JUNE 28, 2023

THE CONTROLLER OF PATENT
THE PATENT OFFICE
NEW DELHI

KIND ATTN.: DR. SUMAN VERMA
ASSISTANT CONTROLLER OF PATENTS AND DESIGNS

Re: REPRESENTATION U/S 25(1) OF THE PATENT ACT – BY POONAM KUMARI AGAINST INDIAN PATENT APPLICATION NO. 201917006277 FILED ON 18/02/2019
TITLE: THERAPEUTIC COMPOUNDS USEFUL FOR THE PROPHYLACTIC OR THERAPEUTIC TREATMENT OF AN HIV VIRUS INFECTION
APPLICANT: GILEAD SCIENCES, INC.
OUR REF.: OPP0422

Respected Madam,

We are filing this representation by way of Pre-Grant Opposition along with annexures u/s 25 (1) of the Patents Act, 1970 and Rule 55 of the Patent Rules, 2003 in Form 7A.

The Learned Controller is requested to take said opposition along with annexures on record and proceed further in the matter and keep the Opponent advised of each and every step taken in the matter.

We crave the leave of the Learned Controller to submit additional documents and/or evidence to support any of the averments in the representation as may be necessitated during the future proceeding.

Lastly, we request the Learned Controller to grant an opportunity of being heard before the present Opposition is finally decided.

Thanking you,

Yours faithfully,

MD. AZHARUDDIN
FOR SILVER LINING IP LLP
AGENT FOR THE OPPONENT

Encl.: As stated

C.C: K & S PARTNERS
Email: ipo@knspartners.com;

BEFORE THE OFFICE OF THE CONTROLLER OF PATENTS, NEW DELHI

IN THE MATTER OF:

The Patents Act, 1970 as amended by the Patents (Amendment) Act 2005, and The Patents Rules, 2003, as amended by The Patents (Amendment) Rules, 2006

AND

IN THE MATTER OF:

An opposition by way of representation under Section 25(1) of The Patents, 1970, as amended by the Patents (Amendment) Act, 2005 read with Rule 55 of The Patents Rules, 2003, as amended by The Patents (Amendment) Rules, 2006 to the Indian Patent Application No. 201917006277 DATED 18/02/2019 by **GILEAD SCIENCES, INC.**

IN THE MATTER OF:

POONAM KUMARI …**OPPONENT**

VS.

GILEAD SCIENCES, INC. …**APPLICANT**

PRE GRANT OPPOSITION BY POONAM KUMARI

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	CA Protein" Journal of Virology p. 6643– 6655, June 2012 Volume 86 Number 12.	
6.	Power of Attorney	Will Follow

Dated this 28th day of June, 2023

MD. AZHARUDDIN
FOR SILVER LINING IP LLP
AGENT FOR THE OPPONENT

TO,
THE CONTROLLER OF PATENTS
THE PATENT OFFICE, NEW DELHI

FORM – 7A

THE PATENTS ACT, 1970

(39 OF 1970)

AND

THE PATENTS RULES, 2003

NOTICE OF OPPOSITION

[see Section 25(1) and rule 55A]

I, **Poonam Kumari**, having address at Vill: - Bentera, P.O: Manjhiar, Teh: - Nadaun, Distt: - Hamirpur (H.P.), 177038, India, hereby give representation by way of opposition to the grant of patent in respect of Indian patent application no. 201917006277 filed on 18/02/2019 made by GILEAD SCIENCES, INC. on the grounds:

a) Section 25(1)(b): Lack of novelty

b) Section 25(1)(e): Lack of inventive step

c) Section 25(1)(f): Invention is not patentable under section 3(d)

d) Section 25(1)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

e) Section 25(1)(h): Failure to disclose the information required by section 8 of the Patents Act.

(Detailed grounds are set out in the Opposition)

My address for service in India is:

SILVER LINING IP LLP
429/909 Gulab Nagar, Mauzzam Nagar Lucknow Chowk
Lucknow, Uttar Pradesh -226003
Mobile No.- 7007769772
Email I'd- info@silverliningip.com;

Dated this 28th day of June, 2023

MD. AZHARUDDIN
FOR SILVER LINING IP LLP
AGENT FOR THE OPPONENT

TO
THE CONTROLLER OF PATENTS
THE PATENT OFFICE, NEW DELHI

BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, NEW DELHI

In the matter of Section 25(1) of The Patents Act,1970 as amended by The Patents (Amendment) Act 2005;

And

In the matter of Rule 55 of The Patents Rules 2003 as amended by the Patents (Amendment) Rules, 2006

And

IN THE MATTER of Indian Patent Application 201917006277 filed on 18/02/2019, in the name of **GILEAD SCIENCES, INC.**

REPRESENTATION BY:

POONAM KUMARI .....OPPONENT

VS.

GILEAD SCIENCES, INC. .....APPLICANT

REPRESENTATION BY WAY OF PRE-GRANT OPPOSITION UNDER SECTION 25(1) OF THE PATENTS ACT, 1970

I, Poonam Kumari, an Indian citizen, hereby submit my representation by way of opposition to the grant of patent in respect of Indian Patent Application 201917006277 filed on 18/02/2019 in the name of Gilead Sciences, Inc. titled "Therapeutic Compounds Useful for the Prophylactic or Therapeutic Treatment of an HIV Virus Infection.".

STATEMENT OF CASE OF OPPONENT

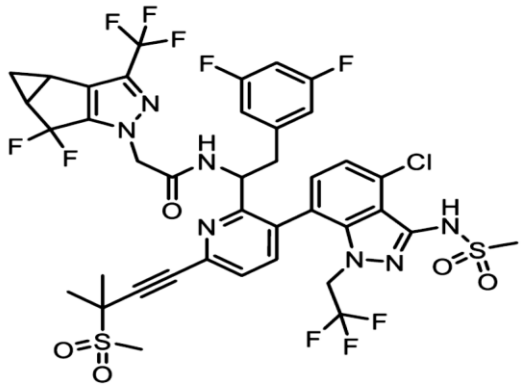
1. The Opponent has learnt that the Applicant has filed an Indian Patent Application 201917006277 (hereinafter referred to as "impugned application") on 18/02/2019 The impugned patent application was published in the official journal of the patent office on 03/05/2019, which is currently pending before the Patent Office. The Impugned Patent

Application is the national phase application of PCT/US2017/047416 and draws its priority from US application 62/377,312 dated 19 August 2016, US application 62/457,555 dated 10 February 2017.

2. The impugned application is entitled "Therapeutic Compounds Useful for the Prophylactic or Therapeutic Treatment of an HIV Virus Infection."

3. The Opponent by way of this present pre-grant opposition submits that the claims currently pending on record are not patentable under the provisions provided in this Act. The claims as filed and currently on record are annexed herewith as **Annexure - A** and reproduced herein below for ready reference:

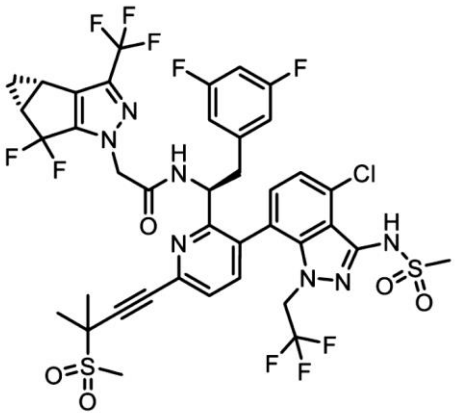
1. A compound of Formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof.

2. The compound as claimed in claim 1, which is a compound of Formula (Ib)

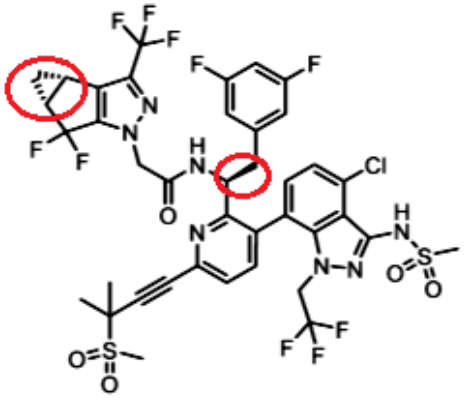


(Ib)

or a pharmaceutically acceptable salt thereof.

DETAILS OF IMPUGNED APPLICATION:

4. The impugned application is drawn towards a compound which has been depicted by a chemical structure in claim 1. The chemical structure recited in claim 1 is devoid of any stereochemical specificities. Claim 2 of the impugned application is dependent on claim 1 and recites a chemical structure which is similar to the chemical structure recited in claim 1 with the difference that the stereochemistry of two specific bonds has been defined in the structure claimed in claim 2. The two specific bonds where the stereochemistry has been defined is shown below in red circles as follows:



5. **PRIOR ARTS:** The opponent wishes to rely on the following prior arts as evidence in support of the grounds of opposition.
   i. WO2014134566 published on 04/Sep/ (annexed here as **Annexure - B**).
   ii. Christopher T. Lemke, et al "Distinct Effects of Two HIV-1 Capsid Assembly Inhibitor Families That Bind the Same Site within the N-Terminal Domain of the Viral CA Protein" Journal of Virology p. 6643– 6655, June 2012 Volume 86 Number 12 (annexed here as **Annexure – C)**.

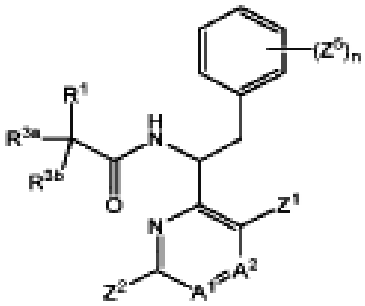
6. It is submitted that the claims of impugned application are liable to be refused on following grounds as below, which are without prejudice to each other:
   (a) Section 25(1)(b): Lack of novelty
   (b) Section 25(1)(e): Lack of inventive step
   (c) Section 25(1)(f): Invention is not patentable under section 3(d)
   (d) Section 25(1)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
   (e) Section 25(1)(h): Failure to disclose the information required by section 8 of the Patents Act.

GROUND 1: Section 25(1)(b) Lack of Novelty

7. It is submitted that the impugned patent application lacks novelty as the compound claimed in claim 1 is disclosed in prior art document WO2014134566 (hereinafter referred to as WO'566).

8. It is submitted that compound Ia of present claims is covered within the Markush disclosure of compound IIId of WO'566 in following manner (the resulting structure formed by the appropriate substituent of WO'566 have been highlighted in yellow for ready reference of the Ld Controller):

1. **A compound of formula IIId:**



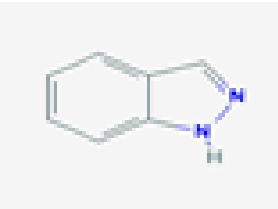
A^1 is CH; A^2 is CH] [-2-pyridinyl]

R^1 is 3-12 member heterocycle [1H-Cyclopropa[3,4]cyclopenta[1,2]pyrazole-1-acetamide]

R^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, wherein the Z^4 groups are same or different [1H-Cyclopropa[3,4]cyclopenta[1,2]pyrazole-1-acetamide]

Each R^{3a} and R^{3b} is independently H [1H-Cyclopropa[3,4]cyclopenta[1,2]pyrazole-1-acetamide]

Z^1 is 3-14 membered heterocycle **[includes Indazole a heterocyclic aromatic compound]** [N-[(1S)-1-[3-[4-chloro-3-[(methylsulfonyl)amino]-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl]



Z^1 3-14 membered heterocycle is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} and Z^{1b} groups, wherein Z^{1a} and Z^{1b} groups are same or different [N-[(1S)-1-[3-[4-chloro-3-[(methylsulfonyl)amino]-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl]

Each Z^{1a} is halogen; $NR^{n1}S(O)_2R^{p1}$, each NR^{n1} is independently H, each R^{p1} is 5-6 membered monocyclic heteroaryl [N-[(1S)-1-[3-[4-chloro-3-[(methylsulfonyl)amino]-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl]

Each Z^{1b} is independently (C_1-C_8) alkyl optionally substituted with 1, 2, 3, 4 or 5 halogen [N-[(1S)-1-[3-[4-chloro-3-[(methylsulfonyl)amino]-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl]

Z^2 is (C_2-C_8) alkynyl optionally substituted with 1, 2, 3, 4 or 5 Z^{2c} groups, wherein Z^{2c} groups are same or different [3-methyl-3- (methylsulfonyl)-1-butyn-1-yl]-2-pyridinyl]

Z^{2c} is independently $–S(O)_2R^{p4}$, each R^{p4} is independently (C_1-C_8) alkyl [3-methyl-3- (methylsulfonyl)-1-butyn-1-yl]-2-pyridinyl]

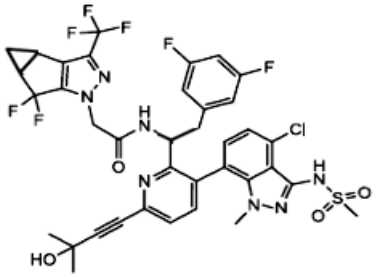
9. It can be seen from the above illustration that the compound claimed in the impugned application is covered in the disclosure of the prior art document WO'566.

10. Therefore, the claimed subject matter of the impugned application lacks novelty and the impugned application ought to be rejected on this ground alone.

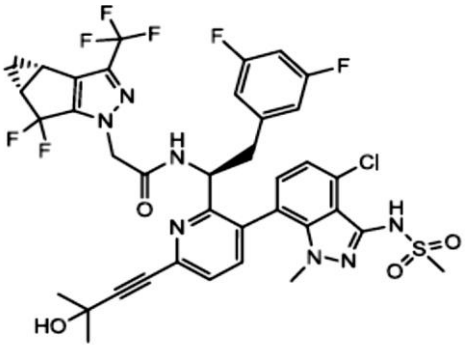
GROUND 2: Section 25(1)(e) Lack of Inventive Step

11. It is submitted that claims 1-26 of the impugned application lack inventive step in view of common general knowledge in art and combined with teachings of the documents as discussed in below paragraphs.

12. It is submitted that the prior art document WO2014134566 relates to capsid inhibitors and discloses compounds with the following structures:



Compound covered in Markush IIId of WO'566



Compound 78, also claimed in Claim 39 of WO'566

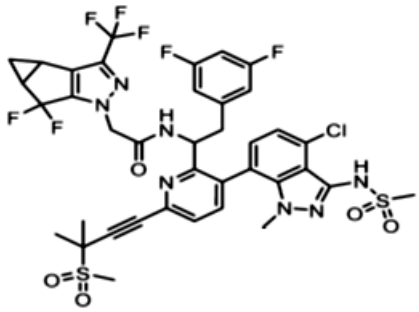
13. The compounds of WO'566 have been disclosed to be potent inhibitors of capsid assembly. Therefore, a person skilled in the art engaged in the pursuit of designing alternate capsid inhibitor compounds is motivated to select said compounds of WO'566 and make minor substitutions in these compounds to arrive at alternate compounds.

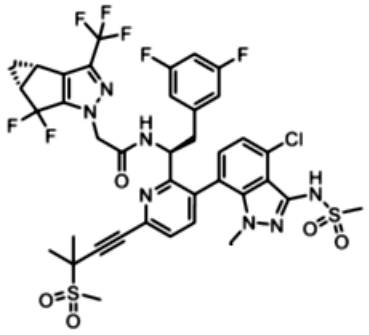
14. The first place of substitution which is apparent to a person skilled in the art is the distal hydroxyl group since it is well known in the field of pharmaceutical drug designing that distal hydroxyl groups are highly prone to metabolism by hydroxylation which results in low half-life of the compound and consequently higher doses of the compound have to be administered which also concurrently causes higher incidence of side effects.

15. Thus, a person skilled in the art is motivated to first protect this distal hydroxyl group of the compounds of WO'566 shown above in para 10 before proceeding to subjecting said compounds to any chemical reaction with the purpose of changing any substituents on said compounds.

16. The most common protecting group which is used for protecting hydroxyl groups by medicinal chemists and which is also known to not affect the pharmacological property of any compound is mesyl group (also known as methanesulfonyl group). Hence, in order to

increase the half-life of a compound by preventing hydroxylation as well as in order to prevent unwanted hydroxylation reactions during modification/addition of substituents, a person skilled in the art would first convert the hydroxyl group to a mesyl group, resulting in a structure as shown below:





17. It is submitted that in another publication by Lemke et al it is disclosed that the emergence of resistance to existing classes of antiretroviral drugs necessitates finding new HIV-1 targets for drug discovery. The viral capsid (CA) protein represents one such potential new target.

18. Lemke et al disclose that CA is sufficient to form mature HIV-1 capsids in vitro, and extensive structure-function and mutational analyses of CA have shown that the proper assembly, morphology, and stability of the mature capsid core are essential for the infectivity of HIV-1 virions.

19. It is disclosed by Lemke et al that CA is composed of two highly helical domains, the N-terminal domain (CA_{NTD}, residues 1 to 146) and the C-terminal domain (CA_{CTD}, residues 151 to 231), which are separated by a short flexible linker. Solution nuclear magnetic resonance (NMR) and high-resolution X-ray crystal structures have been reported for both isolated domains (4, 13, 14, 19, 41). Conical HIV-1 capsids belong to a class of geometric structures called fullerene cones, which comprise hexagonal lattices with 12 pentagonal defects that allow the cones to close at both ends. Although individual HIV-1 capsids differ in size and shape, they typically contain ~250 CA hexagons and have 7 CA pentagons at the wide end and 5 CA pentagons at the narrow end of the cone.

20. The document also discloses that the recent availability of high-resolution structures of CA hexagons and pentagons has enabled molecular modelling of the viral capsid. The capsid lattice is stabilized by four different types of intermolecular CA-CA interactions: a

CA_{NTD}/CA_{NTD} interaction that creates the hexameric (or pentameric) rings, a CA_{NTD}/CA_{CTD} interaction that forms a "girdle" that reinforces the rings, dimeric CA_{CTD}/CA_{CTD} interactions that link adjacent hexamers across local 2-fold axes, and trimeric CA_{CTD}/CA_{CTD} interactions that link adjacent hexamers across local 3-fold axes. Each of these different interfaces has been characterized structurally. Moreover, several distinct but related CA_{CTD}/CA_{CTD} dimers have been observed.

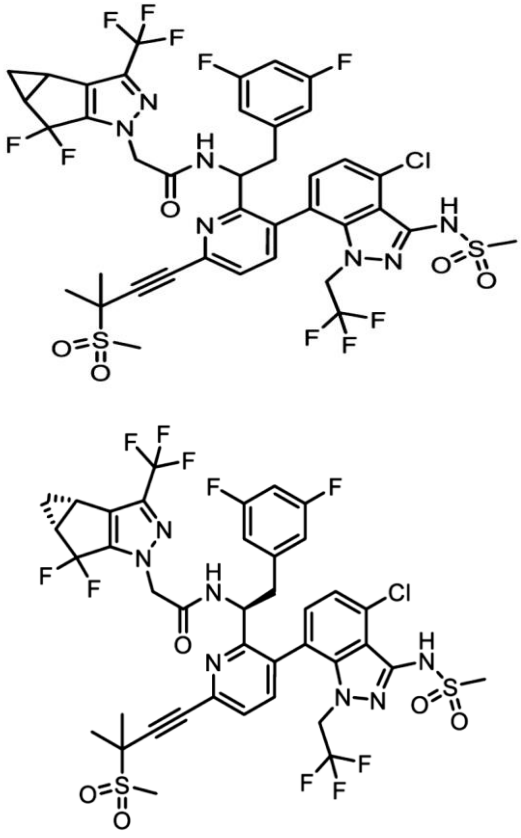
21. Lemke et al also discloses that CA-binding inhibitors of HIV-1 capsid assembly have been reported, thus providing evidence that CA may be a viable drug target. From the disclosure of this document it is established that the binding sites on capsid were well known. It was also well known that various capsid inhibitors were binding to which particular site in the capsid binding site, particularly it was known that a capsid inhibitor CAP-1 binds to a pocket in binding site created by helices-1, 2, 4, and 7; the capsid inhibitor CAI binds to a conserved hydrophobic cleft within the CA_{CTD} four-helix bundle and inhibits both Gag and CA assembly; PF-3450074 and related compounds bind between helix 4 and helix 7 of the CA_{NTD}. This latest class of CA inhibitors disrupts the stability of the viral capsid in both the early and late stages of viral replication, again probably by altering CA_{NTD}/CA_{CTD} interactions.

22. In this 2012 publication Lemke et al have also disclosed that the development of an in vitro capsid assembly assay based on the association of CA-NC subunits on immobilized oligonucleotides is described. This assay was used to screen a compound library, yielding several different families of compounds that inhibited capsid assembly. Optimization of two chemical series, termed the benzodiazepines (BD) and the benzimidazoles (BM), was carried out which resulted in compounds with potent antiviral activity against wild-type and drug-resistant HIV-1. It is disclosed that these inhibitors induce the formation of a pocket that overlaps with the binding site for the previously reported CAP inhibitors.

23. Lemke et al have also disclosed the EC50 values of the benzodiazepines (BD) and the benzimidazoles (BM) series of compounds in Table 1 and it can be seen from said Table that the most potent compounds from both the series have a -CF3 group common at the opposing distal ends of the molecules.

24. Taking into consideration the structure of the binding site and the binding mechanisms as well as binding sites of various capsid inhibitor compounds and motivated to achieve a structure which can cause more extensive binding into the various sites available in the binding pockets of capsid monomers, a person skilled in the art is motivated to have -CF3 group in the similar conformation as found in the most potent benzodiazepine (denoted as BD1 in the document) and the benzimidazole (denoted as BM1 in the document).

25. A person skilled in the art observes that a -CF3 group in the similar conformation as that resent in BD1 compound is already present in the compounds of WO'566. Hence, another -CF3 similar to the conformation as present in BM1 can be added to the compounds of WO'566 to increase their affinity and extent of binding in the binding pocket of the capsid monomers. Making these substitutions a person skilled in the art arrives at the following compounds:



26. Furthermore, as disclosed in Lemke et al adjacent capsid monomers link together at the CA_{NTD}/CA_{CTD} to form the pentameric/hexameric ring which is required for formation of a stable capsid and it is known that molecules like CAP, CAI, and PF-3450074 bind at the

site in capsid monomers which is present at the interface of two capsid monomers and thereby disrupt the formation of proper capsid coating. Thus, a person skilled in the art is motivated to have similar groups at the distal ends of the molecule such as -CF3 and mesyl so as to bind to the adjacent monomers of the capsid and disrupt the formation of a proper capsid.

27. In addition, in view of the fact that the structure of the capsid as well as the structure of the binding site of a capsid monomer was well known, it was merely routine optimization for a person skilled in the art to design modification of known compounds such as compounds of WO'566 and perform docking and ligand binding studies to assess the affinity and binding extent of the modified molecules, thereby, rending the selection of alternate substituents to be merely a software driven exercise devoid of any application of inventive faculty.

28. Hence, the claimed composition fails to provide any technical contribution in the field of endeavour of the invention which was not already known in the field.

29. Therefore, the claimed subject matter is obvious in view of the disclosure of the combination of teachings of the prior art documents discussed above and the impugned application ought to be rejected on this ground alone.

GROUND 3: Claims not patentable under Section 25(1)(f)

The claimed subject matter in not patentable under Section 3(d) of the Act

30. It is submitted that the impugned application falls within the purview of section 3(d) of the Patents Act, 1970 which states that *"the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.*

Explanation -For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy."

31. It is humbly submitted that the claimed compounds are merely new form of the compounds, as shown in para 10 above, disclosed in the prior art document WO'566.

32. The compounds of WO'566 are known to be potent inhibitors of capsid formation and therefore, effective in treatment of HIV.

33. Presently claimed compounds being a new form of the compounds of WO'566, it was incumbent upon the Applicant to establish that the claimed compounds have enhanced therapeutic efficacy as compared to the compounds disclosed in WO'566.

34. The Applicant has failed to discharge this onus. Neither the specification nor any document filed later establishes that the claimed compounds have enhanced therapeutic efficacy as compared to compounds of WO'566.

35. It is the contention of the Applicant that the compounds claimed in the impugned application have better potency i.e IC50 value than the compounds of WO'566. However, it is submitted that potency and therapeutic efficacy are different from each other and merely establishing better potency is not equivalent to establishing better therapeutic enhancement.

36. The specification of impugned application does not contain any comparative data establishing enhanced therapeutic efficacy for the subject matter claimed in claim 1 over the compounds known in the art at the time of the invention.

37. Thus, it is humbly submitted that the impugned application falls squarely within the purview of section 3(d) of the Patents Act 1970 and ought to be rejected.

GROUND 3: INSUFFICIENCY OF DISCLOSURE

38. It is submitted that complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed. It is submitted that it is a well settled law that the specification should clearly and fairly describe the invention and disclose the best mode of working the invention so that the person skilled in the art could perform the invention without any undue efforts. Further, it is submitted that claims of impugned application are not fairly based on the specification and the complete

specification does not fairly describe the invention and the method by which it is to be performed.

39. The impugned application describes compound 24 which is different from the compound claimed in claim 1 of the impugned application. The specification does not provide the method of synthesis or any description about the effect of compound claimed in claim 1 of the impugned application.

40. In absence of this a person of ordinary skilled in the art cannot arrive at the compound claimed in claim 1 without undue experimentation.

41. Similarly for compound of claim 2 specification processes application for separation of various stereochemical compounds formed by the process described in the specification have not been provided in the specification.

42. In absence of this a person of ordinary skilled in the art cannot arrive at the compound claimed in claim 2 in practically relevant levels of purity and percentage without undue experimentation.

43. Therefore, the claims as presently worded are too broad, ambiguous, and encompasses non-working embodiments.

44. Thus, the specification does not clear does not sufficiently and clearly describe the invention or the method by which it is to be performed and the impugned application is liable to be rejected on said ground.

GROUND 5: INFORMATION RELATING TO CORRESPONDING APPLICATIONS UNDER SECTION 8 [SECTION 25(1)(H)]

45. The Applicant has failed to disclose to the Patent Office the information required under Section 8. The Applicant is required to provide all the information regarding the prosecution of the equivalent applications till the grant of the Indian application to the Patent Office in writing from time to time and also within the prescribed time.

46. It is observed that Applicant has not provided information about updated status of corresponding applications in the Form-3 to the learned Controller.

47. Therefore, the applicant has failed to comply with the requirements of the section 8 of the act and the impugned application should be rejected on this ground also.

48. The opponents crave leave to file further submissions and evidence with respect to this ground.

CONCLUSION

49. In view of the above, the claims are not inventive, not patentable and insufficient. The pre-grant opposition as filed may be allowed and the subject patent application may be refused.

HEARING REQUESTED

50. The Opponent hereby requests a hearing under section 25(1) of the Patents Act, 1970 (hereinafter referred to as "the Patents Act") and Rule 55 of the Patents Rules (hereinafter referred to as "the Rules").

P R A Y E R

In the fact and circumstances of the case, the Opponent prays as follows:

i. that the Controller take the present Opposition on record; that the Indian application 201917006277, be rejected under Section 25(1) of the Patents (Amendment) Act, 2005;

ii. that the Opponent may be allowed to file further documents and evidence if necessary to support their averments;

iii. that the Opponent may be allowed to file rejoinder and affidavit if necessary to support their averments;

iv. that the Opponent may be granted an opportunity of being heard in the matter before any final orders are passed;

v. that the Opponent may be allowed to make further submissions in case the Applicant makes any amendments in the claims;

vi. any other reliefs considering the facts and circumstances may be granted in favour of the Opponent in the interest of justice.

Dated this 28th day of June, 2023

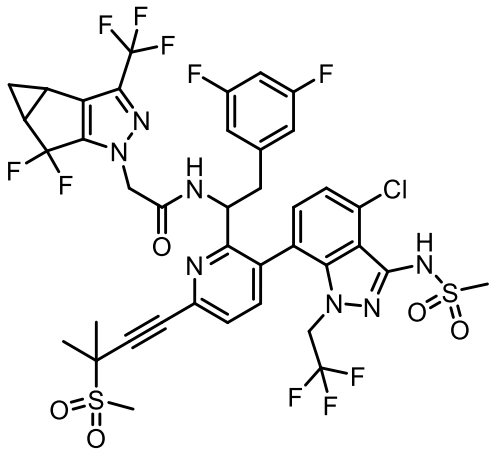
MD. AZHARUDDIN
FOR SILVER LINING IP LLP
AGENT FOR THE OPPONENT

TO,
THE CONTROLLER OF PATENTS
THE PATENT OFFICE, NEW DELHI

We claim:

ANNEXURE-A

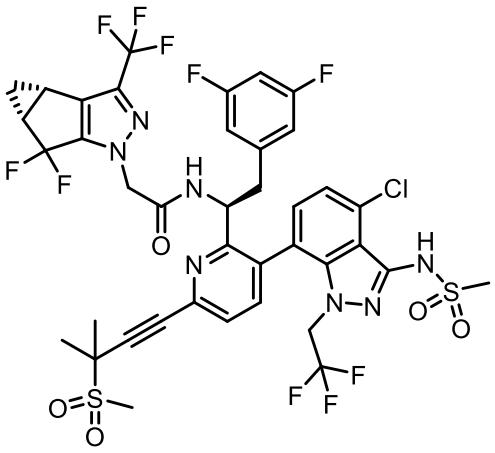
1. A compound of Formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof.

2. The compound as claimed in claim 1, which is a compound of Formula (Ib)



(Ib)

or a pharmaceutically acceptable salt thereof.

Dated this: 18th day of February, 2019

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Sachin

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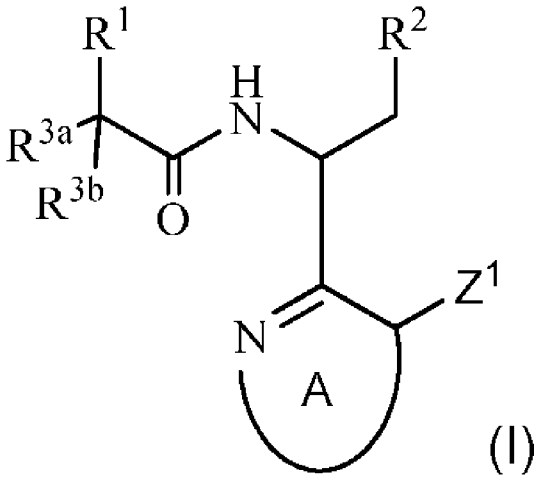

(I)

(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.

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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.

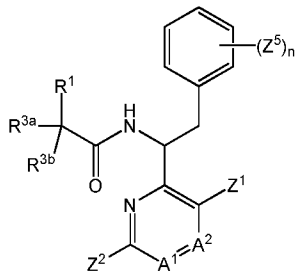
BACKGROUND

[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 $(C_1$-$C_4)$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 $-OR^{n6}$;

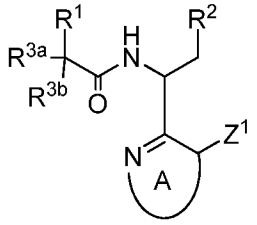
each R^{n5}, R^{p5}, R^{q5}, R^{r5}, and R^{n6} is independently H or $(C_1$-$C_4)$alkyl;

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.

[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 $(C_1$-$C_3)$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;

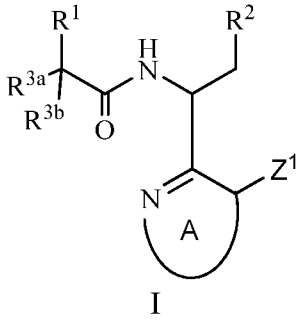
each Z^4 is independently oxo, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, halogen, -CN, $-OR^{n5}$, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-C(O)R^{n5}$, $-C(O)OR^{n5}$, or $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3$-$C_7)$carbocycle or $(C_1$-$C_8)$alkyl of Z^4 is optionally substituted 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., $(C_1\text{-}C_8)$alkyl) or 1 to 6 carbon atoms (i.e., $(C_1\text{-}C_6$ alkyl) or 1 to 4 carbon atoms (i.e., $(C_1\text{-}C_4)$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., $C_2\text{-}C_8$ alkenyl), or 2 to 6 carbon atoms (i.e., $C_2\text{-}C_6$ 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., $C_2\text{-}C_8$ alkyne,) or 2 to 6 carbon atoms (i.e., $C_2\text{-}C_6$ 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, $(C_1\text{-}C_6)$haloalkyl is a $(C_1\text{-}C_6)$alkyl wherein one or more of the hydrogen atoms of the $(C_1\text{-}C_6)$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 $(C_1$-$C_6)$alkyl. For example, $(C_1$-$C_8)$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., $-CH_2-NH_2$. 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

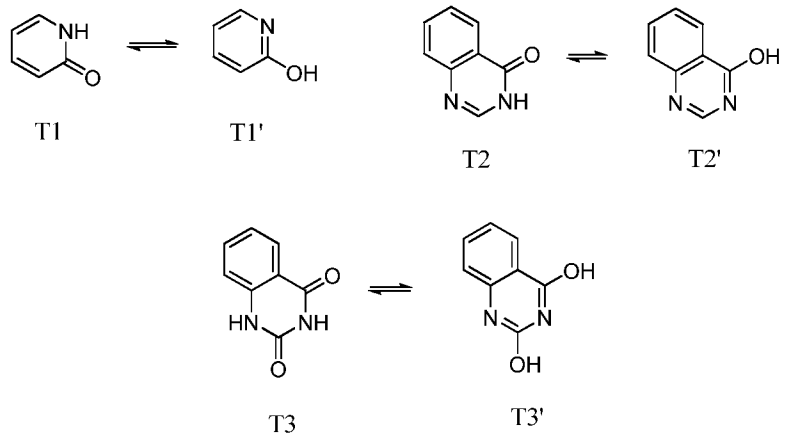
diastereomer. In another embodiment, a compound disclosed herein is at least 99% a single diastereomer.

[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.

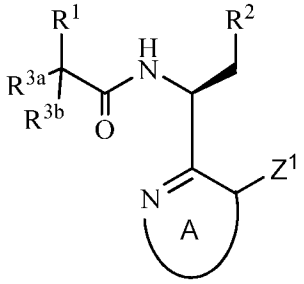
Isotopes

[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.

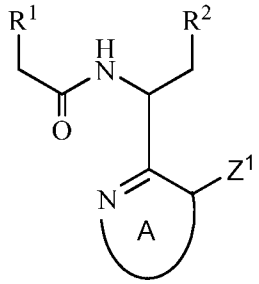
[0063] A specific group of compounds of formula I are compounds of formula Ia.



Ia

or a pharmaceutically acceptable salt thereof.

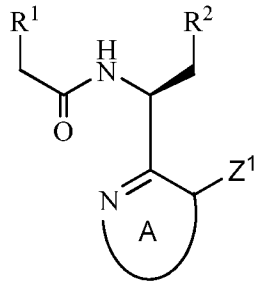
[0064] Another specific group of compounds of formula I are compounds of formula Ib.



Ib

or a pharmaceutically acceptable thereof.

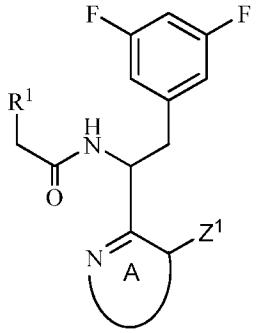
[0065] Another specific group of compounds of formula I are compounds of formula Ic.



Ic

or a pharmaceutically acceptable thereof.

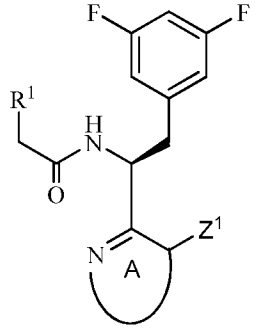
[0066] Another specific group of compounds of formula I are compounds of formula Id.



Id

or a pharmaceutically acceptable thereof.

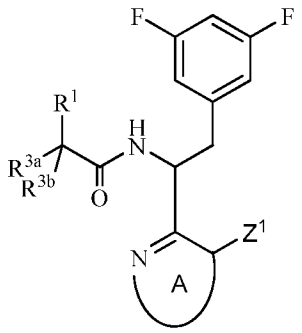
[0067] Another specific group of compounds of formula I are compounds of formula Ie.



Ie

or a pharmaceutically acceptable thereof.

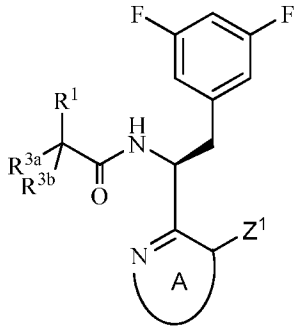
[0068] Another specific group of compounds of formula I are compounds of formula If.



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.

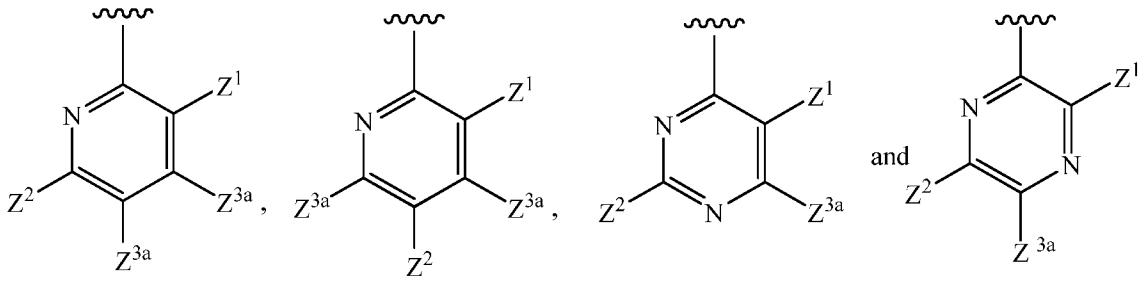
[0088] A specific value for A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein any pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl of A is substituted with one Z^1 group at the position shown, one Z^2 group and optionally substituted with one or more (e.g., 1 or 2) Z^3 groups.

[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.

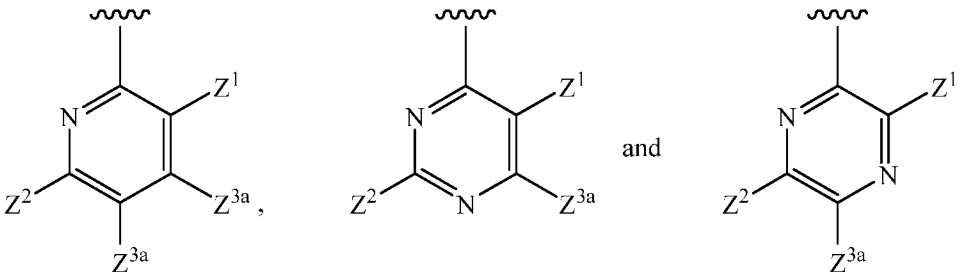
[0091] A specific value for A is pyridinyl, wherein any pyridinyl of A is substituted with one Z^1 group at the position shown and one Z^2 group

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



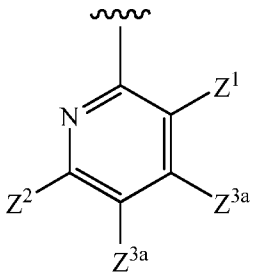
wherein each Z^{3a} is independently selected from H and Z^3.

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

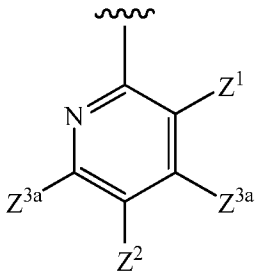


wherein each Z^{3a} is independently selected from H and Z^3.

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

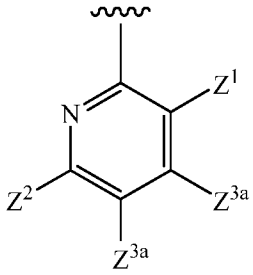


and



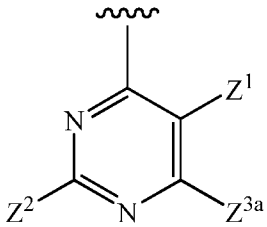
wherein each Z^{3a} is independently selected from H and Z^3.

[0095] A specific value for A is:



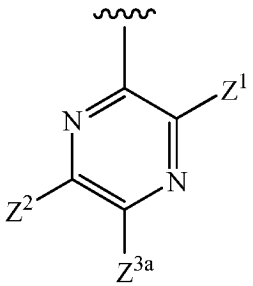
wherein each Z^{3a} is independently selected from H and Z^3.

[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.

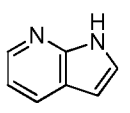
[0110] A specific value for Z^1 is selected from 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle, wherein any from 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle of Z^1 is optionally substituted with one or more Z^{1a} groups.

[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.

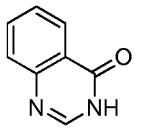
[0112] A specific value for Z^1 is selected from 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle, wherein the 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle have 3-9 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any 8-10 membered bicyclic-heteroaryl 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.

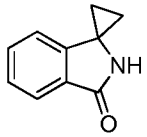
[0114] A specific value for Z^1 is selected from phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 4-oxo-3,4-dihydroquinazolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, 1H-2-oxo-pyridinyl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolinyl as shown by the following formulas;



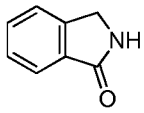
1*H*-pyrrolo[2,3-*b*]pyridinyl



4-oxo-3,4-dihydroquinazolinyl

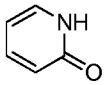


3-oxospiro[cyclopropane-1,1'-isoindolin]-yl



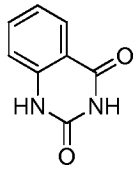
1-oxoisoindolinyl

phenyl

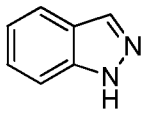
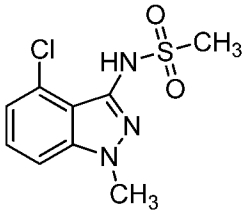
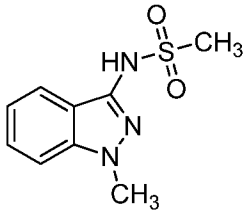


1H-2-oxo-pyridinyl

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.

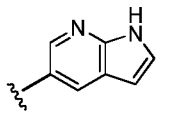
[0117] A specific value for Z^1 is selected from phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, pyridinyl and quinazolinyl, wherein any phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, pyridinyl and 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'-

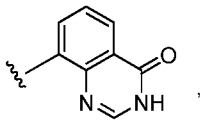
isoindolin]-5'-yl, 1H-2-oxo-pyridin-4-yl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolin-8-yl of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups.

[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.

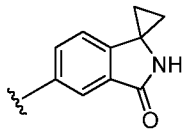
[0120] A specific value for Z^1 is selected from phenyl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1-oxoisoindolin-5-yl, 1-oxoisoindolin-4-yl, 4-oxo-3,4-dihydroquinazolin-8-yl, 3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl, 1H-2-oxo-pyridin-4-yl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolin-8-yl as shown by the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



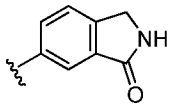
1*H*-pyrrolo[2,3-*b*]pyridin-5-yl



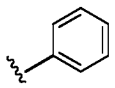
4-oxo-3,4-dihydroquinazolin-8-yl



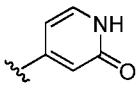
3-oxospiro[cyclopropane-1,1'-isoindolin]-5-yl



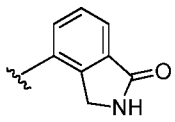
1-oxoisoindolin-6-yl



phenyl

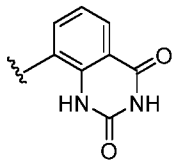


1H-2-oxo-pyridin-4-yl

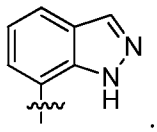
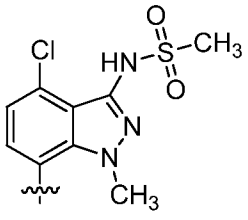
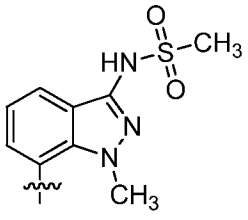


1-oxoisoindolin-4-yl

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 $-C(O)NH_2$.

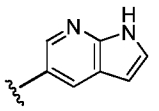
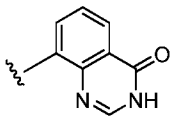
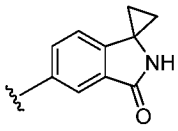
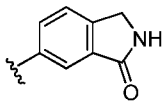
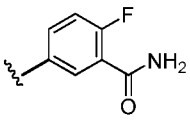
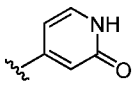
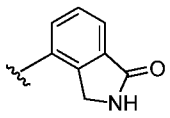
[0129] A specific value for R_{q1} and R_{r1} is H.

[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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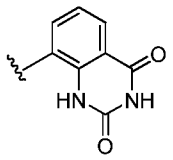
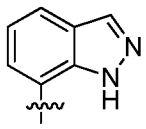
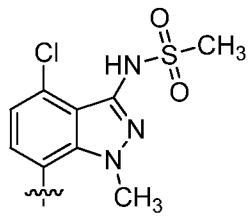
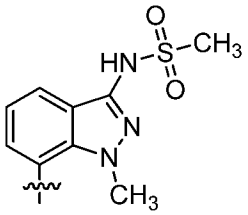


[0134] A specific value for Z^1 is  . A specific value for Z^1 is  or  .

[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.

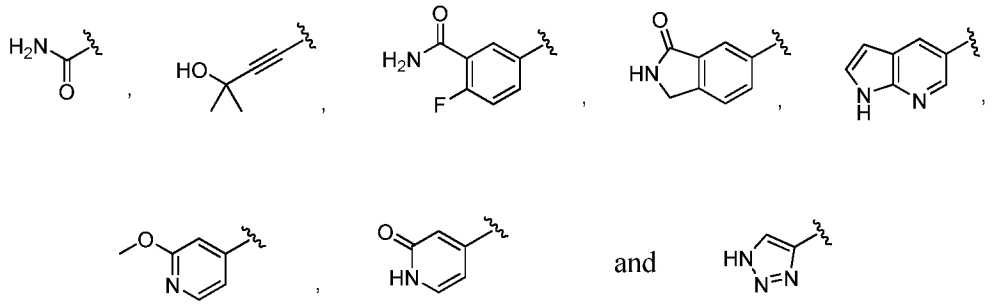
[0147] A specific value for each Z^{2c} is independently selected from halogen, $-OR_{n4}$ and $-C(O)NR_{q4}R_{r4}$.

[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

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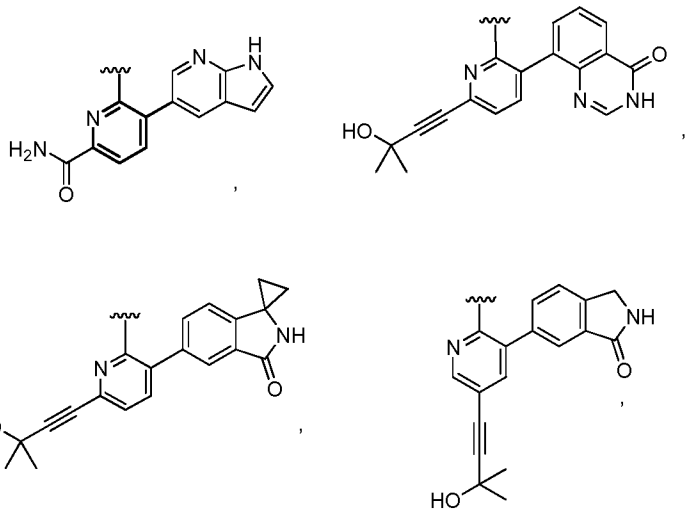
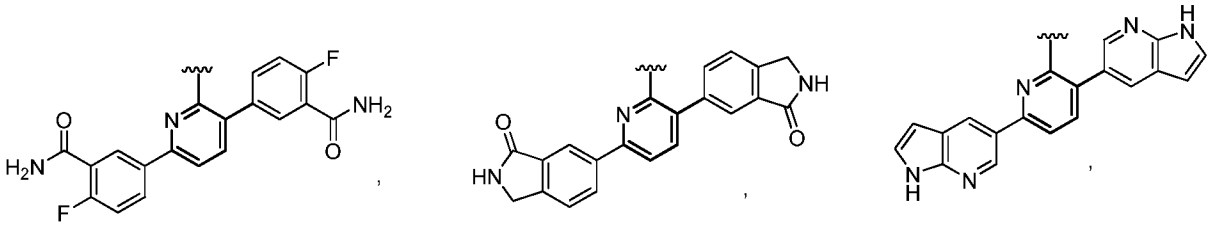
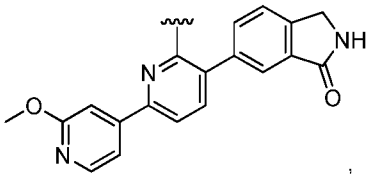
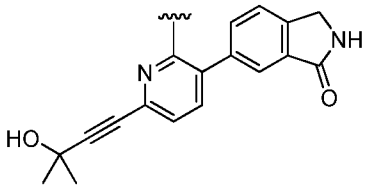
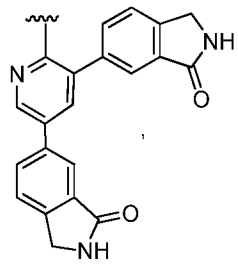
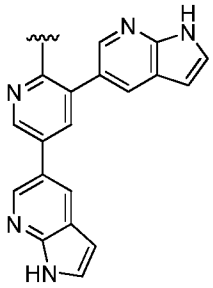
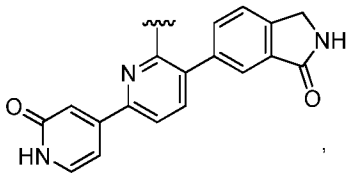
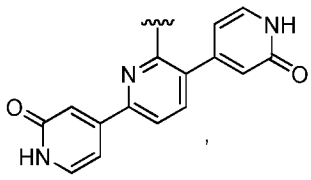
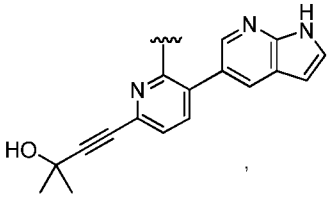
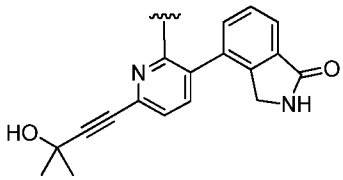
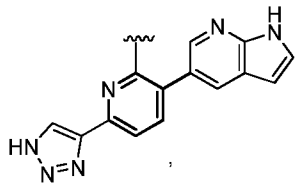
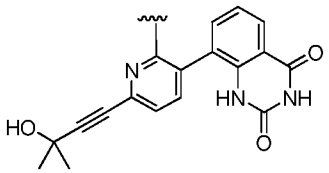
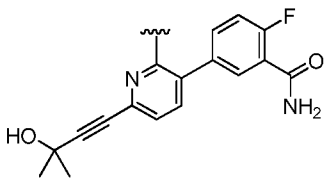
[0152] A specific value for A-Z^1 is selected from:





and



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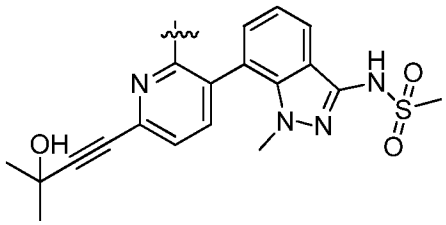
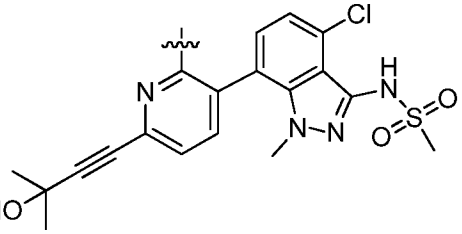
[0153] A specific value for A-Z^1 is selected from:



and.



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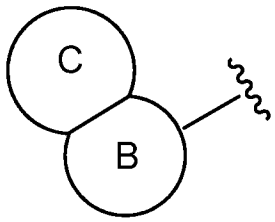
[0154] A specific value for R^1 is a 5-12 membered heteroaryl, wherein any 5-12 membered heteroaryl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) Z^4 groups.

[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:



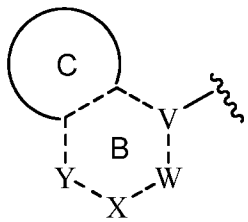
IIa

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;

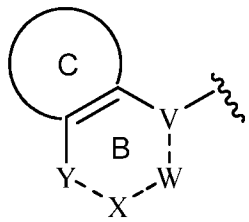
X is CZ^{4c}, NZ^{4c} or N;

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;

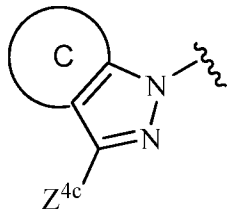
X is CZ^{4c}, NZ^{4c} or N;

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.

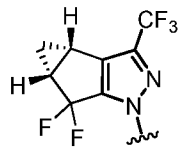
[0162] A specific value for each Z^4 is independently selected from $(C_1\text{-}C_6)$alkyl and halogen, wherein any $(C_1\text{-}C_6)$alkyl of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) halogen.

[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:

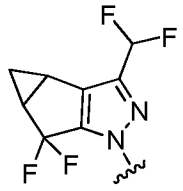
and

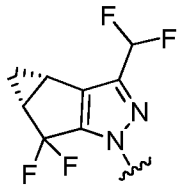
[0165] A specific value for R^1 is selected from:



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.

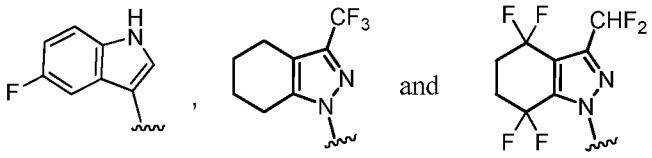
[0174] A specific value for each Z^4 is independently selected from $(C_1\text{-}C_6)$alkyl and halogen, wherein any $(C_1\text{-}C_6)$alkyl of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen.

[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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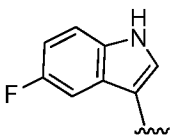
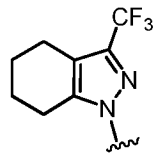

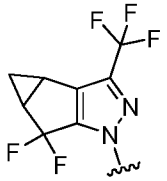

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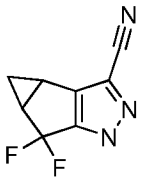
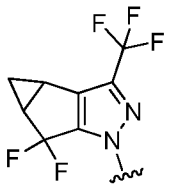


[0180] A specific value for R^1 is selected from:



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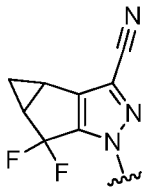
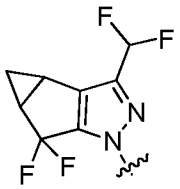
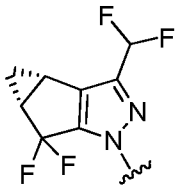


[0181] A specific value for R^1 is  . A specific value for R^1 is  .

[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.

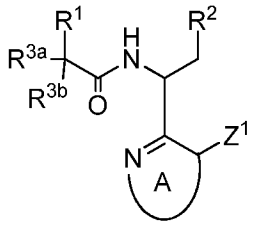
[0192] In one variation of formula I, Z^1 is phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered 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;

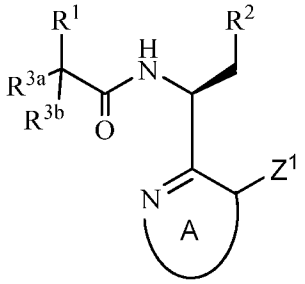
each Z^4 is independently oxo, $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_7)$carbocycle, halogen, -CN, $-OR^{n5}$, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-C(O)R^{n5}$, $-C(O)OR^{n5}$, or $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3\text{-}C_7)$carbocycle or $(C_1\text{-}C_8)$alkyl of Z^4 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.

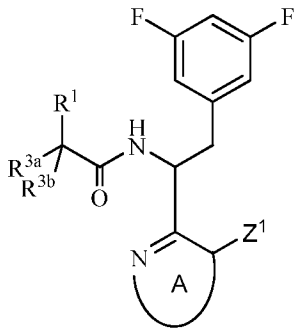
[0196] In certain embodiments, a compound of formula III is a compound of formula IIIa.



IIIa

or a pharmaceutically acceptable salt thereof.

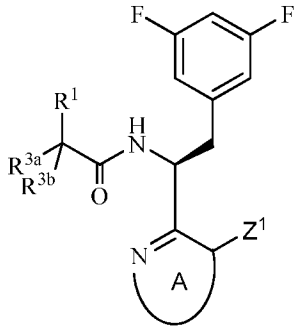
[0197] In certain embodiments, a compound of formula III is a compound of formula IIIb.



IIIb

or a pharmaceutically acceptable thereof.

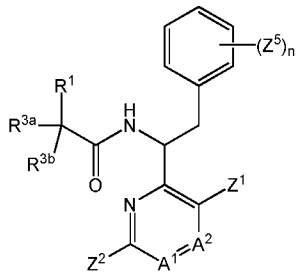
[0198] In certain embodiments, a compound of formula III is a compound of formula IIIc.



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 $-OR^{n6}$;

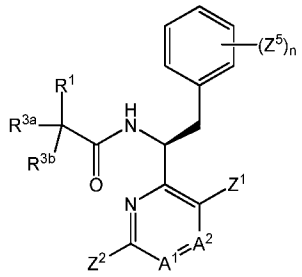
each R^{n5}, R^{p5}, R^{q5}, R^{r5}, and R^{n6} is independently H or $(C_1$-$C_4)$alkyl;

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.

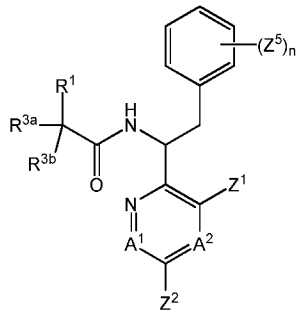
[0200] In certain embodiments, a compound of formula IIId is a compound of formula IIIe.



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 $-OR^{n6}$;

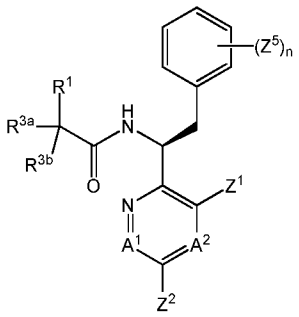
each R^{n5}, R^{p5}, R^{q5}, R^{r5}, and R^{n6} is independently H or $(C_1$-$C_4)$alkyl;

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.

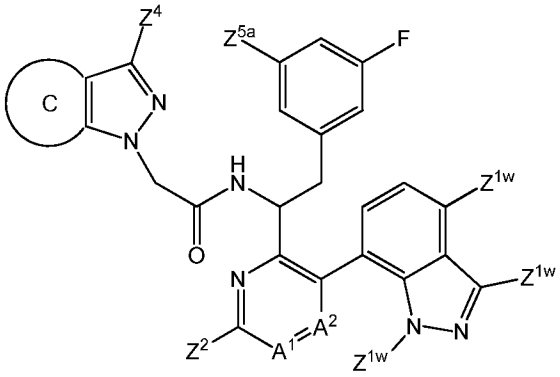
[0202] In certain embodiments, a compound of formula IIIf is a compound of formula IIIg.



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;

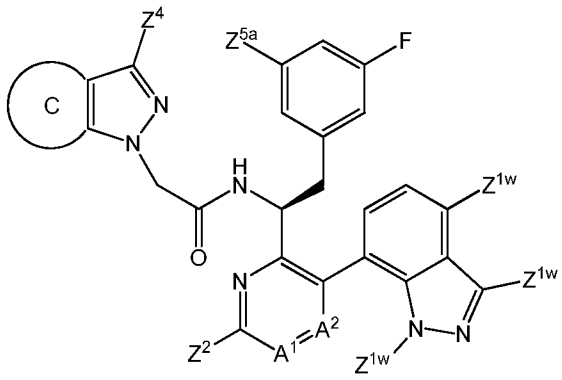
each Z^{4a} is independently halogen, -CN, or -OR^{n6};

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.

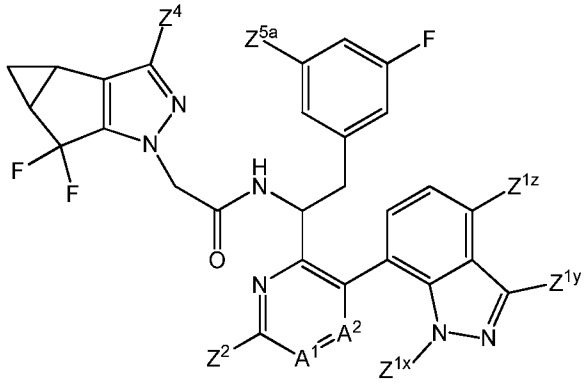
[0204] In certain embodiments, a compound of formula IIIh is a compound of formula IIIi.



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;

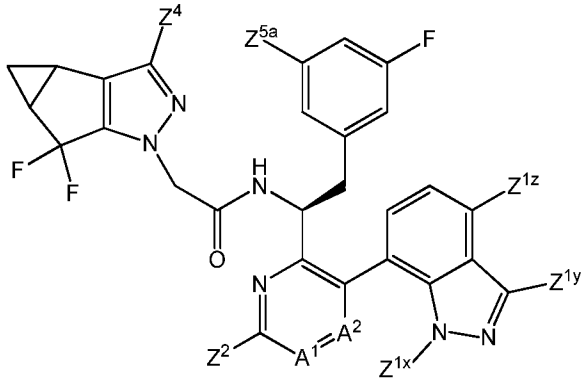
each R^{p5} is independently H or (C_1-C_4)alkyl;

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.

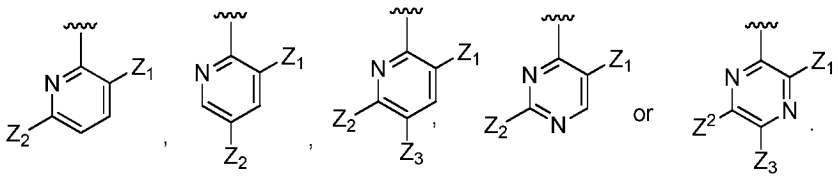
[0223] In certain embodiments, A is pyrimidinyl, wherein any pyridinyl of A is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with 1 or 2 Z^3 groups. In certain embodiments, A is pyrimidinyl, wherein any pyridinyl of A is substituted with one Z^1 group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

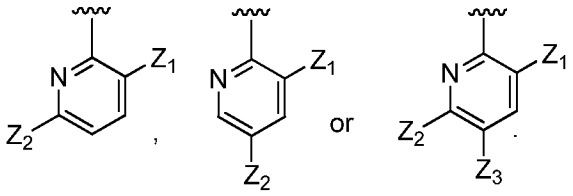
[0225] In certain embodiments, A is pyrazinyl, wherein any pyridinyl of A is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with 1 or 2 Z^3 groups. In certain embodiments, A is pyrazinyl, wherein any pyridinyl of A is substituted with one Z^1 group at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

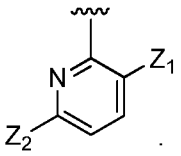
[0227] In certain embodiments, A is:



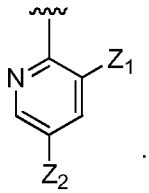
[0228] In certain embodiments, A is:



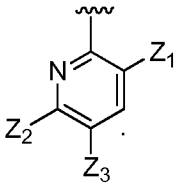
[0229] In certain embodiments, A is:



[0230] In certain embodiments, A is:

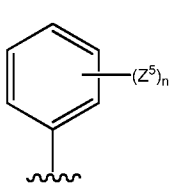
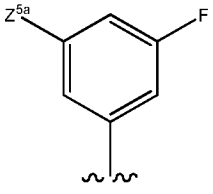


[0231] In certain embodiments, A is:



[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.

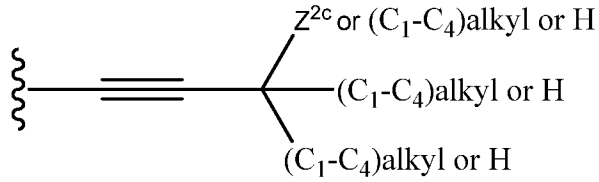
[0241] In certain embodiments, Z^2 is $(C_2$-$C_8)$alkynyl, phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heterocycle, or $-C(O)NR^{q3}R^{r3}$, wherein the 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 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.

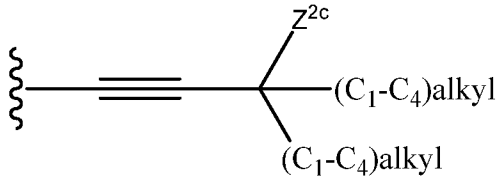
[0243] In certain embodiments of formula III, Z^2 is $(C_2$-$C_8)$alkynyl, optionally substituted with 1, 2, 3, 4, or 5 Z^{2c} groups. In certain embodiments, Z^2 is $(C_2$-$C_8)$alkynyl, optionally substituted with 1, 2, 3, or 4 Z^{2c} groups. In certain embodiments, Z^2 is $(C_2$-$C_8)$alkynyl, optionally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



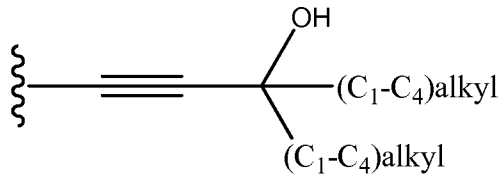
wherein each of the $(C_1$-$C_4)$alkyl moieties of Z^2, if present, is optionally substituted with 1, 2 or 3 Z^{2c} groups, wherein the Z^{2b} groups may be the same or different.

[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.

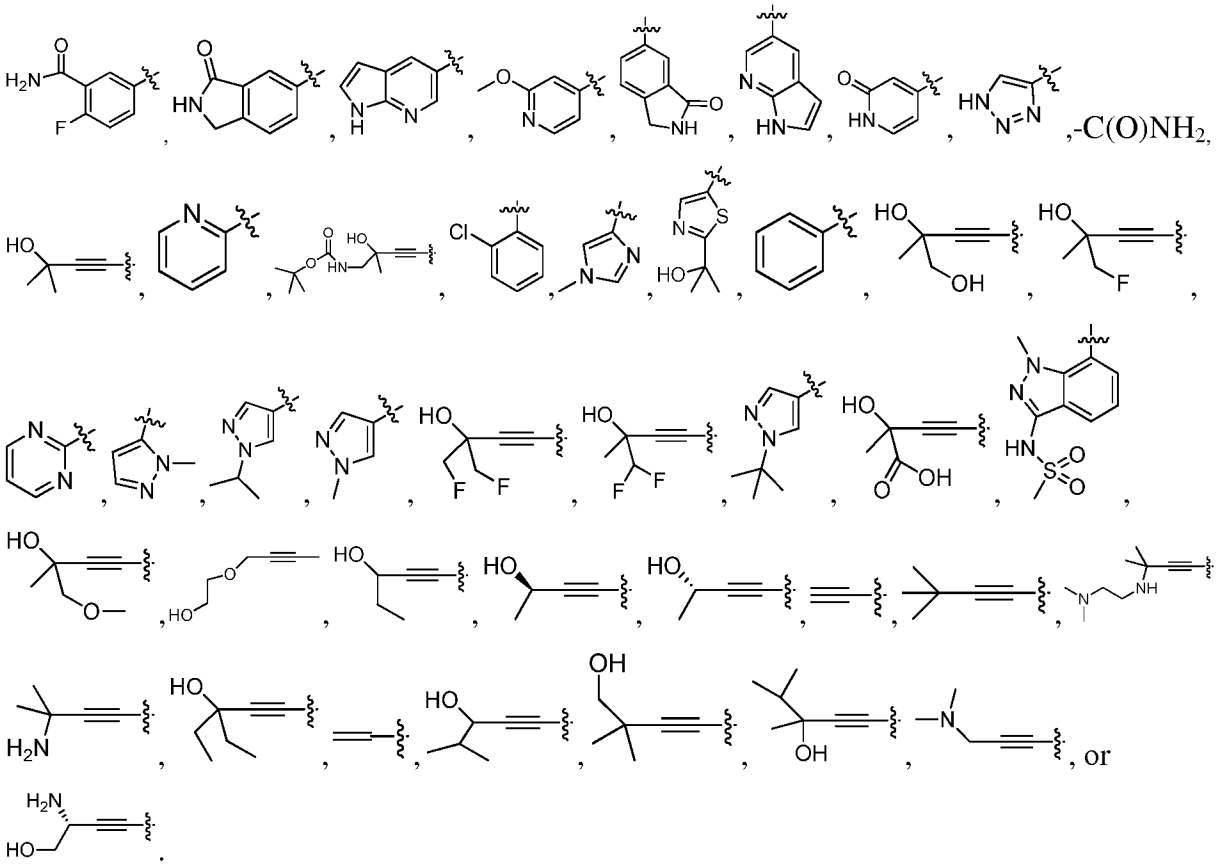
[0248] In certain embodiments of formula III, Z^2 is optionally substituted with 1, 2, or 3 Z^{2b} or Z^{2c} groups, wherein the Z^{2b} and Z^{2c} groups may be the same or different. In certain embodiments, Z^2 is substituted with 1 Z^{2b} or Z^{2c} group. In certain embodiments, Z^2 is substituted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

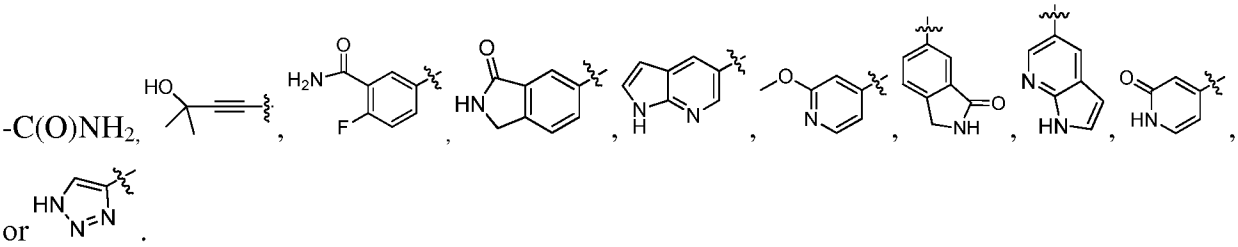
[0250] In certain embodiments of formula III, Z^2 is optionally substituted with 1, 2, or 3 Z^{2c} groups, wherein the Z^{2c} groups may be the same or different. In certain embodiments, Z^2 is substituted with 1 Z^{2c} group. In certain embodiments, Z^2 is substituted with 2 Z^{2c} groups, wherein the 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 $-OR^{n4}$.

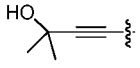
[0252] In certain embodiments, Z^2 optionally substituted with 1, 2, 3, 4, or 5 Z^{2b} or Z^{2c} groups is



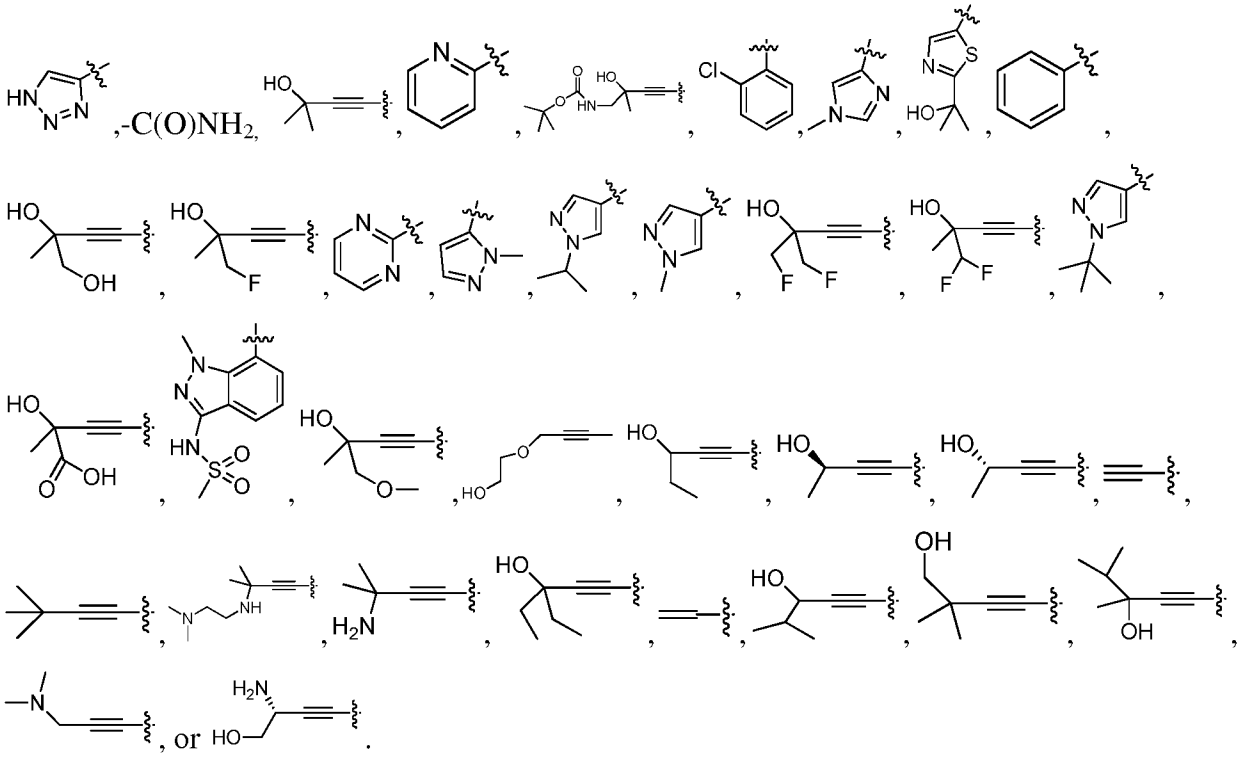
[0253] In certain embodiments, Z^2 optionally substituted with 1, 2, 3, 4, or 5 Z^{2b} or Z^{2c} groups is



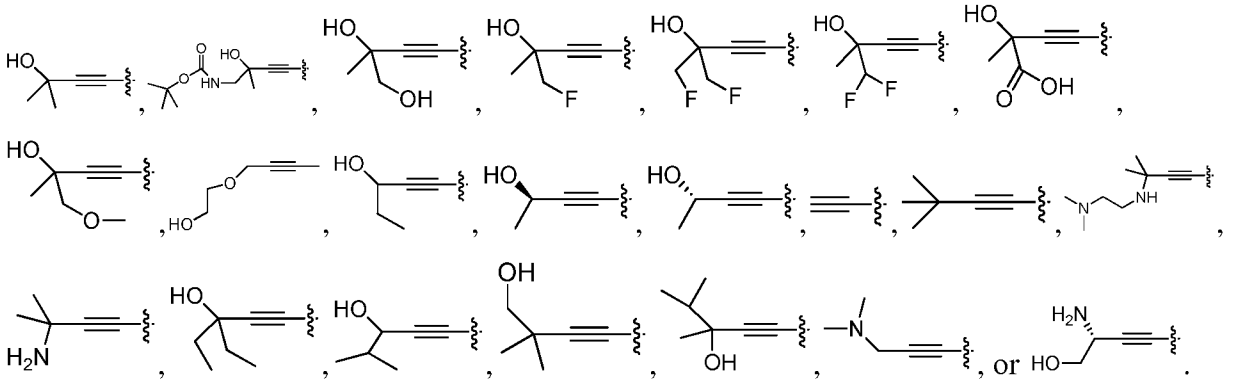
[0254] In certain embodiments, Z^2 optionally substituted with 1, 2, 3, 4, or 5 Z^{2b} or Z^{2c} groups is

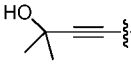


[0255] In certain embodiments, Z^2 optionally substituted with 1, 2, 3, 4, or 5 Z^{2b} or Z^{2c} groups is



[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.

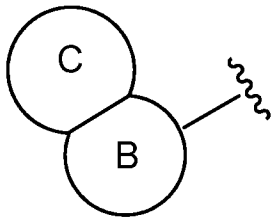
[0263] In certain embodiments, R^1 is a 8-12 membered tricyclic-heteroaryl, wherein the 8-12 membered tricyclic-heteroaryl contains at least one partially unsaturated ring, and wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of R^1 is optionally substituted with 1,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



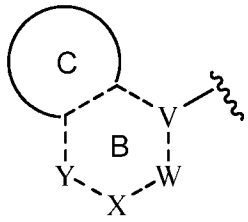
IIa

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;

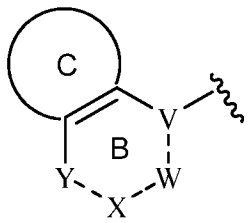
X is CZ^{4c}, NZ^{4c} or N;

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;

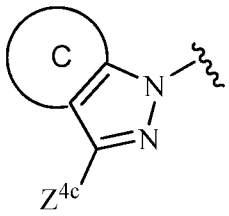
X is CZ^{4c}, NZ^{4c} or N;

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:



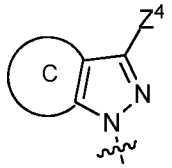
IId

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.

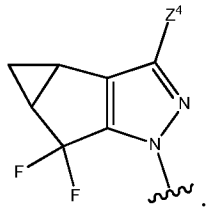
[0271] In certain embodiments of formula III, R^1 has the following formula:



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-

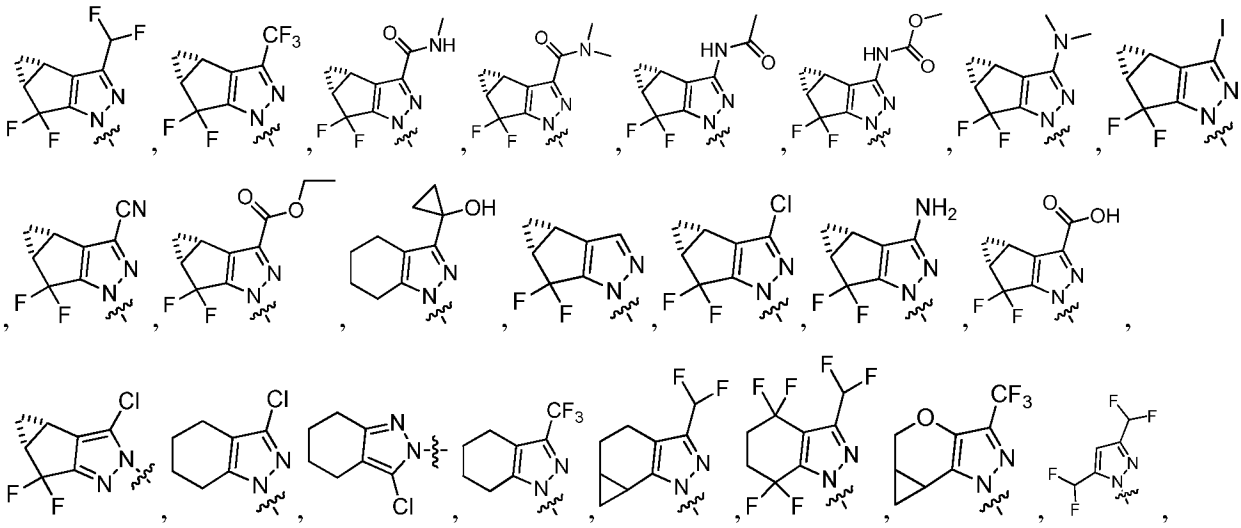
carbocycle, wherein any 5-7 membered monocyclic-carbocycle or 5-7 membered bicyclic-carbocycle of C is optionally substituted with 1, 2, 3, or 4 Z^4 groups, wherein the Z^4 groups are the same or different.

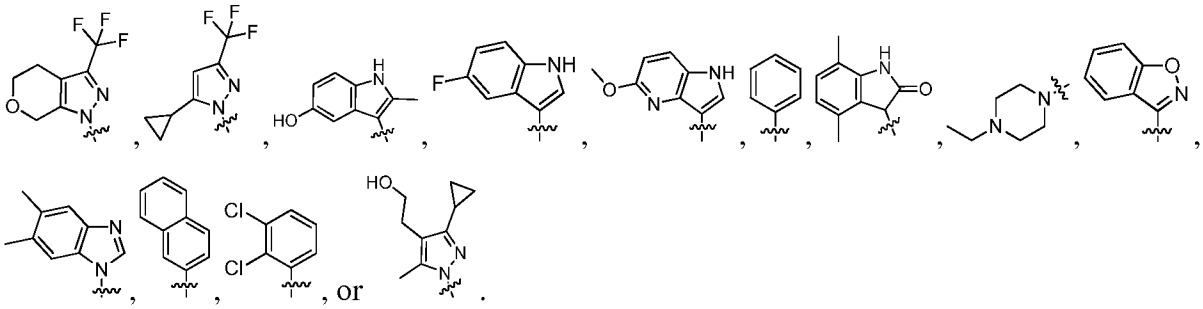
[0274] In certain embodiments of formula III, each Z^4 is independently $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, halogen, -CN, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-C(O)OR^{n5}$, or $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3$-$C_7)$carbocycle or $(C_1$-$C_8)$alkyl of Z^4 is optionally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

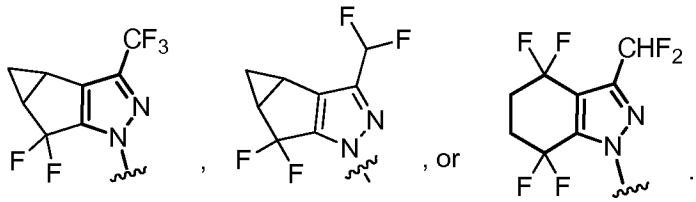
[0276] In certain embodiments, each Z^4 is independently fluoro, trifluoromethyl, or difluoromethyl.

[0277] In certain embodiments of formula III, R^1 optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups is

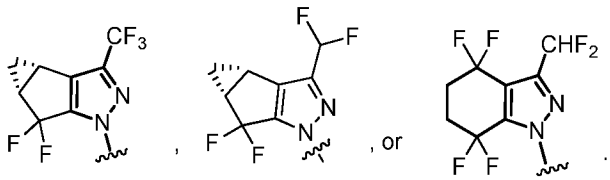




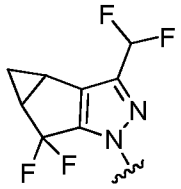
[0278] In certain embodiments, R^1 optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups is



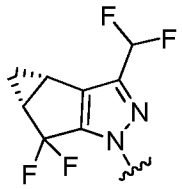
[0279] In certain embodiments, R^1 optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups is



[0280] In certain embodiments, R^1 optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups is

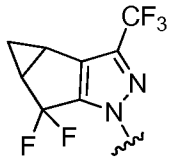


. In certain embodiments, R^1 optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups is

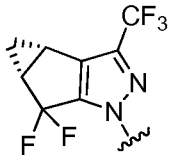


.

[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

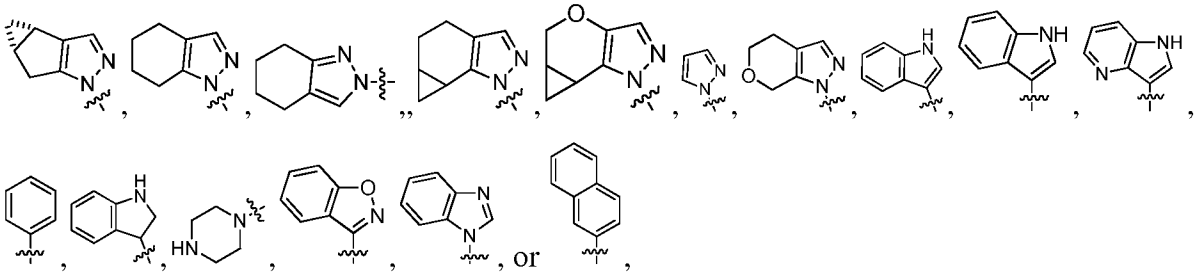


.

[0282] In certain embodiments, R^1 optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups is

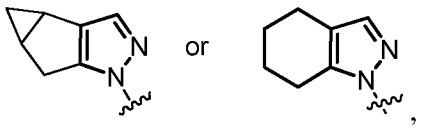
.

[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 $-C(O)NR^{q1}R^{r1}$.

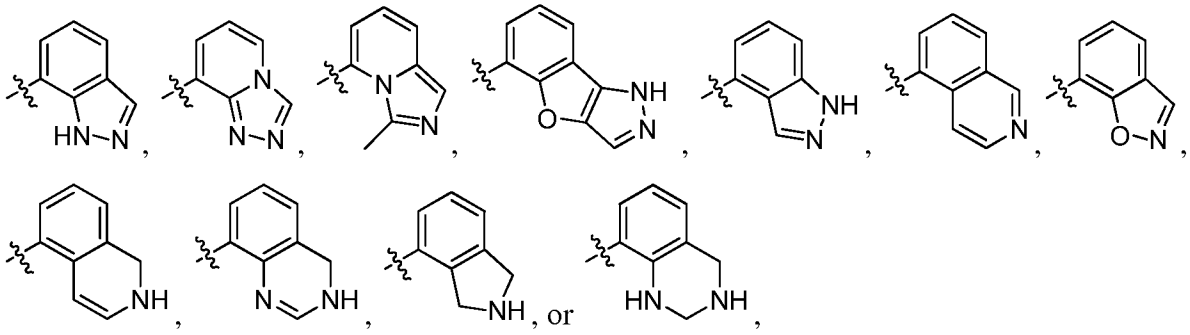
[0311] In certain embodiments, Z^{1a} is halogen, -OH, or $-C(O)NH_2$.

[0312] In certain embodiments, Z^{1a} is fluoro, -OH, or $-C(O)NH_2$.

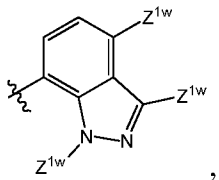
[0313] In certain embodiments, each Z^{1b} is $(C_1\text{-}C_8)$alkyl, which may be same or different.

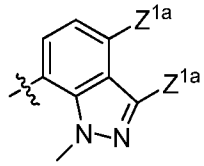
[0314] In certain embodiments, each Z^{1b} is independently methyl or difluoromethyl.

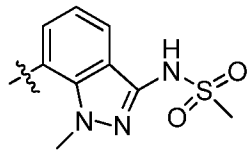
[0315] In certain embodiments of formula III, Z^1 is

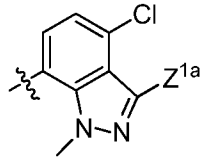


optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b}.

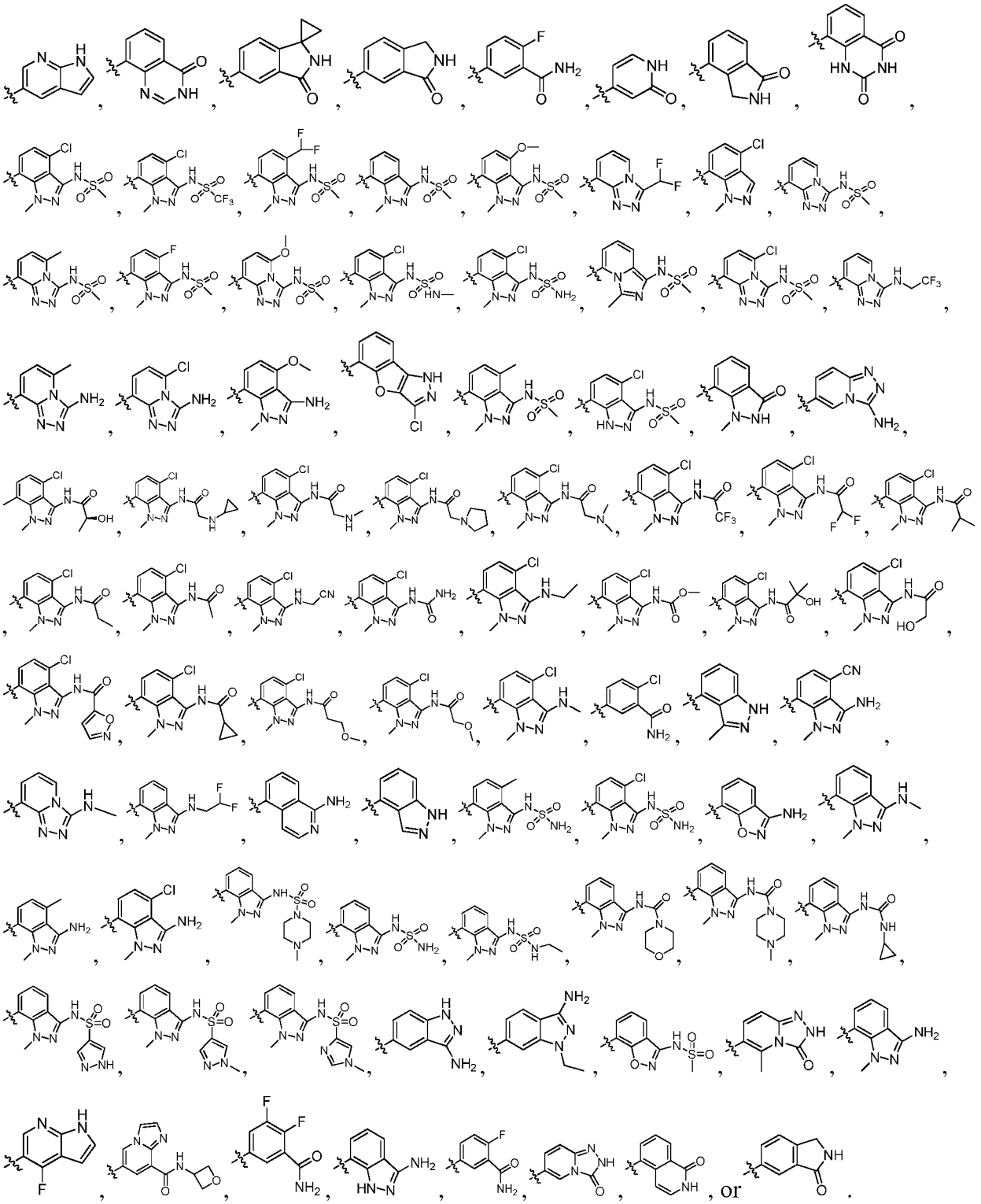
[0316] In certain embodiments, Z^1 is  , wherein each Z^{1w} is independently Z^{1a}, Z^{1b}, or H. In certain embodiments, each Z^{1a} is independently halogen, -CN, -OR^{n1}, -$NR^{n1}S(O)_2R^{p1}$, -$NR^{n1}S(O)_2NR^{q1}R^{r1}$, -$NR^{q1}R^{r1}$, -$NR^{n1}COR^{p1}$, -$NR^{n1}CONR^{q1}R^{r1}$, or -$NR^{n1}CO_2R^{p1}$; 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 -$NR^{n1}S(O)_2NR^{q1}R^{r1}$.

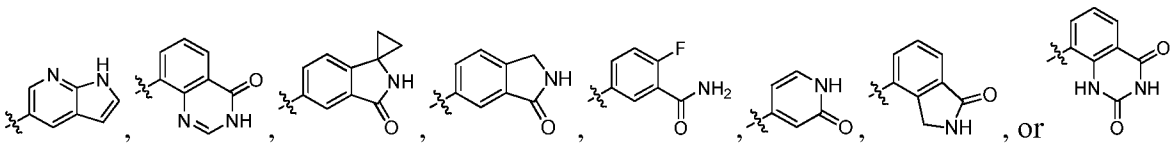
[0318] In certain embodiments, Z^1 is  , optionally substituted with 1, 2, 3, or 4 Z^{1a} or Z^{1b}.

[0319] In certain embodiments, Z^1 is  .

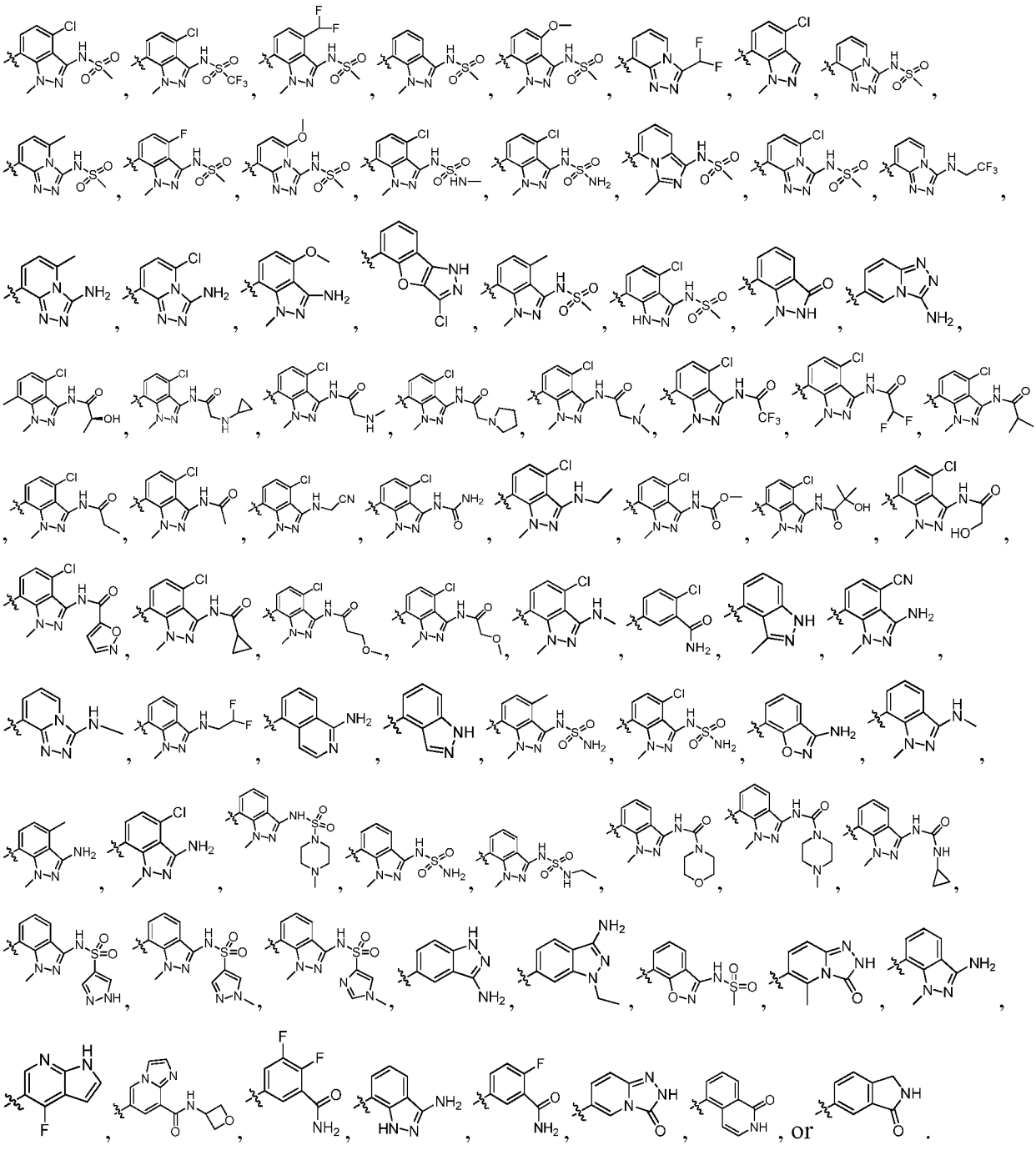
[0320] In certain embodiments, Z^1 optionally substituted with 1, 2, 3, 4, or 5 Z^{1a} or Z^{1b} groups is



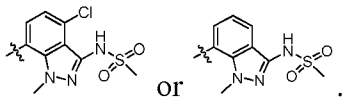
[0321] In certain embodiments, Z^1 optionally substituted with 1, 2, 3, 4, or 5 Z^{1a} or Z^{1b} groups is

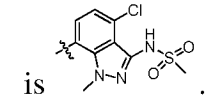


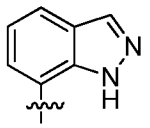
[0322] In certain embodiments, Z^1 optionally substituted with 1, 2, 3, 4, or 5 Z^{1a} or Z^{1b} groups is



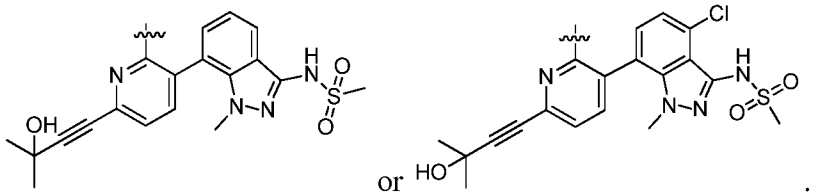
[0323] In certain embodiments, Z^1 optionally substituted with 1, 2, 3, 4, or 5 Z^{1a} or Z^{1b} groups is



[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 $(C_2\text{-}C_8)$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;

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, 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 $(C_1\text{-}C_4)$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 $(C_1\text{-}C_3)$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}, which may be the same or different;

each Z^{1a} is independently oxo, $(C_3\text{-}C_7)$carbocycle, halogen, -CN, -O-$(C_1\text{-}C_8)$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;

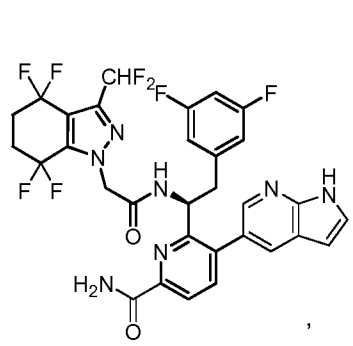
each Z^{4a} is independently halogen, -CN, or $-OR^{n6}$; and

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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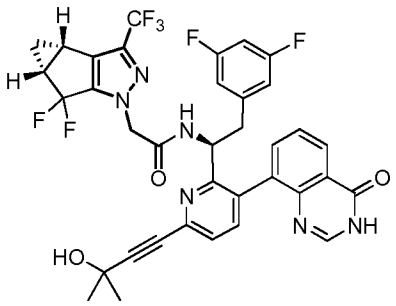

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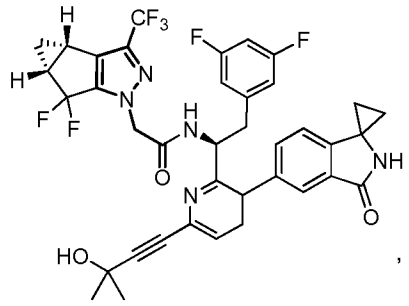

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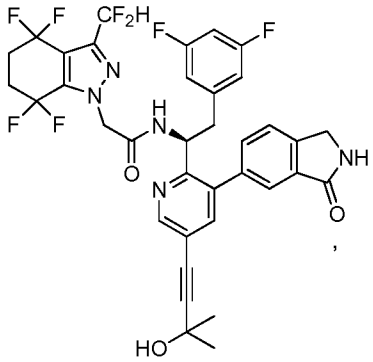

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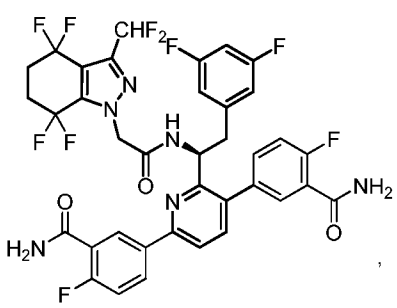

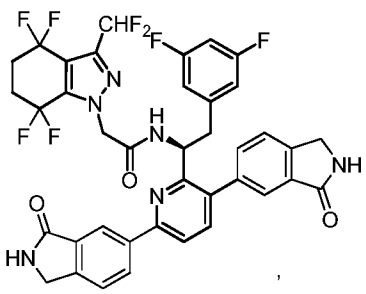

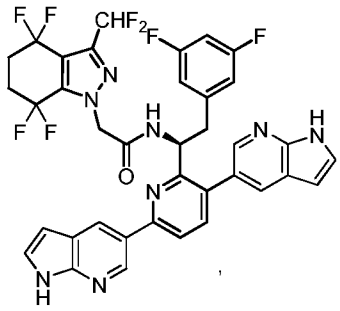

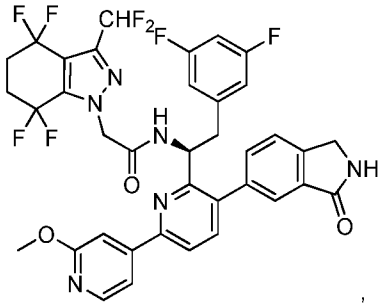

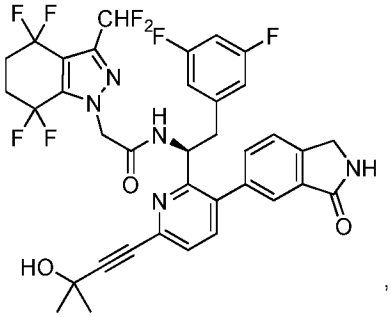

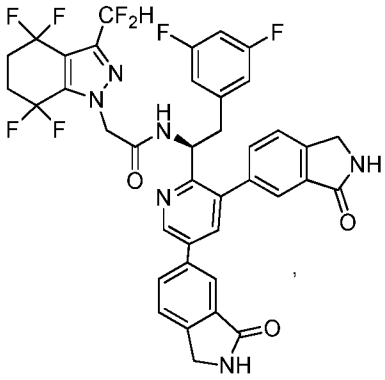

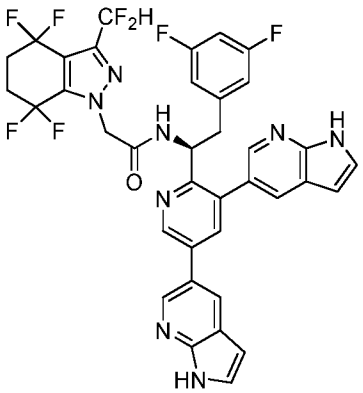

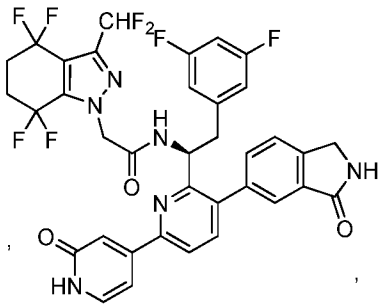

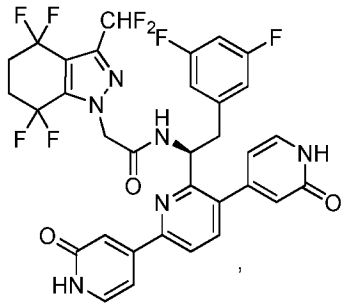

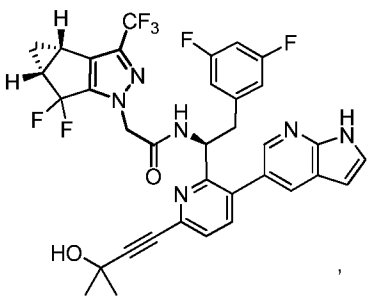

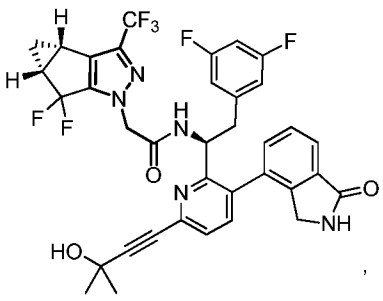

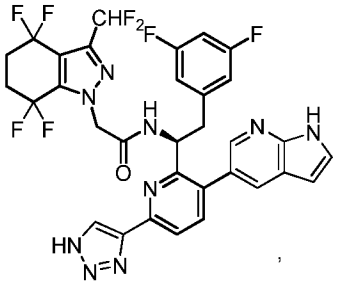

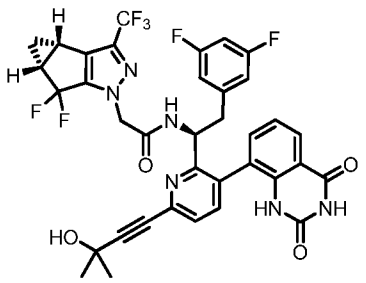
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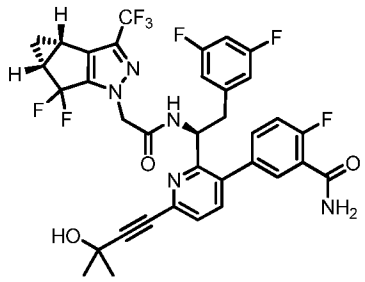
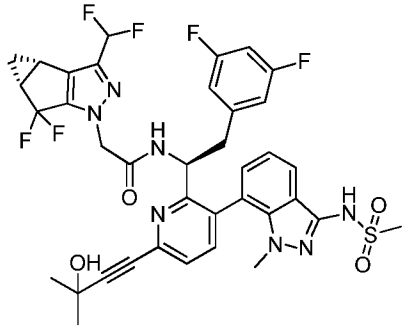
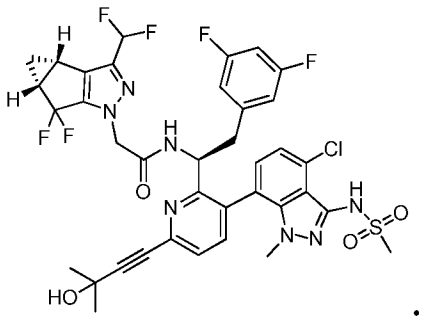


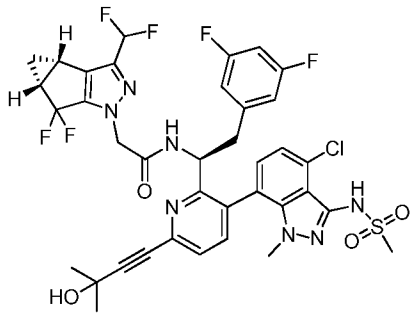
and pharmaceutically acceptable salts thereof.

[0343] In certain embodiments, a compound is:


or

.

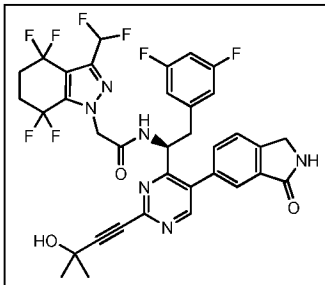
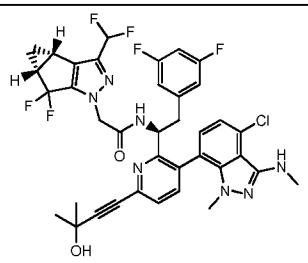
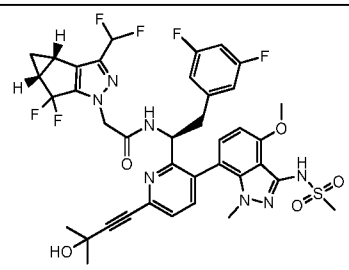
or a pharmaceutically acceptable salt thereof.

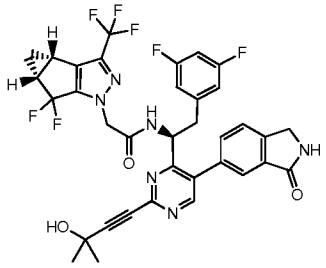
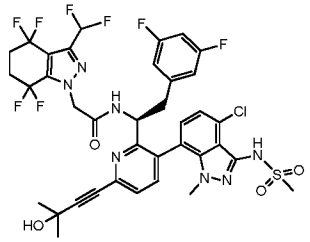
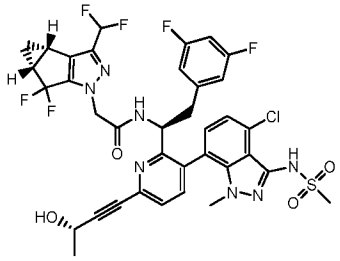
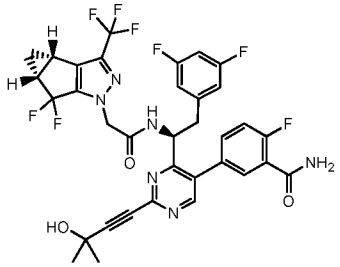
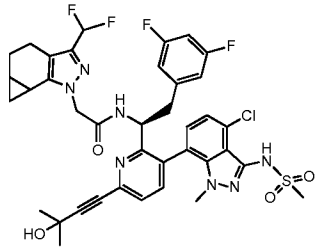
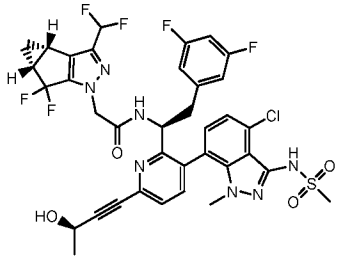
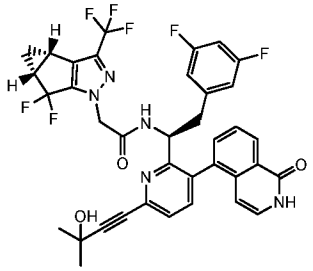
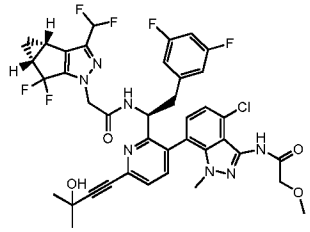
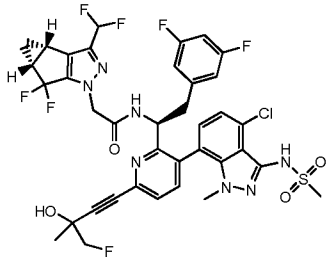
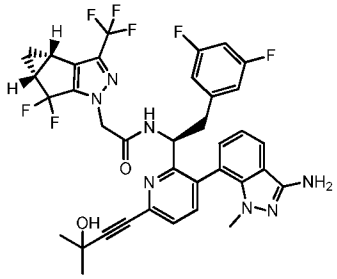
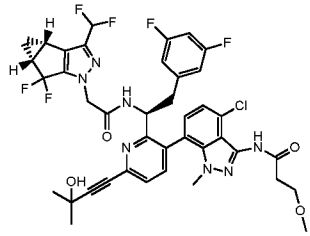
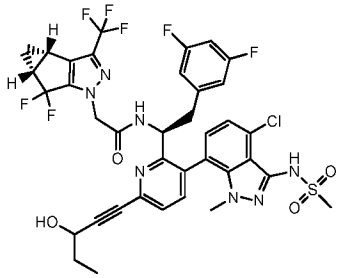
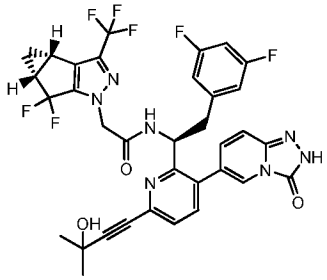
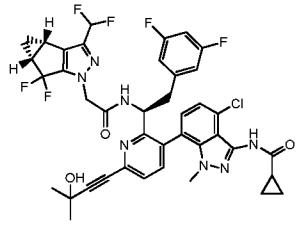
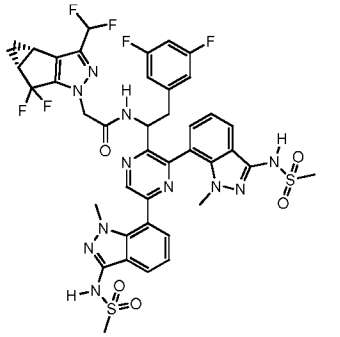
[0344] In certain embodiments, a compound is:

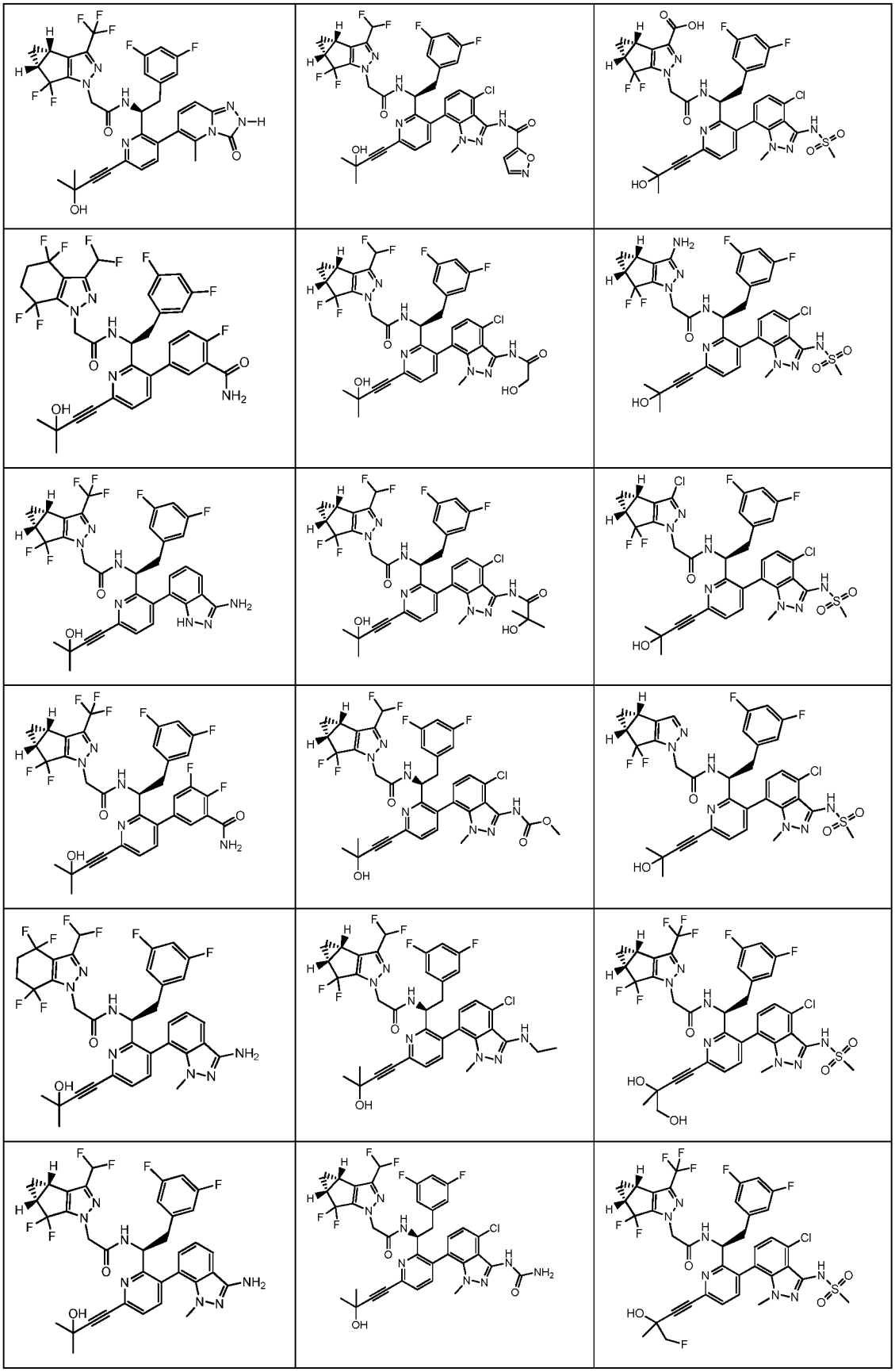


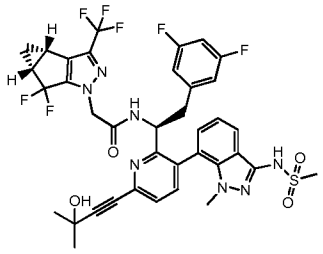
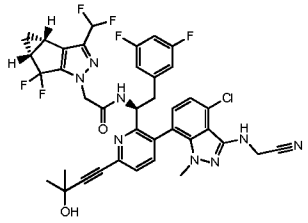
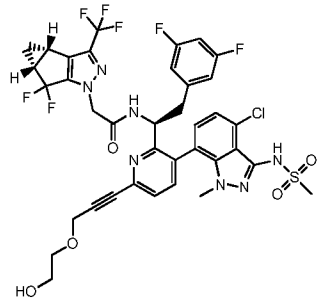
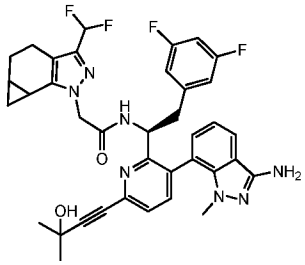
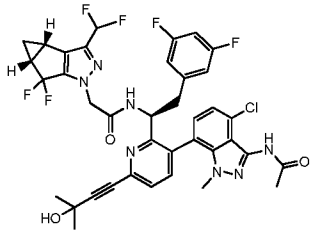
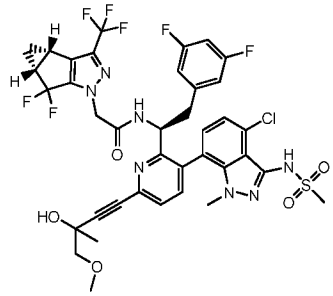
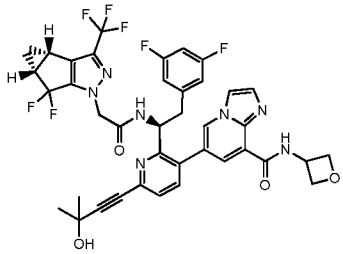
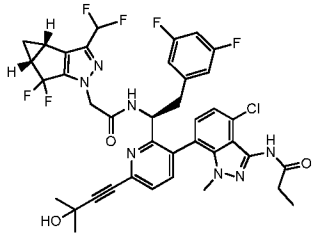
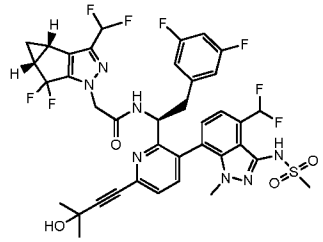
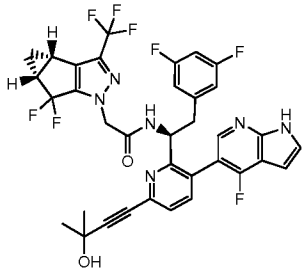
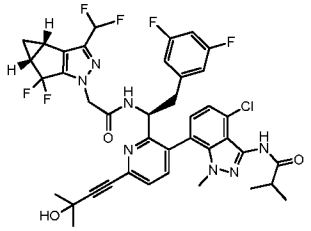
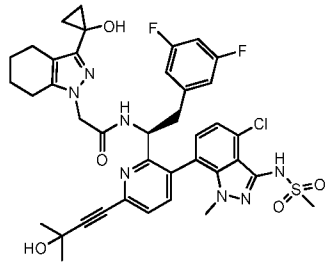
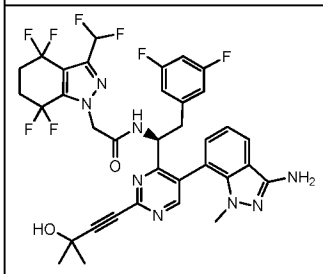
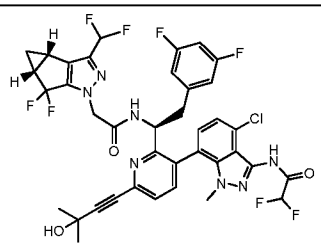
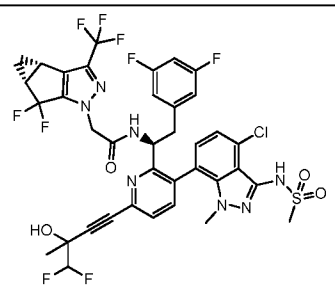
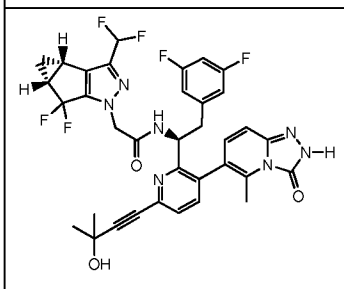
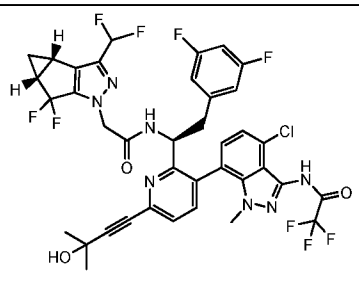
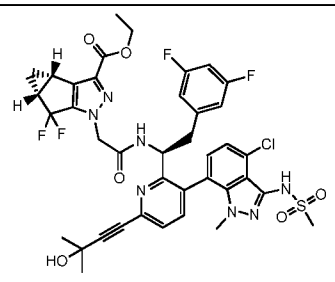
or a pharmaceutically acceptable salt thereof.

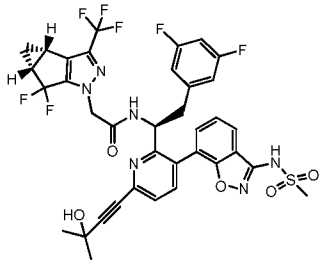
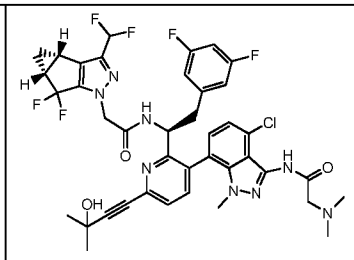
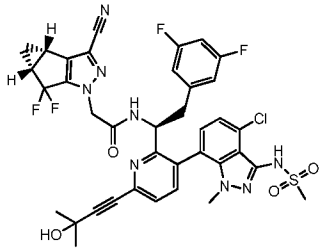
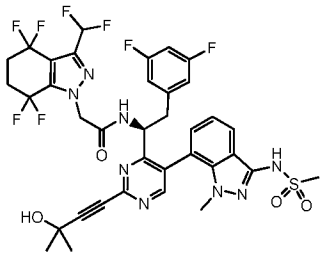
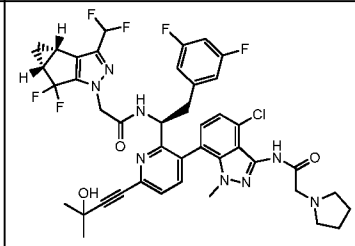
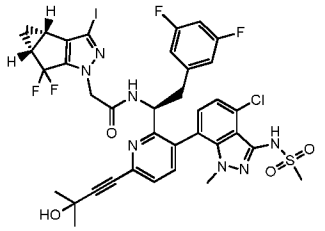
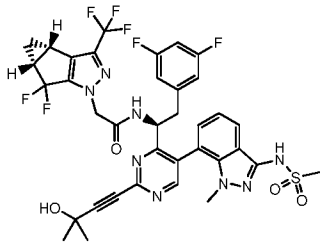
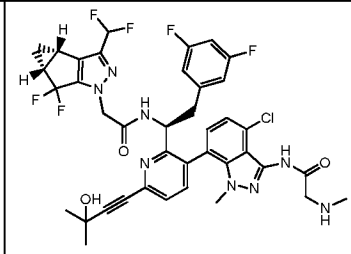
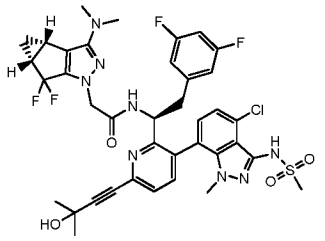
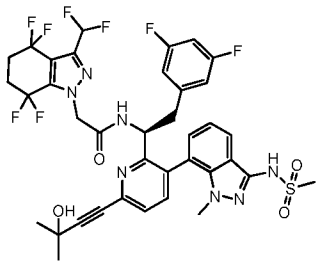
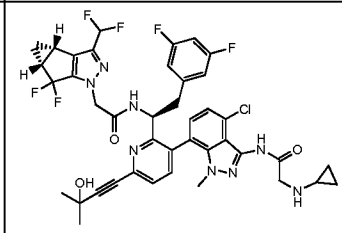
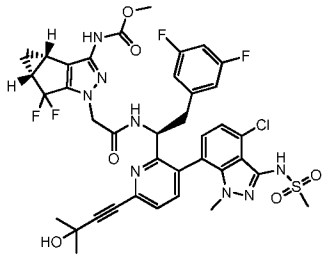
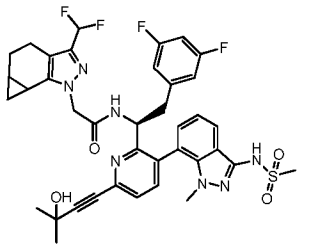
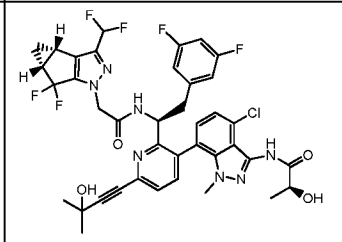
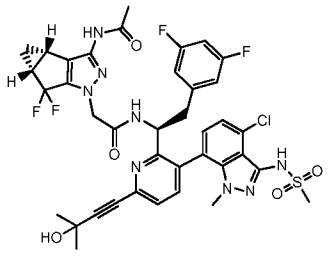
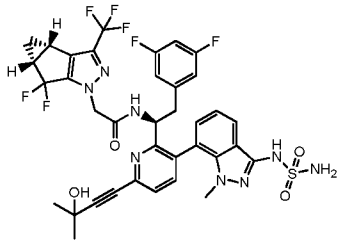
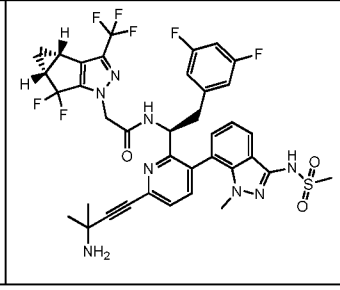
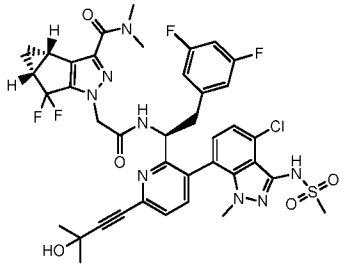
[0345] In certain embodiments, a compound or a pharmaceutically acceptable salt thereof is:

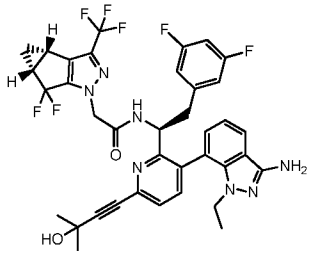
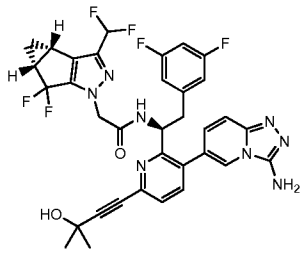
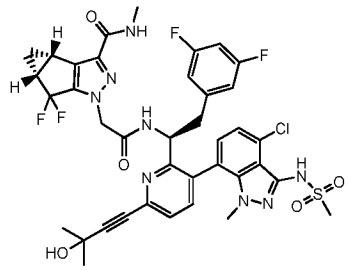
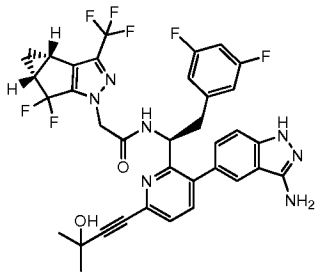
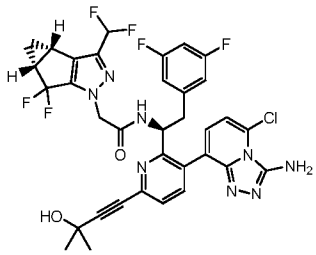
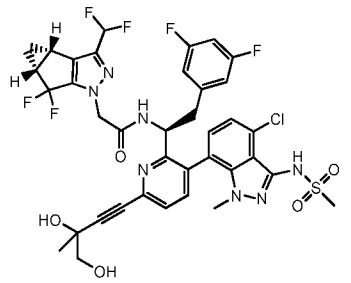
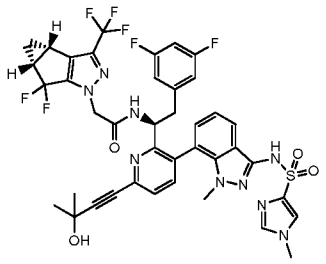
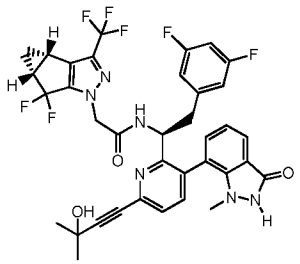
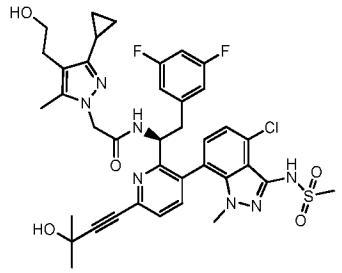
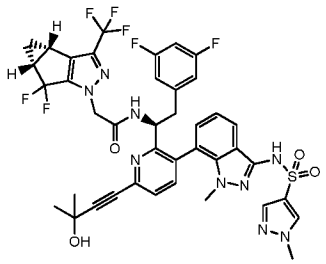
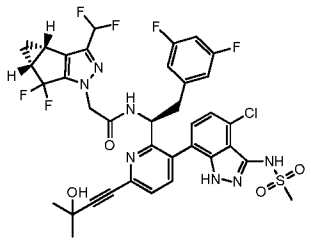
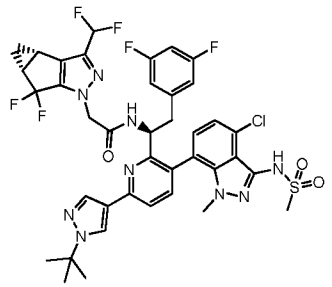
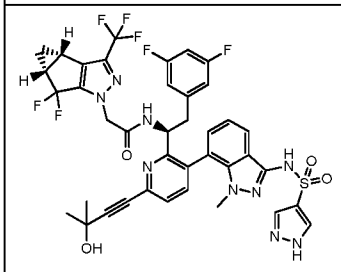
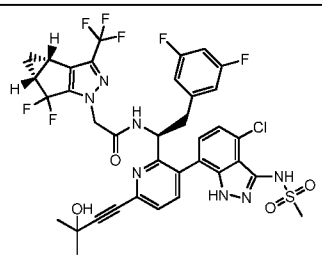
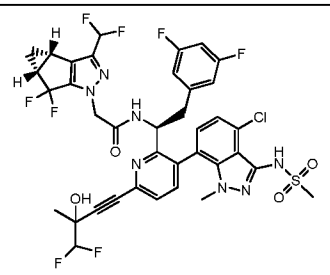
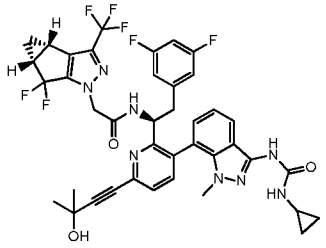
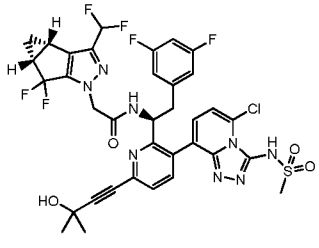
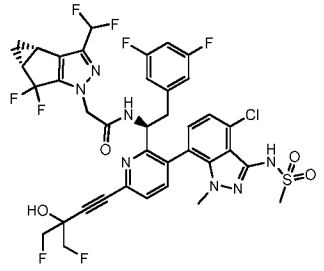
		

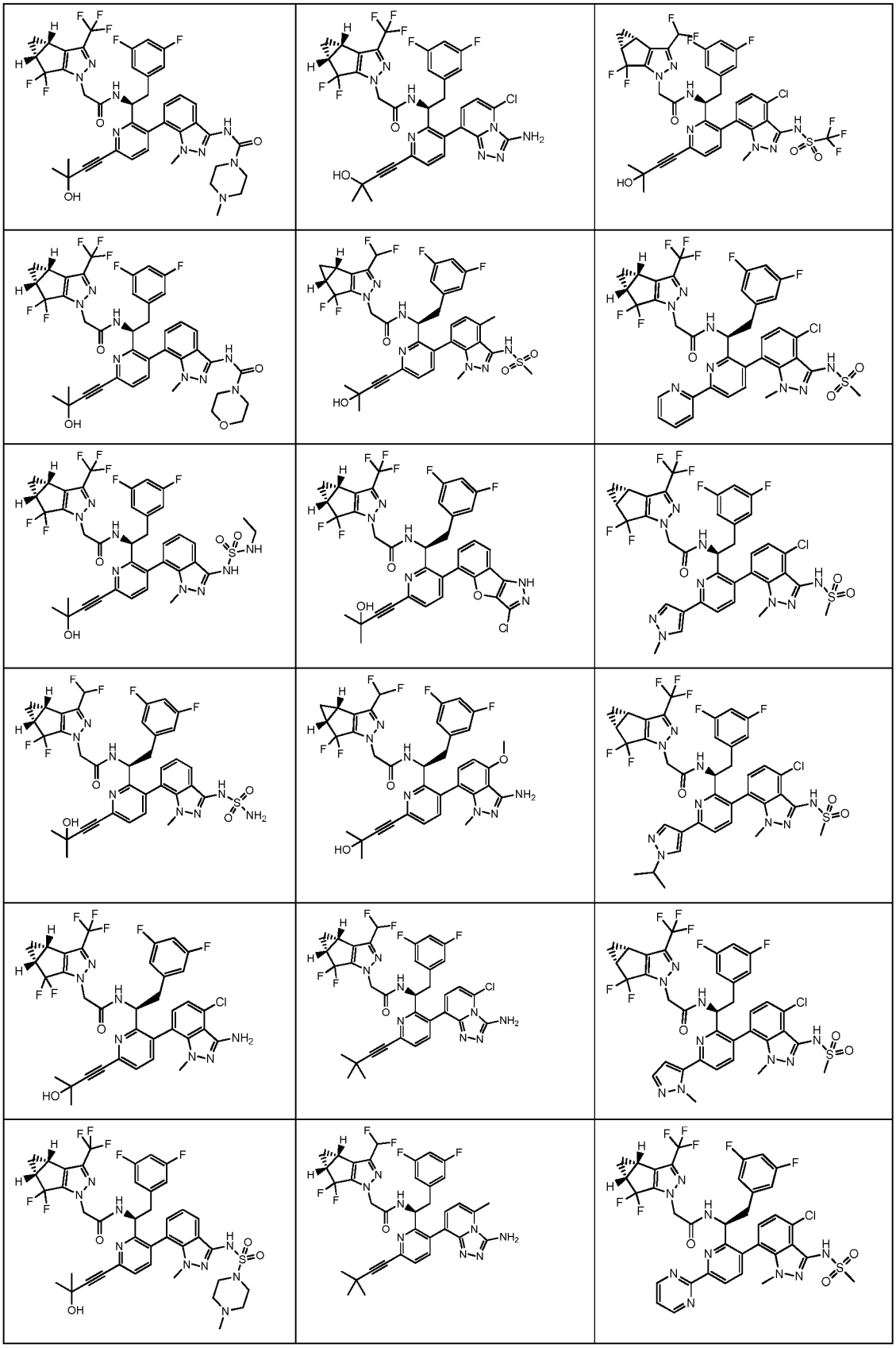
		
		
		
		
		

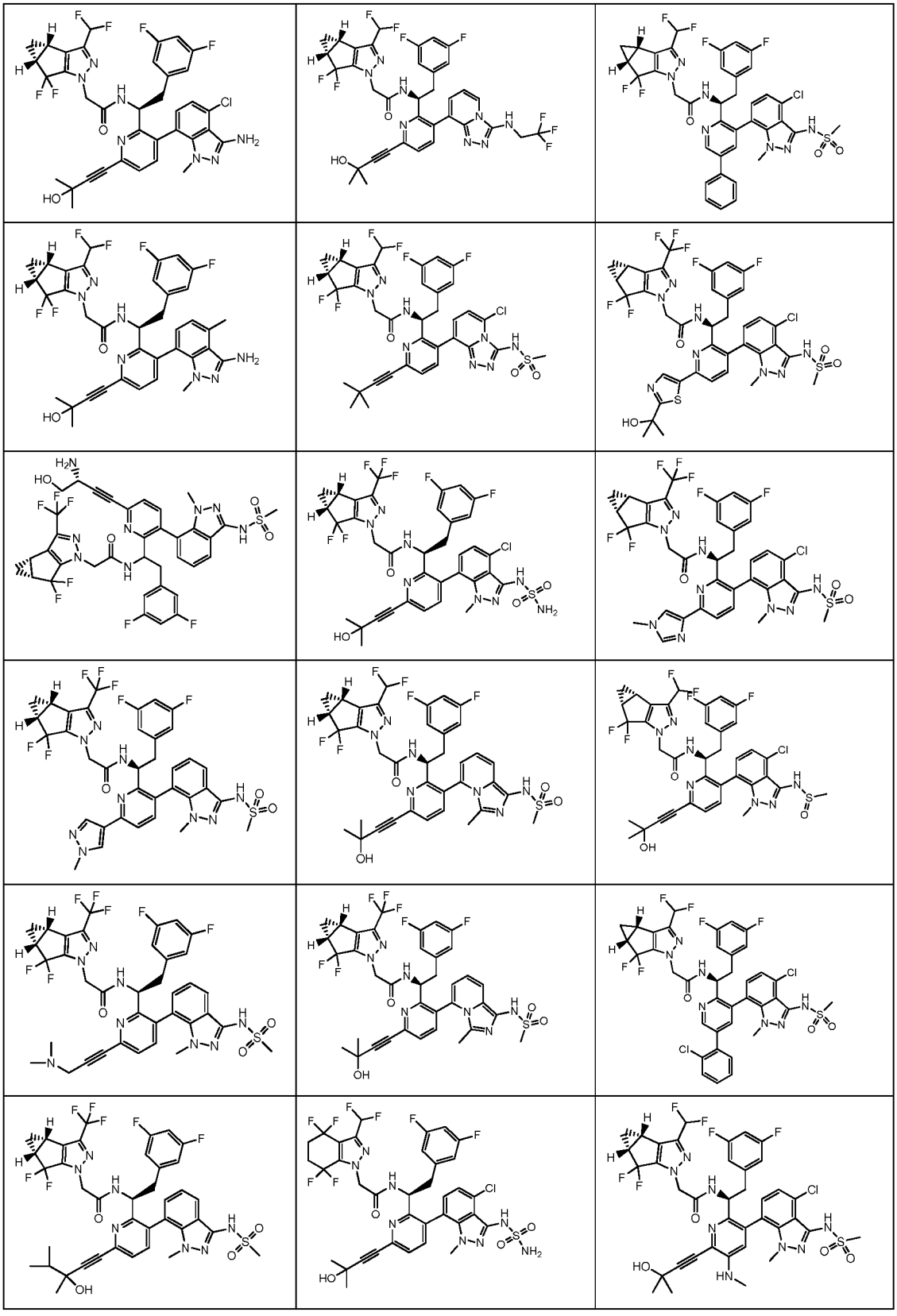


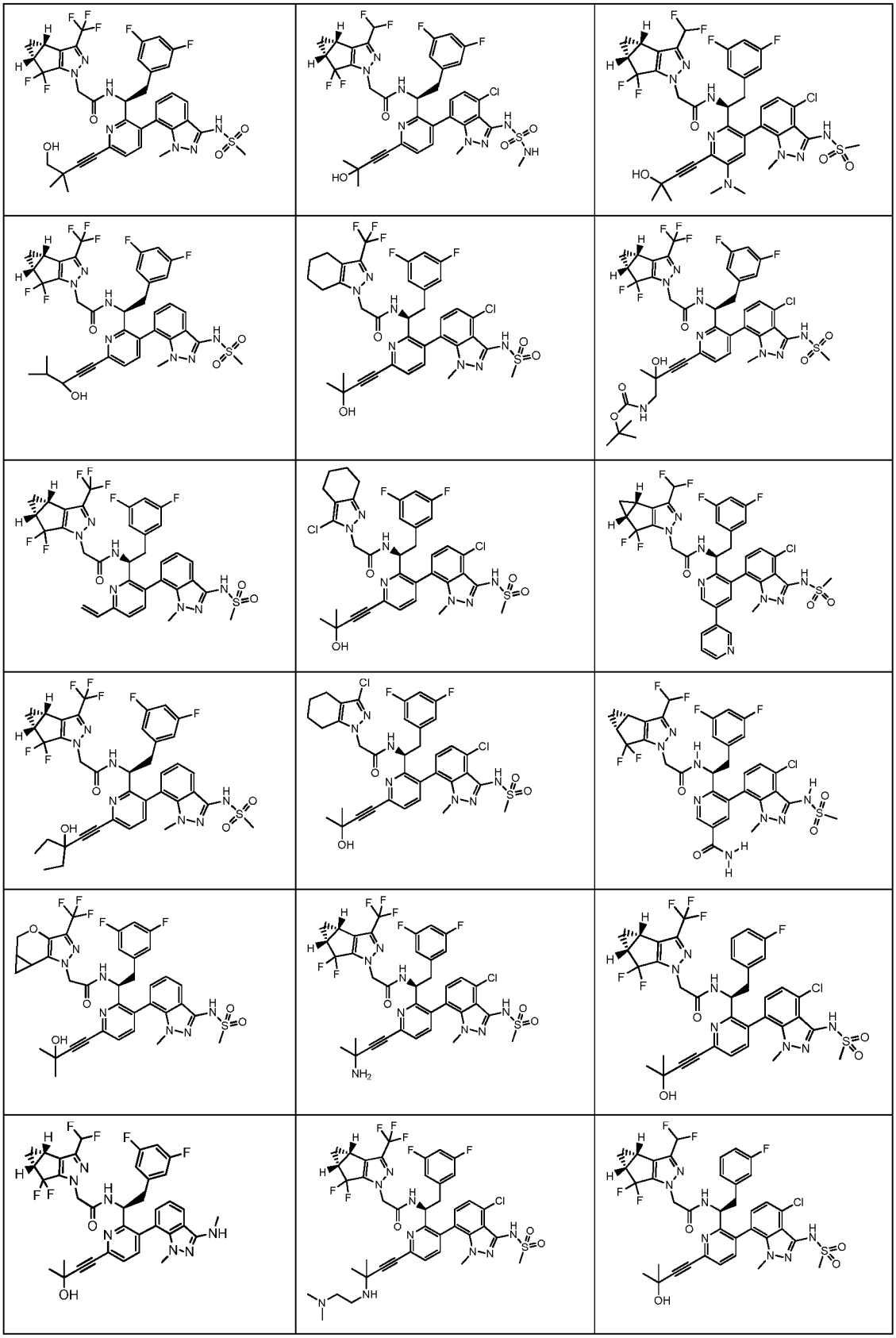
		
		
		
		
		
		

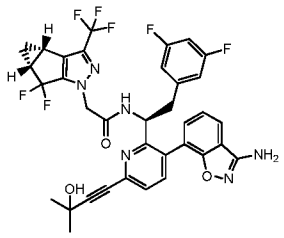
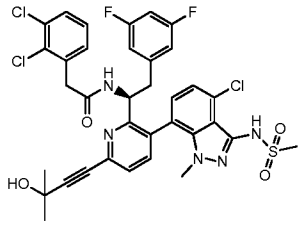
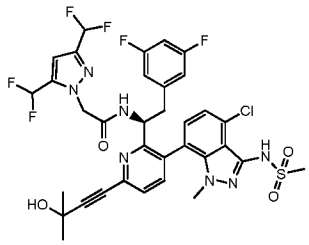
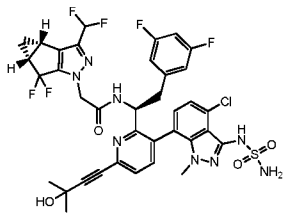
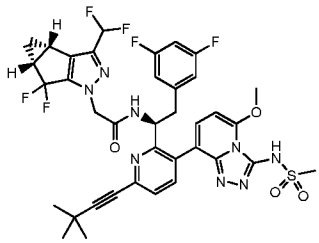
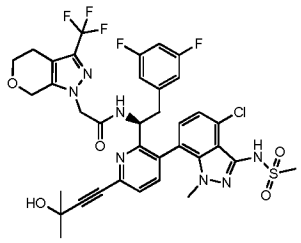
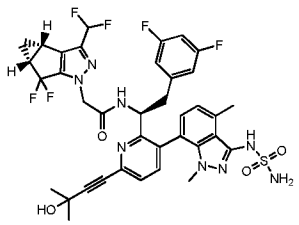
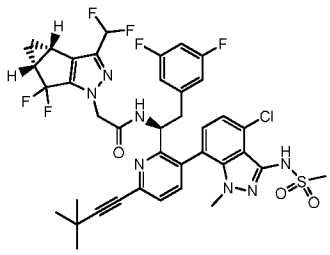
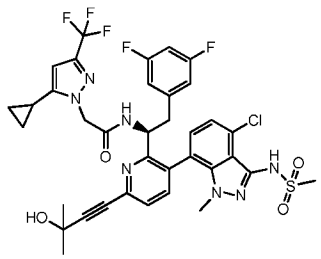
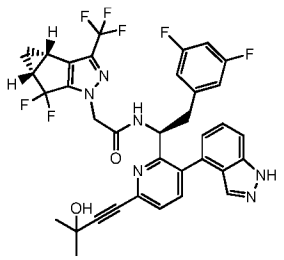
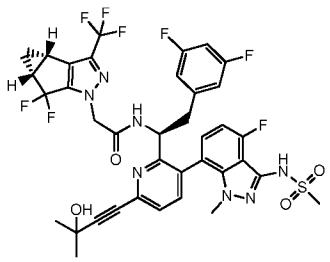
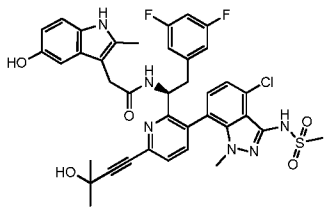
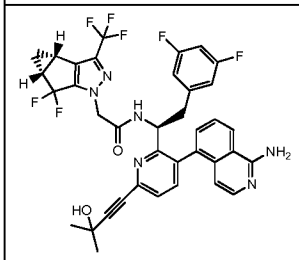
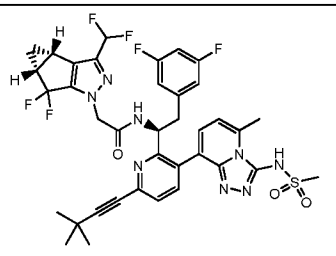
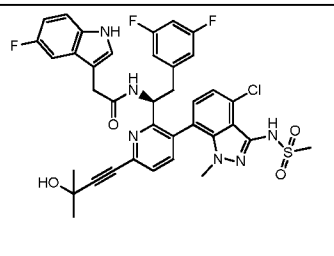
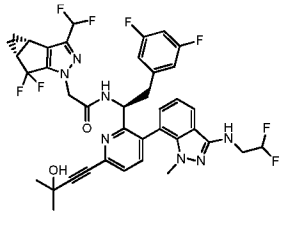
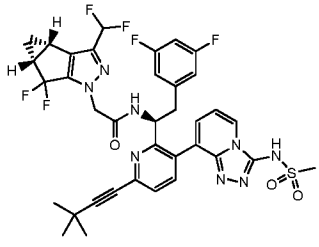
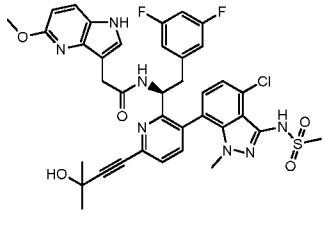
		
		
		
		
		
		

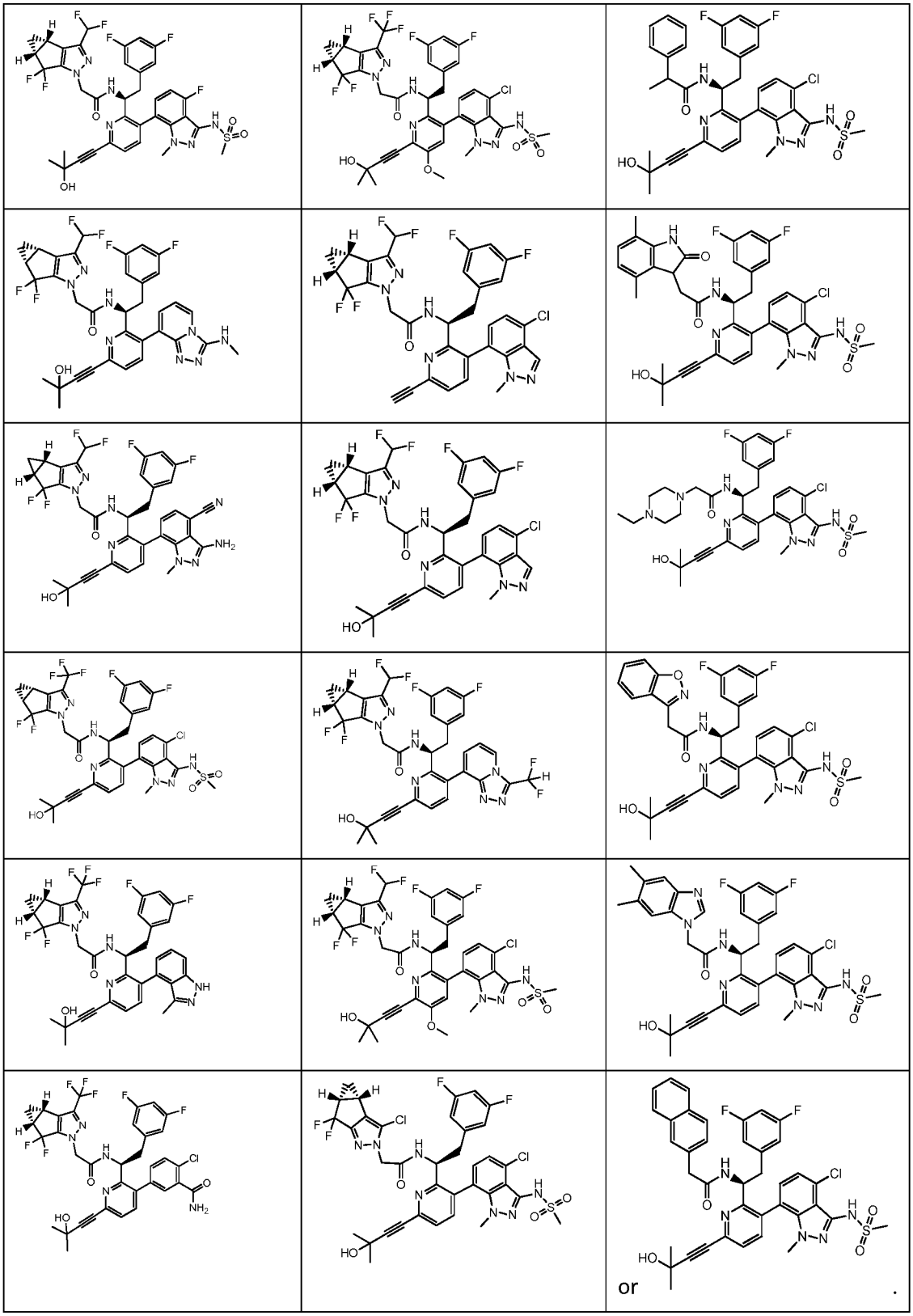
		
		
		
		
		
		





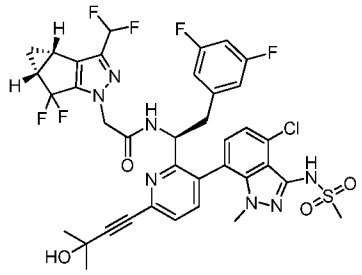




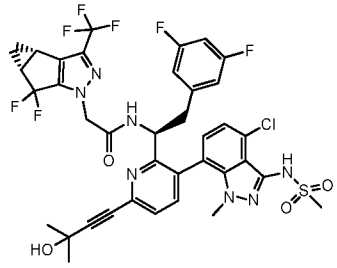
or .

[0346] In certain embodiments, a compound is:



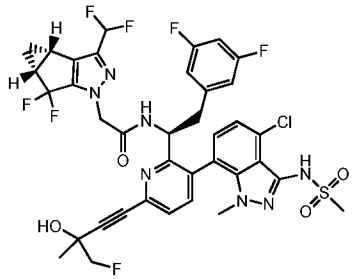
or a pharmaceutically acceptable salt thereof.

[0347] In certain embodiments, a compound is:



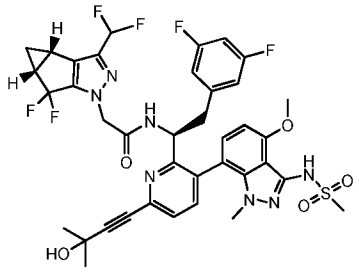
or a pharmaceutically acceptable salt thereof.

[0348] In certain embodiments, a compound is:



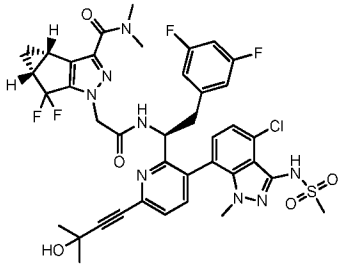
or a pharmaceutically acceptable salt thereof.

[0349] In certain embodiments, a compound is:



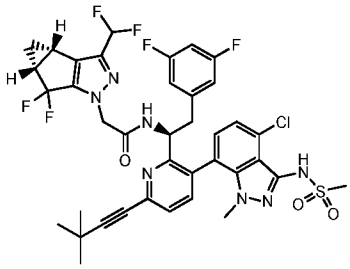
or a pharmaceutically acceptable salt thereof.

[0350] In certain embodiments, a compound is:



or a pharmaceutically acceptable salt thereof.

[0351] In certain embodiments, a compound is:

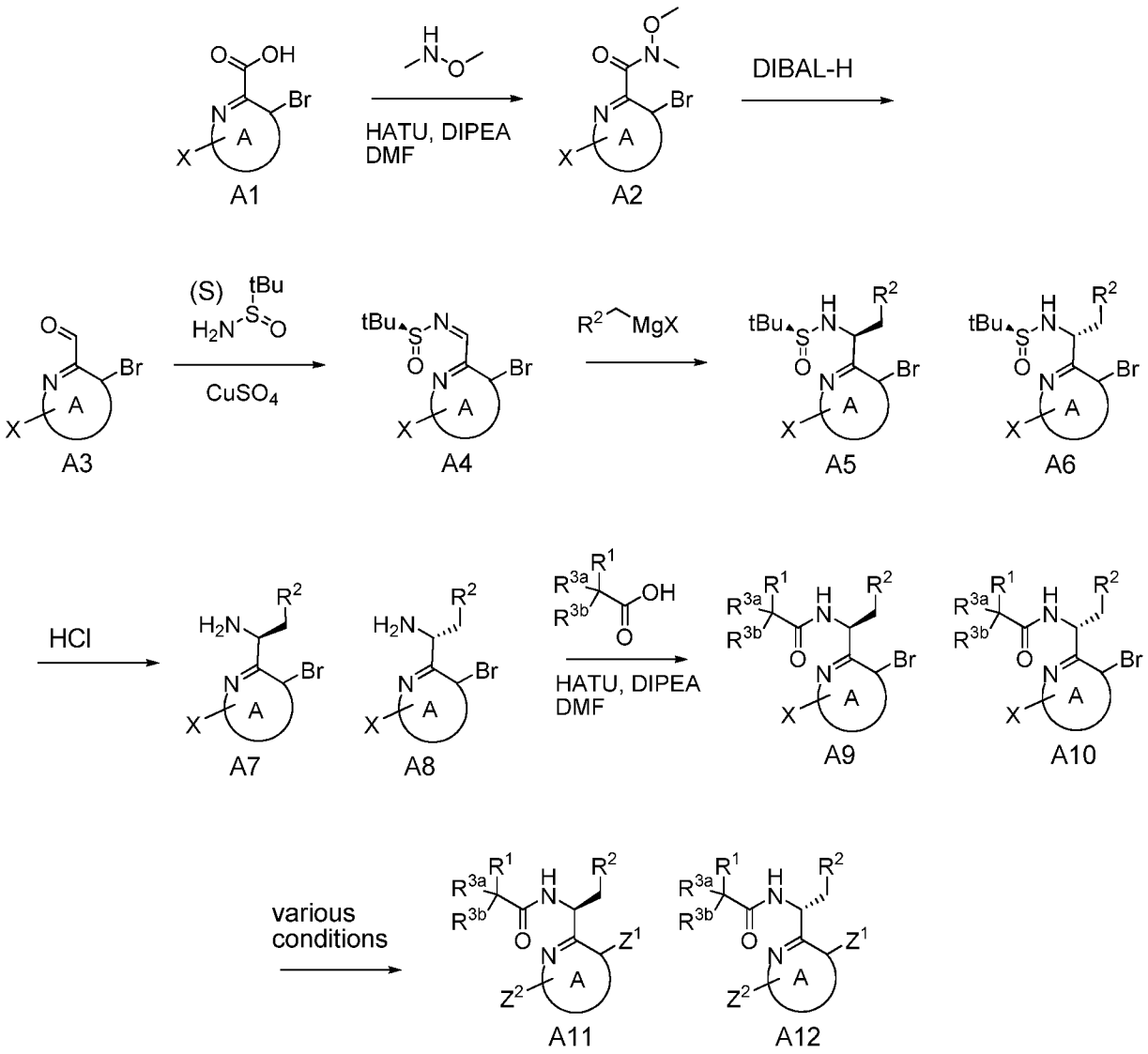


or a pharmaceutically acceptable salt thereof.

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

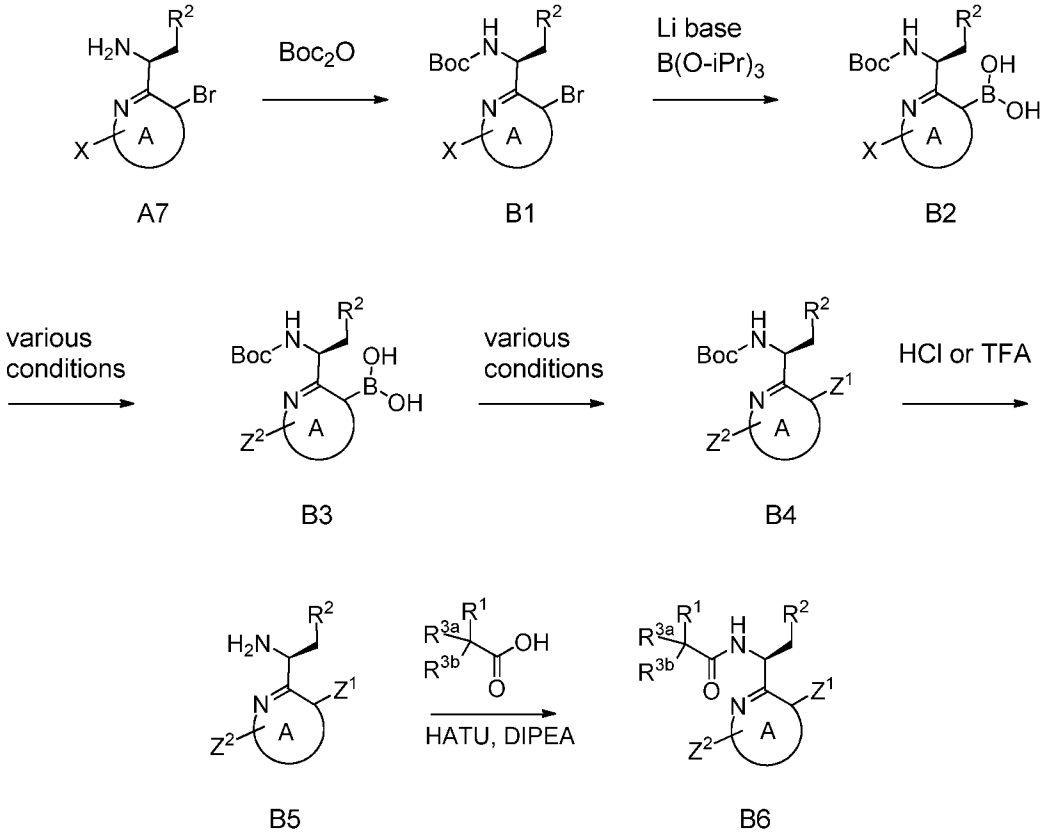


[0353] Scheme 1 describes a general stereoselective route which is used to prepare compounds of formula I. The scheme is also be used to prepare compounds of formula III. Heteroaryl acids of formula A1 (where X represents diversifiable chemical group such as NH_2, SH, or halogen that are suitably protected) 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

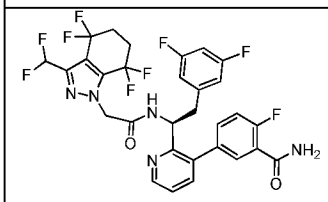
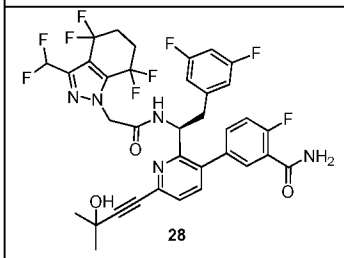
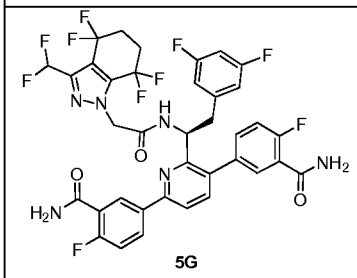
demonstrate >70% inhibition at 2 μM. In one embodiment, the compounds demonstrate >75% inhibition at 2 μM. In one embodiment, the compounds demonstrate >80% inhibition at 2 μM. In one embodiment, the compounds demonstrate >85% inhibition at 2 μM. In one embodiment, the compounds demonstrate >90% inhibition 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.

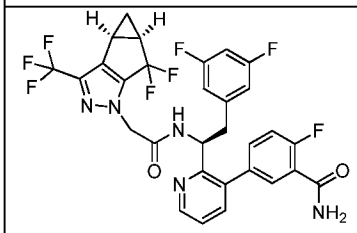
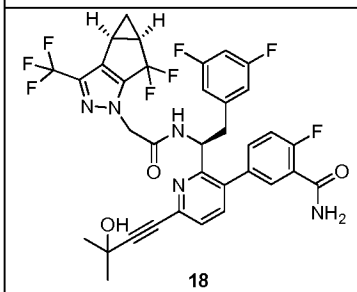
[0391] In one embodiment, the compounds demonstrate >10% inhibition at 0.2 μM. In one embodiment, the compounds demonstrate >30% inhibition at 0.2 μM. In one embodiment, the compounds demonstrate >50% inhibition at 0.2 μM. In one embodiment, the compounds demonstrate >70% inhibition at 0.2 μM. In one 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

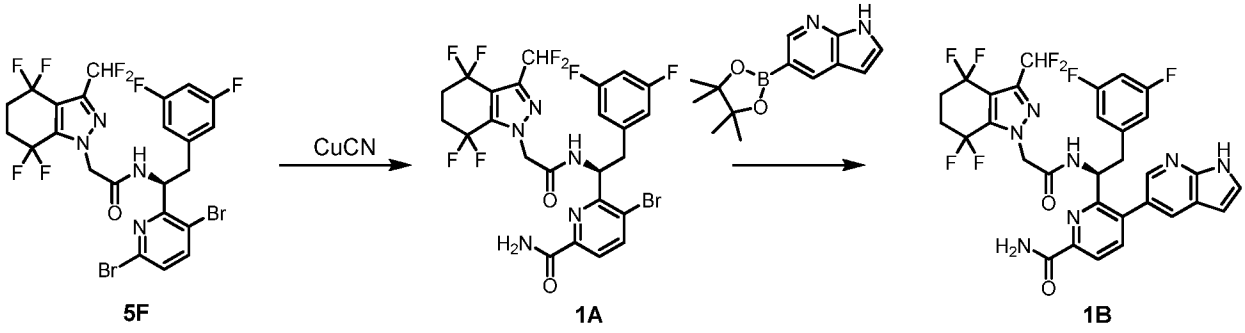
Compound	Response at 2 μM	Response at 0.2 μM
 X2	91	65
 18	90	96

[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.



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**):

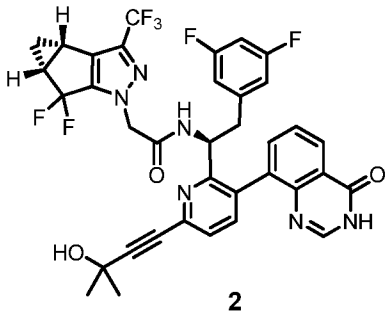
[0397] Compound **5F** (100 mg, 0.15 mmol) and CuCN (16 mg, 0.18 mmol) was dissolved in 0.3 mL of DMF. The reaction mixture was heated at 100 °C overnight. After cooled down to room temperature it was diluted with water and extracted with EtOAc. The organic phase was dried (Na_2SO_4), filtered and concentrated. 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.

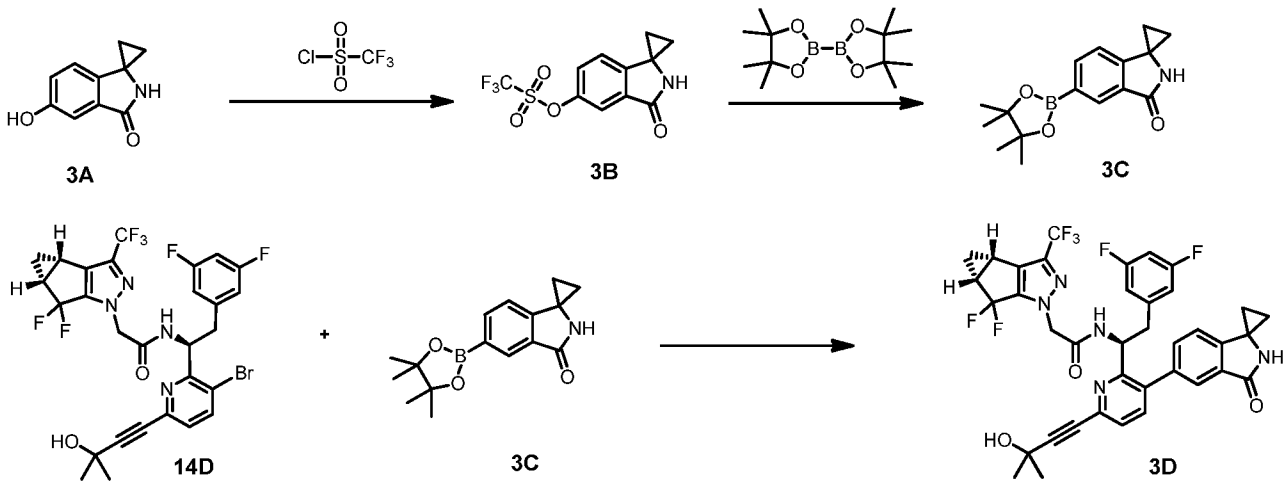


2

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 HCl (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®, 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**):

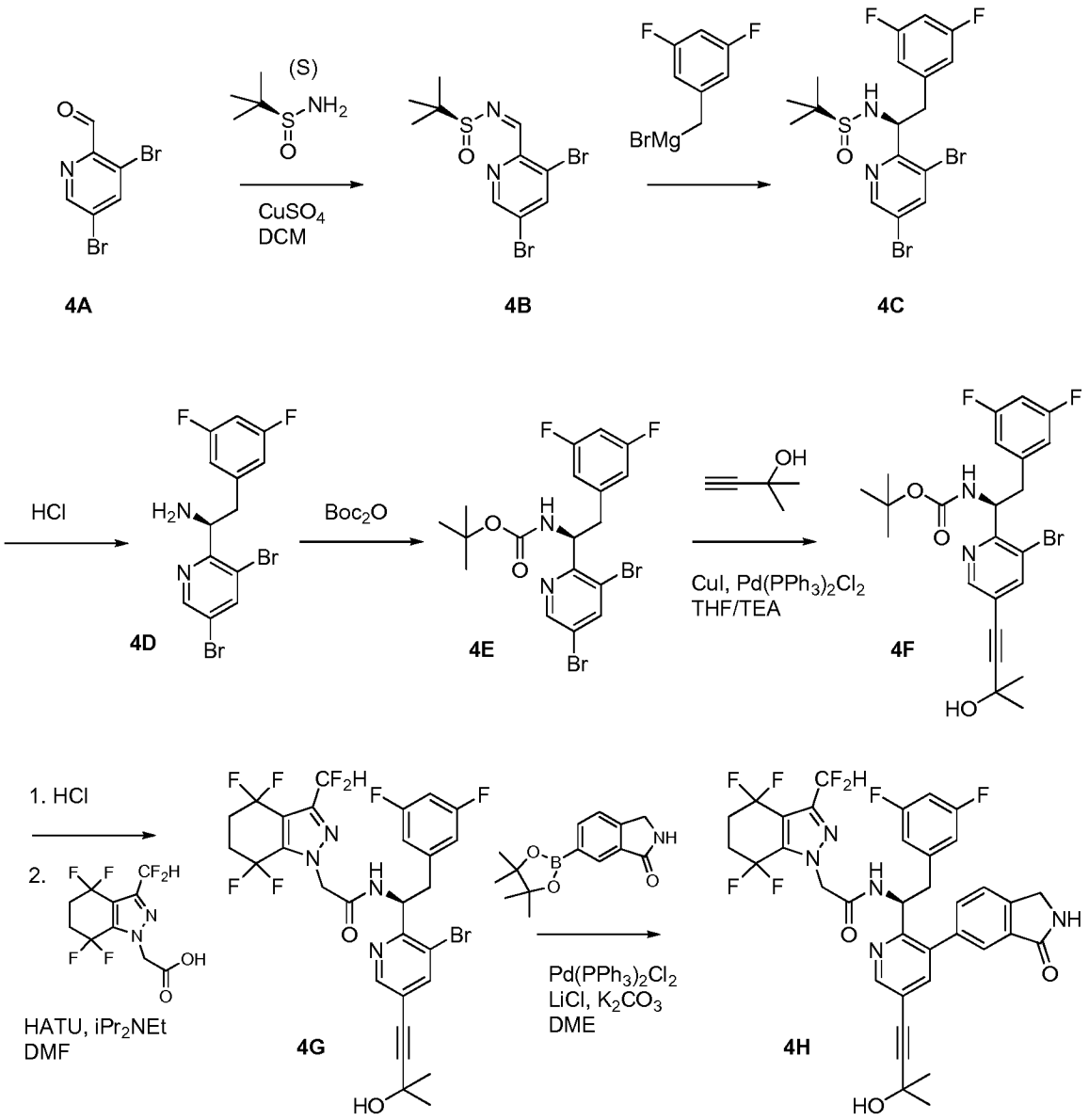
[0401] In a microwave tube were charged **3B** (200 mg, 0.65 mmol), bis(pinacolato)diboron (330 mg, 1.3 mmol) and potassium acetate (191 mg, 1.95 mmol), [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)(14 mg, 0.02 mmol) and 1,4-dioxane (8 mL) The mixture was heated up to 150 °C for 20 min 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 $[M+H]^+$.

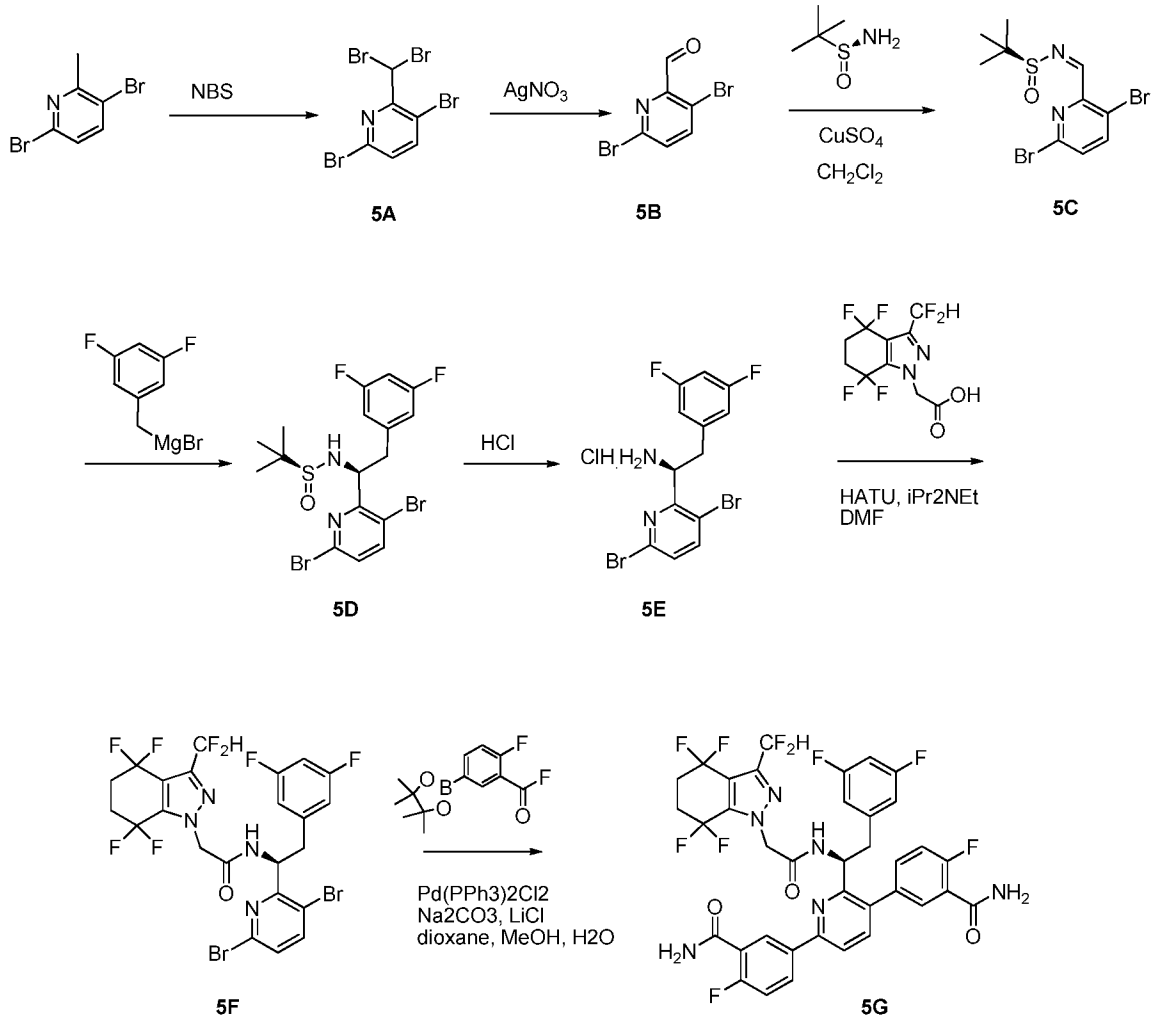
Synthesis of (S)-N-(1-(3-bromo-5-(3-hydroxy-3-methylbut-1-ynyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**4G**):

[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 $[M+H]^+$

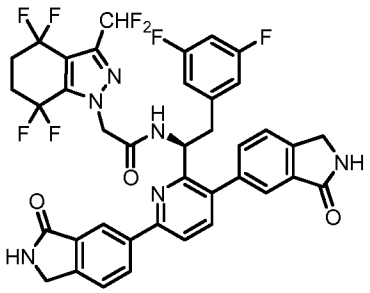
Synthesis of (S)-N-(1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**5F**):

[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.

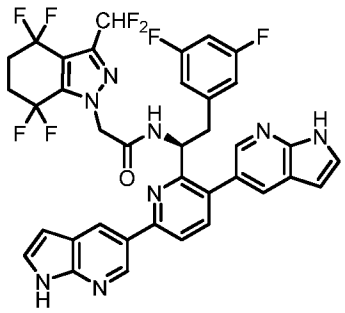


6

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.



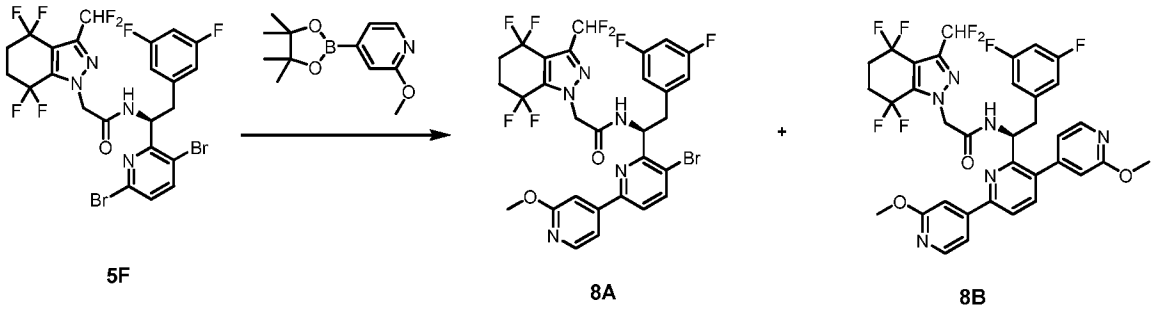
7

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**):

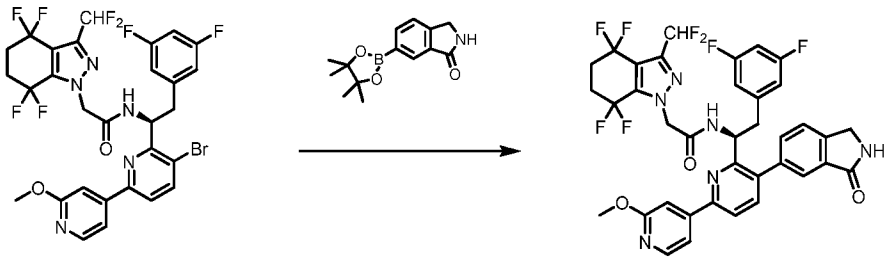
[0418] The title compound (**7**) was prepared according to the method presented for the synthesis of compound **5G** of Example 5 utilizing 6 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine and **5F**. ^1H NMR (400 MHz, CD_3OD) δ 9.23-9.17 (m, 2H), 9.04 (d, *J* = 8.1 Hz, 1H), 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.



5F 8A 8B



8A 8C

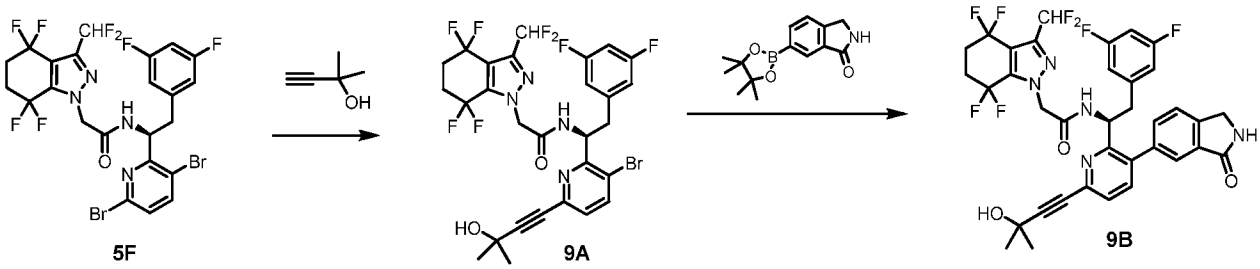
Synthesis of (S)-N-(1-(5-bromo-2'-methoxy-[2,4'-bipyridin]-6-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**8A**) and (S)-N-(1-(2',5'-di(methoxy-[2,4'-bipyridin]-6-yl))-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**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.



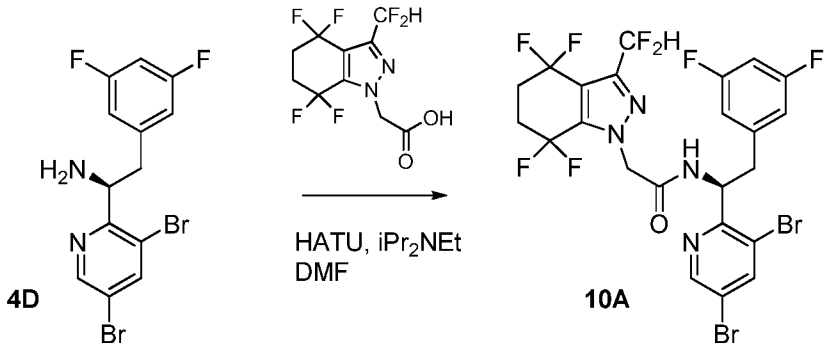
Synthesis of (S)-N-(1-(3-bromo-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**9A**):

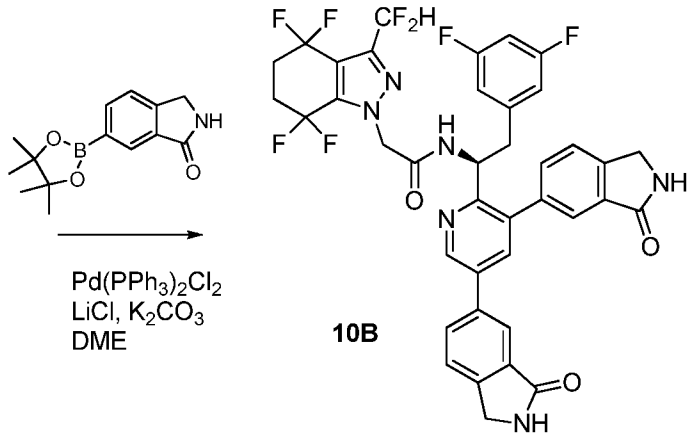
[0421] The title compound (**9A**) was prepared according to the method presented for the synthesis of compound **4F** of Example 4 utilizing 2-methylbut-3-yn-2-ol and **5F**. MS (m/z) 681.17 $[M+H]^+$.

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**):

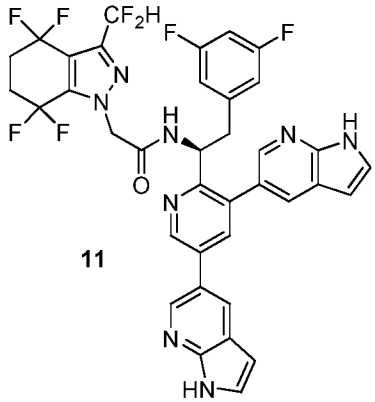
[0423] To (S)-1-(3,5-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethanamine (380 mg, 0.97 mmol) dissolved in DMF (10 mL) was added iPr_2NEt (350 μL, 2 mmol) and 2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid (293 mg, 0.97 mmol). HATU (442 mg, 1.16 mmol) was added 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.

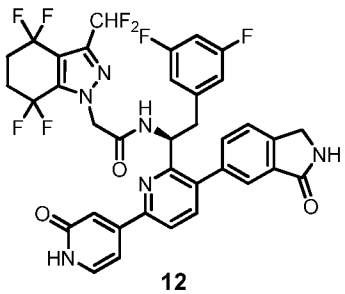


11

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.

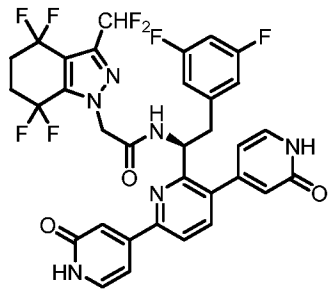


12

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.

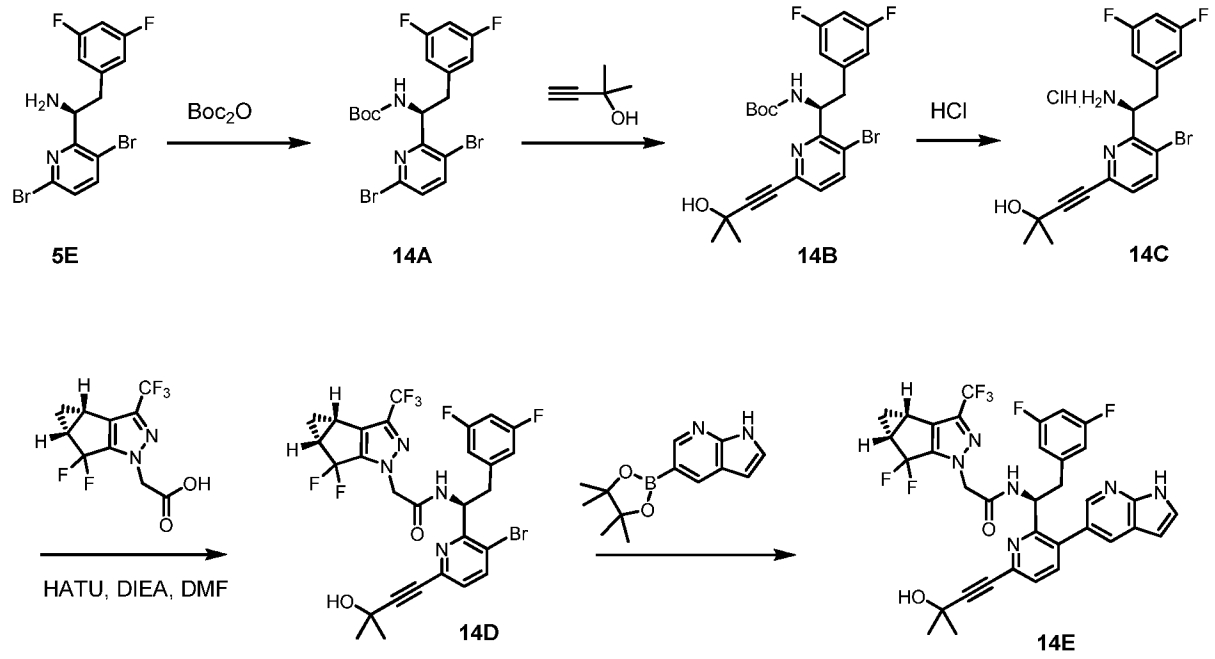


13

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.



5E 14A 14B 14C 14D 14E

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 $[M+H]^+$.

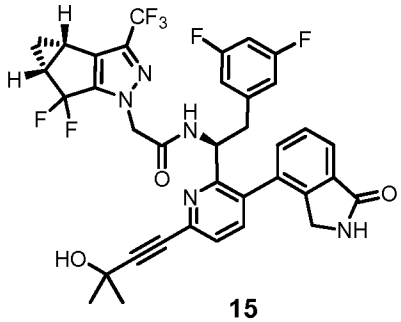
Synthesis of N-((S)-1-(3-bromo-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**14D**):

[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.

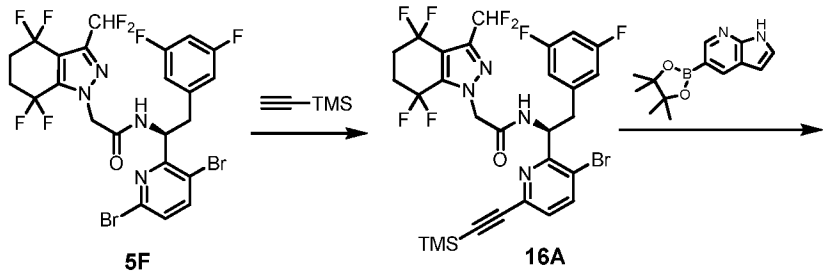


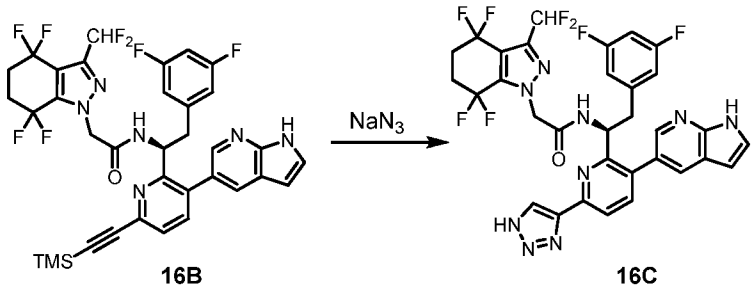
15

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.





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**):

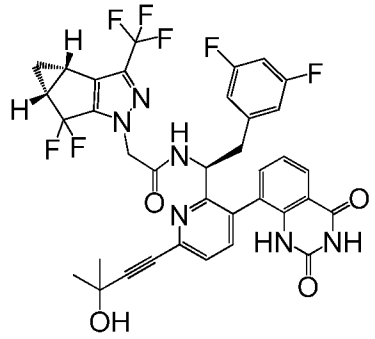
[0435] The title compound (**16B**) was prepared according to the method presented for the synthesis of compound **4H** of Example 4 utilizing 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine and **16A**. MS (m/z) 731.22 $[M+H]^+$.

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.

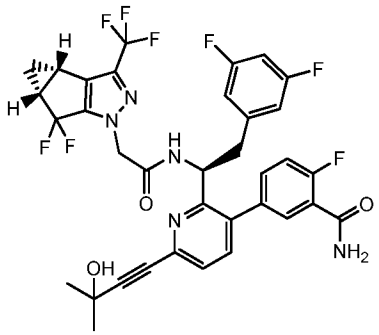


17

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.

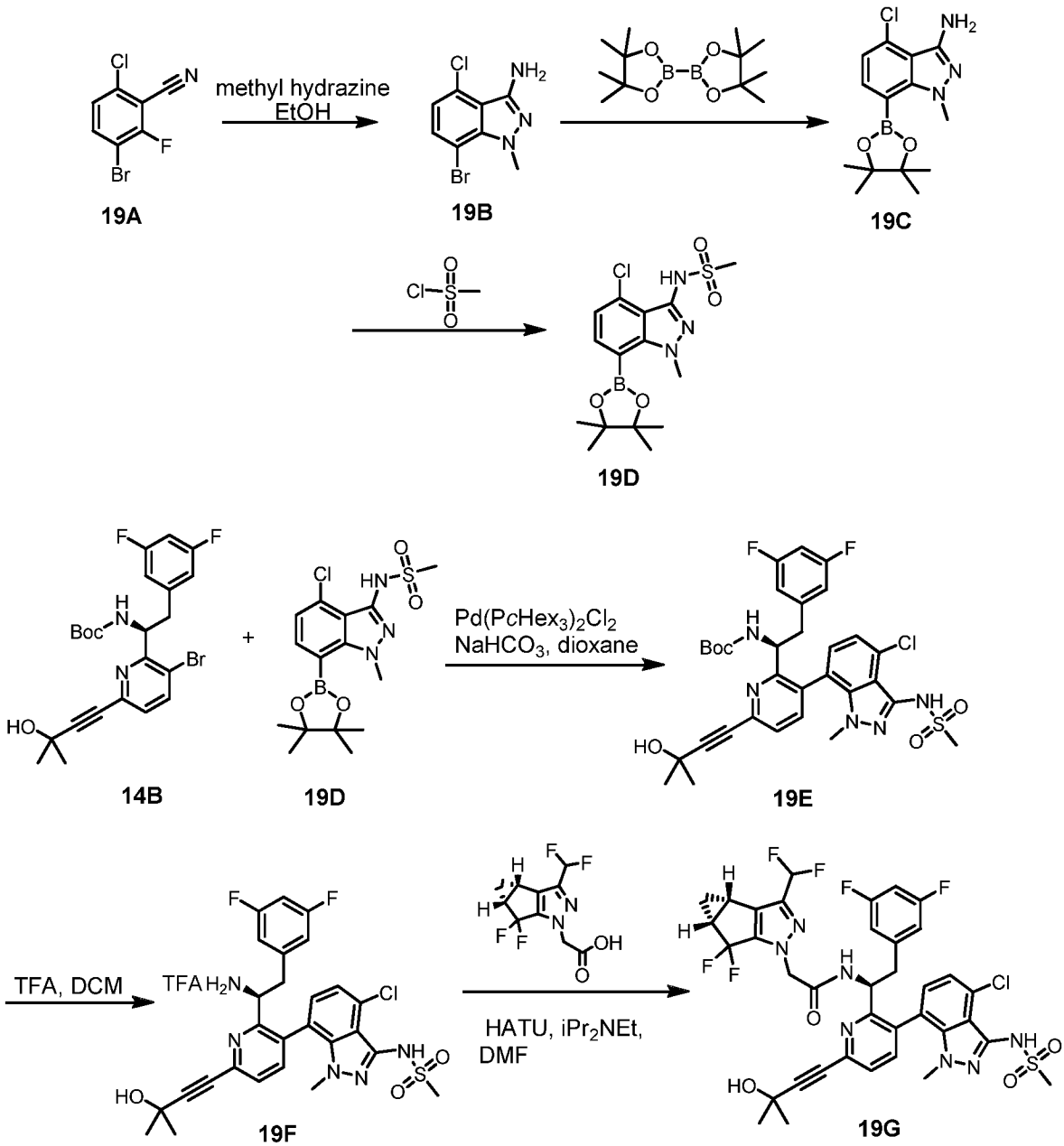


18

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**):

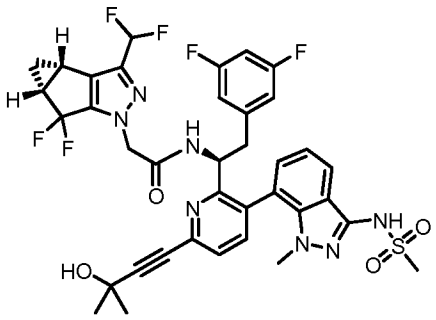
[0443] To (S)-tert-butyl 1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-ynyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (30 mg, 0.04 mmol) in DCM (4 mL) was added TFA (2 ml) . The reaction mixture was stirred for 0.5 hours at RT. The reaction was concentrated 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.



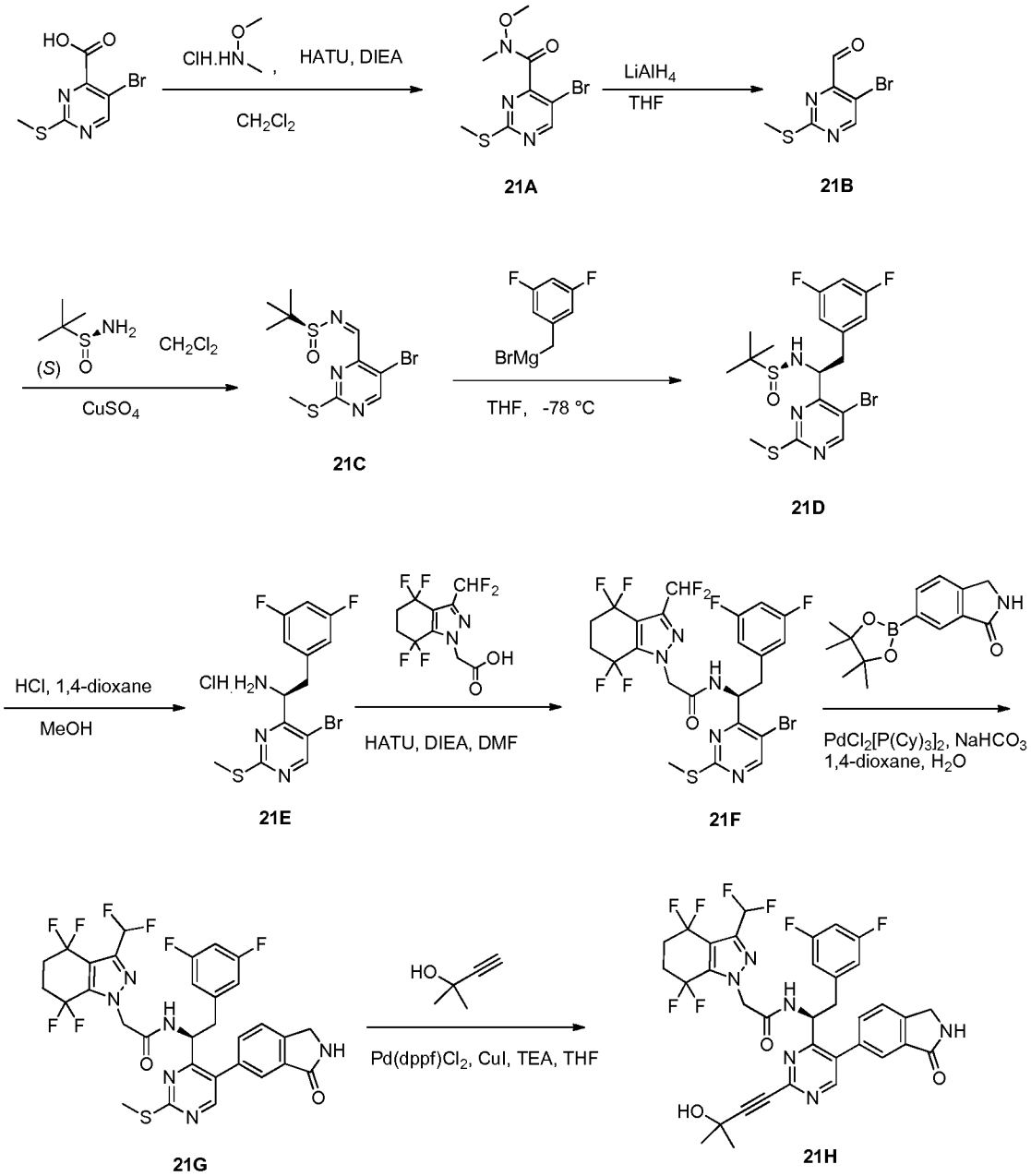
20

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 $[M+H]^+$.

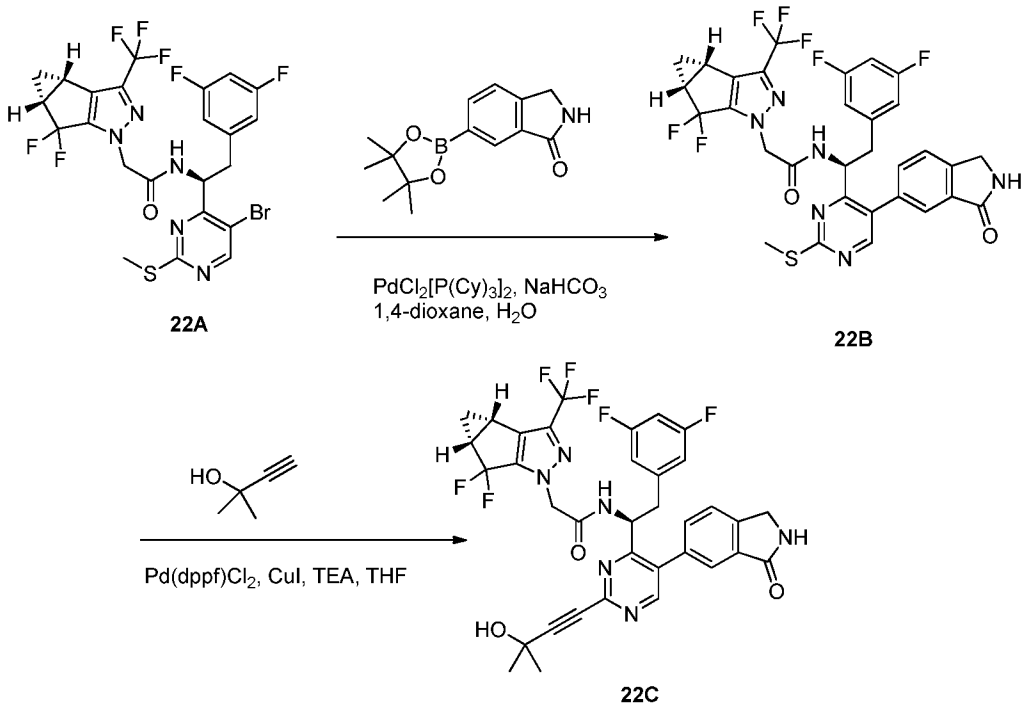
Synthesis of (S)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)-N-(2-(3,5-difluorophenyl)-1-(2-(methylthio)-5-(3-oxoisoindolin-5-yl)pyrimidin-4-yl)ethyl)acetamide (**21G**):

[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.



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**):

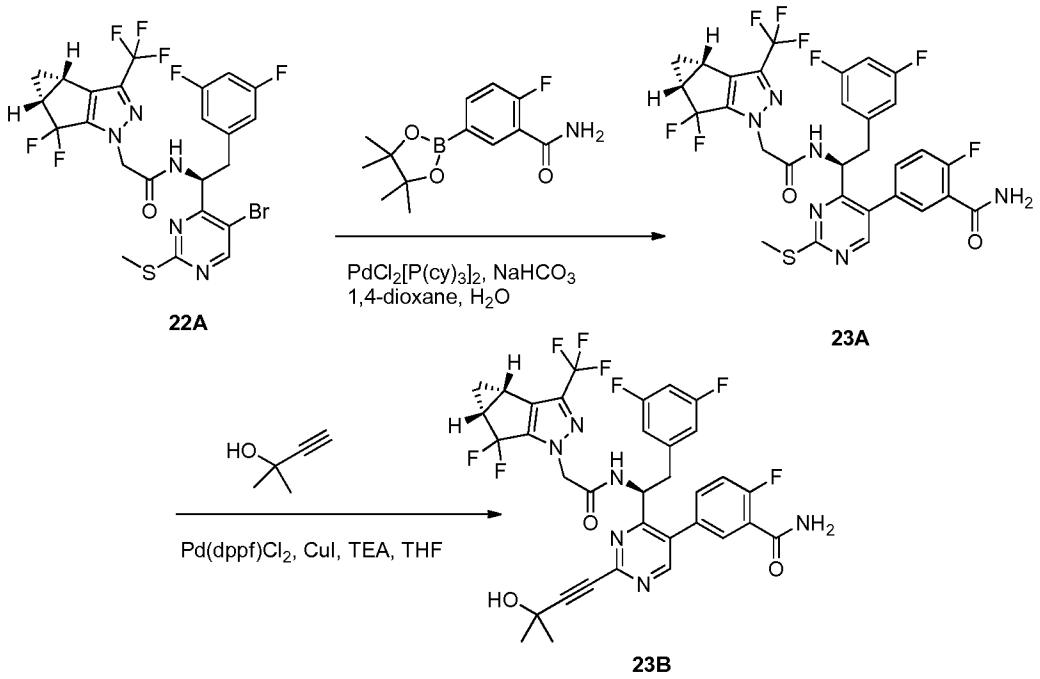
[0457] The title compound (**22B**) was prepared according to the method presented for the synthesis of compound **21G** of Example 21 utilizing compound **22A** and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one. MS (*m/z*) 677.05 $[M+H]^+$.

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.



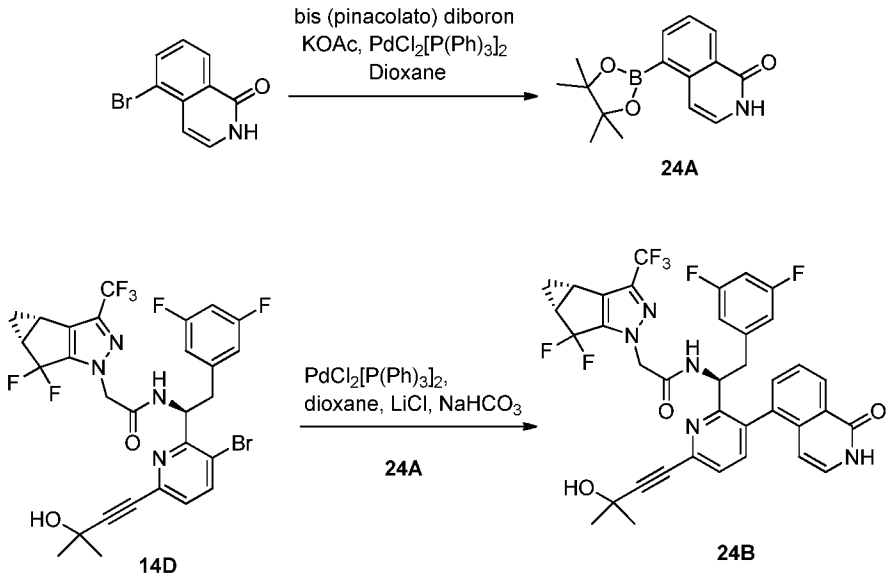
Synthesis of 5-(4-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-2-(methylthio)pyrimidin-5-yl)-2-fluorobenzamide (**23A**):

[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.



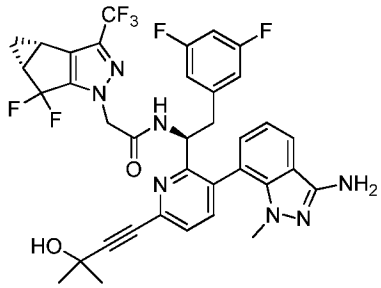
Synthesis of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (**24A**):

[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.

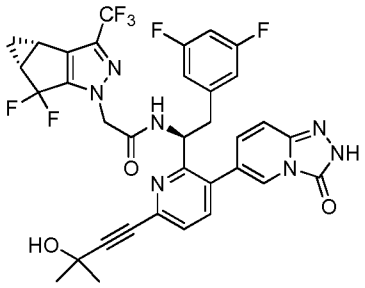


25

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.

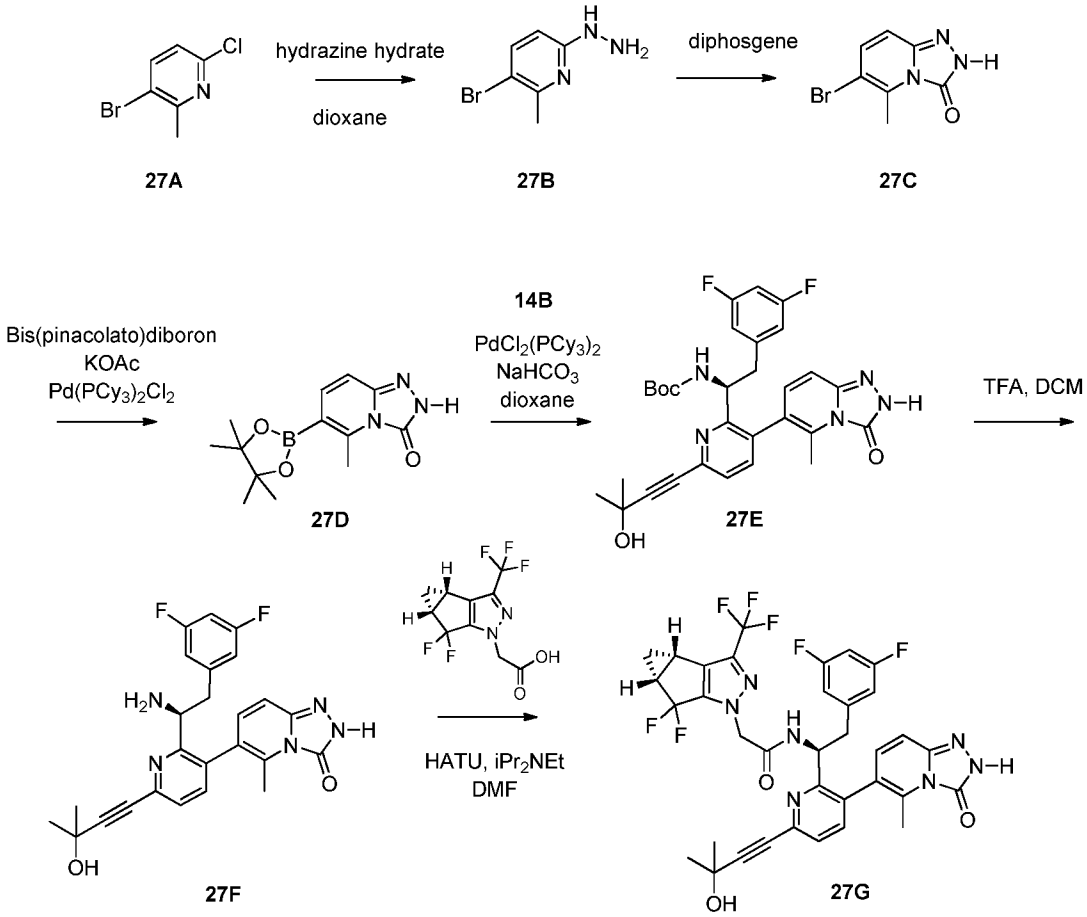


26

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**):

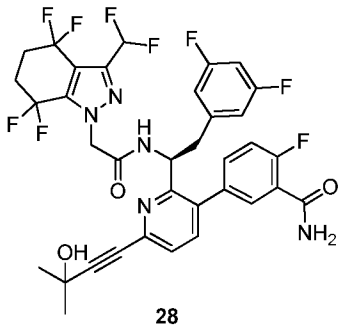
[0469] The title compound (**27F**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of **19F** in Example 19 utilizing **27E**. MS (*m/z*) 464.1 $[M+H]^+$.

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.

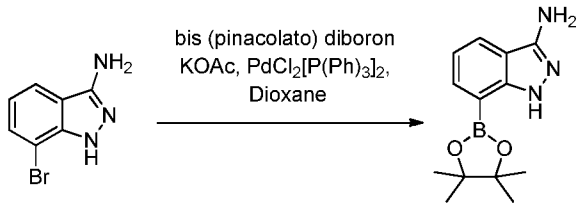


28

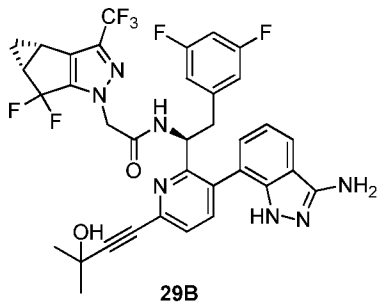
Synthesis of (S)-5-(2-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-2-fluorobenzamide (**28**):

[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

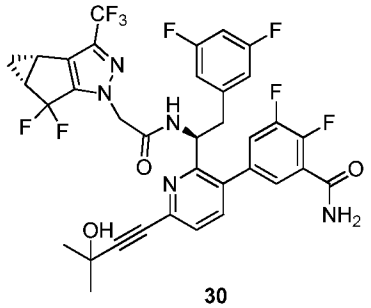
Synthesis of 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-amine (**29A**):

[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.

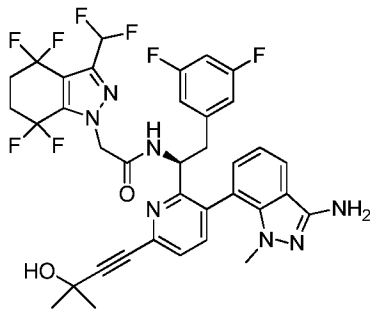


30

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.

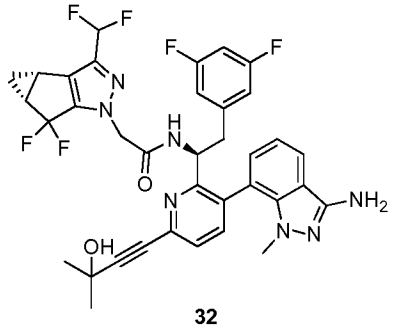


31

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.

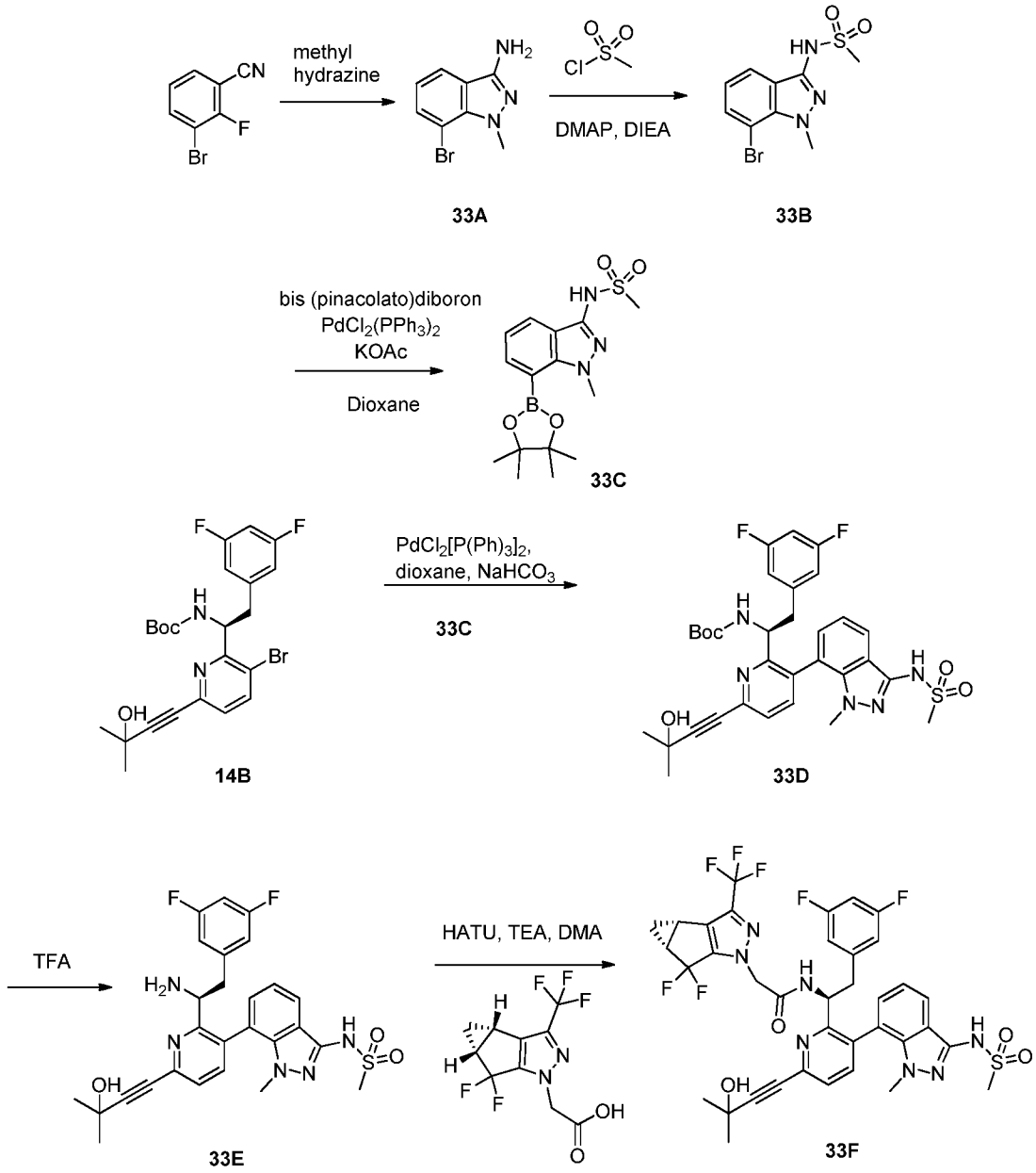


32

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**):

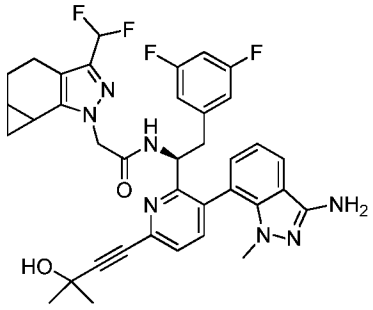
[0481] To a solution of **33D** (47 mg, 0.07 mmol) in DCM was added 4M HCl in dioxane (0.7 mL, 2.9 mmol). The reaction mixture was stirred at room temperature for 0.5 hours. Upon

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.

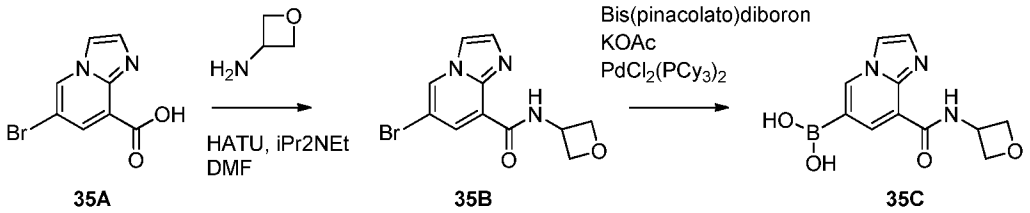


34

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.



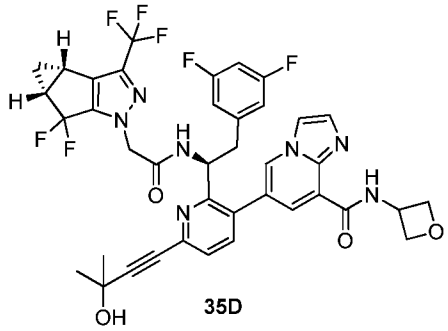
35A 35B 35C

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 $[M+H]^+$.

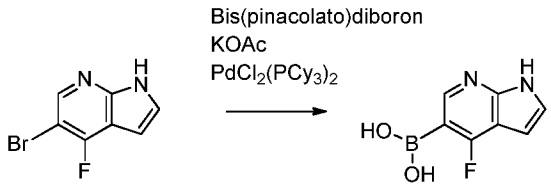


35D

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 $[M+H]^+$.

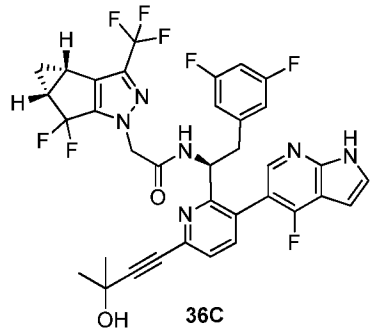
Example 36.



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 $[M+H]^+$.

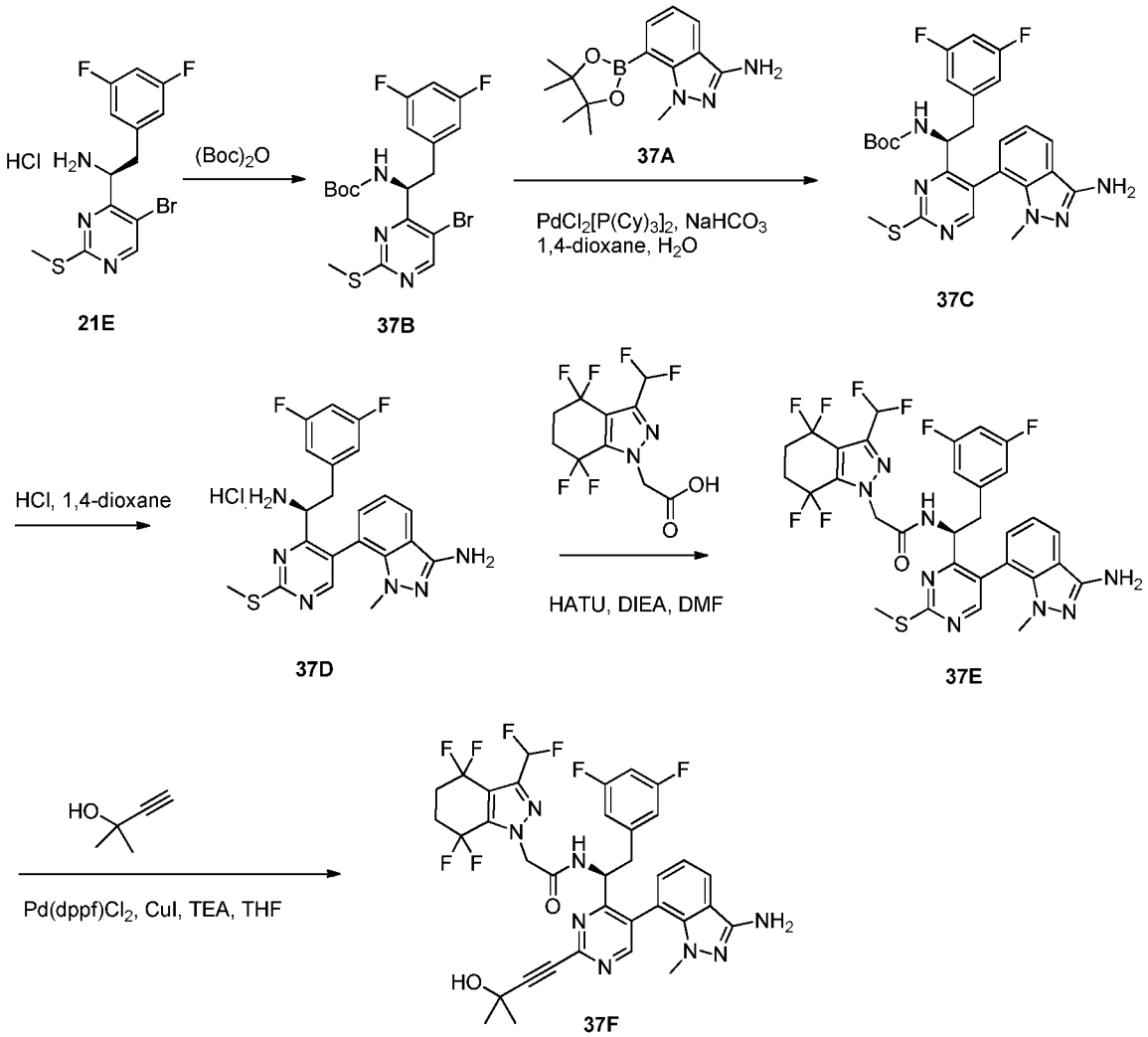


36C

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**. ^1H 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 $[M+H]^+$.

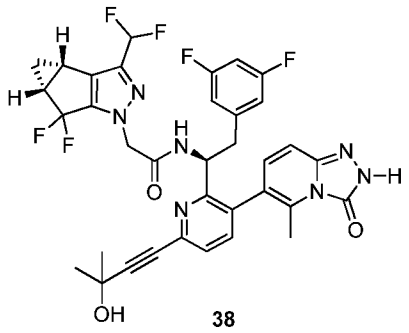
Synthesis of (S)-N-(1-(5-(3-amino-1-methyl-1H-indazol-7-yl)-2-(methylthio)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**37E**):

[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.

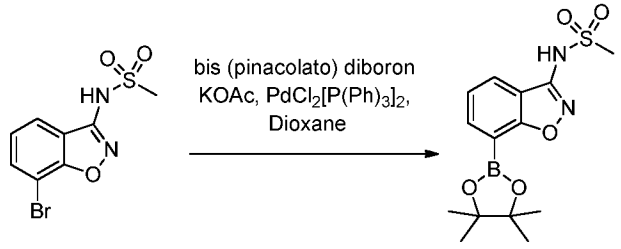


38

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 $[M+H]^+$.

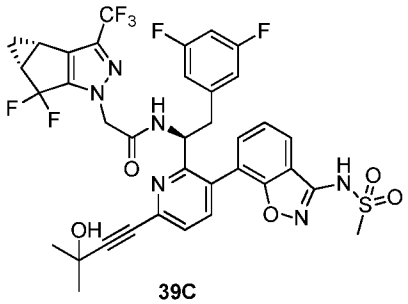
Example 39.



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 $[M+H]^+$.

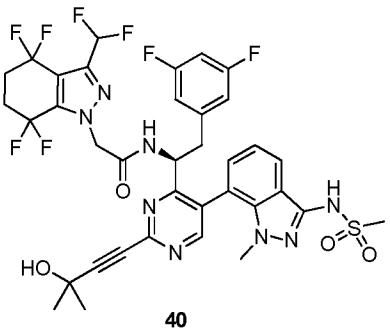


39C

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.

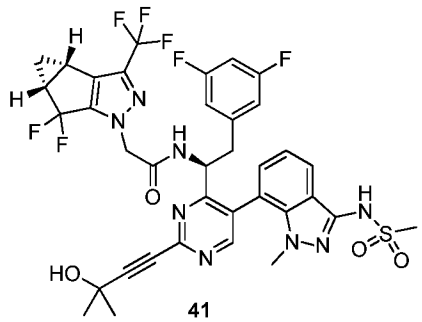


40

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

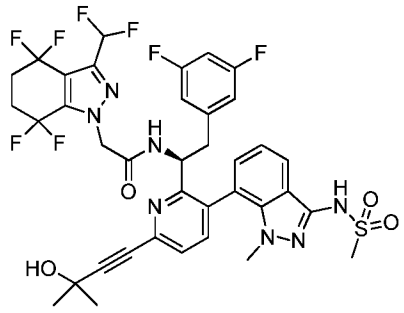


41

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.



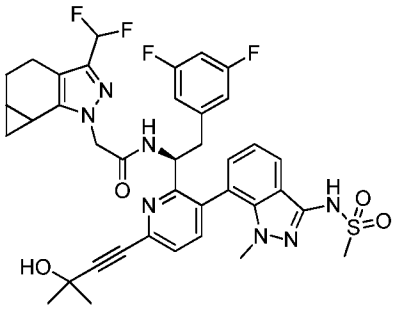
42

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.

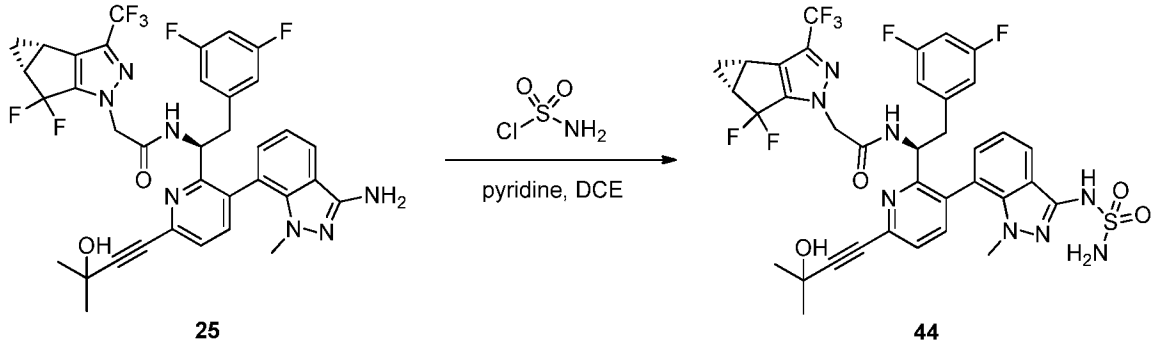


43

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.

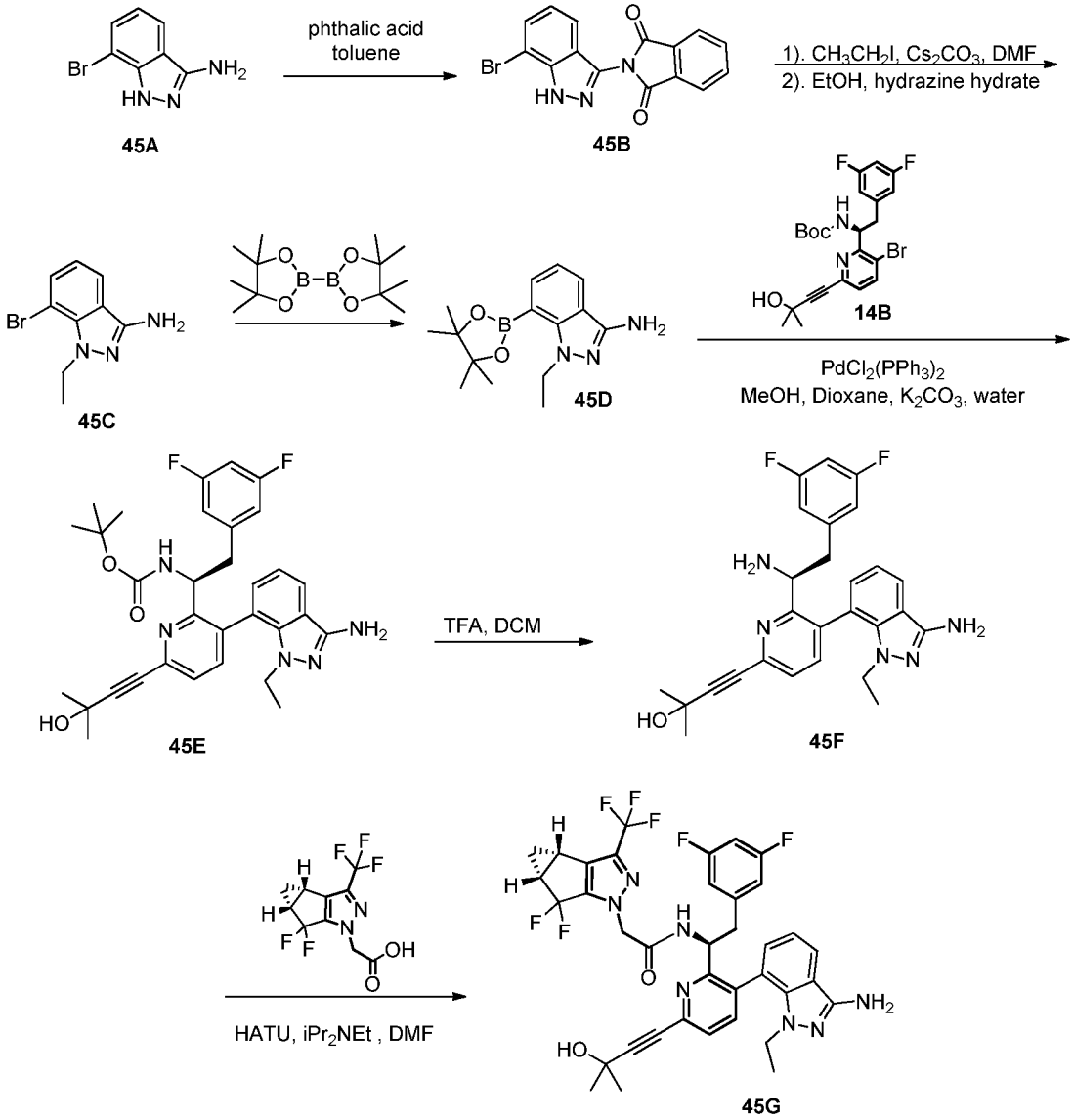


25 44

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 $[M+H]^+$.

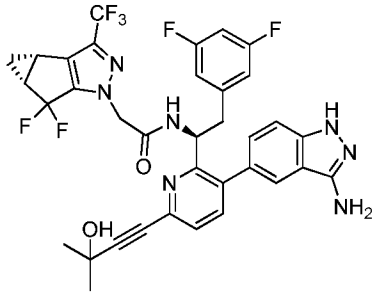
Synthesis of (S)-4-(5-(3-amino-1-ethyl-1H-indazol-7-yl)-6-(1-amino-2-(3,5-difluorophenyl)ethyl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (**45F**):

[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.

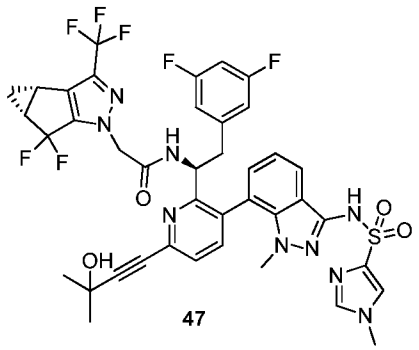


46

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.

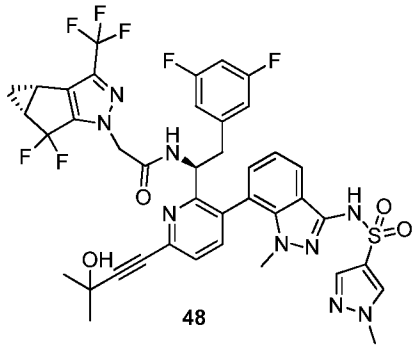


47

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.



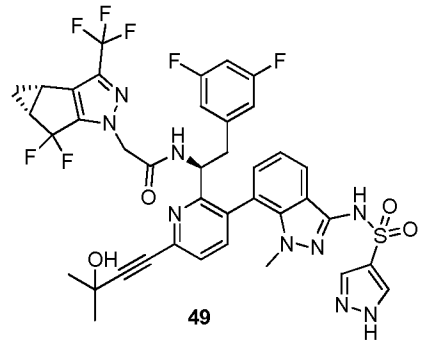
48

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.

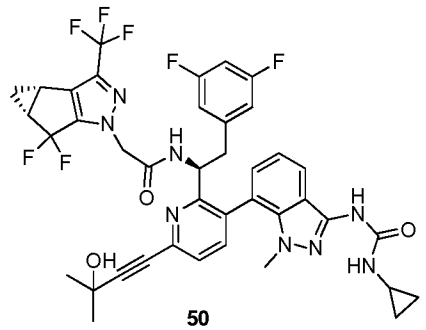


49

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.

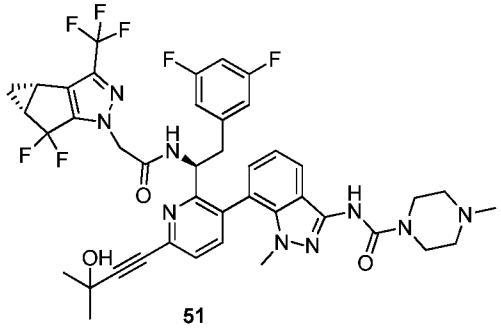


50

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.



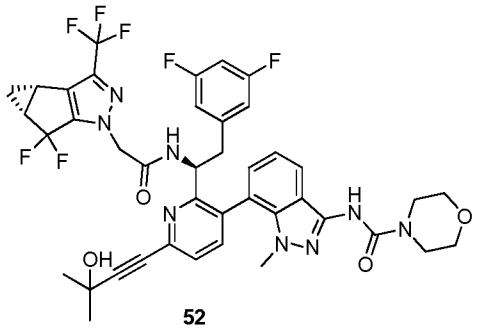
51

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.

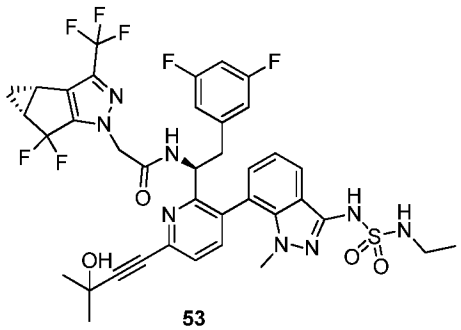


52

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.

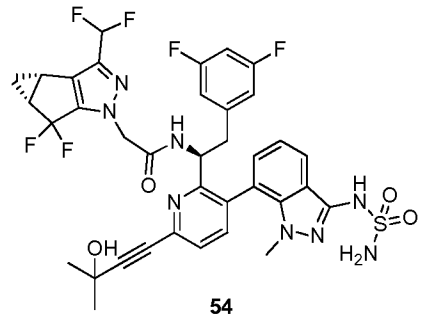


53

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.



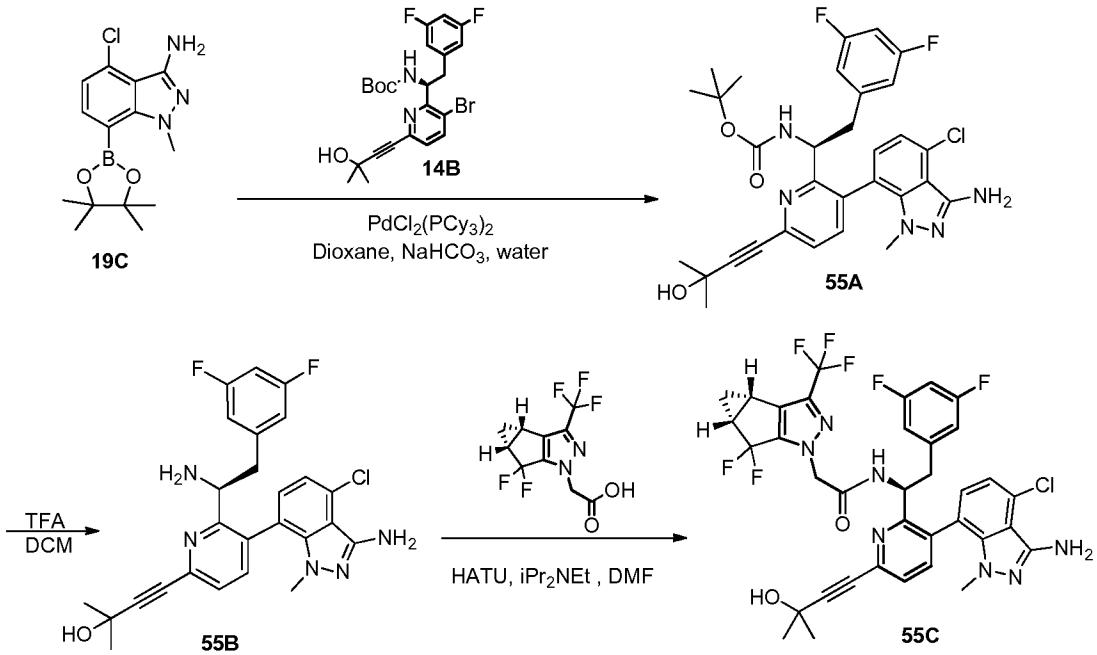
54

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 °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 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**):

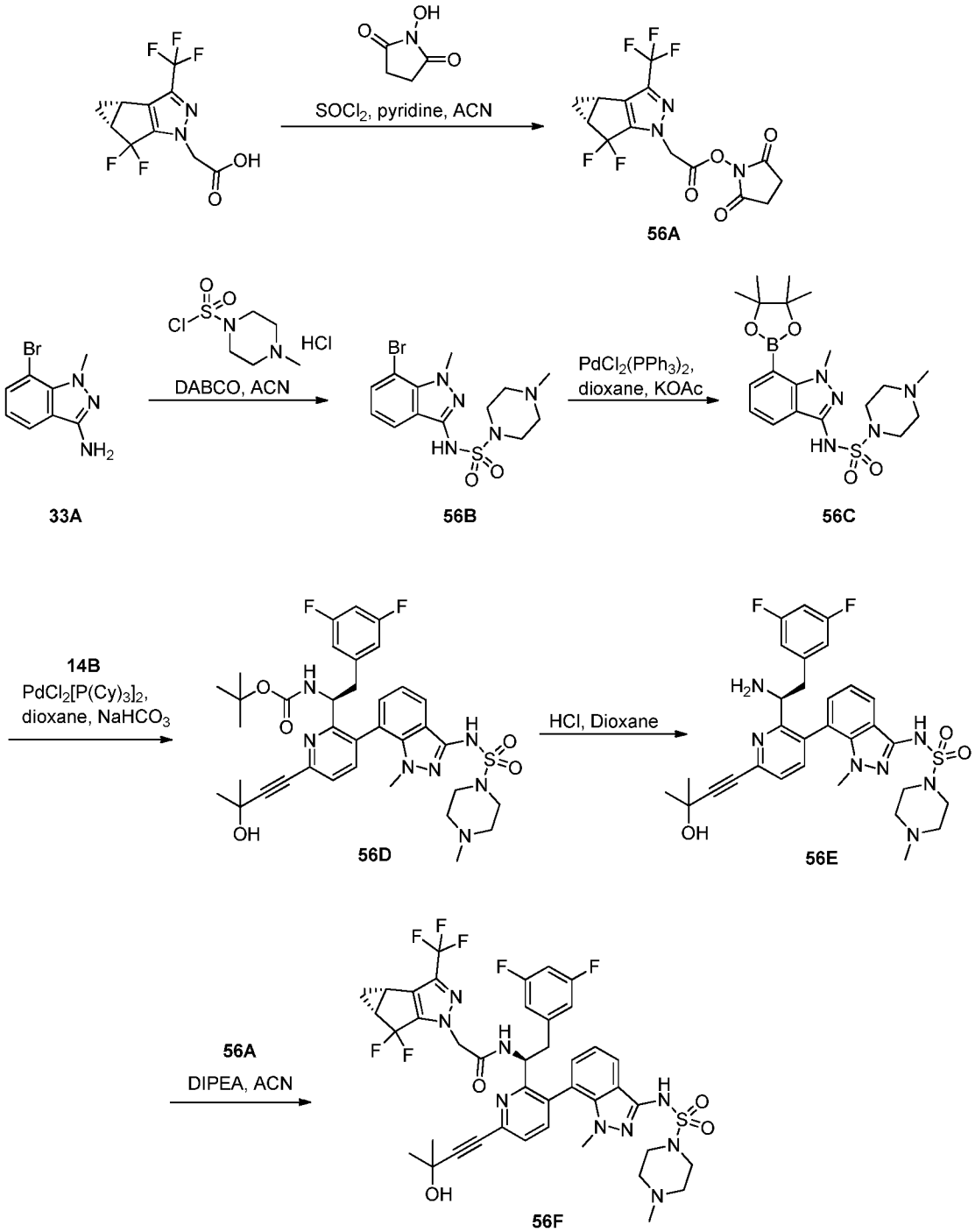
[0520] The title compound (**55B**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19F** of Example 19 utilizing **55A**. MS (m/z) 496.5 $[M+H]^+$.

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**):

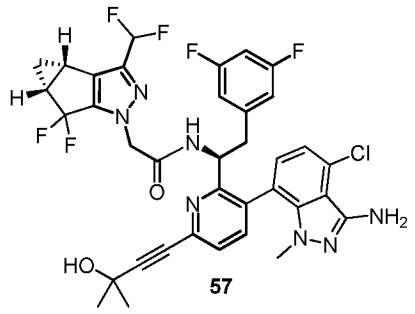
[0526] The title compound (**56E**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound (**14C)** of Example 14 utilizing (S)-tert-butyl (2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-methyl-3-(4-methylpiperazine-1-sulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)carbamate (**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.



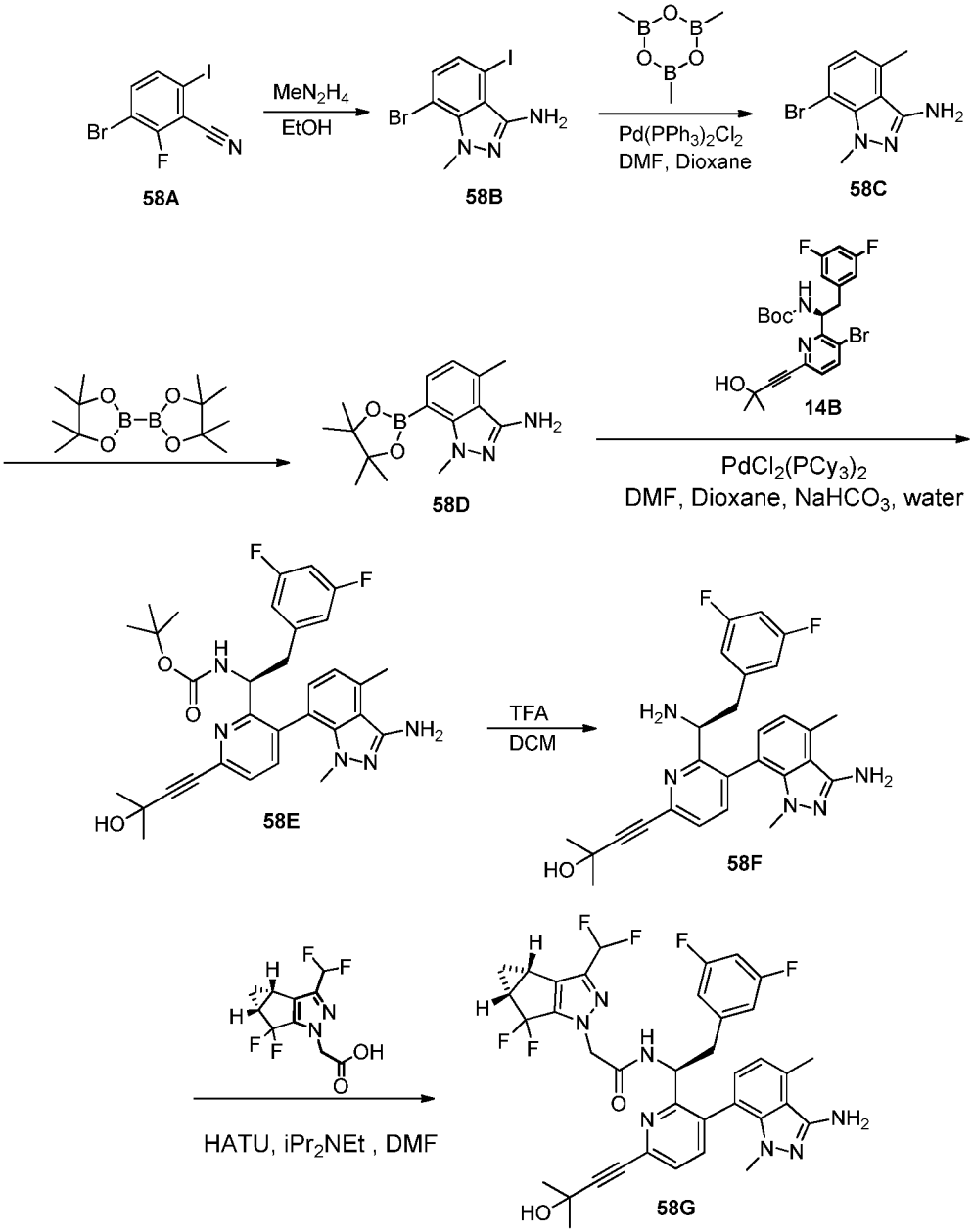
57

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 $[M+H]^+$.

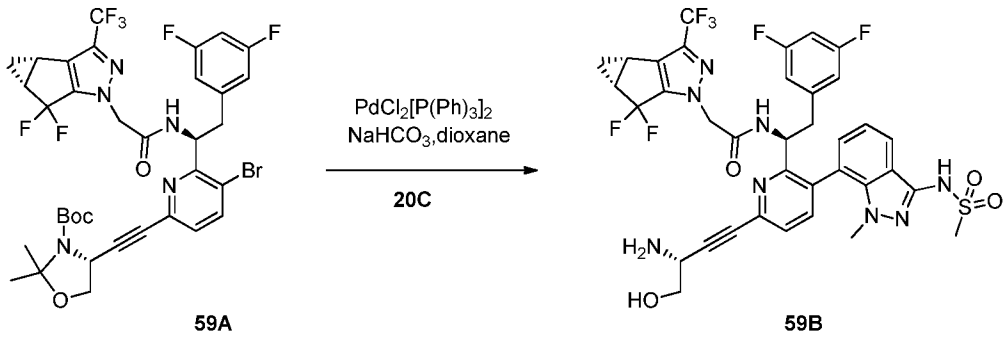
Synthesis of (S)-4-(5-(3-amino-1,4-dimethyl-1H-indazol-7-yl)-6-(1-amino-2-(3,5-difluorophenyl)ethyl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (**58F**):

[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

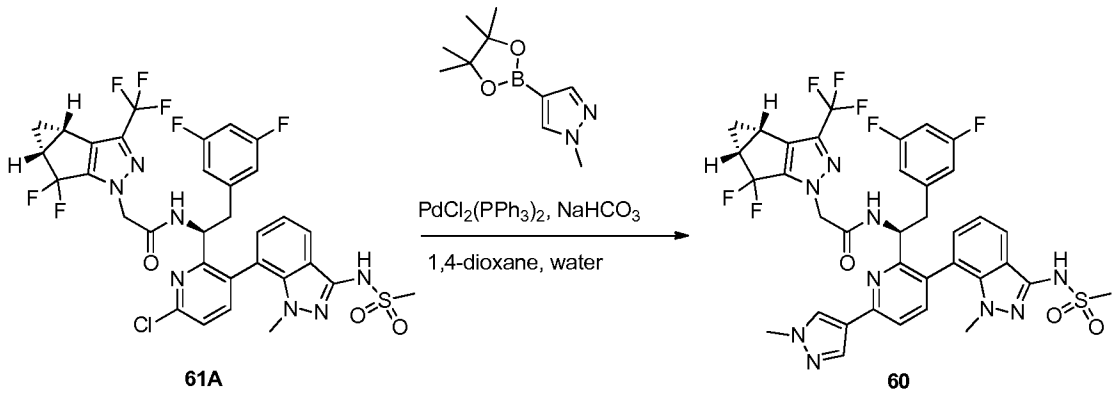
Synthesis of (R)-tert-butyl 4-((5-bromo-6-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-2-yl)ethynyl)-2,2-dimethyloxazolidine-3-carboxylate (**59A**):

[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.

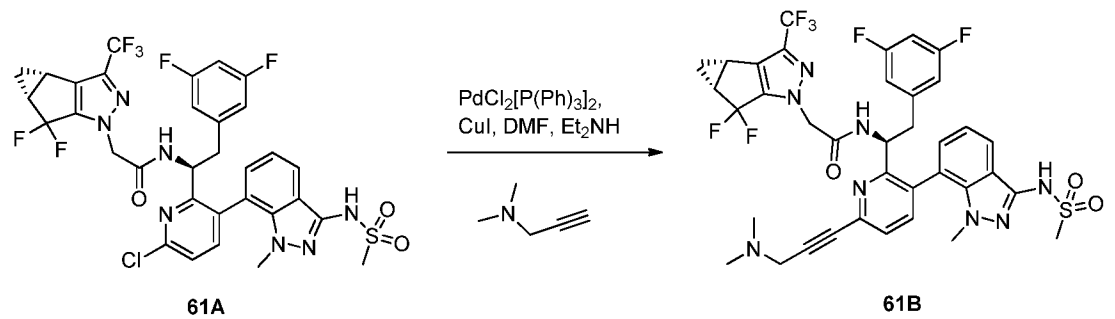


61A 60

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

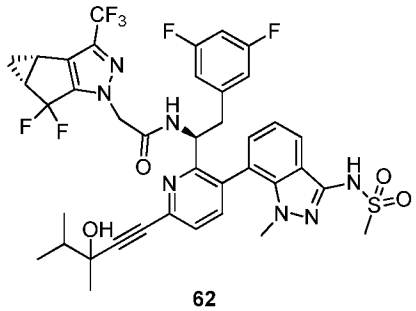
Synthesis of N-((S)-1-(6-chloro-3-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**61A**).

[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.

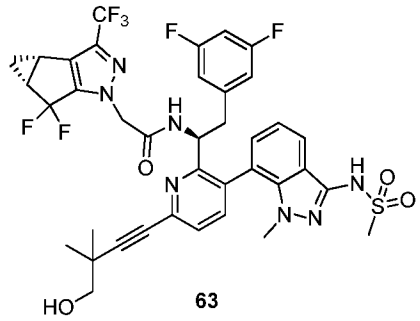


62

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.

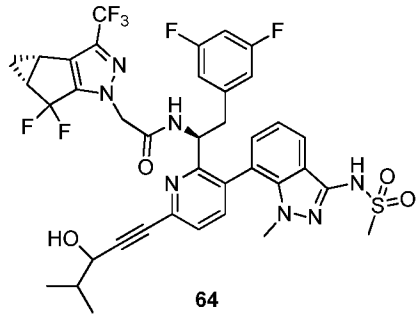


63

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.



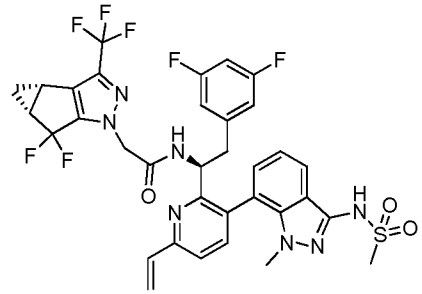
64

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.



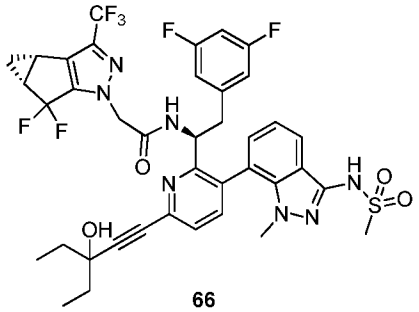
65

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.

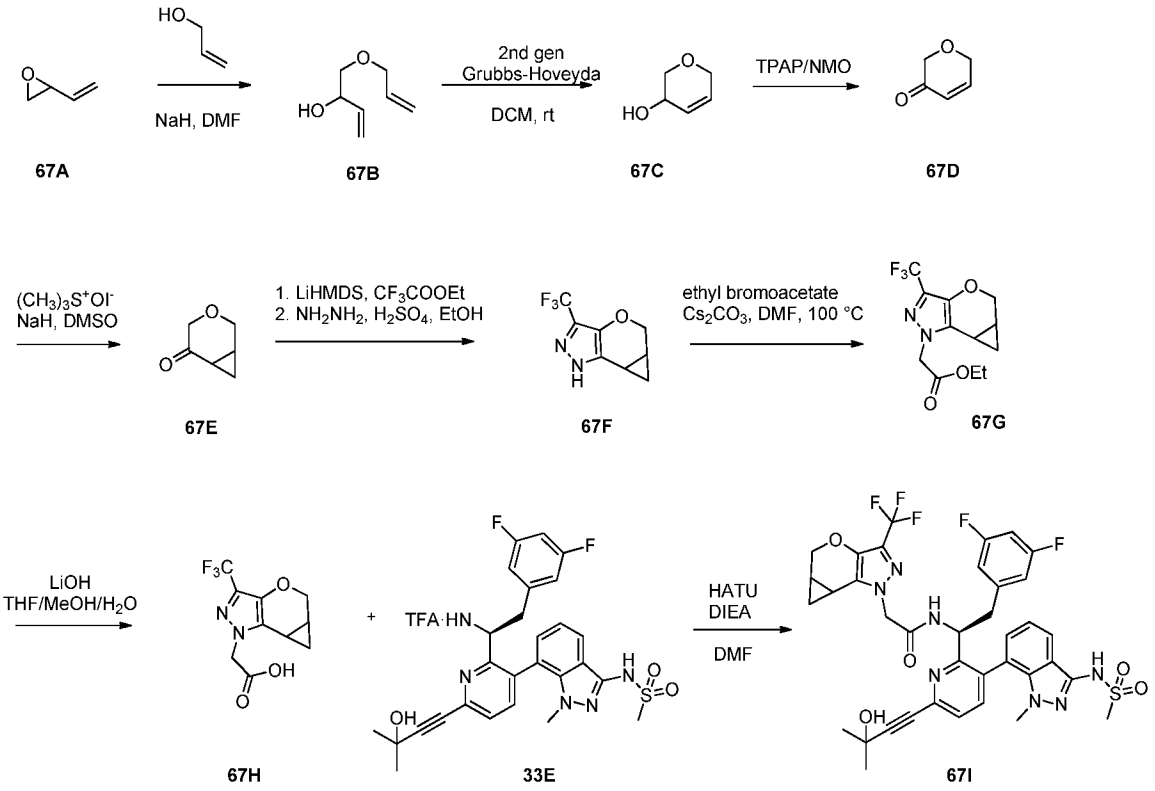


66

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**):

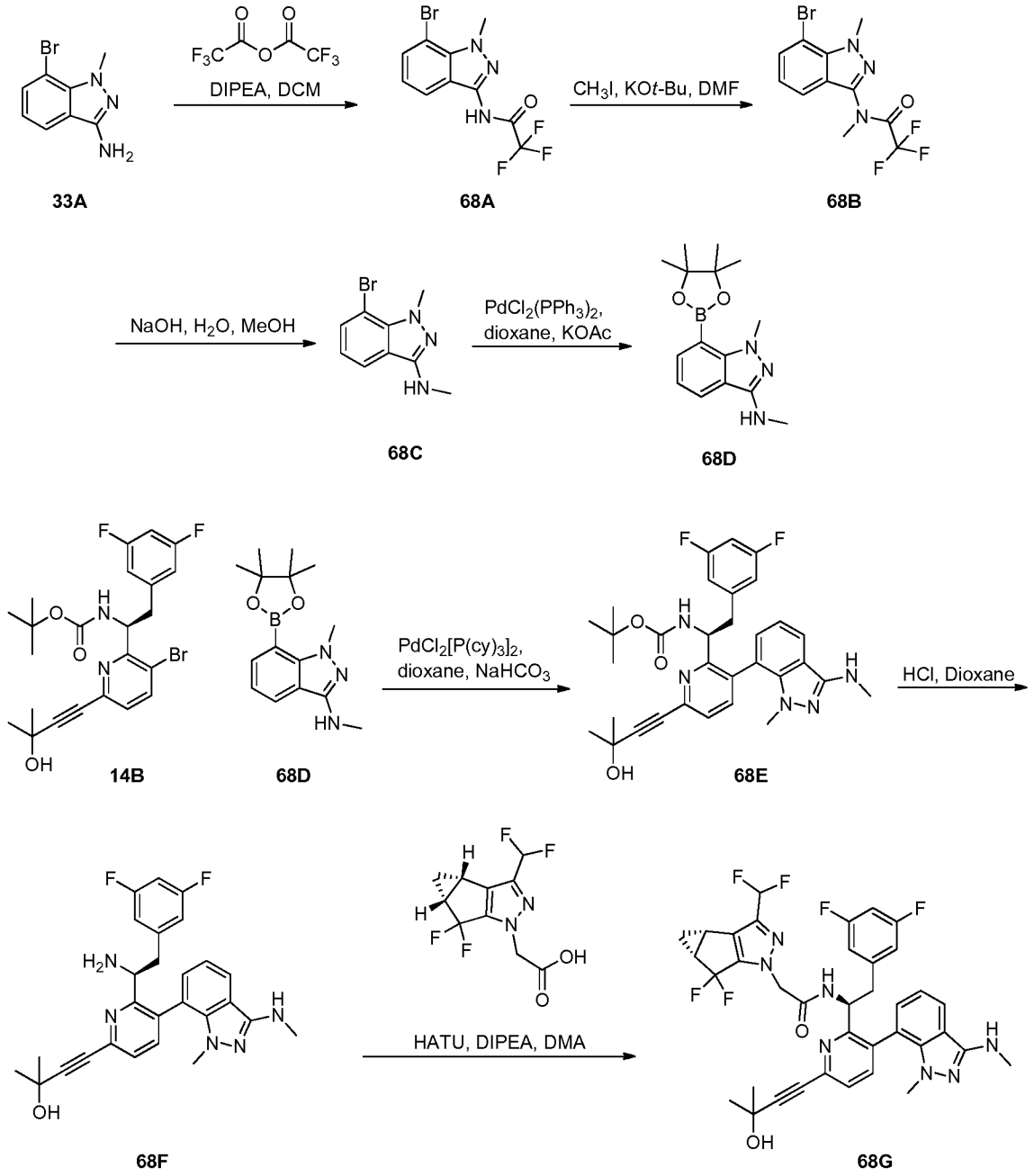
[0552] To a solution of compound **67G** (16 mg, 0.055 mmol) in a mixture of THF:water:MeOH (1 mL : 0.5 mL : 0.5 mL) was added solid LiOH monohydrate (7 mg, 0.165 mmol) at 0 °C. After stirring at room temperature for 10 min, the reaction mixture was poured

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 °C 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 $[M+H]^+$.

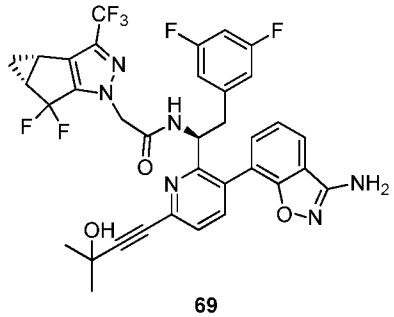
Synthesis of (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(1-methyl-3-(methylamino)-1H-indazol-7-yl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (**68F**):

[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.



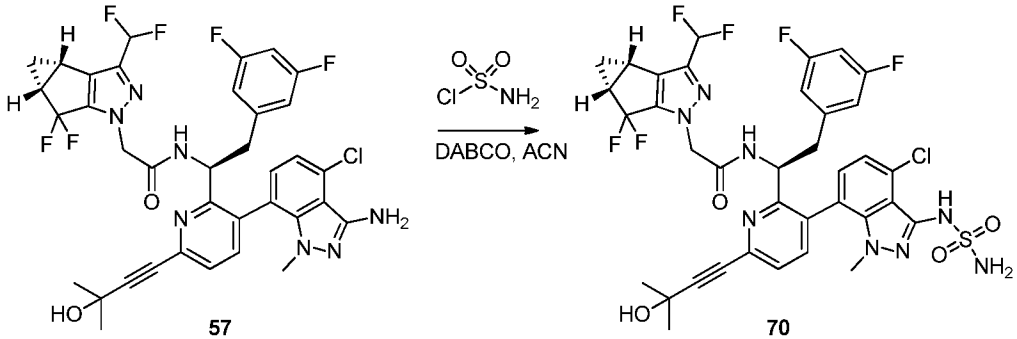
69

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 $[M+H]^+$.

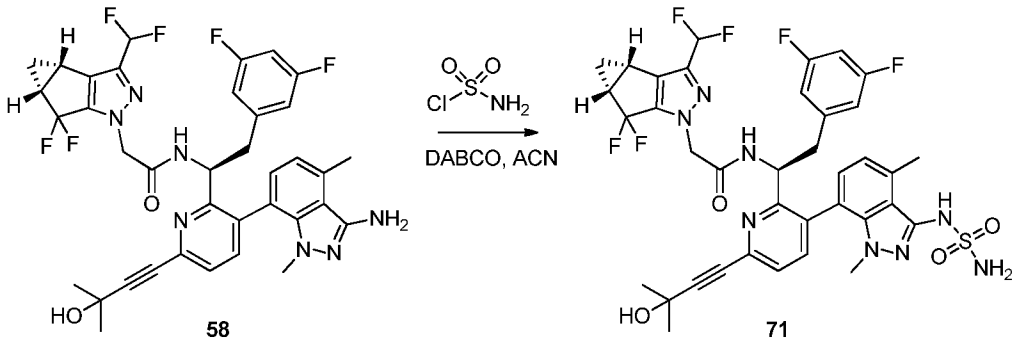
Example 70.



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 $[M+H]^+$.

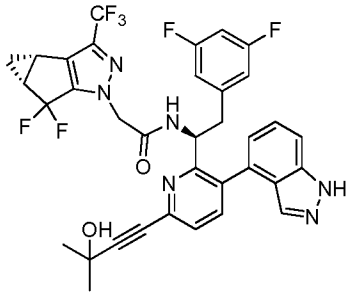
Example 71.



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.

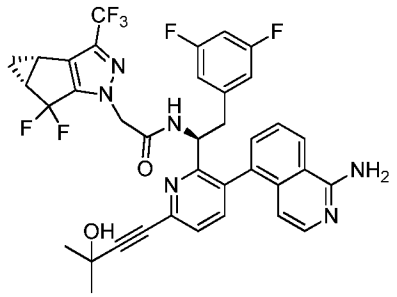


72

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.

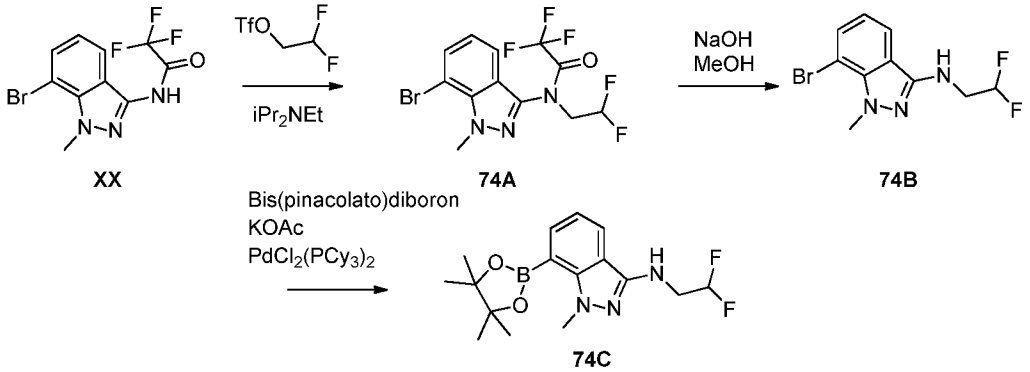


73

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

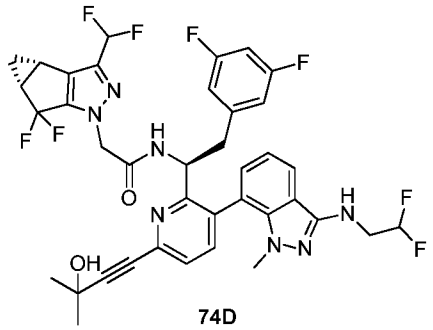
separated, dried, and removed in vacuo to provide the title compound which was used directly in the next reaction. MS (*m/z*) 387.9 $[M+H]^+$.

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 $[M+H]^+$.



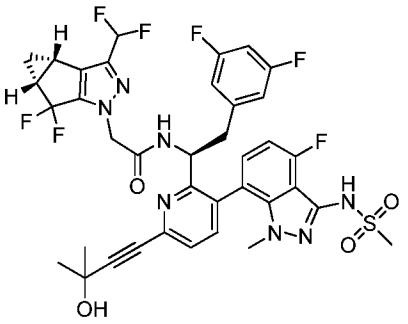
74D

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.

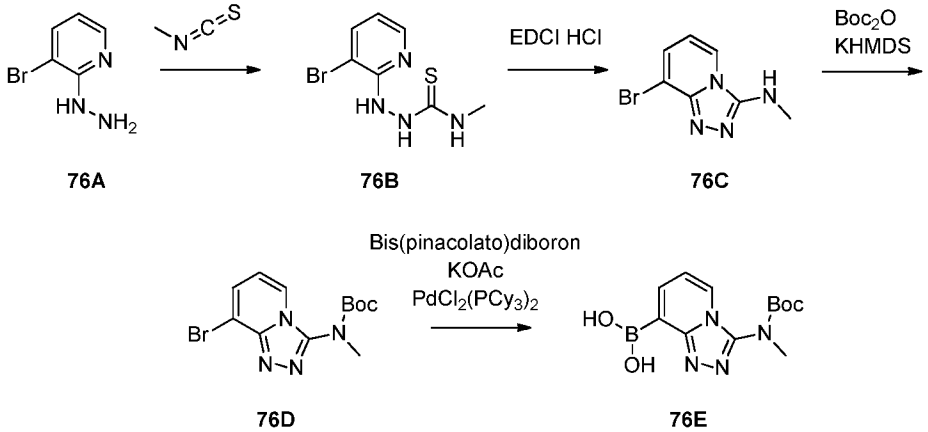


75

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**):

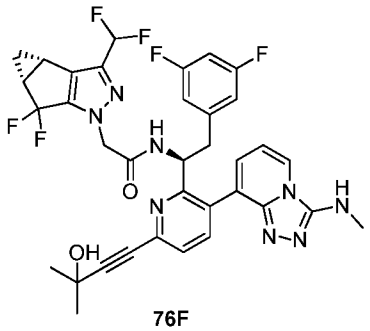
[0572] 2-(3-Bromopyridin-2-yl)-N-methylhydrazinecarbothioamide (1.6 g, 6.1 mmol) was treated with EDCI HCl (1.76 g, 9 mmol) in toluene and heated to 105 °C. After 1 hr, the hot toluene was decanted. To the residue was added H_2O (50 ml). The slurry was mixed thoroughly and heated to 100 °C for 15 min. 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 $[M+H]^+$.



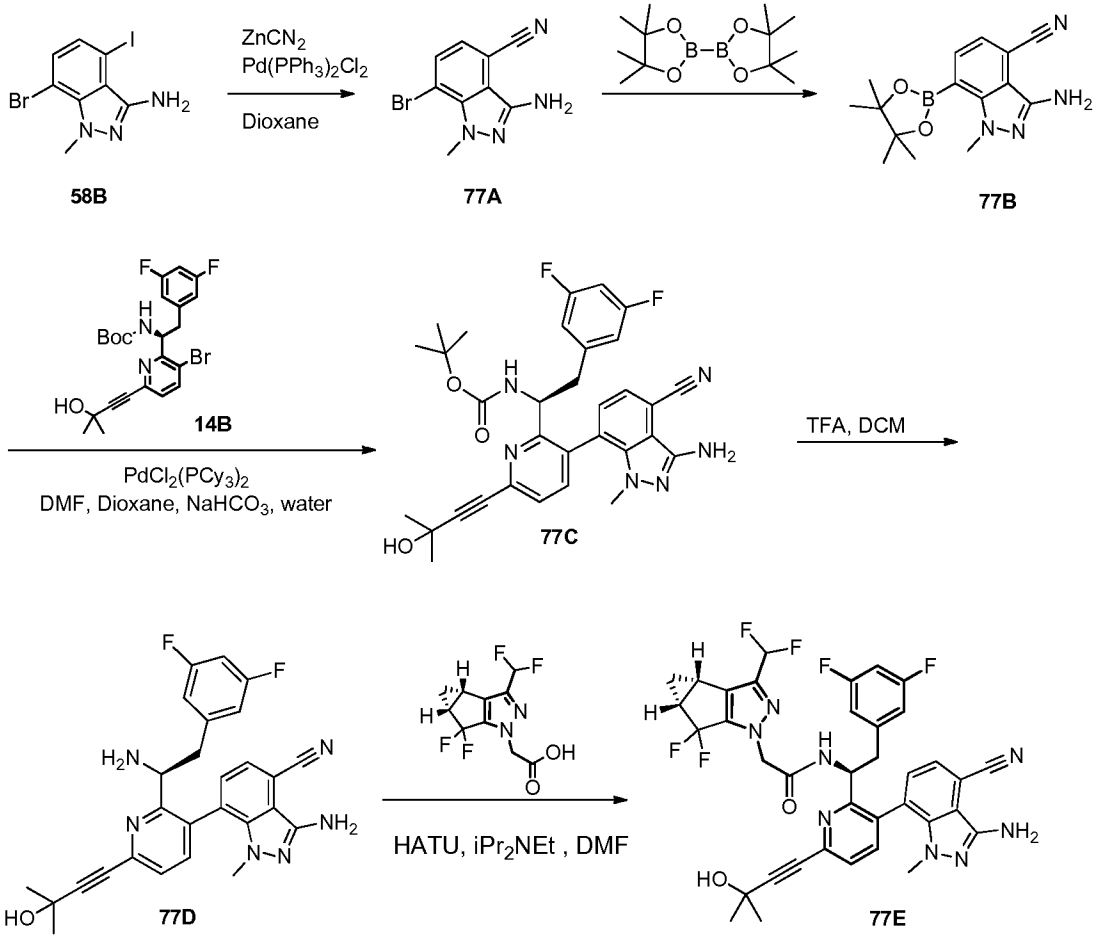
76F

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 $[M+H]^+$.

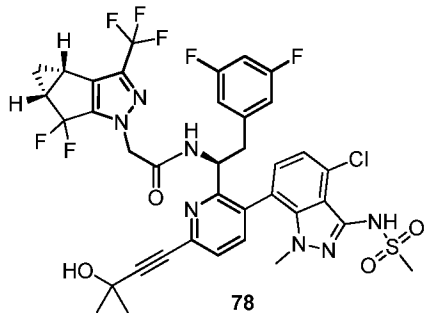
Synthesis of (S)-3-amino-7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazole-4-carbonitrile (**77D**):

[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.

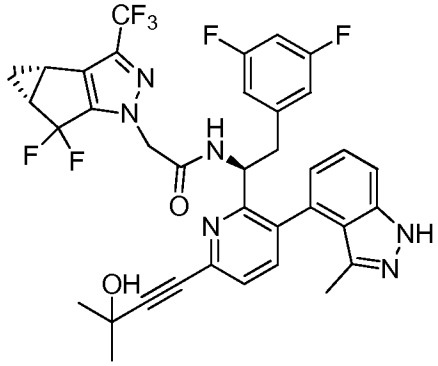


78

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.



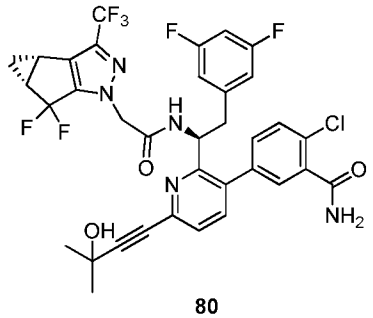
79

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.

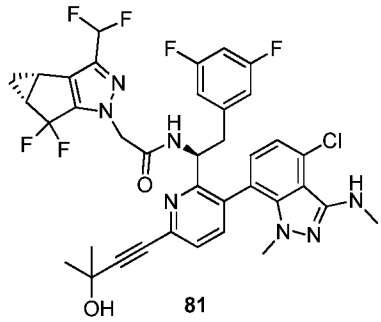


80

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.

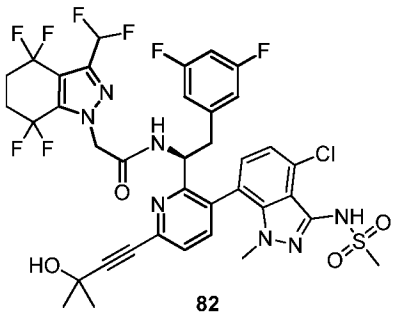


81

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.

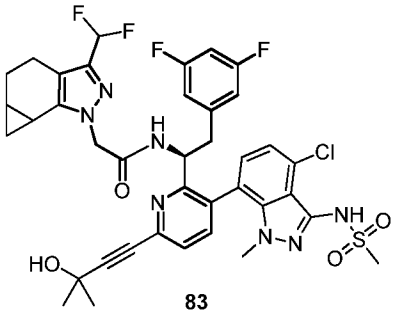


82

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.

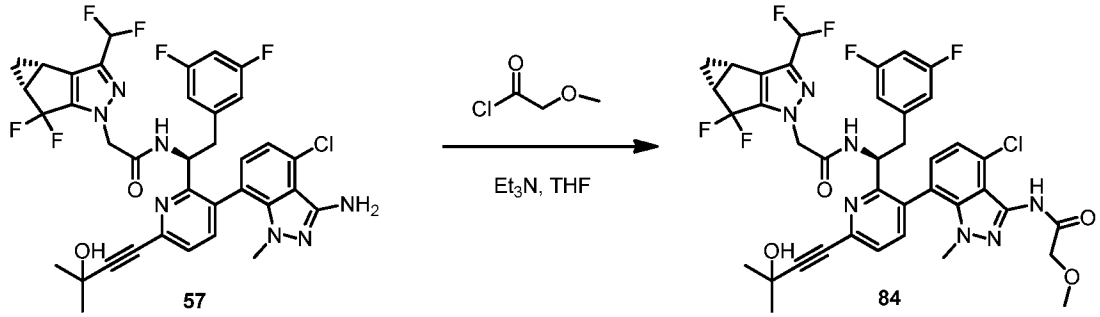


83

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.

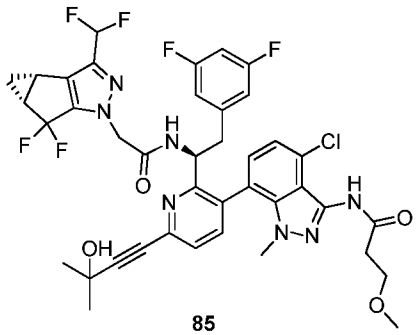


57 84

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.

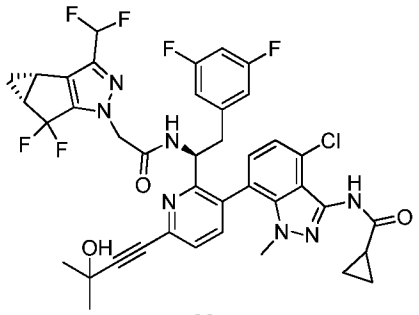


85

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.



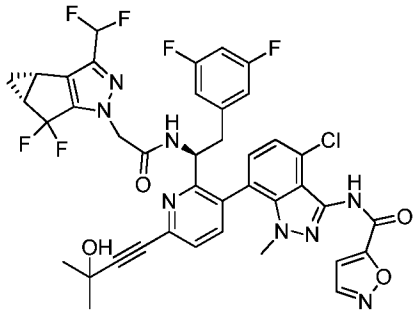
86

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.

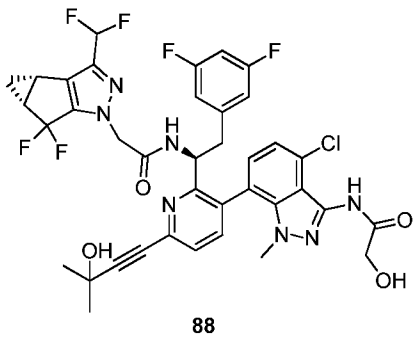


87

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.

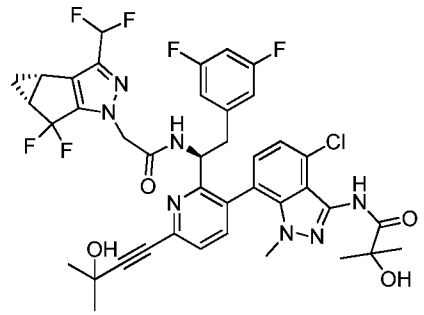


88

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.

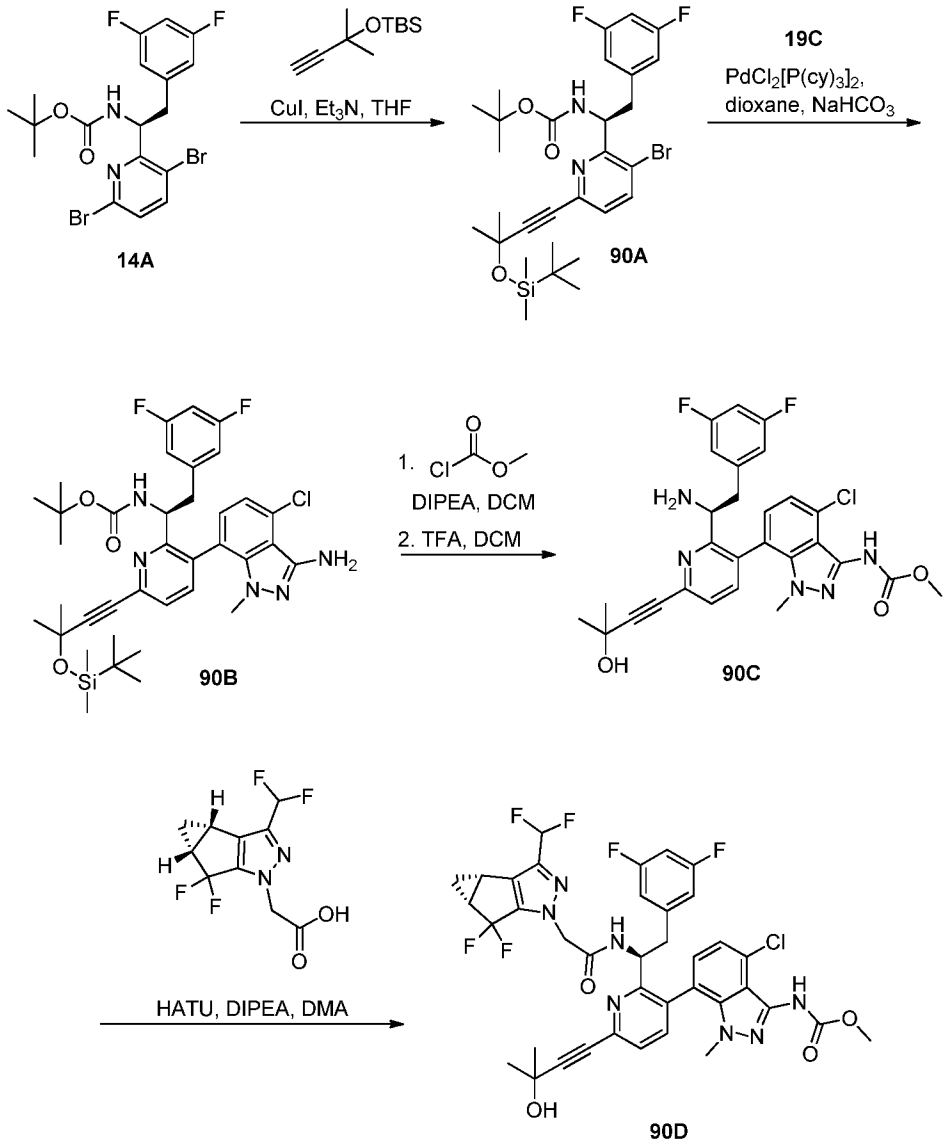


89

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 $[M+H]^+$.

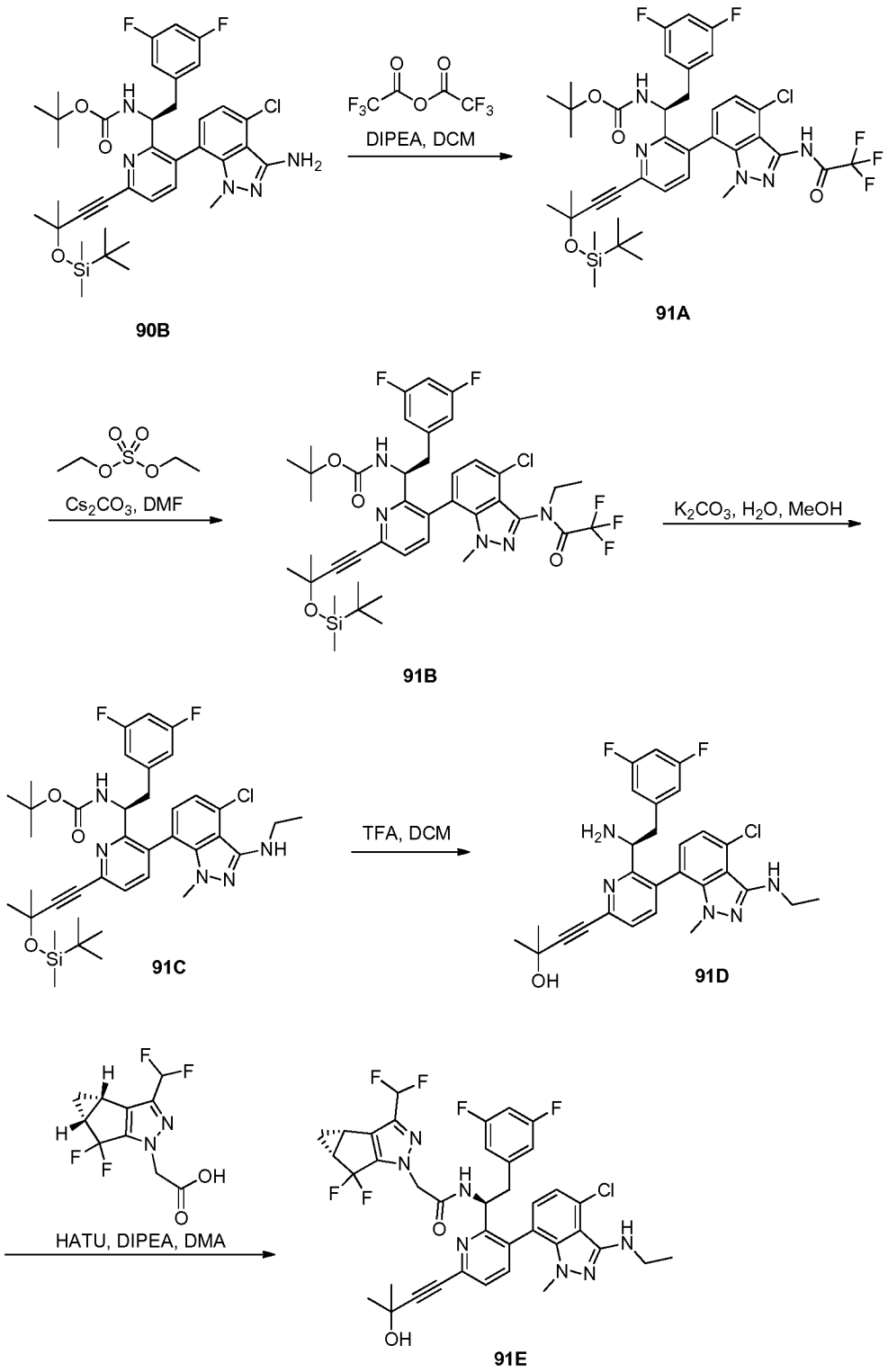
Synthesis of (S)-methyl (7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)carbamate (**90C**):

[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.



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).**

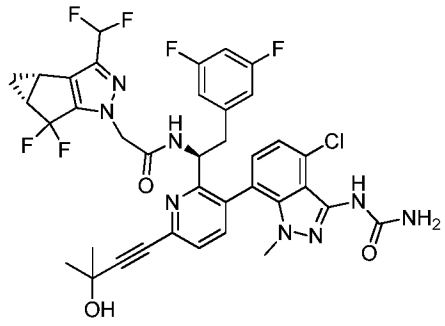
[0600] The title compound (**91D**) was prepared according to the method presented for the synthesis of compound (**90C**) of Example 90 utilizing (S)-tert-butyl (1-(6-(3-((tert-

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.



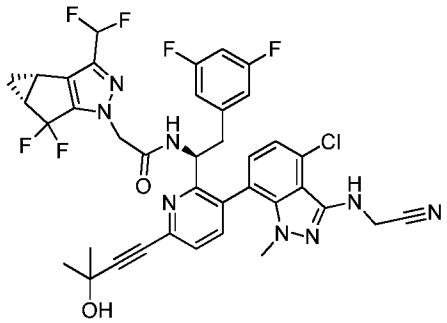
92

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 °C 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.

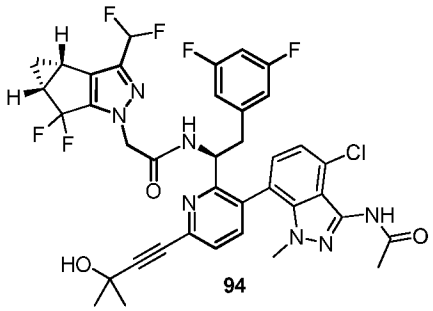


93

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.

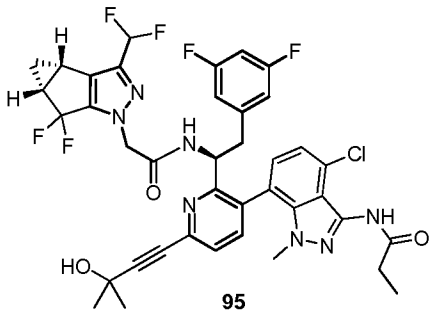


94

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.



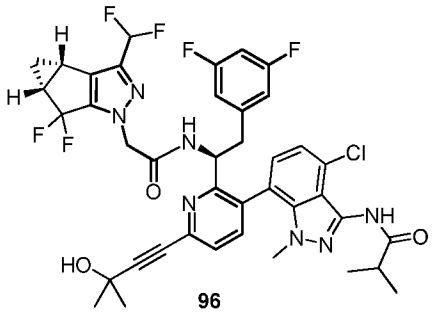
95

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.

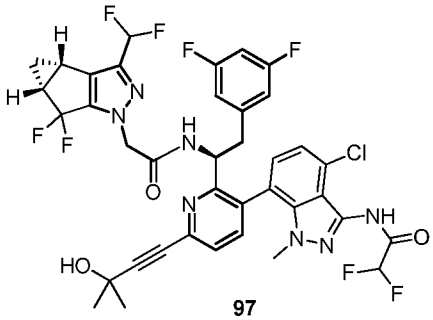


96

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.



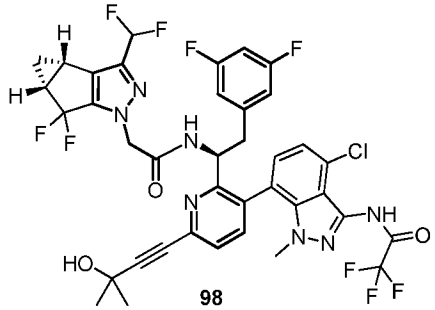
97

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.

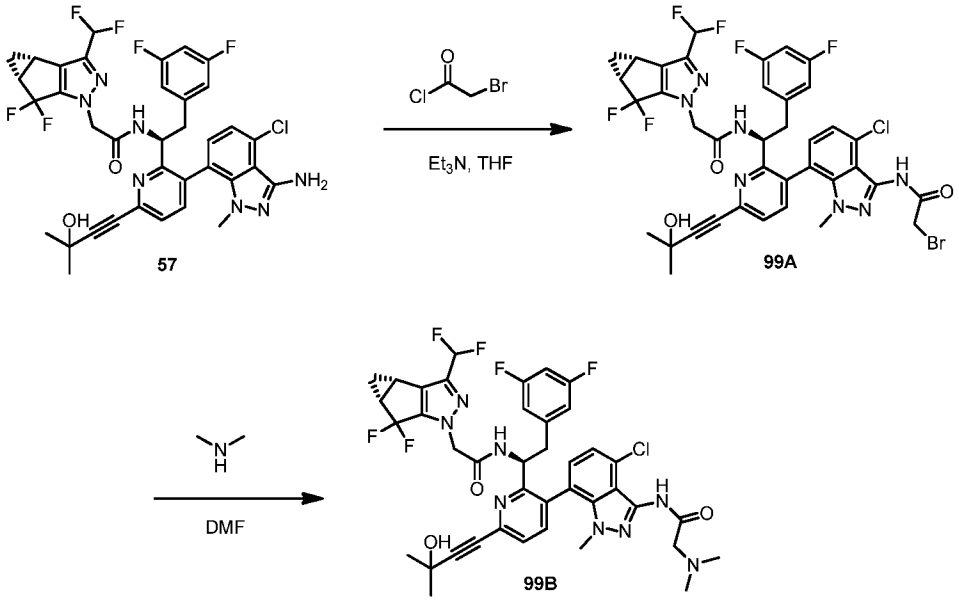


98

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

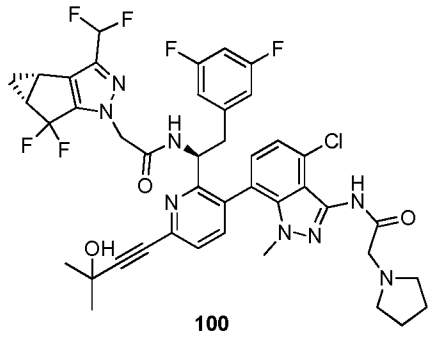
Synthesis of 2-bromo-N-(4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)acetamide (**99A**):

[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.

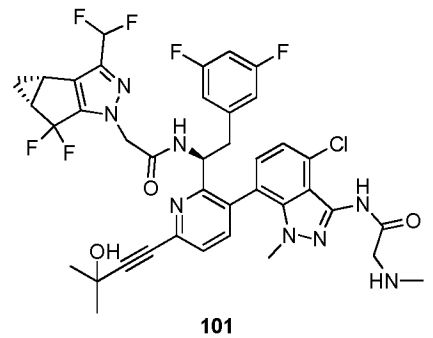


100

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.



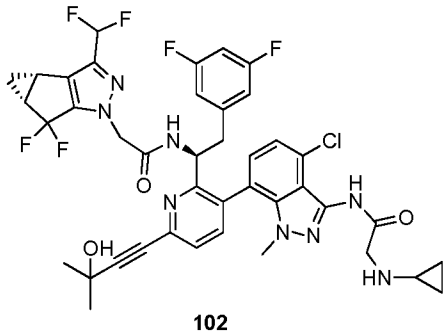
101

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.

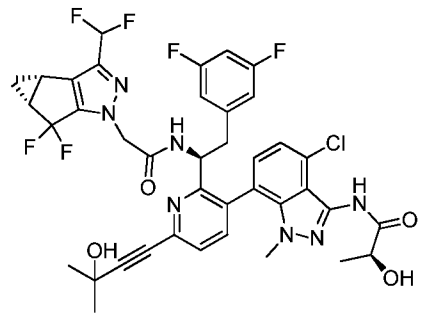


102

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.

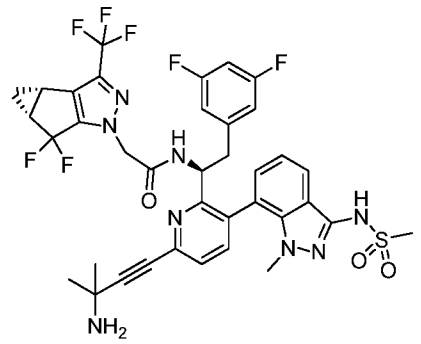


103

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.

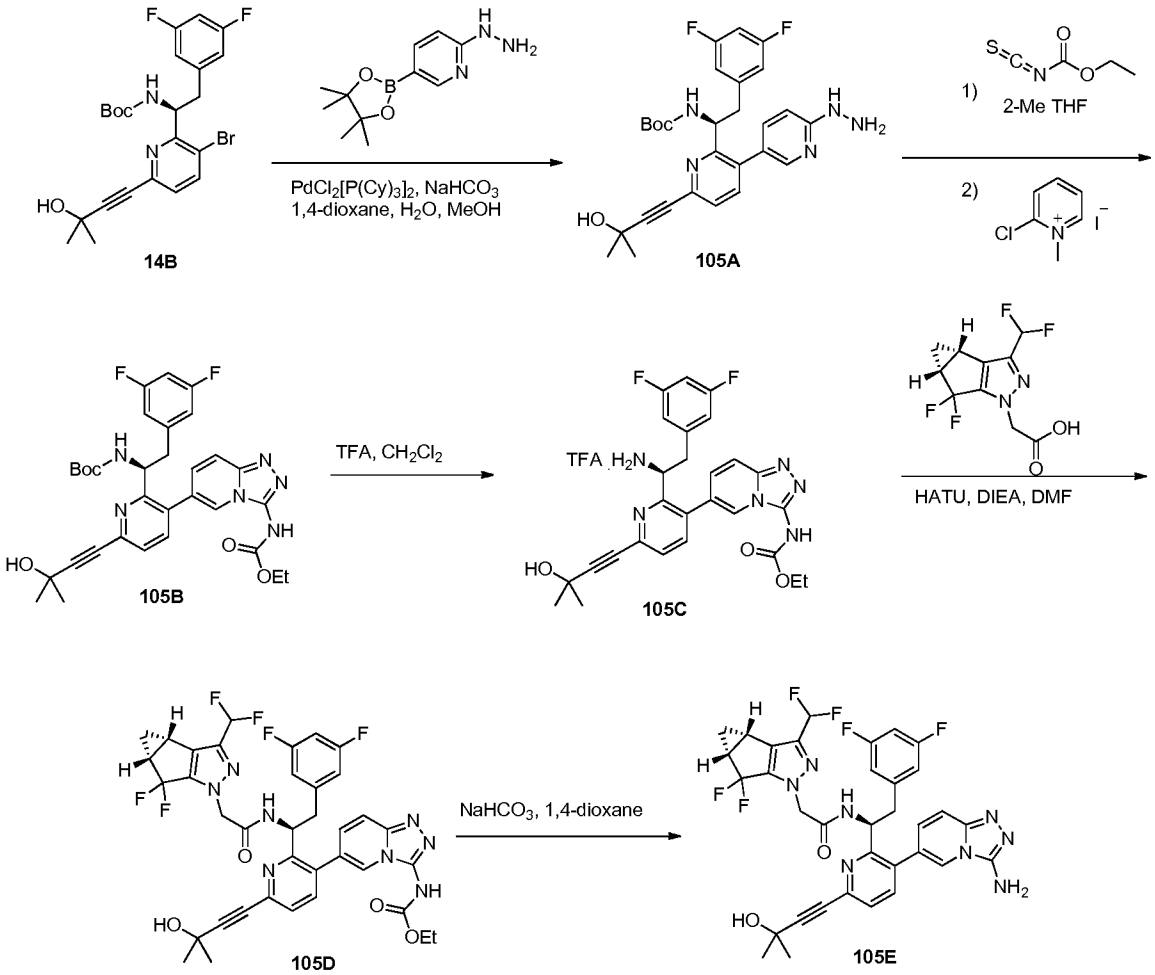


104

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 $[M+H]^+$.

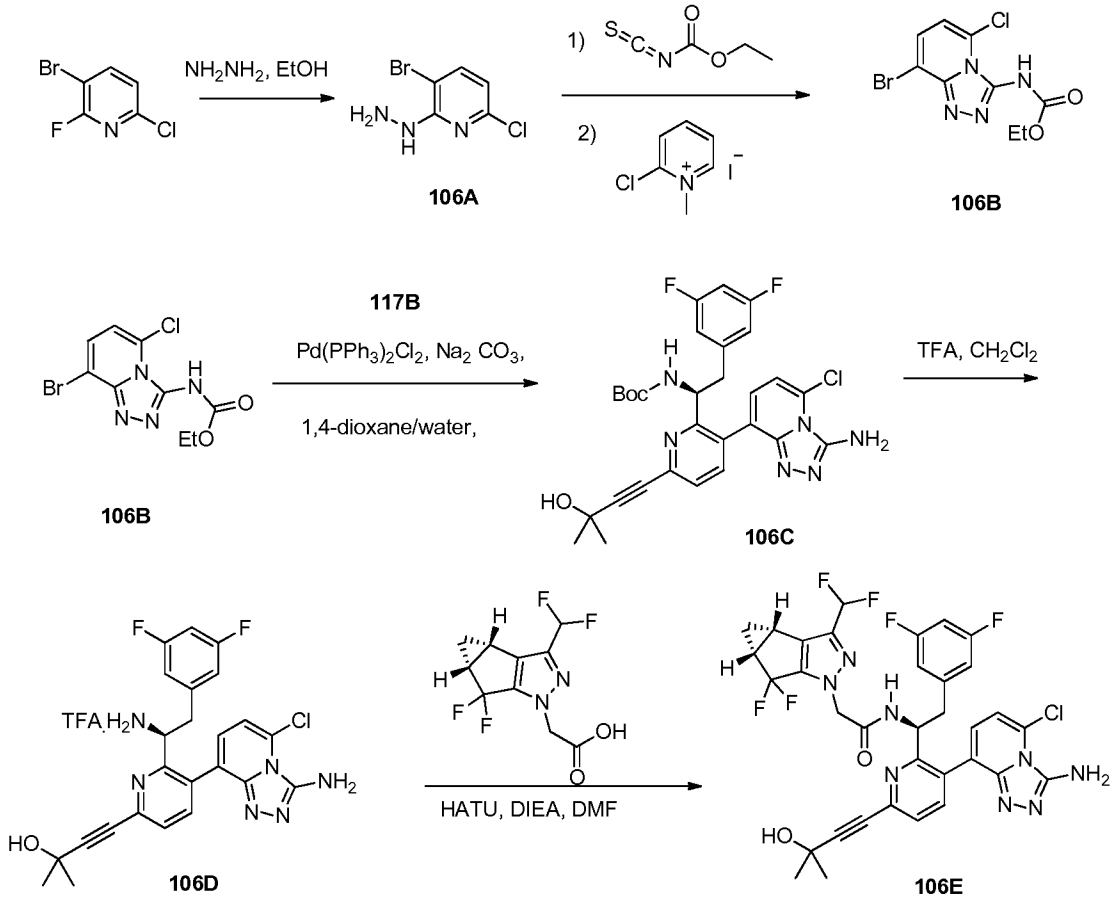
Synthesis of ethyl (6-(2-((S)-1-(2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)carbamate (**105D**):

[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 $[M+H]^+$

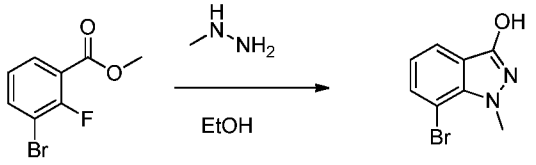
Synthesis of (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(3-amino-5-chloro-[1,2,4]triazolo[4,3-a]pyridin-8-yl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (**106D**):

[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 $[M+H]^+$.

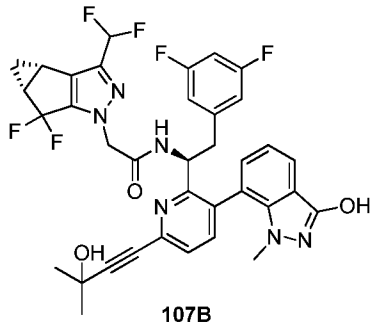
Example 107.



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 $[M+2H]^+$.

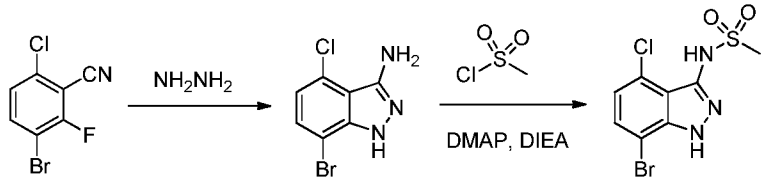


107B

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

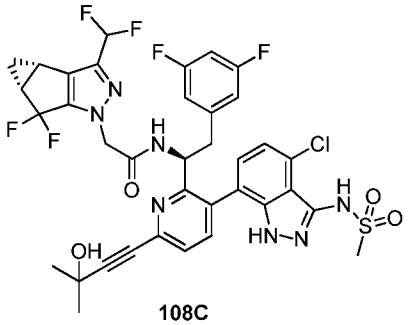
Synthesis of 7-bromo-4-chloro-1H-indazol-3-amine (**108A**):

[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 $[M+H]^+$.

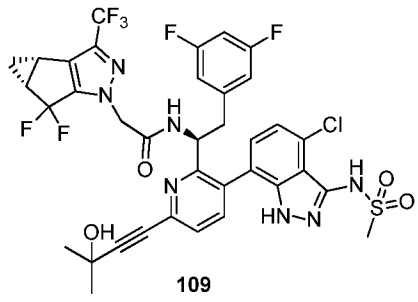


108C

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.



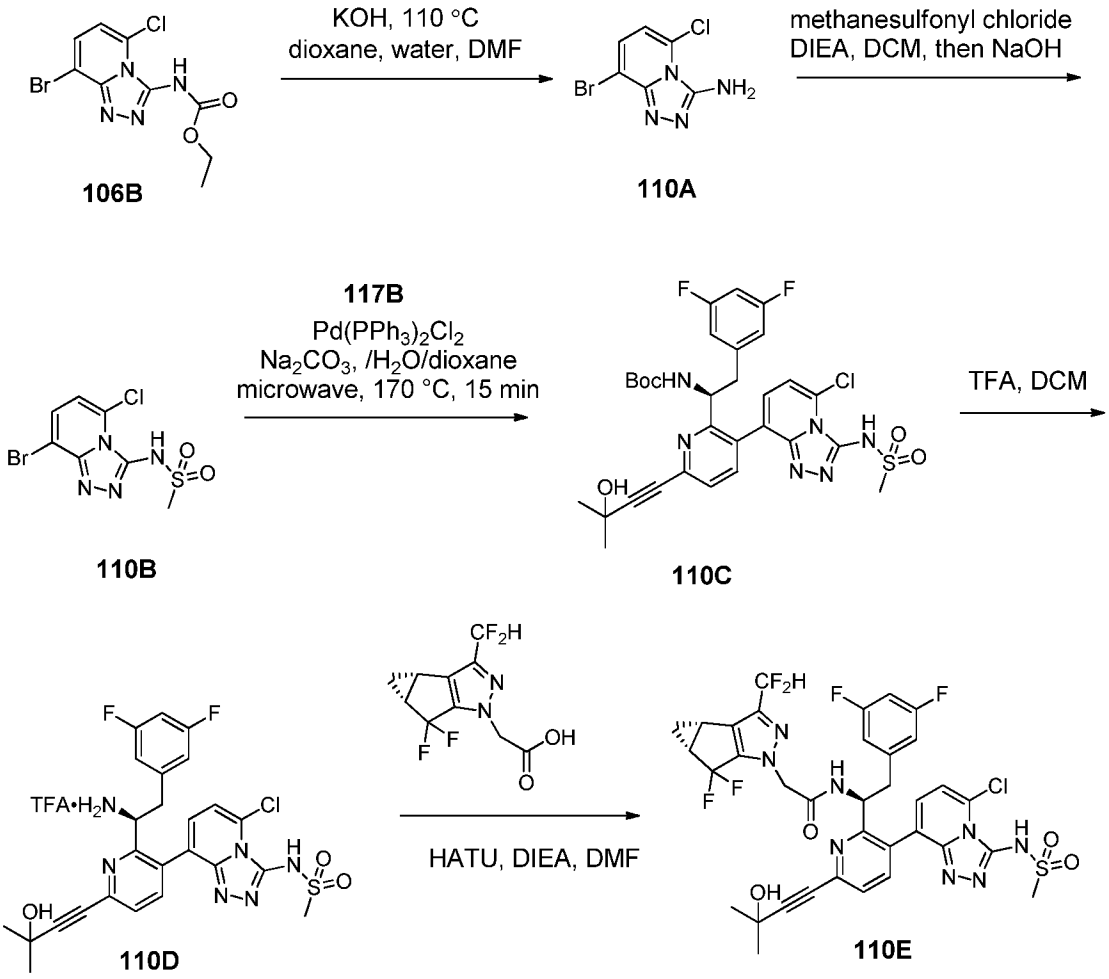
109

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 $[M+H]^+$.

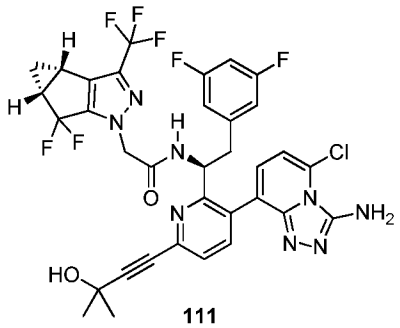
Synthesis of (S)-N-(8-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-5-chloro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methanesulfonamide TFA salt (**110D**):

[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.

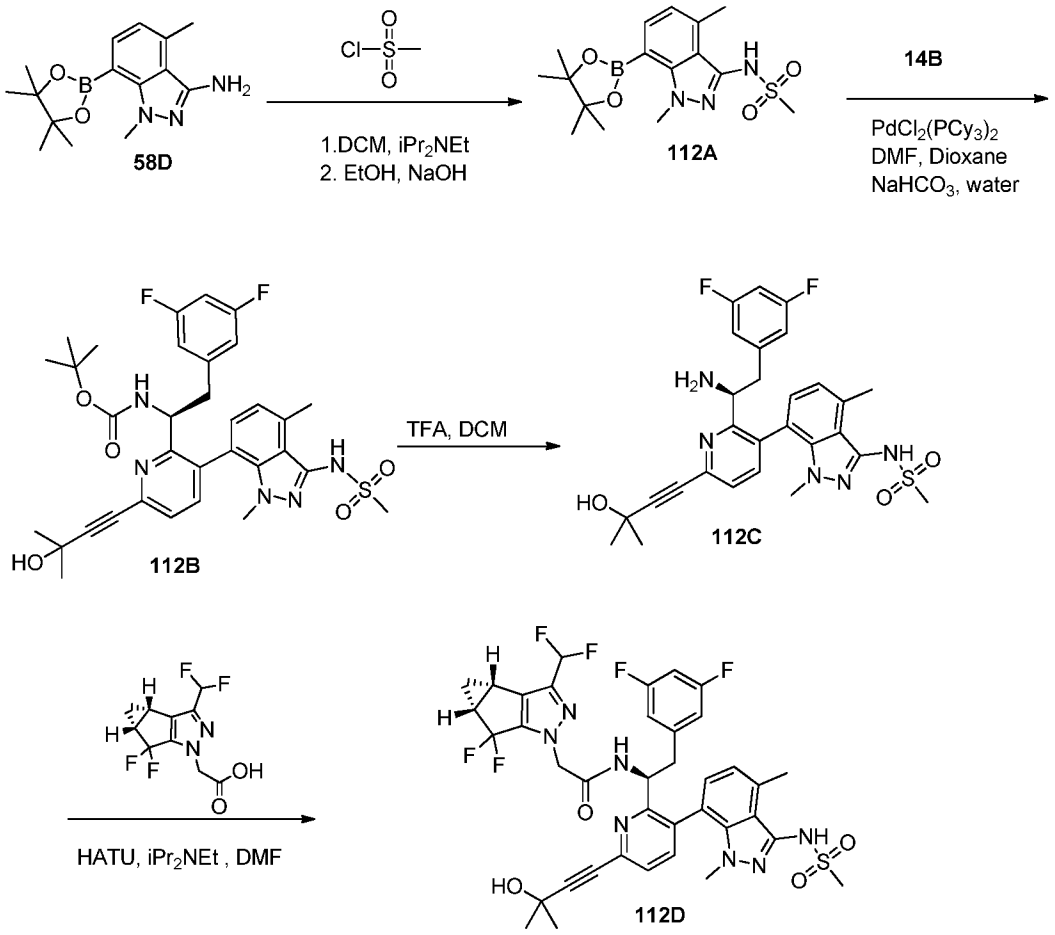


111

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 $[M+H]^+$.

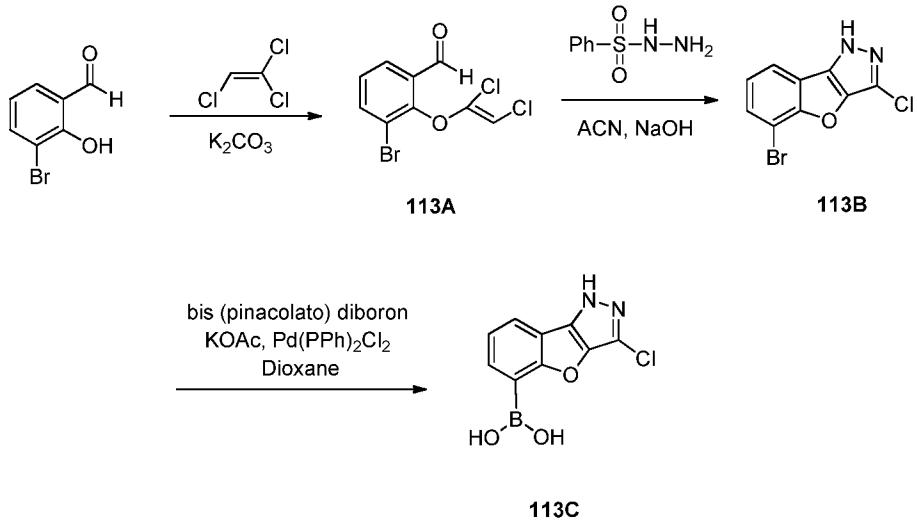
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1,4-dimethyl-1H-indazol-3-yl)methanesulfonamide (**112C**):

[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**):

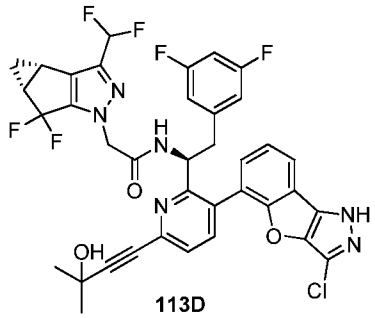
[0642] Trichloroethylene (2.68 mL, 30 mmol) was added drop wise over a period of 30 min to a solution of 3-bromo-2-hydroxybenzaldehyde (2 g, 9.9 mmol) suspended with K_2CO_3 (4.1 g, 30 mmol) in DMF (8 mL) at 60 °C under N_2. The reaction was stirred for 15 h then cooled to room temperature and partitioned 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 $[M+H]^+$.

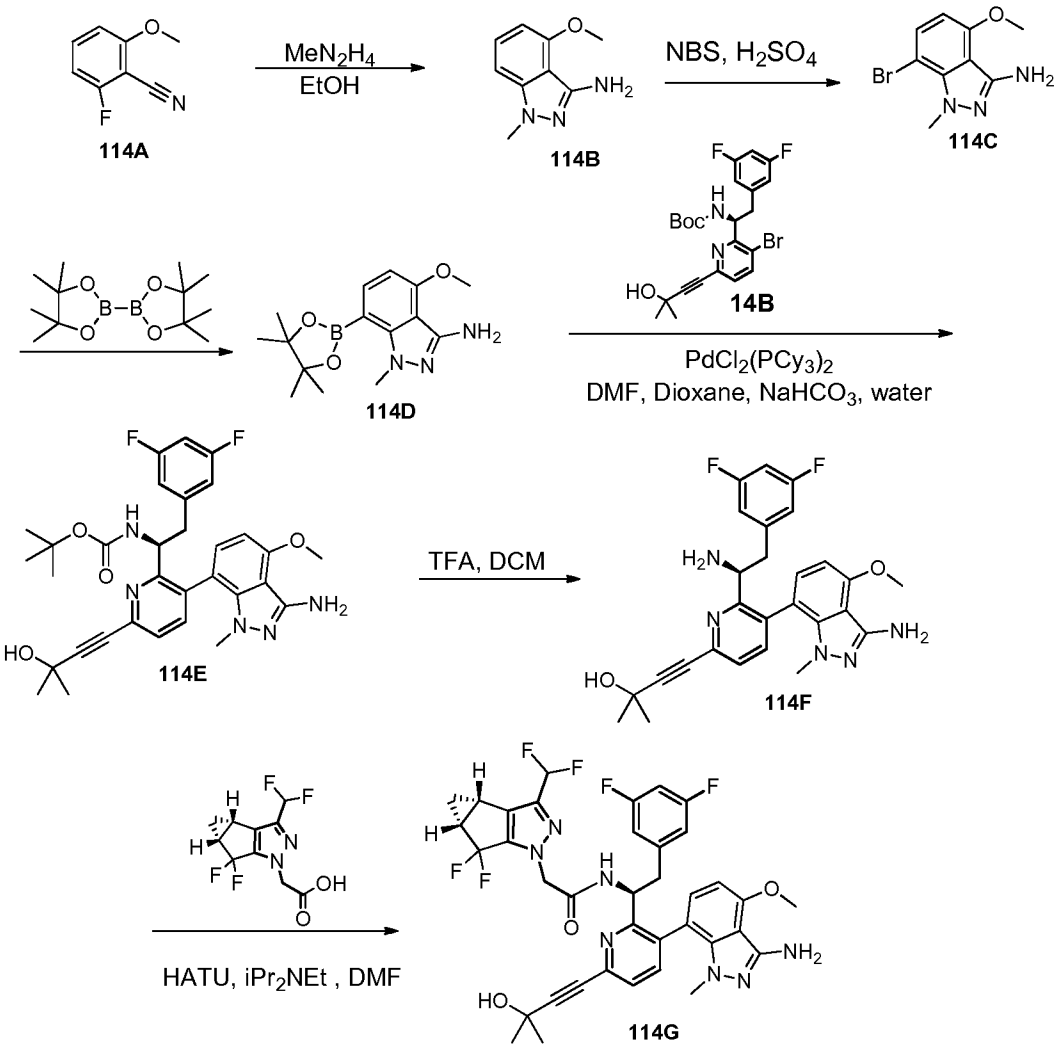


113D

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 $[M+H]^+$.

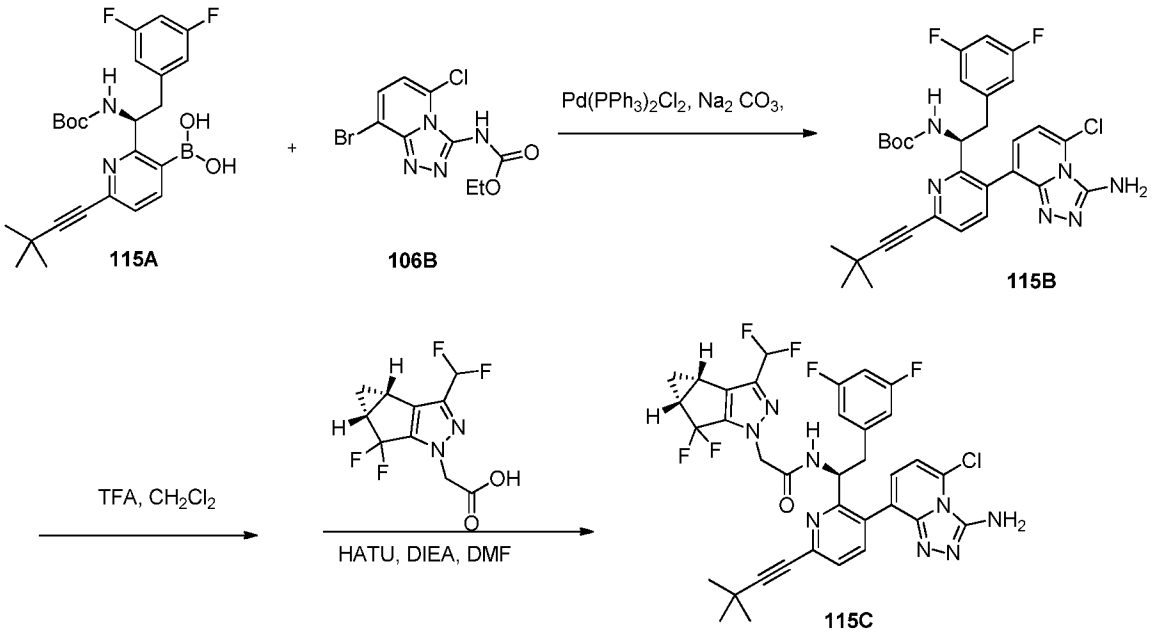
Synthesis of (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(3-amino-4-methoxy-1-methyl-1H-indazol-7-yl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (**114F**):

[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**):

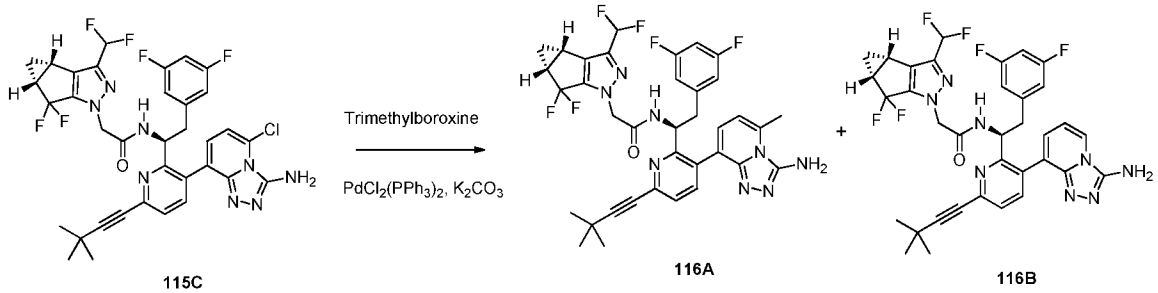
[0653] The title compound (**115B**) was prepared according to the method presented for the synthesis of compound **106C** of Example 106 utilizing compound **115A** and compound **106B**. MS (*m/z*): 581.14 $[M+H]^+$.

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.



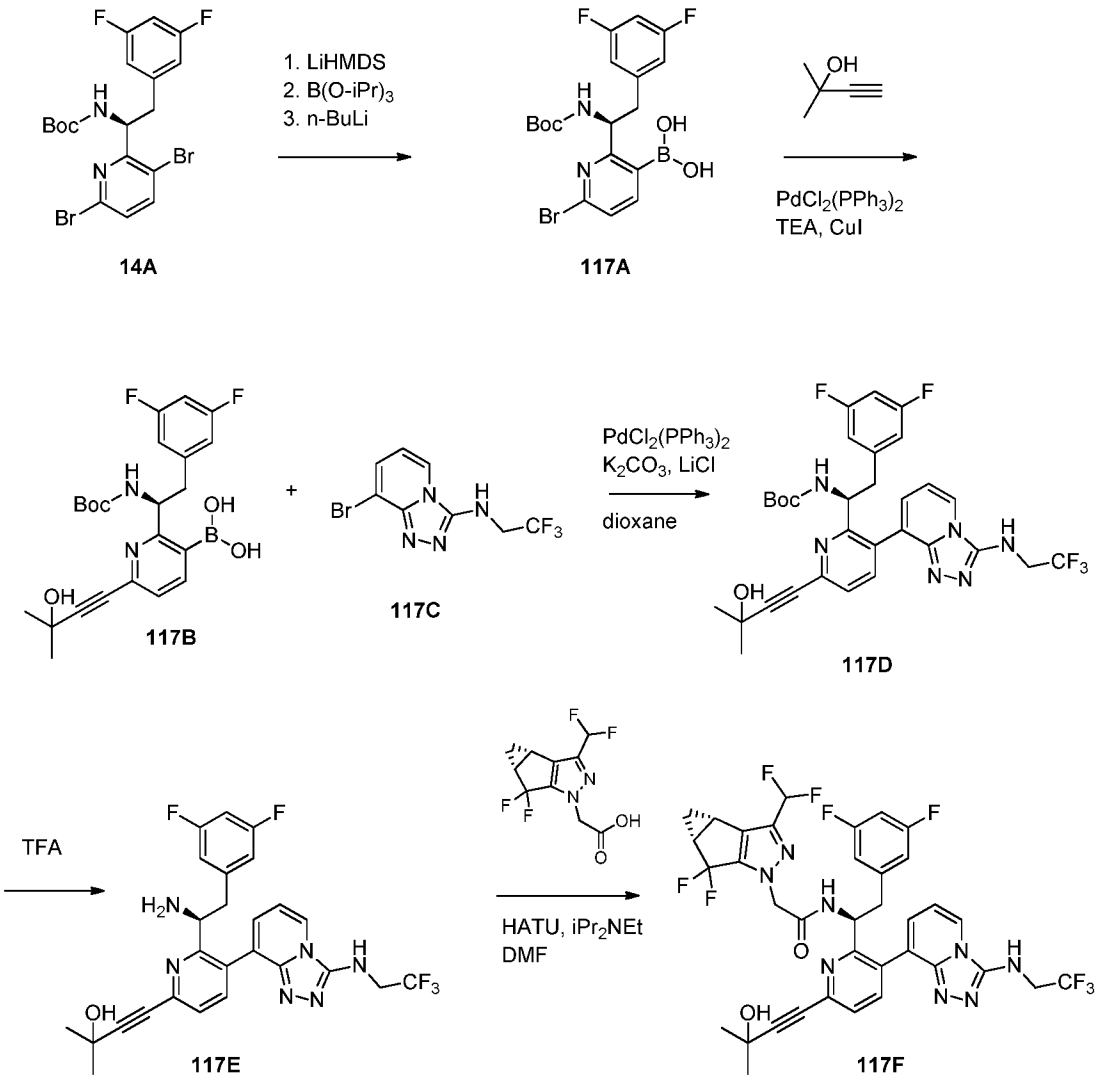
115C 116A 116B

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 $[M+H]^+$.

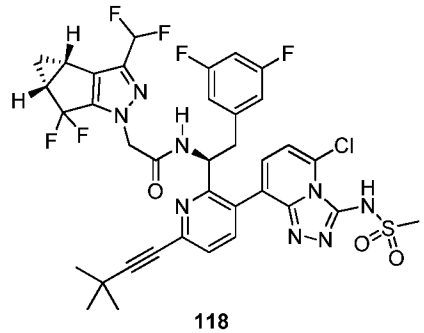
Synthesis of (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(3-((2,2,2-trifluoroethyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (**117E**):

[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.

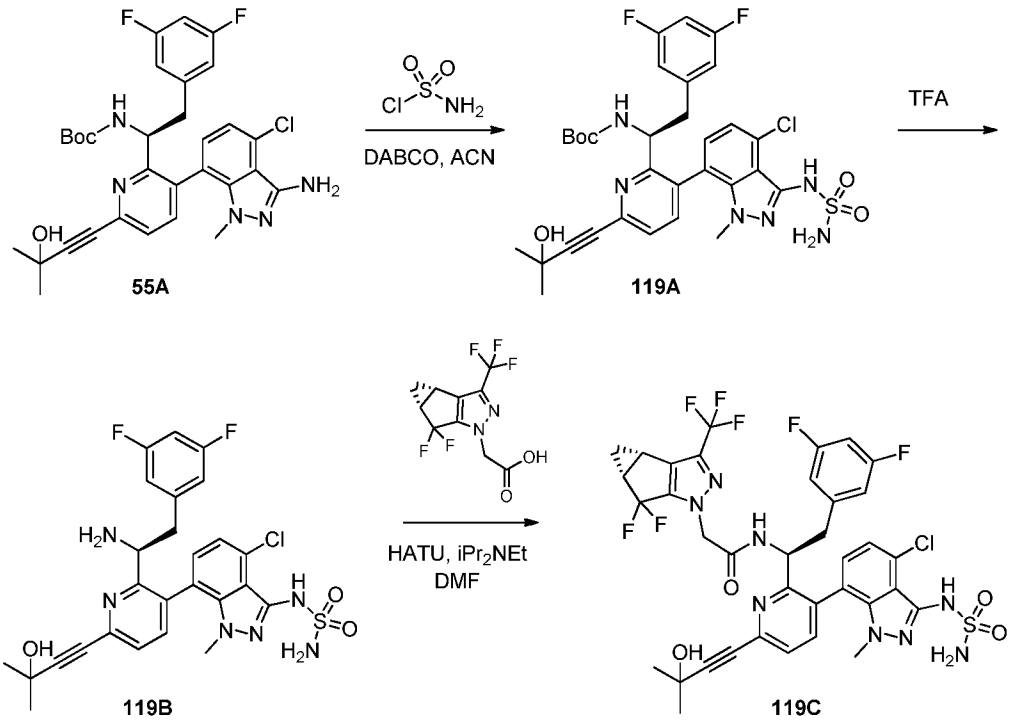


118

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 $[M+H]^+$.

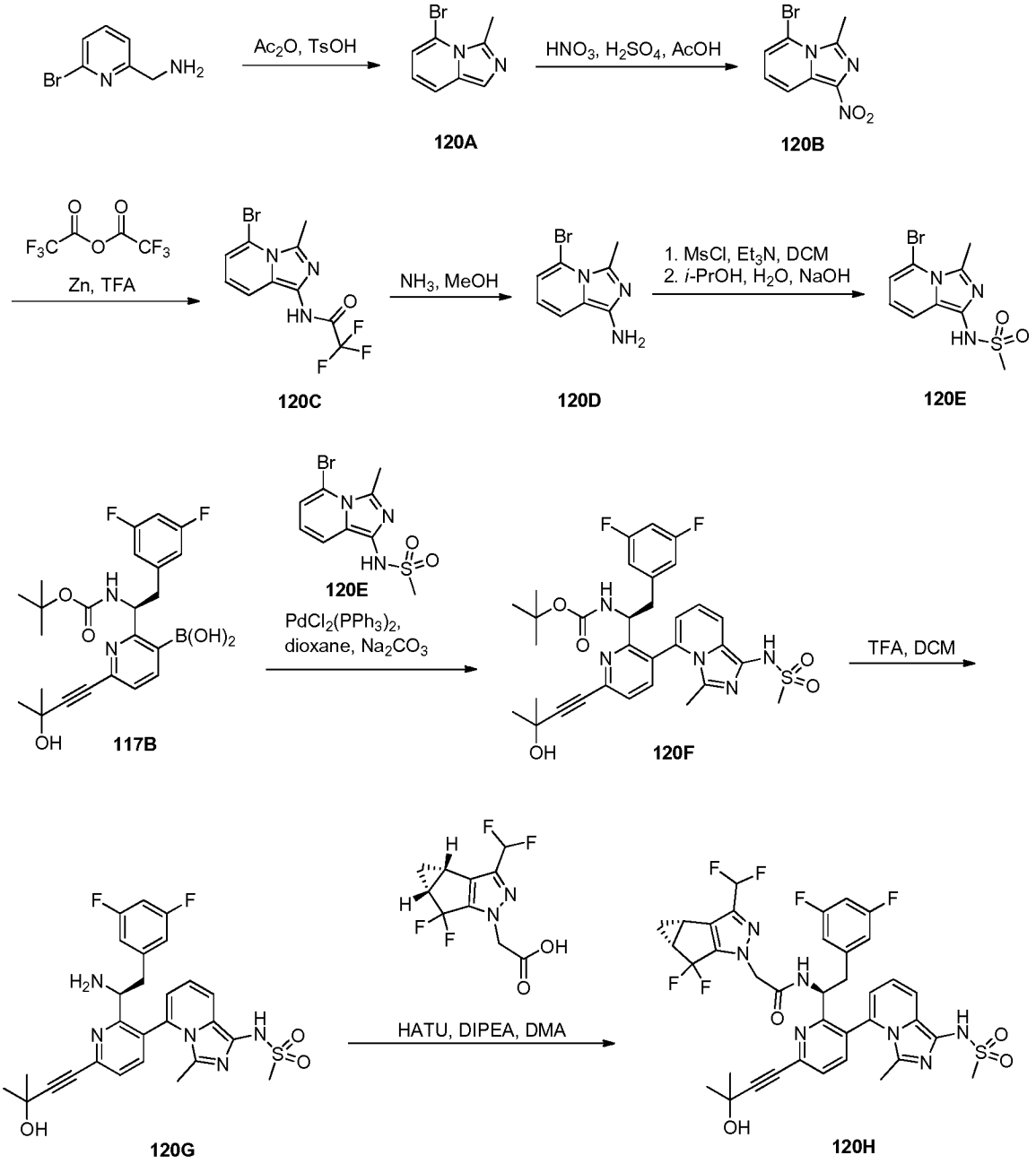
Synthesis of **119B**:

[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**):

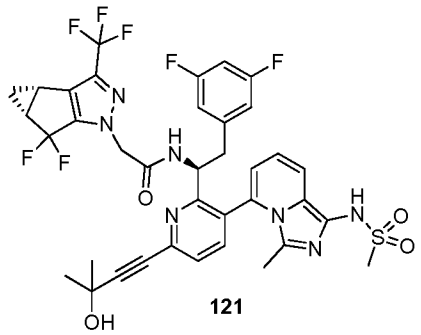
[0673] (S)-tert-butyl (2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(3-methyl-1-(methylsulfonamido)imidazo[1,5-a]pyridin-5-yl)pyridin-2-yl)ethyl)carbamate (**120F**) (75 mg ,0.12 mmol) was dissolved in DCM (1.0 mL) and TFA (0.5 mL) and stirred at room temperature for 30 mins. The resulting 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.

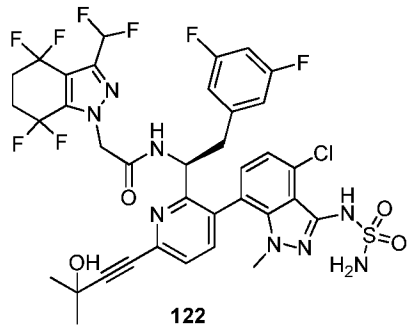


121

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.

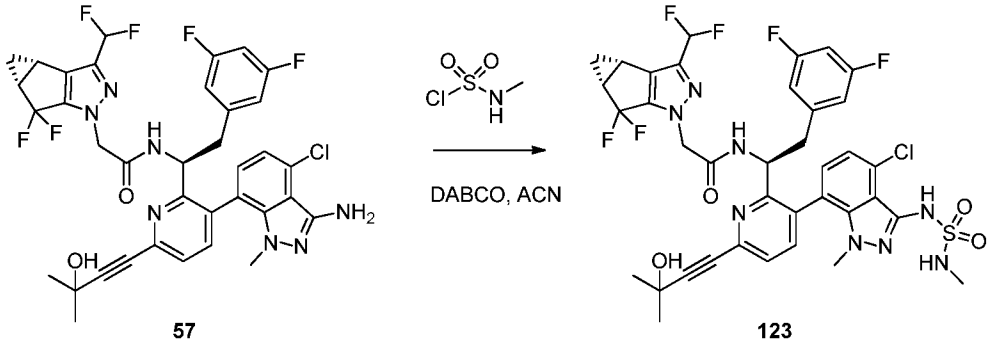


122

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.



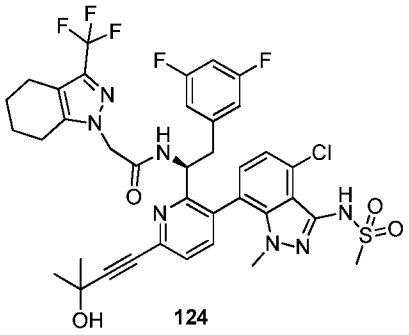
57 123

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.

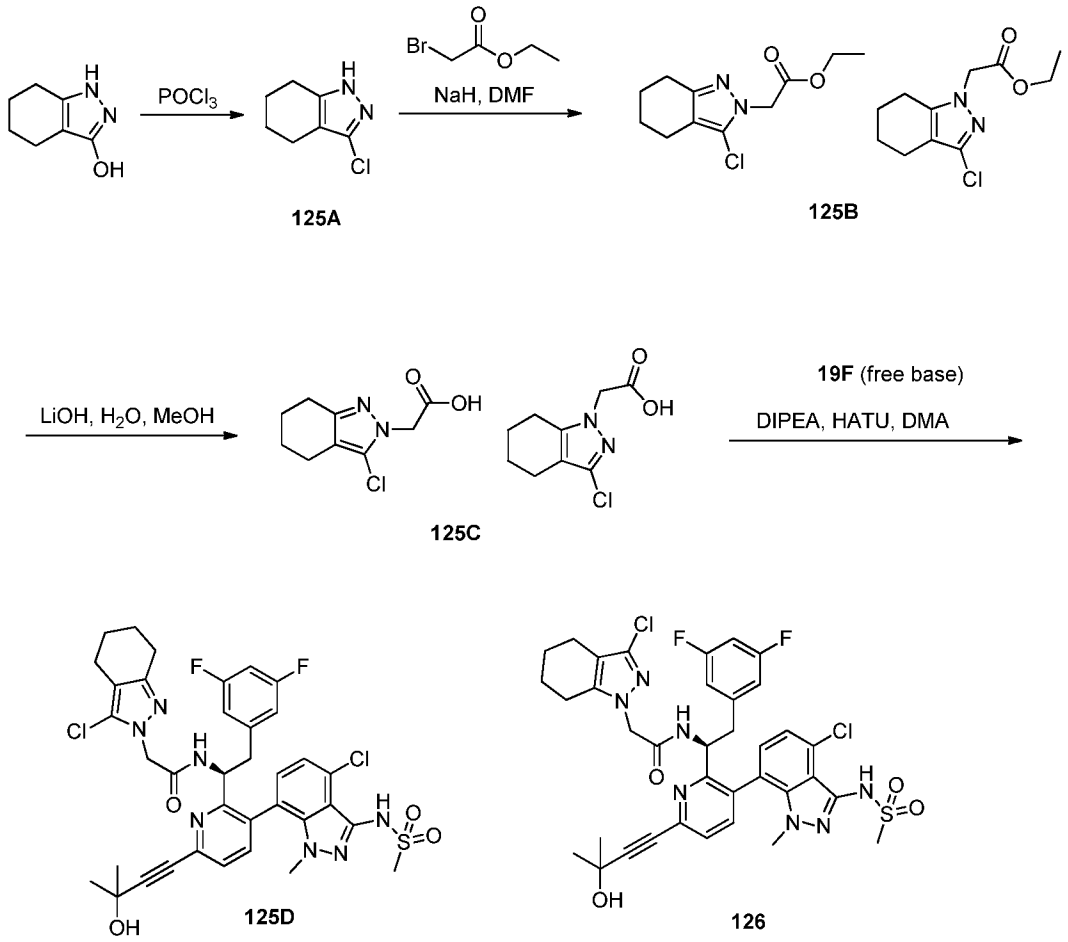


124

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 $[M+H]^+$.

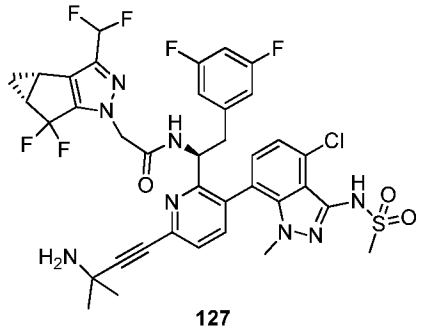
Synthesis of a 1:5 mixture of 2-(3-chloro-4,5,6,7-tetrahydro-2H-indazol-2-yl)acetic acid and 2-(3-chloro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid **(125C)**:

[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.

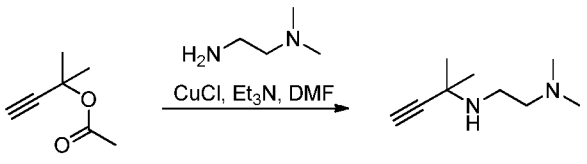


127

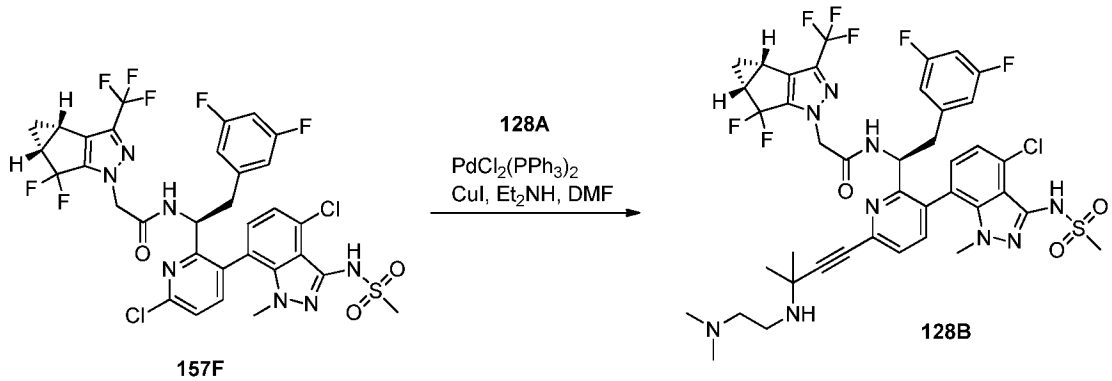
Synthesis of N-((S)-1-(6-(3-amino-3-methylbut-1-yn-1-yl)-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**127**):

[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

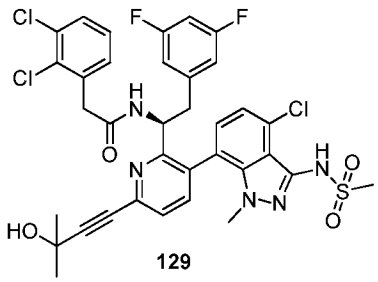
Synthesis of N1,N1-dimethyl-N2-(2-methylbut-3-yn-2-yl)ethane-1,2-diamine (**128A**):

[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.



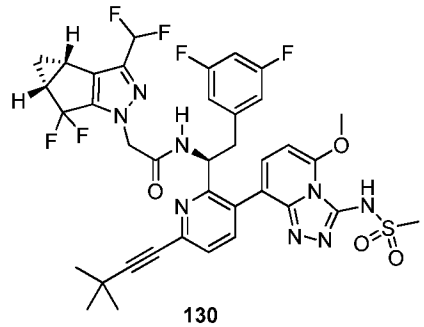
129

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.

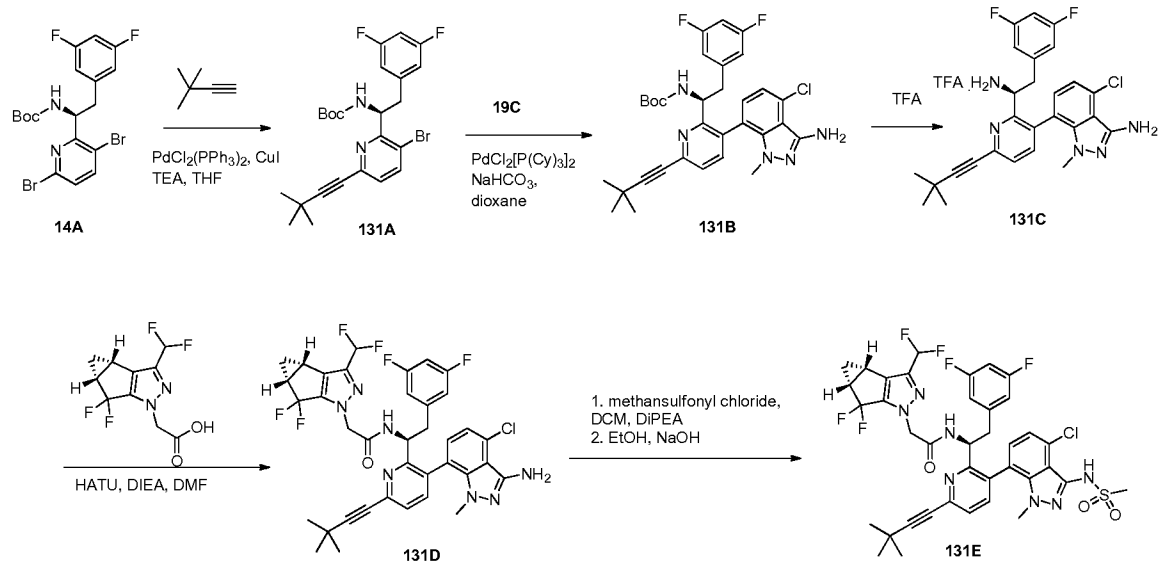


130

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.



14A 131A 131B 131C 131D 131E

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**):

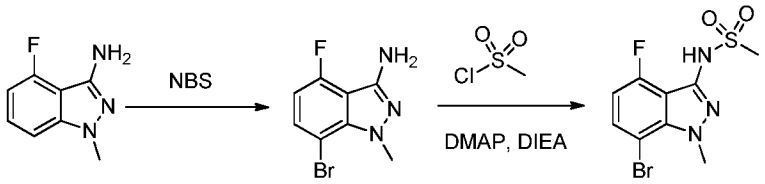
[0691] The title compound **131D** was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **37E** of Example 37 utilizing 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-

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.

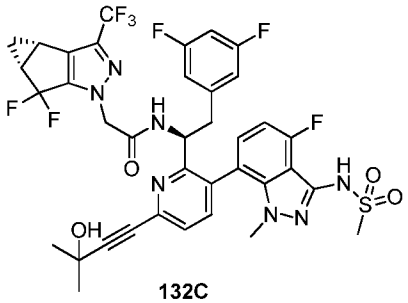


Synthesis of 7-bromo-4-fluoro-1-methyl-1H-indazol-3-amine (**132A**):

[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 $[M-H]^-$.

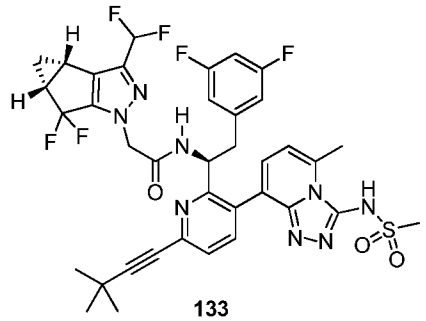


132C

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.



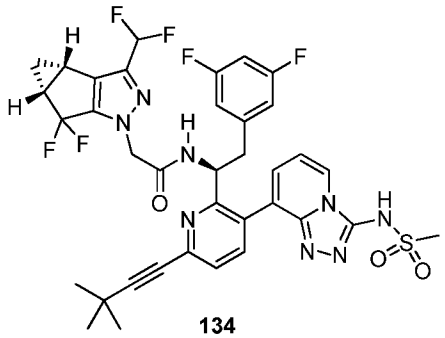
133

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.

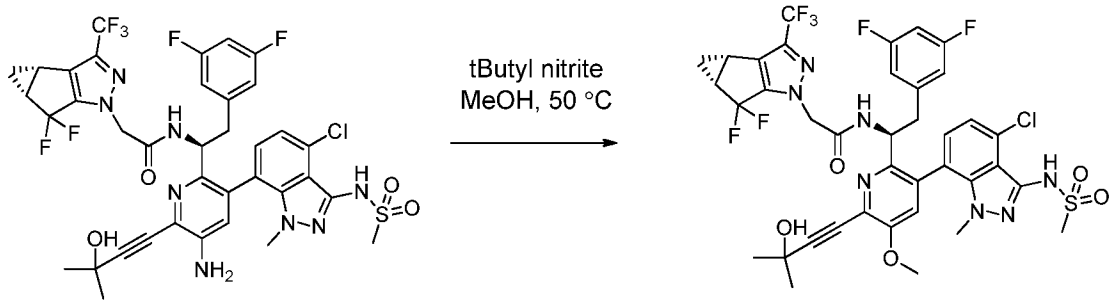


134

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**):

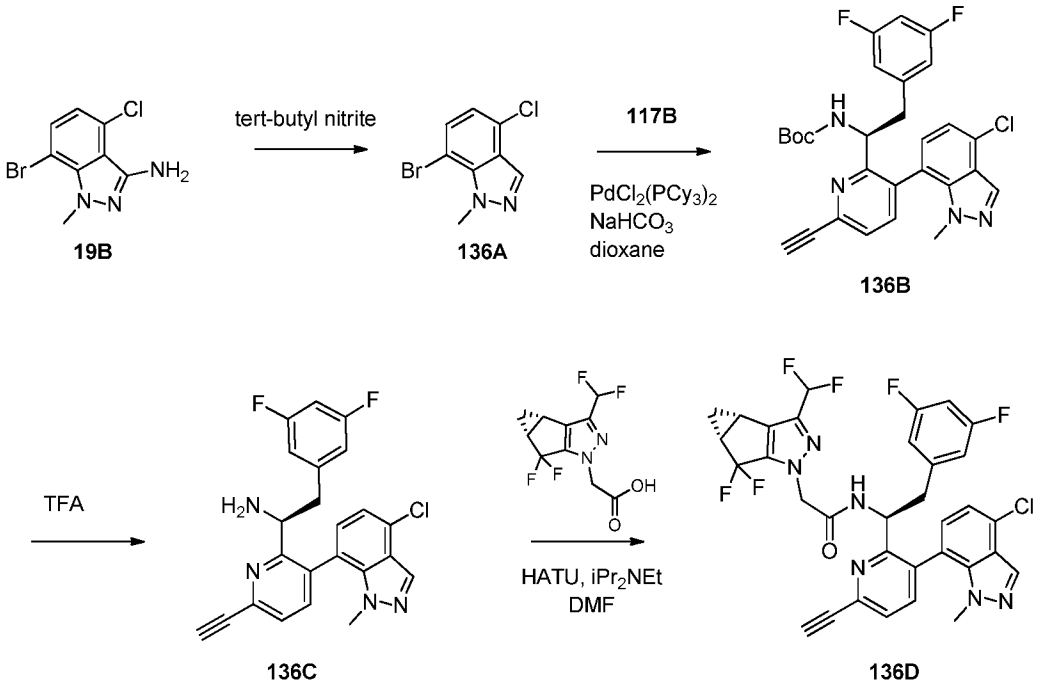
[0698] The title compound (**135A**) may be prepared analogously to the method presented for the synthesis of compound **139A** of Example 139 utilizing 2-((3bS,4aR)-5,5-difluoro-3-

(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 $[M+H]^+$.

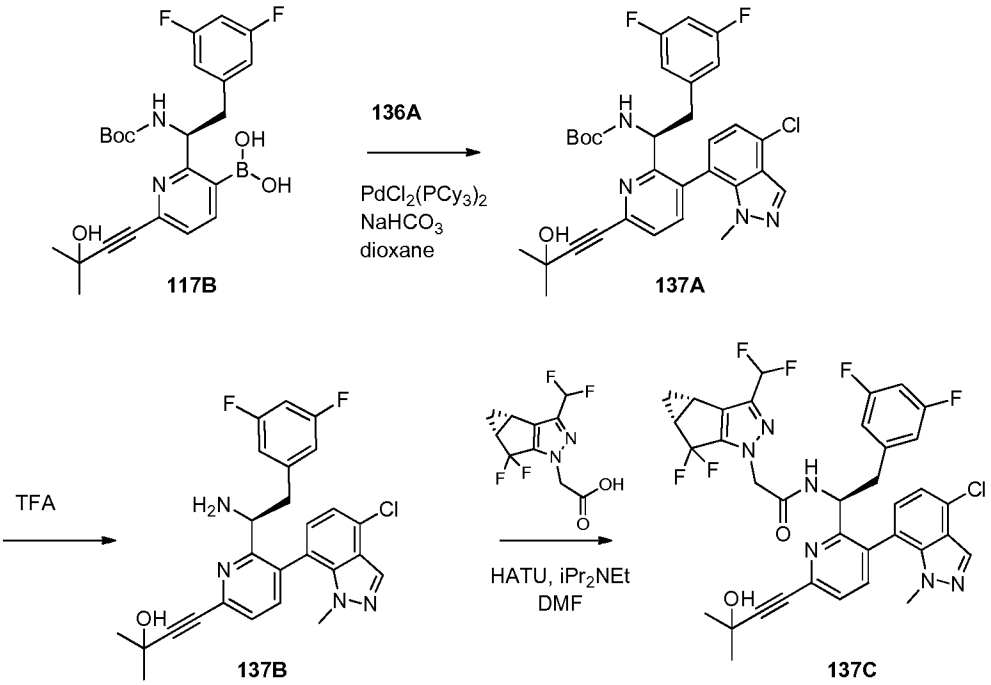
Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-1H-indazol-7-yl)-6-ethynylpyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**136C**):

[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 $[M+H]^+$.

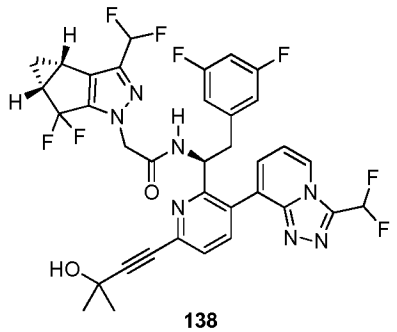
Synthesis of (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(4-chloro-1-methyl-1H-indazol-7-yl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (**137B**):

[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.

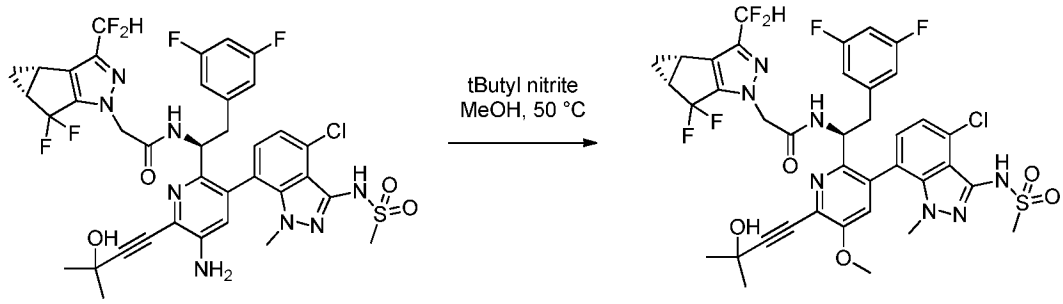


138

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

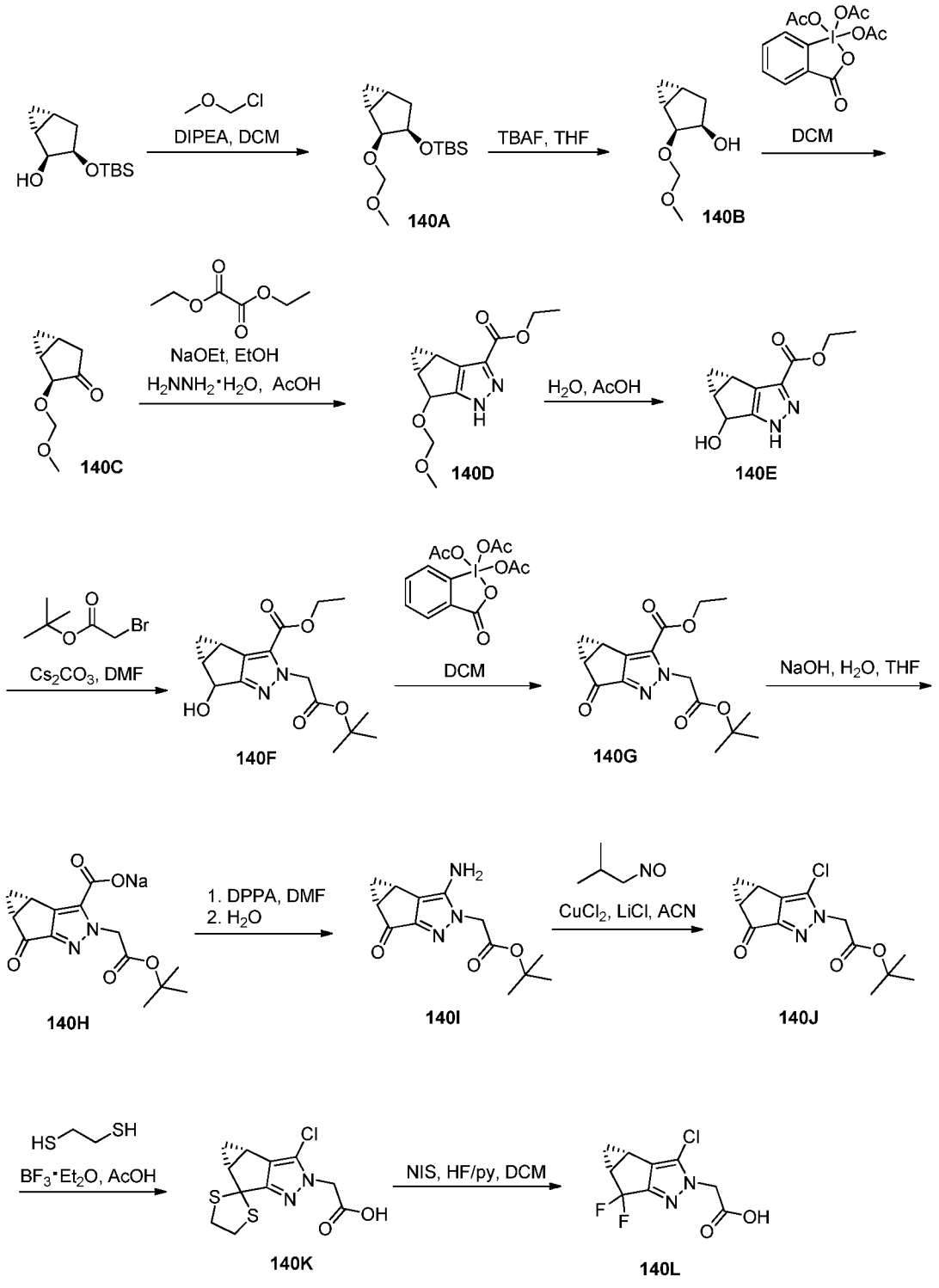
Synthesis of N-((S)-1-(5-amino-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**139A**):

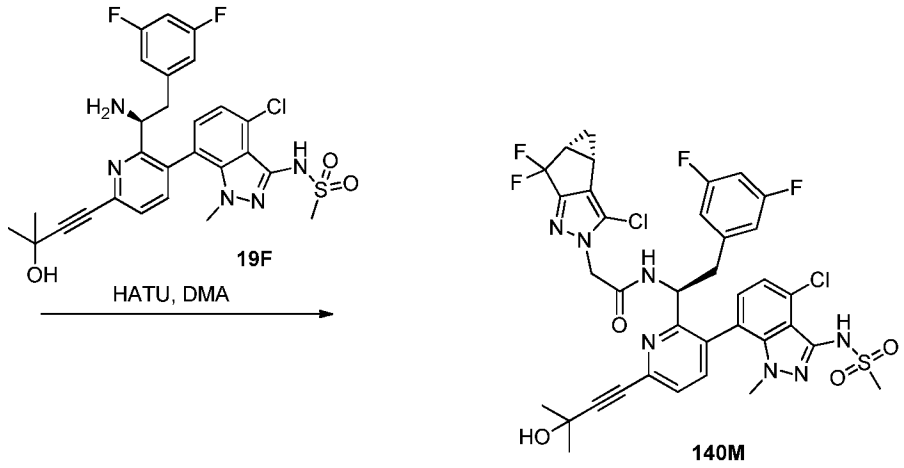
[0708] The title compound (**139A**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19G** of Example 19 utilizing compound **182H.** MS (m/z): 835.67 $[M+H]^+$.

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.


DIPEA, DCM
TBAF, THF
DCM
140A
140B
NaOEt, EtOH
$H_2NNH_2 \cdot H_2O$, AcOH
H_2O, AcOH
140C
140D
140E
Cs_2CO_3, DMF
DCM
NaOH, H_2O, THF
140F
140G
1. DPPA, DMF
2. H_2O
$CuCl_2$, LiCl, ACN
140H
140I
140J
$BF_3 \cdot Et_2O$, AcOH
NIS, HF/py, DCM
140K
140L



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**):

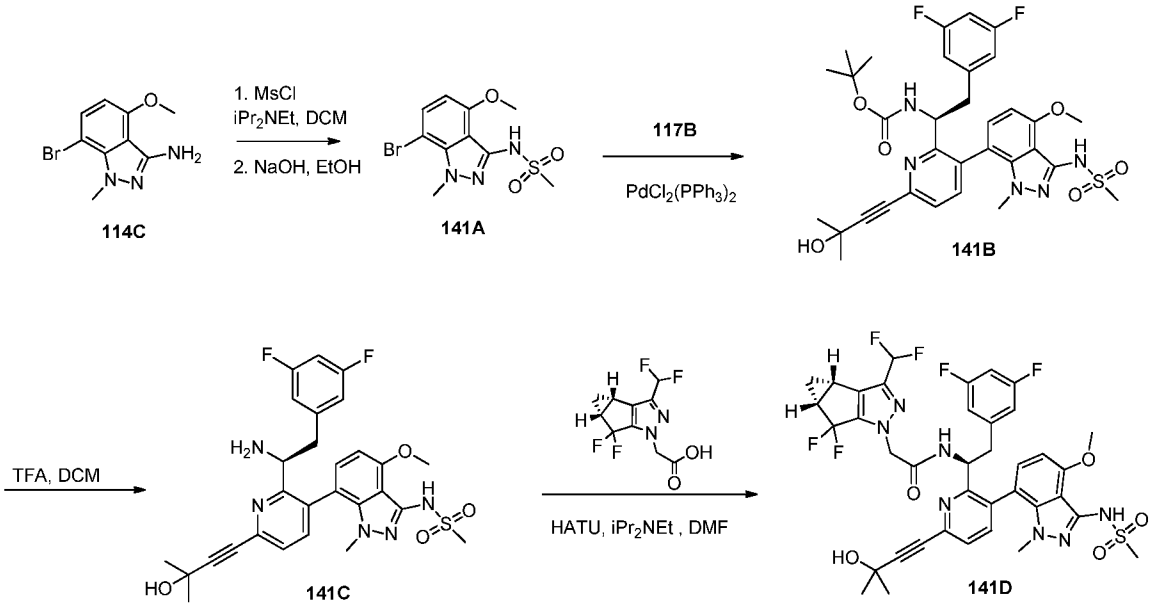
[0721] To a solution of N-iodosuccinimide (27.9 mg, 0.12 mmol) in dichloromethane (0.10 ml) was added dropwise 70% HF in pyridine (0.10 ml) at -78°C. After stirring for 15 minutes, a suspension of **140K** (15 mg, 0.05 mmol) in dichloromethane (0.10 ml) was added and the reaction was gradually warmed 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]$^+$.

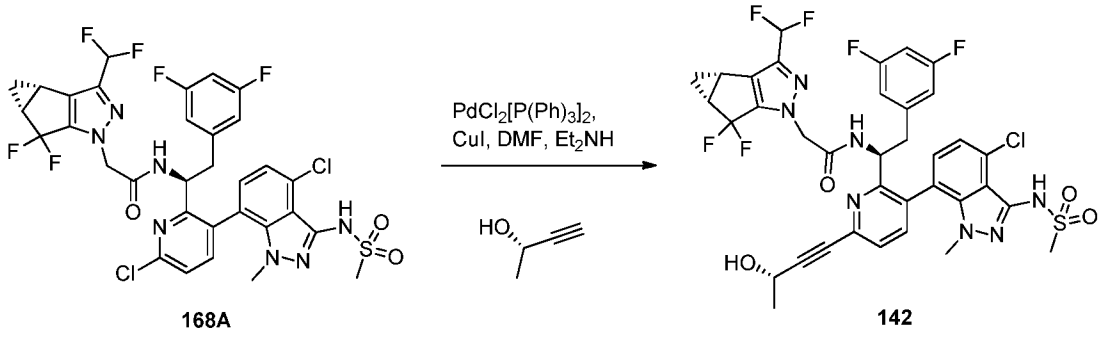
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-methoxy-1-methyl-1H-indazol-3-yl)methanesulfonamide (**141C**):

[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.



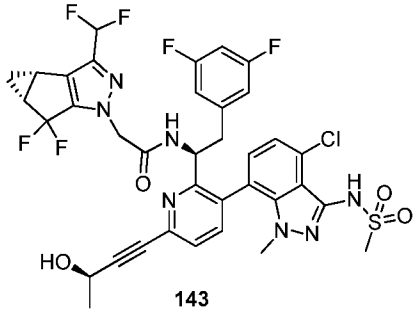
168A 142

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.

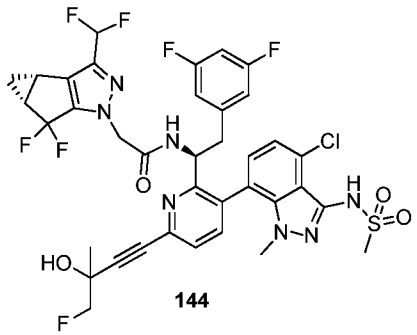


143

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.

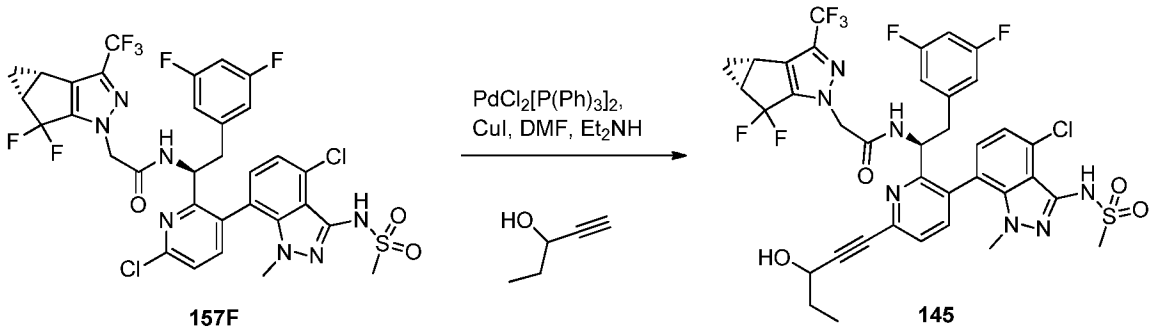


144

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.

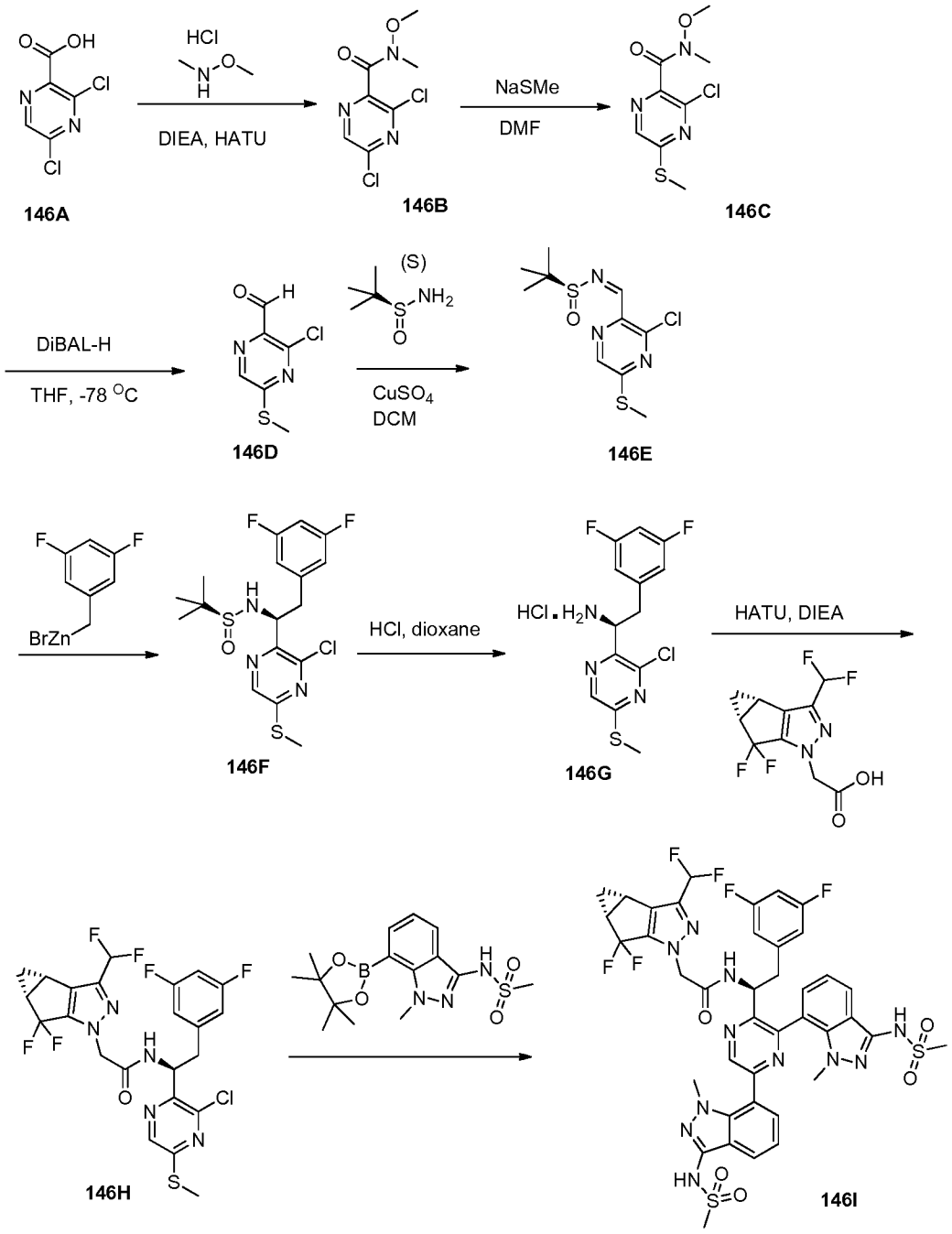


157F 145

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 $[M+H]^+$.

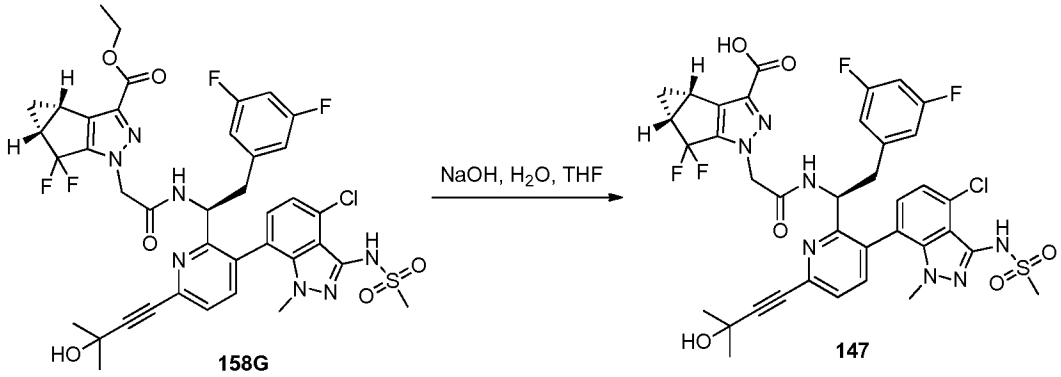
Synthesis of N-((S)-1-(3-chloro-5-(methylthio)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**146H**):

[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.

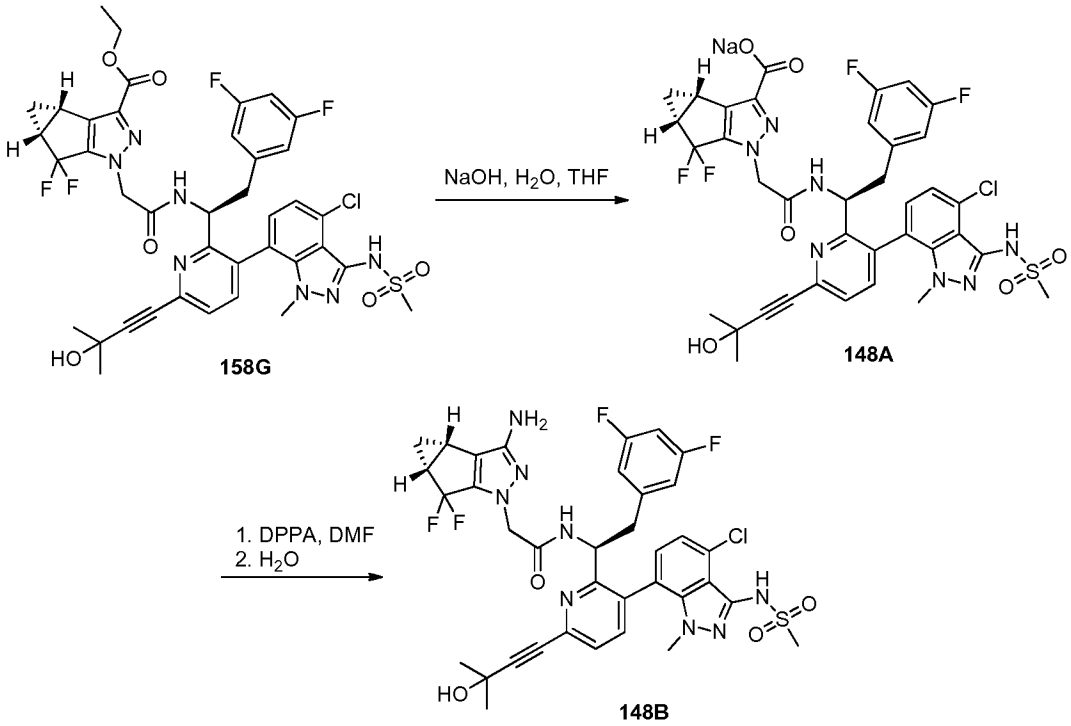


158G 147

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**):

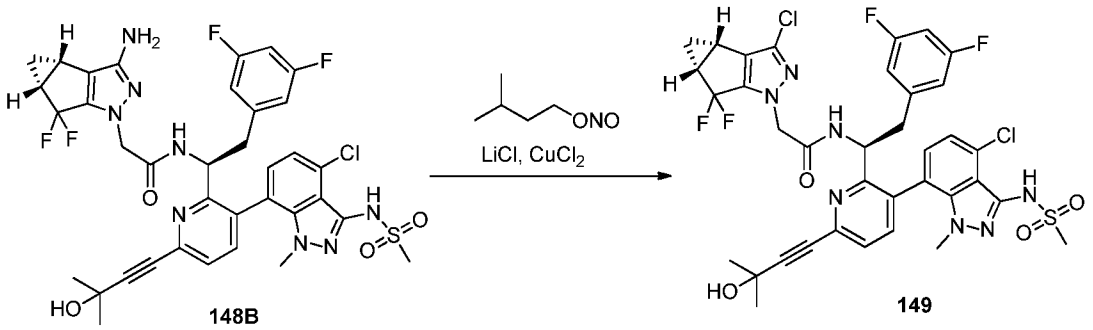
[0740] To a solution of **158G** (0.22 g, 0.26 mmol) in THF (0.65 ml) was added 1M NaOH (0.65 ml). The reaction was stirred at room temperature for 1.5 h. The solution was acidified to ~ pH=4 with AcOH and extracted with with 2-MeTHF (2 x 5 mL) and brine (5 mL). The organic layer was washed with $NaHCO_3$ (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_3od) 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 $[M+H]^+$.

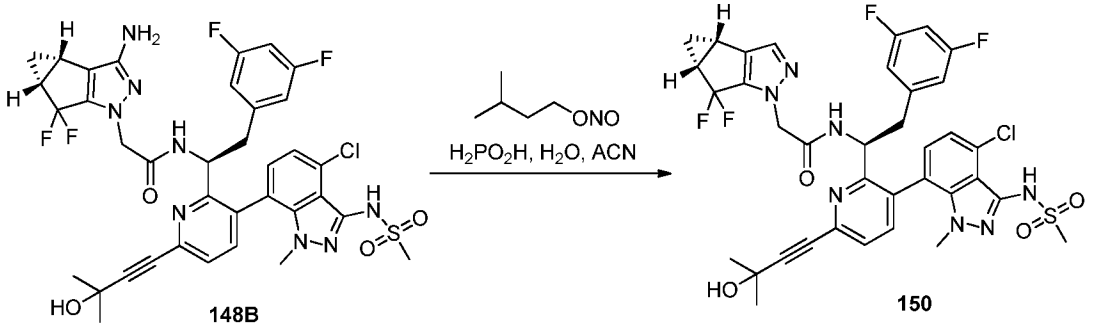
Example 149.



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_3od) 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 $[M+H]^+$.

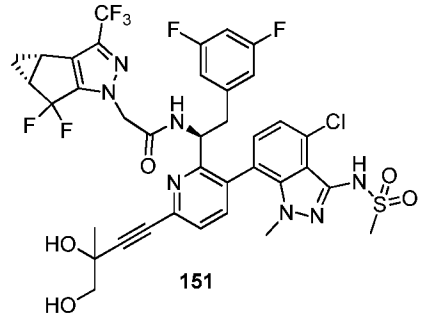
Example 150.



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.

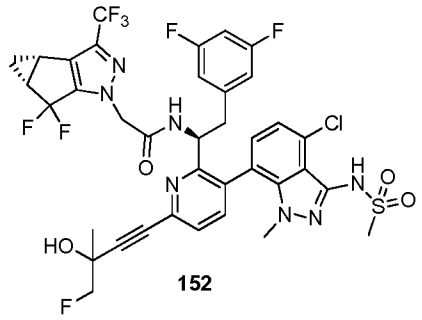


151

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.

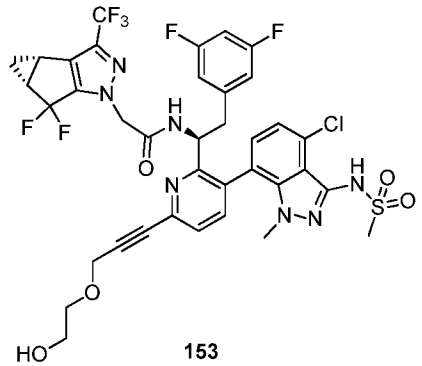


152

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.



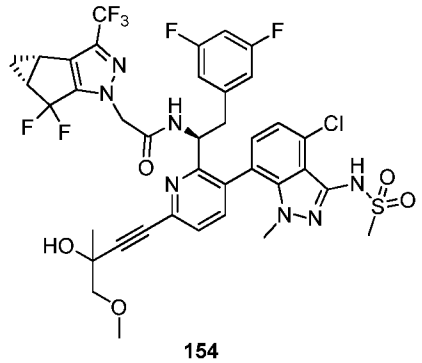
153

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.

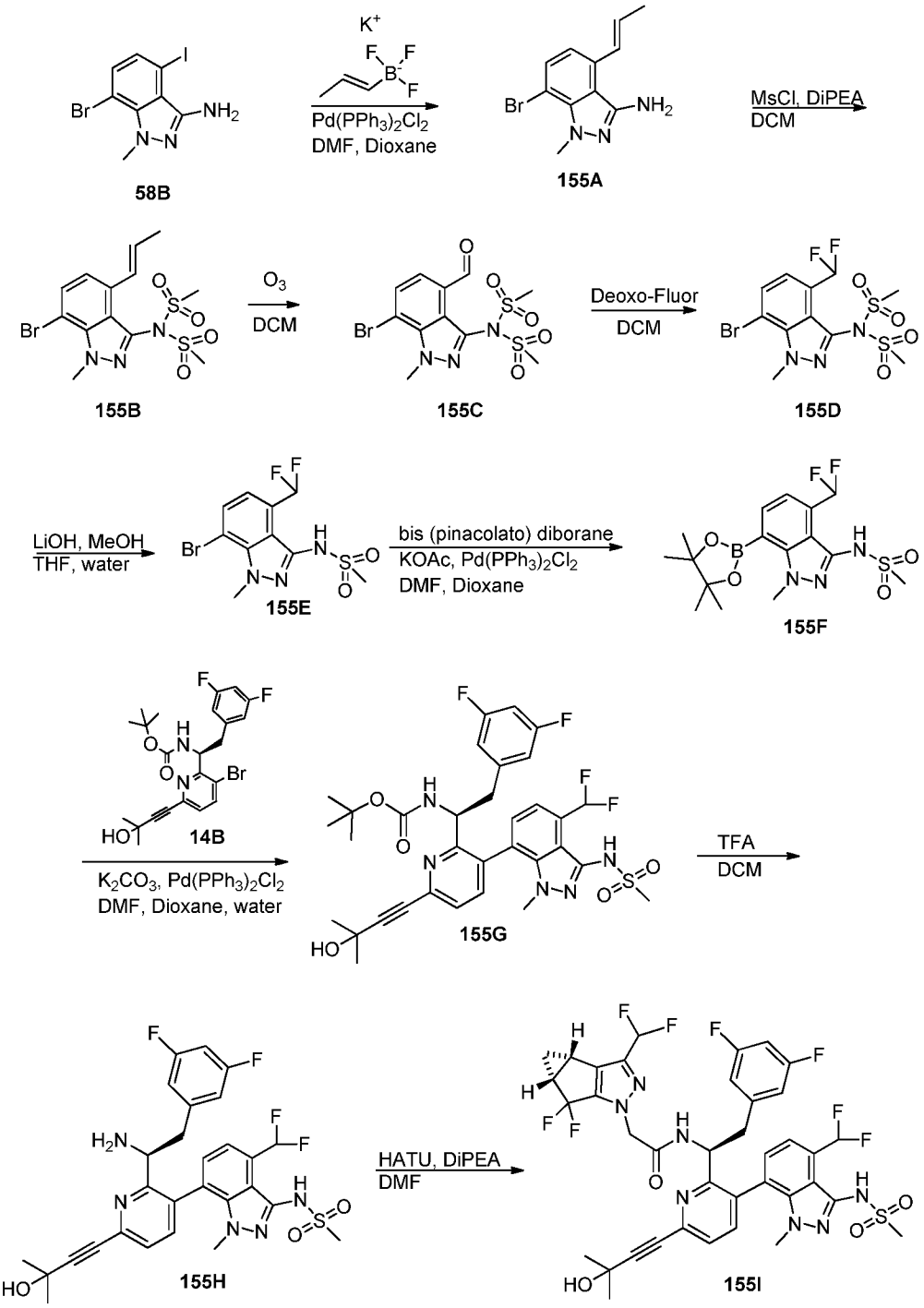


154

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 °C, 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**):

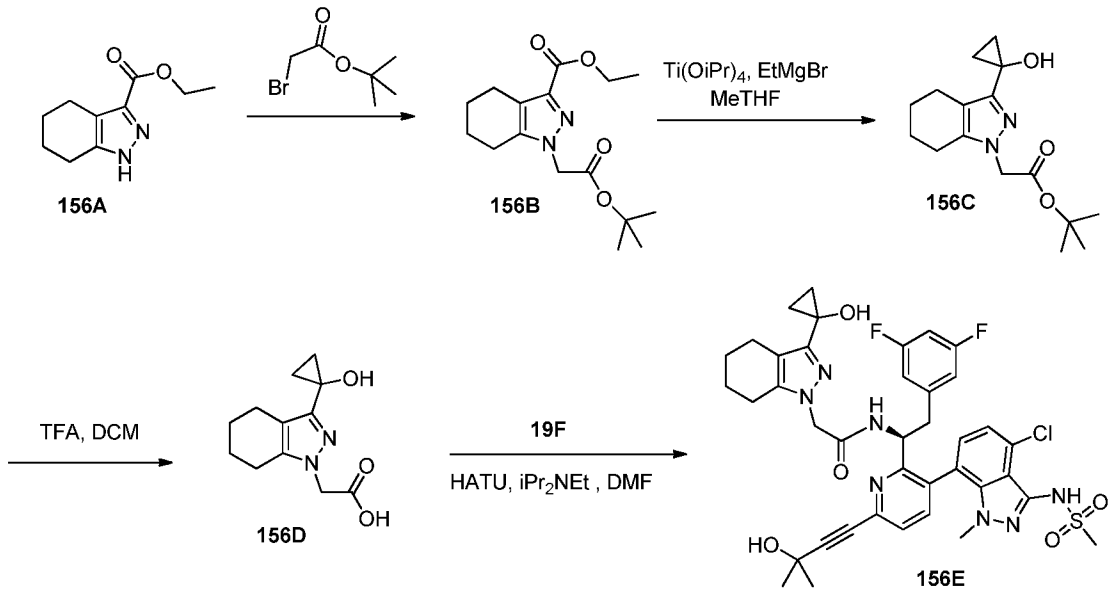
[0755] The title compound (**155H**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19F** of Example 19 utilizing **155G**. MS (m/z) 590.1 $[M+H]^+$.

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 $[M+H]^+$.

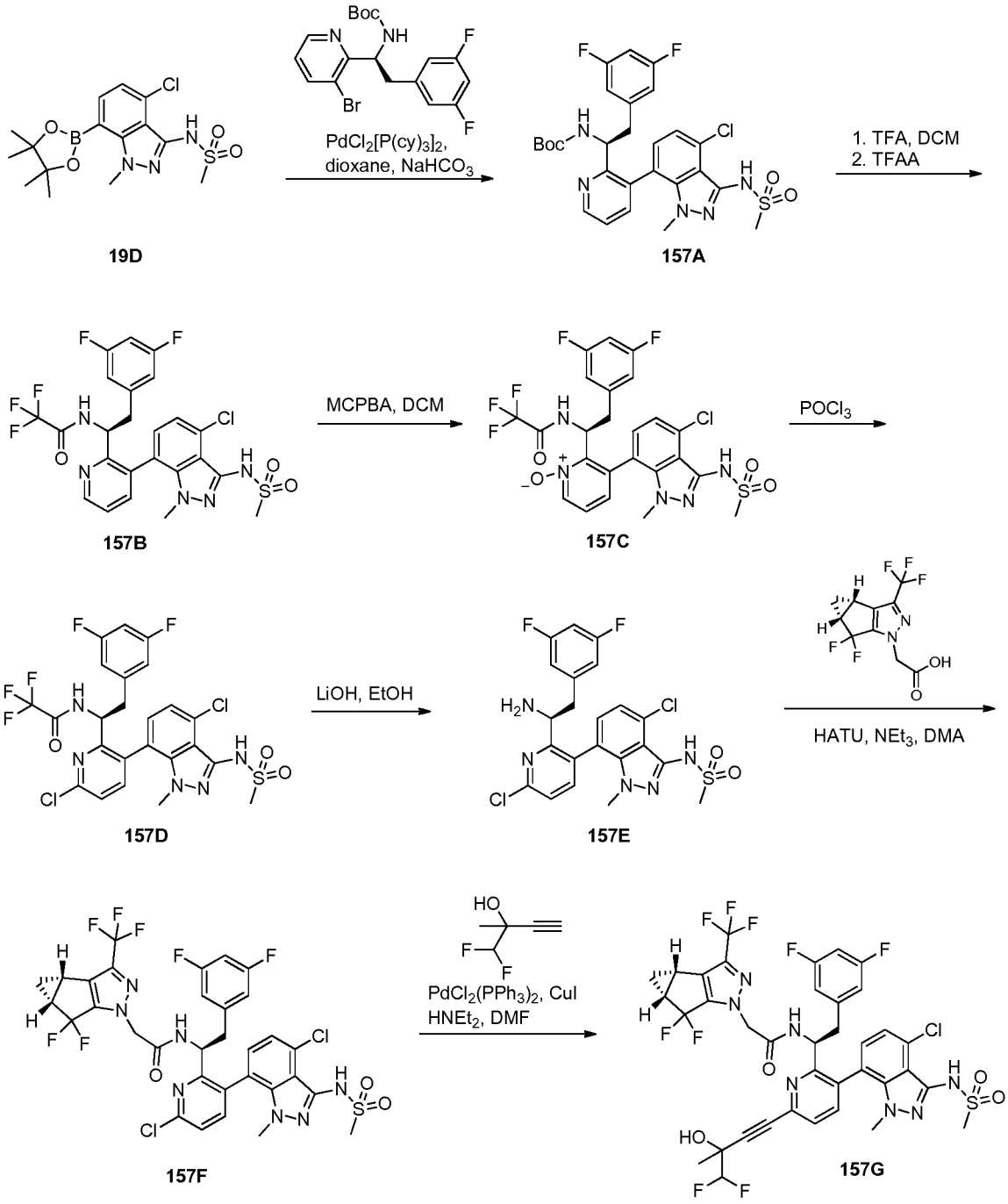
Synthesis of 2-(3-(1-hydroxycyclopropyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid (**156D**):

[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**):

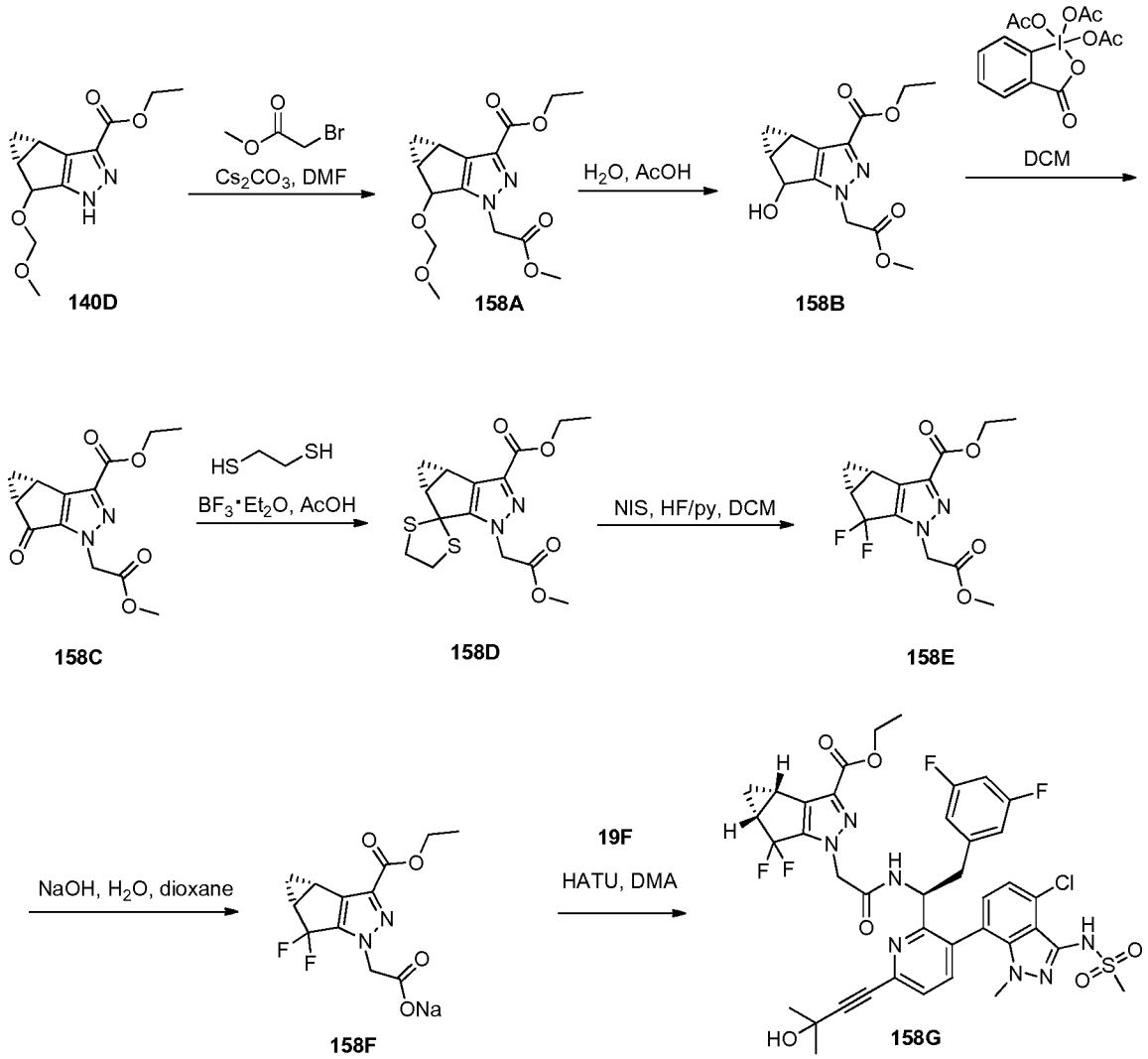
[0766] To a solution of crude (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-chloropyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**157E**, 400 mg, 0.76 mmol) in DMA (6 mL) was added NEt_3 (0.32 mL, 2.28 mmol), 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic 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 $[M+H]^+$.

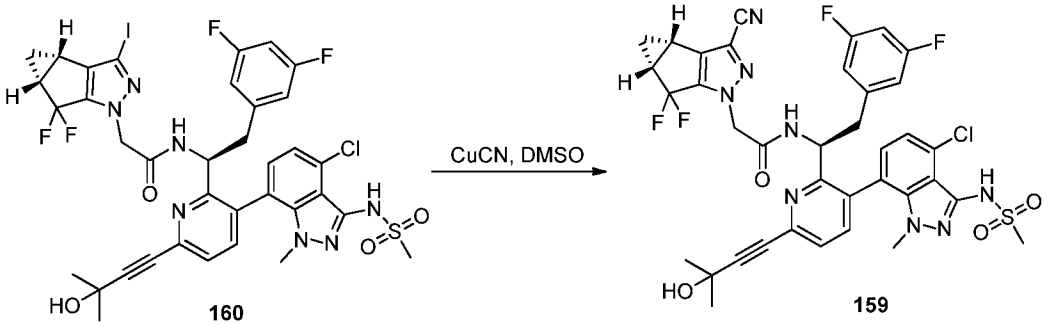
Synthesis of sodium 2-((3bS,4aR)-3-(ethoxycarbonyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**158F**):

[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.



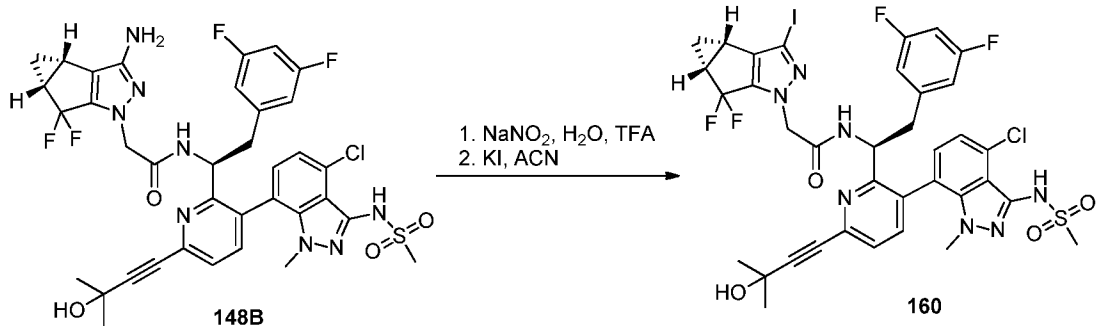
160 159

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.



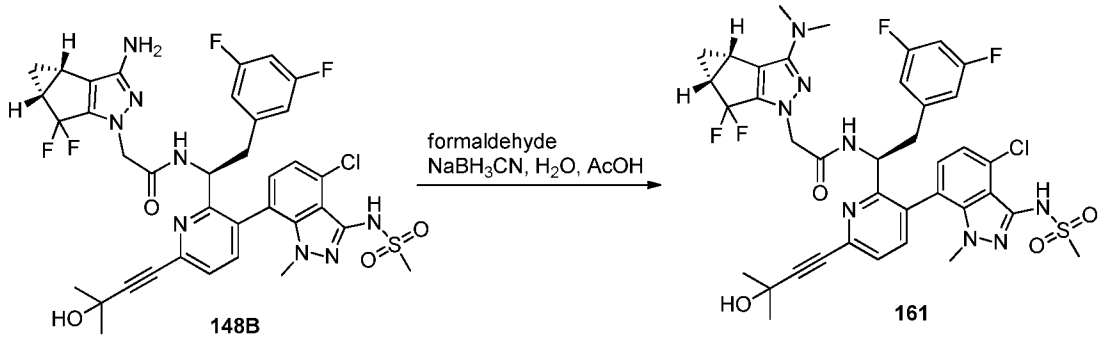
148B 160

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.

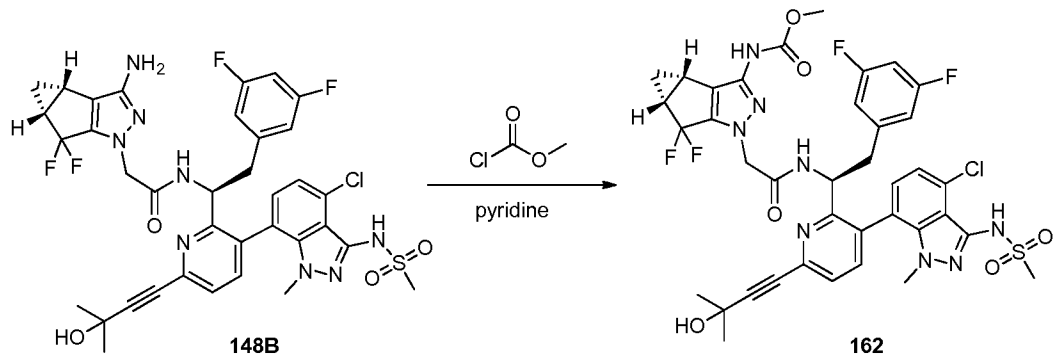


148B 161

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.



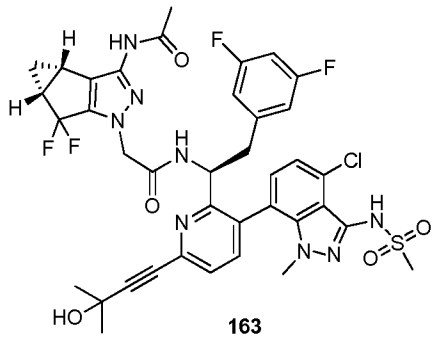
148B 162

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.

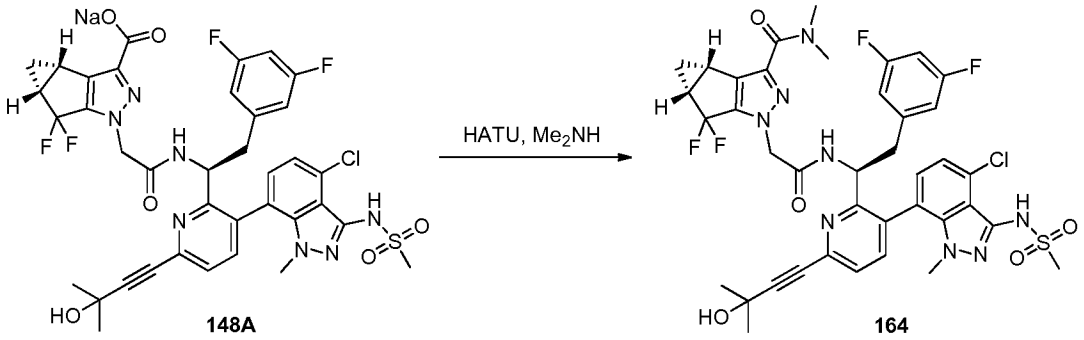


163

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.

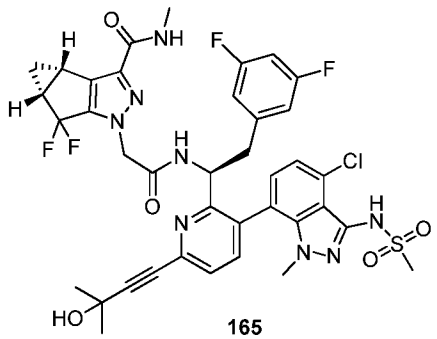


148A 164

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.

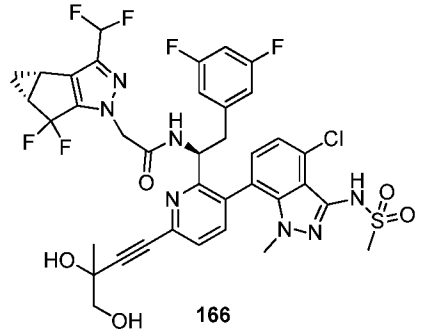


165

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_3od) 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.

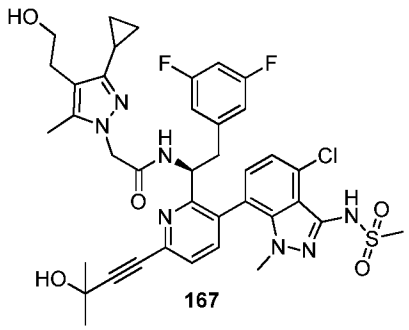


166

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_3od) 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.

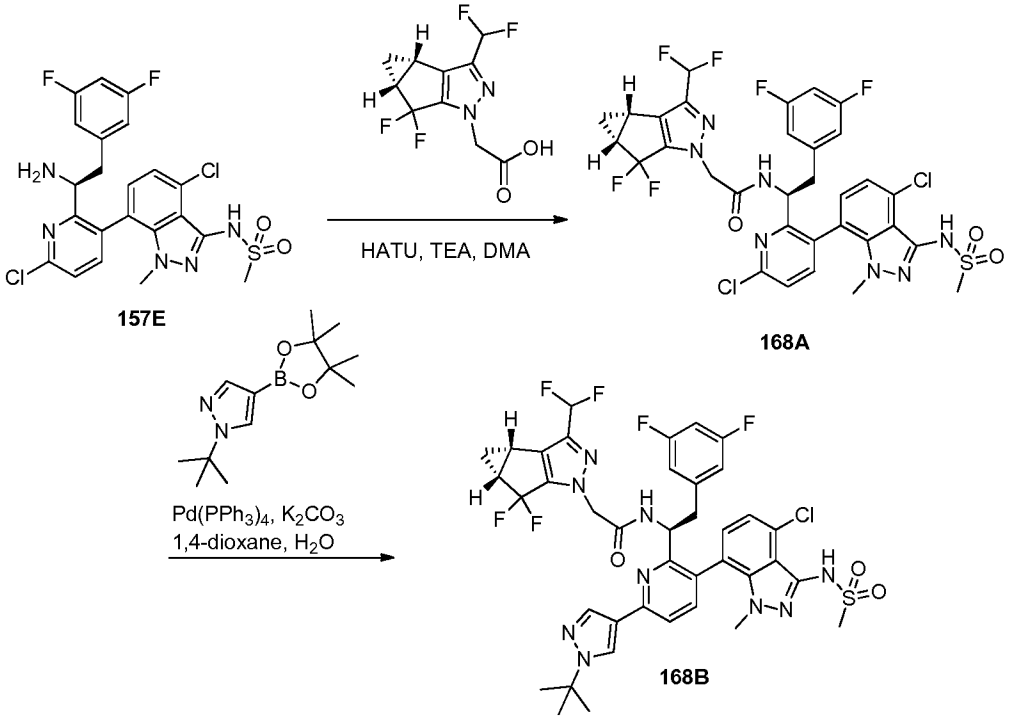


167

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.



157E

168A

168B

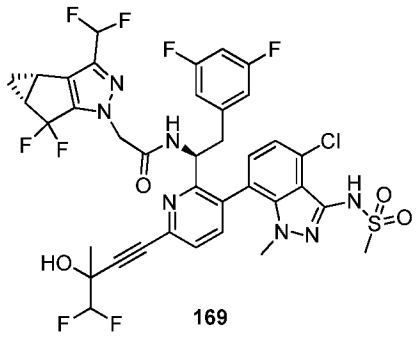
Synthesis of N-((S)-1-(6-chloro-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**168A**):

[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.



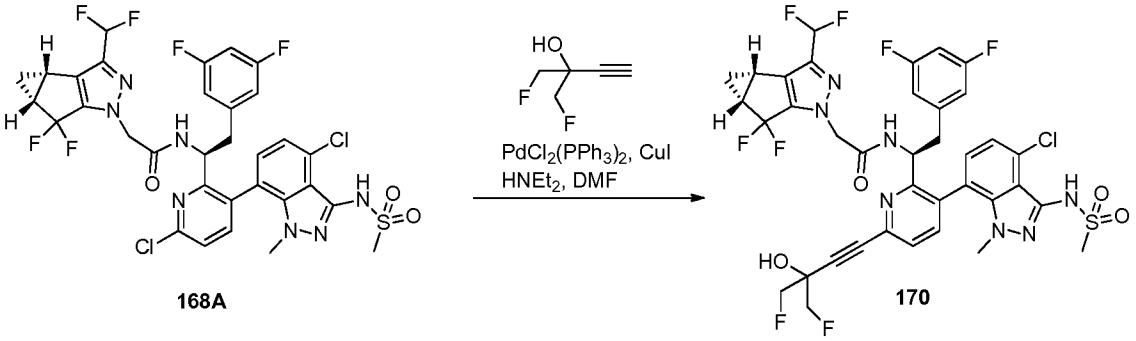
169

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.

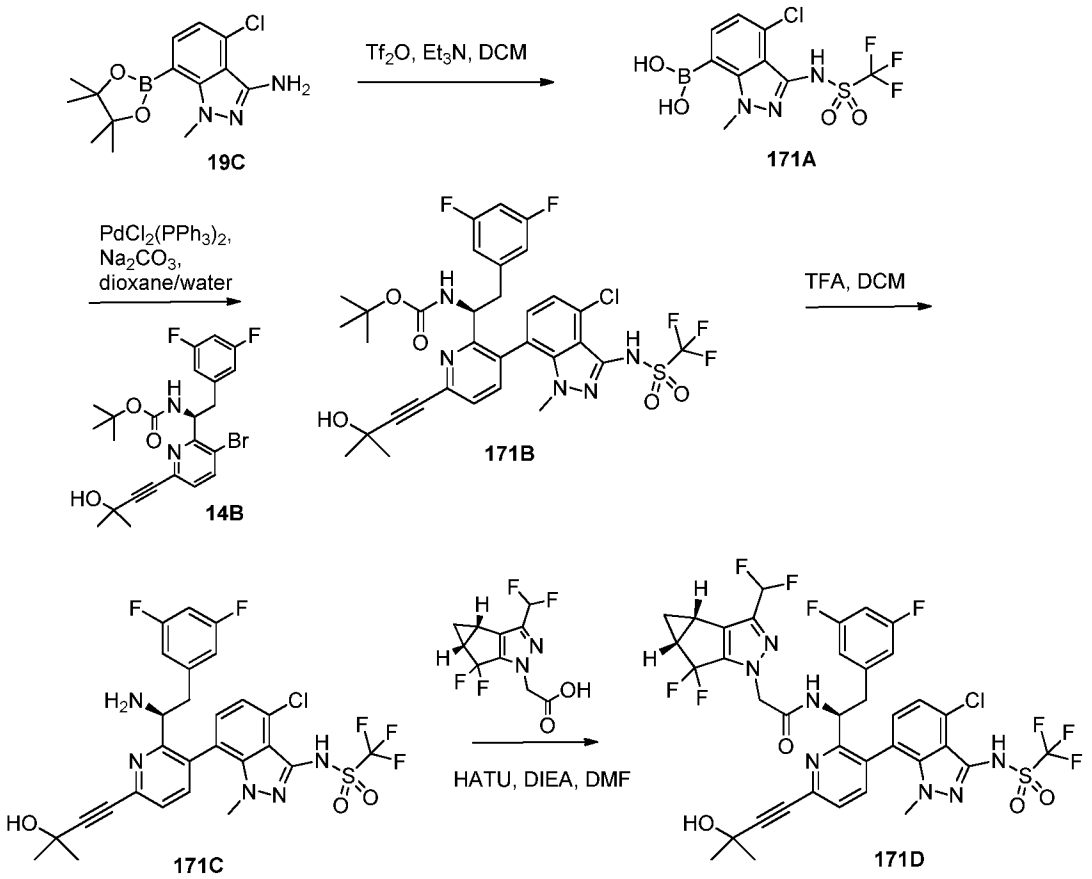


168A 170

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 $[M+H]^+$.

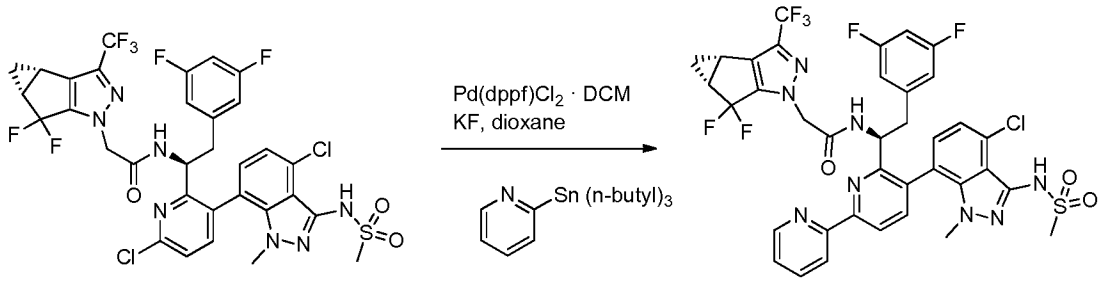
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)-1,1,1-trifluoromethanesulfonamide (**171C**):

[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.

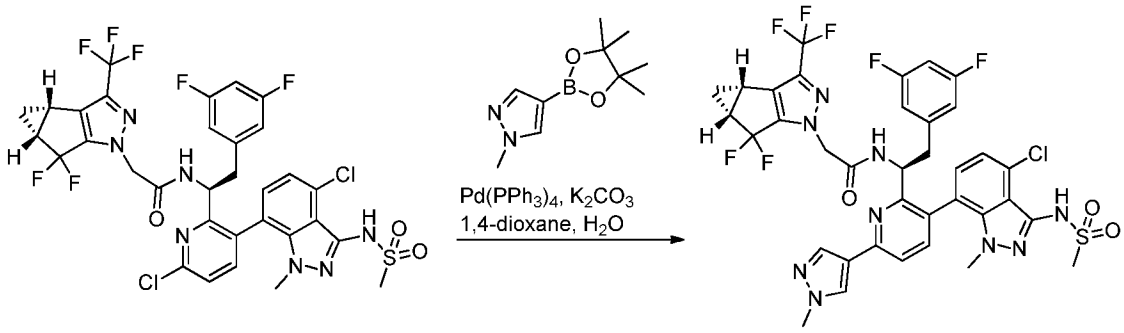


157F 172

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.



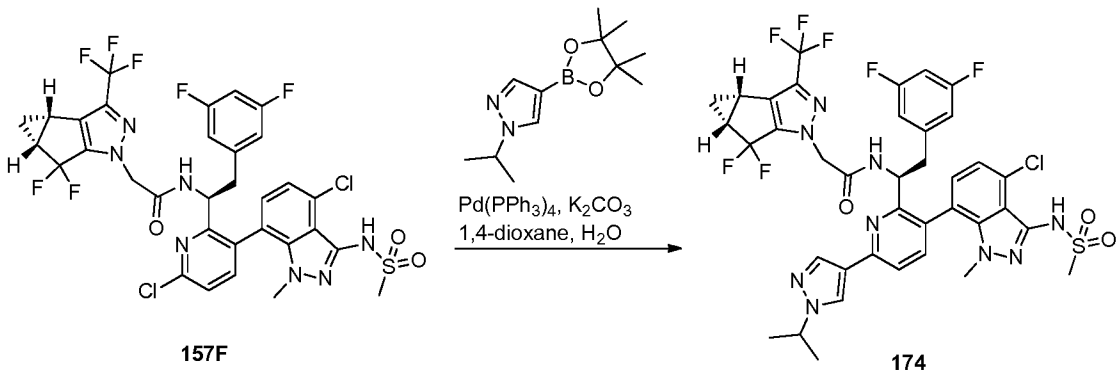
157F 173

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.

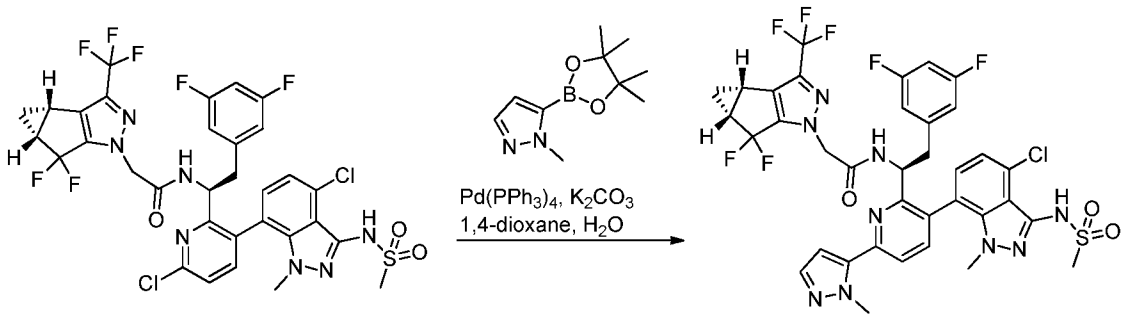


157F 174

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.

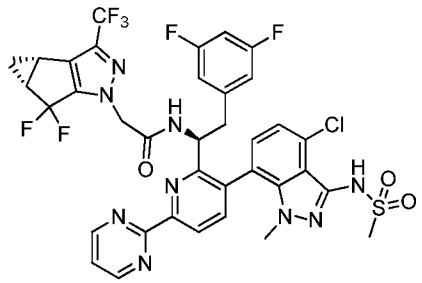


157F 175

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.



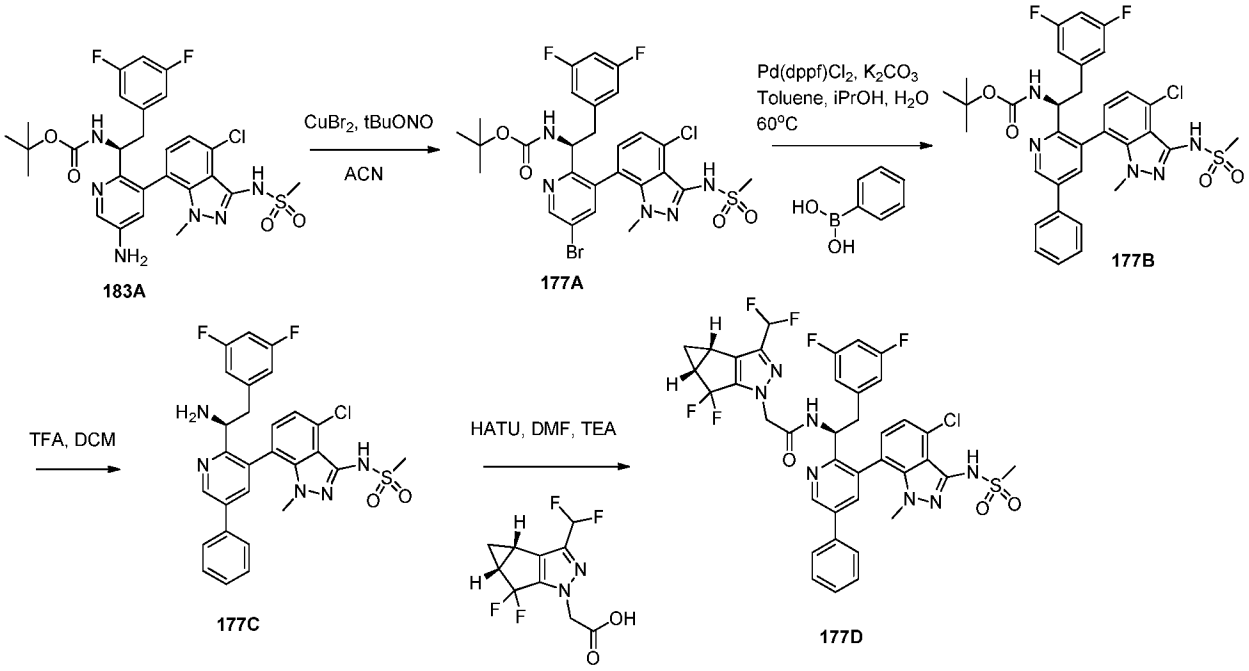
176

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 $[M+H]^+$.

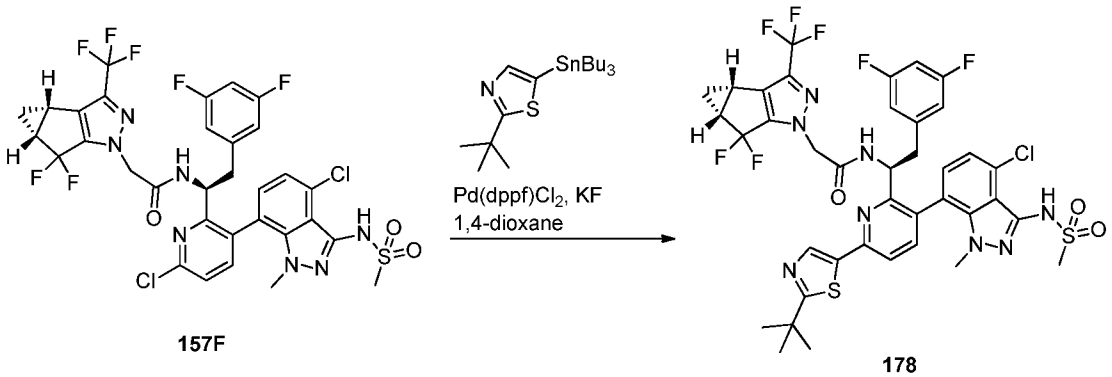
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-phenylpyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**177C**):

[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.

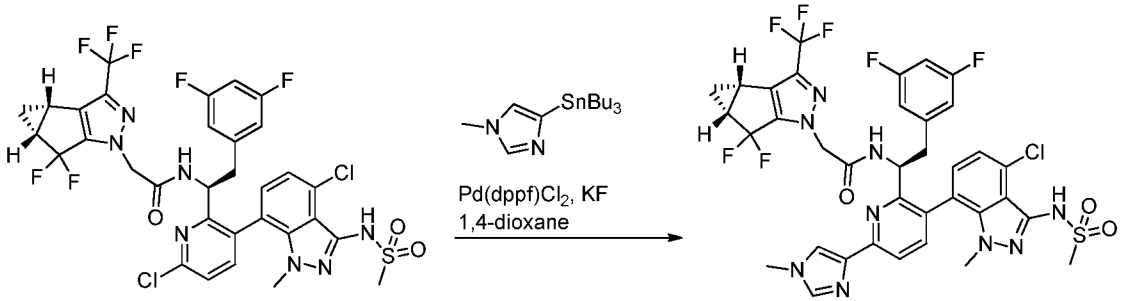


157F **178**

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.

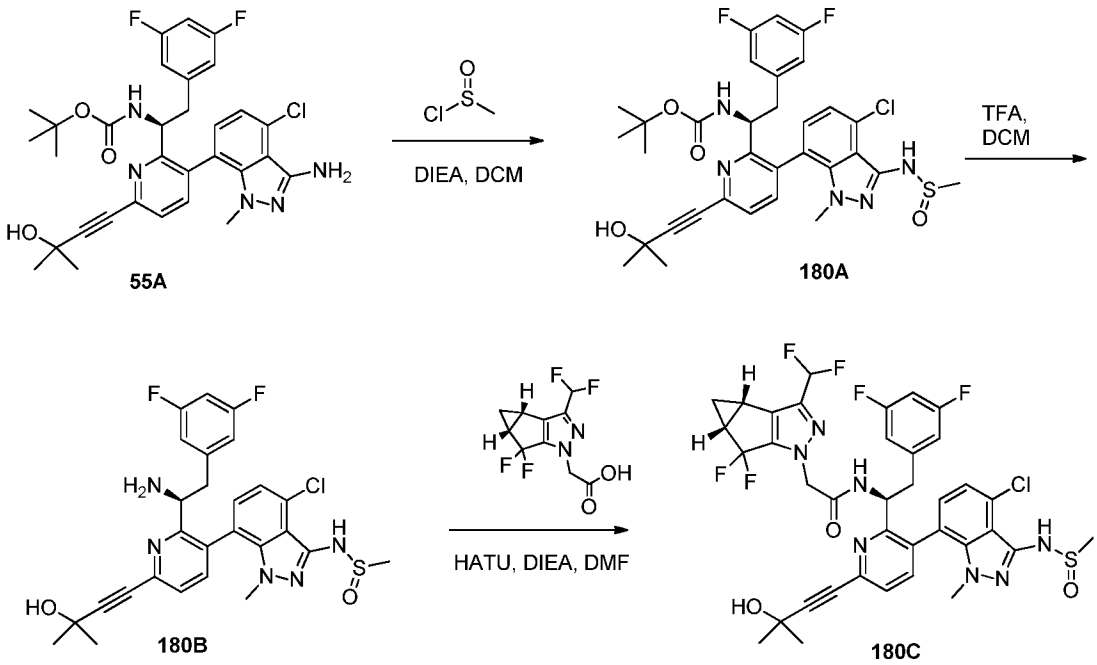


157F **179**

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**):

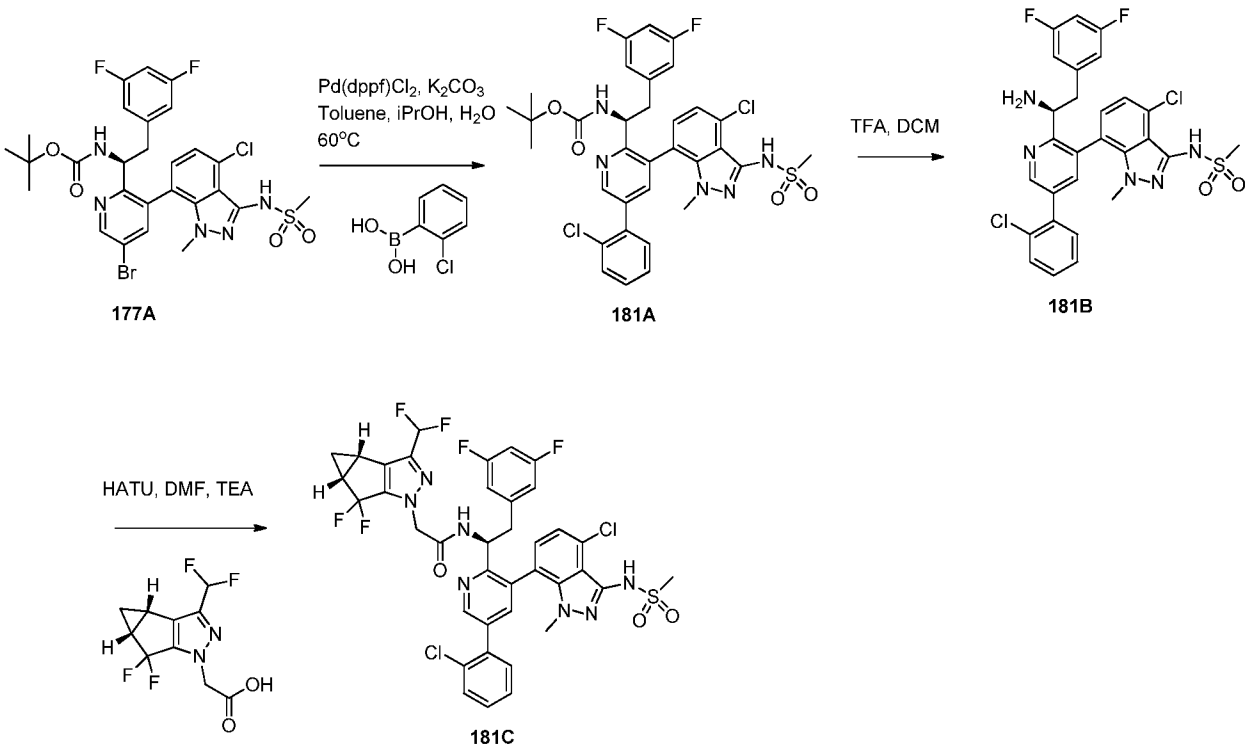
[0804] To a solution of tert-butyl ((1S)-1-(3-(4-chloro-1-methyl-3-(methylsulfinamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**180A**, 50 mg, 0.076 mmol) in DCM (1 mL) was added trifluoroacetic acid (1 mL). The reaction mixture was stirred 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 $[M+H]^+$.

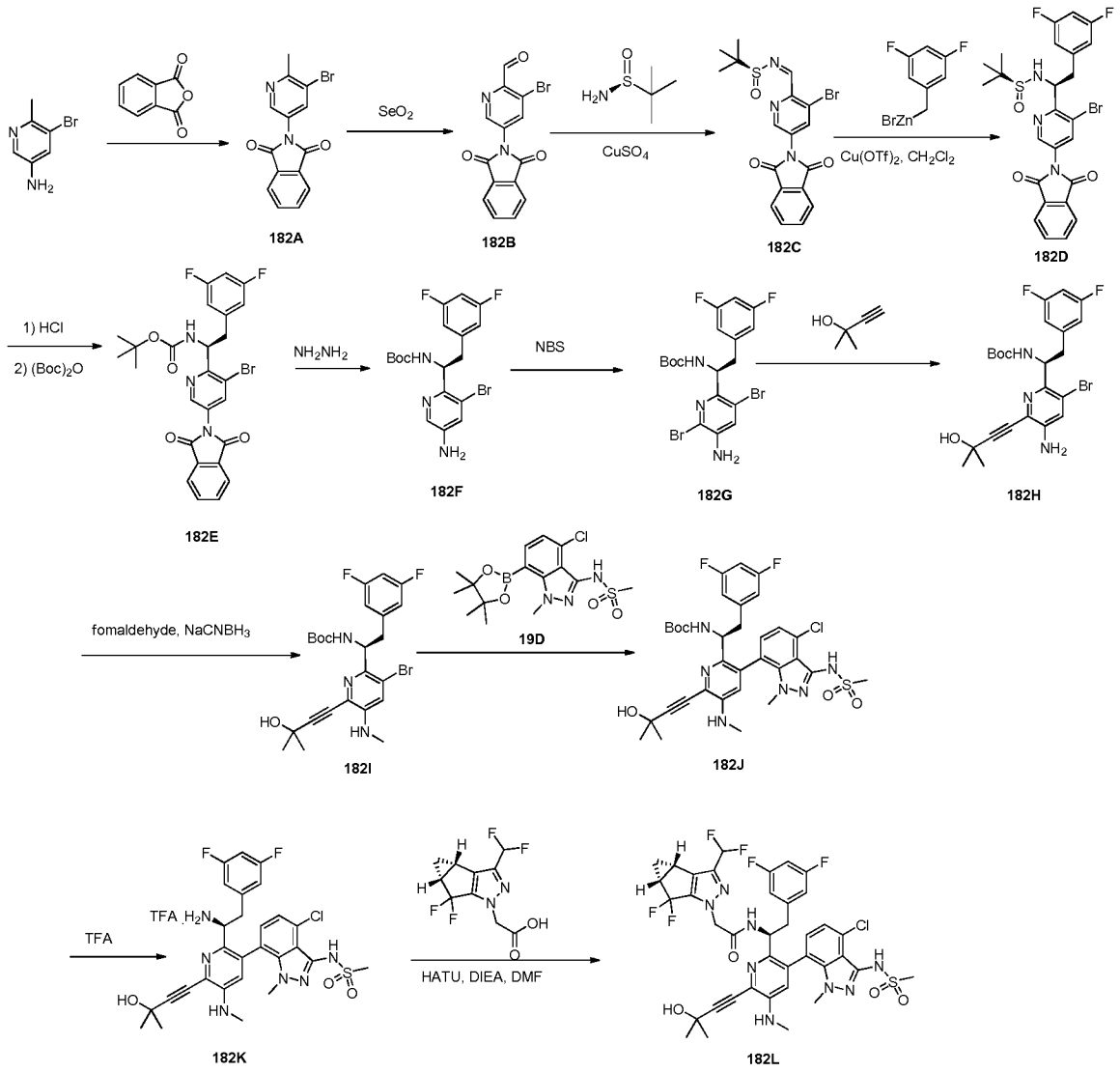
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(2-chlorophenyl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**181A**):

[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 $[M+H]^+$.

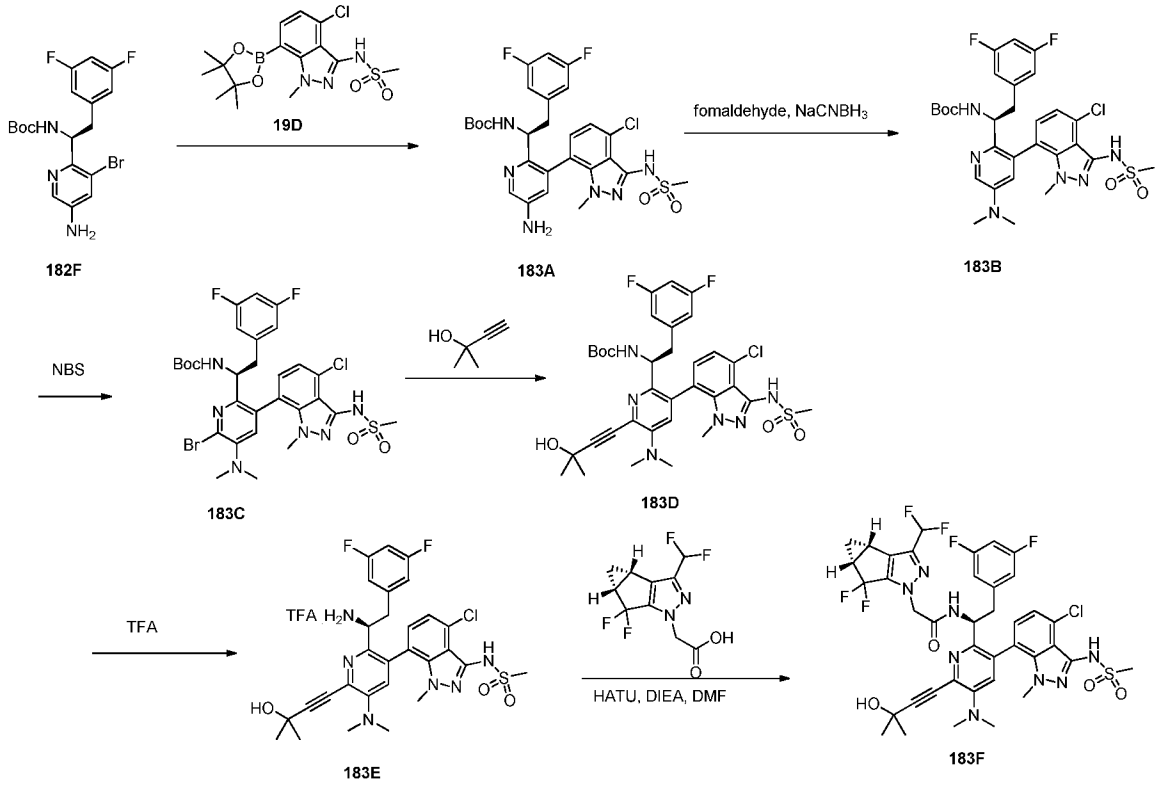
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-(methylamino)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**182K**):

[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 $[M+H]^+$.

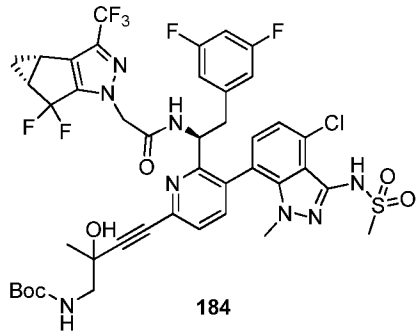
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(dimethylamino)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**183E**):

[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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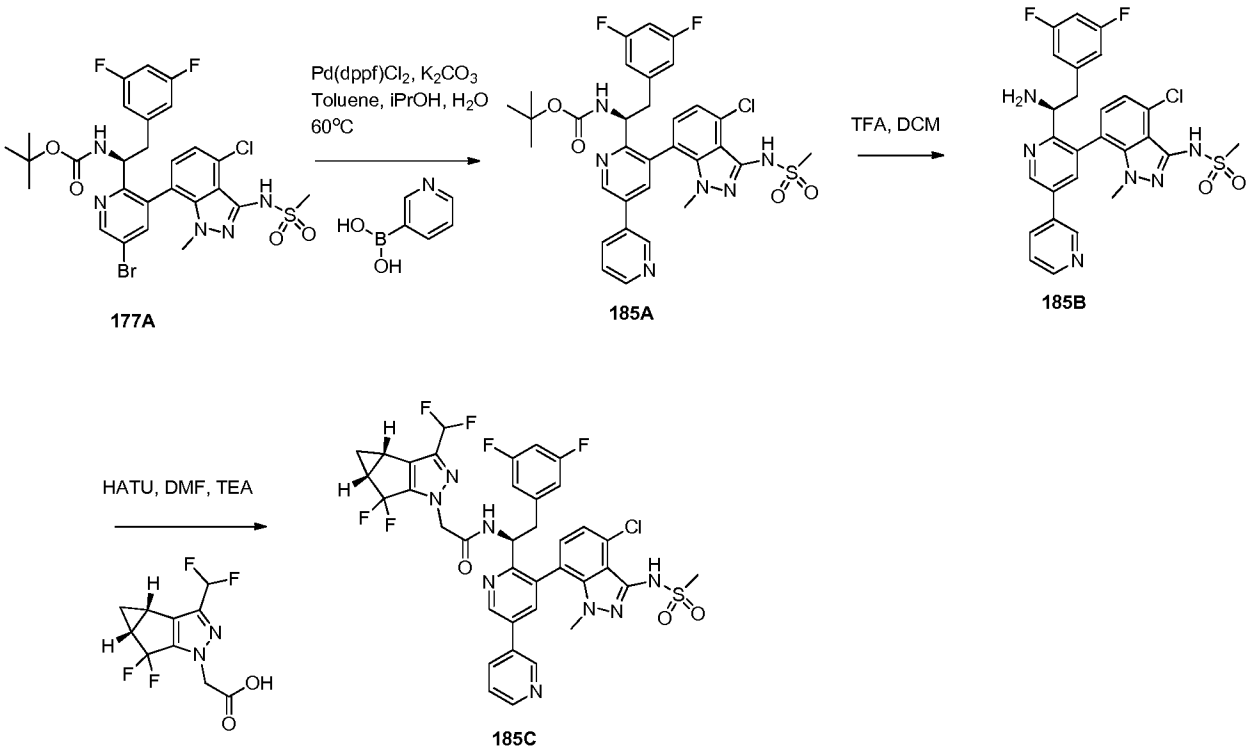
Synthesis of tert-butyl (4-(5-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-2-yl)-2-hydroxy-2-methylbut-3-yn-1-yl)carbamate (**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 $[M+H]^+$.

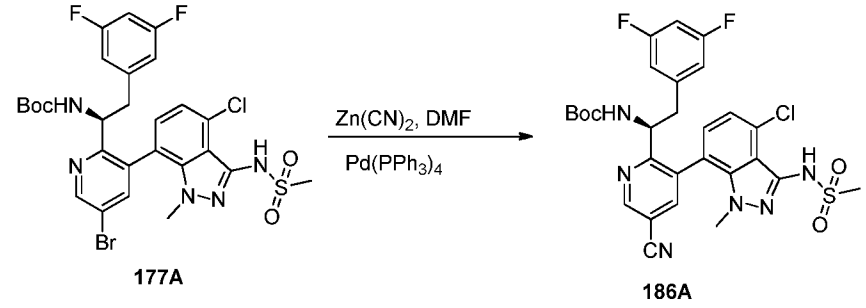
Synthesis of (S)-N-(7-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-[3,3'-bipyridin]-5-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**185B**):

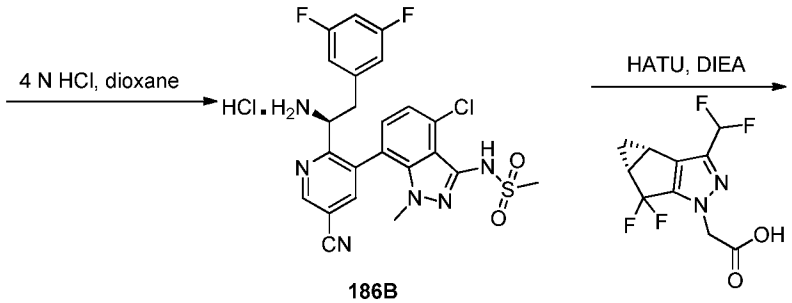
[0829] The title compound as mixture of atropisomers (**185B**) was prepared according to the method presented for the synthesis of compound **177C** of Example 177 utilizing compound **185A**. MS (m/z) 569 $[M+H]^+$.

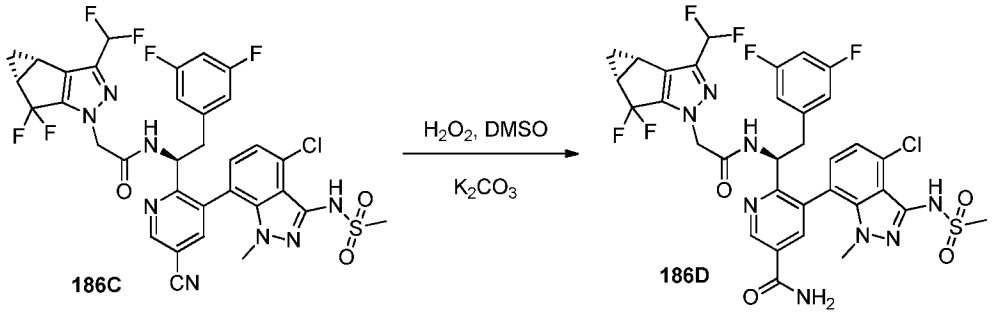
Synthesis of N-((S)-1-(5-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-[3,3'-bipyridin]-6-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**185C**):

[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 $[M+H]^+$.

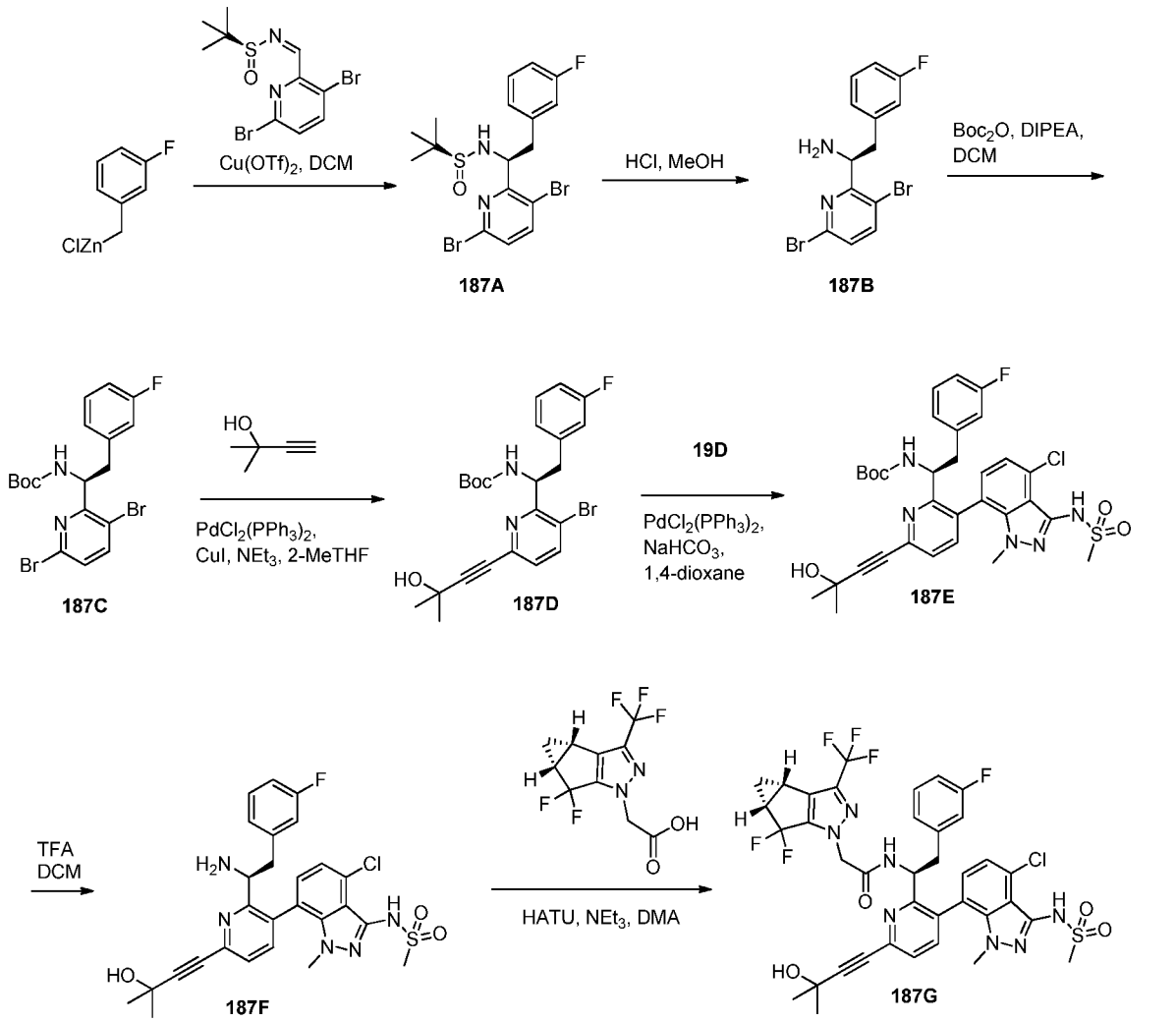
Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-5-cyanopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**186C**):

[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 $[M+H]^+$.

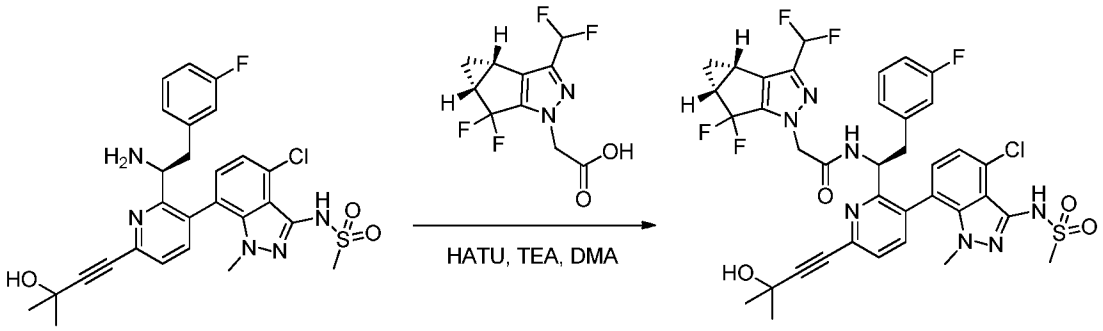
Synthesis of (S)-N-(7-(2-(1-amino-2-(3-fluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**187F**):

[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.



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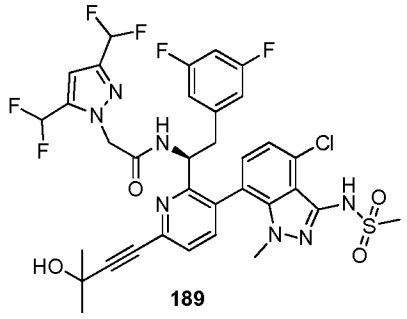
Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3-fluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**188**):

[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.



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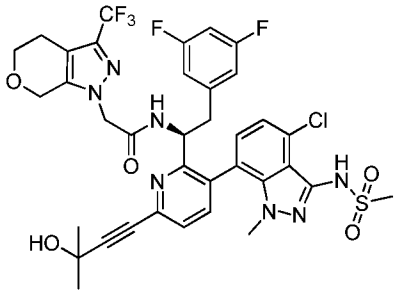
Synthesis of (S)-2-(3,5-bis(difluoromethyl)-1H-pyrazol-1-yl)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)acetamide (**189**):

[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 $[M+H]^+$.

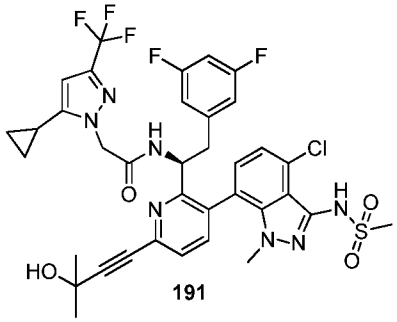
Example 190.



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.



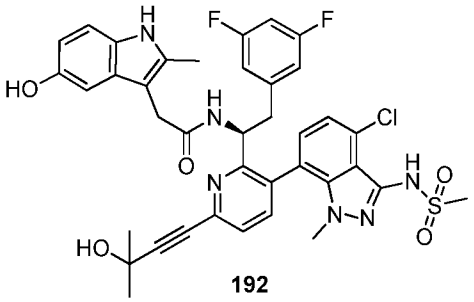
191

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.

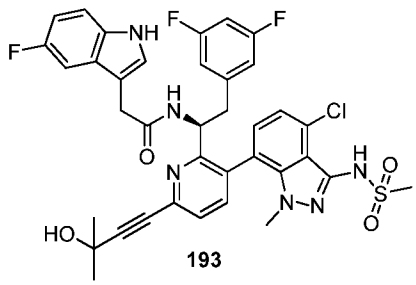


192

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.



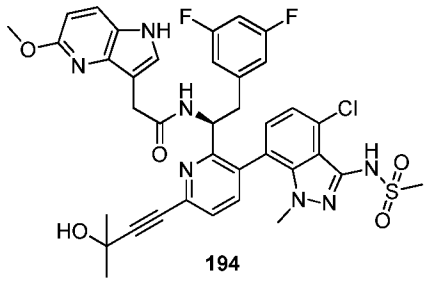
193

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.

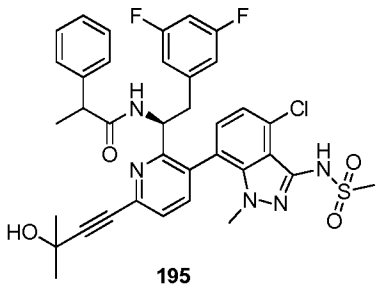


194

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.



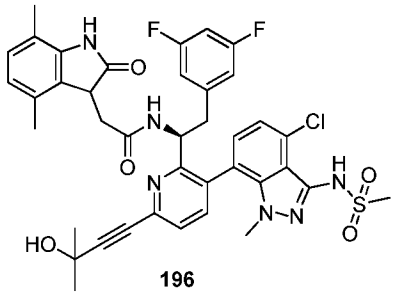
195

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.

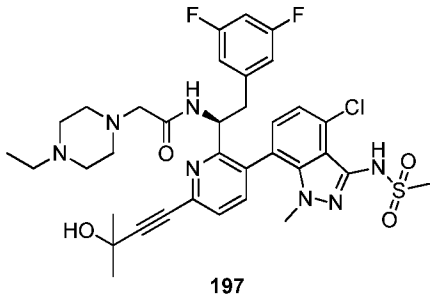


196

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.



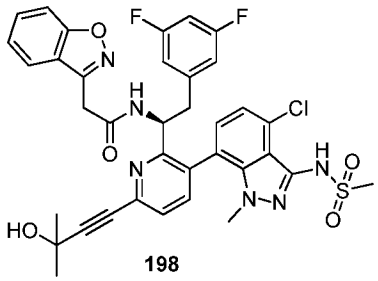
197

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.

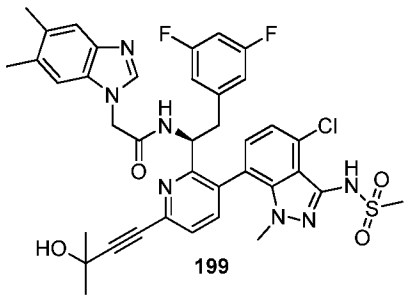


198

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.



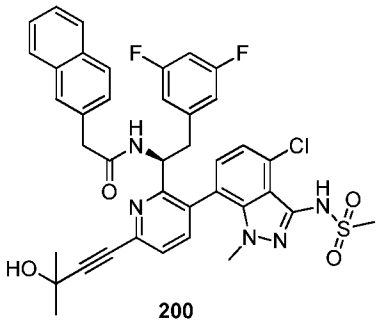
199

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.



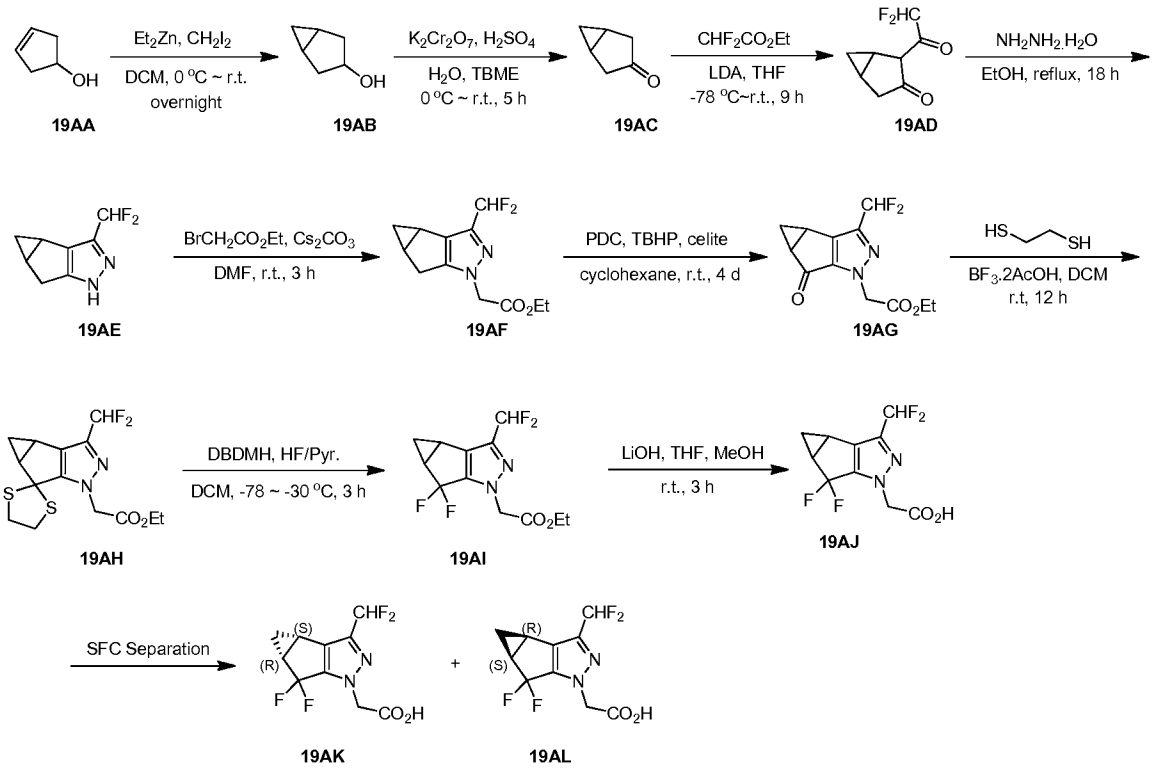
200

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

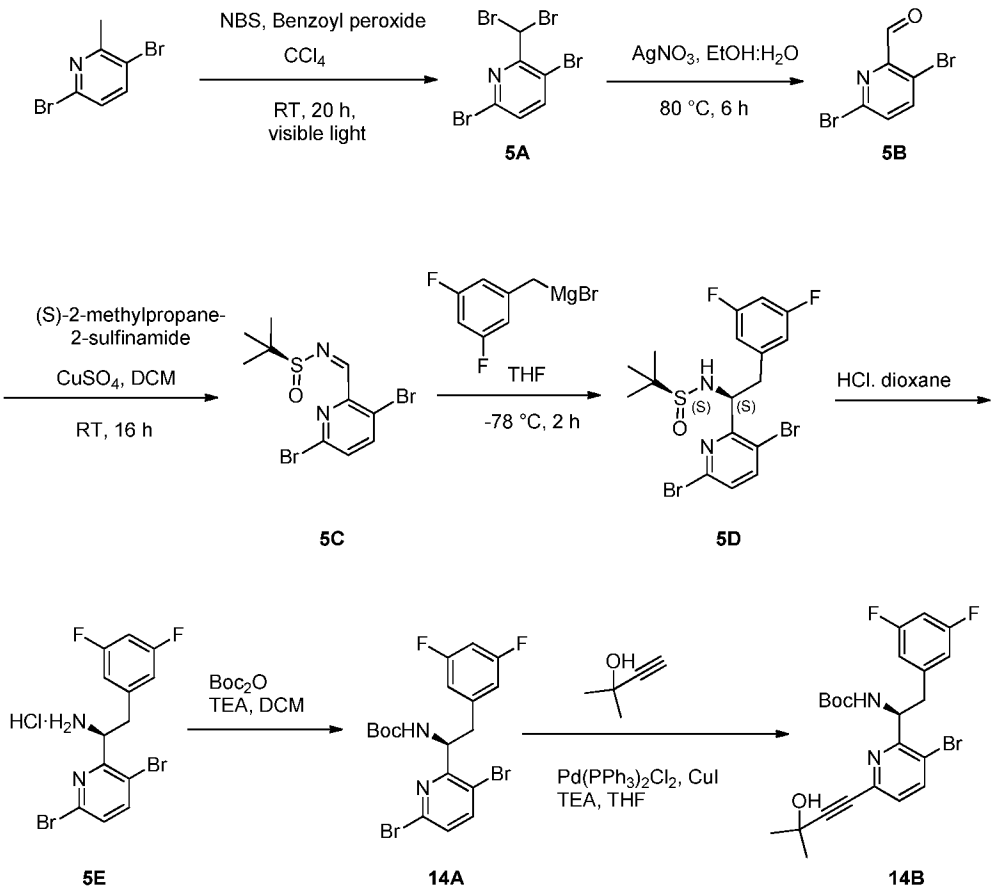
DCM (80 mL) was added drop-wise over a period of 15 min at -78 °C. The resulting mixture was stirred for 30 min at this temperature, then slowly warm to -30 °C and stirred for 1.5 h. The reaction mixture was slowly poured into aq. $NaHCO_3$ (500 mL) and extracted with EA (500 mLx3). The combined organic 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 $[M+H]^+$

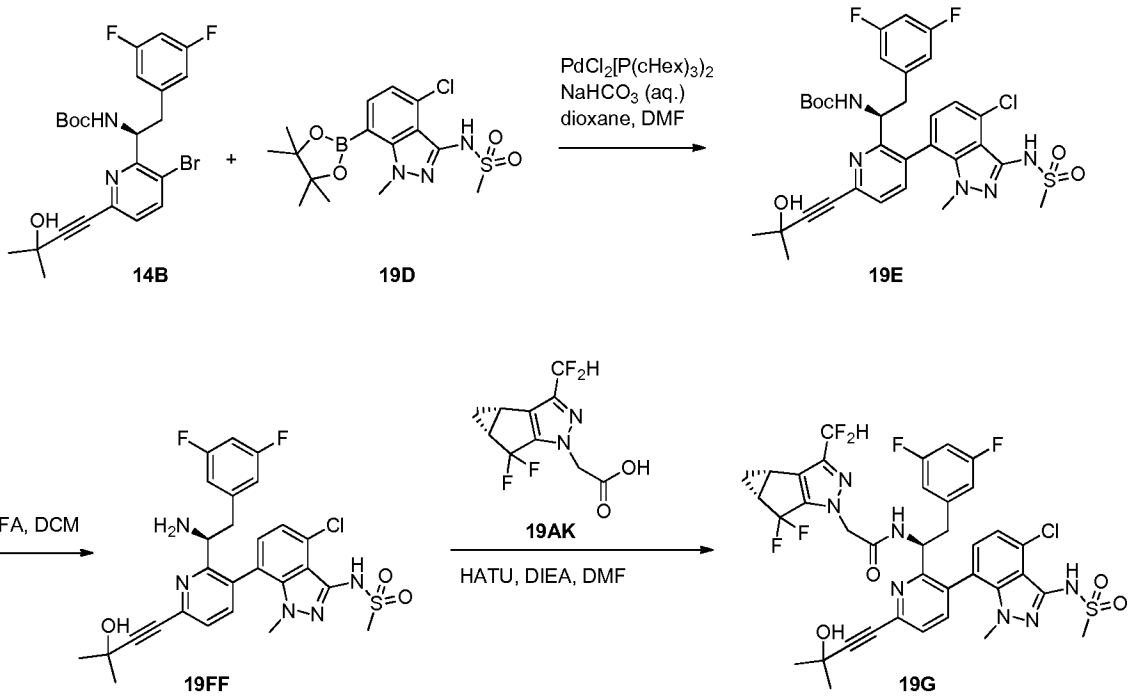
Synthesis of (S)-tert-butyl 1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (**14A**):

[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

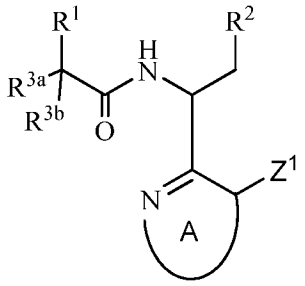
of the element and/or the effect a given amount of variation will have on the performance of the claimed subject matter, as well as other considerations known to those of skill in the art. As used herein, the use of differing amounts of significant digits for different numerical values is not meant to 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;

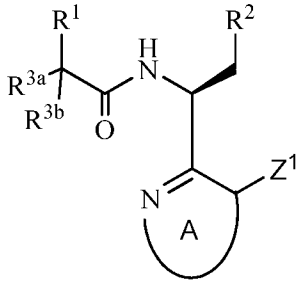
each Z^5 is independently selected from $(C_1$-$C_6)$alkyl, halogen, -CN and $-OR^{n7}$,

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.

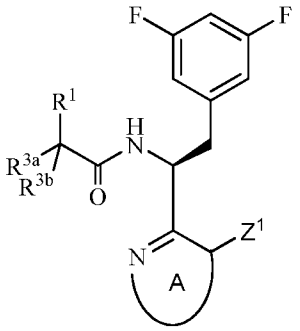
Embodiment I-5. The compound of any one of Embodiments I-1 to I-3 wherein R^2 is phenyl optionally substituted with one or more Z^5 groups.

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.

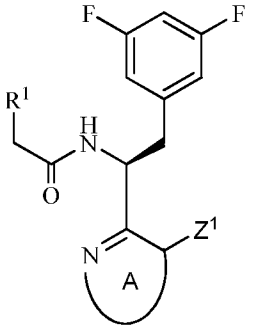
Embodiment I-9. The compound of Embodiment I-1 which is a compound of formula Ig:



Ig

or a pharmaceutically acceptable salt thereof.

Embodiment I-10. The compound of Embodiment I-1 which is a compound of formula Ie:



Ie

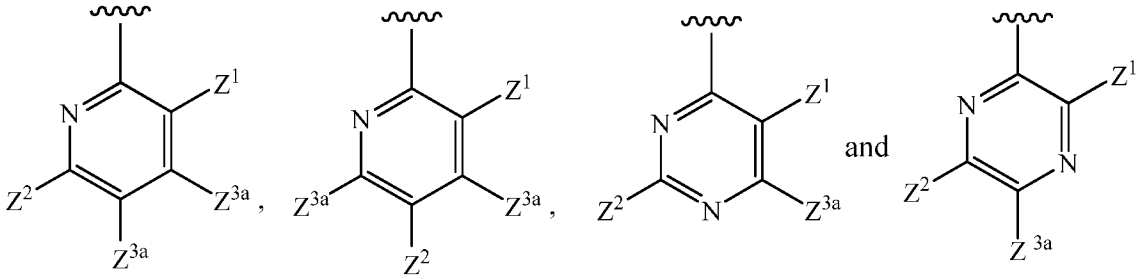
or a pharmaceutically acceptable salt thereof.

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.

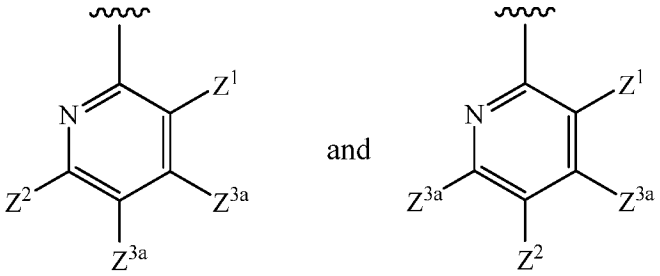
Embodiment I-13. The compound of any one of Embodiments I-1 to I-12 wherein A is substituted with one Z^1 group at the position shown and one Z^2 group.

Embodiment I-14. The compound of any one of Embodiments I-1 to I-10 wherein A-Z^1 is selected from:



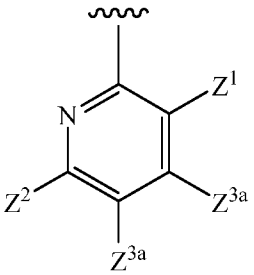
wherein each Z^{3a} is independently selected from H and Z^3.

Embodiment I-15. The compound of any one of Embodiments I-1 to I-10 wherein A-Z^1 is selected from:



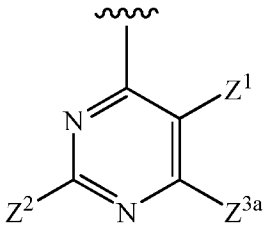
wherein each Z^{3a} is independently selected from H and Z^3.

Embodiment I-16. The compound of any one of Embodiments I-1 to I-10 wherein A-Z^1 is:



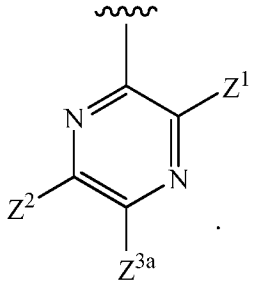
wherein each Z^{3a} is independently selected from H and Z^3.

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.

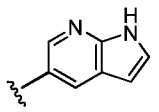
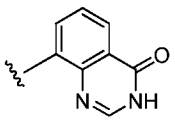
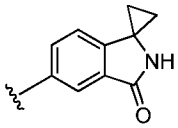
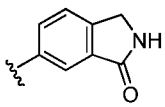
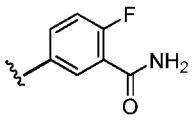
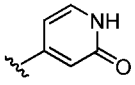
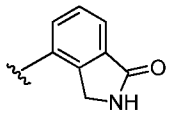
Embodiment I-26. The compound of any one of Embodiments I-1 to I-19 wherein Z^1 is selected from phenyl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1-oxoisoindolin-5-yl, 1-oxoisoindolin-4-yl, 4-oxo-3,4-dihydroquinazolin-8-yl, 3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl, 1H-2-oxo-pyridin-4-yl and 2,4-dioxo-1,2,3,4-tetrahydorquinazolin-8-yl, 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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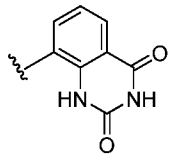


Embodiment I-31. The compound of any one of Embodiments I-1 to I-30 wherein Z^2 is selected from $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle and $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl 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.

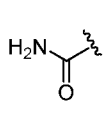
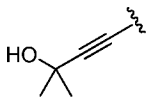
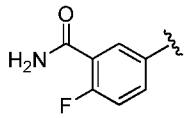
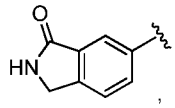
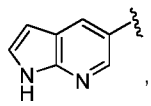
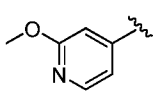
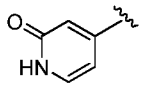
Embodiment I-36. The compound of any one of Embodiments I-1 to I-35 wherein Z^2 is optionally substituted with one or more Z^{2c} groups.

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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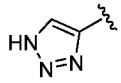
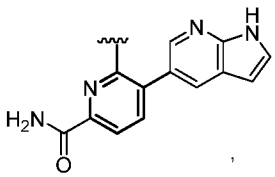
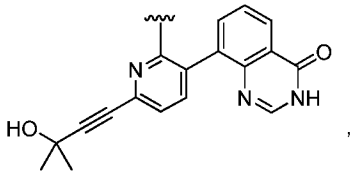
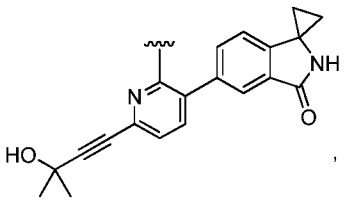
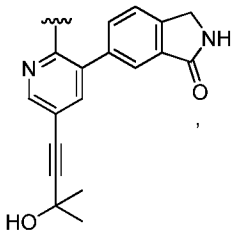
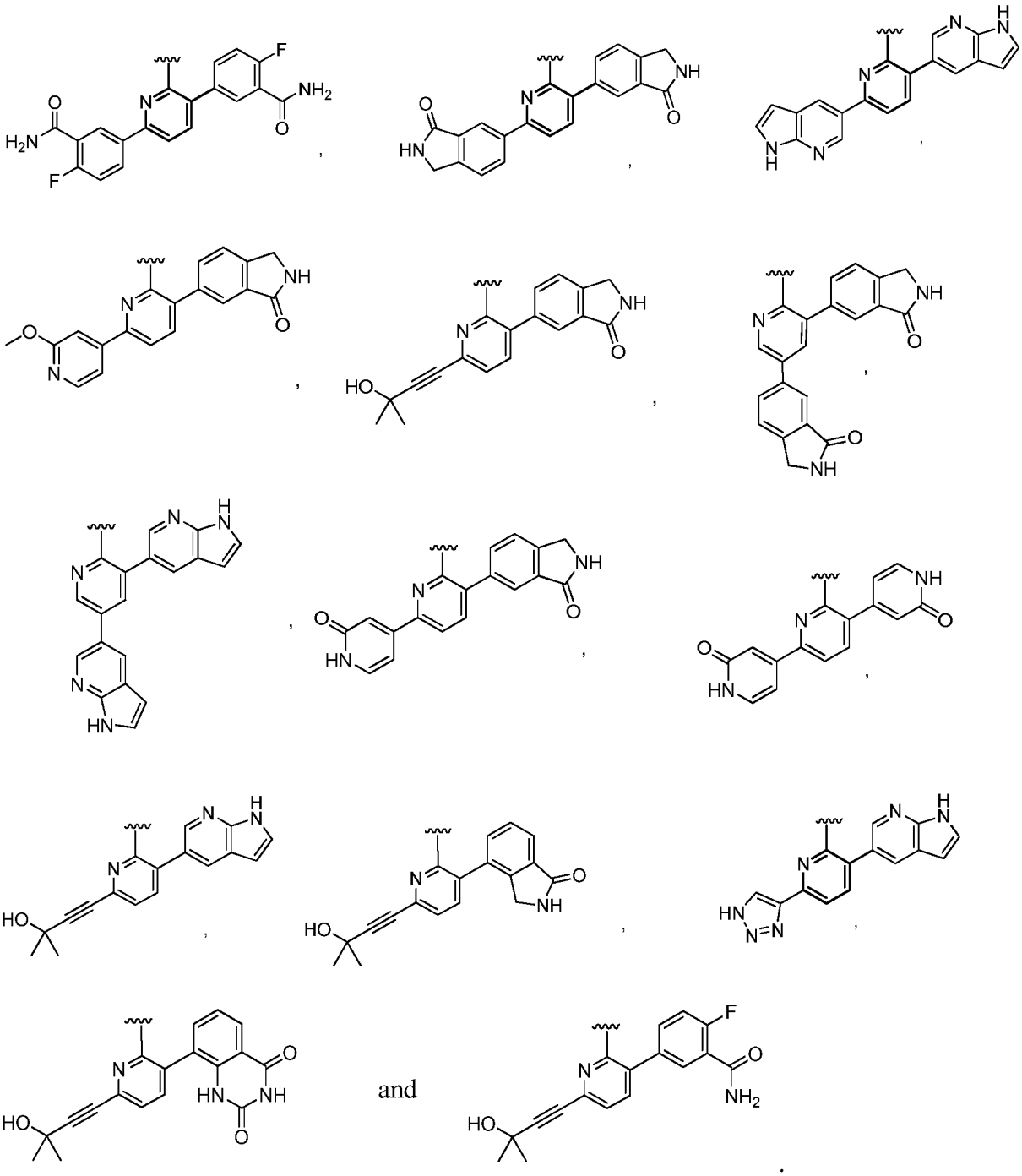


Embodiment I-41. The compound of any one of Embodiments I-1 to I-10 wherein A-Z^1 is selected from:



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.

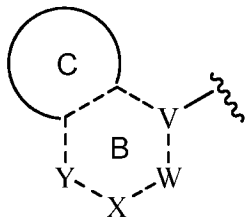
Embodiment I-43. The compound of any one of Embodiments I-1 to I-41 wherein R^1 is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein any 8-12

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;

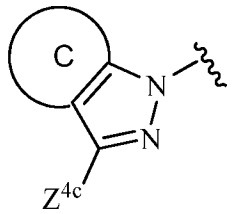
X is CZ^{4c}, NZ^{4c} or N;

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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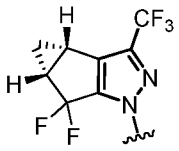
Embodiment I-53. The compound of any one of Embodiments I-1 to I-41 wherein R^1 is selected from:



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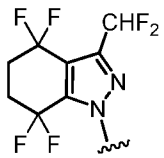

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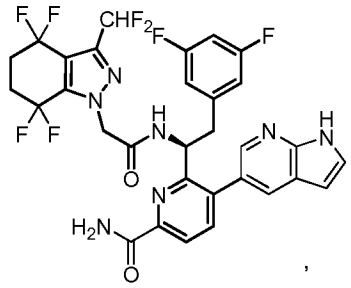
Embodiment I-54. The compound of Embodiment I-1 selected from:



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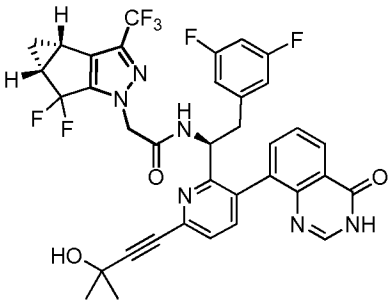

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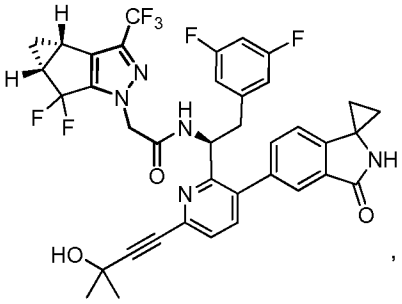

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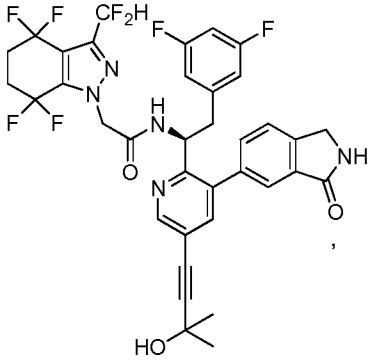

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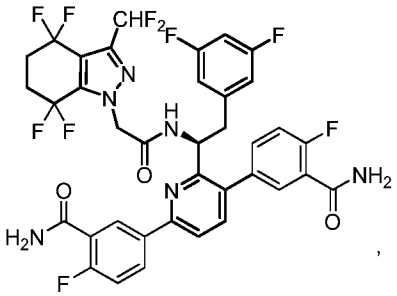

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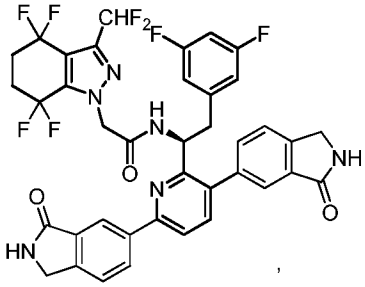

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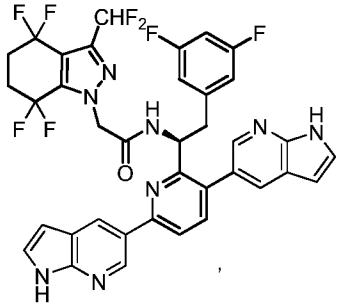

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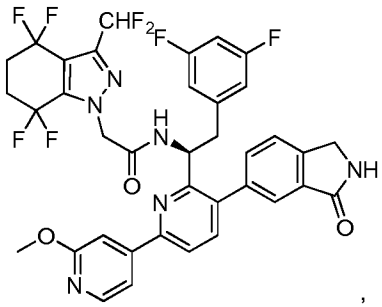
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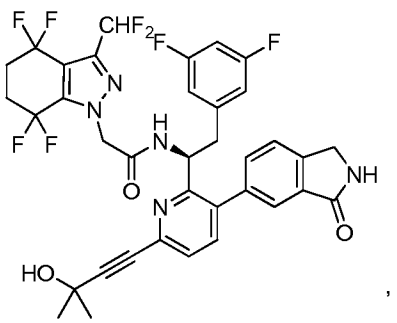
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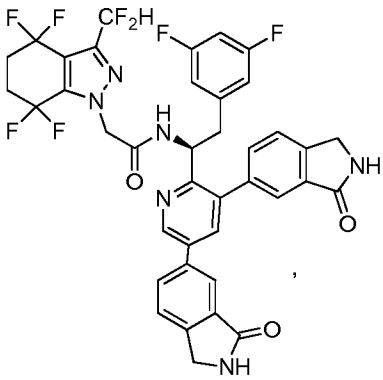
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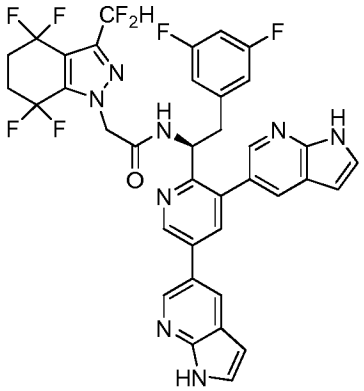
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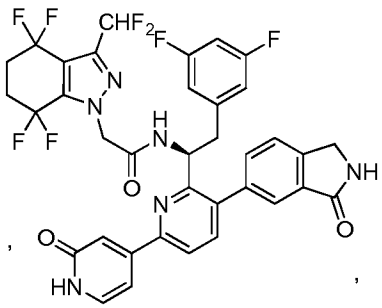
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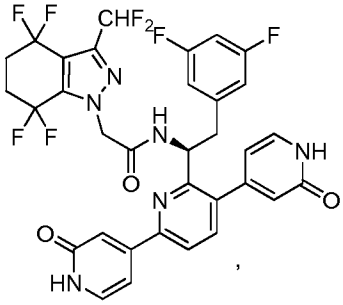
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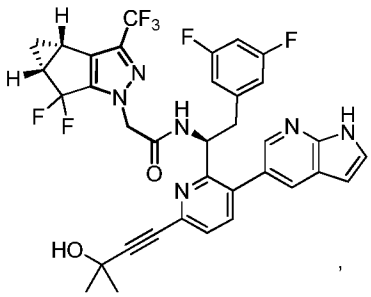
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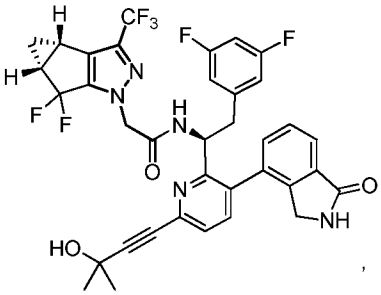
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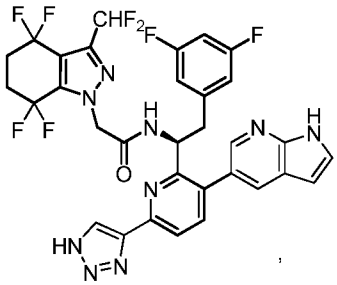
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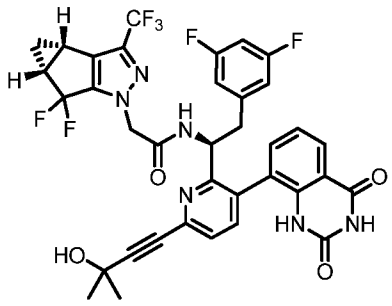
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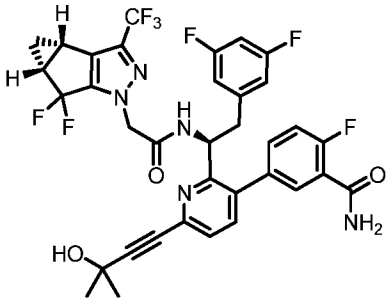


and pharmaceutically acceptable salts thereof.

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.

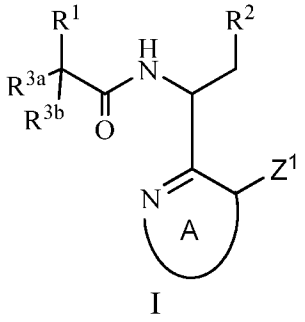
Embodiment I-60. A compound of formula I as described in any one of Embodiments I-1 to I-54 or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of a *Retroviridae* virus infection or an HIV virus infection.

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;

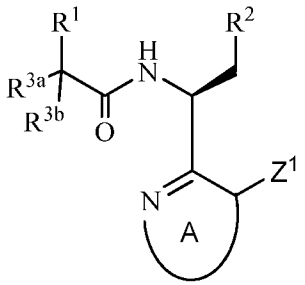
R^{q6} and R^{r6} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

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.

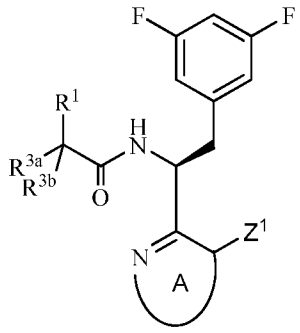
Embodiment II-5. The compound of any one of Embodiments II-1 to II-3 wherein R^2 is phenyl optionally substituted with one or more Z^5 groups.

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.

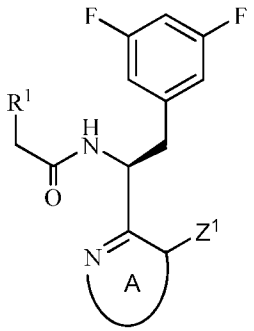
Embodiment II-9. The compound of Embodiment II-1 which is a compound of formula Ig:



Ig

or a pharmaceutically acceptable salt thereof.

Embodiment II-10. The compound of Embodiment II-1 which is a compound of formula Ie:



Ie

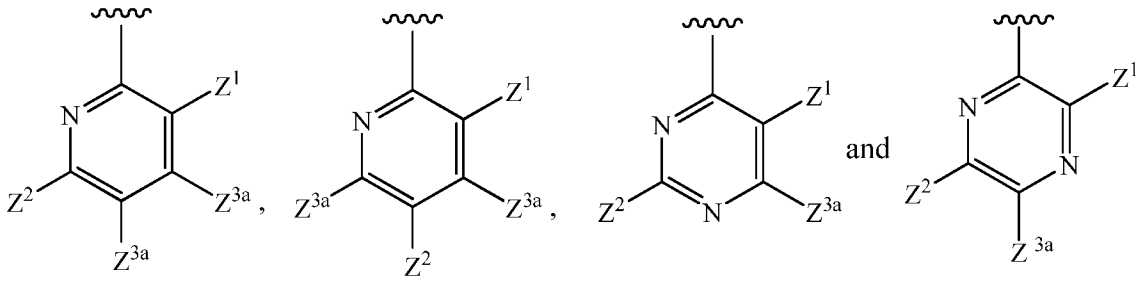
or a pharmaceutically acceptable salt thereof.

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.

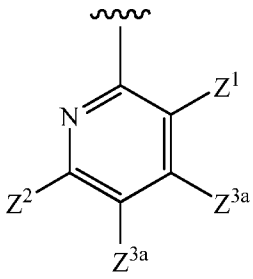
Embodiment II-13. The compound of any one of Embodiments II-1 to II-12 wherein A is substituted with one Z^1 group at the position shown and one Z^2 group.

Embodiment II-14. The compound of any one of Embodiments II-1 to II-10 wherein A-Z^1 is selected from:

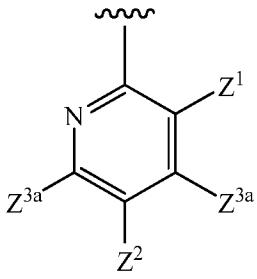


wherein each Z^{3a} is independently selected from H and Z^3.

Embodiment II-15. The compound of any one of Embodiments II-1 to II-10 wherein A-Z^1 is selected from:

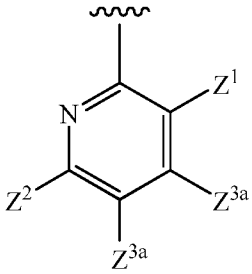


and



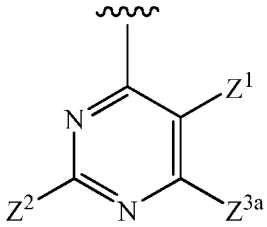
wherein each Z^{3a} is independently selected from H and Z^3.

Embodiment II-16. The compound of any one of Embodiments II-1 to II-10 wherein A-Z^1 is:



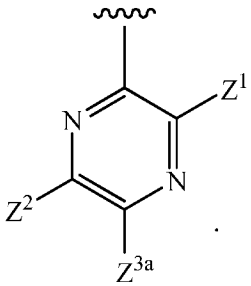
wherein each Z^{3a} is independently selected from H and Z^3.

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:



.

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 $-NR^{n1}S(O)_2R^{p1}$.

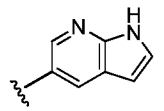
Embodiment II-30. The compound of any one of Embodiments II-1 to II-27 wherein each Z^{1b} is independently selected from $(C_1\text{-}C_8)$alkyl.

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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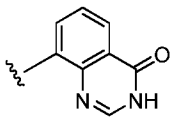
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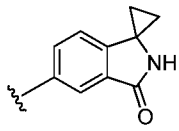
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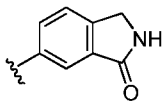
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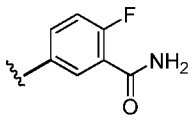
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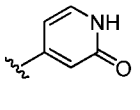
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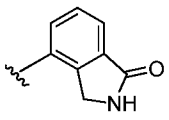
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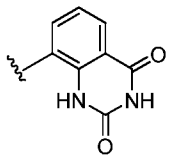
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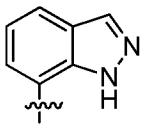
Embodiment II-35. The compound of any one of Embodiments II-1 to II-19 wherein Z^1 is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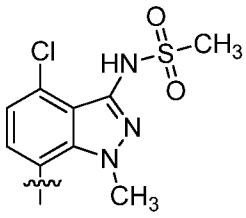
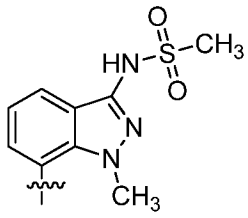
Embodiment II-36. The compound of any one of Embodiments II-1 to II-19 wherein Z^1 is selected from


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.

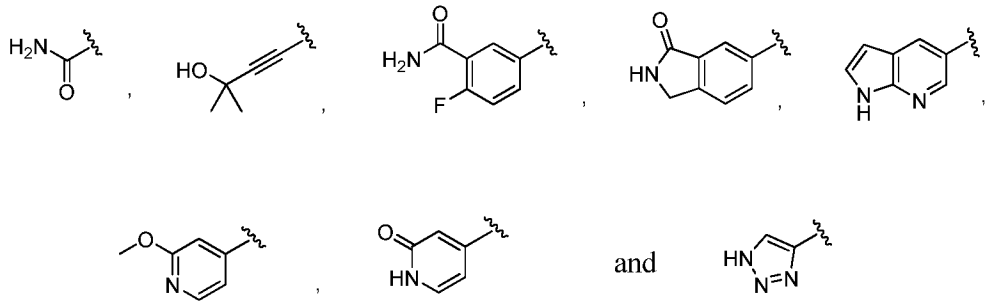
Embodiment II-42. The compound of any one of Embodiments II-1 to II-41 wherein Z^2 is optionally substituted with one or more Z^{2c} groups.

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:



and

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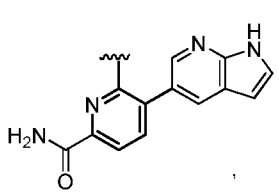
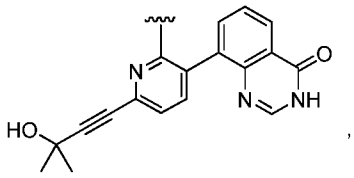
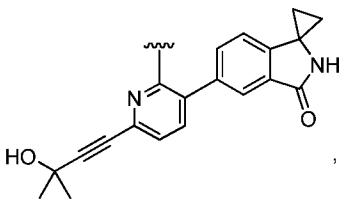
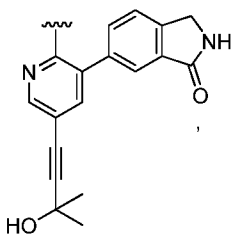
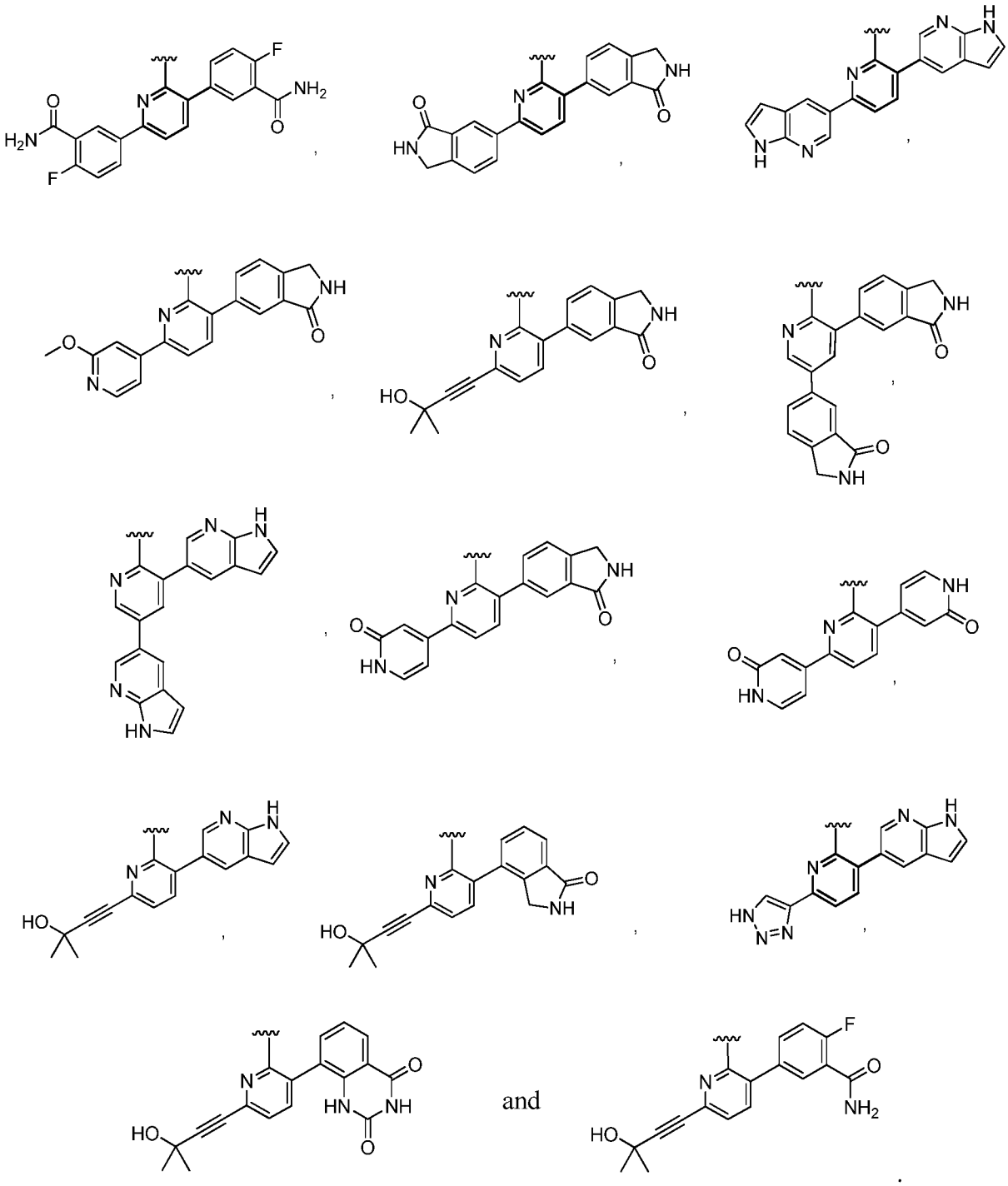
Embodiment II-47. The compound of any one of Embodiments II-1 to II-10 wherein A-Z^1 is selected from:





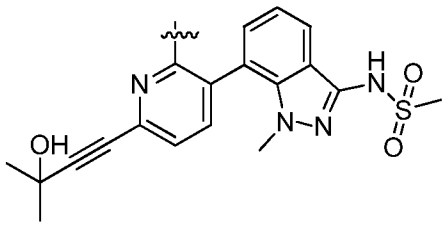




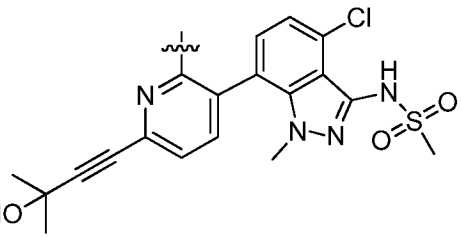


and

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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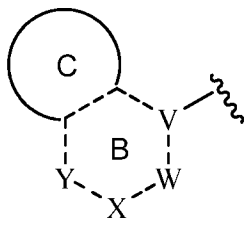
Embodiment II-49. The compound of any one of Embodiments II-1 to II-48 wherein R^1 is a 5-12 membered heteroaryl, wherein any 5-12 membered heteroaryl of R^1 is optionally substituted with one or more Z^4 groups.

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;

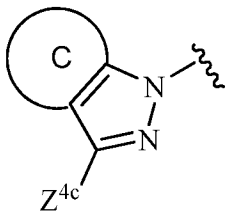
X is CZ^{4c}, NZ^{4c} or N;

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.

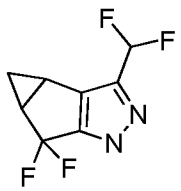
Embodiment II-58. The compound of any one of Embodiments II-1 to II-56 wherein each Z^4 is independently selected from fluoro, trifluoromethyl and difluoromethyl.

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:

and

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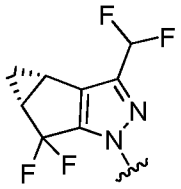
Embodiment II-62. The compound of any one of Embodiments II-1 to II-48 wherein R^1 is



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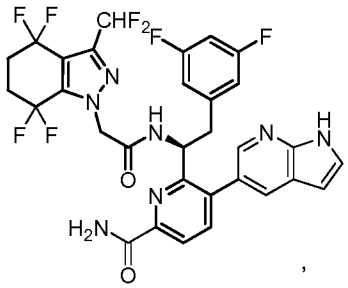
Embodiment II-63. The compound of Embodiment II-1 selected from:



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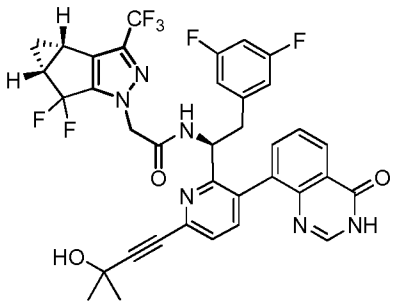

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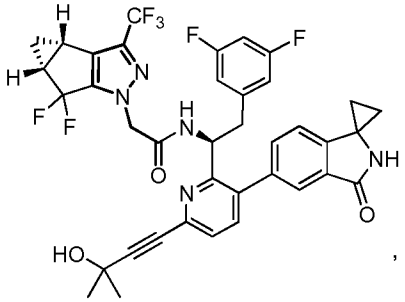

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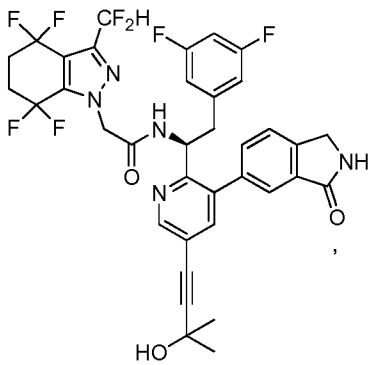

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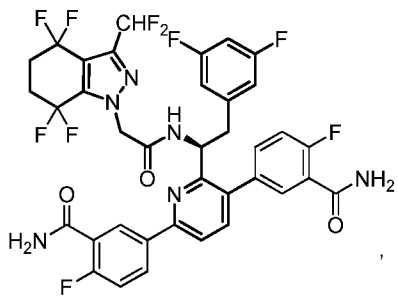

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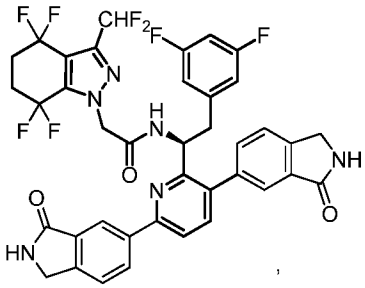

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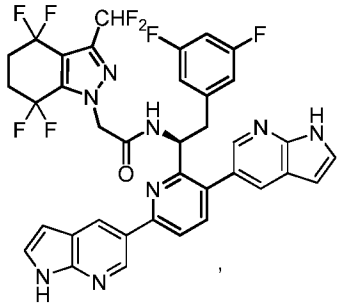

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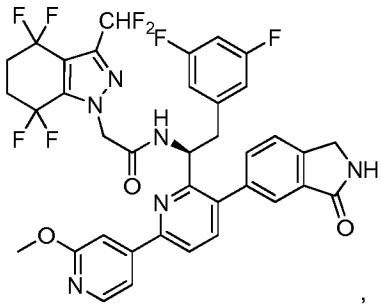

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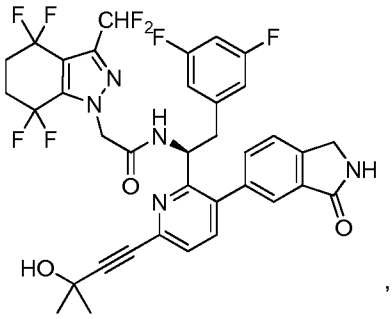

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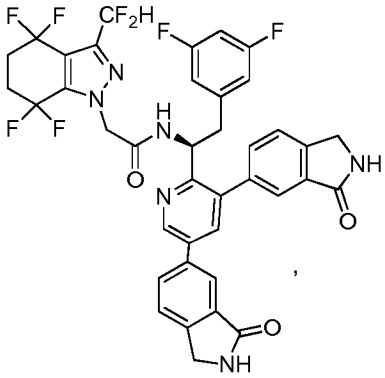

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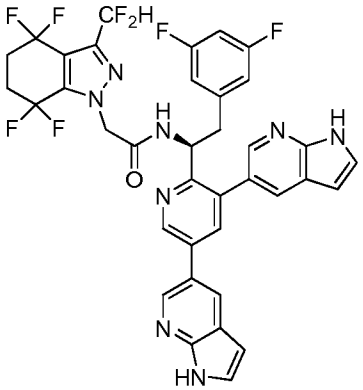

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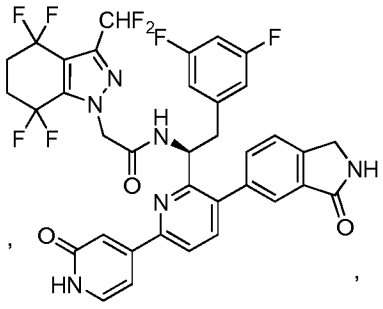

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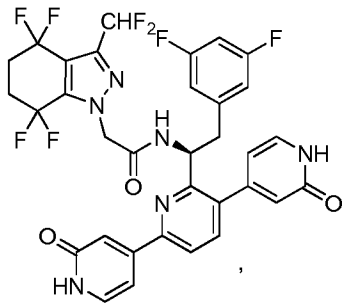

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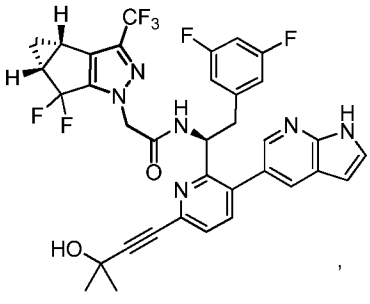

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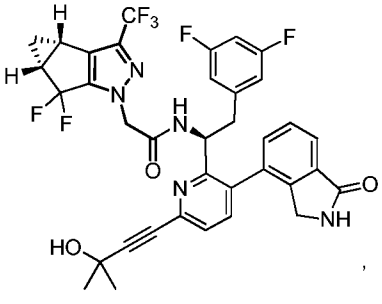

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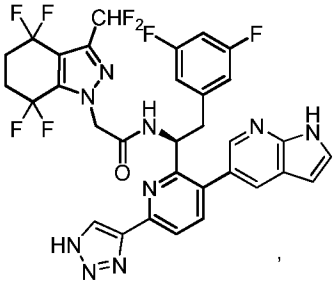

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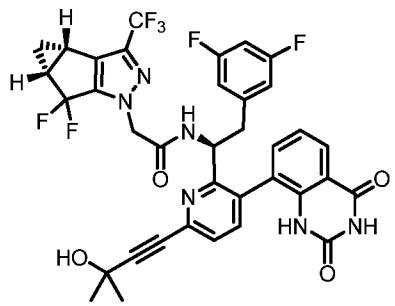

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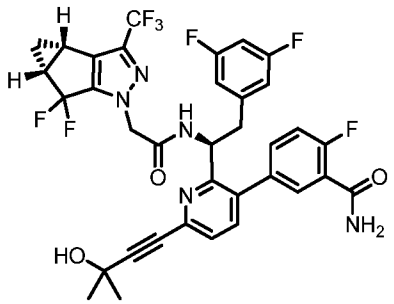
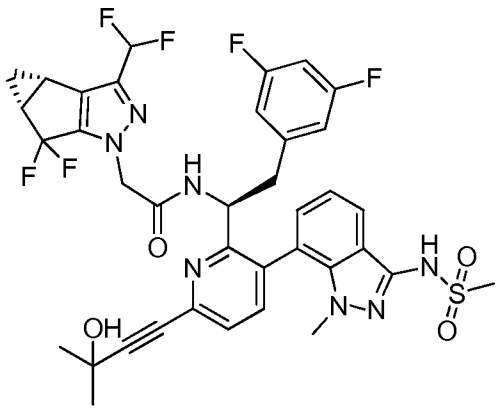
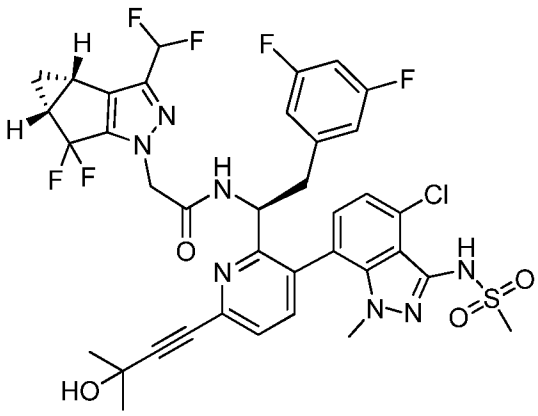


and pharmaceutically acceptable salts thereof.

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.

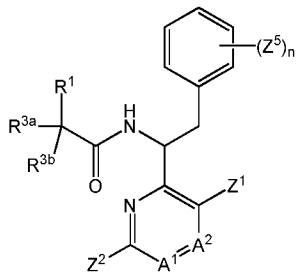
Embodiment II-71. The use of a compound as described in any one of Embodiments II-1 to II-44 or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a *Retroviridae* virus infection or an HIV virus infection in a mammal.

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 $-OR^{n6}$;

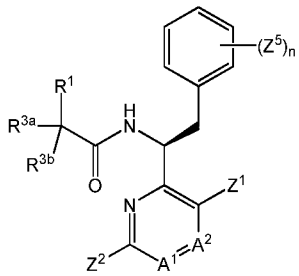
each R^{n5}, R^{p5}, R^{q5}, R^{r5}, and R^{n6} is independently H or $(C_1$-$C_4)$alkyl;

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.

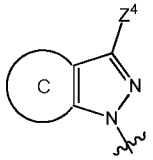
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, which is a compound of formula IIIe:



IIIe

or a pharmaceutically acceptable salt thereof.

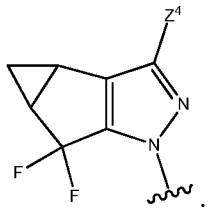
3. The compound of any one of claims 1-2, or a pharmaceutically acceptable salt thereof, wherein R^1 is



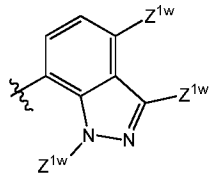
wherein

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:

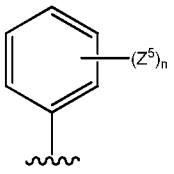
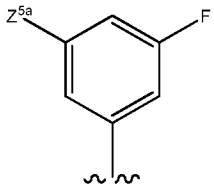
each Z^{1a} is independently halogen, -CN, -OR^{n1}, -$NR^{n1}S(O)_2R^{p1}$, -$NR^{n1}S(O)_2NR^{q1}R^{r1}$, -$NR^{q1}R^{r1}$, -$NR^{n1}COR^{p1}$, -$NR^{n1}CONR^{q1}R^{r1}$, or -$NR^{n1}CO_2R^{p1}$;

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 $-NR^{n1}S(O)_2NR^{q1}R^{r1}$.

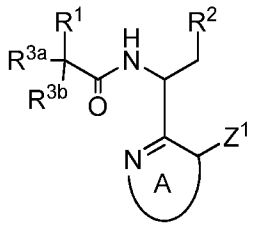
9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein the moiety  is  wherein Z^{5a} is H or halogen.

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)$NR^{q3}R^{r3}$, 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;

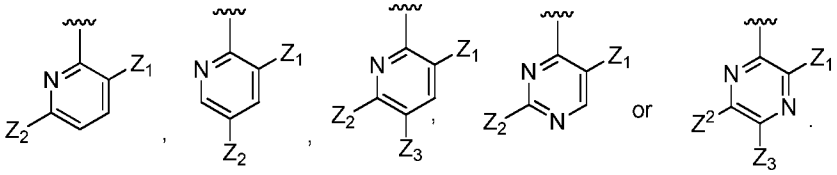
each Z^4 is independently oxo, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, halogen, -CN, $-OR^{n5}$, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-C(O)R^{n5}$, $-C(O)OR^{n5}$, or $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3$-$C_7)$carbocycle or $(C_1$-$C_8)$alkyl of Z^4 is optionally substituted 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

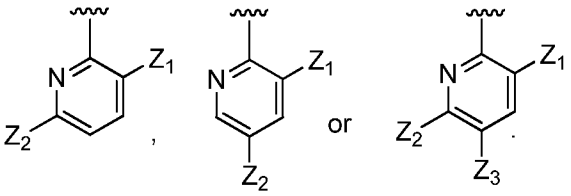
each R^{n5}, R^{p5}, R^{q5}, R^{r5}, and R^{n6} is independently H or $(C_1$-$C_4)$alkyl;

or a pharmaceutically acceptable salt thereof.

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

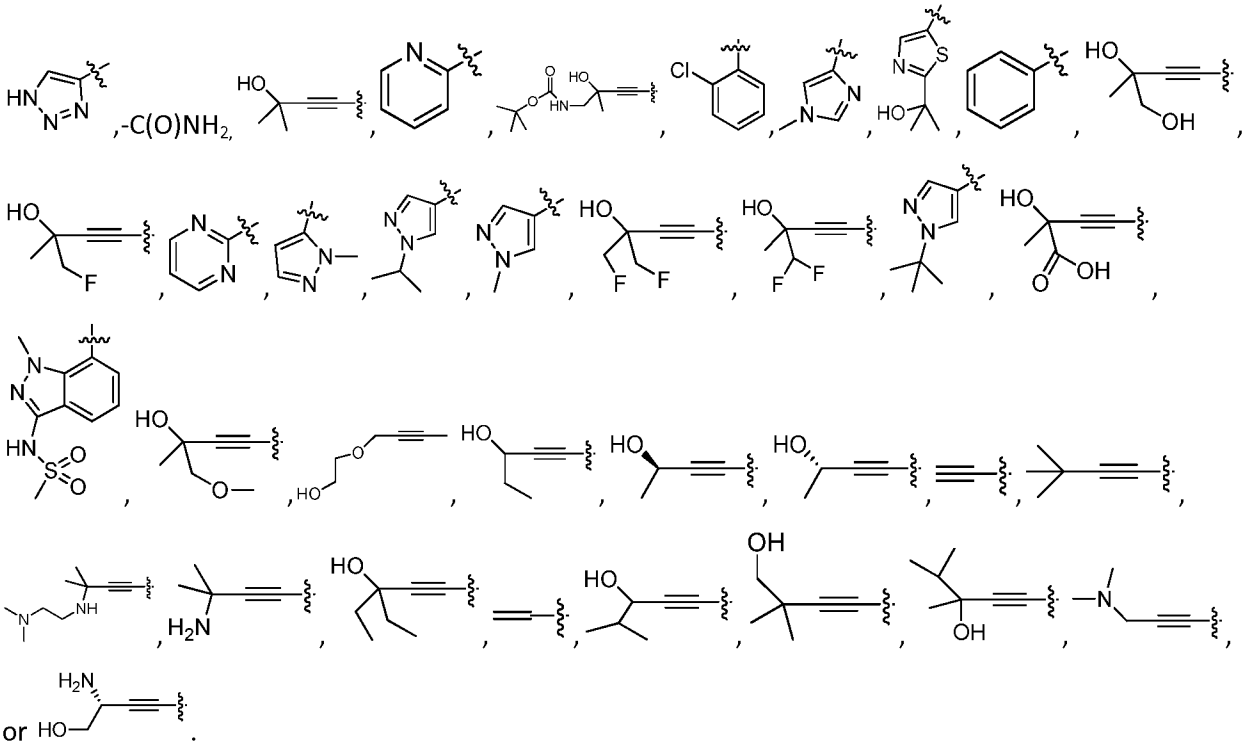
membered C-linked-bicyclic-heteroaryl, or 8-10 membered C-linked-bicyclic-heterocycle of Z^2 is optionally substituted with 1, 2, or 3 Z^{2b} or Z^{2c} groups, and wherein any $(C_2\text{-}C_8)$alkynyl of Z^2 is optionally substituted with 1, 2, or 3 Z^{2c} groups.

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 $-C(O)NR^{q4}R^{r4}$.

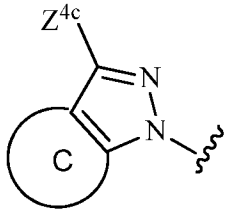
22. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein each Z^{2c} is independently halogen or $-OR^{n4}$.

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

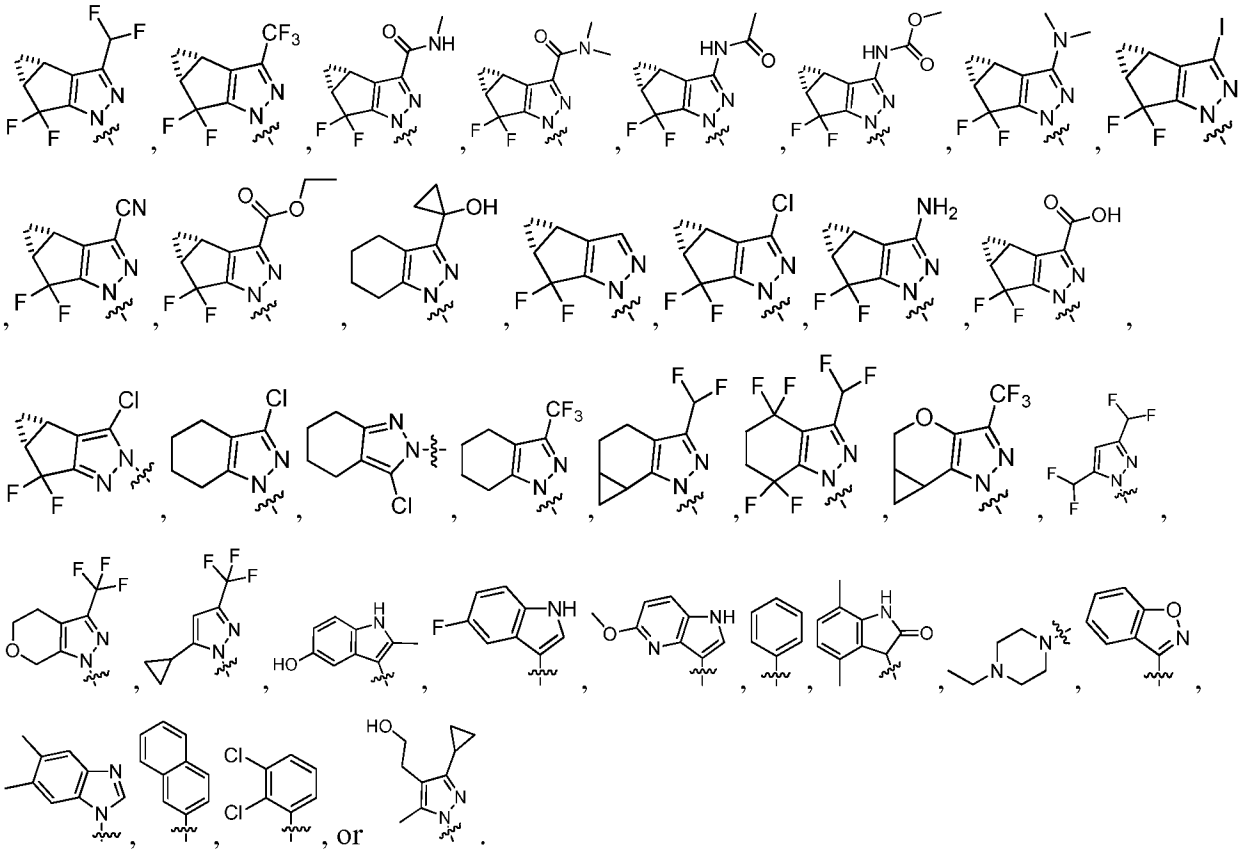
wherein:

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

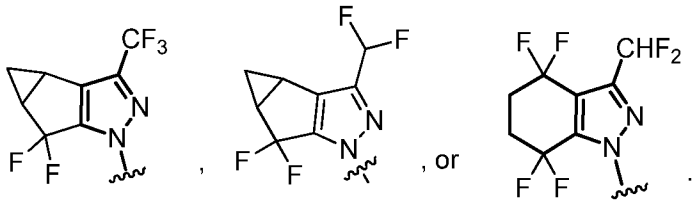
each Z^{4c} is independently selected from H or Z^4, wherein the Z^4 groups are the same or different.

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-

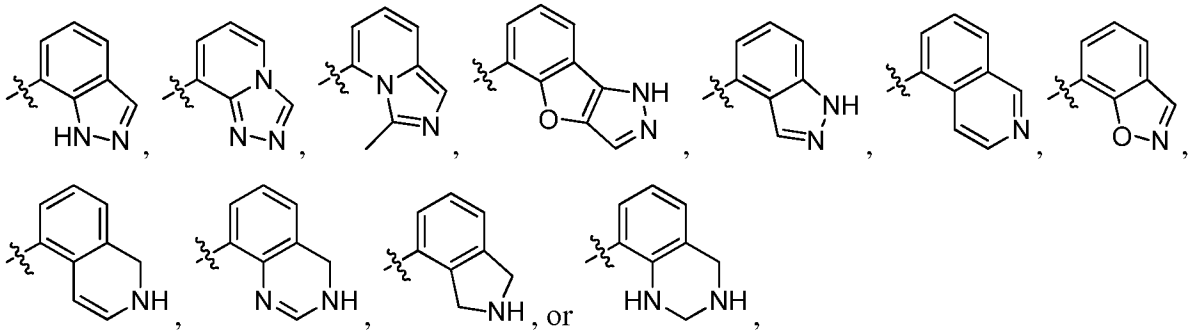
heterocycle, wherein any 8-10 membered bicyclic-heteroaryl or 8-10 membered bicyclic-heterocycle has 3-9 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any 8-10 membered bicyclic-heteroaryl or 8-10 membered bicyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4, or 5 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.

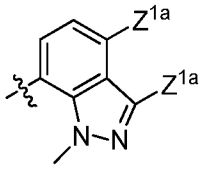
33. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt thereof, wherein Z^1 is substituted with 2 Z^{1a} groups, wherein each Z^{1a} is independently $-NR^{n1}S(O)_2R^{p1}$, $-NR^{n1}S(O)_2NR^{q1}R^{r1}$, or halogen.

34. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein Z^1 is

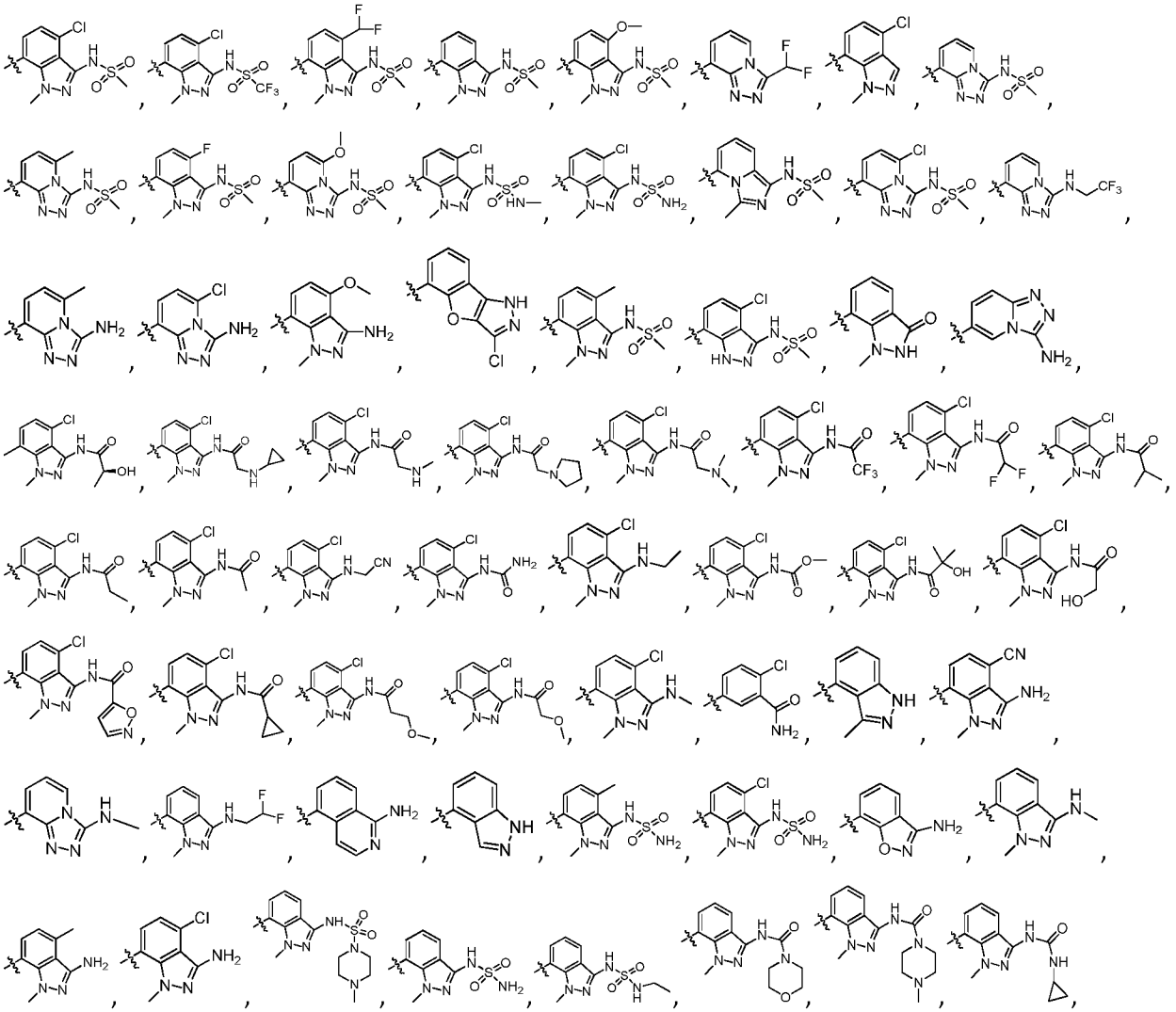


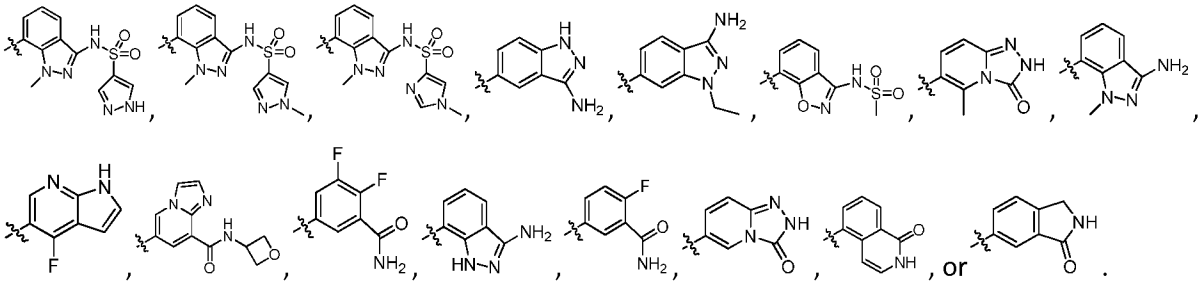
optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b}.

35. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof,

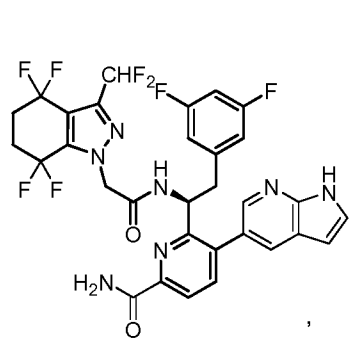
wherein Z^1 is  , wherein each Z^{1a} is independently halogen, $-NR^{n1}S(O)_2R^{p1}$ or $-NR^{n1}S(O)_2NR^{q1}R^{r1}$.

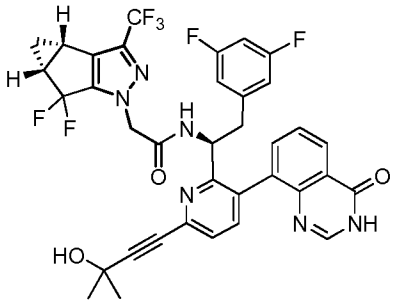
36. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein Z^1 optionally substituted with 1, 2, 3, 4, or 5 Z^{1a} or Z^{1b} groups is

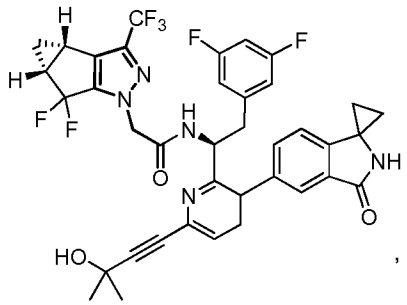


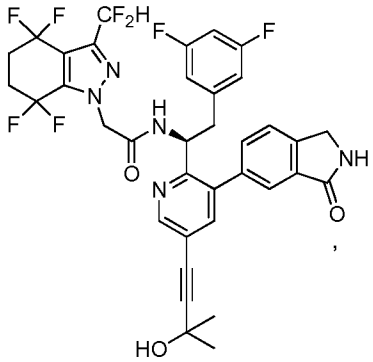


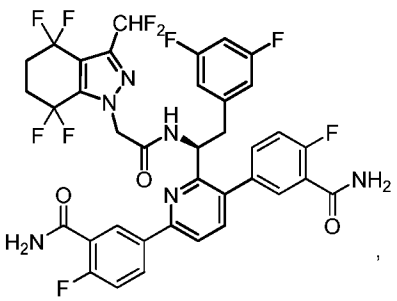
37. A compound or a pharmaceutically acceptable salt thereof, which is

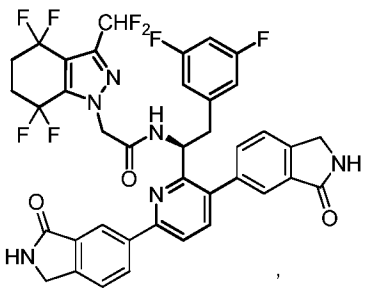


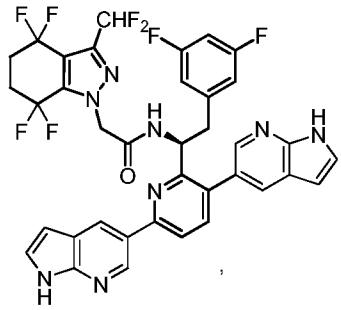


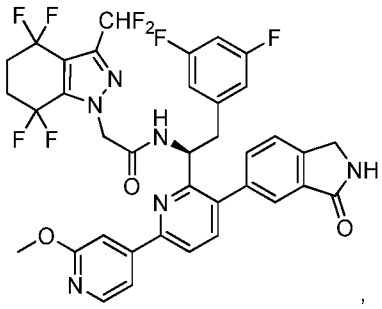


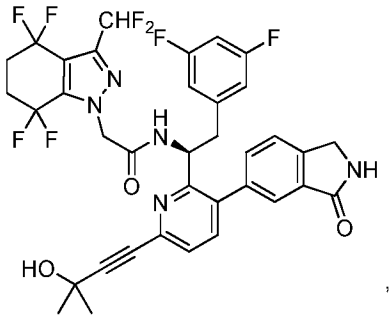


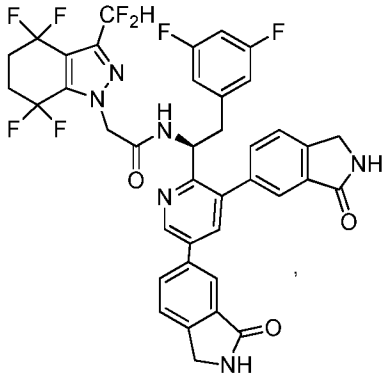


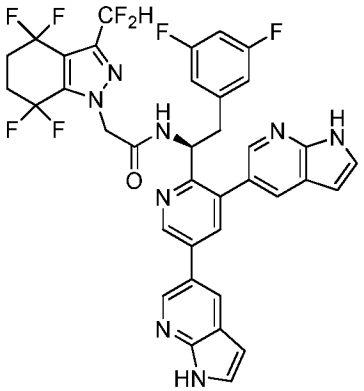


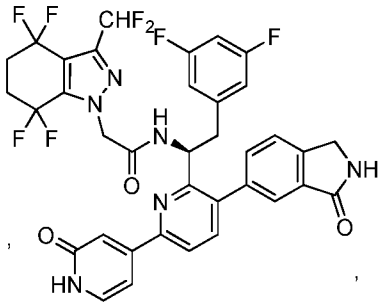


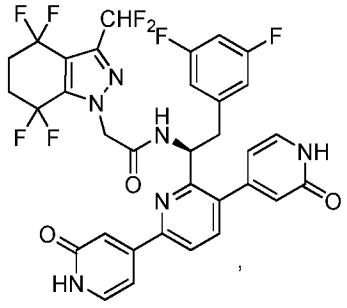


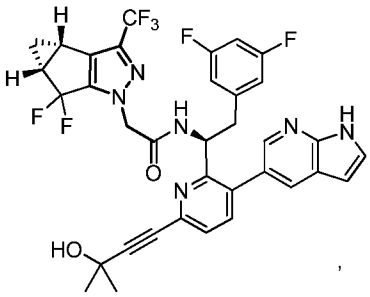


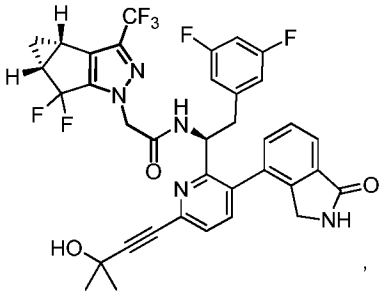


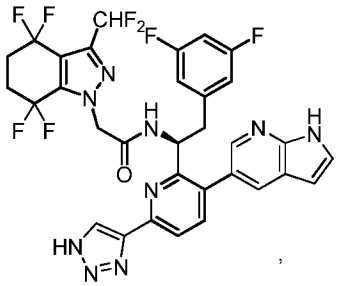


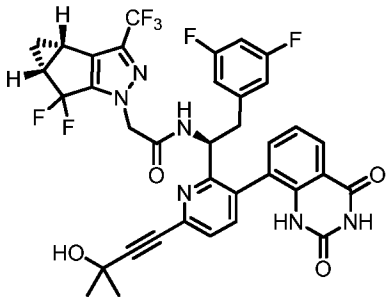


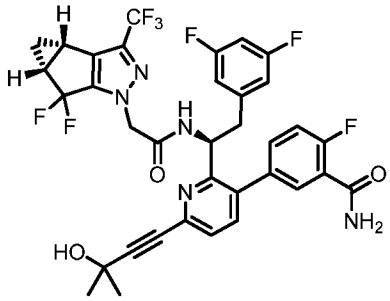


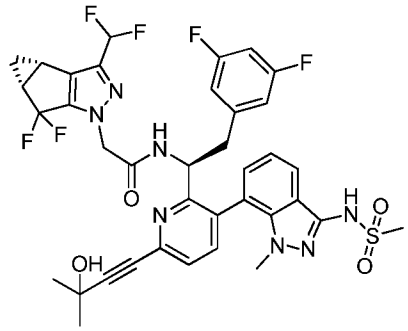


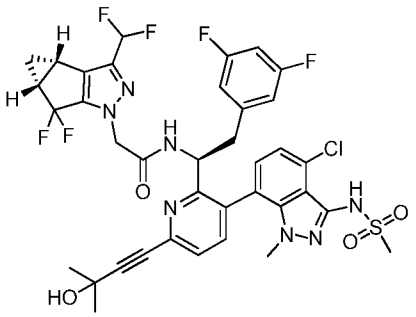


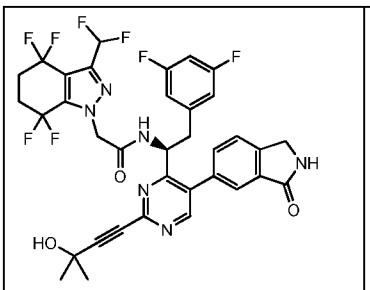


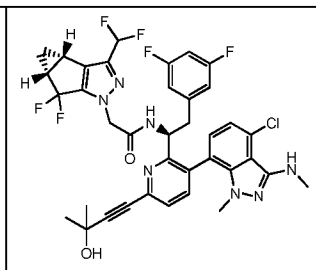


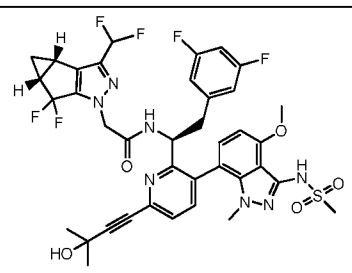


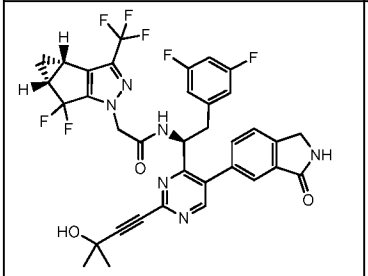


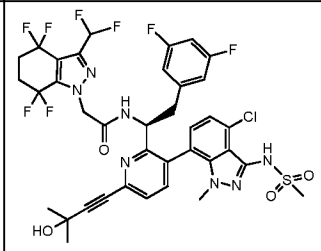


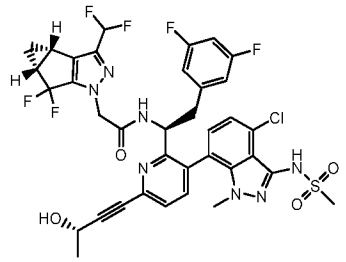


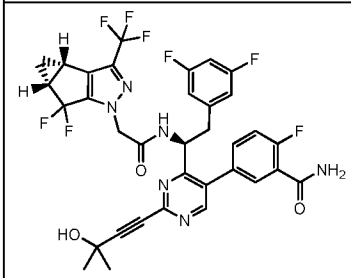


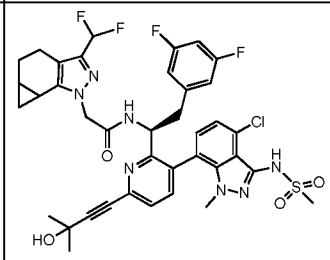


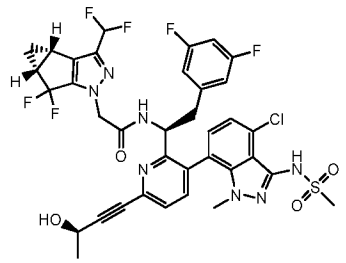


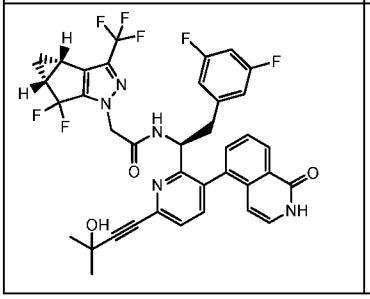


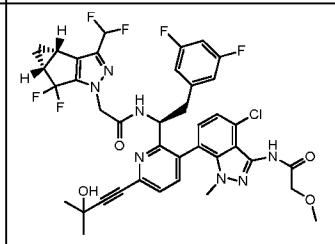


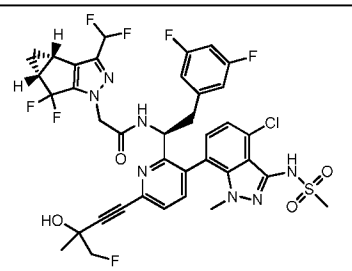


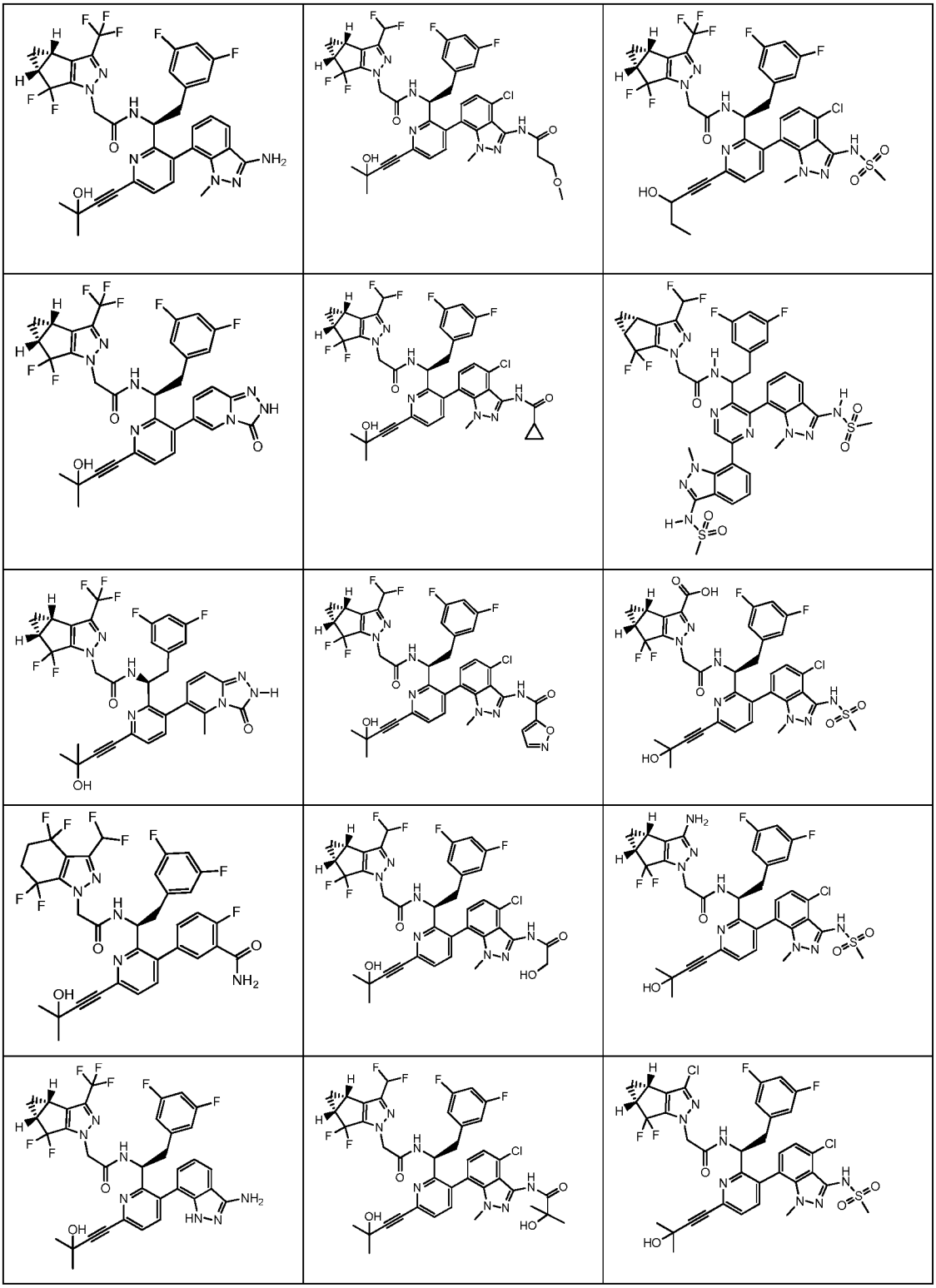


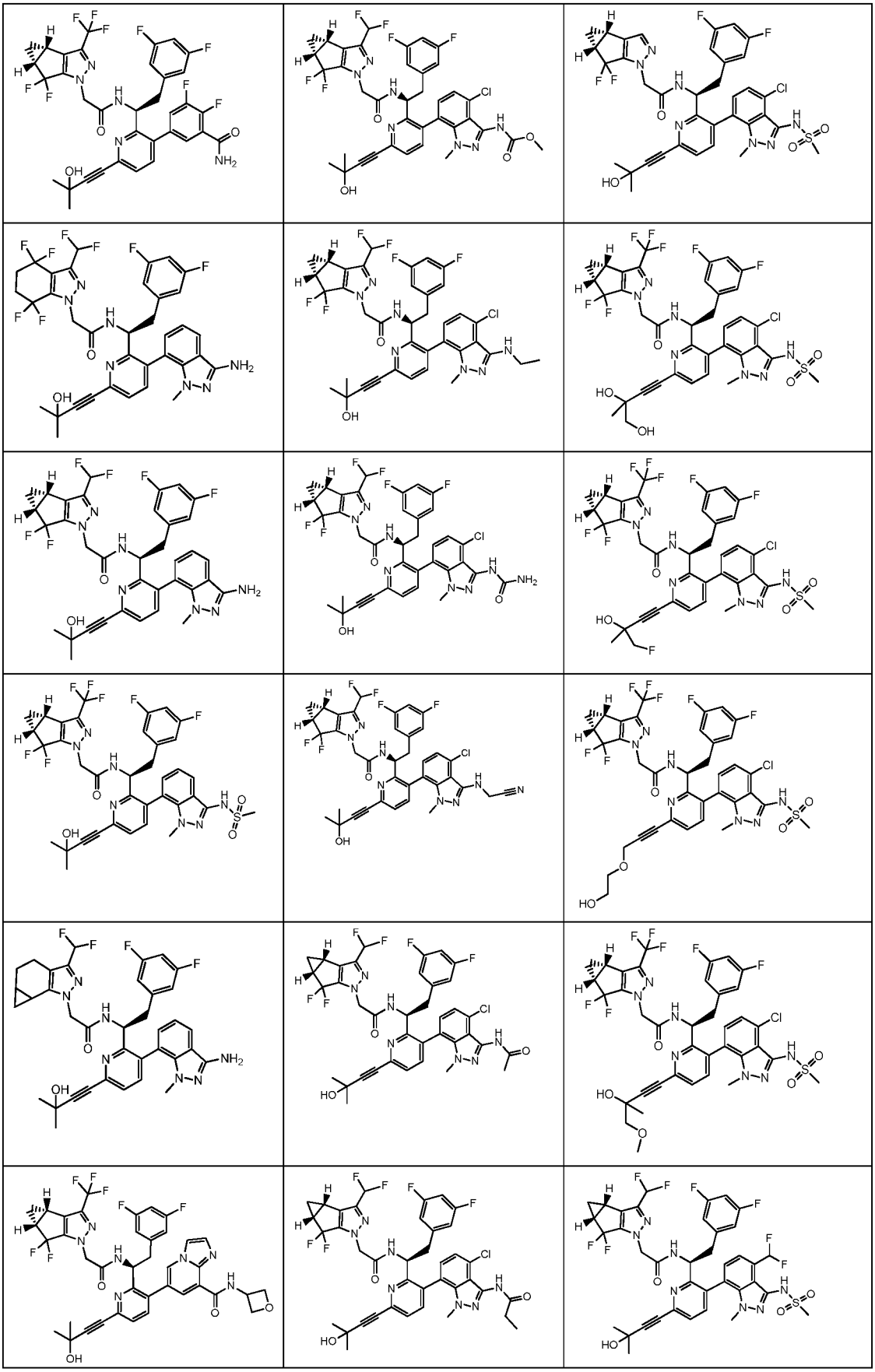


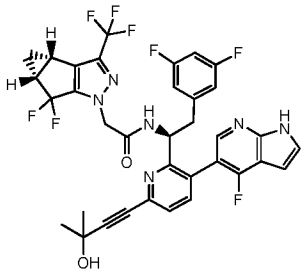
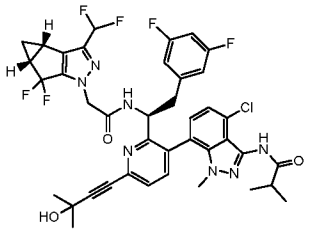
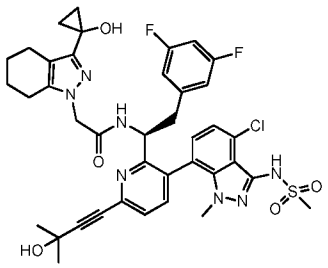
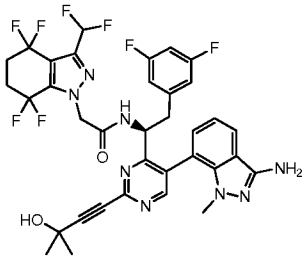
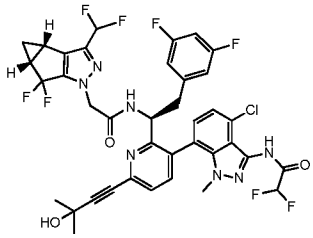
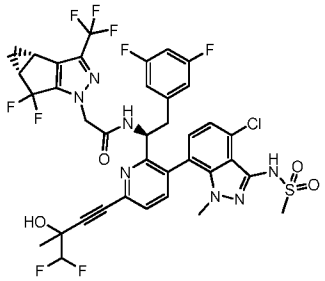
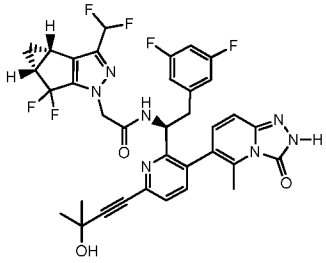
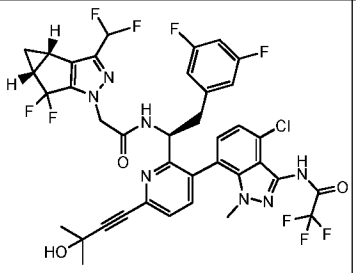
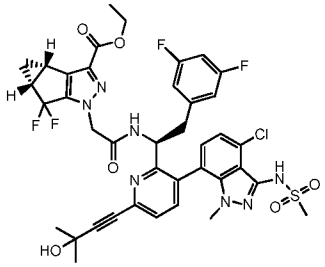
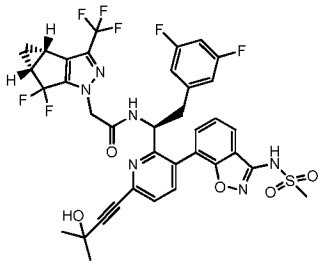
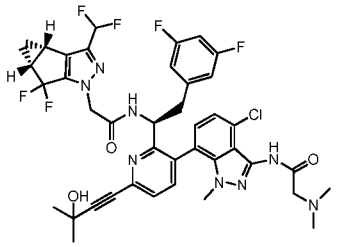
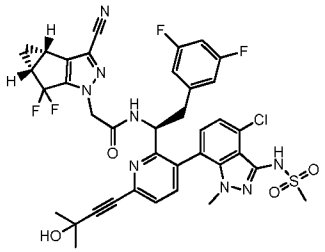
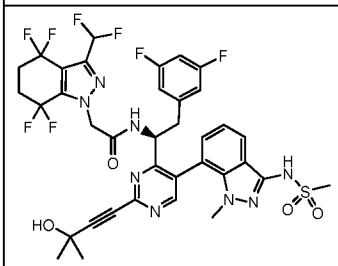
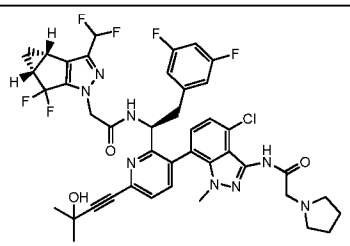
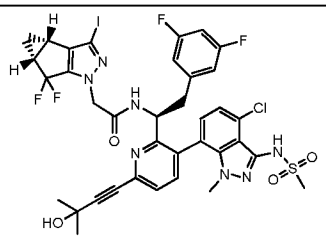
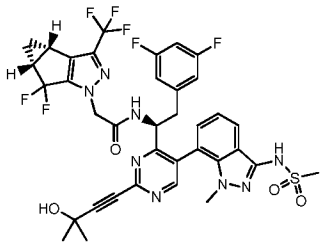
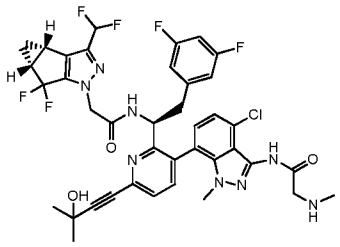
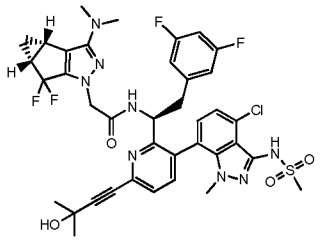


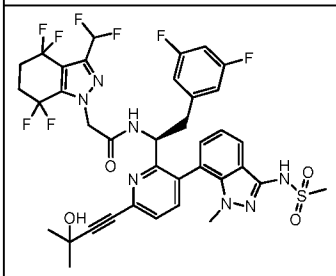
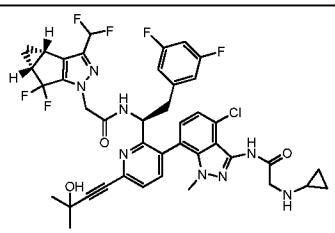
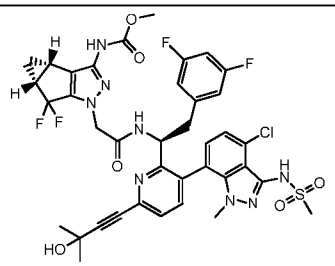
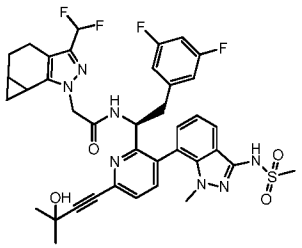
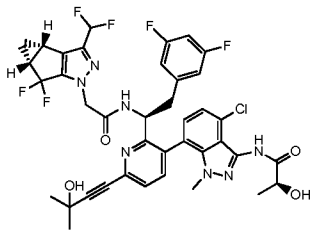
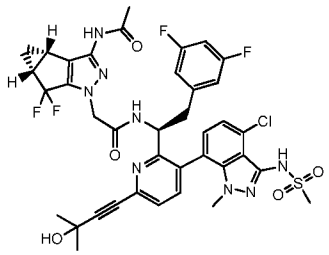
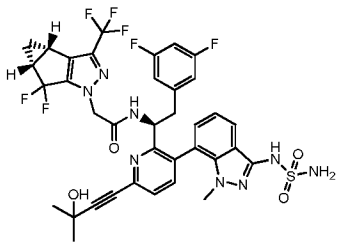
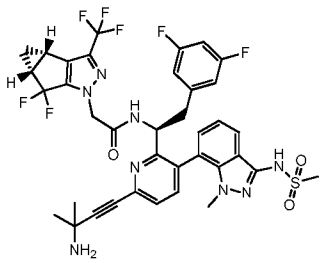
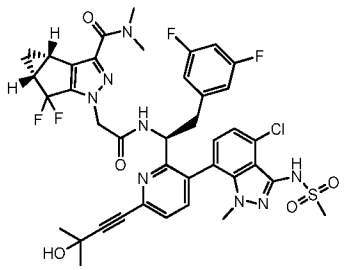
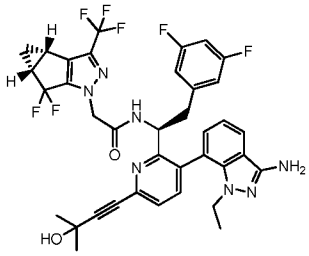
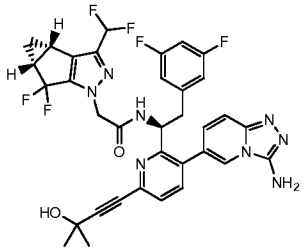
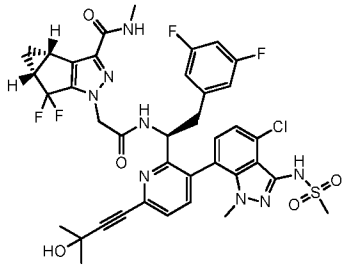
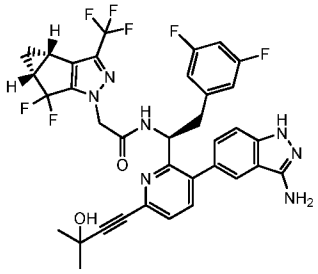
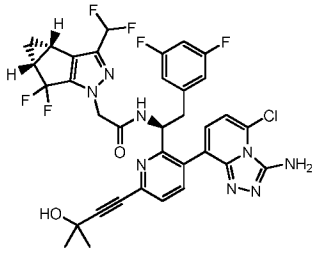
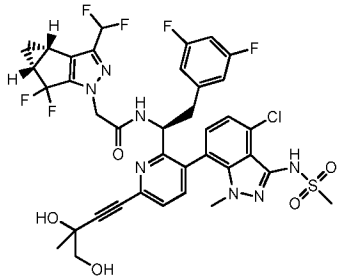
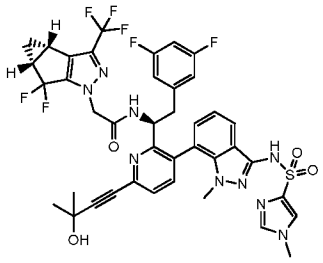
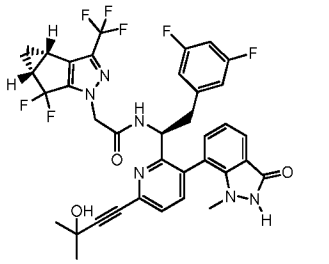
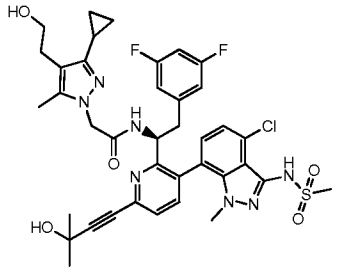


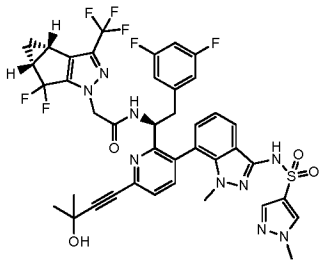
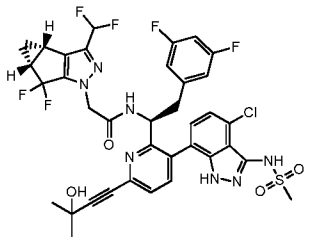
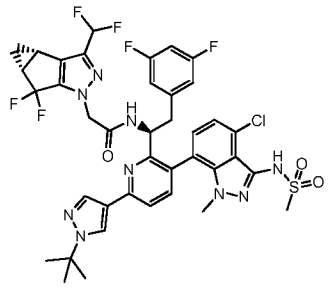
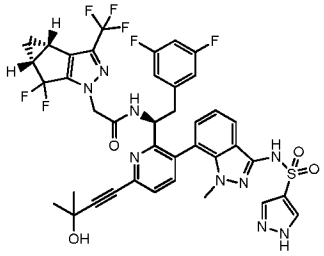
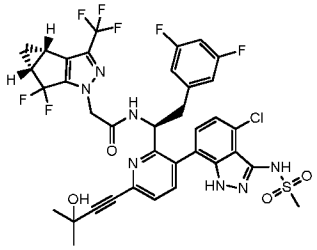
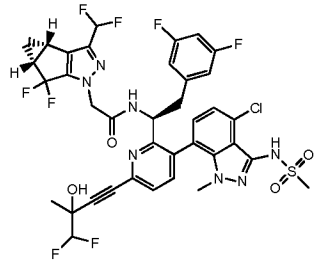
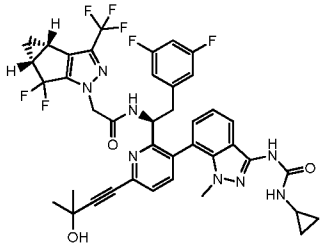
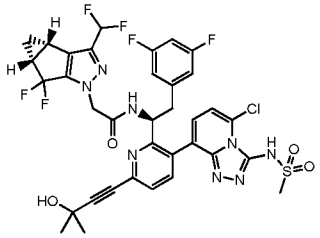
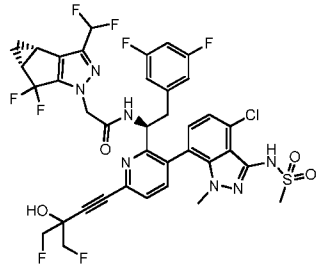
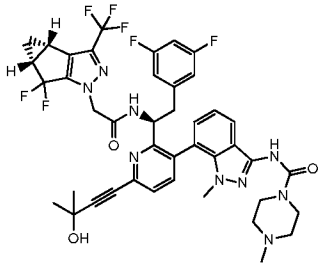
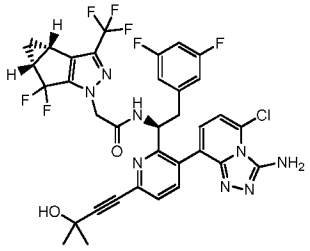
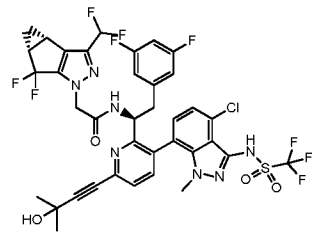
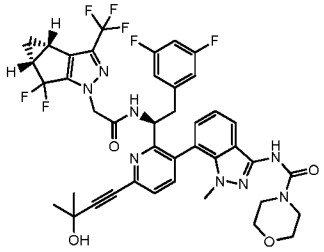
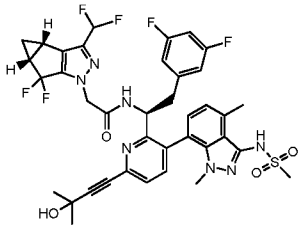
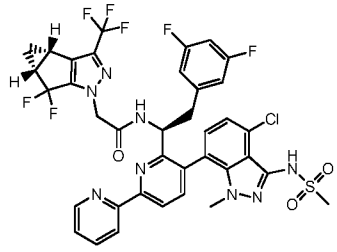
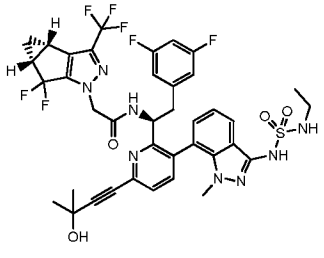
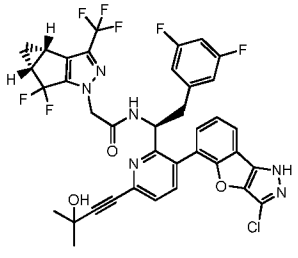
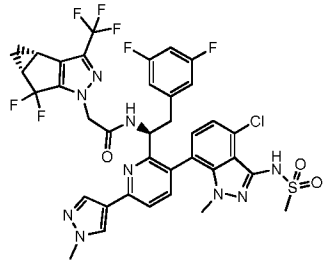


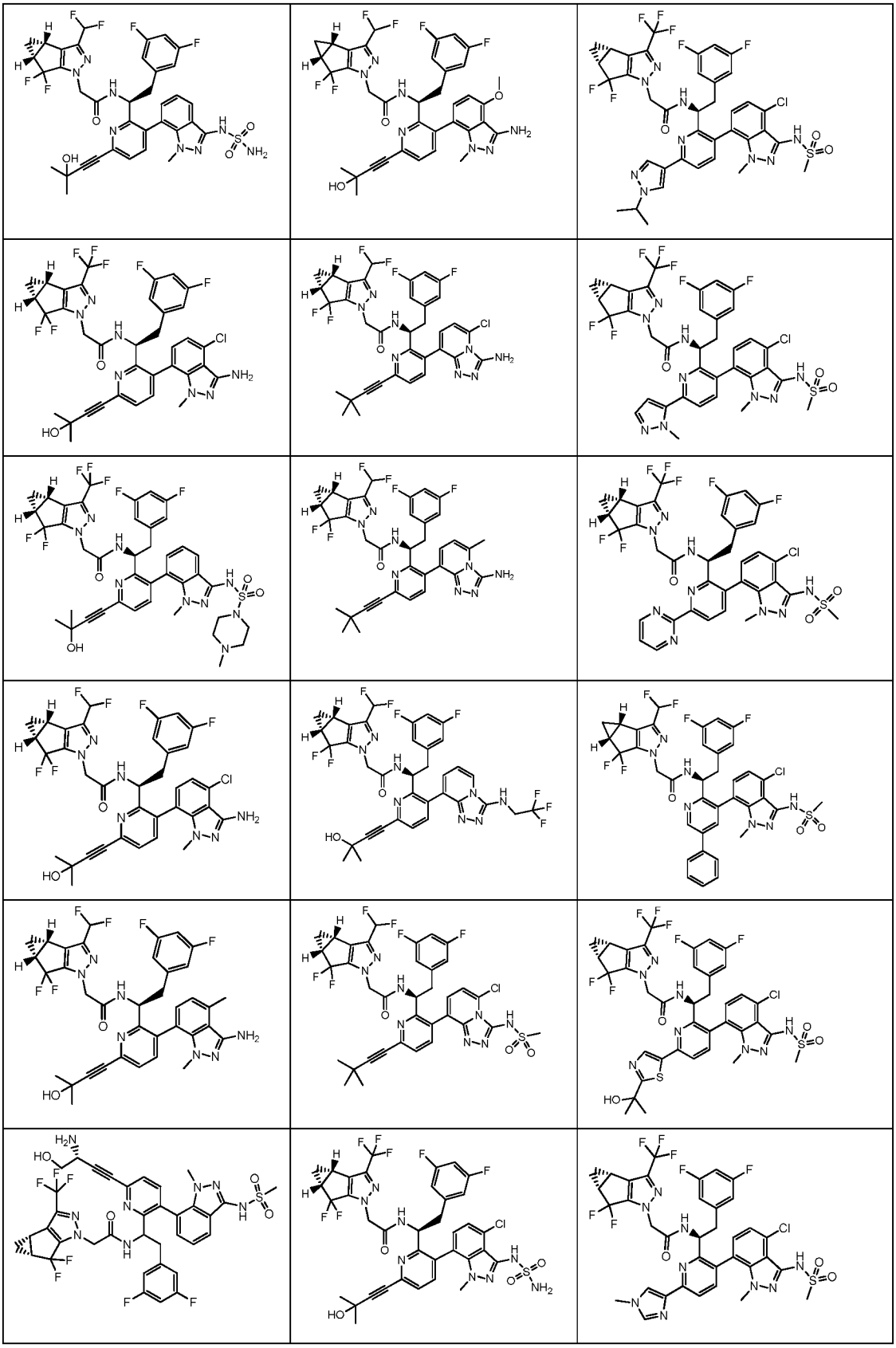


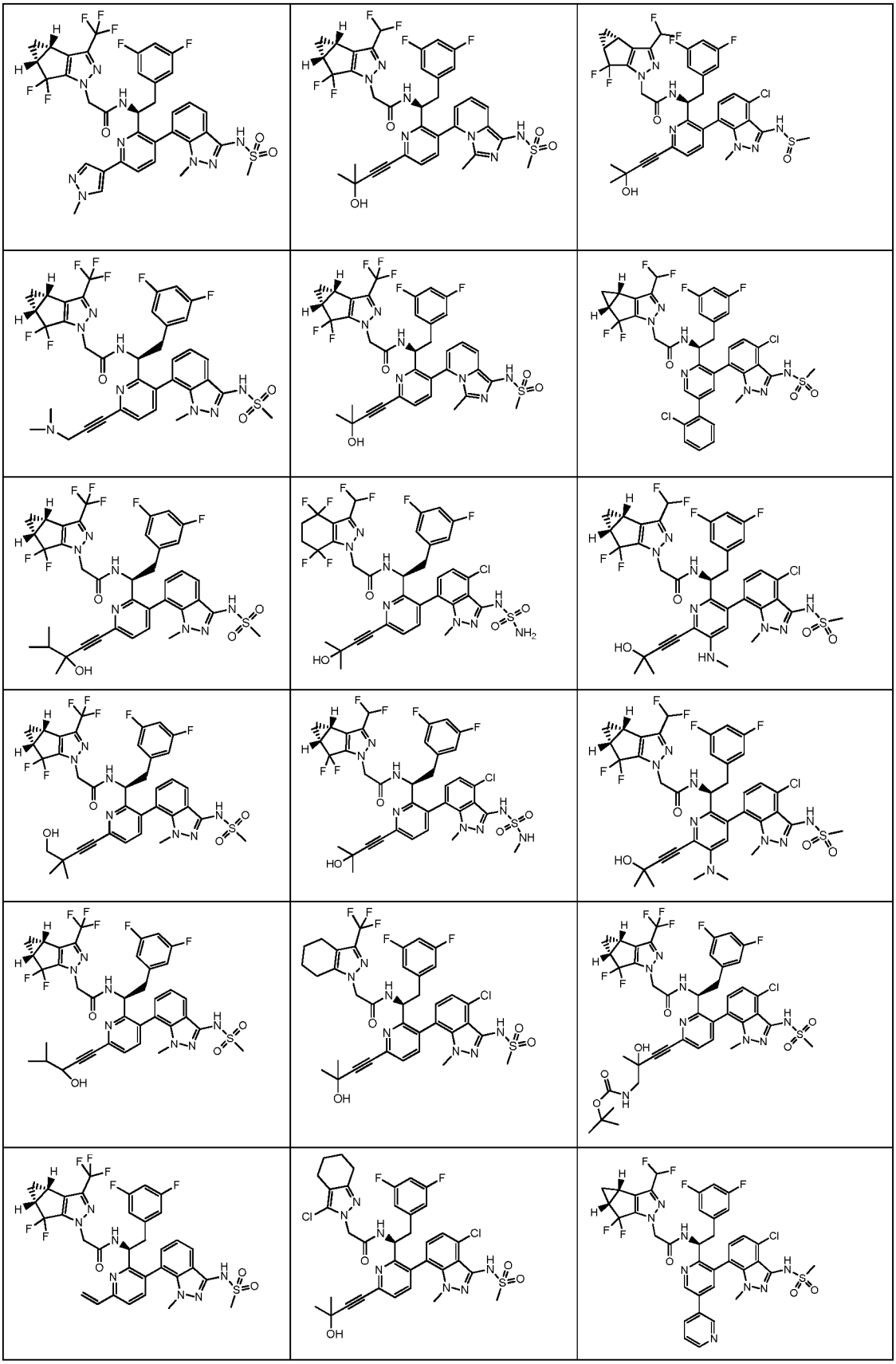


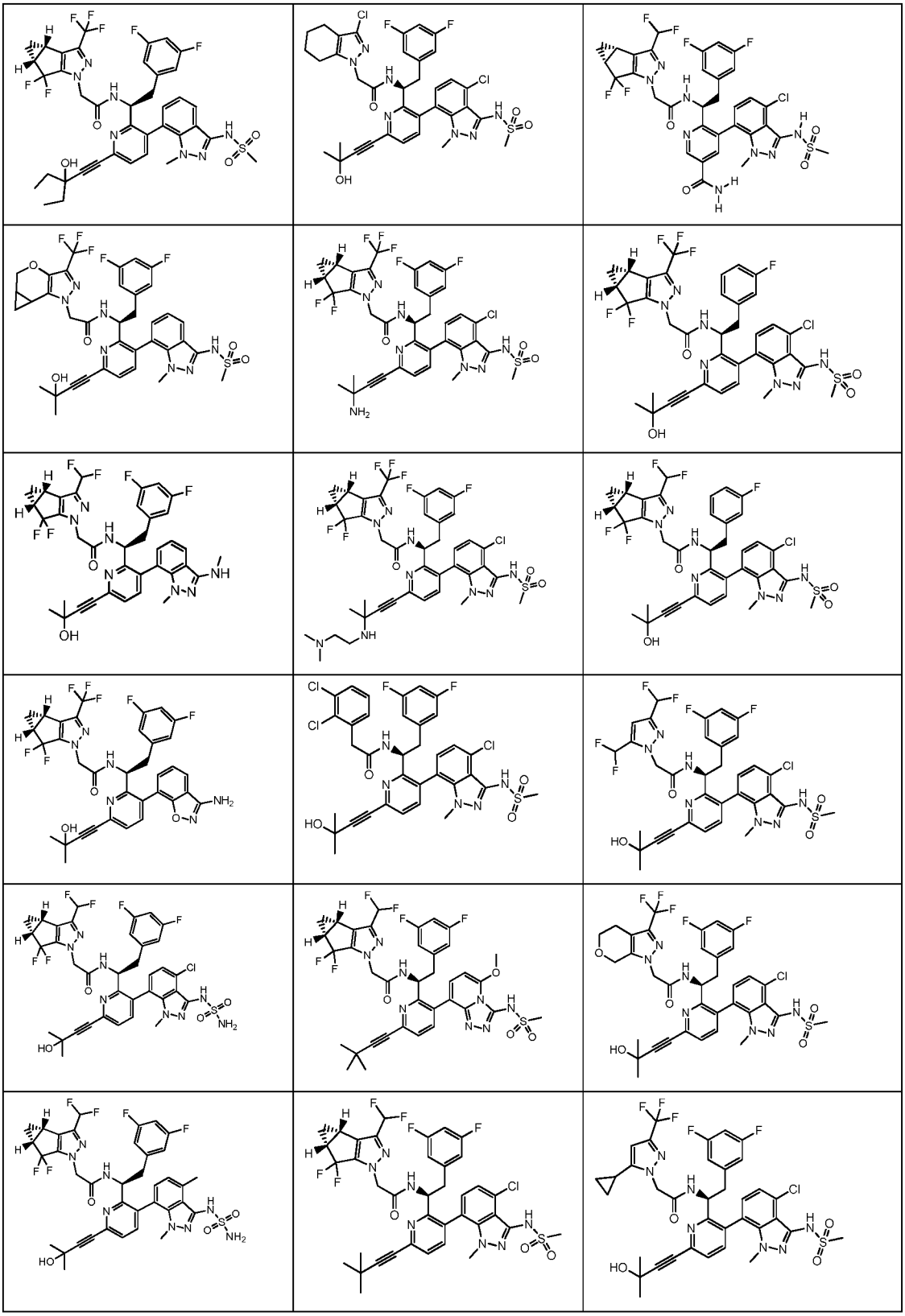
		
		
		
		
		
		

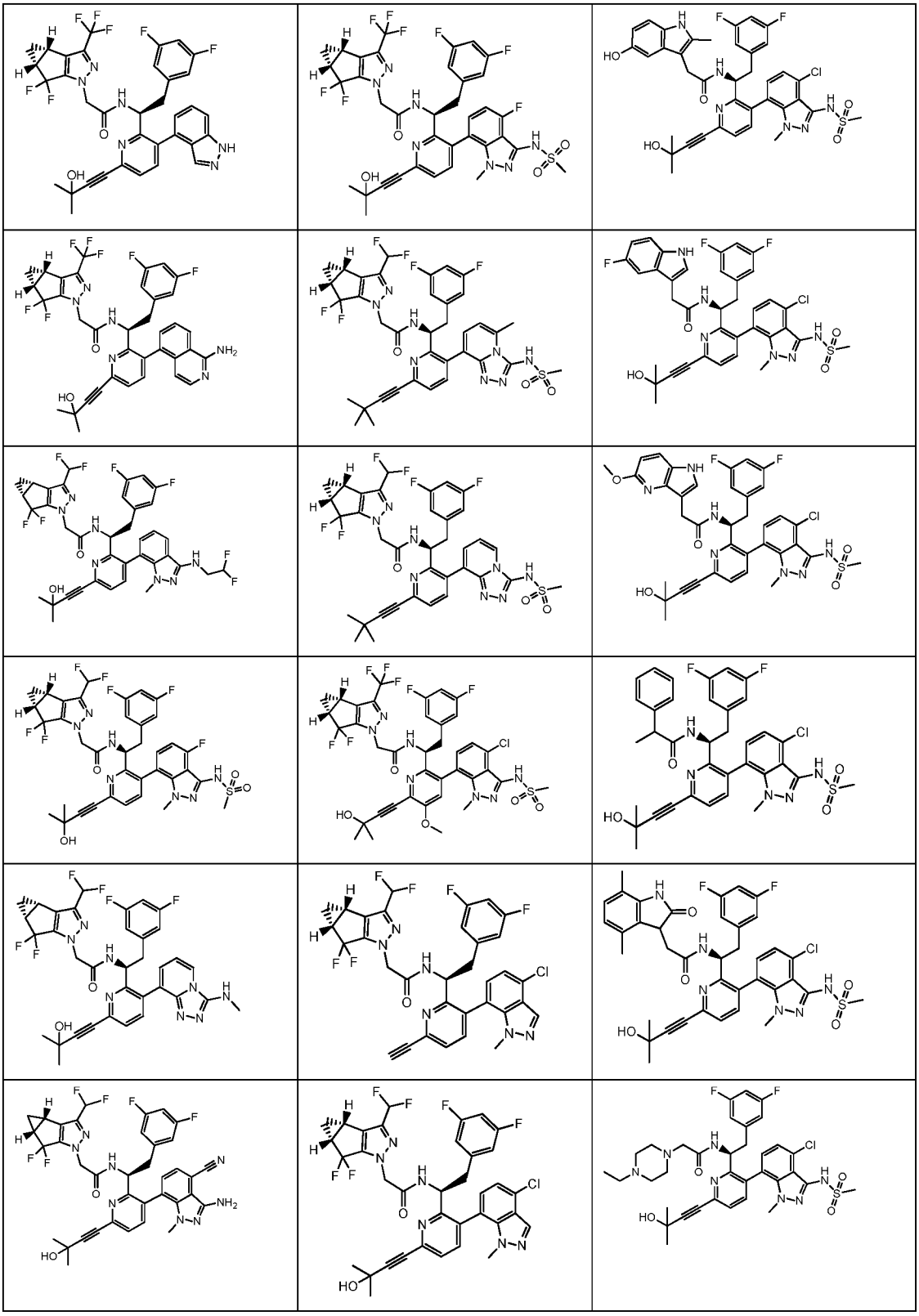
		
		
		
		
		
		

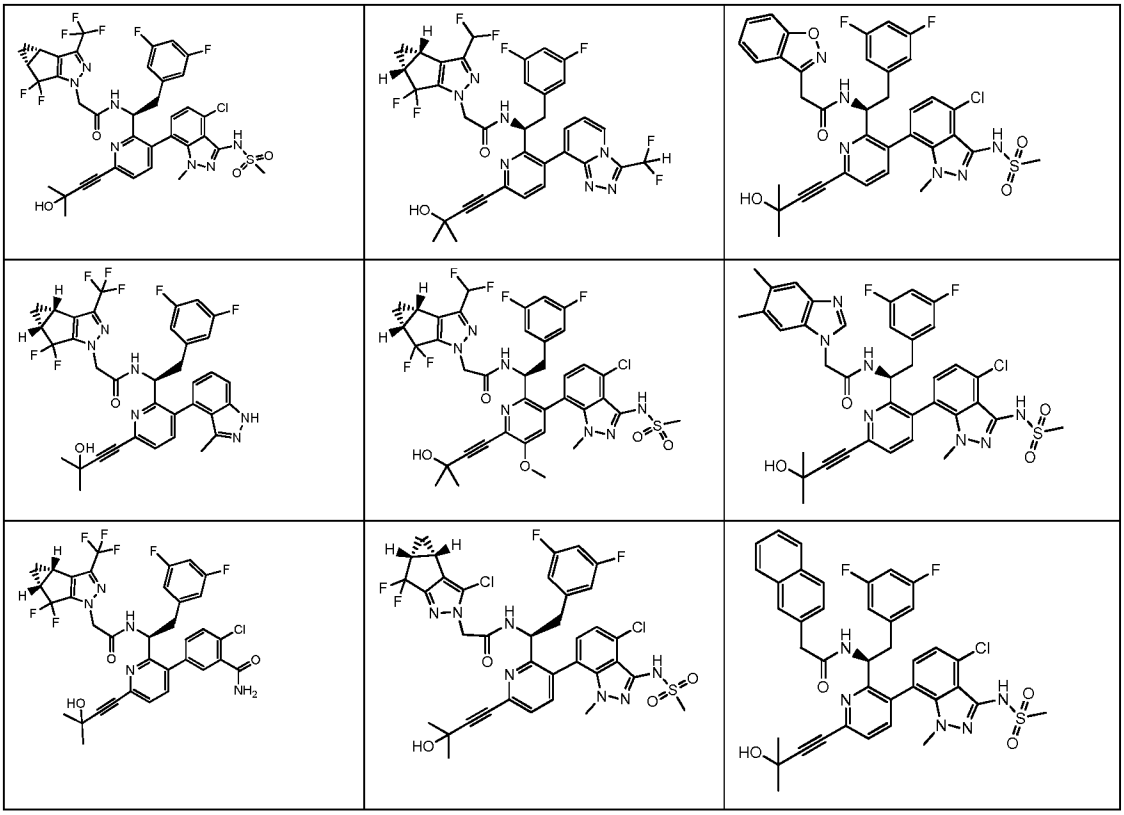
		
		
		
		
		
		



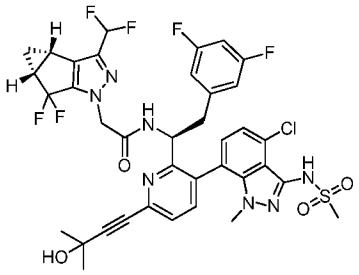






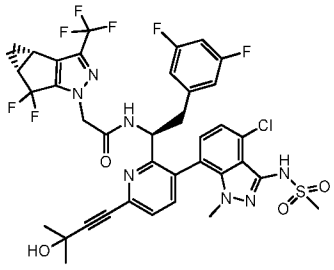


38. A compound of formula:



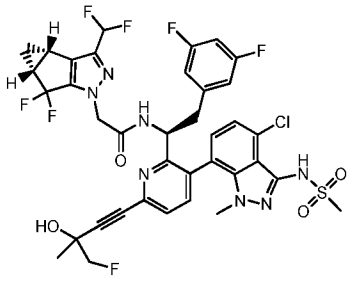
or a pharmaceutically acceptable salt thereof.

39. A compound of formula:



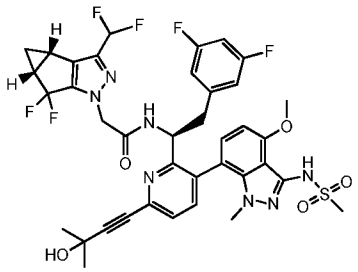
or a pharmaceutically acceptable salt thereof.

40. A compound of formula:



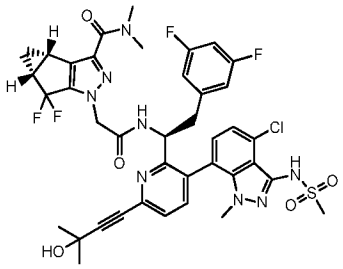
or a pharmaceutically acceptable salt thereof.

41. A compound of formula:



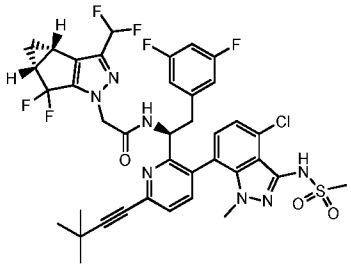
or a pharmaceutically acceptable salt thereof.

42. A compound of formula:



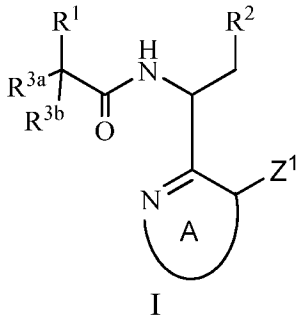
or a pharmaceutically acceptable salt thereof.

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;

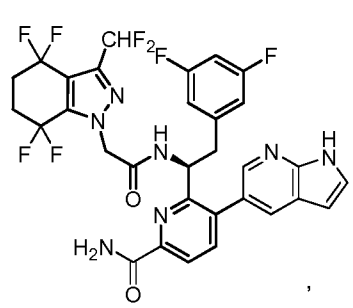
each Z^5 is independently selected from $(C_1\text{-}C_6)$alkyl, halogen, -CN and $-OR^{n7}$,

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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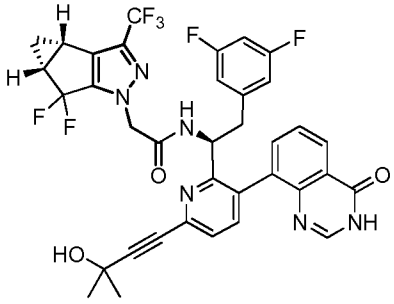

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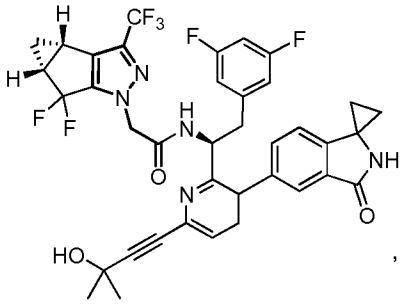

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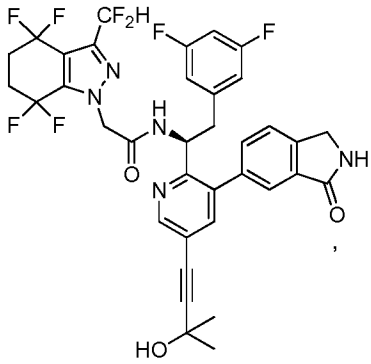

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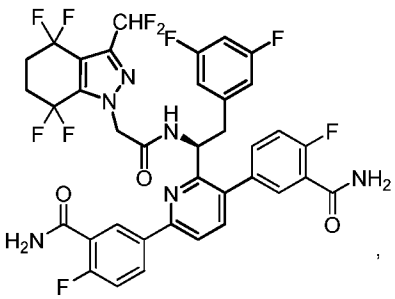

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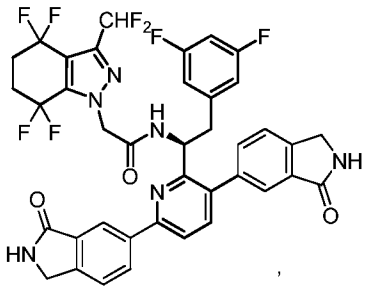

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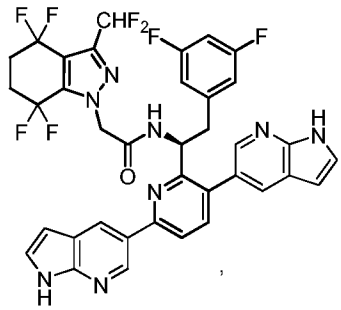

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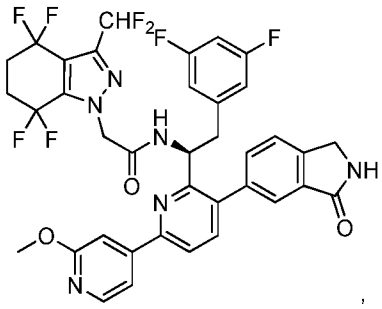

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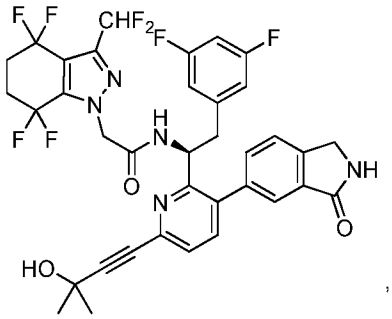

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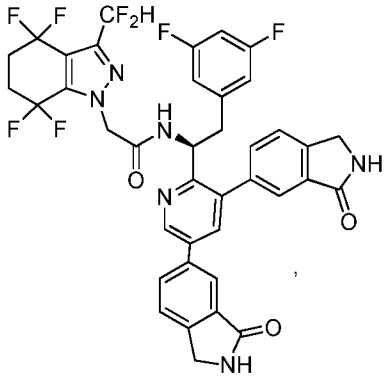

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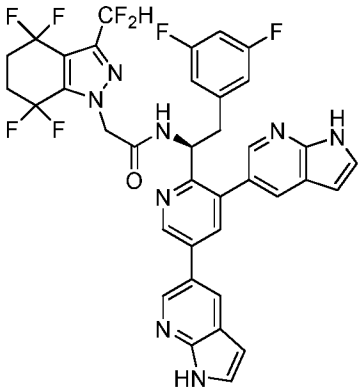

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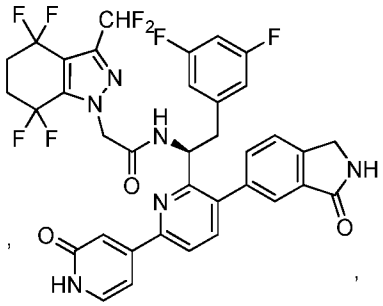

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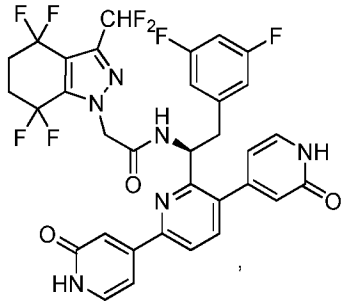

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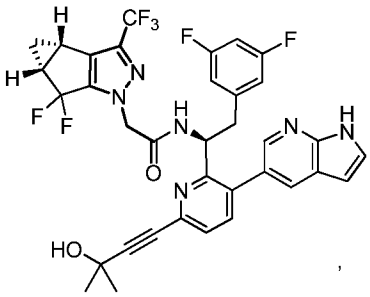

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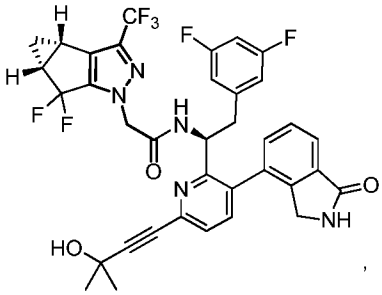

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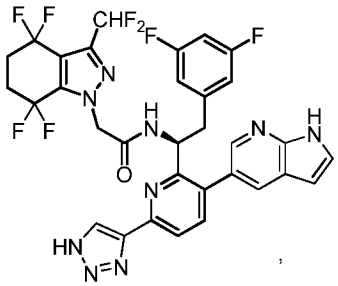

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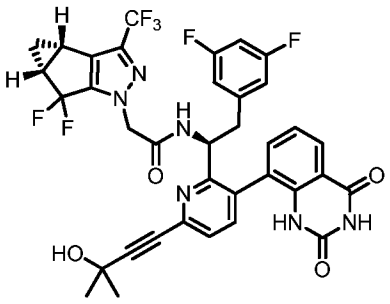

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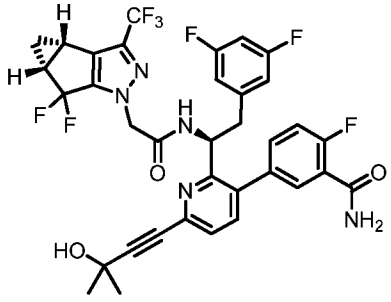

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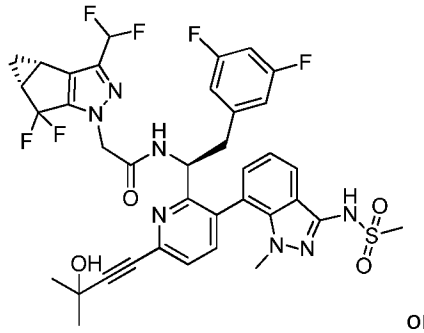
46. The compound of Claim 44, or a pharmaceutically acceptable salt thereof, which is:



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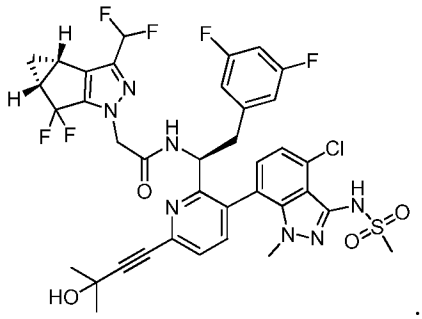

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47. A pharmaceutical composition comprising a compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

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.

Annexure - C

Distinct Effects of Two HIV-1 Capsid Assembly Inhibitor Families That Bind the Same Site within the N-Terminal Domain of the Viral CA Protein

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The emergence of resistance to existing classes of antiretroviral drugs necessitates finding new HIV-1 targets for drug discovery. The viral capsid (CA) protein represents one such potential new target. CA is sufficient to form mature HIV-1 capsids *in vitro*, and extensive structure-function and mutational analyses of CA have shown that the proper assembly, morphology, and stability of the mature capsid core are essential for the infectivity of HIV-1 virions. Here we describe the development of an *in vitro* capsid assembly assay based on the association of CA-NC subunits on immobilized oligonucleotides. This assay was used to screen a compound library, yielding several different families of compounds that inhibited capsid assembly. Optimization of two chemical series, termed the benzodiazepines (BD) and the benzimidazoles (BM), resulted in compounds with potent antiviral activity against wild-type and drug-resistant HIV-1. Nuclear magnetic resonance (NMR) spectroscopic and X-ray crystallographic analyses showed that both series of inhibitors bound to the N-terminal domain of CA. These inhibitors induce the formation of a pocket that overlaps with the binding site for the previously reported CAP inhibitors but is expanded significantly by these new, more potent CA inhibitors. Virus release and electron microscopic (EM) studies showed that the BD compounds prevented virion release, whereas the BM compounds inhibited the formation of the mature capsid. Passage of virus in the presence of the inhibitors selected for resistance mutations that mapped to highly conserved residues surrounding the inhibitor binding pocket, but also to the C-terminal domain of CA. The resistance mutations selected by the two series differed, consistent with differences in their interactions within the pocket, and most also impaired virus replicative capacity. Resistance mutations had two modes of action, either directly impacting inhibitor binding affinity or apparently increasing the overall stability of the viral capsid without affecting inhibitor binding. These studies demonstrate that CA is a viable antiviral target and demonstrate that inhibitors that bind within the same site on CA can have distinct binding modes and mechanisms of action.

The current antiretroviral arsenal against HIV-1 comprises more than 26 FDA-approved drugs from six mechanistic classes that target one of the three viral enzymes or viral entry (5). In spite of this array of drugs and targets and the simplification of therapies, drug resistance can still occur due to lack of adherence, often owing to toxicities associated with the lifelong therapy required for sustained viral suppression (28, 36). Moreover, cross-resistance within mechanistic classes and the emergence of multidrug-resistant isolates can have considerable impact on treatment options and disease outcomes, underscoring the need to discover new classes of HIV inhibitors.

The HIV-1 capsid (CA) protein plays essential roles in viral replication and as such represents an attractive new therapeutic target (11, 18). CA is initially synthesized as the central region of the 55-kDa Gag polyprotein, which is the protein that mediates the assembly and budding of the immature virion. In this context, CA provides key protein-protein interactions required for immature virion assembly (18, 40). During viral maturation, proteolytic cleavage of Gag releases CA, allowing the protein to assemble into the cone-shaped central capsid that surrounds the viral RNA genome and its associated enzymes, reverse transcriptase (RT) and integrase (IN) (34, 35). The capsid is stabilized by multiple weak protein-protein interactions, and CA mutations that impair the assembly and/or stability of the capsid typically inhibit viral replication (10, 17, 40). Thus, HIV-1 CA plays essential roles during the assembly of both the immature virion and the mature viral capsid.

CA is composed of two highly helical domains, the N-terminal domain (CA_{NTD}, residues 1 to 146) and the C-terminal domain (CA_{CTD}, residues 151 to 231), which are separated by a short flexible linker. Solution nuclear magnetic resonance (NMR) and

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high-resolution X-ray crystal structures have been reported for both isolated domains (4, 13, 14, 19, 41). Conical HIV-1 capsids belong to a class of geometric structures called fullerene cones, which comprise hexagonal lattices with 12 pentagonal defects that allow the cones to close at both ends. Although individual HIV-1 capsids differ in size and shape, they typically contain ~250 CA hexagons and have 7 CA pentagons at the wide end and 5 CA pentagons at the narrow end of the cone (15).

The recent availability of high-resolution structures of CA hexagons and pentagons has enabled molecular modeling of the viral capsid (29, 30). The capsid lattice is stabilized by four different types of intermolecular CA-CA interactions: a CA_{NTD}/CA_{NTD} interaction that creates the hexameric (or pentameric) rings (29, 30), a CA_{NTD}/CA_{CTD} interaction that forms a "girdle" that reinforces the rings (16, 29), dimeric CA_{CTD}/CA_{CTD} interactions that link adjacent hexamers across local 2-fold axes (1, 4, 22, 41), and trimeric CA_{CTD}/CA_{CTD} interactions that link adjacent hexamers across local 3-fold axes. Each of these different interfaces has been characterized structurally, although the interactions that stabilize the CA_{CTD}/CA_{CTD} trimer are not yet known in atomic detail (4). Moreover, several distinct but related CA_{CTD}/CA_{CTD} dimers have been observed (1, 4, 22, 41), and it is not yet certain how these different dimers are used to connect the CA hexamers and pentamers within authentic viral capsids (22). Although capsid-like conical assemblies can form *in vitro*, most conditions that drive CA assembly favor CA hexamerization over pentamerization such that recombinant CA proteins typically assemble into long helical tubes composed exclusively of CA hexamers (4, 26).

CA-binding inhibitors of HIV-1 capsid assembly have been reported, thus providing evidence that CA may be a viable drug target (2, 24, 32, 33, 37, 38). These inhibitors have collectively defined three independent inhibitor binding sites on CA. However, each of these sites ultimately appears to interfere with the formation of the CA_{NTD}/CA_{CTD} interface, suggesting that this interaction may be an inhibitory "Achilles' heel" for capsid assembly. The small-molecule inhibitor CAP-1 binds to an induced hydrophobic pocket at the base of the CA_{NTD} helical bundle (24, 37). The pocket is located at the junction of α-helices 1, 2, 4, and 7 and is normally occupied by the aromatic side chain of Phe-32 in structures of uninhibited CA hexamers, pentamers, and monomers. Binding of CAP-1 distorts the loop between helices 3 and 4, which may inhibit the formation of the CA_{NTD}/CA_{CTD} interface (16, 24). A second CA inhibitor, termed the CAI peptide, binds to a conserved hydrophobic cleft within the CA_{CTD} four-helix bundle and inhibits both Gag and CA assembly *in vitro* (33, 38). Superposition of the CA_{CTD}-CAI complex onto the CA_{NTD}/CA_{CTD} interface of assembled CA suggested that binding of the peptide would sterically hinder the CA_{NTD}/CA_{CTD} interaction (16, 29). The peptide may also act allosterically by altering the geometry of CA_{CTD} dimers such that propagation of the mature CA lattice is prevented. More recently, a third small-molecule binding site on CA was identified via a high-throughput screen for inhibitors of HIV replication. PF-3450074 and related compounds bind between helix 4 and helix 7 of the CA_{NTD}. This latest class of CA inhibitors disrupts the stability of the viral capsid in both the early and late stages of viral replication, again probably by altering CA_{NTD}/CA_{CTD} interactions (2, 32).

Here we describe two new and highly potent families of CA inhibitors that were identified by a novel high-throughput screening (HTS) assay. Inhibitors from both families bind to the CA_{NTD} by further expanding the CAP-binding pocket. Moreover, although these two classes of inhibitors target the same binding pocket, they have distinct binding modes, select for unique patterns of resistance mutations, and have different effects on virion morphology.

MATERIALS AND METHODS

Immobilized capsid assembly assay. The 5′-biotin-labeled $(TG)_{25}$ oligonucleotide (Integrated DNA Technology Inc.) was immobilized on Reacti-Bind neutravidin-coated black 384-well plates (Pierce catalog no. 15402) that were washed with 80 μl/well of buffer C {50 mM Tris (pH 8.0), 350 mM NaCl, 10 μM $ZnSO_4$, 0.0025% (wt/vol) 3-[(3-cholamidopropyl)-dimethylammonio]-1-propanesulfonate (CHAPS), 50 μg/ml bovine serum albumin (BSA), 1 mM dithiothreitol (DTT)} prior to the addition of 50 μl/well of a 25 nM solution of oligonucleotide in buffer C plus 5 mg/ml BSA, followed by overnight incubation. Unbound material was removed by two washes with buffer C. Assembly reactions were performed in 60-μl/well reaction mixtures comprising 100 nM 5′-fluorescein-labeled $(TG)_{25}$ oligonucleotide (Integrated DNA Technology Inc.), 2 μM CA-NC protein, and various concentrations of test compounds diluted in buffer C with a final dimethyl sulfoxide (DMSO) concentration of 1%. Assembly reaction mixtures were incubated for 2 h at room temperature, followed by two washes with buffer C, the addition of 80 μl/well of buffer C plus 0.1% sodium dodecyl sulfate (SDS), and a 15-min incubation prior to quantification of captured fluorescence on a Victor^2 plate reader (Perkin-Elmer Life Sciences) equipped with fluorescein excitation and emission filters. The amount of captured fluorescence is proportional to the level of assembly. The concentrations of compound required for 50% inhibition of assembly (IC_{50}s) were generated by fitting inhibition curves from 10-point dilution series to the following equation: % inhibition $= (I_{max^n} \times [I]^n)/([I]^n + IC_{50^n}) \times 100$, where I_{max} is the maximal percent inhibition, $[I]$ is the corresponding concentration of inhibitor, and the superscript n denotes the Hill coefficient.

Protein expression and purification. pET-11a vectors were used to express the HIV-1_{NL4-3} CA-NC (WISP-98-68, Gag residues 133 to 432) carrying the CA G94D mutation, full-length CA (WISP-98-85), CA_{NTD} (WISP-96-19, CA residues 1 to 146), and CA_{CTD} (WISP-97-07, CA residues 146 to 231) (17, 26). Point mutations were introduced using the QuikChange II site-directed mutagenesis kit (Stratagene) according to the manufacturer's instructions.

All proteins were expressed in *Escherichia coli* BL21(DE3) cells (Novagen). Briefly, LB medium was inoculated with overnight precultures, which were grown at 37°C until mid log-phase (A_{600}, ~0.6). Protein expression was induced with 0.5 to 1 mM isopropyl-β-D-thiogalactopyranoside (IPTG) for 4 to 6 h at 30°C. Cells were harvested by centrifugation, and pellets were stored at −80°C until purification. For NMR studies, ^{15}N-labeled proteins were produced using Spectra 9 (^{15}N, 98%) medium (Cambridge Isotope Laboratories Inc.).

Purification of CA-NC (and all mutants) was carried out as follows. Five to 10 g of cell paste was lysed by sonication in 40 ml of buffer A (20 mM Tris [pH 7.5], 1 μM $ZnCl_2$, 10 mM β-mercaptoethanol) supplemented with 0.5 M NaCl and Complete EDTA-free protease inhibitor tablets (Roche). Nucleic acids and cell debris were removed by adding 0.11 volume of 0.2 M ammonium sulfate and an equivalent volume of 10% poly(ethyleneimine) (pH 8.0), stirring the sample for 20 min at 4°C, and centrifuging at 30,000 × *g* for 20 min. CA-NC protein was recovered from the supernatant by adding 0.35 volume of saturated ammonium sulfate solution, followed by centrifugation at 10,000 × *g* for 15 min. The pellet was dissolved in 10 ml of buffer A plus 0.1 M NaCl and was dialyzed overnight in buffer A plus 0.05 M NaCl. The sample was cleared by centrifugation and was chromatographed on a 1-ml HiTrap SP HP column (GE Healthcare) preequilibrated with dialysis buffer. CA-NC protein was eluted with buffer A plus 0.5 M NaCl. Fractions containing the protein were pooled, and the concentration was determined by absorbance at 280

nm using the calculated molar extinction coefficient ($\varepsilon = 40{,}220\ M^{-1}\ cm^{-1}$).

Purification of CA_{NTD} (wild type [WT], all mutants, and ^{15}N labeled) was similar to that of CA-NC, but lysis was performed in buffer B (20 mM morpholineethanesulfonic acid [MES] [pH 6.5], 10 mM β-mercaptoethanol) supplemented with 0.5 M NaCl and Complete EDTA-free protease inhibitor tablets. Nucleic acids and cell debris were removed as described above. CA_{NTD} was recovered from the supernatant by the addition of 0.6 volume of saturated ammonium sulfate. The pellet was dissolved in 10 ml of buffer B and was dialyzed in the same buffer using dialysis tubing with a 10,000-molecular-weight cutoff. The sample was clarified by centrifugation and was sequentially passed through HiTrap SP HP and Q HP columns (GE Healthcare) preequilibrated in buffer B. CA_{NTD} was recovered in the flowthrough and wash fractions and was concentrated, and the protein concentration was determined by the absorbance at 280 nm using the calculated molar extinction coefficient ($\varepsilon = 25{,}320\ M^{-1}\ cm^{-1}$).

Cells. SupT1 and 293FT cells were obtained from the ATCC (CRL-1942) and Invitrogen (R700-07), respectively. C8166 cells were obtained from J. Sullivan, University of Massachusetts Medical Center. C8166-LTR-Luc cells were produced by stable transfection of C8166 cells with an HIV long terminal repeat (LTR)-luciferase construct followed by selection with 5 μg/ml blasticidin S-HCl through three consecutive limiting dilutions. SupT1 and C8166 cells were maintained in RPMI medium (Wisent) supplemented with 10% fetal bovine serum (FBS; HyClone). C8166-LTR-Luc cells were maintained in the same medium supplemented with 5 μg/ml blasticidin S-HCl. Antibiotic was removed for all antiviral activity assays. 293FT cells were maintained in Dulbecco's modified Eagle medium (DMEM; Wisent) supplemented with 10% FBS (37°C, 5% CO_2).

Antiviral activity (EC_{50}) determinations. Inhibitors were prepared in 10 to 20 mM stocks in 100% DMSO and were serially diluted in RPMI medium plus 10% FBS. C8166-LTR-luciferase cells were infected at a multiplicity of infection (MOI) of 0.005 with HIV-1 NL4-3 for 1.5 h and were seeded at 25,000 cells/well in 96-well black microtiter plates, in wells already containing inhibitors or an equivalent concentration of DMSO (0.5%). Plates were incubated for 3 days (37°C, 5% CO_2), and luciferase expression levels were determined by the addition of 50 μl per well of SteadyGlo (Promega) and measurement on the BMG LUMIstar Galaxy luminometer. The inhibitor concentration needed to produce a 50% reduction of viral replication activity (50% effective concentration [EC_{50}]) was determined by nonlinear regression analysis using SAS software (SAS Institute, Cary, NC).

Single-cycle assays for evaluating early- versus late-stage inhibition of HIV-1 replication. Three constructs for the generation of vesicular stomatitis virus G glycoprotein (VSV-G)-pseudotyped HIV-1 were made as follows. HIV-1 helper virus was amplified from SODk1CG2 cells (21) and was cloned into pcDNA 3.1. The helper plasmid, which lacks both LTRs as well as functional gp120 and Nef, has all HIV coding sequences expressed from the immediate-early cytomegalovirus (CMV) promoter. Gag-Pol, Vif, and Vpr were derived from NL4-3, while all other sequences were derived from HXB2. The pTV-linker self-inactivating transfer vector (23) was obtained through the AIDS Research and Reference Reagent Program, Division of AIDS, NIAID, NIH, from Lung-Ji Chang. pTV-linker was further modified by inserting the EF-1α promoter and firefly luciferase gene, creating pTV-Luc. The VSV-G expression plasmid was obtained from Ivan Lessard (Boehringer Ingelheim [Canada] Ltd.).

The activity of the CA compounds in the early phase of the replication cycle was evaluated by transducing SupT1 cells with VSV-G-pseudotyped HIV-1 in the presence of test compounds. VSV-G-pseudotyped HIV-1 was prepared by batch transfection of 293FT cells in a T-75 flask with 2.2 μg of VSV-G plasmid, 6.7 μg of HIV-1 helper plasmid, and 9 μg of pTV-luc by using FuGene (Roche Applied Science). The 293FT supernatant was harvested 48 h posttransfection and was centrifuged for 5 min at 2,000 rpm. p24 levels were quantified using an HIV-1 p24 enzyme-linked immunosorbent assay (ELISA) kit (Beckman Coulter). Viral supernatants were stored at −80°C. In a 96-well microtiter plate, 40,000 SupT1 cells (25 μl) were infected with an amount of virus corresponding to 4 ng of p24 (25 μl) in the presence of 50 μl of the test compound (in 1% DMSO). Forty-eight hours postinfection, 25 μl Steady Glo (Promega) was added to each well, and luciferase activity was measured using a TopCount plate reader (Perkin-Elmer).

Inhibitory activity during the late phase of the replication cycle was evaluated by adding test compounds to 293FT cells during the production of VSV-G-pseudotyped HIV-1. Cells were batch transfected (as described above) in the absence of compounds by using FuGene (Roche Applied Science) for 4 to 6 h in a T-75 (75-cm^2) flask, after which cells were dislodged by pipetting, and ~40,000 cells in 50 μl were transferred to a 96-well microtiter plate (Corning Costar) containing an equivalent volume of test compound from 10-point dose-response curves (in 1% DMSO). Forty-eight hours posttransfection, 10 μl viral supernatant was diluted 1:10 in RPMI medium supplemented with 10% FBS in a second 96-well microtiter plate and was then frozen at −80°C for at least 1 h. Following thawing, 10 μl of diluted viral supernatant was used to infect 40,000 SupT1 cells in a final volume of 100 μl. Thus, compounds were diluted 100-fold in order to minimize any potential inhibitory activity in the early phase of the replication cycle. Forty-eight hours postinfection, firefly luciferase activity was measured as described above. The cytotoxicity of the test compounds was evaluated by adding 50 μl of CellTiter Glo (Promega) to the microplates containing the transfected 293FT cells. Luminescence was measured using a TopCount plate reader.

ITC. Isothermal titration calorimetry (ITC) was performed at 25°C in 50 mM Tris (pH 8.0), 350 mM NaCl, and 1% DMSO by using a VP-ITC microcalorimeter (MicroCal Inc.; GE Health Sciences). Titrations were performed using 200 μM CA_{NTD} in the syringe and approximately 20 μM compound in the sample cell. After degassing, the compound solution was centrifuged at 15,000 × *g* for 15 min and was loaded in the sample cell. The precise compound concentration in the sample cell was assessed by high-performance liquid chromatography (HPLC) using a reference DMSO solution of the compound. Each titration consisted of 19 injections of 15 μl at 280-s intervals. Thermodynamic parameters were derived by fitting the binding isotherms to the single-site binding model algorithm, with stoichiometries (n), enthalpies (ΔH), and equilibrium dissociation constants (K_D) allowed to float during nonlinear least-squares fits of the data. Typically, stoichiometries (n) were between 0.9 and 1.1. The starting concentrations of more-potent compounds were reduced to 5 μM in the sample cell for better assessment of the K_D.

Selection of HIV-1 variants resistant to capsid inhibitors. C8166 cells were infected at an MOI of 0.1 with WT HIV-1 2.12 (7) in complete RPMI medium (RPMI 1640, 10% FBS, 10 μg/ml gentamicin, and 10 μM β-mercaptoethanol) with twice to 5 times the EC_{50} of the capsid inhibitor. At each passage (3 to 4 days), microscopic evaluation of the cytopathic effect (CPE) was performed, and the culture supernatant was used to infect fresh C8166 cells, which were then maintained at the same or a higher concentration of inhibitor depending on the CPE. At passages where viral breakthrough was evident, the genomic DNA was isolated using the DNeasy Blood and Tissue kit (Qiagen). The CA gene was amplified by PCR, and the fragments were cloned into the Zero Blunt TOPO plasmid (Invitrogen) and sequenced by automated sequencing.

Construction of recombinant HIV-1. To create viruses carrying CA mutations, site-directed mutagenesis was carried out using the QuikChange site-directed mutagenesis kit (Stratagene). All mutations were confirmed by sequencing on an ABI Prism 3100 genetic analyzer (Applied Biosystems Inc.). Sequenced DNA fragments containing the confirmed mutation(s) were subcloned into the NL4-3 provirus by standard molecular biology techniques. Viral stocks were produced by transfecting 293 cells by the calcium phosphate method (20). The culture supernatant was collected after 3 days (37°C, 5% CO_2); cell debris was removed; and aliquots were frozen at −80°C. The 50% cell culture infective dose ($CCID_{50}$) was determined by monitoring the formation of syncytia in C8166 cells.

Jurkat cell replication capacity assay. The replication capacity assay was carried out with Jurkat-LTR luciferase cells as described previously (7). Briefly, Jurkat cells expressing an HIV LTR luciferase construct were infected with virus at an MOI of 0.05 for 2 h at 37°C, washed, and seeded at 1×10^5 cells/well in 200 μl RPMI 1640 supplemented with 10% FBS and 10 μg/ml gentamicin in clear-bottom black 96-well microtiter plates. Every 3 to 4 days, the cells were mixed, and 100 μl medium was removed and replaced with fresh medium. Luciferase levels were determined by adding 50 μl/well BrightGlo (Promega) at days 7, 10, 12, and 14 postinfection and reading on the LUMIstar galaxy plate reader (BMG). Replication was not assessed at later times owing to the potential for variability over longer periods.

Assays for inhibition of virion release, infectivity, and assembly. 293T cells were transfected with the proviral HIV-1_{NL4-3} R9 expression construct in the presence of benzodiazepine (BD) and benzimidazole (BM) inhibitors (50-fold over the EC_{50}s). Viral Gag expression, processing, virion release, and viral titers were assayed as described in detail elsewhere (40). Released virions were fixed with gluteraldehyde and osmium tetroxide, stained with uranyl acetate, embedded in epoxy resin, thin sectioned (thickness, 60 to 90 nm), poststained with Reynold's lead citrate, and imaged on a Hitachi H-7100 transmission electron microscope at a magnification of ×50,000, as described in detail elsewhere (39).

X-ray crystallography models. A full description of the crystallization and diffraction data will be reported elsewhere (manuscript in preparation). For the superposition shown in Fig. 3, monomer A of the CA_{NTD}-BD 3 structure and monomer B of the CA_{NTD}-BM 4 structure were superposed on the unliganded CA_{NTD} (residues 1 to 146) of the stabilized hexameric CA structure (PDB identification code [ID] 3H47) (29). Monomer A of the CA_{NTD}-BD 3 structure was selected because it is the only one of the two monomers of the asymmetric unit that bound the BD 3 inhibitor (the other monomer is apo). Monomer B of the CA_{NTD}-BM 4 structure was selected because the bound inhibitor appears to be less affected by neighboring molecules of the crystal lattice. The alignments were based on 300 atoms constituting the backbone of 75 CA_{NTD} residues: Ala47 to Asn57, Ala64 to Leu83, Arg97 to Met118, and Ile124 to Tyr145. This selection focuses on the most immutable portions of CA_{NTD}, avoiding helices 1 and 2 and other highly flexible regions. The calculated root mean square distances (RMSDs) for the fitted CA_{NTD}-BD 3 and CA_{NTD}-BM 4 structures to the unliganded CA_{NTD} were both 0.44 Å.

For the liganded hexameric model shown in Fig. 9, monomer B of the CA_{NTD}-BM 4 structure was superposed on the unliganded CA monomer of the hexameric CA structure (PDB ID 3H47) (29). The superposition was based on 440 atoms constituting the backbone of 110 CA residues: residues 1 to 3, 10 to 24, 33 to 57, 64 to 82, and 97 to 144. This more comprehensive selection of residues includes the major secondary structural elements while avoiding highly flexible regions. A hybrid CA molecule was then made by fusing residues 1 to 140 of the CA_{NTD}-BM 4 structure with residues 141 to 219 of 3H47. The hexamer of this hybrid molecule was then generated by applying the appropriate crystallographic symmetry operations based on the hexagonal (P6) space group of 3H47.

Protein structure accession numbers. The PDB entries for CA_{NTD}-BD 3 and CA_{NTD}-BM 4 are 4E91 and 4E92, respectively.

RESULTS

Efficient HTS assay for inhibitors of HIV-1 CA assembly. In principle, inhibition of CA tube assembly can be used to screen for small molecules that block capsid assembly, but this method generally requires high protein concentrations and must be performed under high-ionic-strength conditions (25, 26). We therefore developed an *in vitro* CA assembly assay that was more amenable to high-throughput screening (HTS).

Our assay employed a Gag fragment that spanned the CA and NC regions and took advantage of the ability of the nucleocapsid (NC) to bind tightly to TG-rich deoxyoligonucleotides (9). The use of $d(TG)_{25}$ as a "scaffold" enabled CA tubes to form at much lower protein and salt concentrations than in previously reported assays. Assembly reactions were performed in neutravidin-coated 384-well plates using both biotin- and fluorescein-labeled $d(TG_{25})$. The biotin-labeled $d(TG_{25})$ oligonucleotide bound on the surface acts to nucleate the assembly of complexes, and further "polymerization" of CA-NC is driven by soluble fluorescein-labeled $d(TG_{25})$. Unbound and unassembled species are washed away from captured assembly products at the end of the assembly reaction.

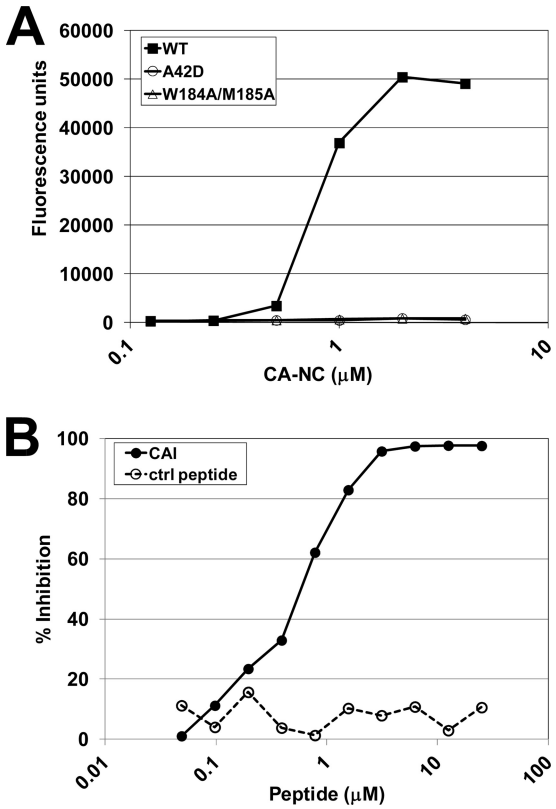


FIG 1 Validation of the capsid assembly assay. (A) Assay showing that wild-type HIV-1 CA-NC assembles in a concentration-dependent fashion, whereas the assembly-defective CA-NC mutants (the A42D and W184A M185A mutants) do not. CA-NC assembly was detected by capture and immobilization of a fluorescent oligodeoxynucleotide. (B) CAI, a known peptide inhibitor of HIV-1 capsid assembly (33), inhibits CA-NC assembly in a concentration-dependent fashion, whereas a scrambled peptide control (ctrl) does not. The assay was performed with wild-type CA-NC under standard assay conditions, and activities are reported as the percentage of inhibition of the control fluorescence signal.

As shown in Fig. 1A, titration of increasing quantities of wild-type (WT) CA-NC in this assay led to a dose-dependent increase in the fluorescence signal up to a level of saturation that corresponded to complete loading of the oligonucleotide with CA-NC protein. In contrast, two control CA-NC proteins with amino acid substitutions previously shown to block capsid assembly *in vitro* and *in vivo* (A42D and W184A/M185A) (17, 40) were inactive in this assay.

The sensitivity of the capsid assembly assay to known inhibitors was confirmed using the CAI peptide as a positive control (33). As shown in Fig. 1B, increasing concentrations of the CAI peptide abrogated the assay signal, with an IC_{50} of 0.6 μM (Fig. 1B). In contrast, a control peptide with the same amino acid com-

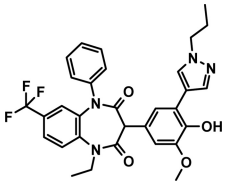
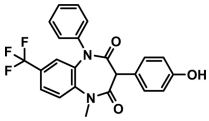
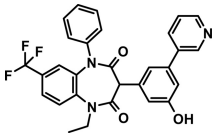
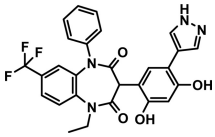
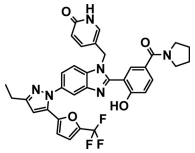
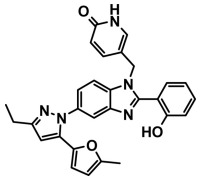
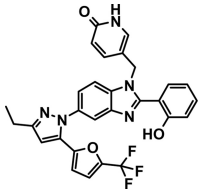
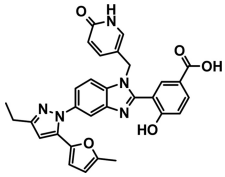
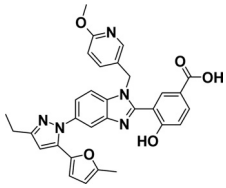
position as CAI, but with a scrambled sequence, failed to inhibit CA-NC assembly, even at concentrations as high as 25 μM (Fig. 1B). Taken together, these results validate the assay and indicate that it recapitulates the formation and inhibition of capsid-like assemblies *in vitro*.

Identification of two classes of HIV-1 CA assembly inhibitors. The CA assembly assay was used to screen the Boehringer Ingelheim corporate compound collection, producing >50 active hit clusters. Hits were triaged based on several criteria, including relative potency in the capsid assembly assay, lack of activity in an analogous assay based on assembly of a Gag CA-NC protein from Rous sarcoma virus (RSV Gag ΔMBD ΔPR protein), cytotoxicity, and assessment of chemical tractability. Compounds that survived this triage showed direct binding to CA_{NTD} as analyzed by NMR chemical shift perturbations and cocrystallization (see below) (data not shown). Based on these hit-to-lead studies, two structurally distinct families of compounds were chosen for lead optimization (Table 1): the benzodiazepines (BDs) and the benzimidazoles (BMs). Significant medicinal chemistry efforts (8; also manuscripts in preparation) led to the synthesis of the most potent inhibitors from the BD and BM series, BD 1 (half-maximal antiviral effective concentration [EC_{50}], 70 ± 30 nM [$n = 21$]; half-maximal cytotoxic concentration [CC_{50}], >28 μM) and BM 1 (EC_{50}, 62 ± 23 nM [$n = 53$]; CC_{50}, ≥20 μM), both of which displayed potent antiviral activity and a large window relative to cytotoxicity (CC_{50}/EC_{50}, >300-fold). These inhibitors, along with related compounds within the same two families (Table 1), were characterized further to establish their mechanisms of action.

Mechanistic studies of the BD and BM inhibitors. To ensure that the BD and BM compounds did not also inhibit the same targets as currently available antiretroviral agents, representative compounds from both the BD and BM series were tested for activity against HIV-1 NL4-3 strains that were resistant to the four major classes of antiretroviral inhibitors: nonnucleoside reverse transcriptase inhibitors (NNRTI) (RT mutations Y188L and V106A), nucleoside reverse transcriptase inhibitors (NRTI) (RT mutations K65R and M184V), protease (PR) inhibitors (PI) (PR mutations V32I I47V and L33F I54L), and integrase strand transfer inhibitors (INSTI) (IN mutation G140S Q148H). As shown in Table 2, BD 1, BM 2, and BM 3 inhibited the replication of the wild-type and all mutant viruses with equal potencies. In contrast, control experiments showed the expected pattern of reduced susceptibility to well-characterized antiretrovirals. These data indicate that the mechanism of action of the BD and BM compounds differs from that of the four major classes of antiretroviral agents.

To determine the stage of the viral replication cycle targeted by the BM and BD compounds, we tested their effects on the efficiency of HIV-1 vector transduction when the compounds were applied either during virus production (late phase) or during infection (early phase). A vesicular stomatitis virus G glycoprotein (VSV-G)-pseudotyped HIV-1 vector containing a luciferase reporter under the control of the HIV-1 LTR was used in these studies, allowing discrimination between the inhibition of early replication events (i.e., virus entry through transcription) and late events (i.e., viral transcription through virus maturation). Control compounds behaved as expected in our assays: nevirapine, which inhibits the early-stage process of reverse transcription, reduced the reporter activity only when added to target cells. In contrast, lopinavir, which inhibits the late-stage processes of Gag proteolysis and viral maturation, inhibited vector transduction

TABLE 1 Compounds used in this study and their antiviral activities

Compound	Structure	EC_{50} (μM)[a]
BD compounds		
BD 1		0.070
BD 2		1.1
BD 3		0.48
BD 4		0.13
BM compounds		
BM 1		0.062
BM 2		0.26
BM 3		0.11
BM 4		>46[b]
BM 5		2.4[c]

[a] Activity determined in a standard antiviral replication assay (see Materials and Methods).
[b] BM 4 was inactive in the viral replication assay but active in the capsid assembly assay.
[c] BM 5 was active in the capsid assembly assay.

TABLE 2 Relative activities of capsid assembly inhibitors against drug-resistant viruses

Inhibitor	EC_{50} (nM) for the WT	Fold change from the EC_{50} for the isogenic WT virus[a] with the following mutation (resistance class)[b]: Y188L (NNRTI)	V106A (NNRTI)	K65R (NRTI)	M184V (NRTI)	V32I I47V (PI)	L33F I54L (PI)	G140S Q148H (INSTI)
BD 1	70	1.1	0.9	0.8	0.9	1.5	0.9	1.2
BM 2	284	1.0	0.7	1.0	0.6	1.1	1.3	1.2
BM 3	112	1.2	0.9	0.7	1.0	0.7	0.6	0.8
Nevirapine	18	**>83**	**130**[b]	0.3	0.5	1.4	1.4	1.3
Lamivudine	89	1.3	0.9	**26.4**	**>96**	0.9	1.2	1.2
Amprenavir	35	0.6	0.8	1.2	0.5	**6.9**	**8.3**	1.3
Raltegravir	1.5	2.8[b]	0.4	1.0	0.6	0.7	1.8	**227**

[a] All values are averages for two independent experiments except for the values for V106A with nevirapine and Y188L with raltegravir, for which experiments were performed once. Significant fold change values are in boldface.
[b] Resistance targets were RT for Y188L, V106A, K65R, and M184V; PR for V32I I47V and L33F I54L; and IN for G140S Q148H.

only when added to producer cells (Table 3). By these criteria, the BD and BM compounds both acted primarily at the late stage of the viral replication cycle, since both BD 1 and BM 2 inhibited replication when added during virus production. Furthermore, the EC_{50}s obtained in the late-stage assay for BD 1 and BM 2 were similar to those obtained in standard, multiple-round HIV-1 replication assays (Table 3). In contrast, EC_{50}s for these compounds were at least 10-fold higher when they were applied during the infection of target cells (early phase). Both compounds did exhibit weak inhibitory activity in the early phase (EC_{50}, ~3 μM), which could be due to effects on viral core stability and disassembly or, alternatively, to cytotoxicity. Regardless, the data establish that both the BD and BM compounds act primarily by inhibiting the late stage(s) of viral replication.

BD and BM inhibitors bind the N-terminal domain of the HIV-1 CA protein. Isothermal titration calorimetry (ITC) and 2-dimensional (2D)-NMR chemical shift perturbation analyses were performed to test whether the BD and BM compounds bound purified recombinant HIV-1 CA proteins and to map their binding sites. The NMR chemical shift perturbation analyses demonstrated that BD and BM inhibitors bound CA_{NTD}, with shifted residues clustered at the bases of helices 1, 2, 4, and 7 and at the flexible loops between helices 1 and 2 and helices 3 and 4 (data not shown). ITC binding isotherms showed that inhibitors from both families of compounds bound CA_{NTD} with 1:1 stoichiometries and submicromolar dissociation constants. For example, two BM compounds, BM 2 and BM 3, and the weak-binding BD compound BD 2 (see Table 1) bound CA_{NTD} with dissociation constants of 210 nM, 87 nM, and 690 nM, respectively (Table 4). These dissociation constants correlated well with the antiviral EC_{50}s for these compounds (260, 110, and 1,100 nM, respectively [Table 1]). Binding of the BM compounds was enthalpically driven (ΔH, −18.3 and −18.7 kcal/mol, respectively), which is a favorable property for viral inhibitors (12). Unfortunately, ITC analyses could not be performed with more-potent compounds in the BD series owing to their limited solubility. Nevertheless, our data establish that both compound classes bind directly to the CA_{NTD}, independently of the CA C-terminal domain, CA dimerization, or higher-order CA assembly.

Crystal structures of BD and BM inhibitors bound to the HIV-1 CA_{NTD}. To explore the inhibitor binding modes in greater detail, representative compounds from each inhibitor family, BD 3 and BM 4 (see Table 1), were cocrystallized in complex with CA_{NTD}. The structures of both complexes were determined at high resolutions and were refined fully (for CA_{NTD}-BD 3, 1.7 Å resolution, R = 22.0%, and R_{free} = 24.3%; for CA_{NTD}-BM 4, 1.8 Å resolution, R = 22.0%, and R_{free} = 26.4%). Complete details of the crystallography will be reported elsewhere.

As shown in Fig. 2, both inhibitor types bind to a pocket located at the base of the central four-helix bundle of the CA_{NTD}, which is the same site described previously for CAP-1 (24). As was the case for the CAP inhibitors, binding of the BD or BM compounds displaces the side chain of Phe32 from the helical bundle to create a new pocket within the hydrophobic core. Although their binding sites overlap, there are interesting differences in the ways in which the two compounds interact with the protein and affect its structure (Fig. 2 and 3). Specifically, the BD compounds bind more deeply and enlarge the pocket to a greater extent, resulting in significant disruptions of the CA_{NTD} tertiary structure (Fig. 3A). In particular, the trifluoromethyl group of BD 3 binds very deeply, displacing the CA Trp23 side chain at the top of the pocket by more than 3 Å, which in turn contributes to a >1.5-Å displacement of the CA α1 helix. The BM compound BM 4 also perturbs the CA tertiary structure, but in this case the native

TABLE 3 Inhibition of postentry (early) versus postintegration (late) stages of virus replication

Compound	Value for single-cycle assays[a]: Early EC_{50} (μM)	Late EC_{50} (μM)	Cytotoxicity[b] (CC_{50} [μM])	EC_{50} (μM) for multiple-cycle assays
BD 1	2.8	0.2	>7.0	0.06
BM 2	3.2	0.2	6.2	0.26
Lopinavir	>0.5	**0.01**	>0.5	0.009
Nevirapine	**0.08**	>2.2	>2.2	0.02

[a] Boldface values denote the expected result for late- and early-stage activities of Lopinavir and Nevirapine, respectively.
[b] Cytotoxicity was determined on virus producer cells (late phase).

TABLE 4 Energetics of inhibitor binding to CA_{NTD}[a]

Compound	K_D (μM)	ΔG (kcal/mol)	ΔH (kcal/mol)	$-T\Delta S$ (kcal/mol)
BM 2	0.210	−9.12	−18.3	9.21
BM 3	0.087	−9.64	−18.7	9.06
BD 2	0.690	−8.40	−7.50	−0.90

[a] Inhibitor binding was quantified by isothermal titration calorimetry (see Materials and Methods).

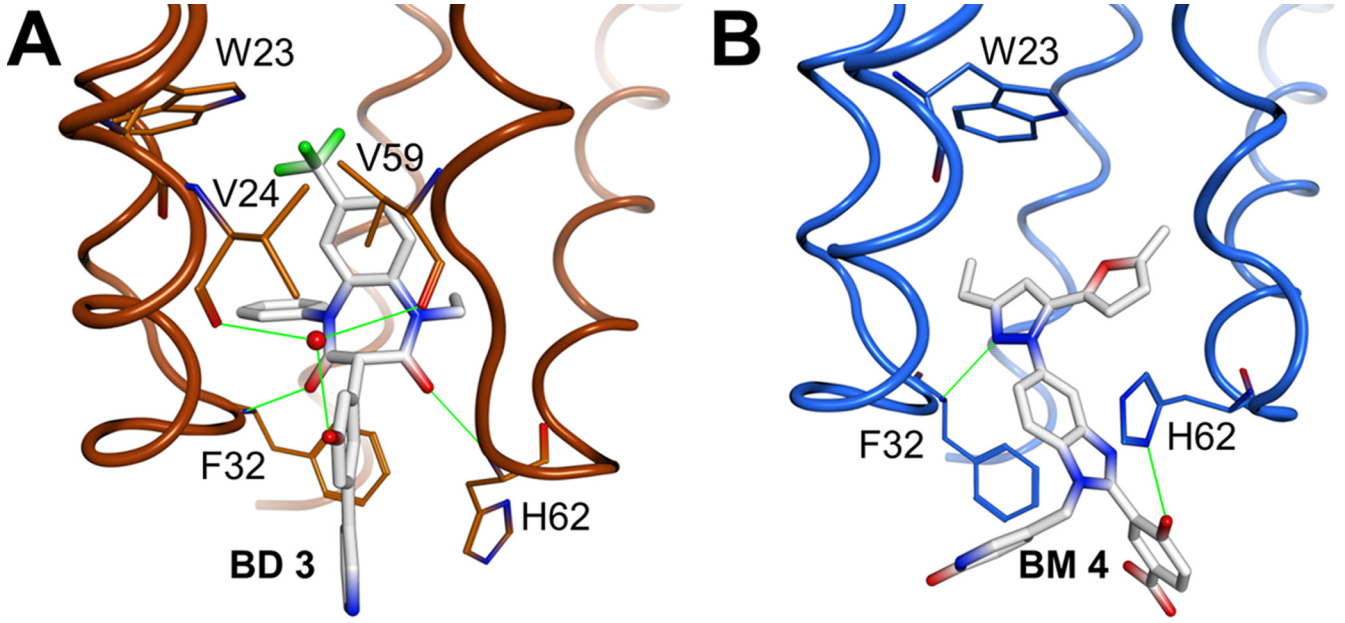


FIG 2 X-ray crystal structures of CA_{NTD} with the BD 3 (A) and BM 4 (B) inhibitors bound within an induced pocket at the base of the HIV-1 CA_{NTD} four-helix bundle. Note that BD 3 binds deeply within the pocket and forms two direct H-bonds (green) with the backbone nitrogen atoms of Phe32 and His62, as well as water-mediated hydrogen bonds with the backbone carbonyl oxygen atoms of Val24 and Val59. BM 4 binds less deeply and forms direct hydrogen bonds with the backbone nitrogen atom of Phe32 and with Nδ of His62. The inhibitors are shown in stick models with carbons in white, nitrogens in blue, oxygens in red, and fluorines in green. CA backbones and key side chains are shown in orange (BD 3 complex) and blue (BM 4 complex).

CA interactions at the top of the pocket are much less disrupted (Fig. 3B).

Additionally, both compounds reposition the flexible loop linking CA helices 3 and 4 (Fig. 3B), but in considerably different ways. BD 3 hydrogen bonds with the backbone NH of His62, thus positioning the imidazole side chain away from the pocket (Fig. 2A), while BM 4 interacts with the His62 imidazole, positioning it nearer to the pocket (Fig. 2B). Both inhibitor-bound loop confor-

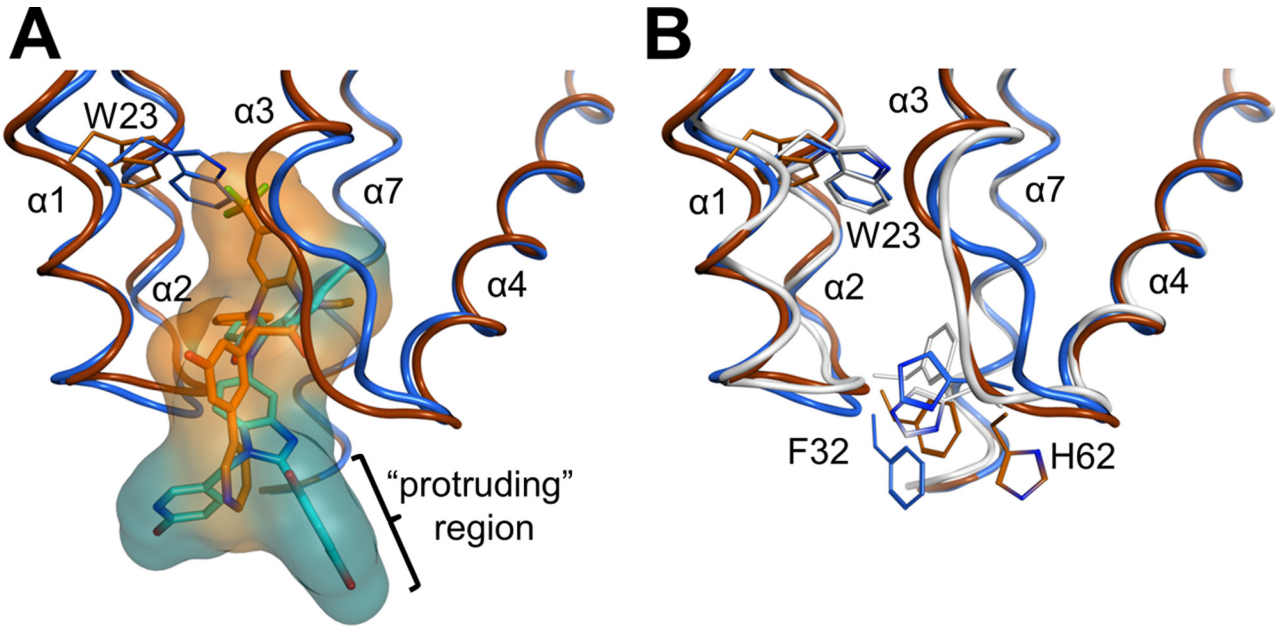


FIG 3 Structural comparisons illustrating the differing effects of BD and BM inhibitor binding on the CA_{NTD} conformation. (A) Overlay of the BD 3 (orange) and BM 4 (blue) complex structures. van der Waals surfaces illustrate how BM 4 protrudes further into the solvent, whereas BD 3 binds more deeply and induces the formation of a larger pocket, primarily by shifting CA-NC helices 1 and 2 and the Trp23 side chain. The "protruding region," or the substituents on the inhibitors that extend outside the pocket, is indicated (see the text). (B) Overlay of the apo (white)-, BD 3 (orange)-, and BM 4 (blue)-bound CA_{NTD} structures detailing shifts of backbones and key residues. The bound inhibitors have been removed for clarity. Residues 1 to 146 of the stabilized hexameric CA structure (PDB ID 3H47) (29) were used as the reference apo structure. Residues of helices 1 and 2 and highly flexible portions of CA_{NTD} were omitted from the superposition calculations, as described in Materials and Methods.

mations differ substantially from that of the apo-CA hexamer structure (29) and would be expected to perturb or inhibit the formation of the CA_{NTD}/CA_{CTD} interface.

Finally, the two classes of compounds protrude from the CA_{NTD} with significantly different trajectories, and the BM compounds extend much further outside the pocket than do the BD compounds (Fig. 3A). Structure-activity relationships within the protruding groups of the BM compounds revealed their importance for potency, suggesting that this region of the inhibitor may make additional interactions within the assembled capsid (or Gag) lattices. In contrast, the activities of the BD inhibitors were not significantly altered by chemical modifications beyond the directly attached phenyl group, implying that this part of the inhibitor does not make other significant contacts. Thus, although both classes of inhibitors bind the same pocket on CA, differences in the details of their binding modes suggest the possibility that they may have distinct effects on capsid assembly.

Differential effects of the BD and BM inhibitors on virus assembly and maturation. The effects of the BD and BM inhibitors on Gag production, processing, and virus release were analyzed by Western blotting of cell- and virion-associated Gag proteins (Fig. 4). Virus was produced in the presence of high concentrations (50-fold over the EC_{50}) of two different inhibitors from each family. As expected, in all cases, viral titers were dramatically reduced from that with the control DMSO treatment (Fig. 4A). Neither class of inhibitor had a significant effect on Gag expression or processing, as analyzed by Western blotting of intracellular and cell-associated viral proteins with antibodies that detected the MA and CA proteins (and their Gag precursors) (Fig. 4B). Virus release was analyzed by Western blotting to detect virion-associated CA proteins released into the culture supernatant. In this case, the two classes of inhibitors exhibited quite different effects. The BM compounds reduced virion release only modestly from that with the DMSO control, whereas the BD inhibitors reduced virion release to nearly undetectable levels. We therefore conclude that the BD inhibitors function primarily by blocking Gag assembly and virion release, whereas the BM inhibitors have a different mode of action.

Electron microscopic (EM) analyses were performed to examine the morphologies of viral particles released in the presence of the two different classes of inhibitors. As expected, control virus produced in the presence of DMSO (Fig. 5A) yielded virions with a mixture of different core morphologies, but a high proportion had discernible conical cores (44% ± 9%, based on 1,005 virions scored in multiple fields). Consistent with the Western blot analysis, very few virions were produced in the presence of BD inhibitors, and most of the visible structures corresponded to amorphous cellular vesicles (Fig. 5B). The few virions that were present had a variety of gross morphological defects, including partially formed immature Gag shells and acentric electron-dense "cores" (see enlargements of individual virions below Fig. 5B for three examples). In contrast, virions produced in the presence of the BM series were much more prevalent and homogeneous (Fig. 5C) but only rarely had conical cores (2% ± 0.2% of 543 virions scored in multiple fields). Instead, they typically contained acentric, electron-dense complexes that lacked discernible capsids. These data indicate that the BM inhibitors act primarily by inhibiting the assembly of mature conical capsids.

Selection of inhibitor resistance mutations. To confirm that CA was the target of the inhibitors and to learn more about how

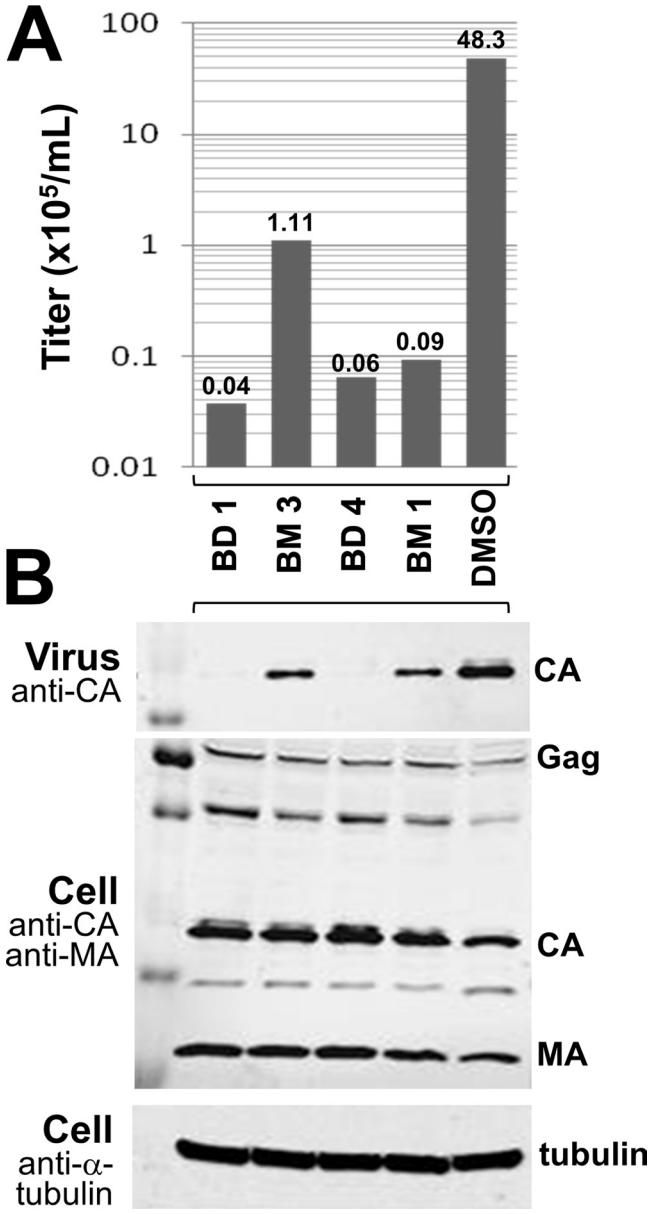


FIG 4 BM and BD compounds inhibit different stages of HIV-1 assembly and maturation. (A) HIV-1_{NL4-3} titers produced from cells treated with the designated inhibitors (concentration, 50-fold over the EC_{50}) or with a DMSO control. (B) Western blots showing levels of virion-associated CA proteins released into the supernatant (top) or levels of Gag, CA, and MA proteins being produced in cells (center). Cellular tubulin levels are shown as a control for toxicity and loading levels (bottom). Note that virus release was nearly normal in cells treated with the two BM inhibitors but was severely impaired in cells treated with the two BD inhibitors. The experiments were performed twice, and similar results were obtained in both cases, although the absolute viral titers differed in the two experiments.

the virus could adapt to inhibition, we selected for viruses that were resistant to BD or BM compounds. To select for resistance, HIV-1_{NL4-3} was cultured in C8166 cells in the presence of increasing concentrations of two representative compounds from each series for as many as 11 passages (see Table S1 in the supplemental material). The development of viral resistance resulted in increased virus replication, which led to cytopathicity. At later pas-

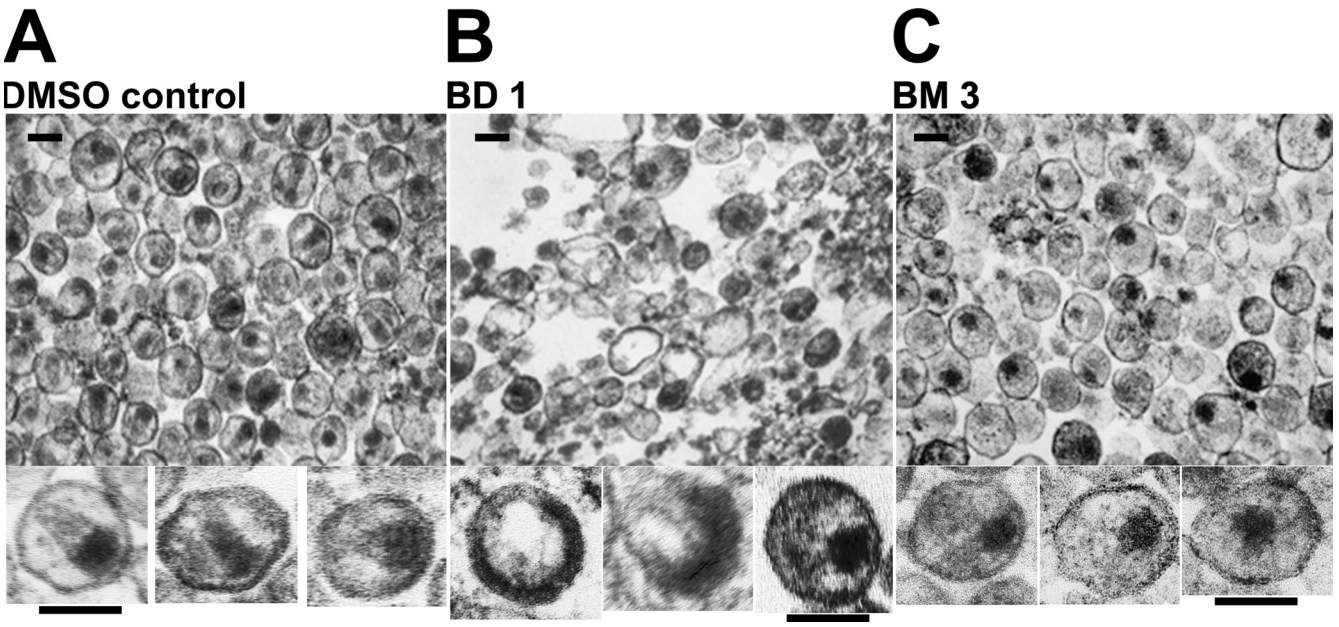


FIG 5 EM analyses showing the different viral assembly and maturation defects induced by BM and BD inhibitors. Images show transmission electron micrographs of thin-sectioned concentrated virions released from cells treated with DMSO (control) (A), BD 1 (B), or BM 3 (C). Enlargements of 3 individual virions are shown below each representative field. Inhibitor treatments were performed as for the experiments shown in Fig. 4. Similar results were also obtained with BD 4 (rare, highly aberrant virions) and BM 1 (acentric, nonconical cores). The experiments were performed twice, and similar results were obtained in both cases. Bars, 100 nm.

sages (between passages 7 and 11), whenever cytopathicity became evident, proviral DNA was cloned; the capsid gene was sequenced to identify candidate resistance mutations; and the inhibitor concentration was raised in subsequent passages to elicit additional resistance mutations.

In most cases, multiple different CA mutations were present when high-level resistance developed. Perhaps not surprisingly, many of the selected amino acid substitutions mapped to the inhibitor binding site (Fig. 6). Interestingly, however, distinct patterns of amino acid substitutions were selected with potent versus weaker inhibitors and with BD versus BM inhibitors. Specifically, the V36T and G61E substitutions were obtained only upon selection with BD inhibitors (Fig. 6A), whereas the K30R and S33G substitutions were obtained only upon selection with BM inhibi-

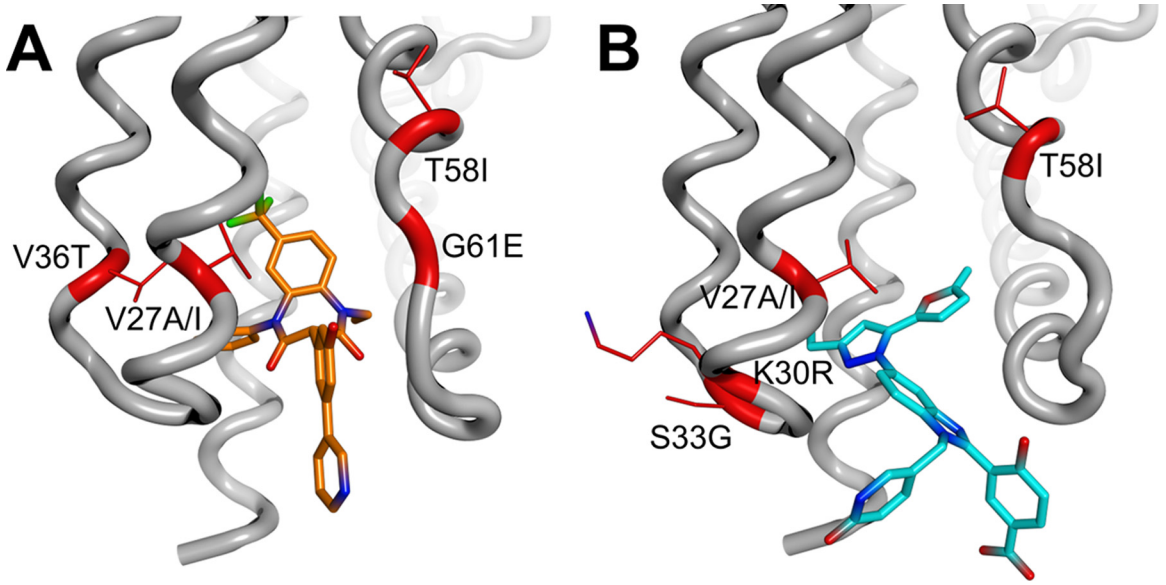


FIG 6 Identities and structural locations of viral resistance mutations selected by treatment with BD (A) and BM (B) inhibitors. Two compounds from each chemical series were used for the selection of resistant virus: BD 1 and BD 2 from the BD series and BM 2 and BM 3 from the BM series (see Table 1 for compound structures and activities). Resistance substitutions (highlighted in red; side chains shown in stick form) selected by these compounds are mapped onto the CA_{NTD} Cα trace (gray), with bound BD and BM inhibitors shown in orange (BD 3) and blue (BM 4).

TABLE 5 Susceptibilities of viruses with resistance mutations to inhibitors of capsid assembly

Compound	Fold change from the EC_{50} of the wild-type virus with the following mutation[a]:							
	V27I (BD)	V36T (BD)	K30R (BM)	T58I[a] (BM and BD)	G208R (BM and BD)	G208A	K30R G208R (BM)	V36T G208R (BD)
BD 1	5	25	1	6	3	1	4	>36
BM 2	1	8	4	16	7	1	16	55
BM 3	1	7	5	22	5	1	5	35

[a] The class(es) of compound with which each mutation was selected is given in parentheses. T58I was a major substitution selected with BM compounds but a minor substitution selected with BD compounds. G208A is a natural polymorphism.

tors (Fig. 6B). The G61E substitution was selected only by a weaker inhibitor from the BD series, BD 2, and was never obtained with the more potent compound BD 1. T58I was selected by both inhibitors from the BM series (BM 2 and BM 3) and was also observed as a minor substitution selected by BD 1. Finally, Val27 alterations to Ala or Ile were observed as minor substitutions for the BD series only. Table S1 in the supplemental material summarizes all major and minor CA amino acid substitutions obtained during selection. All major substitutions, as well as several of the minor substitutions, were chosen for further characterization, as described below.

Interestingly, inhibitors from both families also selected for amino acid substitutions in the CA_{CTD}, including G208R (major for BD 1 and BM 3; minor for BM 2) and E213G (a minor substitution for BM 2 only). At later passages and higher inhibitor concentrations, these CA_{CTD} substitutions were often found together with binding pocket substitutions, and the following double mutants were observed in different clones: the K30R/G208R, S33G/G208R, T58I/G208R, or T58I/E213G (BM) and V36T/G208R (BD) mutants.

Characterization of key inhibitor resistance mutations. To quantify the degree of inhibitor resistance induced by different amino acid substitutions, all major single and double substitutions were introduced separately into the NL4-3 proviral clone, and the mutant viruses were tested for their sensitivities to capsid assembly inhibitors BD 1, BM 2, and BM 3. As shown in Table 5, all of the single substitutions that were selected by BD inhibitors resulted in significant BD drug resistance, ranging from 3-fold (G208R) to 25-fold (V36T). Similarly, single substitution mutations that were selected by BM inhibitors resulted in significant BM inhibitor resistance, ranging from 4-fold (K30R versus BM 2) to 22-fold (T58I versus BM 3). In most cases, resistance mutations selected against one inhibitor family also conferred resistance to the other, presumably reflecting their common binding sites. The demonstration that resistance is engendered by clonal mutations at a series of different CA residues provides formal proof that CA is the functional target of both the BD and the BM inhibitors.

As has been seen in other drug resistance profiles, multiple mutations often synergized to produce high-level drug resistance. For example, although the most prevalent CA_{CTD} resistance substitution, G208R, conferred only modest (3- to 7-fold) resistance to either inhibitor family, this substitution synergized with V36T to produce ≥35-fold resistance to both inhibitor series. Interestingly, CA residue 208 is also highly variable among different virus isolates. Although Arg is found at this position in only 3 of 2,240 reported HIV-1 sequences, Ala substitutions are quite common, particularly in subtype B (44% of all sequences and 90% of subtype B sequences in the Los Alamos National Laboratory HIV Database [http://www.hiv.lanl.gov]). We found, however, that the G208A substitution in HIV-1_{NL4-3}, a subtype B-derived virus, did not confer resistance to any of the capsid assembly inhibitors, implying that viral strains with Ala at position 208 will not exhibit intrinsic resistance to BD or BM inhibitors (Table 5).

Most BD and BM resistance mutations reduce viral replicative capacity. Drug resistance mutations often reduce viral fitness (31). We therefore tested whether this was also the case for the BD and BM resistance substitutions. Viral fitness was assessed in a Jurkat-LTR-luciferase reporter T cell line that provided a more stringent test of replicative capacity than the highly permissive cell lines used for the selection of resistant virus. As shown in Fig. 7, BD and BM resistance substitutions invariably reduced viral replication capacity from that of the wild-type virus, showing impairments that were modest (40 to 80% of wild-type replication for V27I), moderate (5 to 40% for V36T, K30R, T58I, K30R/T58I, and E213G), or profound (less than 5% for G208R, V36T/G208R, and K30R/G208R). The S33G resistance substitution could not be tested in this assay because infectious virus was not produced from the mutated proviral clone, implying that this substitution severely impairs viral replicative capacity. Thus, the development of resistance to either family of capsid inhibitors can be expected to reduce viral fitness.

Effects of resistance mutations on inhibitor binding. To test whether inhibitor resistance mutations reduced inhibitor binding, recombinant CA_{NTD} proteins carrying representative CA inhibitor resistance substitutions were purified and used in ITC experiments to quantify the binding of the BM 2, BM 5, BM 6, and BM 7 inhibitors. As shown in Table 6, and in Table S2 in the supplemental material, three of the substitutions; S33G, V27A, and V36T, reduced the inhibitor binding affinity between 6- and 21-fold. For BM 2, the decrease in binding energy was driven by

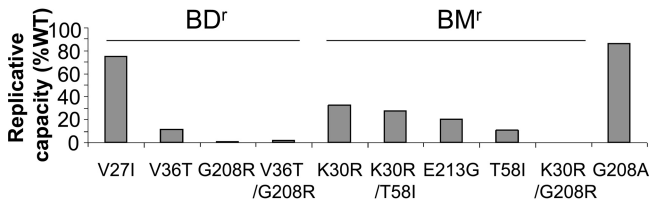


FIG 7 Inhibitor resistance substitutions reduce viral fitness. Shown are levels of luciferase produced by Jurkat LTR-luciferase reporter cells 14 days after infection with wild-type HIV-1 or with viruses carrying the designated mutations within the CA protein that confer resistance to BD inhibitors or BM inhibitors. The major G208A polymorphism was also tested. Luciferase activities are expressed as relative replicative capacities, with that for the wild-type virus set at 100%. Replicative capacities were measured at days 7, 12, and 14. The results for each mutant were similar on days 12 and 14. Replicative capacity was not assessed at additional times owing to the potential for variability over longer periods. Each value represents the average for 6 replicates from a typical experiment.

TABLE 6 Reduction in affinity for BM compounds by resistance substitutions

Compound	Fold change from the K_D of the compound for wild-type CA_{NTD}[a] with the following mutation:				
	S33G	V27A	V36T	T58I	K30R
BM 2	13	6	16	0.9	ND[b]
BM 5	14	10	18	1.1	0.9

[a] The K_Ds of BM 2 and BM 5 for wild-type CA_{NTD} were 210 and 170 nM, respectively.
[b] ND, not determined.

reductions in binding enthalpy, indicating that these substitutions removed favorable interactions (see Table S3 in the supplemental material). Similar reductions in binding affinity were seen for each mutant with all related BM compounds that were tested (see Table S2). Given that all three of these residues are located within the BM inhibitor binding site, it is likely that the mutations confer resistance, at least in part, by directly reducing inhibitor binding. Two other resistance substitutions, K30R and T58I, were of interest because they did not reduce the CA_{NTD} binding affinities of the BM compounds (Table 6; see also Table S2). Thus, the 4- to 22-fold levels of resistance conferred by these substitutions (Table 5) were not attributable to reduced inhibitor binding affinity, implying that they act via an indirect mechanism.

Indirect resistance mutations promote CA-NC assembly *in vitro*. We hypothesized that resistance mutations that did not directly affect inhibitor binding might act indirectly by increasing the efficiency of capsid assembly and/or capsid stability, thereby counteracting the detrimental destabilizing effects of inhibitor binding. To investigate this possibility, we took advantage of previous reports that amino acid substitutions that increase HIV-1 core stability often reduce the ionic strength requirements for CA-NC assembly *in vitro* (6, 10). We therefore examined the assembly properties of purified recombinant CA-NC proteins that carried either the aforementioned T58I resistance substitution or the G208R substitution, which is located in the CA_{CTD} and is therefore distant from the inhibitor binding site. The wild-type and mutant CA-NC proteins were tested for their abilities to assemble *in vitro* under suboptimal (150 mM) salt concentrations, and the "direct" S33G resistance substitution was used as a control.

As predicted, the wild type CA-NC protein assembled efficiently in buffers that contained 350 mM NaCl (Fig. 1), but not at 150 mM NaCl (Fig. 8). Similarly, the control CA-NC mutant (the S33G mutant) also failed to assemble detectably under these low-salt conditions. In contrast, low-salt CA-NC assembly was dramatically stimulated by both of the resistance mutations located outside the inhibitor binding pocket (T58I and G208R). Thus, both of these substitutions enhanced CA-NC assembly efficiency and/or stability *in vitro*, consistent with the idea that they impart inhibitor resistance by "counteracting" the capsid destabilization that accompanies BM inhibitor binding.

DISCUSSION

There is a growing need for drugs that act against new HIV-1 targets. Toward this end, we developed a high-throughput *in vitro* capsid assembly assay and used it to screen a compound library to identify potential inhibitors of capsid assembly. Subsequent optimization of two distinct chemical series produced very potent inhibitors of viral replication. These compounds (i) bind CA_{NTD}, (ii) are fully active against viruses that are resistant to other classes of antiretroviral drugs, (iii) select for resistance mutations that map to CA, (iv) act during the late phase of the viral replication cycle, and (v) inhibit virus assembly. We therefore conclude that both compound classes are *bona fide* capsid assembly inhibitors.

X-ray crystal structures of CA_{NTD} in complex with representative compounds from the BD and BM families revealed that these inhibitors bind to the same site, but with distinct binding modes that lead to different effects on virus assembly. BD compounds bind more deeply within the four-helix bundle, and the trifluoromethyl group induces a large displacement of the α1 helix, which normally makes intersubunit contacts within the mature CA_{NTD} hexameric and pentameric rings (29, 30). This displacement may, therefore, be incompatible with mature CA ring formation. The α1 displacement may also be incompatible with the formation of Gag hexamers that make up the immature virion lattice. Although a high-resolution structure of the Gag hexamer is lacking, modeling studies have suggested that the Gag and CA hexamers may be similar (3, 42), and recent H/D exchange studies support the idea that intersubunit packing within the mature and immature hexamers is similar, albeit with some reorientation of α1 within the hexamer interface (27). The dramatic effects of the BD compounds on both virion production and capsid morphology (Fig. 5B) are consistent with the idea that these inhibitors affect the formation of both immature Gag and mature CA hexamers.

In contrast, BM inhibitors exert their effects primarily by inhibiting the assembly of the mature viral capsid. These inhibitors insert less deeply into the helix bundle and disrupt the surrounding tertiary structure less extensively, but they protrude significantly further outside the CA_{NTD}. The high-resolution structures of CA hexamers and pentamers (29) reveal that this region of the CA_{NTD} makes contact with the CA_{CTD} of the neighboring unit within the hexamer. Indeed, when a BM compound is modeled into the hexamer structure (Fig. 9), the protruding portion of the inhibitor clashes with the neighboring CA_{CTD} domain, particularly with the conserved residues Arg162, Asp163, and Asp166. Moreover, BM inhibitor binding also displaces the CA_{NTD} Phe32 and His62 side chains and reorients the loop between helices 3 and 4. All of these changes are predicted to destabilize the CA_{NTD}/

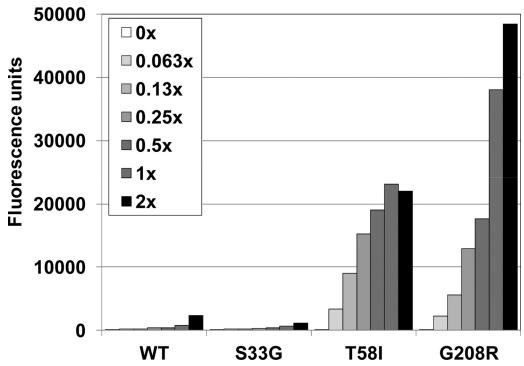


FIG 8 Inhibitor resistance mutations can enhance CA-NC assembly *in vitro*. The assembly of wild-type and mutant CA-NC proteins was assayed as shown in Fig. 1, except that the assembly conditions were more stringent (150 mM NaCl). CA-NC/oligonucleotide ratios were maintained across the 2-fold dilution series, and "1×" represents the concentrations used in the standard assembly assay.

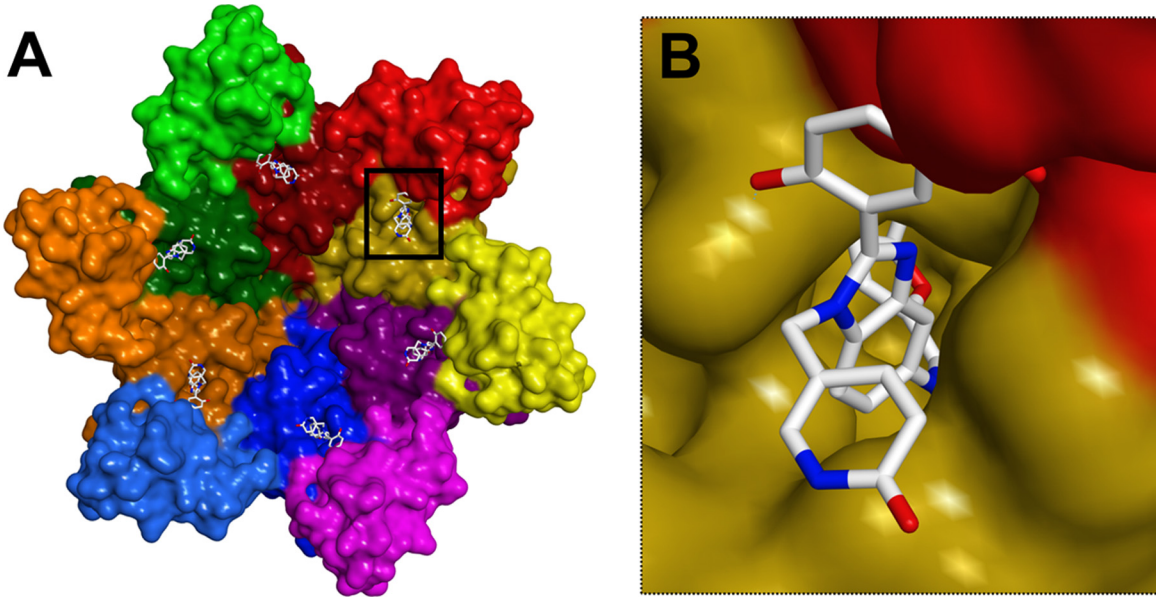


FIG 9 Models showing that BM inhibitors are expected to interfere with the formation of CA_{NTD}/CA_{CTD} interfaces in the CA hexamer. (A) Global view of BM 4 (sticks) bound to the CA hexamer (surface model, with different CA subunits in different colors, and N-terminal domains shown in darker shades). (B) Close-up view of a single CA_{NTD}/CA_{CTD} interface (boxed in panel A) showing how a BM 4 inhibitor bound to the CA_{NTD} (yellow) would be positioned to perturb the interface with an adjacent CA_{CTD} (red). The model was generated by superimposing the structure of the CA_{NTD} BM 4 complex onto the crystal structure of the HIV-1 CA hexamer (PDB ID 3H47) as described in Materials and Methods.

CA_{CTD} interface, and therefore it is likely that this is how the BM compounds prevent or disrupt mature capsid assembly (Fig. 5C). In summary, our data show that the BM and BD capsid assembly inhibitors have distinct binding modes within the four-helix bundle of CA_{NTD} that apparently translate into distinct effects on virion morphology.

Consistent with their differing binding modes, the profile of resistance substitutions selected by the BM and BD inhibitors are also different. Mutations conferring resistance to both classes of compound had two different types of effects. Not surprisingly, substitutions within the inhibitor binding site decreased the affinity of inhibitor binding, consistent with the notion that these mutations exert their effects directly by reducing inhibitor binding. Most of these resistance mutations reduced viral fitness, implying that the integrity of the inhibitor binding pocket is important for viral replication.

More interestingly, other resistance substitutions were located slightly outside (T58I) or much more distant (G208R) from the inhibitor binding site and apparently did not affect inhibitor binding affinity. Remarkably, both these substitutions enhanced CA-NC assembly *in vitro*, implying that these changes conferred resistance by counteracting the destabilizing effects of the binding of the inhibitor to the viral capsid. We speculate that the G208R mutation may stabilize the capsid by making favorable contacts across the local 3-fold axis between adjacent hexamers (4). Although a precise structure of the trimer interface is not yet available, it is believed that the Gly208 residue sits near the Glu231 residue of a neighboring subunit within the trimer. An E231Q mutation stabilizes the viral capsid (4), and it is therefore conceivable that the G208R mutation also exerts a similar stabilizing effect by helping to neutralize the Glu231 side chain. Increases in capsid stability have been reported to inhibit viral replication (10), and both of the indirect resistance substitutions reduced viral replication, with a >95% decrease observed for G208R (Fig. 7).

Viral fitness was reduced by each of the BM and BD resistance mutations tested (Fig. 7), suggesting that there may be a high barrier to the development of resistance against capsid assembly inhibitors binding within this site *in vivo*. It is also noteworthy that most of the resistance substitutions appear to be rare in natural HIV-1 isolates. For example, S33G, E213G (both selected by BM compounds only), V27A, and G208R (selected by both chemotypes) are each present in fewer than 5 of the 2,240 HIV-1 sequences in the Los Alamos database, and the K30R substitution is present in only approximately 2% of sequences. Two of the resistance substitutions did correspond to known polymorphisms: V27I (selected by BD compounds only) is present in 49%, and T58I (selected primarily by BM compounds) is present in 18%, of the database sequences. However, V27I conferred only low-level BD resistance and did not confer cross-resistance to BM compounds (Table 5). Interestingly, T58I was not observed among subtype B sequences and appears to cosegregate with the I54M polymorphism in subtype C viruses. The significance of this observation is not known, but it may represent a compensatory change necessary for efficient replication because, at least in the NL4-3 background, the T58I mutant replicated poorly (Fig. 7). Finally, although the BD and BM compounds selected different patterns of resistance mutations, those selected against one inhibitor class typically also conferred moderate resistance to the other compound class. This is presumably because the inhibitor binding sites overlap and because inhibitor binding likely destabilizes the viral capsid in both cases.

Compounds that bind to a different site on the outer face between helices 4 and 7 of the CA_{NTD} were recently shown to reduce capsid stability and inhibit HIV-1 replication (2, 32). These inhibitors promote the disassembly of purified capsids *in vitro* and during early stages of virus entry (32). They therefore exhibit postentry defects in single-cycle replication assays, in addition to inhibiting late stages of viral replication (2). Our BD and BM

compounds exhibited only modest early-stage effects, although it is conceivable that these effects might be even greater when entry is mediated by wild-type HIV-1 Env (rather than by VSV-G, as in our single-cycle experiments). Nevertheless, the major inhibitory effects occurred during virus assembly, which is consistent with the observation that CAP inhibitors also affect only the late events during replication (37).

In conclusion, we have shown that the HIV-1 CA protein, and in particular the CAP inhibitor binding site within the N-terminal domain, is a tractable inhibitor binding target and that several different classes of inhibitors can bind tightly within this pocket. However, the highly hydrophobic nature of the pocket, as well as the apparent flexibility that allows it to adjust to the binding of different inhibitors, makes it a challenging target for inhibitor optimization. We have disclosed two families of very potent capsid assembly inhibitors. Although chemically tractable, these series were not advanced as drug candidates because of intrinsic limitations in biopharmaceutical properties, such as solubility and metabolic stability. In spite of these challenges, CA is now a validated target for therapeutic intervention and merits additional drug discovery efforts.

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