formulated as an aqueous suspension in 2% poloxamer 338 in saline (about 150 mg/mL). This formulation was then administered as a single subcutaneous (SC) injection to rats and the pharmacokinetic (PK) profile was determined. As can be seen in FIG. 3, Compound 38 maintains plasma concentrations well above paEC95 for > 10 weeks from a single SC injection. This data demonstrates that Compound 38 displays extended release pharmacokinetics.

A suspension of a compound of Formula Ib in 2% poloxamer 188 in saline (200mg/mL) was prepared. The suspension was administered to dogs subcutaneously at a dose of 6mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 4 shows a plot of the plasma concentration of the compound of Formula Ib as a function of time. As the data shows in FIG. 4, the compound of Formula Ib has measurable plasma concentrations at day 70 demonstrating extended release pharmacokinetics.

A suspension of a compound of Formula Ib in 2% poloxamer 188 in saline (100mg/mL) was prepared. The suspension was administered to dogs subcutaneously at a dose of 6mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 5 shows a plot of the plasma concentration of the compound of Formula Ib as a function of time. As the data shows in FIG. 5, the compound of Formula Ib has measurable plasma concentrations at day 70 demonstrating extended release pharmacokinetics.

A suspension of the sodium salt of a compound of Formula Ib in 2% poloxamer 188 in saline (200mg/mL) was prepared. The suspension was administered to dogs subcutaneously at a dose of 6mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 6 shows a plot of the plasma concentration of the compound of Formula Ib as a function of time. As FIG. 6 shows, the compound of Formula Ib has measurable plasma concentrations at day 70 demonstrating extended release pharmacokinetics.

A solution of a compound of Formula Ib in NMP (100mg/mL) was prepared. The solution was administered to dogs subcutaneously at a dose of 6mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 7 shows a plot of the plasma concentration of the compound of Formula Ib as a function of time. As the data shows in FIG. 7, the compound of Formula Ib has measurable plasma concentrations at day 70 demonstrating extended release pharmacokinetics.

A solution of a compound of Formula Ib in NMP (200mg/ml) was prepared. The solution was administered to dogs subcutaneously at a dose of 6mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 8 shows a plot of the plasma concentration of the compound of Formula Ib as a function of time. As the data shows in FIG. 8, the compound of Formula Ib has measurable plasma concentrations at day 70 demonstrating extended release pharmacokinetics.

A solution of the sodium salt of a compound of Formula Ib in NMP (200mg/ml) was prepared. The solution was administered to dogs subcutaneously at a dose of 6mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 9 shows a plot of the plasma concentration of the compound of Formula Ib as a function of time. As the data shows in FIG. 9, the compound of Formula Ib has measurable plasma concentrations at day 70 demonstrating extended release pharmacokinetics.

A solution formulation of a compound of Formula Ib in 10% ethanol, 12% water, and 78% PEG 200 (200mg/ml) was prepared. The solution was administered to dogs subcutaneously at a dose of 6mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 10 shows a plot of the plasma concentration of the compound of Formula Ib as a function of time. As the

data shows in FIG. 10, the compound of Formula Ib has measurable plasma concentrations at day 28 demonstrating extended release pharmacokinetics.

A solution formulation containing 200mg/mL of Formula Ib with 1.2 molar equivalent NaOH to form *in situ* sodium salt in 10% ethanol, 12% water, and 77% PEG are provided. Subjects were orally dosed with this formulation at 6mg/kg. A solution of the the compound of Formula Ib in 10% ethanol, 12% water, and 7% PEG 200 (200mg/ml) with 1.2 molar equivalent NaOH was prepared to form *in situ* sodium salt. The solution was administered to dogs subcutaneously at a dose of 6mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 11 shows a plot of the plasma concentration of the compound of Formula Ib as a function of time. As the data shows in FIG. 11, the compound of Formula Ib has measurable plasma concentrations at day 28 demonstrating extended release pharmacokinetics.

A solution formulation of the compound of Formula Ib in 10% ethanol, 13% water, and 77% glycofurol (200 mg/mL) with 1.2 molar equivalent NaOH was prepared to form in situ sodium salt. The solution was administered to dogs subcutaneously at a dose of 6 mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 12 shows a plot of the plasma concentration of the compound of Formula Ib as a function of time. As the data shows in FIG. 12, the compound of Formula Ib has measurable plasma concentrations at day 28 demonstrating extended release pharmacokinetics.

Oral Formulation Example

[00264] An oral formulation containing a compound of Formula Ib in 10% ethanol, 20% Vitamin E TPGS, and 70% MIGLYOL 812 was prepared in hard gelatin capsules was preapared. Dogs were orally given a fixed 7.5mg dose of the compound of Formula Ib and the pharmacokinetic (PK) profile was determined. FIG. 13 shows the change in plasma concentration over time for the compound of Formula Ib.

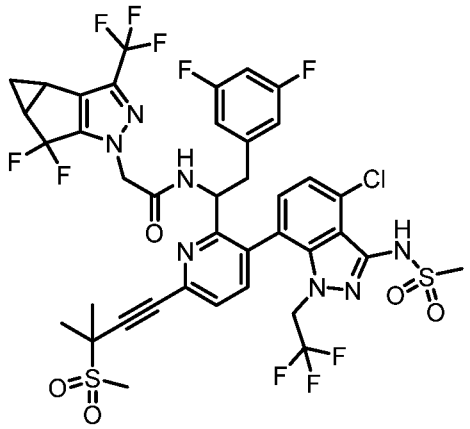
All references, including publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The present disclosure provides reference to various embodiments and techniques. However, it should be

understood that many variations and modifications may be made while remaining within the spirit and scope of the present disclosure.

CLAIMS

What is claimed is:

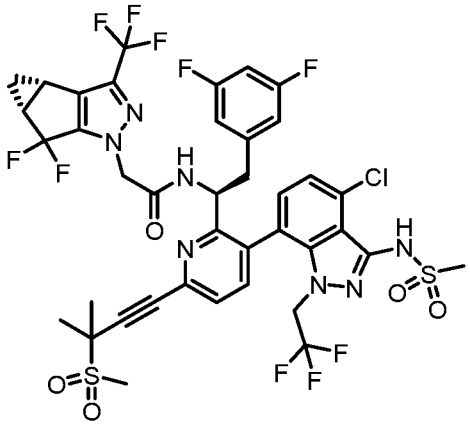
1. A compound of Formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, which is a compound of Formula (Ib)



(Ib)

or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

4. The pharmaceutical composition of claim 3, further comprising one, two, three, or four additional therapeutic agents.

5. The pharmaceutical composition of claim 4, wherein the additional therapeutic agents are selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof.

6. The pharmaceutical composition of claim 4, wherein the additional therapeutic agents are selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120

inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, or any combinations thereof.

7. The pharmaceutical composition of claims 4 to 6, wherein the additional therapeutic agents are selected from the group consisting of abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate.

8. The pharmaceutical composition of claims 4 to 7, wherein the additional therapeutic agents are selected from the group consisting of tenofovir alafenamide, tenofovir alafenamide fumarate and tenofovir alafenamide hemifumarate.

9. A method of treating or preventing a human immunodeficiency virus (HIV) infection comprising administering a therapeutically effective amount of a compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

10. The method of claim 9, wherein the method comprises administering the compound, or a pharmaceutically acceptable salt thereof, in combination with one, two, three, or four additional therapeutic agents.

11. The method of claim 10, wherein the additional therapeutic agents are selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev

protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof.

12. The method of claim 10 or 11, wherein the additional therapeutic agents are selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, or any combinations thereof.

13. The method of claims 10 to 12, wherein the additional therapeutic agents are selected from the group consisting of abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate.

14. The method of claims 10 to 13, wherein the additional therapeutic agents are selected from the group consisting of tenofovir alafenamide, tenofovir alafenamide fumarate and tenofovir alafenamide hemifumarate.

15. A compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, for use in therapy.

16. A compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, for use in a method of treating or preventing a human immunodeficiency virus (HIV) infection comprising administering a therapeutically effective amount of said compound to a subject in need thereof.

17. The compound for use according to claim 16, wherein said method comprises administering one, two, three or four additional therapeutic agents.

18. The compound for use as claimed in claim 17, wherein the additional therapeutic agents are administered simultaneously with the compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof.

19. The compound for use as claimed in claim 18, wherein the compound of formula (Ia) or (Ib) is combined with the additional therapeutic agents in a unitary dosage form for simultaneous administration.

20. The compound for use as claimed in claim 17, wherein the compound of formula (Ia) or (Ib) is administered and the additional therapeutic agents are administered sequentially.

21. The compound for use according to claim 17, wherein the additional therapeutic agents are selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent

kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof.

22. The compound for use according to claim 17, wherein the additional therapeutic agents are selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, or any combinations thereof.

23. The compound for use according to claim 17, wherein said compound is combined with abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, or tenofovir alafenamide hemifumarate.

24. The compound for use according to claim 17, wherein said compound is combined with tenofovir alafenamide, tenofovir alafenamide fumarate or tenofovir alafenamide hemifumarate.

25. The compound for use according to claim 17, wherein said compound is combined with tenofovir disoproxil, tenofovir disoproxil hemifumarate or tenofovir disoproxil fumarate.

26. The compound for use according to claim 17, wherein said compound is combined with a first additional therapeutic agent selected from the group consisting of abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent selected from the group consisting of emtricitabine and lamivudine.

27. The compound for use according to claim 17, wherein said compound is combined with a first additional therapeutic agent selected from the group consisting of tenofovir alafenamide fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a

second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine.

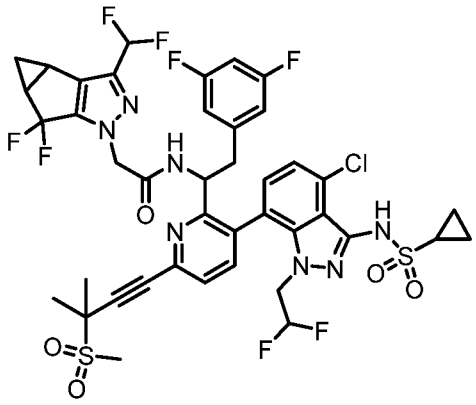
28. The compound for use according to claim 17, wherein said compound is combined with a first additional therapeutic agent selected from the group consisting of tenofovir disoproxil fumarate, tenofovir disoproxil, and tenofovir disoproxil hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine.

29. The pharmaceutical composition of claims 4 to 6, wherein the additional therapeutic agent is 4′-ethynyl-2-fluoro-2′-deoxyadenosine, bictegravir, or a pharmaceutically acceptable salt thereof.

30. The method of claims 10 to 12, wherein the method comprises administering the compound, or a pharmaceutically acceptable salt thereof, in combination with 4′-ethynyl-2-fluoro-2′-deoxyadenosine, bictegravir, or a pharmaceutically acceptable salt thereof.

31. The compound for use according to claims 17 to 22, wherein said compound is combined with 4′-ethynyl-2-fluoro-2′-deoxyadenosine, bictegravir, or a pharmaceutically acceptable salt thereof.

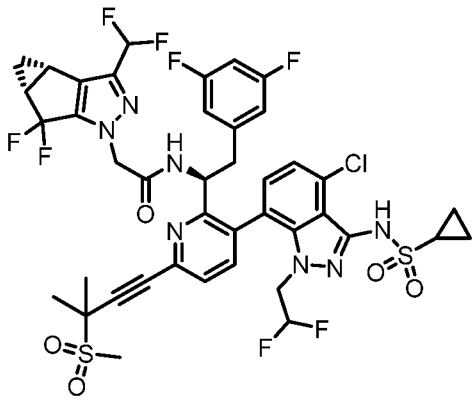
32. A compound of Formula (IIa):



(IIa)

or a pharmaceutically acceptable salt thereof.

33. The compound of claim 32, which is a compound of Formula (IIb)



(IIb)

or a pharmaceutically acceptable salt thereof.

34. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 32 or 33, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

35. The pharmaceutical composition of claim 34, further comprising one, two, three, or four additional therapeutic agents.

36. The pharmaceutical composition of claim 35, wherein the additional therapeutic agents are selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing

inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof.

37. The pharmaceutical composition of claim 35, wherein the additional therapeutic agents are selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, or any combinations thereof.

38. The pharmaceutical composition of claims 35 to 37, wherein the additional therapeutic agents are selected from the group consisting of 4′-ethynyl-2-fluoro-2′-deoxyadenosine, bictegravir or a pharmaceutically acceptable salt thereof, abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate.

39. The pharmaceutical composition of claims 35 to 38, wherein the additional therapeutic agents are selected from the group consisting of 4′-ethynyl-2-fluoro-2′-deoxyadenosine, bictegravir or a pharmaceutically acceptable salt thereof, tenofovir alafenamide, tenofovir alafenamide fumarate and tenofovir alafenamide hemifumarate.

40. A method of treating or preventing a human immunodeficiency virus (HIV) infection comprising administering a therapeutically effective amount of a compound of claim 32 or 33, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

41. The method of claim 40, wherein the method comprises administering the compound, or a pharmaceutically acceptable salt thereof, in combination with one, two, three, or four additional therapeutic agents.

42. The method of claim 41, wherein the additional therapeutic agents are selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof.

43. The method of claim 41 or 42, wherein the additional therapeutic agents are selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120

inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, or any combinations thereof.

44. The method of claims 41 to 43, wherein the additional therapeutic agents are selected from the group consisting of 4′-ethynyl-2-fluoro-2′-deoxyadenosine, bictegravir or a pharmaceutically acceptable salt thereof, abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate.

45. The method of claims 41 to 44, wherein the additional therapeutic agents are selected from the group consisting of 4′-ethynyl-2-fluoro-2′-deoxyadenosine, bictegravir or a pharmaceutically acceptable salt thereof, tenofovir alafenamide, tenofovir alafenamide fumarate and tenofovir alafenamide hemifumarate.

46. A compound of claim 32 or 33, or a pharmaceutically acceptable salt thereof, for use in therapy.

47. A compound of claim 32 or 33, or a pharmaceutically acceptable salt thereof, for use in a method of treating or preventing a human immunodeficiency virus (HIV) infection comprising administering a therapeutically effective amount of said compound to a subject in need thereof.

48. The compound for use according to claim 47, wherein said method comprises administering one, two, three or four additional therapeutic agents.

49. The compound for use as claimed in claim 48, wherein the additional therapeutic agents are administered simultaneously with the compound of formula (IIa) or (IIb), or a pharmaceutically acceptable salt thereof.

50. The compound for use as claimed in claim 49, wherein the compound of formula (IIa) or (IIb) is combined with the additional therapeutic agents in a unitary dosage form for simultaneous administration.

51. The compound for use as claimed in claim 48, wherein the compound of formula (IIa) or (IIb) is administered and the additional therapeutic agents are administered sequentially.

52. The compound for use according to claim 48, wherein the additional therapeutic agents are selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof.

53. The compound for use according to claim 48, wherein the additional therapeutic agents are selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120

inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, or any combinations thereof.

54. The compound for use according to claim 48, wherein said compound is combined with 4′-ethynyl-2-fluoro-2′-deoxyadenosine, bictegravir or a pharmaceutically acceptable salt thereof, abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, or tenofovir alafenamide hemifumarate.

55. The compound for use according to claim 48, wherein said compound is combined with 4′-ethynyl-2-fluoro-2′-deoxyadenosine, bictegravir or a pharmaceutically acceptable salt thereof, tenofovir alafenamide, tenofovir alafenamide fumarate or tenofovir alafenamide hemifumarate.

56. The compound for use according to claim 48, wherein said compound is combined with 4′-ethynyl-2-fluoro-2′-deoxyadenosine, bictegravir or a pharmaceutically acceptable salt thereof, tenofovir disoproxil, tenofovir disoproxil hemifumarate or tenofovir disoproxil fumarate.

57. The compound for use according to claim 48, wherein said compound is combined with a first additional therapeutic agent selected from the group consisting of 4′-ethynyl-2-fluoro-2′-deoxyadenosine, abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent selected from the group consisting of emtricitabine and lamivudine.

58. The compound for use according to claim 48, wherein said compound is combined with a first additional therapeutic agent selected from the group consisting of 4′-ethynyl-2-fluoro-2′-deoxyadenosine, tenofovir alafenamide fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine.

59. The compound for use according to claim 48, wherein said compound is combined with a first additional therapeutic agent selected from the group consisting of 4′-ethynyl-2-fluoro-2′-deoxyadenosine, tenofovir disoproxil fumarate, tenofovir disoproxil, and tenofovir

disoproxil hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine.

60. The pharmaceutical composition of any one of claims 3-8, 29, or 34-39, wherein the composition is a parenteral formulation.

61. The parenteral formulation according to claim 60, wherein the formulation is administered subcutaneously to a subject in need thereof.

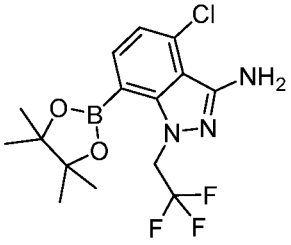
62. The parenteral formulation according to claim 60, wherein the formulation is administered intramuscularly to a subject in need thereof.

63. The parenteral formulation of any one of claims 60-62, wherein the formulation comprises saline.

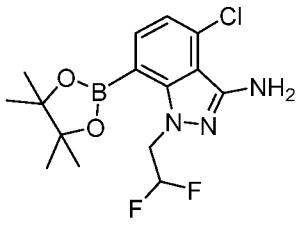
64. The parenteral formulation of any one of claims 60-63, wherein the formulation comprises a poloxamer.

65. The parenteral formulation of claim 64, wherein the poloxamer is poloxamer 338.

66. A compound selected from the group consisting of:

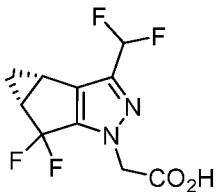


and

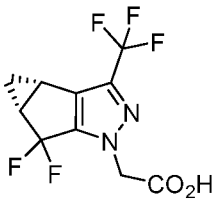


.

67. A compound selected from the group consisting of:

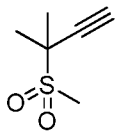


and



.

68. A compound of the formula:



69. The parenteral formulation of claim 64, wherein the poloxamer is poloxamer 188.

70. The parenteral formulation of claim 69, wherein the concentration of poloxamer 188 in saline is about 1 % to about 10%.

71. The parenteral formulation of claim 69 or 70, wherein the concentration of poloxamer 188 in saline is about 1 % to about 3%.

72. The parenteral formulation of claim 69, 70, or 71, wherein the concentration of poloxamer 188 in saline is about 2%.

73. The parenteral formulation of any one of claims 60-62, wherein the formulation comprises N-methyl-2-pyrrolidone.

74. The parenteral formulation of any one of claims 60-62, wherein the formulation consists essentially of N-methyl-2-pyrrolidone.

75. The parenteral formulation of any one of claims 60-62, wherein the formulation comprises dimethyl sulfoxide.

76. The parenteral formulation of any one of claims 60-62, wherein the formulation consists essentially of dimethyl sulfoxide.

77. The parenteral formulation of any one of claims 60-62, wherein the formulation comprises water.

78. The parenteral formulation of any one of claims 60-62 or 77, wherein the formulation further comprises an alcohol.

79. The parenteral formulation of claim 78, wherein the alcohol is ethanol.

80. The parenteral formulation of any one of claims 60-62 or 77 to 79, wherein the formulation further comprises polyethylene glycol.

81. The parenteral formulation of claim 80, wherein the polyethylene glycol has an average molecular weight of about 200 g/mol.

82. The parenteral formulation of any one of claims 77 to 81, further comprising an inorganic base.

83. The parenteral formulation of claim 82, wherein the inorganic base is sodium hydroxide.

84. The parenteral formulation of claims 60-62, and 77-83, wherein the formulation comprises about 5% to about 20% ethanol, about 5% to about 20% water, and about 60% to about 90% polyethylene glycol 200.

85. The parenteral formulation of claims 60-62, and 77-84, wherein the formulation comprises about 10% to about 15% ethanol, about 10% to about 15% water, and about 70% to about 80% polyethylene glycol 200.

86. The parenteral formulation of claims 60-62, and 77-85, wherein the formulation comprises about 10% ethanol, about 12% water, and about 78% polyethylene glycol 200.

87. The pharmaceutical composition of any one of claims 3-8, 29, or 34-39, wherein the composition is an oral formulation.

88. The formulation of any one of claims 60-65 and 69-87, wherein the compound is present as a sodium salt.

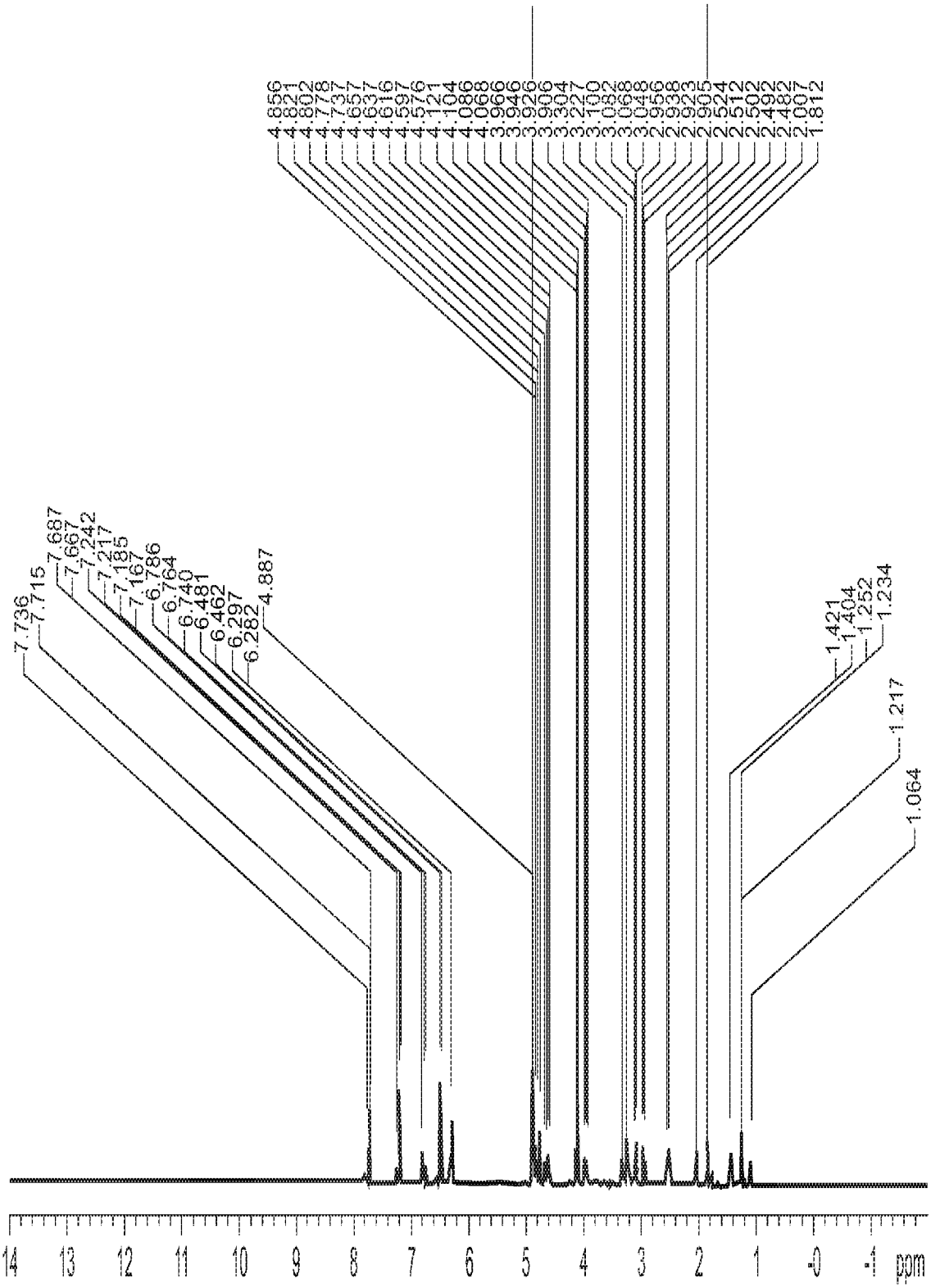


FIG. 1

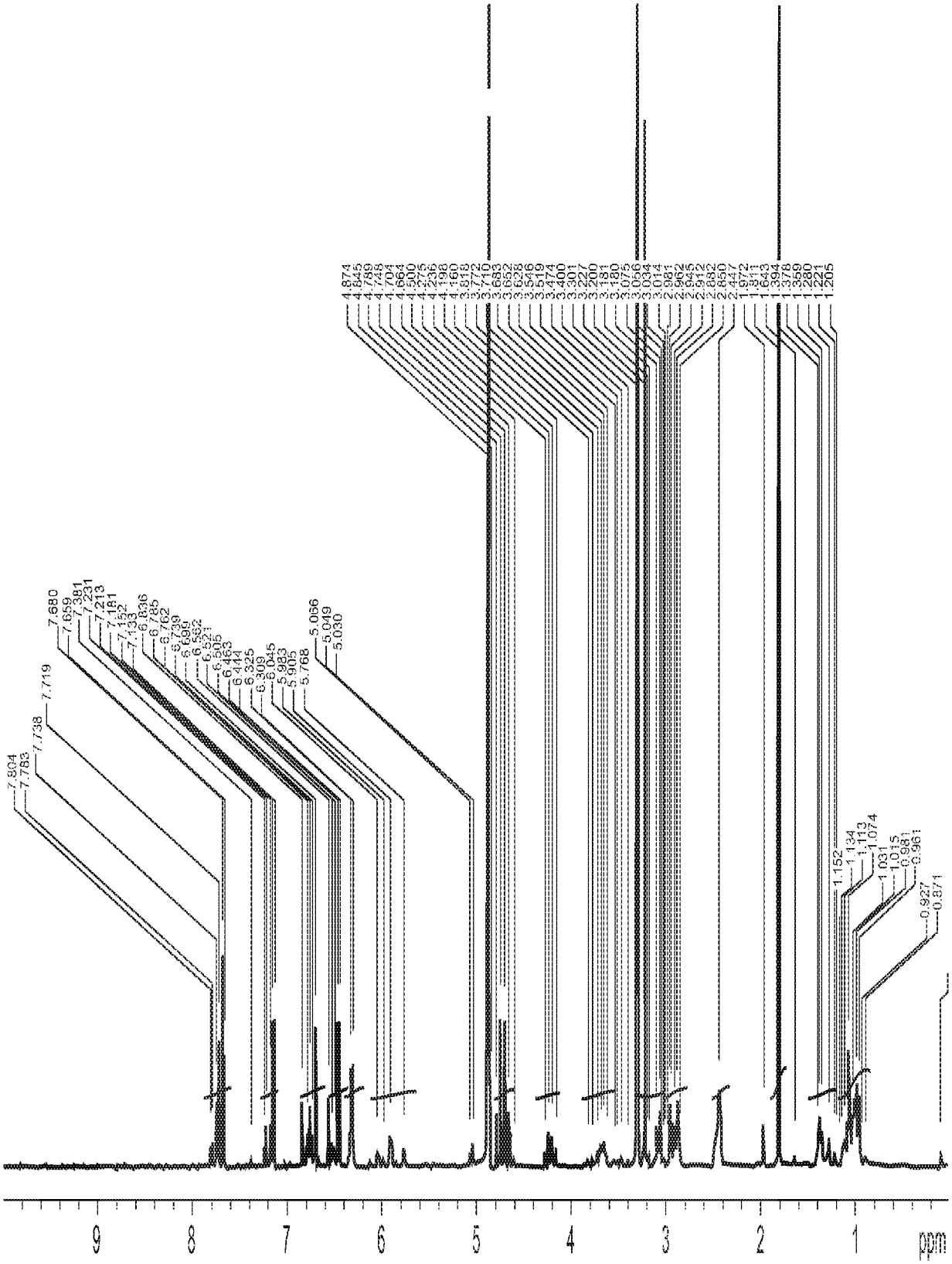


FIG. 2

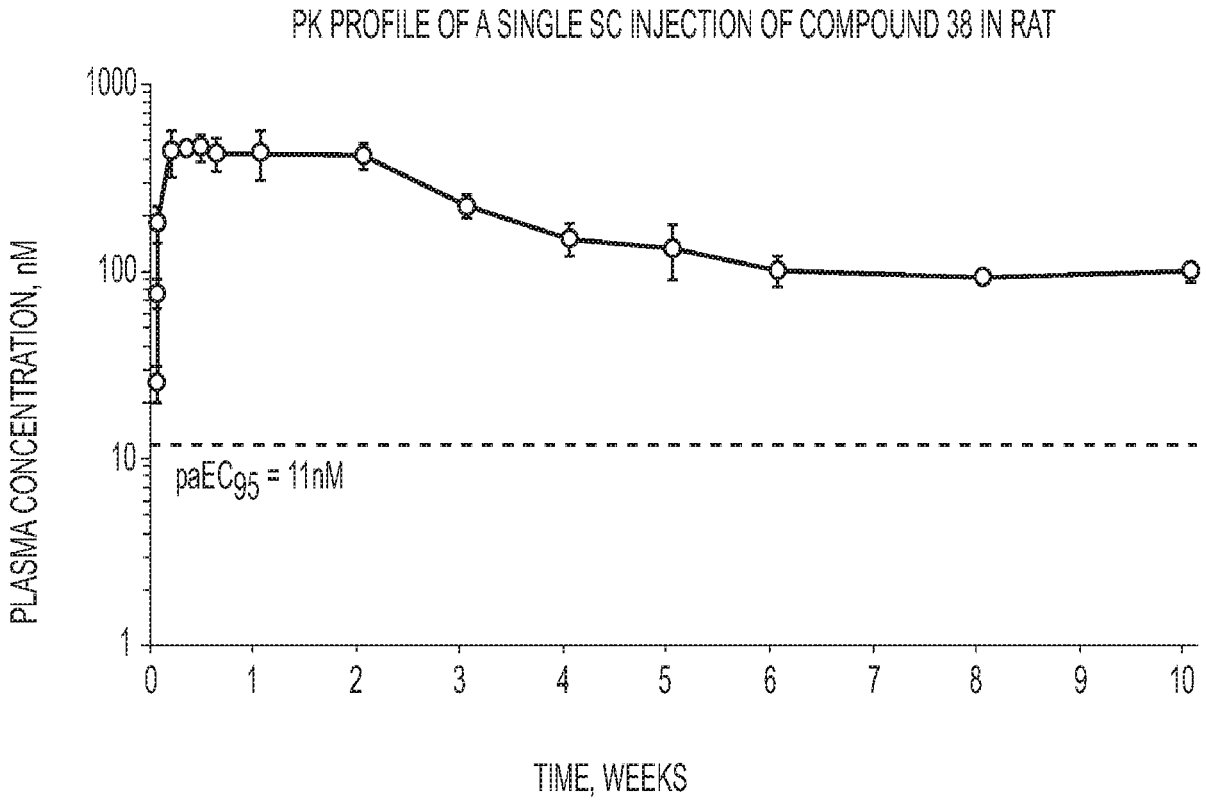


FIG. 3

Concentration over time of 200 mg/mL of Formula Ib free acid form suspended in 2% Poloxamer 188 in saline formulation after subcutaneous dosing in dogs at 6mg/kg

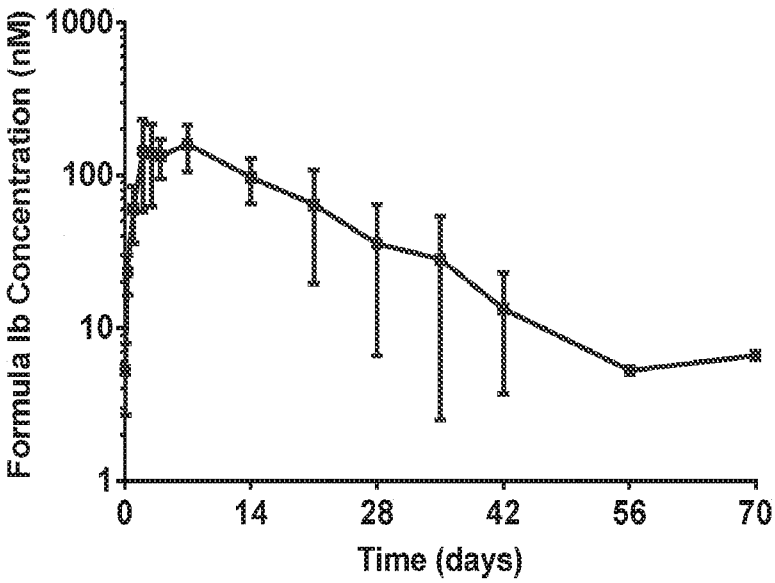


FIG. 4

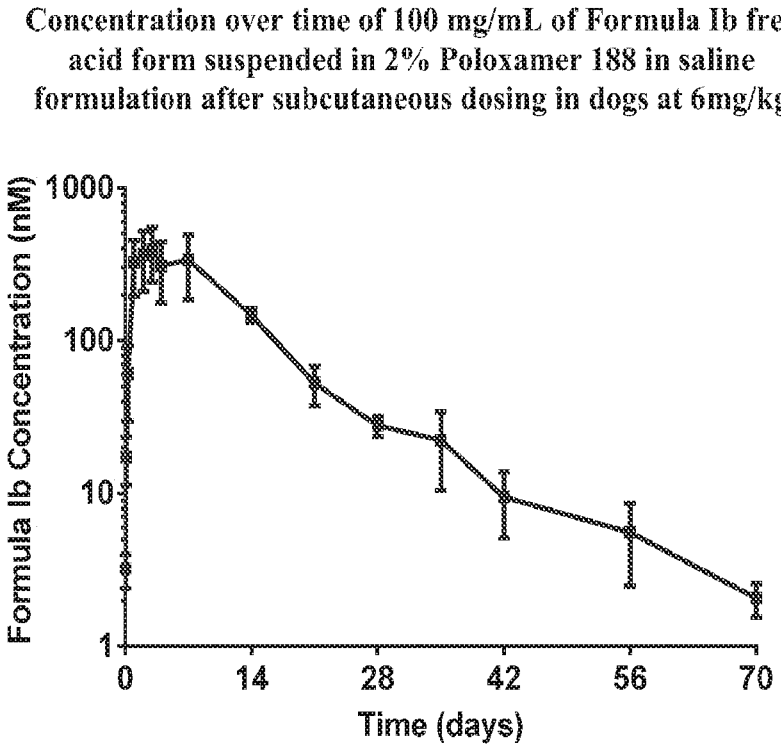


FIG. 5

Concentration over time of 200 mg/mL of Formula Ib, sodium salt form suspended in 2% Poloxamer 188 in saline formulation, after subcutaneous dosing in dogs at 6mg/kg

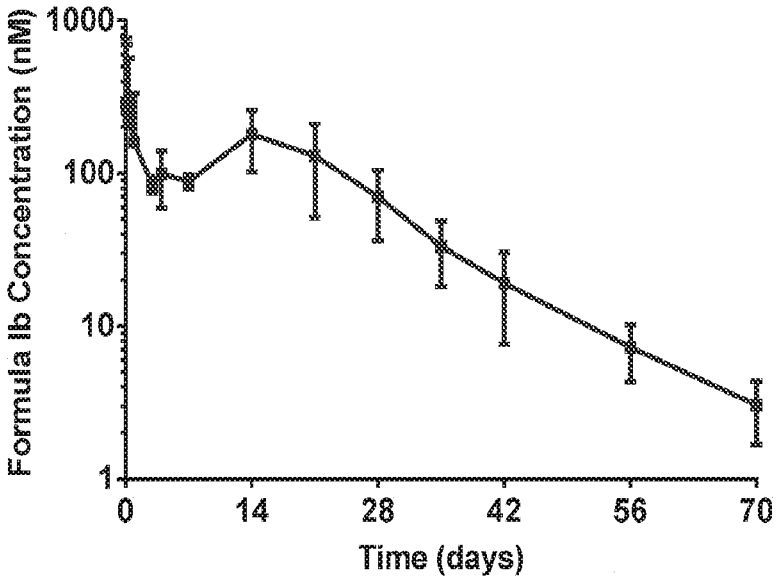


FIG. 6

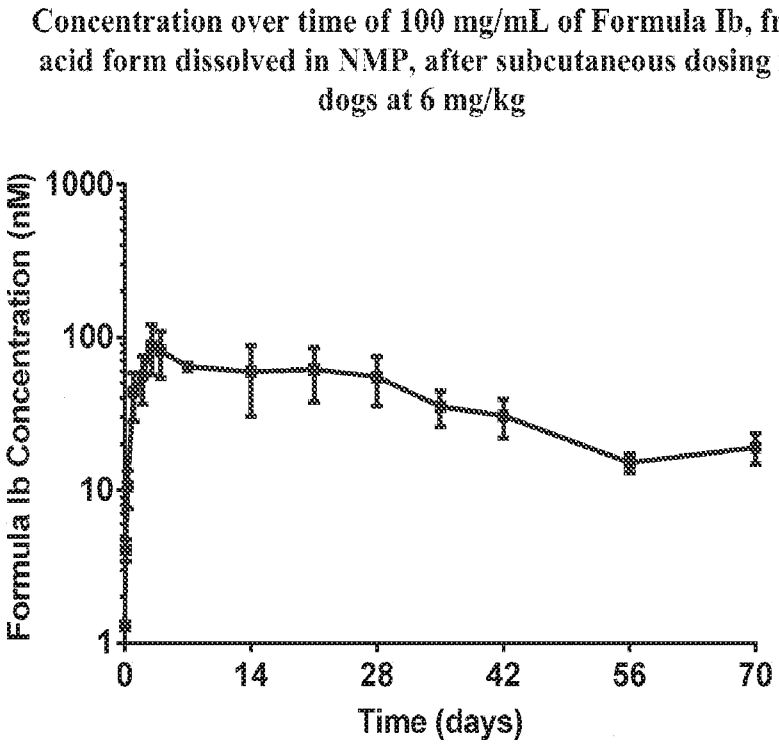


FIG. 7

Concentration over time of 200 mg/mL of Formula Ib, free acid form dissolved in NMP, after subcutaneous dosing in dogs at 6 mg/kg

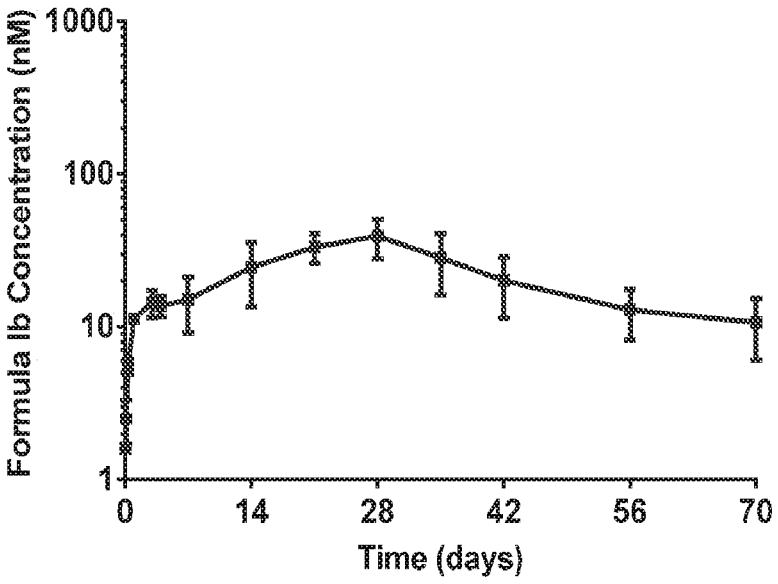


FIG. 8

Concentration over time of 200 mg/mL of Formula Ib, sodium salt form dissolved in NMP, after subcutaneous dosing in dogs at 6mg/kg

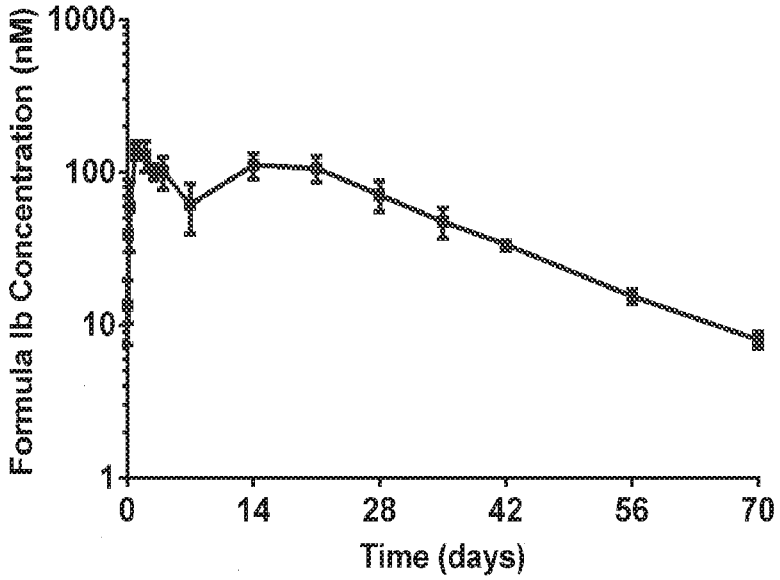


FIG. 9

Concentration over time of 200 mg/mL of Formula Ib free acid form dissolved in 10% ethanol, 12% water, and 78% PEG 200, after subcutaneous dosingin dogs at 6 mg/kg

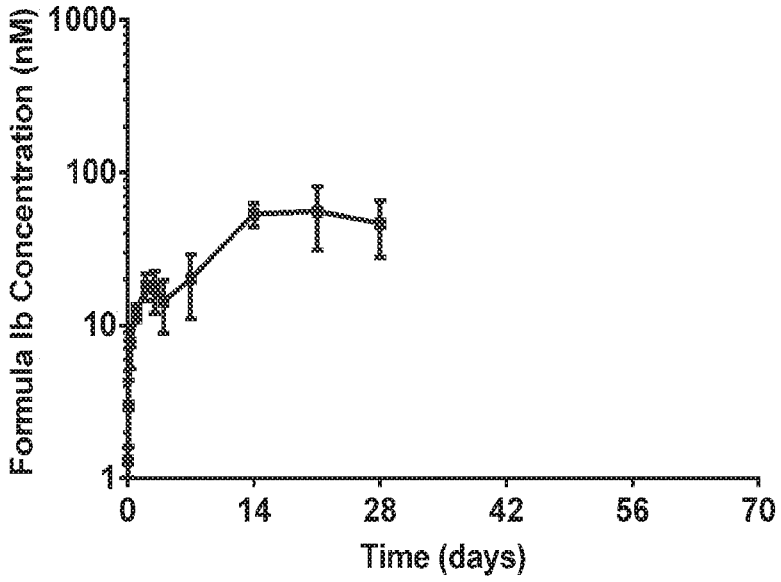


FIG. 10

Concentration over time of 200mg/mL of Formula Ib dissolved in 10% ethanol, 12% water, and 77% PEG 200, with 1.2 mol-eq sodium hydroxide, after subcutaneous dosing in dogs at 6 mg/kg

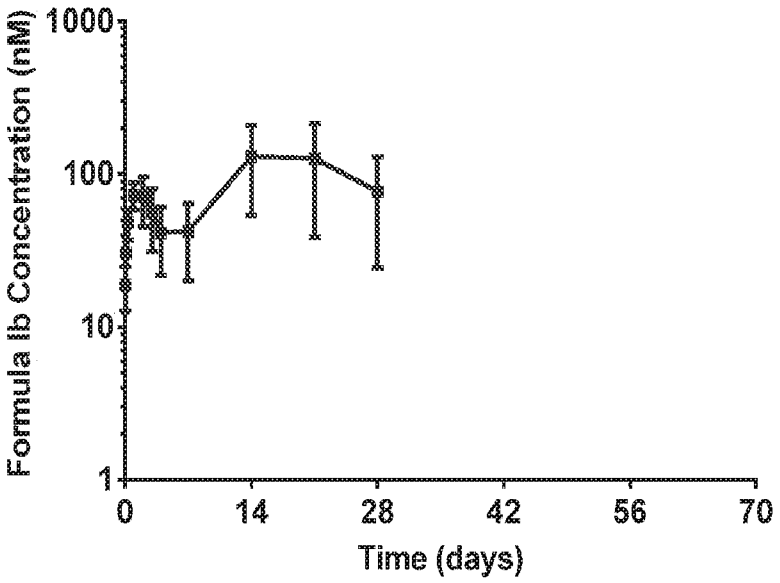


FIG. 11

Concentration over time of 200mg/mL of Formula Ib dissolved in 10% ethanol, 13% water, and 77% glycofurol, with 1.2 mol-eq NaOH, after subcutaneous dosing in dogs at 6mg/kg

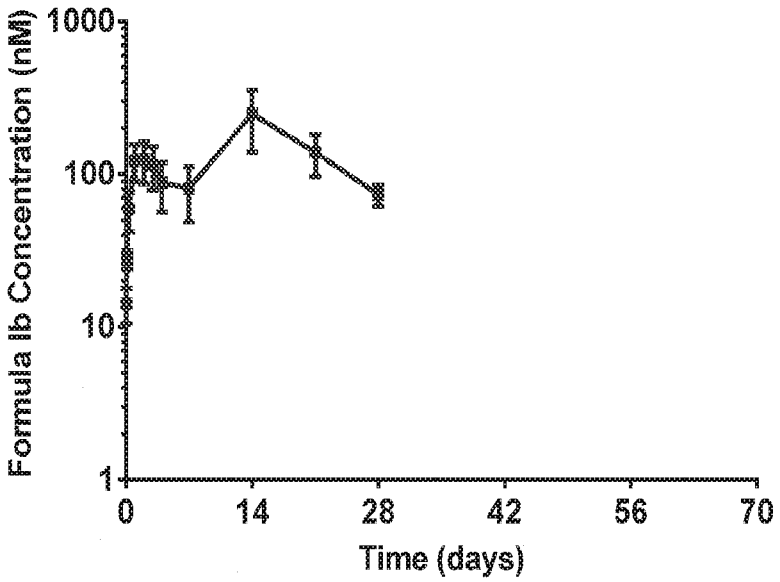


FIG. 12

Concentration over time of fixed 7.5mg oral dose of Formula Ib free acidform dissolved in 10% ethanol, 20% vitamin E TPGS, 70% Miglyol 812, after oral dosing in dogs

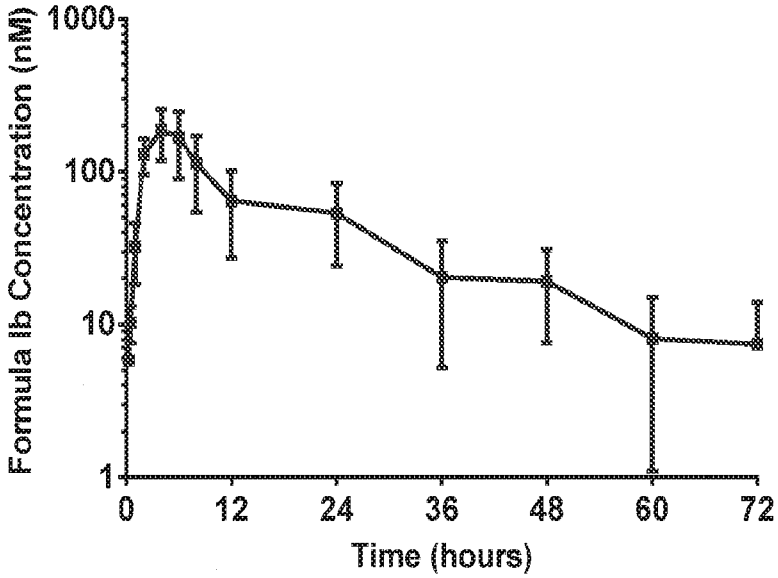


FIG. 13

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/047416

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 A61P31/18 A61K31/4439
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014/303164 A1 (BRIZGYS GEDIMINAS [US] ET AL) 9 October 2014 (2014-10-09) cited in the application	67
A	examples 19,33 claims 28, 46-50	1-65, 68-88
X,P	WO 2017/007689 A1 (GILEAD SCIENCES INC [US]) 12 January 2017 (2017-01-12) example 980	68

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 October 2017	27/10/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fanni, Stefano

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/047416

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 2017152240 A1	01-06-2017
		UY 36771 A	31-01-2017
		WO 2017007689 A1	12-01-2017

Article

Clinical targeting of HIV capsid protein with a long-acting small molecule

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Check for updates

A list of authors and their affiliations appears at the end of the paper.

Oral antiretroviral agents provide life-saving treatments for millions of people living with HIV, and can prevent new infections via pre-exposure prophylaxis[1–5]. However, some people living with HIV who are heavily treatment-experienced have limited or no treatment options, owing to multidrug resistance[6]. In addition, suboptimal adherence to oral daily regimens can negatively affect the outcome of treatment—which contributes to virologic failure, resistance generation and viral transmission—as well as of pre-exposure prophylaxis, leading to new infections[1,2,4,7–9]. Long-acting agents from new antiretroviral classes can provide much-needed treatment options for people living with HIV who are heavily treatment-experienced, and additionally can improve adherence[10]. Here we describe GS-6207, a small molecule that disrupts the functions of HIV capsid protein and is amenable to long-acting therapy owing to its high potency, low in vivo systemic clearance and slow release kinetics from the subcutaneous injection site. Drawing on X-ray crystallographic information, we designed GS-6207 to bind tightly at a conserved interface between capsid protein monomers, where it interferes with capsid-protein-mediated interactions between proteins that are essential for multiple phases of the viral replication cycle. GS-6207 exhibits antiviral activity at picomolar concentrations against all subtypes of HIV-1 that we tested, and shows high synergy and no cross-resistance with approved antiretroviral drugs. In phase-1 clinical studies, monotherapy with a single subcutaneous dose of GS-6207 (450 mg) resulted in a mean $\log_{10}$-transformed reduction of plasma viral load of 2.2 after 9 days, and showed sustained plasma exposure at antivirally active concentrations for more than 6 months. These results provide clinical validation for therapies that target the functions of HIV capsid protein, and demonstrate the potential of GS-6207 as a long-acting agent to treat or prevent infection with HIV.

HIV-1 capsid protein (p24; hereafter abbreviated CA) has essential roles throughout the viral replication cycle, making it an attractive target for therapeutic intervention[11,12]. Unlike the viral enzymes (protease, reverse transcriptase and integrase) that are currently targeted by small-molecule antiretroviral drugs, CA functions through interactions between proteins; targets that function in this way have historically posed considerable challenges for interventions using small-molecule drugs[13]. CA is initially expressed within the Gag and Gag–Pol polyproteins, and provides key interactions between proteins that are necessary for assembly of the virion[14]. In the virion, CA is released by precursor cleavage mediated by HIV-1 protease, and self-assembles into a conical capsid composed of about 250 CA hexamers and 12 pentamers[15]. The correct formation and integrity of the capsid are essential for virus infectivity[14]. Upon infection of a new cell, controlled intracellular transport and disassembly of the viral capsid is regulated, in part, by interactions with host factors, and supports reverse transcription and proviral DNA integration[16–18].

We assayed small molecules for effects on the kinetics of in vitro CA assembly, and identified multiple inhibitor and accelerator series. Potency improvements through chemical modification were limited for compounds that inhibited CA assembly, presumably because these compounds could not overcome mass action and excess of the CA subunit in the virion (about 4 mM)[19,20]. Compounds that worked in concert with mass action to increase the rate and extent of CA assembly proved more amenable to improvement of their antiviral activity. Ultimately, extensive potency and pharmacokinetic optimization was required to discover a clinical candidate directed against HIV CA. The activity of GS-CA1 has previously been reported[21]. Here we report on GS-6207 (Fig. 1a), a CA-targeting inhibitor of HIV replication that is even more potent and more metabolically stable than GS-CA1 and that is suitable for clinical trials[22]. GS-6207 showed a dose-dependent increase in the rate and extent of in vitro CA assembly (Fig. 1b). In a cellular context, this acceleration of CA assembly produced malformed capsids that are morphologically distinct from mature and immature particles (Fig. 1c, d). Importantly, GS-6207 showed a mean half-maximum effective concentration (EC_{50}) of 105 pM in MT-4 cells infected with HIV-1, which makes this inhibitor significantly more potent than all of the approved HIV antiretroviral drugs that we tested (Fig. 1e). GS-6207 showed picomolar mean EC_{50} values in primary human $CD4^+$ T cells (32 pM) and macrophages (56 pM) infected with HIV-1, and remained broadly active against 2 HIV-2 isolates (885 pM) and 23 clinical HIV-1 isolates (50 pM, range of 20 to 160 pM) in human peripheral blood mononuclear cells (Fig. 1f). GS-6207 exhibited minimal cytotoxicity in human cell lines and primary cells, showing a mean half-maximal

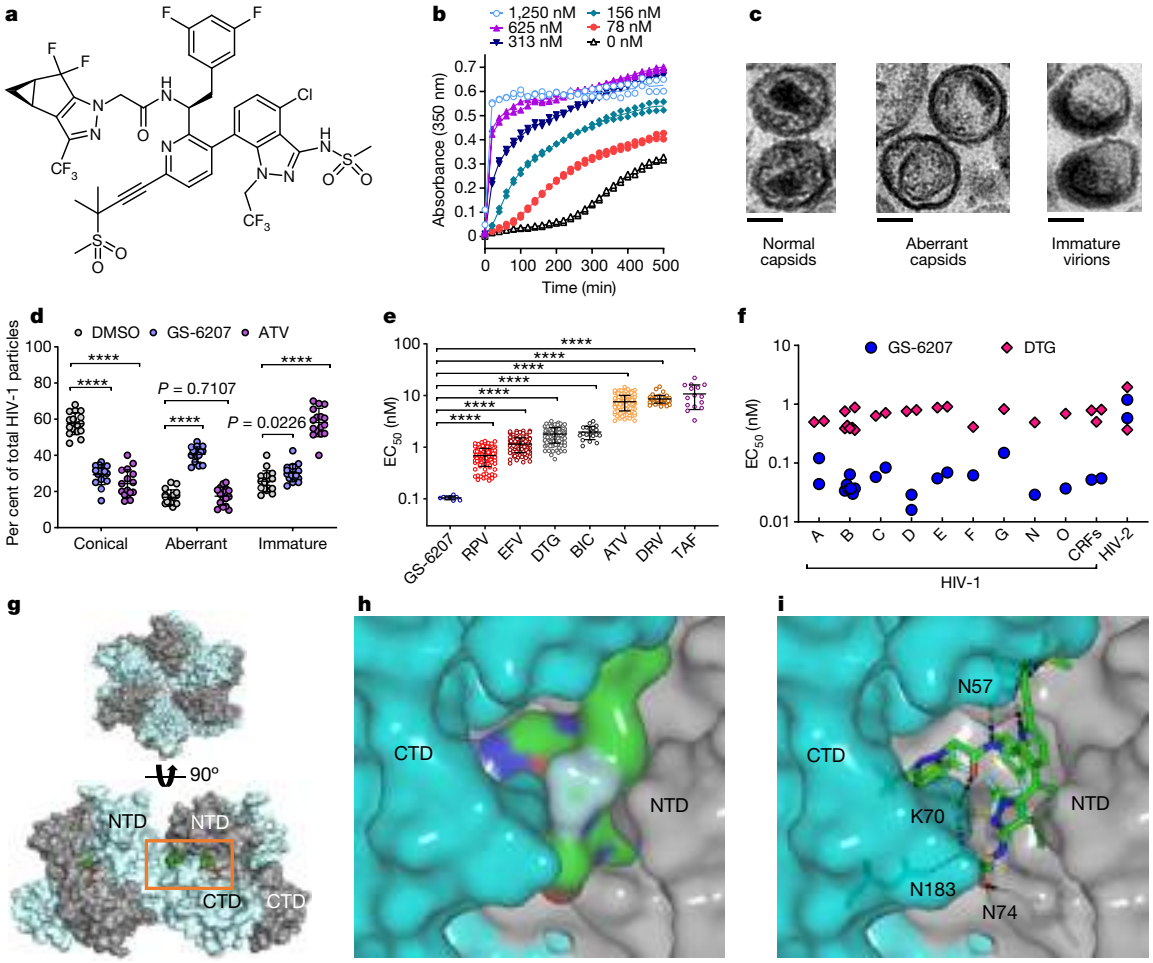

Fig. 1 | GS-6207 is a potent CA-targeting inhibitor of HIV replication. a, GS-6207. **b**, Light scattering (absorbance at 350 nm) responses showing the rate and extent of in vitro CA (20 μM) assembly in 2 M NaCl, in the presence and absence of GS-6207. Data are representative of four independent experiments ($n = 2$ biological replicates each). **c**, Representative thin-section electron micrograph images of HIV-1 produced in the presence of 0.2% dimethyl sulfoxide (DMSO) (left), GS-6207 (15 nM) (middle) or the HIV-1 protease inhibitor atazanavir (500 nM) (right). Scale bars, 50 nm. **d**, Quantification for **c**. Data are mean ± s.d. from representative images of HIV-1 produced in one of two independent experiments. DMSO, $n = 737$ virions; GS-6207, $n = 591$ virions; atazanavir (ATV), $n = 618$ virions. *P* values in all figures are by unpaired two-tailed Student's *t*-test with Welch's correction. ****$P < 0.0001$. **e**, Inhibition of HIV-1 strain IIIB in MT-4 cells. Data are mean ± s.d. from 4 biological replicates in each of 8 to 115 independent experiments. GS-6207 ($n = 8$), rilpivirine (RPV) ($n = 113$), efavirenz (EFV) ($n = 113$), dolutegravir (DTG) ($n = 115$), bictegravir (BIC) ($n = 20$), ATV ($n = 113$), darunavir (DRV) ($n = 60$) and tenofovir alafenamide (TAF) ($n = 15$). ****$P < 1 \times 10^{-15}$. **f**, Inhibition of HIV-2 and HIV-1 group M (subtypes A–G, circulating recombinant forms (CRFs)), N and O clinical isolates. Data represent individual isolates ($n = 3$ biological replicates each). **g**, X-ray crystal structure of GS-6207–CA hexamer complex. Top and side views of CA hexamer (individual CA monomers coloured alternately in cyan and grey). The GS-6207 binding site, located between the NTD of one CA monomer and the CTD of an adjacent monomer, is boxed. **h**, Space-filling view of GS-6207 in its binding site (X-ray structure). **i**, Hydrogen bonds (dashed black lines, $n = 7$) and cation–π interactions (dashed yellow lines, $n = 2$) are shown between GS-6207 and CA residues.

cytotoxic concentration (CC_{50}) in peripheral blood mononuclear cells of >50 μM and a therapeutic index (CC_{50}/EC_{50}) of more than 1,000,000 (Extended Data Table 1). When combined with other antiretroviral agents, GS-6207 displayed synergy (Extended Data Table 2) and retained full activity against HIV-1 variants that are resistant to current drug classes (Extended Data Table 3), which demonstrates its potency in combination and against drug-resistant strains of HIV.

The molecular underpinnings of the role of GS-6207 as an accelerator of CA monomer assembly are apparent in a 2.0 Å resolution X-ray crystal structure of GS-6207 in complex with a cross-linked CA hexamer (Fig. 1g–i, Extended Data Table 4). In this structure, GS-6207 binding is located between the N-terminal domain of one subunit of the CA hexamer (CA_{NTD}) and the C-terminal domain (CA_{CTD}) of an adjacent subunit in the hexamer. GS-6207 exhibits notable shape complementarity with adjacent CA monomers (contacting more than 2,000 $Å^2$ of buried protein surface area), and displays extensive hydrophobic and electrostatic interactions that include two cation–π interactions and seven hydrogen bonds. The GS-6207 sulfonamide is the linchpin in a hydrogen-bonding network that bridges from CA_{NTD} residues N74 and K70 of one subunit to CA_{CTD} residue N183 of the neighbouring subunit, and orders a loop that is unstructured in the apo hexamer crystal (Fig. 1i). Consistent with its binding position between neighbouring CA monomers in this crystal structure, GS-6207 showed saturable dose-dependent binding to Gag and CA; the slow dissociation of GS-6207 from CA multimers is consistent with a tenfold-higher affinity relative to the CA monomer (Extended Data Table 5).

To define the functional consequences of GS-6207 binding to capsid, we measured the potency of GS-6207 during early and late stages of the viral replication cycle in target MT-2 and producer HEK293T cells, respectively. GS-6207 showed sub-nanomolar potency in target cells ($EC_{50} = 23$ pM), in a full-cycle assay ($EC_{50} = 25$ pM) and in producer cells ($EC_{50} = 439$ pM), which indicates that GS-6207 interferes with both the early and late stages of HIV-1 replication but exhibits greater potency against the early stage (Fig. 2a). Time-of-addition

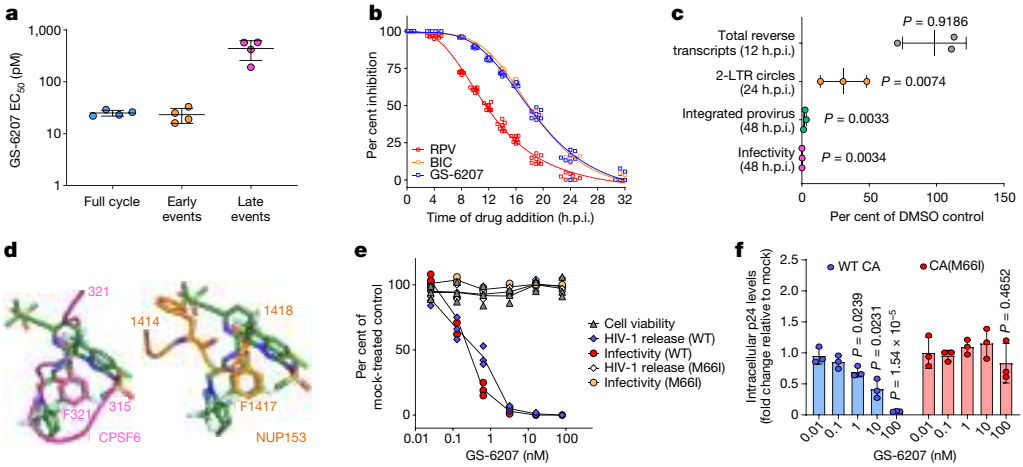

Fig. 2 | GS-6207 inhibits multiple CA-dependent steps of HIV-1 replication. **a**, Antiviral activity of GS-6207 throughout a full replication cycle, or when selectively present during target-cell infection (early events) or virus production (late events). Data are mean ± s.d. from 4 independent experiments ($n = 3$ biological replicates each). **b**, Time-of-addition study indicating when GS-6207 inhibits HIV-1 replication relative to rilpivirine (reverse transcriptase inhibitor) and bictegravir (integrase inhibitor). Data are mean from one of two representative independent experiments ($n = 8$ biological replicates per group in each experiment). h.p.i., hours post-infection. **c**, Effect of GS-6207 (1.25 nM) on the intracellular abundance of various forms of HIV-1 DNA. Data are mean ± s.d. from one of two representative independent experiments ($n = 3$ biological replicates each). **d**, Overlay of GS-6207 with CA-binding peptides from nuclear-import factors CPSF6 and NUP153 (ref. [25]) in their shared binding pocket. **e**, Effect of GS-6207 on HEK293T producer-cell viability, HIV-1 particle production and infectivity. Data are mean from one of three representative independent experiments ($n = 3$ biological replicates each). M66I, GS-6207 resistance-associated CA-binding-site variant; WT, wild type. **f**, Effect of GS-6207 on intracellular p24 levels. Data are mean ± s.d. from 3 independent experiments ($n = 3$ biological replicates each). For gel source data, see Supplementary Fig. 1.

studies relative to a non-nucleoside reverse-transcriptase inhibitor and an integrase strand-transfer inhibitor indicated that GS-6207 targets one or more steps that occur after reverse transcription and before integration (Fig. 2b). In quantitative PCR assays, we measured the accumulation of the products of reverse transcription, the formation of two-long-terminal-repeat (2-LTR) circles (which indicate nuclear localization but aborted integration) and proviral integration (Fig. 2c). GS-6207 at 1.25 nM (12.5-fold EC_{50}) did not alter the synthesis of HIV complementary DNA (cDNA) but significantly reduced formation of 2-LTR circles and integrated proviruses. These data suggest that GS-6207 might prevent the nuclear import of viral cDNA—possibly via direct competition with host-cell nuclear import cofactors (such as nucleoporin 153 (NUP153) and cleavage and polyadenylation specificity factor 6 (CPSF6)[23–26]) that bind CA and share a CA binding site with GS-6207 (Fig. 2d). In addition to these early effects and the effects on capsid formation, GS-6207 inhibited the production of HIV-1 that contains mature wild-type CA but not the CA(M66I) binding-site mutant that reduces GS-6207 binding affinity to CA oligomers (Extended Data Table 5), as measured by a p24 enzyme-linked immunosorbent assay (Fig. 2e). GS-6207 did not inhibit HIV-1 protease cleavage activity in vitro (half-maximal inhibitory concentration of more than 50 μM) but reduced intracellular Gag and processed CA levels in the producer cells (Fig. 2f), which indicates that the loss of p24 production probably reflected GS-6207 binding to CA precursors, and a reduction in Gag and/or Gag–Pol stability, trafficking and/or viral assembly.

To evaluate drug resistance, we serially passaged HIV-1 in MT-2 cells in the presence of increasing concentrations of GS-6207 for more than three months (Fig. 3a). Sequence analysis identified an N74D substitution in CA (passages 4–6) followed by a CA(Q67H/N74D) variant (passages 7–10). The N74D substitution has previously been shown to alter the viral pathway of nuclear entry[27]. Viruses with these GS-6207 resistance-associated mutations remained fully sensitive to agents from other antiretroviral classes (Fig. 3b). Selections performed in the presence of fixed concentrations of GS-6207 in human peripheral blood mononuclear cells independently infected with six HIV-1 isolates similarly identified Q67H and N74D as the major resistance-associated

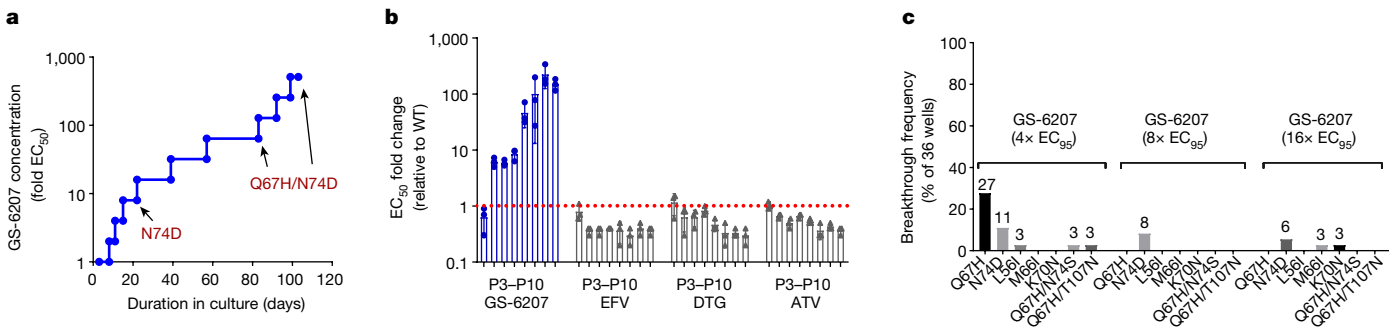

Fig. 3 | Resistance to GS-6207 maps to CA. **a**, Emergent CA substitutions denoted during resistance selection in MT-2 cells infected with HIV-1 strain HXB2D, by escalation of the GS-6207 dose. Data are representative of one of two biological replicates from a single selection experiment. **b**, Fold resistance of GS-6207-selected viral isolate passage (P)3 to 10 (each tick mark corresponds to one passage) to GS-6207, and control antiretroviral agents. Data are mean ± s.d. from 3 independent experiments ($n = 3$ biological replicates each). Red dotted line defines the cut-off for drug resistance. **c**, Frequency of GS-6207-selected CA variants observed at fixed GS-6207 concentrations in peripheral blood mononuclear cells infected with clinical HIV-1 isolates.

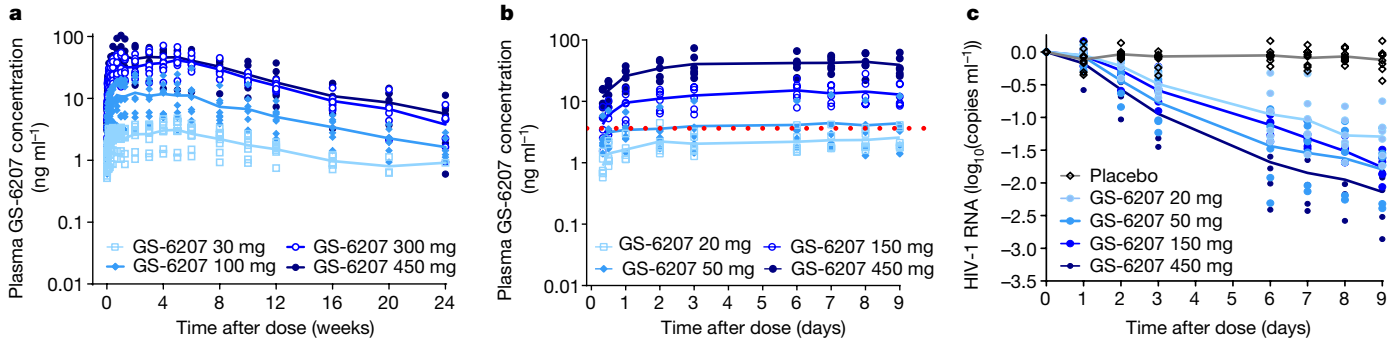

Fig. 4 | Clinical testing of GS-6207 in humans. a, Mean plasma concentration–time profile of GS-6207 after a single subcutaneous administration of 30–450 mg of drug to uninfected individuals ($n = 8$ within each dosing arm). **b**, Mean plasma concentration–time profile of GS-6207 after a single subcutaneous administration of 20–450 mg to individuals infected with HIV ($n = 6$ within each dosing arm). Red dotted line defines protein-adjusted EC_{95} for GS-6207. **c**, Mean log_{10}-transformed change in plasma HIV-1 RNA after a single subcutaneous administration of 20–450 mg GS-6207 to 8 individuals with untreated HIV-1 infection randomized to drug ($n = 6$) or placebo ($n = 2$) within each dosing arm.

mutations, with additional variants (L56I, M66I, K70N, Q67H/N74S and Q67H/T107N) that were each independently detected in a single GS-6207-selected culture (Fig. 3c). These resistance-associated mutations, alone or in combination, conferred reduced susceptibility to GS-6207 (6- to >3,200-fold resistance relative to the wild-type virus), consistent with the assignment of CA as the functional target of GS-6207. All CA residues that confer resistance map to the GS-6207 binding site and are highly conserved across subtypes of HIV-1[21,28–30]. Of the mutants that we tested, all but the low-level-resistant Q67H variant (sixfold resistance to GS-6207 relative to wild-type virus) display reduced replication capacity in vitro (Extended Data Table 6).

Low hepatic clearance is an essential attribute for a long-acting agent. Thus, along with enhancement of potency, the design process that culminated in GS-6207 also focused on blocking metabolically labile sites through incorporation of electron-withdrawing groups (halogens and sulfonyls), metabolically stable ring systems (cyclopropane and pyrazoles) and rigidifying elements. Tritiation ([^{3}H]) of GS-6207 was necessary to accurately measure the low turnover of GS-6207 in primary human hepatocytes, and showed a predicted rate of hepatic clearance of 0.01 l h^{-1} kg^{-1}, or 0.8% of the hepatic extraction.

In a single-ascending-dose clinical study that was randomized, double-blind and placebo-controlled, we administered a suspension formulation of 30 to 450 mg GS-6207 to healthy participants (32 active and 8 placebo)—most of whom were male (27 of 40) and in their 30s (median age of 37 years old, range 19 to 44 years old), and had normal kidney and liver function—as a subcutaneous injection (Fig. 4a). Consistent with nonclinical safety studies, GS-6207 was generally safe and well-tolerated. The most frequent adverse events were mild erythema and/or pain at the injection site that resolved in a few days (Extended Data Table 7). GS-6207 pharmacokinetic profiles showed slow, sustained drug release, with a median apparent terminal half-life ($t_{1/2}$) of about 38 days. Increases in exposure to GS-6207 were approximately dose-proportional. At doses of ≥100 mg, GS-6207 plasma concentrations exceeded the human serum protein-adjusted 95% effective concentration (EC_{95}) for wild-type HIV-1 (4.0 nM or 3.87 ng ml^{-1} in MT-4 cells) for ≥12 weeks, and doses of ≥300 mg exceeded the human protein-adjusted EC_{95} for more than 24 weeks.

In a subsequent clinical study (which was also randomized, double-blind and placebo-controlled), 20 to 450 mg GS-6207 was administered to trial participants with untreated HIV-1 infection (24 active and 8 placebo) as a single-dose subcutaneous suspension. We conducted a prespecified interim analysis of this part of the study. Most of the participants were male (30 of 32), in their 30s (median age of 34 years old, range 19 to 59 years old) and treatment-naive (25 of 32), and had median HIV-1 RNA loads of log_{10}-transformed copies per millilitre of 4.48 (range of 3.86 to 5.01) and median $CD4^+$ T cell counts of 458 cells per microlitre (range of 200 to 1,009). GS-6207 was generally safe and well-tolerated (Extended Data Table 8), and the concentration–time profiles of GS-6207 were consistent with those in HIV-negative participants through to nine days after administration of the dose (Fig. 4b, Extended Data Table 9). A single subcutaneous administration of 20, 50, 150 or 450 mg GS-6207 led to mean maximum log_{10}-transformed reductions of 1.35, 1.79, 1.76 and 2.20, respectively, in plasma HIV-1 RNA by the ninth day (Fig. 4c, Extended Data Table 10). A genetic mixture of wild-type CA and the CA(Q67H) mutant emerged on day 9 in one participant in the 20-mg cohort, which was associated with a 1.6-fold decrease in phenotypic susceptibility but not with viral escape by day 9 of monotherapy.

These data establish GS-6207 as a first-in-class HIV-1 capsid inhibitor with potent antiviral activity against both wild-type virus and variants that are resistant to current antiretroviral agents. The favourable safety profile, prolonged pharmacokinetic exposure and observed antiviral efficacy in humans support continued clinical development of GS-6207 as a long-acting antiretroviral agent for the treatment of infection with HIV-1, including for people living with HIV who are heavily treatment-experienced and have multidrug-resistant virus. In addition, the infrequent subcutaneous dosing renders GS-6207 an attractive candidate for the simplified prevention of the acquisition of HIV in at-risk populations—making this drug a potentially transformative tool in efforts to end the global HIV epidemic.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-020-2443-1.

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Methods

No statistical methods were used to predetermine sample size. The in vitro experiments were not randomized and investigators were not blinded to sample allocation during in vitro experiments and outcome assessment.

Compounds

GS-6207 was synthesized at Gilead Sciences, and chemical identity (^{1}H-nuclear magnetic resonance (NMR), ^{13}C-NMR and high-resolution mass-spectrometry spectra) and sample purity were established using reverse-phase high-performance liquid chromatography (HPLC) (Supplementary Information). The control antiretroviral agents emtricitabine (FTC), tenofovir alafenamide (TAF), elvitegravir (EVG), raltegravir (RAL), bictegravir (BIC), darunavir (DRV), atazanavir (ATV) and bevirimat (BVM) were synthesized at Gilead Sciences, and efavirenz (EFV) and dolutegravir (DTG) were purchased from Toronto Research Chemicals and Porton Shanghai R&D Center, respectively. Puromycin (a control compound for cytotoxicity assays) was purchased from Sigma-Aldrich.

Viruses

The HIV-1 strains IIIB and BaL were obtained from the NIH AIDS Reagent Program and from Advanced Biotechnologies, respectively. Two HIV-2 isolates (CBL20 and CDC310319) and 23 clinical HIV-1 isolates from the Southern Research virus collection were selected for susceptibility profiling: subtype A (92UG031 and 92UG037), subtype B (89BZ_167, 90US_873, YU-2, 91US001, 91US004, 96TH_NP1538, BaL and JR-CSF), subtype C (92BR025 and 98US_MSC5016), subtype D (92UG001 and 98UG_57128), subtype E (CMU02 and CMU08), subtype F (93BR020), subtype G (JV1083), group N (YBF30), group O (BCF01), CRF01_AE (90TH_CM235) and CRF02_AG (01CM0008BBY, 91DJ263). HIV-1 recombinant strains encoding mutation(s) that confer resistance to nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, integrase strand transfer inhibitors, protease inhibitors or maturation inhibitors have previously been described[31,32]. Single-cycle HIV-1 encoding firefly luciferase with and without mutations within the capsid gene was made by co-transfecting HEK293T cells with pKS13ΔEnv and pHCMV-G plasmids. Cell-free viral supernatant was collected 3 days after transfection, clarified using a 0.45-μm syringe filter and stored at −80 °C. The amount of HIV in each sample was quantified by p24 antigen enzyme-linked immunosorbent assay (Perkin Elmer) and a reverse transcriptase activity assay (Southern Research).

Cell lines

Human MT-2 and MT-4 T-cell lines were obtained from the NIH AIDS Reagent Program and maintained in RPMI-1640 medium supplemented with 10% heat-inactivated fetal bovine serum (FBS), 100 units ml^{-1} penicillin, and 10 μg ml^{-1} streptomycin (complete RPMI). MT-2 cells chronically infected with HIV-1 strain IIIB were cultured in complete RPMI. HEK293T cells were obtained from the Gladstone Institute for Virology and Immunology and maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% FBS, 100 units ml^{-1} penicillin, and 10 μg ml^{-1} streptomycin (complete DMEM). The human hepatoma Huh-7 cell line was obtained from ReBLikon and cultured in complete DMEM[33]. The human hepatoblastoma cell line HepG2, human prostate carcinoma cell line PC-3 and normal human fetal-lung-derived MRC-5 cells were obtained from the American Type Culture Collection. PC-3 and HepG2 cells were adapted to grow in 0.2% galactose-containing, glucose-free DMEM supplemented with 10% FBS, 1% non-essential amino acids, 1% pyruvate, and 1% GlutaMAX. MRC-5 cells were maintained in Eagle's Minimum Essential Medium (MEM) supplemented with 10% FBS. Each cell culture medium was further supplemented with 100 units ml^{-1} penicillin and 100 μg ml^{-1} streptomycin. The above eukaryotic cell lines were not authenticated and were judged to be free of mycoplasma contamination using the MycoProbe Mycoplasma Detection Kit (R&D Systems).

Primary cells

Human peripheral blood mononuclear cells (PBMCs) were collected from healthy volunteers under informed consent; their use was approved by an institutional review board at AllCells. The preparation of human PBMCs, CD4$^+$ T lymphocytes and monocyte-derived macrophage cultures have previously been described[31]. Before infection, PBMCs and CD4$^+$ T cells were activated for 48 h at 37 °C by addition of 1 μg ml^{-1} phytohaemagglutinin (PHA) and 50 international units ml^{-1} recombinant human interleukin 2 (IL-2). Primary human hepatocytes from three independent donors were purchased from Invitrogen and cultured in William's Medium E medium containing cell maintenance supplement. Donor profiles were limited to 4–65 years of age, non-smokers with limited alcohol consumption. Upon arrival at Gilead Sciences, hepatocytes were allowed to recover in a 37-°C incubator with 5% CO_2 and 90% humidity for 12–18 h in complete medium with vendor-supplied supplements before treatment with compounds.

Antiviral assays

The five-day cytoprotection antiviral assays using MT-2 and MT-4 T-cell lines have previously been described[31]. Data analysis was performed using GraphPad Prism 7.0 to calculate EC_{50} values. The EC_{95} value for GS-6207 was calculated from the EC_{50} and Hill coefficient, n, determined in MT-4 cells using the equation: $EC_{95} = EC_{50} \times (95/5)^{1/n}$.

For time-of-addition antiviral assays, MT-2 cells were infected with single-cycle reporter HIV-1 for 1 h at 37 °C, washed and seeded into 96-well plates (75-μl aliquots; 1.5×10^4 cells per well). A 25-μl aliquot of complete RPMI medium was added to 8 uninfected and 8 infected wells as respective minimum (0%) and maximal (100%) infection controls. Twenty-five-microlitre aliquots of 4× drug–medium were added to 8 replicate wells at indicated times after infection. GS-6207 and control antiretroviral agents were tested at concentrations equivalent to 10× and 100× EC_{50}, producing similar results. Assay plates were kept in a humidified 37-°C incubator before and after drug–medium additions. Plates were developed 48 h.p.i. using ONE-Glo Luciferase Assay reagent (Promega) and the resulting luminescence data were collected and analysed using EnVision Manager 1.13.3009 and GraphPad Prism 7.0 software, respectively. When investigating inhibitor potency across the phases of viral replication, single-cycle antiviral assays were performed in MT-2 cells in a manner such that GS-6207 was present selectively at early stage, late stage or during a full course of infection as previously described[34]. Assays evaluating the effect of GS-6207 on HIV-1 particle production (by p24 antigen enzyme-linked immunosorbent assay) and intracellular CA levels (by anti-p24 and anti-tubulin western blot analyses) have previously been described[21].

For in vitro two-drug combination studies, compounds within a test pair were combined in 384-well assay plates to create a two-dimensional matrix of diluted drugs. Positive control (EVG) and negative control (DMSO) wells were included in every assay plate to define 100% and 0% protection from viral replication-mediated cytopathic effect (CPE), respectively. The final DMSO concentration in the assay was 0.5%. MT-2 cells were bulk-infected in complete RPMI medium with HIV-1 strain IIIB at a multiplicity-of-infection (MOI) of 0.01 for 3 h at 37 °C, added to the assay plates (3×10^3 cells per well) and incubated at 37 °C for 5 days. Cell viability was determined by adding CellTiter-Glo reagent and the resulting luminescence data were collected using EnVision Manager 1.13.3009. Data were normalized to positive and negative controls in each plate, expressed as per cent CPE protection and analysed with MacSynergy II software[35]. Combination data were analysed at the 95% confidence level, with synergy and antagonism volumes defined as follows: high synergy (>100 μM^2%), moderate synergy (50 to <100 μM^2%), additivity (>-50 to <50 μM^2%) and antagonism (<-50 μM^2%).

Antiviral assays using HIV-1 strain BaL in primary human CD4$^+$ T lymphocytes and macrophage cultures were conducted using a p24 endpoint assay as previously described[36]. A seven-day reverse transcriptase endpoint antiviral assay using fresh human PBMCs independently infected with a panel of clinical HIV-1 and HIV-2 isolates was performed by Southern Research as a contracted research study.

Cytotoxicity assays

For cytotoxicity assessment in MT-4 cells, PBMCs, primary human CD4$^+$ T cells and monocyte-derived macrophages, the protocol was identical to that of the respective antiviral assay, including assay duration, except that no virus was added to the plates. Protocols for cytotoxicity assessments in Huh-7, Gal-HepG2, Gal-PC-3 and MRC-5 cell lines, as well as in primary human hepatocytes, have previously been described[37]. The effect of test compounds on cell viability was measured using CellTiter-Glo. Data analysis was performed using GraphPad Prism 7.0 to calculate CC_{50} values.

GS-6207 resistance analysis

Dose-escalation selections for drug-resistant HIV-1 variants were performed in MT-2 cells infected with HIV-1 strain HXB2D using twofold incremental increases in GS-6207 concentration as previously described[31]. The resistance profile of each emergent virus passage was then assessed in the five-day cytoprotection antiviral MT-2 assay after titrating virus inoculums to normalize the MOI across all samples. Viral breakthrough selections were conducted under conditions of fixed, constant drug concentrations over a period of 35 days in human PBMCs independently infected with 6 different HIV-1 isolates (BaL, 92US657, 91US0006, 7406, 7467 and 7576) as previously described[21]. GS-6207 was tested at fixed drug concentrations equal to 4-fold, 8-fold and 16-fold its EC_{95} value of 0.23 nM (0.92 nM, 1.9 nM, and 3.7 nM GS-6207, respectively), using 6 replicate cell cultures per experimental condition. Viruses that emerged in the presence of GS-6207 were genotyped by population sequencing. Total RNA was isolated from mock- and GS-6207-selected virus-containing supernatants using the QiaAMP Viral RNA Mini Kit (Qiagen). A 986-bp fragment encoding HIV-1 capsid and the adjacent p2 spacer peptide was amplified by PCR with reverse transcription (RT–PCR) using the Qiagen OneStep RT–PCR Kit in combination with primers 5′-CAGTAGCAACCCTCTATTGTGTGC-3′ and 5′-CCTAGGGGCCCTGCAATTT-3′. RT–PCR products were sequenced by Elim Biopharmaceuticals. To identify codon changes, gene sequences from selected HIV-1 variants were aligned using DNA Sequencher 4.9 Software (Gene Codes) with that of the input virus and virus passaged in the absence of GS-6207. For samples containing >1 codon change, PCR products were subcloned, DNA was isolated from individual bacterial colonies and the gene encoding CA was sequenced to assess the linkage of all observed substitutions.

The resistance profile and infectivity of each GS-6207-selected CA variant was determined in MT-2 cells after introducing each substitution, alone and in combination, into wild-type single-cycle reporter HIV-1. The replication level (fitness) of select CA variants introduced into wild-type replication-competent reporter HIV-1 was evaluated in primary human CD4$^+$ T cells over a period of 19 days[21].

Recombinant HIV-1 Gag and CAs

Recombinant HIV-1_{LAI} CA was prepared as previously described[38]. Soluble cross-linked CA hexamers of HIV-1 strain NL4.3 (wild type and the M66I variant), as well as CA pentamers, were prepared as previously described[38–40]. Recombinant Gag protein of HIV-1 strain NL4.3 was prepared as previously described[21].

Crystallization, data collection and structure determination

HIV-1 CA hexamer (25 mg ml^{-1} in 20 mM Tris, pH 8.0) was thawed and diluted to 12 mg ml^{-1} in the same buffer and incubated on ice for 10 min with 1 mM GS-6207. Crystallization droplets were assembled in MRC2 microplates with 100 nl of the complex and 100 nl of 12% polyethylene glycol (PEG) 3350, 0.2 M sodium thiocyanate, 0.1 M sodium cacodylate, pH 6.7. The assembled 200-nl droplet was then subjected to vapour diffusion with 50 µl of 1% PEG 3350, 0.2 M sodium thiocyanate, 0.1 M sodium cacodylate, pH 6.7 in the large reservoir. Large hexagonal crystals (30 µm × 160 µm × 160 µm) grew in 4 d at 25 °C and were subsequently cryo-protected for X-ray diffraction in 30% PEG 3350, 7% glycerol, 0.2 M sodium thiocyanate, 0.1 M sodium cacodylate, pH 6.7, and 0.3 mM GS-6207. X-ray diffraction data to 2.0 Å resolution were collected on a single frozen (−180 °C) crystal at the Advanced Light Source, Beamline 5.0.1. The protein–inhibitor complex crystallized in space group P3 with cell parameters: a = 158.3 Å, b = 158.3 Å, c = 55.6 Å, α = 90.0°, β = 90.0° and γ = 120.0°. The data were processed and scaled with the programs DENZO and SCALEPACK (HKL Research), respectively. Initial models were obtained by molecular replacement using the program EPMR[41] and using the coordinates from a single monomer of a previously determined HIV-1 CA hexamer–inhibitor complex (with coordinates for the inhibitor atoms removed) as the search model. The molecular replacement solution included six monomers. The initial model was further refined using multiple rounds of simulated annealing in the PHENIX software package[42] followed by manual refitting of the model in COOT[43]. In the later stages of refinement, strong residual electron density in the capsid modulator binding site allowed for unambiguous placement of GS-6207 into the structure followed by final refinement of the model (see Supplementary Fig. 2 for sample inhibitor density). Data collection and model refinement statistics are summarized in Extended Data Table 4.

In vitro HIV-1 CA assembly assay

The in vitro assembly of HIV-1 CA in the presence and absence of small-molecule library compounds (10 µM) or twofold serially diluted GS-6207 was monitored by measuring changes in sample absorbance over time at 350 nm. Final assembly reactions contained 20 µM CA, 2 M NaCl, 50 mM sodium phosphate pH 7.5, 0.005% Antifoam 204 (Sigma-Aldrich) and 1% DMSO. Sample absorbance values at 350 nm were monitored over time at 25 °C in 96-well or 384-well plates using an M5 plate reader (Molecular Devices), corrected for absorbance values in the absence of CA or NaCl, and the data analysed using SoftMax Pro 6.3.1 as previously described[38].

GS-6207 binding assay

Surface plasmon resonance biosensor binding experiments were performed using the ProteOn XPR36 platform (CA hexamer and pentamer proteins) or the Biacore T100 platform (CA monomer and Gag proteins) as previously described[21]. Data were analysed using ProteOn Manager 3.1.0 or Scrubber 2.0 and fit with a simple kinetic model with a term for mass transport added when necessary.

Quantification of HIV-1 DNA

MT-2 cells (2×10^6 cells ml^{-1}) were infected with single-cycle reporter HIV-1, added to 24-well plates containing drug medium and transferred to a humidified 37-°C incubator. For each condition, cells from each of 3 replicate wells were collected at 12 h.p.i. for late reverse transcription product quantification, 24 h.p.i. for 2-LTR circle quantification, and 48 h.p.i. for Alu-LTR product quantification. Viral DNA was isolated from cell pellets using a QIAamp DNA mini kit (Qiagen) and quantified using the TaqMan real-time PCR and ABI Prism 7900HT sequence detection system (Applied Biosystems) or the QX200 Droplet Digital PCR System (Bio-Rad) as previously described[21].

Ultrastructural analysis of HIV-1 by electron microscopy

MT-2 cells infected with HIV-1 strain IIIB were washed and cultured at 37 °C in complete RPMI containing 0.25% DMSO, 15 nM GS-6207 or 500 nM ATV. After a four-day incubation, samples were pelleted, fixed, stained, sectioned and imaged on a JEOL JEM-1230 transmission electron microscope as previously described[21].

Metabolic stability of [^{3}H]GS-6207 in primary human hepatocytes

A 500-µl suspension of human hepatocytes (1×10^6 cells ml^{-1}) and 0.25 µM [^{3}H]GS-6207 was prepared in Krebs–Henseleit Buffer (KHB) medium and incubated in a humidified 37-°C incubator with 5% CO_2 in duplicate wells of a 24-well plate. Propranolol (1 µM final), a compound known to be efficiently metabolized by hepatocytes by oxidation and conjugation, was used as a positive control. A cell-free control was incubated in parallel as a negative control. Aliquots (100 µl) were removed after 0, 1, 3 and 6 h, mixed with 200 µl quenching solution, placed on a shaker for 10 min and then centrifuged at 3,000*g* for 60 min. The supernatant was transferred to a new plate, diluted with 100 µl water and placed on a shaker for 10 min. The quantification of [^{3}H]GS-6207 and its metabolites was performed by radio flow chromatography using a Perkin Elmer Radiomatic 625TR flow scintillation analyser with a 500 µl flow cell coupled to a Dionex Ultimate 3000 HPLC system. The scintillation cocktail was Perkin Elmer Ultima-Flo and was mixed with the HPLC effluent at a ratio of 1:1. The sample (100 µl) was injected with a Leap Technologies CTC PAL autosampler. Separation was achieved on a Phenomenex Synergi Fusion-RP 80 Å pore size, 4-µm particle size, 150 × 4.6-mm column maintained at 32 °C. Mobile phase A consisted of 95% water, 5% acetonitrile, and contained 0.1% trifluoroacetic acid (TFA). Mobile phase B consisted of 95% acetonitrile, 5% water, and contained 0.1% TFA. Elution was achieved, at a flow rate of 1 ml min^{-1}, by linear gradients: initial condition was 2% B at 0 min which was increased to 75% B over 45 min, holding for 4 min at 75% B and then returning to initial conditions. The column was allowed to re-equilibrate for 12 min between injections. Quantification was by radiochromatographic peak area.

Competitive equilibrium dialysis

Human serum protein binding to GS-6207 was determined by competitive equilibrium dialysis. Human plasma (10%) was spiked with GS-6207 (2 µM) and blank RPMI cell culture medium containing 2% FBS were placed in duplicate into opposite sides of assembled dialysis cells. After a 24-h equilibration period at 37 °C, GS-6207 concentrations in plasma and cell culture medium were determined by a liquid chromatography with tandem mass spectrometry (LC–MS/MS) method and multiplied by 10 to obtain the protein-adjusted shift for 100% human plasma.

Ethical conduct and consent in clinical trials

The clinical trials were conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonization and in accordance with the ethical principles underlying the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). The protocol and the participant informed-consent form received institutional review board, independent ethics committee approval and/or favourable opinion (Advarra) before initiation of the study. Freely given written informed consent was obtained from every individual before participation in the clinical studies.

Single ascending-dose study in healthy participants

For clinical study GS-US-200-4070, we enrolled healthy men and women uninfected with HIV-1, 18–45 years of age, with normal kidney and liver function, body mass index between 19 and 30 kg/m^2, and no relevant medical history. Ten trial participants in each dosing arm were randomized in a blinded fashion in a 4:1 ratio to receive either the drug (GS-6207) or placebo (vehicle alone). The primary objectives were to assess the safety and tolerability of escalating single subcutaneous doses of GS-6207 compared with placebo in healthy participants and to assess its pharmacokinetics. GS-6207 was formulated as a sterile, preservative-free, injectable aqueous suspension (100 mg m1^{-1}). Serial blood samples were collected for plasma pharmacokinetics analysis through day 197 (30- and 100-mg cohorts) or day 225 (300- and 450-mg cohorts). Plasma samples were analysed using a validated, high-performance LC–MS/MS bioanalytical method with multiple reaction monitoring and electrospray ionization in the positive mode (Covance Laboratories). Quantification was performed using multiple reaction monitoring of the transitions *m/z* 968.2 to 869.2 and *m/z* 974.3 to 875.2 for GS-6207 and an isotopically labelled internal standard, respectively. The bioanalytical method was validated over a calibrated range of 0.5 to 500 ng ml^{-1}. Inter-assay precision, based on coefficient of variation, was ≤ 8.7%, and accuracy ranged from 95.2% to 104.6%. All plasma samples were analysed within the timeframe supported by frozen stability storage data. Pharmacokinetic parameters were estimated using Phoenix WinNonlin 6.4 (Certara, L.P.) software using standard noncompartmental methods. Pharmacokinetics parameters for GS-6207 included area under plasma concentration versus time curve extrapolated to infinity (AUC_{inf}), the per cent of the area that is extrapolated ($AUC_{\%exp}$), and area under the concentration versus time curve from time zero to the last quantifiable concentration (AUC_{last}), maximal concentration (C_{max}), time to C_{max} (t_{max}) and $t_{1/2}$.

Single ascending-dose study in participants living with HIV

For clinical study GS-US-200-4072 (registered with ClinicalTrials.gov, NCT03739866), we enrolled treatment-naive or -experienced, but HIV-capsid-inhibitor-naive and integrase-strand-transfer-inhibitor-naive, men and women, 18–65 years of age with plasma HIV-1 RNA ≥ 5,000 copies ml^{-1} (via amendment; originally 10,000 copies ml^{-1}) but ≤ 400,000 copies ml^{-1} and CD4$^+$ T cell counts >200 cells per mm^3. Eight trial participants in each dosing arm were randomized in a 3:1 ratio to receive either the drug (GS-6207) or placebo (vehicle alone) (part A). GS-6207 was formulated as a sterile, preservative-free, injectable aqueous suspension (100 mg m1^{-1}).

Plasma HIV-1 RNA levels were determined using the Roche COBAS Ampliprep/COBAS TaqMan HIV-1 test v.2, which has a limit of detection of 20 copies ml^{-1} and a range of quantification of 20 to 10,000,000 HIV-1 RNA copies ml^{-1}. All samples were analysed by a central laboratory. Serial blood samples were collected for plasma pharmacokinetics through at least day 9. Pharmacokinetics samples were analysed as above for study 200-4070.

HIV-1 resistance analyses for study GS-US-200-4072 were carried out at Monogram Biosciences using the research-grade gag-protease genotyping (population-level sequencing) and phenotyping assay to assess resistance to GS-6207 using HIV-1 DNA fragment of each participant that encompasses the gag-protease HIV-1 region, and/or using the CLIA-certified PhenoSense GT + Integrase or GenoSure PRIme assay to assess resistance to the components of Biktarvy (which was administered to all participants following the 9-day GS-6207 monotherapy). Resistance analyses were conducted at screening and day 9 (last GS-6207 monotherapy visit).

Within part A, we conducted an interim analysis, which was prespecified in the protocol to be conducted after at least 50% of the participants and/or after all participants within each cohort completed the day-10 visit. The purpose of this interim analysis was to select the doses of GS-6207 to evaluate in each subsequent cohort.

Statistics

GraphPad Prism 7.0 was used for statistical analysis. In each case, an unpaired two-tailed Student's *t*-test with Welch's correction was performed for parametric analysis of two groups. A P value < 0.05 was considered statistically significant.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this paper.

Data availability

All data to understand and assess the conclusions of this research are available in the Article and Supplementary Information. Raw gel source

data for Fig. 2f are available in Supplementary Fig. 1. Small-molecule X-ray crystallographic coordinates and structure factor files have been deposited in the Protein Data Bank (PDB) with accession number 6V2F. Study GS-US-200-4072 was registered with ClinicalTrials.gov, NCT03739866. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Competing interests All authors are current or previous employees of Gilead Sciences (except for G.I.S., P.J.R., G.E.C., C.K.M., W.I.S. and E.S.D.) and received salary and stock ownership as compensation for their employment. M.G., J.O.L., W.R., R.D.S., S.D.S., W.C.T. and J.R.Z. are inventors on granted US patent no. 10,071,985B2 covering GS-6207 composition of matter and methods of use. G.I.S. receives research support from Gilead Sciences, Janssen Pharmaceutica, GlaxoSmithKline, Abbvie and Cepheid, and is on the speaker's bureau and advisory board for Janssen, ViiV Healthcare and Merck. G.E.C. receives grants (investigator research payments) from Gilead Sciences, ViiV Healthcare, Merck and Janssen Pharmaceutica. C.K.M. receives research support from Gilead Sciences, Merck, ViiV Healthcare and Janssen Pharmaceutica, is on the speaker's bureau for Gilead Sciences, Merck and Insmed, and is on an advisory board for Gilead Sciences. E.S.D. receives research support from Gilead Sciences, Merck and ViiV Healthcare, and has served as a consultant for Gilead Sciences.

Additional information

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Extended Data Table 1 | Cytotoxicity of GS-6207 in human cell lines and primary cells

	CC_{50} (μM)	
	GS-6207	**Puromycin**
Human cell lines		
MT-4	24.7 ± 18.3	0.2 ± 0.1
Huh-7	>44.4	0.5 ± 1.7
Gal-HepG2	>44.4	1.0 ± 1.7
Gal-PC-3	>44.4	0.4 ± 1.5
MRC-5	>44.4	0.3 ± 1.5
Human primary cells		
Hepatocytes	>50.0	1.6 ± 0.6
Quiescent PBMCs	>44.4	0.6 ± 1.5
Stimulated PBMCs	>50.0	0.2 ± 0.1
$CD4^+$ T-lymphocytes	>50.0	0.2 ± 0.1
Monocyte-derived macrophages	>50.0	4.5 ± 2.8

Data are mean ± s.d. from 3 independent experiments (n = 4 biological replicates each). Puromycin was assayed in parallel as a positive control for cytotoxicity.

Extended Data Table 2 | In vitro combination studies with GS-6207

	TAF	EFV	DTG	DRV	GS-6207
Synergy volume [μM^2.%]	87 ± 32	101 ± 40	116 ± 13	119 ± 39	18 ± 8
Antagonism volume [μM^2.%]	-8 ± 7	-8 ± 8	-8 ± 7	-3 ± 3	-16 ± 6
Combination effect	Moderately synergistic	Highly synergistic	Highly synergistic	Highly synergistic	Additive

TAF is a nucleotide reverse transcriptase inhibitor; EFV is a nonnucleoside reverse transcriptase inhibitor; DTG is an integrase strand transfer inhibitor); DRV is an HIV protease inhibitor; GS-6207 in combination with itself was included as a positive control for additivity. Data are mean ± s.d. from 3 independent experiments (n = 3 biological replicates each). The high-antagonism control combination of ribavirin and stavudine produced the expected results (synergy volume = 0 ± 0; antagonism volume = −398 ± 23).

Extended Data Table 3 | GS-6207 activity against HIV-1 isolates that are resistant to existing antiretroviral inhibitors

		Fold resistance (*n*)		
Antiretroviral Class	**HIV-1 Mutant**	**GS-6207**	**Control Antiretroviral Agent**	
Nucleotide reverse transcriptase inhibitor (NRTI)	K65R	0.6 ± 0.2 (3)	FTC	14.1 ± 2.6 (3)
	M184V	0.3 ± 0.3 (3)	FTC	>23.0 (3)
	6TAMs	0.2 ± 0.1 (3)	FTC	4.0 ± 2.8 (3)
Nonnucleoside reverse transcriptase inhibitor (NNRTI)	Y188L	0.5 ± 0.1 (3)	EFV	>22.5 (3)
	L100I+K103N	0.5 ± 0.2 (3)	EFV	>22.5 (3)
	K103N+Y181C	0.6 ± 0.2 (3)	EFV	>22.5 (3)
Integrase strand transfer inhibitor (INSTI)	E138K+Q148K	0.6 ± 0.3 (3)	EVG	>53.8 (3)
	G140S+Q148R	0.8 ± 0.3 (3)	EVG	>53.8 (3)
	E92Q+N155H	0.8 ± 0.4 (3)	EVG	>53.8 (3)
	N155H+Q148R	1.2 ± 0.7 (3)	EVG	>52.9 (3)
Maturation inhibitor (MI)	V230I in CA	0.7 ± 0.2 (6)	BVM	>67.5 (6)
	V7A in SP1	0.8 ± 0.4 (8)	BVM	>67.5 (7)
Protease inhibitor (PI)	M46I+I50V	0.7 ± 0.2 (3)	DRV	27.1 ± 23.1 (3)
	I84V+L90M	0.3 ± 0.1 (3)	ATV	32.7 ± 7.8 (3)
	G48V+V82A+L90M	0.5 ± 0.2 (3)	ATV	31.0 ± 11.9 (3)
	G48V+V82S	0.4 ± 0.2 (3)	ATV	15.2 ± 3.2 (3)

SP1, 14-amino-acid spacer peptide 1, located between CA and nucleocapsid (NC) in HIV-1 Gag; 6TAMs, six non-polymorphic HIV-1 reverse-transcriptase mutations (M41L, D67N, K70R, L210W, T215Y and K219Q) that confer resistance to thymidine analogues. Data are geometric mean ± s.d. from three biological replicates in each of at least three independent experiments (exact *n* given in parentheses).

Extended Data Table 4 | Data collection and refinement statistics (molecular replacement)

	HIV-1 Capsid hexamer - GS-6207 complex
Data collection	
Space group	P3
Cell dimensions	
a, *b*, *c* (Å)	158.30, 158.30, 55.65
α, β, γ (°)	90, 90, 120
Resolution (Å)	30.00 - 2.00 (2.07 - 2.00) *
R_{sym} or R_{merge}	0.119 (0.795)
$I / \sigma I$	18.80 (1.94)
Completeness (%)	98.66 (90.82)
Redundancy	5.2 (4.3)
Refinement	
Resolution (Å)	29.18 - 2.00 (2.07 - 2.00)
No. reflections	105,864 (9,768)
R_{work} / R_{free}	0.2051 / 0.2492 (0.2447 / 0.2712)
No. atoms	
Protein	9,456
Ligand/ion	384
Water	896
B-factors	
Protein	30.72
Ligand/ion	25.60
Water	38.83
R.m.s. deviations	
Bond lengths (Å)	0.003
Bond angles (°)	0.570
Ramachandran statistics	
Favored (%)	99.40
Allowed (%)	0.60
Outliers (%)	0.00
Rotamer outliers	0.00

All data were collected from a single crystal. For inhibitor electron density defined by X-ray crystallography, see Supplementary Fig. 2.
*Values in parentheses are for the highest-resolution shell.

Extended Data Table 5 | Biosensor surface-plasmon-resonance assays of GS-6207 binding to recombinant CA

	Immature capsid	Mature capsid			
	Gag polyprotein	CA monomer	CA pentamer	CA hexamer	CA hexamer_M66I
K_D (pM)	1,100 ± 900	2,500 ± 500	220 ± 160	240 ± 90	60,000 ± 20,000
k_{on} ($M^{-1}s^{-1}$)	ND	ND	$2 \pm 1 \times 10^5$	$6.5 \pm 0.3 \times 10^4$	$6 \pm 4 \times 10^4$
k_{off} (s^{-1})	ND	ND	$2.7 \pm 0.4 \times 10^{-5}$	$1.4 \pm 0.4 \times 10^{-5}$	$2.6 \pm 0.3 \times 10^{-3}$

M66I is an in vitro GS-6207-selected CA binding-site mutant that confers high-level resistance to GS-6207. ND, not determined (because the binding rate was too fast to be determined reliably). Data are mean ± s.d. from four independent experiments (or three for the M66I variant), assayed in singlet.

Extended Data Table 6 | Resistance profile of HIV-1 CA mutants identified in viruses selected by GS-6207

HIV-1 CA Sequence	WT	Q67H	N74D	K70N	Q67H N74S	Q67H T107N	L56I	Q67H N74D	M66I
Mean EC_{50} (pM) in MT-2 cells *	31	196	682	741	996	1,910	7,400	34,069	>100,000
Fold GS-6207 resistance †	1	6	22	24	32	62	239	1,099	>3,226
Infectivity (% WT) in a single-cycle replication assay in MT-2 cells ‡	100	95	48	7	34	41	9	29	6
Peak replication level (% WT) in primary human $CD4^+$ T-cells infected with a replication-competent reporter HIV-1 §	100	100	1	1	69	28	3	<1	<1

*Data are mean single-cycle EC_{50} values from 3 independent experiments (n = 3 biological replicates each).

†Data are mean EC_{50} ratios of mutant to wild type, from 3 independent experiments (n = 3 biological replicates each).

‡Data are mean luminescence values expressed as a percentage of those of the wild-type virus, from 3 independent experiments (n = 3 biological replicates each).

§Data are mean luminescence values expressed as a percentage of those of the wild-type virus from 2 independent experiments (n = 6 biological replicates each).

Extended Data Table 7 | Baseline characteristics and clinical adverse events in healthy participants (that affected >1 participant overall) in study GS-US-200-4070

	GS-6207					
Baseline characteristics	**30 mg (*n* = 8)**	**100 mg (*n* = 8)**	**300 mg (*n* = 8)**	**450 mg (*n* = 8)**	**Placebo (*n* = 8)**	**Overall (*n* = 40)**
Age, years, median (range)	40 (29-43)	36 (19-42)	34 (22-41)	36 (27-42)	41 (21-44)	37 (19-44)
Sex at birth: female, n (%)	3 (38)	5 (63)	3 (38)	1 (13)	1 (13)	13 (33)
Race: black, n (%)	3 (38)	2 (25)	1 (13)	3 (38)	2 (25)	11 (28)
Body mass index, kg/m^2, median (range)	28 (23-30)	26 (21-29)	24 (23-30)	28 (23-30)	27 (21-30)	26 (21-30)
Safety: preferred term						
Any AE, n (%)	4 (50)	8 (100)	7 (88)	6 (75)	4 (50)	29 (73)
Injection site erythema	1 (13)	5 (63)	6 (75)	3 (38)	0	15 (38)
Injection site pain	0	3 (38)	6 (75)	3 (38)	2 (25)	14 (35)
Injection site nodule	0	5 (63)	3 (38)	1 (13)	0	9 (23)
Injection site induration	0	0	6 (75)	2 (25)	0	8 (20)
Injection site swelling	1 (13)	5 (63)	1 (13)	0	0	7 (18)
Headache	2 (25)	1 (13)	2 (25)	0	0	5 (13)
Injection site pruritus	1 (13)	0	1 (13)	1 (13)	0	3 (8)
Viral upper respiratory tract infection	0	0	0	2 (25)	1 (13)	3 (8)
Acne	0	0	0	2 (25)	0	2 (5)
Back pain	0	0	2 (25)	0	0	2 (5)
Dizziness	0	0	1 (13)	1 (13)	0	2 (5)
Injection site bruising	0	0	1 (13)	0	1 (13)	2 (5)
Nausea	1 (13)	0	1 (13)	0	0	2 (5)
Oropharyngeal pain	1 (13)	0	0	0	1 (13)	2 (5)
Skin mass	0	0	1 (13)	1 (13)	0	2 (5)

AE, adverse event.

Extended Data Table 8 | Baseline characteristics and clinical serious adverse events (that affected any participant) and adverse events (that affected >1 participant overall) in participants living with HIV in study GS-US-200-4072

Baseline characteristics	GS-6207 20 mg or Placebo (*n* = 8)	GS-6207 50 mg or Placebo (*n* = 8)	GS-6207 150 mg or Placebo (*n* = 8)	GS-6207 450 mg or Placebo (*n* = 8)
Age, years, median (range)	35 (23-50)	28 (19–56)	36 (24–56)	29 (20–59)
Sex at birth: female, n (%)	1 (13)	0	1 (13)	0
Race: black, n (%)	2 (25)	2 (25)	3 (38)	3 (38)
Body mass index (kg/m^2), median (range)	25 (21-38)	25 (21–28)	26 (20–34)	25 (23–29)
HIV-1 RNA, log_{10} copies ml^{-1}, median (range)	4.47 (3.86-5.01)	4.33 (4.01-4.85)	4.57 (4.15-4.92)	4.48 (4.31-4.84)
CD4 count, cells μl^{-1}, median (range)	472 (217-574)	594 (362-1009)	388 (294-800)	430 (200-968)
ARV treatment naïve, n (%)	8 (100)	6 (75)	4 (50)	7 (88)
Median duration of follow up, Days (range)*	38 (17 to 73)	129 (122 to 136)	199 (164 to 199)	122 (113 to 136)
Safety: Preferred term				
Serious AE, n (%)				
Atrial fibrillation	0	0	0	1 (13)†
Any AE, n (%)	5 (63)	6 (75)	7 (88)	6 (75)
Injection site pain	0	4 (50)	5 (63)	4 (50)
Injection site erythema	1 (13)	1 (13)	5 (63)	2 (25)
Injection site induration	0	1 (13)	4 (50)	2 (25)
Injection site nodule	0	1 (13)	1 (13)	2 (25)
Upper respiratory tract infection	0	0	0	4 (50)
Headache	1 (13)	0	1 (13)	1 (13)
Nausea	2 (25)	1 (13)	0	0
Oropharyngeal pain	1 (13)	1 (13)	0	1 (13)
Vomiting	2 (25)	1 (13)	0	0
Arthralgia	0	0	2 (25)	0
Constipation	0	1 (13)	0	1 (13)
Haemorrhoids	0	1 (13)	0	1 (13)
Nasopharyngitis	0	0	2 (25)	0
Rash	1 (13)	1 (13)	0	0
Syphilis	0	1 (13)	0	1 (13)

*All participants were administered the components of Biktarvy (bictegravir, emtricitabine, and tenofovir alafenamide) after nine days of GS-6207 monotherapy.
†One participant who received either 450 mg GS-6207 or placebo experienced a serious adverse event of atrial fibrillation on day 113, while receiving Biktarvy, after amphetamine use.

Extended Data Table 9 | Clinical pharmacokinetic parameters in healthy volunteers and participants living with HIV

	GS-6207 in Healthy Volunteers					GS-6207 in PLWH			
Parameter	**30 mg (*n* = 8)**	**100 mg (*n* = 8)**	**300 mg (*n* = 8)**	**450 mg (*n* = 8)**	**Parameter**	**20 mg (*n* = 6)**	**50 mg (*n* = 6)**	**150 mg (*n* = 6)**	**450 mg (*n* = 6)**
AUC_{inf} ($hr*ng\ ml^{-1}$)	8,700 (27.1)	27,300 (41.5)	86,100 (18.3)	108,000 (24.4)	C_{D9} ($ng\ ml^{-1}$)	2.58 (41.5)	4.40 (89.9)	12.9 (39.3)	38.2 (35.1)
AUC_{last} ($hr*ng\ ml^{-1}$)	5,500 (42.2)	23,600 (45.1)	73,100 (35.4)	97,600 (29.9)	C_{D9} / $paEC_{95}$ (mean)	0.67	1.14	3.33	9.87
AUC_{exp} (%)	17.6 (69.4)	6.78 (65.0)	5.39 (126)	3.29 (69.9)					
C_{max} ($ng\ ml^{-1}$)	3.2 (39.8)	14.7 (58.4)	47.9 (27.7)	58.4 (39.2)					
T_{max} (day)	35.0 (16.5, 38.5)	21.0 (9.50, 39.0)	31.5 (14.0, 35.0)	14.0 (6.00, 31.5)					
$T_{1/2}$ (day)	37.0 (32.8, 46.2)	31.9 (21.3, 48.2)	45.4 (26.6, 62.5)	39.7 (29.7, 48.7)					

Data are shown to three significant figures and are presented as mean (per cent coefficient of variation), except for T_{max} and $t_{1/2}$, which are median (with first and third quartiles in parentheses). PLWH, people living with HIV; C_{D9}, GS-6207 plasma concentration on day 9; C_{D9}/protein-adjusted (pa)EC_{95} = fold EC_{95} coverage on day 9.

Extended Data Table 10 | Plasma HIV-1 RNA levels and genotype in participants living with HIV (GS-US-200-4072)

GS-6207 Dose	Participant ID	Baseline (day 0) HIV-1 RNA (log_{10} copies ml^{-1})	Maximum HIV-1 RNA change through day 9 (log_{10} copies ml^{-1})	Capsid genotype (day 9) (relative to baseline sequence)
20 mg	20-1	4.84	-0.83	wild-type
	20-2	3.86	-1.58	wild-type
	20-3	4.90	-1.74	Q67Q/H
	20-4	4.19	-1.43	wild-type
	20-5	4.21	-1.33	wild-type
	20-6	4.73	-1.21	ND
50 mg	50-1	4.01	-2.39	ND
	50-2	4.81	-1.55	wild-type
	50-3	4.3	-1.61	wild-type
	50-4	4.33	-2.32	ND
	50-5	4.85	-1.16	wild-type
	50-6	4.32	-1.73	ND
150 mg	150-1	4.61	-2.06	ND
	150-2	4.55	-1.68	wild-type
	150-3	4.58	-1.86	wild-type
	150-4	4.25	-1.49	ND
	150-5	4.61	-1.87	wild-type
	150-6	4.31	-1.62	ND
450 mg	450-1	4.31	-2.32	ND
	450-2	4.38	-2.86	ND
	450-3	4.53	-2.11	ND
	450-4	4.84	-1.83	wild-type
	450-5	4.44	-1.58	wild-type
	450-6	4.62	-2.52	ND

ND, not determined owing to repeated sequence assay failures.

nature research

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Reporting Summary

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☒	☐	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	EnVision Manager 1.13.3009 was used to collect luminescence data. JEOL JEM-1230 transmission electron microscope was used to collect images of ultra-thin sectioned HIV-1 virions. SoftMax Pro 6.3.1 was used to collect CA in vitro assembly and p24 ELISA data. ImageJ 1.46 was used to collect and quantify western blot data. VnmrJ (versions 3.2A and 4.2A) and Topspin 4.0.6 and 3.5pl7 softwares were used to acquire NMR data. Thermo Scientific Xcalibur 2.0.0.0 was used to collect LC/MS data. X-ray crystallographic coordinates were collected on beamline 5.0.1 at Advanced Light Source, Berkeley, CA. Quantstudio Real-Time PCR v1.3 was used to acquire quantitative RT-PCR data BioRad Quantasoft Version 1.6.6.0320 was used to collect droplet digital PCR data. Thermo Scientific Xcalibur 4.1.50 was used to collect high-resolution mass spectrometry data.
Data analysis	GraphPad Prism 7.0 was used to represent data and for statistical analyses. SoftMax Pro 6.3.1 was used to analyze CA in vitro assembly and p24 ELISA data. ProteOn Manager 3.1.0 or Scrubber 2.0 was used to analyze surface plasmon resonance biosensor binding data. ImageJ 1.46 was used for quantification of western blots. Sequencher 4.9 was used for DNA sequence analyses. PyMOL 2.3.0 was used to analyze protein/small-molecule X-ray co-crystallography structures. MacSynergy II version 1.0 was used to analyze synergy/antagonism of in vitro drug combinations. Phoenix WinNonlin 6.4 was used for noncompartmental analyses of pharmacokinetic (PK) parameters. MestReNova 11.0.4-18998 was used to analyze NMR data. Waters Empower 3 version FR3 was used to analyze HPLC data. Thermo Scientific Xcalibur 2.0.0.0 and 4.1.50 was used to analyze LC/MS and high-resolution mass spectrometry data, respectively.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

All data to understand and assess the conclusions of this research are available in the main text and Supplementary Information. Raw gel source data for Fig. 2f is available in Supplementary Figure 1. Small molecule X-ray crystallographic coordinates and structure factor files have been deposited in the Protein Data Bank (PDB, www.rcsb.org) with accession number 6V2F. Study GS-US-200-4072 was registered with ClinicalTrials.gov, NCT03739866. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Field-specific reporting

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☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No samples size calculation was performed. Sample sizes were chosen to provide a minimum of two independent samples in each of a minimum of 3 independent experiments in order to generate a convincing and reproducible result. If after doing so, the data did not produce convincing and reliable results with reasonably low standard deviations, additional experiments were performed to better assess the reproducibility of the phenotype under investigation. Exceptions were the virus-based electron microscopy experiment, which was performed twice. To ensure a reliable result in this instance, we analyzed >500 virions across multiple independent image fields at two different magnifications to rigorously assess the effect of each treatment on HIV-1 virion morphology. Results from those studies were quantified in a blinded fashion over 16 representative images to evaluate their statistical significance and to ensure the data presented were truly representative. The time-of-addition studies involved two independent experiments, each using 8 replicate cell cultures for each condition and time point, and produced similar results. The quantitative PCR studies used triplicate cell cultures for each of 3 time points in each of two independent experiments and produced similar results. The determination of peak replication level for wild-type and CA mutant HIV-1 variants involved two independent experiments, each using 6 replicate cell cultures originating from a mixture of CD4+ T cells isolated from 4 independent PBMC donors, and produced similar results. The dose-escalation drug resistance selection with GS-6207 was performed once using two replicate cell cultures and produced similar results. No sample size calculation was performed for clinical Study GS-US-200-4070. The sample size in this study is determined based on practical considerations and past experience with similar types of studies. A sample size of 40 subjects across 4 cohorts (10 subjects per cohort, including 8 active and 2 placebo) will provide a suitable assessment of the descriptive PK and safety profile. For clinical Study GS-US-200-4072, a sample size of 6 subjects in each of 4 GS-6207 dose groups and a total of 8 subjects in the placebo group will provide 99% power to detect a treatment difference of 2.79 log10 copies/mL in maximum reduction of HIV-1 RNA between at least one of the GS-6207 dose groups and the placebo group. In this power analysis, it is assumed that a common standard deviation for maximum reduction in HIV-1 RNA is 0.526 log10 copies/mL (based on Study GS-US-141-1219) and a 2-sided t-test is conducted at an alpha level of 0.05.
Data exclusions	No data sets were excluded.
Replication	The majority of in vitro experiments were repeated at least three times to ensure reproducibility. All attempts at replication were successful. For clinical trial studies, the analyses were performed on individual trial participants. Experiments did not include replicates as all participants and data points are unique.
Randomization	Not relevant to any of the in vitro studies as samples and corresponding controls were always processed at the same time. For each group in clinical studies GS-US-200-4070 and GS-US-200-4072, trial participants were randomized in a 4:1 and 3:1 ratio within each cohort, respectively, to receive either the drug (GS-6207) or placebo (vehicle alone).
Blinding	No blinding was done for any of the in vitro studies, except for each of the two studies evaluating the effect of drug treatment on capsid morphology. In both of these instances, virus-based electron microscopy images were collected in a blinded fashion by one individual at an external organization (Gladstone Institute) and then the associated virion phenotypes within each image (normal, abnormal, and immature) were scored and quantified in a blinded fashion by a research colleague. All other in vitro studies were conducted in an unblinded manner and instead were repeated multiple times each with multiple independent biological replicates to ensure reproducibility and, if appropriate, evaluate statistical significance of any observed phenotypes. Both clinical studies were double-blinded and placebo-controlled.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

Anti-HIV-1-p24 mouse monoclonal antibody (Thermo Fisher Scientific, Cat # MA1-71516, clone N17_05-004, Lot # SH2424811, 1:1000 dilution) was used for Western blot analysis.
Anti-alpha-tubulin rabbit monoclonal antibody (Cell Signaling Technology, Cat # 2125S, clone 11H10, lot # 11, 1:2000 dilution) was used for Western blot analysis.
HRP-conjugated goat anti-rabbit polyclonal antibody (Thermo Fisher Scientific, Cat # 31460, lot # SA245916, 1:5000 dilution) was used for Western blot analysis.
HRP-conjugated goat anti-mouse polyclonal antibody (Thermo Fisher Scientific, Cat # 31430, lot # RK244131, 1:5000 dilution) was used for Western blot analysis.

Validation

All antibodies were validated by manufacturers and in previous publications.

HIV1 p24 Monoclonal Antibody (N17 (05-004)) from Thermo Fisher Scientific is a mouse monoclonal antibody generated using recombinant p24 protein of HIV-1 B-subtype consensus purified from E. coli as the immunogen. It reacts with HIV-1 and has been shown to work in applications such as ELISA (1:10,000) and Western Blot (1:1,000). This antibody reacts with HIV-1 p24 subtypes B, C and A, and has been mapped to the C-terminus, aa 165- 231, which are well outside all of the N-terminal capsid mutations assessed in this new report. The manufacturer shows that this antibody detects recombinant HIV-1 Gag (Han-2 subtype) by Western blot analysis. Our data presented here also confirm this antibody does not cross-react with host cell proteins in mock-transfected samples.

α-Tubulin (11H10) Rabbit mAb #2125 from Cell Signaling Technology is a rabbit monoclonal antibody generated using a synthetic peptide corresponding to the amino terminus of human α-tubulin protein as the immunogen. It has been validated for Western blot applications (1:1,000 dilution) and the manufacturer shows that it detects endogenous levels of total α-tubulin protein and does not cross-react with recombinant β-tubulin. It shows reactivity with Human, Mouse, Rat, Monkey, D. melanogaster, Zebrafish, Bovine, and Pig and is predicted to react with Dog based on 100% sequence homology. There are currently 17 citations using this antibody for Western blot analysis again human α-Tubulin.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

MT-2 and MT-4 cell lines were obtained from the NIH AIDS Reagent Program.
HEK293T cells were obtained from the Gladstone Institute for Virology and Immunology. Huh-7 cells were obtained from ReBLikon GmbH. HepG2, PC-3, and MRC-5 cell lines were obtained from the American Type Culture Collection.

Authentication

No authentication.

Mycoplasma contamination

All cell lines were tested and judged free of mycoplasma contamination using a commercial kit.

Commonly misidentified lines
(See ICLAC register)

None of the cell lines used are commonly misidentified cell lines.

Human research participants

Policy information about studies involving human research participants

Population characteristics

Leucopacks were purchased from AllCells (Alameda, CA, USA). Donors underwent a screening process at three month intervals and attributes, such as age, sex, HLA typing, and medical history, were captured during each screening. Screening is done for viral status, CBC, changes in health status (illness, medication use). Donors utilized herein included both genders, ranged in age from 18 - 50, and most importantly for the sake of the studies described herein, all were negative for HIV-1, hepatitis B virus, and hepatitis C virus infections. All donors were obtained from the Alameda California location and were deemed medication-free

(i.e., no over the counter, prescription, birth control, steroid drugs, or vitamins/supplements used for the 2 days prior to sample collection) to avoid any confounding effects due to unforeseen drug-drug interactions.

For clinical Study GS-US-200-4070, we enrolled HIV-1-uninfected healthy men and women, 18-45 years of age.
For clinical Study GS-US-200-4072 (registered with ClinicalTrials.gov, NCT03739866), we enrolled treatment-naive or -experienced, but HIV capsid inhibitor naïve and integrase strand transfer inhibitor naïve, men or nonpregnant, nonlactating women, 18–65 years of age with plasma HIV-1 RNA levels ≥ 10,000 copies/ml but ≤ 400,000 copies/ml and CD4+ T cell counts > 200 cells/mm3.

Recruitment

For clinical Study GS-US-200-4070, eligible HIV-1-uninfected healthy men and nonpregnant, nonlacting women, 18-45 years of age, negative for HIV-1 and HCV antibodies and HBV surface antigen, were enrolled in the study sequentially. As this study enrolled from a single site (Quotient Sciences - Miami LLC) in Florida, the study participants were mostly young and healthy people who were willing to participate in clinical trials from the Miami metropolitan area. For example, the study participants were mostly Hispanic or Latino males in their 30s.

For clinical Study GS-US-200-4072, eligible viremic participants were pre-screened for sensitivity to BIC/FTC/TAF. Participants harboring sensitive viruses were enrolled in the study sequentially. As this study enrolled mostly treatment naive people, the study population reflected the current HIV epidemic in the US. For example, the study participants were mostly non-Hispanic (or Latino) White or Black males in their 30's.

We acknowledge there is a potential for bias for both studies. However, we believe that the data generated from both studies are valid and sufficient to support further clinical development of GS-6207, where we will evaluate GS-6207 in a larger and more diverse population.

Ethics oversight

The leukopack collection protocols and donor informed consent were approved by an Institutional Review Board (IRB) at AllCells, with strict oversight. HIPAA compliance and approved protocols are also followed. Donors are screened and tissues are collected in accordance with GMP, FDA, CFR 21CFR1271 and EU directives 2004/23/EC and 2006/17/EC.

The clinical trials were conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonisation and in accordance with the ethical principles underlying the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). The protocol and the subject informed consent form received institutional review board/independent ethics committee approval/favorable opinion (Advarra, Columbia, MD) before initiation of the study. Freely given written informed consent was obtained from every subject before participation in the clinical studies.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration

NCT03739866 (GS-US-200-4072).
GS-US-200-4070 is not registered with ClinicalTrials.gov, as it is a Phase 1 study, where the primary goal is to determine the antiviral activity and pharmacokinetics of GS-6207.

Study protocol

The full protocol for Study GS-US-200-4072 is not publicly available, because it is not a Phase 2 or 3 studies, but a Phase 1 study, where the primary goal is to determine the antiviral activity and pharmacokinetics of GS-6207. As Phase 1 studies, CONSORT checklist is not needed per Nature Research policy information about clinical studies.

Data collection

Participants for Study GS-US-200-4070 were enrolled from a single site in the United States: Quotient Sciences (Miami, FL), which specializes in Phase 1 studies in healthy volunteers. First participant was enrolled on 16 February 2018, and the last one on 12 July 2018. Last participant last observation was on 21 February 2019. Database finalization occurred on 24 May 2019, and treatment unblinding on 06 June 2019.

Participants for Study GS-US-200-4072 were enrolled across 5 clinical sites within the United States, which are clinics where people living with HIV are diagnosed, treated, and followed: the Ruane Clinical Research Group, Inc. (Los Angeles, CA), the Lundquist Institute for BioMedical Innovation at Harbor-UCLA Medical Center (Torrance, CA), AIDS Arms, Inc., DBA Prism Health North Texas (Dallas, TX), North Texas Infectious Diseases Consultants (Dallas, TX), Tarrant County Infectious Disease Associates (Fort Worth, TX), and the Crofoot Research Center, Inc. (Houston, TX). The first participant for the 20-450 mg cohorts was enrolled on 08 January 2019, and the last one on 09 July 2019. The last participant, last observation for these cohorts is projected to be on 18 February 2020. Database finalization is projected to occur on 21 August 2020. This study is still blinded and ongoing.

Outcomes

For Study GS-US-200-4070, the primary and secondary outcome measures were pre-defined as per the usual first-in-human study in healthy volunteers. The outcome measures were assessed using conventional methods as follows:
-Primary outcome measures: safety and pharmacokinetics (AUCinf, AUClast, %AUCexp, Cmax, Tmax, Clast, Tlast, lambda z, CL/F, t1/2, and Vz/F).
-Secondary outcome measures: none

For Study GS-US-200-4072, the primary and secondary outcome measures were pre-defined as per the usual proof-of-concept study in people living with HIV. The outcome measures were assessed using conventional methods as follows.
-Primary outcome measures: maximum reduction of plasma HIV-1 RNA (log10 copies/mL) from Day 1 through Day 10
-Secondary outcome measures: safety and pharmacokinetics (AUC0-t, AUCinf, AUClast, CL/F, t1/2, lambda z, Vz/F, Cmax, Tmax, Clast, CD10, Tlast)

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Prodrug and conjugate drug delivery strategies for improving HIV/AIDS therapy

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Despite the wide variety of highly potent anti-HIV drugs that have been developed and made available in clinical practice over the years, eradication of HIV infection has not been achieved. Currently, HIV infection and AIDS are thought to be chronically treatable. HIV attacks host immune cells namely macrophages and CD4⁺T-cells and sequesters itself into sanctuary and reservoir sites such as the lymphoid tissues, testes, and brain. Initial drug delivery efforts with prodrugs and drug conjugates focused on improving the physicochemical (i.e. solubility), biopharmaceutic (i.e. absorption, metabolism), and pharmacokinetic (i.e. blood concentrations) properties of the parent drugs. Eradicating HIV, however, will require advanced drug delivery approaches in order to access and maintain effective drug concentrations for prolonged periods of time in sanctuary sites. The current review discusses prodrug/conjugate efforts, clinical successes and describes drug delivery challenges and approaches for eradicating HIV infection.

Key words: Anti-viral – Conjugate – Fosamprenavir – HIV – Nanocarrier – Prodrug – Targeted drug delivery – Tenofovir disoproxil fumarate.

Since the first report in 1981, more than 67 million persons have been infected with HIV, and more than 27 million have died of AIDS [1, 2]. More than 40% of new infections worldwide occur among adults in the age range of 15-24 years [3]. In fact, AIDS is now the leading cause of premature death among people 15 to 59 years of age. HIV/AIDS remains both a medical and economic challenge in developing countries especially in Sub-Saharan Africa [4]. Unfortunately, after nearly 30 years of research there are still three compelling facts driving the development of new anti-AIDS drugs and delivery systems: i) there is a lack of an effective vaccine or prophylactic agent that would provide protection for the foreseeable future, ii) there is a constant need for both less expensive and more tolerable drug therapies, and iii) the development of resistant viral strains in treatment-experienced patients continue [5]. The late Dr. Paul Janssen described four ideal characteristics of a novel anti-HIV drug. The drug must possess: i) high antiviral activity against both wild-type and mutant virus, thus a drug must be effective despite the genetic flexibility of the virus and it must anticipate resistant strains that may develop once therapy is initiated, ii) high oral bioavailability and a long elimination half-life to allow for once daily dosing, which is considered the gold standard of any therapy, iii) have minimal adverse effects, which will ultimately impact patient compliance, and iv) be easy to synthesize and formulate into dosage forms, which ultimately impact the cost of the drug for both the manufacturer and the patient [6]. However, the development of drugs that meet these criteria is an arduous task. Those drugs that fall short of any of the criterion could benefit from drug delivery strategies, specifically conjugate and prodrug design to improve upon less desirable drug characteristics.

Current anti-HIV drugs include the twenty-four approved agents listed in *Table I*. These drugs are prescribed as part of a multiple drug regimen known as highly active antiretroviral therapy (HAART). Even though current anti-HIV drugs are effective in suppressing viral titers in infected individuals, a cure for HIV infection remains elusive. This is due to several reasons that include poor pharmacokinetics, frequent adverse drug reactions, and the lack of patient adherence to complicated drug administration regimens. Treatment compliance is critical regardless of whether a patient is treatment-naïve or treatment-experienced since poor patient compliance is often a factor in treatment failure and viral rebound. Unfortunately, once first-line drugs fail, second-line drugs are not very effective since they have less than ideal dosing parameters, which can further burden the patient [5, 7].

Recently anti-AIDS therapeutic development efforts have been focusing on improving drug delivery and not just on discovering new chemical entities. Initial efforts using traditional prodrug strategies have had some success resulting in two new important prodrugs, fosamprenavir and tenofovir disoproxil fumarate. These prodrugs demonstrated improved intestinal absorption by increasing water solubility and lipophilicity for fosamprenavir and tenofovir disoproxil fumarate, respectively, resulting in improved clinical efficacy over other HAART drugs [8, 9]. However, traditional prodrugs still face the same challenges as conventional anti-AIDS drugs once the prodrug is absorbed in the intestine (i.e. they are rapidly eliminated or have limited tissue distribution). Efforts to prolong the elimination half-life of anti-AIDS drugs (e.g. by PEGylation) are not expected to be successful in AIDS therapy due to the limited biodistribution of macromolecules to sanctuary sites where infected cells such as macrophages reside (e.g. the brain or lymph). Therefore, novel drug delivery concepts will be required in order to eradicate HIV infection.

In the following review, a brief overview of the molecular and cellular targets that have been identified as points of drug intervention to curtail HIV infection is presented. Prodrug strategies as well as a detailed treatment of two clinically successful prodrug examples (fosamprenavir and tenofovir disoproxil fumarate) are also described. Finally, a detailed discussion of the challenges facing targeted drug delivery for eradicating HIV infection is presented.

I. BACKGROUND

1. Viral life cycle and potential cell surface targets for drug delivery

HIV is a retrovirus, whose mechanism of action involves directly integrating viral DNA into the host cells' DNA by means of several

Table I - FDA approved drugs in HIV therapy (drugs with abbreviations are referred to as such in the article).

Drug	Brand name	Manufacturer
Nucleoside reverse transcriptase inhibitors (NRTIs)		
Zidovudine (AZT)	Retrovir	GlaxoSmithKline
Didanosine (ddI)	Videx	Bristol Myers-Squibb
Zalcitabine (ddC)	Hivid	Hoffmann-La Roche
Stavudine (d4T)	Zerit	Bristol Myers-Squibb
Lamivudine (3TC)	Epivir and Zeffix	GlaxoSmithKline
Abacavir sulfate (ABC)	Ziagen	GlaxoSmithKline
Emtricitabine (FTC)	Emtriva	Gilead Sciences, Inc.
Nucleotide reverse transcriptase inhibitors (NtRTIs)		
Tenofovir disoproxil fumarate	Viread	Gilead Sciences, Inc.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Nevirapine (NVP)	Viramune	Boehringer Ingelheim
Delavirdine (DLV)	Rescriptor	Pfizer
Efavirenz (EFV)	Sustiva and Stocrin	Bristol Myers-Squibb
Entavirine (TMC125)	Intelence	Tibotec, Inc.
Protease inhibitors (PIs)		
Saquinavir mesylate (SQV)	Invirase and Fortovase	Hoffmann-La Roche
Ritonavir	Norvir	Abott Laboratories
Indinavir (IND)	Crixivan	Merck & Co., Inc.
Nelfinavir mesylate (NFV)	Viracept	Agouron Phramaceuticals
Amprenavir	Agenerase and Prozei	GlaxoSmithKline
Fosamprenavir calcium (Prodrug of amprenavir)	Lexiva and Telzir	GlaxoSmithKline
Atazanavir sulfate	Reyataz	Bristol Myers-Squibb
Lopinavir and ritonavir	Kaletra	Abott Laboratories
Tipranavir	Aptivus	Boehringer Ingelheim
Darunavir	Prezista	Tibotec, Inc.
Entry and fusion inhibitors		
Maraviroc	Salzentry	Pfizer
Enfuvirtide	Fuzeon	Hoffmann-La Roche, Trimeris
Integrase inhibitors		
Raltegravir	Isentress	Merck & Co., Inc.

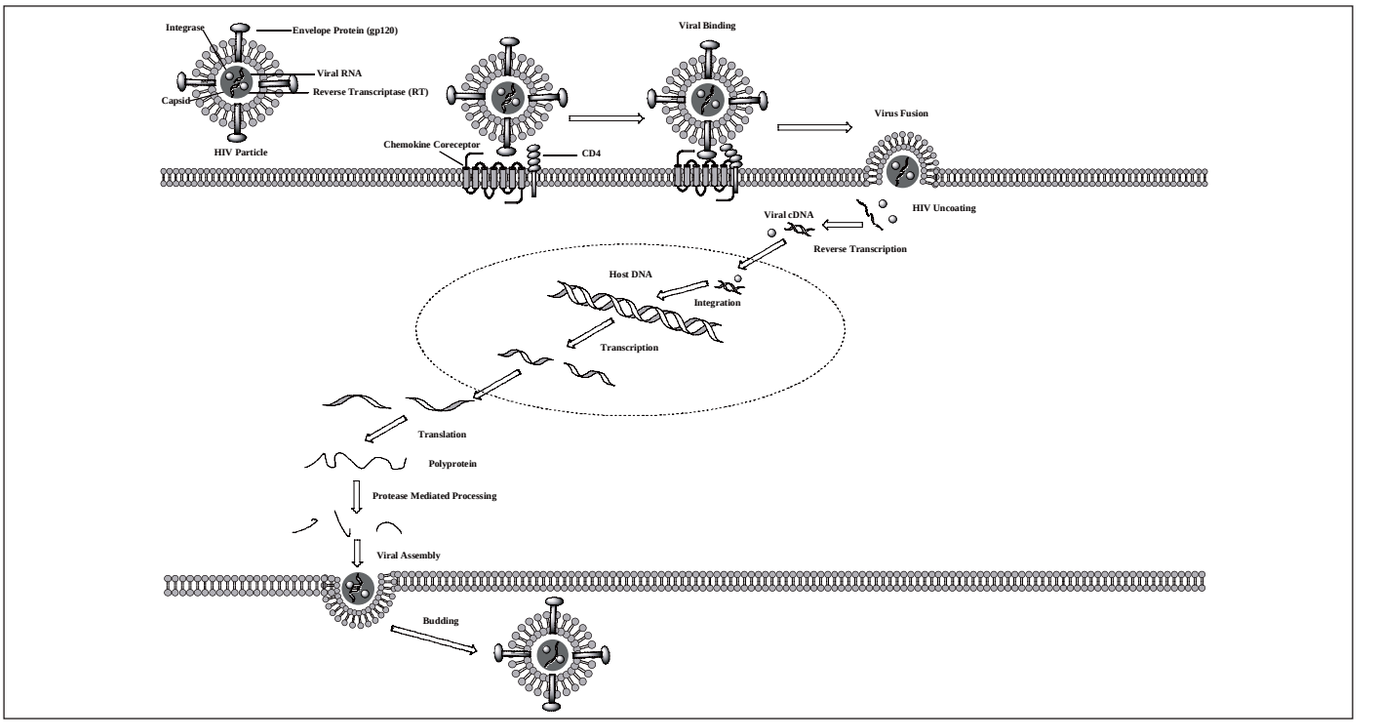

Figure 1 - HIV life cycle. The viral stages include surface adsorption, binding to the cell surface receptors (CD4 and a chemokine coreceptor), fusion of the viral envelope to the cell membrane, capsid uncoating, reverse transcription, nuclear translocation of viral cDNA and integrase, integration of the viral cDNA into the host genome, transcription, translation, protease mediated cleavage, and viral assembly and budding (redrawn from [10] and [15]).

critical steps, upon which it is replicated to produce a new progeny of virus particles (*Figure 1*). HIV adsorption to the cell surface is the first step of infection. This process hinges on the interaction of the negatively charged heparan sulfate molecules on the cell surface with the positively charged viral glycoprotein (gp120) [10].

Once HIV adsorbs to the cell surface, it then binds to the CD4 receptor and a coreceptor, either CXCR4 or CCR5 via gp120 [10]. This interaction stabilizes the virus to the cell surface so that viral-cellular fusion may take place in the subsequent stages of the life cycle. Whether the virus interacts with CXCR4 or CCR5 of $CD4^+$ cells depends upon the protein sequence of the V3 loop of gp120. Therefore, HIV is characterized as X4 tropic, R5 tropic, or dual tropic (X4R5) corresponding to the coreceptor(s) to which it binds [11]. CXCR4 and CCR5 belong to the class of receptors known as chemokine receptors. The chemokine receptors are members of the G protein coupled receptor super family, whose diverse physiological roles include host defense by chemotaxis to sites of inflammation, tumor genesis and metastasis, and embryologic development (for a review see [12]). The endogenous ligands for the chemokine receptors that act as HIV coreceptors are stromal-cell-derived factor 1 (SDF-1) for CXCR4 and regulated upon activation, normal T-cell expressed and secreted (RANTES) and macrophage inflammatory proteins 1α (MIP-1α) and 1β (MIP-1β) for CCR5 [10, 13]. All of these ligands have been shown to possess, to some extent, anti-HIV activity *in vitro* [13, 14].

Following the binding of the virus to CD4 and its coreceptor, a conformational change occurs that allows gp41 to insert itself into the plasma membrane of the cell and begins the process of fusing the viral particle's envelope to the cell [15]. Upon fusion of the viral envelope with the cell membrane, the virus undergoes a process consisting of uncoating its contents within the capsid matrix into the cytosol of the infected cell. These contents include the viral RNA and the viral proteins reverse transcriptase (RT) and integrase. Reverse transcriptase converts the viral RNA into viral cDNA by utilizing the viral RNA as a template for incorporating endogenous nucleotides to elongate the cDNA [10, 16]. After reverse transcription in the cytosol, viral cDNA translocates to the nucleus and is incorporated into the host genome, this process is done by the viral protein integrase. Within each viral particle approximately 40-100 copies of integrase are released into the host cell upon viral fusion and uncoating (for a review see [17]). Viral DNA integration is a critical step in the viral life cycle, because after integration infected cells may be able to enter a period of latency, a phenomenon that will be discussed later.

New copies of viral RNA are produced as a result of host genome transcription. The proteins necessary for the assembly of virus progeny are produced in the cytosol via the translation process. This produces the Gag-Pol protein, a precursor to the other viral proteins. Gag-Pol is self-cleaved upon the folding and dimerization of the protease domain to form the active site of viral protease, thus liberating the enzyme from the Gag-Pol protein [18]. HIV protease is an aspartic-protease whose subsequent enzymatic activity upon the Gag and Gag-Pol proteins forms the components necessary for viral assembly including the structural capsid proteins and functional proteins reverse transcriptase and integrase [16, 18].

2. Eradication of HIV: target cells for therapeutic intervention

HIV infects cells that express CD4 and one of the coreceptors (i.e. CXCR4, CCR5). However these cell types, macrophages, $CD4^+$ T-cells, and follicular dendritic cells (FDCs) occupy physiological spaces that are difficult to penetrate with drugs. Furthermore, cells that are infected can enter varying stages of latency aiding in viral persistence. Latency of the virus occurs when the viral DNA has been integrated into the host genome, but no active transcription occurs [19]. This presents a difficult challenge to eradicating HIV infection since the virus can remain dormant in cells with extended life-cycles and dormant virus cannot be killed by nearly any of currently used drugs.

$CD4^+$ T-cells have been identified as the major contributing cell type in viral replication. Nearly 99% of all viral replication occurs in activated and productively infected $CD4^+$ T-cells of the blood and lymphoid tissues [19]. HIV has been shown to infect several subsets of T-cells, including Th-17 cells, which secrete IL-17. Th-17 cells exist constitutively in the lamina propria of the gut and are responsible for host defense against bacterial infections in the gut [20]. The vast majority of these cells become rapidly depleted during the initial infection, leaving the gut vulnerable to bacterial infections, which results in increased activation of additional T-cells that may further assist in exposing an increased population of susceptible cells to HIV [21]. Other subsets of $CD4^+$ T-cells are responsible for viral latency *in vivo*, including resting memory (CD45RO) T-cells and resting naïve (CD45RA) T-cells [19].

Macrophages and cells derived from that lineage are the other major cellular target of HIV. These cell types have longer cellular turnover (approximately 2 weeks), which contributes to the persistence of HIV. Macrophages are harbored in various organs colonizing the bone marrow, liver, thymus, spleen, lymph nodes, gut, mucosal associated lymphoid tissue, brain, lungs, and kidney. They have been implicated in carrying HIV across the blood brain barrier and establishing and maintaining HIV infection in the central nervous system (CNS) [22]. Because of their distribution to numerous organ systems, macrophages are pharmacologically difficult to reach [23, 24]. Macrophages, unlike T-cells have the ability to continually produce HIV particles with little threat of cell lysis due to viral production. Therefore, they are believed to be responsible for the secondary phase of viral decay in HAART patients and are generally believed to be an important HIV sanctuary [24, 25]. Although macrophages are not responsible for the majority of the viral production *in vivo*, the proportion of infected macrophages within tissues can reach up to 50% depending on the tissue in which they reside. Their physiological proximity to the other cell types involved in HIV infection compound their importance in viral infection (for a review see [26]). For these reasons macrophages play a critical role in HIV persistence.

FDCs are unable to produce HIV particles through replication, however they play a significant role in viral storage *in vivo*. FDCs have the ability to pool HIV and protect it from immune defenses. FDCs are able to preserve HIV infectivity even in the presence of antibodies produced by the host to neutralize the virus [27]. Also FDCs contribute to the expansion of HIV infection by migrating toward T-cells and presenting those cells with the viral particles [27]. Therefore, FDCs are a unique cellular target that has yet to be addressed by HAART approved drugs.

A model of the effect of HAART on HIV load decay in patients revealed that decreasing viral load occurs in three distinct phases: i) a rapid exponential decrease in viral load upon initiation of pharmacotherapy resulting in viral half lives of less than 6 h and virus producing cells' half lives of approximately one day, ii) after several weeks of therapy, a decrease in the viral decay occurs with a half life of approximately two weeks, which corresponds to the slower turnover of specific cell populations such as macrophages, and iii) the final phase includes the time from non-detectable plasma levels to the elimination of virus in latently infected cells. This phase has a dramatically slower decay rate of virus of approximately 44 months, which if the population of the latently infected cells were 1.0×10^5 cells would result in viral eradication after sixty years of therapy. This reflects the inefficiency of the available pharmacotherapy in addressing viral latency and persistence in $CD4^+$ T-cells [28].

3. Physiological barriers

If the ability to generate drug concentrations within the specific cell types did not present a great enough challenge, many physiological

barriers stand in the way of drug accumulation within both latently and actively infected cells. The lymphoid tissues, brain, and testes act as HIV reservoirs or sanctuary sites since most of these drugs do not persist in these tissues at effective concentration for adequate periods of time. Each of these physiological locations poses a unique hurdle in the delivery of effective drug concentrations.

Lymphoid tissues such as the peripheral secondary lymphoid organs, the spleen, lymph nodes, and gut-associated lymphoid tissue (GALT) are the primary sites of HIV infection [24]. It is estimated that only 2% of lymphocytes are in the general circulation at any one time and the remainder are distributed among the lymphoid tissues [24]. Often the lymphoid tissues have a greater extent of infection than the peripheral blood and specifically the GALT is home to large numbers of activated T-cells, which propagate the infection [24]. For example, a few weeks after the initial infection with simian immunodeficiency virus (SIV) (a model of HIV), there is a dramatic increase in infected $CD4^+$ T-cells in the GALT, spleen, and lymph nodes before the virus has even reached the CNS or other accessory sites of infection [23]. Also the primary lymphoid tissues, bone marrow and thymus, are said to be reservoir sites, however the extent of T-cell infection for these sites remains unknown [24]. Despite the uncertainty of the pervasiveness of the infection, the lymphoid tissue reservoir develops quickly and persists throughout the course of infection and remains the primary site of HIV production regardless of the effectiveness of HAART to diminish viral RNA levels to undetectable levels [23].

The blood-brain barrier (BBB) remains one of the most difficult physiological sites to penetrate with pharmacological agents. The barrier itself consists of brain capillary endothelial cells that are densely packed via tight junctions that prevent both endogenous substances and xenobiotics from penetrating the brain and CNS [29]. For HIV specifically, the microglial cells of the CNS are one of the main sanctuary sites of the virus, however very few antiviral drugs have the ability to enter the brain particularly AZT, 3TC, and the protease inhibitors [30, 31]. HIV infection within the CNS has led to the development of HIV associated dementia and other neurological disorders. Therefore, HIV in the brain remains unaffected by drugs that are otherwise effective at suppressing the viral replication in the rest of the body.

Besides the lack of direct penetration of drugs as a result of their charge or lipophilicity (permeability), drugs are also subjected to efflux by drug transporters like P-glycoprotein (Pgp, ABC1), that are expressed by astrocytes at the BBB [29]. Several HIV drugs have been shown to act as substrates for these efflux transporters including the protease inhibitors, ritonavir and SQV, as well as the NRTIs like AZT [29, 32]. A few methods for improving BBB include the modulation of the efflux transporters and/or utilizing drug delivery vehicles that may be conjugated to a ligand that can facilitate BBB penetration [29]. Glucose is one example of an endogenous substance that undergoes carrier-mediated transport across the BBB, whereas peptides like insulin and transferrin pass the BBB via receptor mediated transport [29]. However, in order for conjugation to become successful, a specific BBB receptor must be identified and manipulated for the translocation of a drug into the CNS. Another possibility is to utilize a cell-penetrating peptide (CPP) also known as protein transduction domains to cross the BBB [29]. This class of peptides has been shown to have the ability to act as carrier proteins for drug cargoes and remains a topic of great interest (for reviews see [33, 34]).

Other sanctuary sites include the testes of HIV infected patients. This tissue barrier limits the penetration of drugs due to its reduced vascularization. Replication-competent virus has been found in the seminal cells of men who have been receiving antiviral therapy [19]. The Sertoli cells of the testes form tight junctions with each other creating a physical barrier known as the blood-testis barrier (BTB). The presence of Pgp transporters at the BTB makes it in some ways similar to that of the BBB. The BTB also is home to HIV susceptible immune cells namely macrophages and $CD4^+$ T-cells. Drug penetration into the testes is drug dependent, d4T shows poor penetration, whereas AZT and 3TC show efficient accumulation in the seminal plasma [35]. However, the protease inhibitors and NNRTIs concentrations are generally lower in the seminal plasma compared to blood plasma [35]. Despite the variable penetration of HAART into the BTB, it is important to note that the male reproductive organ is a route of viral transmission between individuals, so elimination of the virus from this sanctuary site is not only beneficial for the infected individual, but for susceptible individuals as well [35].

II. PRODRUG AND CONJUGATE STRATEGIES

There is incredible potential for improving anti-HIV therapy not only by increasing the potency of antiviral drugs, but also by reducing the burden of the dosing regimen. This can be achieved by modifying the physicochemical, biopharmaceutic, and pharmacokinetic properties of drugs through the development of prodrugs. Traditional prodrugs, which only include about 5-7% of marketed drugs, are classified as drugs that are activated by undergoing transformation *in vivo* to form the active drug [8]. Reasons for prodrug development are poor aqueous solubility, chemical instability, low oral bioavailability, lack of BBB penetration, and high first pass metabolism associated with the parent drug [8]. There has been limited prodrug development in HIV HAART despite the fact that most of the antiviral drugs developed thus far suffer from one or more of the above-mentioned limitations. Currently, only two traditional prodrugs have been developed in HIV therapy, fosamprenavir and tenofovir disoproxil fumarate. Although the NTRIs, like AZT, are metabolized intracellularly to their active phosphorylated forms, they are often regarded as active metabolites as opposed to prodrugs that are catabolized enzymatically to their active parent drug in classical prodrugs. Both fosamprenavir and tenofovir disoproxil fumarate improve the drug delivery capabilities of their parent drug by increasing intestinal absorption. A more recent trend in prodrug design has extended the prodrug platform to encompass drug delivery systems with targeting agents and releasable drugs (for a review on prodrug design strategies see [8]).

Improved therapy can be achieved using conjugation chemistry approaches for developing multicomponent and multifunctional drug delivery systems. These systems can incorporate either active or passive targeting moieties to improve distribution to the sanctuary sites in the body, for example to the lymphatics, where the majority of the viral replication and infection exists. Targeted drug delivery to macrophages and T-cells would not only improve the efficacy of antiviral drugs, but would potentially also limit the development of toxicities/adverse effects often associated with the presence of drugs in non-infected cells. Another potential auxiliary benefit of targeted drug delivery is the reduction of HIV resistance by increasing uptake into HIV infected cells. Along the same line of thinking, by accumulating drug into either those cells latently infected or not yet infected, the drug can be within the cell and interfere with early viral life cycle stages upon infection or disrupt virus replication when transitioning from a latent to active state.

1. Prodrugs

1.1. Fosamprenavir

Fosamprenavir (*Figure 2*) is a water-soluble, phosphate ester prodrug of the protease inhibitor drug amprenavir [36-38]. The FDA approved it for the treatment of HIV-1 protease inhibitor-naive patients in 2003 and the EMEA approved it in 2004. The drug is formulated either as a suspension or as a tablet in a dosing regimen of fosamprenavir 1400 mg twice a day or fosamprenavir 700 mg twice a day plus ritonavir 100 mg twice a day for treatment-experienced patients [37, 38].

Amprenavir, the active metabolite of fosamprenavir, is a protease inhibitor with demonstrated antiviral efficacy and good tolerability when used in combination with other antiretroviral agents. Fosampre-

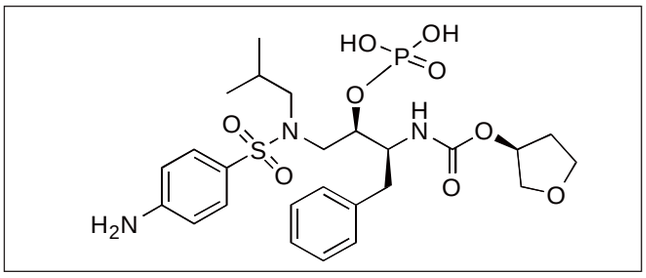

Figure 2 - Structure of fosamprenavir. IUPAC name is [(2R,3S)-1-[(4-aminophenyl)sulfonyl-(2-methylpropyl)amino]-3-{[(3S)-oxolan-3-yl] oxycarbonylamino}-4-phenyl-butan-2-yl]oxyphosphonic acid.

navir has no antiviral activity *in vitro* and any activity detected after administration is due to the presence of amprenavir [37, 39].

The oral bioavailability of amprenavir varies from 35-90% due to its low water solubility (~0.04 mg/mL) [37]. A large percentage of organic excipients were included in the original formulation to aid its dissolution, necessitating a high capsule burden (10/day with ritonavir, 16/day when used alone) [37]. The development of the prodrug, fosamprenavir, greatly enhanced the water solubility of the drug (by ~10 fold) by the addition of the phosphate group to the hydroxyl group, thus reducing the high dosage form burden [8, 37].

Because of fosamprenavir increased water solubility, it has poor membrane permeability and is rapidly converted to amprenavir after oral administration [38, 40]. Preclinical studies have demonstrated that fosamprenavir is converted almost entirely (99%) to amprenavir at or near the intestinal epithelium by alkaline phosphatase, the primary enzyme responsible for conversion (*Figure 3*) [41]. Less than 1% of the prodrug dose was detected in the portal vein of animals confirming nearly complete presystemic conversion. This observation has been further supported by measurement of plasma concentrations of fosamprenavir and amprenavir in clinical studies [42].

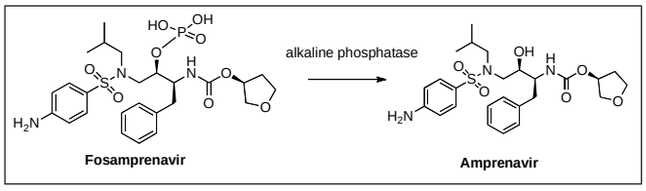

Figure 3 - Metabolic conversion of fosamprenavir to amprenavir by alkaline phosphatase in the intestinal lumen.

As a result of rapid conversion of fosamprenavir in the intestine to the parent drug, amprenavir is predominantly absorbed in the intestine, however it is also a substrate for P-glycoprotein (P-gp), which may play a certain role too in its absorption [38, 43]. Following administration of prodrug, the drug is rapidly absorbed as indicated by plasma drug concentrations that are measurable as early as 15 minutes post dosing, with maximum plasma concentrations occurring at 1.5-2.5 h following single and repeat dose administration [42]. Despite its rapid absorption, a secondary absorption phase appears to take place in the terminal ileum as evident from second peak in the plasma concentration curve at 10-12 h, which is less than the C_{max} [44].

Co-administration of food with fosamprenavir appears to have little effect on drug absorption, therefore fosamprenavir can be taken with or without food [45].

Following oral prodrug administration to humans, the apparent volume of distribution is ~430 L suggesting drug penetration into tissues beyond the systemic circulation [38]. Amprenavir is taken up by lymphocytes with concentrations 2- to 3-fold higher than plasma concentrations [46]. Also amprenavir has been shown to penetrate human semen most likely with Pgp playing a role in the distribution into the tissues [38, 47].

1.2. Tenofovir

Tenofovir disoproxil fumarate is the first nucleotide drug to be approved for the treatment of HIV/AIDS and is classified as an acyclic nucleoside phosphonate (ANP), an analogue of adenosine monophosphate (*Figure 4*) [48, 49]. It has been formulated into once daily tablets (*Figure 5*) [50]. Therapeutically, tenofovir, (R)-9-(2-phosphonomethoxypropyl) adenine also known as bis(isopropyloxyc arbonyloxymethyl)-(R)-9-(2-phosphonomethoxypropyl) adenine (bis-POC-PMPA), is administered as the oral prodrug, tenofovir disoproxil fumarate [51]. Like NRTIs, tenofovir is converted intracellularly by phosphorylation to its active form tenofovir diphosphate, which acts as a chain terminator when HIV reverse transcriptase is actively making viral DNA [52].

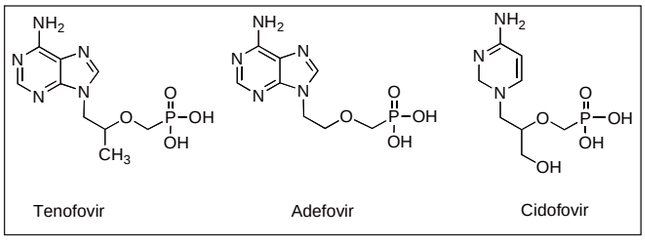

Figure 4 - Nucleoside phosphonate analogues developed for various anti-viral therapies.

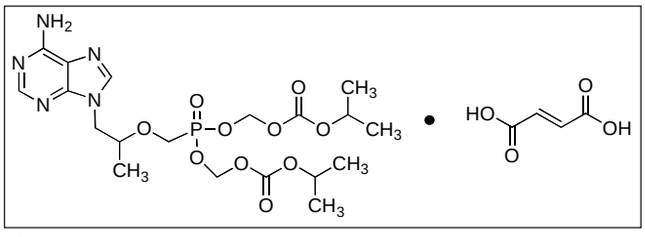

Figure 5 - Tenofovir disoproxil fumarate or bis(isopropyloxycarbonylox ymethyl)-(R)-9-(2-phosphonomethoxypropyl) adenine. IUPAC name is 1-(6-aminopurin-9-yl) propan-2-yloxymethylphosphonic acid.

However unlike the other traditional NRTIs, tenofovir possesses a phosphonate group, which is stable in the biological milieu. The phosphonate group consists of a P-C bond protected from phosphoesterase cleavage. This is different from a phosphate group (P-O-C) that is formed upon phosphorylation of NRTIs, which is susceptible to such cleavage [53-55]. Because of the phosphonate group, tenofovir only needs to be phosphorylated twice and this allows tenofovir to avoid the initial phosphorylation step by virus-induced kinases that has been identified as the rate-limiting step in the conversion of NRTIs to their active metabolites [52, 54, 55].

After cellular uptake of tenofovir, it is converted to its monophosphate form (TMP) by adenylate kinase found in the intermembrane space of the mitochondria, while the secondary phosphorylation takes place rapidly with the aid of nucleoside diphosphate kinase to form the active metabolite TDP (*Figure 6*) [51, 52, 56]. Once in the active form, TDP competes with naturally formed deoxyadenosine 5'-triphosphate (dATP) for incorporation into the viral cDNA. The DNA chain becomes terminated because TDP lacks the deoxyribose sugar moiety necessary to continue reverse-transcription (*Figure 7*) [49, 57, 58].

Tenofovir possesses the ability to be metabolized by non-dividing cells as well as quiescent cells and can reach up to two-fold greater concentration in resting peripheral monocytes compared to stimulated monocytes [56, 61]. The potency of tenofovir in macrophages can be attributed to two factors: i) the phosphonate group that avoids initial phosphorylation as previously mentioned and ii) the low levels of the competitive substrate dATP [25]. The effective concentration of tenofovir in resting $CD4^+$ T-cells is about ten times greater than rest-

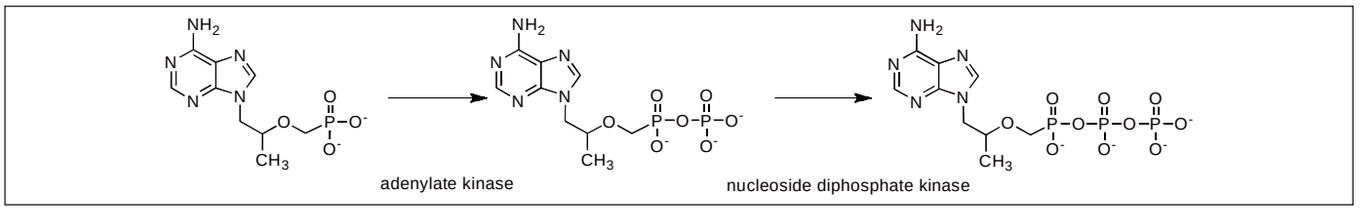

Figure 6 - Intracellular activation of tenofovir to TDP.

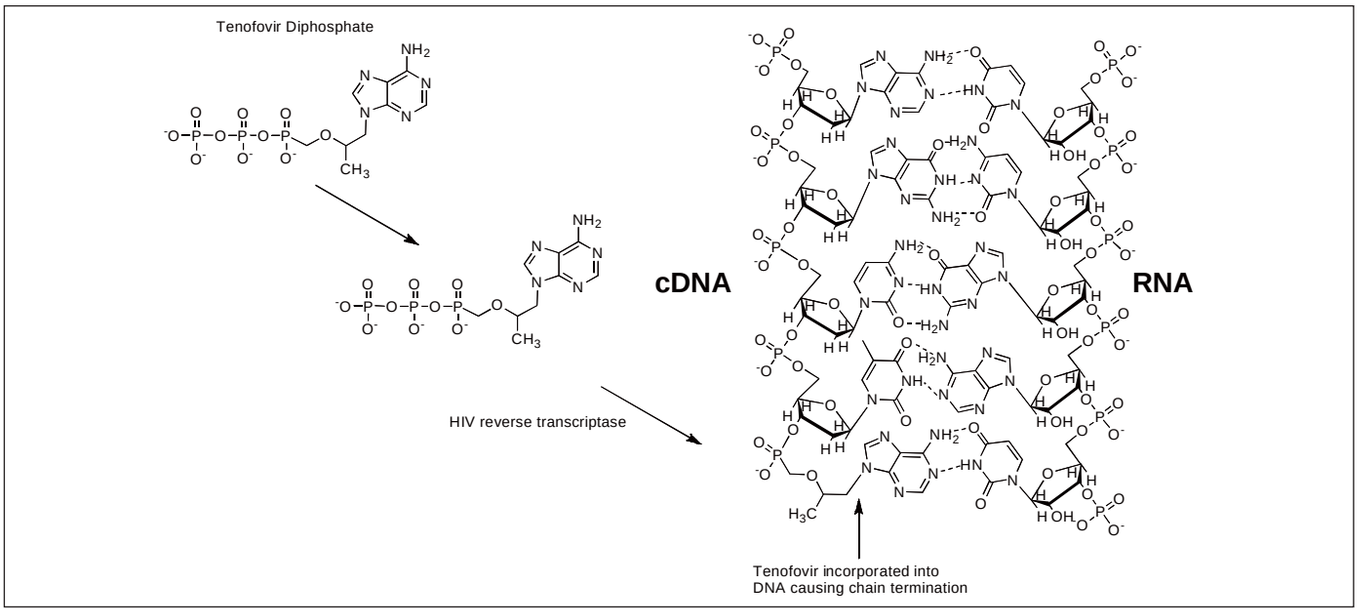

Figure 7 - Incorporation of tenofovir into viral cDNA and mechanism of chain termination.

ing macrophages, however because tenofovir does not require initial phosphorylation, it is seen to be more active than other NTRI alternatives in these cell types [25, 52]. Accumulation of drug in the resting cells means that tenofovir may possess the capability to inhibit HIV in latent cells, which is lacking in previously developed NRTIs like AZT or d4T [51].

Because of the polar nature of tenofovir, intestinal absorption is low. Therefore a prodrug was developed to increase its lipophilicity and to mask the negatively charged phosphonate group. Acyloxyalkyl esters of carboxylic acid were synthesized, since similar drugs with low bioavailability have benefited from ester linkages of phosphate groups [56]. Adefovir (*Figure 4*) another acyclic phosphonate drug similar to tenofovir had improved bioavailability when pivoxil groups were conjugated to the negatively charged phosphonate group [62]. For tenofovir, an isoproxil group was chosen because of its good oral bioavailability (~30%) and stability in both chemical and intestinal milieus [62, 63]. This prodrug formulation increased the lipophilicity of the drug from log P = -2.5 tenofovir to a log P = 1.3 of tenofovir disoproxil fumarate, increasing its ability to cross the intestinal membrane [64].

The conversion of the prodrug after absorption is mediated by enzymatic and non-enzymatic hydrolysis of the ester linkages of the phosphonate functional group [64]. The hydrolytic reactions produce carbon dioxide, formaldehyde, and the parent drug tenofovir (*Figure 8*). This process occurs upon absorption and is believed to be initiated by carboxylesterases, however esterases in general are relatively ubiquitous [63]. The conversion of tenofovir disoproxil fumarate to the parent drug tenofovir is rapid and complete, *in vitro* and *in vivo* studies revealed that the conversion process takes minutes to accomplish and the presence of any intermediates were undetectable by HPLC [56, 63, 65].

The oral bioavailability of tenofovir can be enhanced by the consumption of high-fat meals or ester mixtures for example those derived

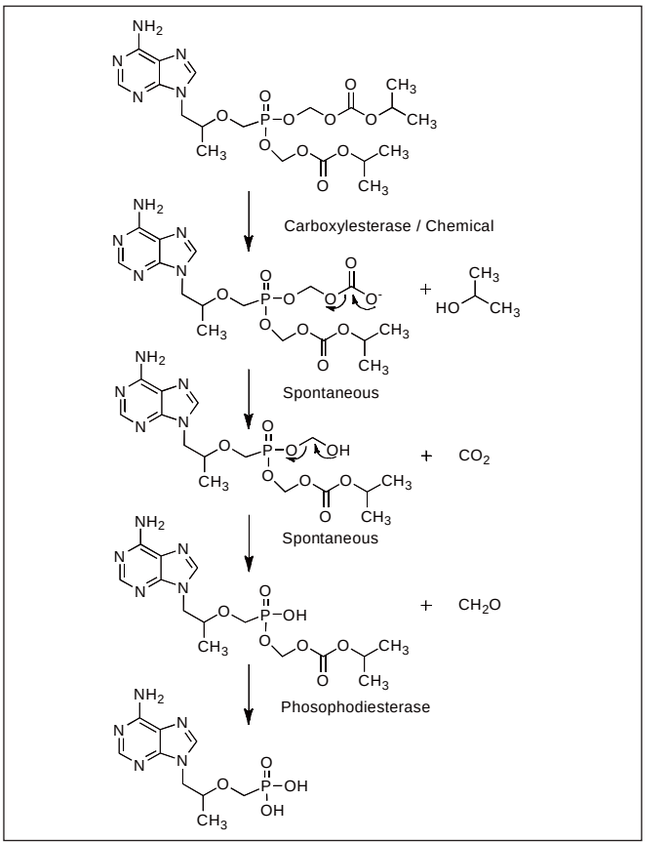

Figure 8 - Conversion of tenofovir disoproxil fumarate to tenofovir upon intestinal absorption.

from strawberry extracts, which prevent premature ester cleavage of the prodrug [49, 66, 67]. These ester mixtures limit the metabolism in the intestinal milieu, prior to absorption, and *in vitro* interfere with P-glycoprotein related efflux, while the consumption of a high-fat meal is related to the increased lipophilicity of the tenofovir prodrug [52, 66, 67].

Although tenofovir disoproxil fumarate shows increased antiviral activity in resting and activated lymphocytes, in reality very little prodrug if any will enter the systemic circulation, because of the predominance of esterases. Since it is believed that cells take up the charged parent drug, the absorption process is most likely receptor- or transporter-mediated. Cellular uptake of a similar drug, adefovir, has been shown not to use the nucleoside transporters utilized by the natural nucleosides and NRTIs [68]. Instead it is believed that tenofovir is internalized via an endocytosis pathway similar to that of adefovir. Adefovir uptake in HeLa cells is protein mediated and saturable [68]. Conflicting claims suggest that tenofovir enters cells passively by endocytosis that is neither transport mediated nor saturable [51].

Tenofovir is extensively distributed throughout the body with steady state distribution reaching approximately 1.3 L/kg from an intravenous dose. An associated volume of this magnitude is greater than the total body water [48, 50, 51, 69]. The extensive distribution throughout much of the body and tissues could be attributed to the polar nature of the parent drug tenofovir. Despite its large volume of distribution, tenofovir is virtually unable to penetrate the blood brain barrier. Although BBB penetration is limited, tenofovir does have the ability to pass the blood cerebral spinal fluid (CSF) barrier of the choroid plexus gaining access to perivascular and meningeal macrophages [70].

Intracellular elimination of tenofovir *in vitro* was markedly different between stimulated and resting peripheral blood mononuclear cells (PBMCs). In stimulated cells, TMP and TDP have half-lives of 15 and 11 h, respectively, which is similar to observed half-lives in T-cell lines [56, 71]. Interestingly in resting cells the half-lives of TMP and TDP reach 33 and 49 hours. The increased intracellular time could translate into increased antiviral activity especially in resting cells, a known viral sanctuary site [56]. The increased intracellular duration may be attributed to the phosphorylation of tenofovir, which locks the active metabolite within the cell.

HIV resistance to NRTIs manifests itself in two mechanisms: i) lack of incorporation and/or ii) increased excision of the drugs from the viral cDNA [72]. Because of the flexible nature of the acyclic linker and the lack of the ribose sugar, which gives the drug torsional freedom and a reduction in size respectively, tenofovir does not develop highly resistant strains of the virus [72, 73]. These properties are also advantageous against viral strains that are resistant to other NRTIs. For example M184V is a strain resistant to 3TC incorporation because its ribose ring is sterically hindered by the mutation, but the lack of the bulky side chains allows tenofovir to still be incorporated [72, 73]. The side chain features keep HIV-RT from developing a mutant that would not incorporate tenofovir, while still being able to incorporate dNTPs [72].

2. Drug conjugates and targeted nanocarrier drug delivery strategies

Traditional prodrug strategies have significantly improved HIV therapy by improving pharmacokinetics and the resulting dosing regimens. However, prodrugs can undergo non-specific activation thus potentially causing significant side effects. A prodrug strategy focusing toward the development of targeted prodrugs, which could allow for the drug release at the site of action, can address these potential problems [78, 79].

Targeting is achieved by conjugating the drug/prodrug molecules to carriers of varying molecular classes, sizes, and shapes, like sugars, growth factors, vitamins, antibodies, peptides and synthetic polymers

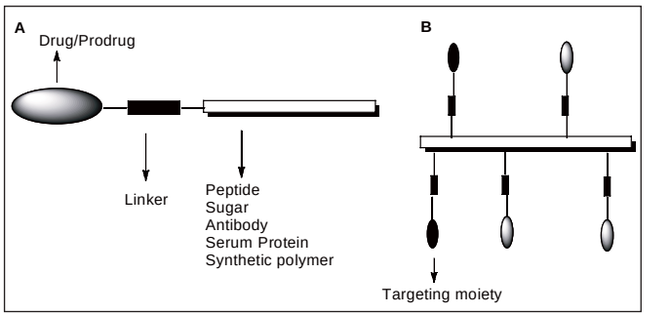

Figure 9 - General design of prodrug conjugates.

that can transport the drugs to the target site. Site-specific release is performed by incorporating chemical linkages that are normally stable, but can be cleaved under the defined conditions at the target site. The general design of prodrug conjugates for targeted therapy is shown in *Figure 9*.

Design and development of target-specific prodrug/drug conjugates is challenging because the functionality of the carriers is often sensitive to subtle structural variations and therefore emphasis must be placed on the chemical aspect of preparing and characterizing them [80]. Extensive chemical experimentation and characterization should be performed to optimize the physicochemical properties (e.g. molecular weight, hydrophilicity/hydrophobicity, three-dimensional structure, and immunogenicity) of the carrier and/or conjugate before evaluating their potential biological effects. Molecular biology is currently being implemented in the design and development of targeted drug/prodrug conjugates to understand the effect of conjugation on drug activity and where relevant, to modify biologically active molecules for conjugation [80].

Our lab has used the conjugate approach to overcome several challenges associated with the physicochemical properties of SQV [4]. SQV was the first approved HIV-1 protease inhibitor used for the treatment of HIV infection. The drug suffers from limitations such as low absorptive and high secretary permeability, bioconversion to inactive metabolites, and poor solubility, all of which are commonly associated with protease inhibitors. SQV absorption in particular, is highly variable and the mean oral bioavailability of the two-marketed SQV capsule formulations range from 4 to 16%. Earlier studies have considered the first-pass intestinal hepatic metabolism by cytochrome P-450 monooxygenases (CYP) as a major determinant in the clearance of SQV, but our group, along with others, have shown that multiple membrane transporters working in concert with P-glycoprotein (P-gp) may also be responsible for this observed behavior [31, 81-84].

Prodrug conjugates of the protease inhibitors, SQV, IND, and NFV, have been developed by conjugating the drugs to fatty acids, L-valine, L-tyrosine, PEG, and D-glucose so as to improve their bioavailability [85, 86]. The only successful prodrug of a protease inhibitor to date is the phosphate-ester prodrug of amprenavir, fosamprenavir, as previously discussed. In each of these cases, the prodrugs were readily converted to active drug molecule either in the intestinal environment or on the first pass through the intestine and liver. Therefore once the prodrug is absorbed only the parent drug remains in the blood and the potential benefits of the prodrug are lost [87].

Our lab has also designed and developed SQV PEG-based nanocarriers to overcome biopharmaceutical problems associated with SQV (*Figure 10*) [87]. Poly(ethylene glycol) (PEG) scaffolds were covalently attached to a SQV molecule to enhance the aqueous solubility, circulation half-life, and prevent nonspecific interactions of the drug in the biological milieu. PEG was used because it is among the most versatile polymers for medical applications due to the chemical inertness of its polyether backbone, as well as its excellent solubility in aqueous media. PEG is nontoxic, non-immunogenic, and non-biodegradable,

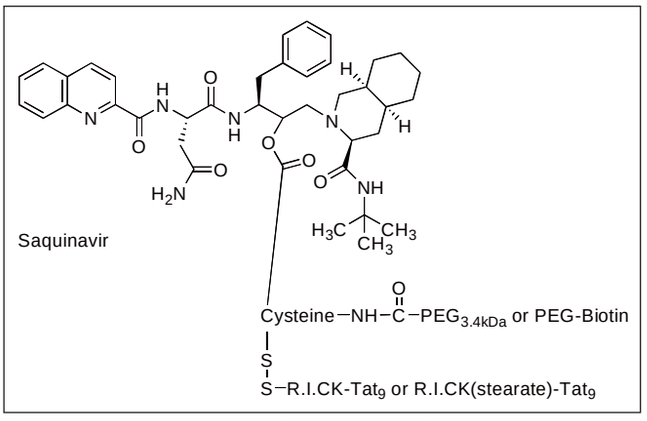

Figure 10 - General design of PEG nanocarriers conjugated to SQV prodrug and biotin / retro-inverso CK-Tat9 or CK(stearate)Tat9 peptides. The prodrug is attached through a reversible ester bond, whereas the cell-penetrating peptides are attached through reducible disulfide bonds. PEG is attached through stable amide bonds and biotin is attached through PEG spacer. The nanocarrier shown here releases the SQV.

which makes it suitable for the modification of various biologically active compounds. The PEG-prodrug conjugates were further attached to either biotin or retro-inverso-cysteine-lysine-Tat_9 (R.I.CK-Tat_9) or R.I.CK-Tat_9(stearate) to achieve enhanced cell association and uptake. R.I.CK-Tat_9 was used not only for its cell-penetrating properties but also its anti HIV-1 properties, which may be useful in combination therapy [88]. The biotin was attached because we have previously shown that conjugation to biotin or biotinylated PEG results in enhanced cellular uptake and transport of R.I.CK-Tat_9 peptide via SMVT, the intestinal biotin transporter [89, 90].

Several prototypes of these PEG nanocarriers were synthesized viz., SQV-Cys (control), SQV-Cys-$PEG_{3.4kDa}$, SQV-Cys-$PEG_{3.4kDa}$-biotin, SQV-Cys(R.I.CK-Tat_9)-$PEG_{3.4kDa}$, and SQV-Cys(R.I.CK(stearate)-Tat_9)-$PEG_{3.4kDa}$ [87]. The PEG was bound to a cysteine residue through stable amide bonds, whereas the prodrug was attached through reversible ester bonds. Similarly, R.I.CK Tat peptides were attached through reducible disulfide bonds. *In vitro* studies showed that the PEG only conjugate was inactive, but further modification with biotin or the peptide restored the prodrug activity. Cytotoxicities were found in the micromolar range, but more importantly the SQV molecule was released from the prodrug conjugates. The prodrug conjugate SQV-Cys(R.I.CK-Tat_9)-$PEG_{3.4kDa}$ was found to be most active among the conjugates investigated. We also demonstrated the combined preclinical *in vitro* effectiveness of R.I.CK-Tat_9 alone or attached with SQV-PEG conjugates for HIV treatment [91].

Our recent efforts have focused on the design and development of PEG-nanocarriers for macrophage targeting. Macrophage targeting represents a key challenge in HIV therapy, since macrophages are not only the primary target of HIV infection, but along with $CD4^+$ T-lymphocytes are an important source of HIV persistence during HAART [22]. They play an important role in the initial stages and throughout the course of HIV-1 infection [92]. Productively infected macrophages have been reported in both untreated patients and those receiving HAART. Also HIV-1 infection of macrophages is noncytopathic, enabling them to serve as sources of HIV production and represent major viral reservoirs, as previously mentioned [25].

Macrophages regulate their biological function in response to environmental stimuli (action of soluble factors, contact with foreign particles or cells). Hence, delivering drugs to macrophages is an extremely challenging task because of their inherent phagocytic ability and inhibition towards foreign particles even though there are drugs known that are capable of modulating macrophage activities [22]. Several liposomes, nanoparticles and microsphere-based delivery systems have been developed for delivering the drug to macrophages [22, 93]. However, another strategy that is being increasingly explored is the design and development of conjugates/nanocarriers containing ligands for specific interaction with receptors expressed on macrophage surfaces.

Macrophages possess various receptors such as formyl peptide, complement, fibronectin, lipoprotein, mannosyl, galactosyl, Fc, and many others [94, 95]. These macrophage surface receptors control the activities of the cells including; activation, recognition, endocytosis, and secretion. Conjugates/nanocarriers containing ligands specific to macrophage surface receptors may enhance uptake due to the receptor-mediated endocytosis. The advantage of using such a targeted system is that drug is delivered selectively to the HIV-infected tissues without affecting the normal tissues. As a result, the side effects are reduced, lower doses are needed, and drug administration regimens are simplified.

An ideal nanocarrier for macrophage targeting should be flexible enough in design so that different combinations of anti-HIV drugs, targeting moieties, and/or imaging agents can easily be incorporated. We have been extensively exploring the possibility of using our modular design of PEG nanocarriers (*Figure 10*) for macrophage targeting. A PEG-based linear copolymer, poly[poly(ethylene glycol)-alt-poly(aspartic acid)] was designed and developed [96]. The copolymer was further modified to obtain multifunctional PEG nanocarriers containing four copies of N-formyl-methionine-leucine-phenylalanine (fMLF) peptide (PEG-$fMLF_4$) and/or four and eight copies of digoxigenin (DIG_4-PEG-$fMLF_4$ and PEG-DIG_8). Branched PEG with three and four arms were used to obtain PEG nanocarriers with three and four copies of fMLF respectively. Similarly, eight-arm PEGs were used to obtain nanocarriers containing 1.1, 5.5 and 8- copies of fMLF respectively (PEG-$fMLF_{1.1}$, PEG-$fMLF_{5.5}$, and PEG-$fMLF_8$) [96]. The fMLF peptides and the surrogate drug (digoxigenin) were attached through stable amide bonds. However in future work, reducible disulfide bonds would be used for the attachment of drugs/prodrugs. The fMLF peptide is recognized by formyl peptide receptors over-expressed on macrophage surfaces [97].

Nanocarriers with a single copy of fMLF were found to reduce the binding avidity for differentiated HL-60 cells when compared to the free fMLF peptide [96]. Increasing the number of fMLF peptides on PEG nanocarrier led to an increase in avidity for HL-60 cells and interestingly the geometry of the polymer backbone (linear/branched) was found to have no influence on the outcome and there was no enhancement observable when fMLF receptor negative Jurkat cells were used. Importantly, none of the nanocarriers investigated above showed an enhanced ability to activate phagocytic cells, a potential cause of various adverse side effects. The advantage of using PEG nanocarriers described herein is that multiple copies of targeting moieties and drug/prodrugs can be incorporated to obtain optimum targeting and drug payload. Furthermore, the lack of enhancement of phagocytic activation suggests that the drugs/prodrugs appended to such nanocarriers are less likely to be inactivated by degradative mechanisms induced by phagocytic activation.

We later developed a series of PEG nanocarriers containing multiple fMLF moieties to optimize the fMLF copy number and PEG size for macrophage uptake [98]. One, two, and four-arm PEG scaffold of molecular weights 5, 10, 20, and 40 kDa were used to conjugate up to four copies of fMLFK(fluorescein)C. The following nanocarriers were synthesized: fMLFK(fluorescein)KC-PEG_{5kDa}, $[fMLFK(fluorescein)KC]_2$-PEG_{5kDa}, $[fMLFK(fluorescein)KC]_2$-PEG_{20k}, $[fMLFK(fluorescein)KC]_2$-PEG_{40kDa}, and $[fMLFK(fluorescein)KC]_4$-PEG_{10kDa} (*Figure 11*). Since, the ability to produce PEGs with a defined number of anchoring moieties is limited, especially in high numbers, a modular PEGylated peptide [(acetyl-Cys-β-Ala-β-Ala-Lys)n-PEG_{5k}] nanocarrier was designed and developed incorporating two and four copies of fMLFK(fluorescein)C [98]. The advantage

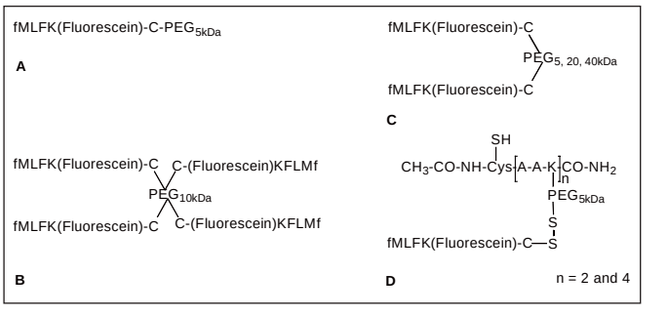

Figure 11 - PEG (A-C) and PEG-peptide (D) based nanocarriers developed for macrophage targeting by receptor-mediated endocytosis. The fMLF copy number was varied to obtain a nanocarrier with optimum binding properties. The molecular weight of PEG was varied to influence the molecular size of the nanocarrier whereas fluorescein molecule was attached to monitor their binding and uptake behavior.

of using PEG-peptide nanocarriers is that the precise copy number of drug/prodrug and targeting moieties can be attached, unlike the PEG alone nanocarriers, where only the average copy numbers were obtainable.

Results from macrophage like differentiated human U937 cell-specific binding and cellular uptake studies conclusively showed that uptake is energy dependant and mediated by fMLF receptor [98]. Similar to our earlier results [96], fMLF copy number was found to influence the binding and uptake behavior. Increasing the number of fMLF moiety from one to two resulted in 4-fold enhanced uptake, but further increase in fMLF copy number to four led only to a modest increase. Molecular size was also found to influence the uptake behavior as increasing the PEG molecular weight from 5 to 20 kDa resulted in an increase in the uptake but further increase to 40 kDa led to a decreased uptake. This is consistent with earlier reports where receptor-mediated endocytosis has been shown to be strongly size dependant with optimal size requirement of ~ 25 nm or < 50 nm [99-102]. Thus, two copies of fMLF along with a molecular size of 20 kDa PEG appears to be a prerequisite for optimum macrophage targeting.

Peritoneal macrophage uptake, pharmacokinetics, and biodistribution of macrophage-targeted PEG nanocarriers for improving the HIV drug delivery were also investigated [103]. In this case the following nanocarriers were used: $[fMLFK(fluorescein)C]_2$-PEG_{5kDa}, $[fMLFK(fluorescein)C]_4$-PEG_{20kDa}, and acetyl-Cys-[β-Ala-β-Ala-Lys{PEG_{20kDa}-CK(fluorescein)FLMf]$_4$. Attachment of one, two or four fMLF copies increased the macrophage uptake by 3.8, 11.3 and 23.6-fold when compared to nanocarrier without the targeting moiety. Incorporation of fMLF moiety also increased the $t_{1/2}$ of PEG_{5kDa} by 3-fold, but decreased by 40% for PEG_{20kDa}. Furthermore, the attachment of targeting moieties to the PEG nanocarriers led to an increased accumulation in liver (1.5-fold), kidney (3.2-fold), and spleen (6.9-fold). However on a molar basis, the penetration was equivalent, suggesting that the nanocarrier size and the targeting moieties are an important determinant. The PEG-peptide nanocarrier with four copies of fMLF was found to be the most promising nanocarrier tested so far. Overall, the results demonstrated the feasibility of targeting macrophages, a primary HIV reservoir site by modularly designed PEG nanocarriers. The studies also suggest a need to balance peripheral tissue penetration with target cell uptake, and we are currently working on the design and development of nanocarriers containing multiple targeting moieties and drug copies to achieve efficient targeted drug delivery [103].

III. SUMMARY AND FUTURE DIRECTIONS

In summary, the antiviral drug development process remains challenging. It has been suggested by many that drugs targeted toward viral proteins will be more specific and less toxic to the host, but they may ultimately select for mutant virus rendering the therapeutic agent ineffective. Others believe that developing drugs that target host proteins will avoid the development of viral resistance, but may have a less than desirable adverse effect profile [10]. In our opinion, a combination of these two methods is necessary to keep HIV at chronically low titers or possibly to eradicate HIV infection altogether.

Most of the antiviral drugs developed so far are viral protein inhibitors designed to disrupt the viral life cycle in HIV infected cells, namely viral DNA synthesis (reverse transcriptase), viral DNA insertion into the host genome (integrase), and viral protein cleavage (protease). Although the prodrug strategy has been successfully used to improve the physicochemical, biopharmaceutic, and pharmacokinetic properties of some anti-HIV drugs, they are unable to eradicate HIV infection because they suffer from poor specificity for the infected cell types or the physiological sites (tissues or organs) that sequester HIV. Also, these drugs do not persist in target cells for a sufficient period of time. Therefore, efforts need to shift in order to improve target cell bioavailability and persistence.

Targeted-delivery to host proteins specific to HIV susceptible cells could improve antiviral therapy because it will potentially increase either the access to the physiological reservoir sites (brain, testes, and lymphatics) or the cellular active site concentrations, unlike the conventional drug/prodrug design, where focus is on improved pharmacokinetics (i.e. blood concentration). Drug delivery to HIV-infected tissues with selectivity can be achieved by macrophage targeting. Microspheres, liposomes, and nanoparticle-based delivery systems have been developed for delivering drugs to macrophages. Macrophage targeting can also be achieved by interaction with receptors expressed on macrophage surfaces. We have shown the advantage of using modularly designed PEG-nanocarriers containing effectors (targeting ligands, drugs, and/or imaging agents) for macrophage targeting. These nanocarriers can be easily modified to incorporate various antiviral drugs/prodrugs, biologics, targeting moieties, and/or imaging agents. It has been also shown that these nanocarriers do not show an enhanced ability to activate phagocytic cells, a potential cause of various adverse side effects. We believe that the design of such nanocarriers will be a key to the development of targeted delivery systems that can accumulate into the difficult to reach physiological locations such as the brain, testes, and lymphatics.

Besides targeting macrophages, the chemokine receptors (CXCR4 and CCR5) that act as the coreceptors to HIV infection can also be used as potential targets. Targeting these receptors can have two effects: i) prophylactic protection of the cell by occupying the receptor necessary for virus-cell interaction, and/or ii) improving the specific uptake of a nanocarrier loaded with anti-viral drugs. There are several other strategies that are being explored to target viral compounds or virus-associated events [10].

Although this review has exclusively focused on anti-HIV prodrugs and conjugates that can be potentially used as chronic therapeutic agents, however new and uniquely designed pharmacological agents and strategies with specificity to the physiological and cellular targets are necessary if eradication of the virus is to become attainable.

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Strategies to improve oral drug bioavailability

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Efforts to improve oral drug bioavailability have grown in parallel with the pharmaceutical industry. As the number and chemical diversity of drugs has increased, new strategies have been required to develop orally active therapeutics. The past two decades have been characterised by an increased understanding of the causes of low bioavailability and a great deal of innovation in oral drug delivery technologies, marked by an unprecedented growth of the drug delivery industry. The advent of biotechnology and consequent proliferation of biopharmaceuticals have brought new challenges to the drug delivery field. In spite of the difficulties associated with developing oral forms of this type of therapeutics, significant progress has been made in the past few years, with some oral proteins, peptides and other macromolecules currently advancing through clinical trials. This article reviews the approaches that have been successfully applied to improve oral drug bioavailability, primarily, prodrug strategies, lead optimisation through medicinal chemistry and formulation design. Specific strategies to improve the oral bioavailability of biopharmaceuticals are also discussed.

Keywords: biopharmaceuticals, formulation, macromolecules, medicinal chemistry, oral bioavailability, prodrugs

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1. Introduction

Oral administration is regarded as the preferred route of drug intake, offering numerous advantages, including convenience, ease of compliance, potential for availability to large patient populations and cost-effectiveness. Not surprisingly, oral bioavailability plays an important role in lead selection at the discovery stage and is a key factor in many go/no-go decisions for the development of new drugs [1-7].

Understanding the causes of low oral absorption and the approaches to improve it is critical for decreasing attrition rates in drug development and successfully bringing new drugs to market. Poor oral bioavailability affects drug performance and leads to high intra- and interpatient variability. The recourse to parenteral administration in these cases faces limitations of cost, patient compliance, especially in chronic therapies, and weak competitive positions compared with alternative oral therapies.

Oral bioavailability depends on a number of factors, primarily drug permeability, aqueous solubility, dissolution rate, presystemic metabolism, first-pass metabolism and susceptibility to efflux mechanisms. Among these factors, low permeability and poor solubility stand as the most frequent causes of low oral bioavailability [8-11]. In 1997, Lipinski and colleagues introduced the so-called 'rule of 5', which became a reference to estimate oral drug absorption [12]. The rule incorporates parameters such as molecular size, hydrogen bonding capability and water/octanol partition coefficient, which determine the hydrophilicity/lipophicicity balance required for appropriate solubility and permeability. Since then, numerous other approaches to estimate oral bioavailability have been proposed. The development of *in vitro* and *in silico* prediction methods is still a very active field and has contributed to a better understanding of the factors influencing systemic drug absorption following oral

administration [13-15]. Initially, predictive methods focused exclusively on passive absorption, giving primary importance to the drug characteristics that determine solubility and permeability through lipid membranes. This was useful for a number of drugs, but often failed with drugs that are absorbed through transporter proteins, as is the case of β-lactam antibiotics, angiotensin-converting enzyme inhibitors and nucleoside antivirals [16-21]. In addition, these early methods overlooked factors such as potential high presystemic and/or first-pass metabolism and susceptibility to efflux pumps, including P-glycoprotein (Pgp) or multi-drug resistance proteins (MRPs), which are known to have a significant impact on the bioavailability of certain drug types [22-26]. Recent approaches recognise that predictive methods are, to a certain extent, drug-class-specific and that it is important to understand the pathway of absorption of a particular drug or drug class in order to select the appropriate *in vitro* and/or *in silico* methods to assess oral bioavailability [27-32].

The advances in the understanding of the causes of low oral bioavailability have led to significant improvements in the design of technologies to address these deficiencies. The past two decades have witnessed a great deal of innovation in oral drug delivery, marked by an unprecedented growth of the drug delivery industry. Overall, the strategies developed to improve oral bioavailability can be grouped into three main categories:

- prodrugs and drug conjugates
- medicinal chemistry
- formulation design

These strategies are not mutually exclusive; on the contrary, they are often applied in combination. For instance, a prodrug designed to improve drug absorption can, in addition, use a formulation approach to enable rapid onset or to target absorption from a particular site in the gastrointestinal tract. Choosing a suitable approach among the vast number of options is often not an easy task. Good knowledge of the causes of low bioavailability and preferred absorption pathways, as well as the impact of the different approaches on drug metabolism and desired pharmacokinetic profile is key to the successful selection of an appropriate strategy for a particular drug or drug candidate.

2. Prodrugs

Prodrugs are inactive drug derivatives that are transformed into the active drug inside the body through chemical hydrolysis or enzymatic reaction. Typically, prodrugs are formed by covalent attachment to a drug of a chemical moiety that alters the physicochemical properties of the drug, to improve bioavailability. This covalent link should be relatively labile and designed to be cleaved, liberating the active drug, once the prodrug is absorbed into the systemic circulation (**Figure 1**), this strategy has worked successfully for a number of drugs [33]. The potential downsides are the reduced solubility of the prodrug, particularly when all the ionisable groups are masked with non-polar moieties, and the risk of entrapment or drug accumulation inside cells where the biotransformation of the prodrug into active drug often occurs.

A well-known prodrug approach relies on the attachment of a non-polar group through an ester bond as a way of masking highly polar or charged moieties, such as phosphates and carboxyl groups. This increases the lipophilicity of the drug molecule and, consequently, its permeability. The ester bond is readily cleaved by esterases in the plasma and liver. Some examples of this approach are etilevodopa, the ethyl ester of Parkinson's disease drug levodopa [34], antivirals such as adefovir dipivoxil [35,36], capecitabine, an oral prodrug of 5-fluorouracil [37,38], oseltamivir [39], docarpamine [40] and tenofovir disoproxil fumarate [41-43].

Other prodrug strategies rely on modified chemical groups that confer appropriate permeability properties and are biotransformed after absorption, to liberate the active drug. This is the case, for example, for sibrafiban and ximelagatran, in which amidoxime groups (neutral) of the inactive prodrug form are transformed after absorption into amidines (charged), to yield the active drug. Following a similar strategy, thioesters have recently been used in a novel approach to design oral prodrugs of promising antimalarial agents [44]. Lactone prodrugs such as simvastatin and lovastatin are also examples of this approach [45-47].

Prodrugs in which the role of the attached moiety is not to mask charged or highly polar groups but rather to promote or enhance transporter-mediated absorption are a growing class. In these cases the attached moiety acts as a recognition site for transporter proteins that can shuttle the molecule across the intestinal epithelium. Oligopeptide transporters, such as peptide transporter 1 (PEPT1) and human intestinal peptide transporter 1 (HPT1), are abundant in the small intestine, have a broad specificity, and are capable of transporting a variety of chemically diverse substrates into the systemic circulation, provided that they contain a minimum of recognition features [48-50]. These transporters have been exploited, for example, to increase the bioavailability of acyclovir and ganciclovir in their respective valine esters, valacyclovir and valganciclovir [51-55]. Another interesting example is the recently proposed valquinidine. This prodrug approach was designed to target absorption via oligopeptide transporters and at the same time avoid Pgp-mediated efflux [56].

Bile acid transporters have also been explored to improve oral bioavailability through the attachment of cholic acid or other bile acids. The attachment site and drug size play an important role in determining affinity for the transporter and, thus, the efficiency of this approach [57,58]. Absorption through bile acid transporters has particular interest for drugs targeting the liver and hepatobiliary system but presents limitations for systemic drug absorption due to the rapid biliary uptake by the liver. Successful systemic absorption requires release of the free drug from the conjugate before reaching the liver. Recent applications of this approach include the

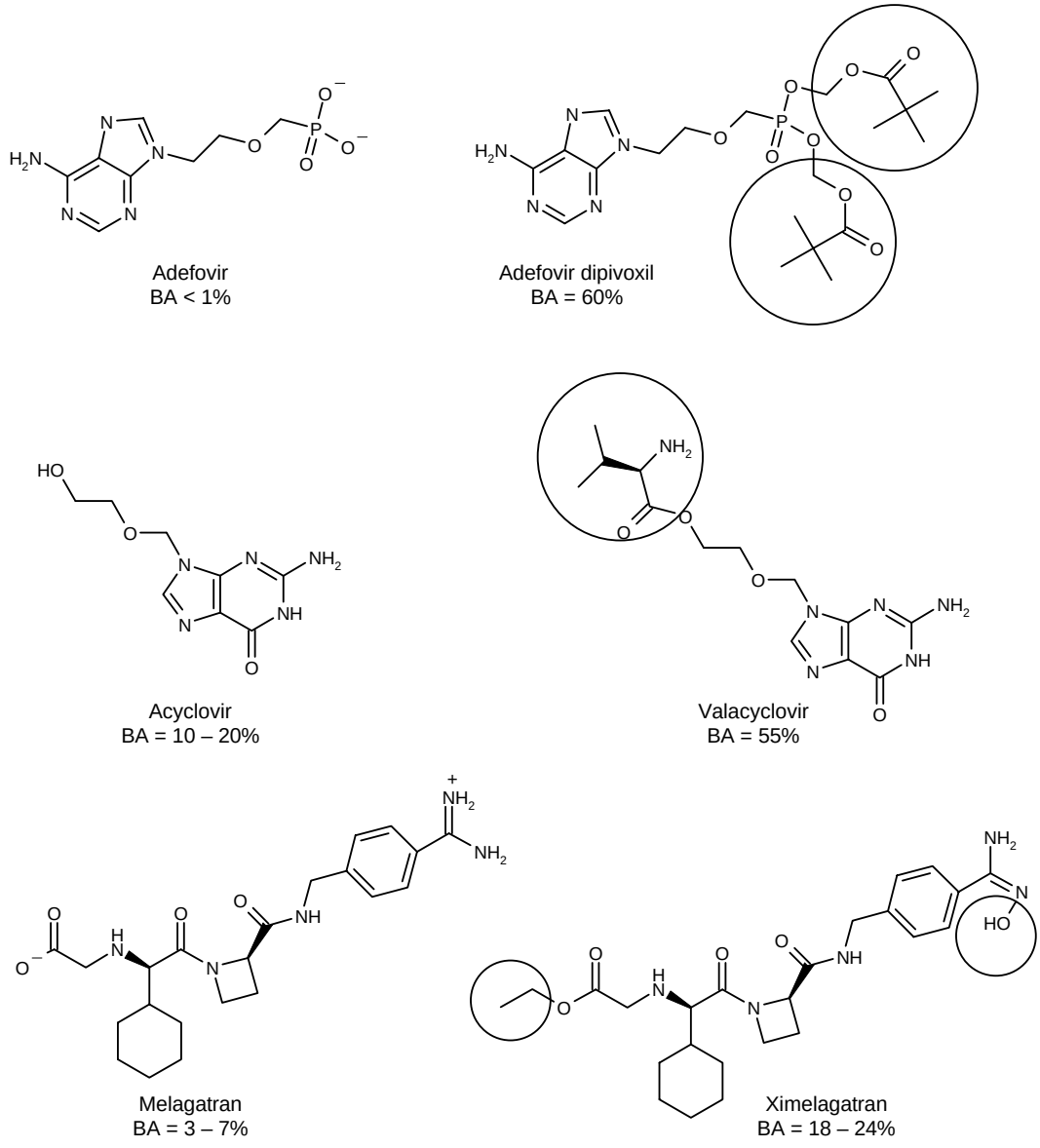

Figure 1. Examples of prodrugs and their impact on the oral bioavailability of the active drug. The attached moieties are marked with a circle and the active drug is shown next to each prodrug. In the case of adefovir dipivoxil and ximelagatran, the attached moieties mask charged groups, to increase the hydrophobicity and permeability of the molecule. In the case of valacyclovir, the attached moiety acts as a recognition site for oligopeptide transporters that transfer the drug across the intestinal epithelium.
BA: Oral bioavailability.

development of oral cisplatin–bile acid conjugates to treat liver tumours [59,60] and conjugates of deoxycholic acid and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors aimed at improving the efficiency of cholesterol-lowering agents [61,62].

XP-13512, a gabapentin prodrug engineered to be absorbed by various nutrient transporters, including the sodium-dependent multivitamin transporter and monocarboxylate transporters, has been shown to improve bioavailability and reduced interpatient variability [63,64]. Mono- and disaccharide conjugates have also been shown to be a potential strategy to target drug absorption through intestinal glucose transporters [65-71]. Other transporter proteins present in the gastrointestinal tract, such as organic anion transporters, nucleoside transporters, vitamin transporters and organic cation transporters, are known to contribute to drug absorption and are being explored in prodrug strategies [72]. The successful application of these strategies requires a good understanding of the transporter recognition characteristics [73-75], gastrointestinal tract distribution [76,77], transport capacity, as well as potential inhibitors, agonists [78-81] and drug–drug interactions [82,83]. It is also important to take into consideration the tissue distribution of these transporters

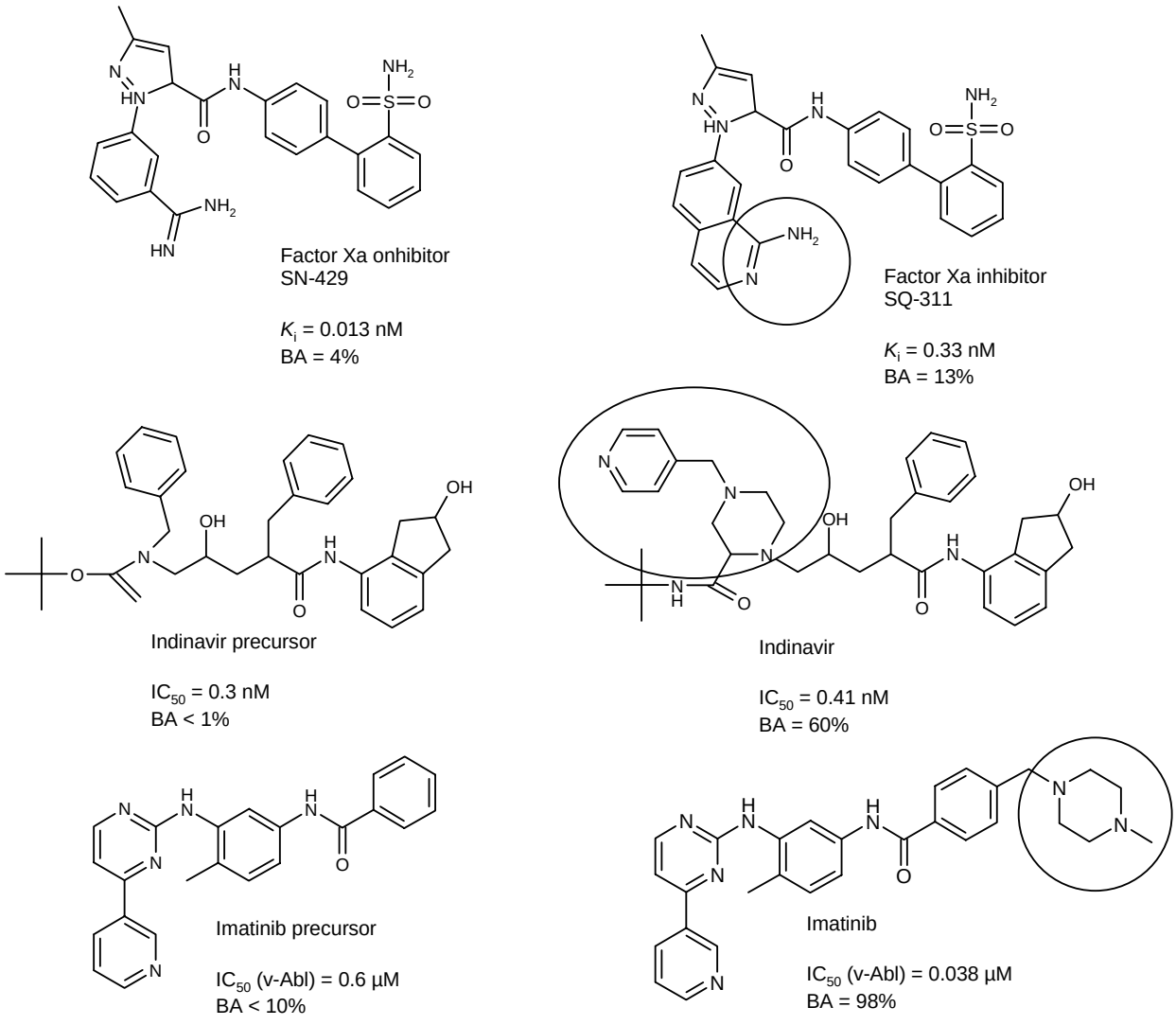

Figure 2. Examples of improved oral bioavailability through medicinal chemistry approaches. The strategy followed in the case of Factor Xa inhibitor SQ-311 was to lower the pK_a of benzamidine by incorporating it into an aromatic ring. This decreased the hydrophilicity and solubility at physiological conditions, thus increasing the permeability. The potency of Factor Xa inhibitor was reduced by an order of magnitude, which was considered a reasonable trade-off in this case [105]. In the case of indinavir and imatinib, the precursors had limited bioavailability due to their poor aqueous solubility. This was addressed by introducing ionisable groups (marked with circles) that increased the overall solubility of the molecule. The impact on activity (IC_{50}) was moderate for indinavir. Interestingly, for imatinib this strategy had a positive impact on activity, improving specificity towards target tyrosine kinases.
BA: Oral bioavailability; IC_{50}: Median inhibitory concentration; K_i: Inhibition constant; pK_a: -Log_{10} dissociation constant for an acid.

and their potential effect on clearance. Many transporters present in the gastrointestinal tract are also abundant in the kidneys and liver, and can contribute to rapid elimination, thus offsetting the absorption advantages [84,85].

Prodrugs have proven to be an effective approach to increase oral bioavailability. In addition, they can provide long-acting pharmacokinetic profiles and increased drug half-lifes by targeting appropriate mechanisms of active drug release and/or slowing down metabolism and clearance. In these cases, prodrugs offer advantages of both lower dosing frequency and improved absorption. Valacyclovir, for example, enables the reduction of dosing regimen from five- to three-times a day because its gradual biotransformation into acyclovir creates a sustained release of active drug into the systemic circulation. Bambuterol and docarpamine are other examples of prodrugs that provide prolonged half-lifes through slow biotransformation and metabolism rates [40]. Bambuterol, a prodrug of terbutalin, has comparable bioavailability to the active drug. Its advantage lies primarily on its relatively slow biotransformation that enables a sustained release of terbutalin into the blood, enabling once-daily dosing regimens instead of three-times a day.

Table 1. Examples of substrates of membrane transporter proteins.

Transporter protein	Substrate
Amino acid transporters	Gabapentin, levodopa, baclofen
Oligopeptide transporters	ACE inhibitors, β-lactam antibiotics, cephalosporins, renin inhibitors, bestatin
Nucleoside transporters	Zidovudine, acyclovir, zalcitabine, gemcitabine
Organic anion transporters	Pravastin, methotrexate

ACE: Angiotensin-converting enzyme.

3. Medicinal chemistry

Medicinal chemistry encompasses the design of drugs with appropriate bioactivity and bioavailability characteristics [7]. Incorporating good oral absorption features into the drug design process entails managing a delicate balance between activity and bioavailability goals (**Figure 2**). Designing for optimal bioavailability profiles often requires compromising on activity; nevertheless, in many instances the advantages of oral absorption compensate for small activity trade-offs [2,86,87].

Drug design efforts targeting good oral bioavailability normally take place at the early stages of lead selection and optimisation, although sometimes this strategy is applied to the development of second-generation drugs, providing novel and competitive proprietary positions [88]. Lead optimisation often involves a significant investment of resources in design, synthesis and testing. The availability of reliable computational methods and high-throughput assays to estimate both activity and bioavailability is critical for the efficiency of this process [31,89-98]. Successful drug design strategies require a good understanding of the specific drug absorption pathways and causes of poor bioavailability, including efflux mechanisms, liver first-pass metabolism and presystemic degradation [99-101]. Typically, lead optimisation strategies targeting oral bioavailability focus on chemistries that confer solubility and permeability characteristics required for passive absorption [102-106]. When transporter proteins are known to be involved in the absorption process, medicinal chemistry strategies concentrate transporter affinity features (**Table 1**). A good understanding of the factors that determine recognition and affinity is key for successful lead optimisation in these cases [73,74,107-113].

4. Formulation strategies

Improving oral bioavailability through formulation design is often the approach of choice, particularly for drugs that are already in development stages or on the market. Formulation strategies offer relatively low-cost opportunities to improve oral bioavailability of new drugs and manage the life cycle of existing ones. As opposed to prodrug and medicinal chemistry approaches, they do not require chemical modification of the drug or creation of new chemical entities. This provides considerable advantages in terms of reduced cost and development time. The use of already approved excipients and generally recognised as safe materials is often preferred due to their reduced risk and development requirements. Nevertheless, the need for innovation in the development of new classes of excipients that can address unmet formulation needs has long been recognised, and substantial efforts are being invested in this direction. Solubility enhancing agents such as cyclodextrins, or permeability increasing agents such as chitosans or medium chain fatty acids, are some examples of these ongoing efforts. Efflux problems are also being addressed through the use of excipients that have properties as efflux pump inhibitors. Examples of reported Pgp inhibitors are grapefruit juice, tocopheryl polyethylene glycol 1000 succinate, polyethylene glycol 400, Tween 80 and Cremophor EL [114-118].

4.1 Solubility and dissolution rate

Formulation approaches vary depending on the unfavourable drug properties that limit bioavailability and the desired pharmacokinetic profiles. Poor aqueous solubility is one factor that frequently affects the oral performance of drugs. It has been successfully tackled with the use of co-solvents, solid dispersions [119], microemulsions, self-emulsifying systems [120,121], nanosuspensions [122-125] and inclusion compounds [126,127]. Solid-state strategies, such as freeze-drying, micronisation and nanocrystals [128,129] have been successfully applied to increase dissolution rates by optimising particle size and surface area. Stabilisation of polymorphs or the development of specific solvates are other solid-state approaches commonly applied to improve dissolution profiles and solubility [130].

Fast-dissolving and orally disintegrating technologies that target rapid dissolution in the mouth and pregastric absorption from the oral cavity have rapidly grown in recent years. They address poor dissolution profiles, are an appropriate strategy for drugs subject to high presystemic or first-pass metabolism, and are suitable for drugs that require a rapid onset and/or present gastrointestinal compatibility or food interaction issues. In addition, this approach offers a dosage form alternative for patient populations with swallowing difficulties. Fast-dissolving technologies targeting absorption from the mouth rely on freeze-drying, effervescence or direct compression (**Table 2**). A good number of medications currently benefit from these types of drug delivery approaches [131-141]. The main requirements for the successful application of orally disintegrating technologies are adequate taste and loading capacity.

4.2 Hydrophilic drugs

The oral bioavailability challenges of drugs with poor permeability, which are normally highly polar or charged, have been addressed primarily through the use of absorption

Table 2. Examples of rapid-disintegration technologies that enable absorption from the oral cavity.

Trade name	Base technology	Example products
Zydis®	Freeze drying	Zyprexa® Zydis®, Zydis® Selegiline, Claritin® RediTabs®, Zofran ODT®
DuraSolv®	Direct compression and mild effervescence	Zomig ZMT®/ Rapidmelt, Nulev™, Parpoca™, Alavert™, Loratadine ODT
OraSolv®	Direct compression and mild effervescence	Remeron®, SolTabs™, FazaClo™, Triaminic®, SoftChews®, Tempra® FirstTabs
Flashtab®	Direct compression	Excedrin®, QuickTabs™
WOWTAB®	Direct compression	Benadryl®, Fastmelt™

enhancers such as medium chain fatty acids, bile salts, surfactants, liposaccharides and chitosans [142-149]. Typically, enhancers facilitate absorption by increasing the permeability of cell membranes and/or opening the tight junctions between adjacent cells to facilitate paracellular absorption, which has sometimes raised safety concerns. Alternative approaches rely on the co-administration with specific delivery agents capable of forming transient, non-covalent complexes with the drugs, which facilitate or enable their transcellular absorption [150,151].

4.3 Sustained-release and gastroretentive approaches

Sustained-release formulations have been applied successfully to improve the oral bioavailability of drugs with inappropriate solubility or dissolution profiles and/or high presystemic metabolism [152]. The added benefits of reduced dosage frequency and improved performance of therapeutics that require sustained blood levels are the clear advantages of this approach [153]. Numerous sustained-release technologies have been developed in recent years, and today, there are close to 100 drugs on the market in sustained-release formulations. Most sustained-release technologies are based on polymeric systems that release the drug through gradual erosion, swelling or diffusion. These different release processes are typically controlled by pH [154,155], osmotic pressure [156], or enzymatic or chemical reaction [157,158]. Some key factors to consider in the selection of the appropriate technology are drug compatibility, loading capacity and manufacturing costs.

Gastroretentive systems are a particular case of sustained-release technologies designed to ensure that the drug is released in the stomach. They aim at avoiding the variability associated with the randomness of intestinal transit times and target drug release into the upper gastrointestinal tract where absorption is high for many drugs. Gastroretentive technologies are based on polymeric materials that swell or expand in the stomach creating a large size matrix unable to escape through the pylorus [159]. Eventually, these polymeric matrices disintegrate and are eliminated or biodegraded. These technologies have found applications in drugs targeting the stomach, as well as in drugs requiring systemic absorption. They are applicable primarily to drugs that are preferentially absorbed in the upper gastrointestinal tract, and are stable and have good solubility and dissolution profiles under the acidic pH conditions typical of the stomach [160-168].

A potential alternative for drugs that are sensitive to the low pH and high enzymatic activity of the upper gastrointestinal tract would be to target absorption from the ileum and/or colon where the pH is close to neutral and enzymatic activity is reduced. This can be achieved by using enteric coatings, time-dependent systems, polymers that disintegrate at neutral or near neutral pH, or polymeric materials that are specifically metabolised by bacteria residing in the colon. pH-dependent polymers are susceptible to the variability of gastrointestinal pHs, whereas bacteria-metabolised polymers can ensure specific release in the colon. Nevertheless, all of these approaches are limited by the variability of transit times. They are applicable to drugs that do not require rapid onset or timely absorption and are stable at body temperature for several hours. So far, these approaches have been more successful in the development of drug products that target local gastrointestinal conditions, such as ulcerative colitis or Crohn's disease, than for systemic drug absorption.

5. Macromolecules and biopharmaceuticals

Macromolecules comprise a particular drug class characterised by their large molecular size (typically > 1000 Da). Most biopharmaceuticals, including proteins, peptides, vaccines, antisense oligonucleotides and heparins, fall within this category. Their oral bioavailability is almost negligible due to their size and high presystemic degradation [8-10]. In addition, most of biopharmaceuticals are very hydrophilic, a property that further limits their oral absorption [169]. Today, most biopharmaceuticals are available only in injections. Exceptions are calcitonin and GnRH analogues, which are available as nasal solutions or sprays, cyclosporin, which is available in oral forms, and desmopressin, which is available in both oral and nasal administration forms. Cyclosporin, desmopressin and GnRH analogues are relatively small peptides subject to low presystemic degradation in the gastrointestinal tract, two characteristics that have greatly facilitated the development of their oral forms. Unfortunately, the formulation approaches pursued with these two peptides are not applicable to most biopharmaceuticals, which have larger molecular sizes and are susceptible to substantial presystemic metabolism.

In spite of the inherent difficulties associated with developing oral biopharmaceuticals, significant progress has been made in recent years; a number of different technologies and approaches have been generated [170-176], and some oral biopharmaceuticals have already advanced into clinical development. The main strategies applied to date to improve the oral bioavailability of macromolecules fall within four main categories:

- drug conjugates
- formulation with permeation enhancers
- co-administration with delivery agents
- micro- and nanoparticle formulations

Drug conjugates aim at increasing oral bioavailability through the attachment of a chemical moiety that either increases the lipophilicity and permeability of the macromolecule [177-179] or enables its absorption via transporter proteins or receptor-mediated endocytosis [180-183]. Conjugates must retain biological activity or release the attached molecule after absorption. Permeation enhancers open tight junctions between adjacent cells, to enable paracellular absorption, and/or to alter the permeability of cell membranes, to increase absorption across the intestinal epithelium [184-189]. Technologies based on co-administration with drug delivery agents rely on specific low molecular weight compounds that interact weakly and reversibly with macromolecules, thus increasing their lipophilicity and enabling their transcellular absorption [190-193]. Micro- and nanoparticle formulation approaches target absorption through the gut-associated lymphoid tissue and are being investigated primarily for the development of oral vaccines [194,195]. These four basic approaches are often combined with other strategies, primarily, co-administration with enzyme inhibitors capable of reducing presystemic degradation [196-199] and/or formulation with mucoadhesive polymers that can improve absorption by increasing the residence time of the formulation on the gastrointestinal epithelium [200-203].

Many of these strategies have been tested *in vitro* and in animal models but, to date, only a few have advanced into clinical development. Among the latter are hexyl–insulin monoconjugate 2; a modified insulin with improved oral permeability due to its conjugation to an amphililic polymer, which has shown efficacy in Type I and II diabetic patients [204-207]. A similar approach has been successfully applied to the oral delivery of calcitonin [208]. Absorption enhancer approaches have been applied to the development of oral forms of an antisense therapeutic [209,210] and heparin [211], and both have initiated Phase I clinical studies. The eligen® technology, which relies on co-administration with drug delivery agents that enable transcellular drug absorption, has been successfully applied to the development of oral forms of several biopharmaceuticals, including heparin, insulin, calcitonin, parathyroid hormone and growth hormone, all of which are advancing through clinical trials [176,212-222]. Oral formulations of calcitonin and parathyroid hormone consisting of a combination of enzyme inhibitors, absorption enhancers and enteric coating also have been evaluated in humans [223]. Technologies based on oral sprays and sublingual tablets that target absorption from the buccal cavity have also advanced into clinical studies with insulin [224,225] and glucagon-like peptide-1 [226,227].

6. Expert opinion

Efforts to improve oral drug bioavailability have led to a great deal of innovation in drug delivery, which has been demonstrated in a good number of breakthroughs and success stories, particularly in the past two decades. It remains a very active field and one that is critical for the successful development of new drugs.

To date, formulation strategies have been far more successful in improving the bioavailability of hydrophobic drugs, with poor solubility, than with hydrophilic, polar drugs, which have good solubility but rather impaired permeability; prodrug and medicinal chemistry approaches have been more successful with the latter. Oral delivery remains a challenge for biopharmaceuticals. Nevertheless, significant progress has been made in the past few years, with some oral proteins, peptides and other macromolecules currently advancing through clinical trials. The first oral macromolecules to reach the market will open the doors to further advances and confidence in this field.

It is important to note that the approaches to improve bioavailability often have a significant impact on pharmacokinetic profiles. This can be exploited to improve drug performance; for example, in the case of fast-dissolving technologies to achieve a rapid onset, or in the case of some prodrugs and sustained-release formulations to reduce dosing frequency. The selection of an appropriate approach for a particular drug is a case-dependent process. It is important to take into consideration not only the compatibility of the approach and the causes of low absorption of the drug, but also the impact on the pharmacokinetic profile, drug distribution, elimination, metabolism, onset, blood levels and duration. All of these factors must be evaluated in order to determine the appropriate strategy for each drug. All approaches have, in principle, a tremendous potential. Their success depends to a large extent on their application to the appropriate drugs. For example, fast-dissolving technologies that target absorption from the mouth may be a good strategy for migraine drugs, but would be inappropriate for a drug such as valacyclovir that targets absorption via oligopeptide transporters, which are not abundant in the buccal cavity.

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Prodrugs: design and clinical applications

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Abstract | Prodrugs are bioreversible derivatives of drug molecules that undergo an enzymatic and/or chemical transformation *in vivo* to release the active parent drug, which can then exert the desired pharmacological effect. In both drug discovery and development, prodrugs have become an established tool for improving physicochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically active agents. About 5–7% of drugs approved worldwide can be classified as prodrugs, and the implementation of a prodrug approach in the early stages of drug discovery is a growing trend. To illustrate the applicability of the prodrug strategy, this article describes the most common functional groups that are amenable to prodrug design, and highlights examples of prodrugs that are either launched or are undergoing human trials.

Combinatorial chemistry
The rapid synthesis or the computer simulation of a large number of different but structurally related molecules.

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The application of modern discovery technologies such as high-throughput screening and combinatorial chemistry can produce novel lead structures with high pharmacological potency, but the physicochemical and biopharmaceutical aspects of the initial leads have frequently been neglected. This can lead to drug candidates with poor drug-like properties that face significant problems later in drug development[1].

The development of prodrugs — chemically modified versions of the pharmacologically active agent that must undergo transformation *in vivo* to release the active drug — is now well established as a strategy to improve the physicochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically potent compounds, and thereby increase the developability and usefulness of a potential drug[2–9] (FIG. 1a). For example, prodrugs provide possibilities to overcome various barriers to drug formulation and delivery such as poor aqueous solubility, chemical instability, insufficient oral absorption, rapid pre-systemic metabolism, inadequate brain penetration, toxicity and local irritation. Prodrugs can also improve drug targeting, and the development of a prodrug of an existing drug with improved properties may represent a life-cycle management opportunity.

In most cases, prodrugs are simple chemical derivatives that require only one to two chemical or enzymatic transformation steps to yield the active parent drug. In some cases, a prodrug may consist of two pharmacologically active drugs that are coupled together in a single molecule so that each drug acts as a promoiety for the other; such derivatives are called co-drugs[10,11]. Prodrugs have also been referred to as reversible or bioreversible derivatives, latentiated drugs or biolabile drug-carrier conjugates[12–14], but the term prodrug is now standard. A bioprecursor prodrug is a prodrug that does not contain a carrier or promoiety, but results from a molecular modification of the active agent itself. This modification (for example, oxidation or reduction) generates a new compound that can be transformed metabolically or chemically, with the resulting compound being the active agent (it can also be referred to as an active metabolite). Finally, soft drugs, which are often confused with prodrugs, also find applications in tissue targeting. However, in contrast to prodrugs, soft drugs are active drugs that are designed to undergo a predictable and controllable deactivation or metabolism *in vivo* after achieving their therapeutic effect[15–17].

Currently, 5–7% of the drugs approved worldwide can be classified as prodrugs, and approximately 15% of all new drugs approved in 2001 and 2002 were prodrugs[2,6]. However, we have only begun to realize their full potential, and this is mainly due to the only recent understanding of various biological phenomena enabling the design of more sophisticated, safer and better-targeted prodrugs. With the aim of illustrating the full potential of the prodrug approach, this article will provide an overview of functional groups that are amenable to prodrug design, and then highlight the major applications of the prodrug strategy, including the ability to improve oral absorption and aqueous solubility, enhance lipophilicity and active transport, as well as achieve site-selective delivery.

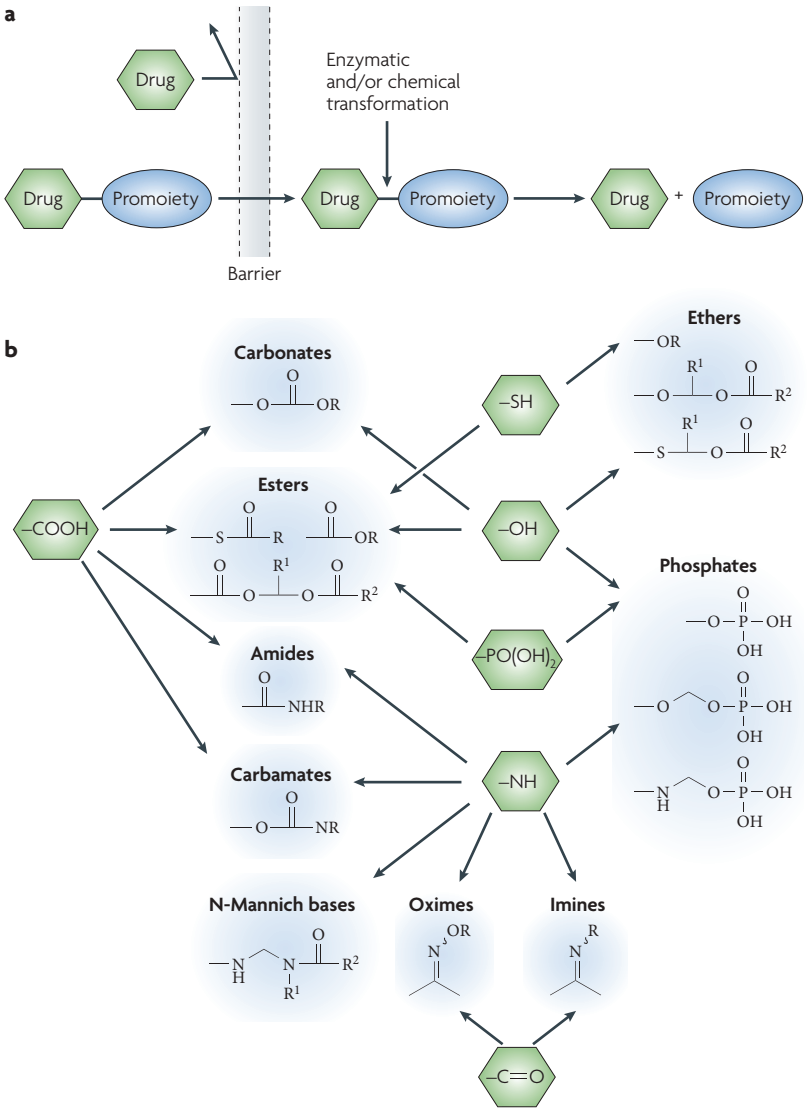


Figure 1 | **A simplified representative illustration of the prodrug concept.** **a** | The drug–promoiety is the prodrug that is typically pharmacologically inactive. In broad terms, the barrier can be thought of as any liability or limitation of a parent drug that prevents optimal (bio)pharmaceutical or pharmacokinetic performance, and which has to be overcome for the development of a marketable drug. The drug and promoiety are covalently linked via bioreversible groups that are chemically or enzymatically labile, such as those shown here. The 'ideal' prodrug yields the parent drug with high recovery ratios, with the promoiety being non-toxic. **b** | Common functional groups on parent drugs that are amenable to prodrug design (shown in green). Most prodrug approaches require a 'synthetic handle' on the drug, which are typically heteroatomic groups.

Functional groups amenable to prodrug design

Ideally, the design of an appropriate prodrug structure should be considered at the early stages of preclinical development, bearing in mind that prodrugs might alter the tissue distribution, efficacy and the toxicity of the parent drug. Several important factors should be carefully examined when designing a prodrug structure, including:

- Parent drug: which functional groups are amenable to chemical prodrug derivatization?
- Promoiety: this should ideally be safe and rapidly excreted from the body. The choice of promoiety should be considered with respect to the disease state, dose and the duration of therapy.
- Parent and prodrug: the absorption, distribution, metabolism, excretion (ADME) and pharmacokinetic properties need to be comprehensively understood.
- Degradation by-products: these can affect chemical and physical stability and lead to the formation of new degradation products.

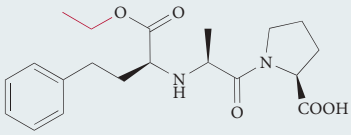
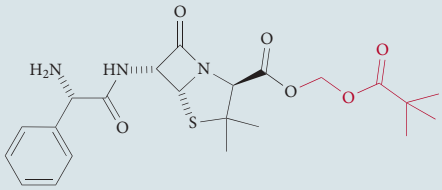
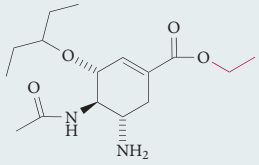
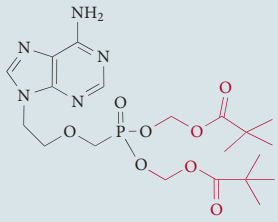
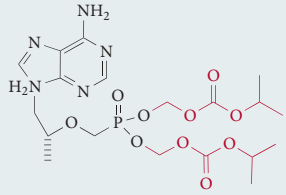
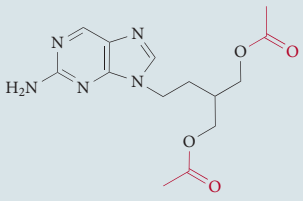
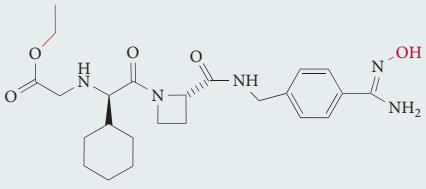
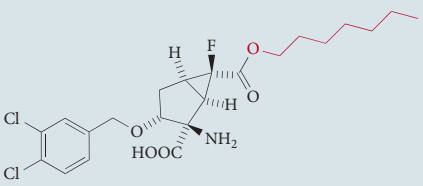
Promoiety
A functional group used to modify the structure of pharmacologically active agents to improve physicochemical, biopharmaceutical or pharmacokinetic properties.

Some of the most common functional groups that are amenable to prodrug design include carboxylic, hydroxyl, amine, phosphate/phosphonate and carbonyl groups. Prodrugs typically produced via the modification of these groups include esters, carbonates, carbamates, amides, phosphates and oximes. However, other uncommon functional groups have also been investigated as potentially useful structures in prodrug design. For example, thiols react in a similar manner to alcohols and can be derivatized to thioethers[18] and thioesters[19]. Amines may be derivatized into imines[20,21] and N-Mannich bases[22]. The prodrug structures for the most common functionalities are illustrated in FIG. 1b and discussed below.

Esters as prodrugs of carboxyl, hydroxyl and thiol functionalities. Esters are the most common prodrugs used, and it is estimated that approximately 49% of all marketed prodrugs are activated by enzymatic hydrolysis[4]. Ester prodrugs are most often used to enhance the lipophilicity, and thus the passive membrane permeability, of water-soluble drugs by masking charged groups such as carboxylic acids and phosphates[3,23]. The synthesis of an ester prodrug is often straightforward. Once in the body, the ester bond is readily hydrolysed by ubiquitous esterases found in the blood, liver and other organs and tissues[24], including carboxylesterases, acetylcholinesterases, butyrylcholinesterases, paraoxonases and arylesterases. However, one significant challenge with ester prodrugs is the accurate prediction of pharmacokinetic disposition in humans, owing to significant differences in specific carboxylesterase activities in preclinical species[25], as reported for the exploratory intravenous diester prodrug of nalbuphine[26]. A comprehensive review on ester prodrugs that enhance oral absorption of predominantly poorly permeable and polar parent drugs was recently published by Beaumont *et al.*[3]

Several alkyl and aryl ester prodrugs are in clinical use[3], of which angiotensin-converting enzyme (ACE) inhibitors are some of the most successful[24], with a representative sample shown in TABLE 1. However, the relatively slow and incomplete bioconversion of some simple alkyl esters in human blood can sometimes result in lower than predicted bioavailability. For example, the oral bioavailability of enalaprilate in humans is 36–44%, despite 53–74% of the administered dose being absorbed[3]. In some cases, faster bioactivation has been achieved by the use of a double prodrug (pro-prodrug), which requires an enzymatic breakdown after which a spontaneous chemical reaction releases the parent drug. The double prodrug approach has been the preferred choice when preparing oral acyloxyalkyl ester prodrugs of β-lactam antibiotics (TABLE 1).

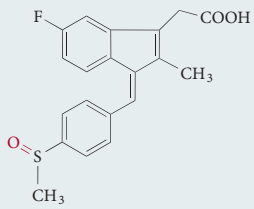
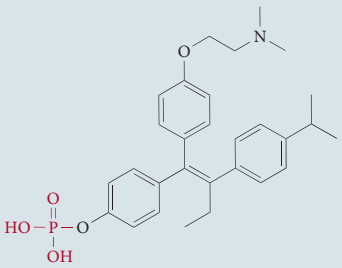
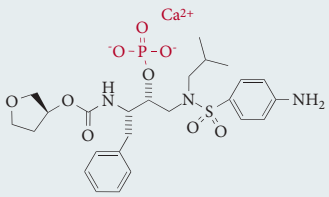
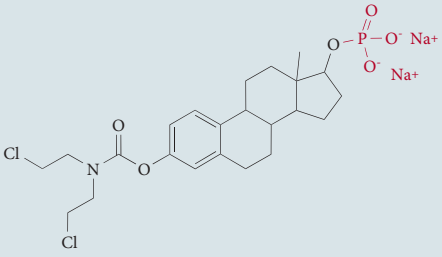
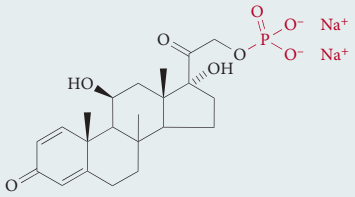
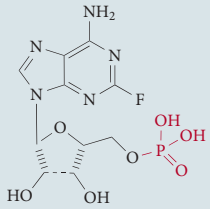
Table 1 | **Prodrugs for improved lipophilicity or permeability**

Prodrug name (therapeutic area)	Functional group	Structure	Prodrug strategy
Enalapril (angiotensin-converting enzyme inhibitor)	Monoethyl ester of enalaprilat		• Bioconversion by esterases • The oral bioavailability of enalaprilat in humans is 36–44% • 53–74% of the administered dose is absorbed[3,172]
Pivampicillin (β-lactam antibiotic)	Pivaloylmethyl ester of ampicillin		• Bioconversion by esterases • The oral bioavailability of 32–55% for ampicillin increased to 87–94% for pivampicillin[173,174]
Oseltamivir (anti-influenza)	Ethyl ester of oseltamivir carboxylate		• Bioconversion by esterases • The oral bioavailability of less than 5% in rat and marmoset for oseltamivir carboxylate increased to 80% for oseltamivir in humans[80–82]
Adefovir dipivoxil (antiviral)	Bis-(pivaloyloxy-methyl) ester of adefovir		• Bioconversion by esterases and phosphodiesterases • The oral bioavailability of ~10% for adefovir increased to 30–45% for adefovir dipivoxil[78,79]
Tenofovir disoproxil (antiviral)	Bis-(isopropyloxy-carbonyloxymethyl) ester of tenofovir		• Bioconversion by esterases and phosphodiesterases • The oral bioavailability of tenofovir from tenofovir disoproxil is 39% in the fed state[74,76,77]
Famciclovir (antiviral)	Dimethyl ester of penciclovir		• Bioconversion by esterases and oxidation from purine to guanide • The oral bioavailability of 4% for penciclovir increased to 75% for famciclovir[175–177]
Ximelagatran (anticoagulant)	Hydroxyamidine and ethyl ester of melagatran		• Bioconversion by esterases and reductive enzymes • The oral bioavailability of 3–7% for melagatran increased to 20% for ximelagatran[84,86]
MGS0210 (glutamate receptor (MGLUR2) antagonist)	*n*-Heptyl ester of MGS0039		• Bioconversion by esterases • The oral bioavailability of less than 13% for MGS0039 in monkeys increased to 44% for MGS0210 in monkeys[41,50]

Co-drug
A chemical structure that undergoes conversion to two or more active drugs within a biological system, such conversion usually involves the metabolism of the co-drug.

Phosphate esters as prodrugs of hydroxyl or amine functionalities. Phosphate ester prodrugs are typically designed for hydroxyl and amine functionalities of poorly water-soluble drugs with an aim to enhance their aqueous solubility to allow a more favourable oral or parenteral administration (see examples in TABLES 2,3). The synthesis of phosphate prodrugs is fairly straightforward, and the presence of the dianionic phosphate promoiety usually raises the aqueous solubility[27,28]. Phosphate prodrugs typically display excellent or adequate chemical stability and rapid bioconversion back to the parent drug by phosphatases present at the intestinal brush border or

Table 2 | **Prodrugs for improved aqueous solubility**

Prodrug name (therapeutic area)	Functional group	Structure	Prodrug strategy
Sulindac (non-steroidal anti-inflammatory)	Oxide prodrug of sulindac sulphide		• Bioprecursor prodrug that is reduced to the active sulphide form after oral absorption • ~ 100-fold increase in aqueous solubility[62,65]
Miproxifene phosphate, TAT-59 (anticancer)	Phosphate ester of miproxifene/DP-TAT-59		• Bioconversion by alkaline phosphatases • Aqueous solubility at pH 7.4 increased by ~1,000-fold[69] • Enhanced bioavailability to 28.8% in rats and 23.8% in the dog[66] • Dose-linear pharmacokinetics in humans[69]
Fosamprenavir (antiviral)	Phosphate ester of amprenavir		• Bioconversion by alkaline phosphatases • 10-fold increased aqueous solubility • More simplified and patient compliant dosage regimen • Prolonged exclusive patent[70–72]
Estramustine phosphate (anticancer)	Phosphate ester of estramustine		• Bioconversion by alkaline phosphatases • Marketed both as injectable and oral formulations for the treatment of prostate carcinoma since the mid-1970s[178,179]
Prednisolone phosphate (glucocorticoid)	Phosphate ester of prednisolone		• Bioconversion by alkaline phosphatases • The prodrug enabled the development of a liquid formulation, and thus, improved childrens' compliance to prednisolone treatment[28,180]
Fludarabine phosphate (antiviral)	Phosphate ester of fludarabine		• Bioconversion by alkaline phosphatases • Until recently, fludarabine phosphate was marketed only for parenteral use[181] • Based on a modest advantage over the parent drug, development of an oral prodrug of fludaribine may have only been as a consequence of the prior existence of a commercial parenteral prodrug[28,181]

Bioprecursor prodrug
A prodrug that does not contain a carrier or promoiety, but is metabolically or chemically transformed into an active drug.

Soft drug
Soft drugs are the opposite of prodrugs. They are active drugs that are designed to undergo a predictable and controllable deactivation or metabolism *in vivo* after achieving their therapeutic effect.

Bioconversion
A process in which the pharmacologically active drug is released or formed.

in the liver[27,28]. Unlike carboxylic acid esters, phosphate esters are typically hydrolysed at similar rates in different preclinical species by alkaline phosphatases[29], and there are no published reports on species differences resulting in poor human pharmacokinetic performance.

There are many successful examples of parenteral phosphate prodrugs, but because of the challenges that they may encounter in the development phases, only a few phosphate prodrugs for oral administration have reached the market[27]. A highly ionic phosphate prodrug may, for example, exhibit suboptimal enzymatic bioconversion by phosphatases (usually the aqueous solubility of the phosphate prodrug is enhanced to such an extent that passive diffusion through the intestinal membrane is prevented); lead to precipitation of the parent drug following cleavage in the intestinal lumen — this eventually leads to poor absorption or drug flux of the parent drug, as the parent drug is not in a soluble form[27]; or show reduced bioavailability in the presence of calcium, for example, milk products or antacids[8].

Carbonates and carbamates as prodrugs of carboxyl, hydroxyl or amine functionalities. Carbonates and carbamates differ from esters by the presence of an oxygen or nitrogen on both sides of the carbonyl carbon. They are often enzymatically more stable than the corresponding esters but are more susceptible to hydrolysis than amides. Carbonates are derivatives of carboxylic acids and alcohols, and carbamates are carboxylic acid and amine derivatives. The bioconversion of many carbonate and carbamate prodrugs requires esterases for the formation of the parent drug[30] (see examples in TABLES 1,3,4).

Amides as prodrugs of carboxylic acids and amines. Amides are derivatives of amine and carboxyl functionalities of a molecule. In prodrug design, amides have been used only to a limited extent owing to their relatively high enzymatic stability *in vivo*. An amide bond is usually hydrolysed by ubiquitous carboxylesterases[30], peptidases or proteases[31]. Amides are often designed for enhanced oral absorption by synthesizing substrates of specific intestinal uptake transporters[31,32] (TABLE 4).

Oximes as derivatives of ketones, amidines and guanidines. Oximes (for example, ketoximes, amidoximes and guanidoximes) are derivatives of ketones, amidines and guanidines, thus providing an opportunity to modify molecules that lack hydroxyl, amine or carboxyl functionalities. Oximes are hydrolysed by the versatile microsomal cytochrome P450 (CYP450) enzymes[33,34], better known as xenobiotic metabolizing enzymes[35,36]. Oximes, especially strongly basic amidines and guanidoximes, can be used to enhance the membrane permeability and absorption of a parent drug[37] (see an example in TABLE 1).

Summary. Using the functional groups described above, the prodrug strategy has been successfully applied to a wide range of drug molecules. The major applications of prodrugs are described below, with examples that have been approved for marketing, or that are currently or have been in clinical trials, shown in TABLES 1–6.

Improved oral absorption

The oral bioavailability of a potential drug may be limited by its aqueous solubility, low permeability, propensity to be an efflux substrate, and rapid and extensive hepatic metabolism and biliary excretion. It is imperative to understand the physicochemical and biological factors that are limiting the oral bioavailability of a compound before embarking on a prodrug strategy (BOX 1). For most drugs, the bioavailability is controlled by the fraction absorbed (F_a) and by the clearance of the drug. F_a is largely controlled by the physicochemical parameters of the parent or prodrug, that is, its gastrointestinal permeability, solubility, dissolution rate and dose number[38].

Most marketed oral prodrugs are derived from parent drugs with a low F_a or minimal first-pass metabolism. This Review also assumes negligible gut-wall and pre-systemic metabolism, although there are several prodrugs — for example, bambuterol (Bambec/Oxeol; AstraZeneca) (TABLE 6) — that have been designed to protect against rapid metabolic breakdown[39], with varying degrees of success. F_a can be improved by enhancing the dissolution rate, aqueous solubility or permeability, assuming that the gut-wall metabolism is insignificant. Some prodrug strategies overcome poor absorption by

Box 1 | **Factors affecting oral bioavailability**

The maximum achievable oral bioavailability, F_{max}, of a parent drug is a function of three factors:

$$F_{max} = F_a * F_g * F_h \quad (1)$$

where F_a is the fraction of the dose that is absorbed after oral administration, F_g is the fraction of the dose that escapes intestinal metabolism and F_h is the fraction of the dose that escapes hepatic metabolism. Since $F_h = 1 - E_h$, where E_h is the hepatic extraction ratio (which is a measure of the liver's ability to extract drug from the systemic circulation), and $E_h = CL_h \div Q_h$, one obtains:

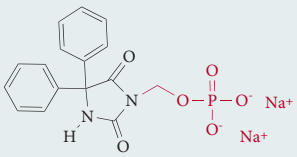
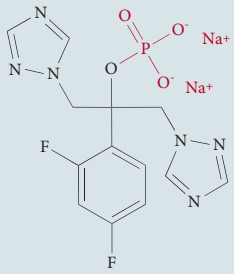
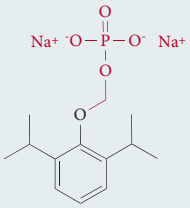
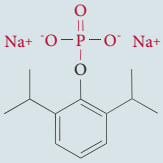
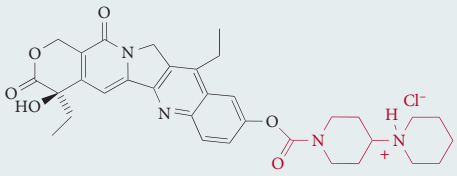
$$F_{max} = F_a * F_g * \left(1 - \frac{CL_h}{Q_h}\right) \quad (2)$$

where CL_h is the hepatic drug blood clearance and Q_h is the hepatic blood flow. When hepatic metabolism is the primary clearance mechanism and the fraction of drug excreted renally, f_e, is small, and with the assumption that drug is equally distributed between blood and plasma (blood/plasma ratio =1), the total blood clearance (CL) is equal to CL_h, since $CL_h = (1 - f_e)\,CL$ and $f_e \sim 0$ (REFS 168,169). For the purposes of this Review it will be assumed that gut-wall metabolism is negligible, that is, F_g is near unity, which leads to a simplified equation:

$$F_{max} = F_a * \left(1 - \frac{CL}{Q_h}\right) \quad (3)$$

Equation 3 states that for most drugs the bioavailability is controlled by the fraction absorbed and by the clearance of the drug. The F_a is largely controlled by the physicochemical parameters of the parent or prodrug, that is, its gastrointestinal permeability, solubility, dissolution rate and dose number[38]. F_a can be calculated in a preclinical species once CL and absolute bioavailability have been determined[170]. Q_h is a known constant in preclinical species and humans[171]; if the clearance is half of the liver blood flow in a given species[171] the theoretically maximum achievable bioavailability is 50%. For example, a compound with a CL of 35 ml per min per kg in the rat will have a calculated maximum bioavailability of only 50%, given the rat liver blood flow of ~70 ml per min per kg[171], even if absorption is complete and gut-wall metabolism is negligible, that is, F_a is near unity. Similarly, if a parent drug series has a rat blood clearance >50 ml per min per kg, then E_h >0.7 and its maximum oral bioavailability is limited to ~30%.

Table 3 | **Prodrugs for improved parenteral administration**

Prodrug name (therapeutic area)	Functional group	Structure	Prodrug strategy
Fosphenytoin (anticonvulsant)	Phosphonooxymethyl amine of phenytoin		• Rapidly converted to phenytoin by alkaline phosphatases (half-lives 7-15 min)[101,102] • Increased aqueous solubility from 20–25 µg per ml of phenytoin to 140 mg per ml of fosphenytoin
Fosfluconazole (antifungal)	Phosphate ester of fluconazole		• Bioconversion by alkaline phosphatases[106] • Allows a low-volume bolus and higher dose product for intravenous administration • Increased aqueous solubility of fosfluconazole (over 300 mg per ml)
Phosphonooxymethyl propofol (anaesthetic)	Phosphonooxymethyl ether of propofol		• Is rapidly converted to propofol after intravenous administration by alkaline phosphatases[106,185] • Significantly increased the aqueous solubility of propofol from 150 µg per ml to ~500 mg per ml
Propofol phosphate (anaesthetic)	Phosphate ester of propofol		• Significantly increased the aqueous solubility of propofol (150 µg per ml) • But bioconversion to propofol after intravenous administration is significantly slower when compared with phosphonooxymethyl propofol[107]
Irinotecan (anticancer)	Dipiperidino carbamate of camptothecin		• Increased aqueous solubility from 2–3 µg per ml (in water) of camptothecin to 20 mg per ml (at pH 3–4) of irinotecan • Undergoes rapid, pH-dependent equilibrium with closed and open forms of the lactone ring • Only the lactone form is active[112,115]

enhancing permeability, which is achieved by masking polar or charged moieties of a poorly permeable parent drug. These prodrugs are often carboxylic acid esters[3,40,41], such as GS-4104, the ethylester of GS-4071 (oseltamivir; marketed as Tamiflu by Gilead/Roche) (TABLE 1), or phosphonic acid esters[42,43] of poorly permeable but aqueous soluble parent drugs. Thus, these are prodrugs of Class III parent drugs in the Biopharmaceutical Classification System (BCS)[38], with parent drugs of low permeability, but high solubility (FIG. 2). As these prodrugs are designed to enhance permeability, and as they typically do not alter the metabolic clearance or half-life of parent drugs, 'ideal' parent drug candidates will have low to moderate clearance in preclinical species with an hepatic extraction ratio (E_h) that is less than 0.5.

For parent drugs that are not significantly metabolized by the liver in preclinical species[44,45], it can be seen from equation 2 in BOX 1 that the bioavailability is determined by the fraction absorbed, that is, $F_{max} \sim F_a$. For example, the bioavailability of adefovir (9-[2-(phosphonomethoxy)ethyl] adenine; PMEA) in rats is low (near 8%)[46], which is in agreement with adefovir's low F_a (reported to be close to 12% using *in silico* methods[47]). The low F_a resulting in low bioavailability is likely to be caused by the low cellular permeability of the charged phosphonic acid[48], and not by poor aqueous solubility or high E_h. The bioavailability of adefovir in the rat was greatly enhanced with the bis-(pivaloyloxy-methyl) prodrug to almost 40%[49]. The bis-(pivaloyloxy-methyl) prodrug, also known as adefovir dipivoxil, is now marketed as Hepsera by Gilead (TABLE 1).

MGS0039 (TABLE 1) is a recent example of a successful prodrug discovery strategy to enhance the bioavailability by increasing the F_a of ester prodrugs of the metabotropic glutamate receptor 2 (MGLUR2; also known as GRM2) antagonist[52,53]. *In vitro* screening experiments included

parent-drug release from the prodrug in human liver S9 fractions as well as *in vivo* testing in rat and monkey. The parent drug is a poorly permeable carboxylic acid, with a low permeability of less than 1×10^{-6} cm per s in the intestinal Caco-2 cell line, and no evidence of intestinal efflux. The clearance of MGS0039 is low in the rat (2.9 ml per min per kg)[50] and in the monkey (5.8 ml per min per kg)[41] with $E_h \leq 0.1$. Using equation 3 in BOX 1, an F_a of less than 0.15 can be calculated from rat and monkey *in vivo* data, indicating incomplete absorption. Combined, the data suggest that the poor bioavailability of less than 13% in rats and monkeys is caused by poor permeability, not by high hepatic extraction[41]. However, it should be noted that theoretically, intestinal metabolism of the parent drug may also be saturated with the prodrug (more accurately increased intestinal availability, F_g), so that increased bioavailability of a prodrug may be the result of an increased $F_a{*}F_g$, or absorption. For MGS0210, alkyl prodrugs did increase the bioavailability to 40–70% in the rat and up to 44% in the monkey. MGS0210 (TABLE 1), the *n*-heptyl prodrug, was chosen as the most promising candidate for further development on the basis of its high bioavailability in the monkey (39%), combined with its high parent-drug-release ratio in human S9 incubations (77%) and little or no formation of additional unknown metabolites[41].

Intestinal drug absorption may also be limited by efflux transporters, which secrete drugs and intracellularly formed metabolites back into the intestinal lumen. Well-known examples of efflux pumps are P-glycoprotein (P-gp)[51–53] and breast cancer resistant protein (BCRP)[54,55], which are expressed on the apical surfaces of the gut wall epithelium among various other tissues. Although intestinal efflux proteins may be reasons for incomplete oral absorption and variable bioavailability of drugs, particularly for parent drugs with low intestinal permeability[52,53,56], these transporters are also important to consider as a liability in terms of clinical drug–drug interactions and inter-individual variability. Various prodrugs intended to avoid efflux-protein-mediated transport of drugs from the intestinal lumen and thereby enhance the oral absorption and bioavailability of the parent drug are under preclinical investigation[57–59].

In the following sections, some of the more common prodrug approaches for improving oral drug delivery are discussed, including improved aqueous solubility, improved lipophilicity and carrier-mediated absorption.

Improved aqueous solubility. Approximately 40% of the drug candidates produced from combinatorial screening programmes have poor aqueous solubility; that is, they have an aqueous solubility of less than 10 μM[60,61]. Sometimes conventional formulation technologies, such as salt formation, particle size reduction, solubilizing excipients and complexation agents, can not provide adequate solubility. In these cases, prodrugs offer an alternative tool to overcome the solubility limitations of poorly soluble drugs when first-pass metabolism is low to moderate and not the main cause of systemic drug availability. Parent drug properties for which a solubility-enhancing prodrug strategy could be appropriate are listed in BOX 2.

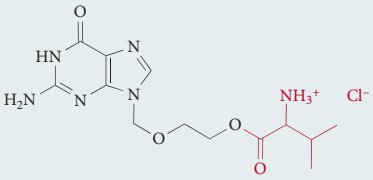
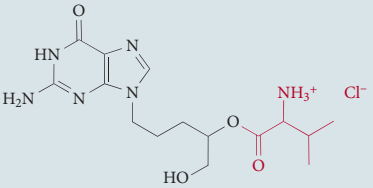
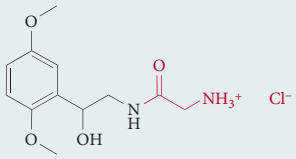
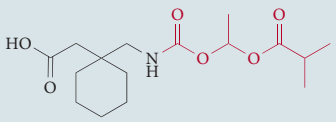
Although there are many examples of successful water-soluble prodrugs for parenteral administration, only a few water-soluble prodrugs have been developed exclusively for oral administration. Many of the water-soluble prodrugs for enhanced oral drug delivery include the addition of an ionizable progroup to the parent compound (such as a phosphate group). However, enhanced water solubility, and thus, better oral bioavailability may also be achieved by decreasing the crystal packing or by affecting the melting point of the parent drug[9].

A good example of a water-soluble oral prodrug is the non-steroidal anti-inflammatory indene derivative, sulindac (TABLE 2). This is a bioprecursor prodrug that does not contain a promoiety, but instead, its inactive sulphoxide form is reduced to the active sulphide form after oral absorption[62,63]. Sulindac sulphoxide, the prodrug, is about 100-times more water-soluble than the pharmacologically active sulphide. Greater solubility incorporated with the prodrug's optimal lipophilicity (logP 1.52 at pH 7.4) provides more efficient oral absorption[64,65].

Phosphate esters can increase the oral bioavailability of many poorly water-soluble drugs. They are especially useful for drug candidates that require a high dose and exhibit a dissolution-rate limited absorption[28]. Nearly all oral phosphate ester prodrugs are rapidly hydrolysed to the parent drug by endogenous alkaline phosphatases at the intestinal cell surface during absorption, leading to low prodrug concentrations in the systemic circulation. An example is a water-soluble phosphate ester miproxifene phosphate (TAT-59; TABLE 2), the prodrug of DP-TAT-59 (REFS 28,66). The parent drug, DP-TAT-59, has low to moderate hepatic clearance (CL_h) compared with the hepatic blood flow (Q_h) in preclinical species[66] and in humans[67], and a low E_h in the rat (0.4) and dog (0.2). DP-TAT-59 is apparently not bioavailable in preclinical species owing to the 'brickdust' nature of this parent drug, with a solubility of less than 1 μg per ml[68]. After TAT-59 prodrug dosing, DP-TAT-59 bioavailability was greatly enhanced to 28.8% in rats and 23.8% in the dog[66], and in human trials DP-TAT-59 showed dose-linear pharmacokinetics after TAT-59 dosing[69].

Another example, fosamprenavir (Lexiva/Telzir; GlaxoSmithKline) (TABLE 2), is a phosphate ester of the HIV protease inhibitor amprenavir (Agenerase; GlaxoSmithKline), which shows improved water solubility and an oral bioavailability that is equivalent or higher to that of amprenavir[70]. While the marginally water-soluble amprenavir (0.04 mg per ml) requires a high dose (1,200 mg twice a day, or 8 capsules), fosamprenavir as a calcium salt has a 10-fold higher water solubility, permitting a more simplified and patient-compliant dosage regimen (4 tablets once a day)[71,72]. Fosamprenavir is rapidly hydrolysed by gut epithelial alkaline phosphatases to amprenavir during absorption, with only minimal concentrations of fosamprenavir reaching the circulation[70,71]. Fosamprenavir is also a good example of prodrugs having improved life-cycle management over the parent drug. The additional costs to develop fosamprenavir will probably be covered by its extended patent life of 6 years over the parent amprenavir[73].

Table 4 | **Prodrugs to exploit carrier-mediated absorption**

Prodrug name (therapeutic area)	Functional group	Structure	Prodrug strategy
Valacyclovir (antiviral)	L-Valyl ester of acyclovir		• Bioconversion by valacyclovir hydrolase (valacyclovirase) • Transported predominantly by hPEPT1 • Oral bioavailability improved from 12–20% (acyclovir) to 54% (valacyclovir)[90–92,182]
Valganciclovir (antiviral)	L-Valyl ester of ganciclovir		• Bioconversion by intestinal and hepatic esterases • Transported predominantly by hPEPT1 • Oral bioavailability improved from 6% (ganciclovir) to 61% (valganciclovir)[183,184]
Midodrine (vasopressor)	Glycyl amide of desglymidodrine		• Bioconversion by unknown peptidase • Transported by hPEPT1 • Oral bioavailability improved from 50% (desglymidodrine) to 93% (midodrine)[94]
XP13512 (restless leg syndrome, neuropathic pain)	Isobutanoyloxy-ethoxy carbamate of gabapentin		• Bioconversion by esterases • Transported by both MCT1 and SMVT • Oral bioavailability improved from 25% (gabapentin) to 84% (XP13512) in monkeys[98,99]

hPEPT1, human peptide transporter 1 (also known as SLC15A1); MCT1, monocarboxylic acid transporter 1 (also known as SLC16A1); SMVT, sodium-dependent vitamin transporter (also known as SLC5A6).

Other orally administered water-soluble phosphate ester prodrugs include estramustine phosphate, prednisolone phosphate, and fludarabine phosphate (Fludara; Bayer) (TABLE 2).

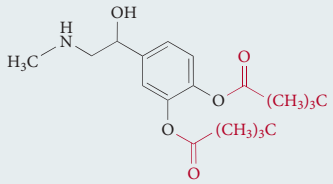
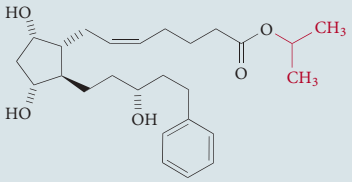
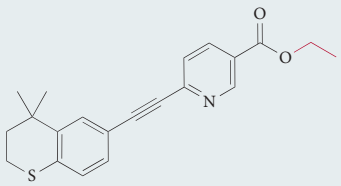
Improved lipophilicity. Prodrugs are most frequently applied to mask polar and ionizable groups within a drug molecule with the aim of improving oral drug delivery. Increasing drug lipophilicity promotes membrane permeation and oral absorption. BOX 2 lists some parent drug properties for which a permeability-enhancing prodrug strategy could be appropriate.

Some of the best examples of prodrugs in this category include ACE inhibitors and ampicillin prodrugs, which have already been described. Most nucleoside antivirals are polar, and thus poorly absorbed after oral administration. In the case of tenofovir and adefovir, high hydrophilicity of the phosphonic acid moieties have been postulated to account for their poor oral bioavailability (<5%). From a series of bis-carbonate esters of tenofovir[74], tenofovir disoproxil (Viread; Gilead) (TABLE 1) was selected for further development. In clinical studies, tenofovir disoproxil has been well tolerated, with an oral bioavailability of approximately 39%[75,76], and is now approved for the treatment of HIV[76,77]. Similarly, the lipophilic adefovir dipivoxil (TABLE 1) was developed and approved as a bis-pivalate ester prodrug for the treatment of hepatitis B after an initial trial for the treatment of HIV[78,79]. Both tenofovir disoproxil and adefovir dipivoxil are rapidly converted back to their parent drugs by esterases[74,78,79].

Oseltamivir (TABLE 1) is an oral prodrug of oseltamivir carboxylate (GS4071, Ro 64-0802), a selective inhibitor of viral neuramidase glycoprotein in influenza A and B[80–82]. As an ethyl ester, oseltamivir is rapidly and well absorbed, and increases the oral bioavailability from 5% to 79%[82,87]. Oseltamivir undergoes fast bioconversion to oseltamivir carboxylate mostly by human carboxylesterase 1 (CES1), resulting in the production of small quantities of ethanol as a by-product[80,83].

A more recent example of an ethyl ester prodrug is ximelagatran (Exanta; AstraZeneca) (TABLE 1), a prodrug of melagatran, which was the first member of orally administered direct thrombin inhibitors[84]. As a zwitterion, melagatran has an oral bioavailability of only 3–7%. Ximelagatran is a double prodrug, as, in addition to an ethyl ester group in the carboxylic acid end, it contains an *N*-hydroxyamidine group in the amidine end of melagatran. Therefore, the formation of melagatran requires two metabolic reactions. The *N*-hydroxy group is reduced to an amidine in the liver, and to some extent also in the intestine, by CYP450 enzymes. The ethyl ester is then hydrolysed to free carboxylic acid in the liver by carboxyl esterases[84,85]. The oral bioavailability of melagatran is improved up to 20% by ximelagatran[86]. Ximelagatran was

Table 5 | **Prodrugs for improved ophthalmic and dermal delivery**

Prodrug name (therapeutic area)	Functional group	Structure	Prodrug strategy
Dipivefrin (glaucoma)	Dipivalic acid diester of adrenaline		• Bioconversion by esterases • More lipophilic (600-fold) dipivefrin is able to permeate the human cornea 17-times faster than adrenaline[119,120]
Latanoprost (glaucoma)	Isopropyl ester of latanoprost acid		• Bioconversion by esterases • Improved lipophilicity achieves better ocular absorption and safety[124,186]
Tazarotene (topical skin disorders, psoriasis, acne)	Ethyl ester of tazarotenic acid		• Bioconversion by esterases • Is both a prodrug and soft drug (undergoes oxidative deactivation) • Improved lipophilicity and maintained adequate aqueous solubility; resulted in better skin permeation[131,132]

approved for marketing in Europe in 2004, but was withdrawn in February 2006 after an extended clinical trial confirmed the initial concerns of severe liver toxicity, possibly caused by the chemical template and not the promoiety[87].

Carrier-mediated absorption. Recent progress in molecular biology has allowed the identification and cloning of nutrient transporters and the elucidation of the functional and structural characteristics and regulation of these proteins[88]. Prodrugs targeted towards specific membrane transporters are designed to have structural features that would allow them to be taken up by one of the endogenous transporters present at the intestinal epithelium[89]. Targeting specific transporters is particularly important for polar or charged drugs that have negligible passive absorption.

Peptide transporters appear to be attractive targets for prodrug design, as they are widely distributed throughout the small intestine and show sufficiently high transport capacity and broad substrate specificity[32,88,89]. Good examples of prodrugs that exploit carrier-mediated transport are valacyclovir (Valtrex; GlaxoSmithKline) (TABLE 4) and valganciclovir (Valcyte; Roche) (TABLE 4). They are L-valyl esters (for example, amino-acid valine as the promoiety) of acyclovir and ganciclovir, which both have limited and variable oral bioavailability owing to their high polarity. These amino-acid prodrugs increased the intestinal permeation of their parent drugs by 3–10-fold, and their membrane transport was not passive but mediated predominantly by the di- and tripeptide transporter (hPEPT1)[90–93] expressed in the intestinal epithelial cells[94]. Following their membrane transport, both prodrugs are readily bioconverted back to their parent drugs by intracellular hydrolysis[93,95,96].

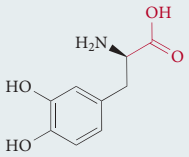
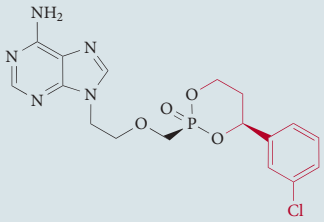
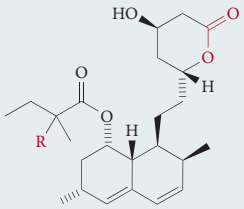
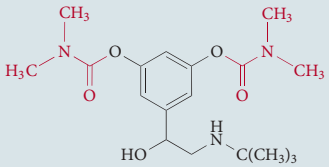
An amino-acid prodrug approach was also used in the development of an oral prodrug of desglymidodrine (DMAE), a selective α1-receptor agonist for the treatment of orthostatic hypotension[94,97]. The prodrug midodrine (TABLE 4) contains a glycine promoiety that is attached to the amine functionality of DMAE and it is converted into its active drug mainly in the liver and in the systemic circulation by unknown peptidases[97]. Midodrine is a substrate for hPEPT1, and this carrier-mediated transport raises the bioavailability of midodrine to 93%, compared with 50% for DMAE[94].

Gabapentin (Neurontin; Pfizer) is a structural analogue of GABA (γ-aminobutyric acid) that is marketed for the treatment of epilepsy and post-herpetic neuralgia. Gabapentin has suboptimal pharmacokinetic properties including saturable absorption, high inter-patient variability, lack of dose proportionality and a short half-life. XP13512 (TABLE 4) is a carbamate prodrug of gabapentin developed by Xenoport. The prodrug takes advantage of both a monocarboxylate transporter type 1 (MCT1), which is highly expressed in all segments of the colon and upper gastrointestinal tract, and a sodium-dependent multivitamin transporter (SMVT), responsible for absorption of multiple essential nutrients[98,99]. The oral bioavailability of gabapentin was increased from 25% to 84% by use of the prodrug (XP13512) in monkeys, and showed dose-proportional gabapentin exposure in humans[98]. XP13512 is currently in Phase III development for restless legs syndrome and in Phase II development for neuropathic pain.

Improved parenteral administration

There are numerous successful prodrugs with improved aqueous solubility properties for parenteral administration. The most commonly used prodrug-based approach

Table 6 | **Prodrugs for other purposes**

Prodrug name (therapeutic area)	Functional group	Structure	Prodrug strategy
Levodopa (Parkinson's disease)	Carboxylic acid of dopamine		• Crosses the blood–brain barrier and enters the brain by using LAT1 • Is decarboxylated to dopamine by aromatic amino-acid decarboxylase[136,137]
Pradefovir mesylate (antiviral)	2-(3-chlorophenyl)-[1,3,2]di oxaphosphinane of adefovir		• Undergoes cytochrome P450-catalyzed oxidation to adefovir predominantly in the liver[154,155,187]
Simvastatin, R= CH_3; lovastatin, R=H (hypercho-lesterolaemia)	Inactive lactone forms		• Bioprecursor prodrugs that are converted into the active hydroxyl acid forms in the liver[156,157,188]
Bambuterol (asthma)	Bisdimethylcarbamate of terbutaline		• Prolongs duration of drug action • Undergoes cascade of hydrolysis and oxidation reactions to terbutaline[163,165]

LAT1, type 1 L-type amino-acid transporter.

to increase water solubility is to introduce an ionizable/polar promoiety to the parent drug. As the increase in solubility imparted by the dianionic phosphate group is often of several orders of magnitude, several phosphoric acid esters have been developed as potential water-soluble prodrugs for parenteral administration and, less commonly, for oral administration.

Fosphenytoin (Cerebyx; Pfizer/Eisai) (TABLE 3) is a phosphate ester prodrug of poorly water-soluble phenytoin for the acute treatment of seizures, and can be used for both intravenous and intramuscular administration[100,101]. In fosphenytoin, a phosphate ester is attached to a weakly acidic (pK_a = 8.3) amine functionality of phenytoin via an oxymethyl spacer group, leading to a remarkable increase in aqueous solubility (from 20–25 μg per ml to 140 mg per ml)[102]. Following intravenous administration in patients with epilepsy, endogenous alkaline phosphatases completely convert fosphenytoin back to phenytoin, with a half-life ranging from 7–15 minutes[101,102]. As an oxymethyl-linked prodrug, the bioconversion of fosphenytoin leads to the liberation of formaldehyde within the body[103]. The recovery of phenytoin is almost quantitative, with only 1–5% of the fosphenytoin dose being recovered in urine[100].

A phosphate prodrug approach was also applied to fluconazole (Diflucan; Pfizer), which is a broad-spectrum antifungal drug marketed in both oral and intravenous formulations[104]. The phosphate prodrug fosfluconazole (Procif; TABLE 3) has been marketed in Japan since 2003. It exhibits an aqueous solubility of over 300 mg per ml as its disodium salt, which allows lower dosing volumes for bolus administration as well as higher intravenous doses. Fosfluconazole is almost completely converted to fluconazole in humans following an intravenous bolus dose of up to 2,000 mg, with less than 4% of the given dose excreted intact in the urine[105].

Two different phosphate prodrugs of propofol, a highly lipophilic but potent anaesthetic agent, have been developed and tested in clinical trials. Phosphonooxymethyl propofol (TABLE 3) is an oxymethyl-linked phosphate derivative of propofol[106], and propofol phosphate (TABLE 3) is a simple phosphate derivative of propofol[107]. Phosphonooxymethyl propofol forms propofol and gives a maximum plasma concentration (T_{max}) more rapidly than propofol phosphate. This may be due to steric hindrance from two large isopropyl groups on either side of the hydroxyl group of the parent drug. The oxymethyl group of phosphonooxymethyl propofol reduces this

steric hindrance around the hydroxyl group, and the rate of bioconversion is enhanced and T_{max} is achieved earlier[108].

Irinotecan (CPT-11, Camptosar; Pfizer) (TABLE 3) is a parenteral water-soluble carbamate prodrug of the lipophilic antineoplastic topoisomerase I inhibitor, camptothecin (SN-38). It represents an alternative ionizable promoiety for improved aqueous solubility[109–112]. In the irinotecan molecule, a dipiperidino promoiety is attached to the phenol moiety of camptothecin by a carbamate bond. The bioconversion back to camptothecin occurs primarily in the liver, and to a minor extent in tumours[113], by human carboxylesterases[110]. Both irinotecan and camptothecin exist in a pH-dependent equilibrium between lactone and carboxylate forms, of which the lactone is the pharmacologically active form[114]. The T_{max} of camptothecin was reached in 2.3 hours after intravenous administration of irinotecan[114]. It should be noted that the dose-limiting toxicities of the parent drug camptothecin are not altered with the prodrug[115].

Improved topical administration

The topical administration of drugs encompasses all external membranes, but here we consider only ocular and dermal prodrug applications.

Ophthalmic drug delivery. The corneal barrier limits the permeation of topically administered ophthalmic drugs into the intraocular tissues. As a result, only a small percentage of the applied dose is absorbed, most (50–99%) of which escapes into the systemic circulation[116]. Prodrugs were introduced to ophthalmology about 30 years ago when ocular absorption of adrenaline was substantially improved by the use of its prodrug, dipivalyl adrenaline (dipivefrin)[117,118]. Dipivefrin (TABLE 5), a dipivalic acid diester of adrenaline, penetrates the human cornea 17-times more rapidly than adrenaline[119], owing to its 600-fold increase in lipophilicity (at pH 7.2) compared with that of adrenaline[120]. Consequently, a 0.1% dipivefrine eyedrop is only slightly less effective at lowering intraocular pressure than a 2% adrenaline hydrochloride eyedrop[121]. In addition, systemic side effects are greatly reduced[122].

The prostaglandin analogues latanoprost (Xalatan; Pfizer) (TABLE 5), bimatoprost (Lumigan; Allergan), travoprost (Travatan; Alcon) and unoprostone isopropyl (Rescula; Santen/Novartis) represent a new class of active ocular hypotensive agents for the treatment of glaucoma. They are lipophilic isopropyl ester (latanoprost, travoprost, unoprostone) or ethanolamine amide (bimatoprost) prodrugs that are rapidly hydrolysed inside ocular tissue to biologically active prostaglandins[123–126]. In their carboxylic acid forms, these agents are poorly permeable and cause irritation, whereas the lipophilic prodrugs achieve improved ocular absorption and safety.

Dermal drug delivery. The unfavourable physicochemical properties of many drug molecules lead to poor permeation across the skin, in particular through the most superficial layer, the stratum corneum, which provides high resistance for topical drug delivery. Numerous studies have demonstrated that both water and lipid solubilities, or a balance of the two, are important in the optimization of drug permeation[127–130]. These optimal features can often be achieved by prodrugs. In the case of tazarotene (Tazorac; Allergan) (TABLE 5), its active carboxylic acid form is esterified to a more lipophilic ethyl ester, which still maintains adequate water solubility[131,132]. Tazarotene was effectively and reliably absorbed percutaneously, exerted less skin irritation and was rapidly converted to tazarotenic acid[133,134]. The less lipophilic tazarotenic acid subsequently released, showed no accumulation in fat and other tissues in part due to the reduced systemic half-life of this parent drug[135], achieved by the introduction of a metabolically labile sulphur group that undergoes rapid oxidative deactivation and thus prevents accumulation in tissues. Thus, tazarotene is not only a carboxylic acid prodrug with enhanced skin permeability, but it is also a soft drug with enhanced systemic metabolism. Both can be important features for drugs aimed at topical treatment.

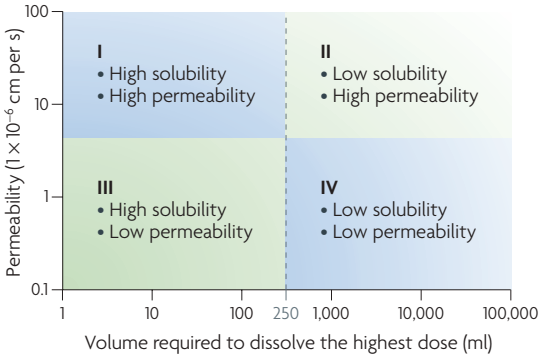


Figure 2 | **Biopharmaceutical Classification System (BCS) characterization of drugs based on solubility and permeability measures.** Many successful prodrugs are those of parent drugs from BCS Classes II and III (shown in green). Prodrugs of BCS Class II parent drugs enhance solubility, whereas prodrugs of BCS Class III parent drugs are designed to enhance permeability[38]. The x-axis shows the volume (ml) required to dissolve the highest dose strength of the parent drug at the lowest solubility over the pH 1–7.5. A parent drug is considered 'highly soluble' when the highest dose strength is soluble in <250 ml water over a pH range of 1–7.5, in which 250 ml reflects the so-called FDA glass of water. Permeability is defined by various *in vivo* or *in vitro* assays, and a permeable drug is one associated with ≥90% oral bioavailability or ≥90% absorption as assessed by urinary excretion data.

Site-selective drug delivery

An ultimate goal in drug delivery is that it is site selective, and this may be the most exciting possibility that prodrugs offer. Site selectivity may be achieved in four different ways: by passive drug enrichment in the organ; through transporter-mediated delivery; by selective metabolic activation through enzymes; and by antigen targeting[4]. Examples of the most frequently studied applications are listed in sub-sections below. It is to be noted, however, that possible prodrug applications are not restricted to those listed.

Box 2 | **Parent-drug properties and prodrug strategies**

Solubility-enhancing strategy

A solubility-enhancing strategy can be applied when low intestinal solubility or dissolution rate of the parent drug is a barrier to bioavailability, but not hepatic metabolism:

- Parent is a Biopharmaceutical Classification System (BCS) Class II drug (low solubility, high permeability).
- High dose/solubility ratio, that is, the highest targeted parent drug dose will only dissolve in volumes much larger than 250 ml over a pH range of 1–7.5.
- Low or moderate hepatic clearance, CL_h, in rats or preclinical species.
- Hepatic extraction ratio, E_h, is less than 0.5.
- High permeability in *in vitro* assays such as Caco-2.
- Fraction of dose absorbed after oral administration, F_a, is calculated or measured to be low (less than ~25%).

Permeability-enhancing strategy

A permeability-enhancing strategy can be applied when low intestinal permeability of the parent drug is a major barrier to bioavailability, but not hepatic metabolism:

- Parent is a BCS Class III drug (high solubility, low permeability).
- Low or moderate CL_h in the rat or other preclinical species.
- E_h less than 0.5.
- Low *in vitro* permeability in screening assays such as Caco-2.
- F_a is calculated or measured to be low (less than ~25%).

Central nervous system (CNS) drug delivery. Clinically, the CNS is one of the most challenging organs to target, mainly due to the blood–brain barrier (BBB). However, by understanding the transport mechanisms and enzymatic activity at the BBB, it is often possible to achieve substantially enhanced CNS delivery relative to other sites of the body. For example, the prodrug of dopamine, Levodopa (TABLE 6), is a substrate for the neutral amino-acid transporter (LAT1) expressed at the BBB[136,137]. Having entered the brain tissue, Levodopa is rapidly converted back to dopamine, and being a very hydrophilic molecule, it is trapped there, enabling its pharmacodynamic effects.

A traditional approach to increase CNS drug concentration has been to increase the lipophilicity of the parent drug. For this approach to be successful the prodrug must have easy access to the brain tissue, bioconversion back to the parent drug should be highly site-selective, and the parent drug should exhibit prolonged retention within the brain tissue[138]. Once the lipophilicity of the drug is increased by the development of a prodrug, it has improved access to the CNS. However, increased lipophilicity alone does not ensure a higher concentration of the parent drug in the target tissue. Bioconversion in the target tissue needs to be rapid and selective enough to compete with elimination, and also to ensure that any premature bioconversion of the prodrug is kept to a minimum.

Tumour targeting. The aim in cancer therapy is to target an inactive prodrug selectively to tumour cells, where the active drug may then be released without causing toxicity to normal, healthy tissue[139,140]. Owing to the high proliferation rates of tumour cells, in addition to bioreductive activity, the levels of certain enzymes are often elevated in these cells and have been exploited in targeted prodrug-tumour delivery[141]. A need for reduced normal tissue exposure of the cytotoxic drug, 5-fluorouracil (5-FU), has led to the development of a prodrug that is activated by tumour-selective enzymes[142,143]. Capecitabine (Xeloda; Roche) (FIG. 3) is an orally administered carbamate prodrug of 5-FU that requires a cascade of three enzymes for the bioconversion to the active drug[144] (FIG. 3). Intact capecitabine is absorbed from the intestine and undergoes bioconversion in tumours, thus, avoiding any systemic toxicity[144,145]. The bioavailability of 5-FU after oral administration of cabecitabine is almost 100% and the T_{max} of 5-FU is reached within 1.5–2 hours[143].

To expand the range of tumours susceptible to enzyme-prodrug cancer therapy, prodrug-activating exogenous enzymes can be delivered to tumour cells by using antibodies or genes. The most common approaches are antibody-directed enzyme prodrug therapy (ADEPT) and gene-directed enzyme prodrug therapy (GDEPT). ADEPT is a two-step therapy, in which the enzyme–antibody conjugate first binds to a tumour-specific antigen on the malignant cell membrane[139,140,146,147]. The inactive prodrug is then administered and activated to a cytotoxic drug by the localized enzyme. The principle of GDEPT is similar, but the enzyme is localized to tumour cells using a targeting vector to deliver the gene encoding the enzyme[148,149]. Some ADEPT systems have progressed to clinical Phase I studies[150–152], and one GDEPT has reached Phase III clinical trials[149].

Liver-targeted delivery. Of all organs, the liver may hold the greatest potential for organ-specific targeted drug delivery, because, as the metabolizing organ, it possesses a wide variety of liver-specific metabolizing enzymes[153] that are capable of prodrug activation. Pradefovir mesylate (TABLE 6) is a cyclic 1,3-propanyl ester prodrug of a nucleoside monophosphate (NMP), adefovir, that is under development for the treatment of hepatitis B[154,155]. Pradefovir undergoes a CYP450-catalysed oxidation reaction predominantly in hepatocytes in the liver[155]. In Phase II clinical trials in patients with hepatitis B, pradefovir has demonstrated good efficacy with low systemic adefovir levels, which is indirect evidence for liver targeting[154].

Simvastatin (Zocor; Merck) and lovastatin (for example, Mevacor; Merck) are bioprecursor prodrugs of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors used in the treatment of hypercholesterolaemia (TABLE 6). Simvastatin and lovastatin are administered in their inactive hydrophobic lactone forms, which are then transformed into the active hydroxy acid forms in the liver[156,157]. Moreover, the lactone ring present in cyclic lactone undergoes relatively rapid metabolism by CYP450 enzymes. Lipophilic simvastatin and lovastatin are well absorbed from the gastrointestinal tract and are taken up by hepatocytes by a transport mechanism[157–159]. Both prodrugs are highly extracted by the liver, and their bioavailability is only 5% or less, in part due to CYP3A4 /P-gp-mediated clearance and metabolism of prodrugs in the intestine and in the liver[157].

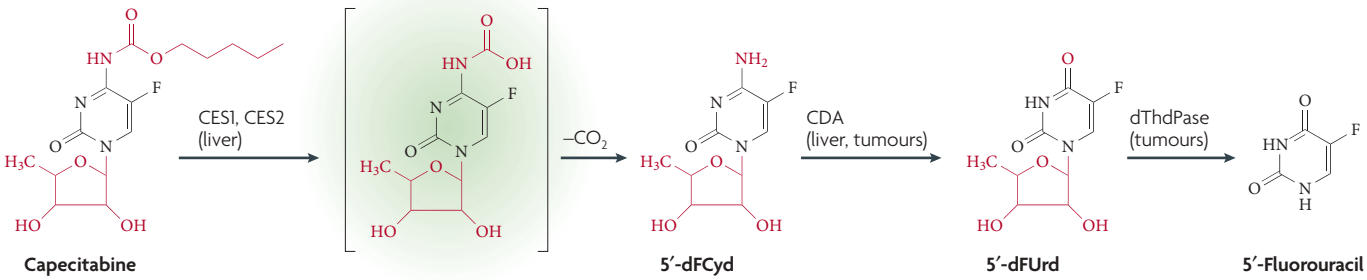


Figure 3 | **Capecitabine as an example of a prodrug that requires multiple enzymatic activation steps.** Capecitabine (Xeloda) is a prodrug that has reduced gastrointestinal toxicity and high tumour selectivity. The enzymatic bioconversion pathway initiates in the liver, where human carboxylesterases 1 and 2 (CES1 and CES2) cleave the ester bond of the carbamate[142]. This is followed by a fast, spontaneous decarboxylation reaction resulting in 5′-deoxy-5-fluorocytidine (5′-dFCyd)[144]. Generation of the parent drug continues in the liver, and to some extent in tumours, by cytidine deaminase (CDA), which converts 5′-dFCyd to 5′-deoxyuridine (5′-dFUrd). Finally, thymidine phosphorylase (dThdPase; also known as ECGF1) liberates the active drug 5′-fluorouracil in tumours[7,144].

Prolonged duration of drug action

Although various pharmaceutical formulations are frequently used to prolong the duration of drug action, a few examples that use prodrugs exist. Highly lipophilic prodrugs of several steroids (for example, testosterone nandrolone) and neuroleptics (for example, fluphenazine, flupenthixol, haloperidol) are slowly released in the circulation from the site of intramuscular injection and result in a prolonged duration of action[160,161]. Once released from the injection site, prodrugs are usually rapidly bioconverted, with no attenuation of their therapeutic action in most cases. As an example, the onset of action of fluphenazine is generally between 24–72 hours after injection of its lipophilic decanoate ester prodrug, which continues for 1–8 weeks with an average duration of 3–4 weeks[162].

In the case of the bronchodilator and β_2-agonist terbutaline, sustained drug action is provided with its bisdimethylcarbamate prodrug, bambuterol (TABLE 6). Protection of a phenolic moiety, which is susceptible for rapid and extensive pre-systemic metabolism, also avoids first-pass intestinal and hepatic metabolism. After oral administration, bambuterol is slowly bioconverted to terbutaline, predominantly outside the lungs via a cascade of hydrolysis and oxidation reactions[163,164]. As a result of prolonged action, a once-daily bambuterol treatment provides relief of asthma symptoms with a lower incidence of side effects than terbutaline, which is taken three times a day[165].

Safety assessment of prodrugs

In general, while the fundamental process of safety assessment for a prodrug is no different to that of any other drug molecule, the extra facets provided by prodrugs are likely to require additional consideration and, therefore, effort and cost. However, considering the high cost of drug development and the low rate of drug success, carefully designed prodrugs will warrant the increased costs of additional complexity. The safety assessment of prodrugs was recently comprehensively reviewed[166], and is briefly discussed below.

When considering prodrugs, a prerequisite is the lack of toxicity of the promoieties. The choice of promoiety should be considered with respect to the disease state, dose and the duration of therapy. A risk assessment is often worthwhile if a questionable structure provides properties superior to that of other structures. Two frequently discussed examples are formaldehyde- and pivalate-releasing promoieties. There are several marketed prodrugs (for example, fosphenytoin, tenofovir disoproxil fumarate, propofol phosphate), in which formaldehyde is being released in the body during the bioactivation process. A good example of pivaloyl derivatives that form the pivalate-group (trimethylacetic acid) and that may interrupt carnitine homeostasis in humans[167] is adefovir dipivoxil. Despite common concerns, normal formaldehyde input from the diet and the environment exceeds the exposure from formaldehyde-releasing prodrugs[2], and simultaneous carnitine supplementation may be administered with a pivalate-generating prodrug[167].

Perspectives

The prodrug approach to drug design is a versatile, powerful method that can be applied to a wide range of drug administration routes and formulations for many types of parent drug molecule. However, for prodrug strategies to be successful, analysis of parent-drug properties and the proper identification of barriers are crucial. Clinically, the majority of prodrugs are used with the aim of enhancing drug permeation by increasing lipophilicity and more recently by improving water solubility.

However, there are significant needs that have not yet been adequately addressed by prodrugs. It is surprising how few marketed prodrug examples exist for cancer therapy, such as those designed to increase site-selective drug delivery, despite the prominent side effects of anticancer agents. In addition prevention of pre-systemic drug metabolism and the circumvention of efflux-limited drug absorption and distribution have not received enough attention in prodrug research, despite great possibilities.

In summary, prodrugs have become an integral part of the drug design and delivery process, as illustrated by the increasing number of approved prodrugs and patents. We anticipate that an increased application of rational prodrug approaches at early stages of the drug discovery process by multidisciplinary teams including medicinal chemists, pharmaceutical chemists, and drug metabolism and pharmacokinetic scientists will lead to the development of compounds with better drug-like properties.

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FURTHER INFORMATION

Biopharmaceutical Classification System:
http://www.fda.gov/cder/OPS/BCS_guidance.htm

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3.3

Prodrugs of Amines

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Introduction

The amine group is one of the most frequently found functional groups in today's armory of commercially available drugs. Like many pharmaceuticals, compounds containing an amine can have physicochemical attributes that present obstacles to their safe and effective delivery to desired sites of action. Amines are generally considered to be amenable to derivatization reactions and thus provide a "synthetic handle" that can be exploited in chemical modifications. As a result, numerous prodrugs of amines have been evaluated in an effort to overcome formulation and delivery barriers, which include low aqueous solubility, toxicity of the vehicle, poor membrane permeability, chemical and metabolic instability, and lack of specificity

An amine, by definition, is considered to be any hydrocarbon derivative of ammonia. Amines are generally classified as primary, secondary, tertiary or quaternary, depending on the degree of hydrocarbon substitution, and they can be further classified as aliphatic, aromatic or heterocyclic. Aliphatic amines typically have alkyl substituents whereas aromatic amines are coupled to at least one aromatic group. Heterocyclic amines have a nitrogen contained within a ring system, which may be partially or fully unsaturated.

An important physicochemical characteristic of amines is their basicity, or propensity to accept a proton and form the respective conjugate acid, according to the Brönsted-Lowrey classification. Accordingly, the pKa value associated with an amine is a reflection of its ability to share the associated lone pare of electrons in the formation of a bond with hydrogen. This pKa value is influenced by electronic and steric properties as well as the hybridization state. Electron-withdrawing substituents decrease the strength of the base (*i.e.*, lower pKa). Alternatively, electron-donating substituents (*i.e.*, methoxy) increase the basicity and assist in stabilization of the positively charged conjugate acid. These influences on basicity can occur either through inductive or resonance effects. Steric factors can hinder hydrogen bond formation and result in reductions in basicity. Amines bonded to bulky alkyl groups will generally have lower pKa values than corresponding amines with more exposed lone pairs of electrons. The hybridization state of the amine is also an important determinant in basicity as it reflects how close electrons are to the nitrogen nucleus. Aliphatic sp^3 hybridized amines are generally more basic than sp^2 hybridized heterocyclic amines.

From a synthetic point of view, it is also important to consider the nucleophilicity of the amine. Basicity and nucleophilicity often correlate with one another; however, it is important to realize the distinction between these two properties. Basicity, expressed by pKa values, is an equilibrium constant for reversible protonation whereas nucleophilicity refers to the rate of a chemical reaction at an electrophilic center. Many of the same factors that influence pKa will influence nucleophilicity; however, as previously mentioned, steric factors often lead to greater reduction in chemical reactivity than they do in basicity.

Produgs highlighted in this chapter were created in order to overcome many different barriers. It is important to consider how the addition of the promoiety will change the properties of the parent drug and how this fits in with the intended

purpose. One important consideration is the influence of derivatization on the pKa of the parent drug. Typically, derivatizations of amines will result in reductions in both basicity and nucleophilicity. Reductions in basicity would be favorable for improving the rate of diffusion across biological membranes since at a given pH the percent of the molecule existing in the unionized state will increase. Reductions in nucleophilicity have been exploited in efforts to improve the chemical stability of parent amines that are prone to intermolecular aminolysis reactions.

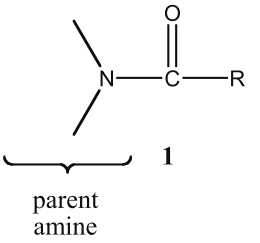
It is also important to focus on the physicochemical and structural properties of the promoiety itself. Some promoieties are considered hydrophilic and are designed to improve the water solubility of parent drugs. Conversely, others are lipophilic and are designed to improve membrane permeability. Another, less obvious, effect of amine derivatization is changes in intermolecular interactions between molecules in the crystalline state. Prodrugs that decrease the extent of these interactions will be expected to have increased dissolution rates and possibly higher water solubility. Therefore, it is conceivable that a prodrug could have both increased water solubility and membrane permeability relative to the parent amine.

Additionally, structural design of promoieties has been optimized in order to make prodrugs with improved specificity for target sites. This has been accomplished by designing promoieties that are substrates for enzymes specifically localized at the desired sites of action. Obviously, one must consider all of these contributions collectively when designing a successful prodrug.

With this introduction, the remainder of this chapter will focus on specific chemical strategies to derivatize amines. The prodrug strategies reviewed here will be categorized according to the type of promoiety employed rather than the intended use of the prodrug. There are several excellent and comprehensive reviews that pertain to prodrug strategies for amines that follow a similar format. The most extensive reviews, although somewhat dated, were compiled by Pitman (1981) and Bundgaard (1985). Since these early reviews, several book chapters and reviews have focused on this topic as well (Roche, 1987; Sloan, 1992; Hu 2005). Testa and Mayer (2003) have also recently published a book devoted to the hydrolysis mechanisms of prodrugs that also include various amine prodrugs.

This chapter includes examples of some earlier work on prodrugs covered in previous reviews to give a historical perspective and for the sake of completeness. However, emphasis is given to newer prodrug concepts as well as how some of the more classical approaches have been used and optimized in recent years.

N-Acyl derivatives



Structure 1.

Acylated amines are defined here as the category of prodrugs that take on the general structure 1. When R is a hydrocarbon, the prodrug is a true acyl prodrug; however, very few successful examples of such prodrugs exist in the literature. Simple acylation of amines leads to the creation of amides, which are well known for their resistance to both chemical and enzymatic hydrolysis.

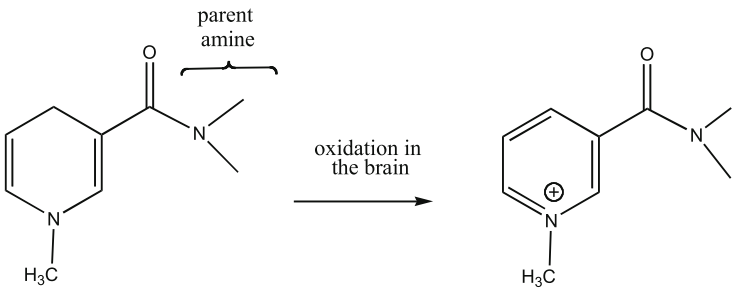
Prodrugs of dopamine (**1**, R = glycosyl) were synthesized and were shown to be too stable for use as prodrugs in *in vivo* mice studies (Fernandez *et al.*, 2000). Zhu *et al.* (2001) have tried to capitalize on this slow release profile; they coupled a model primary amine to oxidized cellulose and evaluated its usefulness as a prodrug for sustained release purposes. The authors found that the hydrolysis in buffer and in rat liver homogenate was minimal even after days of incubation, thus illustrating the stability of this hindered amide linkage.

Both amidases and esterases exist that can facilitate the hydrolysis of certain amide prodrugs (Testa and Mayer, 2003). Typically, these enzymes have a fairly narrow window of substrates that they can hydrolyze. Steric factors, both at the amine and acyl ends of the amide, play a significant role in affecting the enzymes' activity. Stark *et al.* (2001) synthesized a prodrug (**1**, R = palmityl) on the primary amine of (R)-α-methylhistamine and showed that it was subject to a relatively fast *in vivo* hydrolysis in studies with mice. The specific enzyme responsible for the accelerated hydrolysis was not identified.

The lability of amides in buffer can be relatively high depending on the characteristics of the parent amine. The chemical hydrolysis is pH dependent and has been shown to increase if the lone pair of electrons associated with the acylated amine are substantially delocalized. This was demonstrated with a variety of amide prodrugs of theophylline and allopurinol, which have half-lives of less than 30 min at pH 7.4 (Higuchi *et al.*, 1971; Lee *et al.*, 1979; Bundgaard and Falch, 1985).

Bodor and colleagues have pioneered work in central nervous system (CNS) targeted delivery of prodrugs (**2**) which contain an amide linkage (Simpkins and Bodor, 1994). This strategy has been applied to phenyethylamine and dopamine (Bodor and Farag, 1983a,b).

These prodrugs were designed specifically to enhance penetration of amines across the blood-brain barrier (BBB) into the CNS. Amines, normally ionized at physiological pH, have difficulty crossing the BBB unless an endogenous



2 **3**

Structures 2 and 3.

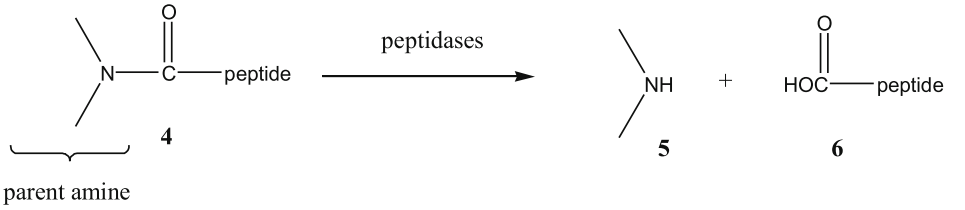
transport mechanism is involved. Linking such drugs to dihydropyridine gave the prodrugs the ability to penetrate all membranes, including the BBB. The prodrug is subsequently oxidized enzymatically to the quaternary salt (**3**) in the CNS. The quaternary intermediate is considered to be membrane impermeable and thus "trapped" in the brain. Slow hydrolysis of the amide then yields sustained delivery of the parent amine in the brain.

In the previous strategy, slow hydrolysis *in vivo* was acceptable because the clearance of the prodrug from the CNS was extremely slow due to the quaternary nature of the oxidized salt. In most other prodrug applications, faster *in vivo* conversion is required. A number of creative strategies have been described that have led to N-acylated prodrugs with dramatically accelerated bioreversion characteristics. The majority of these approaches utilize two different methods for increasing hydrolysis rates. The first strategy exploits peptidases and the second utilizes an intramolecular cyclization approach to catalyze the cleavage of the amide. These strategies are highlighted in the following two sections.

Peptidase-assisted Cleavage

Peptidase proteolytic activity can be found in all biological tissues and fluids. One strategy to facilitate the *in vivo* hydrolysis is to design prodrugs that are substrates for these enzymes. This strategy is depicted in Scheme 1.

The first prodrugs designed to be substrates for peptidase-assisted cleavage utilized γ-glutamic acid. Prodrugs of dopamine, L-dopa, and sulfamethoxazole (**4**, R = L-glutamine) were readily hydrolyzed after *in vivo* administration in a variety of animals (Orlowski and Wilk, 1977; Wilk *et al.*, 1978). Interestingly, the



4 **5** **6**

Scheme 1.

enzyme responsible for the cleavage, γ-glutamyl transpeptidase, is highly concentrated in kidneys. Such prodrugs have been shown to provide kidney-specific release of parent amine (**5**) and the conjugated peptide or amino acid (**6**). However, Drieman *et al.* (1993) demonstrated that the strategy was not universally applicable to all drugs coupled to L-glutamine. Some prodrugs studied were either susceptible to kidney active transport mechanisms or were not substrates for γ-glutamly transpeptidase.

Other amino acid and peptide derivatives of amines have been shown to be enzymatically labile to varying degrees. Some were designed to be substrates of plasmin, a protease that is shown to have higher activity in tumor cells (Evers *et al.*, 1982). The anticancer agents acivicin, phenylenediamine and doxorubicin were all derivatized with the tri-peptide D-Val-Leu-Lys to create prodrugs that were shown to have increased conversion to the respective parent compounds in cancer cell lines compared to non-transformed fibroblasts (Carl *et al.*, 1980; Chakravarty *et al.*, 1983a,b).

Tumor-selective delivery of anticancer drugs by a prostate-specific antigen (PSA)-targeted peptide conjugates of drugs has been described. Wong *et al.* (2001) investigated a prodrug of doxorubicin containing the substrate for PSA, a seven amino acid peptide. The peptide was conjugated to the primary amine of doxorubicin in an attempt to specifically localize the free drug to prostate cancer cells, which have high expression of PSA. Following intravenous administration of the prodrug in a nude mouse xenograft model of human prostate cancer, a 2.5-fold increase in tumor-associated doxorubicin was observed relative to equimolar injections of parent drug.

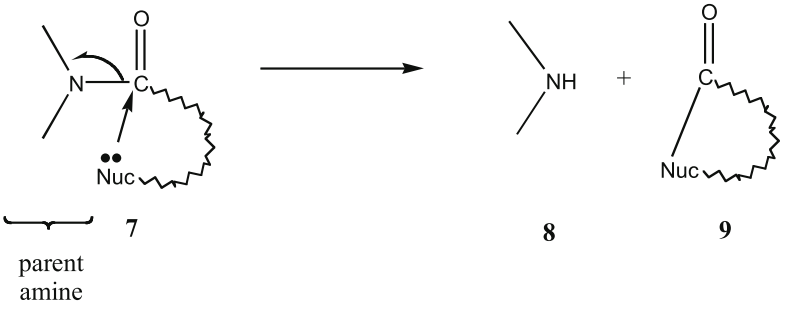
In an attempt to improve water solubility of amines, Pochopin and co-workers (1994) evaluated the utility of amino acid prodrugs of dapsone. The authors compared the *in vivo* conversion kinetics in rabbits of prodrugs that contained L and D amino acids. The D amino acid prodrugs had half-lives in the range of 30 min to 1 h whereas L forms had corresponding values of less than 2 min. This work suggests that the peptidase responsible for cleavage is stereospecific. Another possibility is that different enzymes are responsible for the different prodrug isoforms, as the authors noted, and that D-amino acid analogs were not labile in whole blood samples while L-forms were.

Several prodrugs utilizing peptidase assisted cleavage have been commercially quite successful. Examples include N-acetyl-L-cysteine and midodrine. N-Acetyl-L-cysteine is probably the most successful example (Chasseaud, 1974; Zera and Nagasawa, 1980). This prodrug is enzymatically deacetylated *in vivo* to yield cysteine, which is a biosynthetic precursor of glutathione. Midodrine is a glycinamide prodrug that yields desglymidodrine, an α agonist, following *in vivo* exposure (McClellan *et al.*, 1998; Cruz, 2000).

Promoetiy-assisted Cleavage

A second method for increasing the hydrolysis rate of N-acyl prodrugs is to design promoieties that undergo an intramolecular cyclization reaction to release

the parent amine (**8**) and the cyclized promoiety (**9**). A general diagram for this approach is shown in Scheme 2.



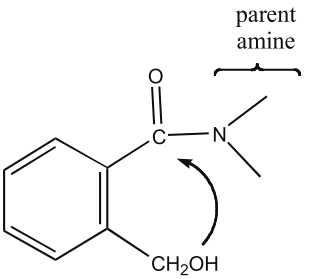
Scheme 2.

Specially designed acyl groups that participate in such a reaction have been described. One of the first applications of this strategy was with 2-hydroxymethylbenzamide conjugates (**10**), which undergo cyclization in aqueous solution to release phthalide and the free amine (Belke *et al.*, 1971; Okuyama *et al.*, 1973; Chiong *et al.*,1975).

Although the intramolecular catalysis was shown to increase the hydrolysis rate, it was still quite slow. Subsequent studies have demonstrated that substitutions of the ring and methylene hydrogens of **10** lead to derivatives with hydrolysis rates 10,000-fold faster than those of underivatized analogs (Fife and Benjamin, 1974; Chiong *et al.*, 1975). Replacement of the primary hydroxyl group in **10** with a primary amine has also been shown to lead to prodrugs with rapid intramolecular aminolysis to give the parent amine and phthalimidine (Fife and DeMark, 1976). Other structural variations on this basic strategy have been investigated, many of which were able to display significant improvements in ring cyclization rates (Cain, 1976; Nielsen and Bundgaard, 1986).

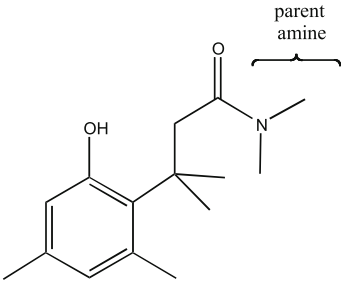
A noteworthy example was described by Amsberry and Borchardt (1990) who have shown a dramatic enhancement in the lactonization rate of hydroxyamides by incorporating a "trimethyl lock" series of substitutions (**11**), which led to a half-life of 65 s at pH 7.5 for release of the parent amine.

The authors subsequently described a double prodrug strategy that involved esters on the phenol groups of **11** (Amsberry *et al.*, 1991). In doing so the authors



10

Structure 10.



11

Structure 11.

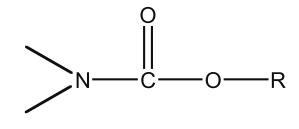
demonstrated that the rate-determining step in the formation of the parent drug was now controlled by esterase activity. This approach is attractive in that the prodrugs are quite stabile at neutral pH conditions but rapidly release parent amine after *in vivo* exposure to esterases. This same methodology has been used to link amine-containing drugs to polyethylene glycol for potential applications in targeting drugs to tumors, relying on the enhanced permeation and retention effect of polymeric molecules (Greenwald *et al.*, 1999).

In a similar approach to the trimethly lock system, Wang *et al.* (1998) have shown that lactonization of O-hydroxy-cis-cinnamic amides to coumarins is fast and can be considered to be a useful prodrug strategy for derivatizing amines

A number of other triggering mechanisms to initiate the lactonization steps in prodrug release have been described. For reviews see Shan *et al.* (1997) and Testa and Mayer (1998). Because of the high reductive capacity of many tumor cells, potential tumor specific prodrugs have been designed that rely upon reduction as a triggering mechanism for bioconversion. Amsberry and Borchardt (1991) also developed a double prodrug concept that requires quinine reduction to trigger the timethyl lock lactonization reaction. Similarly, Sykes *et al.* (1999) have investigated a series of model prodrugs that require nitro-to-hydroxylamine reduction, which can then undergo fast intramolecular cyclization to release the parent amine.

Carbamates

The carbamate functionality has been utilized in many prodrug strategies designed for amines (**12**). As will be discussed, all carbamate-type derivatives are at least double prodrugs, some are considered to be higher order (*i.e*, triple, etc.).



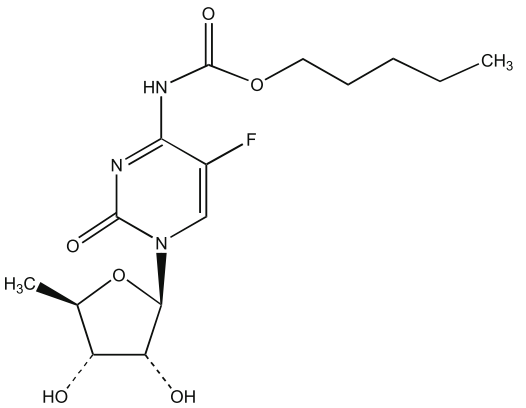
12

Structure 12.

Simple carbamic acids of amines (**12**, R = H) are too unstable for use as prodrugs as they quickly break down to generate carbon dioxide and the parent amine. Esters of carbamic acids are therefore employed in prodrug strategies. In such cases, the rate-determining step in bioreversion is the removal of the alcohol (R in **12**). The hydrolysis of the carbamic acid esters *in vivo* is generally thought to be catalyzed by esterases as there does not appear to be a carbamate-specific enzyme in mammals. Cholinesterases have been shown to specifically hydrolyze some carbamates; however, their rates for doing so are quite slow and could not account for the relatively fast *in vivo* hydrolysis (Wilson *et al.*, 1961).

When R in **12** is a simple hydrocarbon, the resultant prodrugs are quite stable and typically are not very effective (Kupchan and Isenberg, 1967). A notable exception to this generalization is capecitabine (**13**), the commercially available prodrug of 5-fluorouracil (5-FU), an anticancer agent (Tsukamoto *et al.*, 2001).

This prodrug was designed to improve the oral bioavailability and specificity of 5-FU to tumor cells. The ester in **13** is readily removed by liver carboxylesterase following oral absorption and the remaining transformations to 5-FU are catalyzed by cytidine deaminase and thymidine phosphorylase. The latter enzyme is highly enriched in tumors, thus providing selective release of 5-FU in cancer cells. This prodrug is currently approved as a first line of therapy for colorectal and breast cancers, and is also approved for use in combination with other anticancer drugs (Walko and Lindley, 2005).



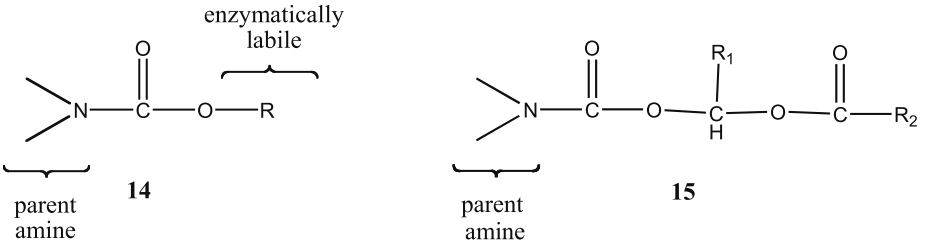
13

Structure 13.

Double Prodrugs

Considering the inherent stability of most simple carbamic acid alkyl esters, a variety of double prodrug strategies have been designed that take on the general structure **14**. R groups are designed to be enzymatically labile and will, in turn, release the carbamic acid that readily decomposes to give the parent amine.

Theoretically, such prodrugs could then have good chemical stability and *in vivo* lability. Accordingly, (acyl-oxy)alkylcarbamates (**15**) have been explored as bioreversible prodrugs of amines. Some of the pioneering work in this area was

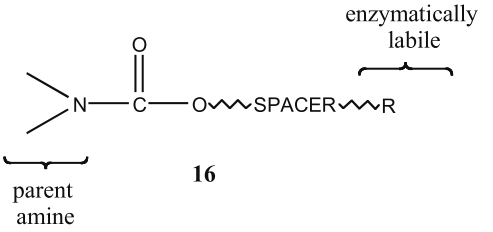


Structures 14 and 15.

done by Alexander and coworkers (Alexander *et al.*, 1988; Gogate *et al.*, 1987, Gogate and Repta, 1987). The results from these studies indicated that prodrugs had good chemical stability (shelf life of greater than 3 years at physiological pH) and are substrates for plasma esterases. It is important to note that this strategy may be limited to secondary amines since primary amines were shown to be subject to an intramolecular O to N-acyl migration in solution.

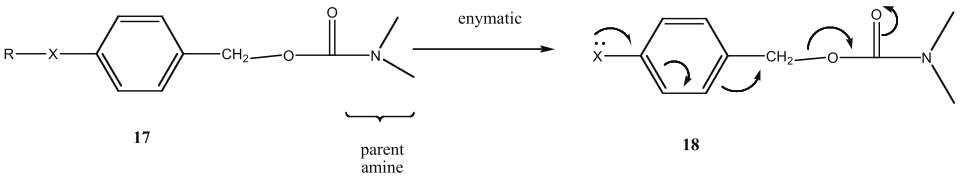
Higher Order Prodrugs

A problem inherent in simple double prodrugs obtained by directly attaching an enzymatically labile group to the carbamic acid group in **14** is that the ability of the enzyme to interact with its substrate may be compromised if the parent amine is bulky. In such circumstances the addition of a spacer to physically separate the enzymatically labile group from the drug was expected to normalize hydrolysis rates. The prototypic structure of this strategy is illustrated in **16**.



Structure 16.

An example of this prodrug approach utilizing an electronic cascade type spacer was originally proposed by Carl *et al.* (1981). The elimination mechanism is illustrated in Scheme 3.



Scheme 3.

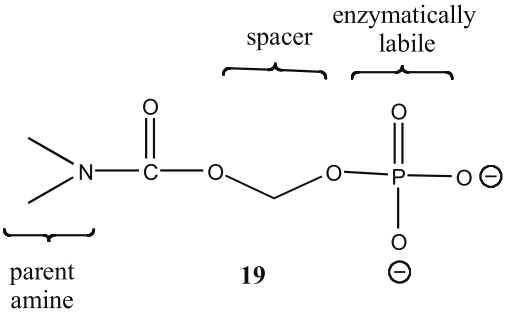
Model prodrugs (**17**, X = O, R = N-Boc-Lys) were designed to be substrates for proteolytic cleavage by trypsin to generate **18**. The available lone pair electrons associated with X on **18** can resonate to stabilize the development of the positive charge on the benzylic carbon and, therefore, favor the solvolytic cleavage of the benzyl-carbamate bond. The authors stated that the potential drawback to this strategy lies in the generation of the iminoquinone methide byproduct, which may present toxicity issues.

A number of prodrug strategies have been developed with variations in the triggering event that catalyzes the release of the parent amine. Senter *et al.* (1990) described a related prodrug strategy to target mitomycin C to tumor cells that have higher reductive capacity. In their approach, X in **17** represents sulfur, which exists in a disulfide linkage. After reduction of the disulfide, the elimination cascade is initiated and free amine is released as previously described. Interestingly, the prodrugs were approximately 50-fold more potent than mitomycin itself, indicating that either the prodrug showed enhanced permeation into cancer cells or, possibly, the formation of the thioquinone methide may have contributed to the toxicity. Mauger *et al.* (1994) synthesized prodrugs of anticancer agents in which X was NO_2 in **17** . These prodrugs were used in antibody-directed enzyme prodrug therapy (ADPET) with a nitroreductase enzyme. A variety of similar strategies using this self-immolating spacer strategy have been described and are covered in more detail elsewhere in this book. de Groot *et al.* (1999) utilized this technique to target cancer cells by designing prodrugs where the R in **17** represents the peptide substrates of plasmin, an enzyme shown to have higher activity at the surface of cancer cells.

Linking polyethylene glycol to this promoiety has also been investigated in an attempt to take advantage of the enhanced permeation and retention phenomenon that has been shown to promote tumor specificity to macromolecules (Greenwald *et al.*, 1999).

The use of multiple electronic cascade spacer groups in prodrugs has also been investigated (de Groot *et al.*, 2001). This approach was shown to increase the rate of enzyme hydrolysis by up to 10 times for bulky amine-containing drugs such as paclitaxel. As expected, the benefit of multiple spacers was less pronounced for the smaller and less bulky anthracycline class of anticancer agents.

Safadi *et al.* (1993) evaluated the utility of oxymethyloxycarbonyl spacer group to link aromatic and aliphatic amines to a phosphate moiety (**19**).



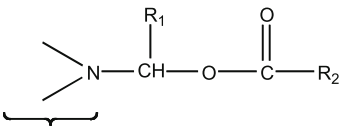
19

Structure 19.

These prodrugs were engineered to improve the aqueous solubility of amines; they have also been applied to hindered alcohols. The bioconversion mechanism involves an initial rate-determining dephosphorylation step followed by fast release of the spacer group (formaldehyde and carbon dioxide) to generate the parent amine. The prodrugs were rapidly hydrolyzed in the presence of alkaline phosphatase to the corresponding amine. The prodrugs were also susceptible to chemical hydrolysis that was attributed to the intramolecular hydrolytic catalysis by the neighboring phosphate group on the carbamate carbonyl functionality. Prodrugs derived from an aliphatic amine were chemically more stable than those derived from an aromatic amine.

N-acyloxyalkyl Derivatives

The general structure of N-acyloxyalkyl derivatives is illustrated in **20**. Most often, this type of promoiety has found its application in improving the delivery of drugs containing acidic NH groups (*i.e.*, imides, sulfonamides, amides, carbamates, ureas, etc.), which are discussed in detail in the chapter in this book by Guarino and Stella. One reason for this is that more basic amine groups derivatized with this functionality tend to be chemically quite unstable (Sloan and Koch, 1983). It is thought that the stability of these analogs is inversely proportional to the ability of the lone pair of electrons on the amine to stabilize the positive charge that builts up on the alpha carbon during solvolysis. As will be discussed in the next section, derivatization of tertiary amines with this group is possible.



20

Structure 20.

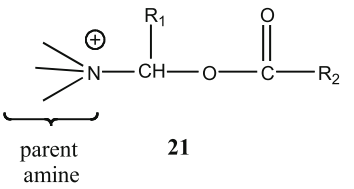
Quaternary Ammonium Derivatives

The majority of prodrug strategies discussed in this chapter will inevitably cause a reduction in the pKa value of the parent amine. This can be expected to result in reduced water solubility and enhanced membrane permeability. Derivatization of tertiary amines is different in that it results in the creation of a quaternary ammonium compound that is ionized regardless of solution pH and therefore would be expected to have improved water solubility. As a result, the majority of the strategies discussed in this section are intended to improve aqueous solubility of parent tertiary amines.

Most successful prodrug strategies described here can be classified as double prodrugs that require enzymatic hydrolysis to trigger initiation of a fast chemical

degradation of a spacer group to produce the parent tertiary amine. This is because simple alkylations of tertiary amines, albeit effective in improving water solubility (Nielsen *et al.*, 2005), typically result in quaternary ammonium salts that are very stable *in vivo* and fail to hydrolyze.

As previously mentioned, N-acyloxyalkyl-type prodrug derivatives of most primary and secondary amines (**20**) are very unstable. However, when applied to tertiary amines, the resultant quaternary analogs (**21**) are typically stable and can be enzymatically hydrolyzed *in vivo*.



21

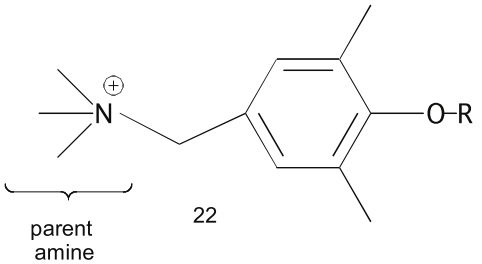
Structure 21.

Vinogradova *et al.* (1980) investigated a variety of N-(alkyloxymethyl) and N-(acyloxymethyl) derivatives on a number of different tertiary amine-containing drugs. Their work illustrated that both prodrug types were chemically stable; however, only N-(acyloxymethyl) prodrugs were able to release parent tertiary amine after intravenous administration in rats.

A more recent application of the N-(acyloxyalkyl) prodrug strategy was employed to a platelet-activating factor antagonist in order to improve its water solubility (Davidsen *et al.*, 1994; Albert *et al.*, 1996). The prodrugs displayed significantly enhanced water solubility, and their buffer and plasma stability could be adjusted through variations in the promoiety (R_1 and R_2 in **21**). The acetoxymethyl promoiety was subsequently selected for Phase I clinical evaluations in man, where rapid release of the parent amine was observed (Albert *et al.*, 1997).

Ichikawa *et al.* (2001) also applied this derivatization strategy to the triazole ring of a water-insoluble antifungal agent. Nine different prodrugs with variations in the acyl portion (R_2) of **21** were synthesized. The promoiety with R_1 = H and R_2 = CH_3 was ultimately selected for *in vivo* evaluations in rats, and the prodrug half-life was shown to be approximately 6 min after intravenous administration.

Bogardus and Higuchi (1982) studied the kinetics and mechanism of hydrolysis of a labile quaternary ammonium prodrug that has a general structure depicted in **22**. When R is a methyl or acyl group, the prodrugs were chemically very stable. When R is H, the prodrug is relatively unstable and undergoes



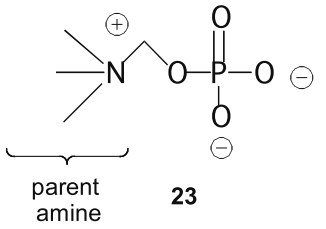
22

Structure 22.

unimolecular dissociation to generate quinone methide and the parent tertiary amine. The authors speculated that when R is an acyl group the breakdown *in vivo* would be controlled by esterase activity.

The previously described quaternary derivatives have been shown to behave as prodrugs and to lead to improved solubility; however, they may experience somewhat limited interest because of the association between quaternary compounds and *in vivo* toxicity (Cooper, 1988; Dimmock *et al.*, 1994; Sanders *et al.*,1995).

To overcome the perceived *in vivo* toxicity of quaternary ammonium prodrugs, a novel prodrug approach using N-phosphonooxymethyl promoeities (**23**) was applied to tertiary amines with poor aqueous solubility. Three model drugs—loxapine, cinnarizine, and amiodarone—were selected as model compounds to examine the utility of the N-phosphonooxymethyl prodrug concept. This prodrug strategy incorporated a negatively charged phosphate group in the promoiety as a means of overcoming the potential toxcicity limitation associated with quaternary ammonium prodrugs (Krise *et al.*, 1999a). The net charge of the molecule can vary from anionic (at physiological pH) to zwitterionic (at pH values near 3), thus masking the quaternary center. The rate-determining step in bioconversion involves enzyme-catalyzed dephosphorylation followed by a rapid breakdown of the hydroxymethyl intermediate to yield one mole of formaldehyde and the parent tertiary amine.



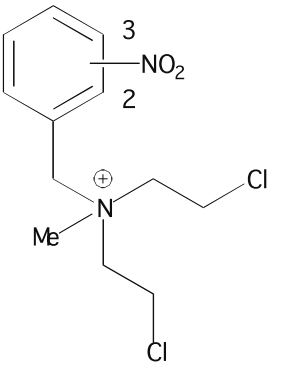
23

Structure 23.

The prodrugs were shown to be chemically stable and water soluble and to rapidly convert to the parent tertirary amine with no apparent toxicity after intravenous administration in dogs and rats (Krise *et al.*, 1999a,b).

Tercel *et al.* (1993) have proposed a prodrug strategy for tertiary amines with the intent of improving selectivity of cancer drugs using a bioreductive prodrug strategy. The nitrogen mustard anti-cancer agent mechlorethamine was quaternized using a nitro-reductive electronic cascade elimination strategy (**24**).

The nitrobenzyl promoiety was designed to undergo selective bioconversion in hypoxic cancer cells. One-electron reduction of the nitroaromatic portion causes the release of the reactive aliphatic mustard. The quaternary nature of the prodrug is considered attractive because it essentially deactivates the cytotoxicity of the mustard as well as increasing its water solubility. More recently, this group has evaluated additional prodrugs of mechlorethamine with modifications to the nitroheterocyclic ring (*i.e.*, nitroimidazole and nitropyrrole) to optimize reduction pathways in order to activate prodrug release via radiotherapy (Tercel *et al.*, 2001).



24

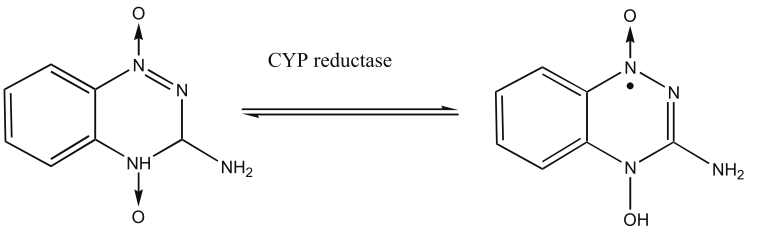
Structure 24.

Soft Quaternary Drugs

Bodor (1984) has coined a term "soft drug" to signify a transiently modified molecule that is essentially designed to behave as an active drug, but contains a readily biodegradable chemical appendage that, when cleaved through metabolism, renders the molecule inactive, facilitating a predictable clearance and, thus, improved safety. An important distinction between prodrugs and soft drugs is that the latter are designed to be active themselves whereas, by definition, prodrugs should have no activity. Soft quaternary drugs do, however, behave like prodrugs in that they are both designed to undergo a conversion event after systemic exposure. Examples of soft drug approaches relevant to prodrugs of tertiary amines can be found in applications with antimicrobials, anticholinergics and antitumor agents (Bodor and Kaminski, 1980; Bodor *et al.*, 1980a,b). Generally, the described strategies have employed N-(acyloxyalkyl) groups as the biodegradable moiety (see **21**).

N-Oxides of Amines

N-oxides represent a class of prodrugs that capitalize on the hypoxia associated with many cancer cells. Numerous N-oxide and related bioreductive prodrug strategies have been described (for a review on this topic see Denny (2004)). Two clinically promising prodrugs in this category will be highlighted



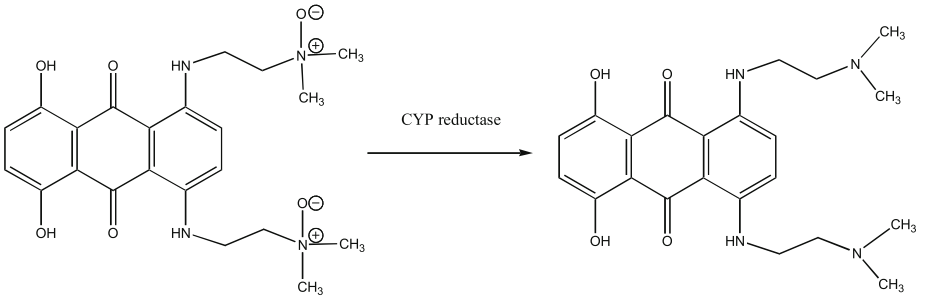
25 **26**

Structures 25 and 26.

here. Tirapazamine (**25**) is currently in clinical trials and, if successful, may be the first tumor-activated prodrug to reach the market.

This prodrug undergoes one-electron reduction (Scheme 4), which is thought to be carried out by NADPH cytochrome P450 reductase (Riley and Workman, 1992), to produce the cytotoxic nitroxide (**26**). This agent is believed to generate high concentrations of radicals in the vicinity of DNA, which results in double strand breaks (Brown, 1999).

The anticancer agent AQ4N (**27**) is an example of an aliphatic N-oxide that is reduced selectively in tumor cells to produce the parent tertiary amine (**28**, see Scheme 5) (Raleigh *et al.*, 1998). The tertiary amine is a strong binder of DNA and inhibitor of DNA topoisomerase II (Smith *et al.*, 1997).



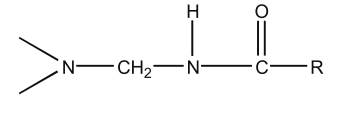
27 **28**

Scheme 5.

N-Mannich Bases

The N-Mannich reaction can be considered a prodrug strategy for derivatizing amines or amides (**29**). This section will focus on the use of the strategy for derivatizing amines since the application to amides is highlighted elsewhere in this book.

The principal reason for making N-Mannich bases of amines has been to improve membrane permeation. N-Mannich bases typically have better membrane permeation relative to parent amines because of the lowering of the amine pKa values that occur through this derivatization reaction. The pKa values of amines have repeatedly been shown to decrease by approximately 3 units after derivatization (Johansen and Bundgaard, 1980). Prodrugs, therefore, will be less ionized at physiological pH values than will the parent amines. Log D octanol-buffer partition coefficients (at pH 7.4) have been shown to increase over 100-fold



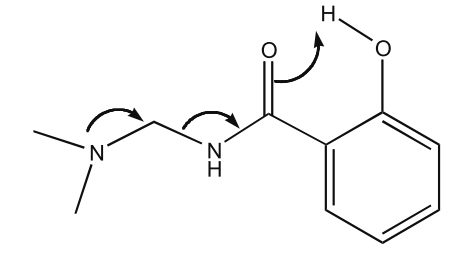
parent amine **29**

Structure 29.

for weak bases with pKa values above neutrality. The majority of this increase can be attributed to the change in ionization state at physiological pH rather than to the lipohilic contribution of the amide promoiety. In addition to increasing lipohilicity, N-Mannich bases have also been used to limit pre-systemic metabolic inactivation by N-acetylation (Bundgaard and Johansen, 1981).

Variations in the amide functionality (R in **29**) used in the N-Mannich reaction can significantly influence the bioreversion rates of resultant prodrugs. Bundgaard (1985) investigated a series of 24 N-Mannich prodrugs at pH 7.4 at 37°C and found their half-lives to vary between 0.06 and 1,400 min. Generalized characteristics that facilitate hydrolysis include availability of the lone pair of electrons associated with the amine and the propensity of the carbonyl to accept a proton. Interestingly, it was also found that having a proton donor group (*i.e.*, salicylamide **30**) in close proximity to the amide carbonyl dramatically increases the hydrolysis rate. As will be discussed, a number of N-Mannich prodrugs utilize this group in the promoiety because of the fast hydrolysis.

Cogan and coworkers (2004) have made several N-Mannich base derivatives of anthracycline drugs. Several prodrugs with variations in the amide region (R in **29**) were synthesized and evaluated. After initial characterizations, the authors focused their efforts on the salicylamide derivative (**30**) because of its rapid bioconversion properties. Interestingly, the authors reported that the reason for making these prodrugs was to take advantage of release of formaldehyde in the vicinity of DNA in cancer cells, which has been shown to promote covalent coupling of the drug to DNA (Taatjes *et al.*, 1996). The authors also investigated the effect of esterification of the phenol group of the salicylamide N-Mannich prodrugs in a double prodrug strategy aimed at improving the chemical stability of the resultant prodrug for purification and storage purposes. The hydrolysis of the prodrugs by esterases was shown to occur readily after *in vivo* administration. The same group has also recently investigated phenolic esters of **30** that are recognized by the androgen receptor in an effort to promote the specific localization of the prodrugs to cancer cells (Cogan and Koch, 2003).

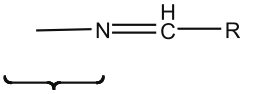


30

Structure 30.

Schiff bases

Amine prodrugs that are considered to be Schiff bases take on the general structure shown in **31**.



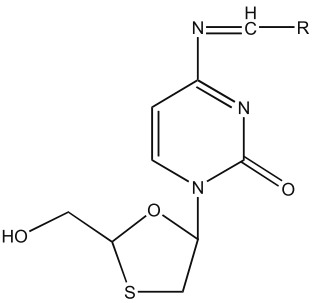
31

Structure 31.

In many regards, Schiff base prodrugs are similar to N-Mannich prodrugs because both derivatives result in substantial reductions in the pKa of the parent amine and are useful for improving membrane permeability. Some of the early applications of this approach were undertaken to improve the blood-brain barrier permeability of γ-aminobutric acid (Worms *et al.*, 1982). This approach was also applied to the histamine derivative (R)-α-methylhistamine, a potent H3-receptor agonist, which suffers from poor bioavailability and CNS delivery. Krause *et al.* (1996) have investigated a variety of azomethine prodrugs of this drug. Of the Schiff bases synthesized, the alkyl imines were found to be too unstable for isolation whereas diaryl and benzaryl imines were sufficiently stable and permitted increased bioavailability and CNS delivery *in vivo* in mice.

More recent examples include prodrugs of antiviral nucleoside type drugs. Many prodrugs originating from the free exocyclic amine of various pyrimidine and purine nucleic bases have been prepared and evaluated in an attempt to increase lipophilicity (see Anastasi *et al.*, 2003, for a review).

Formamidine-type prodrugs represent a type of Schiff base prodrug that has received considerable attention. A representative structure of these prodrugs is shown in **32**, where the parent drug is 3TC.



32

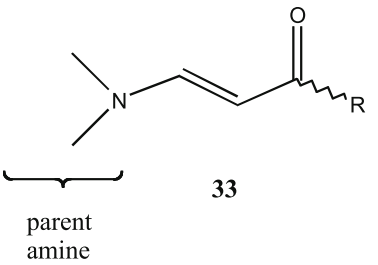
Structure 32.

Prodrugs with a lipophilic R group in **32** were shown to increase membrane permeability and water solubility. The improvements in solubility are thought to

occur through the loss of intermolecular hydrogen-bonding potential associated with the parent amine. It was shown that electron-donating R groups tended in have increased hydrolysis rates as opposed to electron-withdrawing groups, which stabilize the Schiff base (Anastasi *et al.*, 2004).

Enaminones

The general structure of enaminone type prodrugs is shown in **33**. Related enamine prodrugs have not found much application primarily because of their high degree of chemical instability in aqueous solutions. Enaminones, however, have been shown to have improved chemical stability due to the intramolecular hydrogen bond between the parent amine and the γ carbonyl. This can also be due to the extended conjugation of the vinylic double bond with the carbonyl group.



33

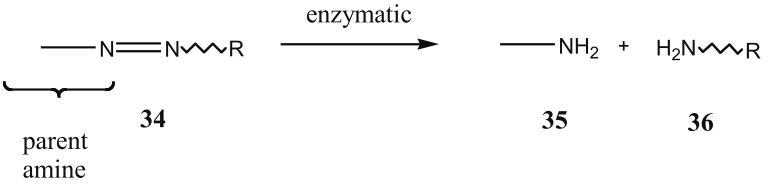
Structure 33.

This class of prodrugs has been used to reduce the nucleophilicity of parent amines. For example, Jensen *et al.* (1980) have synthesized an acetylacetone prodrug of cycloserine in order to prevent a nucleophilic dimerization reaction that was shown to occur in both the solid and concentrated aqueous solutions.

Murakami *et al.* (1981) evaluated enaminone prodrugs of a variety of β-lactam antibiotics in an effort to enhance their membrane permeability. The authors concluded that these prodrugs were more lipophilic than the parent compounds, but the prodrugs improved the bioavailability of the drugs only after rectal administration. Oral administration did not lead to increased bioavailability, presumably due to stability problems with these prodrugs in the acidic gastric environment. This finding is consistent with the work of Naringrekar and Stella (1990), who studied the mechanism of hydrolysis of enaminones as prodrugs for amines. They came to the conclusion that the concept of emaminone prodrugs intended to improve oral delivery may be unrealistic. If such prodrugs are designed to have adequate chemical stability at acidic pH values (similar to what is encountered in the GI tract), then hydrolysis at pH 7.4 would be too slow. Similarly, if these prodrugs were designed to have fast hydrolysis at pH 7.4, they would be far too unstable in acidic conditions and thus fail to be attractive prodrugs for amines.

Azo compounds

The formation of azo compounds (**34**) has been a widely utilized prodrug strategy for targeting drugs to the colon. The enzyme responsible for reducing the azo bond and releasing the parent amine (**35**) and the amine promoiety (**36**) is azoreductase. A variety of prodrugs have been developed that foster the delivery of 5-amino salicylic acid (5-ASA) to the colon. Examples include sulfasalazine, ipsalazine, balsalazine, and olsalazine (see Sinha and Kumria, 2001; Chourasia and Jain, 2003). The prodrugs are quite chemically stable and are poorly absorbed from the small intestine. When these prodrugs reach the colon, they are cleaved by azoreductase, an enzyme specifically produced by the colon microflora.

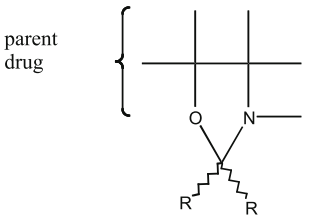


Scheme 6.

More recently polymers and dendrimers have been used as prodrug-type carriers that release 5-ASA in the colon (Wiwattanapatapee *et al.*, 2003). One advantage of the polymer linkage is that the large size of the prodrugs would preclude any absorption in the small intestine. Some polymers were designed with mucoadhesive properties (Kopecek *et al.*, 1992). Such bioadhesive polymers have also been coupled to 9-aminocamptothecin through an azo linkage (Sakuma *et al.*, 2001).

Oxazolidines

The general structure of oxazolidine prodrugs is depicted in **37**. The application of this prodrug approach is limited to primary or secondary amines with a β-alcohol group present. This strategy has received considerable attention since several marketed drugs, including selected sympathomimetics and β-blockers, contain this arrangement of functional groups.



37

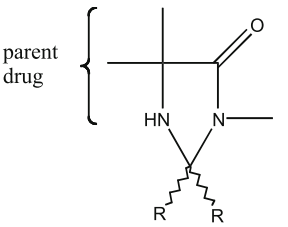
Structure 37.

The creation of prodrugs involves a cyclic condensation of the β-aminoalochol with an aldehyde or ketone. The resultant prodrugs have lower pKa associated with the amine functionality and, therefore, are considered useful in increasing the membrane permeation of drugs. The hydrolysis of a number of oxazolidine prodrugs derived from (–)-ephedrine and (+)-pseudoephedrine have been studied (Bundgaard and Johansen, 1982; Johansen and Bundgaard, 1983). Resultant prodrugs have been shown to be more lipophilic than parent drugs and to experience fast chemical hydrolysis to release the parent drug and aldehyde or ketone at physiological pH. The hydrolysis rates have been shown to decrease with increasing basicity of the oxazolidine moiety. Increasing the steric bulkiness of substituents of the aldehyde linker was also associated with decreased hydrolysis rates. Generally, prodrugs were shown to have a 3-4 h half-life at pH 1, which decreased to approximately 5 min at pH 7.4. The fast hydrolysis at neutral pH may limit the usefulness of this strategy in many applications.

More recently, Fenick and coworkers (1997) evaluated prodrugs of daunorubicin and doxorubicin where the aminoalcohol was condensed with formaldehyde. Like the previously described N-Mannich prodrugs of anthracyclines, these prodrugs were made in an attempt to take advantage of formaldehyde release, which can promote covalent attachment of these drugs to DNA. The prodrugs showed promising behavior in cultured cancer cells; however, the hydrolysis rate was extremely rapid and thus compromised the ability to formulate and deliver these prodrugs.

4- Imidazolidinones

A concept similar to the oxazolidine strategy is also applicable to drugs containing the α aminoamide moiety. The general structure of 4-imidazolidinone-type prodrugs is shown in **38**. These prodrugs can also be regarded as cyclic N-Mannich base derivatives.



38

Structure 38.

Most of the work in this area has been concentrated on improving the delivery of peptide type drugs in which this functional group arrangement is almost always present. However, this technique has also been successfully employed to make the prodrug hetacillin through the condensation of ampicillin with acetone (Tsuji and

Yamana, 1974). The prodrug was useful in stopping the concentration dependent intermolecular aminolysis problem associated with this ampicillin.

A more recent application of this technique was demonstrated by condensing prilocaine with either formaldehyde or acetaldehyde (Larsen *et al.*, 2003). These prodrugs were synthesized to make a lipophilic prodrug that could provide sustained delivery from an oil vehicle following subcutaneous administrations.

Conclusion

In summary, this review, although not comprehensive, has attempted to highlight and assess examples of prodrug approaches applied to various aliphatic and aromatic amines. Over the past 25 years, nearly 1000 papers that pertain to prodrugs of amines have been published. Obviously, this review has referenced only a fraction of this body of work. It is somewhat disappointing to realize how few commercially available prodrugs have arisen from these efforts. However, it is important to give credit to those systematic evaluations of prodrug strategies that were done to understand, on a mechanistic level, why prodrugs did or did not work. It is only with this foundation that successful strategies have evolved. Likewise, development of prodrugs of the future will certainly rely on the lessons learned from the work done to date, even though the intended applications may be considerably different. We hope that this chapter will further encourage and guide research into the use of prodrugs for improved delivery, targeting, and pharmacokinetic profiles of amine-containing drugs.

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Review

Prodrugs for Amines

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Abstract: The purpose of this work is to review the published strategies for the production of prodrugs of amines. The review is divided in two main groups of approaches: those that rely on enzymatic activation and those that take advantage of physiological chemical conditions for release of the drugs. A compilation of the most important approaches is presented in the form of a table, where the main advantages and disadvantages of each strategy are also referred.

Keywords: Prodrugs, amines, enzymatic activation, chemical activation

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Introduction

The prodrug strategy may be defined as the temporary derivatisation of a functional group of a drug in order to improve its pharmaceutical utility. Sometimes the functional group is merely a handle for the introduction of a moiety that confers on the new entity some desirable characteristic; more frequently, the group is intimately connected with the pharmaceutical deficiency and its masking directly addresses the deficiency. Of the commonly occurring drug functional groups, perhaps greatest effort has been directed at temporarily masking the amino group. The most easily identified liability of candidate amino drugs is their tendency to ionise under physiological conditions, leading to poor

membrane penetration by passive diffusion. The impact of this is amplified for the large number of amino drugs that are required to penetrate the blood brain barrier in order to reach their pharmacological targets. A second issue that can affect the development of amino drugs is instability. An example of this is the tendency of primary amines to undergo first-pass metabolism due to *N*-acetylation and oxidation by monoaminooxidase (MAO) [1]. The same applies to peptides [2] containing basic amino acid side-chains. Low water solubility, poor stability and low permeability through biological membranes often hinder the clinical development of biologically active peptides [3]. The major problem in designing amine prodrugs is the general robustness of amine derivatives particularly those, such as amides, in which the capacity to ionize has been obviated. On the other hand, the very robustness of amino derivatives means that subtle drug targeting effects can be achieved if an appropriate local vector can be identified and accommodated in the design process. A number of prodrugs of cytotoxic agents fit this description. In structuring the review we have in the first instance sought to classify prodrugs according to whether in vivo activation is enzymatic or pH/redox dependent. Within this major division the various types are identified by the nature of the derivative functional group. The approach is admittedly somewhat arbitrary as prodrug systems rarely undergo activation exclusively by one route. Also, a derivative type that undergoes unmasking enzymatically in one prodrug, may be removed primarily chemically in another because of overall structural differences. Finally, although peptides can be derivatised on other functionalities, we have included only those approaches that involve the amino group alone or conjointly with other functional groups. Table 1 presents a summary of the most important amine prodrug designs along with their dominant activation mechanism and the advantages/disadvantages of each approach. The table should be consulted where difficulties arise in identifying the chemical structure of a group from its name.

Prodrugs that rely (mostly) on enzymatic activation

N-Alkylation

Secondary and tertiary alkyl amines are reported to undergo dealkylation mediated by MAO-B to an amine and the corresponding aldehyde or ketone [4]. This has been investigated as a prodrug approach for the CNS active agent 2-phenylethylamine (PEA). In comparison with the free drug, *N*,*N*-dipropargyl-2-phenylethylamine and *N*-propargyl-2-phenylethylamine produced increased levels of PEA in the brain of rats [5,6]. *N*-(2-cyanoethyl)-2-phenylethylamine [7] and *N*-(3-chloropropyl)-2-phenylethylamine (**1**) [8] also caused sustained elevations of PEA in rat brain.

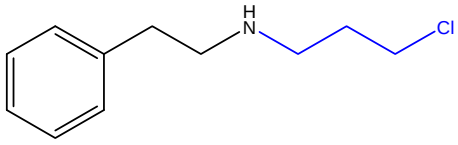

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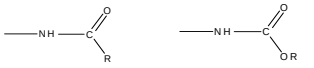
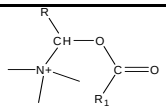
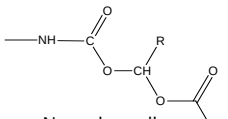
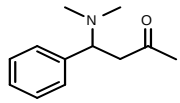
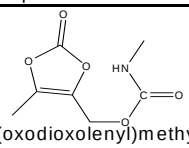
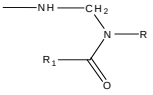
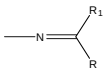
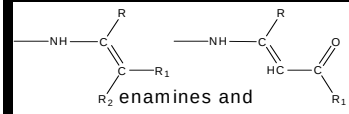
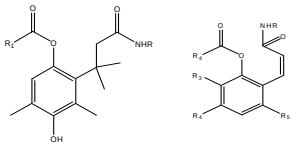
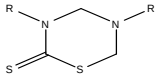
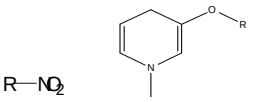
Table 1. Compilation of a series of published prodrug approaches to amine drugs.

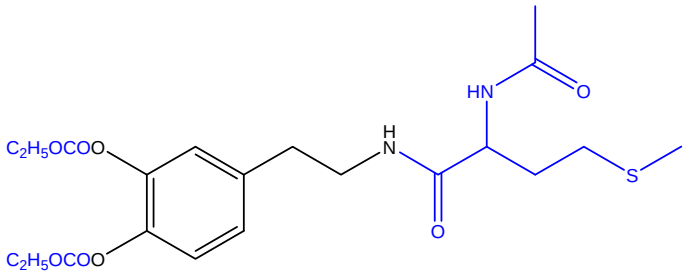
Prodrug type	mechanism of transformation	advantages	disadvantages
 amides and carbamates	enzymatic, pH activated	lipid solubility may be improved slow release	Needs to be activated by an electron withrawing substitute
 N-acyloxyakylderivatives	enzymatic followed by spontaneous	improved lipophilicity	only applicable to tertiary amines
 N-acyloxyalkoxy carbonyl derivatives	enzymatic followed by spontaneous	produces neutral compounds	usually not suitable for primary amines
 β-aminoketones	pH activated	lowers pKA increases lipophilicity	easily hydrolysed in aqueous solution
 (oxodioxolenyl)methyl derivatives	base catalysis and/or enzymatic	also applicable to primary amines	
 N-Mannich bases	base catalysis	lowers pKa up to 3 units	formation of formaldehyde low stability
 imines (Schiff bases)	pH activated	lowers pKa	easily hydrolysed in aqueous solution
 enamines and enaminones	chemical	lowers pKa improved lipophilicity	not stable enough at low pH
azo compounds	azo-reductases	possibility of targeting	only applicable to aromatic amines
 lactonization systems	enzymatic followed by spontaneous	possible to manipulate phys/chem characteristics	poor aqueous solubility in most cases
 THTT	enzymatic and chemical	improved lipophilicity	only applicable to primary amines
 redox sytems	chemical or enzymatic activation	possibility of targeting	oxidation in solid state
PEG	chemical and enzymatic activation	improved solubility	need association with other systems

N-Acylation: amides and simple carbamates

Bioreversible masking of the hydroxyl group with an ester functionality is a practical prodrug approach as ester compounds are in general readily hydrolysed by the rich variety of hydrolase enzymes present in the human body. Acylation of amines is ostensibly less promising because of the chemical and enzymatic stability of amides and carbamates: in this context, mammalian amidases appear to be less promiscuous than esterases. Indeed amides also undergo hydrolysis by esterases *in vitro* [9], but the rates are usually too slow and insufficiently competitive to be used for amine release *in vivo*.

Nevertheless, several successful *N*-acyl prodrugs are in clinical use or in development. In some cases, activation relies on specific substrate-peptidase relationships while in others, slow prodrug hydrolysis by non-specific enzymes is not undesirable. A well-known example of the former is the exploitation of renal γ-glutamyl transpeptidase as a vector for amino drug release from γ-glutamic acid conjugates [10]. Dopamine has been a candidate for this and numerous other prodrug approaches because it is inactivated by sulfotransferase, MAO and COMT in the intestinal wall and liver [11] following oral administration [12]. The dopamine double prodrug, γ-glutamyl-L-dopa (gludopa), achieves kidney dopamine levels about five-fold higher than those obtained with an equimolar quantity of the single prodrug L-dopa [13]. Gludopa itself however, suffers from poor oral bioavailability [14].

Docarpamine, [*N*-(*N*-acetyl-L-methionyl)-*O*,*O*-*bis*(ethoxycarbonyl)dopamine), **2**], a pseudopeptide prodrug of dopamine, is administered orally in the treatment of renal and cardiovascular pathologies [15,16].



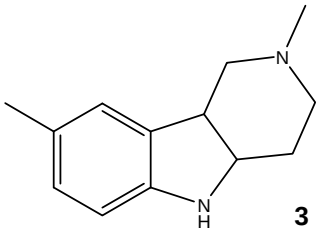
2

Docarpamine is well absorbed from the oral route, has weak intrinsic vasodilatory effects [17], has no effect in the CNS even at high doses [11], and is easily converted to dopamine *in vivo* [15]. Non-peptide *N*-acyl derivatives of dopamine have also been evaluated [18]. Several other amine conjugate with amino acids via amide bonds have been investigated with significant improvement in solubility, for example, dapsone [19,20].

More recently, amino acids have been linked to anti-tumour amines to produce water-soluble amide prodrugs that release, *in vivo*, the parent amine [21]. Glycine and valine amides of monoaminooxidase A (MAO-A) inhibitors were also prepared as an attempt to deliver the active compounds to the brain before inhibiting MAO-A in the intestinal mucosa which leads to the potentiation of tyramine induced hypertension [22].

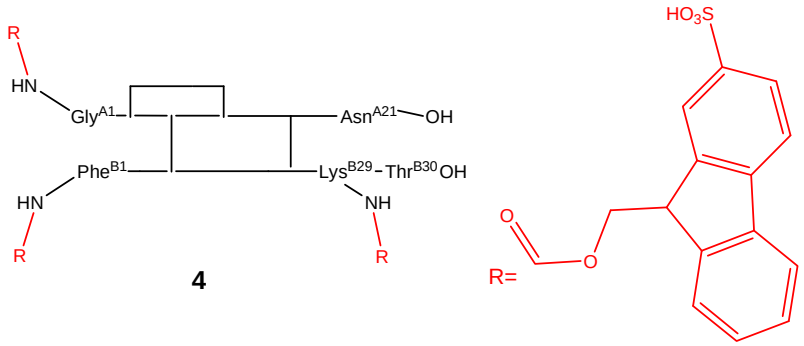
Derivatization with amino acids has also been used to target intestinal transporters such as PEPT1. One such case is the vasoconstrictor midodrine, which releases the active form 1-(2',5'-dimethoxy-phenyl)-2-aminoethanol) following cleavage of the glycine residue [23].

One synthetic amide prodrug type system that has been extensively studied are the *N*-acyl derivatives of allopurinol, which are more lipophilic than the parent drug, while at the same time being in some cases more water soluble [24]. The acetyl, veleroyl and nicotinoyl amides of stobadine (**3**) are highly lipophilic and penetrate the BBB [25].

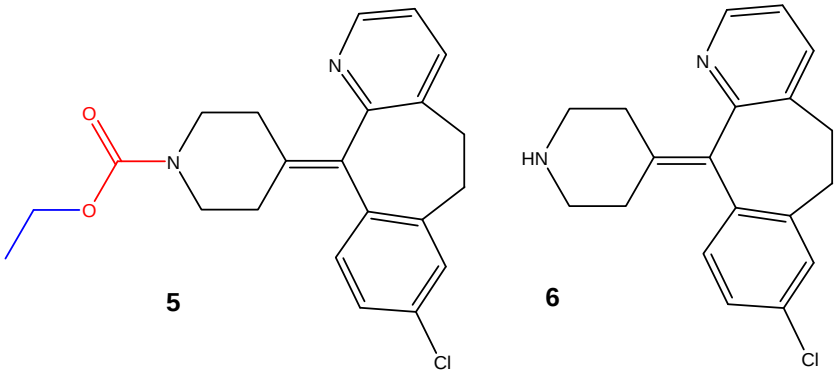


3

Simple *N*-acyl prodrugs in which slow cleavage is desirable are the [(2-sulfo)-9-fluorenylmethoxycarbonyl]-3 derivatives of glucose lowering drugs like insulin [26] (**4,** R=H) and exendin-4 [27]. These prodrugs have the advantage of delivering the drugs slowly to the systemic circulation reducing the risk of hypoglycaemia.



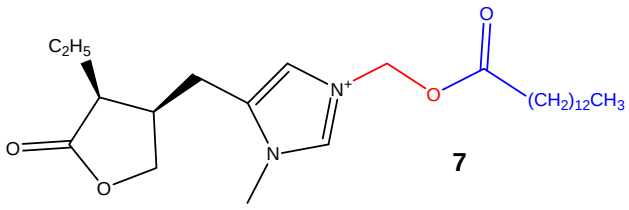
Another system that involves carbamate and urea prodrugs has been developed for antibody-directed enzyme prodrug therapy [ADEPT]. In this system, the carbamate and the urea groups are substrates for the enzyme tyrosinase present in melanomas, where it triggers the release of the drug [28]. New cephalosporins have also been subjected to acyl derivatisation in order to increase solubility [29]. The prototypical non-sedating antihistamine loratadine (**5**) is an ethyl carbamate, which undergoes a CP450–mediated conversion *in vivo* to the active desloratadine (**6**) [30]. It is interesting to note that loratadine was not designed in response to any apparent pharmaceutical liability in desloratadine, and it was certainly not clear at the outset that one acted as a precursor for the other [31].



The anti-cancer drug capecitabine is a cascade-type prodrug that produces 5-fluorouracil (5-FU) in the liver and in response to enzymes overexpressed in cancer cells. The first step in the cascade is hydrolysis of a pentyl carbamate mediated by liver carboxylesterase (CES-1). Significant species differences were observed when a panel of homologous carbamates was subjected to hydrolysis by human, monkey and mouse carboxylesterases and the discovery scientists point out that the correct analogue would not have been selected for development without the availability of human intestinal and liver carboxylesterases [32]. Capecitabine has lower gastrointestinal toxicity than 5FU, better tumour targeting and is widely used now clinically [33]. Pentyl PABC-Doxaz (PPD) is a doxaz carbamate prodrug that contains a pentylcarbamate of an anilide, though in this case hydrolysis is mainly mediated by human intestinal carboxylesterase (CES-2) [34]. Neither of these pentyl carbamates is an amine prodrug in the truest sense, since in neither case is the pharmacologically active moiety an amine. However they illustrate that carbamates of anilides may be processed by intestinal or liver carboxylases, predominantly CES-2 or CES-1 respectively.

N-Acyloxyalkylation, N-hydroxyalkylation and N-(phosphoryloxy)alkylation

N-Acyloxyalkyl derivatives of primary and secondary amines are not usually suitable as prodrugs due to their high lability in aqueous solution. However, with tertiary or *N*-heterocyclic amines it is possible to produce stable quaternary ammonium salts that are nonetheless susceptible to enzymatic hydrolysis by esterases and subsequent spontaneous decomposition. An example of this type is the tetradecyloxymethyl quaternary salt of pilocarpine (**7**) [35].



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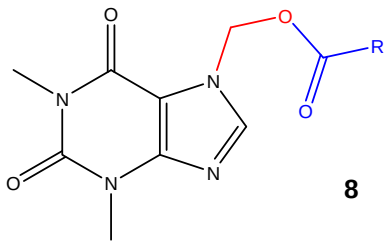
N-acyloxyalkyl derivatives **8** of the topical antiproliferative drug theophylline have been evaluated. No increase in skin permeability was apparent with alkyl chains of up to five carbons; however, the intermediate 7-hydroxymethyltheophylline, possesses twice the permeability of the drug itself [36].

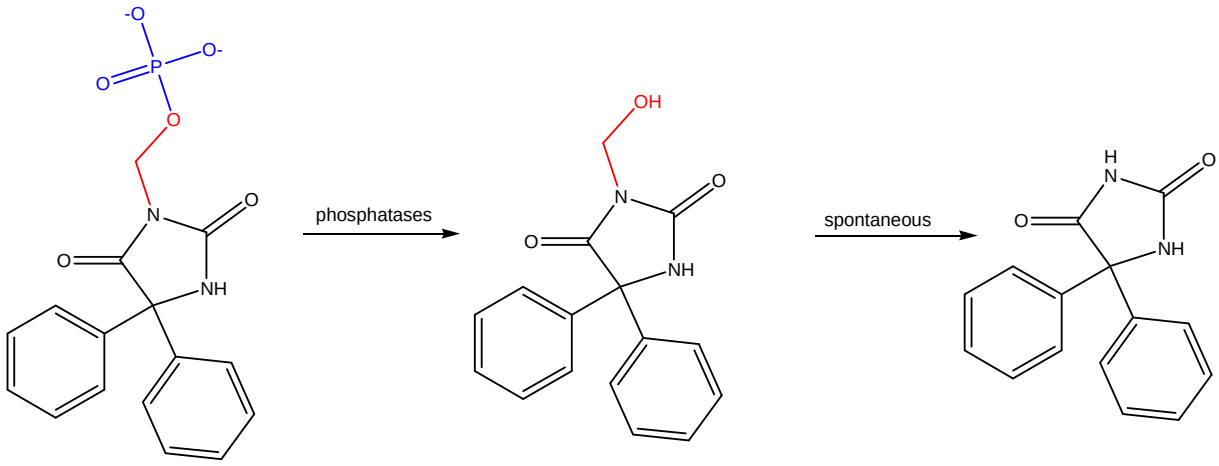


8

Some quaternary derivatives of tertiary amines have been mentioned as potential prodrugs since these compounds degrade at physiological pH releasing the parent amine [10] in a similar fashion to the acyloxyalkyl derivatives. Another approach involves a salt form of an *N*-phosphoryloxymethyl prodrug, from which the parent drug is released by a first step enzyme-catalysed rate-determining dephosphorylation, followed by spontaneous chemical breakdown of the *N*-hydroxymethyl intermediate [37]. This approach which has been applied to loxapine, improves the aqueous solubility

and stability of the drug [38] and *in vivo* tests suggest that there is quantitative reversion of the prodrug to the parent drug [39]. The phosphoryloxymethyl spacer approach has also been successfully employed in fosphenytoin (Scheme 1), a prodrug of the anti-epileptic phenytoin [40].

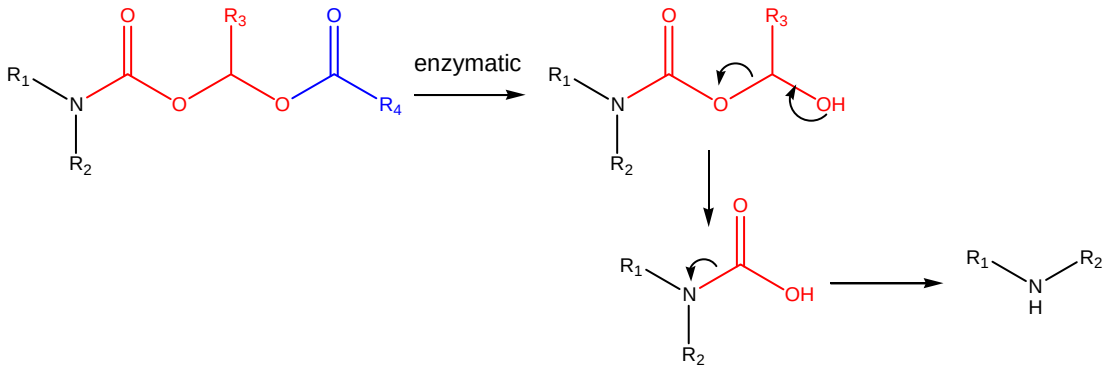
Scheme 1. Tripartite prodrug system for tertiary amines (illustrated for fosphenytoin).



(Acyloxy)alkyl and (phosphoryloxy)alkyl carbamates

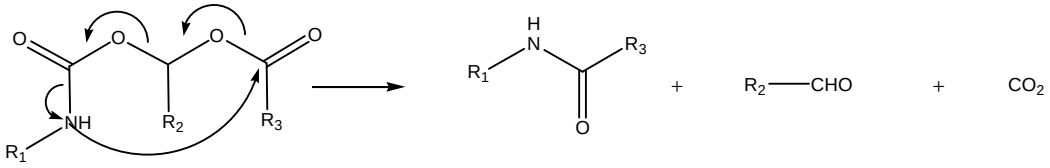
N-Acyloxyalkoxycarbonyl derivatives or (acyloxy)alkyl carbamates (R_4= alkyl or aryl), have received attention as possible prodrug types for amines [41-44]. The compounds possess an esterase sensitive terminal group, whose hydrolysis triggers a spontaneous decomposition of the intermediate (hydroxyalkoxy)carbonyl derivative liberating the parent amine (Scheme 2). This approach neatly addresses the relative enzymatic stability of simple *N*-acyl groups.

Scheme 2. Hydrolysis of (acyloxy)alkyl carbamate and amine prodrugs.

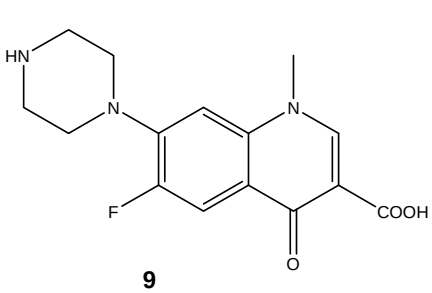


The system has limited applicability to primary amines whose *N*-acyloxyalkoxycarbonyl adducts can undergo intramolecular acyl transfer, leading to the formation of stable *N*-acyl compounds (Scheme 3) [45].

Scheme 3. Intramolecular acyl transfer in *N*-acyloxyalkoxycarbonyl derivatives of primary amines.



(Acyloxy)alkyl carbamates derivatives of hydrophilic beta-blockers exhibited several fold increase in rat skin and rabbit cornea permeation in comparison with the original drugs [46]. Other examples of (acyloxy)alkyl carbamates are the taste-masking prodrugs **9** of the bitter anti-bacterial norfloxacin (**10**) [47] and XP13512, a prodrug of gabapentin recognized by MCT1 and the sodium-dependent multivitamin transporter (SMVT) [48]. XP13512 was efficiently absorbed and rapidly converted to gabapentin after oral dosing. In monkeys, the oral bioavailability of gabapentin from XP13512 was about 84% compared to 25% after similar oral administration of gabapentin [49].



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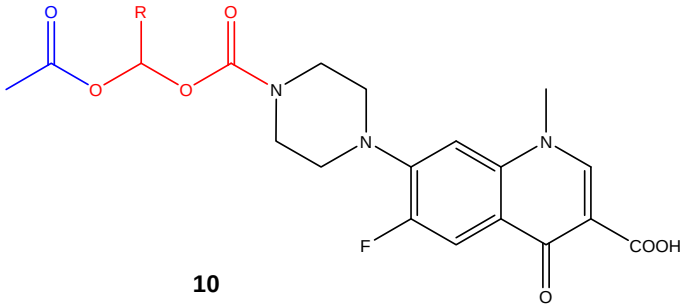
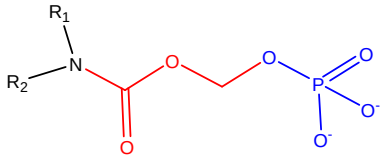


10

The use of (acyloxy)methyl esters as bridging groups (Scheme 2, R_2=H) is generally a topic of controversy due to the generation of formaldehyde during breakdown. For this reason, (acyloxy)ethyl esters (Scheme 2, R_2=CH_3) are usually preferred. On the other hand, (acyloxy)ethyl derivatives introduce a chiral centre into the system; if the drug already has a chiral centre, diastereomers are formed, which can display very different hydrolytic rates [50].

(Alkoxycarbonyloxy)methyl carbamates have also been prepared (Scheme 2, R_4= alkoxy or aryloxy) [43], as well as (phosphoryloxy)methyl carbamates **11** which would, *in vivo*, be cleaved by alkaline phosphatases. *In vitro* tests with the phosphate esters showed that following the initial enzymatic triggering, a spontaneous cascade leads to the release of the amine [51].

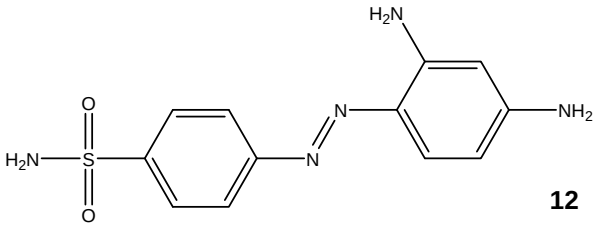


11

Azo compounds

Numerous azo compounds have been investigated as site-specific prodrugs that exploit the facile reduction of the azo linkage by azo-reductase enzymes. A remarkable story of an early amine azo prodrug is that of Prontosil (**12**), which was used for the treatment of streptococcal infections. Prontosil is a prodrug of sulphanilamide (**13**) and it was developed by Gerhard Domagk in 1932,

probably for commercial reasons rather than pharmacokinetic ones, as the active compound was not patentable. A group at the Pasteur Institute later speculated that the azo link might not be necessary for therapeutic efficacy, and that the active principal might be formed by reduction of the azo bond. They later proved that the antibacterial activity resided in the sufanilamide portion of the molecule [52].



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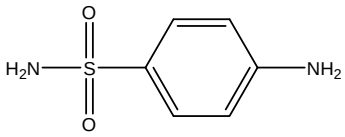
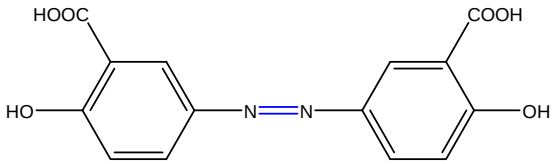


13

A well-known azo-drug class that exploits azoreductases for site-specific drug release are the 5-aminosalicylic acid prodrugs (e.g. olsalazine, **14**). These pass unaffected through the intestine where they are poorly absorbed [10, 45], but are reduced by azoreductases associated with the high levels of colonic bacteria.



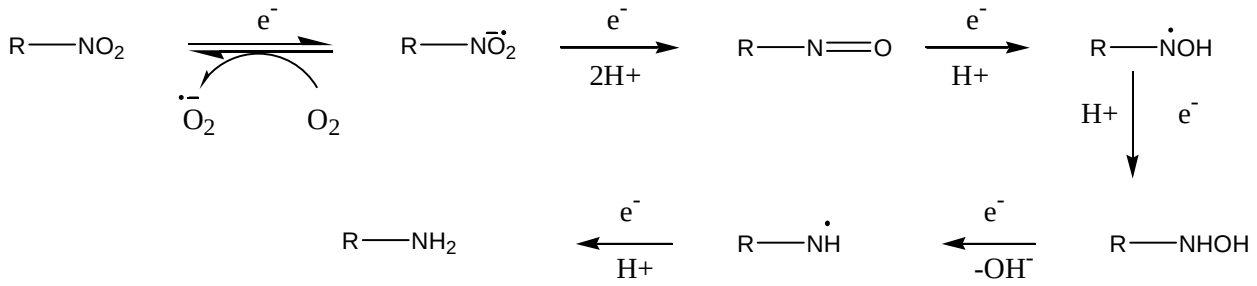
14

Other clinically used prodrugs in this class include balsalazide and ipsalazide, in which the 5-aminosalicylic acid moiety is conjugated to 4-aminobenzoyl-*β*-alanine and 4-aminobenzoylglycine, respectively [53]. It should be noted that the azo-approach is generally restricted to primary aromatic amines, azo derivatives of aliphatic amines being unstable. More recently, conventional *N*-acyl type conjugates of 5-aminosalicylic acid with various amino acid derivatives were evaluated for colon specific delivery. 5-Aminosalicylic acid-L-aspartic acid was effectively delivered to the large intestine, releasing about half of the administered dose of 5-aminosalicylic acid [54].

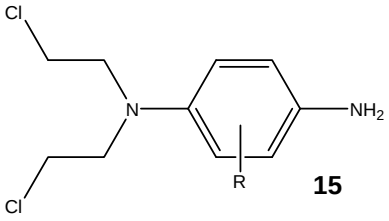
Redox systems

The design of prodrug systems poised to undergo redox reaction receives growing attention. The principal merit of this type of drug-release triggering mechanism is its potential to achieve site-specific delivery. For example, several reductive systems which are selectively activated in hypoxic conditions have been developed and applied in cancer therapy. The systems involve amines latent as nitro groups which, after conversion, form adducts with DNA. The reduction pathway involves several radical intermediates as well as nitroso, hydroxylamine and amine intermediates (Scheme 4).

Scheme 4. Generalised reduction pathway for nitro-heterocycles [55].



This type of drug delivery system has been evaluated for the 2-nitroimidazoles, mitomycin C, tirapazamine [55] and indolequinones [56], amongst others. The reduction can be facilitated by the action of endogenous or specially delivered enzymes [ADEPT or GDEPT]. A similar approach has been applied to aromatic mustards **15** to produce prodrugs to target hypoxic tumours. Although the direct use of nitroaromatic mustards **16** could be envisaged as a hypoxic activated system, its application is limited because both the nitro and the alkylating groups are attached to the same aromatic rings and have opposing electronic requirements. This means that the prodrug has a very low reduction potential with consequent low hypoxic selectivity. Substitution on the aromatic ring with electron-withdrawing groups greatly reduced the cytotoxicity of the drug [57]. Nevertheless a water-soluble phosphate ester of a 3,5-dinitrobenzamide-2-nitrogen mustard is currently under clinical trials. The prodrug is converted in vivo to the corresponding alocohol and afterwards activated by reduction to the corresponding 5-hydroxylamine and 5-amine [58].



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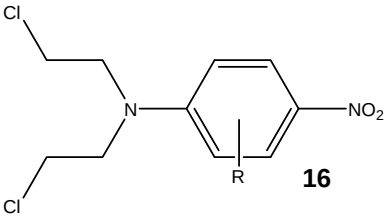

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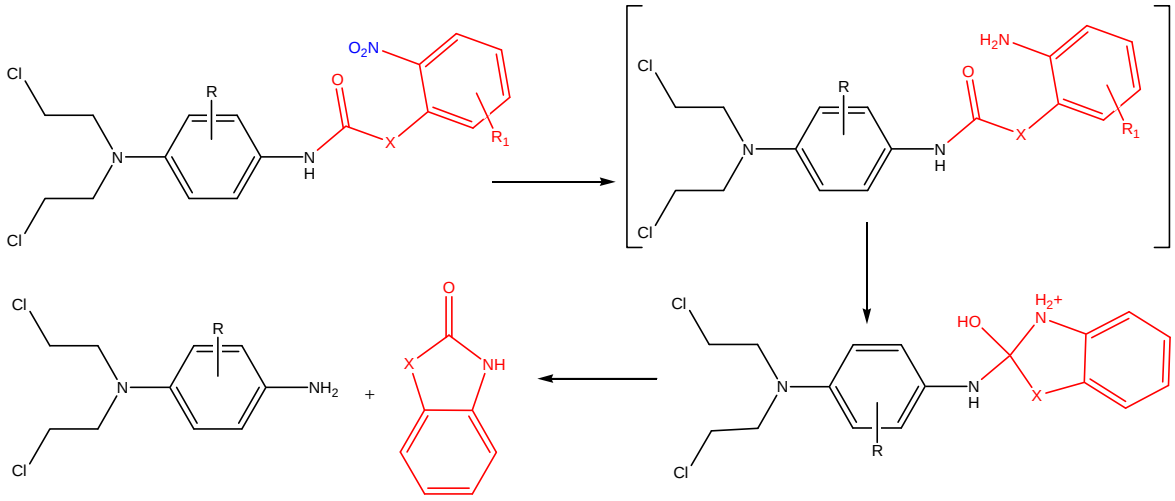
However, the design of a reductively activated system where the reduction potential can be manipulated independently (R_1) allows the production of prodrugs of the more cytotoxic non-substituted mustards. Moreover, the selection of the linker group X (Scheme 5) allows some control over the rates of cyclization [57].

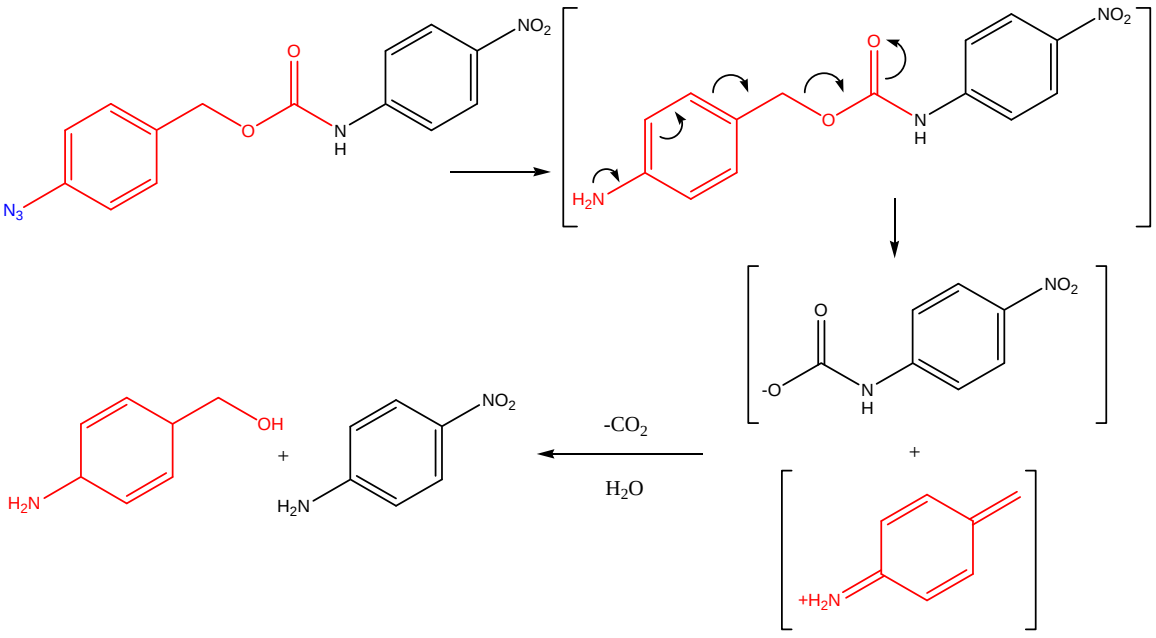
A series of *N*-dinitrophenylamino acid amides that also release primary amines via nitroreduction and intramolecular cyclization has been studied. This system does not seem to be efficiently activated by nitroreductases but the reduction can be radiation-induced, which is a possible approach in cancer therapy [59].

Scheme 5. Mechanism of activation of 2-aminoaryl derivatives.



Another system that can be activated by reduction is the 4-azidobenzyloxycarbonyl (Scheme 6). In this system the drug is linked through a carbamate to an aromatic azide that is converted by reduction to an amine: a cascade reaction eliminates the carbamic acid, which is readily converted to the amine drug [60].

Scheme 6. Activation of the 4-azidobenzyloxycarbonyl prodrug system.

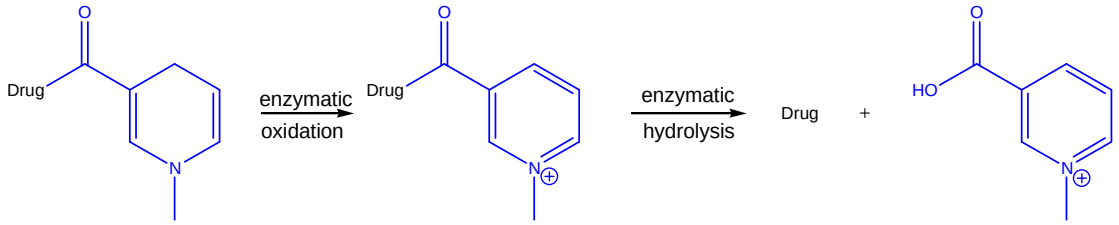


N-oxides have been suggested as bioreductive prodrugs for tertiary amines. *N*-oxidation masks the cationic charge of the amine reducing their DNA binding affinity and toxicity. The prodrugs are activated by metabolic reduction under hypoxic conditions [61].

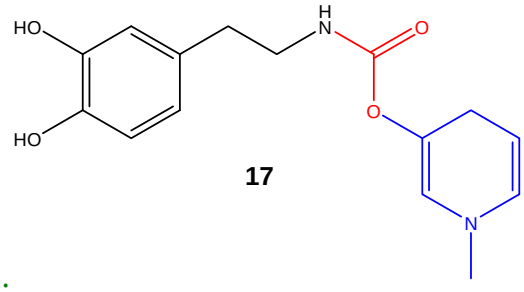
The dihydropyridinepyridinium salt system [62,63] (Scheme 7) is an example of a site-specific prodrug, developed for brain penetration of amines (but that is also applicable to alcohols and carboxylic acids), which employs an oxidative pathway for prodrug localisation. Application of this system to amines was illustrated for desipramine, amongst others. In this case, although there was no

evidence of a more efficient delivery, there was a prolonged presence of the drug in the rat brain at a constant level [64].

Scheme 7. Redox carrier system to the brain.



The system has also been applied to dopamine [65,66]. A dimeric form of this progroup has also been used [17]. The system has also been modified to include an activated carbamate ester **17**.



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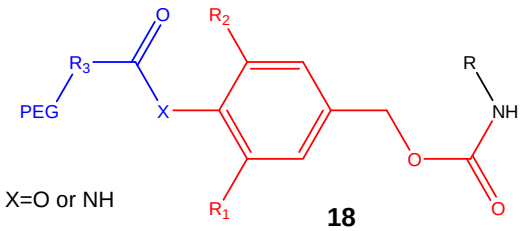
The relatively lipophilic prodrug penetrates the BBB and the salt obtained after oxidation is trapped in the brain, where it slowly releases the drug. Any oxidation in periphery results in rapid elimination of the intermediate due to its high polarity. This way, the drug can be preferentially accumulated in the brain. The approach has wide applicability to other functional groups such as alcohols and carboxylic acids [67,68]. One significant limitation to the design is the facile oxidation of the dihydropyridine function, which makes the development of a stable formulation difficult [13]. The application of this method to several different drugs has been reviewed [69]. An analogous thiazolium system [70] and carrier groups that involve alkoxycarbonyl methyl derivatives of 7,4-dihydropyridine-3,5-dicarboxilate [71] have been proposed to overcome the stability problems of the dihydropyridine type prodrugs.

PEG and other macromolecular systems

Double prodrug systems that consist of poly(ethylene glycol) (PEG) linked through a spacer to the amine drug (**18**) have been explored for drug solubilization and for extending the plasma half-life of the drug. In one approach, ester, carbonate, carbamate or amide bonds are introduced as spacers and triggers for enzymatic activation and release of the PEG group. After that, the drug, latentiated in the form of a carbamate or an ester, is released by a spontaneous 1,4- or 1,6-benzyl elimination [72,73].



18

PEG can also be used in conjunction with the "trimethyl lock" system to produce prodrugs for amines with improved solubility and potentially capable of targeting specific tumors. In this system, which has been applied to Daunorubicin, PEG is connected through a spacer to the phenol group of the open lactone. Manipulation of the spacer or the substituents in the aromatic ring allows for tuning of release rates [73-76]. Analogous conjugates have been prepared for Doxorubicin with different results from the ones obtained for Daunorubicin [77], revealing that individual compounds should be evaluated with different linkers in order to determine the most effective combination.

Low molecular weight proteins (LMWP) have also been used to prepare systems for kidney targeting that can be cleaved by aminopeptidases or lysosomal lysates. The LMWP can also be linked to the drug through an acid sensitive spacer. Using *β*-naphthylamine (*β*-naph) as a model compound, it was found that the Leu-*β*-naph and the Gly-Phen-*β*-naph conjugates were stable in buffer solution, but released the amine completely in cortex homogenates and lysosomal lysates solutions. However the results were not as promising with adriamycin, triametrene and sulfamethoxasole as model drugs [78].

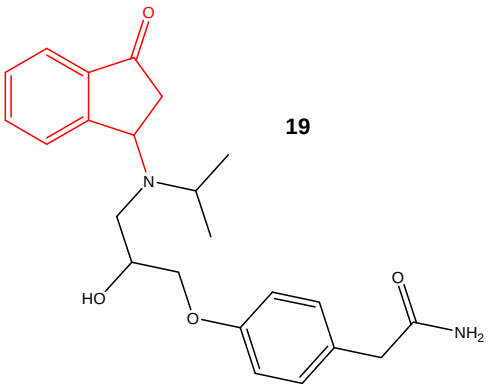
Dextran conjugates have also been prepared using aminocarboxilic acids as spacers [79]. The concept has been applied for slow release of Mitomycin C; different release rates were observed for different linkers.

Prodrugs that rely mostly on chemical activation

β-aminoketones

A recently reported design involves the preparation of *β*-aminoketones, which are usually stable in acidic conditions but cleave into the parent amine and an *α,β*-unsaturated ketone at neutral to basic pH [80,81]. Elimination from *β*-aminoketones by retro-Michael reaction is well known, but hadn’t been used previously in prodrug systems for amines. Placement of the amine in a benzylic position seems to have a positive effect on the rate of elimination in comparison with aliphatic systems. This is probably due to the extended conjugation of the double bond upon elimination of the amine.

Half-lives at pH=7.4 range from less than one minute to several hours depending on the amine and on the progroup. The indanone prodrug of atenolol **19** has a half-life of 1.3 minutes in pH=7.4 buffer and 2.3 minutes in plasma.

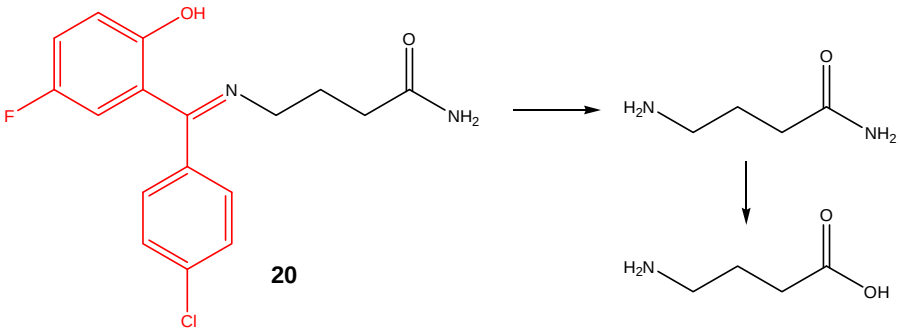


19

Schiff bases

Imines (Schiff bases), are usually too easily hydrolysed to be useful as amine prodrugs. Nevertheless, in some particular cases they may be surprisingly stable and useful as they impart increased lipophilicity to the parent amine and depress the pKa values. The anticonvulsant progabide under the trade name Gabrene© (**20**) was prepared as a prodrug form of γ-aminobutyric acid (GABA) since it crosses the BBB, while the free drug doesn't. The prodrug is converted to γ-aminobutiramide and GABA (Scheme 8), which are then trapped if produced in the brain. However, it might not be considered a true prodrug as it possesses intrinsic pharmacological activity [10].

Scheme 8. Metabolism of progabide.



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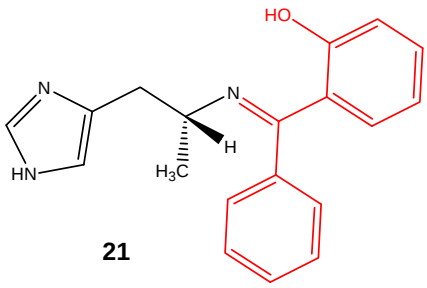
Chemically activated azomethine prodrugs **21** [82,83] of the reference histamine H3 receptor agonist *R*-α-methylhistamine have been evaluated, as well as enzymatically [84] activated prodrugs (amide, esters and carbamates).



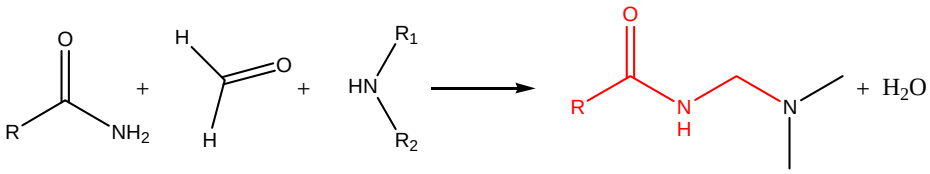
21

The new compounds, being more lipophilic, have improved oral absorption and better BBB penetration than the original drug.

S and N-Mannich bases

N-Mannich bases are synthesised through the Mannich reaction, which involves a NH-acidic compound, an aldehyde (usually formaldehyde) and an amine in ethanol (Scheme 9).

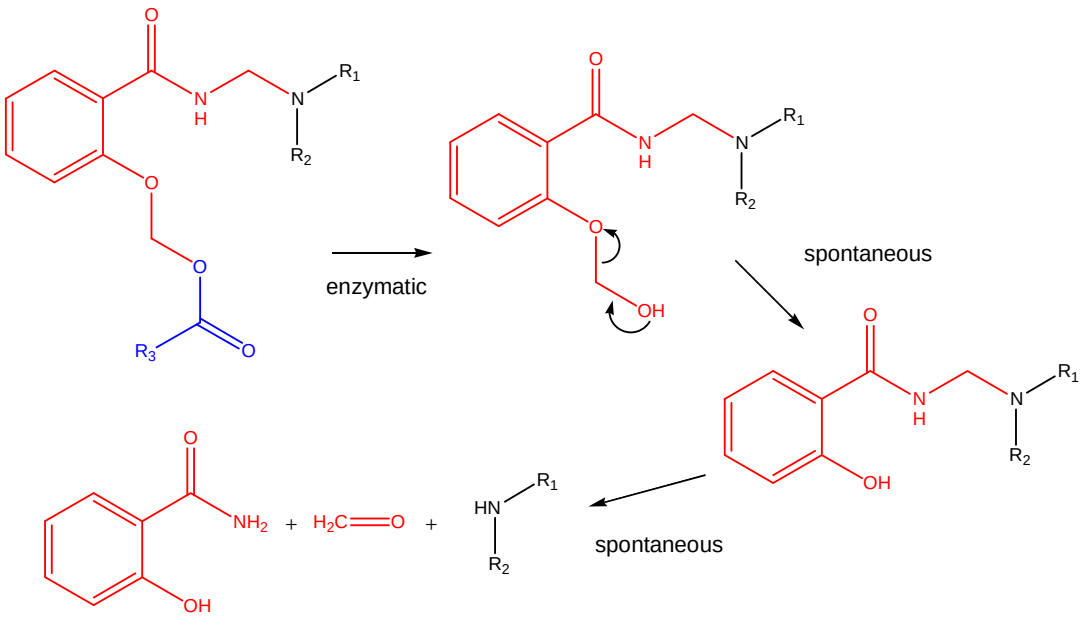
Scheme 9. Synthesis of *N*-Mannich bases.



This system can be used to produce prodrugs that are more soluble than the parent [85], not only for amines but also for amides, as in the case of rolitetracycline [45]. *N*-Mannich bases are useful when an increase in the lipophilicity of amines is desirable. *N*-Mannich base formation also suppresses the pKa (a difference of up to 4 units) with respect to the amine, which means that an important proportion remains unionized at the pH of the intestine [1]. However, the range of biologically acceptable amide type transport groups affording an appropriate cleavage rate is limited [86].

Cleavage of the prodrug in this case is strictly pH dependent: it has been found that *N*-Mannich bases of salicylamide and different aliphatic amines and amino acids show a bell shaped pH/rate profile with a high breakdown rate at pH 7.4. In the case of salicylamide, the hydroxyl group is thought to be responsible for the high reactivity, possibly by intramolecular catalysis, when the compound is in the neutral or zwitterionic forms. At high pH, when the compound is in the anionic form, the reactivity decreases markedly [87]. However, derivatisation of this group by acyloxymethylation, provides new possibilities of controlling *in vivo* cleavage as well as improved *in vitro* stability (Scheme 10) [88].

Scheme 10. Esterase sensitive *N*-Mannich bases of salicylamide as prodrugs for amines.



It was established that the acidity of the parent amide and steric effects within the amine component correlate with reactivity [85,89]. For amines with similar steric properties, a decreasing basicity is associated with decreasing reactivity [85]. For example, the rate of breakdown of *N*-Mannich bases of aromatic amines with succinamide increases markedly with increasing amine basicity [1]. For amines with similar pKas, some correlation was found between reaction rates and the difference in pKa between the amine and the corresponding Mannich base (for the same amide) [90].

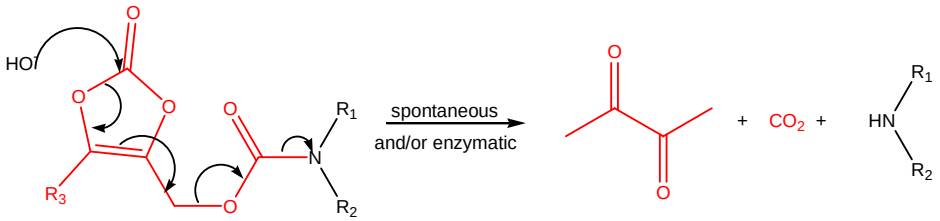
A drawback of the *N*-Mannich bases is their limited *in vitro* stability, raising some stability/formulation problems [45]. The unavoidable release of formaldehyde during decomposition is another factor that has to be taken into consideration due to its toxicity [85].

An example of an S-Mannich base is dipyrone (metamizole) the methanesulfonic acid of the analgesic 4-(methylamino)antipyrine, which is highly water soluble and therefore more suitable for parenteral administration. When administered orally, dipyrone appears to undergo fast hydrolysis in the stomach followed by intestinal absorption of the active form [91].

(Oxodioxolenyl)methyl carbamates and other selfimmolative systems

(Oxodioxolenyl)methyl carbamates were prepared as an attempt to avoid the drawbacks of (acyloxy)ethyl and (acyloxy)methyl esters. The prodrugs break by base catalysis according to Scheme 11, but the rate of hydrolysis in plasma solutions is higher than in pH 7.4 buffer solutions [43,50].

Scheme 11. (Oxodioxolenyl)methyl carbamate prodrugs of amines: mechanism of base-catalysed cleavage.



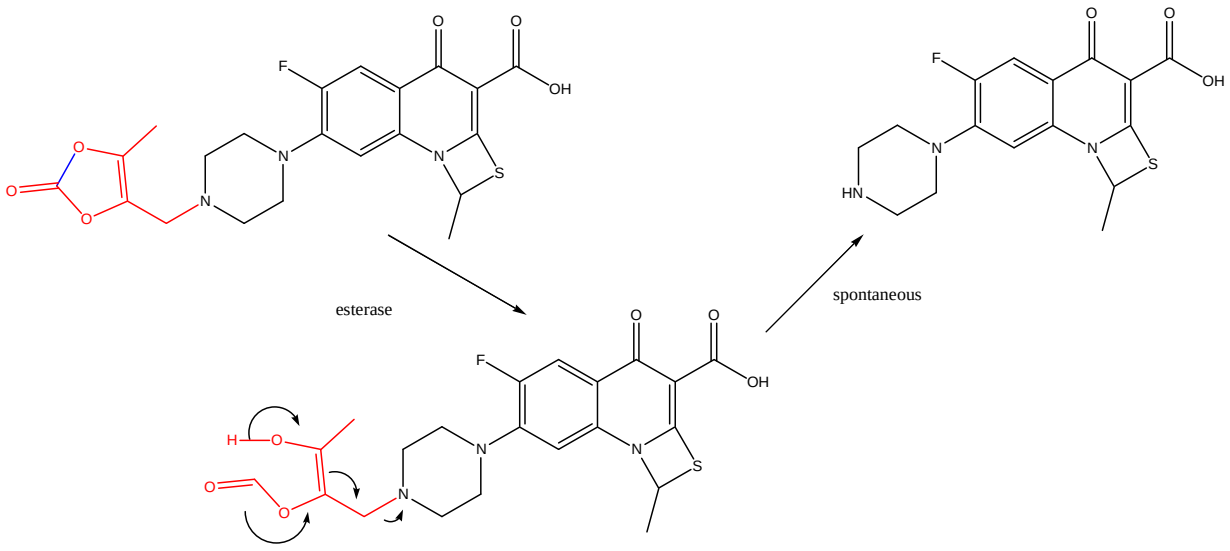
In these systems, the cleavage of the dioxolenone ring by the amino group attack on the reactive vinylene carbonate function is precluded, which makes this approach potentially applicable to primary amines. Aryl R_3 substituents generally have a destabilising influence, reducing the half-life of the prodrugs [50]. The system has been applied to pseudomycins and some of the prodrugs exhibited comparable *in vivo* efficacy to that achieved by the parent compounds, with reduced side effects [92].

In a similar approach a selfimmolative linker was used to attach tryptophan to a bisphosphonate component through a carbonate-labile linker, 4-hydroxy-3,5-dimethoxybenzyl alcohol, which was further attached through a stable carbamate linkage to the amine group of tryptophan [93]. The carbonate linkage hydrolysed with a half-life of 90 h, but it can be modulated through the nature of the substituent on the aromatic ring of the self-immolative linker.

Another example using oxodioxolenyl group is that of Prulifloxacin (Scheme **12**) which is a fluoroquinolone antibacterial agent with a broad spectrum of activity against Gram-positive and -negative bacteria [94] currently under clinical phase 3 trials. The prodrug uses the (5-methyl-2-oxo-1,3-dioxolyl)methyl promoiety linked to the secondary amine group of the active form by N-alkylation. Amine release is triggered by esterase attack on a distal oxodioxolenyl group, but formally

speaking, the connection to the amine group being masked is an alkyl group. Prulifloxacin is available for oral use, and after absorption is metabolized to the active form ulifloxacin by esterases, mainly paraoxonase [95].

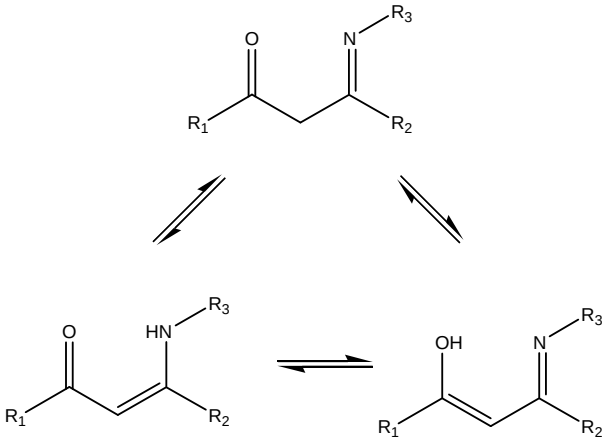
Scheme 12. Enzymatic hydrolysis of Prulifloxacin [95].



Enamines and enaminones

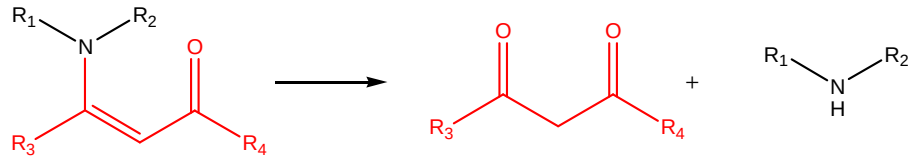
Enamines [96], (*α,β*-unsaturated amines), just like imines, are generally unstable particularly at low pH, which make them unsuitable for the preparation of prodrugs for oral delivery. Nevertheless, an enamine prodrug of ampicillin was found to promote the rectal absorption of the drug [97]. Enaminones, which are enamines of β-dicarbonyl compounds are more stable, probably due to keto-enol and imine-enamine tautomeric equilibria (Scheme 13) [91], and were thought to have potential use as prodrugs [10].

Scheme 13. Stabilisation of enaminones.



The hydrolysis of enaminones derived from some amino acids and antibiotics is rapid, releasing the amine and a diketone (Scheme 14).

Scheme 14. Hydrolysis of enaminones.



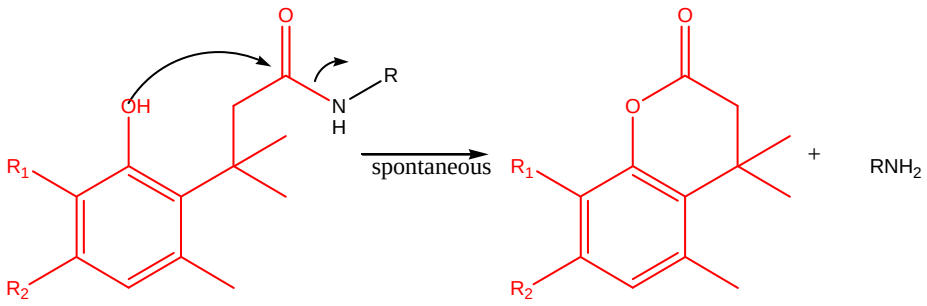
The prodrugs are more lipophilic than the corresponding drugs, which usually results in improved absorption [10]. The system seems to be relatively insensitive to the type of amine used, but very sensitive to minor changes in the structure of the 1,3-dicarbonyl compound used to produce the prodrug. Closed structures like the compounds derived from cyclohexane-1,3-dione show considerably lower rates of hydrolysis. This is probably due to their rigid geometry and the inherent stability of this system. The maximum rate of hydrolysis occurs in the pH range 2-5 [98].

Based on chemical stability considerations, enaminones do not seem promising as prodrugs. However it has been speculated that enaminones obtained from ketoesters and lactones may be better candidates as they may be subjected to enzyme-catalysed degradation [99].

"Trimethyl lock" and coumarin systems

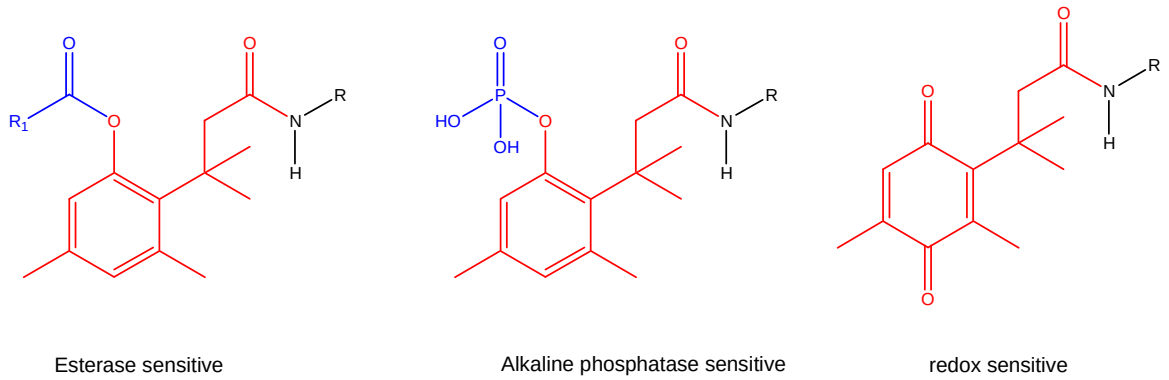
Phenolic amides derived from lactones can be used as amine prodrug systems as they release the amine and a lactone at physiological pH [100] (Scheme 15). In this system, referred to generally as a "trimethyl lock", the side chain is folded back to bring the amide carbonyl group into proximity with the nucleophilic phenolic oxygen. This conformation may account for the facile cyclisation that occurs independently of the drug attached to the side chain. However the half-lives of these systems are usually less than 1 min, which is too short for useful application [101].

Scheme 15. "Trimethyl lock" prodrug system for amino drugs.



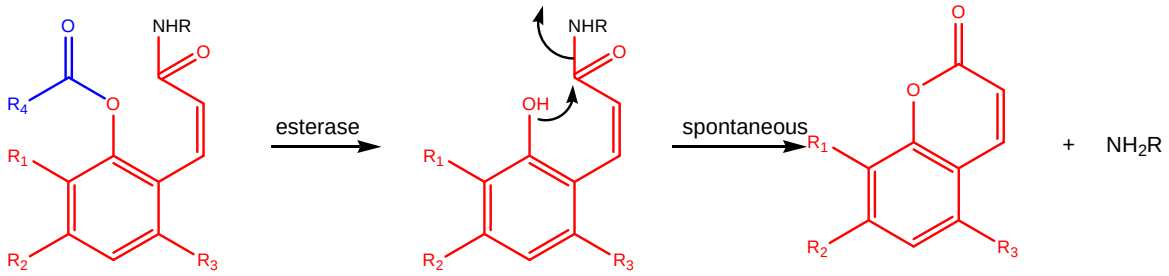
The design has been has been modified to produce compounds that are esterase [102] or redox [103] sensitive (Figure 1). These derivatisations involve the protection of the nucleophilic hydroxyl in a bioreversible manner. The rate-limiting step then becomes the enzymatic exposure of the phenolic group. A further variation to this system involved the introduction of phosphate esters as the phenolic masking group [104].

Figure 1. Tripartite "trimethyl lock" systems.



A conceptually similar system exploits the facile cyclization of coumarinic acid and its derivatives [105] (Scheme 16). The presence of the phenolic hydroxyl group and the *cis*-geometry of the double bond allows lactonization at rates comparable to those of the "trimethyl lock" system. The phenol group is protected by an ester or a phosphate group that serves as an esterase or phosphatase sensitive biological triggering mechanism.

Scheme 16. Coumarin-based esterase sensitive system for amino drugs.



The lactonization rate is higher for primary amines than for secondary amines; it also depends on steric features of the amine to be released [106]. For secondary amines with higher pKas, the system is sometimes undesirably slow. A further refinenment to the design is the use of ring mesomeric effects to tune drug release rates: increases of up to 16-fold can be achieved by placing electron releasing groups on the aromatic ring [107,108].

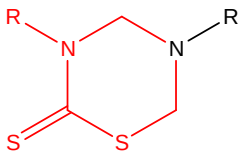
More recently, an attempt was made to prepare a tripartite prodrug (double prodrug) that uses the coumarin system as a spacer between the drug (linked to the side chain) and a carrier group, a peptide or an amino acid, connected to the hydroxyl group of the coumarin. The advantage of this system would be the possibility of targeting drug specific proteases for the cleavage that would release the carrier, which would be followed by spontaneous lactonization, releasing the drug. Poor aqueous solubility has, however, limited the exploitation of this system [109].

THTT

A tetrahydrothiadiazine-2-thione (THTT, Figure 2) was proposed as a prodrug system for primary amines [110], amino acids [111] and peptide drugs [112]. In this system the nitrogen atom from the drug is included in a six membered ring, which is more lipophilic than the original drug. The prodrugs

are enzyme and chemically sensitive at physiological pH, but are stable under acidic conditions. Despite the apparent promise of this system, it does not seem to have been subjected to further development.

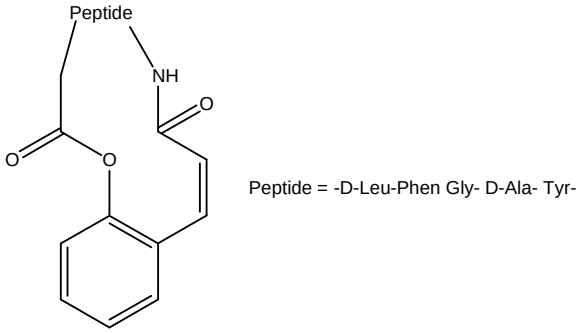
Figure 2. THTT prodrug system for amines and amino acids.



Cyclic derivatives of polyfunctional drugs containing the amino group

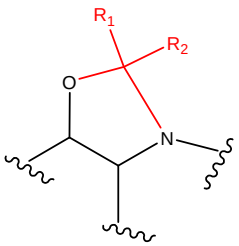
Making prodrugs of compounds with multiple functional groups may be a challenge, particularly in the case of peptides, where the amine group poses a problem of its own due to the lack of suitable biologically reversible masking groups. The "trimethyl lock" and coumarin systems mentioned before as prodrug systems for amines, have also been tested as prodrugs for peptides (linked to the progroup through an amide and an ester link) with promising results (Figure 3) [113-116].

Figure 3. Coumarin system applied to peptides.



The concept has been applied to peptides such as DADLE, an opioid peptide. The *C* and *N* terminal ends of the linear peptide are masked by forming an ester and an amide bond with the phenol hydroxyl and side chain carboxyl groups, respectively, of the linker [107]

Oxazolidines **22**, which are cyclic condensation products of *β*-aminoalcohols and aldehydes or ketones, are a possible means of formation of peptide prodrugs [86]. These compounds are less basic and more lipophilic than the corresponding *β*-aminoalcohols and hydrolyse completely in aqueous solution [117]. Thiazolidines can be used for *β*-aminothiols.



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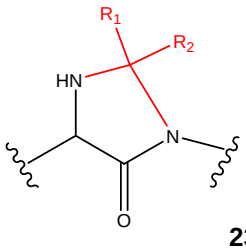
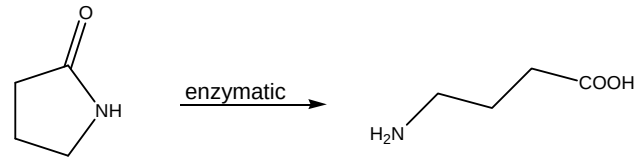


23

4-Imidazolidinones **23** [118-120] have been proposed for the α-aminoamide moiety, in particular as prodrugs of Leu-enkephalin and prilocaine. The derivatives of Leu-enkephalin afford protection against aminopeptidase-N and angiotensin converting enzyme (ACE) and are cleaved slowly in buffered solutions at pH=7.4, with half-lives of some hundred minutes [120]. The hydrolysis of some prilocaine derivatives, at basic pHs, proceeds to an equilibrium due to reversible kinetics [119]. Lactams and pyrrolines have been shown to revert to the corresponding amino acids by enzymatic action. Moreover, they pass the BBB while the opened structures don't. One example is the cyclic derivative (**24**) of GABA depicted in Scheme 17.

Scheme 17. Conversion of 2-pyrrolidinone to GABA.



. **24**

Conclusions

Three major themes emerge in amine prodrug chemistry: (i) suppression of ionization in order to promote passive diffusion; (ii) increasing the metabolic stability especially of primary amines and peptides; (iii) tissue targeting, particularly tumor tissue targeting. Other objectives include increasing the water solubility of the amine. Overall then, amino drugs may benefit significantly from prodrug design, but designing appropriate prodrugs for amines has been challenging. This challenge has provoked a markedly disparate variety of responses from pharmaceutical researchers. We considered it timely to gather these into one review article as a sort of catalogue that developers might find useful to consult during the development of new amino drugs or improvement of existing ones. Predicting the suitability of any single approach to a new situation, however, is still problematic. It seems prudent to investigate a number of approaches in parallel with appraisal in a panel of the most relevant human biological matrices, for example, intestinal and liver microsome preparations as well as plasma.

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ESTATUTO SOCIAL DA ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS - ABIA

CAPÍTULO I - DENOMINAÇÃO, SEDE, DURAÇÃO E FINS

Artigo 1º - A Associação Brasileira Interdisciplinar de AIDS - ABIA, doravante designada simplesmente ABIA, é uma associação, de direito privado, sem fins lucrativos e de fins não econômicos, de natureza social e filantrópica, fundada em 12 de março de 1987, cujas atividades reger-se-ão pelo presente Estatuto Social, devidamente aprovado por Assembleia Geral, e pela legislação em vigor.

Parágrafo Único – Para a sua identificação, o ABIA poderá adotar logomarca.

Artigo 2º - A ABIA tem sua sede, foro e administração no município do Rio de Janeiro, Estado do Rio de Janeiro, na Av. Presidente Vargas n. 446, 13º andar, Centro, CEP: 20.071-907.

Parágrafo Primeiro – Por decisão da Assembleia Geral, a sede poderá ser transferida para outro local.

Parágrafo Segundo - A ABIA poderá atuar em todo território nacional, abrindo filiais, escritórios ou credenciando representantes regionais, no Brasil ou no exterior, respeitada a legislação aplicável.

Artigo 3º - A ABIA terá prazo de duração indeterminado.

Artigo 4º - A ABIA desenvolve ações voltadas à prevenção ao vírus da imunodeficiência humana (HIV), à Síndrome da Imunodeficiência Adquirida (AIDS/SIDA) e doenças associadas, a garantia dos direitos, à assistência à saúde de pessoas atingidas pelo HIV, promovendo o respeito aos direitos humanos e, em particular, pelo respeito aos direitos das pessoas vivendo com HIV/AIDS e dos grupos mais vulneráveis ao HIV/AIDS, cabendo-lhe:

I. Promover a assistência social;

II. Promover a educação e a informação visando prevenir e controlar a epidemia de AIDS/SIDA baseando suas ações no princípio da solidariedade;

III. Elaborar e implementar campanhas de prevenção adequadas à realidade brasileira.

IV. Acompanhar a formulação e a implementação de políticas públicas.

V. Coletar, armazenar e interpretar dados oriundos de pesquisas desenvolvidas.

VI. Reunir, sistematizar e divulgar informações, atualizadas e cientificamente fundamentadas sobre a epidemia, através de estudos, relatórios, e publicações por conta própria ou de terceiros.

VII. Fornecer assessoria a diferentes grupos da sociedade tais como: empresas, escolas, universidades, sindicatos, associações comunitárias, igrejas, entidades de comunicação, prefeituras e outras instituições governamentais ou não governamentais.

VIII. Planejar, promover, coordenar e exercer atividades de promoção cultural e humana em suas áreas de atuação.

IX. Promover e/ou realizar projetos culturais, inclusive através das leis federais, estaduais e municipais de incentivo à cultura.

Parágrafo Primeiro - A ABIA não distribui entre os seus sócios, associados, conselheiros, diretores, empregados ou doadores eventuais excedentes operacionais, brutos ou líquidos, lucros, dividendos, bonificações, participações, resultados ou parcelas do seu patrimônio, auferidos mediante o exercício de suas atividades, e os aplica integralmente no território nacional, na manutenção e desenvolvimento de seus objetivos institucionais.

Parágrafo Segundo - À ABIA é vedada qualquer atividade político-partidária, eleitoral ou religiosa.

Parágrafo Terceiro – É vedado o uso da ABIA para qualquer espécie de promoção pessoal, política-partidária ou religiosa.

Artigo 5º - No desenvolvimento de suas atividades, a ABIA:

I. Não fará qualquer distinção de raça, cor, sexo, idade, condição física ou social, credo político ou religioso.

II. Prestará serviços permanentes e sem qualquer discriminação de clientela.

III. Poderá firmar termos de colaboração, termos de fomento, convênios, contratos, termos de cooperação, e outros instrumentos jurídico contratuais com pessoas jurídicas, públicas ou privadas, nacionais ou estrangeiras.

IV. Estimulará a atuação voluntária de pessoas interessadas em colaborar com suas finalidades.

CAPÍTULO II - DOS ASSOCIADOS

Seção I - Admissão, Exclusão e Penalidades.

Artigo 6º - A ABIA se constitui de número ilimitado de associados, pessoas naturais ou jurídicas, idôneas e interessadas, desde que:

I. Estejam na plenitude de sua capacidade civil.

II. Comunguem com suas finalidades sociais.

III. Concordem com o presente Estatuto Social e obriguem-se a cumpri-lo.

IV. Sejam admitidos como associados pelo Conselho de Administração.

Parágrafo Primeiro - Os associados, membros ou não dos órgãos administrativos e consultivos, não respondem solidária nem subsidiariamente pelas obrigações sociais da ABIA.

Parágrafo Segundo – Os associados serão distribuídos nas seguintes categorias:

I. Associados Fundadores: as pessoas naturais que participaram da Assembleia Geral de Fundação da ABIA.

II. Associados Efetivos: as pessoas naturais, admitidas nesta qualidade, por deliberação da Assembleia Geral.

III. Associados Beneméritos: as pessoas naturais ou jurídicas, de caráter público ou privado, que tenham realizado doação, em bens ou espécie, ou tenham prestado relevantes serviços à ABIA, devendo ser recomendado por outros associados, sendo seus nomes aprovados pela Assembleia Geral.

Parágrafo Terceiro – Os associados, independentemente da sua qualificação, comprometem-se a envidar esforços para a consecução dos objetivos sociais da ABIA.

Parágrafo Quarto – Os associados beneméritos não terão direito a voto na Assembleia Geral.

Parágrafo Quinto – A condição de associado prevista neste Estatuto é intransferível a terceiros, a que título for.

Parágrafo Sexto – A ABIA poderá contar com mantenedores, pessoas naturais ou jurídicas, que não serão associados, mas que auxiliem com recursos financeiros ou com dedicação de atuação voluntária às atividades e projetos da ABIA.

Artigo 7º - O interessado em se associar deverá formular pedido por escrito ao Conselho de Administração da ABIA.

Parágrafo Único – O Conselho de Administração apreciará o pedido de filiação e, deferindo-o, o remeterá à aprovação da Assembleia Geral.

Artigo 8º - A exclusão de qualquer associado se dará apenas por justa causa, a critério do Conselho de Administração, sendo-lhe garantido:

I. Prévia notificação para que possa exercer plenamente seu direito de defesa; e

II. Recurso à Assembleia Geral, com efeito suspensivo.

Parágrafo Primeiro - Para fins do disposto nesse Estatuto, será considerado como justa causa:

I. A ausência não justificada em três Assembleias Gerais consecutivas;

II. O não cumprimento do disposto no presente Estatuto Social ou em qualquer outro documento a que a ABIA seja submetida.

Parágrafo Segundo – Alternativamente à exclusão prevista no *caput* deste artigo, o Conselho de Administração poderá deliberar pela advertência do associado ou suspensão deste por até 90 (noventa) dias, contados da decisão.

Parágrafo Terceiro - O associado poderá se desligar a qualquer tempo se assim expressar formalmente e por escrito a sua intenção ao Conselho de Administração.

Seção II - Direitos e Deveres dos Associados

Artigo 9º - São direitos de todos os associados:

I. Frequentar a sede da ABIA.

II. Obter informações que desejarem sobre os objetivos sociais e funcionamento dos diversos órgãos da ABIA.

III. Participar das Assembleias Gerais e todos os eventos sociais, culturais e esportivos e demais atividades promovidos pela ABIA.
IV. Receber exemplares de todas as publicações da ABIA.

V. Propor a admissão de novos associados.

Parágrafo Único - Somente os associados fundadores e efetivos terão direito a voto.

Artigo 10 - São deveres dos associados, independente da categoria:

I. Colaborar com os órgãos da administração da ABIA, na realização dos atos necessários para a consecução de suas finalidades sociais.

II. Cumprir e fazer cumprir as disposições do presente Estatuto Social.

III. Pagar a contribuição financeira que venha a ser fixada pelo Conselho de Administração.

IV. Zelar pelos interesses morais, éticos e materiais da ABIA, cooperando com o seu desenvolvimento e maior prestígio.

CAPÍTULO III – ADMINISTRAÇÃO

Artigo 11 - A ABIA será administrada por:

I. Assembleia Geral

II. Conselho de Administração

III. Conselho Fiscal

IV. Conselho Consultivo e de Sustentabilidade

Parágrafo Primeiro - Cada um desses órgãos será regido pelos artigos dispostos nas seções subsequentes e nos termos da legislação vigente.

Parágrafo Segundo – A ABIA poderá remunerar seus dirigentes e as pessoas naturais e jurídicas que lhe prestem serviços específicos, respeitados, em ambos os casos, as disposições legais aplicáveis.

Seção I - Assembleia Geral

Artigo 12 - A Assembleia Geral é o órgão soberano da ABIA, sendo constituída por todos os associados em pleno gozo de seus direitos estatutários.

Parágrafo Único - As decisões tomadas pela Assembleia Geral obrigam a todos os associados, ainda que ausentes ou discordantes.

Artigo 13 – Compete privativamente à Assembleia Geral:

I. Deliberar sobre todo e qualquer assunto de interesse da ABIA para o qual for convocada.

II. Eleger os membros do Conselho de Administração e do Conselho Fiscal.

III. Destituir os membros do Conselho de Administração e do Conselho Fiscal.

IV. Alterar o presente estatuto social.

V. Deliberar sobre a extinção da ABIA.

VI. Aprovar a Prestação de Contas, incluindo o Relatório de Atividades e Demonstrações Financeiras, formulados pelo Conselho de Administração, que deverão ser previamente aprovadas pelo Conselho Fiscal.

VII. Aprovar a admissão e exclusão de associados, após manifestação do Conselho de Administração.

VIII. Aprovar a Programação e o Orçamento anuais, formulados pelo Conselho de Administração.

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IX. Autorizar a aquisição, alienação e oneração de bens imóveis.

Parágrafo Primeiro – Todas as deliberações, salvo a prevista no parágrafo seguinte, da Assembleia Geral, inclusive as definidas nos incisos III e IV, deverão ser aprovadas pela maioria simples dos votos dos associados presentes.

Parágrafo Segundo – A deliberação quanto à extinção da ABIA e destinação do patrimônio remanescente, prevista no inciso V deste artigo, deverá ser aprovada por 2/3 (dois terços) dos associados presentes à Assembleia Geral especialmente convocada para esse fim.

Artigo 14 – A Assembleia Geral reunir-se-á, ordinariamente, por convocação do Presidente:

I. Anualmente, em até cento e vinte dias após o encerramento do exercício social da ABIA, para, dentre outros assuntos, examinar e aprovar o Relatório de Atividades, o Balanço Patrimonial e as demais demonstrações financeiras e contábeis.

II. A cada três anos, para a eleição dos membros do Conselho de Administração e do Conselho Fiscal.

Artigo 15 – A Assembleia Geral reunir-se-á, extraordinariamente, sempre que se faça necessário, quando convocada:

I. Pelo Presidente;

II. A qualquer tempo, por 1/5 (um quinto) dos associados.

Parágrafo Primeiro – Dentre os assuntos a ser objeto de Assembleia Geral Extraordinária estão:

I. Reforma estatutária.

II. Destituição de membros do Conselho de Administração e do Conselho Fiscal.

III. Dissolução ou liquidação da ABIA.

IV. Julgamento de recurso de exclusão de associado.

Parágrafo Segundo – As deliberações previstas neste artigo, inclusive as que dispuserem sobre os incisos I e II do parágrafo primeiro, deverão ser aprovadas pela maioria simples dos votos dos associados presentes à Assembleia Geral, especialmente convocada para esses fins.

Parágrafo Terceiro – A deliberação quanto à extinção da ABIA e destinação do patrimônio remanescente, prevista no inciso III do parágrafo primeiro, deverá ser aprovada por 2/3 (dois terços) dos associados presentes à Assembleia Geral especialmente convocada para esse fim.

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Artigo 16 – A Assembleia Geral será convocada para fins determinados, mediante prévio e geral anúncio, através de edital afixado na sede da ABIA, por carta enviada aos associados ou qualquer outro meio eficiente, inclusive eletrônicos, com antecedência mínima de cinco dias.

Parágrafo Primeiro – Qualquer Assembleia Geral instalar-se-á, em primeira convocação, com, no mínimo, 2/3 (dois terços) dos associados, e, em segunda convocação, decorridos trinta minutos, com qualquer número.

Parágrafo Segundo – Para melhor gestão operacional, as Assembleias Gerais poderão ser realizadas virtualmente.

Parágrafo Terceiro - Os atos relativos à reforma do Estatuto, para valerem contra terceiros, ficam sujeitos às formalidades de registro e arquivamento nos órgãos competentes.

Seção II – Conselho de Administração

Artigo 17 – O Conselho de Administração é o órgão de gestão estratégica e administração da ABIA, sendo composto por até oito membros, sendo um Presidente, um Vice-Presidente e um Tesoureiro.

Artigo 18 – O Conselho de Administração é eleito em Assembleia Geral, por maioria simples de votos, para um mandato de três anos, sendo permitida a reeleição.

Artigo 19 - Compete ao Conselho de Administração:

I. Definir as diretrizes estratégicas da ABIA, cumprindo suas prioridades.

II. Cumprir e fazer cumprir rigorosamente o Estatuto e as decisões da Assembleia Geral.

III. Deliberar sobre a convocação de Assembleias Gerais.

IV. Nomear e destituir os membros do Conselho Consultivo e de Sustentabilidade.

V. Estabelecer e fiscalizar as normas básicas de funcionamento.

VI. Elaborar o Orçamento Anual da ABIA e autorizar receitas e despesas extraordinárias.

VII. Autorizar investimentos e outros atos jurídicos, que representem ônus ou diminuição patrimonial para a ABIA.

VIII. Fixar a periodicidade e o valor da contribuição mínima a ser paga pelos associados.

IX. Elaborar o Relatório Anual de Atividades e as demonstrações financeiras, submetendo-os, em seguida, à aprovação do Conselho Fiscal e da Assembleia Geral.

X. Nomear os membros do Conselho Supervisor do Fundo Patrimonial e deliberar sobre as demais matérias relativas ao referido Fundo, nos termos deste Estatuto.

XI. Decidir sobre quaisquer matérias que não sejam da competência de outros órgãos ou instâncias da ABIA, inclusive as omissões e interpretações ao presente Estatuto.

Artigo 20 – O Conselho de Administração se reúne ordinariamente uma vez por semestre e, extraordinariamente, sempre que necessário, quando convocado por qualquer um de seus membros ou pelo Conselho Fiscal, sendo suas reuniões presididas pelo seu Presidente.

Parágrafo Único – O Conselho de Administração delibera, validamente, com a presença da maioria simples dos seus membros, sendo vedada a representação, reservado o voto de desempate ao Presidente.

Artigo 21 - Compete ao Presidente:

I. Representar institucionalmente a ABIA, ativa ou passivamente, judicial e extrajudicialmente.

II. Auxiliar nas atividades de mobilização de recursos.

III. Convocar e presidir as reuniões do Conselho de Administração e da Assembleia Geral.

IV. Autorizar pagamentos e movimentação bancária, observadas as diretrizes definidas neste Estatuto.

V. Coordenar, supervisionar e acompanhar as atividades, programas e projetos em realização.

VI. Admitir e demitir os empregados, colaboradores, estagiários e prestadores de serviços a qualquer título e definir as respectivas atribuições.

Parágrafo Único – Compete ao Vice-Presidente substituir o Presidente em suas ausências e impedimentos.

Artigo 22 – Compete ao Tesoureiro:

I. Se responsabilizar pela escrituração patrimonial da ABIA em livros próprios, tendo sob sua guarda e conservação todos os papéis, documentos, títulos e valores de qualquer interesse.

II. Fornecer ao Conselho de Administração balancetes periódicos extraídos da escrituração, bem como informes minuciosos sobre a vida financeira da ABIA.

Artigo 23 – Todos os documentos oficiais da ABIA, incluindo cheques e demais documentos bancários e financeiros, assim como todos os instrumentos contratuais, para serem válidos, deverão ter duas assinaturas, em conjunto, podendo ser:

I. A do Presidente em conjunto com a do Vice-Presidente.

II. A do Presidente em conjunto com a do Tesoureiro.

III. A do Vice-Presidente em conjunto a do Tesoureiro.

III. A do Vice-Presidente em conjunto com a de um Procurador nomeado pelo Presidente.

IV. A do Tesoureiro em conjunto com a de um Procurador nomeado pelo Presidente.

Parágrafo Único – As procurações deverão ser firmadas, por instrumento público ou particular, pelo Presidente, com firma reconhecida.

Seção III - Conselho Fiscal

Artigo 24 - O Conselho Fiscal é um órgão colegiado, de avaliação, acompanhamento e controle, constituído por três membros, eleitos em Assembleia Geral para um mandato de três anos, permitida a reeleição.

Artigo 25 - Compete ao Conselho Fiscal:

I. Examinar os livros de escrituração da ABIA.

II. Fiscalizar a administração econômica, financeira e contábil, sugerindo ações e diretrizes ao Conselho de Administração, bem como à Assembleia Geral.

III. Emitir parecer sobre o Relatório Anual e as Demonstrações Financeiras apresentadas pelo Conselho de Administração.

IV. Contratar, quando necessário ou conveniente, auditoria externa independente, à custa da ABIA, devendo pronunciar-se sobre o relatório emitido pelos auditores.

V. Requisitar, para análise, a qualquer tempo, documentação comprobatória das operações econômico-financeiras realizadas.

Artigo 26 - O Conselho Fiscal se reunirá ordinariamente uma vez ao ano e, extraordinariamente, sempre que necessário.

Parágrafo Único - As reuniões do Conselho Fiscal deverão ser convocadas com antecedência mínima de cinco dias.

Seção V - Conselho Consultivo e de Sustentabilidade

Artigo 27 - O Conselho Consultivo e de Sustentabilidade, órgão auxiliar do Conselho de Administração, será constituído por número ilimitado de membros, escolhidos entre os associados, ou composto por pessoas

de notório saber e reconhecimento em suas áreas de atuação, que possam contribuir tecnicamente com o desenvolvimento das finalidades da ABIA.

Parágrafo Único – Os membros do Conselho Consultivo e de Sustentabilidade serão nomeados pelo Conselho de Administração, que poderá destituí-los.

Artigo 28 - Compete ao Conselho Consultivo e de Sustentabilidade:

I. Orientar trabalhos de pesquisas.

II. Opinar em projetos, programas e orçamentos.

III. Colaborar com o aperfeiçoamento das atividades da ABIA.

IV. Auxiliar o Conselho de Administração no planejamento e implementação de ações que objetivem assegurar a sustentabilidade da ABIA.

V. Opinar sobre outras matérias que lhe sejam encaminhadas.

Artigo 29 - O Conselho Consultivo e de Sustentabilidade reunir-se-á anualmente ou sempre que convocado pelo Conselho de Administração.

CAPÍTULO IV – DAS FONTES DE RECURSOS E DO PATRIMÔNIO

Artigo 30 – Constituem fontes de recursos da ABIA:

I. As doações, dotações, legados, heranças, subsídios e quaisquer auxílios que lhe forem concedidos por pessoas físicas ou jurídicas, de direito privado ou de direito público, nacionais ou estrangeiras, bem como os rendimentos produzidos por esses bens e seu patrimônio.

II. As receitas provenientes dos serviços prestados atinentes às suas finalidades.

III. As receitas patrimoniais.

IV. A receita proveniente de contratos administrativos, termos de fomento, termos de colaboração, convênios e termos de cooperação, celebrados com o Poder Público.

V. A receita proveniente de contratos, convênios, parcerias ou acordos celebrados com pessoas jurídicas de direito público ou privado, nacionais ou estrangeiras.

VI. A receita proveniente das contribuições feitas pelos associados.

VII. Verbas provenientes de promoções organizadas pelos associados.

VIII. Recursos provenientes de projetos culturais enquadrados nas leis federais, estaduais e/ou municipais de incentivo à cultura.

IX. Recursos advindos do recebimento de direitos autorais, conexos e de propriedade intelectual.

X. As receitas advindas da comercialização de produtos afins às atividades institucionais.

XI. Rendimentos financeiros e outras rendas eventuais.

Parágrafo Primeiro – As rendas, recursos, bens, direitos e eventuais resultados operacionais da ABIA serão aplicados integralmente no território nacional, na manutenção e desenvolvimento de seus objetivos institucionais.

Parágrafo Segundo - A ABIA se compromete a manter escrituração de suas receitas e despesas em livros revestidos de formalidades regulamentares capazes de comprovar sua exatidão.

Artigo 31 – O patrimônio da ABIA poderá ser constituído por bens móveis, imóveis, veículos, semoventes, ações e títulos da dívida pública ou privada.

Artigo 32 – No caso de dissolução da ABIA, o respectivo patrimônio líquido será transferido a outra entidade sem fins lucrativos e econômicos, com o mesmo objetivo social, congênere, registrada no Conselho Nacional de Assistência Social (CNAS), ou a entidade pública.

Artigo 33 - O exercício financeiro e fiscal da ABIA coincide com o ano civil.

Artigo 34 - O Fundo Patrimonial da ABIA, composto pelas aplicações financeiras da ABIA, tem por objetivo fortalecer, através de uma política de longo prazo, a sustentabilidade patrimonial da ABIA e a rentabilidade de suas reservas.

Parágrafo Primeiro - O Fundo Patrimonial, inclusive sua política de investimento, rege-se pelo disposto na legislação e regulamentação aplicáveis.

Parágrafo Segundo – Poderá ser constituído um Conselho Supervisor do Fundo Patrimonial com a função específica de acompanhar e supervisionar a administração, gestão e performance do Fundo Patrimonial.

Parágrafo Terceiro - O Conselho Supervisor do Fundo Patrimonial, quando constituído, será composto por três membros, todos com experiência em gestão de recursos de terceiros e indicados pelo Conselho de Administração.

Parágrafo Quarto - Observadas as disposições legais aplicáveis, o Fundo Patrimonial poderá ser usado também como instrumento de captação de recursos para a ABIA, inclusive mediante contribuições a ele destinadas, sendo certo que a sua existência não visa substituir ou diminuir outras fontes de receita da ABIA.

Artigo 35 - A prestação de contas da ABIA observará, no mínimo:

I. Os princípios fundamentais de contabilidade e as Normas Brasileiras de Contabilidade.

II. A publicidade, por qualquer meio eficaz, no encerramento do exercício fiscal, do relatório de atividades e das demonstrações financeiras da entidade, incluindo as certidões negativas de débitos junto ao INSS e FGTS, colocando-os à disposição para o exame de qualquer pessoa jurídica ou cidadão.

III. A realização de auditoria, inclusive por auditores externos independentes se for o caso, da aplicação de eventuais recursos objeto de Termo de Parceria, observada a legislação aplicável.

IV. A prestação de contas de todos os recursos e bens recebidos de origem pública será feita conforme determina o parágrafo único do artigo 70 da Constituição Federal.

CAPITULO V – DISPOSIÇÕES GERAIS

Artigo 36 - A ABIA será dissolvida por deliberação da Assembleia Geral Extraordinária, especialmente convocada para esse fim, pelo voto concorde de 2/3 (dois terços) dos presentes, quando se tornar impossível a continuação de suas atividades, ou nos casos previstos em Lei.

Parágrafo Único – Em qualquer caso serão observados os dispositivos legais aplicáveis e o fixado no presente Estatuto.

Artigo 37 - Os membros da ABIA e seus empregados difundirão as finalidades e a filosofia da entidade, motivando a participação de outros membros da sociedade civil.

Artigo 38 - Os casos omissos serão resolvidos pelo Conselho de Administração, de acordo com a lei.

Rio de Janeiro, 06 de dezembro de 2016.

Richard Guy Parker
Presidente da Assembleia

Regina Maria Barbosa
Secretária da Assembleia

CARTÓRIO VANELE FALCÃO
21º OFÍCIO DE NOTAS - Vanele Falcão - Tabelia de Notas
Av. Erasmo Braga nº 295 - RJ - Tel. (21)2532-2121 11 de Abril de 2017
Reconheço por SEMELHANÇA as firmas de
REGINA MARIA BARBOSA.....
Em testemunho da verdade.
Mat. Jorge José da Silva Filho Escrevente
Emolumentos R$ 5,28 TJ+Fundos R$ 1,86 Total R$ 7,14
ECAR74853-RQE
Consulte em https://www3.tjrj.jus.br/selopublico/

Pedro Carpenter Genescá (OAB/RJ 121.340)

REGISTRO CIVIL DAS PESSOAS JURÍDICAS DA CIDADE DO RIO DE JANEIRO

Rua México, n° 148, 3° andar, Centro, Rio de Janeiro
www.rcpj-rj.com.br email: atendimento@rcpj-rj.com.br

C E R T I D Ã O

O Oficial do Registro Civil das Pessoas Jurídicas do Rio de Janeiro, conforme o art. 19, § 1º, da lei 6015/73 e do art.217 da Lei Civil, CERTIFICA que esta é a cópia fiel da ata da AGO datada de 11/11/2020 e arquivada em 14/12/2020 da ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS, constituída neste ofício na matricula nº 92.514, num total de 09 páginas, numeradas e chanceladas digitalmente.

Rodolfo Pinheiro de Moraes
Mat. 90-00.00.00.00.02

Poder Judiciário - TJERJ
Corregedoria Geral de Justiça
Selo de Fiscalização Eletrônico
EDNC 38371 DQY
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1202101121434027

Rio de Janeiro, 22 de janeiro de 2021

Emol.: 153,16 Trib.: 58,79

AAA 19710179

TERMO DE RESPONSABILIDADE E REQUERIMENTO DE REGISTRO

Requeiro ao Registro Civil de Pessoas Jurídicas o registro da presente documentação da

Pessoa Jurídica: **ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS**

Matrícula da PJ: **92514** CNPJ: **29.263.068/0001-45**

Reconheço como verdadeiras todas as informações constantes neste documento, inclusive a autenticidade das assinaturas, sob pena de nulidade do ato, assumindo responsabilidade pessoal nos termos do **art. 14 da Lei 13874/19 e art. 6° §4° do Provimento 62/2018 CGJ publicado no DOJERJ de 20/12/18 pag. 42.**

[x] **Envio a documentação digitalmente com a minha assinatura ICP-BRASIL.**

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OBS: Caso seja optado pelo envio de vias adicionais será cobrado os emolumentos referentes a quantidade de vias para este serviço em decorrência do processo.

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Rio de Janeiro, 17 de novembro de 2020

Pedro Carpenter Genesca
OAB/RJ 121.340
Advogado

ICP BRASIL do Advogado, Contador ou Participante do ato (Sócio, Administrador, Presidente, Diretor, Presidente da Assembleia e Testemunhas)

(*) OBS: 1) Em caso de registro de livro PDF as assinaturas digitais caberão aos: Representantes Legais e o Contador.
2) O Registro do documento será feito digitalmente, vias em papel deverão ser solicitadas acima.

CERTIDÃO
22/01/2021 EDNC 38371 DQY 1

AAA 19710180

ABIA
ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS

ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS – ABIA

CNPJ 29.263.068.0001/45

Assembleia Geral Ordinária

Convocação

São convocados os associados da ABIA, a se reunirem em Assembleia Geral Ordinária no dia 11 de novembro de 2020, em primeira convocação às 10:00 e, em segunda convocação, às 10:30 horas, a ser realizada de forma virtual, pela plataforma Zoom, a fim de deliberarem sobre a seguinte pauta:

1 – Apresentação das Demonstrações e relatório de Auditoria do Exercício de 2019;

2- A situação da ABIA em 2020;

3 - Caminhos e perspectivas em 2021;

4 – Eleição do Conselho de Administração;

5 – Solicitação para compartilhamento de salas;

6 – Solicitação para baixa do imobilizado, doação e descarte.

Rio de Janeiro, 20 de outubro de 2020.

Richard Guy Parker
Diretor Presidente

ABIA
ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS

Lista de Presença da Assembleia Geral Ordinária da Associação Brasileira Interdisciplinar de AIDS – ABIA

1. Veriano de Souza Terto Júnior
2. Richard Guy Parker
3. Simone Souza Monteiro
4. Regina Maria Barbosa
5. Luis Felipe Rios de Nascimento
6. Fátima Maria Gomes da Rocha
7. Alexandre Domingues Granjeiro
8. Carlos Alberto Ebeling Duarte
9. Kenneth Rochel Camargo Júnior
10. Fernando Seffener
11. Simone Lima

Rio de Janeiro, 11 de novembro de 2020.

Richard Guy Parker
Presidente da Assembleia

Veriano de Souza Terto Júnior
Secretário da Assembleia

Av. Presidente Vargas, 446/13º andar - Centro • CEP- 20071-907 • Rio de Janeiro/RJ • Brasil
Tel.: +55 (21) 2223-1040 • (21) 2223-1185 • (21) 2223-1391
E-mail: abia@abiaids.org.br • Site: www.abiaids.org.br

ABIA
ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS

ATA DA ASSEMBLEIA GERAL ORDINÁRIA DA ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS – ABIA - CNPJ 29.263.068.0001/45

Em segunda convocação, às 10:30 horas, do dia 11 de novembro de 2020, por convocação do Diretor Presidente, Sr. Richard Guy Parker, reuniram-se de forma virtual, pela plataforma Zoom, os senhores e senhoras associados da Associação Brasileira Interdisciplinar de Aids - ABIA, devidamente convocados por meio de correio eletrônico, atingindo o quórum estatutário, com a presença de 11 membros, sendo a Assembleia presidida pelo Sr. Richard Guy Parker e secretariada pelo Sr. Veriano de Souza Terto Júnior.

O Sr Richard Guy Parker deu início à reunião cumprimentando os presentes e abrindo a discussão da pauta, acerca dos seguintes itens:

1 - Apresentação das Demonstrações e relatório de Auditoria do Exercíco de 2019: A Sra. Simone Lima apresentou para o relatório da auditoria referente ao exercício de 2019 e parecer dos auditores independentes. Após votação, foi aprovada por unanimidade as Demonstrações Financeiras de 2019.

2- A situação da ABIA em 2020: Foi feito informe da situação da ABIA em 2020, com projetos iniciados e concluídos e situação financeira.

3 - Caminhos e perspectivas em 2021: Foi conduzida discussão sobre caminhos e perspectivas para 2021, com iniciativas para a sustentabilidade, possíveis mudanças e adaptações, perspectiva financeira.

4 – Eleição do Conselho de Administração: Foram eleitos, por unanimidade, os seguintes membros para o Conselho de Administração, para o mandato que se iniciará em 16/12/2020 e terminará em 15/12/2023: como Diretor-Presidente, **RICHARD GUY PARKER**, americano, solteiro, antropólogo, residente à Avenida Nossa Senhora de Copacabana, 13/1101, Leme. Rio de Janeiro RJ, CEP: 22.010-120, portador do CPF 017.881.517-98 e da identidade VO 62673-P CGP/DIREX/DPF; como Diretor Vice-Presidente, **VERIANO DE SOUZA TERTO JÚNIOR**, brasileiro, solteiro, psicólogo, residente à Rua Visconde de Figueiredo, nº 72 aptº 301- Tijuca – Rio de Janeiro CEP:20.550-050, portador do CPF 667.972.337-04 e da identidade 06.677.516-4, emitida pelo IFP/RJ; e como Tesoureira, **SIMONE SOUZA MONTEIRO**, brasileira, casada, psicóloga, residente à Rua Visconde de Pirajá, 592/503 – Ipanema, RJ, CEP: 22410-002. Rio de Janeiro, RJ, portadora do CPF 986.589.997-34 e da identidade n. 06210329-6, IFP/RJ. Os demais cargos do Conselho de Administração permanecem vacantes.

Declaração de Desimpedimento: Para fins de cumprimento de exigências legais, o administrador, abaixo assinado, declara, sob as penas da lei, de que não está impedido de exercer a administração da associação, por lei especial, ou em virtude de condenação criminal, ou por se encontrar sob os efeitos dela, a pena que vede, ainda que temporariamente, o acesso a cargos públicos; ou por crime falimentar, de prevaricação, peita ou suborno, concussão, peculato; ou contra a economia popular, contra o sistema financeiro nacional, contra normas de defesa da concorrência, contra as relações de consumo, fé pública ou a propriedade.

ABIA
ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS

5 – Solicitação para compartilhamento de salas: Foi aprovada por unanimidade autorização para o compartilhamento de salas da sede da ABIA com o IBASE, outra associação sem fins lucrativos.

6 – Solicitação para baixa do imobilizado, doação e descarte: Foi aprovada por unanimidade a baixa do ativo imobilizado da ABIA, dos bens móveis abaixo listados, podendo ser descartados ou doados a terceiros:

Nº DO PATRIMÔNIO	DESCRIÇÃO DO BEM	DATA DE AQUISIÇÃO	FINANCIADOR
MU 006	Cadeira tipo secretária s/braços com rodízio estofado preto.	25.04.03	HIVCENTER
MU 014	Mesa medindo 120x60, mobicom com 3 gavetas cinza/preto.	25.04.03	HIV CENTER
MU 026	Mesa medindo 106x60, mobicom, cor cinza.	25.04.03	HIV
MU 034	Cadeira tipo secret. s/braço giratória tecido preto.	05.04.04	EED
MU 049	Mesa de madeira c/03 gavts. c/tampo de 1,20x0,60m	30.06.92	FORD
MU 057	Estante de aço c/06 prateleiras	28.08.92	FORD
MU 058	Estante de aço c/06 prateleiras	28.08.92	FORD
MU 059	Estante de aço c/06 prateleiras	28.08.92	FORD
MU 135	Cadeira estofada, cor preta c/rodízio	23.11.92	MACARTHUR
MU 175	Estante de aço c/06 prateleiras	30.06.92	FORD
MU 220	Mesa em madeira c/03 gavts. medindo 1,30x0,40x0,70m	06.05.93	MACARTHUR
MU 271	Estante de aço c/04 prateleiras	02.02.96	EZE
MU 273	Estante de aço c/06 prateleiras.	02.02.96	EZE
MU 294	Mesa com 3 gavetas 1.20 x 60, cor ovo/preto.	23.09.02	FORD
MU 358	Banqueta alta com 60cm de alt. Cor preta.	22.03.07	ABIA
MU 362	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 363	Cadeira giratória tipo secretária fixa preta.	06.06.07	PRISMA

ABIA
ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS

MU 365	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 366	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 367	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 368	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 369	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 370	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 371	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 372	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 373	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 374	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 375	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 376	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 377	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 378	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 379	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 380	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 381	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 382	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 383	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 384	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 385	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 387	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 388	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 389	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA

ABIA
ASSOCIAÇÃO BRASILEIRA INTERNACIONAL DE ARTE

MU 390	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
M U 391	Cadeira giratória tipo secretária fixa preta.	05.06.07	PRISMA
MU 392	Cadeira secretária giratória cor preta.	05.06.07	PRISMA
MU 393	Cadeira secretária giratória cor preta.	05.06.07	PRISMA
MU 394	Mesa diretor cor cinza méd. 75x150, c/gaveteiro, pé.	05.06.07	PRISMA
MU 395	Mesa diretor cor cinza méd. 75x150, c/gaveteiro, pé.	05.06.07	PRISMA
MU 397	Armário multi uso cinza méd. 170x75x35.	05.06.07	PRISMA
MU 398	Armário multi uso cinza méd. 170x75x35.	05.06.07	PRISMA
MU 399	Armário multi uso cinza méd. 170x75x35.	05.06.07	PRISMA
MU 400	Arquivo 4 gavetas cinza arte 24.	05.06.07	PRISMA
MU 401	Arquivo móvel	26.11.07	PRISMA
MU 402	Arquivo móvel 2 gavetões.	16.08.07	PRISMA
MU 403	Armário ferramenta 1 porta	16.08.07	PRISMA
MU 404	Mesa tampo quadrado	16.08.07	PRISMA
MU 405	Armário Multi PA25 CZ	02.04.08	PRISMA
MU 406	Armário Multi PA 25 CZ.	02.04.08	PRISMA
MU 409	Armário Multi uso CE N. fiscal 67693	02.06.08	PRISMA
MU 410	Armário Multi uso CE N. fiscal nº 67693	02.06.08	PRISMA
MU 411	Arquivo 4 gavetas CZ. N. fiscal 63855	13.05.08	PRISMA
MU 412	Arquivo 4 gavetas CZ. N. fiscal 63855	13.05.08	PRISMA
MU 413	Armário 25 CZ N. Fiscal 55951	01.04.08	PRISMA
MU 414	Armário 25 CZ N. Fiscal 55951	01.04.08	PRISMA
MU 415	Arquivo 25 CZ N. Fiscal 55951	01.04.08	PRISMA
MU 416	Arquivo 25 CZ N. Fiscal 55951	01.04.08	PRISMA
MU 442	Arquivo deslizante c/28 faces mod. 1.6 ½	21.11.06	EED

ABIA
ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS

MU 444	POLTRONA PRESIDENTE MILANO LUXO EM CREPE	23.05.14	PRISMA
MU 445	CADEIRA EMPILHAVÉL 120 KG 1003 MS SYSTEM	23.05.14	PRISMA
MU 446	CADEIRA GIRATÓRIA 658 MS SYSTEM VENEZA	23.05.14	PRISMA
MU 447	ARQUIVO DE AÇO 4 GAVETAS PARA PASTA SUSPENSA EM CHAPA	23.05.14	PRISMA
MU 448	VENTILADOR DE COLUNA OSCILANTE PREMIUM 60 CM	23.05.14	PRISMA
MU 449	MESA AUXILIAR SEM GAVEYEIRO A 74 CM X L 1,06 CM X 60 CM ALFAMOB GAMA	23.05.14	PRISMA
MU 450	GAVETEIRO DE MESA ALFAMOB LIGTH 15 MM	23.05.14	PRISMA
MU 451	BEBEDOURO ELETRÔNICO NEO MASTERFRIO 110 BRANSCO GRANDE	23.05.14	PRISMA
MU 463	Mesa reta 40 MM 1200x600x740 castanho	08.12.16	UNITAID
MU 464	GAVETEIRO VOLANTE 03 GAVETAS 15MM VINHO	08.12.16	UNITAID
MU 466	Mesa de reunião méd. 2,00 x 1,00m.	08.12.16	UNITAID

Nada mais havendo a tratar, foi encerrada a reunião.

Rio de Janeiro, 11 de novembro de 2020.

Richard Guy Parker
Presidente da Assembleia

Veriano de Souza Terto Júnior
Secretário da Assembleia

REPÚBLICA FEDERATIVA DO BRASIL

Registro Civil de Pessoas Jurídicas
Comarca da Capital do Rio de Janeiro
Rua Mexico, 148, 3º andar, Centro

CERTIFICO A AVERBAÇÃO NA MATRÍCULA, PROTOCOLO E DATA ABAIXO.
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20201123113212 1 14/12/2020

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Roberto F. de Moraes
Oficial

CERTIDÃO
22/01/2021 EDNC 38371 DQY 9

AAA 19710188

ABIA
ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS

PROCURAÇÃO *ad judicia*

ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS, pessoa jurídica de direito privado, sem fins lucrativos, constituída na forma da lei, registrada no CNPJ sob o n° 29.263.068/0001-45, com sede na Avenida Presidente Vargas, n° 446, 13° andar, Centro, Rio de Janeiro - RJ, CEP: 20071-907, na pessoa de seu representante nos termos de seu Estatuto Social, por seu Diretor Vice-presidente **VERIANO DE SOUZA TERTO JÚNIOR**, brasileiro, solteiro, psicólogo, RG n° 06.677.516-4 emitido pelo IFP/RJ, e inscrito no CPF n° 667.972.337-04, e por seu Coordenador de projetos **JUAN CARLOS DE LA CONCEPCION RAXACH**, cubano, naturalizado brasileiro, solteiro, médico, RG n° 32.847.134-7 emitido pelo DETRAN/RJ, e inscrito no CPF n° 052.549.417-07, vem pelo presente instrumento outorgar procuração *ad* judicia à advogada **SUSANA RODRIGUES CAVALCANTI VAN DER PLOEG**, inscrita no CPF 013.497.254-63 e na **OAB/MG 181.599**, com escritório na Avenida Presidente Vargas, 446, 13º andar, Centro - Rio de Janeiro - RJ, CEP 20071-907, concedendo-lhe poderes da cláusula *ad judicia et extra*, inclusive substabelecer com reserva de poderes, especificamente para apresentação de subsídio ao exame técnico e/ou processo administrativo de nulidade perante o INPI - Instituto Nacional da Propriedade Industrial relacionado à patente de invenção **BR112024010162-2**.

Rio de Janeiro, 25 de novembro de 2025.

Veriano de Souza Terto Júnior
Diretor Vice-presidente da Abia

Juan Carlos de La Concepcion Raxach
Coordenador de projetos

Av. Presidente Vargas, 446/13º andar . 20071 907 . Rio de Janeiro/RJ . Brasil
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E-mail: abia@abiaids.org.br . Site: www.abiaids.org.br

4º Oficial de Registro de Títulos e Documentos e Civil de Pessoa Jurídica da Comarca de São Paulo

Oficial de Registro: Robson de Alvarenga

Rua Líbero Badaró, n. 425 / Pq. Anhangabaú, n. 350 - 28º andar, CEP 01007-040 - Centro
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REGISTRO CIVIL DE PESSOA JURÍDICA

Nº 725.064 de 26/09/2025

Certifico e dou fé que o documento eletrônico, contendo **33 (trinta e três) páginas** (arquivo anexo), foi apresentado em 26/08/2025, protocolado sob nº 444.341, tendo sido registrado eletronicamente sob nº **725.064** e averbado no registro nº 237636/92 no Livro de Registro A deste 4º Oficial de Registro Civil de Pessoas Jurídicas da Comarca de São Paulo, na presente data.

Denominação
FEDERACAO NACIONAL DOS FARMACEUTICOS FENAFAR
CNPJ nº 00.679.357/0001-48

Natureza:
ALTERAÇÃO DE ESTATUTO ELETRÔNICO

Certifico, **ainda**, que consta no documento eletrônico registrado as seguintes assinaturas digitais:
FABIO JOSE BASILIO:(Padrão: Gov-BR)
MARIA MARUZA CARLESSO:(Padrão: Gov-BR)
ANDRE NUNES CAVALCANTE:(Padrão: Gov-BR)
PAULO HENRIQUE REZENDE:(Padrão: Gov-BR)

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São Paulo, 26 de setembro de 2025

Assinado eletronicamente

Carlos Augusto Peppe
Escrevente

Este certificado é parte **integrante e inseparável** do registro do documento acima descrito.

Emolumentos	Estado	Secretaria da Fazenda	Registro Civil	Tribunal de Justiça
R$ 324,15	R$ 91,99	R$ 62,97	R$ 17,15	R$ 22,21
Ministério Público	ISS	Condução	Outras Despesas	Total
R$ 15,45	R$ 6,79	R$ 0,00	R$ 0,00	R$ 540,71

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Página
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Registro Nº
725.064
26/09/2025

Protocolo nº 444.341 de 26/08/2025 às 08:05:45h: Documento **registrado eletronicamente para fins de publicidade e/ou eficácia contra terceiros** sob nº **725.064** em **26/09/2025** e averbado no registro nº 237636/92 neste **4º Oficial de Registro Civil de Pessoas Jurídicas da Comarca de São Paulo**. Assinado digitalmente por Carlos Augusto Peppe - Escrevente.

Oficial	Estado	Secretaria Fazenda	Reg. Civil	T. Justiça	M. Público	ISS	Condução	Despesas	Total
R$ 324,15	R$ 91,99	R$ 62,97	R$ 17,15	R$ 22,21	R$ 15,45	R$ 6,79	R$ 0,00	R$ 0,00	R$ 540,71

ILUSTRÍSSIMO SENHOR OFICIAL DO 4º REGISTRO DE TÍTULOS E DOCUMENTOS E CIVIL DE PESSOA JURÍDICA DA CAPITAL – SP

A Federação Nacional dos Farmacêuticos, inscrita no CNPJ sob o nº 00.679.357/0001-48, com sede à Rua Barão de Itapetininga, 255, Sala 302, Centro, São Paulo/SP, CEP 01042-001, representada neste ato por seu representante legal Fábio José Basílio (GO), domiciliado na Rua RB 16, QD 41, LT 22, Goiânia/GO, CEP:74474-377, Casado, RG:3207835 - 22/12/2022 – SSP/GO, CPF:830.864.801-06 vem, respeitosamente, à presença de Vossa Senhoria requerer o registro da Ata de Reforma de Estatuto e anexos, declarando que foram cumpridos todos os requisitos estatutários vigentes.

São Paulo, 19 de agosto de 2025

Documento assinado digitalmente
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Verifique em https://validar.iti.gov.br

Fábio José Basílio

ATA DA ASSEMBLEIA CONGRESSUAL DA FEDERAÇÃO NACIONAL DOS FARMACÊUTICOS – FENAFAR

Aos cinco dias do mês de agosto do ano de dois mil e vinte e cinco, às treze horas e trinta minutos nas dependências do **Centro de Artes e Convenções da Universidade Federal de Ouro Preto (UFOP)**, situado à Rua Diogo Vasconcelos, nº 328, Bairro Pilar, Ouro Preto – MG, CEP 35400-000, realizou-se a **Assembleia Congressual da Federação Nacional dos Farmacêuticos – FENAFAR**, convocada conforme edital publicado no Diário Oficial da União de 27 de janeiro de 2025, Seção 3, página 185. Constatou-se a presença de **21 sindicatos filiados**, totalizando **179 (cento e setenta e nove) delegados(as)** aptos(as) a votar, conforme lista de eleitores anexa a esta ata. Assumiu a presidência dos trabalhos o **Presidente da Fenafar, Fábio José Basílio**, que compôs a mesa com o **Primeiro Vice-Presidente, André Cavalcanti**, e a **Secretária, Maria Maruza Carlesso**. O Presidente deu início aos trabalhos, agradecendo a presença de todas as delegações e ressaltando a importância da Assembleia Congressual como instância máxima de deliberação da Federação para a reforma estatutária. Em seguida, passou-se à análise da pauta estabelecida:

I – Alteração Estatutária

Foi apresentada à Assembleia a proposta de alteração do Estatuto Social da Fenafar, cujas alterações sugeridas foram lidas e explicadas em detalhes pela mesa diretora. As mudanças propostas foram: I – Alteração do art. 15, passando o Congresso a ser realizado quadrienalmente; II – Alteração do art. 22, passando o mandato da diretoria da Fenafar de 3 (três) para 4 (quatro) anos; III – Desmembramento do inciso XXII do art. 23, passando referido inciso a ser denominado “Diretoria da juventude”, e o inciso XXIII passando a ser “Diretoria dos direitos humanos”; IV – Inclusão da “Diretoria de meio ambiente e crise climática”, que receberá o inciso XXIV do art. 23, com a consequente renumeração dos demais incisos; V – Inclusão, no art. 38-E, de 4 (quatro) incisos, além da adequação da redação; VI – Inclusão do art. 38-F, com as competências da diretoria de direitos humanos, assim como do art. 38-G, com as competências da diretoria de meio ambiente e crise climática, com a renumeração do atual art. 38-F para 38-H; VII – Acrescer, no capítulo X – Das disposições gerais – art. nº 50, que trata das modalidades de reuniões deliberativas, com a renumeração dos artigos subsequentes; VIII – Inclusão de 2 (dois) artigos nas disposições transitórias, referentes à adequação do mandato para os termos do novo estatuto, além de posse das diretorias de juventude, de Direitos Humanos e de Meio Ambiente e Crise Climática, IX – Adequação textual de todos dispositivos e renumeração de artigos em conformidade com as alterações/inclusões deliberações.

Feitas as considerações, o Presidente passou a expor a proposta de alteração/reforma estatutária:

Com base no Estatuto vigente da Federação Nacional dos Farmacêuticos (FENAFAR) e nas deliberações do 11º Congresso da FENAFAR, apresenta-se as seguintes propostas de alteração estatutária para apreciação e deliberação:

1ª Alteração – Alteração da data de realização do Congresso

O Artigo 15 do Estatuto passa a vigorar com a seguinte redação:

Art. 15 – O Congresso reunir-se-á ordinariamente quadrienalmente, ou em caráter extraordinário, quando convocado por dois terços dos membros do Conselho de Representantes.

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2ª Alteração – Alteração do prazo do mandato da diretoria da Fenafar

O Artigo 22 do Estatuto passa a vigorar com a seguinte redação:

Art. 22 – O mandato da Diretoria será de 4 (quatro) anos, eleita pelo Congresso da FENAFAR.

3ª Alteração – Desmembramento da Diretoria de Juventude e Direitos Humanos

O inciso XXII do Art. 23 do Estatuto, passa a vigorar com a seguinte redação:

XXII – Diretoria da Juventude.

O inciso XXIII do Art. 23 do Estatuto, passa a vigorar com a seguinte redação:

XXIII – Diretoria dos Direitos Humanos.

4ª Alteração - Inclusão de Nova Diretoria

Fica alterado o inciso XXIV do Art. 23 do Estatuto, com as consequentes renumerações dos incisos posteriores, passando a vigorar com a seguinte redação:

XXIV – Diretoria de Meio Ambiente e Crise Climática.

5ª Alteração – Atribuições da Diretoria da Juventude

O Art. 38-E, incisos I e II foram adequados, passando a vigorar com as seguintes redações:

Art. 38-E – Caberá a diretoria da Juventude

I – Promover atividades e eventos culturais como seminários, palestras, programações artísticas, etc, de interesse da(o)s jovens farmacêutica(o)s;

II – Coletar, sistematizar e processar dados de interesse da categoria, elaborando análise sobre as relações de trabalho envolvendo a(o)s jovens farmacêutica(o)s;

Ficam incluídos no art. 38-E os seguintes incisos, de II a VI:

III - manter permanente e efetiva integração com entidades sindicais e/ou movimentos sociais, pautando os interesses e defesas da juventude trabalhadora;

IV - Trabalhar junto aos sindicatos a renovação das diretorias sindicais a da federação, visando a formação de novas lideranças.

V - propor estudos e projetos de sua área e compartilhar as informações à diretoria da federação.

VI - Realizar diálogo constante com o Movimento Estudantil de Farmácia, com o objetivo de fortalecer as relações institucionais;

6ª Alteração – Atribuições da Diretoria dos Direitos Humanos

Fica estabelecido, no Art. 38-F, o seguinte artigo:

Art. 38-F – Caberá a(o) Diretor(a) de Direitos Humanos

I – Planejar, propor e coordenar ações da FENAFAR relacionadas aos direitos humanos, com foco nos impactos à saúde pública e às condições de trabalho das farmacêuticas e dos farmacêuticos

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II – Articular-se com movimentos, entidades e organismos governamentais e da sociedade civil, nacionais e internacionais, voltados à justiça social;

III – Apoiar campanhas, estudos e políticas públicas que promovam práticas inclusivas e antidiscriminatórias nos sistemas de saúde e no ambiente de trabalho da categoria farmacêutica;

IV – Promover ações de formação e conscientização da categoria quanto às intersecções entre saúde e direitos humanos.

V - Ampliar a participação da FENAFAR e seus sindicatos em Conselhos Populares relacionados aos Direitos Humanos.

7ª Alteração – Atribuições da Nova Diretoria de Meio Ambiente e Crise Climática

Altera-se ao Estatuto o Art. 38-F, com a readequação do atual 38-F para 38-G, com a seguinte redação:

Art. 38-F – Compete à Diretoria de Meio Ambiente e Crise Climática:

I – Planejar, propor e coordenar ações da FENAFAR relacionadas à defesa ambiental e ao enfrentamento da crise climática, com foco nos impactos à saúde pública e às condições de trabalho das farmacêuticas e dos farmacêuticos;

II – Articular-se com movimentos, entidades e organismos governamentais e da sociedade civil, nacionais e internacionais, voltados à justiça ambiental e climática;

III – Apoiar campanhas, estudos e políticas públicas que promovam práticas sustentáveis nos sistemas de saúde e no ambiente de trabalho da categoria farmacêutica;

IV – Promover ações de formação e conscientização da categoria quanto às intersecções entre saúde, meio ambiente e mudanças climáticas.

8ª Alteração – Modalidades das Reuniões Deliberativas

Fica acrescido ao Estatuto um novo artigo nas Disposições Gerais, que ocupará o art. 50, com a renumeração dos artigos posteriores:

Art. 50 – As reuniões dos fóruns deliberativos da FENAFAR, incluindo Diretoria, Conselho de Representantes e o próprio Congresso, poderão ser realizadas presencialmente, de forma híbrida ou totalmente online, desde que garantidas as condições de participação democrática e votação segura.

9ª – Inclusão de Disposições Transitórias

Ficam acrescidos os arts. 2º e 3º às disposições transitórias

Art. 2º – Excepcionalmente, para garantir a implementação da nova duração de mandato a partir do 11º Congresso da FENAFAR, o mandato da Diretoria eleita no 11º Congresso será prorrogado conforme decisão desta assembleia por mais um ano de 01/09/2028 a 31/08/2029.

Art. 3º – As Diretorias da Juventude, de Direitos Humanos e de Meio Ambiente e Crise Climática serão implementadas ainda nesta gestão (2025-2029), será exercido por Diretores indicados em plenária do11º Congresso da FENAFAR e empossados na primeira reunião do Conselho de Representantes que ocorrer após o registro deste estatuto no órgão competente.

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Aberta a palavra para manifestações, registraram-se intervenções de diversos(as) delegados(as), que apresentaram sugestões e destaques. As contribuições foram discutidas e deliberadas uma a uma, sendo incorporadas ao texto final quando aprovadas pela maioria.

Submetida à votação, a proposta de alteração estatutária, com as devidas emendas, foi **aprovada por unanimidade** dos(as) delegados(as) presentes, passando a integrar a versão atualizada do Estatuto Social da Fenafar, que será registrada em cartório e divulgada aos sindicatos filiados.

Nada mais havendo a tratar, o Presidente da Assembleia agradeceu a presença de todos(as) e encerrou os trabalhos às 14h30. Eu, Maria Maruza Carlesso responsável pela redação, lavrei a presente ata, que vai assinada por mim e pelos(as) membros da mesa.

Ouro Preto – MG, 05 de agosto de 2025.

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FABIO JOSE BASILIO
Data: 19/08/2025 15:53:28-0300
Verifique em https://validar.iti.gov.br

Fábio José Basílio
Presidente da Assembleia

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ANDRE NUNES CAVALCANTE
Data: 21/08/2025 10:17:59-0300
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André Cavalcanti
Primeiro Vice-Presidente

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MARIA MARUZA CARLESSO
Data: 25/08/2025 17:41:43-0300
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Maria Maruza Carlesso
Secretária

ESTATUTO DA FEDERAÇÃO NACIONAL DOS FARMACÊUTICOS

CAPÍTULO I

DA ENTIDADE, SEUS FINS, SEDE E DURAÇÃO

Art. 1 - A Federação Nacional dos Farmacêuticos, entidade Sindical de 2° grau, também denominada FENAFAR, fundada em 25 de outubro de 1974 e reconhecida pela Carta Sindical outorgada pelo Ministério do Trabalho em 1 de outubro de 1981 (Mtb - 11.448/75, Mtb - 318-408/80), é uma entidade autônoma, de natureza civil, sem fins lucrativos, desvinculada do Estado e de duração indeterminada, que representa o conjunto dos trabalhadores da categoria dos Farmacêuticos, independentemente das suas convicções políticas, partidárias e religiosas.

Art. 2 - A Federação Nacional dos Farmacêuticos tem sua sede jurídica e administrativa em São Paulo/SP, à Rua Barão de Itapetininga, 255 – Sala 302 – Centro – CEP: 01042-917 – São Paulo/SP e sua jurisdição em todo o território nacional, ficando a critério do Conselho de Representantes criar subsedes regionais e ou transferir a sede para a Capital Federal.

Ar. 3 - A Federação Nacional dos Farmacêuticos tem por finalidades precípuas a união, a defesa de direitos e interesses da categoria e a assistência a seus Sindicatos filiados.

Art. 4 - A Federação Nacional dos Farmacêuticos tem por objetivos precípuos:

I - Congregar e representar os sindicatos farmacêuticos e seus filiados em todo o País;

II - Expressar as reivindicações e lutas dos Farmacêuticos nos planos educacional, econômico, social, cultural e político;

III - Defender condições adequadas para o bom desempenho do trabalho do profissional Farmacêutico, condizentes com sua formação superior;

IV - Incentivar a participação dos filiados nas reuniões, congressos e demais atividades inerentes à Entidade;

V - Fortalecer e estimular a organização da categoria, respeitando sua autonomia, nos limites deste Estatuto;

VI - Coordenar e unificar o movimento dos Farmacêuticos nas iniciativas de alcance nacional, respeitando as dinâmicas regionais e setoriais;

VII - Buscar a Integração com movimentos e entidades nacionais e internacionais dos Farmacêuticos, dos trabalhadores em geral e de outros setores, na luta pela democracia e pelos interesses do povo brasileiro;

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VIII - Defender a saúde enquanto bem público, conceituada nos termos da Constituição Federal e garantida mediante políticas sociais de alimentação, habitação, moradia, acesso e posse da terra, visando assegurar através de sua promoção e proteção o exercício pleno da cidadania;

IX - Defender o direito à assistência farmacêutica entendida como o conjunto de atividades e pesquisa, produção, distribuição, armazenamento e dispensação, que garanta o acesso qualitativo e quantitativo da população ao medicamento, assim como a sua farmacovigilancia e farmacoepidemiologia;

X - Celebrar convênios com entidades sindicais, órgãos públicos ou privados, com vistas à integração de recursos de esforços, visando a execução dos objetivos expressos neste estatuto;

XI - Prestar assistência jurídica, celebrar dissídios e assinar acordos coletivos de trabalho nas unidades federativas onde não houver Sindicato;

XII - Promover ações de defesa e proteção ao meio ambiente, ao consumidor, à ordem econômica, ao patrimônio artístico, estético, histórico, turístico e paisagístico;

XIII - Promover e organizar estudos, pesquisas, seminários, congressos, palestras, cursos profissionalizantes de qualificação e requalificação profissional, isoladamente ou em convênio com outras entidades da categoria, órgãos governamentais e não governamentais, universidades e demais segmentos da sociedade a fim de:

a) colaborar com a atualização dos conhecimentos dos profissionais sobre temas inerentes às ciências farmacêuticas e demais áreas da saúde;

b) colaborar com o estudo e solução dos problemas que se relacionem direta ou indiretamente com a categoria e o profissional farmacêutico;

c) colaborar com a conscientização e conhecimento dos profissionais sobre o conjunto dos projetos políticos, econômicos, sociais e culturais existentes;

d) colaborar com estudos sobre as relações de trabalho, especialmente as questões sindicais e trabalhistas;

Art. 5 - Constituem prerrogativas e deveres da Federação Nacional dos Farmacêuticos de acordo com este Estatuto:

I - Representar perante as autoridades administrativas e judiciárias os interesses gerais da categoria e os interesses de seus filiados.

II - Estabelecer contribuições financeiras para todos os filiados de acordo com as decisões tomadas no CONGRESSO DA FEDERAÇÃO NACIONAL DOS FARMACEUTICOS, denominado CONGRESSO DA FENAFAR e ou CONSELHO DE REPRESENTANTES.

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CAPÍTULO II

DOS FILIADOS, SEUS DIREITOS E DEVERES

Art. 6 - A todo Sindicato de Farmacêutico no Território Nacional, satisfazendo as exigências da legislação em vigor e do presente Estatuto, assiste o direito de filiar-se à FENAFAR.

Art. 7 - Para filiar-se à FENAFAR. o sindicato encaminhará a solicitação à diretoria da Federação, acompanhada de ata de assembleia, carta sindical ou registro do Estatuto da entidade em cartório, número de associados inscritos, nominata da direção mencionando o respectivo período de mandato.

Art. 8 - Até 30 (trinta) dias após o recebimento do pedido de filiação, a diretoria da FENAFAR aprovará sua filiação de acordo com os requisitos do art. 7°.

Art. 9 - A desfiliação de um sindicato da FENAFAR se dará por deliberação de sua assembleia geral, lavrada em ata própria, na forma que dispuser o respectivo estatuto, não cabendo à Diretoria da FENAFAR o julgamento de mérito da petição e vigorará a partir da entrada da comunicação na secretaria da Federação, contra recibo.

Art. 10 - São direitos dos sindicatos filiados:

I - gozar dos direitos oferecidos pela FENAFAR;

II - solicitar e receber da diretoria da FENAFAR, do Conselho de Representantes e do Congresso da FENAFAR as medidas que julgar necessárias para defender seus interesses e de seus associados. Incluem-se aqui prestação de ajuda material, financeira, jurídica e social, quando for o caso, e o apoio as suas iniciativas e reinvindicações inclusive promovendo a solidariedade nacional e internacional da categoria, desde que não contrarie deliberação adotada pelo Congresso da FENAFAR e pelo Conselho de Representantes, ou este estatuto;

III - desfilar-se da FENAFAR, obedecida as exigências do Art.9°;

IV – participar de todas as atividades e instancias decisórias da FENAFAR nos termos deste estatuto;

V - ser informado regularmente das decisões adotadas pela entidade, assim como das atividades desenvolvidas e programadas;

VI - recorrer de decisões à instância superior, na forma deste Estatuto;

VII - votar e ser votado através de seus representantes e delegados nos organismos da entidade, na forma desde estatuto;

Art. 11 - São deveres dos Sindicatos filiados:

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I - prestigiar a FENAFAR por todos os meios ao seu alcance, cumprindo e fazendo cumprir este estatuto, acatando as deliberações dos Congressos da FENAFAR e de seu Conselho de Representantes, zelando pela unificação do movimento sindical dos farmacêuticos e dos trabalhadores em geral;

II - participar do Conselho de Representantes da FENAFAR, por Intermédio de seus delegados, através de intercâmbio constante e permanente, comparecendo às plenárias e reuniões para as quais for convocado;

III - executor em sua base territorial, os planos de trabalho conjunto propostos e aprovados pelo plenário do Conselho de Representantes da FENAFAR ou Congresso de caráter nacional da categoria, procurando também entrosar-se com a Federação e os demais sindicatos filiados, nos planos de âmbito regional;

IV - recolher à FENAFAR a anuidade de filiado, conforme deliberação, valor e prazo definido pelo Congresso da FENAFAR e/ou Conselho de Representantes:

V - informar anualmente à FENAFAR os nomes e endereços profissionais e residenciais de seus delegados representantes, coordenadores e presidentes;

VI - manter atualizado o cadastro dos farmacêuticos em sua base e repassá-lo à FENAFAR;

VII - informar a federação sobre suas atividades, eleições e deliberações de suas instâncias;

CAPÍTULO III

DO CONGRESSO DA FEDERAÇÃO NACIONAL DOS FARMACÊUTICOS

Art. 12 - O Congresso do FENAFAR é o órgão máximo de deliberação da categoria farmacêutica, sendo composto por delegados eleitos na sua base e observadores convidados:

I - Cada entidade sindical filiada poderá se fazer representar por delegados e observadores, com igual direito a voz, cabendo somente aos delegados eleitos o direito a voto.

II – O número de delegados de cada entidade sindical filiada deverá ser proporcional ao número de farmacêuticos inscritos no Conselho Regional de Farmácia de sua base até 31 de dezembro do ano anterior ao CONGRESSO da FENAFAR, sendo garantido 5 (cinco) delegados para cada 2000 (dois mil) farmacêuticos inscritos no Conselho Regional de Farmácia respectivo, e, mais 1 (um) delegado para cada fração superior a 2000 (dois mil) farmacêuticos inscritos no Conselho Regional de Farmácia da sua base;

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III - Cada entidade sindical filiada poderá eleger para o CONGRESSO da FENAFAR delegados suplentes na proporção de 20% (vinte por cento) do número máximo de delegados titulares;

IV - Não haverá restrição à quantidade de observadores por entidade sindical filiada.

V – Os delegados deverão ser credenciados perante a secretaria do Congresso, ficando garantido ao delegado suplente sua inscrição no caso de não comparecimento ou impedimento do delegado titular;

Parágrafo primeiro - o Congresso da FENAFAR delibera sobre:

I - Alterações deste Estatuto;

II - A linha política e organizativa da Entidade;

III - Os planos de ação sindical e de luta para os trabalhadores representados considerando a situação político, social e econômico do país;

IV- Eleição da Diretoria da FENAFAR e Conselho Fiscal, conforme normas estabelecidas no Regulamento Eleitoral.

Parágrafo segundo: é dever do Congresso da FENAFAR promover a solidariedade nacional e internacional da classe trabalhadora;

Art. 13 - O regimento interno do Congresso deverá ser elaborado por uma comissão designada pelo Conselho de Representantes e aprovado na plenária de início do mesmo.

Parágrafo primeiro - O Congresso, que será dirigido pelo Presidente da FENAFAR, sendo substituído em seus impedimentos pelo Primeiro Vice-presidente e assim sucessivamente, observará as competências privativas definidas no Art. 12 deste Estatuto, não necessariamente na ordem que estão elencadas através de seus incisos, podendo ser dispostas de modo diverso, mediante aprovação na plenária de início do mesmo, salvo a eleição da Diretoria Executiva, Conselho Fiscal e Suplentes, que terão que obedecer a data e hora estipulados em edital designado para esse fim.

Parágrafo segundo - Durante os trabalhos eleitorais, o Congresso será presidido pelo Presidente da Comissão Eleitoral;

Parágrafo terceiro - Outras atividades pertinentes aos objetivos sociais da FENAFAR, tais como eventos sociais e culturais, palestras e debates, também poderão ocorrer no Congresso, conforme deliberado na plenária de início do mesmo.

Art. 14 - A pauta e data do Congresso serão definidas pelo Conselho de Representantes da FENAFAR que designará uma comissão organizadora para auxiliar a diretoria nos encaminhamentos necessários,

Art. 15 - O Congresso reunir-se-á ordinariamente quadrienalmente, ou em caráter extraordinário quando convocado por dois terços dos membros do Conselho de Representantes.

Parágrafo primeiro – A publicização do Edital que convoca o Congresso da Fenafar será subscrita pelo Presidente da Federação e deverá conter a pauta, o local, o período e horário de sua realização, o qual será publicado no Diário Oficial da União, com antecedência mínima de 06 (seis) meses de sua realização;

Parágrafo segundo - Em caráter extraordinário a antecedência mínima será de 30 (trinta) dias;

Parágrafo terceiro - O Congresso só poderá se instalar com a presença de delegações de no mínimo 50% (cinquenta por cento) das entidades filiadas em primeira convocação, ou, com o número de presentes em segunda convocação, devendo as deliberações do CONGRESSO da FENAFAR ser tomadas por maioria simples dos presentes.

CAPITULO IV

DO CONSELHO DE REPRESENTANTES DA FEDERAÇÃO NACIONAL DOS FARMACÊUTICOS

Art. 16 - O Conselho de Representantes da Federação Nacional dos Farmacêuticos é a segunda instância deliberativa.

Parágrafo único - O Conselho de Representantes (CR) é composto por um representante de cada sindicato filiado conforme seu estatuto.

Art. 17· São atribuições do Conselho de Representantes:

I - Implantar e cumprir as deliberações do Congresso;

II - Regulamentar, quando necessário, as deliberações do Congresso;

III - Examinar e apresentar parecer ao Congresso dos relatórios financeiros, prestações de contas e previsões orçamentárias apresentadas pela Diretoria.

IV - Decidir sobre os recursos interpostos às decisões da Diretoria;

V - Convocar o Congresso, com antecedência mínima de 6 meses de sua realização, definindo a data e temário do mesmo;

VI - Aplicar penalidades de suspensão aos filiadas da FENAFAR;

VII- As penalidades serão aplicadas quando o filiado se contrapor às normas e objetivos deste estatuto, bem como às deliberações do Conselho de Representantes e de seu Congresso;

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VIII - Propor a criação de comissões ou grupos de trabalho permanentes ou temporários, sobre questões de interesse da categoria e da população em geral, indicando seus componentes;

IX - Alterar o valor e forma da cobrança da anuidade de seus filiados, definida na última reunião anual do Conselho de Representantes para o próximo exercício;

X - Elaborar o Regulamento Eleitoral da Federação Nacional dos Farmacêuticos, eleger uma Comissão eleitoral, que é responsável pelo processo eleitoral de acordo com o previsto neste estatuto.

XI - Aprovar alterações aditivas e complementares ao Estatuto Social, desde que não contrariem as deliberações do Congresso ou qualquer dispositivo deste estatuto.

Parágrafo único: A deliberação da proposta depende do apoio de maioria absoluta de seus membros, devendo ser aprovado por 2/3 dos presentes, em reunião convocada especialmente para este fim.

CAPITULO V

DO CONSELHO FISCAL DA FEDERAÇÃO NACIONAL DOS FARMACÊUTICOS

Art. 18 - O Conselho Fiscal da FENAFAR será composto por três farmacêuticos efetivos e três suplentes eleitos na forma prevista no Art. 12, com mandato coincidente ao da diretoria.

Art. 19 - Compete ao Conselho Fiscal:

I - dar parecer sobre o orçamento do FENAFAR para o exercício financeiro.

II - opinar sobre as despesas extraordinárias, sobre os balancetes mensais e sobre o balanço anual.

III - reunir-se semestralmente coincidindo com a realização da reunião do Conselho de Representantes;

IV - dar parecer sobre o balanço do exercício financeiro.

V - examinar e apresentar parecer sobre os relatórios financeiros, prestação de contas e previsões orçamentárias apresentadas pela diretoria.

CAPITULO VI

DA DIRETORIA DA FEDERAÇÃO NACIONAL DOS FARMACÊUTICOS

Art. 20 - A Diretoria é o órgão executivo da FENAFAR.

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Art. 21 - À Diretoria, coletivamente compete:

I - Representar a Entidade e defender os interesses da categoria perante os poderes públicos, empresas estatais e privadas, fundações e autarquias podendo a diretoria nomear mandatários por procuração, de acordo com o inciso I do artigo 5°;

II - Cumprir e fazer cumprir este estatuto, os regimentos e as normas administrativas da FENAFAR, bem como as decisões do Congresso da FENAFAR e do Conselho de Representantes;

III - Gerir o patrimônio, garantindo sua utilização para cumprimento deste estatuto e das deliberações do Congresso e do Conselho de Representantes:

IV - Organizar os serviços administrativos internos da FENAFAR;

V - Elaborar relatórios financeiros, prestações de contas e previsão orçamentária anuais da FENAFAR, remetendo ao Conselho Fiscal;

VI - Convocar as reuniões ordinárias e extraordinárias do Conselho de Representantes;

VII - Constituir comissões, coordenações e grupos de trabalho permanente e temporários sobre quaisquer assuntos, indicando seus componentes;

VIII - Remeter à reunião do Conselho de Representantes, parecer do pedido de filiação do Sindicato, como disposto no Artigo 7º;

Art. 22 - O mandato da Diretoria será de 4 (quatro) anos, eleita pelo Congresso da FENAFAR.

Parágrafo único: serão permitidas reeleições de qualquer membro da diretoria a qualquer cargo.

Art. 23 - A Diretoria é composta por membros efetivos e suplentes assim distribuídos:

I - Presidente:

II - Primeiro Vice-Presidente;

III - Segundo Vice-Presidente:

IV - Secretario Geral;

V - Primeiro Secretário;

VI - Tesoureiro Geral;

VII - Primeiro Tesoureiro;

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VIII - Diretoria de Comunicação;

IX - Diretoria de Formação Sindical;

X - Diretoria de Relações Institucionais;

XI - Primeira Diretor de Relações Institucionais;

XII - Diretoria de Relações Internacionais;

XIII – Primeiro Diretor de Relações Internacionais;

XIV – Diretoria de Organização Sindical;

XV - Primeiro Diretor de Organização Sindical;

XVI - Diretoria da Mulher;

XVII - Diretoria de Educação;

XVIII – Diretoria de Assuntos Jurídicos;

XIX – Primeiro Diretor de Assuntos Jurídicos;

XX – Diretoria de Saúde e Segurança do Trabalho;

XXI – Diretoria de Relações Trabalhistas;

XXII – Diretoria de Juventude

XXIII - Diretoria de Direitos Humanos;

XXIII – Diretoria da Região Norte;

XXIV – Diretoria de Meio Ambiente e Crise Climática;

XXV – Diretoria da Região Nordeste;

XXVI – Diretoria da Região Centro-Oeste;

XXVII – Diretoria da Região Sudeste;

XXVIII – Diretoria da Região Sul;

Parágrafo primeiro - os suplentes para a Diretoria serão em número de 7 (sete);

Parágrafo segundo - é vedada a acumulação de cargos na Diretoria;

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Parágrafo terceiro - os suplentes poderão assumir outras funções pela diretoria e/ou Conselho da FENAFAR.

Parágrafo quarto - Os diretores devem participar e representar a entidade nas atividades que tenham sido convidados, sempre se orientando nos princípios da unidade dos trabalhadores e do fortalecimento das entidades sindicais.

Art. 24 - A Diretoria se reúne:

I - Ordinariamente, duas vezes ao ano;

II – Extraordinariamente, quando convocada pelo presidente ou por 1/3 (um terço) de seus membros, em data e local fixados.

Art. 25 - As deliberações da Diretoria são adotadas por maioria simples de votos.

Art. 26 - Compele ao Presidente:

I - representar a FENAFAR em Juízo ou fora dele podendo delegar poderes a outro diretor, ou ainda, nomear mandatário por instrumento de procuração, se necessário for, para o desempenho de funções técnicas, burocráticas e ou administrativas da entidade;

II - Abrir, instalar e presidir o Congresso, o Conselho de Representantes e as reuniões da Diretoria:

III - Convocar as eleições para a nova Diretoria de acordo com o previsto no Artigo 41;

IV Abrir, rubricar e encerrar os livros do FENAFAR;

V - Assinar a correspondência oficial da FENAFAR e, juntamente com o Secretário Geral, toda correspondência que estabeleça quaisquer obrigações para a FENAFAR;

VI - Movimentar com o tesoureiro em exercício as contas da FENAFAR;

VII – Dar posse à diretoria e conselho fiscal eleitos para o mandato consecutivo;

Art. 27 - Compete aos Vice-Presidentes:

I - Auxiliar o Presidente em todas as suas atividades e para os quais forem designados;

II - Executar todas as atribuições que lhes forem outorgadas pela Diretoria;

Parágrafo primeiro: além das funções atribuídas pelo artigo 27, incisos I e II, será de responsabilidade do segundo Vice-presidente assumir os assuntos de ordem parlamentar;

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Parágrafo segundo: no caso de afastamento definitivo, vacância e impedimento do Presidente, assume o 1° Vice-presidente a presidência, o 2° Vice-presidente assume a 1° Vice-presidência, e o 1° suplente assume a Vice-presidência.

Art. 28 - Compete ao Secretário Geral:

I - Ter sob sua guarda e responsabilidade o arquivo da Secretaria;

II - Secretariar as reuniões da Diretoria e do Conselho de Representantes;

III - Encarregar-se do expediente e da correspondência da FENAFAR;

Art. 29 - Compete ao Primeiro Secretário, além de assumir a Secretaria Geral, no caso de falta e/ou impedimento do Secretário Geral, cooperar em todas as atividades inerentes ao cargo;

Parágrafo único: no caso de vacância, impedimento ou afastamento definitivo do Secretário geral, compete do Primeiro Secretário assumir a Secretaria Geral e ao suplente assumir a Primeira Secretaria.

Art. 30 Compete ao Tesoureiro Geral:

I - Ter sob sua responsabilidade e guarda os bens e valores da FENAFAR.

II - Ser responsável pelos recebimentos e pagamentos das despesas.

III - Assinar, com o presidente, os cheques para pagamentos em geral.

IV - Movimentar, com o Presidente, as contas bancárias da FENAFAR.

V - Organizar o balancete semestral e o balanço anual.

Parágrafo único – caso o Tesoureiro se afaste definitivamente, deverá apresentar o balanço ao Presidente dentro de 30 (trinta) dias após seu afastamento;

Art. 31 - Compete ao Primeiro Tesoureiro assumir a Tesouraria geral, no caso de falta e/ou impedimento do Tesoureiro geral e cooperar em todas as atividades inerentes ao cargo.

Parágrafo único: No caso de vacância, impedimento ou afastamento definitivo do Tesoureiro Geral, compete ao Primeiro Tesoureiro assumir a Tesouraria Geral e o suplente assumir a Primeira Tesouraria;

Art. 32 - Compele ao Diretor de Comunicação:

I - Promover a divulgação das ações junto aos sindicatos, a categoria e a sociedade;

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II- Desenvolver e acompanhar as campanhas publicitárias definidas pelos órgãos de deliberação da FENAFAR;

III - Ter sob sua responsabilidade os setores de imprensa, comunicação, publicidade, biblioteca e centro de memória;

IV - Manter a publicação e divulgação do "Boletim da FENAFAR".

Parágrafo único - No caso de afastamento do diretor de comunicação, compete ao suplente assumir e cumprir o restante do mandato.

Art. 33 - Compete ao Diretor de Formação Sindical:

I - Implementar o departamento de formação sindical;

II – Propor, organizar e coordenar, em conjunto com o Diretor Intersindical, a realização de seminários, cursos, palestras, encontros de área, dentro dos interesses da categoria e dos trabalhadores em geral, com base nos princípios fixados por este estatuto;

III - Formar dirigentes, representantes sindicais, organizando cursos e seminários de formação sindical e capacitação política:

IV - Elaborar e submeter à apreciação e deliberação do Conselho de Representantes, na última reunião anual o plano de formação sindical a ser executado no exercício seguinte;

Parágrafo único - No caso de afastamento do diretor de formação sindical, compete ao suplente assumir e cumprir o resto do mandato.

Art. 34 - Compete à Diretoria de Relações Institucionais:

I - Planejar, propor e executar as politicas e projetos de relações institucionais da FENAFAR visando o estreitamento das relações institucionais com entidades de representação sindical e de trabalhadores, de associações, fundações, organismos não governamentais, órgãos e poderes governamentais do Brasil e organizações da sociedade civil em geral, especialmente com as entidades farmacêuticas;

Art. 34 A – Compete ao Primeiro Diretor de Relações Institucionais:

I – Auxiliar o Diretor Relacões Institucionais em todas as suas atividades e para as quais for designado e substituí-lo em suas ausências;

Art. 35 - Compete à Diretoria de Relações Internacionais:

I - Planejar e propor atividades que promovam e incrementem as relações internacionais da FENAFAR com as demais entidades sindicais e de trabalhadores das nações estrangeiras, associações internacionais de trabalhadores, entidades

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congêneres da sociedade civil dos diversos povos do mundo, especialmente com as entidades farmacêuticas bem como com governos e representações diplomáticas.

II- Promover a interação sindical, cultural, política e social com as entidades acima nominadas;

III- Executar as políticas e projetos de Relações Internacionais da FENAFAR;

Art. 35-A – Compete ao Primeiro Diretor de Relações Internacionais

I – Auxiliar o Diretor de Relações Internacionais em todas as suas atividades e para as quais for designado e substituí-lo em suas ausências;

Art. 36 - Compete à Diretoria de Organização Sindical

I - Planejar as ações e promover o debate permanente e pontual dos diversos aspectos que envolvem a organização sindical dos trabalhadores no Brasil:

II- Acompanhar lodos os debates e discussões legislativas sobre a Organização Sindical:

III - Ter e dispor à Diretoria e à categoria todas as informações referentes ao tema Organização Sindical;

IV - Fomentar, no âmbito da categoria o debate de questões específicas da organização sindical farmacêutica.

Art. 36 A – Compete ao Primeiro Diretor de Organização Sindical:

I – Auxiliar o Diretor de Organização Sindical em todas as suas atividades e para as quais for designado e substituí-lo em suas ausências;

Art. 37- Compete à Diretoria da Mulher:

I - Planejar e executar as ações e atividades que promovam o debate, a conscientização e o avanço das questões de gênero no meio sindical e da categoria;

II - Propor a realização de estudos, pesquisas e projetos que tenham por finalidade promover a emancipação social, política, econômica e profissional da mulher:

III - Promover a luta permanente pelas conquistas e pela melhoria das condições de vida, trabalho e saúde da mulher;

Art. 38 - Compete à Diretoria de Educação:

I – Planejar, propor e coordenar a execução das ações da FENAFAR relacionadas à Educação, em especial à educação farmacêutica:

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II - Estabelecer e coordenar as relações e interfaces da Fenafar com as demais instituições e organismos, nacionais e internacionais, no campo da educação farmacêutica, participando das atividades relacionadas;

III - Contribuir para a construção e implementação da política pública de educação, como representação formal da categoria farmacêutica;

Art. 38 A – Caberá ao Diretor de Assuntos Jurídicos:

I – Coordenar a elaboração de Assuntos Jurídicos e ter sob seu comando a responsabilidade das tarefas desenvolvidas pelo setor jurídico da Federação e outros correlatos;

Art. 38 B Caberá à Primeiro Diretor de Assuntos Jurídicos:

I – Auxiliar o Diretor de Assuntos Jurídicos em todas as suas atividades e para as quais for designado e substituí-lo em suas ausências;

Art. 38 C– Caberá ao Diretor de Saúde e Segurança do Trabalho:

I – Promover estudos, pesquisas e seminários visando a melhoria das condições de vida, de trabalho e relacionadas ao ambiente do trabalho;

Art. 38 D– Caberá ao Diretor de Relações Trabalhistas:

I – Promover estudos e pesquisas relacionadas a legislação trabalhista aplicáveis à categoria;

II – Promover estudos, pesquisas e seminários relacionados às reivindicações da categoria em negociações coletivas;

Art. 38 E – Caberá ao Diretor de Juventude e Direitos Humanos:

I – Promover atividades e eventos culturais como seminários, palestras, programações artísticas, etc, de interesse da(o)s jovens farmacêutica(o)s;

II – Coletar, sistematizar e processar dados de interesse da categoria, elaborando análise sobre as relações de trabalho envolvendo a(o)s jovens farmacêutica(o)s;

III - manter permanente e efetiva integração com entidades sindicais e/ou movimentos sociais, pautando os interesses e defesas da juventude trabalhadora;

IV - Trabalhar junto aos sindicatos a renovação das diretorias sindicais a da federação, visando a formação de novas lideranças.

V - propor estudos e projetos de sua área e compartilhar as informações à diretoria da federação.

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VI - Realizar diálogo constante com o Movimento Estudantil de Farmácia, com o objetivo de fortalecer as relações institucionais;

Art. 38-F – Caberá a(o) Diretor(a) de Direitos Humanos

I – Planejar, propor e coordenar ações da FENAFAR relacionadas aos direitos humanos, com foco nos impactos à saúde pública e às condições de trabalho das farmacêuticas e dos farmacêuticos

II – Articular-se com movimentos, entidades e organismos governamentais e da sociedade civil, nacionais e internacionais, voltados à justiça social;

III – Apoiar campanhas, estudos e políticas públicas que promovam práticas inclusivas e antidiscriminatórias nos sistemas de saúde e no ambiente de trabalho da categoria farmacêutica;

IV – Promover ações de formação e conscientização da categoria quanto às intersecções entre saúde e direitos humanos.

V - Ampliar a participação da FENAFAR e seus sindicatos em Conselhos Populares relacionados aos Direitos Humanos.

Art. 38-F – Compete à Diretoria de Meio Ambiente e Crise Climática:

I – Planejar, propor e coordenar ações da FENAFAR relacionadas à defesa ambiental e ao enfrentamento da crise climática, com foco nos impactos à saúde pública e às condições de trabalho das farmacêuticas e dos farmacêuticos;

II – Articular-se com movimentos, entidades e organismos governamentais e da sociedade civil, nacionais e internacionais, voltados à justiça ambiental e climática;

III – Apoiar campanhas, estudos e políticas públicas que promovam práticas sustentáveis nos sistemas de saúde e no ambiente de trabalho da categoria farmacêutica;

IV – Promover ações de formação e conscientização da categoria quanto às intersecções entre saúde, meio ambiente e mudanças climáticas.

Art. 38 G - Caberá às Diretorias Regionais:

I - exercer juntamente com os demais membros da Diretoria a representação política e institucional da Fenafar dentro da respectiva área regional;

II - apresentar e desenvolver um planejamento regional no sentido de promover a capilaridade e efetivar maior presença federativa nos respectivos estados;

III - apresentar aos demais Diretores planos e propostas de ampliação e fortalecimento da base e da representatividade da Federação;

Registro Nº
725.064
26/09/2025

Protocolo nº 444.341 de 26/08/2025 às 08:05:45h: Documento **registrado eletronicamente para fins de publicidade e/ou eficácia contra terceiros** sob nº **725.064** em **26/09/2025** e averbado no registro nº 237636/92 neste **4º Oficial de Registro Civil de Pessoas Jurídicas da Comarca de São Paulo**. Assinado digitalmente por Carlos Augusto Peppe - Escrevente.

Oficial	Estado	Secretaria Fazenda	Reg. Civil	T. Justiça	M. Público	ISS	Condução	Despesas	Total
R$ 324,15	R$ 91,99	R$ 62,97	R$ 17,15	R$ 22,21	R$ 15,45	R$ 6,79	R$ 0,00	R$ 0,00	R$ 540,71

Art. 39 - Qualquer membro da Diretoria poderá ser destituído em Congresso, convocado para este fim, sendo que o mesmo se aplica a Diretoria coletivamente;

Parágrafo primeiro: Fica garantido o direito de ampla defesa às partes;

Parágrafo segundo: No caso de destituição de metade mais um dos membros da Diretoria, efetivos e suplentes, o Congresso deverá eleger uma diretoria provisória que promoverá novas eleições congressuais no prazo de até 180 dias.

Parágrafo terceiro: O diretor que for destituído ficará impedido de se candidatar pelo período correspondente a dois mandatos seguintes ao da sua destituição, não considerado o tempo da diretoria provisória.

CAPÍTULO VII

DO CONSELHO CONSULTIVO

Artigo 40 - O Conselho Consultivo é um órgão permanente e de auxílio aos órgãos deliberativo e executivo da Federação Nacional dos Farmacêuticos, composto por profissionais farmacêuticos, cabendo a ele, quando solicitado, se pronunciar emitindo pareceres, estudos e reflexões, com a finalidade de aconselhamento, consultar orientação à Diretoria da Fenafar sobre os temas de relevância nacional e que possam representar grande interesse ao exercício profissional e aos rumos que serão adotados pela entidade, respeitadas as atribuições de seus órgãos deliberativos;

Parágrafo primeiro - O Presidente do Conselho Consultivo será eleito na Plenária da Assembleia estatutária do Congresso da Fenafar que deliberar a sua criação, sendo que os demais membros serão indicados Executiva após consulta aos sindicatos de base e aprovados pelo Conselho de Representantes;

Parágrafo segundo - O Conselho de Representantes deverá regulamentar a composição, critérios de participação, o funcionamento e atribuições do Conselho Consultivo;

Parágrafo terceiro - O Conselho Consultivo, quando solicitado pela Diretoria, se reunirá junto com uma das Reuniões do Conselho de Representantes da Fenafar;

Parágrafo quarto - Em caso de desistência, saída ou afastamento de quaisquer membros do Conselho Consultivo, a vacância será recomposta na primeira reunião posterior do Conselho de Representantes, por proposta da Diretoria Executiva.

CAPÍTULO VIII

DAS ELEIÇÕES

Registro Nº
725.064
26/09/2025

Protocolo nº 444.341 de 26/08/2025 às 08:05:45h: Documento **registrado eletronicamente para fins de publicidade e/ou eficácia contra terceiros** sob nº **725.064** em **26/09/2025** e averbado no registro nº 237636/92 neste **4º Oficial de Registro Civil de Pessoas Jurídicas da Comarca de São Paulo**. Assinado digitalmente por Carlos Augusto Peppe - Escrevente.

Oficial	Estado	Secretaria Fazenda	Reg. Civil	T. Justiça	M. Público	ISS	Condução	Despesas	Total
R$ 324,15	R$ 91,99	R$ 62,97	R$ 17,15	R$ 22,21	R$ 15,45	R$ 6,79	R$ 0,00	R$ 0,00	R$ 540,71

Art. 41 - A eleição da Diretoria é convocada para o mês de agosto, pelo Presidente em exercício com pelo menos 90 (noventa) dias de antecedência ressalvando o disposto no parágrafo segundo do Artigo 39:

Parágrafo primeiro: A diretoria da FENAFAR, bem como seus suplentes serão eleitos pelo Congresso da FENAFAR;

Parágrafo segundo: A eleição dar-se-á pelo voto direto dos Delegados, conforme o regulamento eleitoral e regimento interno do Congresso.

Parágrafo terceiro: Não sendo convocada a eleição nos prazos previstos neste artigo, cabe ao Conselho de Representantes convocá-la no máximo 30 (trinta) dias após este prazo ter se esgotado;

Art. 42 - O Conselho de Representantes elaborará o Regulamento Eleitoral, elegerá uma Comissão Eleitoral que será responsável pelo processo eleitoral, de acordo com o previsto neste estatuto;

CAPITULO IX

DO PATRIMÔNIO E FINANÇAS, DA AQUISIÇÃO E ALIENAÇÃO DE BENS DO ATIVO PERMANENTE

Art. 43 - O patrimônio da FENAFAR é constituído por:

I - O valor do rateio que lhe couber, na forma da legislação vigente, do produto das arrecadações das contribuições confederativa e sindical;

II - O valor da contribuição (anuidade) dos sindicatos para custeio das suas despesas, como disposto no Artigo 43;

III - Bens e imóveis que a FENAFAR venha a adquirir;

IV - Móveis e utensílios:

V - Doações e legados recebidos com especificações para o patrimônio;

Art. 44 – Aquisição, alienação ou aceitação de doações de bens imóveis e títulos de valores mobiliários, classificados como investimentos de caráter permanente da FENAFAR, deverão ter a aprovação do Conselho de Representantes;

Parágrafo único: excetuam-se do disposto neste artigo as aquisições de móveis e utensílios caracterizados como investimentos transitórios, que podem ser efetuados por deliberação da Diretoria;

CAPÍTULO X

DA RECEITA E DESPESA

Registro Nº
725.064
26/09/2025

Protocolo nº 444.341 de 26/08/2025 às 08:05:45h: Documento **registrado eletronicamente para fins de publicidade e/ou eficácia contra terceiros** sob nº **725.064** em **26/09/2025** e averbado no registro nº 237636/92 neste **4º Oficial de Registro Civil de Pessoas Jurídicas da Comarca de São Paulo**. Assinado digitalmente por Carlos Augusto Peppe - Escrevente.

Oficial	Estado	Secretaria Fazenda	Reg. Civil	T. Justiça	M. Público	ISS	Condução	Despesas	Total
R$ 324,15	R$ 91,99	R$ 62,97	R$ 17,15	R$ 22,21	R$ 15,45	R$ 6,79	R$ 0,00	R$ 0,00	R$ 540,71

Art. 45 - A receita da FENAFAR é classificada em ordinária e extraordinária:

I - Constituem receita ordinária:

a) produto das contribuições dos Filiados, como disposto no artigo 43;

b) juros provenientes de depósitos bancários realizados pela FENAFAR, bem como de títulos incorporados ao patrimônio;

c) repasses dos contribuições sindical e confederativa;

d) renda dos imóveis, dos bens e valores de propriedade da FENAFAR, quando os possuir;

II - Constituem receita extraordinária:

a) subvenções de qualquer natureza;

b) multas e rendas eventuais;

c) renda de doações feitas à FENAFAR:

Art. 46 - Os sindicatos filiados deverão pagar anuidade a FENAFAR de acordo com o Artigo 5º, inciso II;

CAPÍTULO XI

DAS DISPOSIÇÕES GERAIS

Art. 47 - Nenhuma entidade filiada, individual ou coletivamente, responderá subsidiariamente pelos encargos que seus representantes contraírem.

Art. 48 - Os membros da Diretoria não receberão remuneração pelas atividades que desempenharem na FENAFAR, ressalvando o ressarcimento de despesas feitas para o desempenho de atividades sindicais, bem como eventual ônus de liberação de diretor (es) pela categoria, aprovado em Conselho de Representantes;

Art. 49 - A posse dos membros da Diretoria e do Conselho Fiscal ocorrerá na data do início do mandato para o qual foram eleitos;

Art. 50 – As reuniões dos fóruns deliberativos da FENAFAR, incluindo Diretoria, Conselho de Representantes e o próprio Congresso, poderão ser realizadas presencialmente, de forma híbrida ou totalmente online, desde que garantidas as condições de participação democrática e votação segura.

Art. 51 - A FENAFAR poderá ser voluntariamente dissolvida em Congresso convocado especificamente para este fim;

Registro Nº
725.064
26/09/2025

Protocolo nº 444.341 de 26/08/2025 às 08:05:45h: Documento **registrado eletronicamente para fins de publicidade e/ou eficácia contra terceiros** sob nº **725.064** em **26/09/2025** e averbado no registro nº 237636/92 neste **4º Oficial de Registro Civil de Pessoas Jurídicas da Comarca de São Paulo**. Assinado digitalmente por Carlos Augusto Peppe - Escrevente.

Oficial	Estado	Secretaria Fazenda	Reg. Civil	T. Justiça	M. Público	ISS	Condução	Despesas	Total
R$ 324,15	R$ 91,99	R$ 62,97	R$ 17,15	R$ 22,21	R$ 15,45	R$ 6,79	R$ 0,00	R$ 0,00	R$ 540,71

Parágrafo único - No caso de dissolução, o destino dos bens da FENAFAR será definido pelo congresso que a dissolver;

Art. 52 - O presente Estatuto poderá ser reformado pelo Congresso da Fenafar e observando-se o disposto no inciso XI e parágrafo único do artigo 17, pelo Conselho de Representantes, em reunião convocada para este fim;

Art. 53 - Os casos omissos neste Estatuto serão resolvidos pelo Congresso da FENAFAR.

Art. 54 - Este estatuto entra em vigor na data de seu registro no órgão competente.

Art. 55 - Revogam-se as disposições em contrário.

DISPOSIÇÕES TRANSITÓRIAS

Art. 1 – Excepcionalmente o primeiro mandato para os cargos de Primeiro Diretor de Relações Institucionais, Primeiro Diretor de Organização Sindical e Primeiro Diretor de Assuntos Jurídicos, será exercido por Diretores indicados em plenária do 9º Concresso da FENAFAR e empossados na primeira reunião do Conselho de Representantes que ocorrer após o registro deste estatuto no órgão competente.

Art. 2 – Excepcionalmente, para garantir a implementação da nova duração de mandato a partir do 11º Congresso da FENAFAR, o mandato da Diretoria eleita no 11º Congresso será prorrogado conforme decisão desta assembleia por mais um ano de 01/09/2028 a 31/08/2029.

Art. 3 – As Diretorias da Juventude, de Direitos Humanos e de Meio Ambiente e Crise Climática serão implementadas ainda nesta gestão (2025-2029), será exercido por Diretores indicados em plenária do11º Congresso da FENAFAR e empossados na primeira reunião do Conselho de Representantes que ocorrer após o registro deste estatuto no órgão competente.

São Paulo, 11 de agosto de 2025.

gov.br Documento assinado digitalmente
FABIO JOSE BASILIO
Data: 20/08/2025 12:26:59-0300
Verifique em https://validar.iti.gov.br

Fábio José Basílio
Presidente

gov.br Documento assinado digitalmente
PAULO HENRIQUE REZENDE
Data: 19/08/2025 19:22:55-0300
Verifique em https://validar.iti.gov.br

Paulo Henrique Rezende
OAB/MG 136.643

CONSÓRCIO INTERMUNICIPAL MULTISSETORIAL DO VALE DO PIRANGA

AVISO DE LICITAÇÃO
PREGÃO ELETRÔNICO Nº 1/2025

Processo Licitatório nº 07.0016.2025.14
Consórcio Intermunicipal Multissetorial do Vale do Piranga - CIMVALPI, torna pública a abertura do Processo Licitatório nº 07.0016.2025.14 - Pregão Eletrônico 009/2025. Objeto: Registro de preço para eventual e futura contratação de empresa especializada para o fornecimento de kits de materiais escolares para o ano letivo de 2025. A data da sessão pública será: 10/02/2025, às 09:00h, horário de Brasília - DF, no sítio eletrônico www.licitardigital.com.br. O cadastramento de propostas inicia-se quando for publicado na plataforma e encerra-se, automaticamente, na data e hora marcadas para a realização da sessão do pregão. O Edital na íntegra, poderá ser obtido nos sites www.licitardigital.com.br ou www.cimvalpi.mg.gov.br. Maiores informações poderão ser obtidas na sede do CIMVALPI, na Rua Jaime Pereira, 127, ou através da plataforma www.licitardigital.com.br

Ponte Nova, 24 de janeiro de 2025.
MICHELE AP. SILVA DE JESUS
Agente de Contratação

FEDERAÇÃO DAS EMPRESAS DE TRANSPORTE DE PASSAGEIROS DOS ESTADOS DO PARANÁ E SANTA CATARINA

CNPJ/MF 82.703.042/0001-53

EDITAL DE CONVOCAÇÃO
ASSEMBLEIA GERAL EXTRAORDINÁRIA

(AGE) DO CONSELHO DE REPRESENTANTES. Ficam convocados os membros do Conselho de Representantes, composto pelos delegados nomeados pelos Sindicatos filiados à FEPASC, para se reunirem virtualmente em AGE, em 05/02/2025, às 10h, em primeira convocação, e, nos termos dos artigos 23º, I, 24º, caput, 25º, §1º e 46º do Estatuto, às 10:30h, em segunda convocação, para deliberarem sobre a seguinte Ordem do Dia: para adequar a redação aos termos da Portaria/MTE nº 1.472/2025, ratificar a ata da AGE realizada em 16/05/2023, que teve por objeto a eleição dos membros da Diretoria, do Conselho Fiscal e dos delegados representantes junto à Confederação Nacional de Transportes. O link para acessar a videoconferência será enviado, por e-mail, aos membros do Conselho de Representantes em até 30 (trinta) minutos antes do início da AGE.

Curitiba, 24 de janeiro de 2025
FELIPE BUSNARDO GUUN
Presidente da Federação

FEDERAÇÃO NACIONAL DOS FARMACÊUTICOS

EDITAL DE CONVOCAÇÃO
11º CONGRESSO DA FEDERAÇÃO NACIONAL DOS FARMACÊUTICOS

A Federação Nacional dos Farmacêuticos - FENAFAR, pessoa jurídica de direito privado, inscrita no CNPJ nº 00679357/0001- 48, com sede à rua Barão de Itapetininga, 255, 1º andar, sala 302, CEP 01042-010, São Paulo/SP, entidade de representação sindical de 2º grau da categoria dos farmacêuticos, com fundamento em seu Estatuto Social, torna público que o Conselho de Representantes da Fenafar, reunido no dia 23 e 24 de outubro de 2024, de forma presencial, CONVOCOU o 11º Congresso da FENAFAR para realizar-se entre os dias 05, 06, 07 e 08 de agosto de 2025 no Centro de Convenções da Universidade Federal de Ouro Preto, na cidade de Ouro Preto/MG, e ainda que o mesmo Conselho de Representantes designou a Comissão Organizadora do 11º Congresso, a Comissão Eleitoral e aprovou o Regulamento Eleitoral. O Congresso delibera sobre as disposições contidas no Art. 12 do Estatuto da entidade, que dispõe: "Art. 12 - O Congresso da FENAFAR é o órgão máximo de deliberação da categoria farmacêutica, sendo composto por delegados eleitos na sua base e observadores convidados. Parágrafo primeiro - o Congresso da FENAFAR delibera sobre: I - Alterações deste Estatuto; II - A linha política e organizativa da Entidade; III - Os planos de ação sindical e de luta para os trabalhadores representados considerando a situação política, social e econômica do país; IV- Eleição da Diretoria da FENAFAR e Conselho Fiscal, conforme normas estabelecidas no Regulamento Eleitoral. Parágrafo segundo: é dever do Congresso da FENAFAR promover a solidariedade nacional e internacional da classe trabalhadora". A Fenafar informa ainda que a Eleição deverá ser convocada pelo Presidente com pelo menos 90 dias de antecedência, da qual será publicado Edital específico, com as informações pertinentes a este processo eleitoral. Informa ainda que outras informações serão oportunamente fornecidas tais como o local, a programação etc., e que quaisquer informações sobre o 11º Congresso e a Eleição poderão ser obtidas na sede da entidade junto à sua secretaria e através do sítio eletrônico da FENAFAR.

São Paulo, 24 de janeiro de 2025.
FÁBIO JOSÉ BASÍLIO
Presidente da Federação Nacional dos Farmacêuticos

FEDERAÇÃO DOS TRABALHADORES NO SERVIÇO PÚBLICO MUNICIPAL DO ESTADO DA PARAÍBA

EDITAL DE CONVOCAÇÃO
ASSEMBLÉIA GERAL EXTRAORDINÁRIA DE FUNDAÇÃO ELEIÇÕES GERAIS E POSSE

Pelo presente edital, o Presidente da FEDERAÇÃO DOS TRABALHADORES NO SERVIÇO PÚBLICO MUNICIPAL DO ESTADO DA PARAÍBA - FETAM/PB, Senhor, Serildo Henrique da Silva e membro da Comissão de Pró-Fundação, brasileiro, professor, divorciado, categoria dos servidores públicos municipais, residente e domiciliado na Rua São Luis, nº 14, Bairro do Cruzeiro, Cidade de Itapororoca/PB, neste ato no exercício do cargo que lhe foi conferido, convoca pelo presente edital de acordo com a legislação vigente, toda a categoria dos Servidores Públicos Municipais da Educação de Areias/PB, para participarem da Assembleia Geral Extraordinária de Fundação do Sindicato dos Servidores Públicos Municipais da Educação de Areias/PB - SINDSPMEA/PB, a ser realizada de forma presencial, no dia de 15 de fevereiro de 2025, às 9h00 em primeira convocação e às 9h30 em segunda convocação com qualquer número de participantes nas dependências da sede da Associação dos Servidores Públicos do Município de Areias/PB, situado na Rua João Batista, nº 50, Areias/PB para tratar da seguinte ordem do dia: 1 - Fundação do Sindicato dos Servidores Públicos Municipais da Educação de Areias/PB - SINDSPMEA/PB; 2 - Aprovação do Estatuto Social do SINDSPMEA/PB; 3 - Eleição e Posse da Diretoria Executiva e Conselho Fiscal do SINDSPMEA/PB, para o Quadriênio 2025/2029; 4 - Aprovação do valor da contribuição da mensalidade dos associados; 5 - Autorizar à Diretoria eleita para filiar o SINDSPMEA/PB as entidades representativas de Graus superiores, CUT - Central Única dos Trabalhadores, CONFETAM E FETAM/PB e; 6 - Outros assuntos pertinentes a Fundação da Entidade e encaminhamentos.

João Pessoa/PB, 24 de janeiro 2025
SENILDO HENRIQUE DA SILVA

FUNDAÇÃO DE DESENVOLVIMENTO CIENTÍFICO E CULTURAL

AVISO DE ADJUDICAÇÃO

RATIFICAÇÃO DE CONTRATAÇÃO DIRETA - Processo nº 60798/2024
A Fundação de Desenvolvimento Científico e Cultural - FUNDECC, inscrita no CNPJ sob o n. 07.906.323/0001-07, representada por sua Diretora Executiva, ratifica a contratação direta dos bens objetos da Seleção Pública nº 11/2024 julgada deserta por ausência de interessados, aplicando-se o disposto no art. 9º, §3º, do Decreto n. 8241/2014, mantendo-se as mesmas condições previstas no Edital. Diante do Processo no Campo nº 60798/2024, adjudica o objeto à empresa CREACOM INFORMÁTICA COMÉRCIO E SERVIÇOS LTDA - CNPJ 17.603.733/0001-13, no valor de R$54.641,30, regularmente habilitada.

Lavras-MG, 10 de janeiro de 2025.
ANA PAULA PROVESAN MELCHIOR
Diretora Executiva

FUNDAÇÃO ESCOLA POLITÉCNICA DA BAHIA

EXTRATO DE INEXIGIBILIDADE DE LICITAÇÃO

Inexigibilidade nº 008/2024. Projeto: FEP UFRB BNB CONVÊNIO FUNDECI 2024.0005. Contratada: OVV do Brasil Tecnologia e Comercio LTDA - CNPJ: 35.252.465/0001-07. Objeto: aquisição ultrassom com doppler e um transdutor para avaliação de carcaça. Fundamento Legal: Art. 74, inciso I da Lei nº 14.133/2021. Parecer de inexigibilidade exarado 44/2024 emitido por HUMBERTO COSTA JUNIOR E GABRIEL MIRANDA GALLO ADVOGADOS ASSOCIADOS. Valor: R$ 145.000,00 (cento e quarenta e cinco mil reais) ASS: Yuri Guarnieri Pereira, CAR (Diretor Geral).

FUNDAÇÃO NORTE RIO-GRANDENSE DE PESQUISA E CULTURA

EXTRATO DE DISPENSA DE LICITAÇÃO

Processo nº 14000029. Contratante: Fundação Norte-rio-grandense de Pesquisa e Cultura (FUNPEC). Contratada: 24.398.681/0001-02 - ARPLAN ENGENHARIA TERMICA LTDA. Objeto: SERVIÇO DE ADEQUAÇÃO DO SISTEMA DE HVAC. Valor: R$ 85.992,04 (OITENTA E CINCO MIL E NOVECENTOS E NOVENTA E DOIS REAIS E QUATRO CENTAVOS), possibilidade de contratação direta, em respeito ao exposto no art. 29, VI, do Decreto nº 8.241/14, por dispensa de licitação. Autorização: Francisco Alexandre M. M. Costa - Coordenador de grupo de compras. Ratificação: Luiz Cledston de Noronha Freire - gerente de materiais. Natal/RN, 22 de janeiro de 2025.

FUNDAÇÃO SÃO FRANCISCO XAVIER

AVISOS DE LICITAÇÃO
PREGÃO ELETRÔNICO PÚBLICO HMC Nº 423/2025

Encontra-se aberto na Fundação São Francisco Xavier Hospital Instrumento Convocatório na modalidade Pregão Eletrônico Público HMC N.º 423/2025, para Aquisição de Faca Cirúrgica. Acolhimento das propostas: 24/01/25 a 05/02/25. Abertura das propostas: 05/02/25 às 07:30h, início da disputa: 05/02/25 às 09:00h. O presente instrumento Convocatório estará disponível na íntegra no site da plataforma eletrônica Publinexo: www.publinexo.com.br/publico

PREGÃO ELETRÔNICO PÚBLICO HMC Nº 424/2025

Encontra-se aberto na Fundação São Francisco Xavier Hospital Instrumento Convocatório na modalidade Pregão Eletrônico Público HMC N.º 424/2025, para Aquisição de Aparelho Raio-x Móvel Tipo Arco Cirúrgico. Acolhimento das propostas: 24/01/25 à 05/02/25. Abertura das propostas: 05/02/25 às 07:30h, início da disputa: 05/02/25 às 14:00h. O presente instrumento Convocatório estará disponível na íntegra no site da plataforma eletrônica Publinexo: www.publinexo.com.br/publico.

Ipatinga, 22 de janeiro de 2025
CRISTIANE CARVALHO
Pregoeira

FUNDAÇÃO DA UNIVERSIDADE FEDERAL DO PARANÁ

AVISOS DE LICITAÇÃO
PREGÕES ELETRÔNICOS

Edital nº 3896/2024 Objeto: Aquisição de Reinpedância Tetrapolar Savvy, para atender a demanda do Projeto nº 3963 - Integralização da Extensão na UFPR. Acolhimento Propostas: até 06/02/2025 às 09:00min. Data do Pregão: 06/02/2025 às 09:30min. O edital está disponível no site www.bll.org.br ou bllcompras.com. Dúvidas entrar em contato pelo e-mail: licitacao@fuspar.ufpr.br.

Edital nº 3818/2024 Objeto: Aquisição de Cadeira Fisa de Poliprolileno, para atender a demanda do Projeto nº 3963 - Integralização da Extensão na UFPR. Acolhimento Propostas: até 06/02/2025 às 09:00min. Data do Pregão: 06/02/2025 às 09:30min. O edital está disponível no site www.bll.org.br ou bllcompras.com. Dúvidas entrar em contato pelo e-mail: licitacao@fuspar.ufpr.br.

Edital nº 3806/2024 Objeto: Aquisição de Kit Touca EGG, para atender a demanda do Projeto nº 3963 - Integralização da Extensão na UFPR. Acolhimento Propostas: até 06/02/2025 às 09:00min. Data do Pregão: 06/02/2025 às 09:30min. O edital está disponível no site www.bll.org.br ou bllcompras.com. Dúvidas entrar em contato pelo e-mail: licitacao@fuspar.ufpr.br.

Edital nº 3821/2024 Objeto: Aquisição de HD Externo Portátil 2TB, para atender a demanda do Projeto nº 3963 - Integralização da Extensão na UFPR. Acolhimento Propostas: até 06/02/2025 às 09:00min. Data do Pregão: 06/02/2025 às 09:30min. O edital está disponível no site www.bll.org.br ou bllcompras.com. Dúvidas entrar em contato pelo e-mail: licitacao@fuspar.ufpr.br.

MARCIA DE JESUS DE MEIRA MORILHAS
Pregoeira

FUNDAÇÃO UNIVERSIDADE PARA O DESENVOLVIMENTO DO ALTO VALE DO ITAJAÍ

CNPJ: 85.786.621/0001-97

AVISO
REGISTRO DE DIPLOMAS

Para fins do disposto no art. 21 da portaria MEC Nº 1.095, de 25 de outubro de 2018, esta instituição de Educação Superior informa que foram registrados 3 (três) diplomas no período de 31/10/2024 a 31/12/2024, no seguinte livro de registro e sequência numérica: Livro 23, Registro de 587 a 589.
A relação dos diplomas registrados poderá ser consultada em até ninta dias, no endereço https://www.unidavi.edu.br/)

Rio do Sul, 15 de janeiro de 2025
ALCIR TEIXEIRA
Reitor

LISTA DE DELEGADOS E SUPLENTES 11º CONGRESSO DA FENAFAR

Estado: ALAGOAS

DELEGADOS	CRF	ASSINATURA
ALEXANDRE CORREIA DOS SANTOS	541	
CARLOS HENRIQUE ACIOLE TAVARES	439	
ELINE CRISTINA SOUTO MAIOR BARACHO	910	
LEONICE PEREIRA DA SILVA	1209	
LINDOMAR FEITOZA DA HORA	1820	
ROBERTO GALDINO DA SILVA	874	

ESTADO: AMAZONAS

DELEGADOS	CRF	ASSINATURA
ALEXSANDRA FERRAZ DA ROSA	2711	
EDMUNDO TIBÚRCIO FERREIRA ARAÚJO	5929	
ISAIAS DA SILVA OLIVEIRA	5404	
JARDEL ARAÚJO DA SILVA INÁCIO	2570	
LITUANIA MUSTAFA PAES DE ALMEIDA	1996	
LUANA KELLY LIMA SANTANA	1710	
MARA RUBIA HAYDEN FREIRE CAMARA	1423	
MARCOS ROBERTO RODRIGUES DOS SANTOS	1850	
RONIERY LIMA DE SOUZA	1614	
SUPLENTES	**CRF**	**ASSINATURA**
RODRIGO RAMOS DE SENA	2051	

ESTADO: AMAPÁ

DELEGADOS	CRF	ASSINATURA
ALBERTO ISSA PUREZA CALLINS	344	
CLEBER DA CRUZ RODRIGUES DE LIMA	446	
JONE DE ARAÚJO MORAES	298	
OTAVIO EUTIQUIO VASCONCELOS PINHEIRO DA SILVA	404	
ROBERTO FÁBIO DA SILVA PORTELA	551	
SUPLENTES	**CRF**	**ASSINATURA**
LUCIENE MAIA PINHEIRO GADELHA	1155	

Registro Nº
725.064
26/09/2025

Protocolo nº 444.341 de 26/08/2025 às 08:05:45h: Documento **registrado eletronicamente para fins de publicidade e/ou eficácia contra terceiros** sob nº **725.064** em **26/09/2025** e averbado no registro nº 237636/92 neste **4º Oficial de Registro Civil de Pessoas Jurídicas da Comarca de São Paulo**. Assinado digitalmente por Carlos Augusto Peppe - Escrevente.

Oficial	Estado	Secretaria Fazenda	Reg. Civil	T. Justiça	M. Público	ISS	Condução	Despesas	Total
R$ 324,15	R$ 91,99	R$ 62,97	R$ 17,15	R$ 22,21	R$ 15,45	R$ 6,79	R$ 0,00	R$ 0,00	R$ 540,71

ESTADO: BAHIA

DELEGADOS	CRF	ASSINATURA
ARIEL RIOS REZENDE	3749	
ALTAMIRO JOSÉ DOS SANTOS	2429	
CLOVIS DE SANTANA REIS	3030	
ELIANE ARAÚJO SIMÕES	953	
GIBRAN SOUZA EVANGELISTA	4124	
HESROM FERNANDES SERRA MOURA	16375	
IRENE PORTO PRAZERES	1790	
JOSÉ JORGE SILVA JÚNIOR	5644	
MAGNO LUIZ TEIXEIRA SILVEIRA	3743	
MAGNO OLIVEIRA RAMOS	5839	
MARIA SORAYA PINHEIRO DE AMORIM	2114	
RODRIGO NOVAIS OLIVEIRA	8292	
VIVICA KAROLINE DE OLIVEIRA XAVIER	9167	
SUPLENTES	**CRF**	**ASSINATURA**
LEILIANE FERREIRA SARAIVA	6735	
SILVIO ROBERTO DO BOMFIM CARVALHO	13398	
TAYRA BARRETO CUNHA	5591	

ESTADO: CEARÁ

DELEGADOS	CRF	ASSINATURA
ANDRÉ NUNES CAVALCANTE	3042	
ALESSANDRO SIMÕES DE MOURA	2930	
CARLOS JOSÉ MATOS FRANCO	2340	
EXPEDITO ROGILDO CORDEIRO CARLOS	2305	
FÁBIO FROTA DE VASCONCELOS	2689	
FRANCINALDA XAVIER DE SOUSA	3160	
FRANCISCO IELANO VASCONCELOS MESQUITA	3392	
MARIA IRACEMA ROCHA DE ANDRADE	3020	
MÔNICA HELENA SANTOS SOUSA	3083	
SUPLENTES	**CRF**	**ASSINATURA**
ERNESTO DA ROCHA TOME	2446	
MALENA GADELHA CAVALCANTE	3651	

Registro Nº
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ESTADO: ESPÍRITO SANTO

DELEGADOS	CRF	ASSINATURA
ANTÔNIO HENRIQUE NASCIMENTO DA SILVA	8816	
GABRIELA SALES DE SOUZA	8916	
ANDRÉ VICTORIO DA SILVA	1975	
LAIS MARANGON	7871	
MARIA JOSE SARTORIO	738	
MONALISA QUINTÃO CHAMBELLA	3789	
SHEILA FRANCO TRÊS	7909	
YASMINNE DANNAE ROSA ANDRADE	7785	

ESTADO: GOIAS

DELEGADOS	CRF	ASSINATURA
DOUGLAS MACHADO DA SILVA	13915	
EDMAR GODOY VIGGIANO PEREIRA	2415	
ELISTER DE OLIVEIRA RODRIGUES	3907	
FÁBIO JOSÉ BASÍLIO	3104	
GEOVANE DE SOUZA FLÁVIO	18092	
IVANA CLÁUDIA ROCHA SANTOS DE OLIVEIRA	3705	
LORENA BAIA DE OLIVEIRA ALENÇAR	3055	
MARIA CRISTINA RAMIREZ	11473	
RICARDO SOUSA MANZI	2744	
SANDRA MARIA ALVES DA COSTA	6403	
VIVIANE ALVES DE OLIVEIRA	2574	
SUPLENTES	**CRF**	**ASSINATURA**
MIRTES BARROS BEZERRA	1904	
SOLIMAR SILVA	1708	

ESTADO: MARANHÃO

DELEGADOS	CRF	ASSINATURA
ADRIANO DOS ANJOS COSTA	2546	
GIZELLI SANTOS LOURENÇO	2246	
HENRIQUE GOMES DA SILVA	4849	
JAIZA LIMA LEITE LIRA	5939	
OLNIVANIA M. CARDOZO ALMEIDA	4383	
ROBERT DOS SANTOS SOUSA	9777	
ROSÁLIA DOS SANTOS RODRIGUES	4794	
TAYSA CANTANHEDE CARVALHO	4715	

ESTADO: MINAS GERAIS

DELEGADOS	CRF	ASSINATURA
ALBANO RUBENS DO VALLE VERONA	7833	
ANA EMÍLIA AHOUAGI	21339	
CHRISTIAN FRANCISCO DE MATOS	34333	
CRISTIANE MENDONÇA DE OLIVEIRA	15282	
DENISON DE SOUZA SILVEIRA	7966	
ELIANA CAMARGO DE SOUSA	8748	
GEAN LUCAS DE ARAÚJO ALVES	40292	
JÚNIA DARK VIEIRA LELIS LIGÓRIO	14135	
MARCELO SILVA SILVÉRIO	20371	
MARCONY RAIMUNDO FIGUEIREDO DE CARVALHO	15337	
MARIA CLAUDIA MOREIRA DE FARIA	6568	
MARIA HELENA BRAGA	3814	
PAULO FELIX DE ALMEIDA PENA	8831	
RAMON FRANCESCO DE ARAÚJO PEIXOTO	23895	
RAQUEL REZENDE MENEZES	18280	
RATSA FERRAZ AGUIAR	10451	
RILKE NOVATO PÚBLIO	7851	
SEBASTIÃO FORTUNATO DE FARIA FILHO	8078	
SEBASTIÃO JOSÉ FERREIRA	7933	
WALTOVÂNIO CORDEIRO DE VASCONCELOS	8717	
SUPLENTES	**CRF**	**ASSINATURA**
RONDINELLI GOMES PEREIRA	14416	

ESTADO: MATO GROSSO

DELEGADOS	CRF	ASSINATURA
ANTÔNIO APARECIDO CASARIN	1475	
DEVANIL ROZA FERNANDES	548408	
EDNÉIA DUARTE	4631	
JEFFERSON WILLIAM DE OLIVEIRA	1031	
JOEL ALVES DA SILVA	2361	
LETICIA PALÚ	1532	
PEDRO ARANTES DE ASSUNÇAO	538639	
WILLE MARCIO NASCIMENTO CALAZANZ	931	
SUPLENTES	**CRF**	**ASSINATURA**
ANA PAULA SILVA LIMA	5778	
FLÁVIO EDUARDO AFANACI	4885	

Registro Nº
725.064
26/09/2025

Protocolo nº 444.341 de 26/08/2025 às 08:05:45h: Documento **registrado eletronicamente para fins de publicidade e/ou eficácia contra terceiros** sob nº **725.064** em **26/09/2025** e averbado no registro nº 237636/92 neste **4º Oficial de Registro Civil de Pessoas Jurídicas da Comarca de São Paulo**. Assinado digitalmente por Carlos Augusto Peppe - Escrevente.

Oficial	Estado	Secretaria Fazenda	Reg. Civil	T. Justiça	M. Público	ISS	Condução	Despesas	Total
R$ 324,15	R$ 91,99	R$ 62,97	R$ 17,15	R$ 22,21	R$ 15,45	R$ 6,79	R$ 0,00	R$ 0,00	R$ 540,71

ESTADO: PARÁ

DELEGADOS	CRF	ASSINATURA
DEICK RODRIGUES QUARESMA	2235	
LUIS HENRIQUE DE OLIVERA RODRIGUES	5318	
ANDREZA DA SILVA ROCHA	1984	
ANTONIO CESAR RODRIGUES GOMES	1868	

ESTADO: PARAIBA

DELEGADOS	CRF	ASSINATURA
HARIAD RIBEIRO MOAIS DA SILVA	3307	
IARA MATIAS GOMES DE ANDRADE	2496	
JAILSON VILBERTO DE SOUSA E SILVA	2469	
PATRÍCIA AVELAR NAVARRO	2135	
SÉRGIO LUIS GOMES DA SILVA	1813	
VALDIR LEITE DE ARAUJO	4020	

ESTADO: PARANÁ

DELEGADOS	CRF	ASSINATURA
ALLAN KARDEC DE LIMA	30671	
FÁBIO AUGUSTO DO CARMO SANTANA	16985	
GRACIELE DE PINTOR	19181	
JOSÉ CARLOS TOZETTO VETTORAZZI	4579	
LIA MELLO DE ALMEIDA	3532	
MARCOS ANTONIO RECH	3858	
MARSELLME NOBRE DE CARVALHO	29320	
MURILO CEREDA DA SILVA	26087	
NILSON HIDEKI NISHIDA	14793	
SERGIO SATORU MORI	4244	
SORAYA BARRIONUEVO FRANZENER	10995	
TEREZA EMIKO IWAMOTO	1190	

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ESTADO: PERNAMBUCO

DELEGADOS	CRF	ASSINATURA
ALISSON RODRIGO DA SILVA OLIVEIRA	6016	
DALMARE ANDERSON BEZERRA DE OLIVEIRA FALCÃO E SÁ	7736	
DIMAS FELIPE DE SOUZA ARAÚJO	5461	
HOLDACK VELÔSO GOMES PEDROZA	5397	
IVAN SILVA DE SOUZA	11225	
LUCIANO BARROS COSTA	4969	
RENAN DE FIGUEIREDO FERRAZ	5286	
RODRIGO VASCONCELOS DE SALES	3873	

ESTADO: PIAUÍ

DELEGADOS	CRF	ASSINATURA
ADRIANO MARTINS FERREIRA	545	
ANDRAWS HANS SALES RAMOS	3457	
FRANSCISCO ELRICK DE SOUSA OLINDA	624	
JACKSON HENRIQUE ALVES ARAUJO	2973	
SUSANA DE SOUSA ALVES	1332	
ULISSES NOGUEIRA DE AGUIAR	607	
SUPLENTES	**CRF**	**ASSINATURA**
ILUSKA MARTINS PINHEIRO	522	

ESTADO: RIO DE JANEIRO

DELEGADOS	CRF	ASSINATURA
CATARINE BEZERRA CAVALCANTI	23233	
ELIZOMARY ANDRÉA MENDES MEIRELES	19827	
GLEICIANO DE ARAÚJO FÉLIX	22550	
LEONARDO LÉGORA DE ABREU	13010	
SYLVANIA RODRIGUES DOS SANTOS	18297	
TALITA BARBOSA GOMES	15254	
TANIA MARIA LEMOS MOUÇO	3032	

SUSANA JASKARA BORCHES HERRERA 24183 São Paulo

Registro Nº
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ESTADO: RIO GRANDE DO SUL

DELEGADOS	CRF	ASSINATURA
CELIA MACHADO GERVASIO CHAVES	1894	
DEBORA RAYMUNDO MELECCHI	5911	
DENISE BUENO	3317	
DIEGO GNATTA	12061	
EDSON LUIZ ARAUJO CAVALHEIRO	5595	
HELENA CAVALCANTI RANSOLIN	3427	
LISIA HAUSEN GABE	3047	
MARCOS EVANGELISTA CARANHA	547418	
MASURQUEDE DE AZEVEDO COIMBRA	7421	
MAURICIO SCHULER NIN	10395	
NATALIA AZEREDO PAIM	563930	
OTÁVIO AMÉRICO AUGUSTIN	535258	
RAQUEL DENISE PETRY	6177	
VIVIANE MAURA RUBERT	8418	
SUPLENTES	**CRF**	**ASSINATURA**
BIBIANA SCHVANTES DE AGUIAR BOTTINI	6981	
MARCOS SAMARONI DA SILVEIRA	10674	
RENATO CHAGAS RIBEIRO	4184	

ESTADO: SANTA CATARINA

DELEGADOS	CRF	ASSINATURA
FABIO RODRIGO MESQUITA BORGES	6491	
FERNANDA MANZINI	8314	
ISABEL CARDOSO DE CARVALHO	19508	
LETICIA LIS BARSOTI	20908	
LUCIANO SOARES	3798	
LUIZ HENRIQUE COSTA	2258	
MATHEUS NASCIMENTO FUCHINA	22272	
NORBERTO RECH	1328	
RONALD FERREIRA DOS SANTOS	2592	
VANESSA MARIA CORREA	24361	
VINICIUS ANDRÉ BOFF	21747	
SUPLENTES	**CRF**	**ASSINATURA**
BEATRIZ MELIM	21845	

ESTADO: SERGIPE

DELEGADOS	CRF	ASSINATURA
ALLAN JOHN DE OLIVEIRA MELO	1514	
DANIELA SANTOS OLIVEIRA	610	
DANIELA SANTOS SILVA FERREIRA DE ALMEIDA	612	
LOÍDE OLIVEIRA ALVES	1.099	
LUCAS SANTOS DE SOUZA	1.818	
QUÊNNIA GARCIA MORENO RESENDE	543	
SUPLENTES	**CRF**	**ASSINATURA**
JAMILE CAROLINA SANTOS SOUZA	678	

ESTADO: SÃO PAULO

DELEGADOS	CRF	ASSINATURA
ADRYELLA DE PAULA FERREIRA LUZ	40.699	
ANA CLAUDIA SILVA NAVARRO	17.205	
ANDERSON FREIRE CARNIEL	24.500	
ANDERSON JOSE DE ALMEIDA	38.147	
CARLOS ALEXANDRE ALVES DE SILVA	36.948	
DANYELLE CRISTINI MARINI	25.937	
ERICA TIE MIAI	10.895	
FÁBIO CRISTIANO GARCIA	32.073	
FLAVIA GONÇALVES FERREIRA	37.628	
GILDA ALMEIDA DE SOUSA	6.430	
GUSTAVO LEMOS GUERRA	53.572	
JOSÉ LUZIVAN DE HOLANDA	7.552	
LUCIANA CANETTO FERNANDES	18.989	
LUCIANA RODRIGUES PEREIRA	84.198	
MARCEL PEREIRA DOS SANTOS	44.894	
MARCOS MACHADO FERREIRA	32.635	
MARIA ANTONIA GARCIA	18.040	
MARIA JOSÉ MARTINS DE SOUZA	13.625	
PAULA PAIS DOS SANTOS	49.118	
PAULO JOSE TEIXEIRA	20.544	
PAULO PAIS DOS SANTOS	6.068	
PRISCILA VAUTIER	24.728	
RENATA TEREZA GONÇALVES PEREIRA	18.176	
ROBERTO PELLEGRINI	4.705	
ROGERIO ANTONIO DE FREITAS BICHIAROV	62.686	
ROGERIO GOMES DA SILVEIRA	24.525	
SARA KANTEK SOUZA	5 554	

4º Oficial de Registro de Títulos e Documentos e Civil de Pessoa Jurídica da Comarca de São Paulo

Oficial de Registro: Robson de Alvarenga

Rua Líbero Badaró, n. 425 / Pq. Anhangabaú, n. 350 - 28º andar, CEP 01007-040 - Centro
Tel.: (11) 37774040 - Email: contato@4rtd.com.br - Site: www.4rtd.com.br

REGISTRO CIVIL DE PESSOA JURÍDICA

Nº 725.065 de 26/09/2025

Certifico e dou fé que o documento eletrônico, contendo **32 (trinta e duas) páginas** (arquivo anexo), foi apresentado em 16/09/2025, protocolado sob nº 444.897, tendo sido registrado eletronicamente sob nº **725.065** e averbado no registro nº 237636/92 no Livro de Registro A deste 4º Oficial de Registro Civil de Pessoas Jurídicas da Comarca de São Paulo, na presente data.

Denominação
FEDERACAO NACIONAL DOS FARMACEUTICOS FENAFAR
CNPJ nº 00.679.357/0001-48

Natureza:
ATA ELETRÔNICA

Certifico, **ainda**, que consta no documento eletrônico registrado as seguintes assinaturas digitais:
MASURQUEDE DE AZEVEDO COIMBRA:(Padrão: Gov-BR)
FABIO JOSE BASILIO:(Padrão: Gov-BR)
Elister De Oliveira Rodriguês:(Padrão: Privado(não ICP-Brasil))
D4S SERVICOS EM TECNOLOGIA LTDA:23691353000180(Padrão: ICP-Brasil)
Devanil Roza Fernandes:(Padrão: Privado(não ICP-Brasil))
Erica Tie Miai:(Padrão: Privado(não ICP-Brasil))
Albano Rubens do Valle Verona:(Padrão: Privado(não ICP-Brasil))
Masurquede de Azevedo Coimbra:(Padrão: Privado(não ICP-Brasil))

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São Paulo, 26 de setembro de 2025

Assinado eletronicamente

Carlos Augusto Peppe
Escrevente

Este certificado é parte **integrante e inseparável** do registro do documento acima descrito.

Emolumentos	Estado	Secretaria da Fazenda	Registro Civil	Tribunal de Justiça
R$ 259,14	R$ 73,52	R$ 50,33	R$ 13,73	R$ 17,75
Ministério Público	ISS	Condução	Outras Despesas	Total
R$ 12,34	R$ 5,42	R$ 0,00	R$ 0,00	R$ 432,23

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Registro Nº
725.065
26/09/2025

Protocolo nº 444.897 de 16/09/2025 às 15:49:24h: Documento **registrado eletronicamente para fins de publicidade e/ou eficácia contra terceiros** sob nº **725.065** em **26/09/2025** e averbado no registro nº 237636/92 neste **4º Oficial de Registro Civil de Pessoas Jurídicas da Comarca de São Paulo**. Assinado digitalmente por Carlos Augusto Peppe - Escrevente.

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R$ 259,14	R$ 73,52	R$ 50,33	R$ 13,73	R$ 17,75	R$ 12,34	R$ 5,42	R$ 0,00	R$ 0,00	R$ 432,23

ILUSTRÍSSIMO SENHOR OFICIAL DO 4º REGISTRO DE TÍTULOS E DOCUMENTOS E CIVIL DE PESSOA JURÍDICA DA CAPITAL – SP

A Federação Nacional dos Farmacêuticos, inscrita no CNPJ sob o nº 00.679.357/0001-48, com sede à Rua Barão de Itapetininga, 255, Sala 302, Centro, São Paulo/SP, CEP 01042-001, representada neste ato por seu representante legal Fábio José Basílio (GO), domiciliado na Rua RB 16, QD 41, LT 22, Goiânia/GO, CEP:74474-377, Casado, RG:3207835 - 22/12/2022 – SSP/GO, CPF:830.864.801-06 vem, respeitosamente, à presença de Vossa Senhoria requerer o registro da Ata de Eleição da Diretoria, do Conselho Fiscal e seus respectivos suplentes para o mandato 2025/2028 anexos, declarando que foram cumpridos todos os requisitos estatutários vigentes.

São Paulo, 18 de agosto de 2025

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725.065
26/09/2025

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Oficial	Estado	Secretaria Fazenda	Reg. Civil	T. Justiça	M. Público	ISS	Condução	Despesas	Total
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Ata Geral da Eleição da Diretoria, do Conselho Fiscal e dos Suplentes da Federação Nacional dos Farmacêuticos – FENAFAR, CNPJ 00.679.357/0001-48, TRIÊNIO 2025/2028.

Às 12hs05mim, dos oito dias do mês de agosto de 2025, na sede do 11º CONGRESSO DA FEDERAÇÃO NACIONAL DOS FARMACÊUTICOS – FENAFAR, nas dependências do Centro de Artes e Convenções da Universidade de Ouro Preto (UFOP), situado na rua Diogo Vasconcelos N.º 328, no Bairro de Pilar, na cidade de Ouro Preto – MG - CEP 35400-000, reuniram-se os membros da Comissão Eleitoral, Farmacêuticos Albano Rubens Verona, Elister de Oliveira Rodrigues 1ª Secretária, Erica Tie Miai 2º Secretária, Devanil Roza Fernandes e Masurquede de Azevedo Coimbra Presidente, para proceder a confecção/redação/elaboração da ata de eleição e posse da Diretoria, do Conselho Fiscal e Suplentes eleitos em eleição realizada por meio virtual/eletrônico iniciada às 10hs e encerrada, precisamente, às 12hs. Registrando que o processo eleitoral foi realizado através de sistema de votação eletrônica desenvolvido pela empresa de Razão Social Rafaelly Duarte Silva Cunha, CNPJ 33290416/0001-40, sediada na rua do Bordado, Quadra 59, Lote 17 no Bairro do Jardim Atlântico, na cidade de Goiânia – GO, CEP 74343-110, sistema denominado Electios que utiliza plataforma virtual, e que permite relatório de zerésima, antes da abertura da votação, de apuração dos votos e de votantes pela identificação do CPF do eleitor e do IP do equipamento utilizado para votação, que garante ao sistema, a inviolabilidade e sigilo do voto. Inicialmente, avaliou-se o relatório inicial denominado Zerésima da urna eleitoral (em anexo a essa ata), com duas páginas, emitido anteriormente as 09hs00mim do dia oito de agosto, definindo que a eleição iria ocorrer das 10hs às 12hs do dia 08 de agosto com 179 pessoas delegadas previamente credenciadas e aptas a votarem, destaca-se que a relação nominal das pessoas delegadas foi impressa e disponibilizada na Secretaria do Congresso, após o encerramento do período de credenciamento. Terminado o prazo, estabelecido em publicação, foi homologada como candidata apenas a Chapa 1, representada pelo Farmacêutico Fábio José Basílio do Estado de Goiás, candidato a Presidente da FENAFAR. Às 12hs iniciou-se a apuração dos votos através do sistema de votação supracitado com a utilização de chave criptografada de segurança. Em seguida, procedeu-se a avaliação do relatório da eleição, com 11 páginas, emitido às 12hs e 01 mim do dia 08 de agosto, identificaram-se pelo IP todos os 158 delegados eleitores, onde houve 1 voto nulo, 1 voto em branco, 21 pessoas delegadas não manifestaram voto e 156 delegados votantes elegeram para presidência da FENAFAR a Chapa 1, que tem como candidato a presidente o Farmacêutico Fábio José Basílio e todos os seus outros membros Farmacêuticos nominados e qualificados como segue a seguir: **Presidente**: Fábio José Basílio (GO), domiciliado na Rua RB 16, QD 41, LT 22, Goiânia/GO, CEP:74474-377, Casado, RG:3207835 - 22/12/2022 – SSP/GO,

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CPF:830.864.801-06; **Primeira Vice-Presidente:** Renata Tereza Gonçalves Pereira (SP) domiciliada na Av. Manoel da Nobrega, N.º 200 – Apto 106 – São Vicente/SP – CEP 11320-200 – Casada – RG 209558325 – 09/11/2015 – SSP/SP – CPF 159.144.598-18; **Segunda Vice-Presidente:** Débora Raymundo Melecchi (RS) domiciliada na Rua Ramiro Barcelos, N.º 1552, Apto 11 Porto Alegre/RS – CEP 90420-132 – Solteira – RG 4051802314 – 01/06/2012 – SSP/RS – CPF 632.756.430-53; **Secretário Geral:** André Nunes Cavalcante (CE) domiciliado na Rua Barão de Aratanha, N.º 444 – Casa, – Fortaleza/CE – CEP 60050-071 – Casado – RG 95002322087 – 23/10/2000 – SSP/CE – CPF 868.401.773-00; **Primeiro Secretário:** Fábio Augusto do Carmo Santana (PR) domiciliado na Rua Theodorico dos Santos N.º 91 – Casa Fundos – Paranaguá/PR – CEP 83203-450 – Divorciado – RG 88799968 – 03/12/2024 – DETRAN/PR – CPF 006.086.049-92; **Tesoureiro:** Rilke Novato Públio (MG) domiciliado na Rua Geraldo Magela Pereira, N.º 35 – Apto 35 – Belo Horizonte/MG - CEP 30840 – 380 – Solteiro - RG Mg 3 231 185 – 16/08/2016 – Policia Civil – CPF 545.826.796-68; **Primeiro Tesoureiro:** Deick Rodrigues Quaresma (PA) domiciliado na Travessa Monte Alegre, N.º 397, Casa, Cidade Velha, Belém/PA – CEP 66023-040 – Divorciado – RG 2868019 – 24/09/1996 – PC/PA – CPF 628.511.102-25; **Diretor de Comunicação:** Clóvis de Santana Reis (BA) domiciliado na Rua Nivaldo Domingos, N.º 439 – Condomínio Residencial Boulevard Ipitanga – Casa 2 - Lauro de Freitas/BA – CEP 42706-320 – Casado – RG 480872201 – 18/01/2024 – SSP/BA – CPF 928.939.455.20; **Diretor de Formação Sindical:** Allan John de Oliveira Melo (SE) domiciliado na Rua Gumercindo Bessa, N.º 32, Bairro Santo Antônio, – Casa - Aracaju/SE – CEP 49060-280 – Casado – RG 32477627 – 01/02/2010 – SSP/SE – CPF 044.520.725-69; **Diretora de Relações Institucionais:** Isabela de Oliveira Sobrinho (AC) domiciliada na domiciliado na Rua dos Engenheiros, N.º 464 - Casa - Rio Branco/AC – CEP 69919-053 – Solteira- RG 303082 – 11/01/2001 – SSP/AC – CPF 741.123.332-34; **Primeira Diretora de Relações Institucionais:** Gizelli Santos Lourenço (MA) domiciliada na Rua Duque de Vizeu, N.º 17 – Altos do Calhau – Casa 17 – São Luís/MA– CEP 65071-391 – Separada – RG 32507394-5 - 03/03/2023 – SSP/MA – CPF 899.790.283-00; **Diretora de Relações Internacionais:** Gilda Almeida de Souza (SP) domiciliada na Rua Inácio Manoel Álvares - Apto 34 – Bloco A – São Paulo/SP – CEP 05372-110 – Divorciada – RG 10 153 588 – 0 – 02/07/2010 – SEC. Segurança Pública/SP – CPF 912.544.008–00; **Primeira Diretora de Relações Internacionais:** Maria Maruza Carlesso (ES) domiciliada na Avenida Luiz Manoel Vellozo, N.º 121 - AP 302 – Vitória/ES – CEP 29060-040 – Solteira - RG 167541 – 04/04/2013 – SSP/ES – CPF 252.227.327-20; **Diretor de Organização Sindical:** Alexandre Correia dos Santos (AL) domiciliado na Rua Rosalvo Ribeiro, N.º 92, Centro – Casa – Alagoas/AL – CEP 57150-000 – Casado - RG 1.027.718 – 05/07/2017 – SSP/AL – CPF 563.359.544-00; **Primeiro Diretor de Organização Sindical:** Francisco Ielano Vasconcelos Mesquita (CE) domiciliado na Rua das Gaivotas, N.º 1403 – Casa – FortalezaCE –

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CEP 60.821-160 – Casado – RG 95002523147 – 22/05/1997 – SSP/CE – CPF 771.922.653-49; **Diretora da Mulher:** Maria Soraya Pinheiro de Amorim (BA) domiciliada na Travessa Orlando Moscoso, N.º 1 – Boca do Rio – Casa – Salvador/BA – CEP 41706-665 – Solteira – RG 142154890 – 16/05/2024 – SSP/BA – CPF 373.979.665-00; **Diretora de Educação:** Célia Machado Gervásio Chaves (RS) domiciliada na Rua Marcilio Dias, N.º 589 – Apto 1701 – Porto Alegre/RS – CEP 90130-001 – Solteira – RG1017839836 – 08/11/2012 – SSP/RS – CPF 262.770.000-63; **Diretor de Assuntos Jurídicos:** Ulisses Nogueira de Aguiar (PI) domiciliado na Rua Vila da FAB, Casa 5 – Teresina/PI – CEP 64006-030 – Casado – RG 3103636 – 03/11/2021 – SSP/PI – CPF 514.451.403-06; **Primeira Diretora de Assuntos Jurídicos:** Monalisa Quintão Chambella de Abreu (ES) domiciliada na Avenida Rio Branco, N.º 311 – Bairro Santa Lúcia – Ed. West Plaza – Vitória/ES – CEP 29056-255 – Casada – RG 1.942.979 – 18/04/2000 – SSP/ES – CPF 097.127.567-00; **Diretor de Saúde e Segurança do Trabalho:** Leonardo Légora de Abreu (RJ) domiciliado na Rua Doutor Sílvio e Silva, N.º 162 – Casa - Duque de Caxias/RJ – CEP 25071-030 – Casado - RG 121590236 – 28/11/2024 – DETRAN/RJ – CPF 054.409.627-43; **Diretor de Relações Trabalhistas:** Holdack Velôso Gomes Pedroza (PE) domiciliado na Rua Sebastião Ribeiro da Silva, N.º 321 – Casa, Olinda/PE – CEP 53240-060 – Casado – RG 1316509 - 11/04/2002 – SDS/PE – CPF 231.312.094-53; **Diretora de Juventude e Direitos Humanos:** Letícia Lis Barsoti (SC) domiciliada na Rua Porto Alegre, N.º 176 – Casa – São José/SC – CEP 88110-440 – Solteira – RG 6276199 – 18/12/2018 – IGP/SC – CPF 078.984.419-23; **Diretor Regional Norte:** Otávio Eutíquio Vasconcelos Pinheiro da Silva (AP) domiciliado na Avenida Brunei, N.º 466 – Condomínio Parque Novo Mundo - Macapá/AP – CEP 68906-802 – Casado – RG1804766 – 23/10/2023 – SSP/AP – CPF 657.454.692-34; **Diretor Regional Nordeste:** Sérgio Luis Gomes da Silva (PB) domiciliado na Rua Professor Cardoso, N.º 105 – Torre Casa – João Pessoa/PA – CEP 58.040-310 – Divorciado – RG 1326941 – 22/04/2024 – DETRAN/PB – CPF 715.004.644-49; **Diretor Regional Centro–Oeste:** Wille Marcio Nascimento Calazans (MT) domiciliado na Rua Mestres Albertino N.º 95, Apto 1302 – Duque de Caxias – Cuiabá/MT – CEP 78043-356 – Casado – RG 373.031 – SSP/MT – 16/01/1992 – CPF 395.361.571-87; **Diretora Regional Sudeste:** Júnia Dark Vieira Lelis Ligório (MG) domiciliada na Rua Geraldo Magela de Almeida, N.º 135 – Apto 601 - Belo Horizonte/MG – CEP 30840640 – Casada – RG 10657902 – 01/09/2015 – CPF 036.133.366-85; **Diretor Regional Sul:** Nilson Hideki Nishida (PR) domiciliado na Travessa dos Jasmins, N.º 32 – Casa – Paranaguá/PR – CEP 83212-350 – Casado – RG 01422608009 – 13/05/2022 – DETRAN/PR – CPF 034.214.969-51; **Suplentes da Diretoria: Primeiro Suplente:** Ronald Ferreira dos Santos (SC) domiciliado na Rua João de Barro 124 – Florianópolis/SC – CEP 88054-620 – Casado - RG 2039575 – 06/06/1990 – CPF 834.631.789-15; **Segunda Suplente:** Tania Maria Lemos Mouço (RJ) domiciliada na Rua Álvaro Ramos, N.º 185 – Apto 305 - Rio de Janeiro/RJ – CEP 22280-110 – Viúva –

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RG 813633418 – 25/02/2022 – DETRAN/RJ – CPF 490.807.687-15; **Terceiro Suplente:** Ricardo Jorge Bouez Ribeiro (RO) domiciliado na Av. Costa Marques, N.º 988 – Centro Casa - Guajará-Mirim/RO – CEP 76850-000 – Solteiro - MG-7.342 340 – 17/07/1995 – SSP-MG – CPF 595.006.702-91; **Quarto Suplente:** Pablo Renoir Fernandes de Sousa (RN) domiciliado na Rua Desportista Jeremias Pinheiro da Câmara Filho, N.º 500 – Villa Park Imperial Park Torre Roma, – Apto 404 – Natal/RN – CEP 59091250 – Divorciado – RG 002426162 – 30/11/2022 – SSP/RN – CPF 057.847.394-17; **Quinta Suplente:** Iohanna Emanuelle Martins (DF) domiciliada na SHVP Rua 06, Chácara 245 – Casa 27 – Brasília/DF – CEP 72006-465 – Casada – RG 2796573 – 14/02/2006. – SSP/DF – CPF 023.448.711-95; **Sexta Suplente:** Clarissa Xavier dos Santos (RR) domiciliada na Rua Rotary, N.º 236 – Residencial Lucas Firminiano – Apto 06 – Boa Vista/RR – CEP 69304-470 – Solteira – RG 6068949541 – 18/04/2018 – CPF 984.669.330-34; **Sétima Suplente:** Márcia Regina Cardeal Gutierrez Saldanha (MS) domiciliada na Rua Túlio Abrão, N.º 53 – Campo Grande, Mato Grosso do Sul/MS – CEP 79.051-610 – Divorciada – RG 738.001 – 10/04/2019 – SSP/MS – CPF 688.789.231-68; **Conselho Fiscal – Efetivos:** Maria Cristina Ramirez (GO), domiciliada na SRES, Q7, Bloco A – Casa 8 fundos – Brasília/DF – CEP 70640-018 – Viúva – RG 94834 – 04/08/2024 – SSP/GO – CPF 215.503.871-20; Eline Cristina Souto Maior Baracho (AL) domiciliada na Rua Estatístico Teixeira de Freitas, N.º 86 – Apto 304 – Maceió/AL – CEP 57055-660 – Solteira – RG 98001246039 – 21/01/2011 – SSP/AL – CPF 009.432.504-98; Joel Alves da Silva (MT) domiciliado na Rua Dr. Antônio Pires Sobrinho, N.º 55 – Casa – Rondonópolis/MT – CEP 78700-396 – Casada – RG 047456-7 – 23/04/1997 – SSP/MT – CPF 452.191.761-63; **Conselho Fiscal – Suplentes:** Lituânia Mustafa Paes de Almeida (AM) domiciliada na Rua Monte Moria, N.º 06 – Conjunto Galileia 2 – Manaus/AM – CEP 69092-015 – Casada – RG 10261320 - 28/10/2022 – CPF 417.095.782-20; Dimas Felipe de Souza Araújo (PE) domiciliado na Rua Oliveira Fonseca, N.º 351 – Apto 1202 A – Recife/PE – CEP 52040-250 – Casado - RG 1277519048 - 05/10/2012 - SSP/BA – CPF 014.233.094-98; Maria do Socorro Cordeiro Ferreira (PI) domiciliada na Rua Desembargador Adalberto Correia Lima, N.º 1882 Ininga – casa – Teresina/PI – CEP 64049-680 – Viúva – RG 135900 – 17/01/2020 – SSP/PI – CPF 022.726.363-49. Em seguida, a Comissão Eleitoral declarou eleita a nova Diretoria Executiva, Conselho Fiscal e Suplentes da FENAFAR para o mandato do triênio 2025/2028, iniciando-se o mandato em 01 de setembro de 2025 e término em 31 de agosto de 2028, conforme Ata do Congresso. Considerando, por fim, que o Congresso que elegeu a nova diretoria executiva aprovou a reforma estatutária, assunto para o qual foi convocada conforme edital publicado no Diário Oficial da União de 27/01/2025 – Seção 3, página 185, alterando o prazo de mandato da diretoria executiva e conselho fiscal e suplentes para 4 (quatro anos), ficou deliberado, desde já, a prorrogação do mandato da nova diretoria eleita, no período de 01/09/2028 a 31/08/2029.

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Nada mais havendo para ser tratado, eu Elister de Oliveira Rodrigues 1ª Secretária lavrei a presente Ata que segue assinada por mim e pelos demais membros da Comissão Eleitoral, Farmacêuticos Albano Rubens Verona, Erica Tie Miai 2ª Secretária, Devanil Roza Fernandes e Masurquede de Azevedo Coimbra Presidente da Comissão Eleitoral.

Ouro Preto, 08 de agosto de 2025.

Masurquede de Azevedo Coimbra
Presidente

Elister de Oliveira Rodrigues
1ª Secretária

Erica Tie Miai
2ª Secretária

Albano Rubens Verona

Devanil Roza Fernandes

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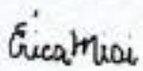

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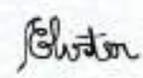

Albano Rubens do Valle Verona
albanodovalleverona@gmail.com
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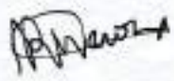

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15 Aug 2025, 11:04:36
Assinaturas **iniciadas** por ADELIR RODRIGUES DA VEIGA (573e50d1-ec16-4cb0-b79c-04191a1e4315). Email: efarmaceuticos@gmail.com. - DATE_ATOM: 2025-08-15T11:04:36-03:00

15 Aug 2025, 11:28:33
ERICA TIE MIAI **Assinou** - Email: erica.miai@sinfar.org.br - IP: 201.69.105.132 (201-69-105-132.dial-up.telesp.net.br porta: 48020) - Documento de identificação informado: 060.223.288-02 - DATE_ATOM: 2025-08-15T11:28:33-03:00

15 Aug 2025, 11:29:49
ALBANO RUBENS DO VALLE VERONA **Assinou** - Email: albanodovalleverona@gmail.com - IP: 201.17.148.243 (c91194f3.virtua.com.br porta: 58328) - Geolocalização: -20.148377391890435 -44.89566020759331 - Documento de identificação informado: 596.140.996-15 - DATE_ATOM: 2025-08-15T11:29:49-03:00

Registro Nº
725.065
26/09/2025

Protocolo nº 444.897 de 16/09/2025 às 15:49:24h: Documento **registrado eletronicamente para fins de publicidade e/ou eficácia contra terceiros** sob nº **725.065** em **26/09/2025** e averbado no registro nº 237636/92 neste **4º Oficial de Registro Civil de Pessoas Jurídicas da Comarca de São Paulo**. Assinado digitalmente por Carlos Augusto Peppe - Escrevente.

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R$ 259,14	R$ 73,52	R$ 50,33	R$ 13,73	R$ 17,75	R$ 12,34	R$ 5,42	R$ 0,00	R$ 0,00	R$ 432,23

D4Sign by ZUCCHETTI

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Certificado de assinaturas gerado em 15 de August de 2025, 14:43:08

ntp.br

15 Aug 2025, 11:34:34
DEVANIL ROZA FERNANDES **Assinou** - Email: devanil.fernandes40@gmail.com - IP: 201.49.174.26 (201.49.174.26 porta: 8940) - Geolocalização: -15.5678586 -56.0758858 - Documento de identificação informado: 142.337.111-91 - DATE_ATOM: 2025-08-15T11:34:34-03:00

15 Aug 2025, 12:09:40
MASURQUEDE DE AZEVEDO COIMBRA **Assinou** - Email: masurr@gmail.com - IP: 200.198.138.130 (200.198.138.130 porta: 61726) - Documento de identificação informado: 924.418.150-91 - DATE_ATOM: 2025-08-15T12:09:40-03:00

15 Aug 2025, 12:44:21
ELISTER DE OLIVEIRA RODRIGUÊS **Assinou** - Email: elisteroliveira20@gmail.com - IP: 191.247.147.23 (191-247-147-23.3g.claro.net.br porta: 51990) - Geolocalização: -16.6839638 -49.2632202 - Documento de identificação informado: 950.556.731-68 - DATE_ATOM: 2025-08-15T12:44:21-03:00

Hash do documento original
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(SHA512):2fe9e5767e48da241019a8c1547e8014a58b028c76e7045cf2e2ae6fa1edf573cb456b7ea292a467fbd507fca29d663dc21ef3e8ee7a2cd26d3f97e40f90838426

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Electios

Sistema Electios
Eleições 2025 - DIRETORIA - FENAFAR

Fenafar Federação Nacional dos Farmacêuticos

Zerésima - Candidatos aptos

Cargo/Partido/Chapa	Nr.	Nome	Votos
CHAPA 1	1	CHAPA 1 - REPRESENTANTE: FÁBIO JOSÉ BASÍLIO (GO)	0,0

Votos Brancos: 0,0

Votos Nulos: 0,0

Data de início: 08/08/2025 às 10:00
Data de encerramento: 08/08/2025 às 12:00

Eleitores aptos (179)

- Votaram: 0
- Não votaram: 179

Relatório emitido em: 08/08/2025 às 09:00

gov.br documento assinado digitalmente
MARQUESES DE AZEVEDO COIMBRA
Data: 15/08/2025 14:39:34 -0300
Verifique em https://validar.iti.gov.br

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Assinatura do Responsável

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Sistema Electios

Eleições 2025 - DIRETORIA - FENAFAR

Relatório de Resultado da Votação

CNPJ: 00679357000148

Mandato: 36 meses

Data de início: 08/08/2025 às 10:00
Data de encerramento: 08/08/2025 às 12:00

Votação

Grupos votantes	Partido/Chapa/Cargo	Número	Nome	Votos
	CHAPA 1	1	CHAPA 1 - REPRESENTANTE: FÁBIO JOSÉ BASÍLIO (GO)	156,0

Votos Brancos: 1,0

Votos Nulos: 1,0

Eleitores aptos: 179

- Votaram: 158
- Não votaram: 21

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Comparecimento de Eleitores aptos

Nome	CPF	Peso voto	Votou	IP/MAC	Grupo votante
ADRIANO DOS ANJOS COSTA	XXX.XXX.XX3-04	1,0	Sim	2804:214:81d6:208e:1:1:8bc5:7066	
ADRIANO MARTINS FERREIRA	XXX.XXX.XX4-19	1,0	Sim	2804:389:b113:493f:1:0:47ce:8c12	
ADRYELLA DE PAULA FERREIRA LUZ	XXX.XXX.XX8-33	1,0	Sim	2804:389:b191:40ad:c13e:4f88:a8ce:d325	
ALBANO RUBENS DO VALLE VERONA	XXX.XXX.XX6-15	1,0	Sim	2804:18:401d:a737:c885:6b97:c47d:ef2b	
ALBERTO ISSA PUREZA CALLINS	XXX.XXX.XX2-39	1,0	Sim	45.171.28.182	
ALESSANDRO SIMÕES DE MOURA	XXX.XXX.XX3-00	1,0	Sim	45.171.28.182	
ALEXANDRE CORREIA DOS SANTOS	XXX.XXX.XX4-00	1,0	Sim	2804:214:818b:104f:e19f:aa68:4fe1:83ad	
ALEXSANDRA FERRAZ DA ROSA	XXX.XXX.XX2-34	1,0	Sim	2804:18:5078:6586:8b2:ad5e:30d0:43f1	
ALISSON RODRIGO DA SILVA OLIVEIRA	XXX.XXX.XX4-08	1,0	Sim	186.248.162.238	
ALLAN JOHN DE OLIVEIRA MELO	XXX.XXX.XX5-69	1,0	Sim	45.171.28.182	
ALLAN KARDEC DE LIMA	XXX.XXX.XX8-10	1,0	Sim	2a04:4e41:63bb:680c::1f3b:680c	
ALTAMIRO JOSÉ DOS SANTOS	XXX.XXX.XX5-91	1,0	Sim	45.171.28.182	
ANA CLAUDIA SILVA NAVARRO	XXX.XXX.XX8-80	1,0	Sim	2804:389:b115:a133:b45a:32ae:cf9b:473	
ANA EMÍLIA AHOUAGI	XXX.XXX.XX6-20	1,0	Sim	201.54.208.55	
ANDERSON FREIRE CARNIEL	XXX.XXX.XX8-70	1,0	Sim	200.149.138.242	
ANDRAWS HANS SALES RAMOS	XXX.XXX.XX3-88	1,0	Não		
ANDRÉ NUNES CAVALCANTE	XXX.XXX.XX3-00	1,0	Sim	189.40.87.182	

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Nome	CPF	Peso voto	Votou	IP/MAC	Grupo votante
ANDREZA DA SILVA ROCHA	XXX.XXX.XX2-34	1,0	Sim	2804:18:4037:2f3d:1:0:9162:836c	
ANTÔNIO APARECIDO CASARIN	XXX.XXX.XX9-68	1,0	Sim	2804:389:b181:d89e:1:0:47b1:53f	
ANTONIO CESAR RODRIGUES GOMES	XXX.XXX.XX2-25	1,0	Não		
ANTÔNIO HENRIQUE NASCIMENTO DA SILVA	XXX.XXX.XX7-11	1,0	Sim	2001:67c:2660:425:25::1aa	
ARIEL RIOS REZENDE	XXX.XXX.XX5-72	1,0	Sim	45.171.28.182	
BEATRIZ MELIM	XXX.XXX.XX9-67	1,0	Sim	45.171.28.182	
CARLOS ALEXANDRE ALVES DE SILVA	XXX.XXX.XX8-59	1,0	Sim	2804:18:5076:9aa9:848a:6bda:234b:1883	
CARLOS HENRIQUE ACIOLE TAVARES	XXX.XXX.XX4-16	1,0	Sim	2804:29b8:5118:219a:4dcb:726:db3c:803a	
CARLOS JOSÉ MATOS FRANCO	XXX.XXX.XX3-04	1,0	Sim	45.171.28.182	
CATARINE BEZERRA CAVALCANTI	XXX.XXX.XX7-46	1,0	Sim	189.115.233.138	
CELIA MACHADO GERVASIO CHAVES	XXX.XXX.XX0-63	1,0	Sim	2804:18:481a:5d3b:d82a:a3ff:fe16:adac	
CLEBER DA CRUZ RODRIGUES DE LIMA	XXX.XXX.XX2-87	1,0	Não		
CLOVIS DE SANTANA REIS	XXX.XXX.XX5-20	1,0	Sim	2804:18:504d:32fb:4051:7c58:83d2:ebbc	
DALMARE ANDERSON BEZERRA DE OLIVEIRA FALCÃO E SÁ	XXX.XXX.XX5-44	1,0	Sim	2804:214:92a2:9a9d:3d69:c600:d4bf:f96a	
DANIELA SANTOS OLIVEIRA	XXX.XXX.XX5-32	1,0	Sim	2804:18:4034:4c12:30ba:280a:99d3:a5e7	
DANIELA SANTOS SILVA FERREIRA DE ALMEIDA	XXX.XXX.XX5-30	1,0	Sim	200.133.41.3	
DANYELLE CRISTINI MARINI	XXX.XXX.XX8-07	1,0	Não		

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Nome	CPF	Peso voto	Votou	IP/MAC	Grupo votante
DEBORA RAYMUNDO MELECCHI	XXX.XXX.XX0-53	1,0	Sim	2804:14d:4cd7:128a:95f5:9070:6d55:3581	
DEICK RODRIGUES QUARESMA	XXX.XXX.XX2-25	1,0	Sim	45.171.28.182	
DENISE BUENO	XXX.XXX.XX0-20	1,0	Sim	2804:18:4811:8ea5:c515:f1af:6d37:d8da	
DEVANIL ROZA FERNANDES	XXX.XXX.XX1-91	1,0	Sim	45.171.28.182	
DIEGO GNATTA	XXX.XXX.XX0-35	1,0	Sim	2804:214:818f:7cd8:9844:b7f6:534a:7caf	
DIMAS FELIPE DE SOUZA ARAÚJO	XXX.XXX.XX4-99	1,0	Sim	45.171.28.182	
DOUGLAS MACHADO DA SILVA	XXX.XXX.XX1-31	1,0	Sim	2804:389:a23c:37be:a485:1839:77d4:a7d5	
EDMAR GODOY VIGGIANO PEREIRA	XXX.XXX.XX1-20	1,0	Sim	45.171.28.182	
EDMUNDO TIBÚRCIO FERREIRA ARAÚJO	XXX.XXX.XX3-35	1,0	Não		
EDNÉIA DUARTE	XXX.XXX.XX6-77	1,0	Sim	45.171.28.182	
EDSON LUIZ ARAÚJO CAVALHEIRO	XXX.XXX.XX0-34	1,0	Sim	45.171.28.182	
ELIANA CAMARGO DE SOUSA	XXX.XXX.XX6-34	1,0	Sim	2804:18:4022:fbc6:1:0:9139:eaf5	
ELINE CRISTINA SOUTO MAIOR BARACHO	XXX.XXX.XX4-98	1,0	Sim	45.171.28.182	
ELISTER DE OLIVEIRA RODRIGUES	XXX.XXX.XX1-68	1,0	Sim	187.68.28.115	
ERICA TIE MIAI	XXX.XXX.XX8-02	1,0	Sim	45.171.28.182	
EXPEDITO ROGILDO CORDEIRO CARLOS	XXX.XXX.XX3-87	1,0	Sim	2804:214:92a5:86b4:c164:86d1:468c:41ca	
FÁBIO AUGUSTO DO CARMO SANTANA	XXX.XXX.XX9-92	1,0	Sim	45.171.28.182	
FÁBIO CRISTIANO GARCIA	XXX.XXX.XX8-00	1,0	Sim	2804:214:818a:bec4:1:1:8bf3:f38a	
FÁBIO FROTA DE VASCONCELOS	XXX.XXX.XX3-53	1,0	Sim	45.171.28.182	

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Nome	CPF	Peso voto	Votou	IP/MAC	Grupo votante
FÁBIO JOSÉ BASÍLIO	XXX.XXX.XX1-06	1,0	Sim	45.171.28.182	
FABIO RODRIGO MESQUITA BORGES	XXX.XXX.XX0-30	1,0	Sim	189.93.234.47	
FERNANDA MANZINI	XXX.XXX.XX8-29	1,0	Não		
FLAVIA GONÇALVES FERREIRA	XXX.XXX.XX2-91	1,0	Sim	45.171.28.182	
FRANCINALDA XAVIER DE SOUSA	XXX.XXX.XX3-25	1,0	Sim	45.171.28.182	
FRANCISCO IELANO VASCONCELOS MESQUITA	XXX.XXX.XX3-49	1,0	Sim	2804:38c4:8:9e75::351:ed63	
FRANSCISCO ELRICK DE SOUSA OLINDA	XXX.XXX.XX3-04	1,0	Sim	189.40.85.110	
GEAN LUCAS DE ARAÚJO ALVES	XXX.XXX.XX6-64	1,0	Sim	45.171.28.182	
GEOVANE DE SOUZA FLÁVIO	XXX.XXX.XX1-25	1,0	Sim	2804:214:90a5:4d7c:5095:9454:c294:6813	
GIBRAN SOUZA EVANGELISTA	XXX.XXX.XX5-03	1,0	Sim	2a09:bac2:785:1c96::2d9:2b	
GILDA ALMEIDA DE SOUSA	XXX.XXX.XX8-00	1,0	Sim	2804:389:b103:4daa:1:0:4555:201	
GIZELLI SANTOS LOURENÇO	XXX.XXX.XX3-00	1,0	Sim	2a04:4e41:6301:122c::f4ba:522c	
GRACIELE DE PINTOR	XXX.XXX.XX9-78	1,0	Sim	45.171.28.182	
GUSTAVO LEMOS GUERRA	XXX.XXX.XX6-85	1,0	Sim	45.171.28.182	
HARIAD RIBEIRO MORAIS DA SILVA	XXX.XXX.XX4-42	1,0	Sim	2804:389:b115:5ff6:60f4:4570:4096:3318	
HELENA CAVALCANTI RANSOLIN	XXX.XXX.XX0-00	1,0	Sim	45.171.28.182	
HENRIQUE GOMES DA SILVA	XXX.XXX.XX3-04	1,0	Sim	45.171.28.182	
HESROM FERNANDES SERRA MOURA	XXX.XXX.XX5-13	1,0	Sim	45.171.28.182	
HOLDACK VELÔSO GOMES PEDROZA	XXX.XXX.XX4-53	1,0	Sim	2804:214:92a9:b602:386e:feff:feb6:2c77	

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Nome	CPF	Peso voto	Votou	IP/MAC	Grupo votante
IARA MATIAS GOMES DE ANDRADE	XXX.XXX.XX4-91	1,0	Sim	45.171.28.182	
IRENE PORTO PRAZERES	XXX.XXX.XX5-72	1,0	Sim	2804:18:4821:52c8:dd9d:330d:c3a6:b4b3	
ISABEL CARDOSO DE CARVALHO	XXX.XXX.XX9-78	1,0	Sim	2804:389:c2a3:51e8:1c94:df92:cc6a:677a	
ISAIAS DA SILVA OLIVEIRA	XXX.XXX.XX2-71	1,0	Sim	45.171.28.182	
IVANA CLÁUDIA ROCHA SANTOS DE OLIVEIRA	XXX.XXX.XX1-87	1,0	Sim	45.171.28.182	
IVAN SILVA DE SOUZA	XXX.XXX.XX4-50	1,0	Sim	45.171.28.182	
JACKSON HENRIQUE ALVES ARAUJO	XXX.XXX.XX3-14	1,0	Não		
JAILSON VILBERTO DE SOUSA E SILVA	XXX.XXX.XX4-66	1,0	Não		
JAIZA LIMA LEITE LIRA	XXX.XXX.XX3-40	1,0	Sim	201.20.86.85	
JARDEL ARAÚJO DA SILVA INÁCIO	XXX.XXX.XX3-33	1,0	Sim	45.171.28.182	
JEFFERSON WILLIAM DE OLIVEIRA	XXX.XXX.XX9-72	1,0	Sim	2804:389:b112:aeb9:1:0:47ec:acb6	
JOEL ALVES DA SILVA	XXX.XXX.XX1-53	1,0	Sim	45.171.28.182	
JOSÉ CARLOS TOZETTO VETTORAZZI	XXX.XXX.XX9-63	1,0	Sim	45.171.28.182	
JOSÉ JORGE SILVA JÚNIOR	XXX.XXX.XX5-54	1,0	Sim	186.248.162.238	
JOSÉ LUZIVAN DE HOLANDA	XXX.XXX.XX4-00	1,0	Sim	2804:214:88e6:866:1859:74b8:6c63:3de	
JÚNIA DARK VIEIRA LELIS LIGÓRIO	XXX.XXX.XX6-85	1,0	Sim	2804:389:b183:a309:1:0:4715:c49e	
LEILIANE FERREIRA SARAIVA	XXX.XXX.XX5-34	1,0	Sim	45.171.28.182	
LEONARDO LÉGORA DE ABREU	XXX.XXX.XX7-43	1,0	Sim	45.171.28.182	
LEONICE PEREIRA DA SILVA	XXX.XXX.XX4-00	1,0	Sim	2804:389:b121:e469:1:0:3fac:16bc	
LETICIA LIS BARSOTI	XXX.XXX.XX9-23	1,0	Sim	189.40.87.50	

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Nome	CPF	Peso voto	Votou	IP/MAC	Grupo votante
LETICIA PALÚ	XXX.XXX.XX1-72	1,0	Sim	45.171.28.182	
LIA MELLO DE ALMEIDA	XXX.XXX.XX9-49	1,0	Sim	2804:214:86ee:6570:1:0:a17:72a8	
LINDOMAR FEITOZA DA HORA	XXX.XXX.XX4-59	1,0	Não		
LISIA HAUSEN GABE	XXX.XXX.XX0-82	1,0	Sim	45.171.28.182	
LITUANIA MUSTAFA PAES DE ALMEIDA	XXX.XXX.XX2-20	1,0	Sim	45.171.28.182	
LOÍDE OLIVEIRA ALVES	XXX.XXX.XX5-88	1,0	Sim	45.171.28.182	
LORENA BAIA DE OLIVEIRA ALENCAR	XXX.XXX.XX1-00	1,0	Sim	45.171.28.182	
LUANA KELLY LIMA SANTANA	XXX.XXX.XX2-49	1,0	Sim	200.208.99.34	
LUCAS SANTOS DE SOUZA	XXX.XXX.XX5-40	1,0	Sim	2804:18:687d:3d9e:7075:abd:49e4:ab41	
LUCIANA RODRIGUES PEREIRA	XXX.XXX.XX6-09	1,0	Sim	45.171.28.182	
LUCIANO BARROS COSTA	XXX.XXX.XX4-70	1,0	Sim	45.171.28.182	
LUCIANO SOARES	XXX.XXX.XX9-00	1,0	Sim	45.171.28.182	
LUIS HENRIQUE DE OLIVERA RODRIGUES	XXX.XXX.XX2-34	1,0	Sim	45.171.28.182	
LUIZ HENRIQUE COSTA	XXX.XXX.XX9-15	1,0	Sim	2804:214:92a6:db2b:186f:57ff:fee9:56d1	
MAGNO LUIZ TEIXEIRA SILVEIRA	XXX.XXX.XX5-91	1,0	Sim	2804:18:7836:7111:1859:c476:5ccb:2966	
MARA RUBIA HAYDEN FREIRE CAMARA	XXX.XXX.XX2-49	1,0	Sim	2804:18:402d:2d01:1:0:916b:7e20	
MARCELO SILVA SILVÉRIO	XXX.XXX.XX6-99	1,0	Sim	2804:389:b183:5db1:1:0:47e3:12c7	
MARCEL PEREIRA DOS SANTOS	XXX.XXX.XX8-71	1,0	Sim	45.171.28.182	
MARCOS ANTONIO RECH	XXX.XXX.XX9-53	1,0	Não		
MARCOS EVANGELISTA CARANHA	XXX.XXX.XX2-34	1,0	Sim	45.171.28.182	

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R$ 259,14	R$ 73,52	R$ 50,33	R$ 13,73	R$ 17,75	R$ 12,34	R$ 5,42	R$ 0,00	R$ 0,00	R$ 432,23

Nome	CPF	Peso voto	Votou	IP/MAC	Grupo votante
MARCOS ROBERTO RODRIGUES DOS SANTOS	XXX.XXX.XX2-87	1,0	Não		
MARIA ANTONIA GARCIA	XXX.XXX.XX8-22	1,0	Sim	2804:389:b120:d9dd:58aa:4a8f:4711:e933	
MARIA CRISTINA RAMIREZ	XXX.XXX.XX1-20	1,0	Sim	45.171.28.182	
MARIA HELENA BRAGA	XXX.XXX.XX6-72	1,0	Sim	2804:18:504c:e986:1:0:9164:13b9	
MARIA JOSÉ MARTINS DE SOUZA	XXX.XXX.XX8-25	1,0	Sim	2804:18:15d:9cb3:1859:c62e:f8d7:52c8	
MARIA JOSÉ SARTÓRIO	XXX.XXX.XX7-91	1,0	Sim	152.255.125.113	
MARIA SORAYA PINHEIRO DE AMORIM	XXX.XXX.XX5-00	1,0	Sim	2804:214:92ae:1a9a:1859:c018:78f7:c96c	
MARSELLHE NOBRE DE CARVALHO	XXX.XXX.XX2-91	1,0	Sim	2804:389:b171:787:542:3c62:8538:ec84	
MASURQUEDE DE AZEVEDO COIMBRA	XXX.XXX.XX0-91	1,0	Sim	2804:389:b126:d598:1:0:4586:ba1e	
MATHEUS NASCIMENTO FUCHINA	XXX.XXX.XX9-60	1,0	Sim	187.25.137.47	
MAURÍCIO SCHULER NIN	XXX.XXX.XX0-04	1,0	Sim	187.69.75.197	
MONALISA QUINTÃO CHAMBELLA	XXX.XXX.XX7-00	1,0	Sim	45.171.28.182	
MÔNICA HELENA SANTOS SOUSA	XXX.XXX.XX3-15	1,0	Sim	45.171.28.182	
MURILO CEREDA DA SILVA	XXX.XXX.XX1-47	1,0	Sim	45.171.28.182	
NATALIA AZEREDO PAIM	XXX.XXX.XX0-58	1,0	Sim	2804:389:b123:7a91:b1ec:f1a:4775:e0fa	
NILSON HIDEKI NISHIDA	XXX.XXX.XX9-51	1,0	Sim	2804:18:4823:155b:ac52:51ff:fee4:660f	
OLNIVANIA M. CARDOZO ALMEIDA	XXX.XXX.XX3-59	1,0	Sim	177.47.39.178	
OTÁVIO AMÉRICO AUGUSTIN	XXX.XXX.XX0-19	1,0	Sim	45.171.28.182	

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Nome	CPF	Peso voto	Votou	IP/MAC	Grupo votante
OTAVIO EUTIQUIO VASCONCELOS PINHEIRO DA SILVA	XXX.XXX.XX2-34	1,0	Sim	2804:389:b163:c7ea:20b6:5cff:fe94:c20d	
PATRÍCIA AVELAR NAVARRO	XXX.XXX.XX4-53	1,0	Sim	2804:389:b172:23c6:f49f:77ff:fe5b:187	
PAULA PAIS DOS SANTOS	XXX.XXX.XX8-18	1,0	Sim	2804:18:504d:ac51:1:0:9171:706e	
PAULO FELIX DE ALMEIDA PENA	XXX.XXX.XX6-72	1,0	Não		
PAULO JOSE TEIXEIRA	XXX.XXX.XX8-54	1,0	Sim	45.171.28.182	
PEDRO ARANTES DE ASSUNÇÃO	XXX.XXX.XX2-14	1,0	Sim	2804:389:b110:4457:8c06:6c5a:f6a4:a260	
PRISCILA VAUTIER	XXX.XXX.XX8-24	1,0	Sim	45.171.28.182	
QUÊNNIA GARCIA MORENO RESENDE	XXX.XXX.XX5-29	1,0	Sim	189.96.25.236	
RAMON FRANCESCO DE ARAÚJO PEIXOTO	XXX.XXX.XX6-27	1,0	Sim	2804:389:b02b:c92b:0:74:e163:7101	
RAQUEL DENISE PETRY	XXX.XXX.XX0-87	1,0	Sim	2804:389:b181:e10:1:0:3842:df9d	
RAQUEL REZENDE MENEZES	XXX.XXX.XX6-12	1,0	Não		
RATSA FERRAZ AGUIAR	XXX.XXX.XX6-91	1,0	Sim	2804:18:4011:5ddb:e9f3:44c1:cd2d:7057	
RENAN DE FIGUEIREDO FERRAZ	XXX.XXX.XX4-60	1,0	Sim	45.171.28.182	
RENATA TEREZA GONÇALVES PEREIRA	XXX.XXX.XX8-18	1,0	Sim	179.226.160.19	
RICARDO SOUSA MANZI	XXX.XXX.XX1-72	1,0	Não		
RILKE NOVATO PÚBLIO	XXX.XXX.XX6-68	1,0	Sim	45.171.28.182	
ROBERT DOS SANTOS SOUSA	XXX.XXX.XX3-73	1,0	Sim	45.171.28.182	
ROBERTO GALDINO DA SILVA	XXX.XXX.XX4-91	1,0	Não		
ROBERTO PELLEGRINI	XXX.XXX.XX8-15	1,0	Sim	191.38.12.201	

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Nome	CPF	Peso voto	Votou	IP/MAC	Grupo votante
ROGERIO ANTONIO DE FREITAS BICHIAROV	XXX.XXX.XX8-12	1,0	Sim	45.171.28.182	
RONALD FERREIRA DOS SANTOS	XXX.XXX.XX9-15	1,0	Sim	2804:18:482f:290b:8970:efbe:708c:4c52	
RONIERY LIMA DE SOUZA	XXX.XXX.XX6-84	1,0	Não		
ROSÁLIA DOS SANTOS RODRIGUES	XXX.XXX.XX3-52	1,0	Sim	170.247.31.201	
SANDRA MARIA ALVES DA COSTA	XXX.XXX.XX1-00	1,0	Sim	2a04:4e41:6301:13ca::f98c:c3ca	
SARA KANTER PINTO DE SOUZA	XXX.XXX.XX0-91	1,0	Sim	45.171.28.182	
SEBASTIÃO FORTUNATO DE FARIA FILHO	XXX.XXX.XX6-72	1,0	Sim	2804:18:402f:ead9:1:0:9175:1d0f	
SEBASTIÃO JOSÉ FERREIRA	XXX.XXX.XX6-00	1,0	Sim	2804:18:5073:fab:8da1:658e:69cc:2d86	
SÉRGIO LUIS GOMES DA SILVA	XXX.XXX.XX4-49	1,0	Sim	45.171.28.182	
SERGIO SATORU MORI	XXX.XXX.XX9-00	1,0	Sim	191.96.5.67	
SILVIO ROBERTO DO BOMFIM CARVALHO	XXX.XXX.XX5-20	1,0	Sim	2804:389:810e:fe1:1:0:439c:22fe	
SORAYA BARRIONUEVO FRANZENER	XXX.XXX.XX9-57	1,0	Não		
SUSANA DE SOUSA ALVES	XXX.XXX.XX3-15	1,0	Não		
SUSANA YASKARA BORCHES HERRERA	XXX.XXX.XX8-89	1,0	Sim	179.84.147.60	
SYLVANIA RODRIGUES DOS SANTOS	XXX.XXX.XX7-02	1,0	Sim	186.248.162.238	
TALITA BARBOSA GOMES	XXX.XXX.XX7-00	1,0	Não		
TANIA MARIA LEMOS MOUÇO	XXX.XXX.XX7-15	1,0	Sim	2a09:bac2:e4d:188c::272:7d	
TAYRA BARRETO CUNHA	XXX.XXX.XX5-08	1,0	Sim	2804:18:6872:d251:4d3e:9a7d:a1d7:aa65	

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Nome	CPF	Peso voto	Votou	IP/MAC	Grupo votante
TAYSA CANTANHEDE CARVALHO	XXX.XXX.XX3-51	1,0	Sim	2804:214:92a7:d405:fce0:a851:1660:69de	
TEREZA EMIKO MAMOTO	XXX.XXX.XX9-00	1,0	Sim	152.255.113.91	
ULISSES NOGUEIRA DE AGUIAR	XXX.XXX.XX3-06	1,0	Sim	45.171.28.182	
VALDIR LEITE DE ARAUJO	XXX.XXX.XX7-16	1,0	Não		
VANESSA MARIA CORREA	XXX.XXX.XX9-94	1,0	Sim	2804:389:b181:bb9a:1:0:4570:707	
VINICIUS ANDRÉ BOFF	XXX.XXX.XX9-80	1,0	Sim	45.171.28.182	
VIVIANE ALVES DE OLIVEIRA	XXX.XXX.XX1-68	1,0	Sim	45.171.28.182	
VIVIANE MAURA RUBERT	XXX.XXX.XX0-87	1,0	Sim	2804:389:b131:e958:4c9e:f66a:6ed1:7fb1	
VIVICA KAROLINE DE OLIVEIRA XAVIER	XXX.XXX.XX5-98	1,0	Sim	2804:389:b162:17d:d0fe:d1fd:5328:8564	
WALTOVÂNIO CORDEIRO DE VASCONCELOS	XXX.XXX.XX6-04	1,0	Não		
WILLE MARCIO NASCIMENTO CALAZANZ	XXX.XXX.XX1-87	1,0	Sim	2804:214:92a4:8233:1859:c88b:f3c7:dce2	
YASMINNE DANNAE ROSA ANDRADE	XXX.XXX.XX7-31	1,0	Sim	45.171.28.182	

Relatório emitido em: 08/08/2025 às 12:01

Assinatura do Responsável

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Sistema Electios
Eleições 2025 - FENAFAR

Lista de eleitores aptos

Nome	CPF	Telefone	E-mail	E-mail funcional	Peso voto	Notificado em	Grupo	
ADRIANO DOS ANJOS COSTA	72328266304	(98) 98867-9181	adrianodosanjoscosta1@gmail.com		1,0			
ADRIANO MARTINS FERREIRA	02219376419	(89) 99922-9265	adrianom.f@hotmail.com		1,0			
ADRYELLA DE PAULA FERREIRA LUZ	27559139833	(11) 98981-8581	adryellaluz@yahoo.com.br		1,0			
ALBANO RUBENS DO VALLE VERONA	59614099615	(37) 99986-3630	albanodovalleverona@gmail.com		1,0			
ALBERTO ISSA PUREZA CALLINS	00289182239	(96) 98115-9573	issalberto@hotmail.com		1,0			
ALESSANDRO SIMÕES DE MOURA	82420491300	(85) 98805-9909	asmceara@gmail.com		1,0			
ALEXANDRE CORREIA DOS SANTOS	56335954400	(82) 99625-1833	alexandresantoa57@gmail.com		1,0			
ALEXSANDRA FERRAZ DA ROSA	44151225234	(92) 99152-5271	afrcompras2@gmail.com		1,0			
ALISSON RODRIGO DA SILVA OLIVEIRA	09345994408	(81) 99915-7220	alissonrodrigoo20@gmail.com		1,0			
ALLAN JOHN DE OLIVEIRA MELO	04452072569	(79) 98890-1959	allan.farmaceutico@gmail.com		1,0			

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ALLAN KARDEC DE LIMA	11750678810	(41) 99585-1412	lima.allan@gmail.com		1,0			
ALTAMIRO JOSÉ DOS SANTOS	41502728591	(72) 99966-2317	altamirojose@gmail.com		1,0			
ANA CLAUDIA SILVA NAVARRO	07133834880	(16) 99244-4507	anaclaudianav@gmail.com		1,0			
ANA EMÍLIA AHOUAGI	06851349620	(31) 99738-3038	ana.emilia@pbh.gov.br		1,0			
ANDERSON FREIRE CARNIEL	24865989870	(11) 99205-4723	afcarniel@gmail.com		1,0			
ANDRAWS HANS SALES RAMOS	06186582388	(86) 99907-4819	andrawshanss88@gmail.com		1,0			
ANDRÉ NUNES CAVALCANTE	86840177300	(85) 99992-5654	andrefarma@gmail.com		1,0			
ANDREZA DA SILVA ROCHA	51032058234	(91) 98860-2311	andrezasofia90@yahoo.com.br		1,0			
ANTÔNIO APARECIDO CASARIN	41424719968	(65) 99245-1757	antoniocasarin25@hotmail.com		1,0			
ANTONIO CESAR RODRIGUES GOMES	45993050225	(91) 98832-8287	sinfarpa@gmail.com		1,0			
ANTÔNIO HENRIQUE NASCIMENTO DA SILVA	13188979711	(27) 99278-7379	ahenriquefts@gmail.com		1,0			
ARIEL RIOS REZENDE	96164492572	(77) 98836-4704	arielrezende78@gmail.com		1,0			
BEATRIZ MELIM	06394092967	(48) 98420-6620	beatrizmelimsc@hotmail.com		1,0			
CARLOS ALEXANDRE ALVES DE SILVA	21922188859	(11) 99527-4047	carlosalexxandre@gmail.com		1,0			
CARLOS HENRIQUE ACIOLE TAVARES	00753639416	(82) 99981-9556	odontoceutico@hotmail.com		1,0			
CARLOS JOSÉ MATOS FRANCO	38209012304	(85) 99131-8888	carlos.franco.jm@gmail.com		1,0			
CATARINE BEZERRA CAVALCANTI	08191829746	(21) 97369-5333	cavalcanti.cathy@gmail.com		1,0			
CELIA MACHADO GERVASIO CHAVES	26277000063	(51) 99954-2639	celiagchaves@hotmail.com		1,0			
CLEBER DA CRUZ RODRIGUES DE LIMA	68897146287	(96) 99173-5176	drcleberrodrigues@gmail.com		1,0			
CLOVIS DE SANTANA REIS	92893945520	(71) 99924-3767	clovissreis@gmail.com		1,0			
DALMARE ANDERSON BEZERRA DE OLIVEIRA FALCÃO E SÁ	02842573544	(79) 99158-2221	dalmare.anderson@gmail.com		1,0			
DANIELA SANTOS OLIVEIRA	00558385532	(79) 99990-1253	daniefarma@yahoo.com.br		1,0			
DANIELA SANTOS SILVA FERREIRA DE ALMEIDA	81926740530	(79) 99814-1857	danyfarmaferreira@yahoo.com.br		1,0			

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DANYELLE CRISTINI MARINI	26841520807	(19) 99804-3933	danyelle.marini@crfsp.org.br		1,0			
DEBORA RAYMUNDO MELECCHI	63275643053	(51) 99323-7092	dmelecchi@gmail.com		1,0			
DEICK RODRIGUES QUARESMA	62851110225	(91) 98114-8858	deickrq@gmail.com		1,0			
DENISE BUENO	38471965020	(51) 99968-5262	aquariobueno@gmail.com		1,0			
DEVANIL ROZA FERNANDES	14233711191	(65) 99668-8023	devanil.fernandes40@gmail.com		1,0			
DIEGO GNATTA	00079261035	(54) 98134-5370	diegognatta@gmail.com		1,0			
DIMAS FELIPE DE SOUZA ARAÚJO	01423309499	(81) 99690-5871	dimasfelipe@gmail.com		1,0			
DOUGLAS MACHADO DA SILVA	01714672131	(62) 99285-9154	douglasmachadofarmaceutico@gmail.com		1,0			
EDMAR GODOY VIGGIANO PEREIRA	50006398120	(62) 99811-2909	edmar@crfgo.org.br		1,0			
EDMUNDO TIBÚRCIO FERREIRA ARAÚJO	00390064335	(92) 99105-0085	edmundotiburcio@hotmail.com		1,0			
EDNÉIA DUARTE	03245631677	(65) 99658-7703	edneiaduarte@icloud.com		1,0			
EDSON LUIZ ARAÚJO CAVALHEIRO	59557656034	(51) 99832-3183	edfarma@gmail.com		1,0			
ELIANA CAMARGO DE SOUSA	59176644634	(31) 98534-4930	elianacds1@gmail.com		1,0			
ELINE CRISTINA SOUTO MAIOR BARACHO	00943250498	(82) 99944-8127	elinesoutomaior@gmail.com		1,0			
ELISTER DE OLIVEIRA RODRIGUES	95055673168	(62) 99117-0404	elisteroliveira20@gmail.com		1,0			
ERICA TIE MIAI	06022328802	(11) 99550-1565	erica.miai@sinfar.org.br		1,0			
EXPEDITO ROGILDO CORDEIRO CARLOS	41888847387	(85) 99998-0428	rogildo@unifor.br		1,0			
FÁBIO AUGUSTO DO CARMO SANTANA	00608604992	(41) 98410-7984	fabiosantana23@yahoo.com.br		1,0			
FÁBIO CRISTIANO GARCIA	22319819800	(11) 98447-5428	garciafabiocristiano@gmail.com		1,0			
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Oficial	Estado	Secretaria Fazenda	Reg. Civil	T. Justiça	M. Público	ISS	Condução	Despesas	Total
R$ 259,14	R$ 73,52	R$ 50,33	R$ 13,73	R$ 17,75	R$ 12,34	R$ 5,42	R$ 0,00	R$ 0,00	R$ 432,23

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Total de eleitores aptos: 179

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Total de Eleitores não aptos: 10

Relatório emitido em: 07/08/2025 às 17:50

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Assinatura do Responsável

mercado

Consumidor reage, e PIB da China cresce 5,4% no 1º trimestre

Nelson de Sá

PEQUIM O crescimento do PIB da China no primeiro trimestre fechou em 5,4% em comparação com o período no ano anterior, às vésperas da escalada de tarifas com os Estados Unidos. Economistas ouvidos pela consultoria financeira chinesa Wind e por agências ocidentais projetavam entre 5,1% e 5,2%.

O consumidor chinês foi um dos responsáveis pelo resultado. As vendas no varejo subiram 5,9%, também em comparação com o período no ano anterior, com a alta concentrada em março, o terceiro mês.

Por outro lado, na comparação com o trimestre anterior, o crescimento econômico foi de 1,2% —abaixo do que havia sido registrado no último trimestre do ano passado, de 1,6% em relação ao trimestre anterior.

Os números foram anunciados na manhã desta quarta (16) pelo Escritório Nacional de Estatísticas, que alertou para o "ambiente externo se tornando mais grave e complexo".

Segundo um dos diretores do órgão, Sheng Laiyun, "o impulso para o crescimento da demanda interna é insuficiente, e a base para um crescimento sustentado ainda não está consolidada".

Em 16 de março, a China anunciou um pacote de estímulo ao consumo, com medidas para a renda das famílias e o setor imobiliário, entre outras. Ele deve ser complementado nas próximas semanas por outras ações, agora em debate.

Medidas de incentivo à economia vêm sendo adotadas desde setembro e garantiram a meta de crescimento para o ano, de 5%. Para 2025, a meta é novamente de cerca de 5%, percentual ameaçado pelas restrições no comércio com os EUA.

Shen creditou o resultado "bom e firme" do primeiro trimestre em parte à inovação, que representa "um papel cada vez mais protagonista" na economia chinesa.

Além do consumo, outro ponto que pesou para os 5,4% foi a produção industrial, que saltou 7,7% em março, ano a ano, no melhor resultado desde junho de 2021.

No início da semana, a Alfândega chinesa havia informado um crescimento de 12,4% nas exportações em março, ano a ano. Sheng creditou esse resultado à resiliência da economia do país.

CONSÓRCIO INTERMUNICIPAL MULTISSETORIAL DO VALE DO PIRANGA

AVISO DE LICITAÇÃO
PREGÃO ELETRÔNICO Nº 1/2025

Processo Licitatório nº 07.0014.2025.14

Consórcio Intermunicipal Multissetorial do Vale do Piranga - CIMVALPI, torna pública a abertura do Processo Licitatório nº 07.0016.2025.14 - Pregão Eletrônico 009/2025. Objeto: Registro de preço para eventual e futura contratação de empresa especializada para o fornecimento de kits de materiais escolares para o ano letivo de 2025. A data da sessão pública será: 10/02/2025, às 09:00h, horário de Brasília - DF, no sítio eletrônico www.licitardigital.com.br. O cadastramento de propostas inicia-se quando for publicado na plataforma e encerra-se, automaticamente, na data e hora marcadas para a realização da sessão do pregão. O Edital na íntegra, poderá ser obtido nos sites www.licitardigital.com.br ou www.cimvalpi.mg.gov.br. Maiores informações poderão ser obtidas na sede do CIMVALPI, na Rua Jaime Pereira, 127, ou através da plataforma www.licitardigital.com.br

Ponte Nova, 24 de janeiro de 2025.
MICHELE AP. SILVA DE JESUS
Agente de Contratação

FEDERAÇÃO DAS EMPRESAS DE TRANSPORTE DE PASSAGEIROS DOS ESTADOS DO PARANÁ E SANTA CATARINA

CNPJ/MF 82.703.042/0001-53

EDITAL DE CONVOCAÇÃO
ASSEMBLEIA GERAL EXTRAORDINÁRIA

(AGE) DO CONSELHO DE REPRESENTANTES. Ficam convocados os membros do Conselho de Representantes, composto pelos delegados nomeados pelos Sindicatos filiados à FEPASC, para se reunirem virtualmente em AGE, em 03/02/2025, às 10h, em primeira convocação, e, nos termos dos artigos 23º, I, 24º, caput, 25º, §1º e 46º do Estatuto, às 10:30h, em segunda convocação, para deliberarem sobre a seguinte Ordem do Dia: para adequar a redação aos termos da Portaria/MTE nº 1.472/2025, ratificar a ata da AGE realizada em 18/05/2023, que teve por objeto a eleição dos membros da Diretoria, do Conselho Fiscal e dos delegados representantes junto à Confederação Nacional de Transportes. O link para acessar a videoconferência será enviado, por e-mail, aos membros do Conselho de Representantes em até 30 (trinta) minutos antes do início da AGE.

Curitiba, 24 de janeiro de 2025
FELIPE BUSNARDO GUUN
Presidente da Federação

FEDERAÇÃO NACIONAL DOS FARMACÊUTICOS

EDITAL DE CONVOCAÇÃO
11º CONGRESSO DA FEDERAÇÃO NACIONAL DOS FARMACÊUTICOS

A Federação Nacional dos Farmacêuticos - FENAFAR, pessoa jurídica de direito privado, inscrita no CNPJ nº 00679357/0001- 48, com sede à rua Barão de Itapetininga, 255, 1º andar, sala 302, CEP 01042-010, São Paulo/SP, entidade de representação sindical de 2º grau da categoria dos farmacêuticos; com fundamento em seu Estatuto Social, torna público que o Conselho de Representantes da Fenafar, reunido no dia 23 e 24 de outubro de 2024, de forma presencial, CONVOCOU o 11º Congresso da FENAFAR para realizar-se entre os dias 05, 06, 07 e 08 de agosto de 2025 no Centro de Convenções da Universidade Federal de Ouro Preto, na cidade de Ouro Preto/MG, e ainda que o mesmo Conselho de Representantes designou a Comissão Organizadora do 11º Congresso, a Comissão Eleitoral e aprovou o Regulamento Eleitoral. O Congresso delibera sobre as disposições contidas no Art. 12 do Estatuto da entidade, que dispõe: "Art. 12 - O Congresso da FENAFAR é o órgão máximo de deliberação da categoria farmacêutica, sendo composto por delegados eleitos na sua base e observadores convidados. Parágrafo primeiro - o Congresso da FENAFAR delibera sobre: I - Alterações deste Estatuto; II - A linha política e organizativa da Entidade; III - Os planos de ação sindical e de luta para os trabalhadores representados considerando a situação política, social e econômica do país; IV- Eleição da Diretoria da FENAFAR e Conselho Fiscal, conforme normas estabelecidas no Regulamento Eleitoral. Parágrafo segundo: é dever do Congresso da FENAFAR promover a solidariedade nacional e internacional da classe trabalhadora". A Fenafar informa ainda que a Eleição deverá ser convocada pelo Presidente com pelo menos 90 dias de antecedência, da qual será publicado Edital específico, com as informações pertinentes a este processo eleitoral. Informa ainda que outras informações serão oportunamente fornecidas tais como o local, a programação etc., e que quaisquer informações sobre o 11º Congresso e a Eleição poderão ser obtidas na sede da entidade junto à sua secretaria e através do sítio eletrônico da FENAFAR.

São Paulo, 24 de janeiro de 2025.
FÁBIO JOSÉ BASÍLIO
Presidente da Federação Nacional dos Farmacêuticos

FEDERAÇÃO DOS TRABALHADORES NO SERVIÇO PÚBLICO MUNICIPAL DO ESTADO DA PARAÍBA

EDITAL DE CONVOCAÇÃO
ASSEMBLÉIA GERAL EXTRAORDINÁRIA DE FUNDAÇÃO ELEIÇÕES GERAIS E POSSE

Pelo presente edital, o Presidente da FEDERAÇÃO DOS TRABALHADORES NO SERVIÇO PÚBLICO MUNICIPAL DO ESTADO DA PARAÍBA - FETAM/PB, Senhor, Serildo Henrique da Silva e membro da Comissão de Pró-Fundação, brasileiro, professor, divorciado, categoria dos servidores públicos municipais, residente e domiciliado na Rua São Luis, nº 14, Bairro do Cruzeiro, Cidade de Itapororoca/PB, neste ato no exercício do cargo que lhe foi conferido, convoca pelo presente edital de acordo com a legislação vigente, toda a categoria dos Servidores Públicos Municipais da Educação de Areia/PB, para participarem da Assembleia Geral Extraordinária de Fundação do Sindicato dos Servidores Públicos Municipais da Educação de Areia/PB - SINDSPMEA/PB, a ser realizada de forma presencial, no dia de 15 de fevereiro de 2025, às 9h00 em primeira convocação e às 9h30 em segunda convocação com qualquer número de participantes nas dependências da sede da Associação dos Servidores Públicos do Município de Areia/PB, situado na Rua João Batista, nº 50, Areia/PB para tratar da seguinte ordem do dia: 1 - Fundação do Sindicato dos Servidores Públicos Municipais da Educação de Areia/PB - SINDSPMEA/PB; 2 - Aprovação do Estatuto Social do SINDSPMEA/PB; 3 - Eleição e Posse da Diretoria Executiva e Conselho Fiscal do SINDSPMEA/PB, para o Quadriênio 2025/2029; 4 - Aprovação do valor da contribuição da mensalidade dos associados; 5 - Autorizar à Diretoria eleita para filiar o SINDSPMEA/PB as entidades representativas de Graus superiores, CUT - Central Única dos Trabalhadores, CONFETAM E FETAM/PB e; 6 - Outros assuntos pertinentes a Fundação da Entidade e encaminhamentos.

João Pessoa/PB, 24 de janeiro 2025
SERILDO HENRIQUE DA SILVA

FUNDAÇÃO DE DESENVOLVIMENTO CIENTÍFICO E CULTURAL

AVISO DE ADJUDICAÇÃO

RATIFICAÇÃO DE CONTRATAÇÃO DIRETA - Processo nº 60798/2024

A Fundação de Desenvolvimento Científico e Cultural - FUNDECC, inscrita no CNPJ sob o n. 07.906.323/0001-07, representada por sua Diretora Executiva, ratifica a contratação direta dos bens objetos da Seleção Pública nº 11/2024 julgada deserta por ausência de interessados, aplicando-se o disposto no art. 9º, §3º, do Decreto n. 8241/2014, mantendo-se as mesmas condições previstas no Edital. Diante do Processo no Campo nº 60798/2024, adjudica o objeto à empresa CREACOM INFORMÁTICA COMÉRCIO E SERVIÇOS LTDA - CNPJ 17.603.733/0001-13, no valor de R$54.641,30, regularmente habilitada.

Lavras-MG, 10 de janeiro de 2025.
ANA PAULA PROVESAN MELCHIOR
Diretora Executiva

FUNDAÇÃO ESCOLA POLITÉCNICA DA BAHIA

EXTRATO DE INEXIGIBILIDADE DE LICITAÇÃO

Inexigibilidade nº 008/2024. Projeto: FEP UFRB BNB CONVÊNIO FUNDECI 2024.0005. Contratada: OMV do Brasil Tecnologia e Comercio LTDA - CNPJ: 35.252.465/0001-07. Objeto: aquisição ultrassom com doppler e um transdutor para avaliação de carcaça. Fundamento Legal: Art. 74, inciso I da Lei nº 14.133/2021. Parecer de inexigibilidade exarado 43/2024 emitido por HUMBERTO COSTA JUNIOR E GABRIEL MIRANDA GALLO ADVOGADOS ASSOCIADOS. Valor: R$ 145.000,00 (cento e quarenta e cinco mil reais) ASS: Yuri Guarnieri Pereira, CAR (Diretor Geral).

FUNDAÇÃO NORTE RIO-GRANDENSE DE PESQUISA E CULTURA

EXTRATO DE DISPENSA DE LICITAÇÃO

Processo nº 14000029. Contratante: Fundação Norte-rio-grandense de Pesquisa e Cultura (FUNPEC). Contratada: 24.398.681/0001-02 - ARPLAN ENGENHARIA TERMICA LTDA. Objeto: SERVIÇO DE ADEQUAÇÃO DO SISTEMA DE HVAC. Valor: R$ 85.992,04 (OITENTA E CINCO MIL E NOVECENTOS E NOVENTA E DOIS REAIS E QUATRO CENTAVOS), possibilidade de contratação direta, em respeito ao exposto no art. 26, VI, do Decreto nº 8.241/14, por dispensa de licitação. Autorização: Francisco Alexandre M. M. Costa - Coordenador de grupo de compras. Ratificação: Luiz Cledston de Noronha Freire - gerente de materiais. Natal/RN, 22 de janeiro de 2025.

FUNDAÇÃO SÃO FRANCISCO XAVIER

AVISOS DE LICITAÇÃO
PREGÃO ELETRÔNICO PÚBLICO HMC Nº 423/2025

Encontra-se aberto na Fundação São Francisco Xavier Hospital Instrumento Convocatório na modalidade Pregão Eletrônico Público HMC N.º 423/2025, para Aquisição de Faca Cirúrgico. Acolhimento das propostas: 24/01/25 a 05/02/25. Abertura das propostas: 05/02/25 às 07:30h, início da disputa: 05/02/25 às 09:00h. O presente instrumento Convocatório estará disponível na íntegra no site da plataforma eletrônica Publinexo: www.publinexo.com.br/publico

PREGÃO ELETRÔNICO PÚBLICO HMC Nº 424/2025

Encontra-se aberto na Fundação São Francisco Xavier Hospital Instrumento Convocatório na modalidade Pregão Eletrônico Público HMC N.º 424/2025, para Aquisição de Aparelho Raio-x Móvel Tipo Arco Cirúrgico. Acolhimento das propostas: 24/01/25 à 05/02/25. Abertura das propostas: 05/02/25 às 07:30h, início da disputa: 05/02/25 às 14:00h. O presente instrumento Convocatório estará disponível na íntegra no site da plataforma eletrônica Publinexo: www.publinexo.com.br/publico.

Ipatinga, 22 de janeiro de 2025
CRISTIANE CARVALHO
Pregoeira

FUNDAÇÃO DA UNIVERSIDADE FEDERAL DO PARANÁ

AVISOS DE LICITAÇÃO
PREGÕES ELETRÔNICOS

Edital nº 3896/2024 Objeto: Aquisição de Reinpedância Tetrapolar Sawy, para atender a demanda do Projeto nº 3963 - Integralização da Extensão na UFPR. Acolhimento Propostas: até 06/02/2025 às 09:00min. Data do Pregão: 06/02/2025 às 09:30min. O edital está disponível no site www.bll.org.br ou bllcompras.com. Dúvidas entrar em contato pelo e-mail: licitacao@fuspar.ufpr.br.

Edital nº 3818/2024 Objeto: Aquisição de Cadeira Fisa de Poliprolileno, para atender a demanda do Projeto nº 3963 - Integralização da Extensão na UFPR. Acolhimento Propostas: até 06/02/2025 às 09:00min. Data do Pregão: 06/02/2025 às 09:30min. O edital está disponível no site www.bll.org.br ou bllcompras.com. Dúvidas entrar em contato pelo e-mail: licitacao@fuspar.ufpr.br.

Edital nº 3806/2024 Objeto: Aquisição de Kit Touca EGG, para atender a demanda do Projeto nº 3963 - Integralização da Extensão na UFPR. Acolhimento Propostas: até 06/02/2025 às 09:00min. Data do Pregão: 06/02/2025 às 09:30min. O edital está disponível no site www.bll.org.br ou bllcompras.com. Dúvidas entrar em contato pelo e-mail: licitacao@fuspar.ufpr.br.

Edital nº 3821/2024 Objeto: Aquisição de HD Externo Portátil 2TB, para atender a demanda do Projeto nº 3963 - Integralização da Extensão na UFPR. Acolhimento Propostas: até 06/02/2025 às 09:00min. Data do Pregão: 06/02/2025 às 09:30min. O edital está disponível no site www.bll.org.br ou bllcompras.com. Dúvidas entrar em contato pelo e-mail: licitacao@fuspar.ufpr.br.

MARCIA DE JESUS DE MEIRA MORILHAS
Pregoeira

FUNDAÇÃO UNIVERSIDADE PARA O DESENVOLVIMENTO DO ALTO VALE DO ITAJAÍ

CNPJ 85.786.621/0001-97

AVISO
REGISTRO DE DIPLOMAS

Para fins do disposto no art. 21 da portaria MEC Nº 1.095, de 25 de outubro de 2018, esta instituição de Educação Superior informa que foram registrados 3 (três) diplomas no período de 31/10/2024 a 31/12/2024, no seguinte livro de registro e sequência numérica: Livro 23, Registro de 587 a 589.

A relação dos diplomas registrados poderá ser consultada em até ninta dias, no endereço https://www.unidavi.edu.br/)

Rio do Sul, 15 de janeiro de 2025
ALCIR TEIXEIRA
Reitor

PROCURAÇÃO *ad judicia*

FEDERAÇÃO NACIONAL DOS FARMACÊUTICOS (FENAFAR), pessoa jurídica de direito privado, sem fins lucrativos, constituída na forma da lei, registrada no CNPJ sob o n°00.679.357/0001-48, com sede na Rua: Barão de Itapetininga nº 255, 3º andar sala 302, Centro - São Paulo – SP, CEP:01042-001, na pessoa de seu representante nos termos de seu Estatuto Social, por seu Presidente, **Fábio José Basilio**, brasileiro, casado, Farmacêutico, RG n°3207835 emitido pelo SSP-GO, e inscrito no CPF n°830.864.801.06, vem pelo presente instrumento outorgar procuração *ad* judicia à advogada **SUSANA RODRIGUES CAVALCANTI VAN DER PLOEG**, inscrita no CPF 013.497.254-63 e na **OAB/MG 181.599**, com escritório na Avenida Presidente Vargas, 446, 13º andar, Centro - Rio de Janeiro - RJ, CEP 20071-907, concedendo-lhe poderes da cláusula *ad judicia et extra*, inclusive substabelecer com reserva de poderes, especificamente para apresentação de subsídio ao exame técnico e/ou processo administrativo de nulidade perante o INPI - Instituto Nacional da Propriedade Industrial relacionado à patente de invenção **BR112024010162-2**.

São Paulo, 25 de novembro de 2025.

FEDERACAO NACIONAL DOS FARMACEUTICOS:00679357000148

Assinado de forma digital por FEDERACAO NACIONAL DOS FARMACEUTICOS:00679357000148
Dados: 2025.11.27 09:53:24 -03'00'

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Fábio José Basílio

Presidente da Fenafar

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Data: 27/11/2025 11:23:58-0300
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ESTATUTO - FÓRUM ONG AIDS RS

CAPÍTULO I
DA DENOMINAÇÃO, SEDE E FINS

Art 1º O Fórum ong aids RS, fundado em 28 de agosto de 1999, com sede e foro em Porto Alegre, capital do Rio Grande do Sul, é uma Associação civil, privada, autônoma, sem vinculação político-partidária, social e / ou religiosa, sem fins econômicos e de duração indeterminada.
Parágrafo único: O Fórum não distribui a Dirigentes, Coordenadores, Associados, Instituidores, Credenciados, Conselheiros, Benfeitores ou Mantenedores, qualquer parcela de seu patrimônio ou de suas rendas, a título de lucro ou participação no seu resultado.

Art 2º O Fórum ong aids RS é uma articulação Estadual de organizações da sociedade civil que atuam no âmbito da síndrome da imunodeficiência adquirida (aids), e suas implicações.
Parágrafo único: A missão do Fórum ong aids RS é ampliar e articular políticas de prevenção e assistência às DST/HIV/aids e suas coinfecções, bem como colaborar no fortalecimento político das instituições que atuam no âmbito da aids no Rio Grande do Sul, incluindo o acesso aos direitos humanos e justiça social.

Art 3º São objetivos do Fórum ong aids RS:
I- Incentivar o intercâmbio e interajuda entre as associações e movimentos;
II- Analisar, incentivar e promover campanhas de prevenção, apoio e educação;
III- Orientar, acompanhar e denunciar qualquer tipo de violação das leis vigentes que prejudiquem os direitos e os deveres das associações que participam, ou não, do Fórum ong aids RS;
IV- Elaborar propostas conjuntas, visando fortalecer a ação das Instituições e movimentos sociais que atuam na luta contra a aids e suas coinfecções, no estado do Rio Grande do Sul, perante as autoridades públicas, civis e religiosas;
V- Influir na legislação pertinente no sentido de conquistar e assegurar novos direitos e/ou alterar dispositivos contrários ou prejudiciais à prevenção das DST/HIV/aids e suas coinfecções, bem como a assistência as pessoas infectadas pelo HIV/aids;
VI- Intervir e participar no processo de formulação de políticas públicas de saúde para que sejam definidas políticas de prevenção e controle da aids, bem como de assistência as pessoas que vivem com HIV/aids;
VII- Incentivar a participação das Instituições associadas nos Conselhos Municipais e Estaduais de Saúde, Assistência Social, Educação, Criança e Adolescente, Idosos, Direitos Humanos e Cidadania e outras instâncias deliberativas e nas comissões Municipais, Estadual e Nacional de DST/aids e outras instâncias consultivas, a fim de fortalecer o papel político-social das Instituições no desenvolvimento do controle social;
VIII- Denunciar todas as formas de omissão, transgressão e violação dos direitos humanos, civis, políticos e sociais, resultados de discriminação as pessoas que vivem com HIV/aids e buscar mecanismos para responsabilizar e punir os (as) infratores (as) de tais atos;
IX- Apoiar e repercutir as ações das Instituições associadas, sempre que estas coincidirem com os princípios do coletivo do Fórum, respeitando suas identidades, autonomia e dinâmicas próprias de funcionamento;
X- Divulgar informações e incentivar / promover ações (palestras, seminários, cursos, oficinas, assessorias e outros eventos) que visem a sustentabilidade das Instituições e seu desenvolvimento técnico e político.
XI- Promover campanhas e outros eventos com finalidade de levantar recursos que possibilitem a consecução da missão da Associação, bem como o fortalecimento político e técnico;
XII- Entrar em contato, desenvolver ações conjunta com entidades civis, públicas ou privadas, nacionais ou internacionais, para viabilizar o cumprimento dos objetivos;
XIII- Buscar financiamentos que propiciem a execução das atividades e ações, visando garantir o alcance da missão.
Parágrafo único – Para cumprir seu propósito, o Fórum ong aids RS atuará por meio da execução direta ou indireta de projetos, programas ou planos de ações, ou execução de ações e atividades de apoio a outras organizações e a órgãos do setor público que atuam em áreas afins.

CAPÍTULO II
DOS ASSOCIADOS, DIREITOS E DEVERES

Art 4º Poderão associar-se ao Fórum ong aids RS as Instituições, Redes e Movimentos que atuam no âmbito da aids, apresentando os seguintes documentos:
a) ata de fundação da Instituição;
b) ata de posse da atual Diretoria;
c) estatuto;
d) c n p j ;

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e) ofício solicitando adesão indicando um representante titular e um suplente, assinado pela coordenação da instituição
§ 1º: Em se tratando de Movimentos ou Redes não institucionalizados, esses poderão participar do Fórum, com um representante do seu coletivo, e mediante apresentação de ata de eleição de reunião do seu coletivo. § 2º - Os interessados em associar-se ao Fórum ong aids RS terão o prazo máximo de 06 (seis) meses para regularização de sua situação jurídica dentro dos critérios supramencionados.

Art 5º O Fórum ong aids RS se comporá e funcionará com a participação de pelo menos um representante titular – ou seu suplente – de cada Instituição a ele associado.
I – somente terá direito a voto os representantes titulares ou, na sua ausência, os suplentes das Instituições associadas.
II – os representantes titulares e suplentes deverão defender posicionamentos de suas Instituições, responder por deliberações defendidas nos encontros do Fórum ong aids RS, bem como repassar as informações, propostas e encaminhamentos para os membros de suas organizações.
III – o Fórum ong aids RS está aberto à participação de qualquer pessoa física ou jurídica, interessada em colaborar para o crescimento do movimento de luta contra as DST/HIV/aids garantindo, no entanto, o direito a voto somente as Instituições associadas.
IV – em situações especiais, havendo interesse, o Fórum ong aids do RS poderá convidar profissionais ou representante de Órgãos, Instituições , Conselhos, Câmaras Éticas e Técnicas e outros que possam contribuir com os objetivos definidos neste estatuto, bem como auxiliar na execução da missão.
V – quando houver ações ou projetos em nome do Fórum ong aids RS, envolvendo recursos financeiros, cabe à Coordenação, o gerenciamento e a prestação de contas dos mesmos.

Art 6º São direitos dos associados, em dia com seus deveres:
a) participar das AssembleiaAssembleias
b) participar de todas as atividades a que esteja o Fórum ong aids RS direta ou indiretamente ligado;
c) ter acesso às atas de reuniões e Assembleias e aos livros contábeis
d) representar o Fórum ong aids RS, desde que autorizado pela Coordenação, em contatos com o público e com outras Instituições;
e) votar e ser votado em indicações para representações e participações.
Parágrafo Único: O direito a ser votado para os cargos que compõem a Coordenação do Fórum é privativo das Instituições associadas.

Art 7º São deveres dos associados:
a) respeitar, cumprir e fazer cumprir o estatuto e demais atos normativos do Fórum ong aids RS;
b) zelar pelo nome e imagem do Fórum ong aids RS, seu patrimônio e empenhar-se pela consecução de seus objetivos;
c) acatar os atos e decisões dos órgãos diretivos;
d) exercer o cargo para o qual for eleito, salvo se houver motivo de força maior, plenamente justificável;
e) manter-se informado e prestar informações ao público em geral sobre as formas de infecção e meios de prevenção das DST/HIV/aids e suas coinfecções, sempre que possível;
f) estimular atitudes que neutralizem o preconceito e a discriminação social às pessoas que vivem com HIV/aids e suas coinfecções;
g) denunciar à Coordenação qualquer atitude individual, coletiva ou institucional que seja lesiva aos direitos humanos das pessoas que vivem com HIV/aids;
h) guardar sigilo ético sobre informações, nomes, dados pessoais que venha a receber sobre as pessoas que vivem com HIV/aids;

Art 8º Os associados não respondem, individual ou subsidiariamente pelas obrigações sociais do Fórum ong aids RS.
Parágrafo único: Não há entre as Instituições associadas, direitos e obrigações recíprocos.

CAPÍTULO III
DAS PENALIDADES

Art 9º Os associados que infringirem este Estatuto e as demais normas internas estarão sujeitos às seguintes penalidades:
I. advertência escrita;
II. Suspensão de 15 (quinze) dias a 12 (doze) meses;
III. Exclusão
Parágrafo único – No caso de aplicação das penalidades dos incisos "II" e "III" desse artigo, o associado poderá interpor recurso a Assembleia Ordinária no prazo de 15 dias, dirigido a Coordenação que deverá

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convocar uma Assembleia nos termos e prazos determinados neste estatuto, contado da data em que teve ciência da penalidade, devendo, enquanto pendente a decisão, permanecer afastado da Instituição.

CAPÍTULO IV
DOS ÓRGÃOS CONSTITUITIVOS DO FÓRUM ONG AIDS RS

Art 10 São órgãos constitutivos do FÓRUM ONG aids RS:
I – Assembleia Ordinária
II – Coordenação
III - Conselho

SEÇÃO I
DA ASSEMBLEIA GERAL

Art 11 A Assembleia Ordinária é o órgão supremo do Fórum ong aids RS, dentro dos limites deste estatuto, para tomar toda e qualquer decisão, sendo para tanto soberana, reunindo-se ordinariamente uma vez por ano, em local determinado pela Coordenação, e convocada com antecedência mínima de 30 (trinta) dias. Poderá reunir-se extraordinariamente quando convocada pela Coordenação ou por 1/5 (um quinto) dos associados, obedecendo a antecedência mínima de 10 (dez) dias.
§ 1º Na realização da Assembleia Ordinária seguir-se-ão as seguintes normas:
a) instalar-se-á em primeira chamada com a presença mínima de 2/3 (dois terços) dos associados ou, em segunda chamada, com qualquer número de associados presentes, sendo as deliberações tomadas pela aprovação de maioria simples;
b) será dirigida por um membro da Coordenação;
c) a própria Assembleia decidirá sobre as normas específicas para o seu funcionamento.
§ 2º A Assembleia extraordinária será realizada sempre que algum assunto urgente de interesse social o exija, inclusive para eleger vacâncias de cargos da Coordenação e do Conselho.
§ 3º Na Assembleia ordinária será proibido o voto por representação
§ 4º A convocação das Assembleias gerais ordinárias e extraordinárias será feita através de correspondência para as Instituições associadas, podendo ser por meio eletrônico.

Art. 12 Em especial compete à Assembleia Ordinária:
I - Eleger a Coordenação e o Conselho;
II - Destituir a Coordenação e o Conselho;
III - Aprovar a escrituração contábil, balanços anuais e planos de trabalho;
IV -Realizar e aprovar alteração estatutária.
Parágrafo único: Para aprovar alteração no Estatuto e destituir a Coordenação é necessário o voto concorde de 2/3 dos associados presentes à Assembleia convocada especialmente para este fim, não podendo esta deliberar em 1ª convocação sem a maioria absoluta dos associados e nas convocações seguintes com menos de 1/3 dos associados.

SEÇÃO II
DA COORDENAÇÃO

Art 13 A Coordenação do Fórum ong aids RS é o órgão deliberativo e normativo no intervalo das Assembleias e com funções executivas através de seus membros; será eleita por voto direto, durante a Assembleia geral ordinária dos associados, e será constituída de três representantes titulares e três suplentes das Instituições associadas a saber :
I - Coordenação Técnica
II - Coordenação Executiva
III - Coordenação Financeira
§ 1º A duração do mandato dos membros da Coordenação é de 03 (três) anos renovado em 1/3 a cada ano, podendo cada um dos seus membros ser reeleito ou eleito mais de uma vez para outro cargo, em períodos consecutivos, desde que sujeitos a processo eleitoral. § 2º A posse da Coordenação dar-se-á após o término do ato eleitoral.
§ 3º Os membros da Coordenação são voluntários e não receberão, sob título algum remuneração por suas funções diretivas do Fórum ong aids RS.
§ 4º **Compete a Coordenação**:
a) Representar o Fórum ong aids RS – ativa, passiva, judicial e extrajudicialmente;
b) Reunir-se pelo menos uma vez ao mês;
c) Cumprir e fazer cumprir este Estatuto e Regimento Interno;
d) Interpretar e fiscalizar a observância do Estatuto e as decisões da Assembleia Geral;

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e) Redigir, submeter à aprovação da Assembleia Geral Ordinária e por em execução o plano de ação para cada exercício;
f) Aprovar balancetes anuais;
g) Autorizar a celebração de contratos e distratos;
h) Aceitar subvenções, doações, donativos e legados;
i) Aplicar os fundos sociais;
j) Autorizar operações de crédito e a compra de títulos, móveis e imóveis;
k) Gerir bens patrimoniais;
l) Apresentar à Assembleia geral ordinária o balanço do exercício anterior e o orçamento do exercício futuro para aprovação;
m) Convocar Assembleia Geral;
n) Autorizar despesas orçamentárias e extraordinárias;
o) Tomar conhecimento e apreciar os atos dos seus, praticados no desempenho de suas funções;
p) Apreciar e deliberar sobre os planos de trabalho do Fórum ong aids RS;
q) Apreciar e deliberar sobre os relatórios do Fórum ong aids RS.

§ 5º **Em especial compete a Coordenação Técnica**
a) Convocar as Assembleias Gerais;
b) Assinar e rubricar todos os livros do Fórum ong aids RS;
c) Representar o Fórum ong aids RS nas suas relações externas ou designar associados para representá-lo nesta função;
d) Defender, perante as autoridades, os interesses do Fórum ong/aids RS, assim como representá-lo em juízo;
e) Constituir advogado e acompanhar as causas judiciais do Fórum ong aids RS, ou designar associados para tanto;
f) Promover sindicância ou inquérito quando ocorrer irregularidade;
g) Decidir e tomar providências, em caso inadiável e imprevisto, submetendo o seu ato à Coordenação na primeira Assembleia ordinária que esta realizar;
h) Substituir o Coordenar Executivo ou Financeiro, em suas faltas ou impedimentos.

§ 6º **Em especial compete a Coordenação Executiva:**
a) Substituir o Coordenador Técnico ou Financeiro, nas suas faltas e impedimentos;
b) Lavrar e ler as atas das reuniões e Assembleias;
c) Organizar o arquivo, tendo sob sua responsabilidade papéis, livros e documentos;
d) Expedir e receber correspondências, designando associados para auxiliá-lo nesta tarefa;
e) Elaborar ao final de cada exercício, relatório geral das atividades do Fórum ong aids RS, que será submetido à Assembleia ordinária;
f) Assinar todos os livros, juntamente com o Coordenador Técnico; § 7º **Em especial compete a Coordenação Financeira**:
a) Ter sob sua guarda os valores e fundos pertencentes ao Fórum ong aids RS;
b) Controlar movimento financeiro;
c) Promover arrecadação de rendas e o recebimento de importâncias creditadas ao Fórum ong aids RS;
d) Realizar pagamentos;
e) Assinar, com a Coordenação Técnica ou com a Coordenação Executiva os livros contábeis;
f) Organizar e assinar toda a escrituração contábil, apresentando balanços anuais para apreciação da Coordenação e Conselho Fiscal em Assembleias Gerais.
g) Substituir o Coordenador Técnico ou Executivo, nas suas faltas ou impedimentos.

SEÇÃO III
DO CONSELHO

Art. 14 O Conselho será composto de três representantes titulares e três representantes suplentes dos associados, eleitos pelos associados votantes.
Parágrafo único: Compete ao Conselho:
a) Prestar assessoria e auxiliar a Coordenação em suas funções;
b) Reunir-se sempre que necessário ou por convocação da Coordenação;
c) Eleger, entre seus membros, um coordenador para dirigir os trabalhos do Conselho;
d) . Auxiliar a Coordenação nas representações externas.

Art 15 Cabe aos suplentes substituir qualquer membro do Conselho em caso de vacância do cargo.

Art 16 O mandato do Conselho é de 03 (três) anos, renovando 1/3 cada ano, podendo cada um dos seus membros ser reeleito, em períodos consecutivo, desde que sujeitos a processo eleitoral.

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CAPÍTULO IV
DO PATRIMÔNIO, ECONOMIA E FINANÇAS

Art 17 O patrimônio do Fórum ong aids RS será constituido pela totalidade de bens, direitos e obrigações que o mesmo venha a possuir ou contrair a qualquer titulo.
§ 1º: Em caso de extinção da Instituição, por nitida impossibilidade de funcionamento, a critério da Assembleia I Extraordinária especialmente convocada para este fim, e por decisão de 2/3 (dois terços) dos associados votantes presentes, seu patrimônio liquido será destinado à entidade de fins não econômicos, estadual ou federal, de fins idênticos.
I - Inexistindo esta, o remanescente do patrimônio será encaminhado para Instituições afins do Estado do Rio Grande do Sul, registrada no Conselho Estadual de Assistência Social.
II - Não existindo no Estado Instituições nas condições indicadas, o patrimônio será devolvido a Fazenda do Estado.
§ 2º - Para instalação da Assembleia Extraoridnária para este fim específico se requer a presença de 2/3 (dois terços) dos associados do Fórum ong aids RS.

Art 18 Constituem rendas as subvenções, legados, auxilios, remissões, doações, contribuições que forem feitas, os juros, aluguéis, dividendos provenientes de serviços e por outros recursos legalmente adquiridos.

Art 19 O Fórum ong aids RS poderá abrir contas e fazer operações bancárias de qualquer natureza.
Parágrafo único: Em todas as operações bancárias e outras do mercado financeiro, terá competência para assinar sempre o Coordenador Financeiro, podendo estar acompanhado de mais um Coordenador em conjunto.

Art 20 O Fórum ong aids RS poderá contratar serviços remunerados, tanto com vínculo empregaticio, como por prestação de serviços, segundo a legislação em vigor, de acordo com as necessidades das ações e projetos a serem desenvolvidos.
Parágrafo único: Os membros dirigentes do Fórum ong aids RS, só responderão, individual ou subsidiariamente, pelas obrigações contraídas em nome da instituição, em caso de atos lesivos ao seu patrimônio e infringentes ao presente Estatuto.

CAPÍTULO V
DAS DISPOSIÇÕES GERAIS E TRANSITÓRIAS

Art 21 Como exercicio será considerado o ano civil.

Art 22 As eleições do Fórum ong aids RS serão regulamentadas pela Coordenação Geral resguardando o disposto neste estatuto.

Art 23 Os casos omissos neste Estatuto serão resolvidos pela Coordenação e ratificados pela Assembleia.
Parágrafo único: A organização, direção e forma de funcionamento da Instituição serão regidas pelo presente Estatuto, complementados, internamente pelo Regimento Interno.

Art. 24 O presente Estatuto, entrará em vigor, após o seu registro no Cartório competente da cidade de Porto Alegre.

Porto Alegre, 27 de setembro de 2012.

OAB RS 32459

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Confere com o original

1º TÍTULOS E DOCUMENTOS
PESSOAS JURÍDICAS
SERVIÇO DE REGISTROS DE PORTO ALEGRE

Av. Borges de Medeiros, 308 - 2º andar - CEP 90020-020 - Centro - Porto Alegre - RS - Fone/Fax: (51) 3211.3608
www.titulosedocumentos.com.br - titulosedocumentos@titulosedocumentos.com.br
Oficial: Bel. Péricles Brinckmann Filho

CERTIDÃO

Certifico que, nesta data, foi registrada a alteração estatutária da associação denominada "FORUM ONG AIDS RS", sob nº 81331, a folhas 046 F do Livro A nº 164 de Registro Civil das Pessoas Jurídicas. O referido é verdade e dou fé. Porto Alegre, RS, 5 de dezembro de 2012. Selos: (0449011200001239978; 0449011200001239979; 0449011200001239980; 0449011200001239981; 0449020800000716659; 0449031000000166518; 0449031000000166519; 0449031000000166520; 0449041200000200129)

Luciana Vedin dos Santos
Escrevente Autorizado

R$ 27,00

CRISTINA DE SIQUEIRA MÜLLER
Escrevente Autorizada

FÓRUM ONG AIDSRS

ATA DA ASSEMBLEIA ORDINÁRIA Nº 01/2025 PARA ELEIÇÃO DA COORDENAÇÃO E CONSELHO DO FÓRUM ONG AIDS RS

Ata de Assembleia do Fórum Ong aids RS para tratar da renovação de coordenação e do conselho. Aos oito dias do mês de setembro de dois mil e vinte e cinco, reuniram-se os representantes de instituições integrantes do Fórum Ong aids RS, inscrito no CNPJ nº 07.959.716/0001-60, às doze horas e dez minutos em segunda chamada, através de link da plataforma zoom < https://us06web.zoom.us/j/82299935590?pwd=fcHFUcAKMttCpopIMGNCVKrZERfcLJ.1 >, com quórum suficiente conforme artigo 11 do Estatuto, para realizar processo de eleição de para a Coordenação e Conselho. Instalou-se a mesa eleitoral nomeando-se como secretaria **Soila Mar Silveira da Silva**, portadora do CPF nº 70610860097 e presidente **José Marciano Oliveira Silveira**, portador do CPF nº 46497579087. Dando início aos trabalhos apresentaram-se os candidatos aos cargos da Coordenação, sendo eles: Coordenação Técnica – Carlos Alberto Ebeling Duarte, Coordenação Executiva – Márcia de Avila Berni Leão, Coordenação Financeira – Horizontina Taborda Rovira; e para o Conselho as instituições: Construindo a Igualdade; GAPA RS; Fonte Colombo; APVHA; SOMOS e Coletivo Feminino Plural. Após informou-se sobre o procedimento para a eleição, com as necessárias explicações e em acordo com o Estatuto. Conduzido o processo eleitoral, a chapa única apesentada foi eleita por unanimidade, ficando o quadro diretivo da Associação, assim composto: a) **Coordenação Técnica – Carlos Alberto Ebeling Duarte,** brasileiro, solteiro, aposentado, portador do RG nº 7004976754 e CPF nº 369.562.600-34, residente e domiciliado à Avenida Neuza Goulart Brizola, 555/702, CEP 90460-230, Porto Alegre, para desempenhar as funções constantes do art. 13, § 5º do citado dispositivo; b) **Coordenação Executiva – Márcia de Avila Berni Leão**, brasileira, solteira, maior, advogada, portadora do RG nº 1044601753 e CPF nº 549329630-68, residente e domiciliada a Rua Albion, 398/105, CEP 91530-010, Porto Alegre, para desempenhar as funções constantes do art. 13, § 6º do Estatuto da Instituição e, c) **Coordenação Financeira – Horizontina Taborda Rovira**, brasileira, casada, técnica em enfermagem, portadora do RG nº 2032624062 e CPF nº 178090100/34, residente e domiciliada nesta Capital, na Rua Upamaroti 400, bloco 4, apto 202, CEP 90820-140, Porto Alegre, para desempenhar as funções constantes do art. 13 § 7º do Estatuto do Fórum Ong aids RS; a composição do Conselho, para exercer o determinado no art. 14 e 15 do já citado dispositivo fica com: **Construindo a Igualdade; GAPA RS; Fonte Colombo; APVHA; Vale a Vida;** e, **Coletivo Feminino Plural** sendo os três primeiros titulares e os seguintes suplentes, todos com **mandato vigente até oito de setembro de dois mil e vinte e oito.** Nada mais havendo a tratar, eu secretária *ad hoc* encerro os trabalhos e lavro a presente ata que vai por mim e pelo presidente da Assembleia, assinada.

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JOSE MARCIANO OLIVEIRA SILVEIRA
Data: 08/09/2025 14:49:23-0300
Verifique em https://validar.iti.gov.br

José Marciano Oliveira Silveira
Presidente

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SOILA MAR SILVEIRA DA SILVA
Data: 08/09/2025 14:38:08-0300
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Soila Mar Silveira da Silva
Secretária

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MARCIA DE AVILA BERNI LEAO
Data: 08/09/2025 14:56:31-0300
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Marcia de Avila Berni Leao
OAB-RS 32459

1º R T D P J PORTO ALEGRE - RS

1º TÍTULOS E DOCUMENTOS
PESSOAS JURÍDICAS
SERVIÇO DE REGISTROS DE PORTO ALEGRE
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Fone/Fax: (51) 3211.3666
Oficial Registrador: Sérgio Mersserschmidt

AUTUAÇÃO

Protocolado no Livro A-95, sob o nº 1808177, em 08/09/2025. Averbado no Livro A-Eletrônico, sob o nº Av.1 do registro 54307, em 18/09/2025. O referido é verdade e dou fé.

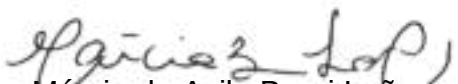
Henrique Souza Mersserschmidt-Substituto do Registrado

Total: R$ 179,27 + R$ 16,70 = R$ 195,97
Exame documentos: R$ 59,30 (0449.04.2400001.15499 - R$ 5,20)
Averbação p/ s/ fins econômicos: R$ 88,40 (0449.04.2400001.15500 - R$ 5,20)
Digitalização: R$ 8,80 (0449.01.2400001.44397 - R$ 2,10)
Processamento eletrônico: R$ 6,90 (0449.01.2400001.44398 - R$ 2,10)
Conf. Documento Público: R$ 6,90 (0449.01.2400001.44399 - R$ 2,10)

PROCURAÇÃO *ad judicia*

FÓRUM ONG AIDS RS, pessoa jurídica de direito privado, sem fins lucrativos, constituída na forma da lei, registrada no CNPJ sob o nº 07.959.716/0001-60 com sede na Rua Uruguai, 300 – sala 101 – Porto Alegre/RS – CEP 90010-140, na pessoa de seu representante nos termos de seu Estatuto Social, por sua Coordenadora Executiva, Márcia de Avila Berni Leão, brasileira, solteira, maior, advogada, RG 1044601753-SSP/RS e CPF 549.329.630-68, vem pelo presente instrumento outorgar procuração *ad* judicia à advogada **SUSANA RODRIGUES CAVALCANTI VAN DER PLOEG**, inscrita no CPF 013.497.254-63 e na **OAB/MG 181.599**, com escritório na Avenida Presidente Vargas, 446, 13º andar, Centro - Rio de Janeiro - RJ, CEP 20071-907, concedendo-lhe poderes da cláusula *ad judicia et extra*, inclusive substabelecer com reserva de poderes, especificamente para apresentação de subsídio ao exame técnico e/ou processo administrativo de nulidade perante o INPI - Instituto Nacional da Propriedade Industrial relacionado à patente de invenção **BR112024010162-2**.

Porto Alegre, 25 de novembro de 2025.



Márcia de Avila Berni Leão
Coordenadora Executiva

3o. R.P.J. DE FORTALEZA-CE
Averbacao No.: 5016463
10 Dez 2010 - PAGINA 1/12
Emls. 05 30,07

3º RTD/RPJ
Fco. Clanton Palácio de M. Santos
Escrevente Compromissado

ILUSTRÍSSIMO SENHOR TERCEIRO OFICIAL DE REGISTRO DE PESSOAS JURÍDICAS DE FORTALEZA, CE.

O(A) signatário(a), Francisco Xavier Lauro Pedrosa Filho

(nome, nacionalidade,estado civil,profissão,domicilio;RG e CIC constáveis apenas SE não figurarem nos documento anexados)

REQUER ( ) o REGISTRO, ( ) a MATRICULA, (X) a AVERBAÇÃO, ( ) o CANCELAMENTO, do (a)

Averbação do Aditivo

(descrever o ato solicitado: adaptação, 2º aditivo, baixa etc),

da entidade denominada:

Grupo de Resistencia Asa Branca

sediada no (a):

Rua Teresa Cristina 1050 centro

pelo que instrui esta petição com os documentos necessários.

Fortaleza, 10 de Dezembro de 2010

GRUPO DE RESISTÊNCIA ASA BRANCA – GRAB
ESTATUTO SOCIAL

Fortaleza – Ceará
2010

Grupo de Resistência Asa Branca – GRAB
Estatuto Social

CAPITULO 1 – DA DENOMINAÇÃO, SEDE, DURAÇÃO E FINALIDADES

Art. 1º - Com a denominação social de "Grupo de Resistência Asa Branca", sob a sigla GRAB, fica constituída uma associação civil, sem fins lucrativos, de personalidade jurídica de direito privado, fundado em 17 de março de 1989, com sede provisória em foro jurídico em Fortaleza – Estado do Ceará à rua Teresa Cristina, 1050, Centro, 60015-141, de caráter cultural, educativo e social, por tempo de duração indeterminado, sem vinculação política partidária nem religiosa, regendo-se pelo presente estatuto e por leis que regulam a espécie.

Art. 2º - O GRAB tem como objetivo o seguinte:

a- A sociedade visa especificamente promover a defesa da saúde e assistência médico-social dos portadores da SIDA – Síndrome da Imunodeficiência Adquirida;

b- Organizar o maior número de homossexuais, bissexuais e heterossexuais, interessados no assunto, independente do sexo, cor, credo, condição social, idade, profissão, postura moral ou física, na busca da defesa de sua sexualidade;

c- Conscientizar os homossexuais de sua importância enquanto ser humano e de seu papel na sociedade, constituindo assim, um movimento de Emancipação Homossexual;

d- Combater toda manifestação de opressão, violência física e moral, preconceito e discriminação de todas as formas, quer de heterossexual para homossexual ou de outra forma qualquer;

e- Promover ou participar junto às Universidades, Escolas, Associações de Classe ou Sociedades Civis, Partidos Políticos, meios de comunicação de massa, etc, debates, palestras, pronunciamentos, reuniões, congressos, etc., que visem o fim da discriminação aos homossexuais;

f- Protestar contra qualquer propaganda preconceituosa, bem como qualquer arbitrariedade de autoridade pública contra os homossexuais;

g- Promover a realização de pesquisas sobre a questão homossexual, criar e/ou fortalecer os laços de solidariedade entre os homossexuais, através de eventos culturais, educacionais e sociais, buscando para tanto, recursos próprios;

h- Estudar e levar à comunidade homossexual, temas científicos relacionados, principalmente com as doenças sexualmente transmissíveis, dando mais ênfase e prioridade a SIDA – Síndrome da Imunodeficiência Adquirida;

i- Criar e desenvolver um Centro de Apoio e Acompanhamento, aos portadores do vírus da SIDA/Aids;

j- Promover o intercâmbio com outras organizações afins, Nacionais e Internacionais, solidarizando-se com as demais entidades que lutam contra as formas de preconceitos e discriminações de que são alvos os demais grupos minoritários: **Consciência Negra, Movimento Indígena, Ciganos, Mulheres, Operários, etc., bem como os órgãos, OAB, Anistia Internacional**, etc.

k- Promover ações e cursos de qualificação profissional, dirigidos à população de LGBTT (lésbicas, gays, bissexuais, travestis e transexuais) e comunidade em geral, com foco para o público jovem, com a finalidade de capacitação para o mercado de trabalho, nas áreas do turismo e desenvolvimento do turismo sócio-ambiental; informática e estética, visando à geração de emprego e renda.

Art. 3º - O GRAB poderá estabelecer núcleos em localidades do interior do Estado, através de deliberação em Assembléia Geral, ficando integrados e supervisionados pelo Grupo Metropolitano.

CAPÍTULO II – DOS MEMBROS – DIREITOS E DEVERES

Art. 4º - O GRAB está constituído por número ilimitado de sócios, sem distinção de cor, sexo, nacionalidade, profissão, credo religioso ou político, que sejam maiores de 16 (dezesseis) anos, que aceitam o presente Estatuto seu regimento e Programa de Ação da Entidade, e, que tenha participado de 05 (cinco) reuniões consecutivas com assiduidade ou que tenha participado pelo menos de 02 (duas) atividades promovidas pelo GRAB, preenchendo a ficha de inscrição individual.

Parágrafo 1º - Estarão aptos a votar, todos os sócios maiores de 16 (dezesseis) anos, quites com suas obrigações sociais;
Parágrafo 2º - São elegíveis à cargos da Diretoria e do Conselho Fiscal, apenas os sócios maiores de 21 (vinte e um) anos;
Parágrafo 3º - Em qualquer circunstância, somente terão acesso guardando assim o direito a inviolabilidade concernente a pessoa humana.

Art. 5º - O GRAB será constituído da seguinte categoria de membros:
I – Sócios Fundadores
II – Sócios Efetivos
III – Sócios Beneméritos

Parágrafo Único: Sócios Fundadores são aqueles que participaram da fundação da entidade e assinaram a Ata da Constituição do GRAB e, que tenham continuado participando e contribuindo financeiramente com Grupo. Sócio Efetivo são aqueles que pagam suas contribuições mensais e participam assiduamente da atividade do GRAB. Sócios Beneméritos, são as pessoas físicas ou jurídicas que prestaram relevantes serviços e doações de grande monta ao GRAB, e que sejam aprovados na Assembléia Geral por 1/3 dos sócios.

Art. 6º - São direitos dos sócios:
- a- Propor, discutir e votar em Assembléia Geral;
- b- Votar e ser votado para os cargos diretivos, segundo as restrições estabelecidas no presente Estatuto Social;
- c- Usufruir todas as vantagens e regalias conferidas aos membros do GRAB, freqüentando as dependências do mesmo tomando parte nos cursos, palestras, congressos, etc.;

Art. 7º - São deveres dos sócios:
- a- Comparecer às Assembléias Gerais;
- b- Atender as convocações da diretoria;
- c- Exercer com probidade e dedicação o cargo para o qual tenha sido eleito ou designado;
- d- Zelar pelo material e pelo patrimônio do GRAB, que lhe for confiado respondendo pelos danos e extravios;
- e- Efetuar pontualmente o pagamento das mensalidades ou outras obrigações a que estiver sujeito, de acordo com o critério de cada um;

f- Aceitar, salvo por motivo de força maior, qualquer cargo para o qual tenha sido eleito ou designado, desempenhando com dedicação a proficiência;
g- Portar-se com dignidade e decência nas dependências do GRAB e nas atividades que tomar parte;
h- Respeitar e fazer respeitar o Estatuto do GRAB, e procurar por todos os meios o desenvolvimento do mesmo;

Art. 8º - Serão aplicados sanções (advertência, suspensão e exclusão) aos membros do Grupo que ferirem os interesses e objetivos do GRAB, cabendo sempre recurso da decisão de exclusão à Assembléia Geral.

Parágrafo Único – Os membros associados não respondem solidária ou subsidiariamente pelas obrigações sociais contraídas pelo GRAB.

3o. R.P.J. DE FORTALEZA-CE
Averbacao No.: 5016463
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3ª RTD/RPJ
Fco. Clarton Palácio de M. Santos
Escrevente Compromissado

CAPÍTULO III – DOS PODERES DIRETIVOS

Art. 9º - São poderes Diretivos do GRAB.
a- Assembléia Geral
b- Diretoria
c- Conselho Fiscal

Seção I
Assembléia Geral

Art. 10º - A Assembléia Geral é o órgão do Grab, formado por todos os sócios em pleno gozo de seus direitos estatutário e tem por finalidade.
a- Eleger os membros da Diretoria e do Conselho Fiscal;
b- Apreciar e aprovar a prestação de contas apresentada pela Diretoria com o parecer do Conselho Fiscal;
c- Apreciar relatórios, balanço, autorizar a alienação, venda ou permuta de bens imóveis e definir as diretrizes e programas do GRAB;
d- Cassar mandato de qualquer membro diretivo;
e- Reformar o Estatuto Social,
f- Deliberar sobre a extinção da Sociedade (observando as determinações dos artigos 40, 41 e 43 deste estatuto) e a destinação do patrimônio social (conforme o que dita o art. 42 deste),
g- Trocar planos comuns de ação.

Art. 11º - A Assembléia Geral reunir-se á:
a- **Ordinariamente** de 02 (dois) anos, para eleição dos membros da Diretoria e do Conselho Fiscal;
b- **Extraordinariamente**, sempre que for necessário, mediante convocação do Presidente ou Conselho Fiscal, ou por requerimento de no mínimo 1/5 (um quinto) dos sócios em pleno gozo de seus direitos estatutários.

Art. 12º - A Assembléia Geral somente poderá deliberar em convocação com a presença de maioria absoluta dos sócios em gozo de seus direitos, e não havendo "Quorum", reunir-se- á em 2ª convocação 01 (uma) hora depois, sendo neste caso, válida as decisões qualquer que seja o número de presentes.

Parágrafo Único – Para tratar dos temas constantes no artigo 10º alíneas "d" e "e", exige-se voto concorde de 2/3 (dois terços) dos presentes à Assembléia que tenha sido especialmente convocada para este fim, somente podendo a mesma deliberar se tiver, em primeira convocação, maioria absoluta dos associados no gozo dos seus direitos, ou pelo menos 1/3 (um terço) dos mesmos nas convocações seguintes.

Art. 13º - As deliberações serão tomadas por meio de voto, podendo desde que a Assembléia Geral concorde, ser adotado o sistema de aclamação, ou votação secreta, podendo qualquer pessoa participar das Assembléias Gerais ou Reuniões da Diretoria com direito a voto.

Seção II
Diretoria

Art. 14º - A Diretoria é o órgão de administração do GRAB, será eleita em Assembléia Geral Ordinária e terá mandato de 02 (dois) anos, constituída por 06 (seis) membros, entre os sócios da seguinte forma:

a- Presidente
b- Vice-presidente
c- 1º Secretário
d- 2º Secretário
e- 1º Tesoureiro
f- 2º Tesoureiro

Art. 15º - Compete a Diretoria:

a- Executar os programas aprovados pela Assembléia Geral;
b- Coordenar todas as atividades do GRAB e distribuir as tarefas entre os seus membros;
c- Organizar um quadro de associados com ampla participação de todos; objetivando os fins a que se propõe o GRAB;
d- Convocar Assembléia Geral, quando julgar necessárias, especialmente para reforma estatutária, extinção da sociedade e destinação do patrimônio social, alienação de imóveis, etc.;
e- Executar e fazer cumprir as decisões da Assembléia Geral.

Parágrafo Único – Compete a Diretoria vetar a utilização do cargo eleito par fins políticos-partidário (eleitoral), sob pena de destituição deste. A candidatura a cargo político ou o seu exercício, implicará no afastamento do cargo que exercer no GRAB.

Art. 16º - Compete ao Presidente:

a- Representar o GRAB ativa e passivamente, judicialmente e extrajudicialmente, podendo, contudo delegar poderes para tais fins;
b- O voto de qualidade e quantidade nas reuniões da diretoria;
c- Coordenar e presidir reuniões e Assembléias Gerais;
d- Coordenar os trabalhos do Grupo e orientar as diversas atividades sociais condizentes com as finalidades do mesmo;
e- Executar o pagamento das despesas autorizadas, bem como, assinar, juntamente com o Tesoureiro, todas as contas de responsabilidade do Grupo e movimentar as contas bancárias;
f- Assinar o expediente e rubricar todos os livros de uso do GRAB;

g- Convocar sessões extraordinárias quando julgá-las necessária e de interesse do GRAB;
h- Cumprir e fazer o Estatuto e Regimento Interno do Grupo.

Art. 17º - Compete ao Vice-presidente:
a- Auxiliar e substituir o Presidente em suas faltas ou impedimentos legais e, colaborar no desempenho de suas funções;
b- Estar apto a desempenhar qualquer cargo ou função que lhe foi designado;
c- Cumprir e fazer cumprir o presente Estatuto e Regulamentos.

Art. 18º - Compete ao 1º Secretário:
a- Lavrar as Atas das Reuniões e das Assembléias Gerais do Grupo;
b- Supervisionar os serviços administrativos do GRAB, na melhor boa vontade;
c- Colher assinaturas dos presentes em Assembléias Gerais e Reuniões de Diretoria;
d- Elaborar convites, informativos com visitas a divulgação dos objetivos do GRAB;
e- Escriturar os documentos do GRUPO, bem como organizar o arquivo e registro do Grupo, fichário pessoal dos associados, mantendo-o sob sua guarda;
f- Estar apto a desempenhos múltiplos que lhe for designado pela Diretoria ou Presidente do GRAB;
g- Cumprir e fazer cumprir o Estatuto e Regimento do Grupo.

Art. 19º - Compete ao 2º Secretário:
a- Auxiliar o 1º Secretário em suas atribuições e substitui-lo em caso de ausência ou impedimento legal;
b- Desenvolver outras tarefas que for designada pela Diretoria ou pelo Presidente;
c- Cumprir e fazer cumprir o presente Estatuto e Regimento do GRAB.

Art. 20º - Compete ao 1º Tesoureiro:
a- Ter sob a sua guarda todos os valores do GRAB; preservando-os e zelando-os na melhor forma possível;
b- Controlar todo o movimento financeiro do GRAB;
c- Apresentar balancetes nas Assembléias Gerais, bem como a prestação de contas nas Reuniões da Diretoria;
d- Assinar, juntamente com o Presidente em exercício, todas as contas de responsabilidade do GRAB e, movimentar as contas bancárias;
e- Depositar dinheiro em bancos e movimentar as contas bancárias, sempre em conjunto com o Presidente;
f- Prestar quaisquer informações sobre serviços da Tesouraria, quando solicitado;
g- Providenciar e receber as contribuições dos associados e outras taxas ou doações, depositando em agência bancária indicada pela Diretoria do GRAB;
h- Estar apto a desempenhar múltiplos que lhe for atribuído pela Diretoria ou pelo Presidente;
i- Zelar o patrimônio social e tê-lo sob sua guarda;
j- Cumprir e fazer cumprir o Estatuto do Grupo e Regimentos.

Art. 21º - Compete ao 2º Tesoureiro:
a- Auxiliar o 1º Tesoureiro em suas atribuições e substitui-lo em sua ausência e/ou impedimento;

b- Estar apto a desempenhos múltiplos que lhe for designado pela Diretoria ou pelo Presidente;
c- Cumprir e fazer cumprir o Estatuto e Regimento do GRAB.

Seção III
Conselho Fiscal

Art. 22º - O Conselho Fiscal é o órgão fiscalizador do GRAB e é constituído por 03 (três) membros efetivos e 03 (três) membros suplentes, que serão eleitos juntamente com a Diretoria pelo voto secreto ou por aclamação.

Art. 23º - O Conselho Fiscal reunir-se-á ordinariamente de 03 (três) meses e extraordinariamente quando convocado pelo Presidente do GRAB, por iniciativa ou por requerimento de no mínimo 2/3 (dois terços) dos associados em forma de abaixo-assinado.

Art. 24º - Compete ao Conselho Fiscal:
a- Fiscalizar as despesas realizadas pela Diretoria;
b- Convocar a Diretoria para apresentar a prestação de contas, dando o seu **parecer** na mesma;
c- Pronunciar-se sobre qualquer assunto de interesse do GRAB;
d- Apreciar relatórios, contas, balanços, etc.;
e- Ampliar juntamente com a Diretoria a ação do GRAB a nível de extensão territorial, para que todas as categorias de associados dela participem e, que também aí fique esclarecidos das suas atividades reivindicatórias e financeiras.

Art. 25º - Dos 03 (três) efetivos do Conselho Fiscal que foram eleitos, 01 (um) será escolhido o seu Presidente.

Art. 26º - Compete ao Suplente do Conselho Fiscal:
a- Auxiliar a Diretoria no Desenvolvimento de suas funções;
b- Substituir os cargos vagos do Conselho Fiscal e da própria Diretoria se for o caso;
c- Convocar Assembléia Geral para eleições de cargos vagos na Diretoria, quando a mesma estiver totalmente com 1/3 (um terço) dos seus membros, ou no caso de renúncia coletiva da Diretoria e do Conselho Fiscal.

CÁPITULO V – ELEIÇÕES

Art. 27º - As eleições dos membros da Diretoria e do Conselho Fiscal, realizar-se-á em Assembléia Geral Eleitoral, obedecendo as seguintes instruções:
a- O processo de votação será encaminhado por comissão eleitoral, criada com esta finalidade, que deverá divulgar a data, hora de início e término das eleições;
b- A Diretoria poderá pleitear reeleições;
c- Podem concorrer todas as chapas inscritas até 10 (dez) dias antes da eleição;
d- Poderá ser votado qualquer membro que esteja em dias com suas obrigações, obedecendo ao que está prescrito no Parágrafo 2º Art. 4º deste Estatuto;
e- A comissão eleitoral deverá designar entre os associados, o Presidente e Secretário que comporão a mesa, em acordo com as chapas que disputam as eleições;

Art. 28º - O registro dos candidatos será requerido à Entidade, por quem encabeçar a chapa, na qual figurarão os nomes dos candidatos, não se permitindo inscrições individuais.

Parágrafo Único – O voto é desvinculado, sendo permitido o voto em candidatos de chapas diferentes.

Art. 29º - Antes do inicio das eleições, o Presidente da Assembléia Geral Eleitoral, reunidos com os representantes das chapas concorrentes ao pleito, abrirão as urnas, examinando-as e mostrando aos presentes que a mesma está vazia e perfeita, para em seguida garantir-lhe a inviolabilidade com papel rubricado pelos componentes da mesma.

Art. 30º - A votação para Assembléia Geral Eleitoral poderá ser:

I – **Por Aclamação**, modalidade consistente na manifestação coletiva dos votos, com os associados aplaudindo qualquer manifestação expressa de aprovação;
II – **Secreta,** modalidade consistente na obtenção do voto do associado através de cédula única, onde o associado marcará o seu voto, devendo fazer a marca em cabine que garanta o sigilo do voto e, ato contínuo, colocará a cédula, devidamente dobrada, na urna destinada à recepção dos votos que deverá ser previamente examinada e lacrada, garantida assim sua inviolabilidade. O associado assinará em seguida na folha de votação, o seu nome.

Art. 31º - Encerrada a eleição, dar-se-á inicio à apuração, ou havendo conveniência, serão devidamente vedadas, lacradas e rubricadas as urnas para a apuração no dia seguinte.

Parágrafo Primeiro – Terminados os trabalhos eleitorais, proceder-se-á à contagem dos votos, verificando se o número de cédulas coincide com o de votantes, e que em caso negativo determinará a nulidade do pleito.

Parágrafo Segundo – Findo a contagem de votos, e encerrada a apuração pelo Presidente, será pelo mesmo proclamado o resultado, lavrando-se Ata de Eleição, assinada pelo Presidente, mesários e autoridades presentes, devendo expressamente consignar o número de associados que votaram, o número de votos atribuídos a cada uma das chapas, composição das chapas e a afirmação de que as eleições obedeceram aos sistemas de escrutínio secreto e, registrar as ocorrências que relacionaram com o pleito.

Parágrafo Terceiro – Em caso de empate, será eleito o candidato mais idoso, ou será convocada nova eleição se outro acordo não houver.

Parágrafo Quarto – No impedimento de qualquer mesário ou secretário da mesa eleitoral, o Presidente poderá, se necessário, escolher entre os associados, o respectivo substituto.

Art. 32º - Será proibida a propaganda eleitoral no dia das eleições, sob pena de advertência para o associado que assim proceder.

Art. 33º - O mandato dos membros da Diretoria e do Conselho Fiscal será de 02 (dois) anos com direito a reeleição.

CÁPITULO VI – DOTAÇÕES PATRIMONIAIS

Art. 34º - Os fundos de dotações patrimoniais do GRAB provirão de:

a- Contribuições mensais e regulares dos sócios;
b- Bem móveis, imóveis e valores adquiridos, ações gerais, verbas de organismos assistenciais;
c- Doações, subvenções, legados em dinheiro ou bens que sejam atribuidos ao GRAB e aceitos pela Diretoria;
d- Fundos e rendas provenientes de promoções e atividades diversas promovido pelo GRAB.
e- Quaisquer valores adventícios (empréstimos e financiamentos) realizados;

Art. 35º - Ainda que seja uma associação sem fins lucrativos, o GRAB poderá construir renda visando à sua aplicação na seqüência dos objetivos do mesmo, necessário se faz o registro no **Livro Caixa**.

Art. 36º - Os rendimentos advindos à entidade, serão aplicados para cumprimento de suas finalidades, não havendo distribuições de lucros.

Art. 37º - Os bens imóveis e as ações, incorporadas ao patrimônio social do GRAB, só poderão ser alienados ou gravados com ônus reais, se houver um objetivo certo e determinado, de maior interesse da Entidade, com aprovação da Diretoria e da maioria absoluta dos membros associados.

Art. 38º - Os membros do GRAB, da Diretoria e do Conselho Fiscal, não respondem solidária ou subsidiariamente pelas obrigações assumidas em nome do mesmo no exercício de suas funções, salvo nos casos em que figuram como avalista e usarem de fraude ou de má fé.

Art. 39º - A aprovação da alteração estatutária deverá constar em Livro Ata e, esta deverá ser registrada em Cartório de Título e Documentos e a alteração averbada a margem do registro dos atos constitutivos em Cartório de Registro Civil das Pessoas Juridicas onde teve seus atos registrados.

Art. 40º - O Grupo de Resistência Asa Branca – GRAB só será extinto por lei ou por deliberação de 2/3 (dois terço) dos associados em Assembléia Geral Extraordinária devidamente convocada para essa finalidade, após prévia aprovação da Diretoria e do Conselho Fiscal.

Art. 41º - A proposta para extinção do GRAB, dar-se-á por impossibilidade de reunir e atuar ou por interesse dos sócios na continuidade de suas atividades, em casos de insuperável dificuldade na consecução dos seus objetivos.

Art. 42º - Extinto o GRAB, o patrimônio social por ventura existente, será doado a outra entidade congênere, preferencialmente situada no próprio Estado do Ceará ou na Região Nordestina, que esteja devidamente registrada no Conselho Nacional de Serviço Social e em Cartório de Registro Civil das Pessoas Juridicas.

Parágrafo Único - A destinação do patrimônio social será deliberada em 02 (duas) Assembléias Gerais Extraordinária sucessivas,somente podendo a mesma deliberar se contar com a presença de 2/3 (dois terços) dos associados quites com suas obrigações sociais.

Art. 43º - O GRAB não poderá ser considerado extinto enquanto existir no mínimo 05 (cinco) membros interessados na continuidade de suas atividades sociais.

Art. 44º - O GRAB não remunera os membros de sua Diretoria ou do Conselho Fiscal, não distribui lucros, vantagens ou bonificações e dirigentes, associados ou mantenedores, sob nenhuma forma.

Art. 45º - O presente Estatuto Social foi aprovado em Assembléia Geral de Constituição no dia 17 de março de 1991, entra em vigor nesta mesma data e será registrada no Cartório de Registro Civil das Pessoas Jurídicas desta Comarca de Fortaleza, Estado do Ceará, juntamente com o extrato do Estatuto que foi publicado no Diário Oficial.

Art. 46º - Os casos omissos neste Estatuto Social, serão resolvidos pela diretoria e pelo Regimento Interno do GRAB.

Dra. FASSIANA LIMA ALVES
ADVOGADA
OAB-CE Nº 16.020

X

3º RTD/RPJ
Fco. Clarion Palácio de M. Santos
Escrevente Compromissado

3o. R.P.J. DE FORTALEZA-CE
Averbacao No.: 5016463
10 Dez 2010 - PAGINA 12/12
Emls. R$ 30,07

Branca – GRAB
Estatuto Social

Presidente

Francisco Xavier Ramos Pedrosa Filho, brasileiro, solteiro, jornalista, residente à Rua, Pedro de Queiroz, 1355, Bairro: Amadeu Furtado, Cidade: Fortaleza – CE, portador do CPF: 430.940.314.04

Vice Presidente

Francisco Orlaneudo de Lima, brasileiro, solteiro, tecnólogo em gestão de saúde, residente à Rua, Peru, 488 Bairro: Montese, Cidade: Fortaleza – CE, portador do CPF:312.865.183.34

1º Secretário

Elizio de Araújo Loiola, brasileiro, Solteiro, assistente social, residente à Rua, 02 Nº 80, Aptº 304 Bairro: São Gerardo, Cidade: Fortaleza – CE, portador do CPF: 073.215.463.49

2º Secretário

6º Ofício de Notas - Cartório Melo Júnior - Rua Major Facundo, 980 - Fortaleza - Ce
Reg. Tit. Doc. e de Pessoas Jurídicas
Tit. Bel. José Evocdio de Melo Júnior
Subst. Rogneberto M. Melo Júnior

Adriano Henrique Caetano Costa, brasileiro, solteiro, filósofo, residente à Rua, Franklin Távora, 416, Apto 401 Bairro: Centro, Cidade: fortaleza – CE, portador do CPF: 456.724.903.87

1º Tesoureiro:

Raimundo Ferreira Costa Neto, brasileiro, solteiro, comerciário, residente à Rua, Luciano de Queiroz, 792 Bairro: Henrique Jorge, Cidade: Fortaleza – CE, portador do CPF: 166.559.233.87

2º Tesoureiro:

José Batista de Souza, brasileiro, solteiro, educador social, residente à Rua, Teodoreto Souto, 1007, Apto 04 Bairro: Parque Araxá, Cidade: Fortaleza – CE, portador do CPF: 022.641.323.37

Conselheiros Efetivos

Francisco Antônio Serafim da Silva, brasileiro, solteiro, comerciário residente à Rua, Clarindo de Queiroz, 1584, Apto 10 Bairro: Centro, Cidade: Fortaleza – CE, portador do CPF: 323.766.933.49

Francisco Helio Souza Brito, brasileiro, solteiro, comerciário, residente à Av. Duque de Caxias, 823, Apto 603 Bairro: Centro, Cidade: Fortaleza – CE, portador do CPF: 02º.979.037.79

José Rocha Filho, brasileiro, solteiro, comerciário, residente à Rua, Ducineia, 511 Bairro: Montese, Cidade: Fortaleza – CE, portador do CPF: 674.795.028.34

Emolumentos Conf. Lei 13.582 de 22/Set/2004 C/C Art. 6º da Lei 10.169/00

Código nº 0060	- R$	25,65
Fermoju 5%	- R$	1,62
Ferc	R$	2,78
Outras desp.	- R$	
Desconto	- R$	
Total	R$	30,07

Selo nº 130 096 ª Via

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REGISTRAL
Nº AD 139.092

Dra. TASSIANA LIMA ALVES
ADVOGADA
OAB-CE Nº 16.028

ILUSTRÍSSIMO SENHOR DO TERCEIRO OFICIAL DE REGISTRA DE PESSOAS JURÍDICAS DE FORTALEZA

3º R.P.J. DE FORTALEZA-CE
Averb. Nº 5051200 - 07 abr 2025
Página 1/9 Emls. R$ 177,11

Jessica Cordeiro Barbosa Farias
Escrevente Autorizada

O (A) REPRESENTANTE LEGAL:

NOME COMPLETO: ANTONIO LUIZ DÁRIO BEZERRA

NACIONALIDADE: BRASILEIRA PROFISSÃO: PEDAGOGO

ESTADO CIVIL: SOLTEIRO UNIÃO ESTÁVEL: SIM ( ) NÃO (X)

FILIAÇÃO:
PAI: ANTONIO BEZERRA

MÃE: RAIMUNDA MARIA NAZÁRIO BEZERRA

TELEFONE PARA CONTATO: (85) 98525-9555

RG: 9902934717 CPF: 656.791.213-87

ENDEREÇO: RUA PAULINO NOGUEIRA, 265, ALTOS, BENFICA, CEP: 60020-270, FORTALEZA-CE.

REQUER: O REGISTRO (X) // A AVERBAÇÃO ( ) // O CANCELAMENTO ( )

ATA DE ELEIÇÃO E POSSE

(DESCREVER O ATO SOLICITADO: REGISTRO DO ESTATUTO SOCIAL OU CONTRATO SOCIAL – AVERBAÇÃO DA ATA DE ELEIÇÃO E POSSE – AVERBAÇÃO DO ADITIVO SOCIAL OU ESTATUTO SOCIAL E BAIXA DA ENTIDADE –ETC...)

DA ENTIDADE DENOMINADA (NOME DA RAZÃO SOCIAL):

GRUPO DE RESISTÊNCIA ASA BRANCA - GRAB.

CNPJ Nº 41.302.803/0001-88

SEDIADA NO ENDEREÇO DA ENTIDADE:

RUA K (IPÊ AMARELO), 1022, ITAPERI, CEP: 60714-665, FORTALEZA-CE.

FORTALEZA –CE 07 DE ABRIL DE 2025.

(ASSINATURA DO REPRESENTANTE LEGAL)

Cartório de Notas - 3º RTD/RCPJ de Fortaleza
Reg. Tit. Doc. e de Pessoas Jurídicas
Jane Kaelyla de Oliveira Souza
Interina Delegatária
(Portaria DFCB nº 244/2024
(DJe 27/02/2024)
Rua Major Facundo, 660 - Fortaleza - CE

ATA DA ASSEMBLÉIA GERAL ELEITORAL E DE POSSE DO GRUPO DE RESISTÊNCIA ASA BRANCA – GRAB, ORGANIZAÇÃO DA SOCIEDADE CIVIL, FUNDADA EM 17 DE MARÇO DE 1989, REGISTRADA NO CARTÓRIO DE REGISTRO CIVIL DAS PESSOAS JURÍDICAS (Cartório Melo Júnior), SOB ESTATUTO SOCIAL/REGISTRO Nº 77214, EM 30 DE AGOSTO DE 1991 / CNPJ: 41.302.803/0001 – 88.

Aos vinte e dois dias do mês de março do ano de dois mil e vinte e cinco, às quatorze horas, na sede social da organização, situada à Rua K (Ipê Amarelo) Loteamento Expedicionários II, nº 1022, Itaperi, CEP: 60714-665 Fortaleza, Estado do Ceará, reuniram-se em Assembleia Geral Eleitoral os/as senhores/as membros/as associados/as do Grupo de Resistência Asa Branca – GRAB, com a finalidade de votarem sobre a ordem do dia: a) eleição e posse da diretoria; b) eleição e posse do conselho fiscal. A Assembleia Geral foi presidida por Elizio de Araújo Loiola e secretariada por Delson Souza do Nascimento, ambos aclamados unanimemente pelos presentes. O presidente da Assembleia Geral fez um breve relato sobre o desempenho da última gestão, destacando as potencialidades na condução dos processos políticos e estruturais da organização. Também destacou a importância e resistência do GRAB em manter-se atuando efetivamente na defesa de direitos humanos de LGBTI+ a 36 anos na cidade de Fortaleza e com atuação em alguns municipios cearenses, pois, na atualidade vivenciamos um cenário mundial de ataques às populações LGBTI+, sobretudo às pessoas trans e travestis, e nesse sentido a existência dessa organização atuando nessa pauta se faz de grande relevância para a sociedade em geral. Em seguida foi realizada a leitura do Regimento Eleitoral que foi discutido e aprovado pelos/as presentes. Tendo sido aprovado o Regimento Eleitoral, iniciou-se a eleição da nova Diretoria e do novo Conselho Fiscal. No processo eleitoral houve apenas uma chapa concorrendo ao pleito que por unanimidade dos votos dos/as presentes foi eleita. Assim, a nova Diretoria e Conselho Fiscal formaram-se pela seguinte composição e qualificação: DIRETORIA - PRESIDENTE: Antonio Luiz Dário Bezerra, brasileiro, solteiro, pedagogo, CPF: 656.791.213-87, RG: 99029347717 SSPDS/CE, filho de Raimunda maria Nazário Bezerra e Antonio Bezerra, residente e domiciliada à Rua Paulino Nogueira, 265 A Altos, Benfica, Fortaleza, CEP: 60020-270; VICE-

PRESIDENTE: Dediane Souza, brasileira, solteira, jornalista, CPF: 022.641.323-37, RG: 2004097019783 SSP/CE, filha de Maria Lindalva de Paulo e José Maria Mendes de Souza, residente e domiciliada à Rua Júlio Alcides, 320, Apto. 302 BL 04, Maraponga, Fortaleza, CEP: 60710-680; PRIMEIRO-SECRETÁRIO: Francisco Xavier Ramos Pedrosa Filho, brasileiro, solteiro, jornalista, CPF: 430.940.314-04, RG: 2006009061363 SSP/CE, filho de Linalda Cabral Pedrosa e Francisco Xavier Ramos Pedrosa, residente e domiciliado à Rua Minas Gerais, Nº 149, Bl. C, Aptº 904 - Bela Vista – Fortaleza, CEP: 60441-135; SEGUNDO-SECRETÁRIO: Francisco Orlaneudo de Lima, brasileiro, solteiro, tecnólogo em gestão de saúde, CPF: 312.865.183-34, RG: 107988086 SSP/CE, filho de Francisca das Chagas Nogueira de Lima e Raimundo Nonato de Lima, residente e domiciliado à Rua Peru, Nº 488 – Montese – Fortaleza, CEP: 60740-510; PRIMEIRO TESOUREIRO: Labelle Silva, brasileira, solteira, produtora cultural, CPF: 000.173.033-97, RG: 99012035938 SSP/CE, filha de Maria de Fátima Silva Menezes (pai não consta), residente e domiciliada à Rua Equador, 1198, Apto. 1198 A, CEP: 60740-788; SEGUNDO TESOUREIRO: Raimundo Ferreira Costa Neto, brasileiro, solteiro, comerciário, CPF: 166.559.233-87, RG: 93019008740 SSP/CE, filho de Adelia de Freitas Costa e João Batista Costa, residente e domiciliado à Rua Luciano de Queiroz, Nº 792 - Henrique Jorge – Fortaleza, CEP: 60510-176; CONSELHO FISCAL – MEMBROS EFETIVOS: Renata de Jesus Bispo, brasileira, solteira, cabeleireira, CPF: 804.855.103-91, RG: 93002377187 SSP/CE, filha de Audeise de Jesus Bispo e pai ausente, residente e domiciliada à Rua Do Trilho, Nº 1233 – Moura Brasil – Fortaleza, CEP: 60010-120; Viviane Venâncio Matias, brasileira, solteira, auxiliar administrativa, CPF: 547.440.673-87, RG: 91013019167 SSP/CE, filha de Francisca Liduína Venâncio Matias e Valdecir Matias, residente e domiciliada à Avenida Pau Brasil, nº 160, Condominio 02, Bloco 15, Apto. 103, Cidade Jardim 1 – José Walter, Fortaleza, CEP: 60748-075; Francisco Cleilson Pires da Silva, brasileiro, solteiro, assistente de produção, CPF: 054.812.023-44, RG: 2007138215-6 SSP/CE, filho de Maria Laís Pires da Silva e Antonio Fernando da Silva, residente e domiciliado à Rua Tenente Wilson, nº 167, Aerolândia, Fortaleza, CEP: 60850-810.

CONSELHO FISCAL – MEMBROS SUPLENTES: José Rocha Filho, brasileiro, solteiro, comerciário, CPF: 674.795.028-34 RG: 2000010308637 SSP/CE, filho

de Maria Dijanira Viana Rocha e José Berneval Rocha, residente e domiciliado à Rua Ducineia Gondim, Nº 511 – Montese – Fortaleza, CEP: 60416-480; Francisco Antônio Serafin Da Silva, brasileiro, solteiro, comerciante, CPF: 323.766.933-49, RG: 90003040203 SSP/CE, filho de Rosa Maria da Silva e Expedito Serafim da Silva, residente e domiciliado à Rua Clarindo De Queiroz, Nº 1584 – Centro – Fortaleza, CEP: 60035-130; Domingos Salvis Paula Da Silva, brasileiro, solteiro, comerciário, CPF: 244.885.423-87 RG: 91015001990 SSP/CE, filho de Raimunda Paula da Silva e Antonio André da Silva, residente e domiciliado à Rua 75, Nº 276 – Jereissati Ii – Pacatuba, CEP: 61800-000. Após a aclamação da chapa eleita, Elizio de Araújo Loiola, presidente da Assembleia Geral Eleitoral decretou posse imediata da nova Diretoria e Conselho Fiscal para darem continuidade às atividades e funções da organização. Nesse sentido, a nova Diretoria e Conselho Fiscal iniciaram nesta data, 22 de março de 2025, seus mandatos, com duração de dois anos, com término previsto para 21 de março de 2027. Em seguida a palavra ficou aberta para as considerações da nova Diretoria que relatou as metas, prioridades e perspectivas da gestão, destacando a importância do comprometimento e das responsabilidades dos membros para com a organização. A seguir, a sessão foi suspensa por tempo necessário à lavratura desta ata, que foi realizada por mim, Delson Souza do Nascimento. Após reaberta a sessão, a presente ata foi lida, aprovada e segue assinada pelos/as membros/as da nova diretoria e conselho fiscal eleitos/as; pelo Presidente da Assembleia Geral Eleitoral; por mim, secretário; e pelos/as demais associados/as presentes, membros/as do Grupo de Resistência Asa Branca - GRAB. Fortaleza, 22 de março de 2025.

Elizio de Araújo Loiola
PRESIDENTE DA ASSEMBLEIA GERAL ELEITORAL

Delson Souza do Nascimento
SECRETÁRIO

3º R.P.J. DE FORTALEZA-CE
Averb. Nº 5051280 - 07 abr 2025
Página 5/9 Emls. R$ 177,11

DIRETORIA:

Antonio Luiz Dário Bezerra
PRESIDENTE: brasileiro, solteiro, pedagogo, CPF: 656.791.213-87, RG: 99029347717 SSPDS/CE, filho de Raimunda maria Nazário Bezerra e Antonio Bezerra, residente e domiciliado à Rua Paulino Nogueira, 265 A Altos, Benfica, Fortaleza, CEP: 60020-270.

Dediane Souza
VICE-PRESIDENTE: brasileira, solteira, jornalista, CPF: 022.641.323-37, RG: 2004097019783 SSP/CE, filha de Maria Lindalva de Paulo e José Maria Mendes de Souza, residente e domiciliada à Rua Júlio Alcides, 320, Apto. 302 BL 04, Maraponga, Fortaleza, CEP: 60710-680.

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PRIMEIRO-SECRETÁRIO: brasileiro, solteiro, jornalista, CPF: 430.940.314-04, RG: 2006009061363 SSP/CE, filho de Linalda Cabral Pedrosa e Francisco Xavier Ramos Pedrosa, residente e domiciliado à Rua Minas Gerais, Nº 149, Bl. C, Aptº 904 - Bela Vista – Fortaleza, CEP: 60441-135.

Francisco Orlaneudo de Lima
SEGUNDO-SECRETÁRIO: brasileiro, solteiro, tecnólogo em gestão de saúde, CPF: 312.865.183-34, RG: 107988086 SSP/CE, filho de Francisca das Chagas Nogueira de Lima e Raimundo Nonato de Lima, residente e domiciliado à Rua Peru, Nº 488 – Montese – Fortaleza, CEP: 60740-510.

Labelle Silva
PRIMEIRO TESOUREIRO:,brasileira, solteira, produtora cultural, CPF: 000.173.033-97, RG: 99012035938 SSP/CE, filha de Maria de Fátima Silva Menezes (pai não consta), residente e domiciliada à Rua Equador, 1198, Apto. 1198 A, CEP: 60740-788.

Raimundo Ferreira Costa Neto
SEGUNDO TESOUREIRO: brasileiro, solteiro, comerciário, CPF: 166.559.233-87, RG: 93019008740 SSP/CE, filho de Adelia de Freitas Costa e João Batista Costa, residente e domiciliado à Rua Luciano de Queiroz, Nº 792 - Henrique Jorge – Fortaleza, CEP: 60510-176.

CONSELHO FISCAL – MEMBROS EFETIVOS:

gov.br Documento assinado digitalmente
RENATA DE JESUS BISPO
Data: 02/04/2025 11:00:24-0300
Verifique em https://validar.iti.gov.br

Renata de Jesus Bispo
Brasileira, solteira, cabeleireira, CPF: 804.855.103-91, RG: 93002377187 SSP/CE, filha de Audeise de Jesus Bispo e pai ausente, residente e domiciliada à Rua Do Trilho, Nº 1233 – Moura Brasil – Fortaleza, CEP: 60010-120.

gov.br Documento assinado digitalmente
VIVIANE VENANCIO MATIAS
Data: 03/04/2025 16:39:13-0300
Verifique em https://validar.iti.gov.br

Viviane Venâncio Matias
Brasileira, solteira, auxiliar administrativa, CPF: 547.440.673-87, RG: 91013019167 SSP/CE, filha de Francisca Liduina Venâncio Matias e Valdecir Matias, residente e domiciliada à Avenida Pau Brasil, nº 160, Condomínio 02, Bloco 15, Apto. 103, Cidade Jardim 1 – José Walter, Fortaleza, CEP: 60748-075.

gov.br Documento assinado digitalmente
FRANCISCO CLEILSON PIRES DA SILVA
Data: 02/04/2025 11:13:08-0300
Verifique em https://validar.iti.gov.br

Francisco Cleilson Pires da Silva
Brasileiro, solteiro, assistente de produção, CPF: 054.812.023-44, RG: 2007138215-6 SSP/CE, filho de Maria Laís Pires da Silva e Antonio Fernando da Silva, residente e domiciliado à Rua Tenente Wilson, nº 167, Aerolândia, Fortaleza, CEP: 60850-810.

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Francisco Antonio Serafin da Silva

Francisco Antônio Serafin Da Silva
Brasileiro, solteiro, comerciante, CPF: 323.766.933-49, RG: 90003040203 SSP/CE, filho de Rosa Maria da Silva e Expedito Serafim da Silva, residente e domiciliado à Rua Clarindo De Queiroz, Nº 1584 – Centro – Fortaleza, CEP: 60035-130.

Domingos Salvis Paula da Silva

Domingos Salvis Paula Da Silva
Brasileiro, solteiro, comerciário, CPF: 244.885.423-87 RG: 91015001990 SSP/CE, filho de Raimunda Paula da Silva e Antonio André da Silva, residente e domiciliado à Rua 75, Nº 276 – Jereissati II – Pacatuba, CEP: 61800-000.

ASSINATURA DOS/AS DEMAIS ASSOCIADOS/AS PRESENTES:

- Jorgier Vicente da Silva
- Ivides Fabiana
- Renan Monteiro dos Santos

GRAB

GRUPO DE RESISTÊNCIA ASA BRANCA
C.N.P.J. – 41302.803/0001-88
Rec. Utilidade Pública Conf. Lei Nº 7066 de 27/03/92
Sede: Rua K (Ipê Amarelo), nº 1022, Itaperi, 60714-665, Fortaleza-CE
Fone: (85) 992913699 E-mail: grab.grupoasabranca@gmail.com Site: www.grab.net.br

RELAÇÃO DOS/AS SÓCIOS/AS APTOS/AS A VOTAR:

NOME DO/A SÓCIO/A	ASSINATURA
Antonio Luiz Dário Bezerra	
Dediane Souza	
Delson Sousa do Nascimento	
Domingos Salvis Paula da Silva	
Elízio de Araújo Loiola	
Francisco Antonio Serafin da Silva	
Francisco Cleilson Pires da Silva	
Francisco Orlaneudo de Lima	
Francisco Xavier Ramos Pedrosa Filho	
Jorgier Vicente da Silva	
José Rocha Filho	
Labelle Silva	
Péricles Sabóia	
Raimundo Ferreira Costa neto	
Renan Monteiro dos Santos	
Renata de Jesus Bispo	
Viviane Venâncio Matias	

Este edital será fixado no flanelógrafo da associação e encaminhado nos grupos do whatsapp da Organização a fim de que seja publicizado aos associados.

REPÚBLICA FEDERATIVA DO BRASIL
ESTADO DO CEARÁ
6º Tabelionato de Notas e 3º Registro de Títulos e Documentos e Registro Civil de Pessoas Jurídicas de Fortaleza

Rua Major Facundo, nº 724 - Centro - Fortaleza - Ceará - CEP: 60025-100 - PABX:(85) 3514-5369

REGISTRO PARA FINS DE PUBLICIDADE E EFICÁCIA CONTRA TERCEIROS

Registro nº 5051200

Certifico e dou fé que consta no documento em papel com 9 (nove) páginas, foi apresentado em 07/04/2025, o qual foi protocolado e registrado **sob nº 5051200** em **07/04/2025** e **averbado à margem do registro sob nº 77214**, no Registro Civil das Pessoas Jurídicas deste Cartório do 6º Ofício de Notas e 3º Registro de Títulos e Documentos e Pessoas Jurídicas da Comarca de Fortaleza,

Natureza: Ata de Eleição e Posse

Este certificado é parte **integrante e inseparável** do registro do documento acima descrito.

Fortaleza, 07 de abril de 2025

Jessica Cordeiro Barbosa Farias
Escrevente

3º R.P.J. DE FORTALEZA-CE
Averb. Nº 5051200 - 07 abr 2025
Página 9/9 Emls. R$ 177,11

Jessica Cordeiro Barbosa Farias
Escrevente Autorizada

PODER JUDICIÁRIO
ESTADO DO CEARÁ
REGISTRO DE RTD E RCPJ
ABM082231-F2R9
SELO DIGITAL DE AUTENTICIDADE

PODER JUDICIÁRIO
ESTADO DO CEARÁ
DISTRIBUIÇÃO / MICROFILMAGEM
ABK528676-H4R9
ABK528677-M9R9
SELO DIGITAL DE AUTENTICIDADE

CUSTAS E EMOLUMENTOS INCIDENTES
Nº de atendimento: 20250407000078
Total emolumentos: R$ 142,83
Total FERMOJU: R$ 10,53
Total Selos: R$ 9,49
Total FRMMP: R$ 7,13
Total FAADEP: R$ 7,13
Valor Total: R$ 177,11

Base de cálculo / Atos com Valor Declarado

Detalhamento da cobrança / Listagem dos códigos da tabela de emolumentos envolvidos
Códigos: 5013, 5023

6º Tabelionato de Notas - 3º RTD/RCPJ de Fortaleza-CE
Reg. Tit. Doc. e de Pessoas Jurídicas
Jane Kellyia de Oliveira Souza
Interina Delegatária
(Portaria DFCB nº 244/2024 (Dje 27/02/2024))
Rua Major Facundo, 660 - Fortaleza - CE

PROCURAÇÃO *ad judicia*

Grupo de Resistência Asa Branca - GRAB, pessoa jurídica de direito privado, sem fins lucrativos, constituída na forma da lei, registrada no CNPJ sob o n° 41.302.803/0001-88, com sede na Rua K (Ipê Amarelo), nº 1022, Itaperi, CEP: 60714-665, Fortaleza/Ceará, na pessoa de seu representante nos termos de seu Estatuto Social, por seu/sua Presidente, Antonio Luiz Dário Bezerra, brasileiro, solteiro, pedagogo, RG n° 99029347717 emitido pela SSPDS CE, e inscrito no CPF n° 656.791.213-87, vem pelo presente instrumento outorgar procuração *ad* judicia à advogada **SUSANA RODRIGUES CAVALCANTI VAN DER PLOEG**, inscrita no CPF 013.497.254-63 e na **OAB/MG 181.599**, com escritório na Avenida Presidente Vargas, 446, 13º andar, Centro - Rio de Janeiro - RJ, CEP 20071-907, concedendo-lhe poderes da cláusula *ad judicia et extra*, inclusive substabelecer com reserva de poderes, especificamente para apresentação de subsídio ao exame técnico e/ou processo administrativo de nulidade perante o INPI - Instituto Nacional da Propriedade Industrial relacionado à patente de invenção **BR112024010162-2**.

Fortaleza, 25 de novembro de 2025.

_____

Antonio Luiz Dário Bezerra

Presidente

ESTATUTO SOCIAL DO MOVIMENTO NACIONAL DE DOENÇAS NEGLIGENCIADAS

CAPÍTULO I
DA DENOMINAÇÃO, SEDE E FINS

Art.1º O **MOVIMENTO NACIONAL DE DOENÇAS NEGLIGENCIADAS – MNDN,** fundada em 21 de Setembro de 2024 é uma **associação civil, sem fins lucrativos e ou econômicos**, que terá duração por tempo indeterminado e sede no Município de Cuiabá , no Estado de Mato Grosso, na Rua Monte das Oliveiras, 104, quadra 01, bairro Real Parque, Cuiabá – Mato Grosso – CEP 78095.595, neste Estatuto designada como Movimento Nacional de Doenças Negligenciadas que adotará a sigla MNDN.

Parágrafo único: A Sede poderá ser itinerante, tendo como local de sede o domicílio e residência do Presidente eleito.

Art. 2º A Associação tem por finalidades:

a. Defender uma política pública, junto aos poderes públicos, que contemplem, de forma integral, os aspectos necessários ao controle das doenças tropicais negligenciadas em ações decisória, disseminadora e consultiva dentro da sua atuação na causa das Doenças Tropicais Negligenciadas tais como às Hepatites Virais, Tuberculose, HIV/Aids, Sífilis, Hanseníases, Chagas congênita, VIH/Sida, Raiva humana transmitida por cães, Leishmaniose, Malária, Filariose, Oncocercose, Esquistossomose, Amebíase, Tracoma, Sífilis congênita, Praga, Helmintíase transmitida pelo solo, HIV transmissão de mãe para filho, Hepatite B, transmitida de mãe para filho, Infecções sexualmente transmissíveis, HTLV e demais doenças tropicais negligenciadas.

b. Articular, em âmbito federal, estadual e municipal, o desenvolvimento de projetos de leis e ações políticas voltadas para as DTNS.

c. Defender junto ao Ministério da Saúde, órgãos estauduais e municipais, a construção e gerenciamento de um plano científico de prevenção e controle das Doenças Negligenciadas que contemplem desde os aspectos epidemiológicos aos terapêuticos, dando a conhecer suas ações, metas e resultados.

Art. 3º No desenvolvimento de suas atividades, a Associação não fará qualquer discriminação de raça, cor, sexo ou religião.

Art. 4º A Associação poderá ter um Regimento Interno, que aprovado pela Assembléia Geral, disciplinará o seu funcionamento.

Art. 5º A fim de cumprir suas finalidades, a Associação poderá organizar-se em tantas unidades de prestação de serviços, quantas se fizerem necessárias, as quais se regerão por este Estatuto e pelo Regimento Interno, se houver.

CAPÍTULO II
DOS ASSOCIADOS

Art. 6º A Associação é constituída por número ilimitado de associados, que serão admitidos, a juízo da diretoria, dentre pessoas idôneas.

Art. 7º Haverá as seguintes categorias de associados:

I – **Fundadores** – aqueles que assinarem a ata de fundação da Associação;

II – **Beneméritos** - aqueles a quem a Assembleia Geral conferir esta distinção, espontaneamente ou por proposta da diretoria, em virtude dos relevantes serviços prestados à Associação.

III – **Honorários** - aqueles que se fizerem credores dessa homenagem por serviços de notoriedade prestados à Associação, por proposta da diretoria à assembleia Geral;

IV - **Contribuintes** - os que pagarem a mensalidade estabelecida pela Diretoria.

Art. 8º São direitos dos associados quites com suas obrigações sociais:

I - Votar e ser votado para os cargos eletivos, exceto os associados beneméritos e honorários;

II - Tomar parte nas Assembleias gerais.

Art. 9º São deveres dos associados:

I - Cumprir as disposições estatutárias e regimentais;

II - Acatar as determinações da Diretoria.

Parágrafo único: Havendo justa causa, o associado poderá ser demitido ou

excluído da Associação por decisão da diretoria, após o exercício do direito de defesa. Da decisão caberá recurso à Assembleia Geral.

Art. 10. Os associados não respondem, nem mesmo subsidiariamente, pelas obrigações e encargos sociais da Associação.

CAPÍTULO III
DA ADMINISTRAÇÃO

Art. 11. A Associação será administrada por:

I- Assembleia Geral;

II - Diretoria; e

III- Conselho Fiscal.

Art. 12. A Assembleia Geral, órgão soberano da instituição, constituir-se-á dos associados em pleno gozo de seus direitos estatutários.

Art. 13. Compete à Assembleia Geral:

I - Eleger a Diretoria e o Conselho Fiscal;

II - Destituir os administradores;

III - Apreciar recursos contra decisões da diretoria;

IV - Decidir sobre reformas do Estatuto;

V - Conceder o título de associado benemérito e honorário por proposta da diretoria;

VI - Decidir sobre a conveniência de alienar, transigir, hipotecar ou permutar bens patrimoniais;

VII - Decidir sobre a extinção da entidade;

VIII - Aprovar as contas;

IX - Aprovar o regimento interno.

Art. 14. A Assembleia Geral realizar-se-á, ordinariamente, uma vez por ano para:

I - Apreciar o relatório anual da Diretoria;

II - Discutir e homologar as contas e o balanço aprovado pelo Conselho Fiscal.

Art. 15. A Assembleia Geral realizar-se á, extraordinariamente, quando convocada:

I - Pelo presidente da Diretoria;

II - Pela Diretoria;

III - Pelo Conselho Fiscal;

IV - Por requerimento de 1/5 dos associados quites com as obrigações sociais.

Art. 16. A convocação da Assembleia Geral será feita por meio de edital afixado na sede da Associação, por circulares ou outros meios convenientes, com antecedência mínima de 10 dias.

Parágrafo único: Qualquer Assembléia instalar-se-á em primeira convocação com a maioria dos associados e, em segunda convocação, com qualquer número, não exigindo a lei quorum especial.

Art. 17. A Diretoria será constituída por um Presidente, um Vice-Presidente, Primeiro e Segundo Secretários, Primeiro e Segundo Tesoureiros.

Parágrafo Único: O mandato da diretoria será de 3 anos, podendo disputar apenas duas reeleições consecutivas.

Art. 18. Compete à Diretoria:

I - Elaborar e executar programa anual de atividades;

II - Elaborar e apresentar, à Assembleia Geral, o relatório anual;

III - Estabelecer o valor da mensalidade para os sócios contribuintes;

IV - Entrosar-se com instituições públicas e privadas para mútua colaboração em atividades de interesse comum;

V - Contratar e demitir funcionários;

VI - Convocar a Assembleia Geral.

Art. 19. A diretoria reunir-se-á no mínimo uma vez por mês.

Art. 20. Compete ao Presidente:

I - Representar a Associação ativa e passivamente, judicial e extrajudicialmente;

II - Cumprir e fazer cumprir este Estatuto e o Regimento Interno;

III - Convocar e presidir a Assembleia Geral:

IV - Convocar e presidir as reuniões da Diretoria;

V - Assinar, com o primeiro tesoureiro, todos os cheques, ordens de pagamento e títulos que representem obrigações financeiras da Associação.

Art. 21. Compete ao Vice-Presidente:

I - Substituir o Presidente em suas faltas ou impedimentos;

II - Assumir o mandato, em caso de vacância, até o seu término;

III - Prestar, de modo geral, a sua colaboração ao Presidente.

Art. 22. Compete o Primeiro Secretário:

I - Secretariar as reuniões da Diretoria e Assembleia Geral e redigir as atas;

II - Publicar todas as notícias das atividades da entidade.

Art. 23. Compete ao Segundo Secretário:

I - Substituir o Primeiro Secretário em suas faltas ou impedimentos;

II - Assumir o mandato, em caso de vacância, até o seu término; e

III - Prestar, de modo geral, a sua colaboração ao primeiro secretário.

Art. 24. Compete ao Primeiro Tesoureiro:

I - Arrecadar e contabilizar as contribuições dos associados, rendas, auxílios e donativos, mantendo em dia a escrituração;

II - Pagar as contas autorizadas pelo Presidente:

III - Apresentar relatórios de receita e despesas, sempre que forem solicitados:

IV - Apresentar o relatório financeiro para ser submetido à Assembleia Geral;

V - Apresentar semestralmente o balancete ao Conselho Fiscal;

VI - Conservar, sob sua guarda e responsabilidade, os documentos relativos à tesouraria;

VII - Manter todo o numerário em estabelecimento de crédito;

VIII - Assinar, com o presidente, todos os cheques, ordens de pagamento e títulos que representem obrigações financeiras da Associação;

Art. 25. Compete ao Segundo Tesoureiro:

I - Substituir o Primeiro Tesoureiro em suas faltas ou impedimentos;

II - Assumir o mandato, em caso de vacância, até o seu término;

III - Prestar, de modo geral, a sua colaboração ao Primeiro Tesoureiro.

Art. 26. O Conselho Fiscal será constituído por 03 (três) membros, não tendo suplentes, eleitos pela Assembleia Geral.

I - O mandato do Conselho Fiscal será coincidente com o mandato da Diretoria.

II - Em caso de vacância, o mandato será assumido pelo respectivo suplente, até seu término.

Art. 27. Compete ao Conselho Fiscal:

I - Examinar os livros de escrituração da entidade;

II - Examinar o balancete semestral apresentado pelo Tesoureiro, opinando a respeito;

III - Apresentar relatórios de receitas e despesas, sempre que forem solicitados.

IV - Opinar sobre a aquisição e alienação de bens.

Parágrafo Único: O Conselho reunir-se-á ordinariamente a cada 6 meses e, extraordinariamente, sempre que necessário.

Art. 28. As atividades dos diretores e conselheiros, bem como as dos associados, serão inteiramente gratuitas, sendo-lhes vedado o recebimento de qualquer lucro, gratificação, bonificação ou vantagem.

Art. 29. A associação não distribuirá lucros, resultados, dividendos, bonificações, participações ou parcela de seu patrimônio, sob nenhuma forma ou pretexto.

Art. 30. A Associação se manterá através de contribuições voluntárias dos associados e de outras atividades, sendo que as rendas, recursos e eventual resultado operacional serão aplicados integralmente na manutenção e desenvolvimento dos objetivos institucionais, no território nacional.

CAPÍTULO IV
DO PATRIMÔNIO

Art. 31. O Patrimônio da Associação será constituído de bens móveis, imóveis, veículos, semoventes, ações e apólices de dívida pública.

Art. 32. No caso de dissolução da Associação, os bens remanescentes serão destinados à outra instituição congênere, com personalidade jurídica, que esteja registrada no Conselho Nacional de Assistência Social – CNAS ou entidade Pública.

CAPÍTULO V
DAS DISPOSIÇÕES GERAIS

Art. 33. A Associação será dissolvida por decisão da Assembleia Geral Extraordinária, especialmente convocada para esse fim, quando se tornar impossível a continuação de suas atividades.

Art. 34. O presente estatuto poderá ser reformado, em qualquer tempo, por decisão de 2/3 (dois terços) dos presentes à Assembléia Geral especialmente convocada para esse fim, não podendo ela deliberar, em primeira convocação, sem a maioria absoluta dos associados, ou com menos de 1/3 (um terço) nas convocações seguintes, e entrará em vigor na data de seu registro em Cartório.

Art. 35. As reuniões das Assembléia Geral, ordinária e extraordinária, da Diretoria e do Conselho Fiscal poderão ser realizadas por meio eletrônico, respeitados os direitos previstos de participação e manifestação.

Art. 36. Os casos omissos serão resolvidos pela Diretoria e referendados pela Assembleia Geral.

O presente estatuto foi aprovado pela Assembleia Geral realizada no dia 21 de Setembro de 2024.

Cuiabá, 21 de setembro de 2024.

João Victor P fós kersul de Carvalho

João Victor Pacheco Fós Kersul de Carvalho
Presidente

José Carlos dos Santos Filho
OAB/MT 6698

TABELIONATO E REGISTRO DE TÍTULOS DOCUMENTOS E PESSOAS JURÍDICAS
PESSOA JURÍDICA - O.S. 719938
CERTIDÃO
Certifico que este documento é parte integrante do Registro nº 46543 datado de 17/03/2025
CUIABÁ-MT, 17 de março de 2025
Em testemunho da verdade
Artur Fazzio de Abreu - Escrevente Autorizado

ATA DA ASSEMBLÉIA GERAL EXTRAORDINÁRIA, PARA CONSTITUIÇÃO DE ASSOCIAÇÃO CIVIL, MOVIMENTO NACIONAL DE DOENÇAS NEGLIGENCIADAS que adotará a sigla MNDN. APROVAÇÃO DE ESTATUTO SOCIAL, ELEIÇÃO E POSSE DA PRIMEIRA DIRETORIA E CONSELHO FISCAL.

Aos 21 dias do mês de Setembro do ano de 2024 , reuniram-se em primeira convocação, no horário 08:00, de forma presencial realizada no Teatro da Faculdade de Medicina de São Paulo no endereço (Av. Dr. Arnaldo 455, Cerqueira César, São Paulo - SP CEP: 01246-903).

Fundadores: João Victor Pacheco Fós Kersul de Carvalho, brasileiro, solteiro, vendedor. CPF: 026.105.141-58, RG: 1988522-9 SSP/MT. Residente: Rua Monte das Oliveiras, 104, quadra 01, bairro Real Parque, Cuiabá – Mato Grosso – CEP 78095.595; Bartolomeu Luiz de Aquino, brasileiro, casado, advogado, CPF: 325.327.174-91, RG: 644.769 SSP/RN. Residente: Rua Romualdo Galvão, 1472, bairro Lagoa Nova, Natal – RN, CEP 59056.100; Gisele da Silva Oliveira, brasileira, solteira, vendedora. CPF: 009.496.102-67, RG: 00949610267 SSP/MT. Residente: Rua Monte das Oliveiras, 104, quadra 01, bairro Real Parque, Cuiabá – Mato Grosso – CEP 78095.595; José Candido da Silva, brasileiro, solteiro, aposentado. CPF: 450.212.954-20, RG: 8736131 SDS/PE. Residente: Rua Rio Morno, 145, bairro Linha do Tiro, Recife – PE, CEP 52140.610; Kássia Pollyane Gomes Medeiros, brasileira, solteira, jornalista. CPF: 04749.69.54-16, RG: 6414452 SDS/PE. Residente: Rua Olavo Bilac, 75 casa A, bairro Curado II, Jabotãodos Guararapes – PE, CEP 54220-060; Fábio Correia Costa, brasileiro, solteiro, educador social. CPF: 386.829.664-68, RG: 2.393.228 SDS/PE. Residente: Av. Conde da Boa Vista, 250, apt 1110C, Boa Vista, Recife – PE, CEP 50060-004; Dircelene Mendonça Cavalcanti, brasileira, solteira, aposentada. CPF: 375.392.564-00, RG: 1144289 SDS/PE. Residente a Rua Itaimbé, 35, Ipsep – Recife/PE, CEP 51.350.030; Joanda Gomes Araújo, brasileira, solteira, do lar. CPF: 115.967.138-95, RG: 10794889 SDS/PE. Residente: Rua 11 de setembro, 5, Maraial, Recife – PE, CEP 55405-000; Ana Paula Ferreira dos Santos, brasileira, agricultora, solteira, CPF: 981.815.305-78, RG: 9276669-28 SSP/BA. Residente: Rua São Paulino, Teolândia – BA, CEP 45.465-000; Maurineia Roseno de Vasconcelos, brasileira, solteira, do lar. CPF: 046.257.644-24, RG: 6602426 SDS/BA. Residente: Rua Lage do Uma, bairro Alto José do Pinho, 336, Recife – PE, CEP 52.110.435;Gian Elias da Silva Oliveira, Brasileiro, solteiro, vigilante, CPF: 026.078.052-95 RG: 026.078.052-95 SSP-MT Residente a Rua Maria Tereza Conceição, N 03 Quadra 108 - São Mateus - Várzea Grande - MT CEP: 78152-118; Amélia Bispo Nascimento dos Santos, brasileira, solteira, aposentada, CPF: 922.491.328-87, RG: 00551.626-90 SSP/BA. Residente: Vilarejo de Arembepe Quadra F, Lote 11, Camaçari, Salvador – BA; Maria Susana Nascimento, brasileira, casada, enfermeira, CPF: 35766751320 RG: 96021056018 SSP/CE . Residente : Rua Maria Julia 267, Granja Portugal

– Fortaleza-CE, CEP: 60545255. Daisy Silva de Jesus, brasileira, solteira, vendedora, CPF: 411.211.715-91 RG: 129568643 ssp - BA Residente a Travessa Pedro Gama de baixo 69C condomínio veredas do bosque EDF Cedro ap22 Bairro Federação Salvador – BA; Maria Aucineide Basílio de Albuquerque, Brasileira, união estável, Técnica de enfermagem, CPF: 61652903453 RG: 3776473 SSP-PE residente a Rua São José da Coroa Grande n° 20 Bomba do Hemetério CEP 52.111-595. Que se reuniram para fundar uma associação civil sem fins lucrativos, denominada MOVIMENTO NACIONAL DE DOENÇAS NEGLIGENCIADAS que adotará a sigla MNDN, com sede na rua Monte das Oliveiras, 104, quadra 01, bairro Real Parque, Cuiabá – Mato Grosso – CEP 78095.595; Cuiabá - MT, regida na forma do estatuto aprovado. Assumiu a presidência o fundador Sr. João Victor Pacheco Fos Kersul de Carvalho, que para secretária designou a Sra. Gisele da Silva Oliveira, dando por instalada a assembleia. Foi deliberado sobre o nome e então aprovado o nome: Movimento Nacional de doenças negligenciadas - MNDN com sede na rua Monte das Oliveiras, 104, quadra 01, bairro Real Parque, Cuiabá – Mato Grosso – CEP 78095.595; Cuiabá - MT, em seguida Foi procedida a leitura do projeto do estatuto, o qual foi submetido à discussão e após, colocado em votação, foi aprovado por unanimidade. A seguir, realizou-se a eleição dos membros da primeira diretoria e conselho fiscal, que foi posta em votação e ficou assim constituída: Presidente:João Victor Pacheco Fós Kersul de Carvalho, brasileiro, solteiro, vendedor. CPF: 026.105.141-58, RG: 1988522-9 SSP/MT. Residente: Rua Monte das Oliveiras, 104, quadra 01, bairro Real Parque, Cuiabá – Mato Grosso – CEP 78095.595. Vice-Presidente: Bartolomeu Luiz de Aquino, brasileiro, casado, advogado. OAB/RN 16.279, CPF: 325.327.174-91, RG: 644.769 SSP/RN. Residente: Rua Romualdo Galvão, 1472, bairro Lagoa Nova, Natal – RN, CEP 59056.100. Primeira Secretária: Gisele da Silva Oliveira, brasileira, solteira, vendedora. CPF: 009.496.102-67, RG: 00949610267 SSP/MT. Residente: Rua Monte das Oliveiras, 104, quadra 01, bairro Real Parque, Cuiabá – Mato Grosso – CEP 78095.595. Segundo Secretário: José Candido da Silva, brasileiro, solteiro, aposentado. CPF: 450.212.954-20, RG: 8736131 SDS/PE. Residente: Rua Rio Morno, 145, bairro Linha do Tiro, Recife – PE, CEP 52140.610E para Tesoureiro: Gian Elias da Silva Oliveira, Brasileiro, solteiro, vigilante, CPF: 026.078.052-95 RG: 026.078.052-95 SSP-MT Residente a Rua Maria Tereza Conceição, N 03 Quadra 108 - São Mateus - Várzea Grande - MT CEP: 78152-118 e Para Segundo tesoureiro eleita a Sra: Kássia Pollyane Gomes Medeiros, brasileira, solteira, jornalista. CPF: 04749.69.54-16, RG: 6414452 SDS/PE. Residente: Rua Olavo Bilac, 75 casa A, bairro Curado II, Jabotão dos Guararapes – PE, CEP 54220-060. Na mesma votação foram apresentados os membros do Conselho Fiscal, igualmente eleitos efetivos: Primeiro membro do Conselho Fiscal a Sra: Maria Susana Nascimento, brasileira, casada, enfermeira, CPF: 35766751320 RG: 96021056018 SSP/CE . Residente : Rua Maria Julia 267, Granja Portugual – Fortaleza-CE, CEP: 60545255. Segundo membro do Conselho Fiscal a Sra: Maria Aucineide Basilio de

Albuquerque, Brasileira, união estável, Técnica de enfermagem, CPF: 61652903453 RG: 3776473 SSP-PE residente a Rua São José da Coroa Grande n° 20 Bomba do Hemetério CEP 52.111-595.E terceiro membro do Conselho Fiscal a Sra: Amélia Bispo Nascimento dos Santos, brasileira, solteira, aposentada. CPF: 922.491.328-87, RG: 00551.626-90 SSP/BA. Residente: Vilarejo de Arembepe Quadra F, Lote 11, Camaçari, Salvador – BA. Não tendo membros suplentes para o conselho fiscal. Após a eleição, os eleitos para cargos na diretoria e no conselho fiscal tomaram posse imediatamente para o mandato que se inicia no dia 21 de Setembro de 2024 até o dia 21 de Setembro de 2027. O presidente informou que a documentação da associação será levada ao Cartório de Registro Civil das Pessoas Jurídicas desta Comarca para registro e formalização da constituição.

Nada mais havendo a deliberar, o presidente abriu a palavra para quem quisesse se manifestar. Após, determinou a suspensão da sessão pelo tempo necessário à transcrição do estatuto. Reaberta a sessão foi lavrada a presente ata, que após lida e achada conforme, segue assinada por mim secretária e pelo presidente. Os demais participantes figurarão na lista de presença.

João Victor Profi Kusul de Carvalho

Presidente

Gisele da Silva Oliveira

Secretário

PROCURAÇÃO *ad judicia*

MOVIMENTO NACIONAL DE DONEÇAS NEGLIGENCIADAS (NOME DA ORG, pessoa jurídica de direito privado, sem fins lucrativos, constituída na forma da lei, registrada no CNPJ sob o n° 59.935.301/0001-50 com sede na Rua Monte das Oliveiras, 104, quadra 01, bairro Real Parque, Cuiabá-MT, na pessoa de seu representante nos termos de seu Estatuto Social, por seu vice presidente Sr. Bartolomeu |Luiz de Aquino, brasileiro, casado, advogado RG n°644.769 SSP/RN emitido pelo SSP/RN, e inscrito no CPF n° 325.327.174-91 vem pelo presente instrumento outorgar procuração *ad* judicia à advogada **SUSANA RODRIGUES CAVALCANTI VAN DER PLOEG**, inscrita no CPF 013.497.254-63 e na **OAB/MG 181.599**, com escritório na Avenida Presidente Vargas, 446, 13º andar, Centro - Rio de Janeiro - RJ, CEP 20071-907, concedendo-lhe poderes da cláusula *ad judicia et extra*, inclusive substabelecer com reserva de poderes, especificamente para apresentação de subsídio ao exame técnico e/ou processo administrativo de nulidade perante o INPI - Instituto Nacional da Propriedade Industrial relacionado à patente de invenção **BR112024010162-2**.

Cuiabá-MT, 25 de novembro de 2025.

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BARTOLOMEU LUIZ DE AQUINO
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Bartolomeu Luiz de Aquino

Vice Presidente

Registro Civil de Pessoas Jurídicas
CARTÓRIO DO 1º OFÍCIO
NOVA IGUAÇU
Margarida Maria Gaspar Gomes
Oficiala

ESTATUTOS SOCIAIS

AGANI- ASSOCIAÇÃO DE GAYS E AMIGOS DE NOVA IGUAÇU

CAPÍTULO I - DA DENOMINAÇÃO, SEDE E FINS

Artigo 1º - A AGANI - Associação de Gays e Amigos de Nova Iguaçu é uma associação civil, sem fins lucrativos, por tempo indeterminado, fundado em 17 de dezembro de 1988, com sede em Nova Iguaçu.

Parágrafo Único - Qualquer pessoa poderá tornar-se membro da AGANI conforme este estatuto, não havendo nenhuma forma de discriminação ou preconceito.

Artigo 2º - A AGANI não pertence a nenhuma facção politica, não se furtando, contudo, a apoiar qualquer partido ou candidato que defenda os direitos dos homossexuais e que, ao mesmo tempo, não contrarie o presente Estatuto.

Artigo 3º - A AGANI não tem qualquer vinculo a qualquer partido politico ou credo religioso, não sendo entretanto apolitico, e tem como objetivo a defesa e conscientização dos direitos e liberdades individuais das "minorias" oprimidas, dedicando especial atenção aos homossexuais, constituindo assim um Movimento de Emancipação Homossexual.

Parágrafo Único - Apesar de priorizar a defesa e conscientização dos direitos dos homossexuais a AGANI há de se manter atento e solidarizar-se com todas as iniciativas de combate ao preconceito e discriminação de que são alvo as " minorias".

Artigo 4º - Para atingir seus objetivos a AGANI propõe-se a:

A - Divulgar da maneira mais ampla possivel todos os pronúnciamentos cientificos, politicos, religiosos, etc., pelo fim do preconceito aos homossexuais.

B - Esforçar-se para conseguir junto a universidades, escolas, associações, de classe ou civis, partidos politicos, meios de comunicação de massas, etc., a promoção de debates, palestras e pronúnciamentos que visem o fim da discriminção aos homossexuais.

C - Combater a legislação discriminatória contra os homossexuais.

D - Protestar contra qualquer propaganda preconceituosa em relação aos homossexuais e outros segmentos estigmatizados.

E - Protestar contra qualquer arbitrariedade pública contra os homossexuais.

F - Manter intercâmbio com outros grupos homossexuais e demais instituições públicas e privadas do Brasil e do exterior.

Artigo 5º - Para viabilizar a consecução de seus objetivos a AGANI propõe-se, ainda, a criar e fortalecer os laços de solidariedade entre os homossexuais através de eventos culturais, educacionais e sociais.

CAPÍTULO II - DA ADMINISTRAÇÃO

Artigo 6º - A AGANI é constituido dos seguintes órgãos de administração:

- ASSEMBLEIA GERAL
- DIRETORIA
- CONSELHO FISCAL

SESSÃO I - DA DIRETORIA

Artigo 7º - A AGANI será representado ativa e passivamente, em Juizo ou fora dele, pelo seu Presidente que responderá pessoalmente pela omissão ou negligência na defesa dos interêsses da associação. Para esse efeito, qualquer diretor da AGANI ou 1/3 de seus membros terá legitimidade para adotar as medidas legais compativeis.

Artigo 8º - A Diretoria da AGANI com mandato de 01 (um) ano é composta de:

PRESIDENTE, VICE PRESIDENTE, SECRETÁRIO GERAL, TESOUREIRO, 1ª VOGAL e 2ª VOGAL. As delibrações serão tomadas em comum acordo, exigindo-se para isso o quorum minimo de 1/2 da Diretoria.

Parágrafo Primeiro - Qualquer membro do a AGANI poderá ser eleito para Diretoria, vetado a utilização do cargo para politica eleitoral (partidária) sob pena de destituição do cargo. A candidatura a cargo politico ou o seu exercicio implicará no afastamento automático do cargo que exercer na AGANI.

Parágrafo Segundo - A Diretoria da AGANI será eleita por Assembléia Geral Ordinária convocada com este fim especifico.

Parágrafo Terceiro - O mandato da Diretoria da AGANI poderá ser alterado por Assembléia Geral extraordinária com este fim especifico.

Artigo 9º - A Diretoria do poderá criar, em qualquer momento, ou dissolver, qualquer departamento que julgue necessário ao seu desenvolvimento e finalidades de acordo com os princípios do presente Estatuto.

Parágrafo Primeiro - Tais departamentos terão um Diretor e um Suplente.

Parágrafo Segundo - O mandato dos departamentos se incorpora a Diretoria original.

Parágrafo terceiro- O(s) Diretor(s) e Suplente(s) passam a integrar a Diretoria em igualdade de direitos e deveres.

Artigo 10º- Compete à Diretoria da AGANI:

A - Procurar resolver por todos os meios legais ao seu alcance os problemas de interesse dos associados.

B - Convocar as Assembléias Gerais.

C - Cumprir e fazer cumprir os Estatutos e as decisões das Assembléias Gerais.

D - Providenciar para que a Tesoraria prepare os balancetes mensais e anuais para prestação de contas.

E - Preparar o relatório anual sobre as atividades da AGANI.

F - Reunir-se mensalmente para resolver as questões que lhe competem.

SESSÃO II - DAS ATRIBUIÇÕES DOS MEMBROS DA DIRETORIA

Artigo 11º- São atribuições dos membros da Diretoria da AGANI:

PRESIDENTE - A) Presidir e coordenar as reuniões da Diretoria e das Assembléias Gerais.
B) Assinar juntamente aos outros membros da Diretoria os livros da Secretaria e da Tesouraria.
C) Superintender em caráter geral todas as atividades da Diretoria e de seus membros respeitando sempre as funções de cada um.
D) Delegar poderes para representá-lo a outro membro da Diretoria ou Associado em seus impedimentos.

VICE - PRESIDENTE - A) Substituir o Presidente em todos os seus impedimentos.
B) Cooperar com o Presidente em todas as suas atribuições.

SECRETÁRIO GERAL - A) Redigir as atas de Assembléias Gerais e reuniões da Diretoria, como também todos os eventos promovidos

pela AGANI ou nos quais o mesmo participe.
B) Dirigir os trabalhos da Secretaria Geral e redigir toda a correspondência da AGANI.
C) Fornecer ao Presidente os dados necessários para a confecção de relatórios da AGANI.

TESOUREIRO - A) Promover a arrecadação da receita.
B) Efetuar pagamento de todas as despesas da AGANI.
C) Apresentar à Diretoria da AGANI mensalmente e à Assembléia Geral anualmente, o balanço finaceiro e material.
D) Dirigir todo o serviço de escrita da Tesouraria em livros apropriados.

1ª VOGAL e 2ª VOGAL - A) Substituir as vacâncias da Diretoria.
B) Cooperar com a Diretoria em todas as suas atribuições.

Artigo 12º- Nenhum dos cargos que compõem a Diretoria da AGANI será remunerado.

CAPÍTULO III - DAS ASSEMBLÉIAS GERAIS

Artigo 13º- A ASSEMBLÉIA GERAL é o órgão máximo de deliberação da AGANI, constituida por todos os seus membros admitidos e legalmente registrados no mesmo e somente a eles cabe o direito a voto.

Artigo 14º- A ASSEMBLÉIA GERAL poderá ser convocada em caráter Ordinário ou Extraordinário, com ampla divulgação com antecedência mínima de 15 dias.

Parágrafo Único - Em primeira convocação a ASSEMBLÉIA GERAL delibera com a presença mínima de 1/3 de seus associados e com qualquer número na segunda convocação.

Artigo 15º- A ASSEMBLÉIA GERAL Ordinária será trimestralmente para conhecimento, discussão e deliberação dos relatórios da Diretoria.

Parágrafo Único - A convocação das ASSEMBLÉIAS GERAIS Ordinárias e Extraordinárias serão de competência da Diretoria da AGANI ou de 1/5 de seus membros.

Artigo 16º - Compete à ASSEMBLÉIA GERAL Ordinária:

A) Anualmente eleger a Diretoria bem como o seu programa.

B) Conhecer, discutir e julgar relatórios sobre as atividades da Diretoria da AGANI.

C) Traçar planos comuns de ação.

D) Decidir sobre casos omissos deste Estatuto.

E) Alterar o Estatuto conforme o disposto no artigo 30º.

Artigo 17º- A ASSEMBLÉIA GERAL Extraordinária será convocada para atendimento de situação de emergência sempre que necessário.

Artigo 18º- Qualquer pessoa poderá participar das Assmbléias e Reuniões de Diretoria, com direito à voz mas sem direito a voto.

Artigo 19º- É vetado o voto por procuração.

Artigo 20º- O Conselho Fiscal é composto de:

A) Presidente
B) Dois Conselheiros

Parágrafo Único- O Conselho Fiscal terá mandato e 01 (um) ano coincidente com o da Diretoria, permitindo a recondução de seus membros.

Artigo 21º- Compete ao Conselho Fiscal fiscalizar e indicar aprovação dos reletórios financeiros da Diretoria da AGANI na Assembléia Ordinária.

SESSÃO I - DOS MEMBROS

Artigo 22º- Serão considerados membros da AGANI todos aqueles maiores de 18 (dezoito) anos que estejam de acordo com o presente Estatuto e Programa de Ação, e que tenham participado de pelo menos duas atividades promovidas pela AGANI, preenchendo a ficha de filiação individual.

Parágrafo Único - Em quaisquer circunstâncias somente terão acesso às fichas de filiação a Diretoria da AGANI, resguardando assim o direito a inviolabilidade concernente à pessoa humana.

Artigo 23º- São direitos dos Membros da AGANI:

A) Propor e discutir e votar em ASSEMBLÉIAS GERAIS.

B) Votar e ser votado para cargos de direção segundo as restrições estabelecida no presente estatuto.

C) Usufruir dos serviços prestados pela AGANI.

Artigo 24º - São deveres dos membros da AGANI:

A) Respeitar e fazer respeitar o presente estatuto.

B) Propagar as vantagens decorrentes da união em torno da AGANI.

C) Promover por todos os meios ao seu alcance o progresso da AGANI.

D) Participar na medida do possivel de todas as atividades da AGANI.

E) Manter suas contribuições mensais em dia sujeitando-se os faltosos a perda do direito a voto.

F) Aceitar, salvo motivo de força maior, qualquer cargo para o qual tenha sido designado ou eleito e desempenhá-lo com dedicação e proficiência.

Artigo 25º - Poderão ser aplicadas sanções aos membros da AGANI que firam os intereses e objetivos do mesmo, devendo Assembléia Geral.

CAPÍTULO IV - DO PATRIMÔNIO E FUNDO SOCIAL

Artigo 26º - O patrimônio e fundo social da AGANI será constituido de:

A) Conribuições regulares dos membros decididas em Assembléia Geral

B) Doações e legados.

C) Bens e valores adquiridos

D) Rendas provenientes de qualquer atividade promovida pela AGANI.

E) Quaisquer valores adventicios (empréstimos e financiamentos).

Parágrafo Único - Ainda que sem fins lucrativos a AGANI constituir renda visando a sua aplicação na sequência dos objetivos do mesmo.

CAPITULO V - DAS DISPOSIÇÕES GERAIS E TRANSITÓRIAS

Artigo 27º - Os membros associados não responderão ainda que subsidiáriamente pelas obrigações contraidas pela AGANI.

Artigo 28º - Nenhum membro da AGANI poderá utilizar o patrimônio ou fundo social para beneficio próprio.

Artigo 29º - A reforma estatutária somente será possivel em Assembléia Geral Ordinária que elege a Diretoria da AGANI, ou Assembléia Geral Extraordinaria convocada com este fim especifico.

Artigo 30º - Dar-se à a dissolução da AGANI somente por Assembléia Geral Extraordinária com este fim especifico exigindo quorum especial de 2/3 dos seus membros, e que tal decisão seja por maioria absoluta, isto é, 2/3 do total dos votantes.

Artigo 31º - Em caso de dissolução da AGANI seus bens imóveis e móveis serão doados a critério da Assembléia Geral que o dissolve.

Artigo 32º - O presente estatuto entrará em vigor na data de sua aprovação.

Nova Iguaçu, 17 de dezembro de 1988.

PRESIDENTE: Manoel Ferreira da Cunha

VICE-PRESIDENTE: Sérgio Serafim Pinto

SECRETÁRIO GERAL: Rosa Maria Campos Paiva

TESOUREIRO: Solange Wendt

1º VOGAL: Maria Bárbara Amorim Menezes

2º VOGAL: Odair Santos da Silva

Registro Civil das Pessoas Jurídicas
CARTÓRIO DO 3.º OFÍCIO
NOVA IGUAÇU
Margarida Maria Gaspar Gomes
Oficial

REGISTRO DE PESSOAS JURÍDICAS
Nova Iguaçu
CGC 39.651.640/0001-22
CARTÓRIO 3.º OFÍCIO
Oficial - Margarida Maria Gaspar Gomes
Oficial Substituta - Divanice Rosendo Soares da Silva
Apresentada hoje para registro e aposta sob o n.º de ordem 8957 no PROTOCOLO 2º livro nº 1 Registro sob o n.º de ordem 8957 do livro nº 3 DE REGISTRO DE PESSOAS JURÍDICAS.
Nova Iguaçu 31 de agosto 1995
Jacyra de O. Costa - Sub oficial

Cartório do 3.º Ofício
Nova Iguaçu
Jacyra de O. Costa
Sub Oficial
Matr. 06 1839

AGANIM
DESDE 1988

ASSOCIAÇÃO DE GAYS E AMIGOS DE NOVA IGUAÇU E MESQUITA

ELEIÇÃO DA DIRETORIA 30/07/2024 – 30/07/ 2028

Aos 30 (trinta) dias do mês de julho de 2024, na cidade de Mesquita, Estado do Rio de Janeiro, com a presença do seu fundador, membro efetivo: seu Presidente, Manoel Ferreira da Cunha, técnico em relações públicas, solteiro, inscrito no RG sob o nº 27.391.408-5, expedida pelo DETRAN-RJ, em 27/11/2017, e inscrito no CPF sob o nº 876.553.737-87, residente e domiciliado na Rua Marcial, 42, Juscelino, Mesquita, Rio de Janeiro e demais membros da diretoria a seguir: Vanessa Aparecida Coelho da Silva, artesã, casada, inscrita no RG sob o nº 21.069.559-9, Vice-presidente, expedida pelo DETRAN RJ, inscrita no CPF sob o nº 111.010.517-79, Vice-presidente, residente e domiciliada na Rua Tenente Audir Soares Adriano, 118, casa 8, Mesquita, RJ e Regina Célia de Oliveira Bueno, advogada aposentada, solteira, inscrita na OAB-RJ sob o nº 156.275 e no CPF 510.502.267-04, Diretora Geral e de Articulação, residente e domiciliada na Rua Cinco de Julho, 335, ap. 301, Copacabana, RJ, foi realizada a Assembleia Ordinária da AGANI - Associação de Gays e Amigos de Nova Iguaçu, conhecida pelo nome fantasia de INSTITUTO AGANIM – ASSOCIAÇÃO DE GAYS E AMIGOS DE NOVA IGUAÇU E MESQUITA e RIO DE JANEIRO, CNPJ nº 00.790.968/0001-69, entidade civil sem fins lucrativos, com sede na Rua Marcial, 42, o Bairro Juscelino, Mesquita, RJ, tendo essa apenas a seguinte pauta: ELEIÇÃO DA NOVA DIRETORIA para cobrir a gestão de 2024 a 2028 e deliberado, a seguir: dado início aos trabalhos do pleito eleitoral da AGANIM 2024-2028 , foi convidado a presidir a assembleia, o Senhor Presidente da organização, Manoel Ferreira da Cunha, que aceitou o encargo e como secretária a Sra. Regina Celia de Oliveira Bueno, que igualmente aceitou o encargo dessa. Diretamente ao encaminhamento da presente pauta o Senhor Presidente informa sobre as competências necessárias para atendimento aos preceitos estabelecidos pelo estatuto vigente da organização quanto aos cargos, para que ninguém tivesse dúvida sobre os compromissos ora assumidos. Ato contínuo, informa a saída da Sra. Vanessa Aparecida Coelho da Silva que deixa o cargo de Vice-Presidente sendo substituída pela Sra. Regina Célia de Oliveira Bueno, acima qualificada e a saída da Sra. Adriana Vieira Ferreira que deixa o cargo de Diretora Executiva e Financeira não sendo substituída por nenhum dos integrantes da ONG e que no cargo da Sra. Regina Célia de Oliveira Bueno ficará a Moacyr

Cajueiro da Silva, solteiro, brasileiro, portador da RG nº 08.619.410-7 e inscrito no CPF sob o nº 004.528.777-50, residente e domiciliada na Rua Mercúrio, 559,casa 3, Mesquita, RJ, para o cargo de Diretor Geral e de Articulação. Em seguida submeteu aos/as presentes os nomes escolhidos para a nova diretoria, que foi totalmente votada e aprovada, por unanimidade, inclusive seu Conselho Fiscal, que será formado por: Presidente: Manoel Ferreira da Cunha, Vice-presidente: Regina Célia de Oliveira Bueno e a Diretora Geral e de Articulação: Moacyr Cajueiro da Silva.

Nada mais havendo a se pronunciar o presente ato foi firmado entre as partes e ora apresenta ata firmado sendo, posteriormente, registrado no Cartório de Registro Civil de Pessoas Jurídicas.

Mesquita, RJ, 30 de julho de 2024.

CARTÓRIO MESQUITA

MANOEL FERREIRA DA CUNHA

Presidente

CARTÓRIO MESQUITA

MOACYR CAJUEIRO DA SILVA

Diretor Geral e de Articulação

Cartório do 1º Ofício de Mesquita - RJ
Rua Mister Watkins, nº 300 - Centro - Mesquita/RJ - CEP 26553-090 - Tel.: (21) 3769-8034
TABELIÃO: CLÁUDIO DE FREITAS F. ALMEIDA

Reconheço por semelhança a(s) firma(s) de MANOEL FERREIRA DA CUNHA - EEWP57014-PEE, MOACYR CAJUEIRO DA SILVA - EEWP57015-AEE, e dou fe
Mesquita-RJ, 07 de fevereiro de 2025.
Gabrielle Silva dos Santos Escrevente
Qtd 2 Emolumentos R$ 15,72 Taxas: R$ 12,14 Total R$ 27,86
Consulte em https://www3.tjrj.jus.br/sitepublico
153346AA

Gabrielle Silva dos Santos
ESCREVENTE
CGJ-RJ: 94/17047

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CARTORIO DO 2 OFICIO DE MESQUITA
RUA PREFEITO JOSE MONTES PAIXAO, 1623
CNS: 154302
REGISTRO CIVIL DE PESSOA JURIDICA
Apres. no dia 07/02/2025 p/ Reg.Int. e Prot. 2717, Lv. A1
Reg.N.2717 no livro A-40,Fls.167/168.
No dia de hoje. MESQUITA, 13/02/2025.
Emol.: R$325,11. Fetj: R$65,02. Fund: R$16,25. Funp: R$16,25.
Funa.: R$19,50. Pmcmv: R$6,50. Iss: R$16,25. Selo: R$2,71.
Dist.: R$0,00. Total: R$467,59
EDEF 23471 WCZ Consulte www4.tjrj.jus.br/Portal-Extrajudicial/consultaselo/

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PROCURAÇÃO *ad judicia*

AGANI – ASSOCIAÇÃO DE GAYS E AMIGOS DE NOVA IGUAÇU, conhecida pelo nome fantasia de AGANIM-ASSOCIAÇÃO DE GAYS E AMIGOS DE NOVA IGUAÇU, MESQUISTA E RIO DE JANEIRO, pessoa jurídica de direito privado, sem fins lucrativos, constituída na forma da lei, registrada no CNPJ sob o n° 00.790.968/0001-69, com sede na Rua Marcial, nº 42, Bairro Juscelino, Mesquita, RJ, na pessoa de seu representante nos termos de seu Estatuto Social, por seu Regina Célia de Oliveira Bueno, brasileira, advogada, solteira, Vice-Presidente, inscrita na OAB/RJ sob o nº 156.275, e no CPF sob o nº 510.502.267-04, vem pelo presente instrumento outorgar procuração *ad* judicia à advogada **SUSANA RODRIGUES CAVALCANTI VAN DER PLOEG**, inscrita no CPF 013.497.254-63 e na **OAB/MG 181.599**, com escritório na Avenida Presidente Vargas, 446, 13º andar, Centro - Rio de Janeiro - RJ, CEP 20071-907, concedendo-lhe poderes da cláusula *ad judicia et extra*, inclusive substabelecer com reserva de poderes, especificamente para apresentação de subsídio ao exame técnico e/ou processo administrativo de nulidade perante o INPI - Instituto Nacional da Propriedade Industrial relacionado à patente de invenção **BR112024010162-2.**

Mesquita (RJ), 25 de novembro de 2025.

gov.br Documento assinado digitalmente
REGINA CELIA DE OLIVEIRA BUENO
Data: 01/12/2025 [illegible]
Verifique em https://validar.iti.gov.br

REGINA CÉLIA DE OLIVEIRA BUENO
Vice-Presidente

Pague via Pix com o QrCode ao lado

Recibo do pagador

BANCO DO BRASIL | 001-9 | 00190.00009 02940.916238 49029.570170 5 13100000014500

Nome do Pagador / CPF / CNPJ / Endereço
ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS, CPF/CNPJ: 29263068000145
AVENIDA PRESIDENTE VARGAS, 446 - 13° ANDAR, RIO DE JANEIRO, RJ, CEP: 20071-907
Sacador/Avalista

Nosso-Número	Nr. Documento	Data de Vencimento	Valor Documento	(=) Valor Pago
29409162349029570	29409162349029570	29/12/2025	R$ 145,00	

Nome do Beneficiário/CPF/CNPJ/Endereço
INSTITUTO NACIONAL DA PROPRIEDADE INDUST CPF/CNPJ: 42.521.088/0001-37
RUA MAIRINK VEIGA, 9 24 ANDAR ED WHITE MARTINS - CENTRO, RIO DE JANEIRO - RJ, CEP 20090-910

Agencia/Código do Beneficiário	Autenticação Mecânica
2234-9/333028-1	

BANCO DO BRASIL | 001-9 | 00190.00009 02940.916238 49029.570170 5 13100000014500

Local de Pagamento
PAGÁVEL EM QUALQUER BANCO ATÉ O VENCIMENTO

Data Vencimento
29/12/2025

Nome do Beneficiário/CPF/CNPJ
INSTITUTO NACIONAL DA PROPRIEDADE INDUST CPF/CNPJ: 42.521.088/0001-37

Agência / Código do Beneficiário
2234-9/333028-1

Data do Documento	Nr. Documento	Espécie DOC	Aceite	Data do processamento	Nosso-Número
30/11/2025	29409162349029570	DS	N	30/11/2025	29409162349029570

Uso do Banco	Carteira	Espécie	Quantidade	x Valor	(=) Valor documento
29409162349029570	17	R$			R$ 145,00

Informações de Responsabilidade do Beneficiário

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(-) Desconto / Abatimento

(+) Juros/Multa

(=) Valor Cobrado

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ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS, CPF/CNPJ: 29263068000145
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Código de Baixa

Sacador/Avalista

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Comprovante BB

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Recebedor

Inpi

CNPJ
42.521.088/0001-37

Instituição
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Pagador

Carolinne Thays Scopel

CPF
***.253.509-**

Agência
1243-2

Conta
39129-8

Instituição
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Informações adicionais

ID: E00000000202511302220076983946 35

Devedor: SILEIRA INTERDISCIPLINAR DE AIDS - ABIA

Nome da cobrança: Pagamento referente ao Boleto

Cód.Produto: BOLETO29409162349029570DATA30112025

CEP: 20.071-907

Endereço: Avenida Presidente Vargas, 446 - 13° a

UF: RJ

Comprovante emitido em: 30/11/2025 às 19:20:25

Documento: 000000000120101

Autenticação SISBB: 3.BAC.0BE.260.670.A2B

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0800 729 0001 Demais localidades.
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Ouvidoria: 0800 729 5678
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