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September 14, 2021

THE CONTROLLER OF PATENT  
THE PATENT OFFICE  
BOUDHIK Sampada Bhawan, Plot No. 32  
Sector 14, Dwarka, New Delhi-110078

**Re: REPRESENTATION u/s 25(1) of the Patent act - By  
SANKALP REHABILITATION TRUST against Indian Patent  
Application No. 202017007904 filed on 25/02/2020**  
**Applicant: GILEAD SCIENCES INC.**

Respected Sir,

We submit herewith Pre-Grant Opposition under Section 25(1) of the Patent Act, 2005 along with evidence and Form 7A.

The Controller is requested to take the documents on record and proceed further in the matter and keep the Petitioner advised of each and every step taken in the matter.

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

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

Thanking you,

Yours faithfully,

RAJESHWARI H. IN/PA - 0358  
AGENT FOR THE OPPONENT  
OF RAJESHWARI AND ASSOCIATES

Encl: As stated

**C.C:** K & S PARTNERS  
515-B, Platinum Tower, 5th Floor, Sohna Road, Sector 47,  
Gurgaon - 122002, National Capital Region, India  
Email.: gurgaon@knspartners.com;

**Also at:** A - 202, First Floor, Shivalik Colony, Malviya Nagar, New Delhi-110017

**BEFORE 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 Pre-grant opposition under Section 25(1)

AND

IN THE MATTER of Indian Patent Application No. 202017007904

**IN THE MATTER OF:**

**SANKALP REHABILITATION TRUST**

**.....OPPONENT**

**VS.**

**GILEAD SCIENCES, INC.**

**.....APPLICANT**

**PRE-GRANT OPPOSITION BY SANKALP REHABILITATION CENTRE**

**INDEX**

<b>S. No.</b>	<b>PARTICULARS</b>	<b>Page Nos.</b>
1.	Form 7A	1
2.	Representation u/s 25(1) by the Opponent	2-27
3.	<b>Annexure 1:</b> Copy of claims currently on record	28-32
4.	<b>Annexure 2:</b> Copy of WO2014134566/7440/DELNP/2015	33-463
5.	<b>Annexure 3:</b> Copy of Article Elaine Fontes Ferreira da Cunha	464-477
6.	<b>Annexure 4:</b> Copy of Article L. Yang et al. / Bioorg. Med. Chem.	478-489
7.	<b>Annexure 5:</b> Copy of Article Silvestri et al.	490-501
8.	Power of Attorney	Will follow

Dated this 14<sup>th</sup> day of September, 2021



**RAJESHWARI H.**  
AGENT FOR THE OPPONENT  
OF RAJESHWARI AND ASSOCIATE

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

**FORM 7A**  
**THE PATENTS ACT,**  
**1970 (39 OF 1970)**  
**AND**  
**THE PATENTS RULES, 2003**  
**REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT**  
**[See Rule 55]**

We, **SANKALP REHABILITATION TRUST**, having its registered office at SS Bengali Municipal School, First Floor, Thakurdwar Road, Charni Road East, Mumbai – 400002, hereby give Notice of opposition to the grant of patent in respect of Indian Patent Application No. 202017007904 filed on 25/02/2020 made by GILEAD SCIENCES INC. on the grounds.

- (a) Section 25(1)(b): The invention is anticipated by disclosure in prior art;
- (b) Section 25(1)(c): Anticipation/lack of novelty by prior claiming in India;
- (c) Section 25(1)(e): Lack of inventive step;
- (d) Section 25(1)(f): Invention is not patentable under section 2(1)(ja) and 3(d);
- (e) 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.
- (f) Section 25(1)(h): Failed to disclose to the Controller the information required by section 8.

**(Detailed grounds are set out in the Opposition)**

Our address for service in India is:

**RAJESHWARI H.**  
**RAJESHWARI & ASSOCIATES**  
**A – 202, FIRST FLOOR**  
**SHIVALIK COLONY**  
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**Email: [rajeshwari@ralegal.co.in](mailto:rajeshwari@ralegal.co.in); [Opposition@ralegal.co.in](mailto:Opposition@ralegal.co.in)**

Dated this 14<sup>th</sup> day of September, 2021



RAJESHWARI H. IN/PA – 0358  
AGENT FOR THE OPPONENT  
OF RAJESHWARI AND ASSOCIATES

TO  
THE CONTROLLER OF PATENTS  
PATENT OFFICE, NEW DELHI

**BEFORE THE CONTROLER OF PATENTS, THE PATENT OFFICE, 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 thePatent (Amendment) Rules, 2006

And

IN THE MATTER of Indian Patent Application 202017007904 filed on 25/02/2020 by GILEAD SCIENCES, INC.

**REPRESENTATION BY:**

**SANKALP REHABILITATION TRUST** ..... **OPPONENT**

**VS.**

**GILEAD SCIENCES, INC.** .....**APPLICANT**

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

We, **SANKALP REHABILITATION TRUST**, an Indian organization, hereby submit our representation by way of oppostion to the grant of patent in respect of application no. 202017007904 filed on 25/02/2020 entitled “CHOLINE SALT FORMS OF AN HIV CAPSID INHIBITOR” on the following grounds.

**STATEMENT OF CASE OF OPPONENT**

1. The Opponent has learnt that the Applicant has filed an Indian Patent Application No. 202017007904 (hereinafter “the Impugned Patent Application”). The Impugned patentapplication was published in the

Official Journal of the patent office on 28/08/2020, which is currently pending before the Patent Office. This Impugned application is the national phase entry of PCT (PCT/US2018/000248), which was filed on 25/02/2020. The Impugned application takes the priority of US62/546,974 dated 17/08/2017.

2. The Impugned patent application is entitled "CHOLINE SALT FORMS OF AN HIV CAPSID INHIBITOR".
3. The impugned patent application has been examined by the Indian patent office, FER is issued and the reply to FER is filed by the Applicant.
4. 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-1** and reproduced herein below for ready reference:

**Claim 1:**

A crystalline form of N-((S)-1-(3-(4-chloro-3-(methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide N,N,N-trimethylethanolammonium salt.

**Claim 2:**

The crystalline form as claimed in claim 1, which is selected from crystalline Form I, crystalline Form II, crystalline Form III, crystalline Form IV, crystalline Form V, crystalline Form VI, and crystalline Form VII.

**Claim 3:**

The crystalline form as claimed in claim 2, wherein the crystalline Form I has at least three XRPD peaks, in terms of  $2\text{-theta} \pm 0.2^\circ$ ,

selected from 5.5°, 7.5°, 7.9°, 14.9°, 15.7°, 16.8°, 17.6°, 19.3°, and 22.4° as measured at a radiation wavelength of 1.5406 Å.

**Claim 4:**

The crystalline form as claimed in claim 2, wherein the crystalline Form is crystalline Form I, wherein the crystalline Form I has at least three XRPD peaks, in terms of 2-theta  $\pm$  0.2°, selected from 5.5°, 7.5°, 7.9°, 14.9°, 15.7°, 16.8°, 17.6°, 19.3°, and 22.4° as measured at a radiation wavelength of 1.5406 Å.

**Claim 5:**

The crystalline form as claimed in any one of claims 2 to 4, wherein the crystalline Form I is characterized by a DSC thermogram having a melting onset of 157 °C as measured at a heating rate of 10 °C/min.

**Claim 6:**

The crystalline form as claimed in claim 2, wherein the crystalline Form II has at least three XRPD peaks, in terms of 2-theta  $\pm$  0.2°, selected from 7.5°, 9.6°, 14.0°, 14.9°, 16.1°, 16.9°, 20.8°, 21.0°, and 26.5° as measured at a radiation wavelength of 1.5406 Å.

**Claim 7:**

The crystalline form as claimed in claim 2, wherein the crystalline Form is crystalline Form II, wherein the crystalline Form II has at least three XRPD peaks, in terms of 2-theta  $\pm$  0.2°, selected from 7.5°, 9.6°, 14.0°, 14.9°, 16.1°, 16.9°, 20.8°, 21.0°, and 26.5° as measured at a radiation wavelength of 1.5406 Å.

**Claim 8:**

The crystalline form as claimed in any one of claims 2 and 6 to 7, wherein the crystalline Form II is characterized by a DSC thermogram having a melting onset of about 147 °C as measured at a heating rate of 10 °C/min.

**Claim 9:**

The crystalline form as claimed in claim 2, wherein the crystalline Form III has at least three XRPD peaks, in terms of 2-theta  $\pm$  0.2°, selected from 7.8°, 8.1°, 8.3°, 15.0°, 15.7°, 16.7°, 20.0°, 21.1°, and 21.7° as measured at a radiation wavelength of 1.5406 Å.

**Claim 10:**

The crystalline form as claimed in claim 2, wherein the crystalline Form is crystalline Form III, wherein the crystalline Form III has at least three XRPD peaks, in terms of 2-theta  $\pm$  0.2°, selected from 7.8°, 8.1°, 8.3°, 15.0°, 15.7°, 16.7°, 20.0°, 21.1°, and 21.7° as measured at a radiation wavelength of 1.5406 Å.

**Claim 11:**

The crystalline form as claimed in any one of claims 2 and 9 to 10, wherein the crystalline Form III is characterized by a DSC thermogram having a melting onset of 144 °C as measured at a heating rate of 10 °C/min.

**Claim 12:**

The crystalline form as claimed in claim 2, wherein the crystalline Form IV has at least three XRPD peaks, in terms of 2-theta  $\pm$  0.2°, selected from 7.5°, 8.0°, 14.8°, 16.1°, 17.0°, 20.3°, 21.1°, 24.6°, and 26.7° as measured at a radiation wavelength of 1.5406 Å.

**Claim 13:**

The crystalline form as claimed in claim 2, wherein the crystalline Form is crystalline Form IV, wherein the crystalline Form IV has at least three XRPD peaks, in terms of 2-theta  $\pm$  0.2°, selected from 7.5°, 8.0°, 14.8°, 16.1°, 17.0°, 20.3°, 21.1°, 24.6°, and 26.7° as measured at a radiation wavelength of 1.5406 Å.

**Claim 14:**

The crystalline form as claimed in any one of claims 2 and 12 to 13, wherein the crystalline Form IV is characterized by a DSC thermogram having a melting onset of 136 °C as measured at a heating rate of 10 °C/min.

**Claim 15:**

The crystalline form as claimed in claim 2, wherein the crystalline Form V has at least three XRPD peaks, in terms of 2-theta  $\pm$  0.2°, selected from 6.9°, 7.9°, 10.7°, 16.7°, 17.6°, 21.1°, 21.8°, 22.8°, and 26.9° as measured at a radiation wavelength of 1.5406 Å.

**Claim 16:**

The crystalline form as claimed in claim 2, wherein the crystalline Form is crystalline Form V, wherein the crystalline Form V has at least three XRPD peaks, in terms of 2-theta  $\pm$  0.2°, selected from 6.9°, 7.9°, 10.7°, 16.7°, 17.6°, 21.1°, 21.8°, 22.8°, and 26.9° as measured at a radiation wavelength of 1.5406 Å.

**Claim 17:**

The crystalline form as claimed in any one of claims 2 and 15 to 16, wherein the crystalline Form V is characterized by a DSC thermogram having a melting onset of about 159 °C as measured at a heating rate of 10 °C/min.

**Claim 18:**

The crystalline form as claimed in claim 2, wherein the crystalline Form VI has at least three XRPD peaks, in terms of 2-theta  $\pm$  0.2°, selected from 6.1°, 8.6°, 9.5°, 15.4°, 20.4°, 21.9°, 22.5°, 24.2°, and 25.2° as measured at a radiation wavelength of 1.5406 Å.

**Claim 19:**

The crystalline form as claimed in claim 2, wherein the crystalline Form is crystalline Form VI, wherein the crystalline Form VI has at least three XRPD peaks, in terms of 2-theta  $\pm$  0.2°, selected from 6.1°, 8.6°, 9.5°, 15.4°, 20.4°, 21.9°, 22.5°, 24.2°, and 25.2° as measured at a radiation wavelength of 1.5406 Å.

**Claim 20:**

The crystalline form as claimed in any one of claims 2 and 18 to 19, wherein the crystalline Form VI is characterized by a DSC thermogram having a melting onset of 121 °C as measured at a heating rate of 10 °C/min.

**Claim 21:**

The crystalline form as claimed in claim 2, wherein the crystalline Form VII has at least three XRPD peaks, in terms of 2-theta  $\pm$  0.2°, selected from 4.7°, 7.3°, 8.9°, 9.5°, 18.3°, 20.5°, 22.3°, 24.9°, and 28.4° as measured at a radiation wavelength of 1.5406 Å.



or the amount of an isomeric compound of Isomer B relative to the amount of an isomeric compound of Isomer A, in a starting mixture comprising both isomeric compounds, the process comprising:

contacting the starting mixture with N,N,N-trimethylethanolammonium hydroxide in the presence of a solvent to form a N,N,N-trimethylethanolammonium salt mixture of both isomeric compounds, wherein the salt mixture has an increased amount of the isomeric salt of

Isomer A relative to the amount of the isomeric salt of Isomer B, or an increased amount of the isomeric salt of Isomer B relative to the amount of the isomeric salt of Isomer A, when compared with the relative amounts of the isomeric compounds of Isomer A and Isomer B in the starting mixture.

**Claim 25:**

The process as claimed in claim 24, wherein the process comprises increasing the amount of an isomeric compound of Isomer A relative to an amount of an isomeric compound of Isomer B.

**Claim 26:**

The process as claimed in claim 24, wherein the process comprises increasing the amount of an isomeric compound of Isomer B relative to an amount of an isomeric compound of Isomer A.

**IMPUGNED PATENT APPLICATION**

5. The present pre-grant opposition is against Indian Patent Application 202017007904, entitled "CHOLINE SALT FORMS OF AN HIV CAPSID INHIBITOR" which is drawn towards a choline salt forms of an HIV capsid inhibitor i.e. N-((S)-1-(3-(4-chloro-3-(methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl) but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa [3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide N,N,N-trimethylethanolammonium salt, and pharmaceutical compositions thereof, which is

useful in the treatment and prevention of a Retroviridae viral infection including an infection caused by the HIV virus.

#### **DISCLOSURE IN THE IMPUGNED PATENT APPLICATION:**

6. The impugned patent application recites crystalline form of N-((S)-1-(3-(4-chloro-3-(methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)-ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (INN name: Lenacapavir) N,N,N-trimethylethanolammonium salt and pharmaceutical compositions thereof, which is useful in the treatment and prevention of a Retroviridae viral infection including an infection caused by the HIV virus. Further, the impugned patent application reports the different forms of the compound Lenacapavir and their characterization by different techniques including XRD pattern, 2-theta ( $\Theta$ ) values (peak values), and DSC thermograms. Also, the process for increasing the amount of an isomeric compound of Isomer A relative to Isomer B or of increasing amount of Isomer B relative to Isomer A of the compound Lenacapavir is claimed in the impugned patent application.

#### **LACK OF UNITY OF INVENTION**

7. It is submitted that the claims of the impugned application lack Unity of Invention as Claims 1 to 23 of the impugned application pertain to crystalline form while Claims 24 to 26 pertain to process of preparation of isomer A in excess of isomer B or vice versa.
8. It is well settled law that a single patent must pertain to a single invention and for that that claims sought in any patent application must pertain to a single invention. The criteria for ascertaining that the claims of a patent application pertain to a single invention call for single inventive concept by way of presence of a “special technical feature” which is common to all the claims of an application.

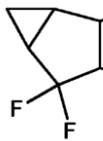
9. In present case the technical feature common to claims 1 to 23 is the “crystalline form” and the technical feature common to claims 24 to 26 is “process of increasing the amount of isomeric compound of isomer A relative to an amount of an isomeric compound of Isomer B or increasing the amount of isomeric compound of isomer B relative to an amount of an isomeric compound of Isomer A”.
10. While the Act allows product and process of preparation thereof to be claimed in a single patent, however, in present application as the product being claimed is a crystalline form and the process of preparation being claimed is of the product “isomeric compound of isomer A and/or isomeric compound of isomer B”.
11. Hence, the present claims of the impugned application lack Unity of Invention and ought to be rejected on this basis alone.

#### **GROUNDS OF OPPOSITION**

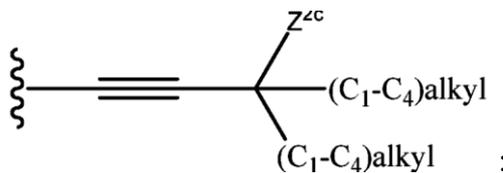
12. Accordingly, the Opponent submits its opposition by way of representation under Section 25(1) in respect of the said Indian Patent Application 202017007904 on the following grounds below, which are without prejudice and in the alternative to each other.
13. It is submitted that all claims of the impugned patent application are liable to be refused on following grounds as below:
  - i. Section 25(1)(b): The invention is anticipated by disclosure in prior art;
  - ii. Section 25(1)(c): Anticipation/lack of novelty by prior claiming in India;
  - iii. Section 25(1)(e): Lack of inventive step;
  - iv. Section 25(1)(f): Invention is not patentable under section 2(1)(ja) and 3 (d);



Wherein:

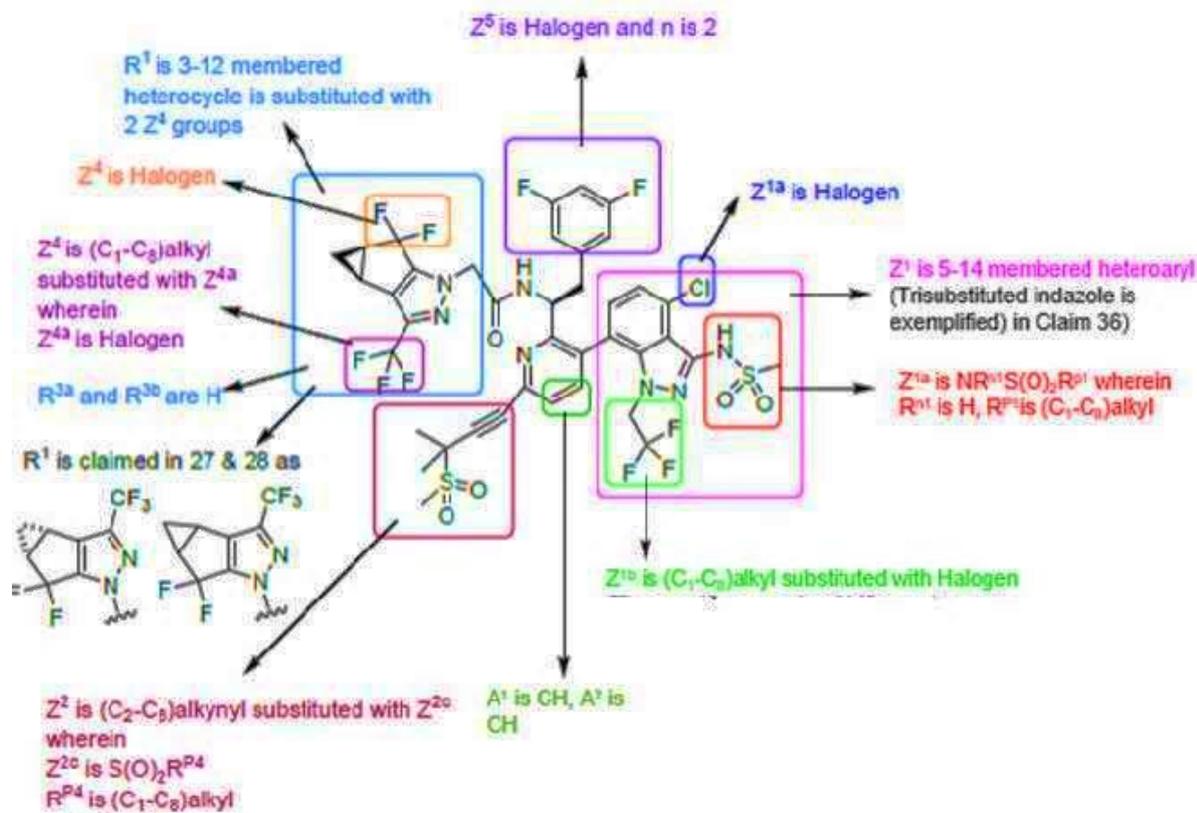


- i. C is
- ii. A<sup>1</sup> is CH; A<sup>2</sup> is CH;
- iii. Z<sup>5a</sup> is F;
- iv. Z<sup>1wis</sup> is C1-C4 alkyl substituted with halogen;
- v. Z<sup>1wis</sup> is -NR<sup>nl</sup>S(O)<sub>2</sub>R<sup>pl</sup>;
- vi. R<sup>nl</sup> is H and R<sup>pl</sup> is (C1-C8)alkyl
- vii. Z<sup>1wis</sup> is Cl;

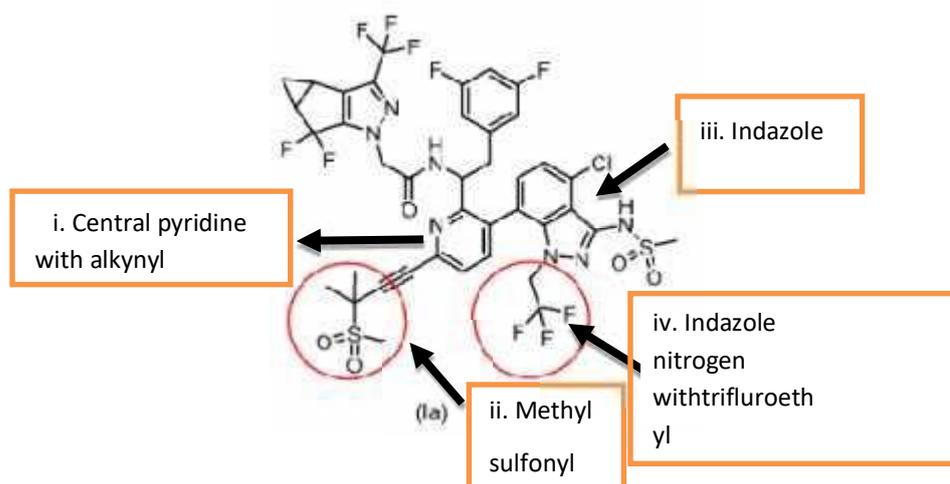


- viii. Z<sup>2</sup> is of the formula
- ix. Z<sup>2cis</sup> is -S(O)<sub>2</sub>R<sup>P4</sup>;
- x. R<sup>P4</sup> is (C1-C8)alkyl;
- xi. Z<sup>4</sup> is (C1-C3)alkyl and is optionally substituted with three Z<sup>4a</sup> groups, wherein the Z<sup>4a</sup> group is fluoro;
- xii. or a pharmaceutically acceptable salt thereof.

17. Substitutions with appropriate substituents as shown above in formula IIIId of WO566 discloses the compound Lenacapvir and pharmaceutical acceptable salt thereof as represented below:



wherein substitutions with the groups exemplified in WO566(IN7440) leads to following molecule which is Lenacapavir:



18. WO566(IN7440) also discloses Pharmaceutically acceptable salt of Lenacapavir which includes **ammonium and NX<sub>4</sub> + (wherein X is C<sub>1</sub>-C<sub>4</sub> alkyl)** salt form, also defined therein as **substituted or quaternized**

**ammonium salts** which includes N,N,N-trimethylethanolammonium pharmaceutical salt derivative of Lenacapavir.

19. In the Para [0056] of D1 it is disclosed that “*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<sub>4</sub> + (wherein X is C<sub>1</sub>-C<sub>4</sub> alkyl).*

*... 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.*

*... **All salts**, whether or not derived from a physiologically acceptable acid or base, **are within the scope of the present invention.**”*

20. The Applicant of the impugned patent has claimed the N,N,N-trimethylethanolammonium pharmaceutical salt derivative of Lenacapavir which is disclosed in IN7440 as **ammonium and NX<sub>4</sub> + (wherein X is C<sub>1</sub>-C<sub>4</sub> alkyl)** includes N,N,N-trimethylethanolammonium.

21. Further, it is stated in the Para [0060] of document WO566 (IN7440) that “*Often crystallizations produce a solvate of the compound of the invention.....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*”. Therefore, crystalline forms of Lenacapavir are inherent in the disclosure of said document.

22. Hence, as per the disclosure of document D1 all crystalline forms of Lenacapavir which, therefore, includes crystalline Forms I, II, III, IV, V, VI, VII of Lenacapavir, too.

23. Claims 2-23 of the impugned patent application claim different crystalline forms of the compound Lenacapavir by their XRD 2-theta ( $\theta$ ) values and DSC thermograms. It is submitted that D1 is silent about specific XRD and DSC values of the crystalline forms of Lenacapavir though, since D1 covers all crystalline forms of Lenacapavir by virtue of this D1 covers crystalline forms of specific XRD and DSC values as recited in claims 2 to 23 as well.
24. Further, the specification as filed of impugned patent application does not provide any comparative data to prove that claimed forms of compound Lenacapavir are different from crystalline forms disclosed in prior art document D1. Mere provision of  $2\theta$  values of an earlier known form does not make a form novel.
25. Therefore, the claimed Form I or II or III or IV or V or VI or VII of the compound Lenacapavir in the claims 2-23 of the impugned patent application are disclosed by prior publication in document D1.
26. Claims 24-26 of the impugned patent application recite process for increasing the amount of an isomeric compound of Isomer A as compared to isomer B of the compound Lenacapavir. It is submitted that said claims of the impugned patent application are not novel as the process for synthesis of different isomeric forms of the compound Lenacapavir is already disclosed in document D1 in Para [0049-54] of D1, wherein in the Para [0049] it is disclosed that, *“The compounds disclosed herein may have chiral centers, e.g., chiral carbon atoms. Such compounds thus include racemic mixtures of all stereoisomers.....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 stereo specific reactions, beginning with the appropriate stereoisomer of the desired starting material”*.

27. Therefore, the process for increasing the amount of an isomeric compound of Isomer A and isomer B of the compound Lenacapavir as disclosed in the impugned patent application is already reported in the cited document D1. Therefore, the process disclosed in the claims 24-26 of the impugned patent application should be construed to be the same as disclosed in D1 as explained above. Therefore, the claims 24-26 of the impugned patent application are anticipated by D1.

28. In view of the above it is submitted that that the subject matter of claims 1 to 26 of the impugned application is lacks novelty and the impugned application ought to be rejected on this ground alone.

## **GROUND 2**

### **SECTION 25 (1)(c): ANTICIPATION/LACK OF NOVELTY BY PRIOR CLAIMING IN INDIA**

29. It is submitted that all claims 1 to 23 are anticipated by prior claiming in Indian application IN201917006277 (hereinafter referred as IN'277 or D2) which has the priority date earlier than that of the impugned application and was published after the priority date of the impugned application. IN277 was published on May 03, 2019 after the priority date i.e. August 17, 2017 of the impugned patent application but the priority date of IN277 is August 19, 2016 which is earlier than the priority date of the impugned patent application which is August 17, 2017.

30. Claims 1 and 2 of IN277 claim the compound N-((S)-1-(3-(4-chloro-3-(methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoro methyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide i.e. Lenacapavir and its pharmaceutically acceptable salt thereof.

31. Further, the specification of IN277 specifically Para 0072 states that the invention covers polymorphic forms of Lenacapavir or pharmaceutically acceptable salt thereof. Thus, claim 1 and 2 of IN277 read in conjunction with the specification of IN277 implies that the subject matter of claim 1 and 2 of IN277 encompasses crystalline forms of Lenacapavir or pharmaceutical salt thereof (which includes Lenacapavir N,N,N-trimethylethanolammonium salt).
32. Since subject matter claimed in claim 1 and 2 of IN277 claims all polymorphic forms of Lenacapavir or pharmaceutical salt thereof, said claims also cover the subject matter claimed in claims 2 to 23 of the impugned application.
33. In view of the above it is submitted that the subject matter of the claims 1 to 23 of the impugned application is anticipated by prior claiming in IN277.
34. Therefore, the impugned application ought to be rejected on this basis alone.

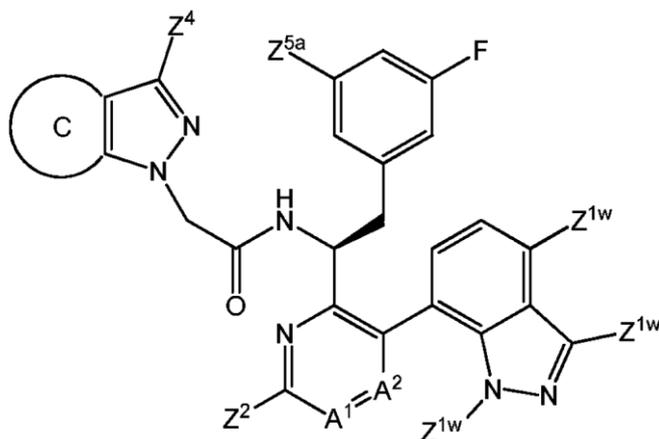
### **GROUND 3**

#### **SECTION 25(1)(e): LACK OF INVENTIVE STEP**

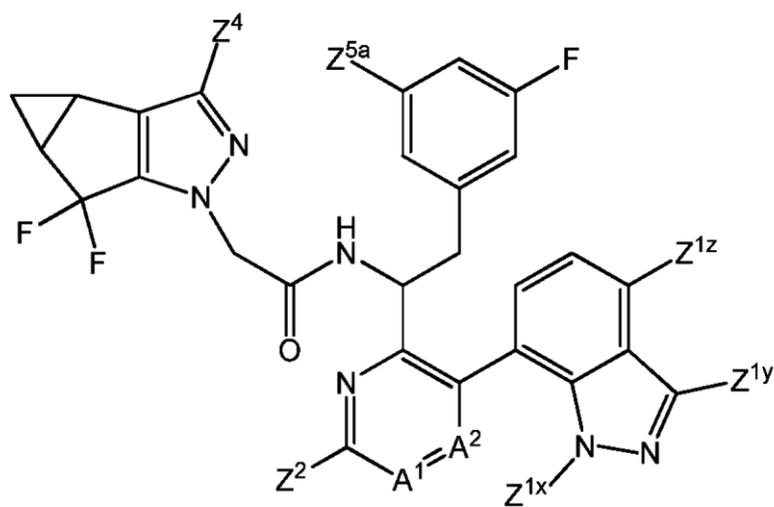
35. The invention so far as claimed in any claim of the complete specification of the impugned patent application is obvious and clearly does not involve any inventive step, having regard to the matter published as mentioned in clause (b) or having regard to what was used in India before the priority date of the claim.
36. The technical teaching of the impugned invention applies to limited knowledge and techniques which are well known in art without any inventiveness. It is submitted that the claims are obvious and lack any inventive step in view of various developments that took place in the art.

37. Document D1 relates to compounds and methods for the treatment of HIV (i.e., human immunodeficiency virus) infection.

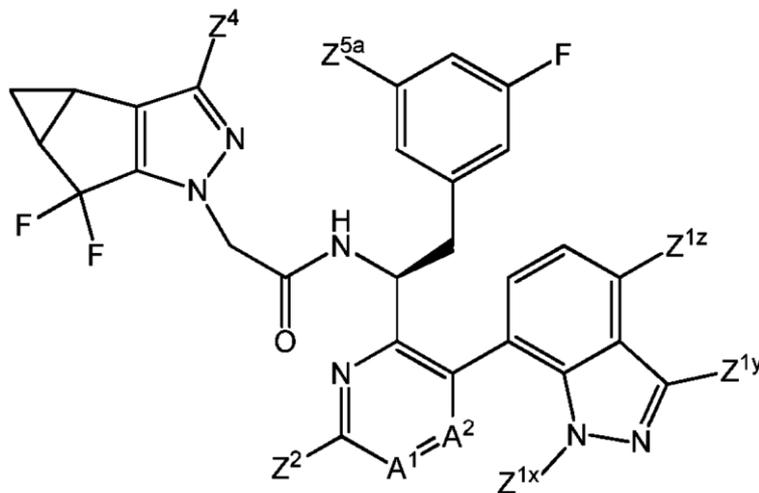
38. Document D1 discloses a narrowed down specific structures named as IIIi, IIIj and IIIk, reproduced below for ready reference:



**IIIi**

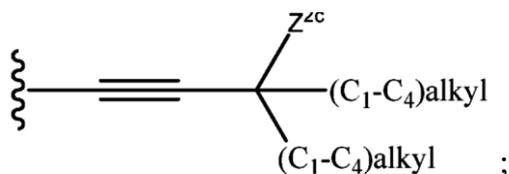


**IIIj**



### IIIk

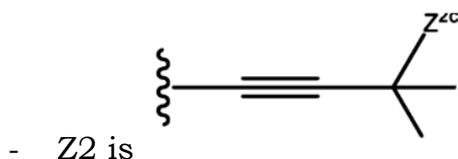
39. Further, WO566 discloses certain preferred substituents of above structures which are as follows:



- Z<sup>2</sup> is of the formula
- A<sup>1</sup> and A<sup>2</sup> are CH;
- Z<sup>5a</sup> is Fluoro;
- Z<sup>1z</sup> is Chloro;
- Z<sup>1y</sup> is -NHS(O)<sub>2</sub>alkyl;
- Z<sup>4</sup> is alkyl substituted with halogen;

40. Further, perusal of the exemplified compounds of WO566 reveals that certain substituents are used more often than others which are as follows:

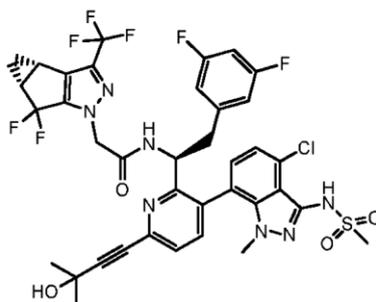
- Z<sup>4</sup> is -CF<sub>3</sub>;
- Z<sup>5a</sup> is Fluoro;
- Z<sup>1z</sup> is Chloro;
- Z<sup>1y</sup> is NHS(O)<sub>2</sub>CH<sub>3</sub>;



41. WO566 also discloses that the preferred combination that Z<sup>x</sup> is (C1-C4)alkyl; Z<sup>y</sup> is -N<sup>R</sup> S(O)<sub>2</sub>R<sup>pl</sup>; and Z<sup>z</sup> is halogen.

42. It is further taught by WO566 that when A is pyridine, then it has substituents Z<sup>1</sup> and Z<sup>2</sup> wherein Z<sup>2</sup> can either be an alkyl or ring substituent. On further perusal of the preferred embodiments of WO566 it is apparent that the preferred Z<sup>2</sup> substituent when A is pyridine is an alkynyl group further substituted by two methyl and an OH group.

43. The above discussed preferred embodiments lead to a molecule with following structure:



44. However, a perusal of the common general knowledge in art prevalent in the field at the time of the invention reveals that the presence of a sulphonyl alkyl group was considered essential for HIV inhibition and was found to be part of the molecule of many HIV inhibitors of various classes. Some the prior art documents which reflect this state of common general knowledge at the time of the invention are – Cunha et al 2005, Yang et al March 2016, Silvestri 2003. (**annexed herewith as Annexure 3, 4, 5 respectively**).

45. It is submitted that a person skilled in the art engaged in designing an alternative HIV inhibitor molecule is motivated to replace the terminal OH group of the molecules depicted in para 43 since first, WO566 gives

the option of replacing said OH group by other groups wherein many of the alternate groups have sulphonyl; secondly, sulphonyl and sulphonyl alkyl groups were commonly used in anti-HIV drugs known at the time and were considered to play an important role HIV inhibition; thirdly, presence of S(O)<sub>2</sub>Me group in the same plane as the said OH group further suggests that to a person skilled in the art to that replacement of OH with S(O)<sub>2</sub>Me has high expectation of success.

46. Further, a person skilled in the art understands that presence of sulphonyl group and/or sulphonyl alkyl [S(O)<sub>2</sub>Me] group means that a strong electron withdrawing group at terminal position following aromatic/heteroaromatic ring is the main stay of anti-HIV drugs. The same is seen in the various other anti-molecules known in prior art at the time of invention. It is also evident in the compounds of WO566 wherein pyrazole ring which is part of bicyclic system has a -CF<sub>3</sub> group, all the alternative substituents to OH disclosed are more electron withdrawing, and aromatic rings have either -CF<sub>2</sub> or S(O)<sub>2</sub>Me groups at terminal position. Thus, it calls to the common sense of a person skilled in the art that addition of a electron withdrawing group to the other pyrazole ring which is also part of the bicyclic system is likely to produce a molecule which is expected to have similar, if not better, activity profile.
47. Thus, the compound Lenacapavir is obvious in view of the disclosure of WO566 and common general knowledge.
48. WO566 also discloses that the compounds recited therein can exist as pharmaceutically acceptable salts such as **NX<sub>4</sub> + (wherein X is C1-C4 alkyl)** salt form which includes N,N,N-trimethylethanolammonium. A person skilled in the art is motivated to select said salt form since WO566 especially mentions quaternized ammonium salts.
49. Furthermore, WO566 discloses that the compounds disclosed therein yield various polymorphs upon crystallization and that different isomeric

forms of said products also exist which can be obtained as a product rich in a particular isomeric form compared to other isomers by use of either conventional techniques or by reaction with acid or bases and conversion back into desired isomer or by using desired isomeric form as the starting material in a stereo-specific reaction.

50. It is submitted that the Applicant has provided comparative data in the specification as filed establishing that Lenacapavir named as Compound 1 has lower EC50 and CC50 values as well as has better pharmacokinetic profile than certain compounds named as compound A and B of WO566.
51. However, as submitted under the ground of novelty, the compound Lenacapavir is disclosed in the prior art document WO566. WO566 also covers all the salt forms and polymorphs including crystalline forms of Lenacapavir. Moreover, as submitted in preceding paragraphs the specific substitutions in Lenacapavir over and above the substitutions present in Compound A and B are in line with the common understanding and practise in the field of anti-HIV drug development at the time of the invention. Thus, there already existed a preponderance of expectation of success.
52. Therefore, it was incumbent upon the Applicant to establish why and how the crystalline and isomeric forms of Lenacapavir claimed in impugned applicant are technically advanced as compared to the Lenacapavir disclosed in WO566 and all its salt and polymeric forms disclosed therein. However, the Applicant has not disclosed any such data in the specification as filed.
53. Furthermore, while the claims of present application are drawn to a particular salt crystalline form and the process of preparation of an isomerically rich compound, the data provided in specification regarding EC50, CC50 and Pharmacokinetics ought to have been established using the claimed salt crystalline form or the particular isomer. However, the

data given in impugned specification pertains to simply Compound 1 i.e. Lenacapavir and not its claimed salt crystalline form or isomeric form.

54. In addition, the impugned application does not state any difference from or any advantage compared to the process of preparation of isomerically rich product as disclosed in prior art.
55. Therefore, the Applicant has failed to establish any technical advancement of the claimed subject matter over what was already known in the art at the time of the invention.
56. In light of the above submissions, it is evident that the claimed subject matter of the impugned application lacks inventive merit and therefore, the impugned application ought to be rejected on this ground alone.

#### GROUND 4

#### **SECTION 25(1)(f): SUBJECT MATTER IS NOT AN INVENTION WITHIN THE MEANING OF THIS ACT OR IS NOT PATENTABLE UNDER THIS ACT:**

57. **The claimed subject matter is not patentable under Section 3(d) of the Act.** According to Section 3(d), "*the mere discovery of a new form of a substance which does not result in the enhancement of a known efficacy of that substance or the mere discovery of a new property or new 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 purpose 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."*

58. As submitted under the grounds of lack of novelty by prior publication, lack of novelty by prior claiming and lack of inventive step the subject matter claimed in impugned application is neither novel nor inventive and hence, squarely falls under the ambit of Section 3(d) of the Act.
59. Further, it is submitted that the Applicant has provided comparative data in the specification as filed establishing that Lenacapavir named as Compound 1 has lower EC50 and CC50 values as well as has better pharmacokinetic profile than certain compounds named as compound A and B of WO566.
60. However, as submitted under the ground of novelty, the compound Lenacapavir is disclosed in the prior art document WO566. WO566 also covers all the salt forms and polymorphs including crystalline forms of Lenacapavir. Moreover, as submitted in preceding paragraphs the specific substitutions in Lenacapavir over and above the substitutions present in Compound A and B are in line with the common understanding and practise in the field of anti-HIV drug development at the time of the invention. Thus, there already existed a preponderance of expectation of success.
61. Therefore, it was incumbent upon the Applicant to establish why and how the crystalline and isomeric forms of Lenacapavir claimed in impugned applicant are technically advanced as compared to the Lenacapavir disclosed in WO566 and all its salt and polymeric forms disclosed therein. However, the Applicant has not disclosed any such data in the specification as filed.
62. Furthermore, while the claims of present application are drawn to a particular salt crystalline form and the process of preparation of an isomerically rich compound, the data provided in specification regarding EC50, CC50 and Pharmacokinetics ought to have been established using the claimed salt crystalline form or the particular isomer. However, the

data given in impugned specification pertains to simply Compound 1 i.e. Lenacapavir and not its claimed salt crystalline form or isomeric form.

63. Therefore, the Applicant has failed to establish enhanced therapeutic efficacy of the claimed salt crystalline form of Lenacapavir over salt crystalline forms of Lenacapavir known in the art such as in the prior art document WO566.

64. In addition, the impugned application does not state any difference from or any advantage compared to the process of preparation of isomerically rich product as disclosed in prior art. The impugned application does not recite any new reactant being used in or any new product directly resulting from the claimed process.

65. In light of the above submissions, it is evident that the claimed subject matter of the impugned application falls within the purview of Section 3(d) of the Act and therefore, the impugned application ought to be rejected on this ground alone.

#### **GROUND 5**

#### **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**

66. It is submitted that the Applicant has broadly claimed all crystalline forms of Lenacapavir trimethylethanolammonium salt form in claim 1 of the impugned application whereas the specification of impugned application discloses the synthesis process of select few crystalline forms.

67. Hence, subject matter of claim 1 is too broad and lacks support in the specification due to lack of enablement.

68. It is submitted that claims 24 to 26 pertain to process of preparation of isomerically rich product. However, said claims lack essential steps and

process parameters. In absence these essential features a person of average skill in the art has to undergo undue experimentation in order to arrive at the claimed invention.

69. Therefore, it is submitted that the claims as currently worded lack support.

70. In view of the afore mentioned submissions, it is respectfully submitted that the impugned patent application lacks clarity and sufficiency.

71. Therefore, the impugned patent application should be rejected on this ground alone.

#### **GROUND 6**

#### **SECTION 25(1)(h): THE APPLICANT HAS FAILED TO DISCLOSE TO THE CONTROLLER THE INFORMATION REQUIRED BY SECTION 8**

72. The patentee has failed to disclose to the Controller 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 Controller in writing from time to time and also within the prescribed time.

73. Therefore, the applicant has failed to comply with the requirements of Section 8 of the Act. It is submitted that the Applicant has failed to disclose the details and all the information of corresponding foreign applications and hence, the impugned patent application should be refused on this ground alone.

74. The Opponent craves leave to submit further arguments, documents, and/or evidences in this ground in future.

75. The Opponent that the Indian application 202017007904, be rejected under Section 25(1) of the Patents (Amendment) Act, 2005;

**PRAYER**

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

- i. that the Controller take the present Opposition on record;
- ii. that the Indian application 202017007904, be rejected under Section 25(1) of the Patents (Amendment) Act, 2005;
- iii. that the Opponent may be allowed to file further documents and evidence if necessary to support their averments;
- iv. that the Opponent may be allowed to file rejoinder and affidavit if necessary to support their averments;
- v. that the Opponent may be granted an opportunity of being heard in the matter before any final orders are passed;
- vi. that the Opponent may be allowed to make further submissions in case the Patentee makes any amendments in the claims;
- vii. any other reliefs considering the facts and circumstances may be granted in favour of the Opponent in the interest of justice.

Dated this 14<sup>th</sup> day of September, 2021



RAJESHWARI H.  
AGENT FOR THE OPPONENT  
RAJESHWARI AND ASSOCIATE

TO  
THE CONTROLLER OF PATENTS  
PATENT OFFICE, NEW DELHI

# Annexure - 1

We claim:

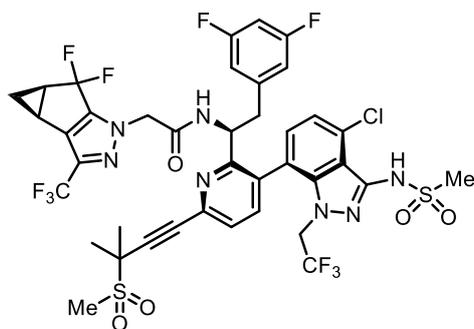
1. A crystalline form of *N*-((*S*)-1-(3-(4-chloro-3-(methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1*H*-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3*bS*,4*aR*)-5,5-difluoro-3-(trifluoromethyl)-3*b*,4,4*a*,5-tetrahydro-1*H*-cyclopropa[3,4]cyclopenta[1,2-*c*]pyrazol-1-yl)acetamide *N,N,N*-trimethylethanolammonium salt.
2. The crystalline form as claimed in claim 1, which is selected from crystalline Form I, crystalline Form II, crystalline Form III, crystalline Form IV, crystalline Form V, crystalline Form VI, and crystalline Form VII.
3. The crystalline form as claimed in claim 2, wherein the crystalline Form I has at least three XRPD peaks, in terms of 2- $\theta \pm 0.2^\circ$ , selected from  $5.5^\circ$ ,  $7.5^\circ$ ,  $7.9^\circ$ ,  $14.9^\circ$ ,  $15.7^\circ$ ,  $16.8^\circ$ ,  $17.6^\circ$ ,  $19.3^\circ$ , and  $22.4^\circ$  as measured at a radiation wavelength of 1.5406 Å.
4. The crystalline form as claimed in claim 2, wherein the crystalline Form is crystalline Form I, wherein the crystalline Form I has at least three XRPD peaks, in terms of 2- $\theta \pm 0.2^\circ$ , selected from  $5.5^\circ$ ,  $7.5^\circ$ ,  $7.9^\circ$ ,  $14.9^\circ$ ,  $15.7^\circ$ ,  $16.8^\circ$ ,  $17.6^\circ$ ,  $19.3^\circ$ , and  $22.4^\circ$  as measured at a radiation wavelength of 1.5406 Å.
5. The crystalline form as claimed in any one of claims 2 to 4, wherein the crystalline Form I is characterized by a DSC thermogram having a melting onset of  $157^\circ\text{C}$  as measured at a heating rate of  $10^\circ\text{C}/\text{min}$ .
6. The crystalline form as claimed in claim 2, wherein the crystalline Form II has at least three XRPD peaks, in terms of 2- $\theta \pm 0.2^\circ$ , selected from  $7.5^\circ$ ,  $9.6^\circ$ ,  $14.0^\circ$ ,  $14.9^\circ$ ,  $16.1^\circ$ ,  $16.9^\circ$ ,  $20.8^\circ$ ,  $21.0^\circ$ , and  $26.5^\circ$  as measured at a radiation wavelength of 1.5406 Å.
7. The crystalline form as claimed in claim 2, wherein the crystalline Form is crystalline Form II, wherein the crystalline Form II has at least three XRPD peaks, in terms of 2- $\theta \pm 0.2^\circ$ , selected from  $7.5^\circ$ ,  $9.6^\circ$ ,  $14.0^\circ$ ,  $14.9^\circ$ ,  $16.1^\circ$ ,  $16.9^\circ$ ,  $20.8^\circ$ ,  $21.0^\circ$ , and  $26.5^\circ$  as measured at a radiation wavelength of 1.5406 Å.

8. The crystalline form as claimed in any one of claims 2 and 6 to 7, wherein the crystalline Form II is characterized by a DSC thermogram having a melting onset of about 147 °C as measured at a heating rate of 10 °C/min.
9. The crystalline form as claimed in claim 2, wherein the crystalline Form III has at least three XRPD peaks, in terms of 2-theta  $\pm$  0.2°, selected from 7.8°, 8.1°, 8.3°, 15.0°, 15.7°, 16.7°, 20.0°, 21.1°, and 21.7° as measured at a radiation wavelength of 1.5406 Å.
10. The crystalline form as claimed in claim 2, wherein the crystalline Form is crystalline Form III, wherein the crystalline Form III has at least three XRPD peaks, in terms of 2-theta  $\pm$  0.2°, selected from 7.8°, 8.1°, 8.3°, 15.0°, 15.7°, 16.7°, 20.0°, 21.1°, and 21.7° as measured at a radiation wavelength of 1.5406 Å.
11. The crystalline form as claimed in any one of claims 2 and 9 to 10, wherein the crystalline Form III is characterized by a DSC thermogram having a melting onset of 144 °C as measured at a heating rate of 10 °C/min.
12. The crystalline form as claimed in claim 2, wherein the crystalline Form IV has at least three XRPD peaks, in terms of 2-theta  $\pm$  0.2°, selected from 7.5°, 8.0°, 14.8°, 16.1°, 17.0°, 20.3°, 21.1°, 24.6°, and 26.7° as measured at a radiation wavelength of 1.5406 Å.
13. The crystalline form as claimed in claim 2, wherein the crystalline Form is crystalline Form IV, wherein the crystalline Form IV has at least three XRPD peaks, in terms of 2-theta  $\pm$  0.2°, selected from 7.5°, 8.0°, 14.8°, 16.1°, 17.0°, 20.3°, 21.1°, 24.6°, and 26.7° as measured at a radiation wavelength of 1.5406 Å.
14. The crystalline form as claimed in any one of claims 2 and 12 to 13, wherein the crystalline Form IV is characterized by a DSC thermogram having a melting onset of 136 °C as measured at a heating rate of 10 °C/min.

15. The crystalline form as claimed in claim 2, wherein the crystalline Form V has at least three XRPD peaks, in terms of  $2\text{-theta} \pm 0.2^\circ$ , selected from  $6.9^\circ$ ,  $7.9^\circ$ ,  $10.7^\circ$ ,  $16.7^\circ$ ,  $17.6^\circ$ ,  $21.1^\circ$ ,  $21.8^\circ$ ,  $22.8^\circ$ , and  $26.9^\circ$  as measured at a radiation wavelength of  $1.5406 \text{ \AA}$ .
16. The crystalline form as claimed in claim 2, wherein the crystalline Form is crystalline Form V, wherein the crystalline Form V has at least three XRPD peaks, in terms of  $2\text{-theta} \pm 0.2^\circ$ , selected from  $6.9^\circ$ ,  $7.9^\circ$ ,  $10.7^\circ$ ,  $16.7^\circ$ ,  $17.6^\circ$ ,  $21.1^\circ$ ,  $21.8^\circ$ ,  $22.8^\circ$ , and  $26.9^\circ$  as measured at a radiation wavelength of  $1.5406 \text{ \AA}$ .
17. The crystalline form as claimed in any one of claims 2 and 15 to 16, wherein the crystalline Form V is characterized by a DSC thermogram having a melting onset of about  $159^\circ\text{C}$  as measured at a heating rate of  $10^\circ\text{C}/\text{min}$ .
18. The crystalline form as claimed in claim 2, wherein the crystalline Form VI has at least three XRPD peaks, in terms of  $2\text{-theta} \pm 0.2^\circ$ , selected from  $6.1^\circ$ ,  $8.6^\circ$ ,  $9.5^\circ$ ,  $15.4^\circ$ ,  $20.4^\circ$ ,  $21.9^\circ$ ,  $22.5^\circ$ ,  $24.2^\circ$ , and  $25.2^\circ$  as measured at a radiation wavelength of  $1.5406 \text{ \AA}$ .
19. The crystalline form as claimed in claim 2, wherein the crystalline Form is crystalline Form VI, wherein the crystalline Form VI has at least three XRPD peaks, in terms of  $2\text{-theta} \pm 0.2^\circ$ , selected from  $6.1^\circ$ ,  $8.6^\circ$ ,  $9.5^\circ$ ,  $15.4^\circ$ ,  $20.4^\circ$ ,  $21.9^\circ$ ,  $22.5^\circ$ ,  $24.2^\circ$ , and  $25.2^\circ$  as measured at a radiation wavelength of  $1.5406 \text{ \AA}$ .
20. The crystalline form as claimed in any one of claims 2 and 18 to 19, wherein the crystalline Form VI is characterized by a DSC thermogram having a melting onset of  $121^\circ\text{C}$  as measured at a heating rate of  $10^\circ\text{C}/\text{min}$ .
21. The crystalline form as claimed in claim 2, wherein the crystalline Form VII has at least three XRPD peaks, in terms of  $2\text{-theta} \pm 0.2^\circ$ , selected from  $4.7^\circ$ ,  $7.3^\circ$ ,  $8.9^\circ$ ,  $9.5^\circ$ ,  $18.3^\circ$ ,  $20.5^\circ$ ,  $22.3^\circ$ ,  $24.9^\circ$ , and  $28.4^\circ$  as measured at a radiation wavelength of  $1.5406 \text{ \AA}$ .
22. The crystalline form as claimed in claim 2, wherein the crystalline Form is crystalline Form VII, wherein the crystalline Form VII has at least three XRPD peaks, in terms of

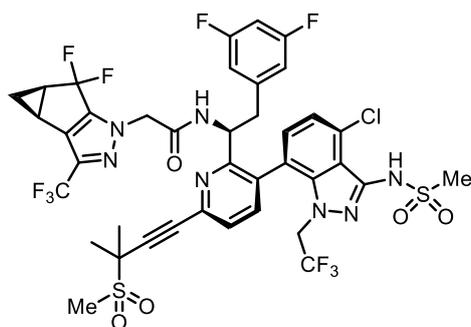
2-theta  $\pm$  0.2°, selected from 4.7°, 7.3°, 8.9°, 9.5°, 18.3°, 20.5°, 22.3°, 24.9°, and 28.4° as measured at a radiation wavelength of 1.5406 Å.

23. The crystalline form as claimed in any one of claims 2 and 21 to 22, wherein the crystalline Form VII is characterized by a DSC thermogram having a melting onset of about 144 °C as measured at a heating rate of 10 °C/min.
24. A process of increasing the amount of an isomeric compound of Isomer A:



**Isomer A**

relative to an amount of an isomeric compound of Isomer B:



**Isomer B**

or the amount of an isomeric compound of Isomer B relative to the amount of an isomeric compound of Isomer A, in a starting mixture comprising both isomeric compounds, the process comprising:

contacting the starting mixture with *N,N,N*-trimethylethanolammonium hydroxide in the presence of a solvent to form a *N,N,N*-trimethylethanolammonium salt mixture of both isomeric compounds, wherein the salt mixture has an increased amount of the isomeric salt of Isomer A relative to the amount of the isomeric salt of Isomer B, or an increased amount of the isomeric salt of Isomer B relative to the amount of the isomeric salt of Isomer A, when

compared with the relative amounts of the isomeric compounds of Isomer A and Isomer B in the starting mixture.

25. The process as claimed in claim 24, wherein the process comprises increasing the amount of an isomeric compound of Isomer A relative to an amount of an isomeric compound of Isomer B.
26. The process as claimed in claim 24, wherein the process comprises increasing the amount of an isomeric compound of Isomer B relative to an amount of an isomeric compound of Isomer A.

Dated this 25.02.2020

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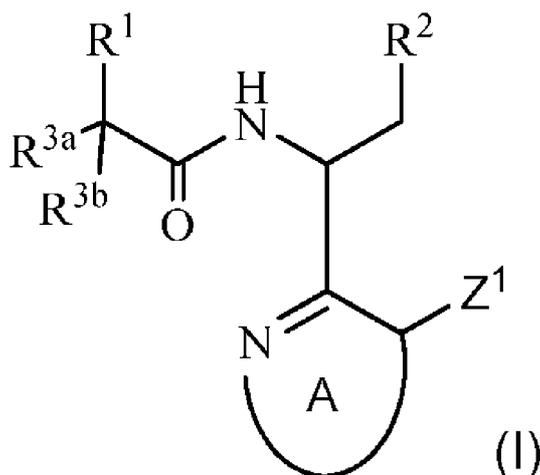
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DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,  
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KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,  
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,  
OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,

[Continued on next page]

(54) Title: AMIDE COMPOUNDS FOR THE TREATMENT OF HIV

(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.

WO 2014/134566 A3

WO 2014/134566 A3



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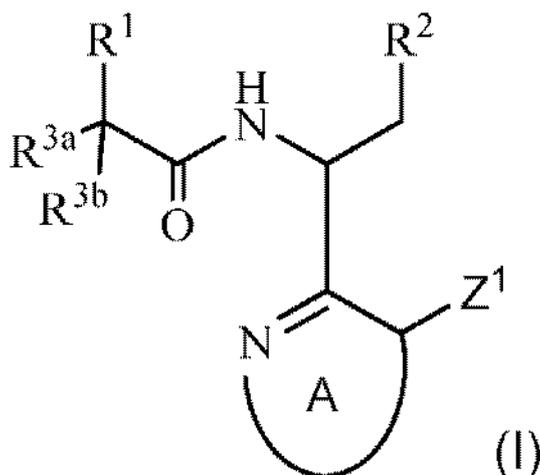
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[Continued on next page]

(54) Title: THERAPEUTIC COMPOUNDS



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

WO 2014/134566 A2



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# FORM 2

THE PATENTS ACT, 1970

(39 of 1970)

&

The Patent Rules, 2003

## COMPLETE SPECIFICATION

(See section 10 and rule 13)

### TITLE OF THE INVENTION

**“AMIDE COMPOUNDS FOR THE TREATMENT OF HIV”**

We, **GILEAD SCIENCES, INC.**, a US corporation, of 333 Lakeside Drive, Foster City, California 94404, United States of America,

*The following specification particularly describes the nature of the invention and the manner in which it is performed:*

## 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.

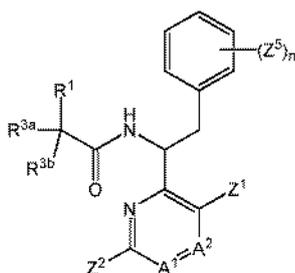
### BACKGROUND

[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 III d:



III d

wherein

A<sup>1</sup> is CH, C-Z<sup>3</sup>, or nitrogen;

A<sup>2</sup> is CH or nitrogen;

R<sup>1</sup> 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<sup>1</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>4</sup> groups, wherein the Z<sup>4</sup> groups are the same or different;

each R<sup>3a</sup> and R<sup>3b</sup> is independently H or (C<sub>1</sub>-C<sub>3</sub>)alkyl;

Z<sup>1</sup> 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<sup>1</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1a</sup> or Z<sup>1b</sup>, wherein the Z<sup>1a</sup> and Z<sup>1b</sup> groups are the same or different;

each Z<sup>1a</sup> is independently (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, -OR<sup>n1</sup>, -OC(O)R<sup>p1</sup>, -OC(O)NR<sup>q1</sup>R<sup>r1</sup>, -SR<sup>n1</sup>, -S(O)R<sup>p1</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p1</sup>, -S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>COR<sup>p1</sup>, -NR<sup>n1</sup>CO<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>CONR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>OR<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -C(O)R<sup>n1</sup>, -C(O)OR<sup>n1</sup>, -C(O)NR<sup>q1</sup>R<sup>r1</sup> and -S(O)<sub>2</sub>NR<sup>n1</sup>COR<sup>p1</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z<sup>1a</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1c</sup> or Z<sup>1d</sup> groups, wherein the Z<sup>1c</sup> and Z<sup>1d</sup> groups are the same or different;

each Z<sup>1b</sup> is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl optionally substituted with 1, 2, 3, 4 or 5 halogen, which are the same or different;

each Z<sup>1c</sup> is independently halogen, -CN, -OH, -NH<sub>2</sub>, -C(O)NR<sup>q2</sup>R<sup>r2</sup>, or (C<sub>1</sub>-C<sub>8</sub>)heteroalkyl;

each Z<sup>1d</sup> is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl or (C<sub>1</sub>-C<sub>8</sub>)haloalkyl;

each R<sup>n1</sup> is independently H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R<sup>n1</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1c</sup> or Z<sup>1d</sup> groups, wherein the Z<sup>1c</sup> and Z<sup>1d</sup> groups are the same or different, and wherein any (C<sub>1</sub>-C<sub>8</sub>)alkyl of R<sup>n1</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1c</sup> groups, wherein the Z<sup>1c</sup> groups are the same or different;

each R<sup>p1</sup> is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)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<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)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<sup>q3</sup>R<sup>r3</sup>, 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<sub>2</sub>-C<sub>8</sub>)alkenyl or (C<sub>2</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl;

each  $R^{q3}$  and  $R^{r3}$  is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

each  $Z^{2b}$  is independently oxo, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl or (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

each  $Z^{2c}$  is independently oxo, halogen, -CN, -OR<sup>n4</sup>, -OC(O)R<sup>p4</sup>, -OC(O)NR<sup>q4</sup>R<sup>r4</sup>, -SR<sup>n4</sup>, -S(O)R<sup>p4</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p4</sup>, -S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>COR<sup>p4</sup>, -NR<sup>n4</sup>CO<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>CONR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>OR<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NO<sub>2</sub>, -C(O)R<sup>n4</sup>, -C(O)OR<sup>n4</sup>, or -C(O)NR<sup>q4</sup>R<sup>r4</sup>;

each  $R^{n4}$  is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $R^{p4}$  is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $R^{q4}$  and  $R^{r4}$  is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $Z^3$  is independently a (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $Z^4$  is independently oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, halogen, -CN, -OR<sup>n5</sup>, -NR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>n5</sup>COR<sup>p5</sup>, -NR<sup>n5</sup>CO<sub>2</sub>R<sup>p5</sup>, -C(O)R<sup>n5</sup>, -C(O)OR<sup>n5</sup>, or -C(O)NR<sup>q5</sup>R<sup>r5</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle or (C<sub>1</sub>-C<sub>8</sub>)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<sup>n6</sup>;

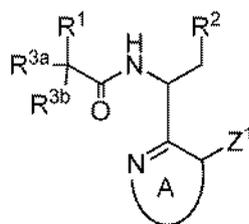
each R<sup>n5</sup>, R<sup>p5</sup>, R<sup>q5</sup>, R<sup>r5</sup>, and R<sup>n6</sup> is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

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<sup>3a</sup> and R<sup>3b</sup> is independently H or (C<sub>1</sub>-C<sub>3</sub>)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<sub>3</sub>-C<sub>7</sub>)carbocycle, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, -OR<sup>n1</sup>, -OC(O)R<sup>p1</sup>, -OC(O)NR<sup>q1</sup>R<sup>r1</sup>, -SR<sup>n1</sup>, -S(O)R<sup>p1</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p1</sup>, -S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>COR<sup>p1</sup>, -NR<sup>n1</sup>CO<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>CONR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>OR<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -C(O)R<sup>n1</sup>, -C(O)OR<sup>n1</sup>, -C(O)NR<sup>q1</sup>R<sup>r1</sup> and -S(O)<sub>2</sub>NR<sup>n1</sup>COR<sup>p1</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)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<sub>2</sub>, -C(O)NR<sup>q2</sup>R<sup>r2</sup>, or (C<sub>1</sub>-C<sub>8</sub>)heteroalkyl;

each  $Z^{1d}$  is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl or (C<sub>1</sub>-C<sub>8</sub>)haloalkyl;

each R<sup>n1</sup> is independently H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R<sup>n1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl of R<sup>n1</sup> 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<sup>p1</sup> is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R<sup>p1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl of R<sup>p1</sup> 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<sup>q1</sup> and R<sup>r1</sup> is independently H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R<sup>q1</sup> or R<sup>r1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl of R<sup>q1</sup> or R<sup>r1</sup> 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<sup>q1</sup> and R<sup>r1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)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<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)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<sup>q3</sup>R<sup>r3</sup>, 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<sub>2</sub>-C<sub>8</sub>)alkenyl or (C<sub>2</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl;

each  $R^{q3}$  and  $R^{r3}$  is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

each  $Z^{2b}$  is independently oxo, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, or (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

each  $Z^{2c}$  is independently oxo, halogen, -CN, -OR<sup>n4</sup>, -OC(O)R<sup>p4</sup>, -OC(O)NR<sup>q4</sup>R<sup>r4</sup>, -SR<sup>n4</sup>, -S(O)R<sup>p4</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p4</sup>, -S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>COR<sup>p4</sup>, -NR<sup>n4</sup>CO<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>CONR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>OR<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NO<sub>2</sub>, -C(O)R<sup>n4</sup>, -C(O)OR<sup>n4</sup>, or -C(O)NR<sup>q4</sup>R<sup>r4</sup>;

each  $R^{n4}$  is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $R^{p4}$  is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $R^{q4}$  and  $R^{r4}$  is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $Z^3$  is independently a (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl or halogen;

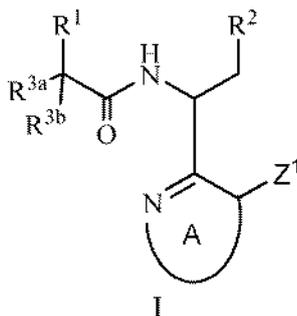
each  $Z^4$  is independently oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, halogen, -CN, -OR<sup>n5</sup>, -NR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>n5</sup>COR<sup>p5</sup>, -NR<sup>n5</sup>CO<sub>2</sub>R<sup>p5</sup>, -C(O)R<sup>n5</sup>, -C(O)OR<sup>n5</sup>, or -C(O)NR<sup>q5</sup>R<sup>r5</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle or (C<sub>1</sub>-C<sub>8</sub>)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<sup>n6</sup>; and

each  $R^{n5}$ ,  $R^{p5}$ ,  $R^{q5}$ ,  $R^{r5}$ , and  $R^{n6}$  is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

or a pharmaceutically acceptable salt thereof.

[0006] One embodiment provides a compound of formula 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<sup>n1</sup>, -OC(O)R<sup>p1</sup>, -OC(O)NR<sup>q1</sup>R<sup>r1</sup>, -SR<sup>n1</sup>, -S(O)R<sup>p1</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p1</sup>, -S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>COR<sup>p1</sup>, -NR<sup>n1</sup>CO<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>CONR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>OR<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, NO<sub>2</sub>, -C(O)R<sup>n1</sup>, -C(O)OR<sup>n1</sup>, -C(O)NR<sup>q1</sup>R<sup>r1</sup> and -S(O)<sub>2</sub>NR<sup>n1</sup>COR<sup>p1</sup>, 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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)alkynyl, wherein any (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)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<sub>3</sub>-C<sub>7</sub>)carbocycle, phenyl, 5-6 membered monocyclic-heteroaryl, 3-7 membered heterocycle, halogen, -CN, -OR<sup>n2</sup>, -OC(O)R<sup>p2</sup>, -OC(O)NR<sup>q2</sup>R<sup>r2</sup>, -SR<sup>n2</sup>, -S(O)R<sup>p2</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p2</sup>, -S(O)<sub>2</sub>NR<sup>q2</sup>R<sup>r2</sup>, -NR<sup>q2</sup>R<sup>r2</sup>, -NR<sup>n2</sup>COR<sup>p2</sup>, -NR<sup>n2</sup>CO<sub>2</sub>R<sup>p2</sup>, -NR<sup>n2</sup>CONR<sup>q2</sup>R<sup>r2</sup>, -NR<sup>n2</sup>S(O)<sub>2</sub>R<sup>p2</sup>, -NR<sup>n2</sup>S(O)<sub>2</sub>OR<sup>p2</sup>, -NR<sup>n2</sup>S(O)<sub>2</sub>NR<sup>q2</sup>R<sup>r2</sup>, NO<sub>2</sub>, -C(O)R<sup>n2</sup>, -C(O)OR<sup>n2</sup>, -C(O)NR<sup>q2</sup>R<sup>r2</sup>, halophenyl, 5-6 membered haloheteroaryl, 3-7 membered haloheterocycle and (C<sub>1</sub>-C<sub>8</sub>)heteroalkyl;

each  $Z^{1d}$  is independently selected from (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl and (C<sub>1</sub>-C<sub>8</sub>)haloalkyl;

each R<sup>n1</sup> is independently selected from H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R<sup>n1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)alkynyl of R<sup>n1</sup> is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5)  $Z^{1c}$  groups;

each R<sup>p1</sup> is independently selected from (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R<sup>p1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)alkynyl of R<sup>p1</sup> is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5)  $Z^{1c}$  groups;

R<sup>q1</sup> and R<sup>r1</sup> are each independently selected from H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R<sup>q1</sup> or R<sup>r1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)alkynyl of R<sup>q1</sup> or R<sup>r1</sup> is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5)  $Z^{1c}$  groups, or R<sup>q1</sup> and R<sup>r1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, (C<sub>1</sub>-C<sub>8</sub>)haloalkyl and (C<sub>1</sub>-C<sub>8</sub>)heteroalkyl;

each  $R^{p2}$  is independently selected from (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, (C<sub>1</sub>-C<sub>8</sub>)haloalkyl and (C<sub>1</sub>-C<sub>8</sub>)heteroalkyl;

$R^{q2}$  and  $R^{r2}$  are each independently selected from H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, (C<sub>1</sub>-C<sub>8</sub>)haloalkyl and (C<sub>1</sub>-C<sub>8</sub>)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<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, -C(O)R<sup>n3</sup> and -C(O)NR<sup>q3</sup>R<sup>r3</sup>, 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<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)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<sub>3</sub>-C<sub>7</sub>)carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, -OR<sup>n4</sup>, -OC(O)R<sup>p4</sup>, -OC(O)NR<sup>q4</sup>R<sup>r4</sup>, -SR<sup>n4</sup>, -S(O)R<sup>p4</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p4</sup>, -S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>COR<sup>p4</sup>, -NR<sup>n4</sup>CO<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>CONR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>OR<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, NO<sub>2</sub>, -C(O)R<sup>n4</sup>, -C(O)OR<sup>n4</sup> and -C(O)NR<sup>q4</sup>R<sup>r4</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl and (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

each  $Z^{2c}$  is independently selected from halogen, -CN, -OR<sup>n4</sup>, -OC(O)R<sup>p4</sup>, -OC(O)NR<sup>q4</sup>R<sup>r4</sup>, -SR<sup>n4</sup>, -S(O)R<sup>p4</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p4</sup>, -S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>COR<sup>p4</sup>, -NR<sup>n4</sup>CO<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>CONR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>OR<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, NO<sub>2</sub>, -C(O)R<sup>n4</sup>, -C(O)OR<sup>n4</sup> and -C(O)NR<sup>q4</sup>R<sup>r4</sup>;

each  $R^{n3}$  is independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl and (C<sub>2</sub>-C<sub>4</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl and (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $R^{p4}$  is independently selected from (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>2</sub>-C<sub>4</sub>)alkynyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl and (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

$R^{q4}$  and  $R^{r4}$  are each independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>2</sub>-C<sub>4</sub>)alkynyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl and (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $Z^3$  is independently selected from halogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, -OH, -CN, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl and (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

each  $Z^4$  is independently selected from (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, halogen, -CN, -OR<sup>n5</sup>, -OC(O)R<sup>p5</sup>, -OC(O)NR<sup>q5</sup>R<sup>r5</sup>, -SR<sup>n5</sup>, -S(O)R<sup>p5</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p5</sup>, -S(O)<sub>2</sub>NR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>n5</sup>COR<sup>p5</sup>, -NR<sup>n5</sup>CO<sub>2</sub>R<sup>p5</sup>, -NR<sup>n5</sup>CONR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>n5</sup>S(O)<sub>2</sub>R<sup>p5</sup>, -NR<sup>n5</sup>S(O)<sub>2</sub>OR<sup>p5</sup>, -NR<sup>n5</sup>S(O)<sub>2</sub>NR<sup>q5</sup>R<sup>r5</sup>, NO<sub>2</sub>, -C(O)R<sup>n5</sup>, -C(O)OR<sup>n5</sup> and -C(O)NR<sup>q5</sup>R<sup>r5</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)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<sup>n6</sup>, -OC(O)R<sup>p6</sup>, -OC(O)NR<sup>q6</sup>R<sup>r6</sup>, -SR<sup>n6</sup>, -S(O)R<sup>p6</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p6</sup>, -S(O)<sub>2</sub>NR<sup>q6</sup>R<sup>r6</sup>, -NR<sup>q6</sup>R<sup>r6</sup>, -NR<sup>n6</sup>COR<sup>p6</sup>,

$-\text{NR}^{\text{n}6}\text{CO}_2\text{R}^{\text{p}6}$ ,  $-\text{NR}^{\text{n}6}\text{CONR}^{\text{q}6}\text{R}^{\text{r}6}$ ,  $-\text{NR}^{\text{n}6}\text{S}(\text{O})_2\text{R}^{\text{p}6}$ ,  $-\text{NR}^{\text{n}6}\text{S}(\text{O})_2\text{OR}^{\text{p}6}$ ,  $-\text{NR}^{\text{n}6}\text{S}(\text{O})_2\text{NR}^{\text{q}6}\text{R}^{\text{r}6}$ ,  $\text{NO}_2$ ,  $-\text{C}(\text{O})\text{R}^{\text{n}6}$ ,  $-\text{C}(\text{O})\text{OR}^{\text{n}6}$  and  $-\text{C}(\text{O})\text{NR}^{\text{q}6}\text{R}^{\text{r}6}$ ;

each  $\text{Z}^{\text{4b}}$  is independently selected from (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl (C<sub>2</sub>-C<sub>4</sub>)alkynyl and (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

each  $\text{R}^{\text{n}5}$  is independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

each  $\text{R}^{\text{p}5}$  is independently selected from (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

$\text{R}^{\text{q}5}$  and  $\text{R}^{\text{r}5}$  are each independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

each  $\text{R}^{\text{n}6}$  is independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

each  $\text{R}^{\text{p}6}$  is independently selected from (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

$\text{R}^{\text{q}6}$  and  $\text{R}^{\text{r}6}$  are each independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

each  $\text{Z}^5$  is independently selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, -CN and -OR<sup>n7</sup>, wherein any (C<sub>1</sub>-C<sub>6</sub>)alkyl of  $\text{Z}^5$  is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen; and

each  $\text{R}^{\text{n}7}$  is independently selected from H, (C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>3</sub>)haloalkyl and (C<sub>3</sub>-C<sub>7</sub>)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 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 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, 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, 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<sub>u-v</sub>” or (C<sub>u</sub>-C<sub>v</sub>) indicates that the following group has from u to v carbon atoms. For example, “C<sub>1-6</sub>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<sub>1</sub>-C<sub>8</sub>)alkyl) or 1 to 6 carbon atoms (i.e., (C<sub>1</sub>-C<sub>6</sub>)alkyl) or 1 to 4 carbon atoms (i.e., (C<sub>1</sub>-C<sub>4</sub>)alkyl). Examples of suitable alkyl groups include, but are not limited to, methyl (Me, -CH<sub>3</sub>), ethyl (Et, -CH<sub>2</sub>CH<sub>3</sub>), 1-propyl (n-Pr, n-propyl, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2-propyl (i-Pr, i-propyl, -CH(CH<sub>3</sub>)<sub>2</sub>), 1-butyl (n-Bu, n-butyl, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2-methyl-1-propyl (i-Bu, i-butyl, -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 2-butyl (s-Bu, s-butyl, -CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>), 2-methyl-2-propyl (t-Bu, t-butyl, -C(CH<sub>3</sub>)<sub>3</sub>), 1-pentyl (n-pentyl, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2-pentyl (-CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3-pentyl (-CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 2-methyl-2-butyl (-C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3-methyl-2-butyl (-CH(CH<sub>3</sub>)CH(CH<sub>3</sub>)<sub>2</sub>), 3-methyl-1-butyl (-CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 2-methyl-1-butyl (-CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>), 1-hexyl (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2-hexyl (-CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3-hexyl (-CH(CH<sub>2</sub>CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)), 2-methyl-2-pentyl (-C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3-methyl-2-pentyl (-CH(CH<sub>3</sub>)CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>), 4-methyl-2-pentyl (-CH(CH<sub>3</sub>)CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 3-methyl-3-pentyl (-C(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 2-methyl-3-pentyl (-CH(CH<sub>2</sub>CH<sub>3</sub>)CH(CH<sub>3</sub>)<sub>2</sub>), 2,3-dimethyl-2-butyl (-C(CH<sub>3</sub>)<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 3,3-dimethyl-2-butyl (-CH(CH<sub>3</sub>)C(CH<sub>3</sub>)<sub>3</sub>), and octyl (-CH<sub>2</sub>)<sub>7</sub>CH<sub>3</sub>.

[0026] "Alkenyl" is a straight or branched hydrocarbon with at least one carbon-carbon, *sp*<sup>2</sup> double bond. For example, an alkenyl group can have 2 to 8 carbon atoms (i.e., C<sub>2</sub>-C<sub>8</sub> alkenyl), or 2 to 6 carbon atoms (i.e., C<sub>2</sub>-C<sub>6</sub> alkenyl). Examples of suitable alkenyl groups include, but are not limited to, ethylene or vinyl (-CH=CH<sub>2</sub>), allyl (-CH<sub>2</sub>CH=CH<sub>2</sub>) and 5-hexenyl (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH=CH<sub>2</sub>).

[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<sub>2</sub>-C<sub>8</sub> alkyne,) or 2 to 6 carbon atoms (i.e., C<sub>2</sub>-C<sub>6</sub> alkynyl). Examples of suitable alkynyl groups include, but are not limited to, acetylenic (-C≡CH), propargyl (-CH<sub>2</sub>C≡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<sub>1</sub>-C<sub>6</sub>)haloalkyl is a (C<sub>1</sub>-C<sub>6</sub>)alkyl wherein one or more of the hydrogen atoms of the (C<sub>1</sub>-C<sub>6</sub>)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<sup>q</sup>, (or if the carbon atom being replaced is a terminal carbon with an OH, SH or N(R<sup>q</sup>)<sub>2</sub>) wherein each R<sup>q</sup> is independently H or (C<sub>1</sub>-C<sub>6</sub>)alkyl. For example, (C<sub>1</sub>-C<sub>8</sub>)heteroalkyl includes a heteroalkyl of one to eight carbons and one or more heteroatoms (e.g., O, S, NR<sup>q</sup>, OH, SH or N(R<sup>q</sup>)<sub>2</sub>). Thus, for example, a C<sub>1</sub> heteroalkyl encompasses, e.g., -CH<sub>2</sub>-NH<sub>2</sub>. 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, quinazoliny-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<sup>2</sup> 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 azetidiny, tetrahydrofuranyl and piperidiny. 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-decahydronaphthyridiny), carbocycles (to form for example a decahydroquinoly) 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, azetidiny, 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 carbocycles 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 carbocycles can be connected to each other via a single carbon atom to form a spiro connection (e.g., 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

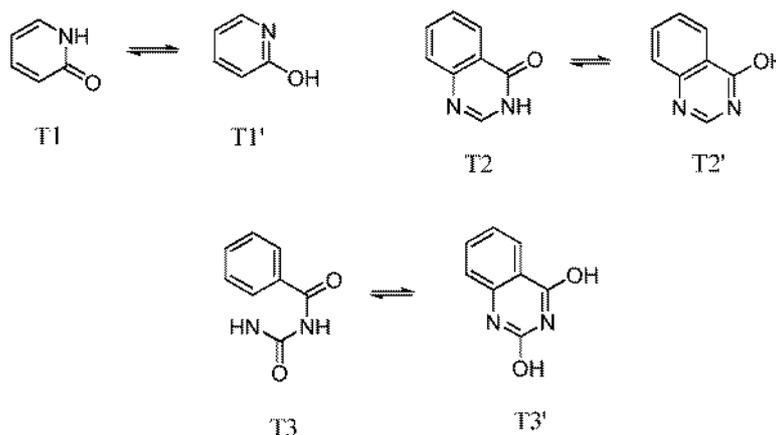
diastereomer. In another embodiment, a compound disclosed herein is at least 99% a single diastereomer.

[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.



### 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-

naphthalenesulfonic, 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  $\text{Na}^+$  and  $\text{NX}_4^+$  (wherein X is independently selected from H or a  $\text{C}_1$ – $\text{C}_4$  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  $\text{Li}^+$ ,  $\text{Na}^+$ , and  $\text{K}^+$ . 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,  $\text{H}_2\text{SO}_4$ ,  $\text{H}_3\text{PO}_4$  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.

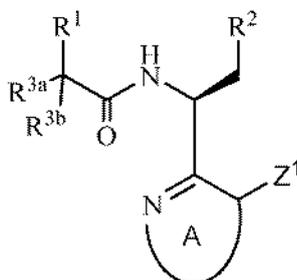
### Isotopes

**[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 ( $^2\text{H}$  or D). As a non-limiting example, in certain embodiments, a  $-\text{CH}_3$  group is replaced with  $-\text{CD}_3$ .

**[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.

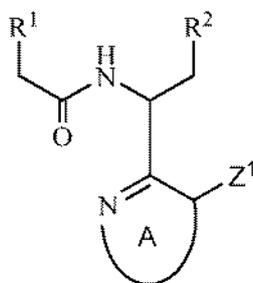
**[0063]** A specific group of compounds of formula I are compounds of formula Ia.



Ia

or a pharmaceutically acceptable salt thereof.

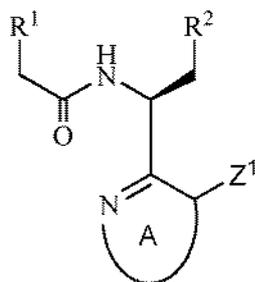
**[0064]** Another specific group of compounds of formula I are compounds of formula Ib.



Ib

or a pharmaceutically acceptable thereof.

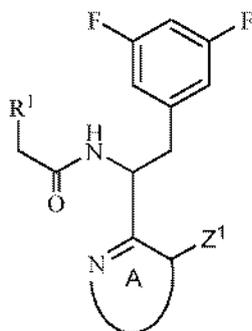
[0065] Another specific group of compounds of formula I are compounds of formula Ic.



Ic

or a pharmaceutically acceptable thereof.

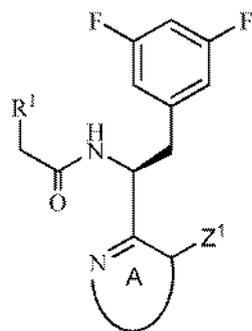
[0066] Another specific group of compounds of formula I are compounds of formula Id.



Id

or a pharmaceutically acceptable thereof.

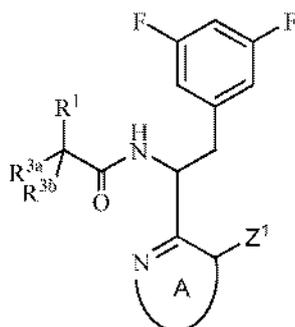
[0067] Another specific group of compounds of formula I are compounds of formula Ie.



Ie

or a pharmaceutically acceptable thereof.

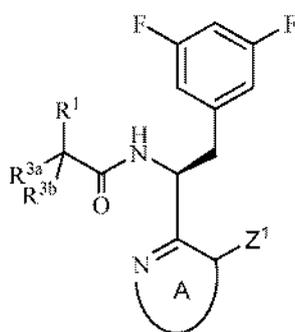
[0068] Another specific group of compounds of formula I are compounds of formula If.



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 be 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<sub>1</sub>-C<sub>3</sub>)alkyl, and (C<sub>1</sub>-C<sub>3</sub>)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<sub>1</sub>-C<sub>3</sub>)alkyl, and (C<sub>1</sub>-C<sub>3</sub>)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<sub>1</sub>-C<sub>3</sub>)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<sub>1</sub>-C<sub>3</sub>)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.

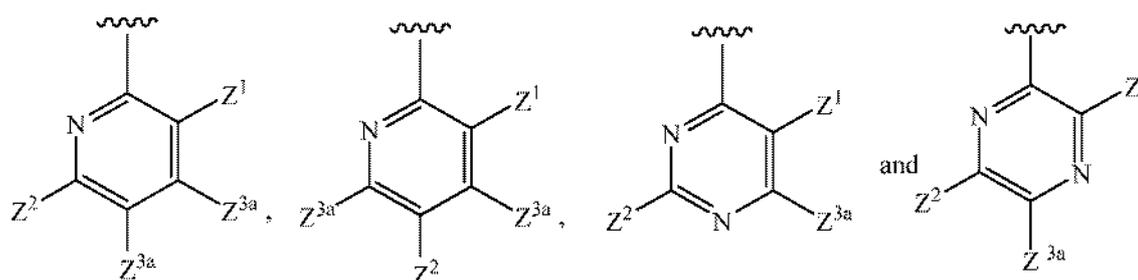
[0088] A specific value for A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein any pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl of A is substituted with one  $Z^1$  group at the position shown, one  $Z^2$  group and optionally substituted with one or more (e.g., 1 or 2)  $Z^3$  groups.

[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.

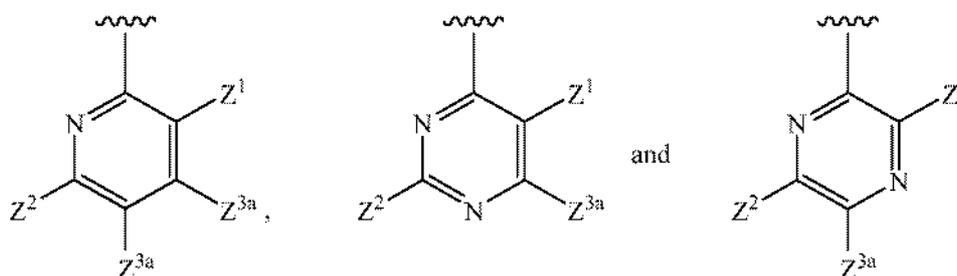
[0091] A specific value for A is pyridinyl, wherein any pyridinyl of A is substituted with one  $Z^1$  group at the position shown and one  $Z^2$  group

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



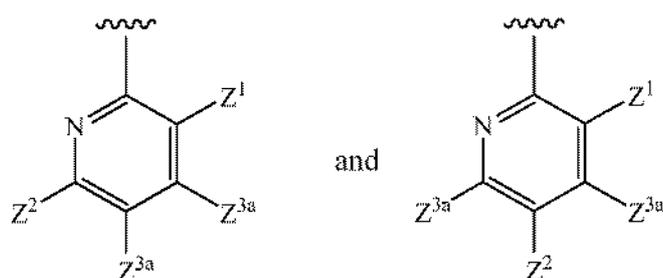
wherein each  $Z^{3a}$  is independently selected from H and  $Z^3$ .

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



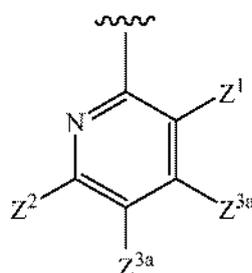
wherein each  $Z^{3a}$  is independently selected from H and  $Z^3$ .

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



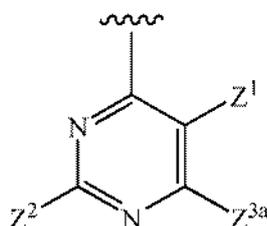
wherein each  $Z^{3a}$  is independently selected from H and  $Z^3$ .

[0095] A specific value for A is:



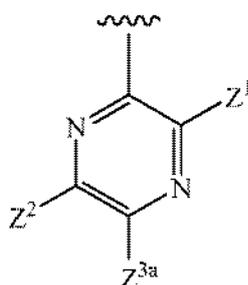
wherein each  $Z^{3a}$  is independently selected from H and  $Z^3$ .

[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.

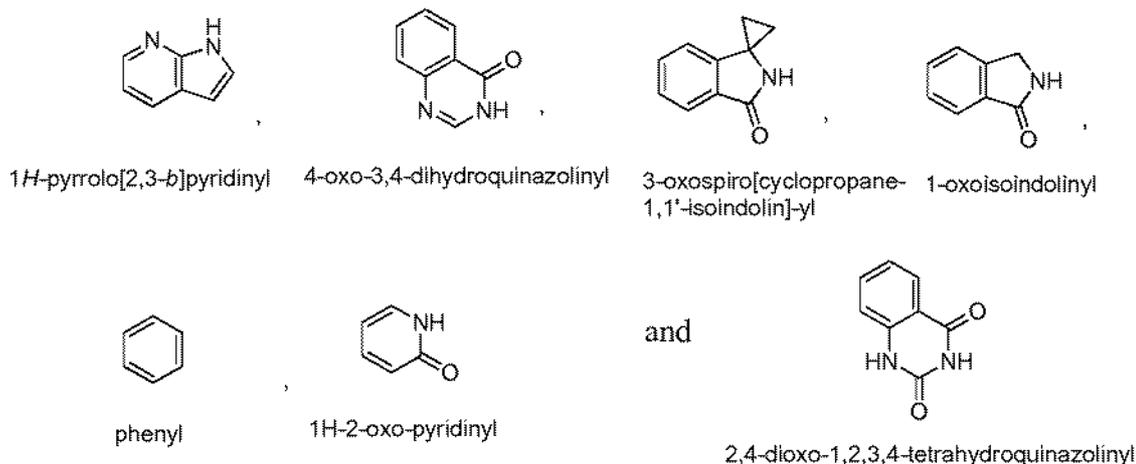
[0110] A specific value for  $Z^1$  is selected from 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle, wherein any from 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle of  $Z^1$  is optionally substituted with one or more  $Z^{1a}$  groups.

[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.

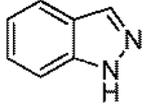
[0112] A specific value for  $Z^1$  is selected from 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle, wherein the 8-10 membered bicyclic-heteroaryl and 8-10 membered bicyclic-heterocycle have 3-9 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any 8-10 membered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

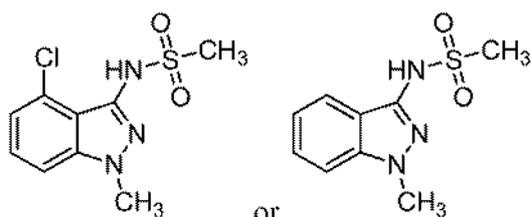
[0113] A specific value for  $Z^1$  is selected from phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 4-oxo-3,4-dihydroquinazoliny, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, 1H-2-oxo-pyridinyl and 2,4-dioxo-1,2,3,4-tetrahydroquinazoliny, wherein any phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 4-oxo-3,4-dihydroquinazoliny, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, 1H-2-oxo-pyridinyl and 2,4-dioxo-1,2,3,4-tetrahydroquinazoliny 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-dihydroquinazoliny, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, 1H-2-oxo-pyridinyl and 2,4-dioxo-1,2,3,4-tetrahydroquinazoliny as shown by the following formulas;



wherein any phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 4-oxo-3,4-dihydroquinazoliny, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, 1H-2-oxo-pyridinyl and 2,4-dioxo-1,2,3,4-tetrahydroquinazoliny 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



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

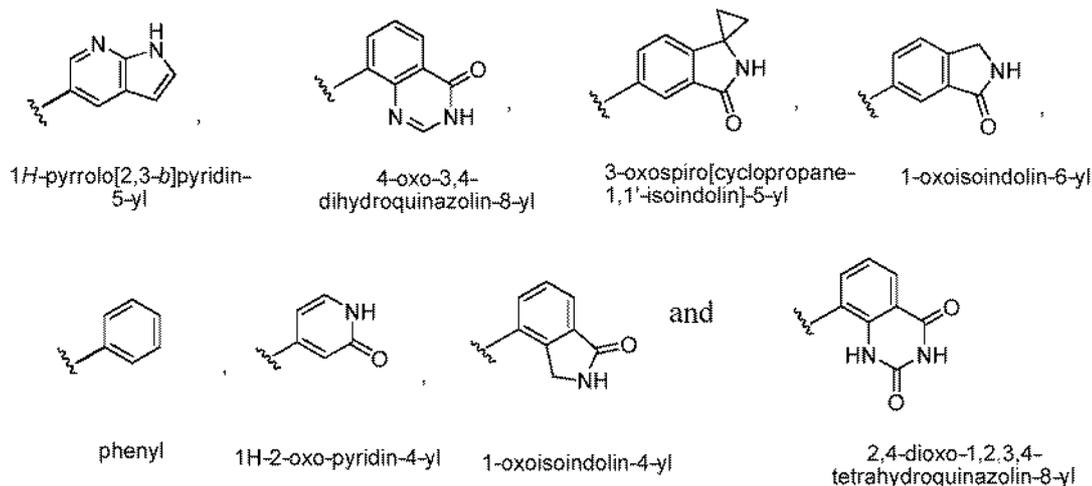
[0117] A specific value for  $Z^1$  is selected from phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, pyridinyl and quinazoliny, wherein any phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisoindolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, pyridinyl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

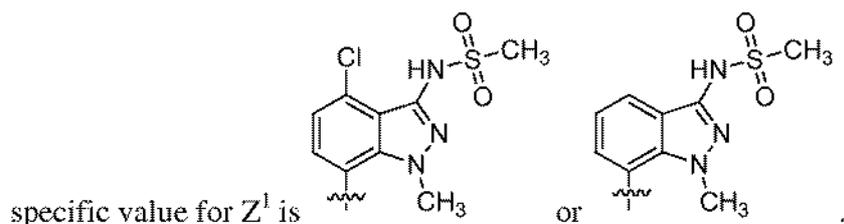
[0119] A specific value for  $Z^1$  is selected from phenyl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1-oxoisoindolin-5-yl, 1-oxoisoindolin-4-yl, 3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl, pyridin-4-yl and quinazolin-8-yl, wherein any phenyl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1-oxoisoindolin-5-yl, 1-oxoisoindolin-4-yl, 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-tetrahydroquinazolin-8-yl as shown by the following formulas;



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-tetrahydroquinazolin-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



[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-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-tetrahydroquinazolin-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  $-C(O)NH_2$ .

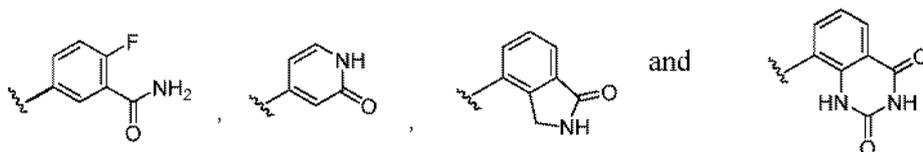
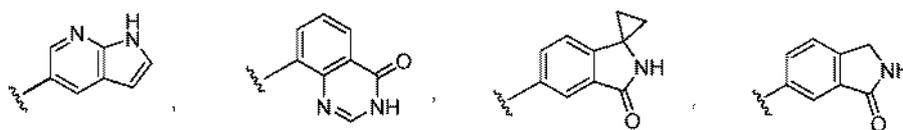
[0129] A specific value for  $R_{q1}$  and  $R_{r1}$  is H.

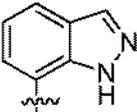
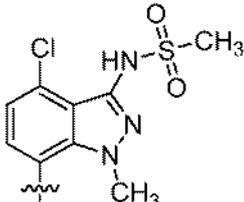
[0130] A specific value for each  $Z^{1a}$  is independently selected from halogen and  $-NR^{n1}S(O)_2R^{p1}$ .

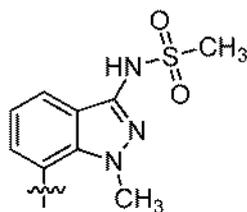
[0131] A specific value for each  $Z^{1b}$  is  $(C_1-C_8)$ alkyl, which may be same or different.

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

[0133] A specific value for  $Z^1$  is selected from:



[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  $(C_2-C_8)$ 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  $(C_2-C_8)$ 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  $(C_2-C_8)$ 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  $(C_2-C_8)$ 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  $(C_2-C_8)$ 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<sub>2</sub>-C<sub>8</sub>)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<sub>2</sub>-C<sub>8</sub>)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<sup>q3</sup>R<sup>r3</sup>, 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<sub>2</sub>-C<sub>8</sub>)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<sub>2</sub>-C<sub>8</sub>)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<sup>q3</sup>R<sup>r3</sup>, 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<sub>2</sub>-C<sub>8</sub>)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<sub>2</sub>-C<sub>8</sub>)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<sup>q3</sup>R<sup>r3</sup>, 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<sub>2</sub>-C<sub>8</sub>)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-oxoisindolinyl, 1H-pyrrolo[2,3-b]pyridinyl and -C(O)NR<sup>q3</sup>R<sup>r3</sup>, wherein any phenyl, pyridinyl, 1H-2-oxo-pyridinyl, triazolyl, 1-oxoisindolinyl 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-oxoisindolinyl, 1H-pyrrolo[2,3-b]pyridinyl and  $-C(O)NR^{q3}R^{r3}$ , wherein any phenyl, pyridinyl, 2-oxopyridinyl, triazolyl, 1-oxoisindolinyl 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-oxoisindolin-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-oxoisindolin-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-oxoisindolin-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-oxoisindolin-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.

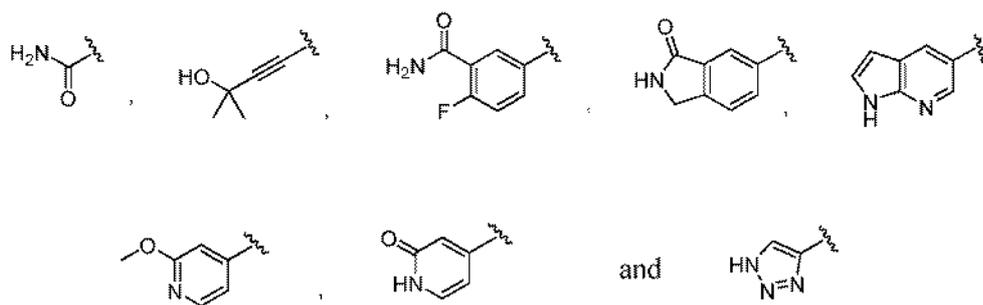
[0147] A specific value for each  $Z^{2c}$  is independently selected from halogen,  $-OR_{n4}$  and  $-C(O)NR_{q4}R_{r4}$ .

[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.

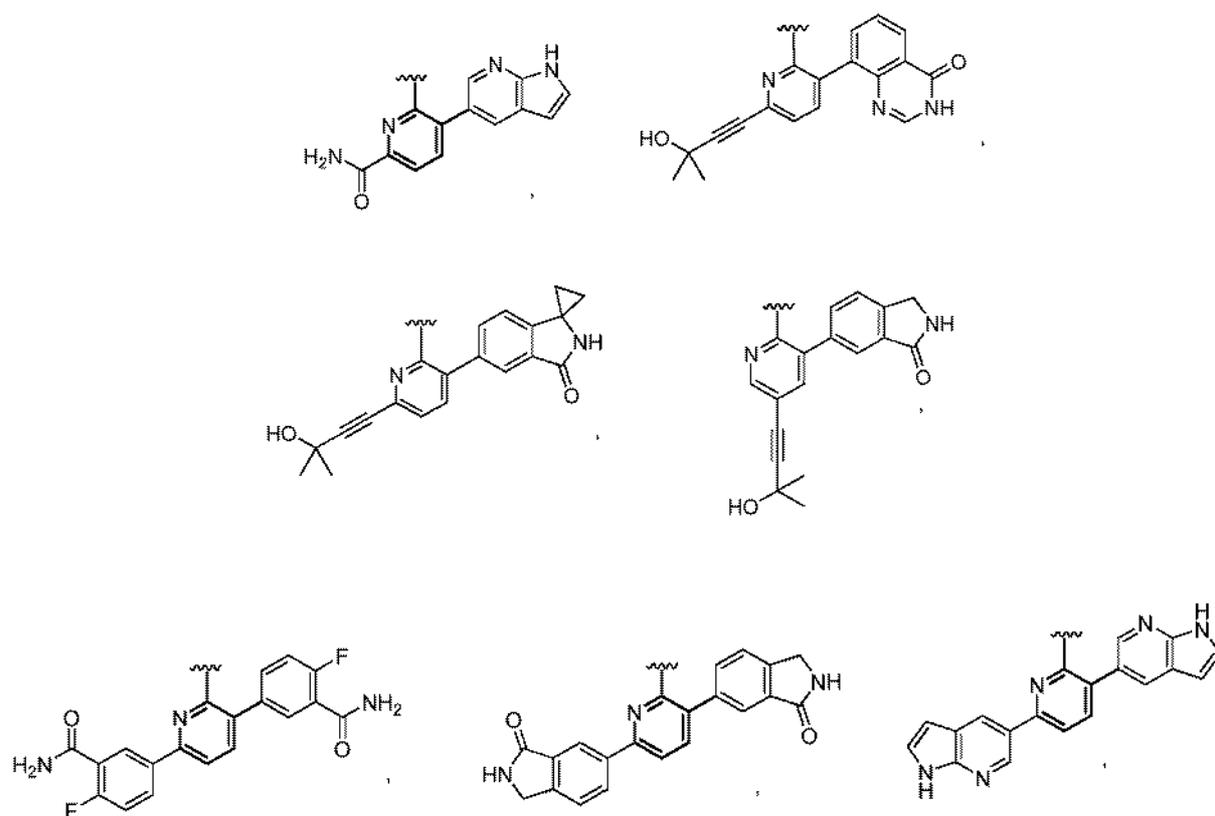
[0149] A specific value for  $R^{n4}$  is H or methyl.

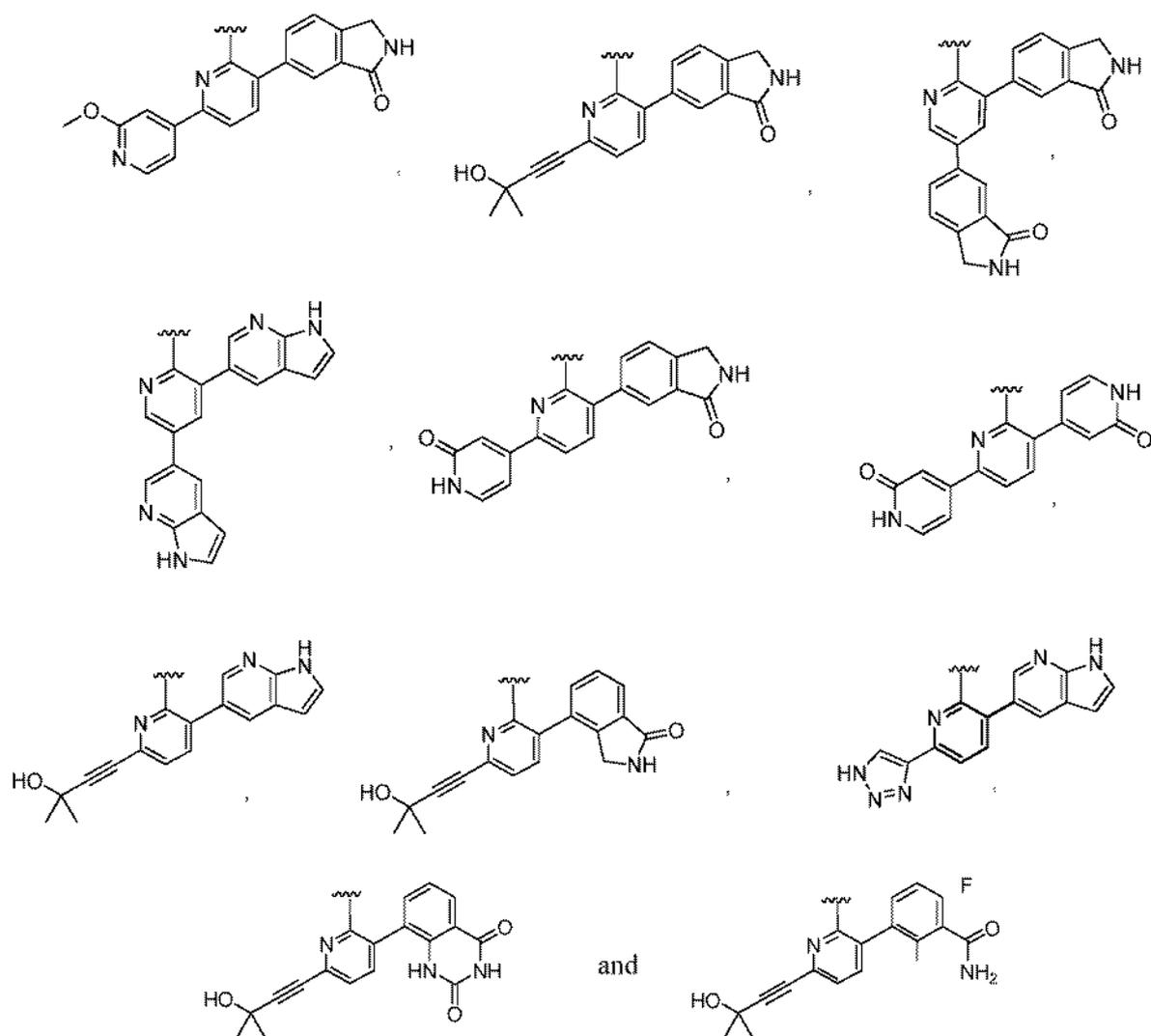
[0150] A specific value for each  $R^{q4}$  and  $R^{r4}$  is H.

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

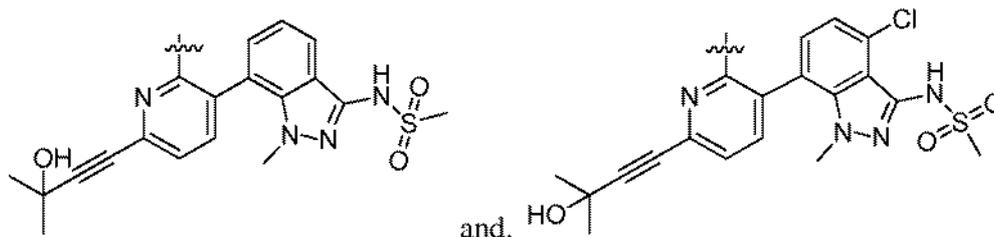


[0152] A specific value for A-Z<sup>1</sup> is selected from:





[0153] A specific value for A-Z<sup>1</sup> is selected from:



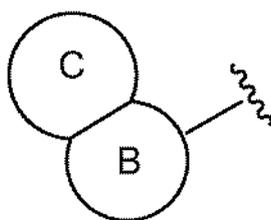
[0154] A specific value for R<sup>1</sup> is a 5-12 membered heteroaryl, wherein any 5-12 membered heteroaryl of R<sup>1</sup> is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) Z<sup>4</sup> groups.

[0155] A specific value for R<sup>1</sup> 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<sup>1</sup> is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) Z<sup>4</sup> 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:



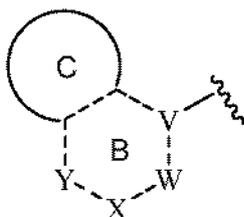
IIa

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;

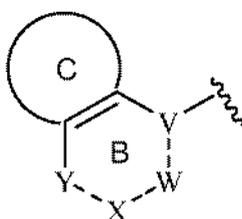
X is  $CZ^{4c}$ ,  $NZ^{4c}$  or N;

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<sup>4c</sup> or N;

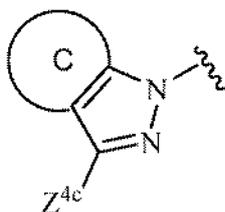
X is CZ<sup>4c</sup>, NZ<sup>4c</sup> or N;

Y is CZ<sup>4c</sup>, 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<sup>4c</sup> is independently selected from H or Z<sup>4</sup>.

[0161] A specific value for R<sup>1</sup> has the following R<sup>1</sup> has the following formula II d:



II d

wherein:

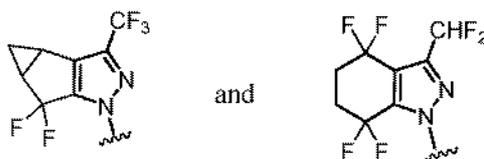
C together with the two carbon atoms to which it is attached forms a 3-7 membered monocyclic-carbocycle, 5-9 membered bicyclic-carbocycle, 3-7 membered monocyclic-heterocycle or 5-9 membered bicyclic heterocycle, wherein any 3-7 membered monocyclic-carbocycle, 5-9 membered bicyclic-carbocycle, 3-7 membered 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<sup>4</sup> groups; and

each Z<sup>4c</sup> is independently selected from H or Z<sup>4</sup>.

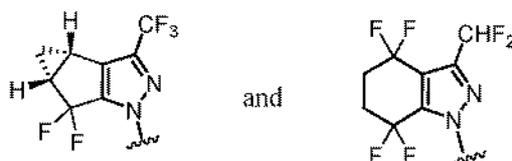
[0162] A specific value for each Z<sup>4</sup> is independently selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl and halogen, wherein any (C<sub>1</sub>-C<sub>6</sub>)alkyl of Z<sup>4</sup> is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) halogen.

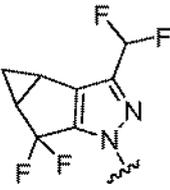
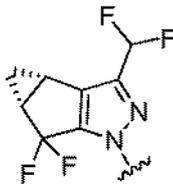
[0163] A specific value for each Z<sup>4</sup> is independently selected from fluoro, trifluoromethyl and difluoromethyl.

[0164] A specific value for R<sup>1</sup> is selected from:



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



[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.

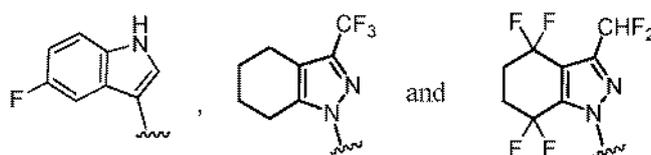
[0174] A specific value for each  $Z^4$  is independently selected from  $(C_1-C_6)$ alkyl and halogen, wherein any  $(C_1-C_6)$ alkyl of  $Z^4$  is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen.

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

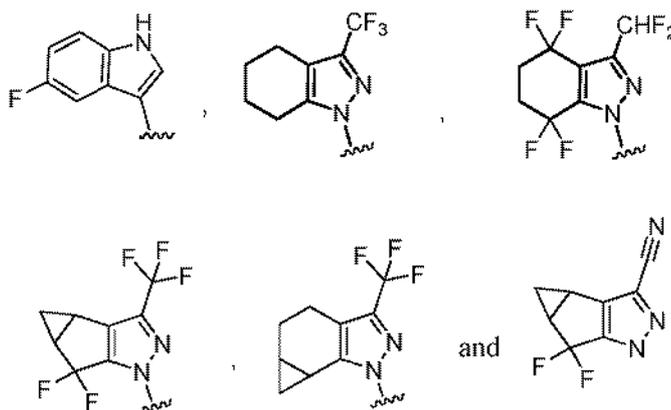
[0176] A specific value for each  $Z^4$  is independently selected from fluoro, trifluoromethyl and difluoromethyl.

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

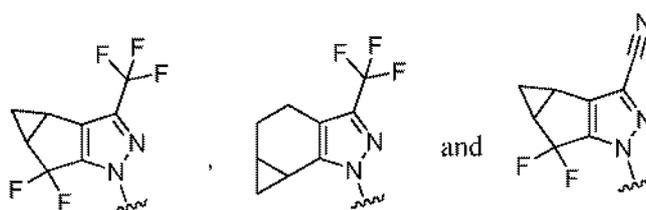
[0178] A specific value for  $R^1$  is selected from:

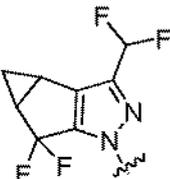
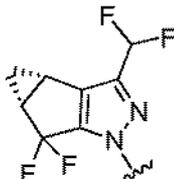


[0179] A specific value for  $R^1$  is selected from:



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



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

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

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

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

[0185] In one variation of formula I, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and Z<sup>1</sup> 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<sup>1</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1a</sup> groups. In another variation, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and Z<sup>1</sup> is phenyl, optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1a</sup> groups. In another variation, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and Z<sup>1</sup> 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<sup>1</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1a</sup> groups. In another variation, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and Z<sup>1</sup> 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<sup>1</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1a</sup> groups.

[0186] In one variation of formula I, A is pyridinyl; and Z<sup>1</sup> 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<sup>1</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1a</sup> groups. In another variation, A is pyridinyl; and Z<sup>1</sup> is phenyl, optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1a</sup> groups. In another variation, A is pyridinyl; and Z<sup>1</sup> 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<sup>1</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1a</sup> groups. In another variation, A is pyridinyl; and Z<sup>1</sup> 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<sup>1</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1a</sup> 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.

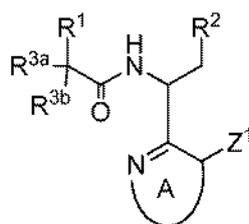
[0192] In one variation of formula I,  $Z^1$  is phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered bicyclic-heterocycle, or 9-12 membered tricyclic-heterocycle wherein any phenyl, 5-6 membered monocyclic-heteroaryl, 8-10 membered bicyclic-heteroaryl, 8-10 membered 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<sub>1</sub>-C<sub>3</sub>)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<sub>3</sub>-C<sub>7</sub>)carbocycle, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, -OR<sup>n1</sup>, -OC(O)R<sup>p1</sup>, -OC(O)NR<sup>q1</sup>R<sup>r1</sup>, -SR<sup>n1</sup>, -S(O)R<sup>p1</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p1</sup>, -S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>COR<sup>p1</sup>, -NR<sup>n1</sup>CO<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>CONR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>OR<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -C(O)R<sup>n1</sup>, -C(O)OR<sup>n1</sup>, -C(O)NR<sup>q1</sup>R<sup>r1</sup> and -S(O)<sub>2</sub>NR<sup>n1</sup>COR<sup>p1</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)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<sub>2</sub>, -C(O)NR<sup>q2</sup>R<sup>r2</sup>, or (C<sub>1</sub>-C<sub>8</sub>)heteroalkyl;

each  $Z^{1d}$  is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl or (C<sub>1</sub>-C<sub>8</sub>)haloalkyl;

each  $R^{n1}$  is independently H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)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<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)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<sup>q3</sup>R<sup>r3</sup>, 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<sub>2</sub>-C<sub>8</sub>)alkenyl or (C<sub>2</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl;

each  $R^{q3}$  and  $R^{r3}$  is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

each  $Z^{2b}$  is independently oxo, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, or (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;  
 each  $Z^{2c}$  is independently oxo, halogen, -CN, -OR<sup>n4</sup>, -OC(O)R<sup>p4</sup>, -OC(O)NR<sup>q4</sup>R<sup>r4</sup>, -SR<sup>n4</sup>, -S(O)R<sup>p4</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p4</sup>, -S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>COR<sup>p4</sup>, -NR<sup>n4</sup>CO<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>CONR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>OR<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NO<sub>2</sub>, -C(O)R<sup>n4</sup>, -C(O)OR<sup>n4</sup>, or -C(O)NR<sup>q4</sup>R<sup>r4</sup>;

each R<sup>n4</sup> is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each R<sup>p4</sup> is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each R<sup>q4</sup> and R<sup>r4</sup> is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each Z<sup>3</sup> is independently a (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl or halogen;

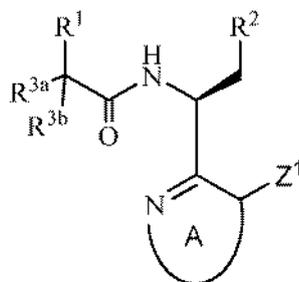
each Z<sup>4</sup> is independently oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, halogen, -CN, -OR<sup>n5</sup>, -NR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>n5</sup>COR<sup>p5</sup>, -NR<sup>n5</sup>CO<sub>2</sub>R<sup>p5</sup>, -C(O)R<sup>n5</sup>, -C(O)OR<sup>n5</sup>, or -C(O)NR<sup>q5</sup>R<sup>r5</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle or (C<sub>1</sub>-C<sub>8</sub>)alkyl of Z<sup>4</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>4a</sup> groups, wherein the Z<sup>4a</sup> groups are the same or different;

each Z<sup>4a</sup> is independently halogen, -CN, or -OR<sup>n6</sup>; and

each R<sup>n5</sup>, R<sup>p5</sup>, R<sup>q5</sup>, R<sup>r5</sup>, and R<sup>n6</sup> is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

or a pharmaceutically acceptable salt thereof.

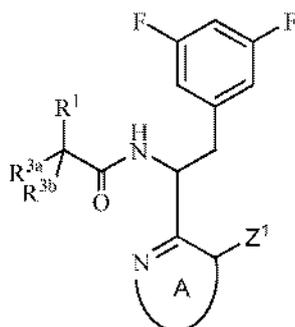
[0196] In certain embodiments, a compound of formula III is a compound of formula IIIa.



IIIa

or a pharmaceutically acceptable salt thereof.

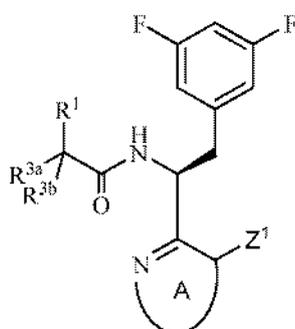
[0197] In certain embodiments, a compound of formula III is a compound of formula IIIb.



IIIb

or a pharmaceutically acceptable thereof.

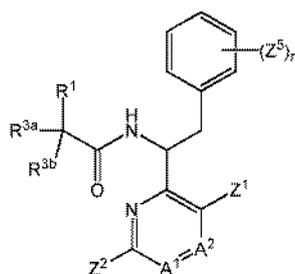
[0198] In certain embodiments, a compound of formula III is a compound of formula IIIc.



IIIc

or a pharmaceutically acceptable thereof.

[0199] The present disclosure provides compounds of formula III d:



III d

wherein

A<sup>1</sup> is CH, C-Z<sup>3</sup>, or nitrogen;

A<sup>2</sup> is CH or nitrogen;

R<sup>1</sup> 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<sup>1</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>4</sup> groups, wherein the Z<sup>4</sup> 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<sup>nl</sup>, -OC(O)R<sup>pl</sup>, -OC(O)NR<sup>q1</sup>R<sup>r1</sup>, -SR<sup>nl</sup>, -S(O)R<sup>pl</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>pl</sup>, -S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>nl</sup>COR<sup>pl</sup>, -NR<sup>nl</sup>CO<sub>2</sub>R<sup>pl</sup>, -NR<sup>nl</sup>CONR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>nl</sup>S(O)<sub>2</sub>R<sup>pl</sup>, -NR<sup>nl</sup>S(O)<sub>2</sub>OR<sup>pl</sup>, -NR<sup>nl</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -C(O)R<sup>nl</sup>, -C(O)OR<sup>nl</sup>, -C(O)NR<sup>q1</sup>R<sup>r1</sup> and -S(O)<sub>2</sub>NR<sup>nl</sup>COR<sup>pl</sup>, 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<sub>2</sub>, -C(O)NR<sup>q2</sup>R<sup>r2</sup>, or  $(C_1-C_8)$ heteroalkyl;

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

each R<sup>nl</sup> 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<sup>nl</sup> 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<sup>nl</sup> 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<sup>pl</sup> 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<sup>pl</sup> 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<sup>pl</sup> 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<sup>q1</sup> and R<sup>r1</sup> 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<sup>q1</sup> or R<sup>r1</sup> 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<sub>1</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)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<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)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<sup>q3</sup>R<sup>r3</sup>, 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<sub>2</sub>-C<sub>8</sub>)alkenyl or (C<sub>2</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl;

each  $R^{q3}$  and  $R^{r3}$  is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

each  $Z^{2b}$  is independently oxo, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl or (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

each  $Z^{2c}$  is independently oxo, halogen, -CN, -OR<sup>n4</sup>, -OC(O)R<sup>p4</sup>, -OC(O)NR<sup>q4</sup>R<sup>r4</sup>, -SR<sup>n4</sup>, -S(O)R<sup>p4</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p4</sup>, -S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>COR<sup>p4</sup>, -NR<sup>n4</sup>CO<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>CONR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>OR<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NO<sub>2</sub>, -C(O)R<sup>n4</sup>, -C(O)OR<sup>n4</sup>, or -C(O)NR<sup>q4</sup>R<sup>r4</sup>;

each  $R^{n4}$  is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $R^{p4}$  is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $R^{q4}$  and  $R^{r4}$  is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $Z^3$  is independently a (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $Z^4$  is independently oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, halogen, -CN, -OR<sup>n5</sup>, -NR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>n5</sup>COR<sup>p5</sup>, -NR<sup>n5</sup>CO<sub>2</sub>R<sup>p5</sup>, -C(O)R<sup>n5</sup>, -C(O)OR<sup>n5</sup>, or -C(O)NR<sup>q5</sup>R<sup>r5</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle or (C<sub>1</sub>-C<sub>8</sub>)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<sup>n6</sup>;

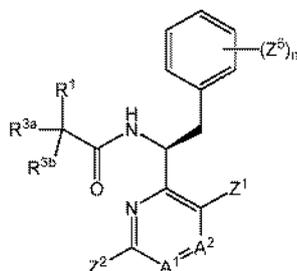
each  $R^{n5}$ ,  $R^{p5}$ ,  $R^{q5}$ ,  $R^{r5}$ , and  $R^{n6}$  is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

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.

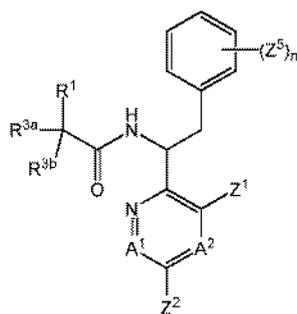
[0200] In certain embodiments, a compound of formula IIIe is a compound of formula IIIe.



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<sub>1</sub>-C<sub>3</sub>)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<sub>3</sub>-C<sub>7</sub>)carbocycle, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, -OR<sup>n1</sup>, -OC(O)R<sup>p1</sup>, -OC(O)NR<sup>q1</sup>R<sup>r1</sup>, -SR<sup>n1</sup>, -S(O)R<sup>p1</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p1</sup>, -S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>COR<sup>p1</sup>, -NR<sup>n1</sup>CO<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>CONR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>OR<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -C(O)R<sup>n1</sup>, -C(O)OR<sup>n1</sup>, -C(O)NR<sup>q1</sup>R<sup>r1</sup> and -S(O)<sub>2</sub>NR<sup>n1</sup>COR<sup>p1</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)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<sub>2</sub>, -C(O)NR<sup>q2</sup>R<sup>r2</sup>, or (C<sub>1</sub>-C<sub>8</sub>)heteroalkyl;

each  $Z^{1d}$  is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl or (C<sub>1</sub>-C<sub>8</sub>)haloalkyl;

each R<sup>n1</sup> is independently H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R<sup>n1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl of R<sup>n1</sup> 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<sup>p1</sup> is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R<sup>p1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl of R<sup>p1</sup> 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<sup>q1</sup> and R<sup>r1</sup> is independently H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R<sup>q1</sup> or R<sup>r1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl of R<sup>q1</sup> or R<sup>r1</sup> 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<sup>q1</sup> and R<sup>r1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)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<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)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<sup>q3</sup>R<sup>r3</sup>, 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<sub>2</sub>-C<sub>8</sub>)alkenyl or (C<sub>2</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl;

each  $R^{q3}$  and  $R^{r3}$  is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

each  $Z^{2b}$  is independently oxo, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl or (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

each  $Z^{2c}$  is independently oxo, halogen, -CN, -OR<sup>n4</sup>, -OC(O)R<sup>p4</sup>, -OC(O)NR<sup>q4</sup>R<sup>r4</sup>, -SR<sup>n4</sup>, -S(O)R<sup>p4</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p4</sup>, -S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>COR<sup>p4</sup>, -NR<sup>n4</sup>CO<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>CONR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>OR<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NO<sub>2</sub>, -C(O)R<sup>n4</sup>, -C(O)OR<sup>n4</sup>, or -C(O)NR<sup>q4</sup>R<sup>r4</sup>;

each  $R^{n4}$  is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $R^{p4}$  is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $R^{q4}$  and  $R^{r4}$  is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $Z^3$  is independently a (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $Z^4$  is independently oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, halogen, -CN, -OR<sup>n5</sup>, -NR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>n5</sup>COR<sup>p5</sup>, -NR<sup>n5</sup>CO<sub>2</sub>R<sup>p5</sup>, -C(O)R<sup>n5</sup>, -C(O)OR<sup>n5</sup>, or -C(O)NR<sup>q5</sup>R<sup>r5</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle or (C<sub>1</sub>-C<sub>8</sub>)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<sup>n6</sup>;

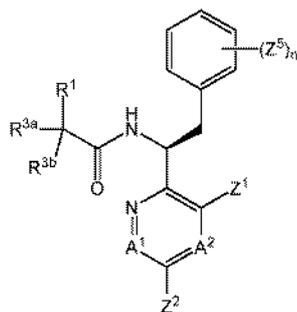
each  $R^{n5}$ ,  $R^{p5}$ ,  $R^{q5}$ ,  $R^{r5}$ , and  $R^{n6}$  is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

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.

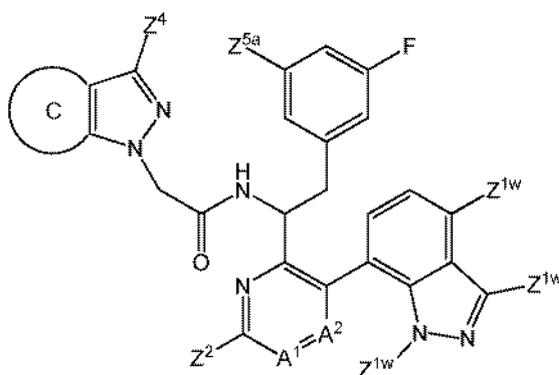
[0202] In certain embodiments, a compound of formula IIIf is a compound of formula IIIg.



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<sub>3</sub>-C<sub>7</sub>)carbocycle, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, -OR<sup>n1</sup>, -OC(O)R<sup>p1</sup>, -OC(O)NR<sup>q1</sup>R<sup>r1</sup>, -SR<sup>n1</sup>, -S(O)R<sup>p1</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p1</sup>, -S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>COR<sup>p1</sup>, -NR<sup>n1</sup>CO<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>CONR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>OR<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -C(O)R<sup>n1</sup>, -C(O)OR<sup>n1</sup>, -C(O)NR<sup>q1</sup>R<sup>r1</sup> and -S(O)<sub>2</sub>NR<sup>n1</sup>COR<sup>p1</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)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<sub>2</sub>, -C(O)NR<sup>q2</sup>R<sup>r2</sup>, or (C<sub>1</sub>-C<sub>8</sub>)heteroalkyl;

each  $Z^{1d}$  is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl or (C<sub>1</sub>-C<sub>8</sub>)haloalkyl;

each R<sup>n1</sup> is independently H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R<sup>n1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl of R<sup>n1</sup> 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<sup>p1</sup> is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R<sup>p1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl of R<sup>p1</sup> 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<sup>q1</sup> and R<sup>r1</sup> is independently H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R<sup>q1</sup> or R<sup>r1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl of R<sup>q1</sup> or R<sup>r1</sup> 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<sup>q1</sup> and R<sup>r1</sup> 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<sup>q2</sup> and R<sup>r2</sup> is independently H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, or R<sup>q2</sup> and R<sup>r2</sup> together with the nitrogen to which they are attached form a 5, 6, or 7-membered heterocycle;

$Z^2$  is (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, -C(O)R<sup>n3</sup>, or -C(O)NR<sup>q3</sup>R<sup>r3</sup>, 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<sub>2</sub>-C<sub>8</sub>)alkenyl or (C<sub>2</sub>-C<sub>8</sub>)alkynyl of Z<sup>2</sup> is optionally substituted with 1, 2, 3, 4, or 5 Z<sup>2c</sup> groups, wherein the Z<sup>2c</sup> groups are the same or different;

each R<sup>n3</sup> is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

each R<sup>q3</sup> and R<sup>r3</sup> is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

each Z<sup>2b</sup> is independently oxo, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl or (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

each Z<sup>2c</sup> is independently oxo, halogen, -CN, -OR<sup>n4</sup>, -OC(O)R<sup>p4</sup>, -OC(O)NR<sup>q4</sup>R<sup>r4</sup>, -SR<sup>n4</sup>, -S(O)R<sup>p4</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p4</sup>, -S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>COR<sup>p4</sup>, -NR<sup>n4</sup>CO<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>CONR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>OR<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NO<sub>2</sub>, -C(O)R<sup>n4</sup>, -C(O)OR<sup>n4</sup>, or -C(O)NR<sup>q4</sup>R<sup>r4</sup>;

each R<sup>n4</sup> is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each R<sup>p4</sup> is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each R<sup>q4</sup> and R<sup>r4</sup> is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

Z<sup>3</sup> is independently a (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each Z<sup>4</sup> is independently oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, halogen, -CN, -OR<sup>n5</sup>, -NR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>n5</sup>COR<sup>p5</sup>, -NR<sup>n5</sup>CO<sub>2</sub>R<sup>p5</sup>, -C(O)R<sup>n5</sup>, -C(O)OR<sup>n5</sup>, or -C(O)NR<sup>q5</sup>R<sup>r5</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle or (C<sub>1</sub>-C<sub>8</sub>)alkyl of Z<sup>4</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>4a</sup> groups, wherein the Z<sup>4a</sup> groups are the same or different;

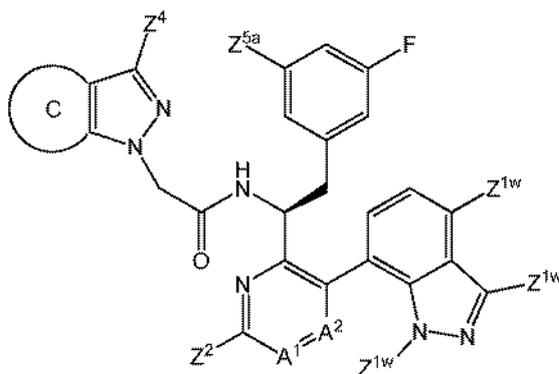
each Z<sup>4a</sup> is independently halogen, -CN, or -OR<sup>n6</sup>;

each R<sup>n5</sup>, R<sup>p5</sup>, R<sup>q5</sup>, R<sup>r5</sup>, and R<sup>n6</sup> is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl; and

Z<sup>5a</sup> is H or halogen;

or a pharmaceutically acceptable salt thereof.

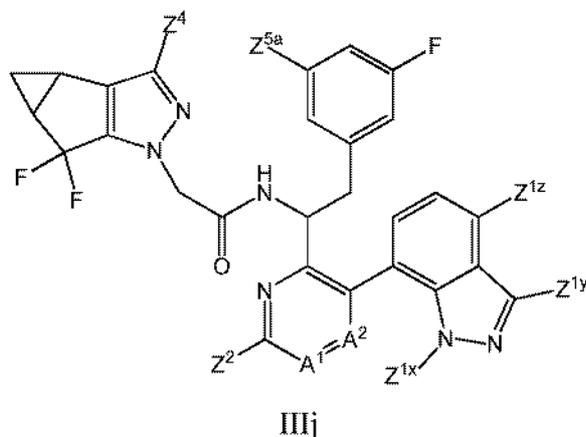
[0204] In certain embodiments, a compound of formula IIIh is a compound of formula IIIi.



IIIi

or a pharmaceutically acceptable salt thereof.

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



wherein

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

$A^2$  is CH or nitrogen;

$Z^{1x}$  is H or (C<sub>1</sub>-C<sub>8</sub>)alkyl;

$Z^{1y}$  is -NR<sup>n1</sup>S(O)<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>COR<sup>p1</sup>, -NR<sup>n1</sup>CONR<sup>q1</sup>R<sup>r1</sup>, or -NR<sup>n1</sup>CO<sub>2</sub>R<sup>p1</sup>;

$Z^{1z}$  is H, halogen, -CN, -OR<sup>n1</sup>, (C<sub>1</sub>-C<sub>8</sub>)alkyl, wherein the (C<sub>1</sub>-C<sub>8</sub>)alkyl is optionally substituted with 1, 2, or 3 halogen, which are the same or different;

each R<sup>n1</sup> is independently H or (C<sub>1</sub>-C<sub>8</sub>)alkyl;

each R<sup>p1</sup> is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl;

each R<sup>q1</sup> and R<sup>r1</sup> is independently H or (C<sub>1</sub>-C<sub>8</sub>)alkyl;

$Z^3$  is (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

$Z^2$  is (C<sub>2</sub>-C<sub>8</sub>)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<sup>n4</sup>, -NR<sup>n4</sup>CO<sub>2</sub>R<sup>p4</sup>, -C(O)OR<sup>n4</sup>, or -NR<sup>q4</sup>R<sup>r4</sup>;

each R<sup>n4</sup> is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

each R<sup>p4</sup> is independently (C<sub>1</sub>-C<sub>4</sub>)alkyl;

each R<sup>q4</sup> and R<sup>r4</sup> is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

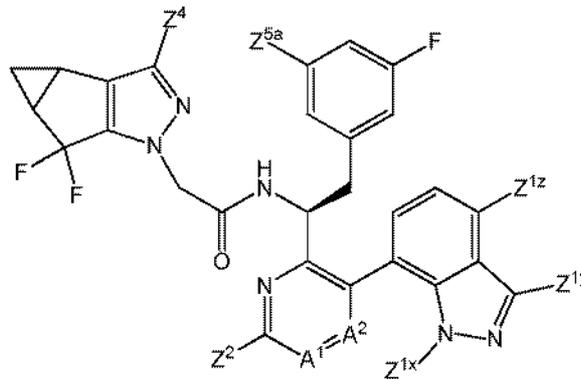
$Z^4$  is hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, halogen, -CN, C(O)R<sup>n5</sup>, -C(O)OR<sup>n5</sup>, -C(O)NR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>n5</sup>COR<sup>p5</sup>, -NR<sup>q5</sup>R<sup>r5</sup>, or (C<sub>3</sub>-C<sub>7</sub>)carbocycle, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle or (C<sub>1</sub>-C<sub>8</sub>)alkyl of  $Z^4$  is optionally substituted with halogen or hydroxyl;

each R<sup>n5</sup> is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

each R<sup>p5</sup> is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

each  $R^{q5}$  and  $R^{r5}$  is independently H or (C<sub>1</sub>-C<sub>4</sub>)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 be 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<sub>1</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl. In certain embodiments,  $Z^{1x}$  is (C<sub>1</sub>-C<sub>4</sub>)alkyl. In certain embodiments,  $Z^{1x}$  is (C<sub>1</sub>-C<sub>3</sub>)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<sub>1</sub>-C<sub>4</sub>)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<sub>1</sub>-C<sub>4</sub>)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.

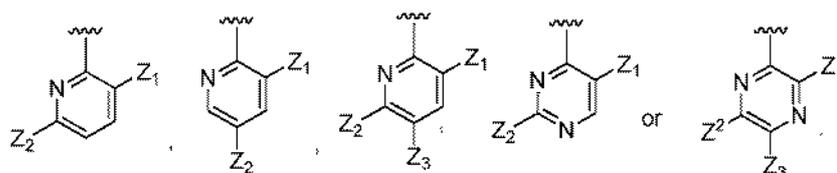
[0223] In certain embodiments, A is pyrimidinyl, wherein any pyridinyl of A is substituted with one  $Z^1$  group at the position shown, one  $Z^2$  group, and optionally substituted with 1 or 2  $Z^3$  groups. In certain embodiments, A is pyrimidinyl, wherein any pyridinyl of A is substituted with one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

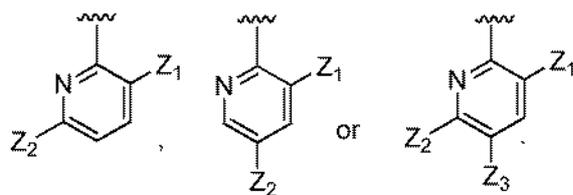
[0225] In certain embodiments, A is pyrazinyl, wherein any pyridinyl of A is substituted with one  $Z^1$  group at the position shown, one  $Z^2$  group, and optionally substituted with 1 or 2  $Z^3$  groups. In certain embodiments, A is pyrazinyl, wherein any pyridinyl of A is substituted with one 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

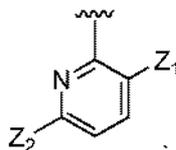
[0227] In certain embodiments, A is:



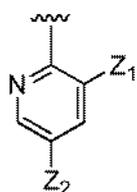
[0228] In certain embodiments, A is:



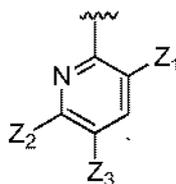
[0229] In certain embodiments, A is:



[0230] In certain embodiments, A is:

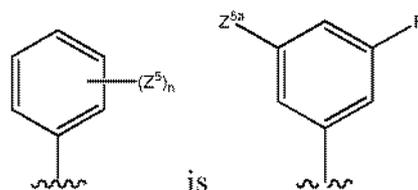


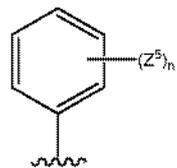
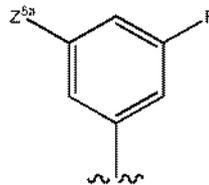
[0231] In certain embodiments, A is:



[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.

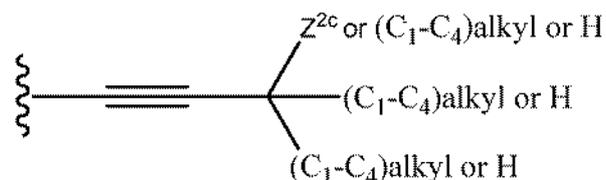
**[0241]** In certain embodiments,  $Z^2$  is  $(C_2-C_8)$ alkynyl, phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heterocycle, or  $-C(O)NR^{q3}R^{r3}$ , wherein the 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered 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<sub>2</sub>-C<sub>8</sub>)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<sub>2</sub>-C<sub>8</sub>)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<sup>q3</sup>R<sup>3</sup>, 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<sub>2</sub>-C<sub>8</sub>)alkynyl of  $Z^2$  is optionally substituted with 1, 2, 3, 4 or 5  $Z^{2c}$  groups.

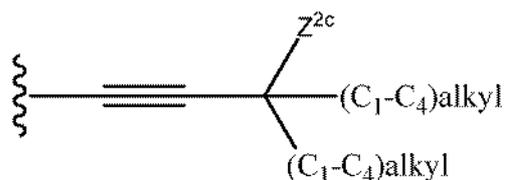
[0243] In certain embodiments of formula III,  $Z^2$  is (C<sub>2</sub>-C<sub>8</sub>)alkynyl, optionally substituted with 1, 2, 3, 4, or 5  $Z^{2c}$  groups. In certain embodiments,  $Z^2$  is (C<sub>2</sub>-C<sub>8</sub>)alkynyl, optionally substituted with 1, 2, 3, or 4  $Z^{2c}$  groups. In certain embodiments,  $Z^2$  is (C<sub>2</sub>-C<sub>8</sub>)alkynyl, optionally substituted with 1, 2, or 3  $Z^{2c}$  groups. In certain embodiments,  $Z^2$  is (C<sub>2</sub>-C<sub>8</sub>)alkynyl, optionally substituted with 1 or 2  $Z^{2c}$  groups.

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



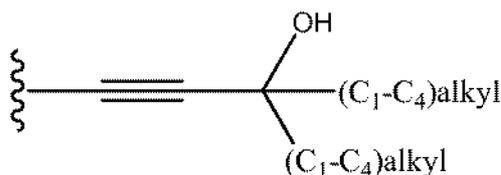
wherein each of the (C<sub>1</sub>-C<sub>4</sub>)alkyl moieties of  $Z^2$ , if present, is optionally substituted with 1, 2 or 3  $Z^{2c}$  groups, wherein the  $Z^{2b}$  groups may be the same or different.

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



wherein each of the (C<sub>1</sub>-C<sub>4</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl moieties of Z<sup>2</sup> is optionally substituted with 1, 2 or 3 Z<sup>2c</sup> groups, wherein the Z<sup>2b</sup> groups may be the same or different.

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

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

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

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

[0251] In certain embodiments, each Z<sup>2c</sup> is independently halogen, -OR<sup>n4</sup>, NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>CO<sub>2</sub>R<sup>p4</sup>, -C(O)OR<sup>n4</sup>, or -C(O)NR<sup>q4</sup>R<sup>r4</sup>. In certain embodiments, each Z<sup>2c</sup> is independently halogen or -OR<sup>n4</sup>.





[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.

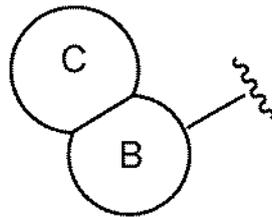
[0263] In certain embodiments,  $R^1$  is a 8-12 membered tricyclic-heteroaryl, wherein the 8-12 membered tricyclic-heteroaryl contains at least one partially unsaturated ring, and wherein any 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl of  $R^1$  is optionally substituted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



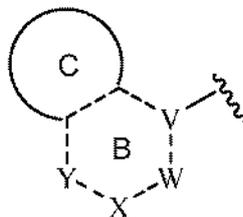
IIa

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;

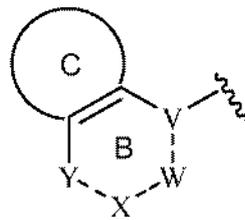
X is  $CZ^{4c}$ ,  $NZ^{4c}$  or N;

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;

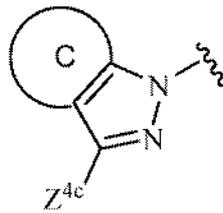
X is  $CZ^{4c}$ ,  $NZ^{4c}$  or N;

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 IIId:



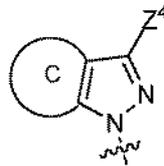
II d

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.

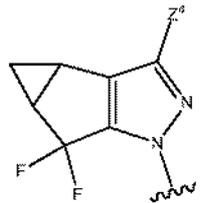
[0271] In certain embodiments of formula III,  $R^1$  has the following formula:



wherein:

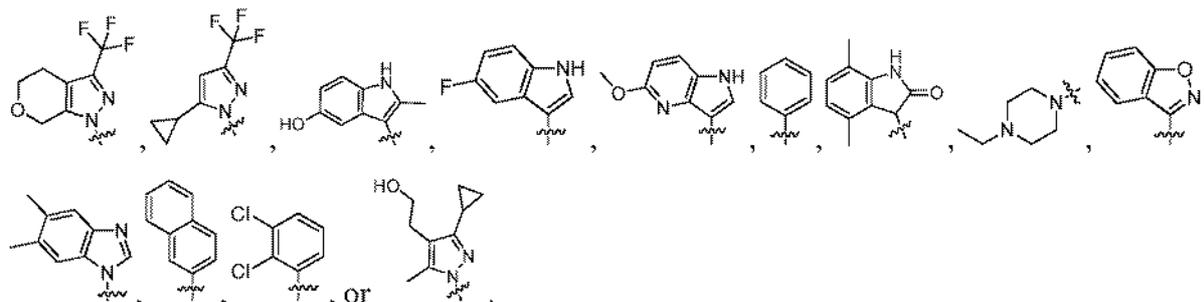
C together with the two carbon atoms to which it is attached forms a 3-7 membered monocyclic-carbocycle or 5-9 membered bicyclic-carbocycle, wherein any 3-7 membered monocyclic-carbocycle or 5-9 membered bicyclic-carbocycle of C is optionally substituted with 1, 2, 3, 4 or 5  $Z^4$  groups, wherein the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

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

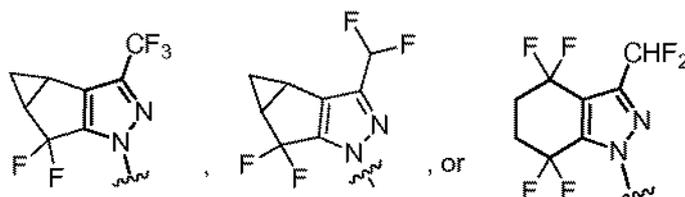


[0273] In certain embodiments of formula III, C together with the two carbon atoms to which it is attached forms a 5-7 membered monocyclic-carbocycle or 5-7 membered bicyclic-

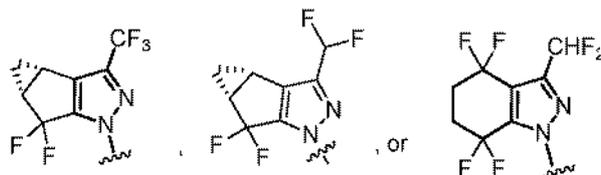




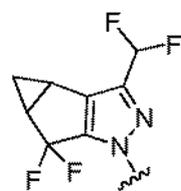
[0278] In certain embodiments,  $R^1$  optionally substituted with 1, 2, 3, 4, or 5  $Z^4$  groups is



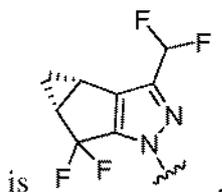
[0279] In certain embodiments,  $R^1$  optionally substituted with 1, 2, 3, 4, or 5  $Z^4$  groups is



[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



[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<sub>3</sub>-C<sub>7</sub>)carbocycle, halogen, -CN, -O-(C<sub>1</sub>-C<sub>8</sub>)alkyl, -NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>COR<sup>p1</sup>, -NR<sup>n1</sup>CO<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>CONR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, or -C(O)NR<sup>q1</sup>R<sup>r1</sup>.

[0305] In certain embodiments, each  $Z^{1a}$  is independently -NR<sup>n1</sup>S(O)<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, or halogen. In certain embodiments, each  $Z^{1a}$  is independently halogen or -NR<sup>n1</sup>S(O)<sub>2</sub>R<sup>p1</sup>. In certain embodiments, each  $Z^{1a}$  is independently halogen or -NR<sup>n1</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>.

[0306] In certain embodiments,  $Z^1$  is substituted with 2  $Z^{1a}$  groups, wherein each  $Z^{1a}$  is independently -NR<sup>n1</sup>S(O)<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, or halogen.

[0307] In certain embodiments, each  $Z^{1a}$  is independently halogen or -NR<sup>n1</sup>S(O)<sub>2</sub>R<sup>p1</sup> and each  $Z^{1b}$  is (C<sub>1</sub>-C<sub>8</sub>)alkyl, which may be same or different.

[0308] In certain embodiments,  $Z^{1a}$  is -NR<sup>n1</sup>S(O)<sub>2</sub>R<sup>p1</sup> or -NR<sup>n1</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>. In certain embodiments,  $Z^{1a}$  is halogen. In certain embodiments,  $Z^{1a}$  is -NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>COR<sup>p1</sup>, -NR<sup>n1</sup>CO<sub>2</sub>R<sup>p1</sup>, or -NR<sup>n1</sup>CONR<sup>q1</sup>R<sup>r1</sup>.

[0309] In certain embodiments,  $Z^{1a}$  is halogen, -OR<sup>n1</sup>, or -C(O)NR<sup>q1</sup>R<sup>r1</sup>.

[0310] In certain embodiments,  $Z^{1a}$  is halogen or -C(O)NR<sup>q1</sup>R<sup>r1</sup>.

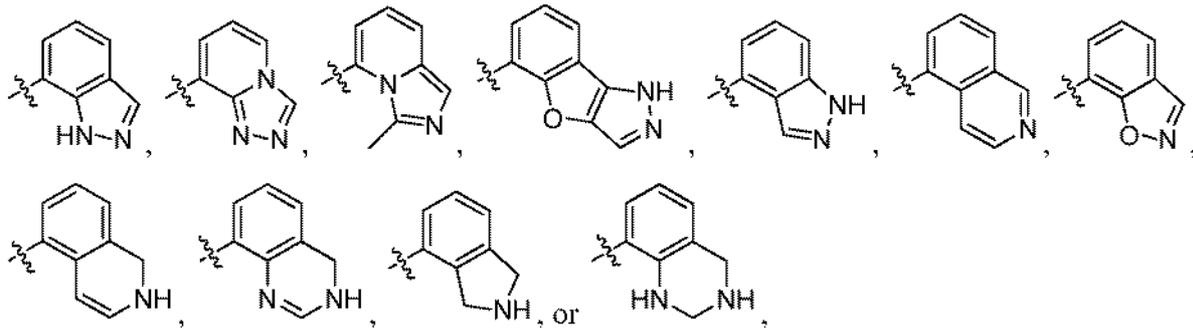
[0311] In certain embodiments,  $Z^{1a}$  is halogen, -OH, or -C(O)NH<sub>2</sub>.

[0312] In certain embodiments,  $Z^{1a}$  is fluoro, -OH, or -C(O)NH<sub>2</sub>.

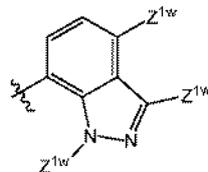
[0313] In certain embodiments, each  $Z^{1b}$  is (C<sub>1</sub>-C<sub>8</sub>)alkyl, which may be same or different.

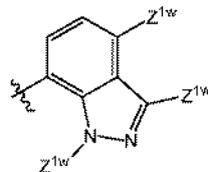
[0314] In certain embodiments, each  $Z^{1b}$  is independently methyl or difluoromethyl.

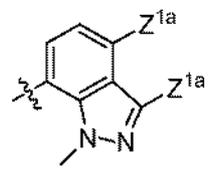
[0315] In certain embodiments of formula III,  $Z^1$  is

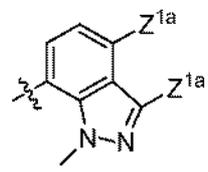


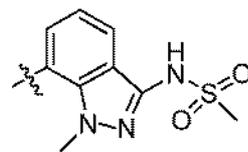
optionally substituted with 1, 2, 3, 4 or 5  $Z^{1a}$  or  $Z^{1b}$ .

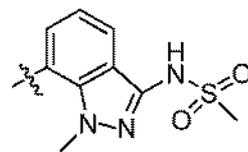


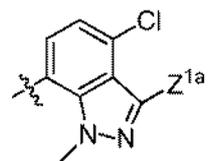
[0316] In certain embodiments,  $Z^1$  is , wherein each  $Z^{1w}$  is independently  $Z^{1a}$ ,  $Z^{1b}$ , or H. In certain embodiments, each  $Z^{1a}$  is independently halogen,  $-\text{CN}$ ,  $-\text{OR}^{n1}$ ,  $-\text{NR}^{n1}\text{S}(\text{O})_2\text{R}^{p1}$ ,  $-\text{NR}^{n1}\text{S}(\text{O})_2\text{NR}^{q1}\text{R}^{r1}$ ,  $-\text{NR}^{q1}\text{R}^{r1}$ ,  $-\text{NR}^{n1}\text{COR}^{p1}$ ,  $-\text{NR}^{n1}\text{CONR}^{q1}\text{R}^{r1}$ , or  $-\text{NR}^{n1}\text{CO}_2\text{R}^{p1}$ ; each  $Z^{1b}$  is independently ( $\text{C}_1$ - $\text{C}_8$ alkyl), wherein the ( $\text{C}_1$ - $\text{C}_8$ alkyl) 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,  $-\text{NR}^{n1}\text{S}(\text{O})_2\text{R}^{p1}$ , or  $-\text{NR}^{n1}\text{S}(\text{O})_2\text{NR}^{q1}\text{R}^{r1}$ .

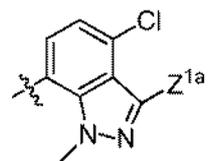


[0317] In certain embodiments,  $Z^1$  is , wherein each  $Z^{1a}$  is independently halogen,  $-\text{NR}^{n1}\text{S}(\text{O})_2\text{R}^{p1}$  or  $-\text{NR}^{n1}\text{S}(\text{O})_2\text{NR}^{q1}\text{R}^{r1}$ .

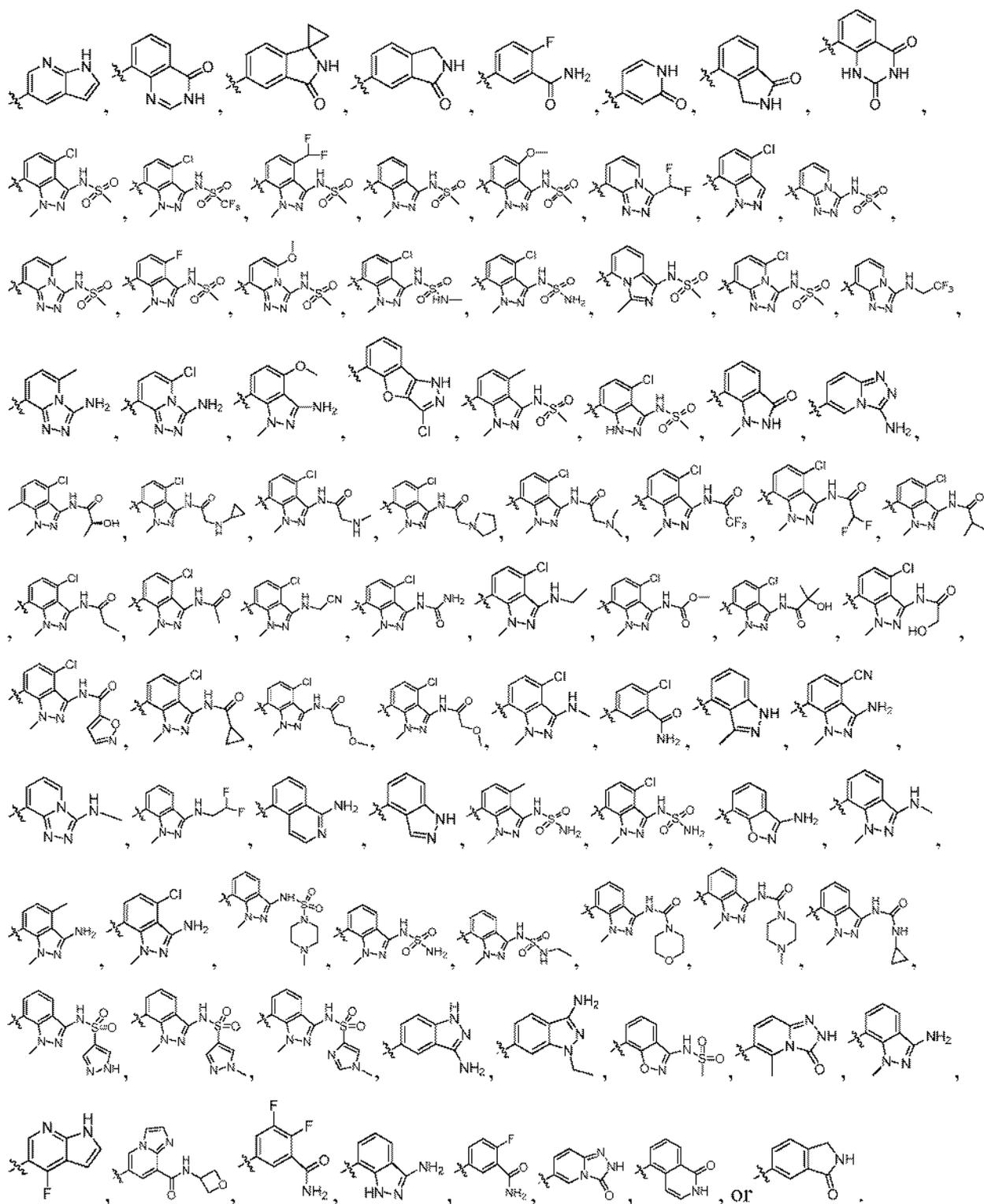


[0318] In certain embodiments,  $Z^1$  is , optionally substituted with 1, 2, 3, or 4  $Z^{1a}$  or  $Z^{1b}$ .



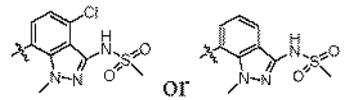
[0319] In certain embodiments,  $Z^1$  is .

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

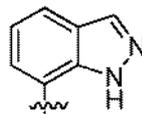
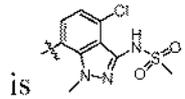


[0321] In certain embodiments, Z<sup>1</sup> optionally substituted with 1, 2, 3, 4, or 5 Z<sup>1a</sup> or Z<sup>1b</sup> groups is



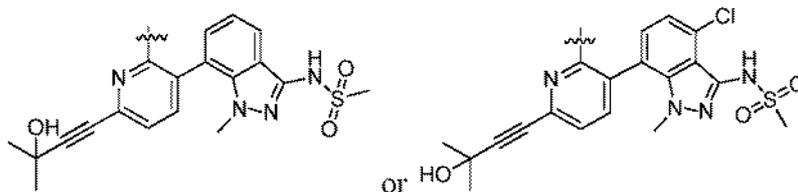


[0324] In certain embodiments,  $Z^1$  optionally substituted with 1, 2, 3, 4, or 5  $Z^{1a}$  or  $Z^{1b}$  groups



[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<sup>1</sup> 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<sup>1</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1a</sup> groups, which may be the same or different. In another variation, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and Z<sup>1</sup> is phenyl, optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1a</sup> groups. In another variation, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and Z<sup>1</sup> 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<sup>1</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1a</sup> groups. In another variation, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and Z<sup>1</sup> 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<sup>1</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1a</sup> groups.

**[0331]** In one variation of formula III, A is pyridinyl; and Z<sup>1</sup> 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<sup>1</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1a</sup> groups, which may be the same or different. In another variation, A is pyridinyl; and Z<sup>1</sup> is phenyl, optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1a</sup> groups. In another variation, A is pyridinyl; and Z<sup>1</sup> 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<sup>1</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1a</sup> groups. In another variation, A is pyridinyl; and Z<sup>1</sup> 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<sup>1</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1a</sup> groups.

**[0332]** In one variation of formula III, A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and Z<sup>2</sup> is (C<sub>2</sub>-C<sub>8</sub>)alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, or -C(O)NR<sup>q3</sup>R<sup>t3</sup>, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z<sup>2</sup> 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<sup>q1</sup> $R^{r1}$ , -NR<sup>q1</sup> $R^{r1}$ , -NR<sup>n1</sup>COR<sup>p1</sup>, -NR<sup>n1</sup>CO<sub>2</sub> $R^{p1}$ , -NR<sup>n1</sup>CONR<sup>q1</sup> $R^{r1}$ , -NR<sup>n1</sup>S(O)<sub>2</sub> $R^{p1}$ , -NR<sup>n1</sup>S(O)<sub>2</sub>NR<sup>q1</sup> $R^{r1}$ , -C(O) $R^{n1}$ , -C(O)OR<sup>n1</sup>, or -C(O)NR<sup>q1</sup> $R^{r1}$ ;

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<sup>q2</sup> $R^{r2}$ , 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<sup>q3</sup> $R^{r3}$ , 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<sub>2</sub>-C<sub>8</sub>)alkenyl or (C<sub>2</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl;

each  $R^{q3}$  and  $R^{r3}$  is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

each  $Z^{2b}$  is independently oxo, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl or (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

each  $Z^{2c}$  is independently oxo, halogen, -CN, -OR<sup>n4</sup>, NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>COR<sup>p4</sup>, -

NR<sup>n4</sup>CO<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>R<sup>p4</sup>, -C(O)R<sup>n4</sup>, -C(O)OR<sup>n4</sup> or -C(O)NR<sup>q4</sup>R<sup>r4</sup>;

each  $R^{n4}$  is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $R^{p4}$  is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl;

each  $R^{q4}$  and  $R^{r4}$  is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $Z^3$  is independently a (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl or halogen;

each  $Z^4$  is independently oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, halogen, -CN, -OR<sup>n5</sup>, -NR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>n5</sup>COR<sup>p5</sup>, -NR<sup>n5</sup>CO<sub>2</sub>R<sup>p5</sup>, -C(O)R<sup>n5</sup>, -C(O)OR<sup>n5</sup>, or -C(O)NR<sup>q5</sup>R<sup>r5</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle or (C<sub>1</sub>-C<sub>8</sub>)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<sup>n6</sup>; and

each  $R^{n5}$ ,  $R^{p5}$ ,  $R^{q5}$ ,  $R^{r5}$ , and  $R^{n6}$  is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl.

[0341] In certain embodiments of formula III,

A<sup>1</sup> is CH, C-Z<sup>3</sup>, or nitrogen;

A<sup>2</sup> is CH or nitrogen;

R<sup>1</sup> 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<sup>1</sup> is optionally substituted with 1, 2, 3, 4 or 5  $Z^4$  groups, which may be the same or different;

each R<sup>3a</sup> and R<sup>3b</sup> is independently H or (C<sub>1</sub>-C<sub>3</sub>)alkyl;

Z<sup>1</sup> 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<sup>1</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>1a</sup> or Z<sup>1b</sup>, which may be the same or different;

each Z<sup>1a</sup> is independently oxo, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, halogen, -CN, -O-(C<sub>1</sub>-C<sub>8</sub>)alkyl, -OC(O)R<sup>p1</sup>, -OC(O)NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>COR<sup>p1</sup>, -NR<sup>n1</sup>CO<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>CONR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -C(O)R<sup>n1</sup>, -C(O)OR<sup>n1</sup>, or -C(O)NR<sup>q1</sup>R<sup>r1</sup>;

each  $Z^{1b}$  is independently (C<sub>1</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl;

each  $R^{p1}$  is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, which may be the same or different, and wherein any (C<sub>1</sub>-C<sub>8</sub>)alkyl of  $R^{p1}$  is optionally substituted with 1, 2, 3, 4 or 5 halogen, hydroxyl, -O(C<sub>1</sub>-C<sub>8</sub>)alkyl, or -NR<sup>q2</sup>R<sup>r2</sup>, which may be the same or different;

each  $R^{q1}$  and  $R^{r1}$  is independently H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, or 3-7-membered heterocycle, wherein any (C<sub>1</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, which may be the same or different;

each  $R^{q2}$  and  $R^{r2}$  is independently H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)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<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, -C(O)R<sup>n3</sup>, or -C(O)NR<sup>q3</sup>R<sup>r3</sup>, 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<sub>2</sub>-C<sub>8</sub>)alkenyl or (C<sub>2</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl;

each  $R^{q3}$  and  $R^{r3}$  is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

each  $Z^{2b}$  is independently oxo, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl or (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

each  $Z^{2c}$  is independently oxo, halogen, -CN, -OR<sup>n4</sup>, NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>COR<sup>p4</sup>, -NR<sup>n4</sup>CO<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>R<sup>p4</sup>, -C(O)R<sup>n4</sup>, -C(O)OR<sup>n4</sup> or -C(O)NR<sup>q4</sup>R<sup>r4</sup>;

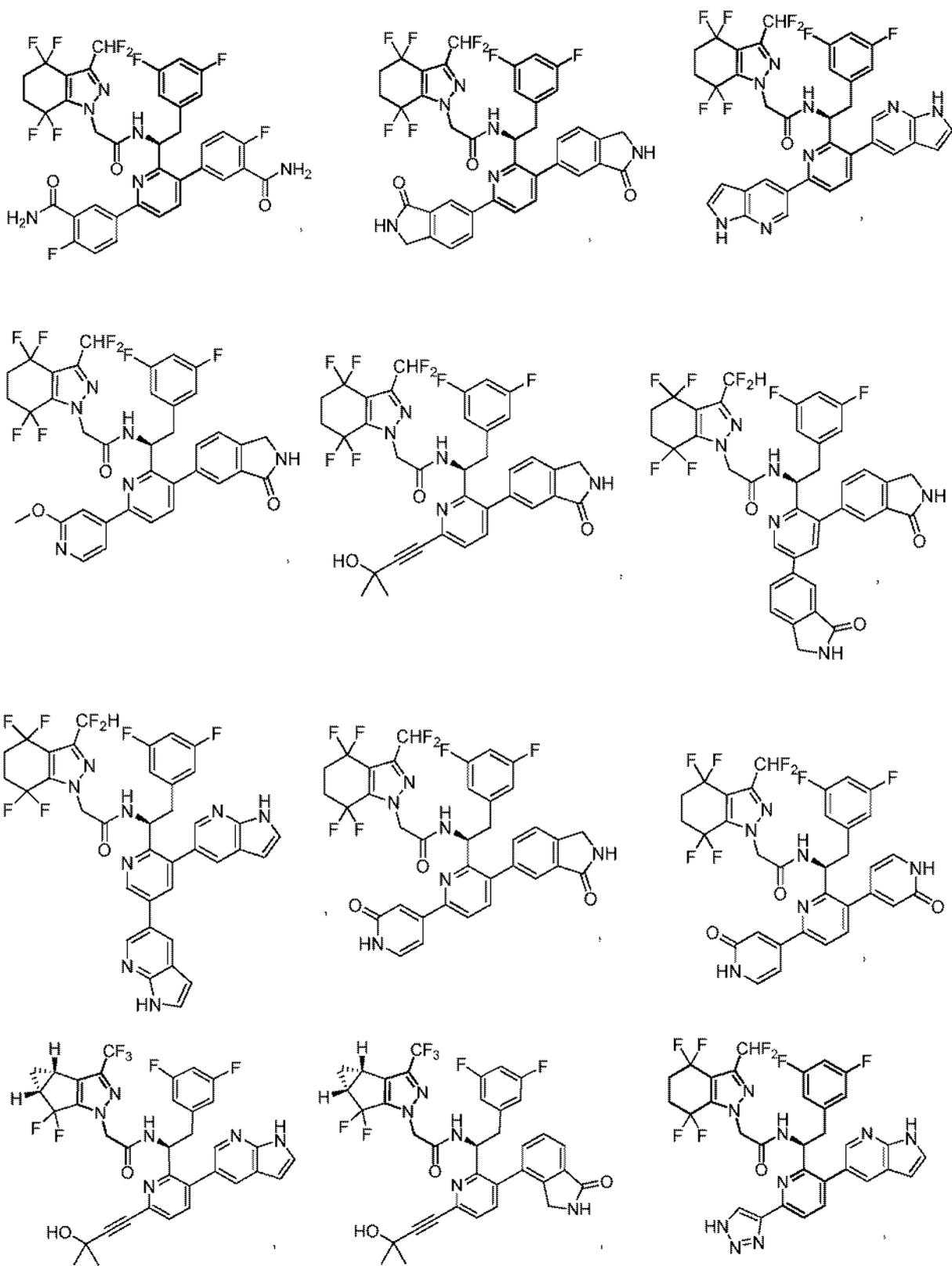
each  $R^{n4}$  is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

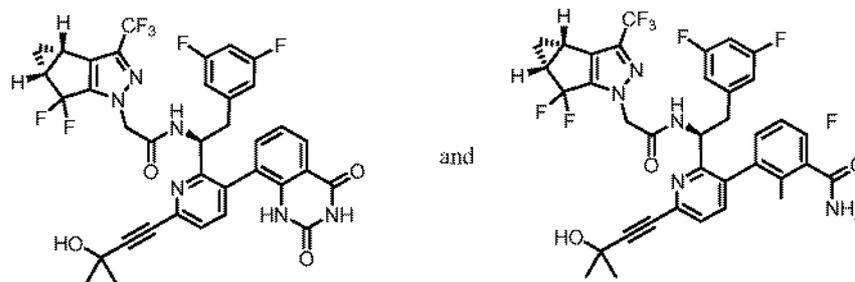
each  $R^{p4}$  is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl;

each  $R^{q4}$  and  $R^{r4}$  is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

$Z^3$  is independently a (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl or halogen;

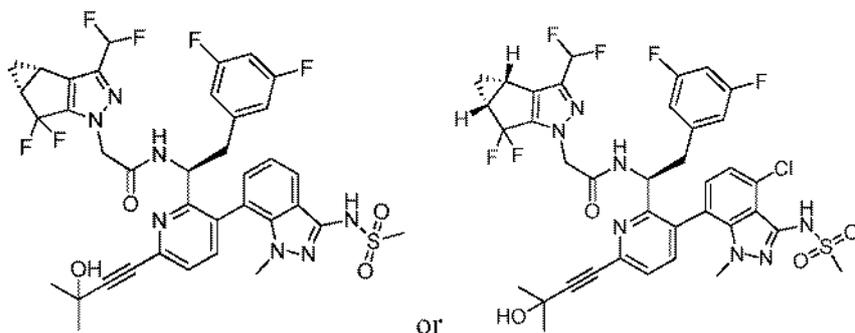






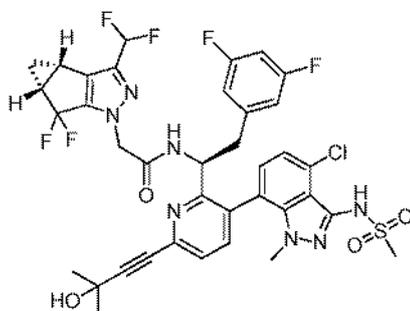
and pharmaceutically acceptable salts thereof.

[0343] In certain embodiments, a compound is:



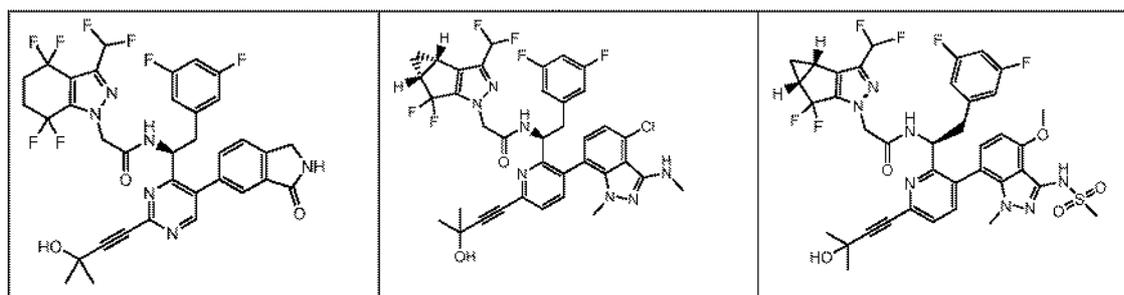
or a pharmaceutically acceptable salt thereof.

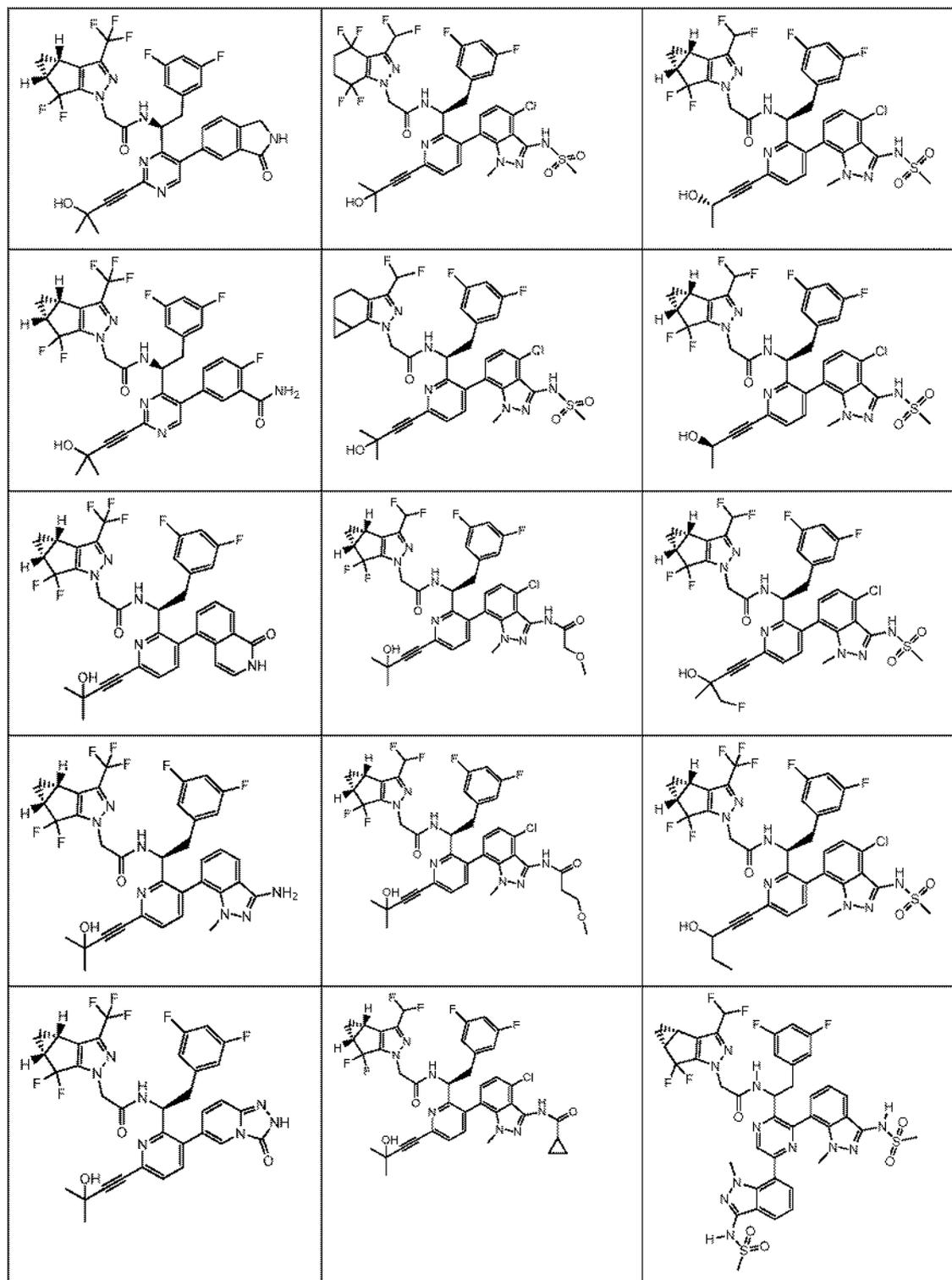
[0344] In certain embodiments, a compound is:

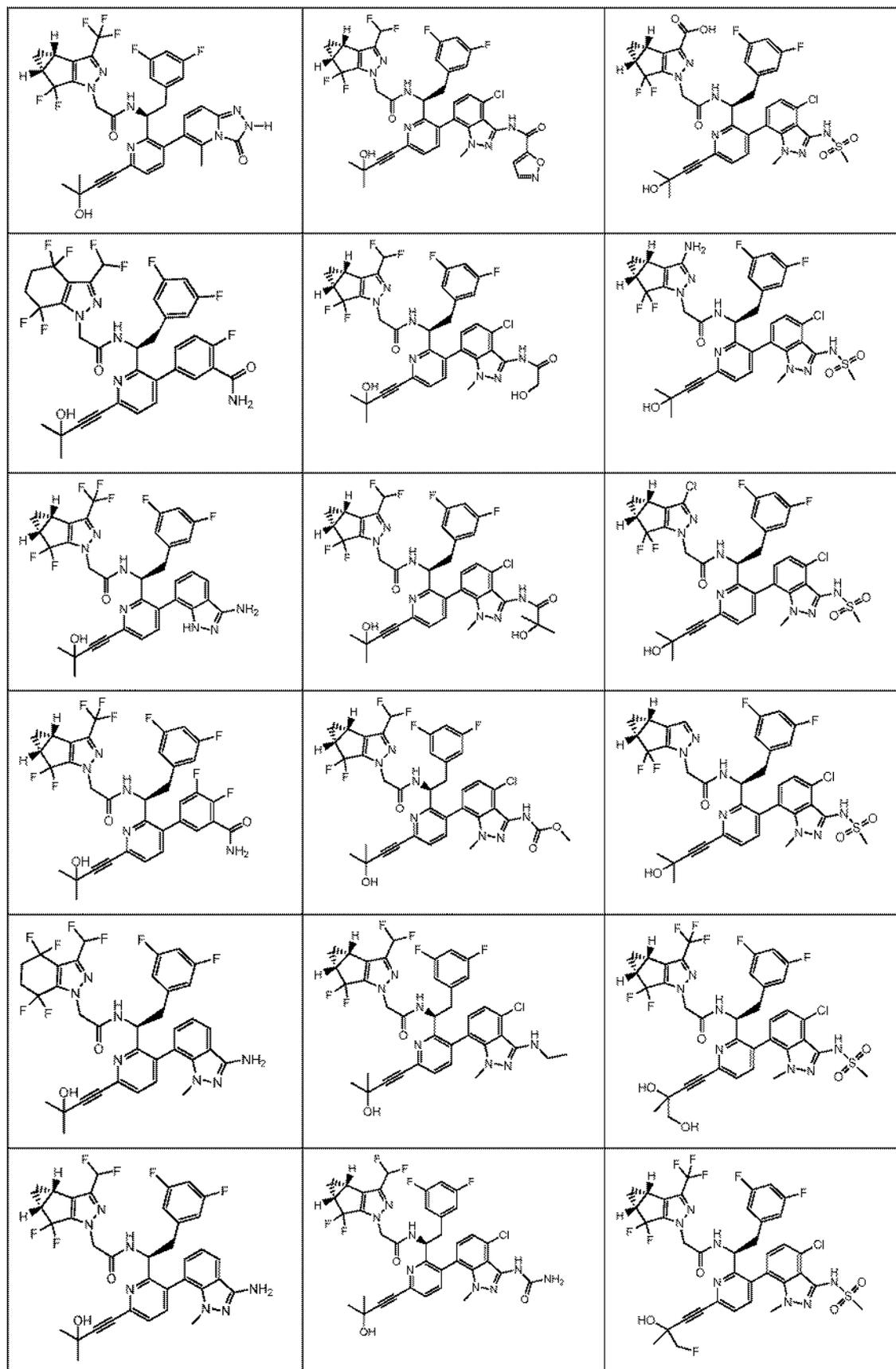


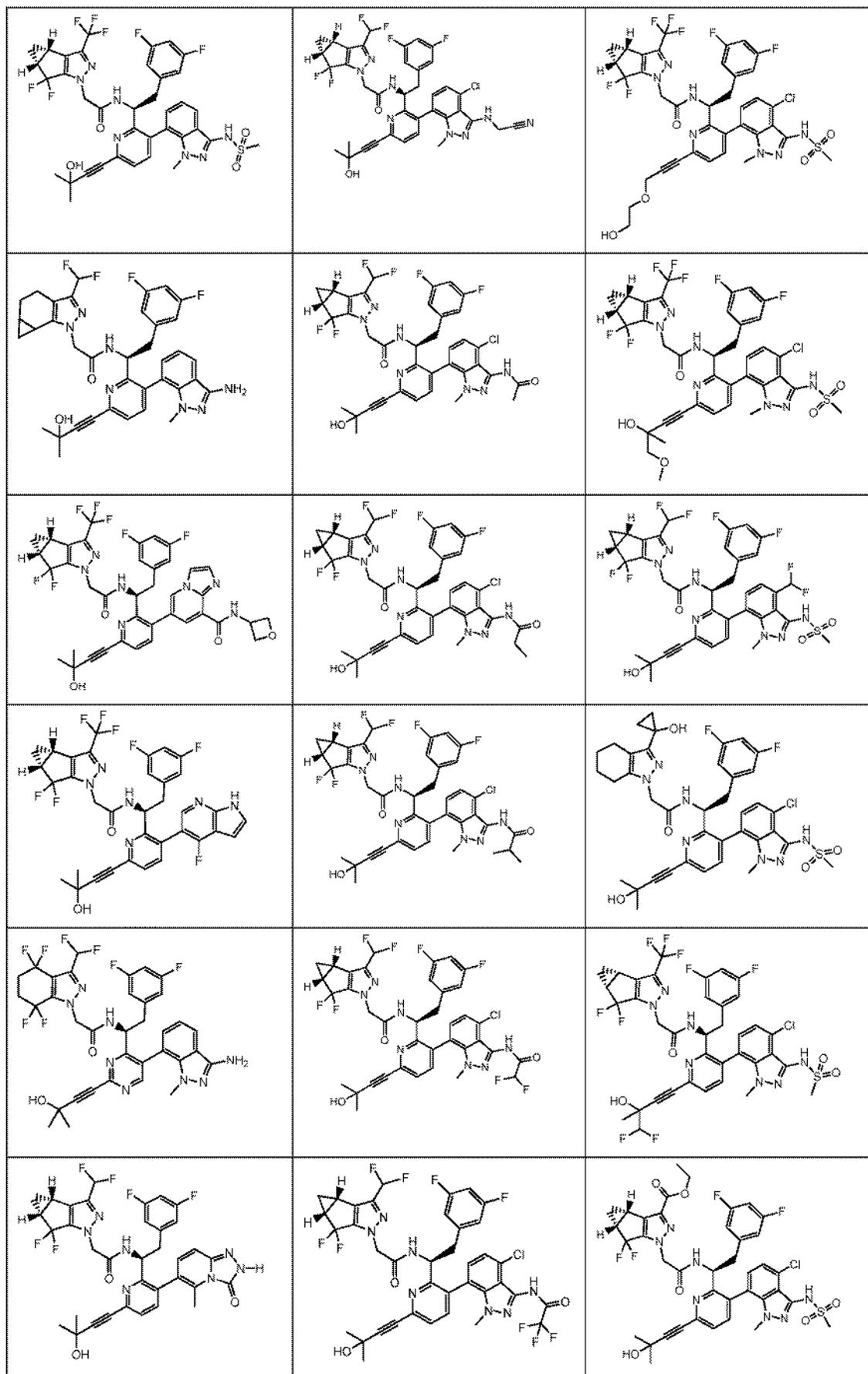
or a pharmaceutically acceptable salt thereof.

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

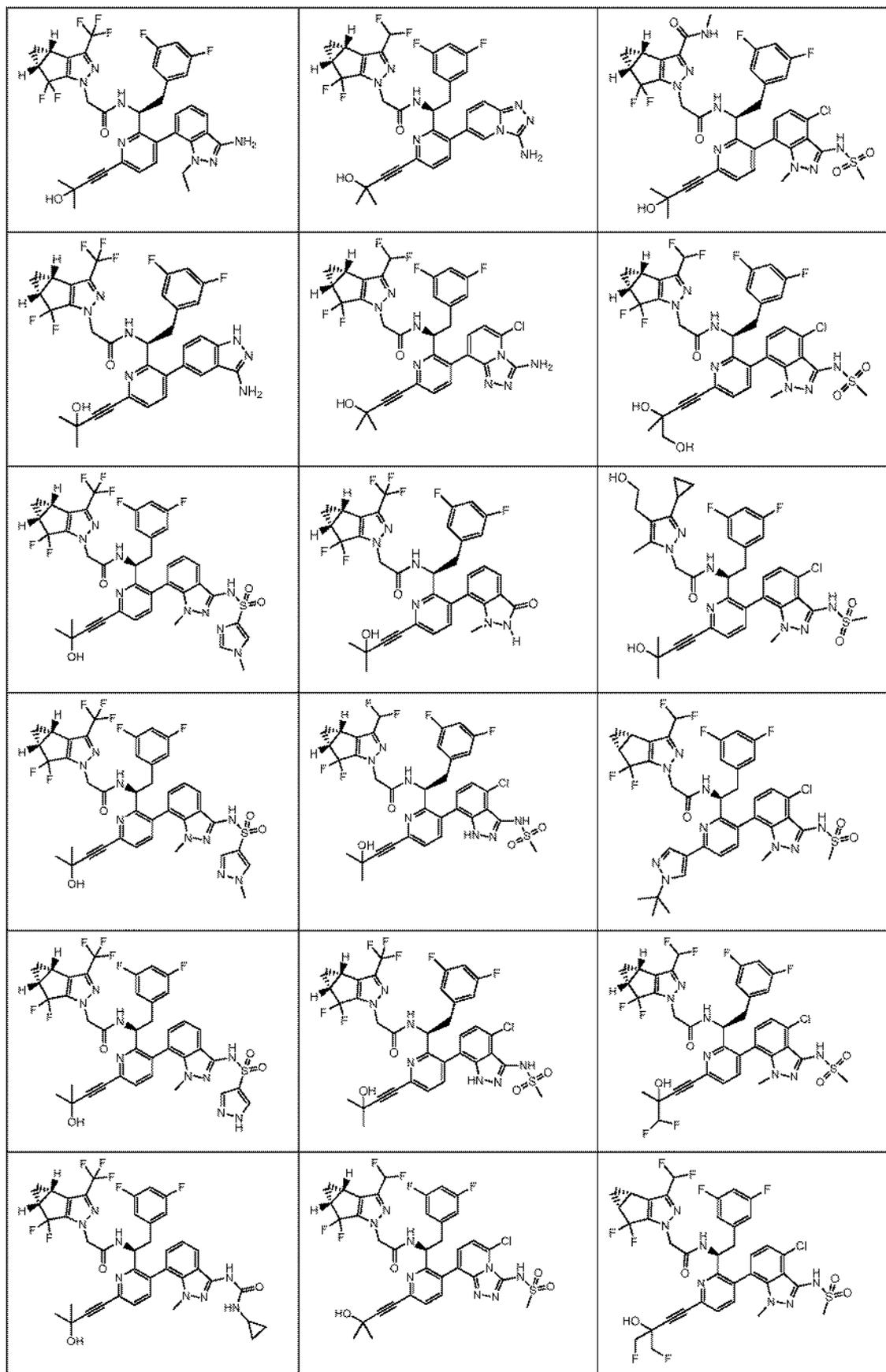




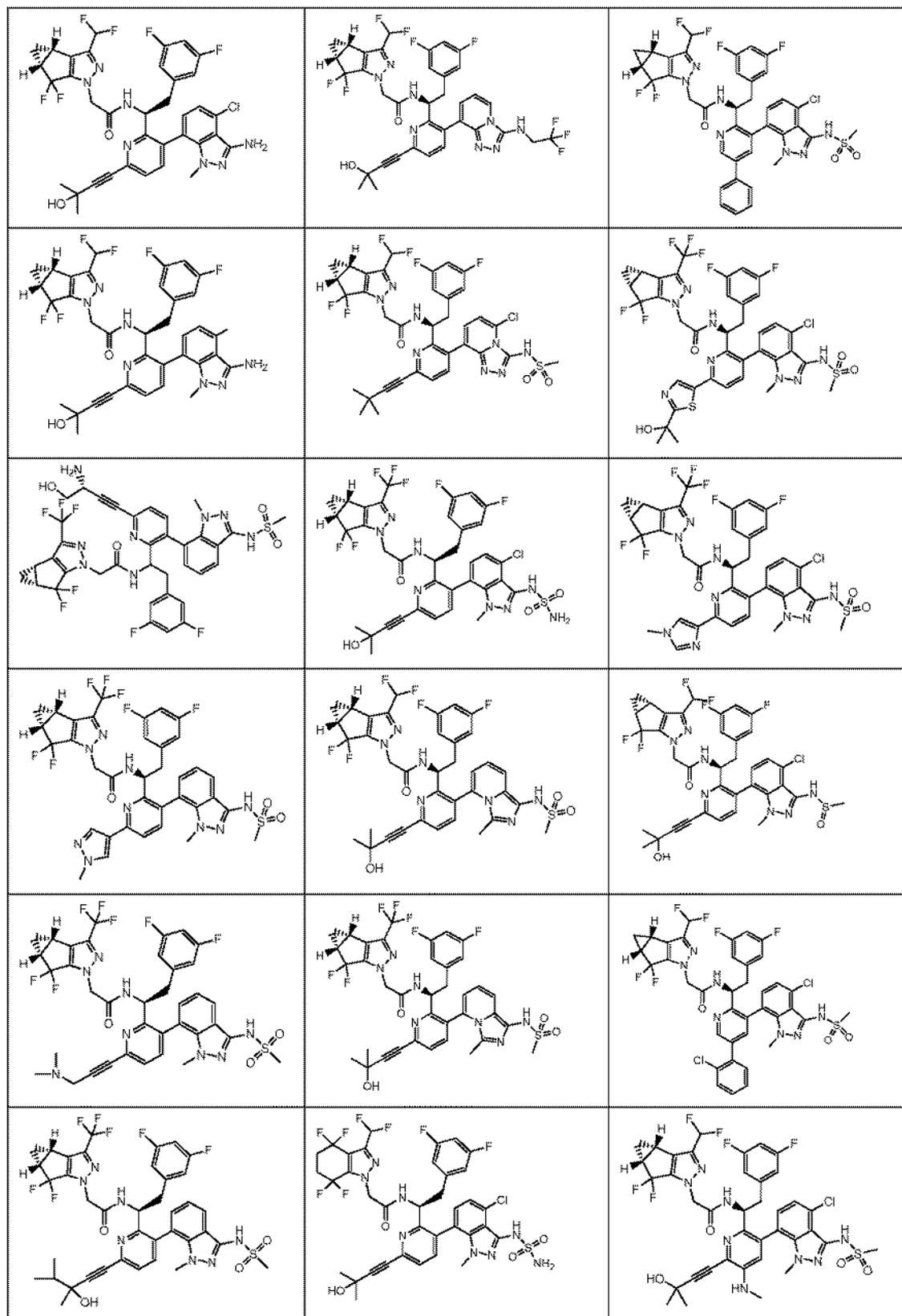


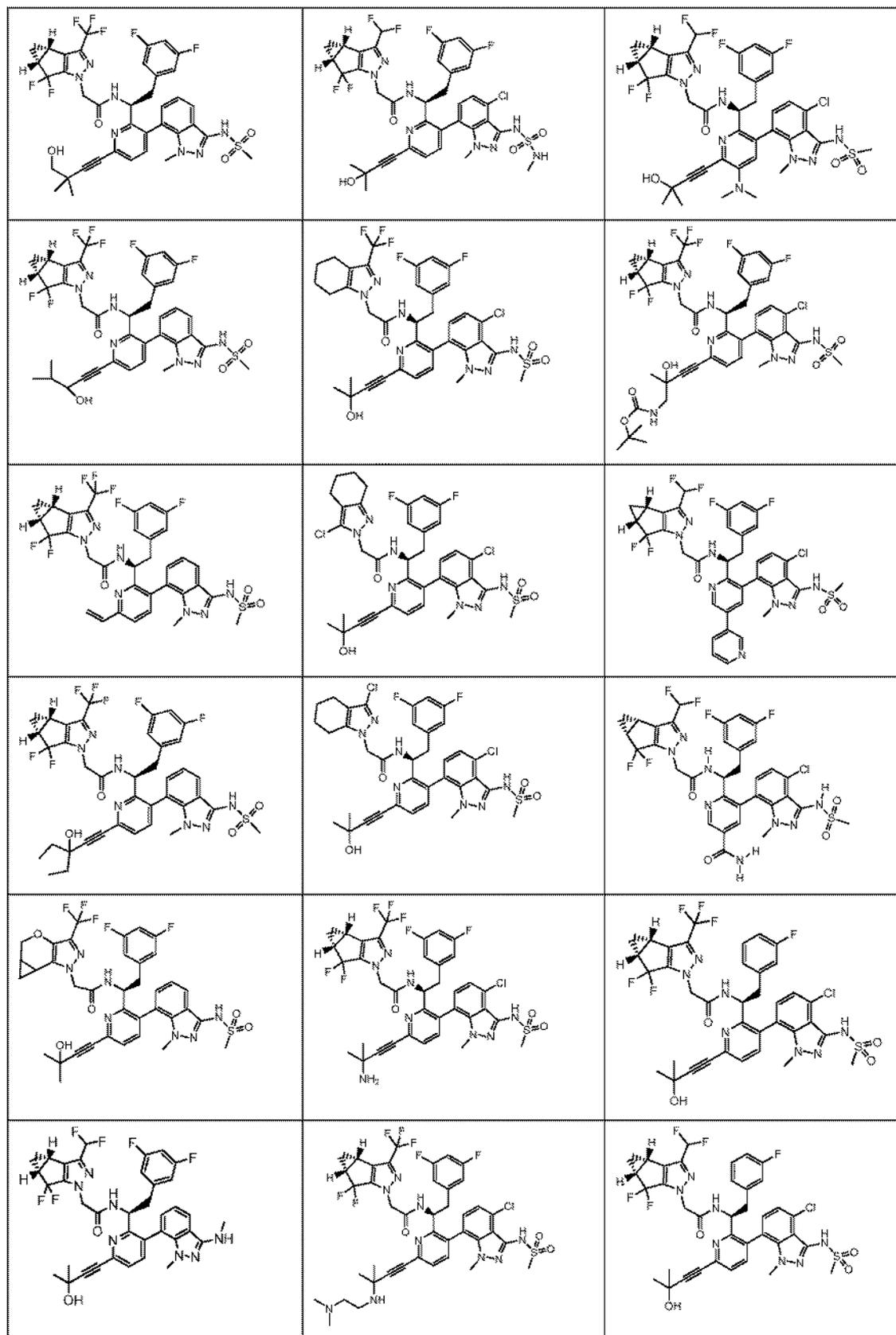


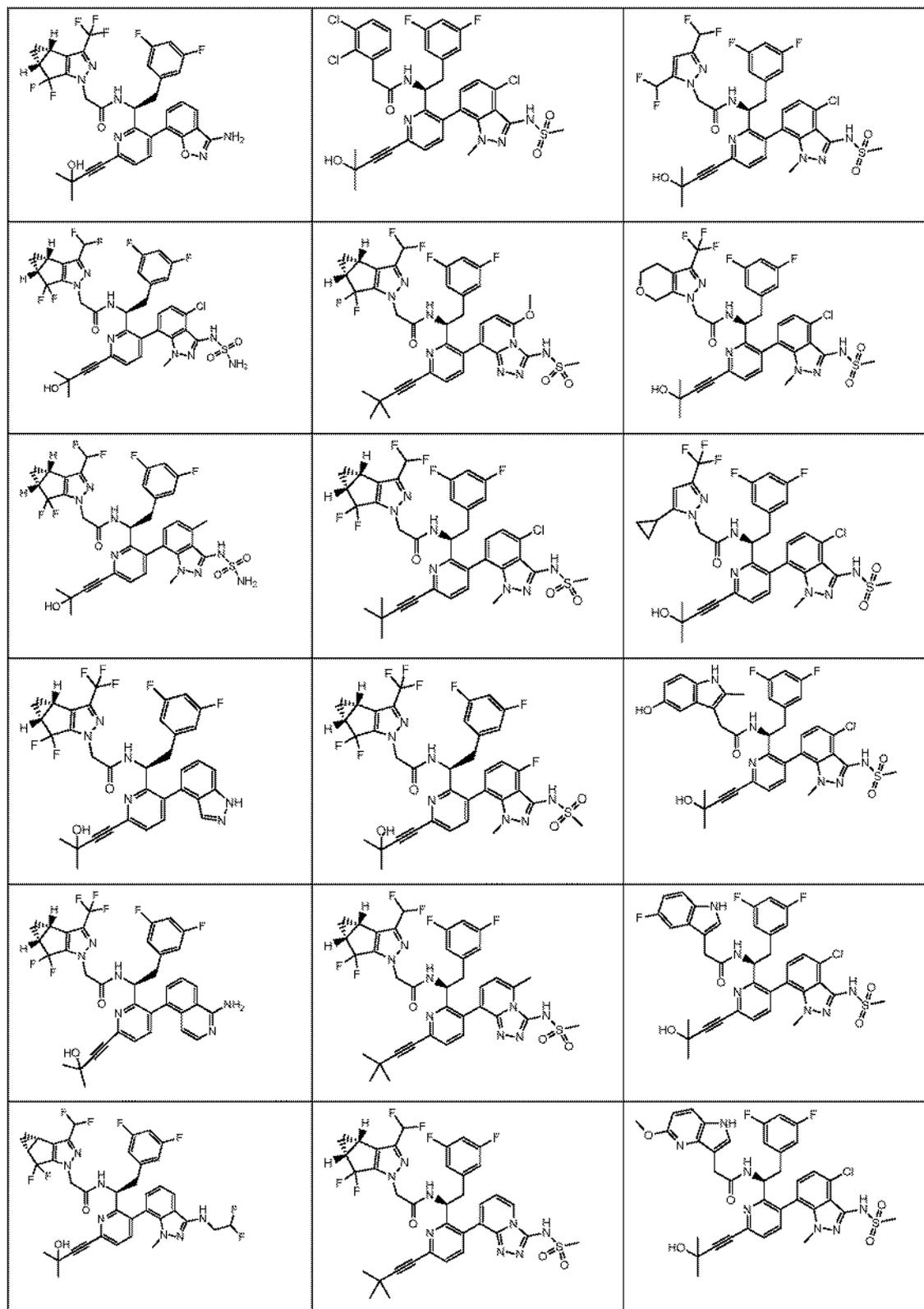


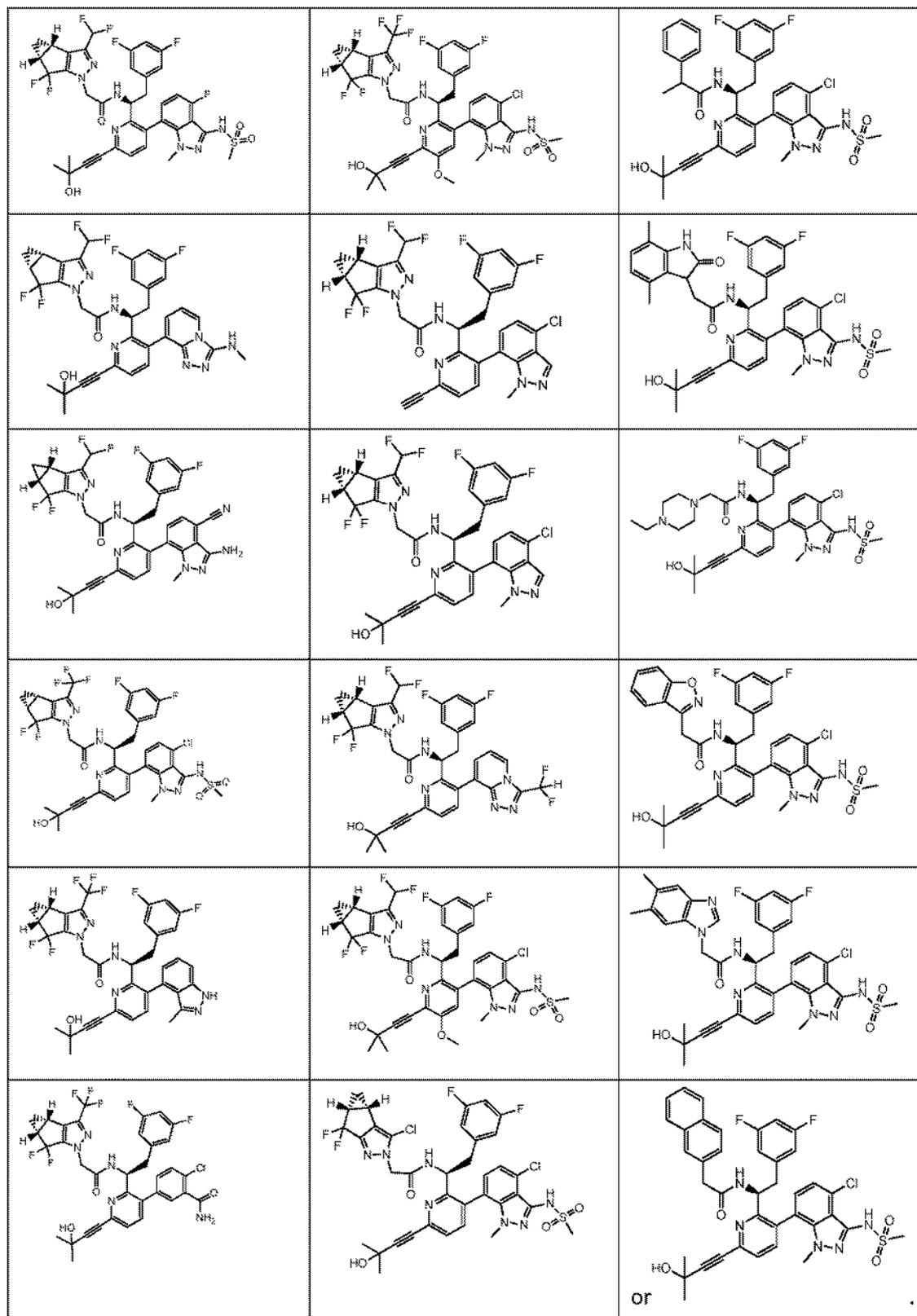


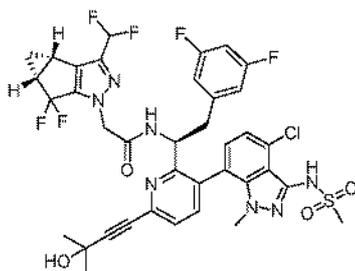






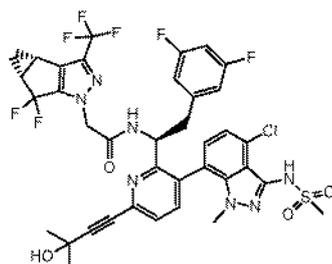






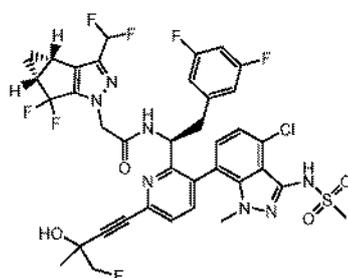
or a pharmaceutically acceptable salt thereof.

[0347] In certain embodiments, a compound is:



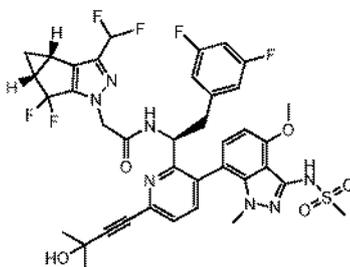
or a pharmaceutically acceptable salt thereof.

[0348] In certain embodiments, a compound is:



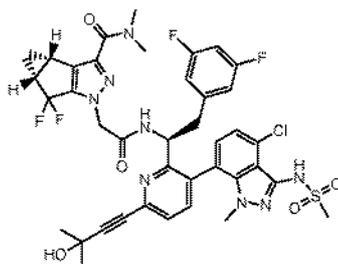
or a pharmaceutically acceptable salt thereof.

[0349] In certain embodiments, a compound is:



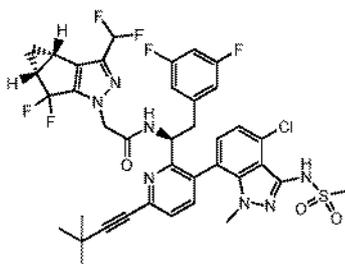
or a pharmaceutically acceptable salt thereof.

[0350] In certain embodiments, a compound is:



or a pharmaceutically acceptable salt thereof.

[0351] In certain embodiments, a compound is:

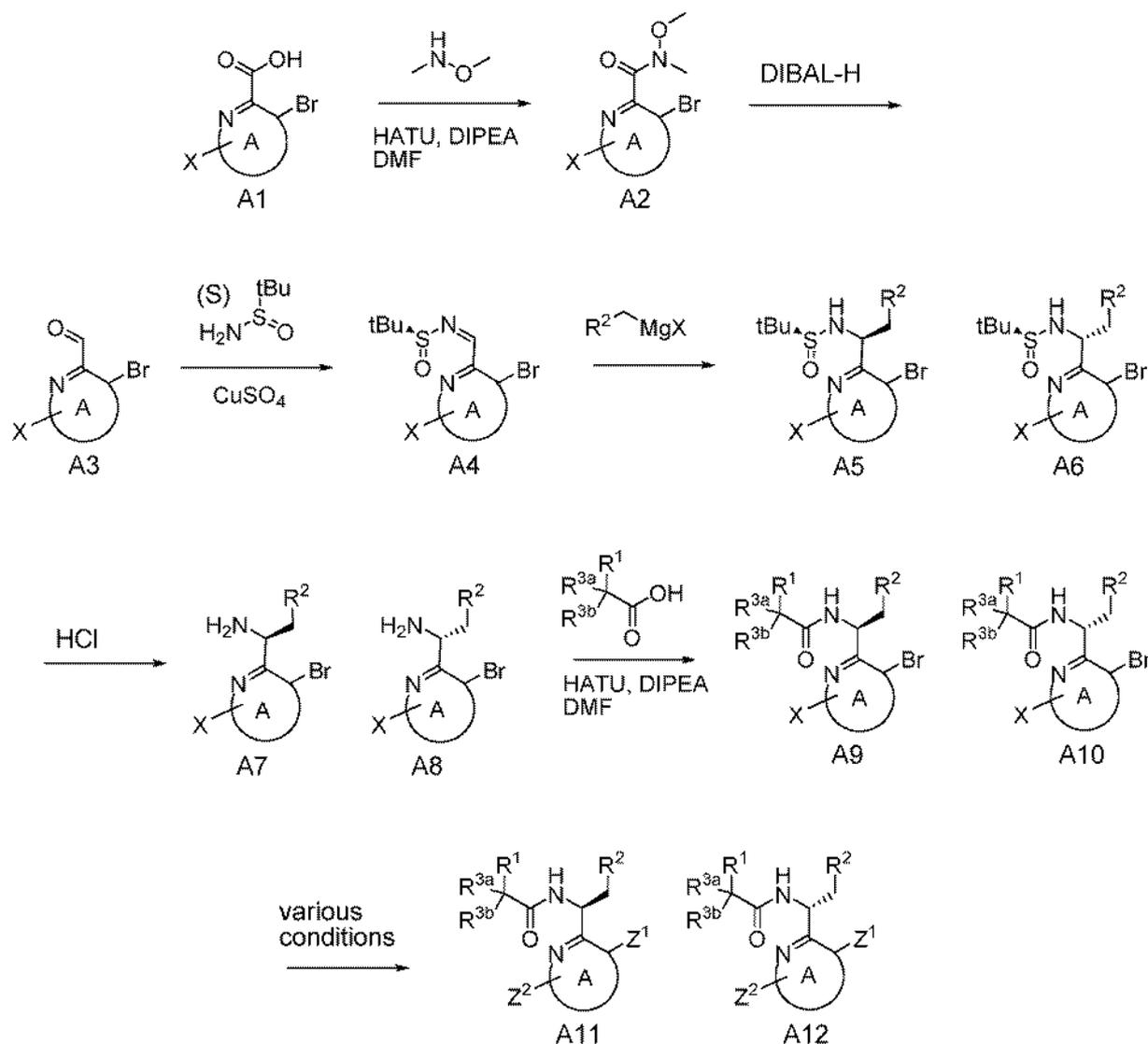


or a pharmaceutically acceptable salt thereof.

#### 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.

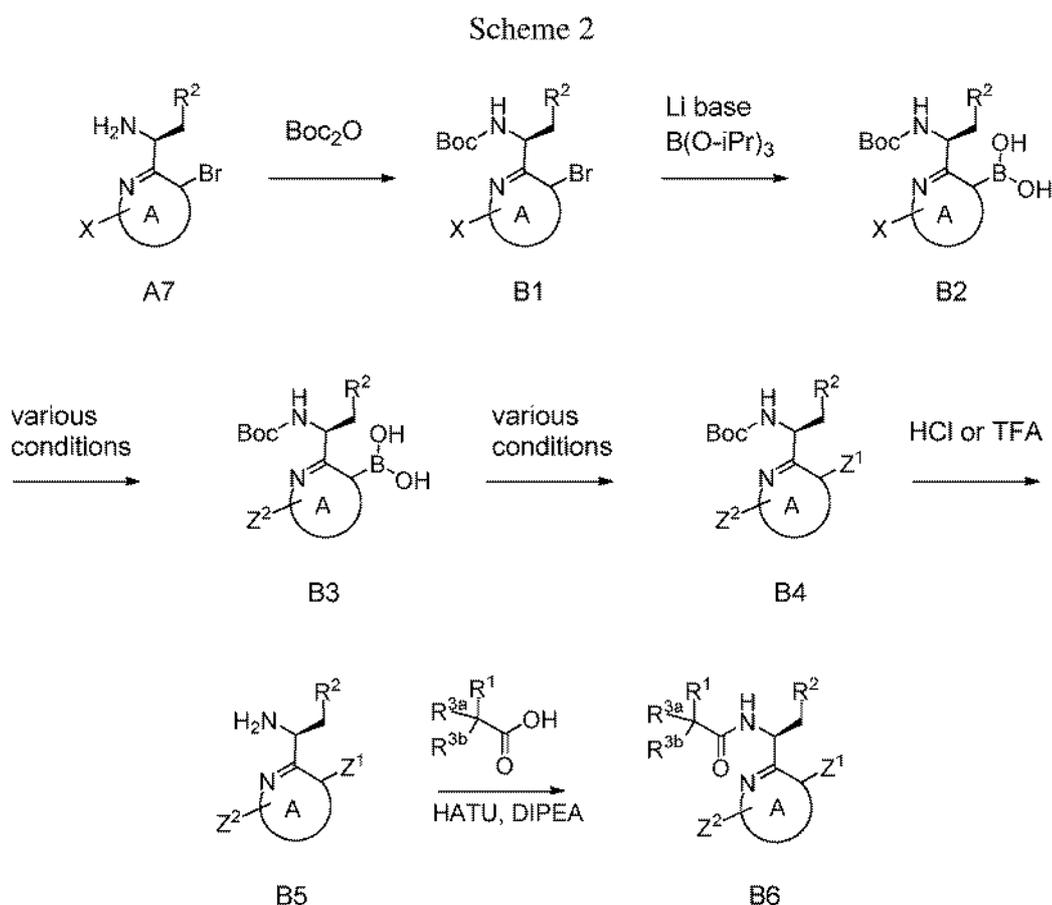
Scheme 1



[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  $\text{NH}_2$ , 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.



**[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, brexanavir, 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,  $\pm$ -FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitabine (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 (bevrimat), 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 than 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  $\mu$ L 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  $\mu$ L of virus/cell mixture (2000 cells) was immediately added to each well containing 40  $\mu$ L of diluted compound. The plates were then incubated at 37°C for 5 days. After 5 days of incubation, 25  $\mu$ L of 2X concentrated CellTiter-Glo<sup>TM</sup> 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  $\mu$ M and 0.2  $\mu$ M 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  $\mu$ M and 0.2  $\mu$ M drug concentration.

Compound	%inhibition at 2 $\mu$ M	%inhibition at 0.2 $\mu$ M	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  $\mu$ M. In one embodiment, the compounds demonstrate >30% inhibition at 2  $\mu$ M. In one embodiment, the compounds demonstrate >50% inhibition at 2  $\mu$ M. In one embodiment, the compounds

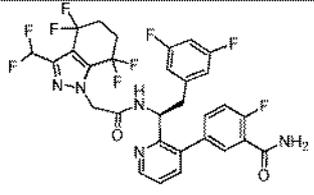
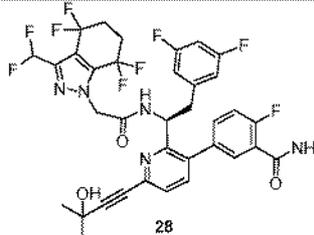
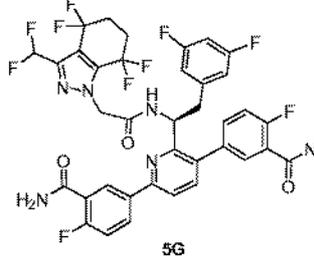
demonstrate >70% inhibition at 2  $\mu$ M. In one embodiment, the compounds demonstrate >75% inhibition at 2  $\mu$ M. In one embodiment, the compounds demonstrate >80% inhibition at 2  $\mu$ M. In one embodiment, the compounds demonstrate >85% inhibition at 2  $\mu$ M. In one embodiment, the compounds demonstrate >90% inhibition at 2  $\mu$ M. In one embodiment, the compounds demonstrate >95% inhibition at 2  $\mu$ M. It is to be understood that the compounds disclosed herein can be grouped according to their % inhibition as described above.

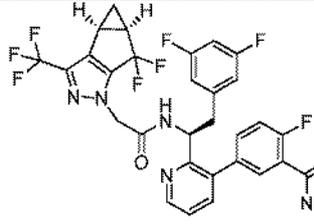
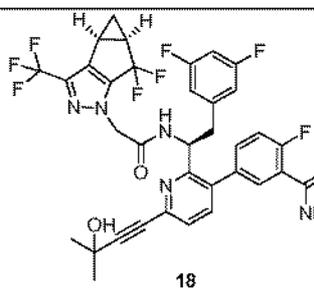
**[0391]** In one embodiment, the compounds demonstrate >10% inhibition at 0.2  $\mu$ M. In one embodiment, the compounds demonstrate >30% inhibition at 0.2  $\mu$ M. In one embodiment, the compounds demonstrate >50% inhibition at 0.2  $\mu$ M. In one embodiment, the compounds demonstrate >70% inhibition at 0.2  $\mu$ M. In one embodiment, the compounds demonstrate >75% inhibition at 0.2  $\mu$ M. In one embodiment, the compounds demonstrate >80% inhibition at 0.2  $\mu$ M. In one embodiment, the compounds demonstrate >85% inhibition at 0.2  $\mu$ M. In one embodiment, the compounds demonstrate >90% inhibition at 0.2  $\mu$ M. In one embodiment, the compounds demonstrate >95% inhibition at 0.2  $\mu$ M. 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  $\mu$ M. 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  $\mu$ M. 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  $\mu$ M or at 0.2  $\mu$ M.

**[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  $\mu$ M or at 0.2  $\mu$ M 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  $\mu$ M and 0.2  $\mu$ M was measured by the method provided in the Test A and Test B sections discussed above.

Compound	Response at 2 $\mu$ M	Response at 0.2 $\mu$ M
 <p>X1</p>	94	21
 <p>28</p>	84	71
 <p>5G</p>	58	3

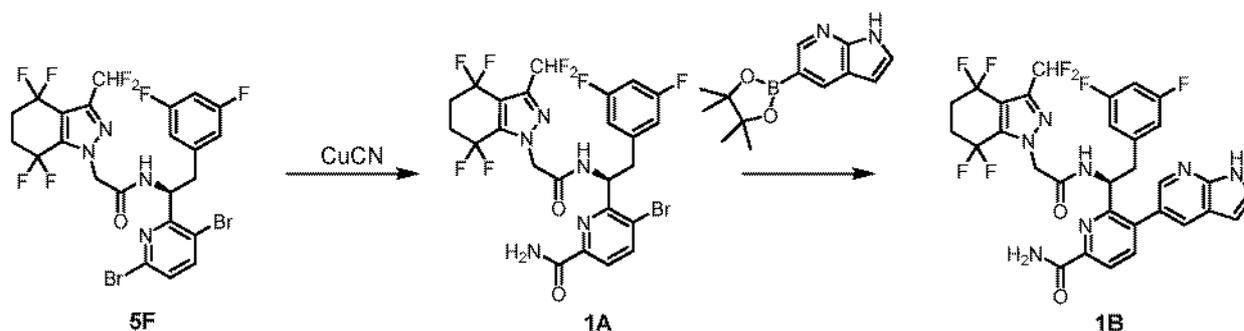
Compound	Response at 2 $\mu$ M	Response at 0.2 $\mu$ M
 <p>X2</p>	91	65
 <p>18</p>	90	96

[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):

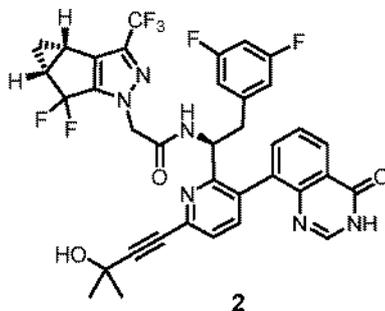
[0397] Compound **5F** (100 mg, 0.15 mmol) and CuCN (16 mg, 0.18 mmol) was dissolved in 0.3 mL of DMF. The reaction mixture was heated at 100 °C overnight. After cooled down to room temperature it was diluted with water and extracted with EtOAc. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>), 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]<sup>+</sup>.

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**. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) 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]<sup>+</sup>.

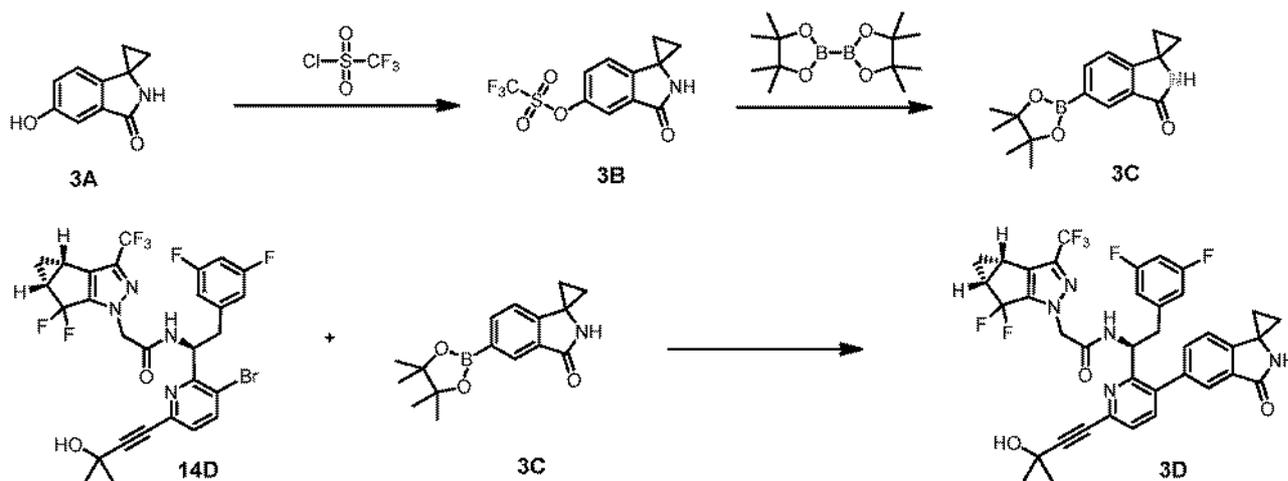
### Example 2.



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**. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) 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]<sup>+</sup>.

### Example 3.



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<sub>3</sub>N (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<sub>4</sub>, filtered through Celite<sup>(R)</sup>, and concentrated in vacuo to give the title product (**3B**). MS (*m/z*) 308.29 [M+H]<sup>+</sup>.

Synthesis of 5'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[cyclopropane-1,1'-isoindolin]-3'-one (**3C**):

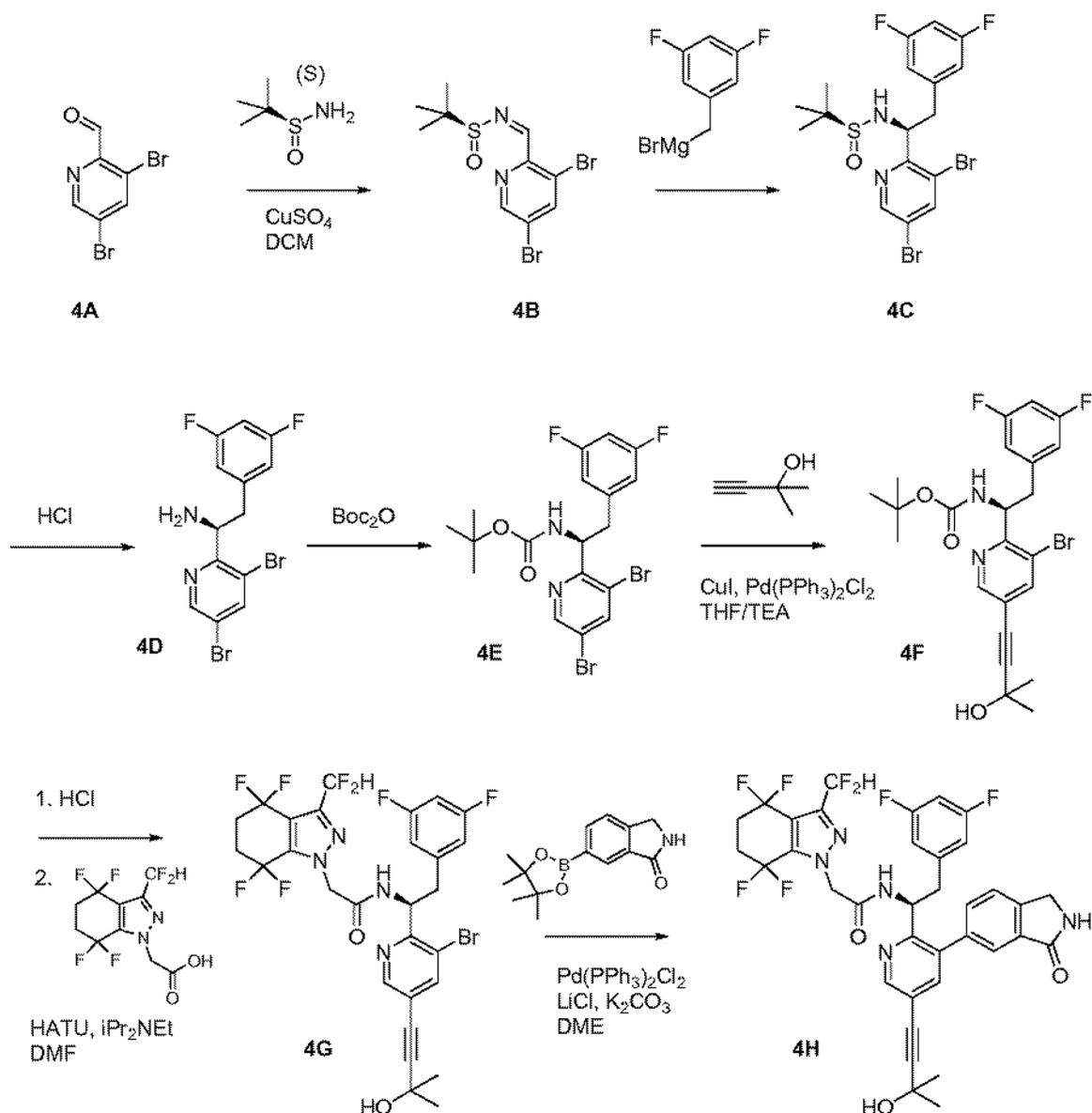
**[0401]** In a microwave tube were charged **3B** (200 mg, 0.65 mmol), bis(pinacolato)diboron (330 mg, 1.3 mmol) and potassium acetate (191 mg, 1.95 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (14 mg, 0.02 mmol) and 1,4-dioxane (8 mL). The mixture was heated up to 150 °C for 20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

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<sub>2</sub>CO<sub>3</sub> (21 mg, 0.15 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (3 mg) and Pd(dppf)Cl<sub>2</sub> (3 mg). To the mixture was added 1 mL of DME and 0.2 mL of H<sub>2</sub>O. 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. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) 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-sulfonamide (**4B**):

**[0403]** To 3,5-dibromopicolinaldehyde (1.9 g, 7.17 mmol) in  $\text{DCM}$  (30 mL) was added (S)-2-methylpropane-2-sulfonamide (870 mg, 7.17 mmol) and  $\text{CuSO}_4$  (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-sulfonamide (**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  $-78\text{ }^{\circ}\text{C}$ . (3,5-difluorobenzyl)magnesium bromide (34 mL, 0.25 M in  $\text{Et}_2\text{O}$ ) was added dropwise. The reaction was stirred at  $-78\text{ }^{\circ}\text{C}$  for 3 hr then let warm to  $0\text{ }^{\circ}\text{C}$  and quenched. The reaction was partitioned between EtOAc and aq.  $\text{NH}_4\text{Cl}$ . 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  $[\text{M}+\text{H}]^+$ .

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  $[\text{M}+\text{H}]^+$ .

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  $\mu\text{L}$ , 3.7 mmol) in DCM (9 mL). The reaction was stirred for 2 hr at ambient temperature. The reaction was partitioned between EtOAc and  $\text{H}_2\text{O}$ . 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  $[\text{M}+\text{H}]^+$ .

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  $\mu\text{L}$ , 0.43 mmol), TEA (0.9 mL),  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  (30 mg) and CuI (16 mg). The reaction was stirred for 2 hr at ambient temperature and then partitioned between EtOAc and  $\text{H}_2\text{O}$ . 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  $[\text{M}+\text{H}]^+$ .

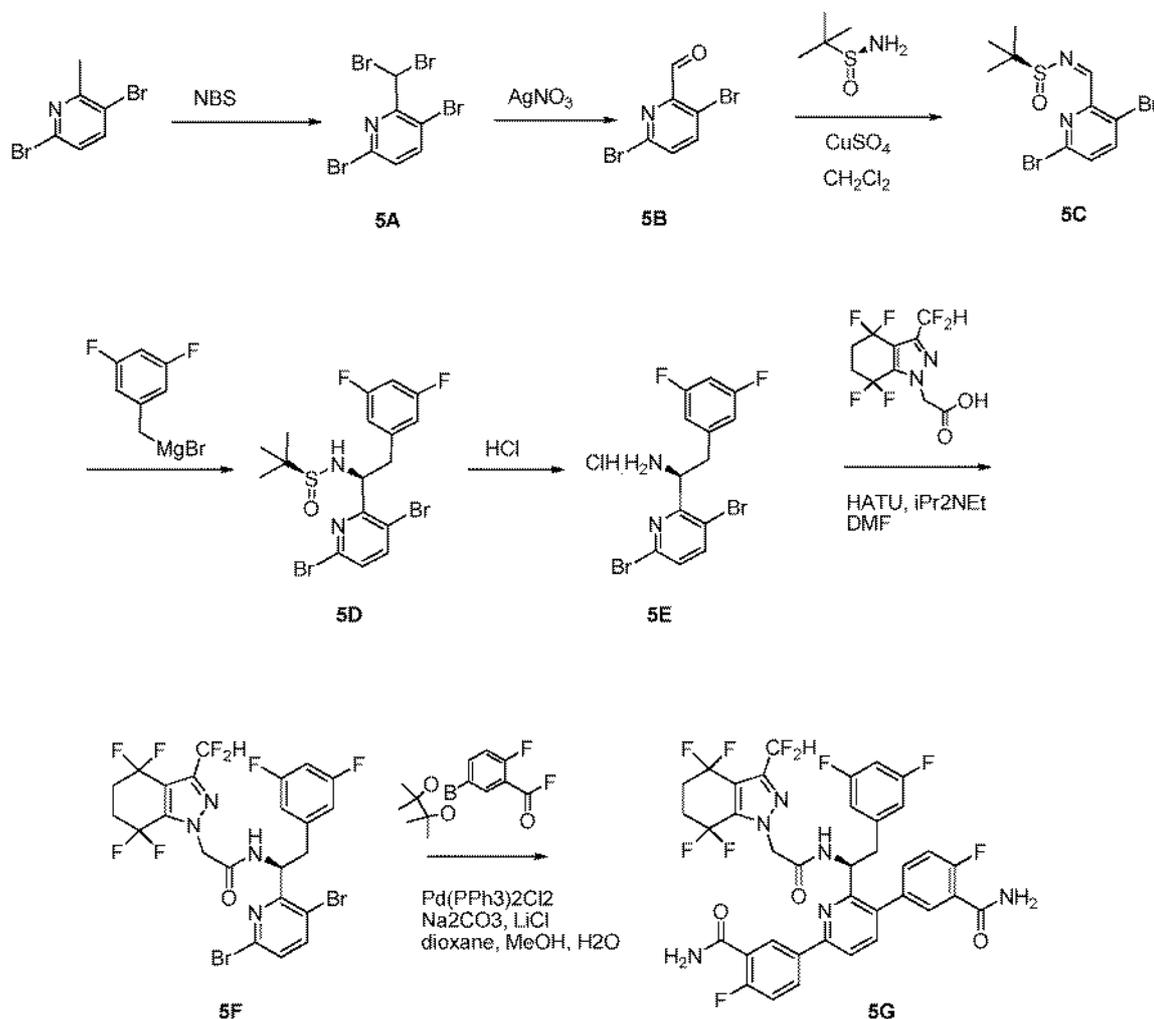
Synthesis of (S)-N-(1-(3-bromo-5-(3-hydroxy-3-methylbut-1-ynyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**4G**):

**[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]<sup>+</sup>). 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<sub>2</sub>NEt (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<sub>2</sub>O. 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]<sup>+</sup>.

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-oxoisindolin-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<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (2 mg), LiCl (1 mg), and aq 2M K<sub>2</sub>CO<sub>3</sub> (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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

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<sub>4</sub> (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 eluting with 0-10 percent EtOAc in hexane (7.36 g). MS (m/z): 409.66 [M+H]<sup>+</sup>

#### 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<sub>2</sub>SO<sub>4</sub>, 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-sulfonamide (**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-sulfonamide (**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  $[M+H]^+$

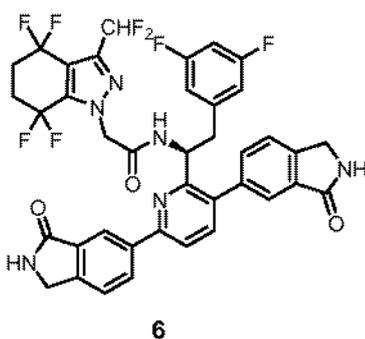
Synthesis of (S)-N-(1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**5F**):

[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),  $\text{Na}_2\text{CO}_3$  ( 50 mg, 0.6 mmol) and 5 mg of  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ . To the mixture was added 1.4 mL of 1,4-dioxane / methanol /  $\text{H}_2\text{O}$  (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.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  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  $[M+H]^+$ .

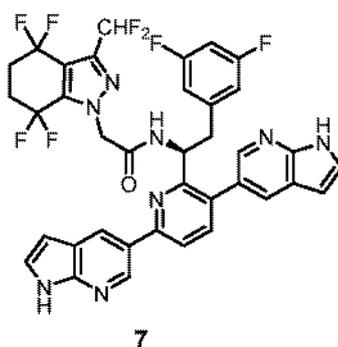
Example 6.



Synthesis of (S)-N-(1-(3,6-bis(3-oxoisindolin-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)isindolin-1-one and **5F**. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) 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]<sup>+</sup>.

Example 7.

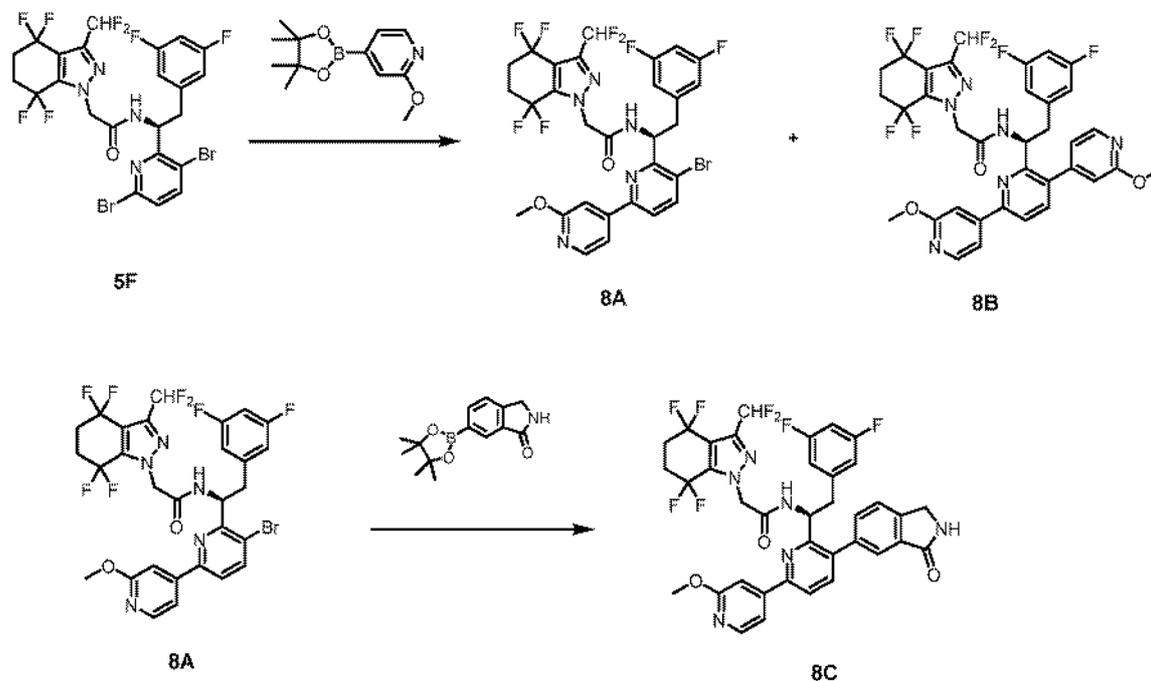


Synthesis of (S)-N-(1-(3,6-bis(1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (7):

**[0418]** The title compound (**7**) was prepared according to the method presented for the synthesis of compound **5G** of Example 5 utilizing 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine and **5F**. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 9.23-9.17 (m, 2H), 9.04 (d, *J* = 8.1 Hz, 1H), 8.03 (m, 3H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.61 (dd, *J* = 7.3, 3.5 Hz, 2H), 6.93 –

6.52 (m, 4H), 6.34 (d,  $J = 6.2$  Hz, 2H), 5.45 (m, 1H), 5.10 (m, 2H), 3.27 – 3.06 (m, 2H), 2.48 (m, 4H).MS ( $m/z$ ) 751.22  $[M+H]^+$ .

### Example 8.



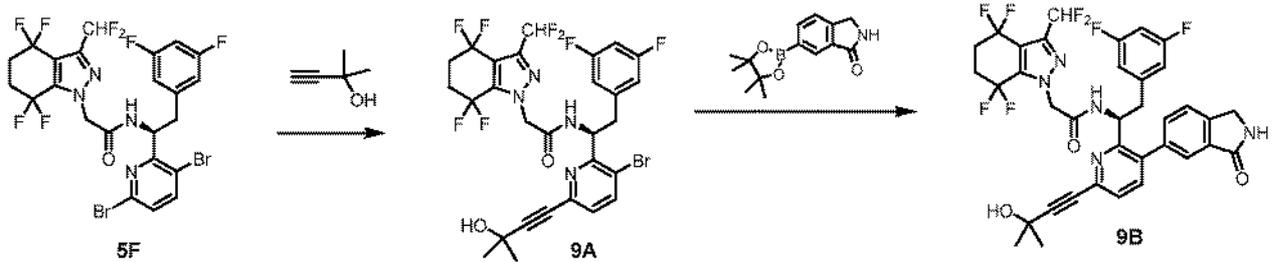
Synthesis of (S)-N-(1-(5-bromo-2'-methoxy-[2,4'-bipyridin]-6-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**8A**) and (S)-N-(1-(2',5'-di(methoxy-[2,4'-bipyridin]-6-yl))-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide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

**[0419]** The title compounds (**8A** and **8B**) were prepared according to the method presented for the synthesis of compound **5G** of Example 5 utilizing 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine(2 equiv.) and **5F**.

Synthesis of (S)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)-N-(2-(3,5-difluorophenyl)-1-(2'-methoxy-5-(3-oxoisindolin-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**.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  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.



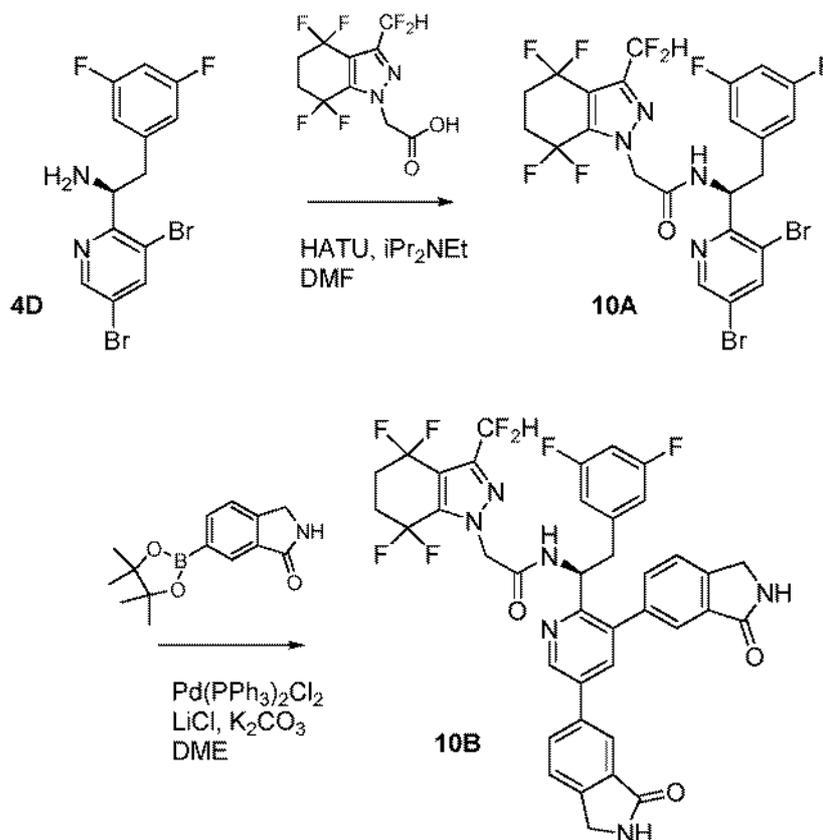
Synthesis of (S)-N-(1-(3-bromo-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (9A):

[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]<sup>+</sup>.

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. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) 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]<sup>+</sup>.

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):

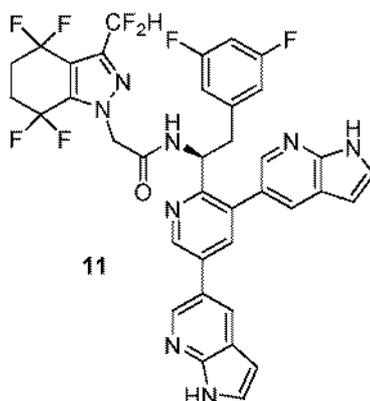
**[0423]** To (S)-1-(3,5-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethanamine (380 mg, 0.97 mmol) dissolved in DMF (10 mL) was added *i*Pr<sub>2</sub>NEt (350  $\mu$ L, 2 mmol) and 2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid (293 mg, 0.97 mmol). HATU (442 mg, 1.16 mmol) was added and the reaction stirred for 30 min. The reaction was partitioned between EtOAc and H<sub>2</sub>O. 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]<sup>+</sup>.

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<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (5 mg), LiCl (2 mg), and aq 2M K<sub>2</sub>CO<sub>3</sub> (110  $\mu$ L). The reaction was heated in a microwave reactor to 150  $^{\circ}$ C for 20 min. The reaction was purified by RP HPLC to provide the desired product. <sup>1</sup>H NMR (400 MHz,

Methanol- $d_4$ )  $\delta$  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]<sup>+</sup>.

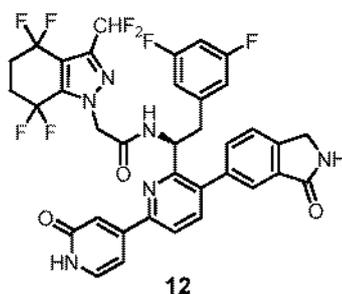
Example 11.



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. <sup>1</sup>H NMR (400 MHz, Methanol- $d_4$ )  $\delta$  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]<sup>+</sup>.

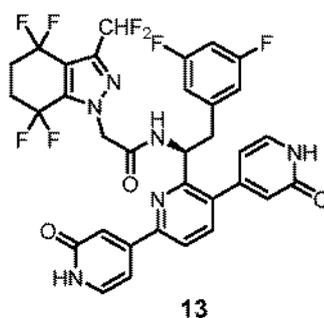
Example 12.



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-oxoisindolin-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-oxoisindolin-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. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) 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]<sup>+</sup>.

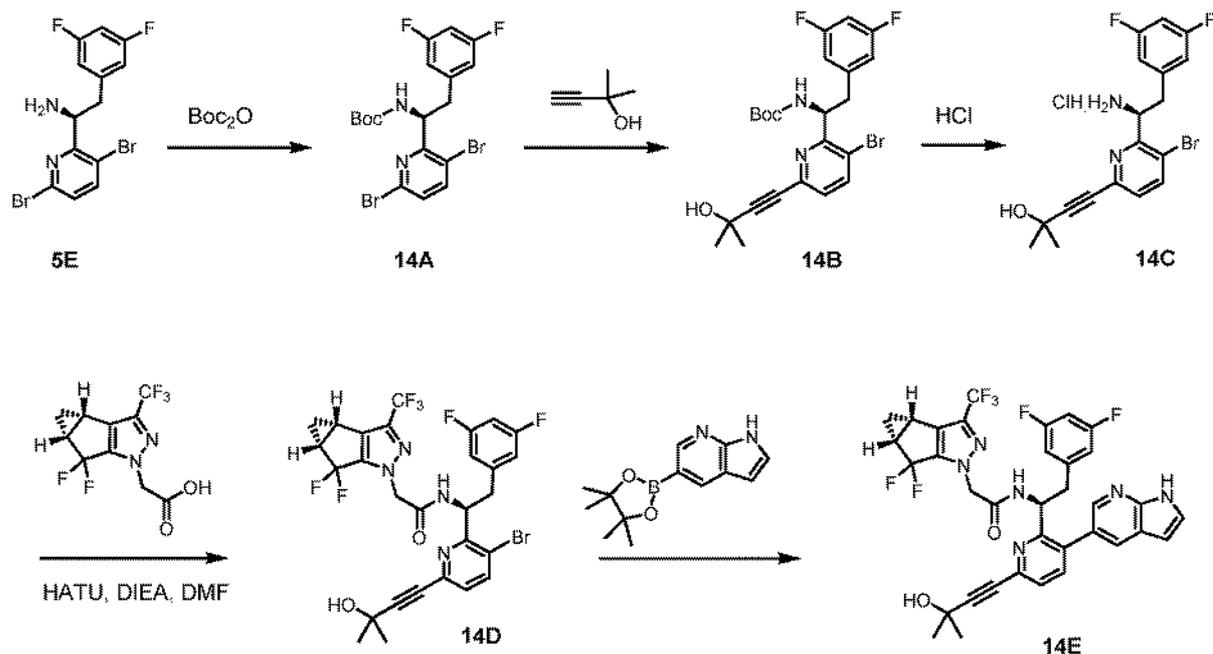
#### Example 13.



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**. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) 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]<sup>+</sup>.

#### Example 14.



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

[0428] The title compound was prepared according to the method presented for the synthesis of compound **4E** of Example 4 utilizing **5E**.

Synthesis of (S)-tert-butyl (1-(3-bromo-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (14B):

[0429] The title compound (**14B**) was prepared according to the method presented for the synthesis of compound **4F** of Example 4 utilizing 2-methylbut-3-yn-2-ol and (S)-tert-butyl (1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate. MS ( $m/z$ ) 496.90  $[\text{M}+\text{H}]^+$ .

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  $[\text{M}+\text{H}]^+$ .

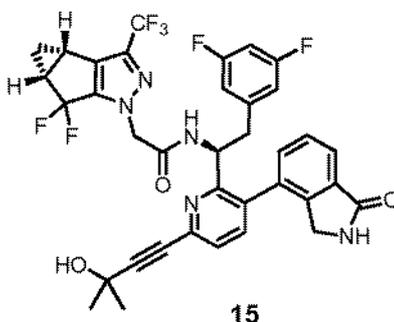
Synthesis of N-((S)-1-(3-bromo-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (14D):

[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  $[\text{M}+\text{H}]^+$ .

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**. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) 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]<sup>+</sup>.

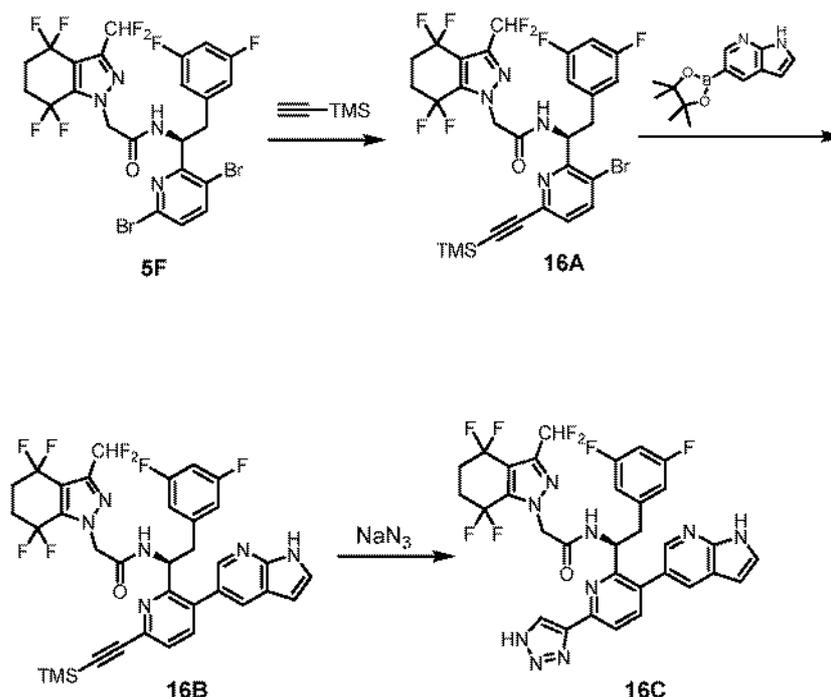
Example 15.



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. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) 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]<sup>+</sup>.

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]<sup>+</sup>.

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**):

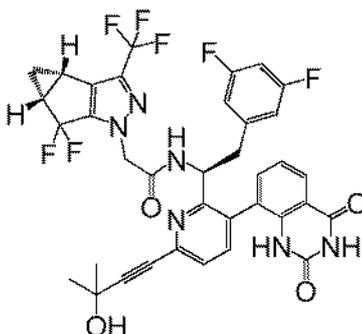
[0435] The title compound (**16B**) was prepared according to the method presented for the synthesis of compound **4H** of Example 4 utilizing 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine and **16A**. MS (m/z) 731.22 [M+H]<sup>+</sup>.

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<sub>3</sub> (13mg, 0.2 mmol) and NH<sub>4</sub>Cl (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<sub>2</sub>SO<sub>4</sub>), 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.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  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  $[\text{M}+\text{H}]^+$ .

Example 17.

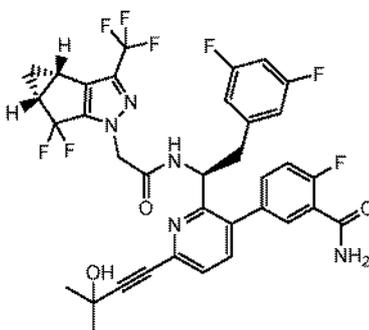


17

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**.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  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  $[\text{M}+\text{H}]^+$ .

Example 18.

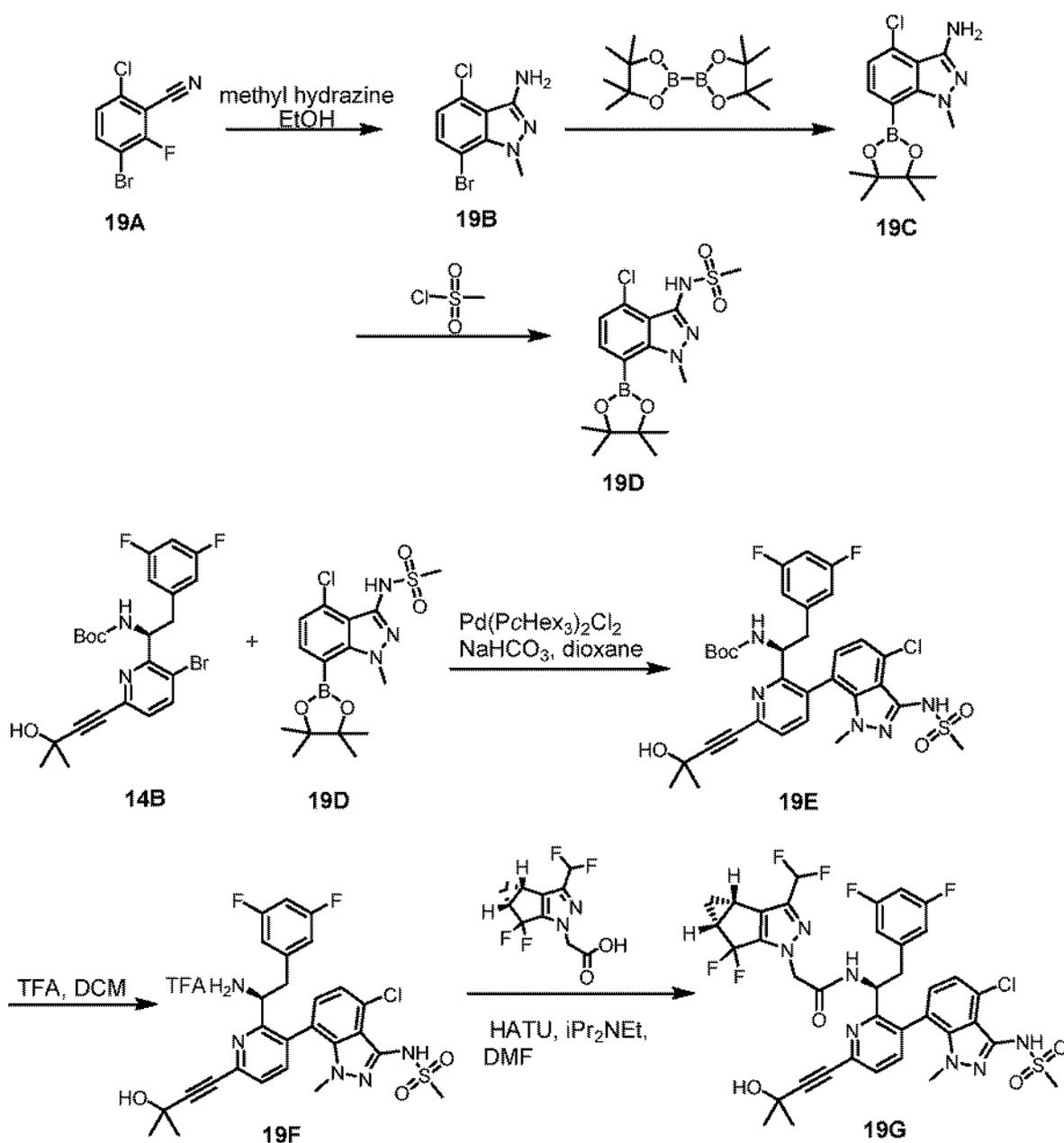


18

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**. <sup>1</sup>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]<sup>+</sup>.

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]<sup>+</sup>.

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]<sup>+</sup>.

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]<sup>+</sup>.

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]<sup>+</sup>.

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]<sup>+</sup>.

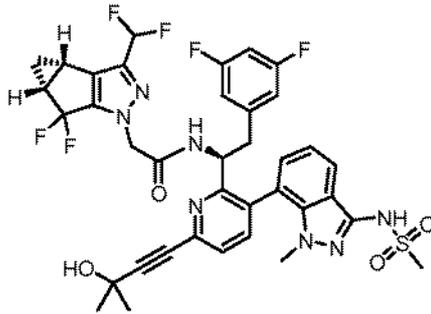
Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-ynyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**19G**):

**[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.

<sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

Example 20.



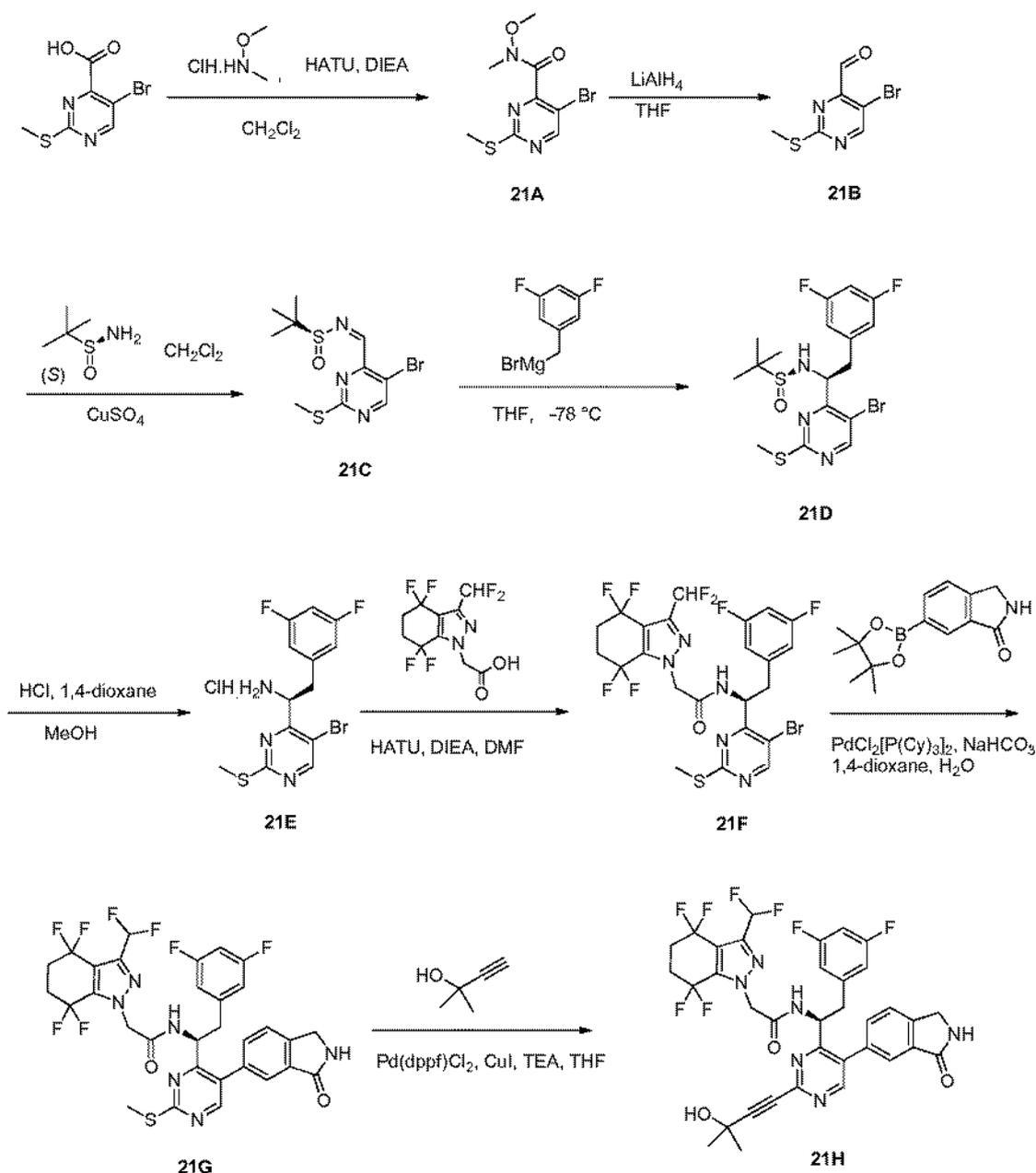
20

Synthesis of (S)-N-(1-(3-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-enyl)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**. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

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<sub>2</sub>Cl<sub>2</sub> 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<sub>2</sub>Cl<sub>2</sub>. It was washed with water and half brine. The organic layer was separated, dried over MgSO<sub>4</sub>, 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]<sup>+</sup>.

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<sub>2</sub>O (1.06 mL), 15% aqueous NaOH solution (1.06 mL) and H<sub>2</sub>O (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]<sup>+</sup>.

Synthesis of (S)-N-((5-bromo-2-(methylthio)pyrimidin-4-yl)methylene)-2-methylpropane-2-sulfonamide (**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-sulfonamide (3.4 g, 28 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The suspension was stirred for 3 days at room temperature. The reaction was filtered and washed with CH<sub>2</sub>Cl<sub>2</sub> (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]<sup>+</sup>

Synthesis of (S)-N-((S)-1-(5-bromo-2-(methylthio)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfonamide (**21D**):

[0451] To a solution of (S)-N-((5-bromo-2-(methylthio)pyrimidin-4-yl)methylene)-2-methylpropane-2-sulfonamide (**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<sub>4</sub>Cl (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<sub>2</sub>SO<sub>4</sub>(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]<sup>+</sup>

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]<sup>+</sup>.

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 °C. To it was drop wise added N,N-diisopropylethylamine (1.05 mL, 6 mmol). The reaction mixture was allowed to stir at 0 °C 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]<sup>+</sup>.

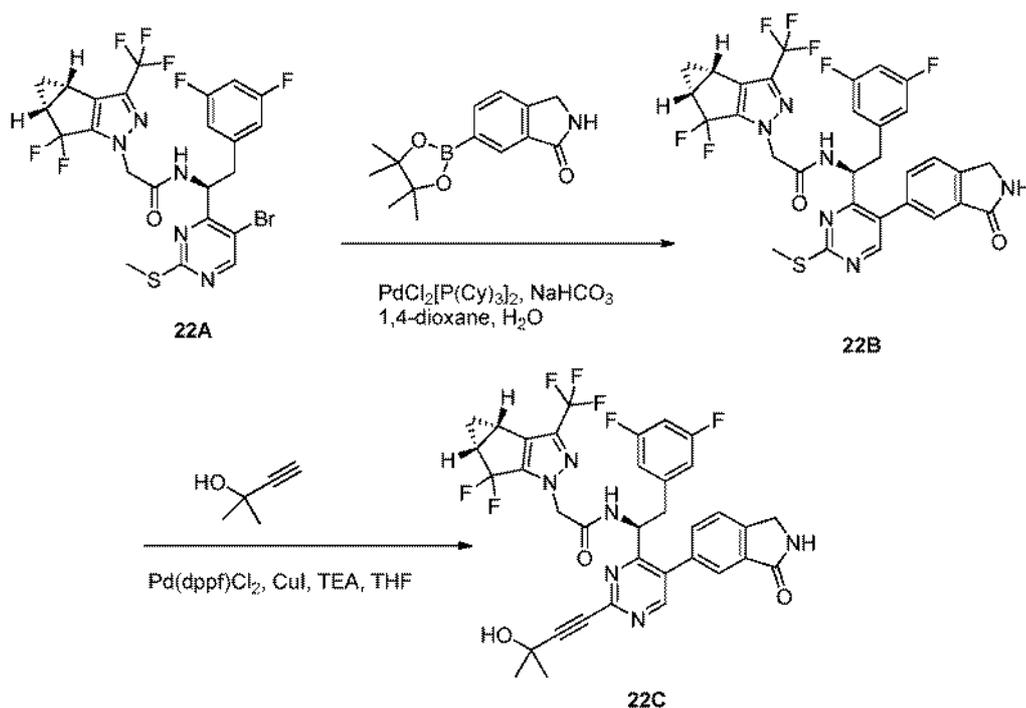
Synthesis of (S)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)-N-(2-(3,5-difluorophenyl)-1-(2-(methylthio)-5-(3-oxoisindolin-5-yl)pyrimidin-4-yl)ethyl)acetamide (**21G**):

[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<sub>2</sub>[P(Cy)<sub>3</sub>]<sub>2</sub> (17 mg, 0.023 mmol). To the mixture was added 10 mL of 1,4-dioxane and 1.4 mL of sodium bicarbonate aqueous solution (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<sub>4</sub>, filtered and concentrated. The residue was purified by silica gel chromatography to afford the title compound **21G**. MS (*m/z*) 697.32 [M+H]<sup>+</sup>.

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-oxoisindolin-5-yl)pyrimidin-4-yl)ethyl)acetamide (**21H**):

[0455] To the mixture of solid CuI (3.3 mg, 0.017 mmol), Pd(dppf)Cl<sub>2</sub> (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<sub>3</sub>N (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<sub>4</sub>OH, water and brine. The organic layer was dried over MgSO<sub>4</sub>, filtered, concentrated, and purified by reverse phase HPLC to afford the title compound (**21H**). <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>): 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]<sup>+</sup>.

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]<sup>+</sup>.

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-oxoisindolin-5-yl)pyrimidin-4-yl)ethyl)acetamide (**22B**):

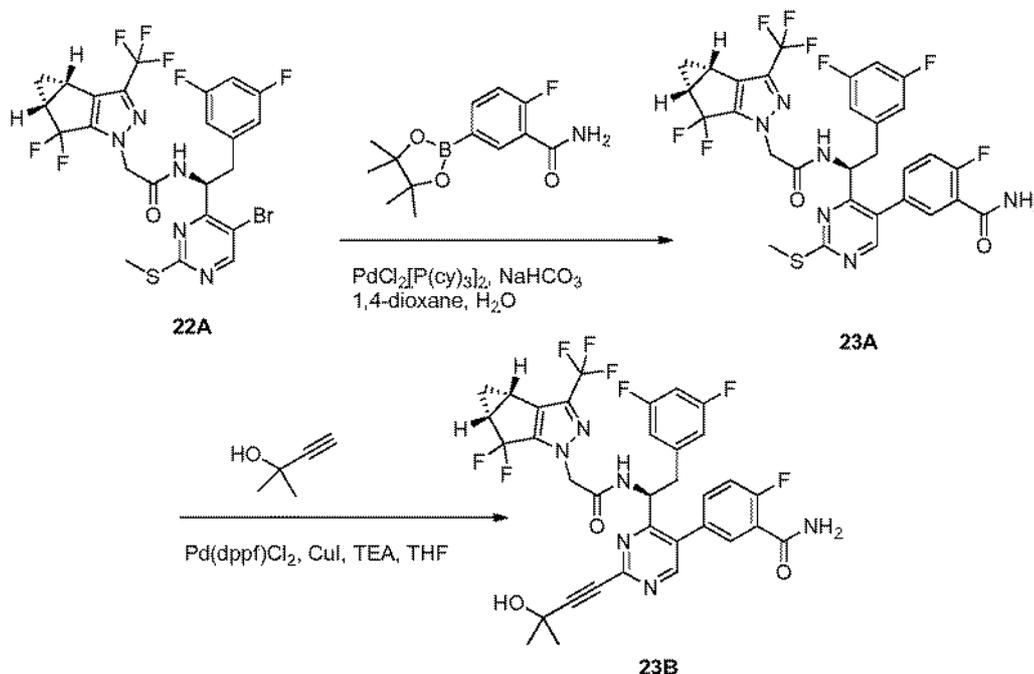
**[0457]** The title compound (**22B**) was prepared according to the method presented for the synthesis of compound **21G** of Example 21 utilizing compound **22A** and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one. MS (*m/z*) 677.05 [M+H]<sup>+</sup>.

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-oxoisindolin-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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>): 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 [ $M+H$ ]<sup>+</sup>.

Example 23.



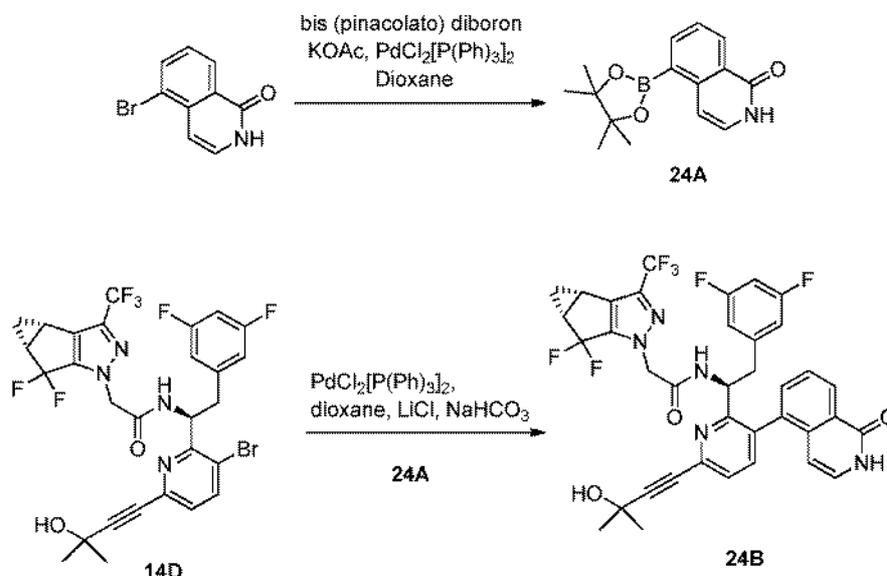
Synthesis of 5-(4-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-2-(methylthio)pyrimidin-5-yl)-2-fluorobenzamide (**23A**):

**[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 [ $M+H$ ]<sup>+</sup>.

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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>): 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 [ $M+H$ ]<sup>+</sup>.

Example 24.



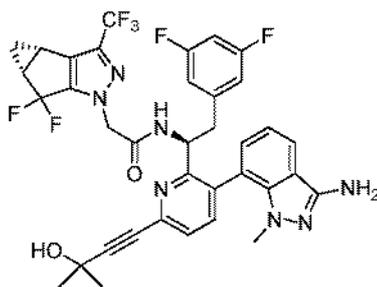
Synthesis of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (24A):

**[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<sub>2</sub>[P(Ph)<sub>3</sub>]<sub>2</sub> (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]<sup>+</sup>.

Synthesis of 2-((3b*S*,4a*R*)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1*H*-cyclopropa[3,4]cyclopenta[1,2-*c*]pyrazol-1-yl)-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<sub>2</sub>[P(Ph)<sub>3</sub>]<sub>2</sub> (5 mg, 0.01 mmol), LiCl (11 mg, 0.22 mmol) and aq 1M NaHCO<sub>3</sub> (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<sub>2</sub>SO<sub>4</sub>, 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]<sup>+</sup>. 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 Phenomenex Kinetex C18 column).

Example 25.

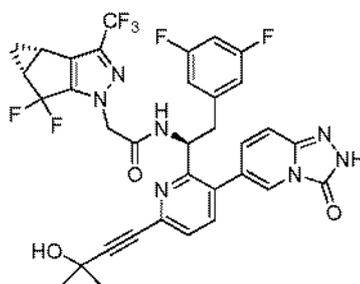


25

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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

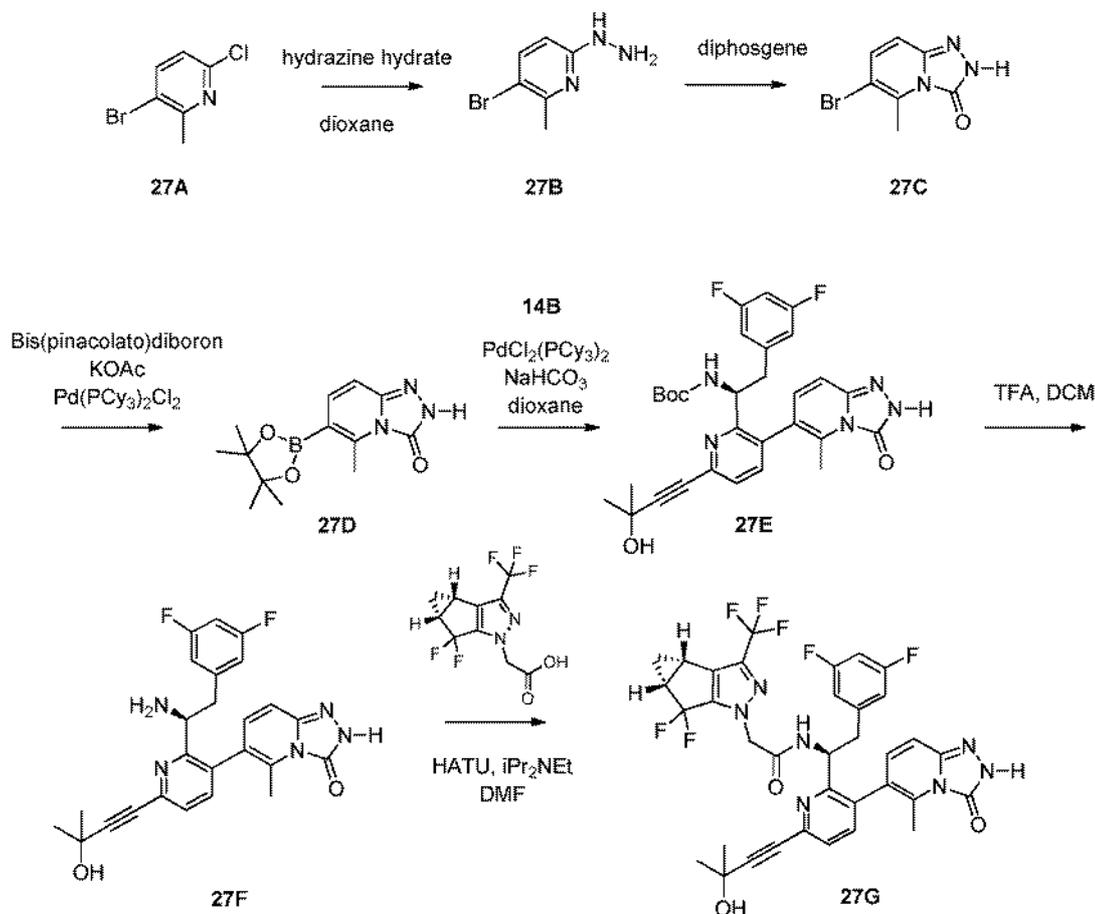
Example 26.



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]<sup>+</sup>. HPLC retention time 6.58 min (2-98% acetonitrile: water with 0.1% trifluoroacetic acid, 8.5 min gradient on a Phenomenex 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]<sup>+</sup>.

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]<sup>+</sup>.

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<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (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<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (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]<sup>+</sup>.

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<sub>3</sub> (0.4 mL) and PdCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (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]<sup>+</sup>.

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):

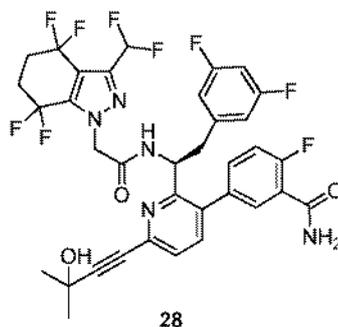
[0469] The title compound (**27F**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of **19F** in Example 19 utilizing **27E**. MS (*m/z*) 464.1 [M+H]<sup>+</sup>.

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.  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  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  $[\text{M}+\text{H}]^+$ .

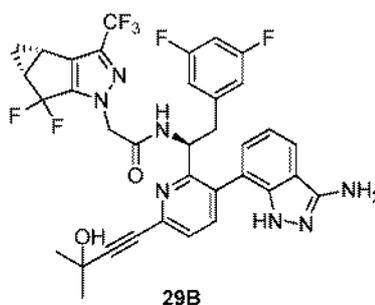
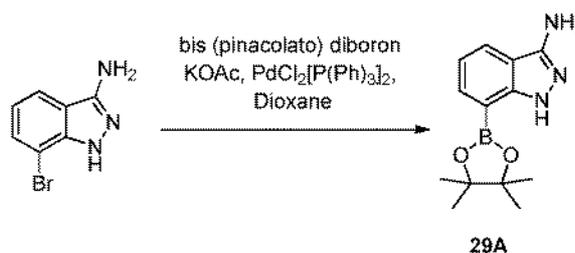
#### Example 28.



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.  $^1\text{H}$  NMR (400 MHz,  $\text{cd}_3\text{od}$ )  $\delta$  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  $[\text{M}+\text{H}]^+$ .

#### Example 29.



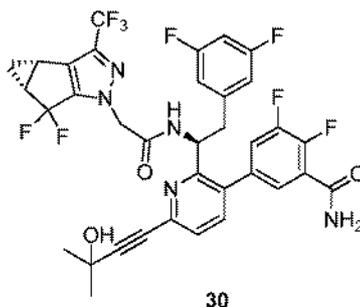
Synthesis of 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-amine (29A):

[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<sub>2</sub>[P(Ph)<sub>3</sub>]<sub>2</sub> (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]<sup>+</sup>.

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]<sup>+</sup>. PLC retention time 6.02 min (2-98% acetonitrile; water with 0.1% trifluoroacetic acid, 8.5 min gradient on a Phenomenex Kinetex C18 column).

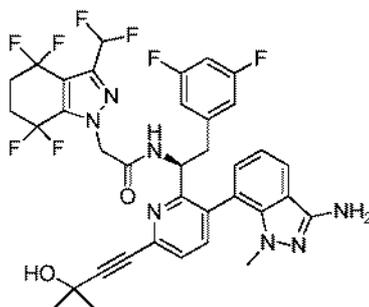
Example 30.



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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

Example 31.

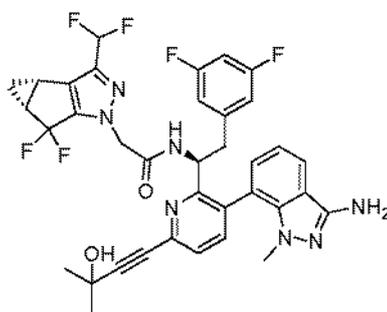


31

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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

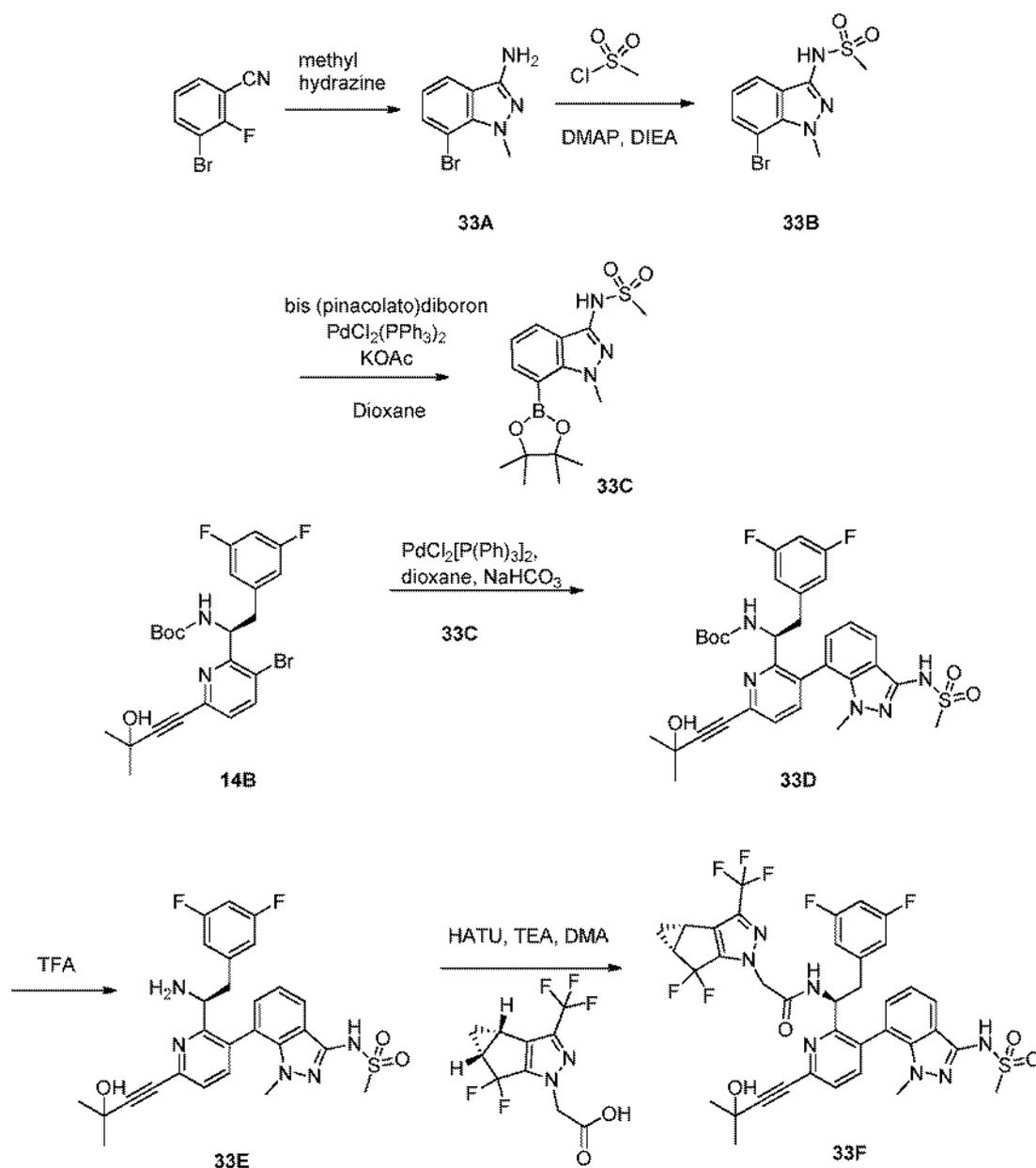
Example 32.



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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

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<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Product was purified by silica chromatography to give the title compound. MS (*m/z*) 227.1 [M+H]<sup>+</sup>.

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<sub>2</sub>SO<sub>4</sub>, 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<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The product was purified by silica chromatography to give the title compound. MS (*m/z*) 305.9 [M+H]<sup>+</sup>.

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<sub>2</sub>[P(Ph)<sub>3</sub>]<sub>2</sub> (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]<sup>+</sup>.

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<sub>2</sub>[P(Ph)<sub>3</sub>]<sub>2</sub> (35 mg, 0.05 mmol), and aq 1M NaHCO<sub>3</sub> (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<sub>2</sub>SO<sub>4</sub>, 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):

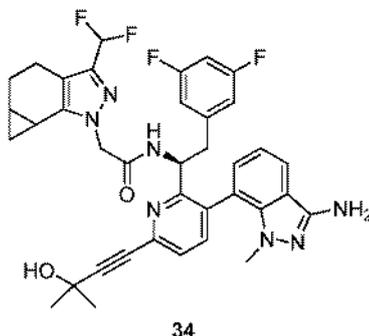
[0481] To a solution of **33D** (47 mg, 0.07 mmol) in DCM was added 4M HCl in dioxane (0.7 mL, 2.9 mmol). The reaction mixture was stirred at room temperature for 0.5 hours. Upon

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**):

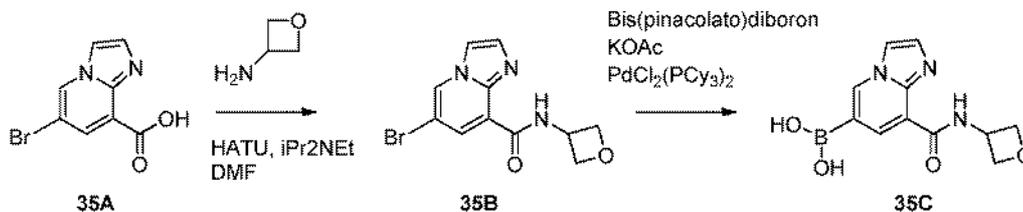
**[0482]** To a solution of **33E** (70 mg) in DMA (3 mL) was added triethylamine (0.046 mL, 0.32 mmol), followed by 2-((3bS,4aR)-3-(trifluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (31 mg, 0.1 mmol) and HATU (46 mg, 0.12 mmol). After stirring for 30 minutes, the reaction mixture was filtered and purified by reverse phase HPLC to provide the product **33F** as a mixture of atropisomers.  $^1\text{H NMR}$  (400 MHz,  $\text{cd}_3\text{od}$ )  $\delta$  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  $[\text{M}+\text{H}]^+$ .

Example 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**):

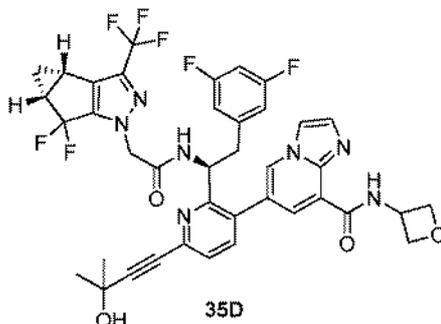
**[0483]** The title compound (**34**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **33F** of Example 33 utilizing **37A** and 2-(3-(difluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetic acid (WO2013006738).  $^1\text{H NMR}$  (400 MHz,  $\text{cd}_3\text{od}$ )  $\delta$  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  $[\text{M}+\text{H}]^+$ .

Example 35.Synthesis of 6-bromo-N-(oxetan-3-yl)imidazo[1,2-a]pyridine-8-carboxamide (35B):

**[0484]** 6-bromoimidazo[1,2-a]pyridine-8-carboxylic acid hydrochloride (235 mg, 0.85 mmol) and HATU (386.16 mg, 1.02 mmol) were combined in DMF (4 ml) and treated with  $iPr_2NEt$  (0.37 ml, 2.12 mmol). 3-Oxetamine hydrochloride (92.31 mg, 0.85 mmol) was added and the reaction stirred at ambient temperature for 1 h. Water (2 ml) was added and a solid precipitated. The solids were collected by filtration to provide the desired product. MS ( $m/z$ ) 296.0  $[M+H]^+$ .

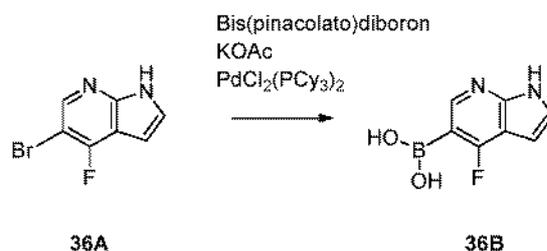
Synthesis of (8-(oxetan-3-ylcarbamoyl)imidazo[1,2-a]pyridin-6-yl)boronic acid (35C):

**[0485]** The title compound (**35C**) was prepared according to the method presented for the synthesis of **27D** in Example 27 utilizing **35B** wherein the boronic ester hydrolyzed and the corresponding boronic acid was isolated. MS ( $m/z$ ) 262.1  $[M+H]^+$ .

Synthesis of 6-(2-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-N-(oxetan-3-yl)imidazo[1,2-a]pyridine-8-carboxamide (35D):

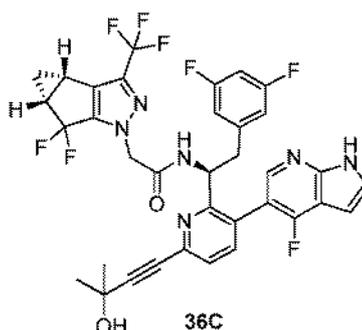
**[0486]** The title compound (**35D**) was prepared according to the method presented for the synthesis of **27G** in Example 27 utilizing **14B** and **35C**.  $^1H$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  9.15 (d), 8.80 (d), 8.27 (d), 8.11 (d), 7.84 – 7.69 (m), 7.65 (dd), 7.53 (dd), 6.89 – 6.64 (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.



Synthesis of (4-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)boronic acid (**36B**):

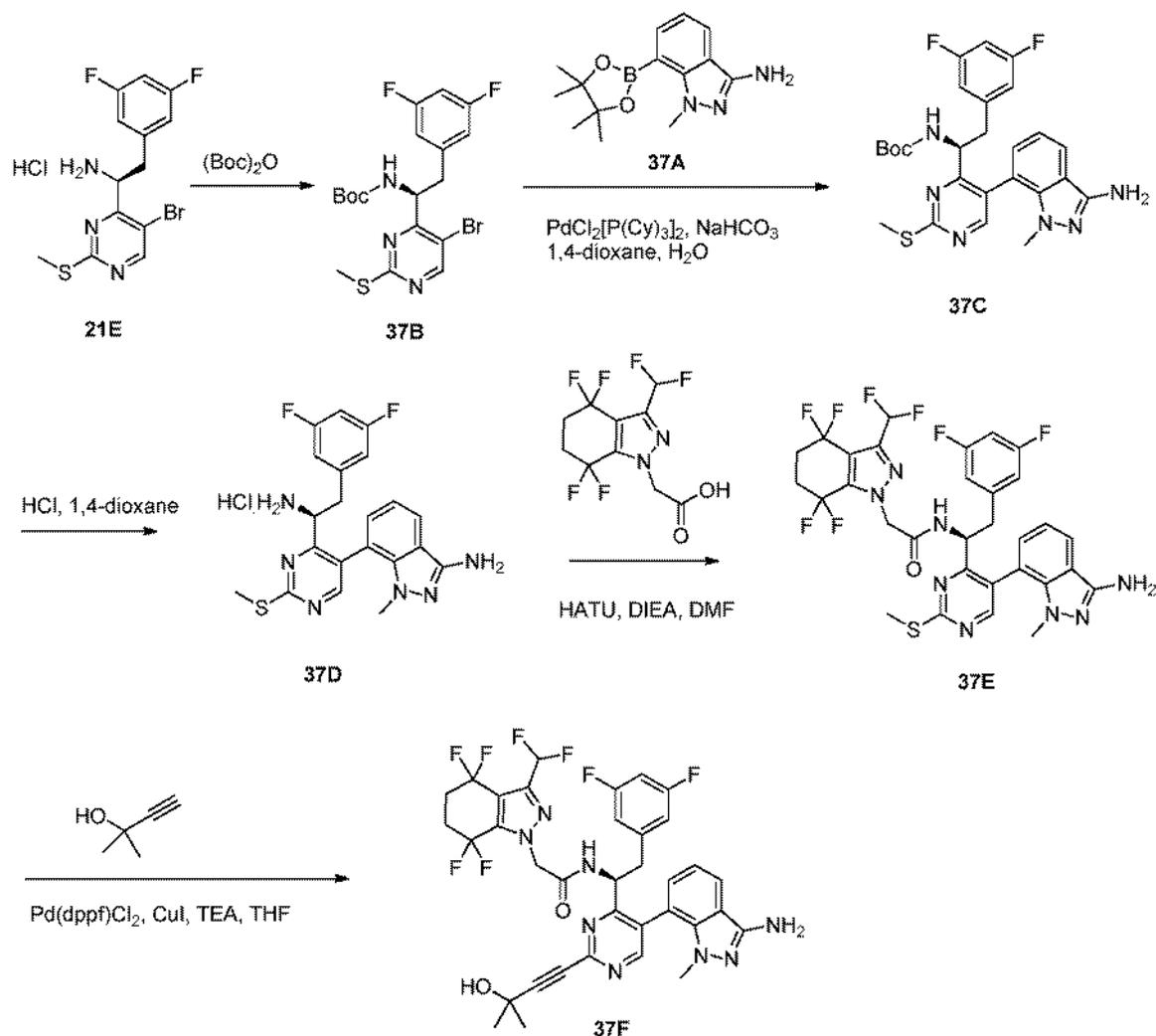
[0487] In a microwave vessel, 5-bromo-4-fluoro-1H-pyrrolo[2,3-b]pyridine (100 mg, 0.47 mmol) was combined with bis(pinacolato)diboron (177 mg, 0.7 mmol), KOAc (91 mg, 0.93 mmol), and PdCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (34 mg) in dioxane (4.5 ml). Argon was bubbled into the reaction solution 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]<sup>+</sup>.



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**. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

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  $[\text{M}+\text{H}]^+$ .

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  $\mu\text{L}$ , 1.56 mmol) and di-tert-butyl dicarbonate (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  $[\text{M}+\text{H}]^+$ .

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]<sup>+</sup>.

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]<sup>+</sup>.

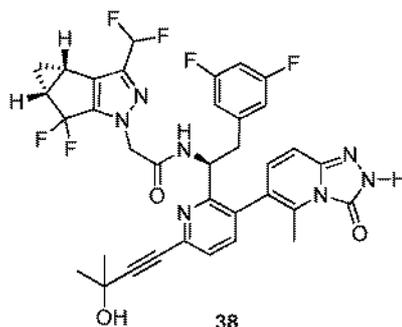
Synthesis of (S)-N-(1-(5-(3-amino-1-methyl-1H-indazol-7-yl)-2-(methylthio)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**37E**):

[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 °C. To it was added N,N-diisopropylethylamine (0.1 mL, 0.6 mmol). The reaction mixture was allowed to stir at 0 °C 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]<sup>+</sup>.

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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

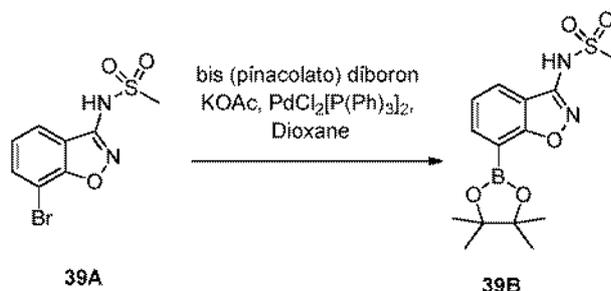
Example 38.



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):

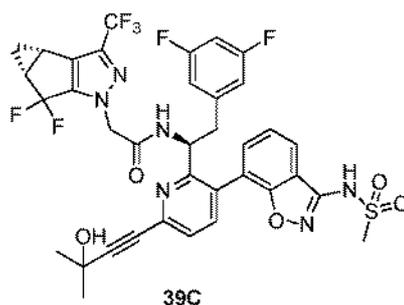
[0496] The title compound (**38**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of **27G** in Example 27 utilizing **27F** and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. 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 Phenomenex Kinetex C18 column 4.6 x 100 mm). MS ( $m/z$ ) 710.1 [M+H]<sup>+</sup>.

Example 39.



Synthesis of N-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]isoxazol-3-yl)methanesulfonamide (39B):

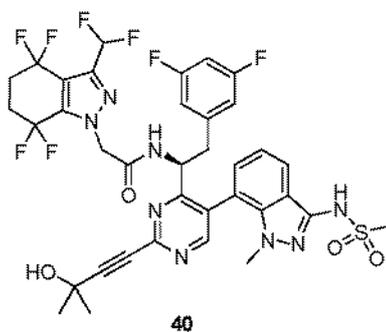
[0497] To **39A** (prepared similarly to **33B** of example 33 utilizing 7-bromobenzo[d]isoxazol-3-amine instead of 7-bromo-1-methyl-1H-indazol-3-amine) (87 mg, 0.3 mmol) in dioxane (3 mL) was added bis(pinacolato)diboron (107mg, 0.4 mmol), and PdCl<sub>2</sub>[P(Ph)<sub>3</sub>]<sub>2</sub> (21 mg, 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]<sup>+</sup>.



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 Phenomenex Kinetex C18 column).

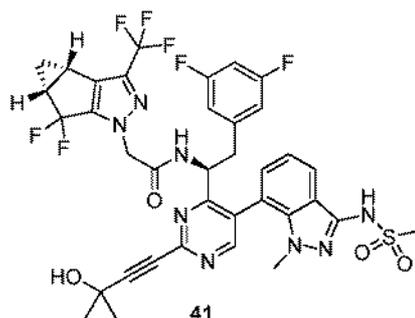
Example 40.



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**).  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ ):  $\delta$  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  $[M+H]^+$

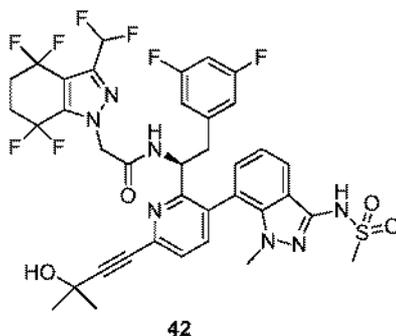
Example 41



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-(methylsulfonylamido)-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**). <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

Example 42.

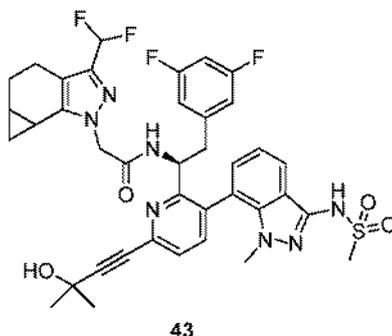


Synthesis of (S)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)-N-(2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl))-3-(1-methyl-3-(methylsulfonylamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)acetamide (**42**):

**[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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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  $[M+H]^+$ .

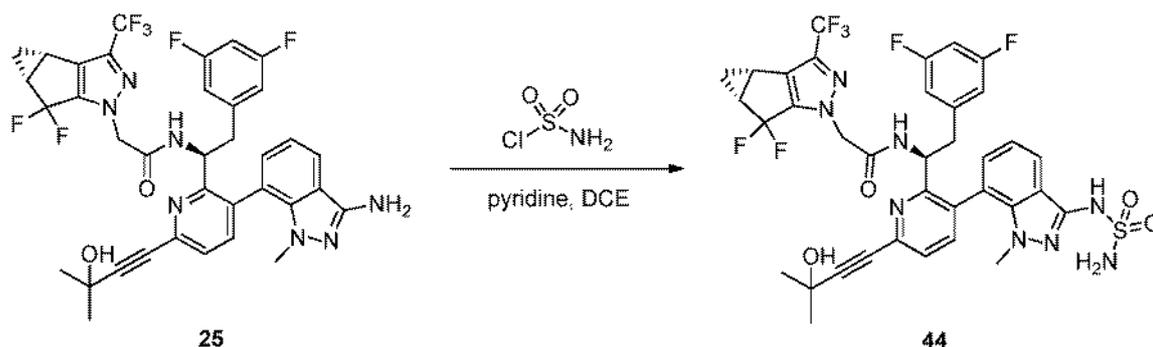
Example 43.



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.  $^1\text{H}$  NMR (400 MHz,  $\text{cd}_3\text{od}$ )  $\delta$  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  $[M+H]^+$ .

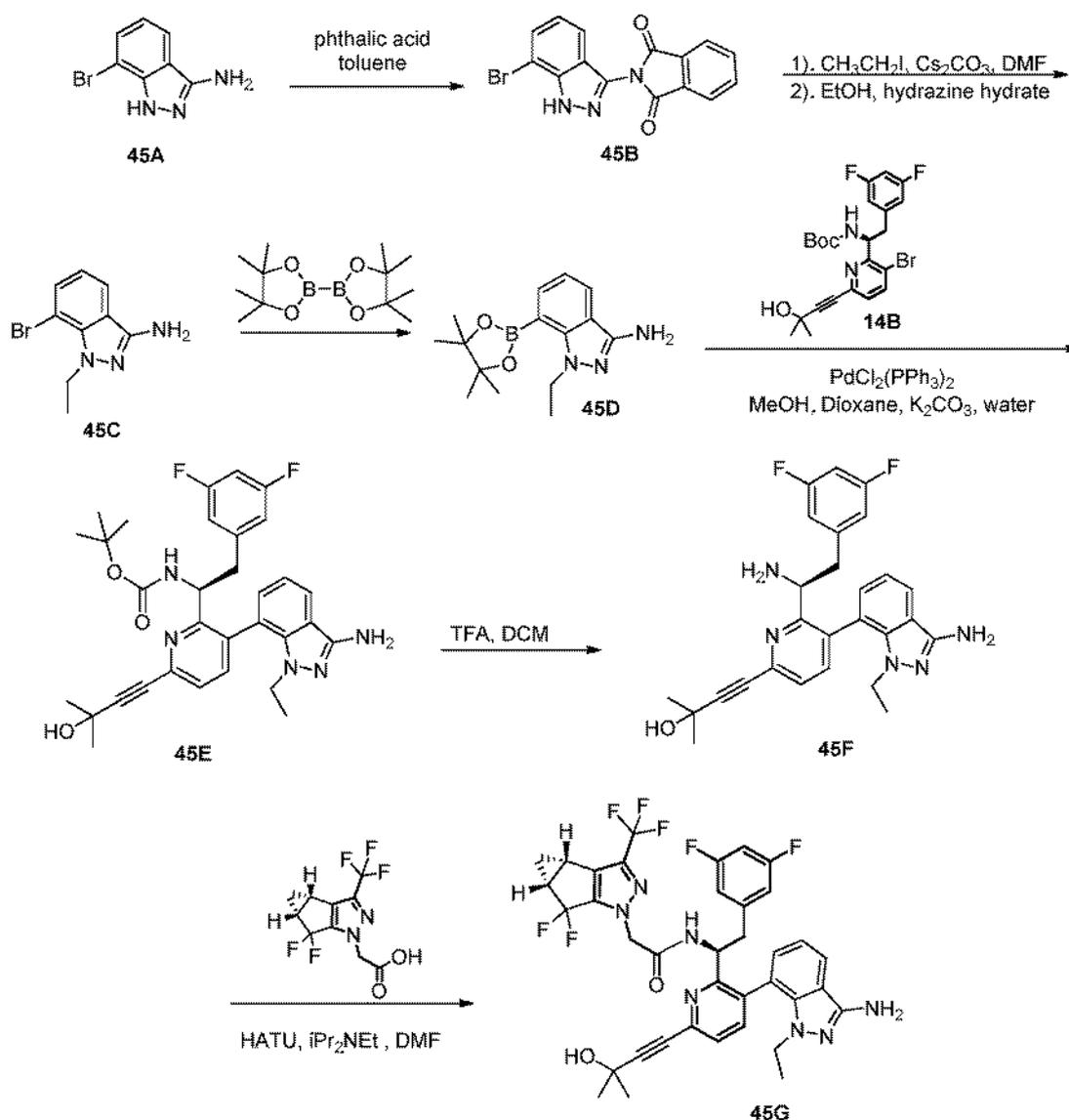
Example 44.



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<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuo, and purified by reverse phase HPLC to provide the title compound **44** as a mixture of atropisomers. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

#### 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]<sup>+</sup>.

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<sub>2</sub>CO<sub>3</sub> (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]<sup>+</sup>.

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<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (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]<sup>+</sup>.

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<sub>2</sub>CO<sub>3</sub> (0.4 ml), LiCl (17.7 mg, 0.4 mmol) and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (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]<sup>+</sup>.

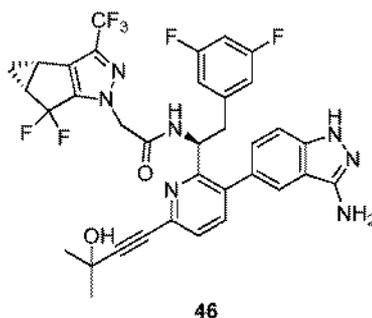
Synthesis of (S)-4-(5-(3-amino-1-ethyl-1H-indazol-7-yl)-6-(1-amino-2-(3,5-difluorophenyl)ethyl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (**45F**):

[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]<sup>+</sup>.

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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

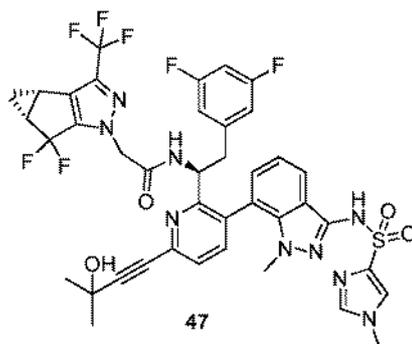
#### Example 46.



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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

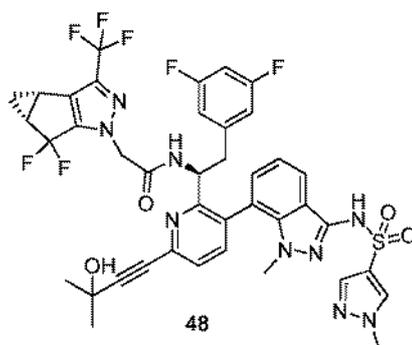
#### Example 47.



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  $\mu$ L, 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.  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  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  $[\text{M}+\text{H}]^+$ .

Example 48.

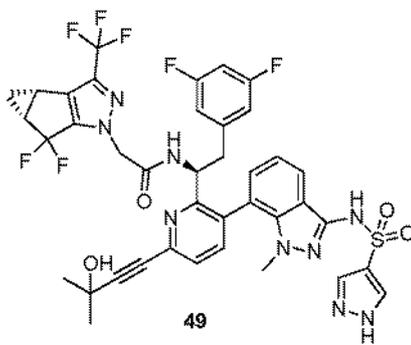


Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-

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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

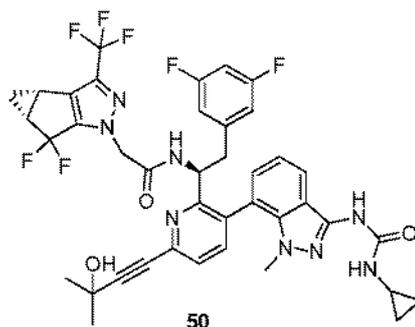
Example 49.



Synthesis of 2-((3b*S*,4a*R*)-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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

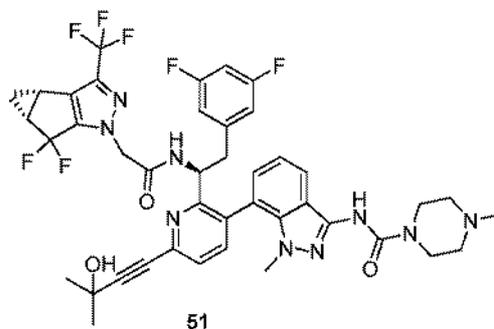
Example 50.



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  $\mu$ L, 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  $\mu$ L, 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.  $^1\text{H NMR}$  (400 MHz, Methanol- $d_4$ )  $\delta$  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 [ $\text{M}+\text{H}$ ] $^+$ .

Example 51.

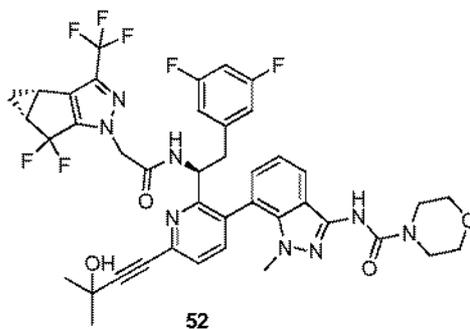


Synthesis of N-(7-(2-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-

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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

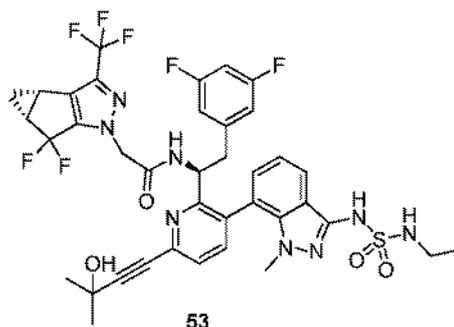
Example 52.



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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

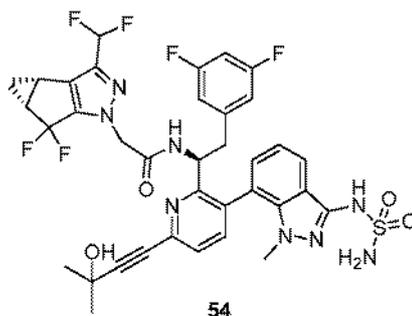
Example 53.



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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

Example 54.

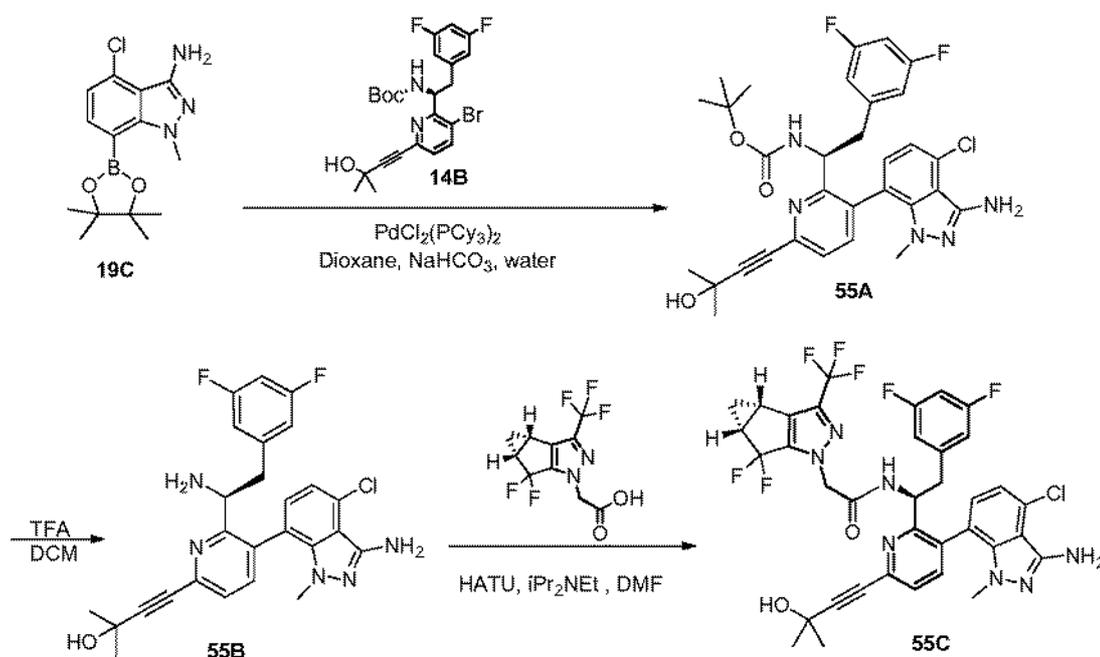


Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-methyl-3-(sulfamoylamino)-1H-indazol-7-yl)pyridin-2-yl)ethyl)acetamide (54):

[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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

### 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<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (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]<sup>+</sup>.

#### 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):

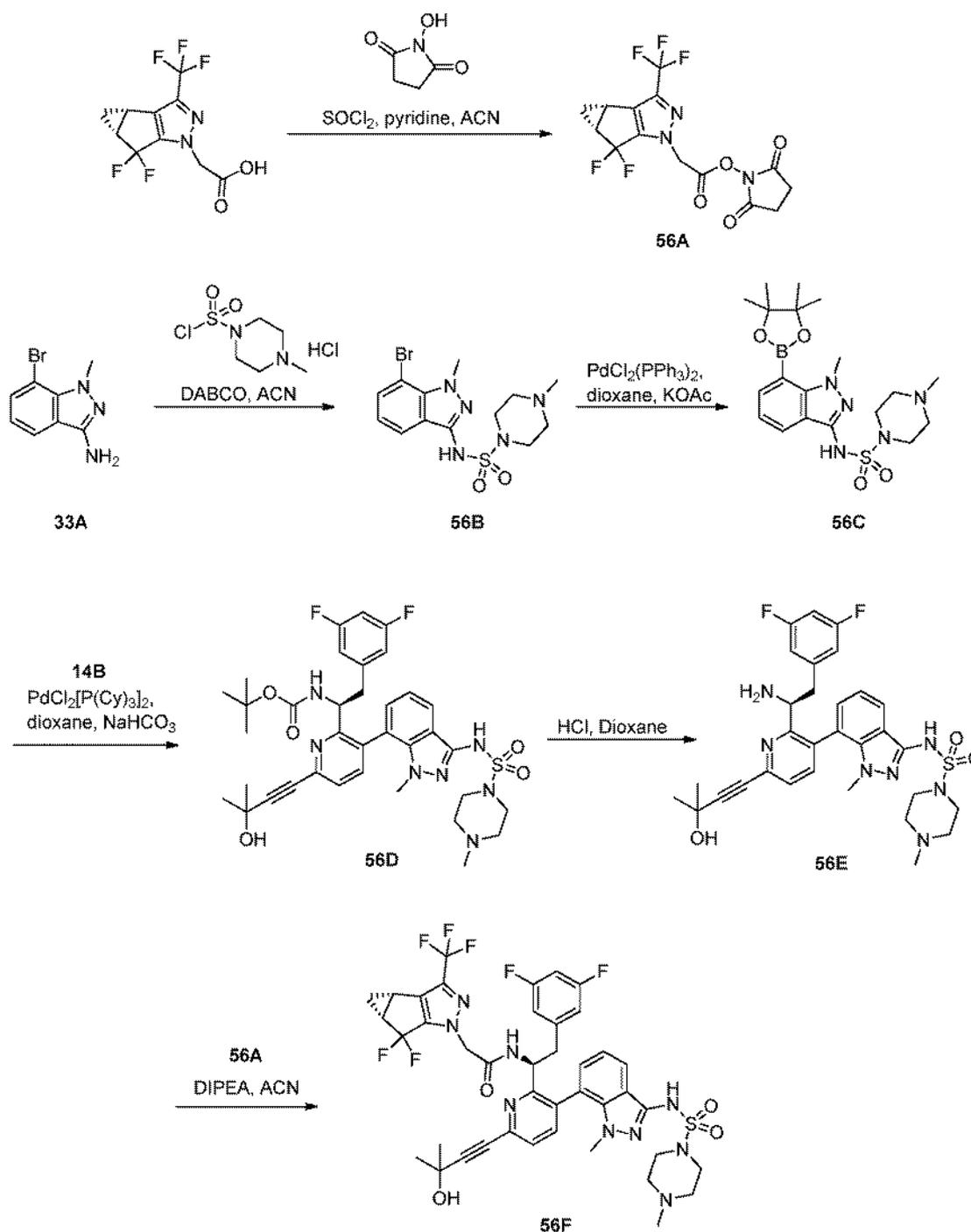
[0520] The title compound (**55B**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19F** of Example 19 utilizing **55A**. MS (*m/z*) 496.5 [M+H]<sup>+</sup>.

#### 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-((3S,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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

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  $-5\text{ }^\circ\text{C}$  thionyl chloride (0.439 mL, 6.02 mmol). After stirring at  $-5\text{ }^\circ\text{C}$  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<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to give the title compound. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) 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 °C for 3 h, the reaction was concentrated, diluted with water and extracted with ethyl acetate. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to give the title compound. MS (*m/z*) 387.97 [M+H]<sup>+</sup>.

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]<sup>+</sup>.

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):

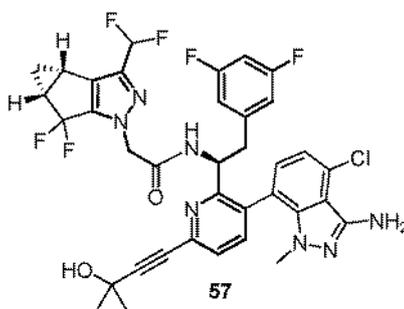
[0526] The title compound (56E) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound (14C) of Example 14 utilizing (S)-tert-butyl (2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(1-methyl-3-(4-methylpiperazine-1-sulfonamido)-1H-indazol-7-yl)pyridin-2-yl)ethyl)carbamate (56D). The resulting crude product was basified to pH~8 with 1M aqueous NaHCO<sub>3</sub> and extracted with

ethyl acetate. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, 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  $\mu$ L, 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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>)  $\delta$  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]<sup>+</sup>.

Example 57.

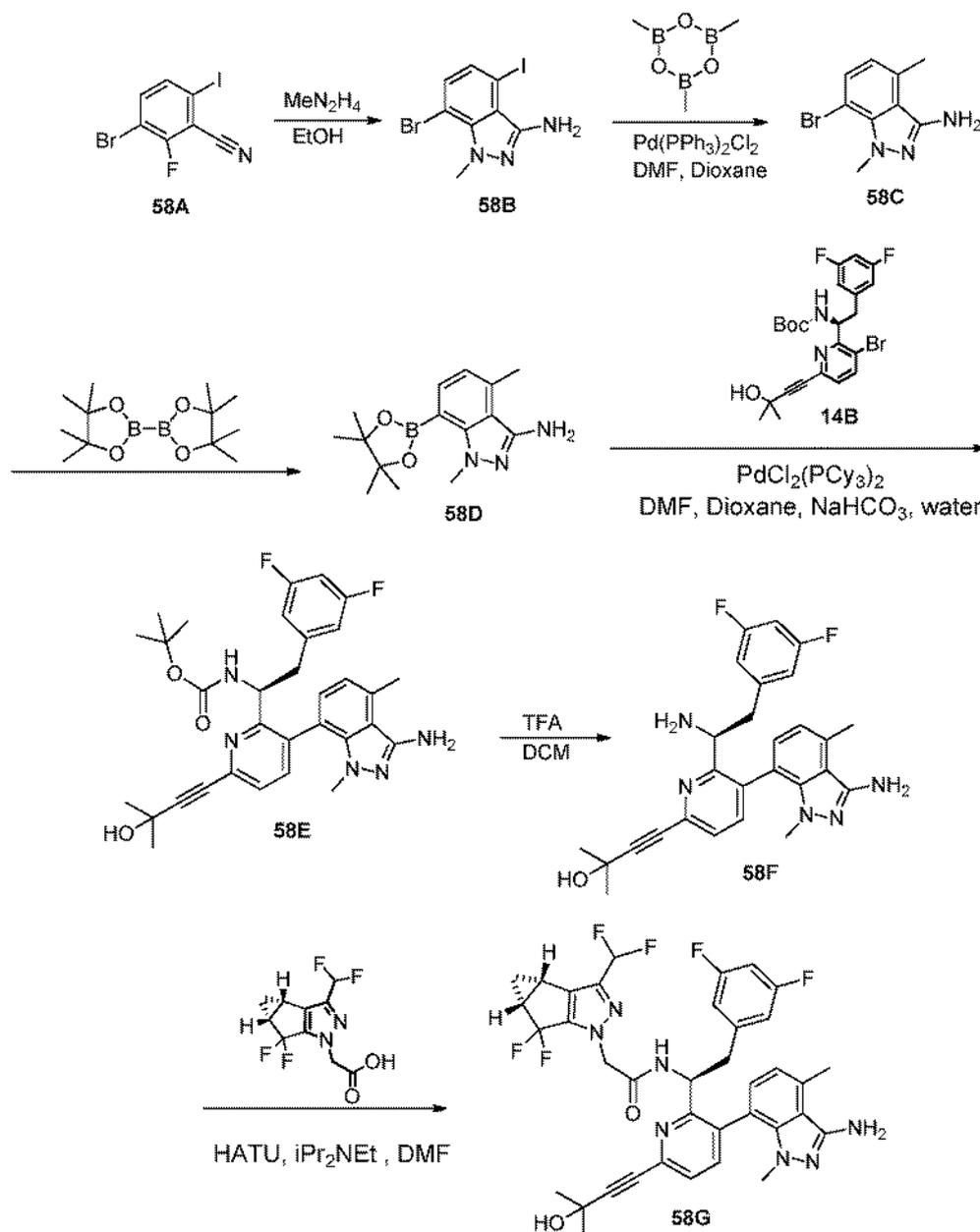


Synthesis of N-((S)-1-(3-(3-amino-4-chloro-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (57):

[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. <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$

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]<sup>+</sup>.

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]<sup>+</sup>.

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<sub>2</sub>CO<sub>3</sub> in water (8.5 ml), and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (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]<sup>+</sup>.

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]<sup>+</sup>.

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]<sup>+</sup>.

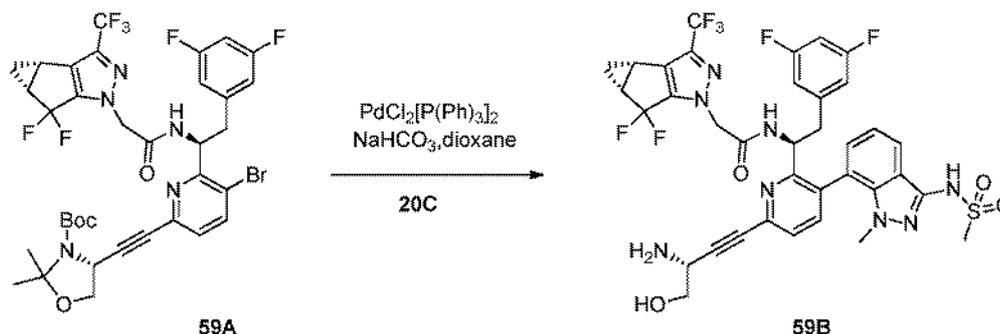
Synthesis of (S)-4-(5-(3-amino-1,4-dimethyl-1H-indazol-7-yl)-6-(1-amino-2-(3,5-difluorophenyl)ethyl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (58F):

[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]<sup>+</sup>.

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. <sup>1</sup>H NMR (Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

## Example 59.



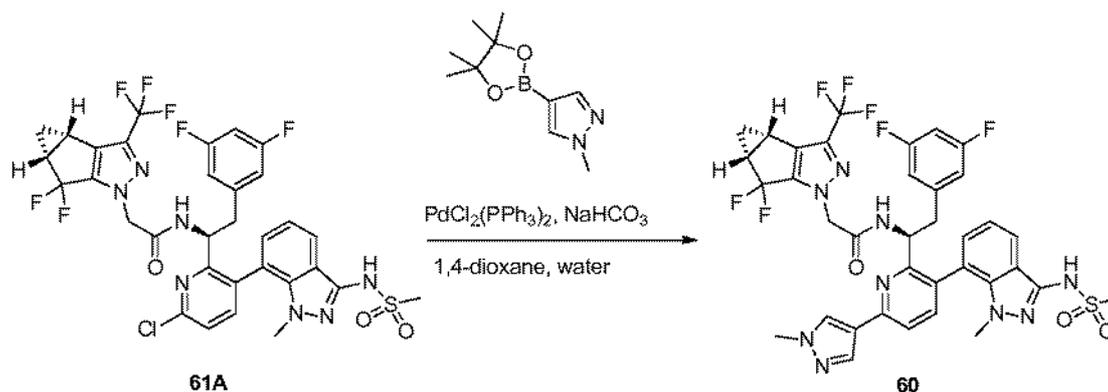
Synthesis of (R)-tert-butyl 4-((5-bromo-6-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-2-yl)ethynyl)-2,2-dimethyloxazolidine-3-carboxylate (**59A**):

[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<sub>2</sub>[P(Ph)<sub>3</sub>]<sub>2</sub> (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<sub>2</sub>SO<sub>4</sub>, 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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

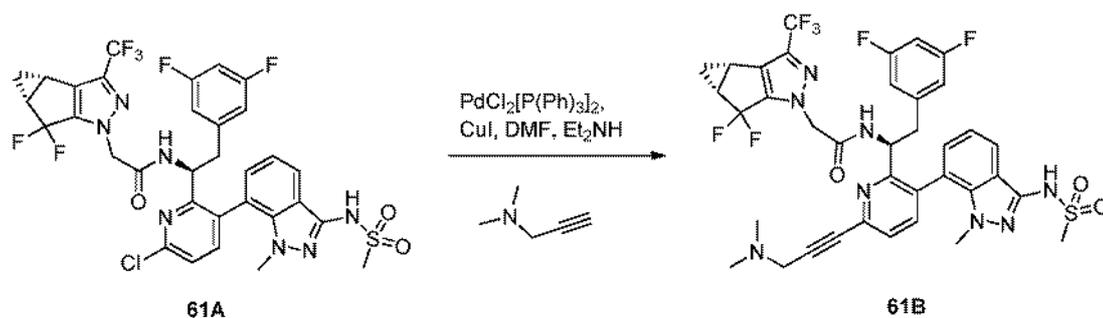
## Example 60.



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  $\text{PdCl}_2[\text{PPh}_3]_2$  (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  $\text{MgSO}_4$ , filtered and concentrated. The residue was purified by reverse phase HPLC to afford the title compound **60** as a mixture of atropisomers.  $^1\text{H NMR}$  (400 MHz, Methanol- $d_4$ )  $\delta$  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  $[\text{M}+\text{H}]^+$

Example 61.



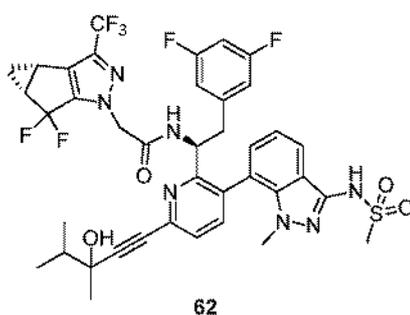
Synthesis of N-((S)-1-(6-chloro-3-(1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (61A).

[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]<sup>+</sup>.

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<sub>2</sub>[P(Ph)<sub>3</sub>]<sub>2</sub> (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. <sup>1</sup>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]<sup>+</sup>.

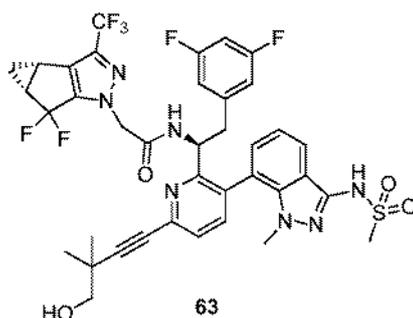
Example 62.



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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

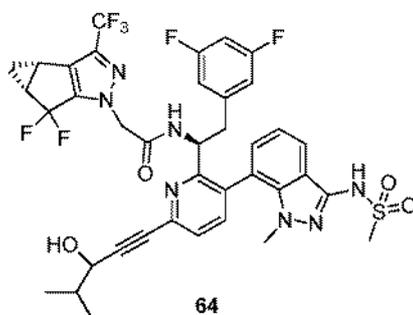
Example 63.



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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

Example 64.

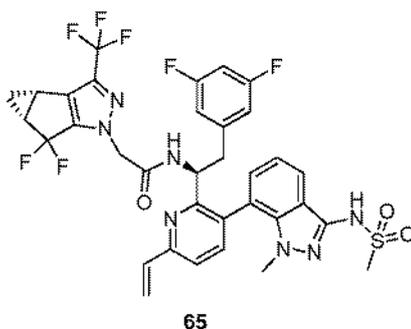


Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((1S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-

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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

Example 65.

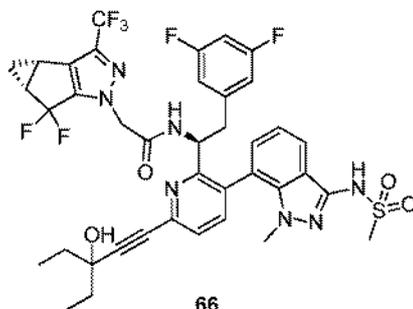


Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(3-(1-methyl-3-(1-methyl-1H-imidazole-4-sulfonamido)-1H-indazol-7-yl)-6-vinylpyridin-2-yl)ethyl)acetamide (65):

[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 °C 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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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  $[M+H]^+$ .

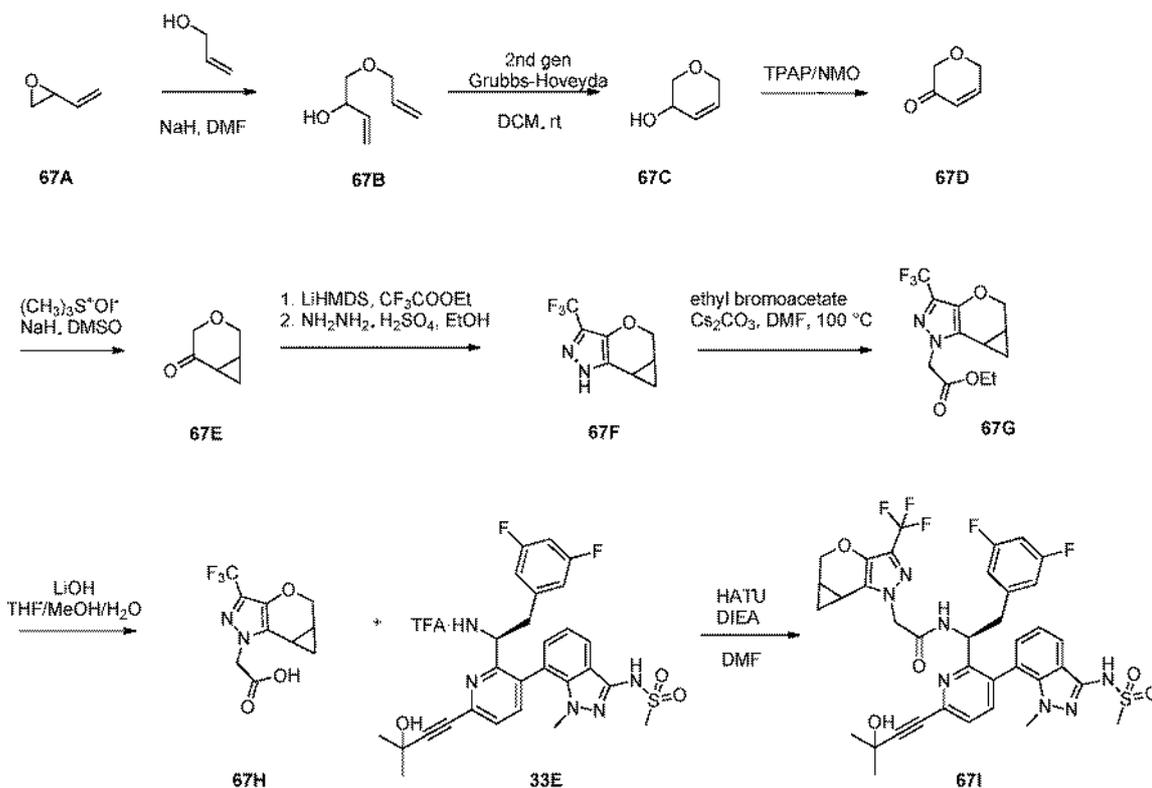
Example 66.



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.  $^1\text{H NMR}$  (400 MHz,  $\text{cd}_3\text{od}$ )  $\delta$  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<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column to yield the title compound **67B**. <sup>1</sup>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. <sup>1</sup>H NMR data: <sup>1</sup>H 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<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to give the title compound. <sup>1</sup>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<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo* to give the title compound which was used without further purification. MS (*m/z*) 209.06 [M+H]<sup>+</sup>.

[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]<sup>+</sup>.

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]<sup>+</sup>.

Synthesis of 2-(3-(trifluoromethyl)-5,5a,6,6a-tetrahydro-1H-cyclopropa[4,5]pyrano[3,2-c]pyrazol-1-yl)acetic acid (67H):

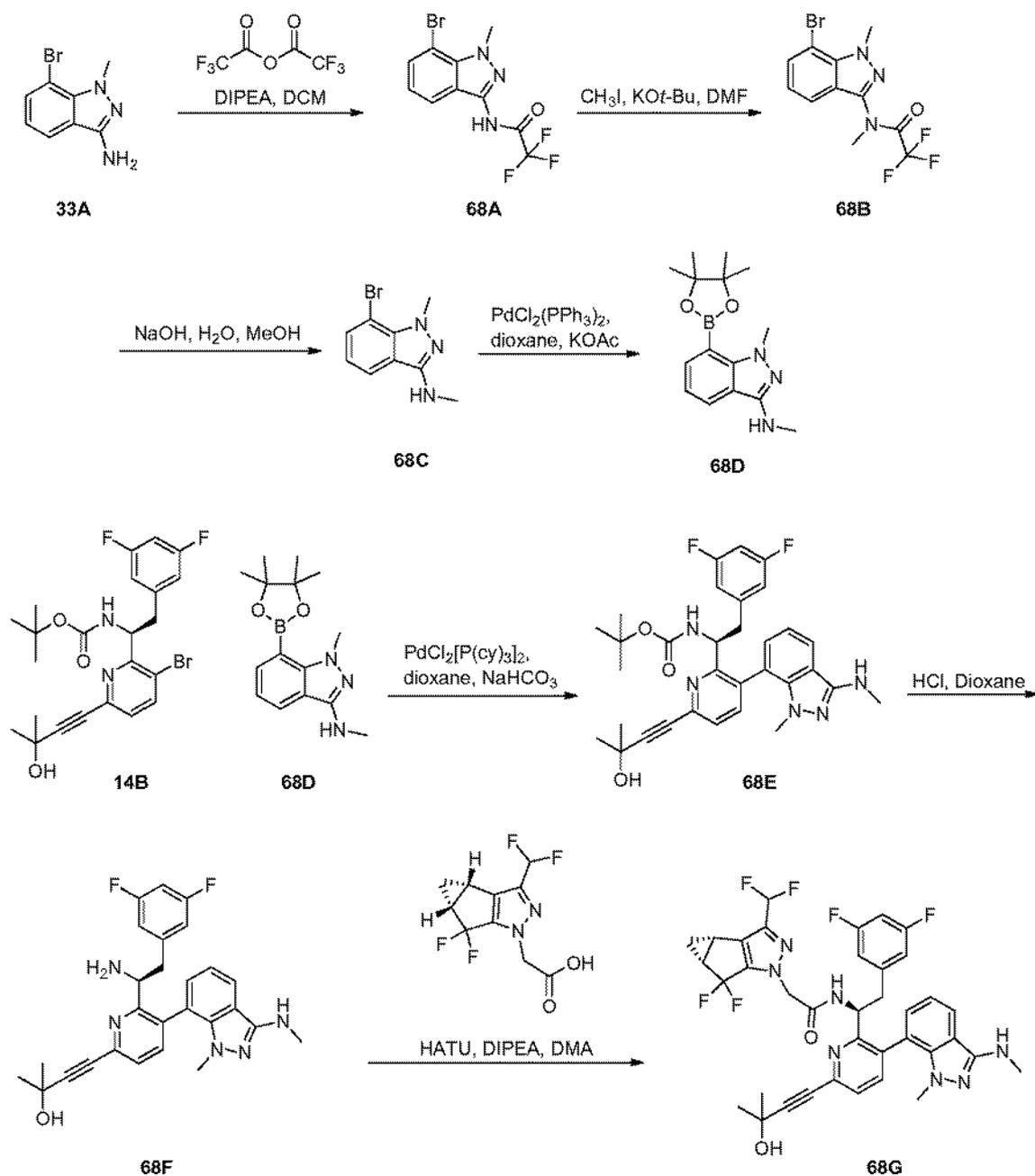
[0552] To a solution of compound **67G** (16 mg, 0.055 mmol) in a mixture of THF:water:MeOH (1 mL : 0.5 mL : 0.5 mL) was added solid LiOH monohydrate (7 mg, 0.165 mmol) at 0 °C. After stirring at room temperature for 10 min, the reaction mixture was poured

into EtOAc and the organic was washed with 2 N HCl. The organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo* to give the title compound which was used in the next step. MS (*m/z*) 263.04 [M+H]<sup>+</sup>.

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**. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

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<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo*, and purified by silica gel column

chromatography to give the title compound. <sup>1</sup>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<sub>2</sub>SO<sub>4</sub>, 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<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The crude product was used in the next step without further purification. MS (*m/z*) 240.15 [M+H]<sup>+</sup>.

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]<sup>+</sup>.

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]<sup>+</sup>.

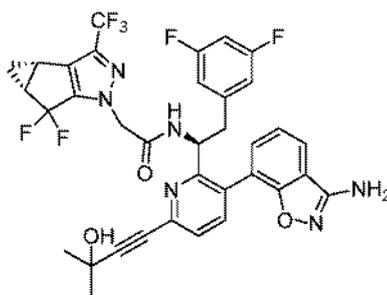
Synthesis of (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(1-methyl-3-(methylamino)-1H-indazol-7-yl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (68F):

[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]<sup>+</sup>.

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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

Example 69.



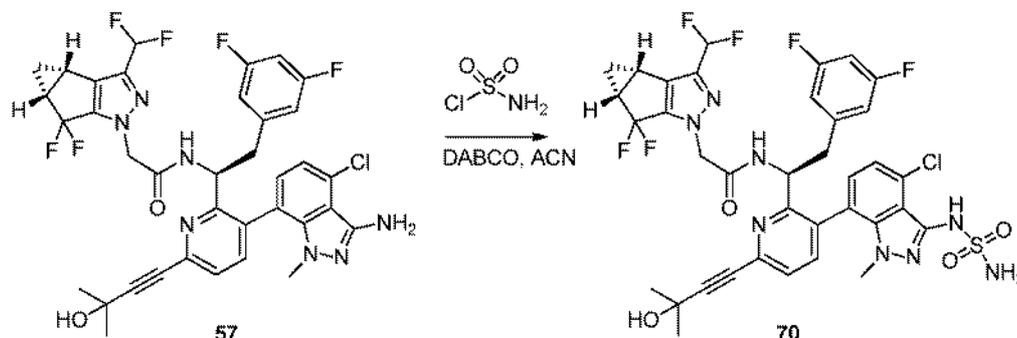
69

Synthesis of N-((S)-1-(3-(3-aminobenzodioxol-5-yl)propyl)-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)benzodioxol-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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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  $[M+H]^+$ .

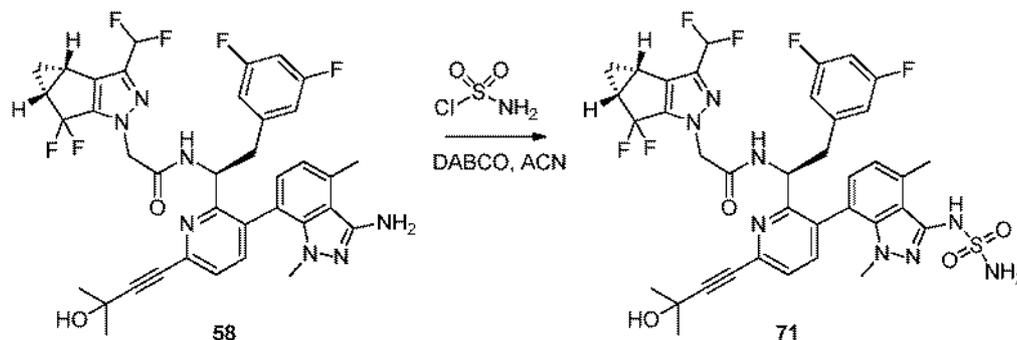
#### Example 70.



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  $-10\text{ }^{\circ}\text{C}$ . 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  $\text{KH}_2\text{PO}_4$  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.  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  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  $[M+H]^+$ .

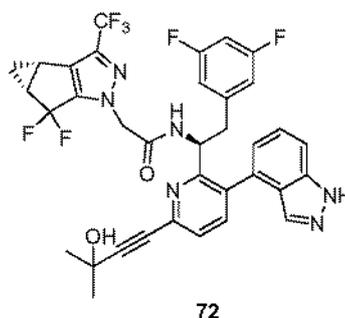
#### Example 71.



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**. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

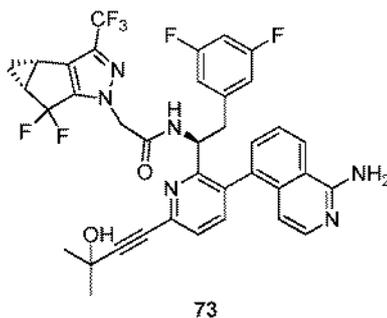
Example 72.



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. <sup>1</sup>H NMR (400 MHz, *cd*<sub>3</sub>od) 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]<sup>+</sup>.

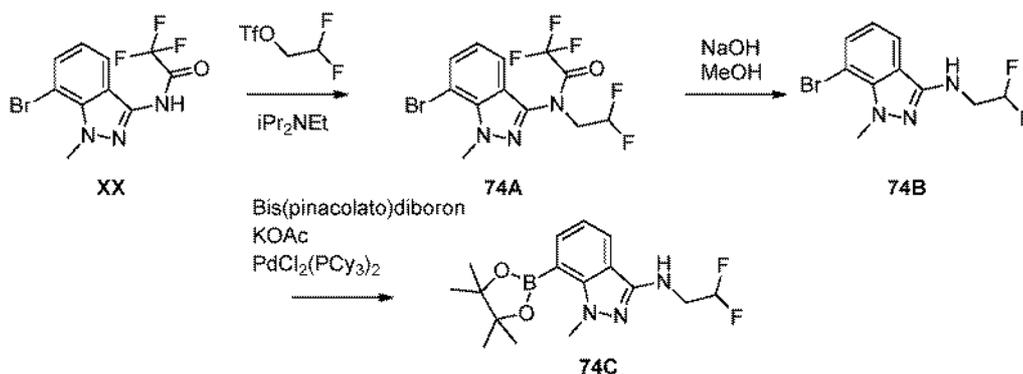
Example 73.



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.  $^1\text{H}$  NMR (400 MHz,  $\text{cd}_3\text{od}$ )  $\delta$  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  $[\text{M}+\text{H}]^+$ .

Example 74.



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  $i\text{Pr}_2\text{NEt}$  (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

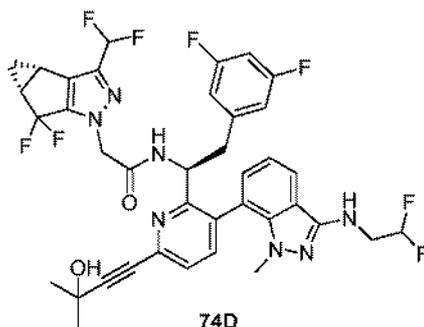
separated, dried, and removed in vacuo to provide the title compound which was used directly in the next reaction. MS ( $m/z$ ) 387.9  $[M+H]^+$ .

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  $[M+H]^+$ .

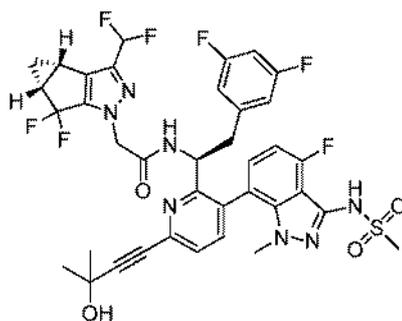


Synthesis of N-((S)-1-(3-(3-((2,2-difluoroethyl)amino)-1-methyl-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (74D):

[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.  $^1H$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  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.

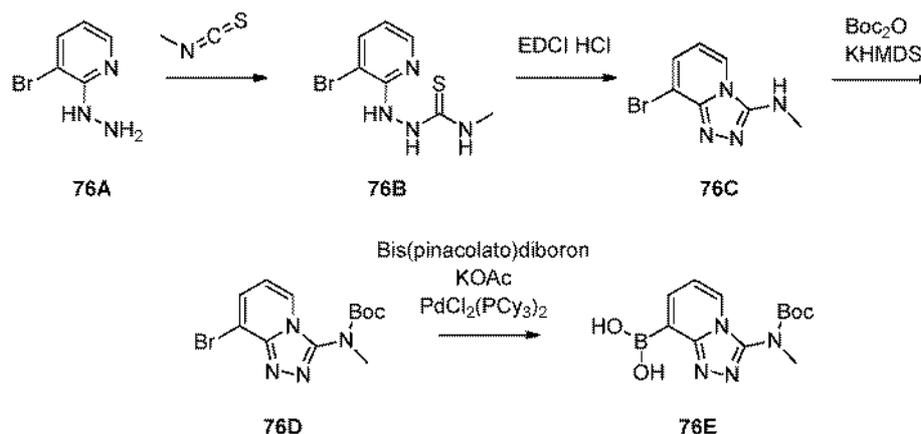


75

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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

Example 76.



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]<sup>+</sup>.

Synthesis of 8-bromo-N-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-amine (76C):

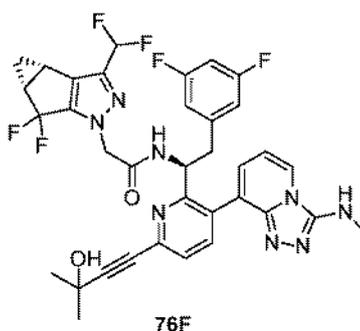
[0572] 2-(3-Bromopyridin-2-yl)-N-methylhydrazinecarbothioamide (1.6 g, 6.1 mmol) was treated with EDCI HCl (1.76 g, 9 mmol) in toluene and heated to 105 °C. After 1 hr, the hot toluene was decanted. To the residue was added H<sub>2</sub>O (50 ml). The slurry was mixed thoroughly and heated to 100 °C 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]<sup>+</sup>.

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]<sup>+</sup>.

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<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (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]<sup>+</sup>.

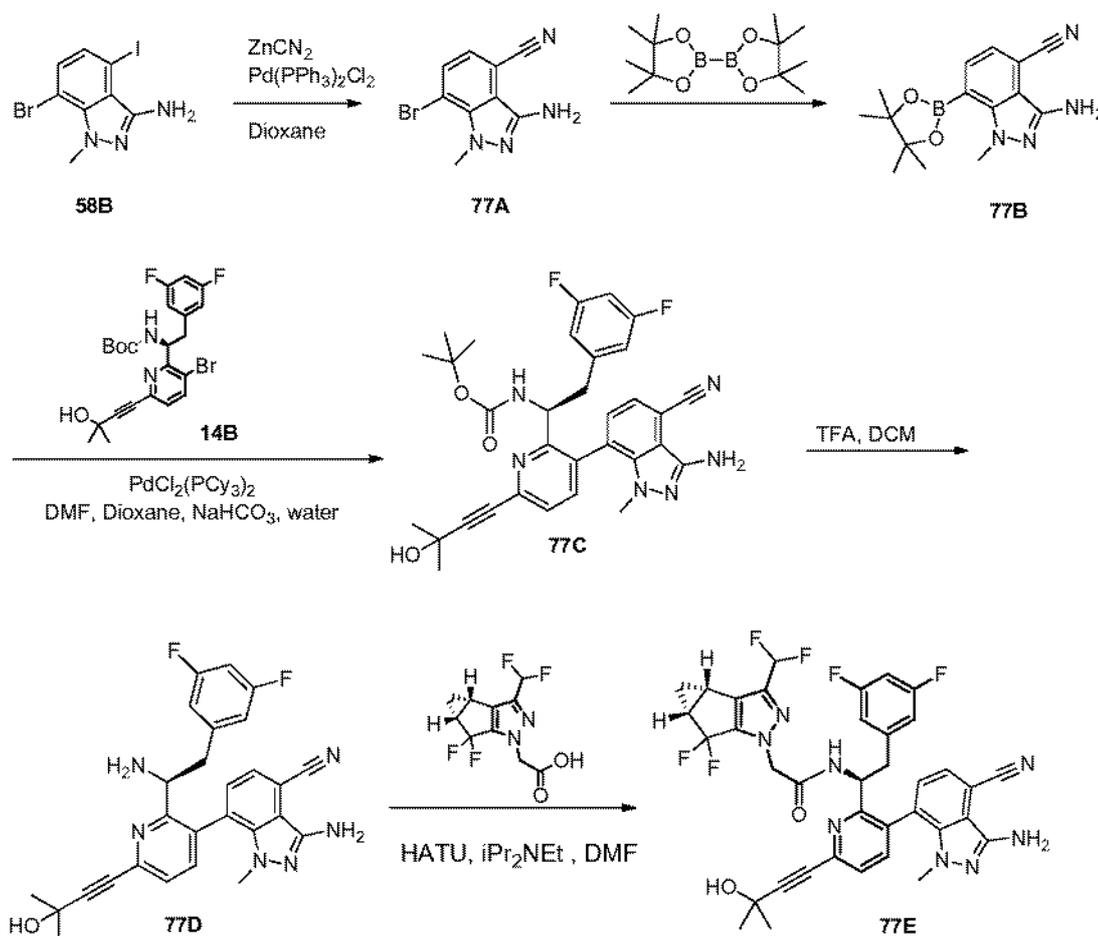


Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-

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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

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<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (600 mg, 0.9 mmol). The reaction mixture was stirred at 160 °C and ZnCN<sub>2</sub> (500 mg, 4.3 mmol) was added to the reaction. After an hour another aliquot of ZnCN<sub>2</sub> (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]<sup>+</sup>.

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]<sup>+</sup>.

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]<sup>+</sup>.

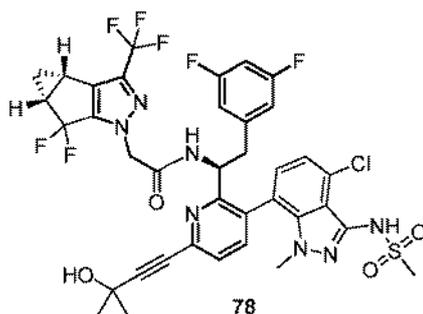
Synthesis of (S)-3-amino-7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazole-4-carbonitrile (77D):

[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]<sup>+</sup>.

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. <sup>1</sup>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]<sup>+</sup>.

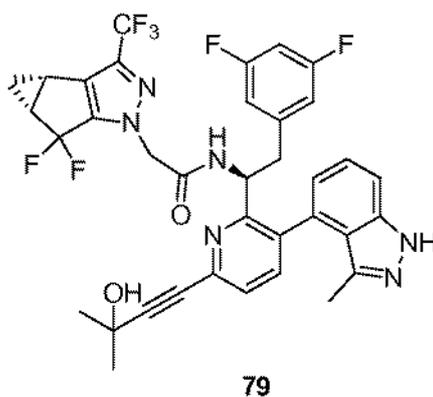
Example 78.



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. <sup>1</sup>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]<sup>+</sup>.

Example 79.

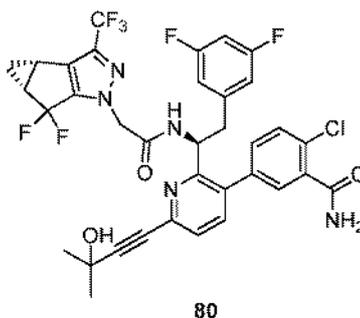


Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(3-methyl-1H-indazol-4-yl)pyridin-2-yl)ethyl)acetamide (79):

[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. <sup>1</sup>H NMR (400 MHz,

cd<sub>3</sub>od)  $\delta$  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]<sup>+</sup>.

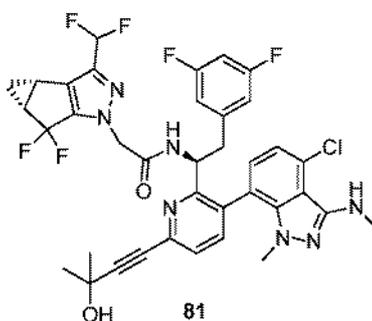
Example 80.



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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od)  $\delta$  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]<sup>+</sup>.

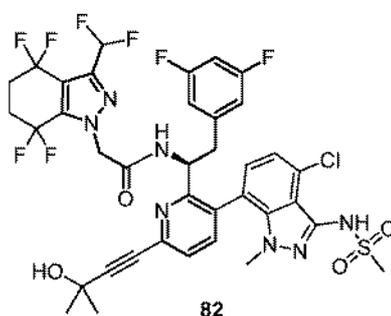
Example 81.



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**). <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

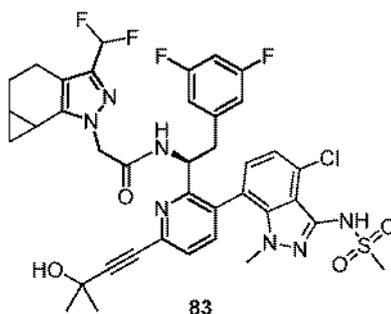
#### Example 82.



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. <sup>1</sup>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]<sup>+</sup>.

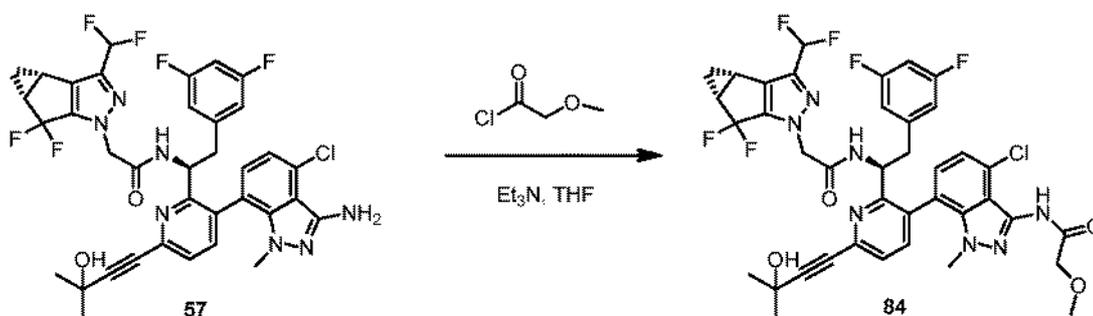
#### Example 83.



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. <sup>1</sup>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]<sup>+</sup>.

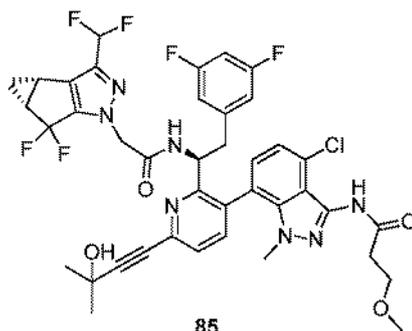
Example 84.



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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

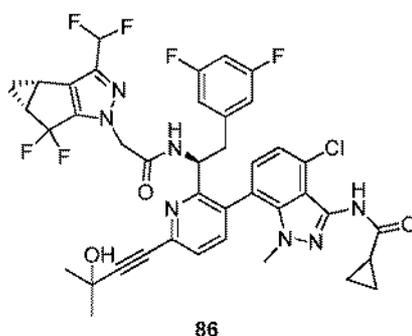
Example 85.



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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

Example 86.

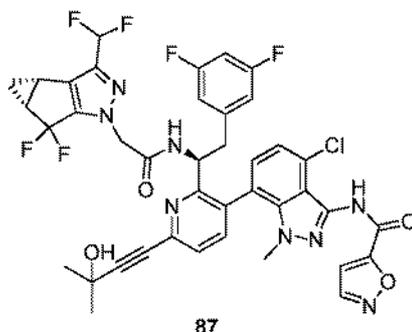


Synthesis of N-(4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)cyclopropanecarboxamide (86):

[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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

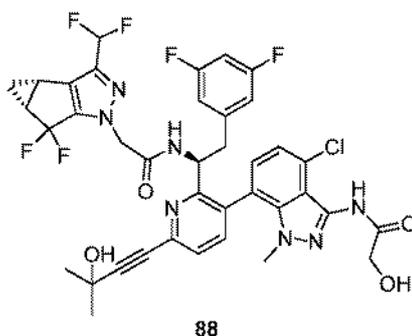
Example 87.



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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

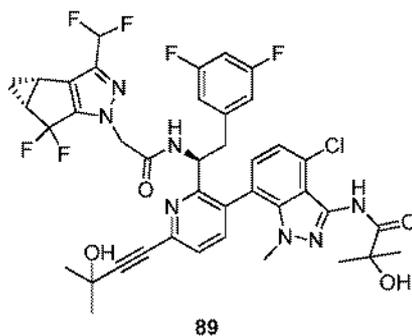
Example 88.



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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

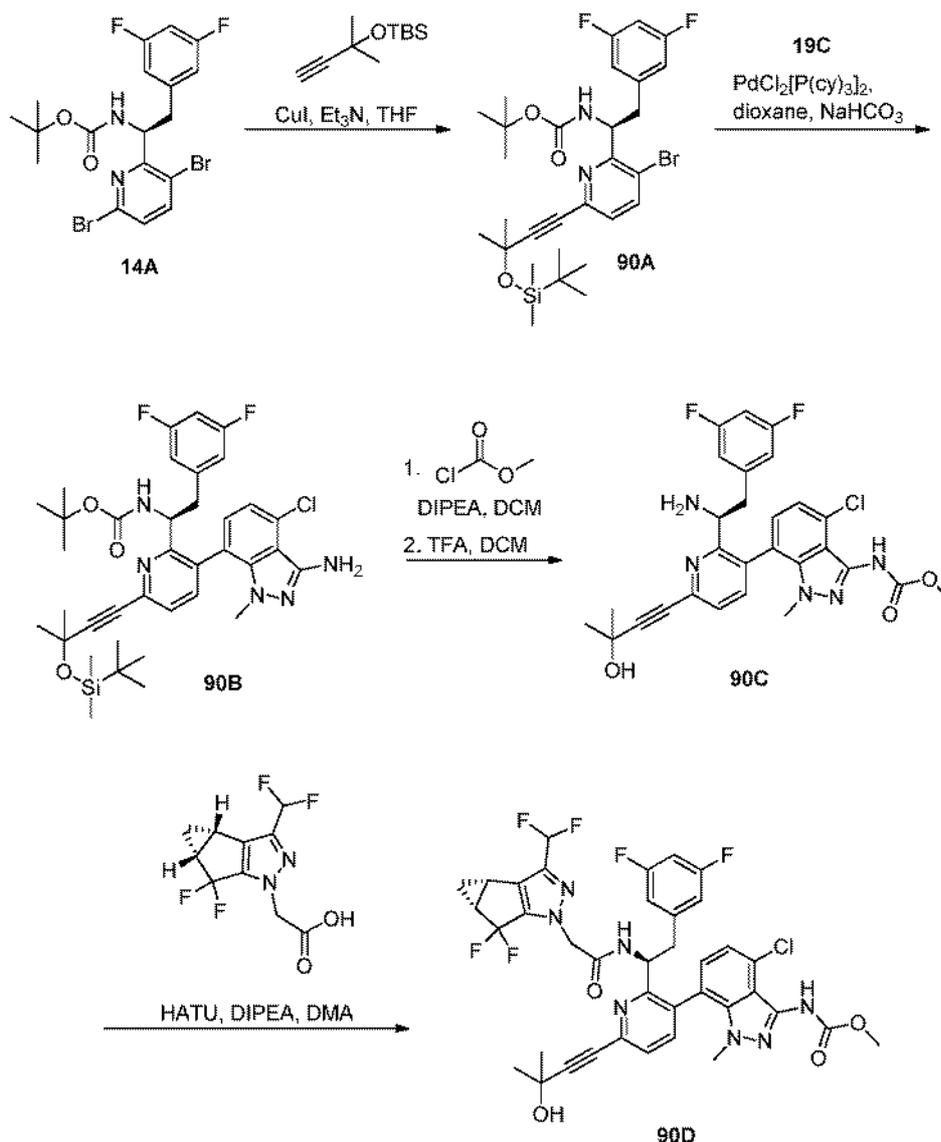
Example 89.



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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

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]<sup>+</sup>.

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]<sup>+</sup>.

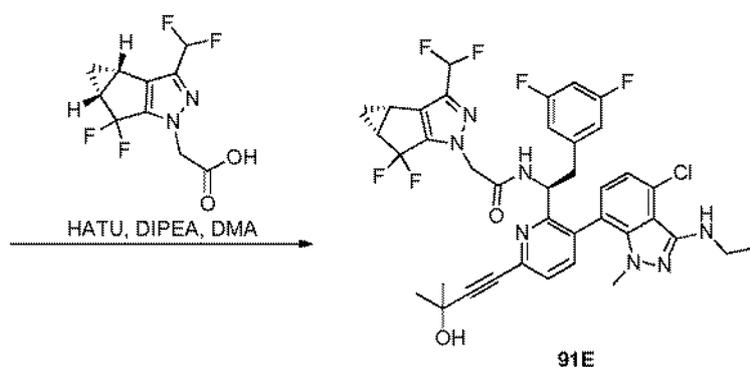
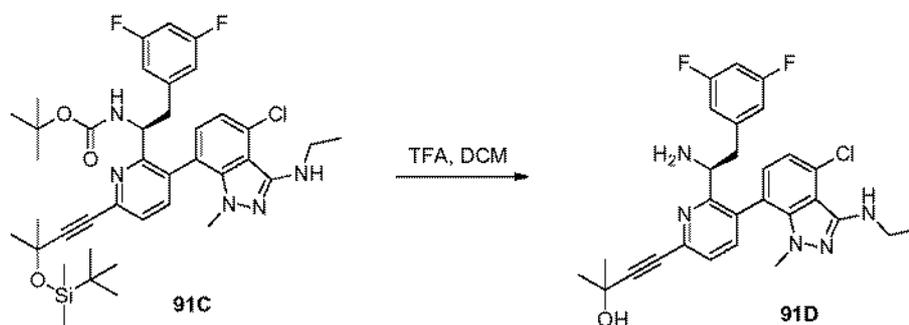
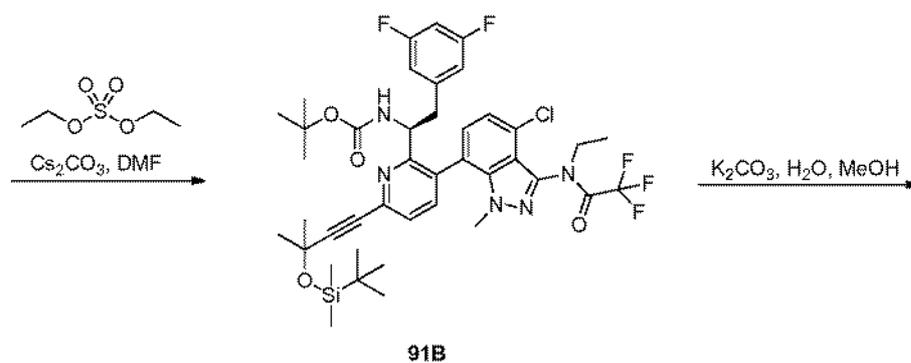
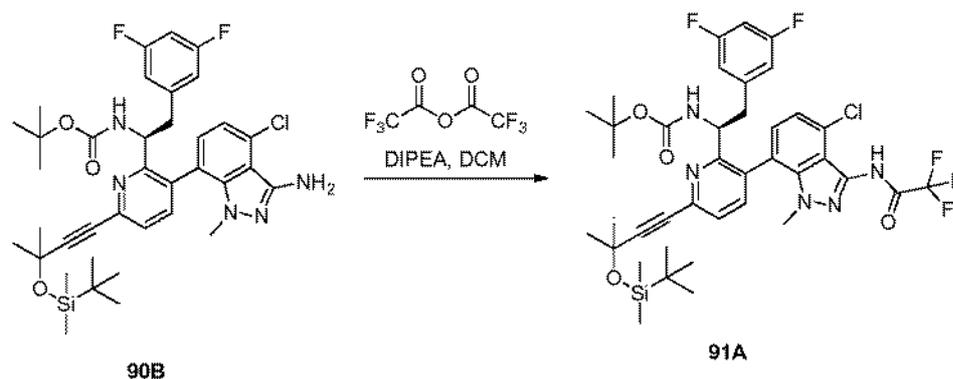
Synthesis of (S)-methyl (7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)carbamate (**90C**):

[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  $\mu$ l, 0.06 mmol) in dichloromethane (0.5 ml) was added methyl chloroformate (3.27  $\mu$ l, 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<sub>2</sub>CO<sub>3</sub>. The organic layer was washed with 0.5 M NaCl and the organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, 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]<sup>+</sup>.

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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>)  $\delta$  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]<sup>+</sup>.

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  $\mu$ l, 0.2 mmol), followed by trifluoroacetic anhydride (25.5  $\mu$ l, 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<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo*, and purified by silica gel chromatography to provide the title compound. MS (*m/z*) 806.04 [M+H]<sup>+</sup>.

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<sub>2</sub>SO<sub>4</sub>, 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<sub>2</sub>CO<sub>3</sub> (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<sub>2</sub>SO<sub>4</sub>, 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**).

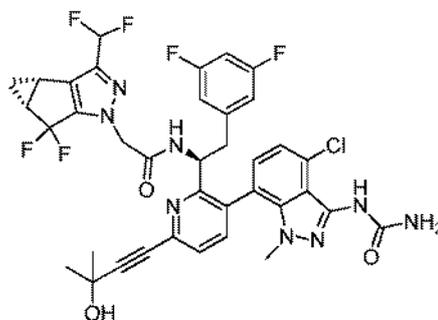
[0600] The title compound (**91D**) was prepared according to the method presented for the synthesis of compound (**90C**) of Example 90 utilizing (S)-tert-butyl (1-(6-(3-((tert-

butyldimethylsilyloxy)-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]<sup>+</sup>.

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**). <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

Example 92.



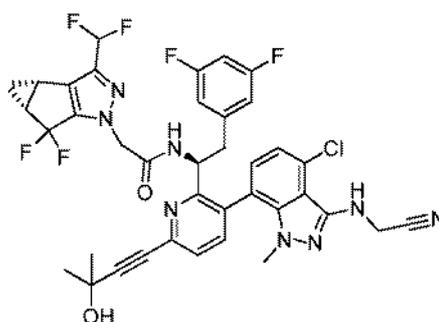
92

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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

Example 93.

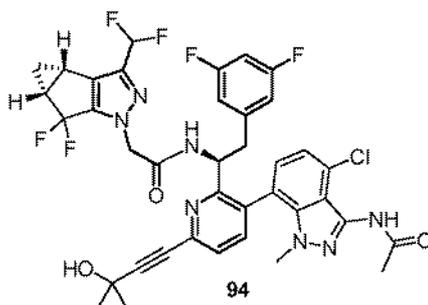


93

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**). <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

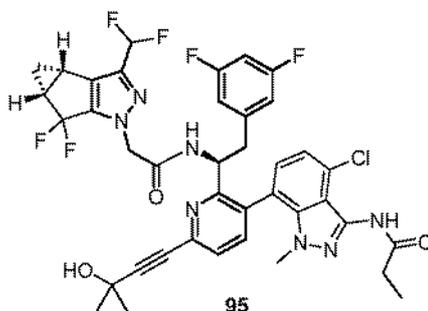
Example 94.



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.  $^1\text{H}$  NMR (Chloroform-*d*)  $\delta$ : 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.

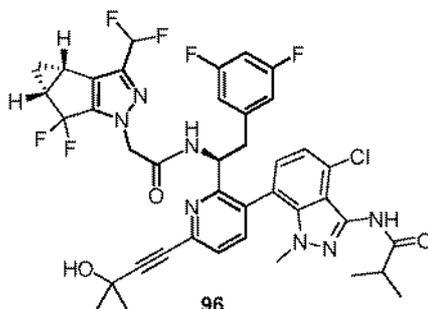


Synthesis of N-(4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)propionamide (**95**):

**[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.  $^1\text{H}$  NMR (Chloroform-*d*)  $\delta$ : 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]<sup>+</sup>.

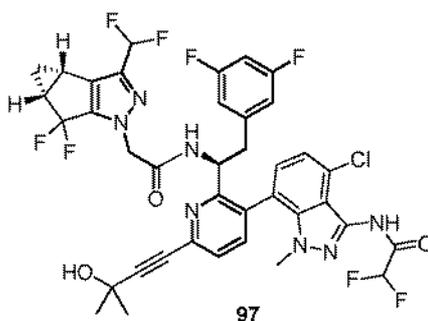
Example 96.



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. <sup>1</sup>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]<sup>+</sup>.

Example 97.

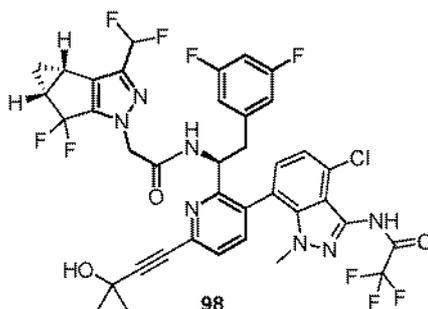


Synthesis of N-(4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)-2,2-difluoroacetamide (97):

[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.  $^1\text{H}$  NMR (Chloroform-*d*)  $\delta$ : 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] $^+$ .

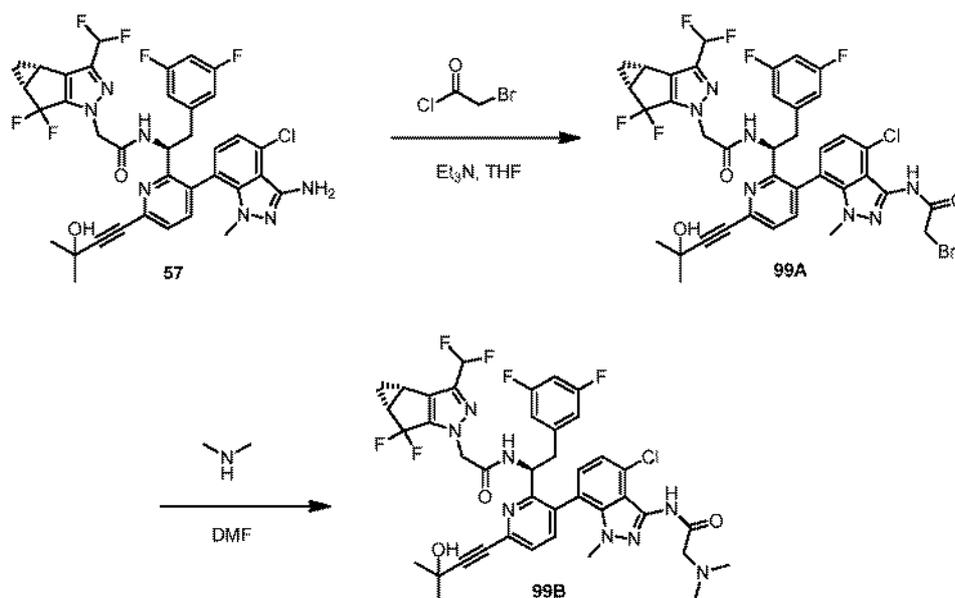
Example 98.



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.  $^1\text{H}$  NMR (Chloroform-*d*)  $\delta$ : 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.



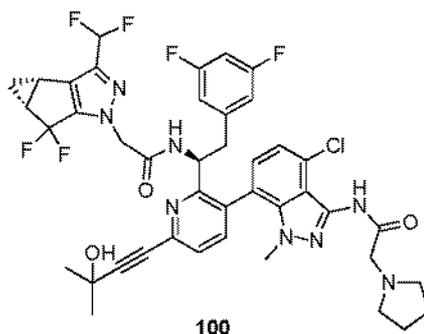
Synthesis of 2-bromo-N-(4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1-methyl-1H-indazol-3-yl)acetamide (99A):

**[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]<sup>+</sup>.

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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

Example 100.

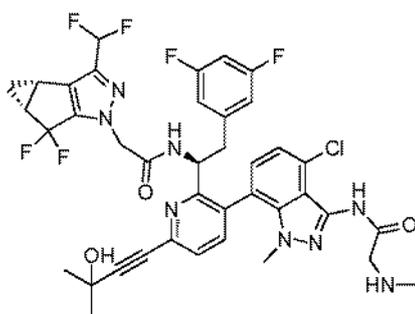


100

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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

Example 101.



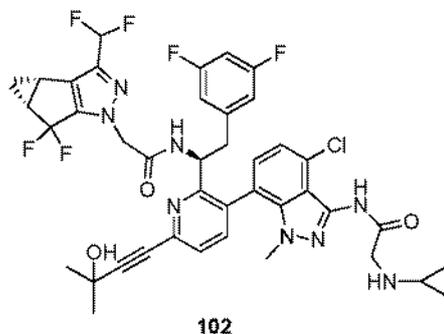
101

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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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  $[M+H]^+$ .

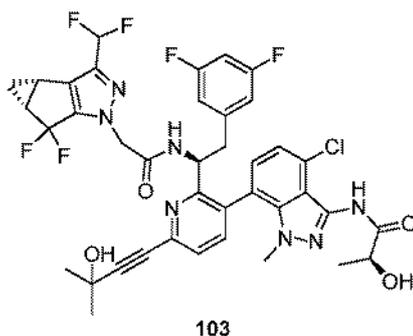
Example 102.



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.  $^1\text{H}$  NMR (400 MHz,  $\text{cd}_3\text{od}$ )  $\delta$  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  $[M+H]^+$ .

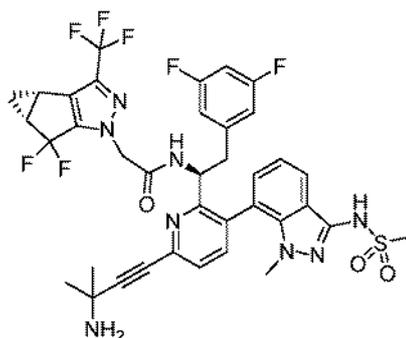
Example 103.



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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

Example 104.

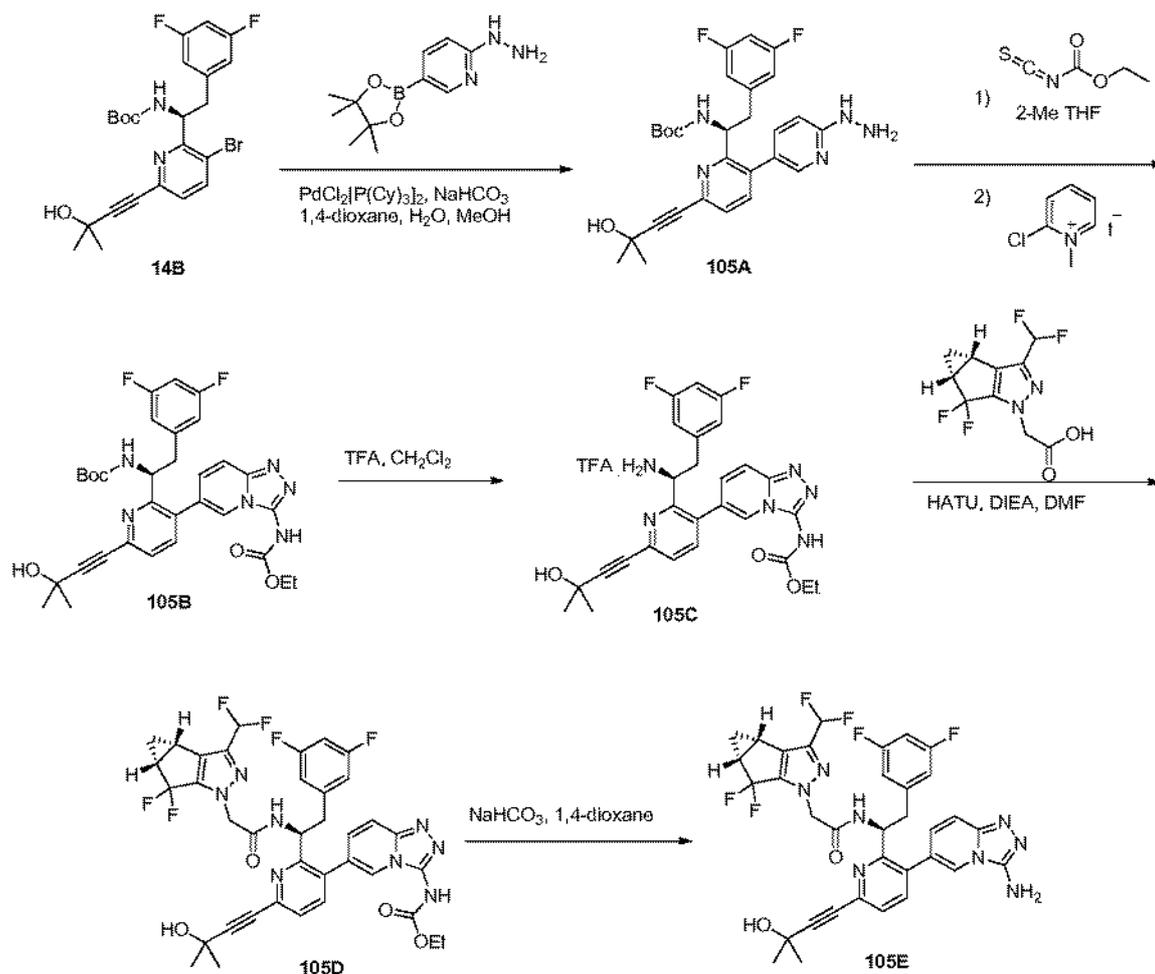


104

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. <sup>1</sup>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]<sup>+</sup>.

Example 105.



Synthesis of (S)-tert-butyl (2-(3,5-difluorophenyl)-1-(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 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  $\text{MgSO}_4$ , filtered and concentrated. The residue was purified by silica gel chromatography to afford the title compound **105A**. MS (m/z): 524.10  $[\text{M}+\text{H}]^+$ ;

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]<sup>+</sup>.

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]<sup>+</sup>.

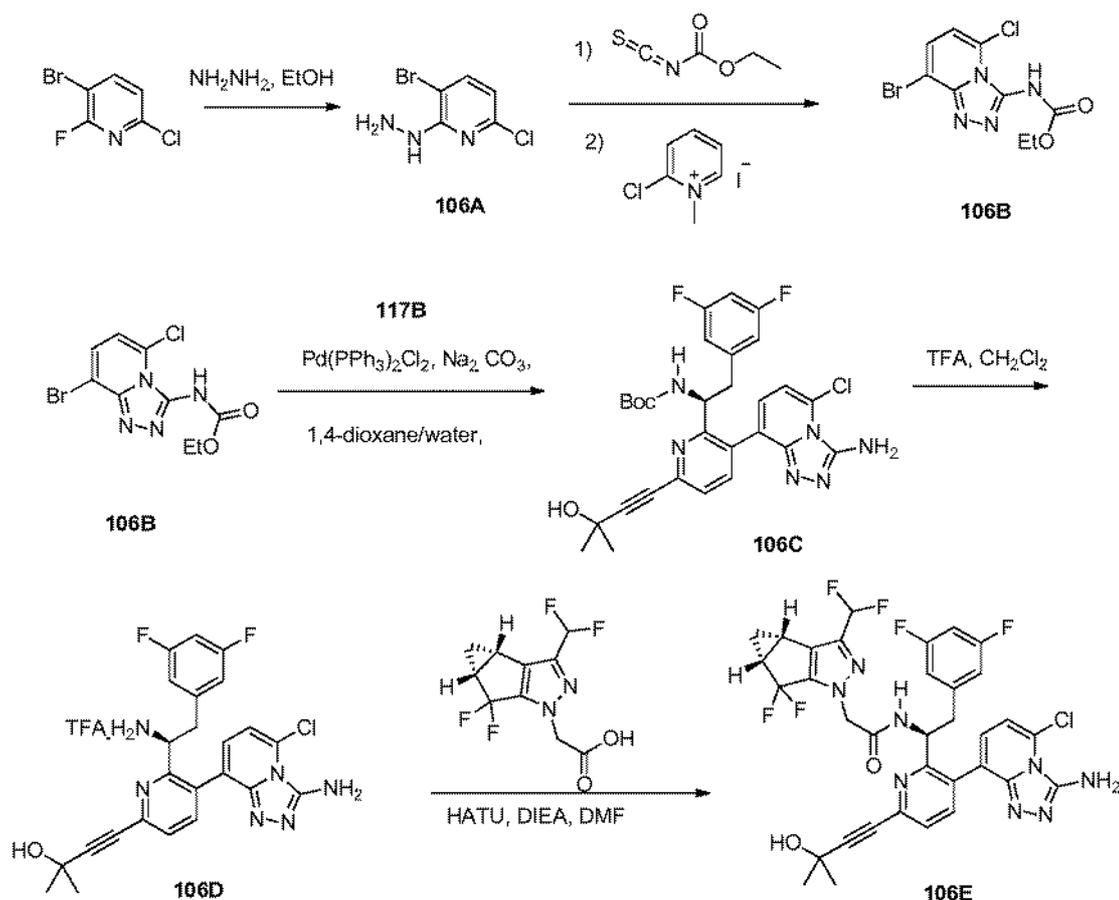
Synthesis of ethyl (6-(2-((S)-1-(2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)carbamate (**105D**):

[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]<sup>+</sup>.

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**. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>): 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]<sup>+</sup>.

## 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 stirred 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]<sup>+</sup>.

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]<sup>+</sup>.

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<sub>2</sub>[PPh<sub>3</sub>]<sub>2</sub> (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<sub>4</sub>, filtered and concentrated. The residue was purified by reverse phase HPLC to afford the title compound **106C**. MS (*m/z*): 583.01 [M+H]<sup>+</sup>

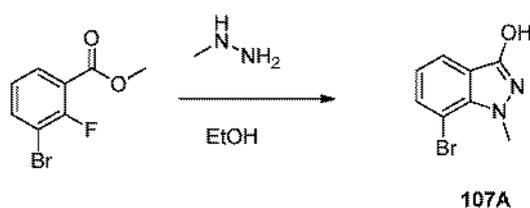
Synthesis of (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(3-amino-5-chloro-[1,2,4]triazolo[4,3-a]pyridin-8-yl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (**106D**):

**[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]<sup>+</sup>.

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**. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>): 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]<sup>+</sup>.

Example 107.

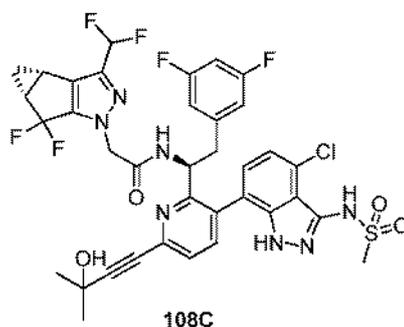


Synthesis of 7-bromo-1-methyl-1H-indazol-3-ol (**107A**):

**[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]<sup>+</sup>.



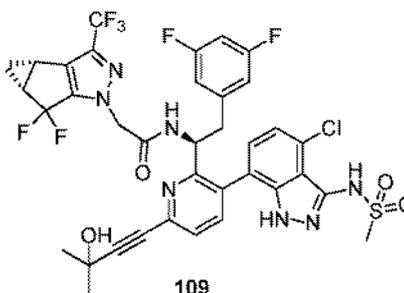
added drop wise methanesulfonyl chloride (156 mg, 1.3 mmol). The ice bath was removed immediately after the addition and the reaction was warmed to room temperature and stirred for 2h. The reaction was washed with water, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product 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  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The product was purified by silica chromatography to give the title compound. MS ( $m/z$ ) 325.9  $[\text{M}+\text{H}]^+$ .



Synthesis of N-((S)-1-(3-(4-chloro-3-(methylsulfonylamino)-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  $[\text{M}+\text{H}]^+$ . HPLC retention time 6.96 min (2-98% acetonitrile: water with 0.1% trifluoroacetic acid, 8.5 min gradient on a Phenomenex Kinetex C18 column).

Example 109.

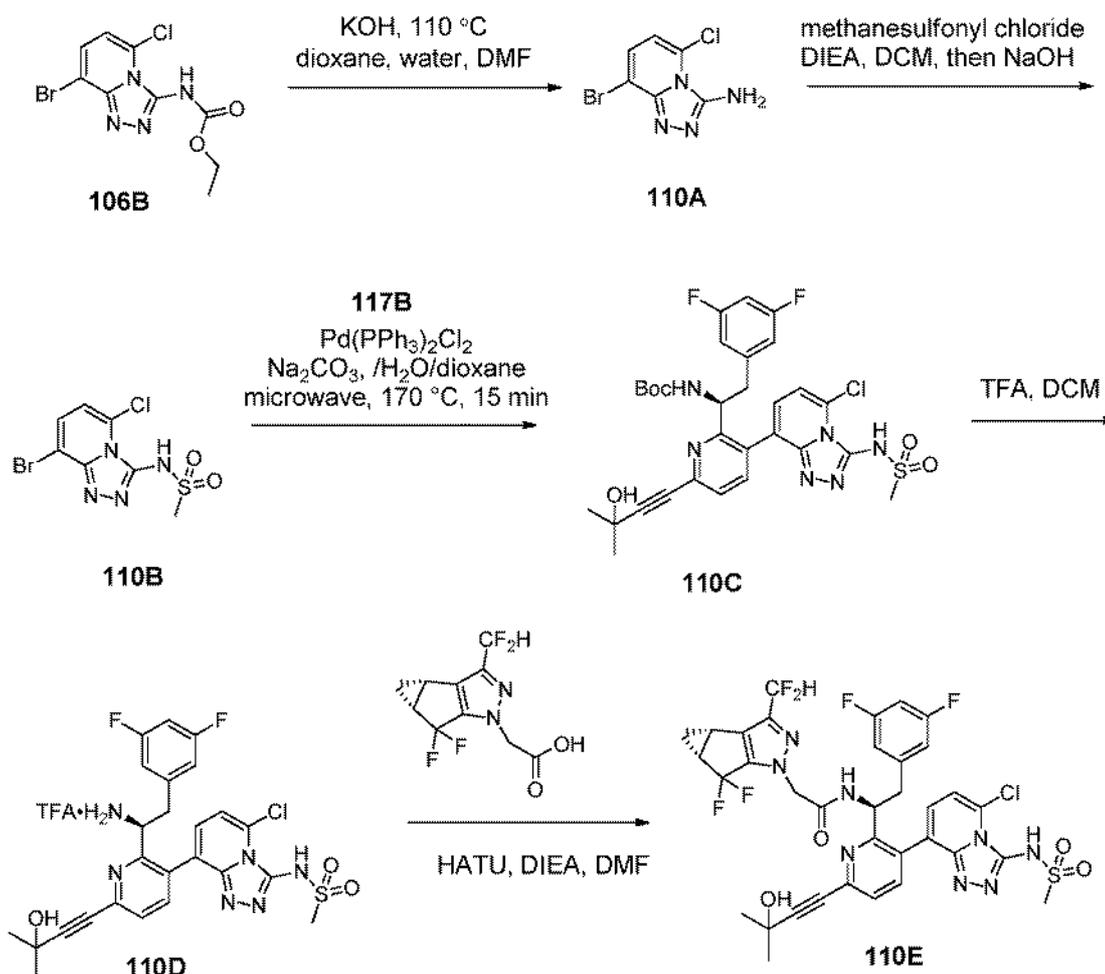


Synthesis of N-((S)-1-(3-(4-chloro-3-(methylsulfonylamino)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-

(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 Phenomenex 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]<sup>+</sup>.

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]<sup>+</sup>.

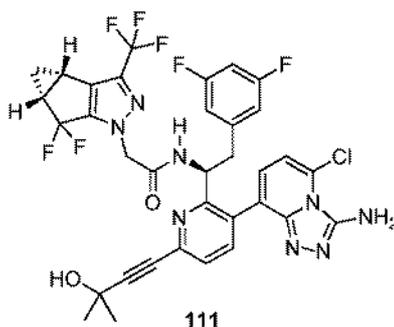
Synthesis of (S)-N-(8-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-5-chloro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methanesulfonamide TFA salt (110D):

[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]<sup>+</sup>.

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]<sup>+</sup>.

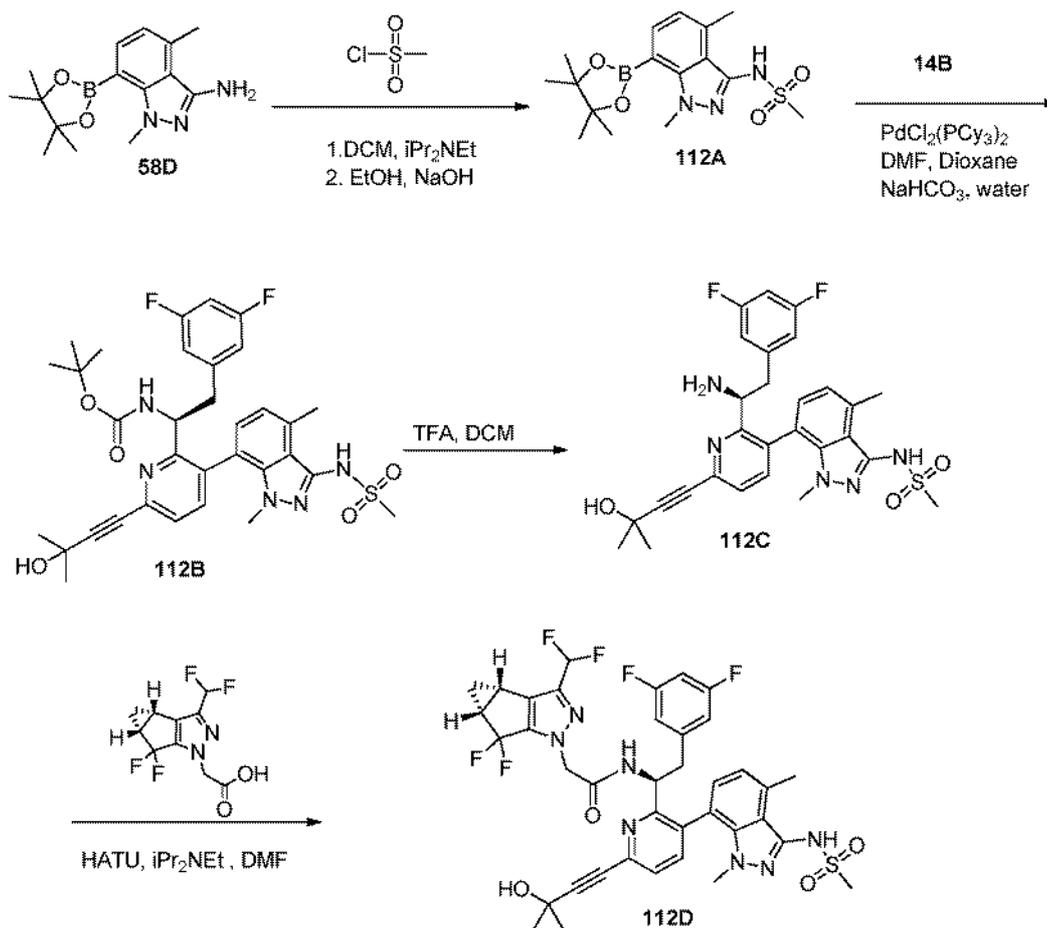
Example 111.



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**. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>): 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]<sup>+</sup>

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-(methanesulfonamido)-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  $[M+H]^+$ .

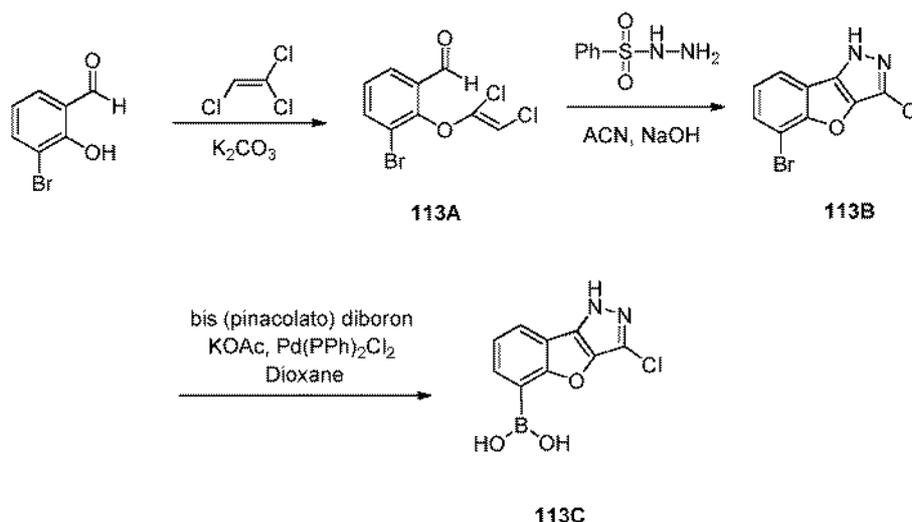
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-1,4-dimethyl-1H-indazol-3-yl)methanesulfonamide (112C):

[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. <sup>1</sup>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]<sup>+</sup>.

Example 113.



Synthesis of (Z)-3-bromo-2-((1,2-dichlorovinyl)oxy)benzaldehyde (113A):

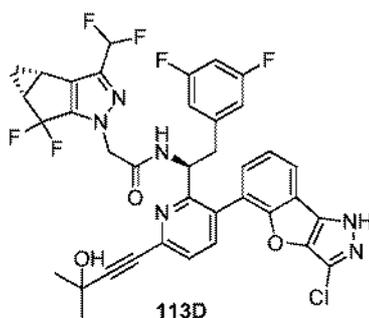
**[0642]** Trichloroethylene (2.68 mL, 30 mmol) was added drop wise over a period of 30 min to a solution of 3-bromo-2-hydroxybenzaldehyde (2 g, 9.9 mmol) suspended with K<sub>2</sub>CO<sub>3</sub> (4.1 g, 30 mmol) in DMF (8 mL) at 60 °C under N<sub>2</sub>. The reaction was stirred for 15 h then cooled 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<sub>2</sub>O. The organic layer was dried over MgSO<sub>4</sub>, 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**):

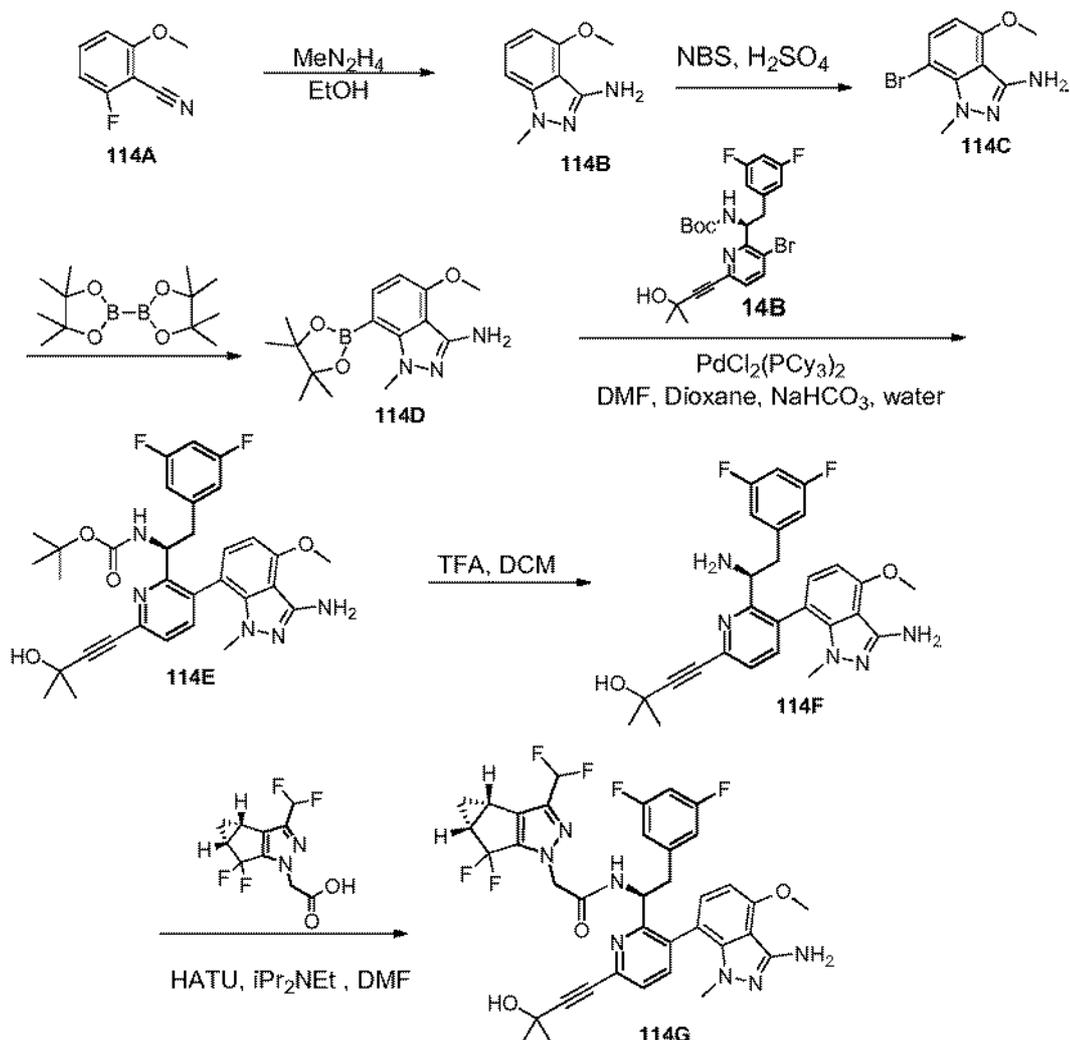
[0644] To **113B** (200 mg, 0.73 mmol) in dioxane (5 mL) was added bis(pinacolato)diboron (262 mg, 1 mmol), potassium acetate (0.144 g, 1 mmol), and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (26 mg, 0.03 mmol). The reaction mixture sealed and heated to 100 °C for 1h. The reaction was cooled to room temperature and telescoped to the next reaction. MS (*m/z*) 237.1 [M+H]<sup>+</sup>.



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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

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 [ $M+H$ ]<sup>+</sup>.

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<sub>2</sub>SO<sub>4</sub> (35 mL) and cooled to 0 °C 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<sub>3</sub> 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 [ $M+H$ ]<sup>+</sup>.

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  $[M+H]^+$ ).

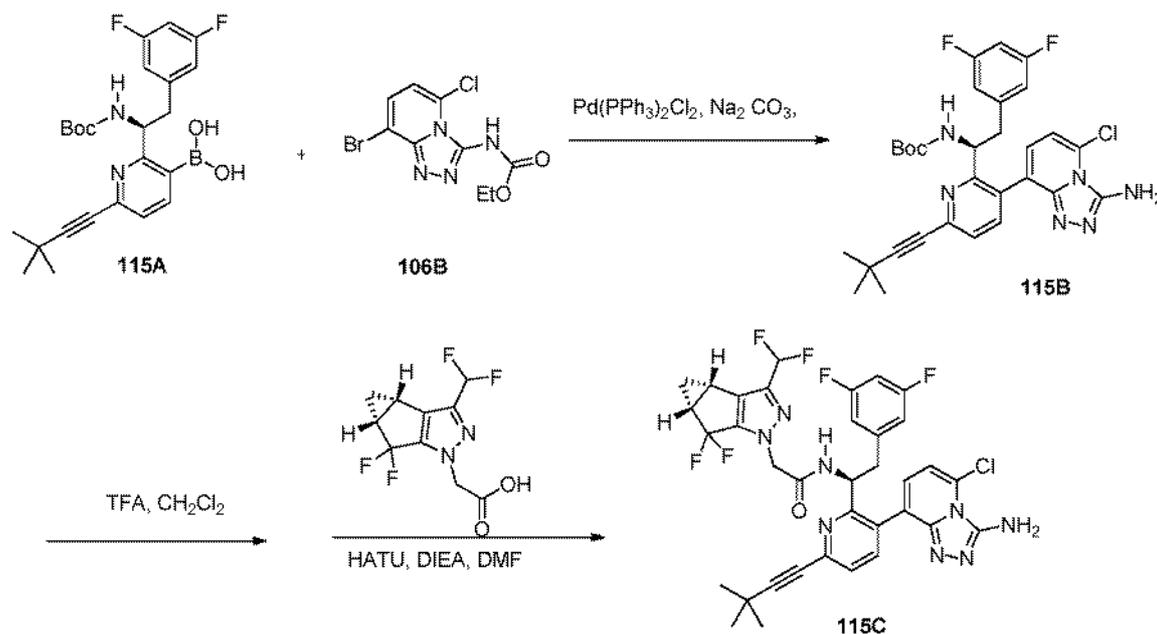
Synthesis of (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(3-amino-4-methoxy-1-methyl-1H-indazol-7-yl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (**114F**):

[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.  $^1\text{H}$  NMR (Methanol- $d_4$ )  $\delta$ : 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]<sup>+</sup>.

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**):

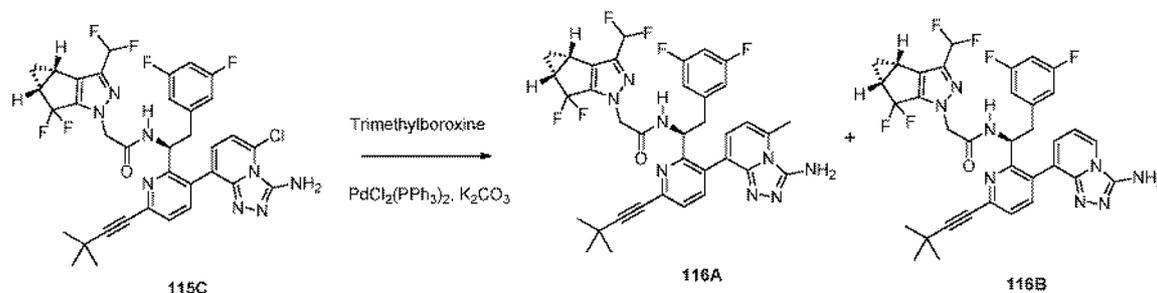
[0653] The title compound (**115B**) was prepared according to the method presented for the synthesis of compound **106C** of Example 106 utilizing compound **115A** and compound **106B**. MS (*m/z*): 581.14 [M+H]<sup>+</sup>.

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**. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>): 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.

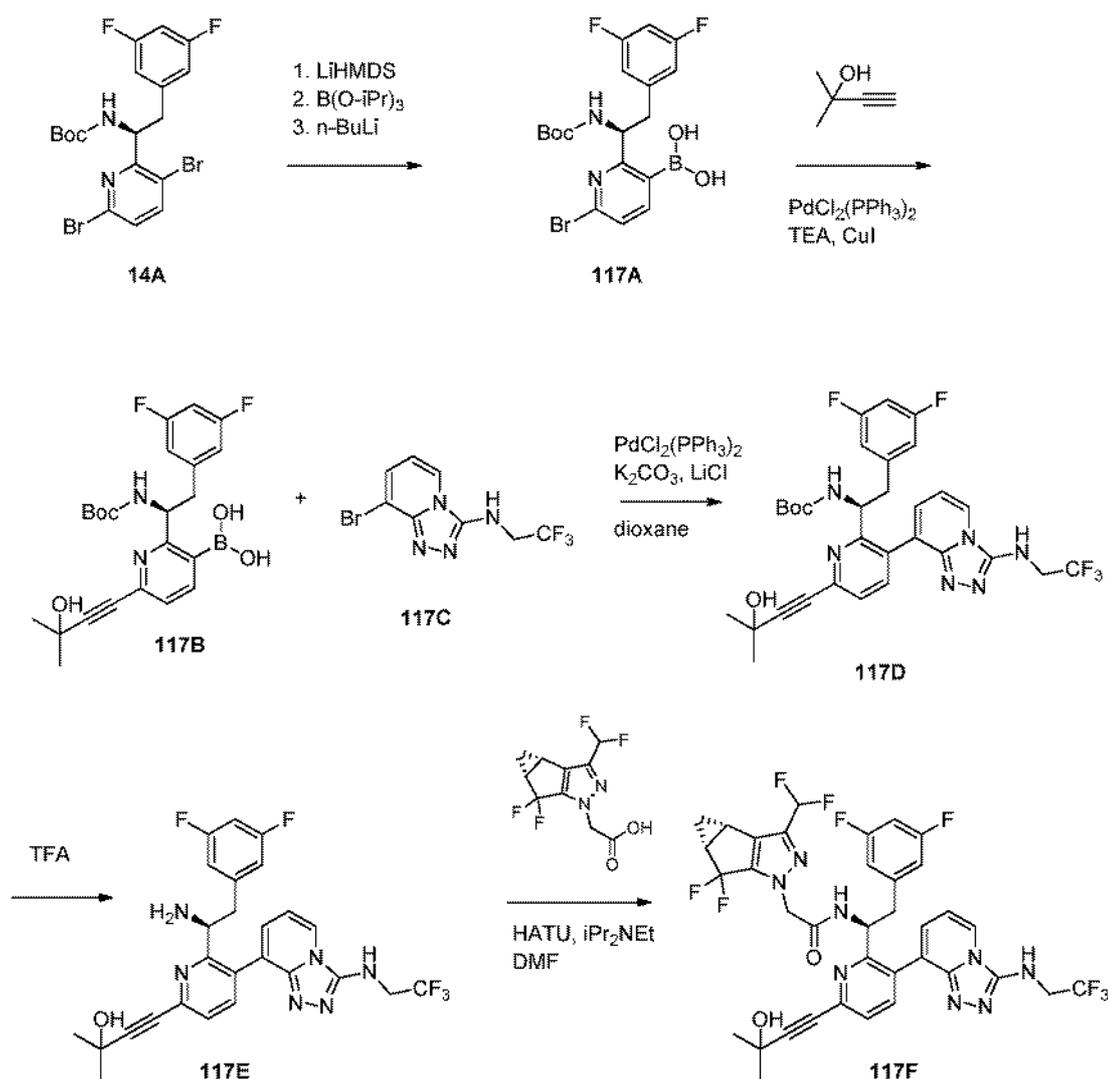


Synthesis of N-((S)-1-(3-(3-amino-5-methyl-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-6-(3,3-dimethylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**116A**):

**[0655]** In a microwave tube were charged with compound **115C** (15mg, 0.02 mmol), trimethylboroxine (9  $\mu$ L, 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  $^{\circ}C$  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- $d_4$ )  $\delta$  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<sub>4</sub>Cl (75mL). Additional 2-MeTHF (25 mL) was added and the organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>,

filtered, and concentrated *in vacuo*. The crude product was taken to the next step without further purification. MS (*m/z*) 456.87 [M+H]<sup>+</sup>.

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<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (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<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo*, and purified by silica chromatography to give the title compound. MS (*m/z*) 460.11 [M+H]<sup>+</sup>.

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]<sup>+</sup>.

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<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (2 mg, 5 mol%), K<sub>2</sub>CO<sub>3</sub> (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]<sup>+</sup>.

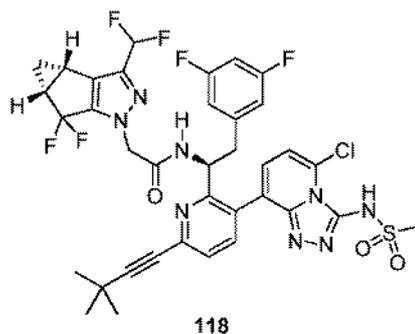
Synthesis of (S)-4-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(3-((2,2,2-trifluoroethyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)pyridin-2-yl)-2-methylbut-3-yn-2-ol (117E):

[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 (**117E**):

[0662] The title compound (**117F**) was prepared according to the method presented for the synthesis of compound **37E** of Example 37 utilizing compound **117E**. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

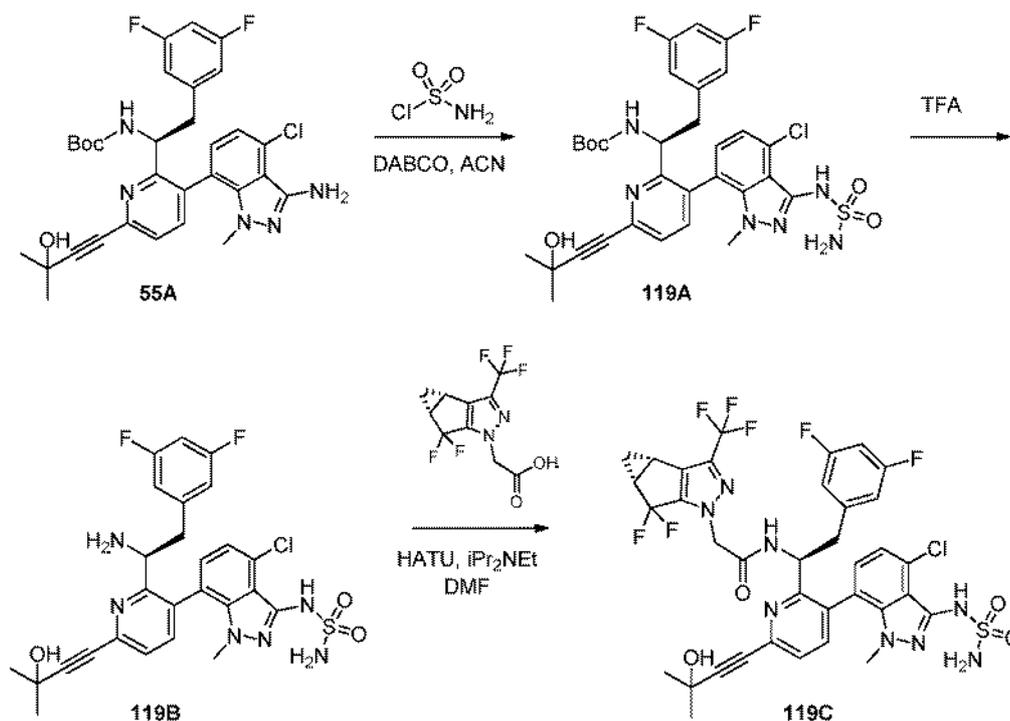
Example 118.



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**. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

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 55A. MS (*m/z*) 675.0 [M+H]<sup>+</sup>.

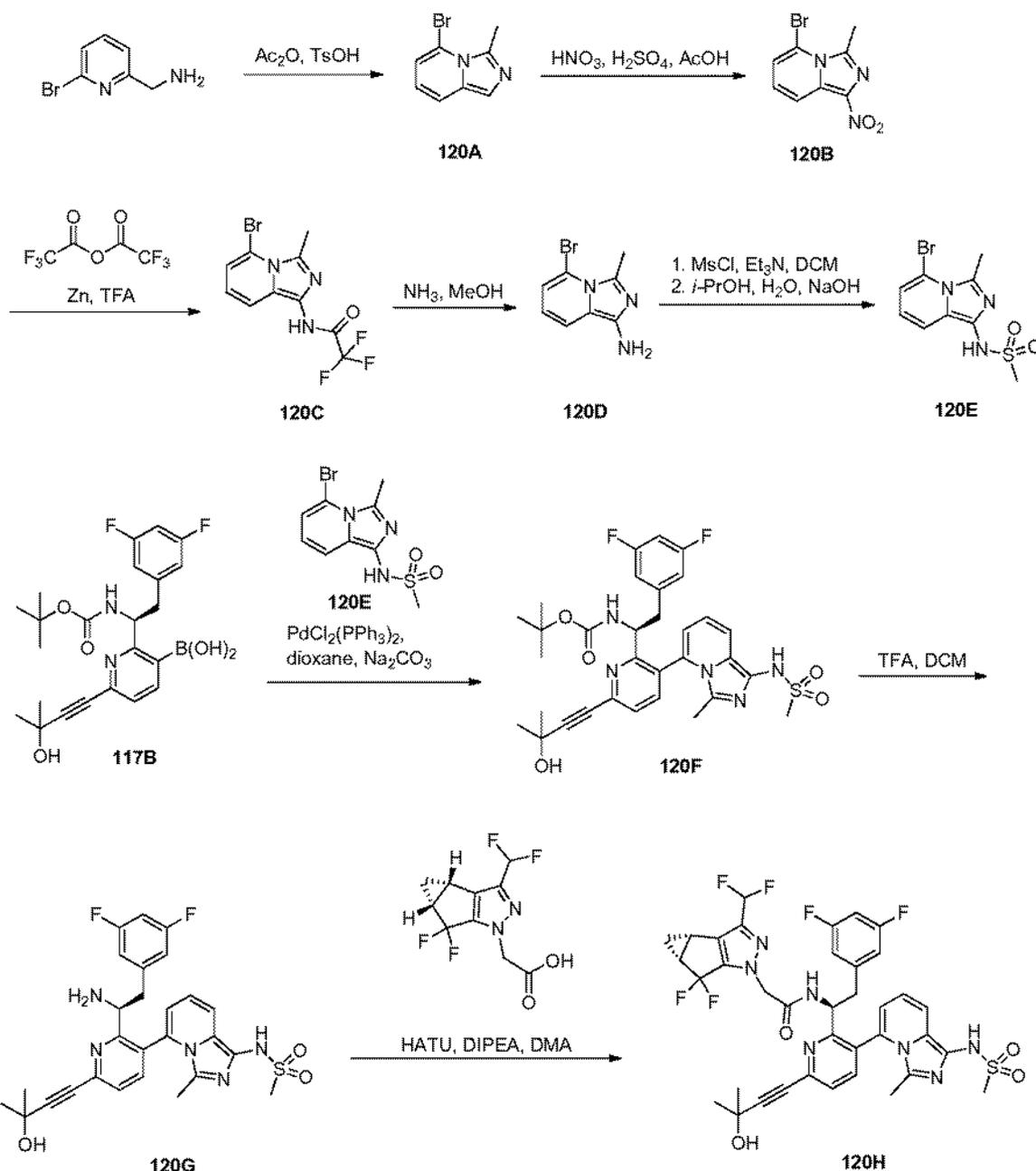
Synthesis of 119B:

[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 119A. MS (*m/z*) 575.2 [M+H]<sup>+</sup>.

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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

## 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  $\text{Na}_2\text{SO}_4$ , filtered, concentrated *in vacuo*, and purified by silica gel chromatography to give the title compound. MS ( $m/z$ ) 213.06  $[\text{M}+\text{H}]^+$ .

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%  $\text{HNO}_3$  (0.82 ml) and conc.  $\text{H}_2\text{SO}_4$  (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  $[\text{M}+\text{H}]^+$ .

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  $\text{NaHCO}_3$ . The organic layer was dried with  $\text{Na}_2\text{SO}_4$ , 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  $[\text{M}+\text{H}]^+$ .

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  $[\text{M}+\text{H}]^+$ .

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  $\mu\text{l}$ , 0.34 mmol) in dichloromethane (0.5 ml) was added methanesulfonyl chloride (24  $\mu\text{l}$ , 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  $\mu$ L), and the resulting mixture was concentrated *in vacuo*. The mixture was extracted with ethyl acetate and water. The organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo*, and purified by silica gel chromatography to give the title compound. MS (*m/z*) 305.88 [M+H]<sup>+</sup>.

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  $\mu$ mol), 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<sub>2</sub>CO<sub>3</sub> (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<sub>2</sub>SO<sub>4</sub>, 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]<sup>+</sup>.

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):

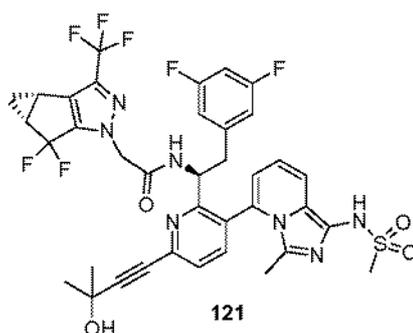
**[0673]** (S)-tert-butyl (2-(3,5-difluorophenyl)-1-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-(3-methyl-1-(methylsulfonamido)imidazo[1,5-a]pyridin-5-yl)pyridin-2-yl)ethyl)carbamate (**120F**) (75 mg, 0.12 mmol) was dissolved in DCM (1.0 mL) and TFA (0.5 mL) and stirred at room temperature for 30 mins. The resulting solution was concentrated *in vacuo* and extracted with ethyl acetate and saturated aqueous NaHCO<sub>3</sub> followed by water. The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, 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]<sup>+</sup>.

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**).  $^1\text{H}$  NMR (400 MHz, Methanol-*d*<sub>4</sub>)  $\delta$  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]<sup>+</sup>.

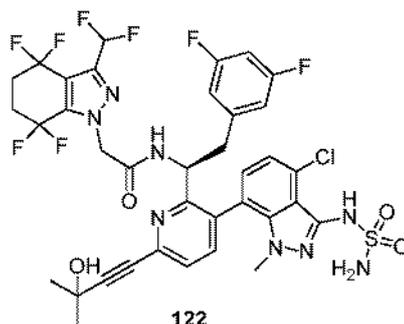
#### Example 121.



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.  $^1\text{H}$  NMR (400 MHz, Methanol-*d*<sub>4</sub>)  $\delta$  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]<sup>+</sup>.

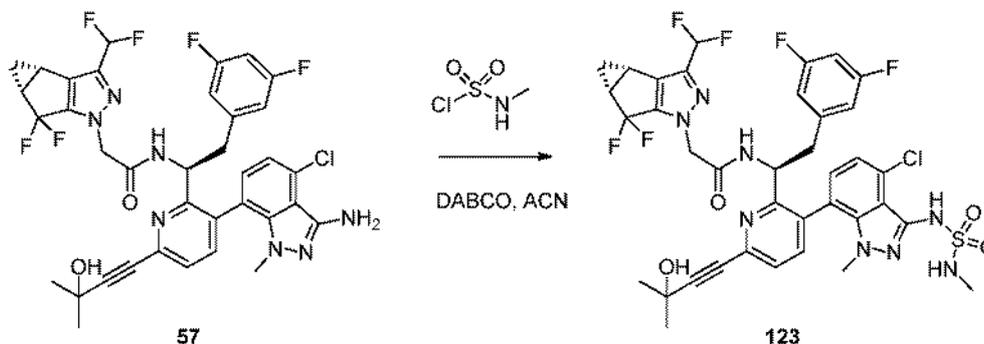
#### Example 122.



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.  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  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 [ $\text{M}+\text{H}$ ] $^+$ .

Example 123.

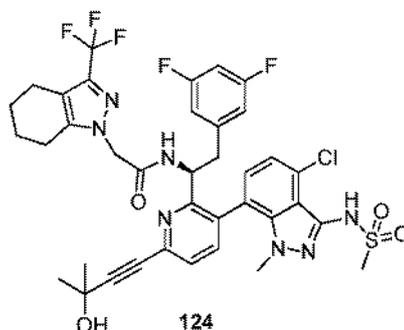


Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-((N-methylsulfamoyl)amino)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**123**):

**[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.  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  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]<sup>+</sup>.

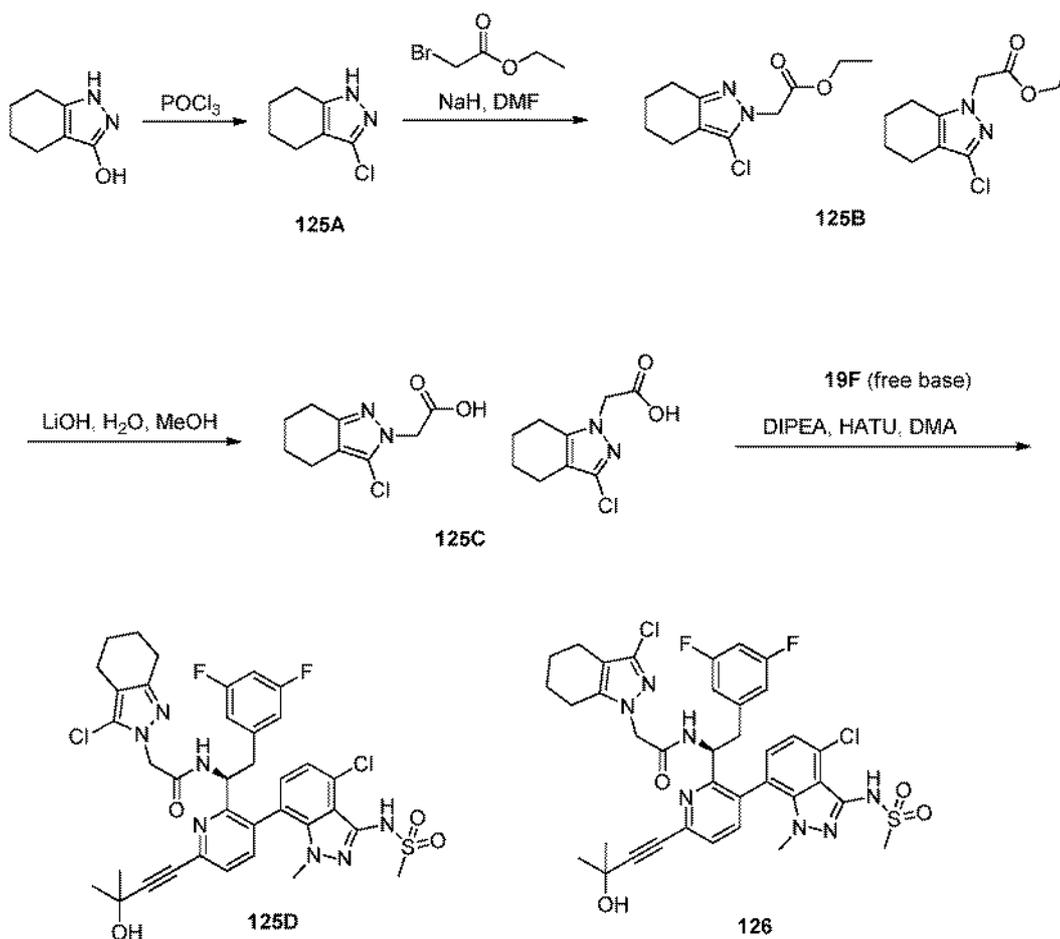
Example 124.



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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

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<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo* and purified by silica gel chromatography to give the title compound. MS (*m/z*) 157.14 [M+H]<sup>+</sup>.

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<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo* and purified by

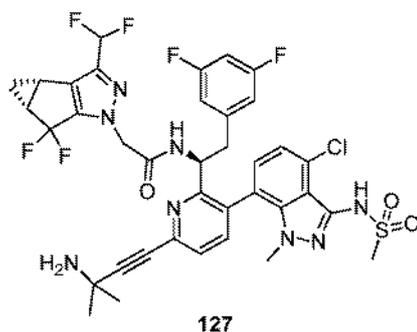
silica gel chromatography to give the title compounds as a 1:5 mixture of ethyl 2-(3-chloro-4,5,6,7-tetrahydro-2H-indazol-2-yl)acetate and ethyl 2-(3-chloro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (**125B**). MS ( $m/z$ ) 243.11 [M+H]<sup>+</sup>.

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  $\mu$ mol) in methanol (250  $\mu$ l) was added 2M aqueous LiOH (62  $\mu$ l). 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<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The crude product was taken to the next step without further purification. MS ( $m/z$ ) 215.14 [M+H]<sup>+</sup>.

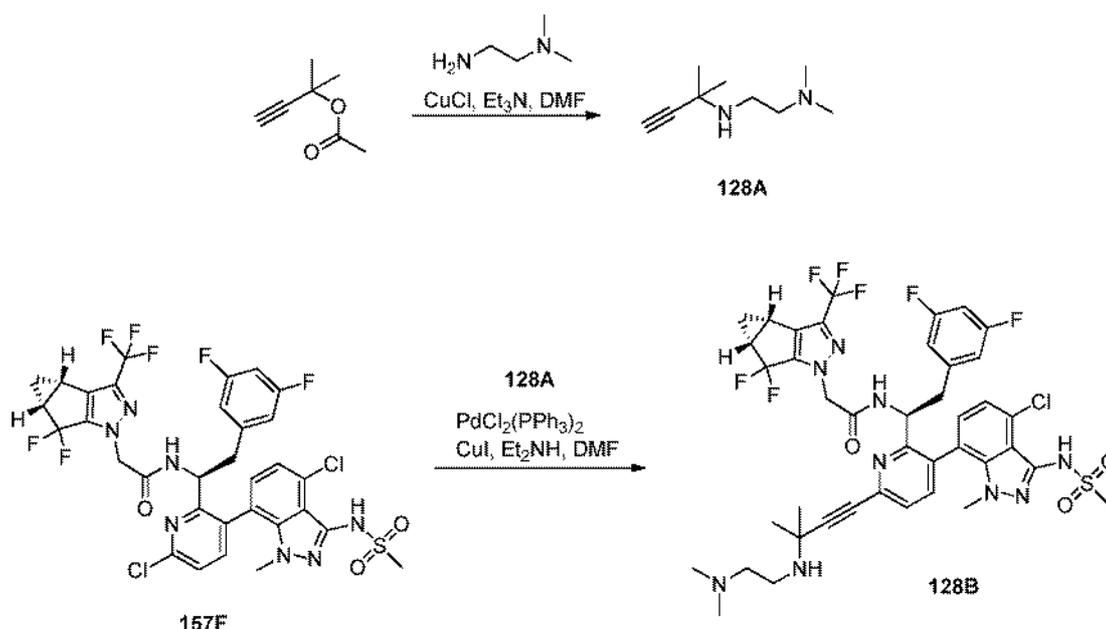
Syntheses of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-chloro-4,5,6,7-tetrahydro-2H-indazol-2-yl)acetamide (**125D**) and of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)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**): <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>)  $\delta$  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]<sup>+</sup>. (**126**): <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>)  $\delta$  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]<sup>+</sup>.

Example 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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

Example 128.

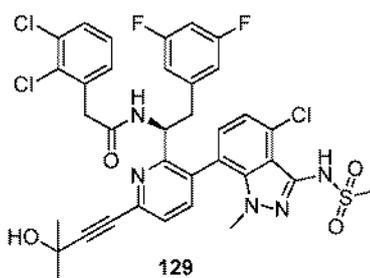
Synthesis of N1,N1-dimethyl-N2-(2-methylbut-3-yn-2-yl)ethane-1,2-diamine (128A):

[0684] Argon was bubbled through a solution of 2-methylbut-3-yn-2-yl acetate (15.96 mg, 126.5  $\mu\text{mol}$ ), copper chloride (0.75 mg, 7.59  $\mu\text{mol}$ ), triethylamine (17.63  $\mu\text{l}$ , 126.5  $\mu\text{mol}$ ), and N,N-dimethylethylenediamine (20.73  $\mu\text{l}$ , 189.74  $\mu\text{mol}$ ) in DMF (0.2 ml). The reaction was heated in a microwave reactor at 110  $^{\circ}\text{C}$  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  $\mu\text{mol}$ ) in DMF (0.2 mL), CuI (1 mg, 5.06  $\mu\text{mol}$ ), and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (3.55 mg, 5.06  $\mu\text{mol}$ ). Argon was bubbled through the reaction and diethylamine (39  $\mu\text{l}$ , 379  $\mu\text{mol}$ ) was added. The reaction was heated in a microwave reactor for 15 mins at 125  $^{\circ}\text{C}$ . 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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od)  $\delta$  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]<sup>+</sup>.

Example 129.

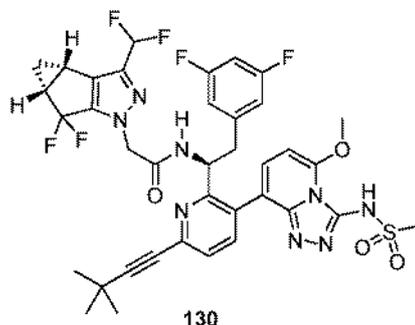


Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(2,3-dichlorophenyl)acetamide (129):

[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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>)  $\delta$  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]<sup>+</sup>.

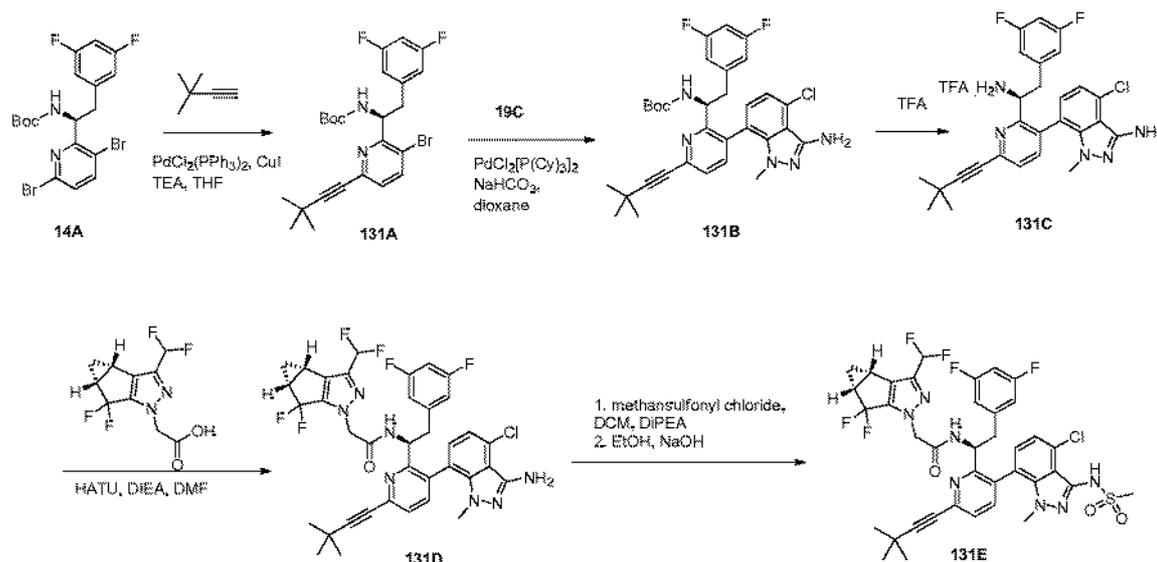
Example 130.



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  $\mu$ L, 0.2 mmol) followed by methanesulfonyl chloride (8  $\mu$ L, 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**. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>)  $\delta$  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]<sup>+</sup>.

Example 131.



Synthesis of (S)-tert-butyl (1-(3-bromo-6-(3,3-dimethylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**131A**):

[0688] The title compound (**131A**) was prepared according to the method presented for the synthesis of compound **4F** of Example 4 utilizing compound **14A** and 3,3-dimethylbut-1-yne. MS ( $m/z$ ) 494.92  $[\text{M}+\text{H}]^+$ .

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  $[\text{M}+\text{H}]^+$ .

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  $[\text{M}+\text{H}]^+$ .

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**):

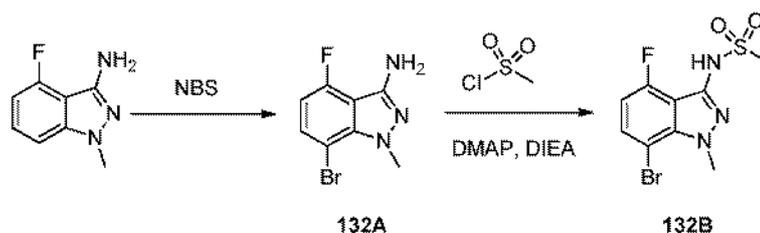
[0691] The title compound **131D** was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **37E** of Example 37 utilizing 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-

cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid and compound **131C**. MS ( $m/z$ ) 740.35 [M+H]<sup>+</sup>.

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**. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

Example 132.

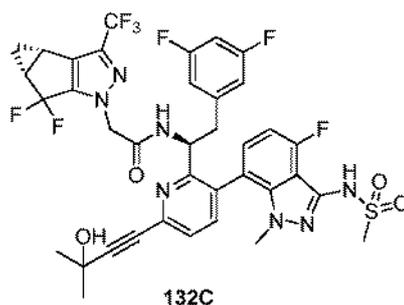


Synthesis of 7-bromo-4-fluoro-1-methyl-1H-indazol-3-amine (**132A**):

**[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]<sup>+</sup>.

Synthesis of N-(7-bromo-4-fluoro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**132B**):

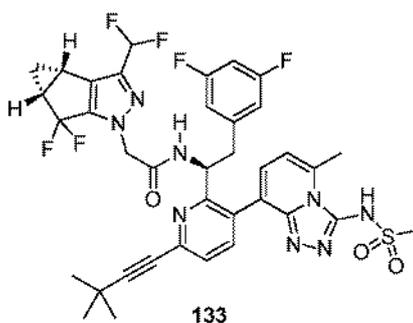
**[0694]** The title compound was prepared similarly to **108B** of Example 108 starting from **132A**. MS ( $m/z$ ) 320.3 [M-H]<sup>-</sup>.



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.  $^1\text{H}$  NMR (400 MHz,  $\text{cd}_3\text{od}$ )  $\delta$  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 [ $\text{M}+\text{H}$ ] $^+$ .

Example 133.

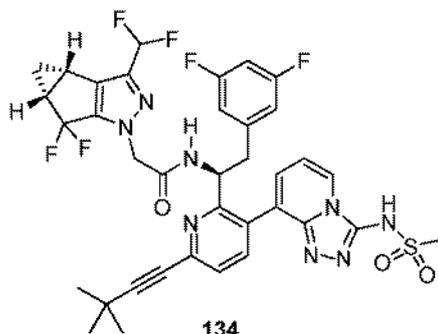


Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(6-(3,3-dimethylbut-1-yn-1-yl)-3-(5-methyl-3-(methylsulfonamido)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)pyridin-2-yl)ethyl)acetamide (**133**):

**[0696]** The title compound (**133**) was prepared according to the method presented for the synthesis of compound **19D** of Example 19 utilizing compound **116A**.  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ ):  $\delta$  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]<sup>+</sup>.

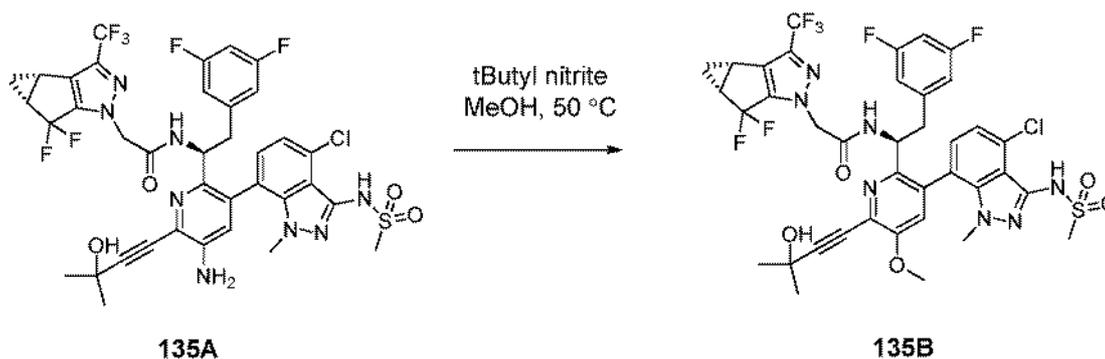
#### Example 134.



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**. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

#### Example 135.



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**):

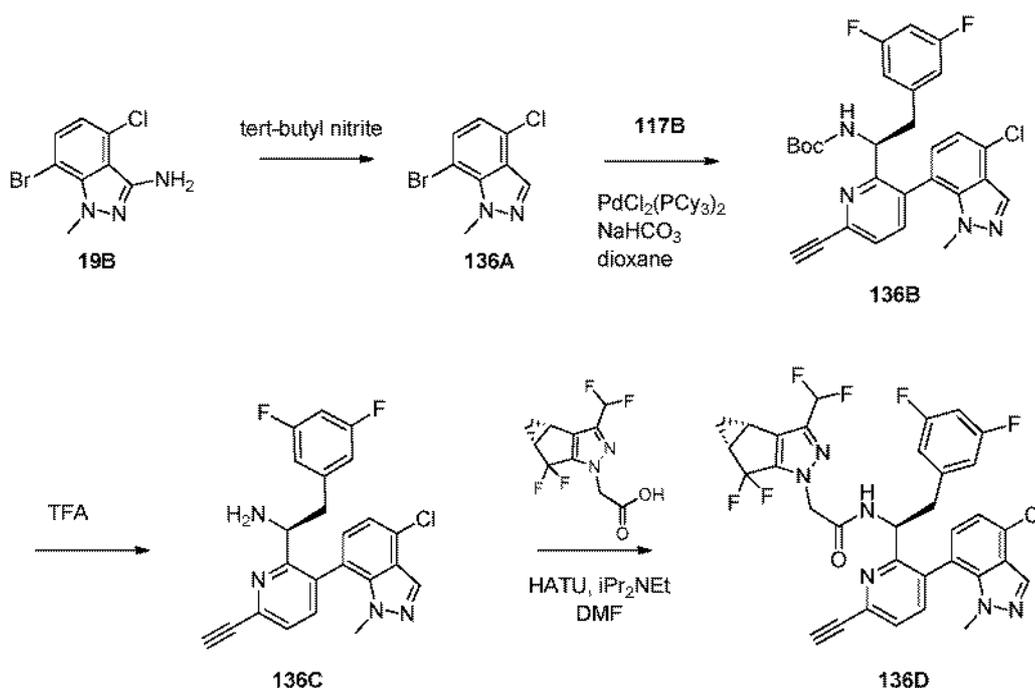
**[0698]** The title compound (**135A**) may be prepared analogously to the method presented for the synthesis of compound **139A** of Example 139 utilizing 2-((3bS,4aR)-5,5-difluoro-3-

(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]<sup>+</sup>.

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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

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]<sup>+</sup>.

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<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (6 mg), and NaHCO<sub>3</sub> (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]<sup>+</sup>.

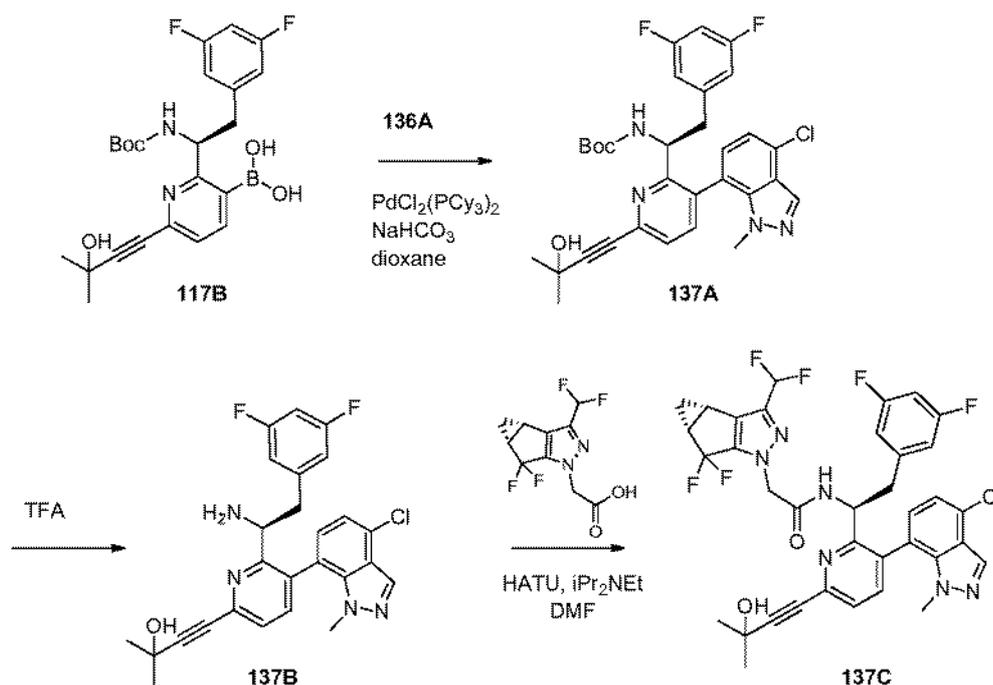
Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-1H-indazol-7-yl)-6-ethynylpyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**136C**):

[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]<sup>+</sup>.

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. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) 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]<sup>+</sup>.

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<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5 mg), and K<sub>2</sub>CO<sub>3</sub> (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]<sup>+</sup>.

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**):

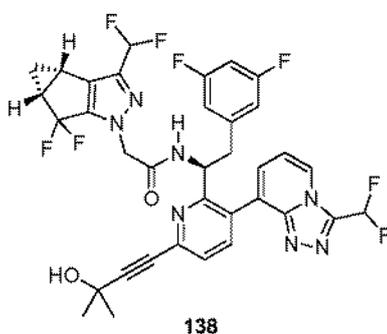
[0705] The title compound (**137B**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19F** of Example 19 utilizing compound **137A**.

MS (*m/z*): 481.1 [M+H]<sup>+</sup>.

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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

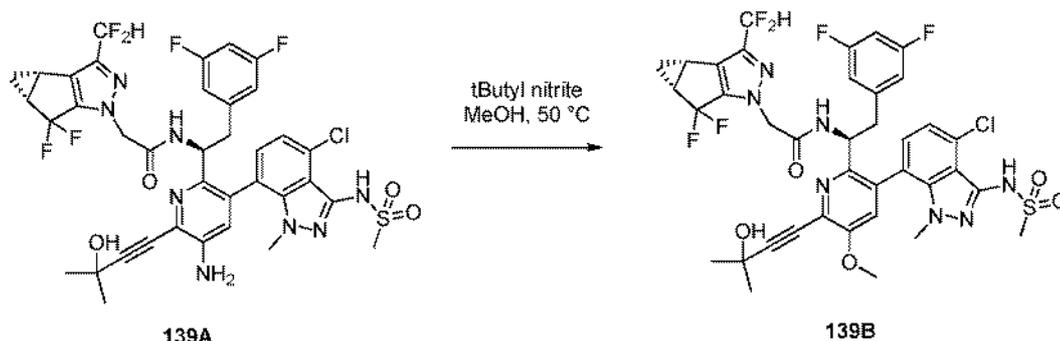
Example 138.



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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

Example 139.

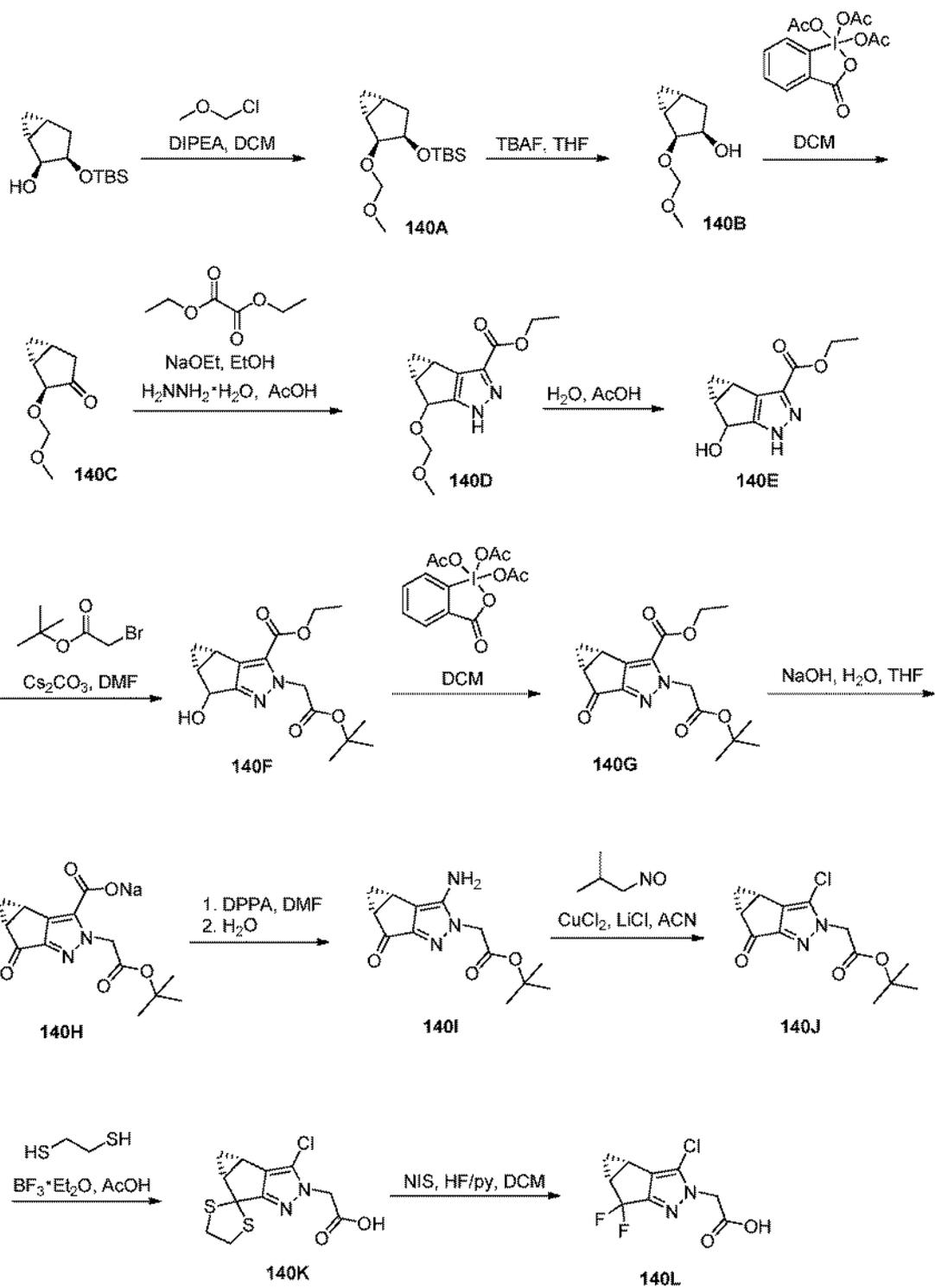


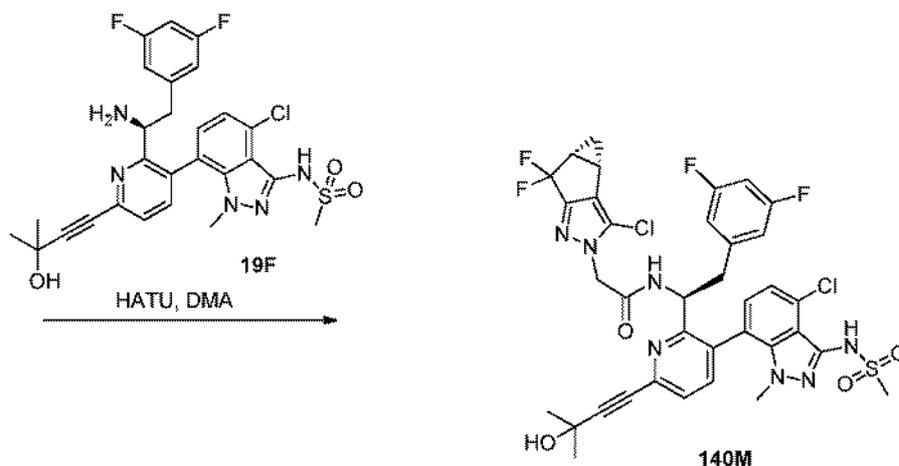
Synthesis of N-((S)-1-(5-amino-3-(4-chloro-1-methyl-3-(methylsulfonylamino)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**139A**):

**[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]<sup>+</sup>.

Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonylamino)-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**. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.  
Example 140.





Synthesis of tert-butyl(((1R,2S,3R,5R)-2-(methoxymethoxy)bicyclo[3.1.0]hexan-3-yl)oxy)dimethylsilane (**140A**):

**[0710]** To a solution of (1R,2S,3R,5R)-3-((tert-butyl(dimethylsilyl)oxy)bicyclo[3.1.0]hexan-2-yl)oxydimethylsilane (**140A**) (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<sub>4</sub>, filtered, and concentrated *in vacuo*. The crude product was taken to next step without further purification. <sup>1</sup>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<sub>4</sub>, 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. <sup>1</sup>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<sub>3</sub> (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<sub>3</sub> (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<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting mixture was slurried in 25% Et<sub>2</sub>O and hexanes, solids filtered, and the filtrate was concentrated *in vacuo* then, purified by silica gel chromatography to give the title compound. <sup>1</sup>H 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<sub>2</sub>SO<sub>4</sub>, filtered, concentrated, and purified by silica gel chromatography to give the title compound. MS (*m/z*) 252.84 [M+H]<sup>+</sup>.

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<sub>2</sub>O (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<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo*, and partially purified by silica gel chromatography eluting with ethyl acetate and hexanes. MS (*m/z*) 208.98 [M+H]<sup>+</sup>.

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<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo*, and purified by silica gel chromatography to give the title compound. MS (*m/z*) 322.83 [M+H]<sup>+</sup>.

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]<sup>+</sup>.

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]<sup>-</sup>.

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]<sup>+</sup>.

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]<sup>+</sup>.

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  $\mu$ l, 0.13 mmol), and acetic acid (19.2  $\mu$ l, 0.34 mmol) in dichloromethane (400  $\mu$ l) was added boron trifluoride diethyl etherate (20.7  $\mu$ l, 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]<sup>+</sup>.

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):

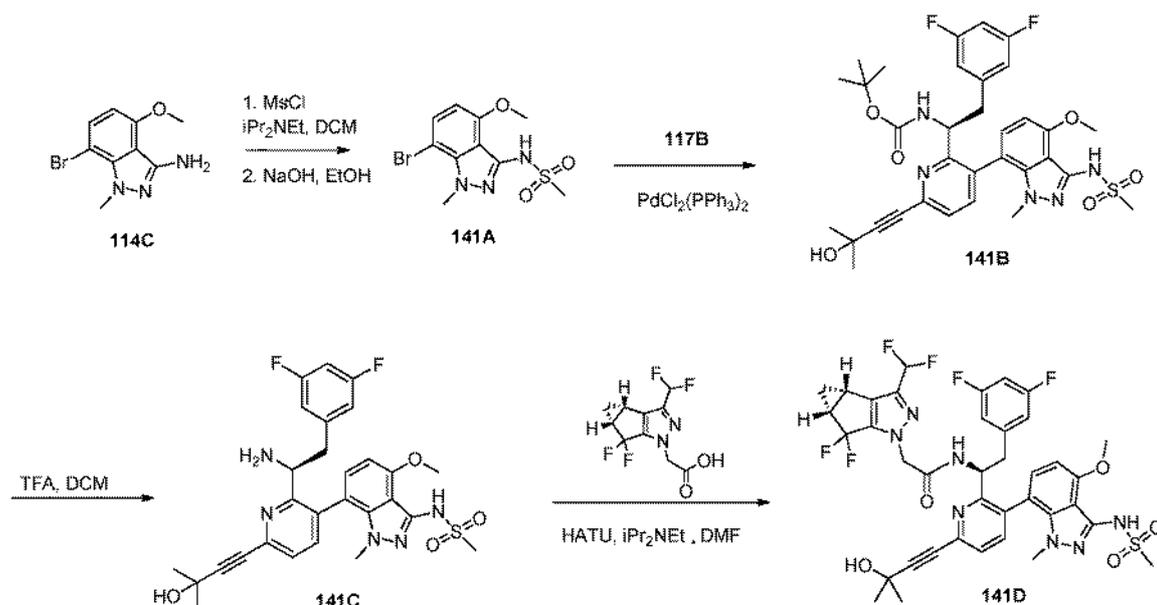
[0721] To a solution of N-iodosuccinimide (27.9 mg, 0.12 mmol) in dichloromethane (0.10 ml) was added dropwise 70% HF in pyridine (0.10 ml) at -78°C. After stirring for 15 minutes, a suspension of **140K** (15 mg, 0.05 mmol) in dichloromethane (0.10 ml) was added and the reaction was gradually warmed 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<sub>2</sub>SO<sub>4</sub>, 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]<sup>+</sup>.

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**). <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>)  $\delta$  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]<sup>+</sup>.

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]<sup>+</sup>.

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<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5 mg, 0.007 mmol), and K<sub>2</sub>CO<sub>3</sub> (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]<sup>+</sup>.

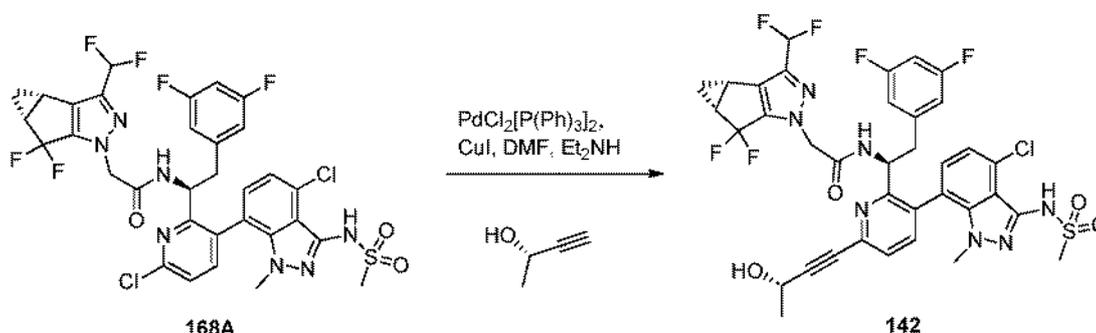
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-methoxy-1-methyl-1H-indazol-3-yl)methanesulfonamide (141C):

[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.  $^1H$  NMR (Chloroform- $d$ )  $\delta$ : 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.

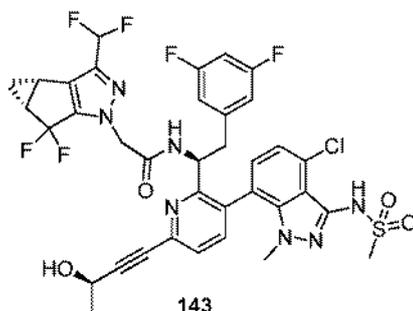


Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-((S)-3-hydroxybut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**142**):

[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.  $^1H$  NMR (400 MHz,  $cd_3od$ )  $^1H$  NMR (400 MHz,  $cd_3od$ )  $\delta$  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  $[M+H]^+$ .

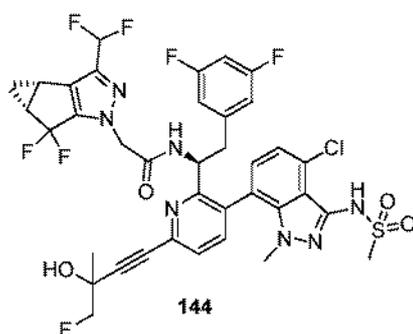
Example 143.



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.  $^1\text{H}$  NMR (400 MHz,  $\text{cd}_3\text{od}$ )  $\delta$  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  $[M+H]^+$ .

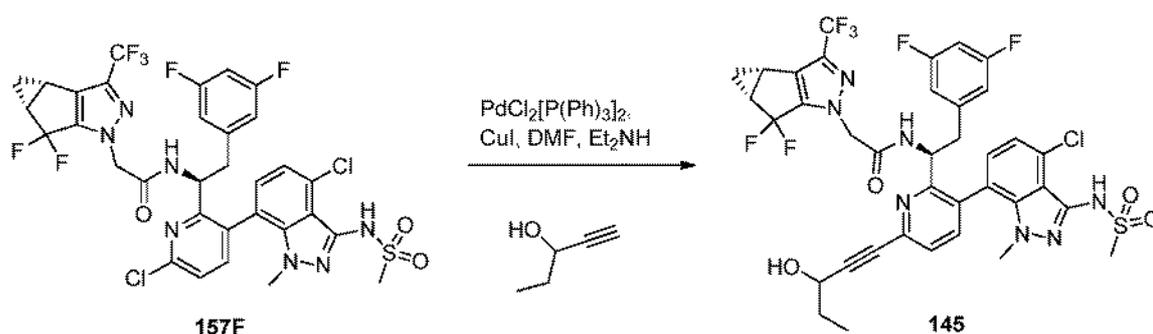
Example 144.



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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

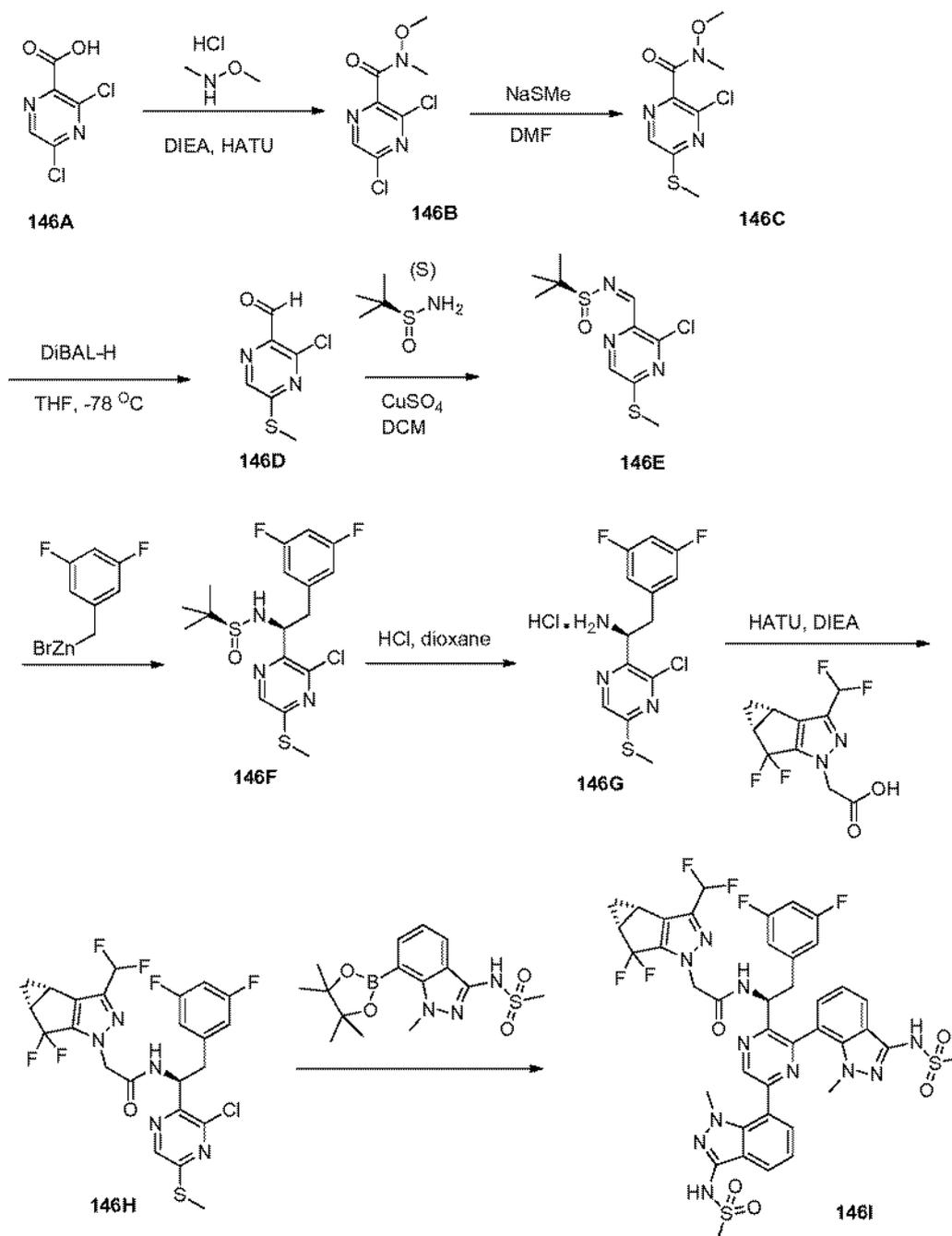
#### Example 145.



Synthesis of N-((1S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxypent-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**145**):

[0730] To the reaction vial containing **157F** (20 mg, 0.025 mmol) in DMF (1 mL) was added pent-1-yn-3-ol (0.011 g, 0.13 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

#### 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]<sup>+</sup>.

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<sub>3</sub>(aq) and brine. The organic layer was concentrated and purified by flash column to provide the title compound. MS (m/z) 248 [M+H]<sup>+</sup>.

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]<sup>+</sup>.

Synthesis of (S,Z)-N-((3-chloro-5-(methylthio)pyrazin-2-yl)methylene)-2-methylpropane-2-sulfonamide (**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]<sup>+</sup>.

Synthesis of (S)-N-((S)-1-(3-chloro-5-(methylthio)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfonamide (**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]<sup>+</sup>.

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]<sup>+</sup>.

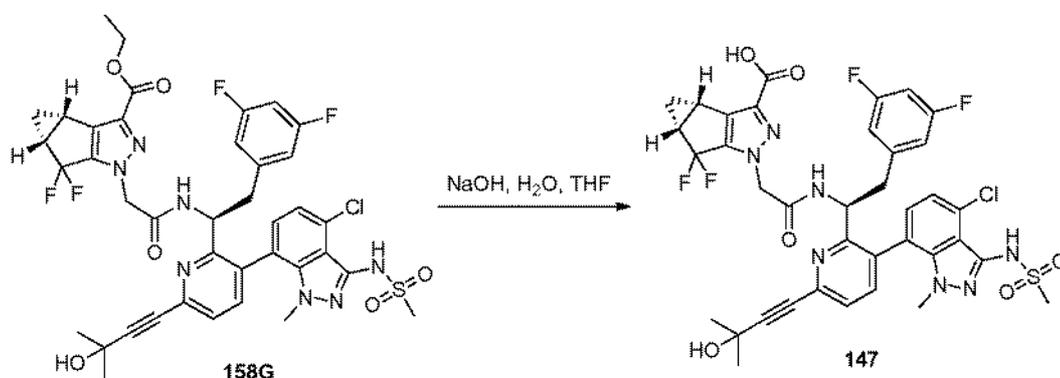
Synthesis of N-((S)-1-(3-chloro-5-(methylthio)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**146H**):

[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]<sup>+</sup>.

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**. <sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>) 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]<sup>+</sup>.

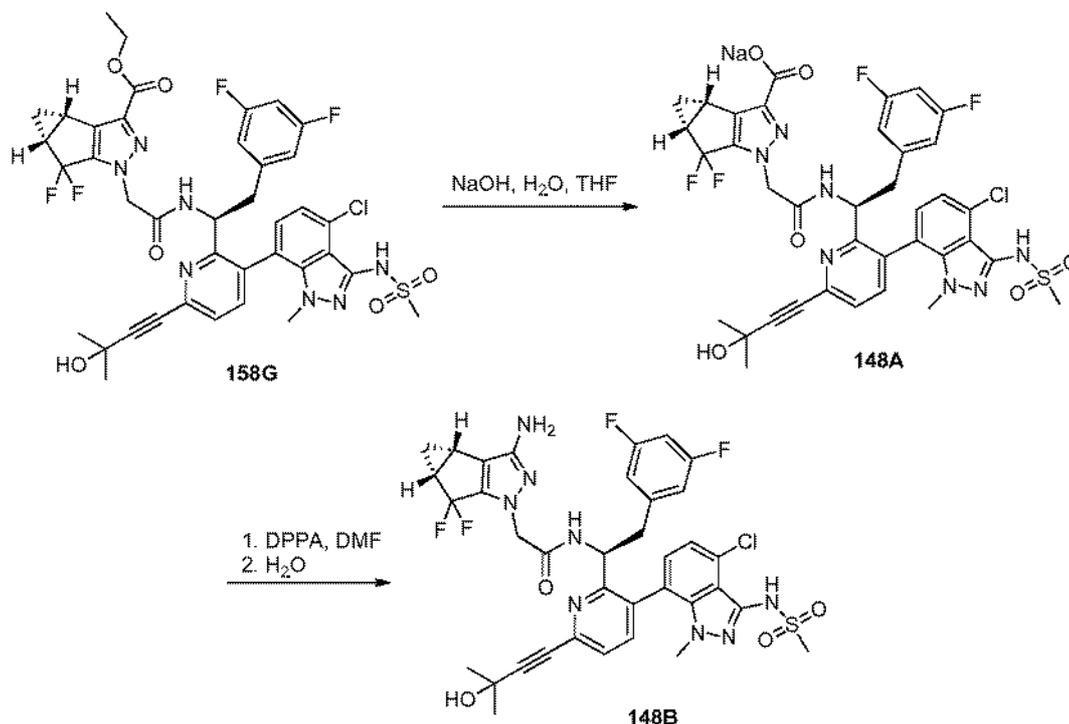
Example 147.



Synthesis of (3bS,4aR)-1-(2-(((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)amino)-2-oxoethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylic acid (**147**):

[0739] A solution of **158G** (0.41 g, 0.49 mmol) in THF (0.5 ml) was treated with 1M NaOH (2 ml). The reaction was stirred at room temperature for 1.5 h. The solution was acidified to ~ pH=4 with AcOH and extracted with 2-MeTHF (2 x 5 mL) and water (5 mL). The organics were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude material was purified by reverse phase HPLC to provide the product **147** as a mixture of atropisomers. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

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**):

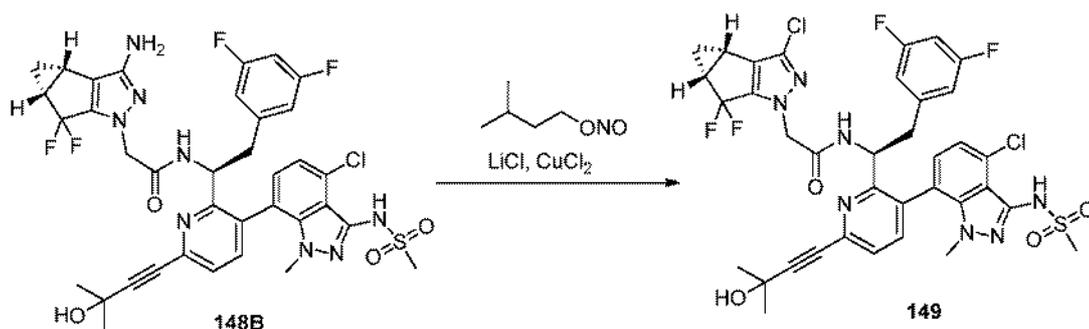
**[0740]** To a solution of **158G** (0.22 g, 0.26 mmol) in THF (0.65 ml) was added 1M NaOH (0.65 ml). The reaction was stirred at room temperature for 1.5 h. The solution was acidified to ~ pH=4 with AcOH and extracted with with 2-MeTHF (2 x 5 mL) and brine (5 mL). The organic layer was washed with NaHCO<sub>3</sub> (10mL). The organics were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The product was taken to the next step without further purification. MS (*m/z*) 814.1 [M+H]<sup>+</sup>.

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  $\mu$ l, 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  $\mu$ l) and purified by prep HPLC to provide the product **148B** as a mixture of

atropisomers.  $^1\text{H NMR}$  (400 MHz,  $\text{cd}_3\text{od}$ )  $\delta$  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  $[\text{M}+\text{H}]^+$ .

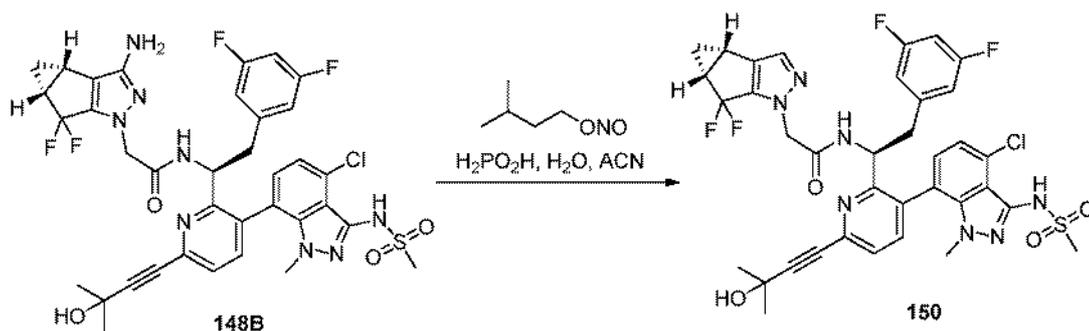
#### Example 149.



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  $\mu\text{l}$ , 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.  $^1\text{H NMR}$  (400 MHz,  $\text{cd}_3\text{od}$ )  $\delta$  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  $[\text{M}+\text{H}]^+$ .

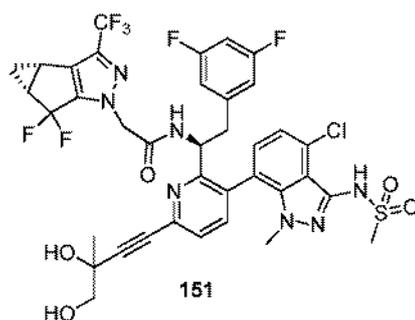
#### Example 150.



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  $\mu$ l) was added isoamyl nitrite (3.41  $\mu$ l, 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.  $^1\text{H}$  NMR (400 MHz,  $\text{cd}_3\text{od}$ )  $\delta$  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 [ $\text{M}+\text{H}$ ] $^+$ .

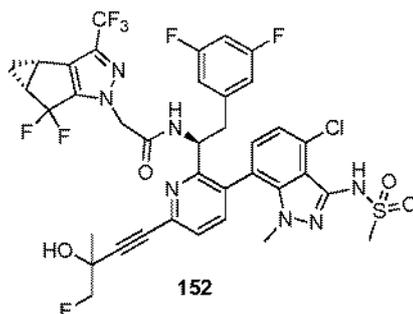
Example 151.



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.  $^1\text{H}$  NMR (400 MHz,  $\text{cd}_3\text{od}$ )  $\delta$  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 [ $\text{M}+\text{H}$ ] $^+$ .

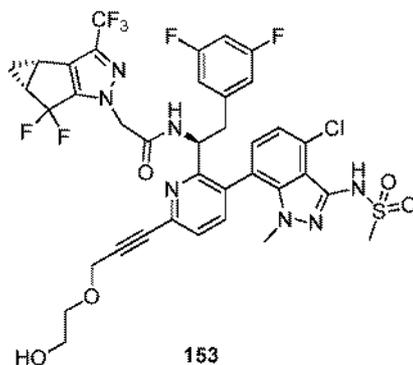
Example 152.



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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

Example 153.

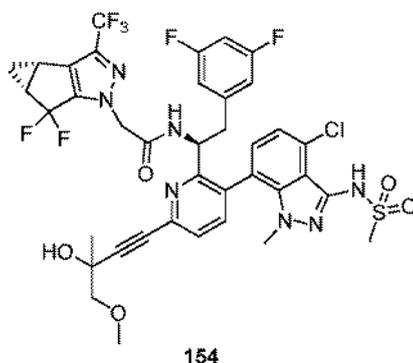


Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-(2-hydroxyethoxy)prop-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**153**):

[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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

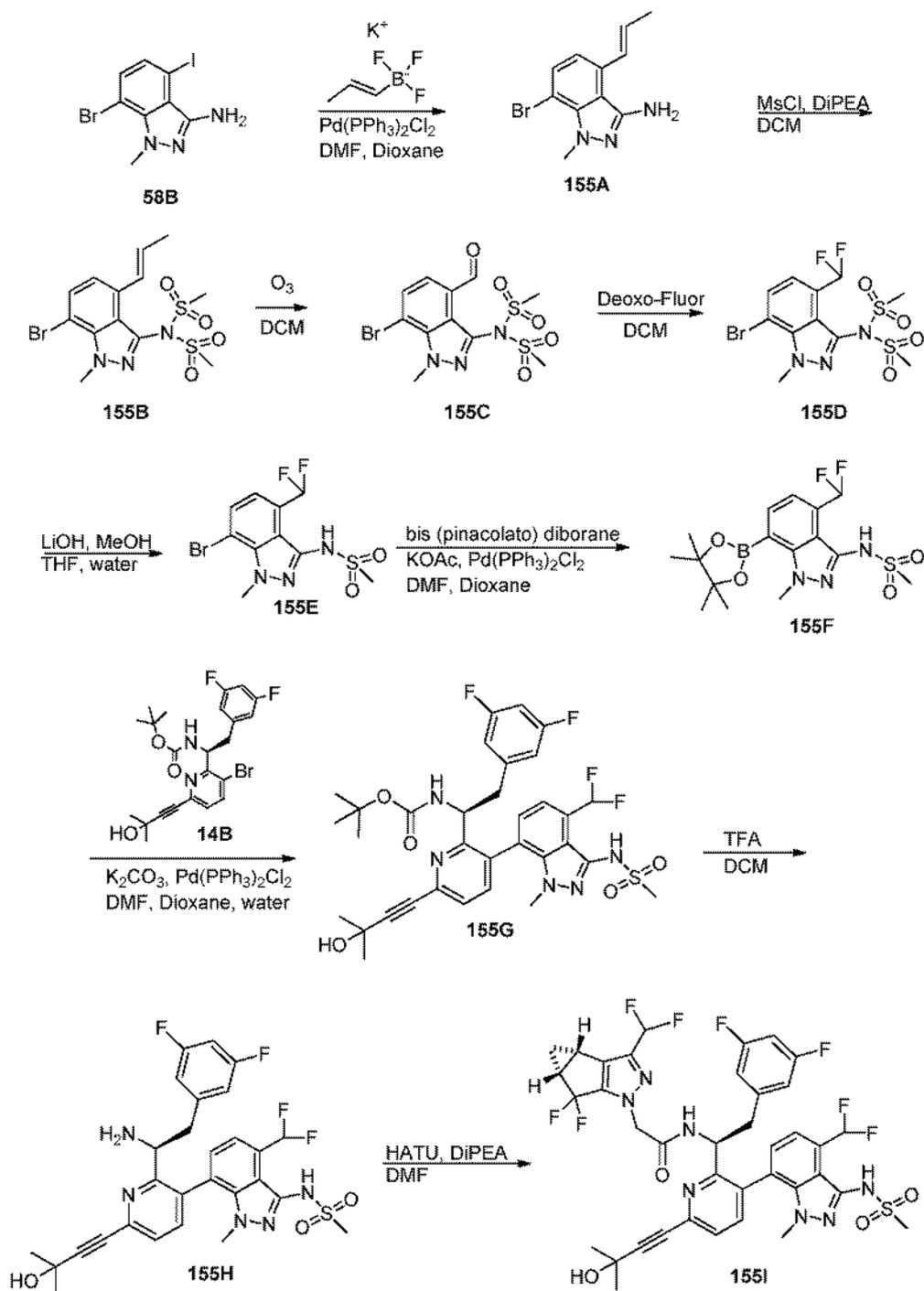
Example 154.



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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

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<sub>2</sub>CO<sub>3</sub> in water (21.0 ml), and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (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]<sup>+</sup>.

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]<sup>+</sup>.

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]<sup>+</sup>.

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]<sup>+</sup>.

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]<sup>+</sup>.

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]<sup>+</sup>.

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<sub>2</sub>CO<sub>3</sub> (0.2 ml), and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (7.1 mg, 0.01 mmol). The reaction mixture was stirred at 110 °C, then **155F** (170 mg, 0.4 mmol) 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]<sup>+</sup>.

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**):

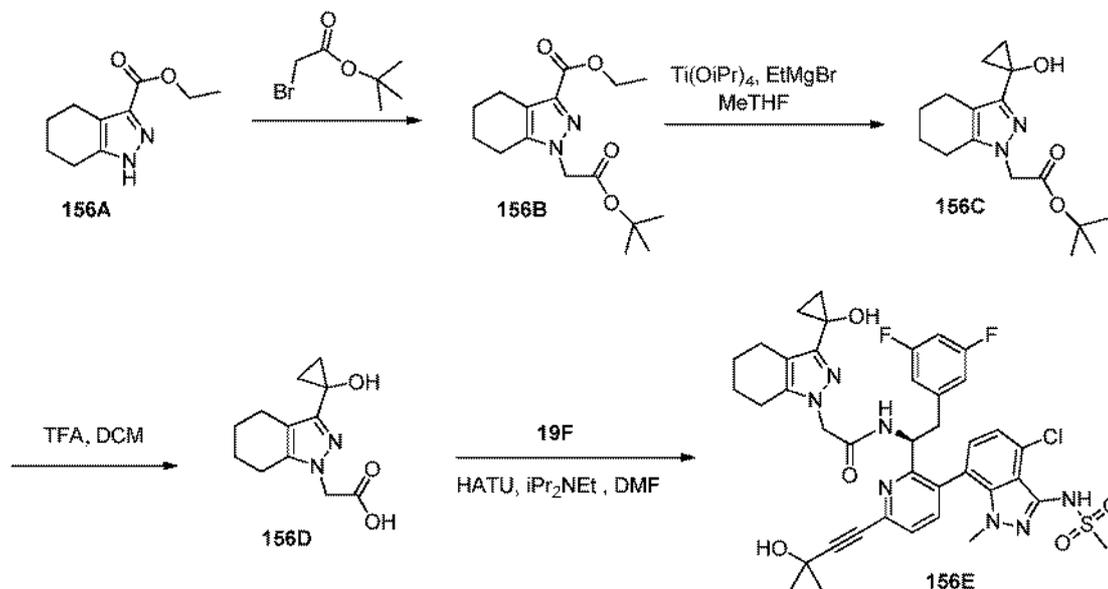
[0755] The title compound (**155H**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **19F** of Example 19 utilizing **155G**. MS (*m/z*) 590.1 [M+H]<sup>+</sup>.

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. <sup>1</sup>H 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  $\text{Cs}_2\text{CO}_3$  (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-(1-hydroxycyclopropyl)-2-oxoethyl)-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  $[M+H]^+$ .

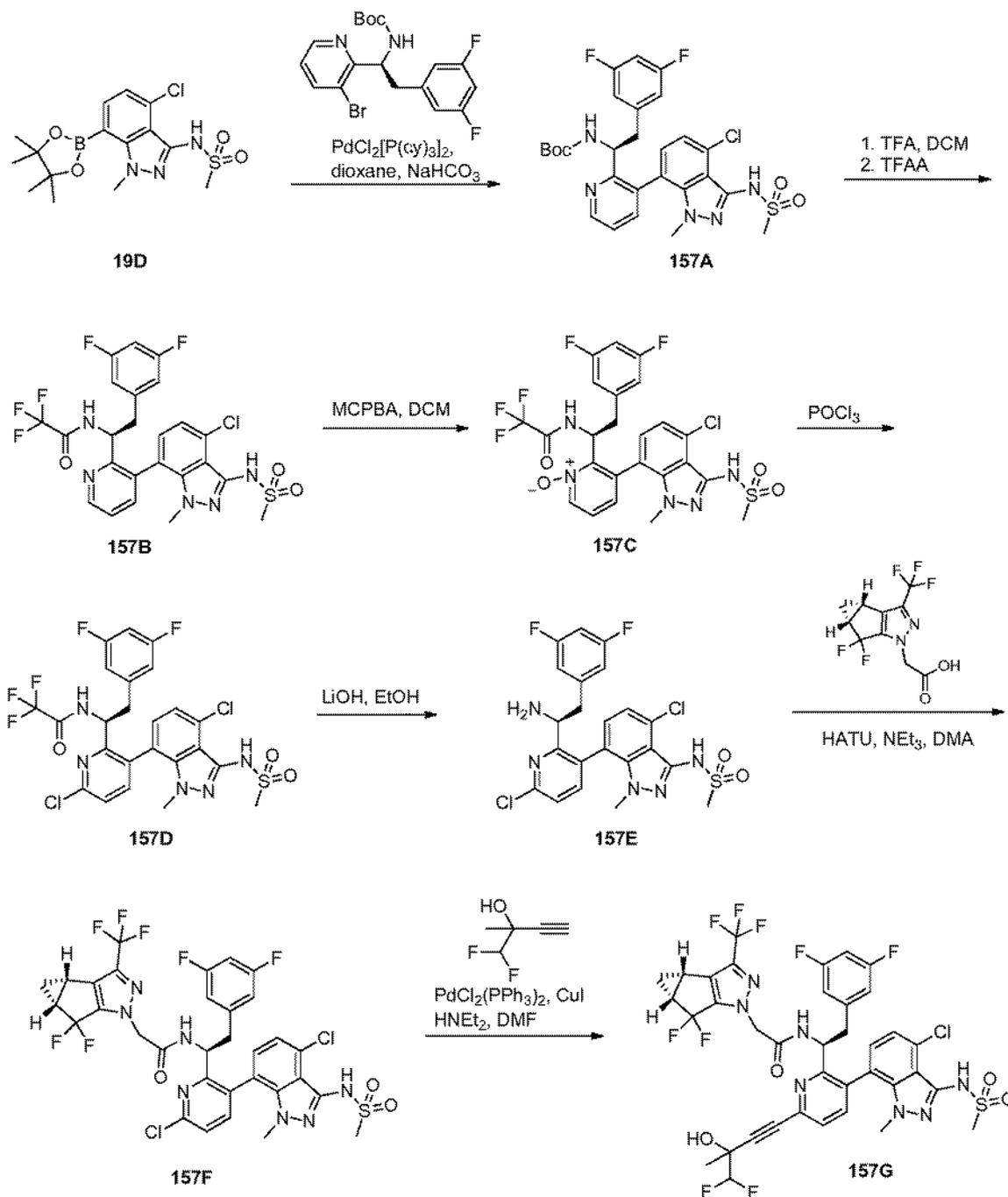
Synthesis of 2-(3-(1-(1-hydroxycyclopropyl)-2-oxoethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid (156D):

[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]<sup>+</sup>.

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**. <sup>1</sup>H NMR (Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

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  $\text{PdCl}_2[\text{P}(\text{cy})_3]_2$  (89.0 mg, 0.121 mmol) were suspended in 1,4-dioxane (12 mL) and 1.0 M aqueous  $\text{NaHCO}_3$  (4 mL). The reaction mixture was degassed by bubbling argon for 5 minutes then sealed and heated at 150 °C 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<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to give the title compound **157A**. MS (*m/z*) 591.72 [M+H]<sup>+</sup>.

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<sub>3</sub> 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<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to give the title compound **157B**. MS (*m/z*) 588.14 [M+H]<sup>+</sup>.

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<sub>3</sub> and saturated aqueous NaHCO<sub>3</sub>. The organic layer was collected and the aqueous layer was extracted an additional time with DCM. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to give the title compound **157C**. MS (*m/z*) 604.10 [M+H]<sup>+</sup>.

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<sub>3</sub> (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<sub>3</sub> 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<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to give the title compound **157D**. MS (*m/z*) 622.13 [M+H]<sup>+</sup>.

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<sub>3</sub> 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<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo*, and used without further purification. MS (*m/z*) 526.06 [M+H]<sup>+</sup>.

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**):

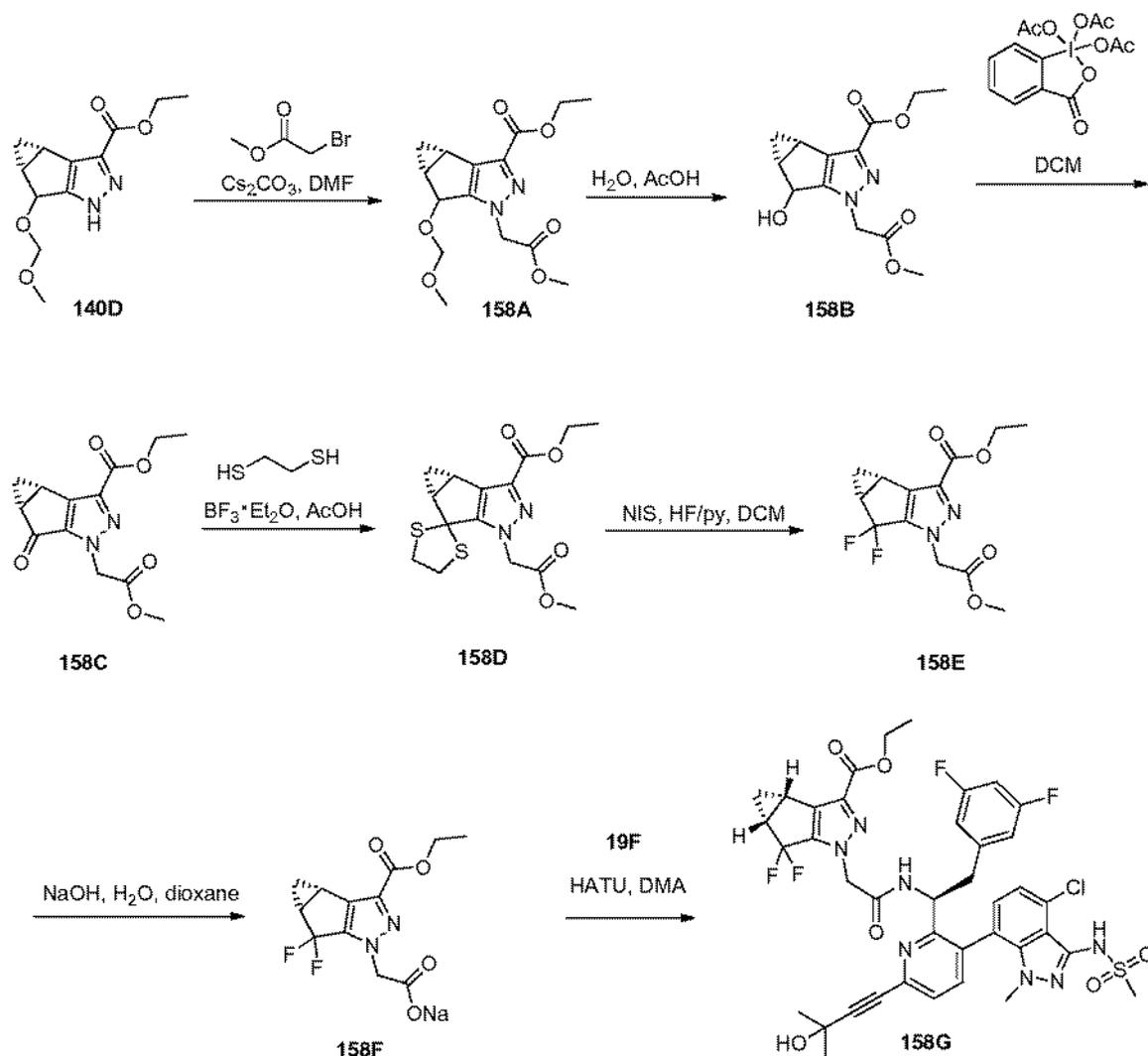
**[0766]** To a solution of crude (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-chloropyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**157E**, 400 mg, 0.76 mmol) in DMA (6 mL) was added NEt<sub>3</sub> (0.32 mL, 2.28 mmol), 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-y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

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<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (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 °C 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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

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<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The crude product was taken to next step without further purification. MS (*m/z*) 324.96 [M+H]<sup>+</sup>.

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<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The crude product was taken to next step without further purification. MS (*m/z*) 281.02 [M+H]<sup>+</sup>.

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]<sup>+</sup>.

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]<sup>+</sup>.

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<sub>3</sub>. The product was extracted with ethyl acetate, washed with NaHSO<sub>3</sub>, brine and water. The combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude material was purified by silica chromatography to give the title compound **158E**. MS (*m/z*) 300.9 [M+H]<sup>+</sup>.

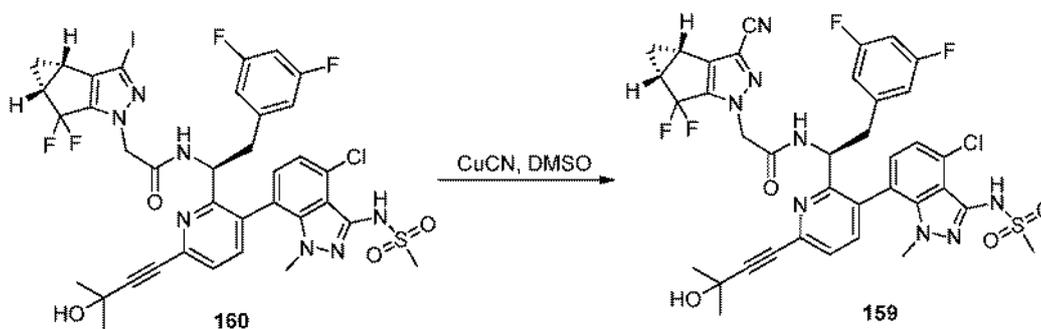
Synthesis of sodium 2-((3bS,4aR)-3-(ethoxycarbonyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**158F**):

[0773] To a solution of **158E** (0.16 g, 532.87  $\mu\text{mol}$ ) 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  $[\text{M}+\text{H}]^+$ .

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  $\mu\text{mol}$ ) and **158F** (164 mg, 532.1  $\mu\text{mol}$ ) in DMA (2 mL) was added HATU (212.31 mg, 558.7  $\mu\text{mol}$ ). 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  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude material was purified by silica chromatography to give the title compound **158G** as a mixture of atropisomers.  $^1\text{H}$  NMR (400 MHz,  $\text{cd}_3\text{od}$ )  $\delta$  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  $[\text{M}+\text{H}]^+$ .

Example 159.

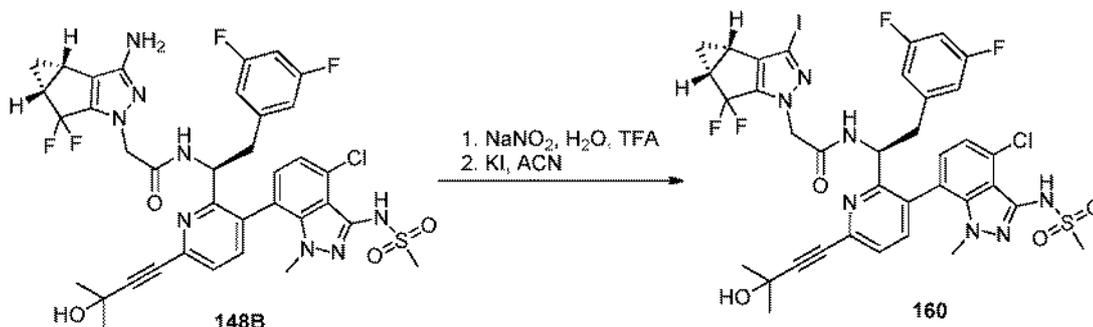


Synthesis of N-(((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-

cyano-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (159):

[0775] To a solution of **160** (11 mg, 12.2  $\mu\text{mol}$ ) in DMSO (0.2 ml) was added cuprous cyanide (2.7 mg, 30.7  $\mu\text{mol}$ ). 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  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The crude material was purified by prep HPLC to provide the product **159** as a mixture of atropisomers.  $^1\text{H}$  NMR (400 MHz,  $\text{cd}_3\text{od}$ )  $\delta$  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  $[\text{M}+\text{H}]^+$ .

Example 160.

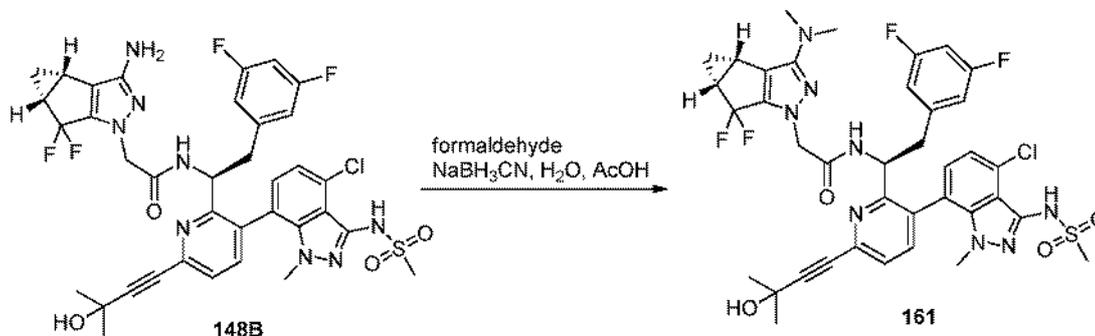


Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-iodo-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (160):

[0776] To a solution of **148B** (75 mg, 95.5  $\mu\text{mol}$ ) 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  $\text{NaHCO}_3$ , quenched with 1M  $\text{NaHSO}_3$ , and extracted with ethyl acetate (20 mL). The organic phase was then dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The crude material was purified by prep HPLC to provide the product **160** as a mixture of atropisomers.  $^1\text{H}$  NMR (400 MHz,  $\text{cd}_3\text{od}$ )  $\delta$  7.75 – 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 (s), 1.65 (s), 1.42 – 1.27 (m), 1.10 – 1.04 (m), 1.04 – 0.99 (m). MS ( $m/z$ ) 896.0  $[M+H]^+$ .

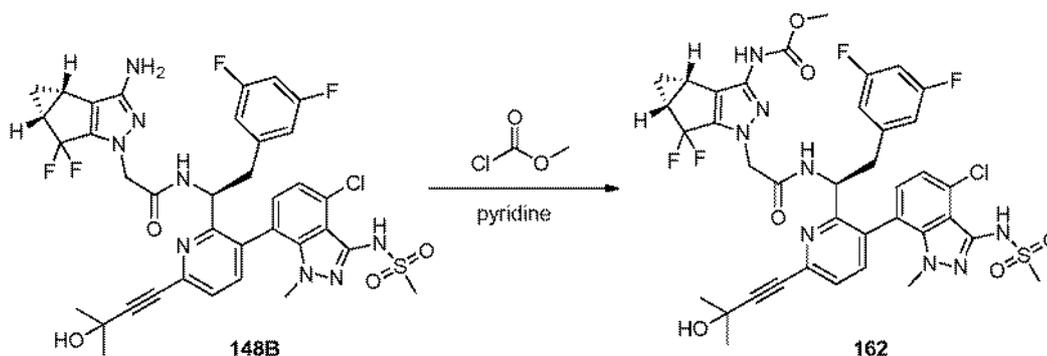
Example 161.



Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(dimethylamino)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**161**):

**[0777]** To a solution of **148B** (10 mg, 12.7  $\mu$ mol) in acetic acid (0.1 ml) and formaldehyde (35% in water, 6.7  $\mu$ l, 63.6  $\mu$ mol) was added sodium cyanoborohydride (1.7 mg, 26.7  $\mu$ mol) 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.  $^1\text{H NMR}$  (400 MHz,  $\text{cd}_3\text{od}$ )  $\delta$  7.74 – 7.64 (m), 7.58 – 7.48 (m), 7.16 (q), 7.07 (d), 6.82 – 6.72 (m), 6.68 – 6.56 (m), 6.45 – 6.30 (m), 5.28 (dd), 4.95 (t), 4.51 (d), 4.47 (d), 3.33 (s), 3.26 (s), 3.25 (s), 3.27 – 3.18 (m), 3.09 (dd), 2.98 (s), 2.92 (s), 2.92 (s), 2.49 – 2.40 (m), 2.40 – 2.28 (m), 1.65 (s), 1.41 – 1.29 (m), 1.09 – 0.98 (m). MS ( $m/z$ ) 813.2  $[M+H]^+$ .

Example 162.

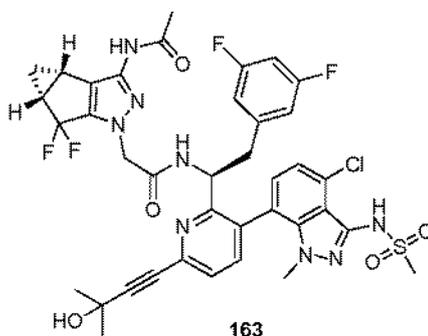


Synthesis of methyl ((3bS,4aR)-1-(2-(((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-

difluorophenyl)ethyl)amino)-2-oxoethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-3-yl)carbamate (**162**):

[0778] To a solution of **148B** (6 mg, 7.64  $\mu\text{mol}$ ) in DCM (0.1 ml) was added pyridine (3.08  $\mu\text{l}$ , 38.21  $\mu\text{mol}$ ) followed by methylchloroformate (0.7 mg, 7.18  $\mu\text{mol}$ ) 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.  $^1\text{H}$  NMR (400 MHz,  $\text{cd}_3\text{od}$ )  $\delta$  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 [ $\text{M}+\text{H}$ ] $^+$ .

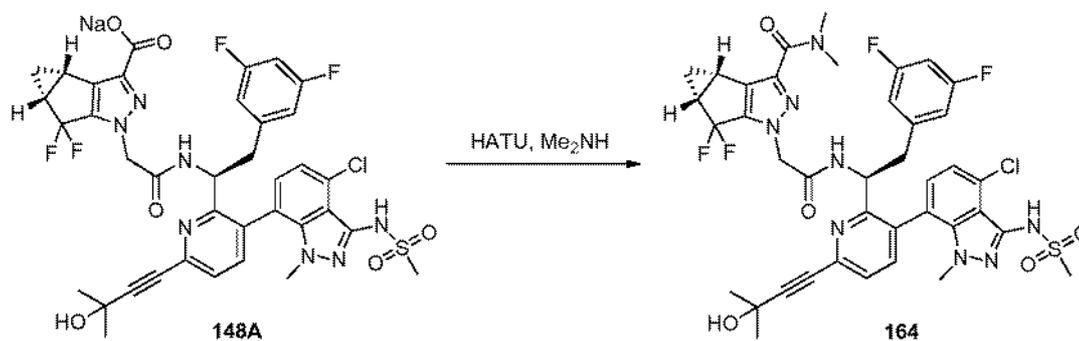
Example 163.



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.  $^1\text{H}$  NMR (400 MHz,  $\text{cd}_3\text{od}$ )  $\delta$  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 [ $\text{M}+\text{H}$ ] $^+$ .

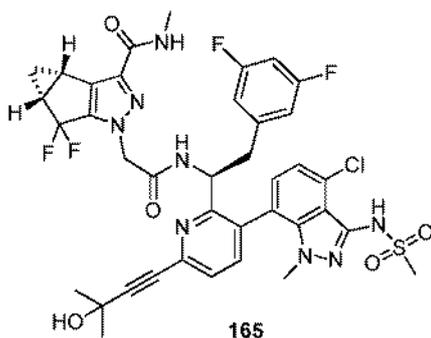
Example 164.



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  $\mu\text{mol}$ ) in DMA (100  $\mu\text{l}$ ) was added a solution of HATU (2.73 mg, 7.18  $\mu\text{mol}$ ) in DMA (50  $\mu\text{l}$ ) followed by dimethylamine (2M in THF, 50  $\mu\text{l}$ , 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.  $^1\text{H}$  NMR (400 MHz,  $\text{cd}_3\text{od}$ )  $\delta$  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 [ $\text{M}+\text{H}$ ] $^+$ .

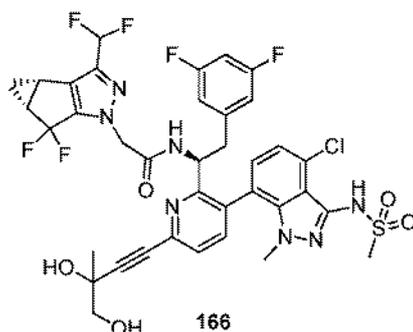
Example 165.



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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

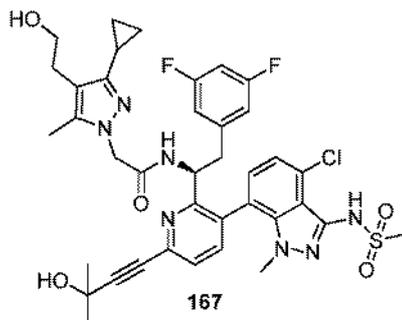
Example 166.



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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) <sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>) 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]<sup>+</sup>.

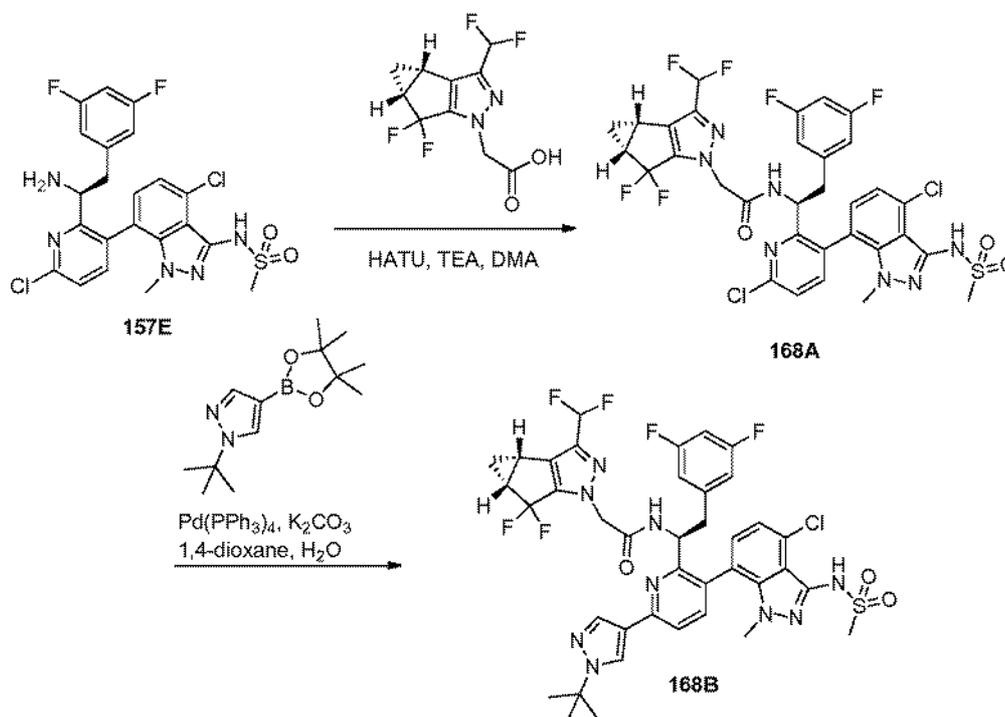
Example 167.



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). <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

Example 168.



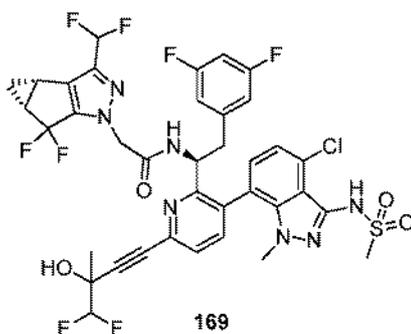
Synthesis of N-((S)-1-(6-chloro-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopro[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (168A):

[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-cyclopro[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. MS (*m/z*) 772.03 [M+H]<sup>+</sup>.

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<sub>3</sub>)<sub>4</sub> (1.50 mg, 0.001 mmol), and K<sub>2</sub>CO<sub>3</sub> (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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

Example 169.

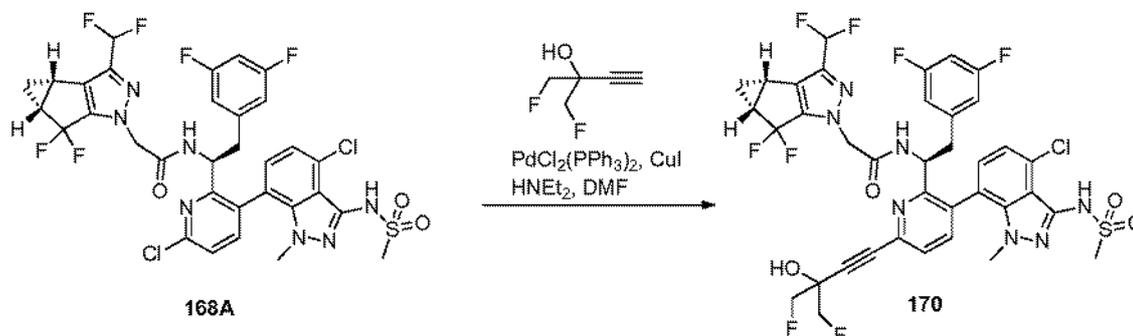


Synthesis of N-((1S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(4,4-difluoro-3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (169):

**[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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

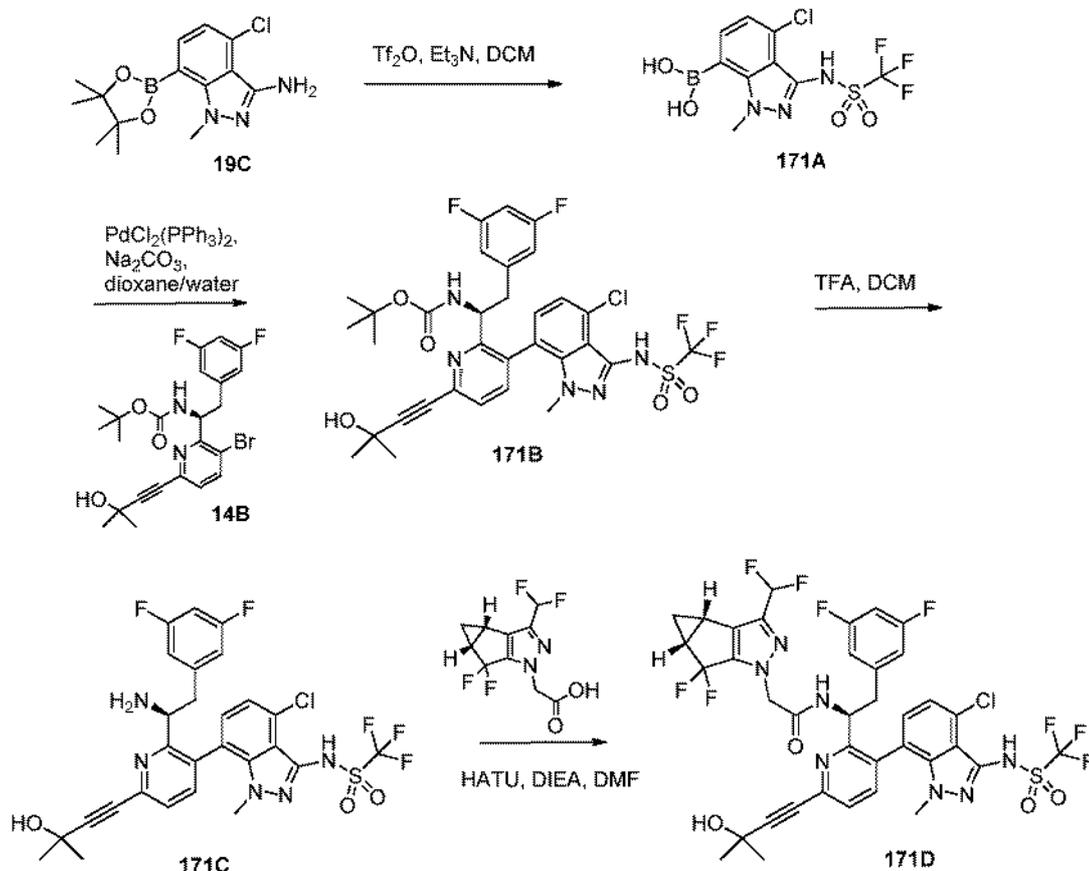
Example 170.



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<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (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 °C 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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

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 °C 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 °C. 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]<sup>+</sup>.

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<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5.1 mg, 0.007 mmol) were suspended in 1,4-dioxane (1 mL) and 1.0 M aqueous NaHCO<sub>3</sub> (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]<sup>+</sup>.

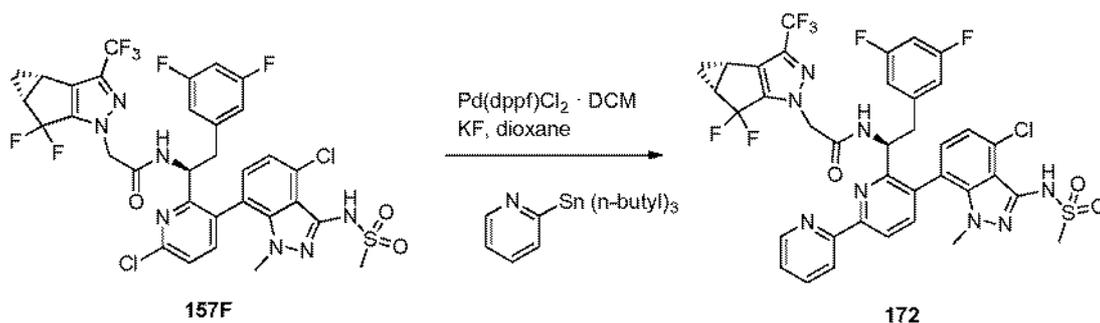
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)-1,1,1-trifluoromethanesulfonamide (**171C**):

**[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]<sup>+</sup>.

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. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) 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]<sup>+</sup>.

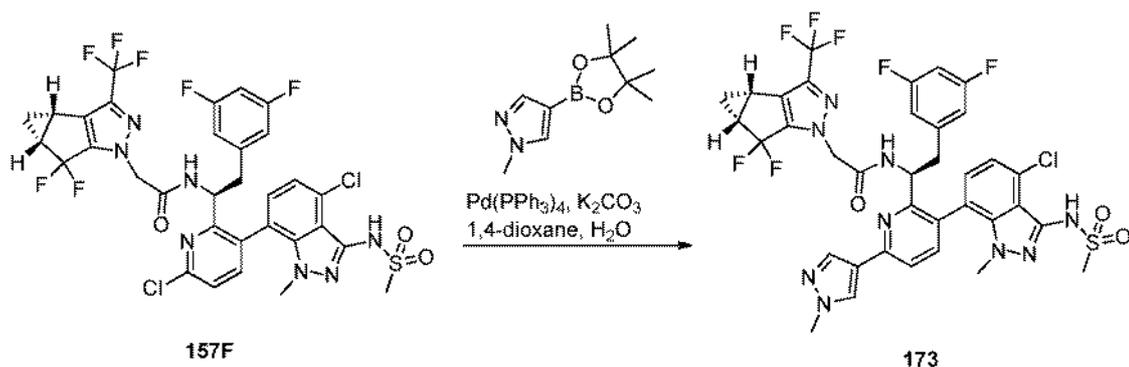
Example 172.



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<sub>2</sub>·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. <sup>1</sup>H NMR (400 MHz, cd<sub>3</sub>od) 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]<sup>+</sup>.

Example 173.

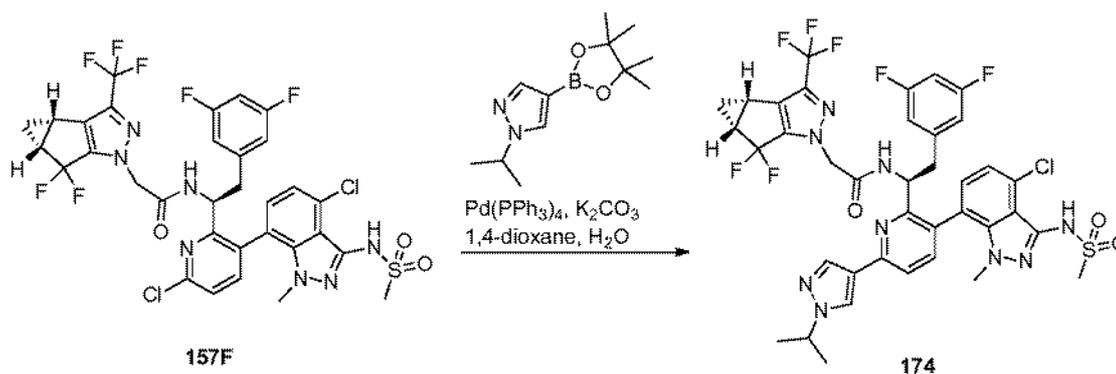


Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**173**):

**[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<sub>3</sub>)<sub>4</sub> (1.5 mg, 0.001 mmol), and K<sub>2</sub>CO<sub>3</sub> (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 °C 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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

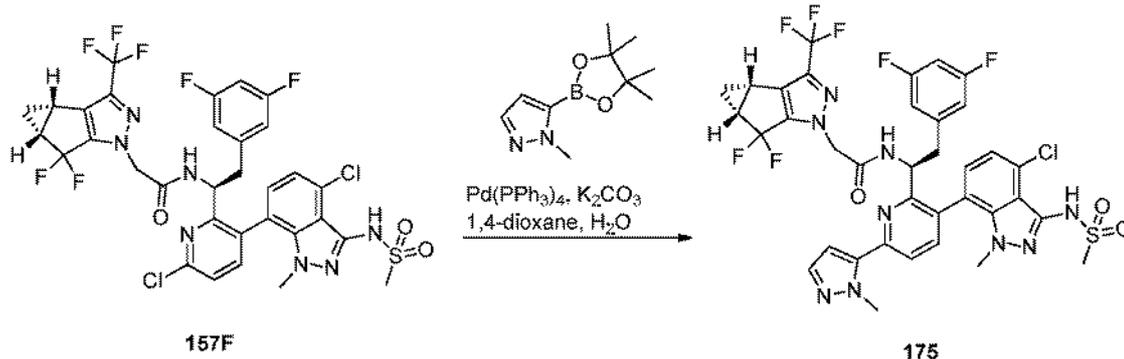
#### Example 174.



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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

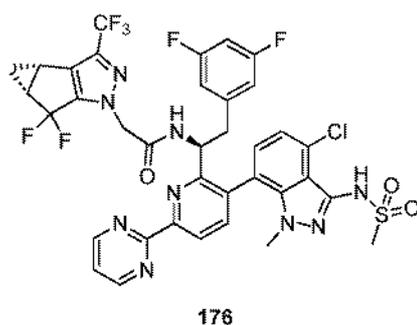
#### Example 175.



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-1H-pyrazole-5-boronic acid pinacol ester. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

Example 176.

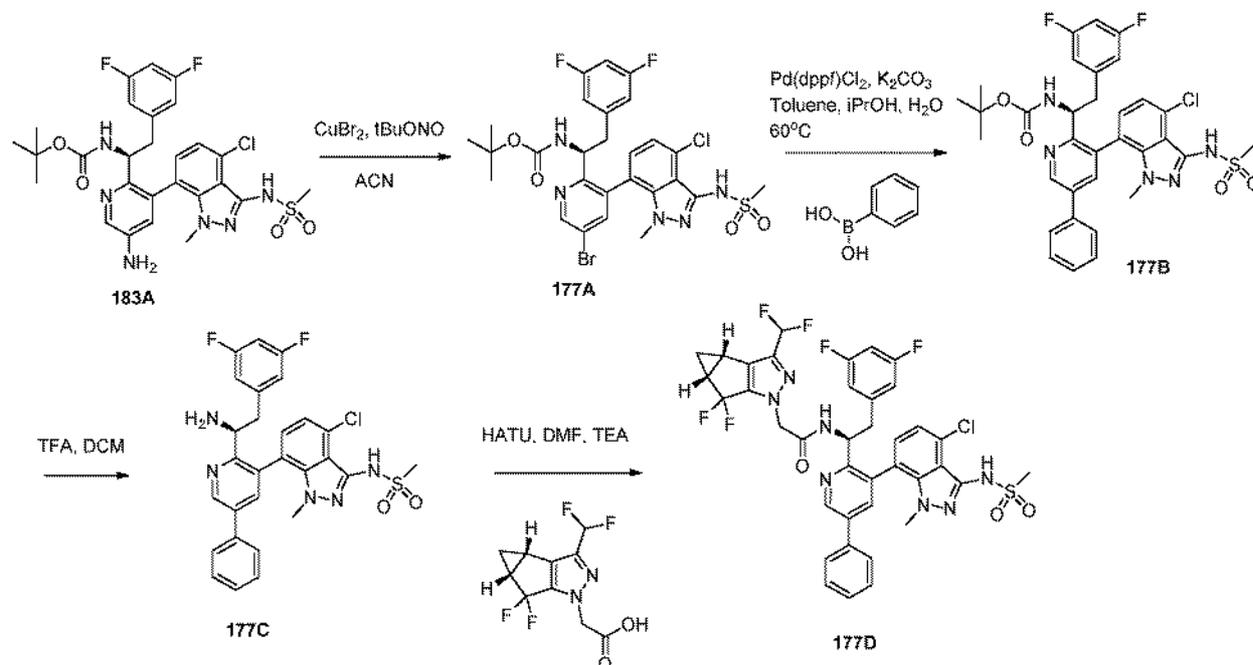


Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(pyrimidin-2-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (176):

[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. <sup>1</sup>H NMR (400 MHz, *cd*<sub>3</sub>od) 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  $\text{CuBr}_2$  (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  $\text{MgSO}_4$ , 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), phenylboronic acid (6.3mg, 0.051mmol),  $\text{K}_2\text{CO}_3$  (39mg, 0.28mmol) and  $\text{Pd}(\text{dppf})\text{Cl}_2$  (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<sub>4</sub> 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]<sup>+</sup>.

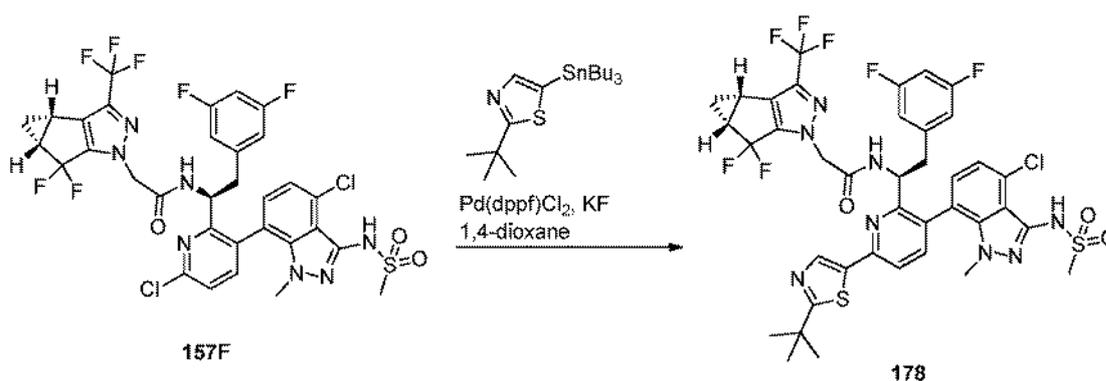
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-phenylpyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**177C**):

[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]<sup>+</sup>.

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**):

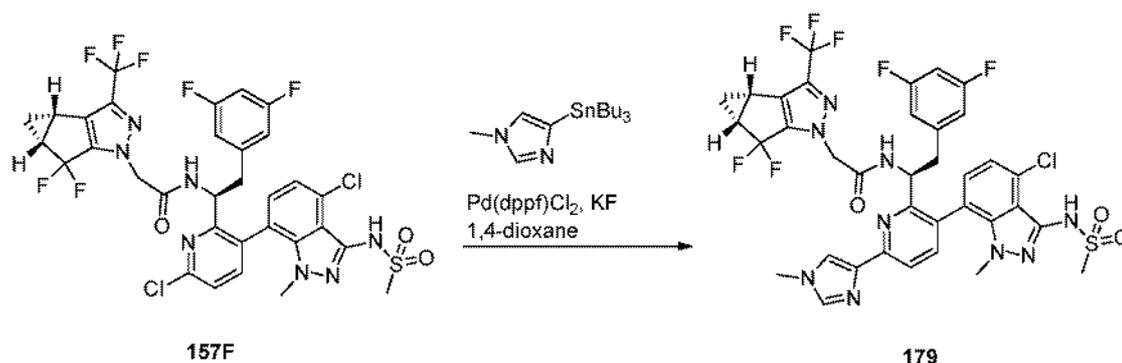
[0800] Compound **177C** (18.4mg, 0.032mmol) and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (8.6mg, 0.032mmol) were dissolved in DMF (1mL). TEA (23uL, 0.162mmol) and HATU (18.5mg, 0.049mmol) were added. Upon completion, a few drops of 1M HCl were added. The reaction was purified by HPLC to afford the title compound as mixture of atropisomers (**177D**). <sup>1</sup>H NMR (400 MHz, Acetonitrile-d<sub>3</sub>) 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]<sup>+</sup>.

Example 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<sub>2</sub> (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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

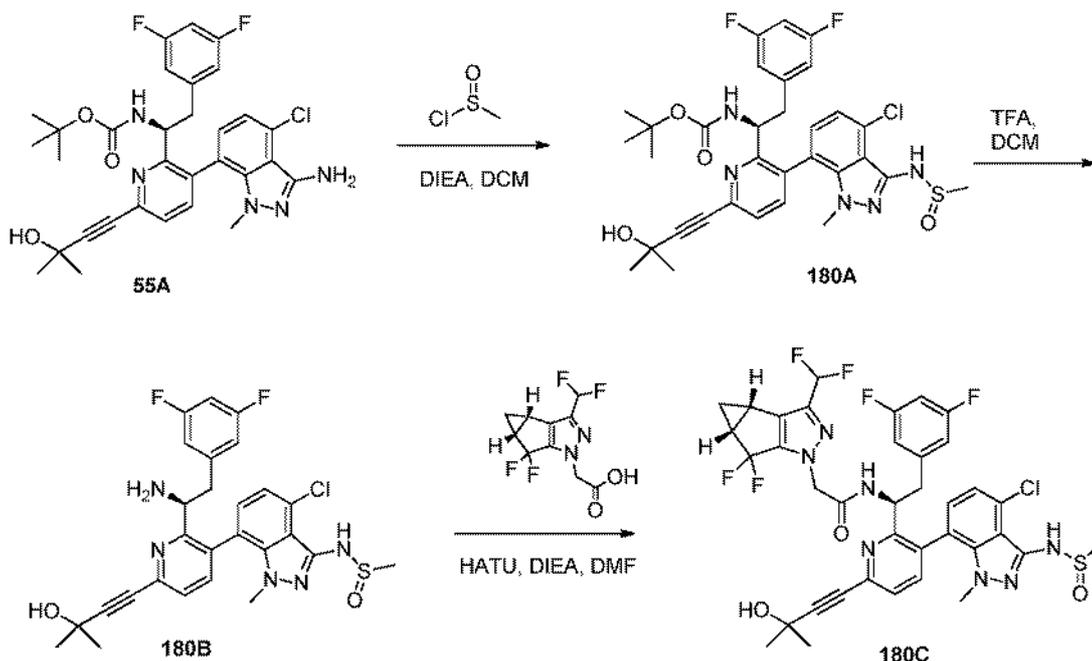
Example 179.



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)-1H-imidazole. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

## 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 °C 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]<sup>+</sup>.

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)methanesulfonamide (180B):

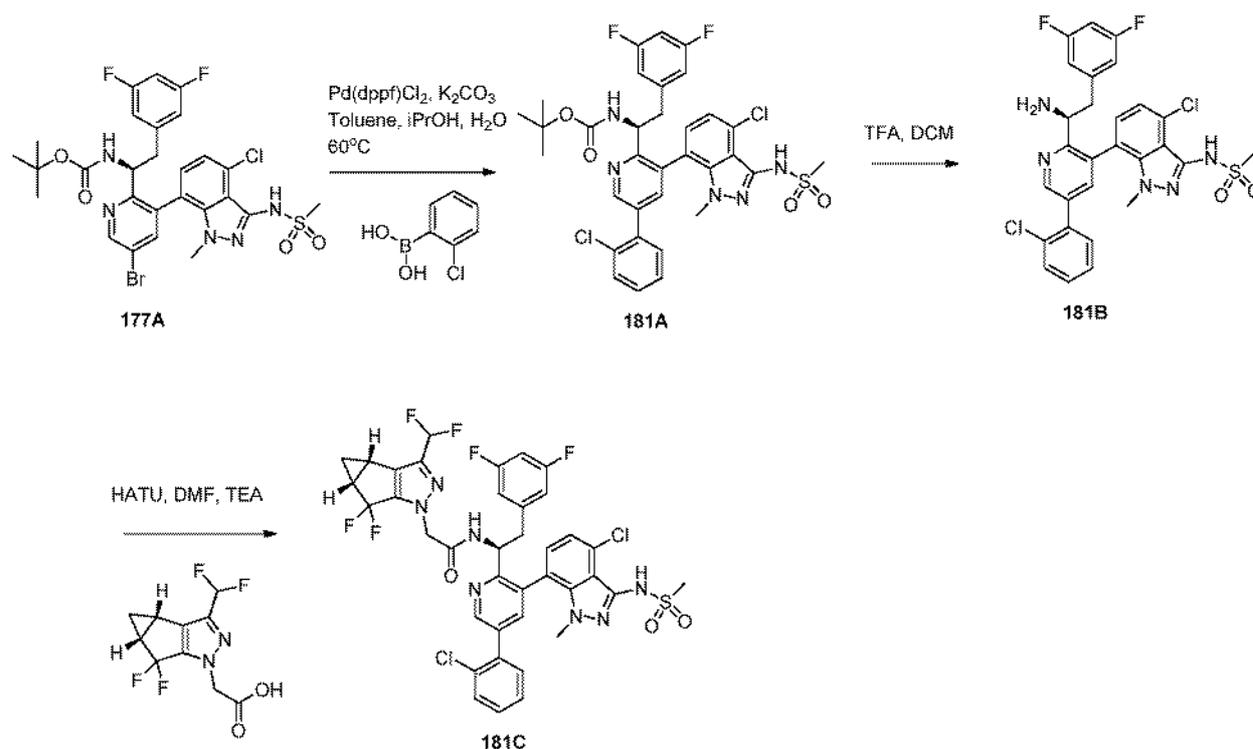
[0804] To a solution of tert-butyl ((1S)-1-(3-(4-chloro-1-methyl-3-(methylsulfinamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**180A**, 50 mg, 0.076 mmol) in DCM (1 mL) was added trifluoroacetic acid (1 mL). The reaction mixture was stirred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

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  $\mu$ L, 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.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  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 [ $\text{M}+\text{H}$ ] $^+$ .

Example 181.



Synthesis of (S)-tert-butyl (1-(3-(4-chloro-1-methyl-3-(methylsulfonylamido)-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-chlorophenylbromic acid. MS (m/z) 702 [M+H]<sup>+</sup>.

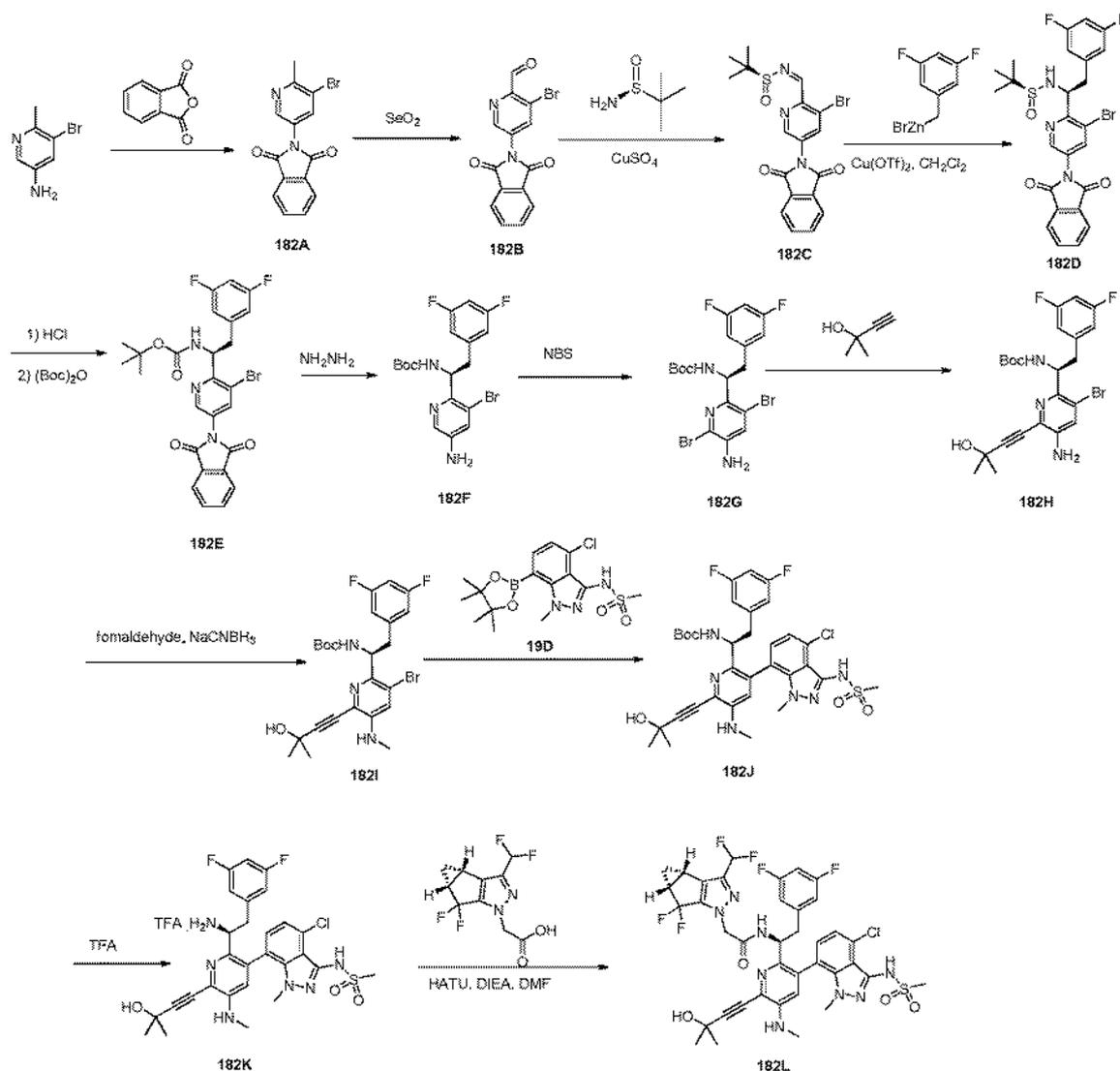
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(2-chlorophenyl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**181A**):

[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]<sup>+</sup>.

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. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) 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]<sup>+</sup>.

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**.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  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-dioxoisindolin-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-dioxoisindolin-2-yl)picolinaldehyde (**182B**, 6 g, 18 mmol) and (S)-2-methylpropane-2-sulfinamide (2.2 g, 18 mmol) in  $\text{CH}_2\text{Cl}_2$  (60 mL). The reaction mixture was stirred at ambient temperature for 2 hours and then filtered and washed with  $\text{CH}_2\text{Cl}_2$ . 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 [ $\text{M}+\text{H}$ ] $^+$ .

Synthesis of (S)-N-((S)-1-(3-bromo-5-(1,3-dioxoisindolin-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  $\text{Cu}(\text{OTf})_2$  (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  $\text{Na}_2\text{SO}_4$ , 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 [ $\text{M}+\text{H}$ ] $^+$ .

Synthesis of (S)-tert-butyl 1-(3-bromo-5-(1,3-dioxoisindolin-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  $\text{CH}_2\text{Cl}_2$  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  $\text{MgSO}_4$ , filtered and concentrated. Then it was purified on silica gel chromatography to yield the title compound **182E**. MS ( $m/z$ ) 559.71 [ $\text{M}+\text{H}$ ] $^+$ .

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]<sup>+</sup>.

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<sub>3</sub>. The organic layer was separated and washed with brine, then dried over MgSO<sub>4</sub> 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]<sup>+</sup>.

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]<sup>+</sup>.

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<sub>2</sub>O) 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<sub>2</sub>SO<sub>4</sub> 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]<sup>+</sup>.

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]<sup>+</sup>.

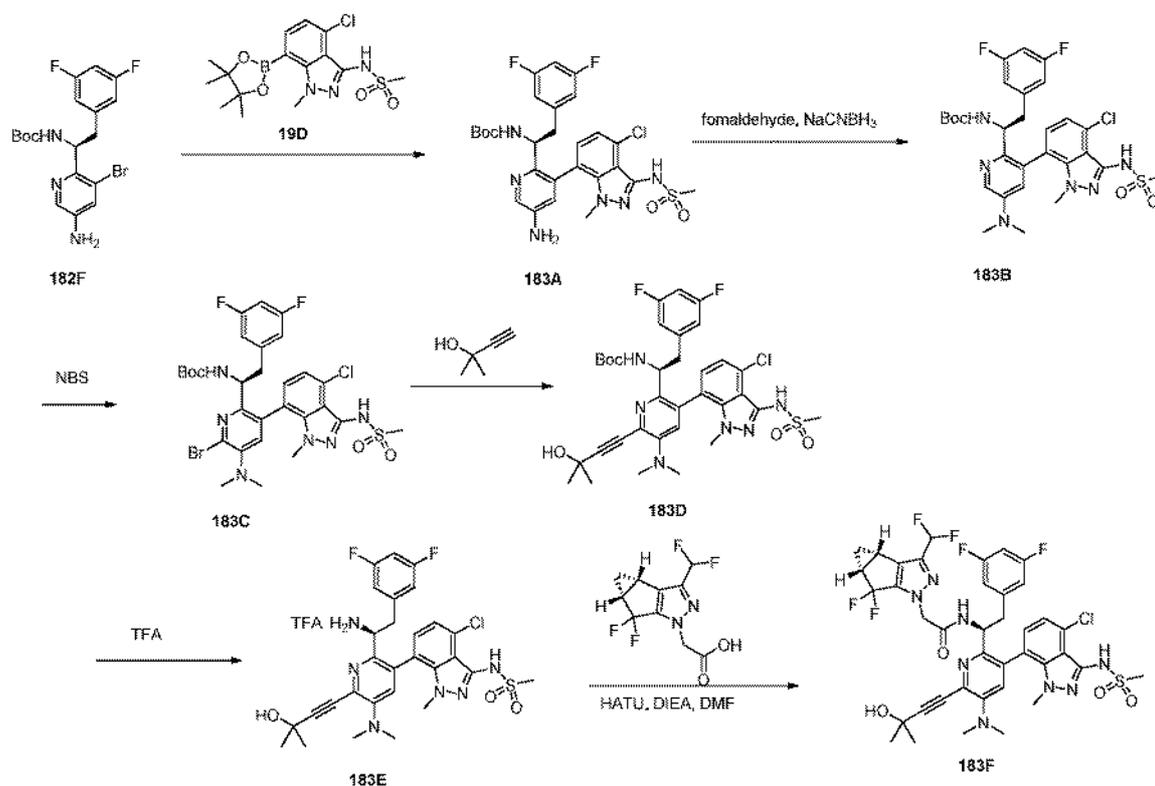
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-(methylamino)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (182K):

[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]<sup>+</sup>.

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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

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]<sup>+</sup>.

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]<sup>+</sup>.

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]<sup>+</sup>.

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]<sup>+</sup>.

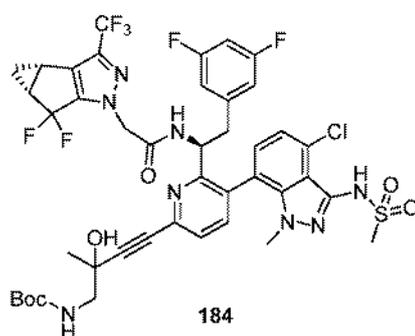
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-(dimethylamino)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**183E**):

[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]<sup>+</sup>.

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**. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

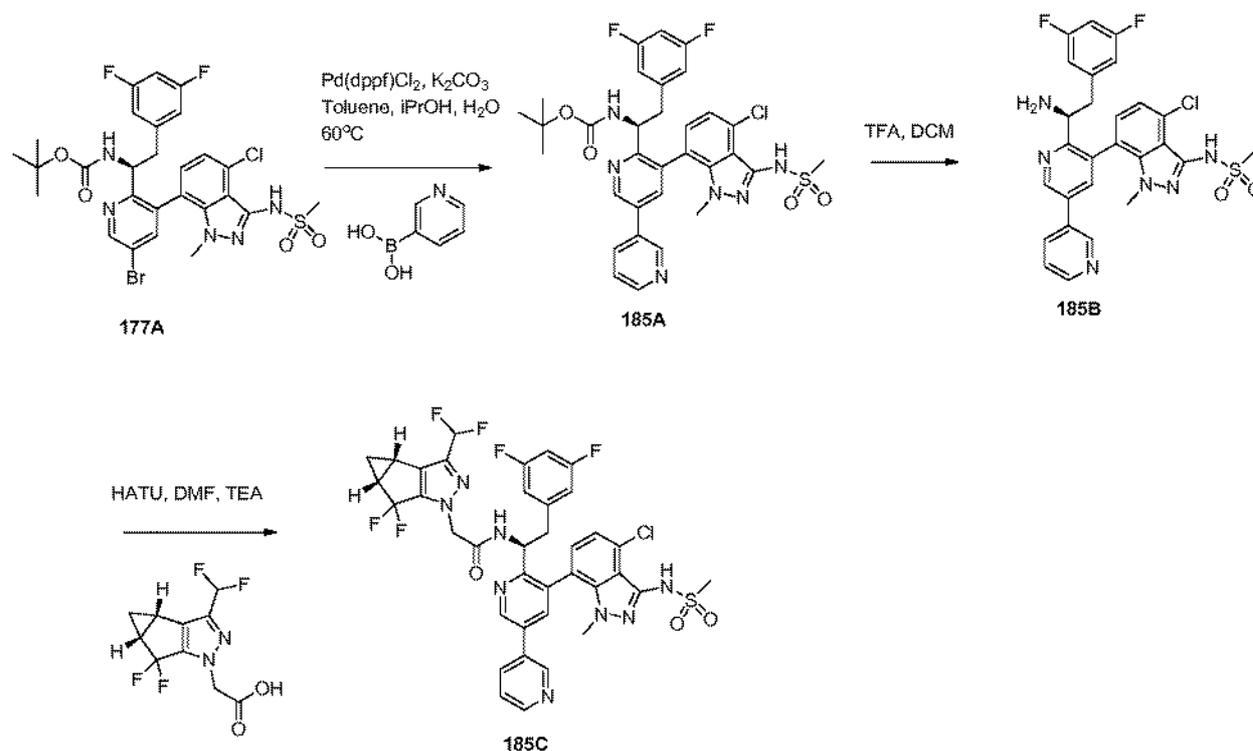
Example 184.



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 Phenomenex 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-pyridineboronic acid. MS ( $m/z$ ) 669  $[M+H]^+$ .

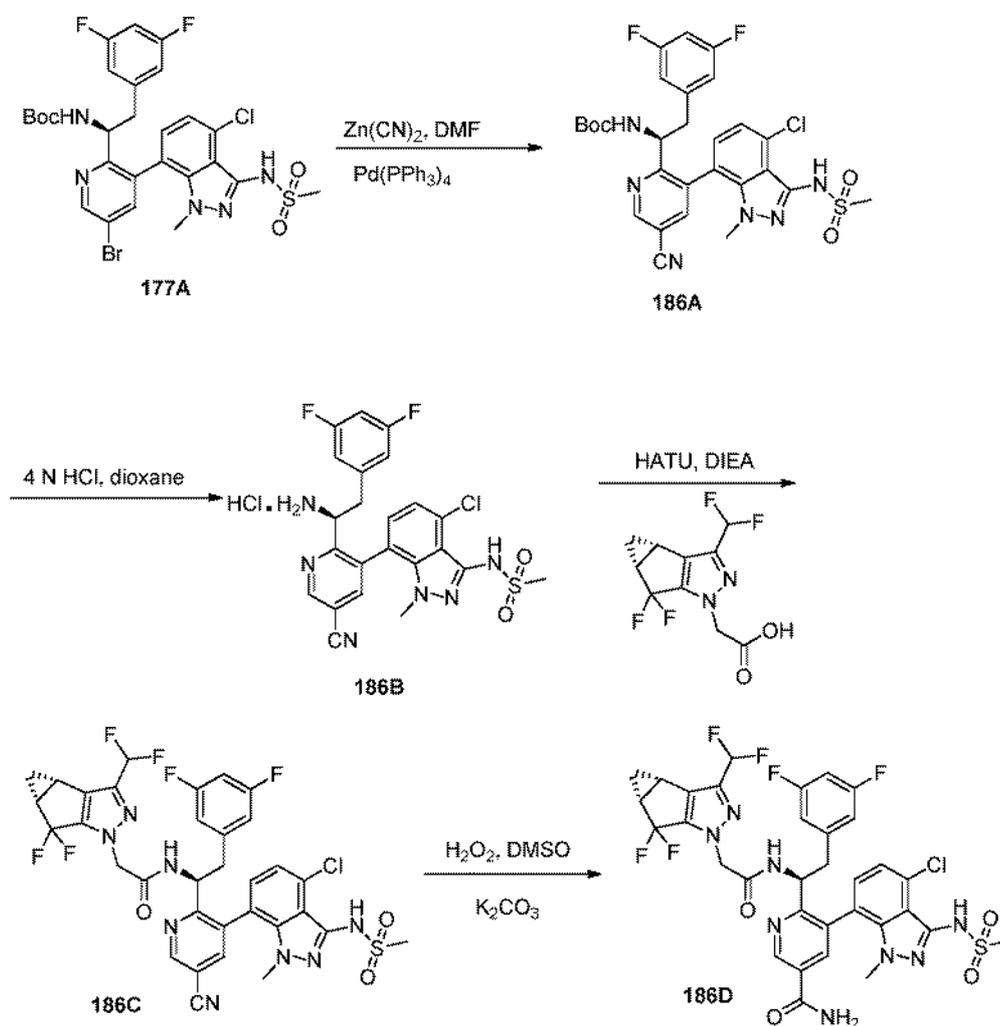
Synthesis of (S)-N-(7-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-[3,3'-bipyridin]-5-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**185B**):

[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**. <sup>1</sup>H NMR (400 MHz, Acetonitrile-d<sub>3</sub>) 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]<sup>+</sup>.

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  $[M+H]^+$ .

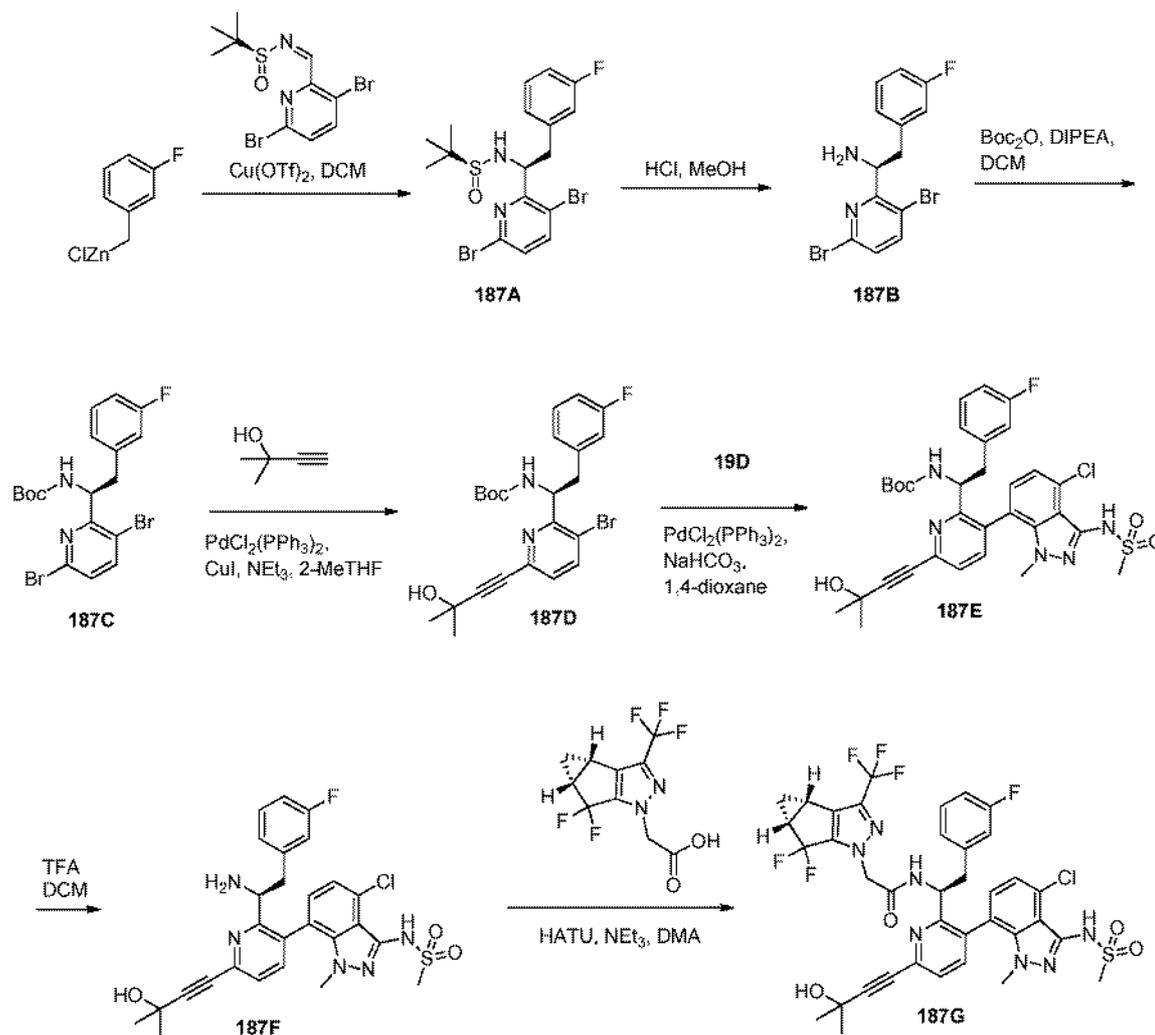
Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-5-cyanopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**186C**):

[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- $d_4$ )  $^1H$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  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-sulfonamide (187A):

[0835] To a solution of (S,Z)-N-((3,6-dibromopyridin-2-yl)methylene)-2-methylpropane-2-sulfonamide (1.0 g, 2.717 mmol) and Cu(OTf)<sub>2</sub> (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 minutes at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, then quenched with saturated aqueous NH<sub>4</sub>Cl 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<sub>2</sub>SO<sub>4</sub>, 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]<sup>+</sup>.

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-sulfonamide (**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]<sup>+</sup>.

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<sub>2</sub>O (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]<sup>+</sup>.

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<sub>3</sub> (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<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (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<sub>2</sub>SO<sub>4</sub>, 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]<sup>+</sup>.

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<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (27.9 mg, 0.04 mmol) were taken in 1,4-dioxane (10 mL) and NaHCO<sub>3</sub> (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]<sup>+</sup>.

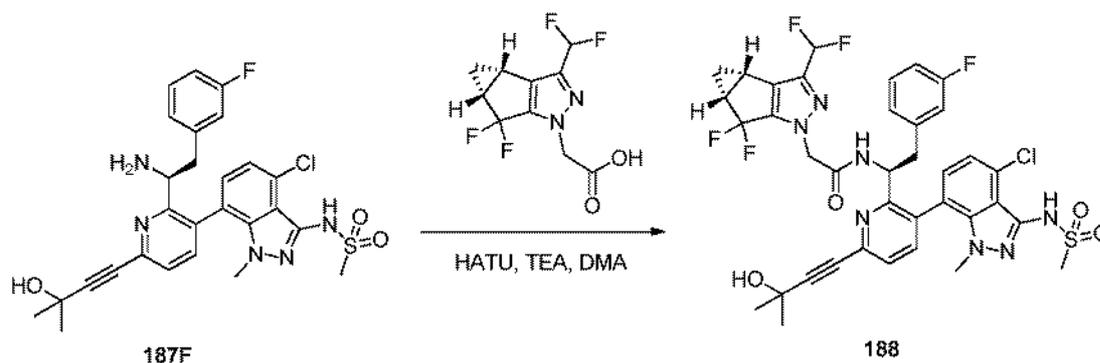
Synthesis of (S)-N-(7-(2-(1-amino-2-(3-fluorophenyl)ethyl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (**187F**):

**[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]<sup>+</sup>.

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<sub>3</sub> (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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

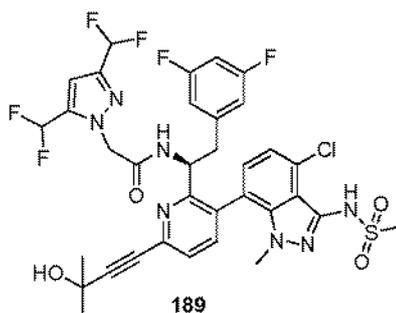
Example 188.



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

**[0842]** The title compound (**188**) was prepared as a mixture of atropisomers according to the method presented for the synthesis of compound **187G** of Example 187 utilizing 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

Example 189.

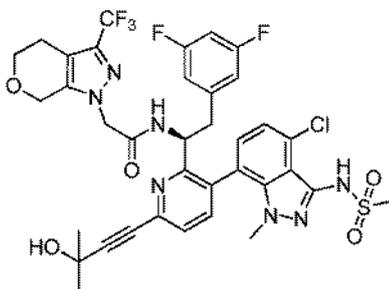


Synthesis of (S)-2-(3,5-bis(difluoromethyl)-1H-pyrazol-1-yl)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)acetamide (189):

**[0843]** The title compound (**189**) was prepared as a mixture of atropisomers according to the method presented in the synthesis of **10A** in Example 10 utilizing **19F** and 2-(3,5-bis(difluoromethyl)-1H-pyrazol-1-yl)acetic acid. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

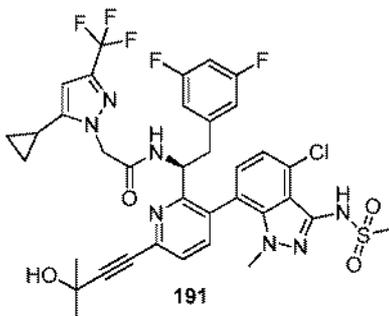
Example 190.



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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

Example 191.

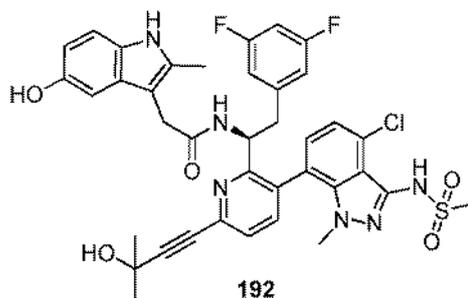


Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (191):

**[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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

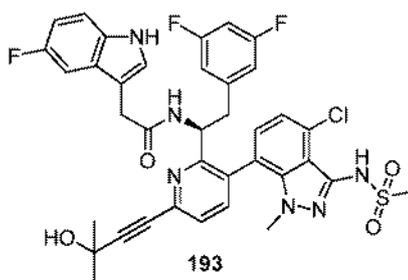
Example 192.



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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

Example 193.

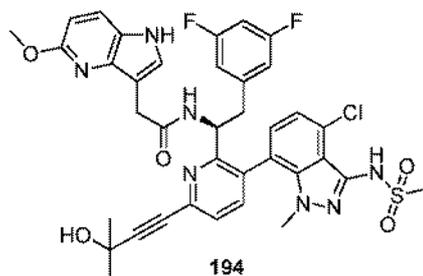


Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (193):

[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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

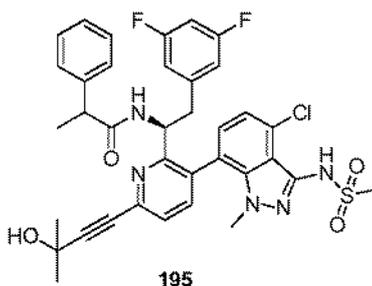
Example 194.



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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

Example 195.

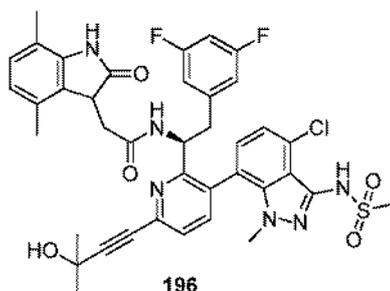


Synthesis of N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-phenylpropanamide (195):

[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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

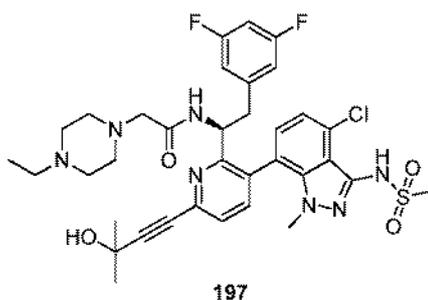
Example 196.



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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

Example 197.

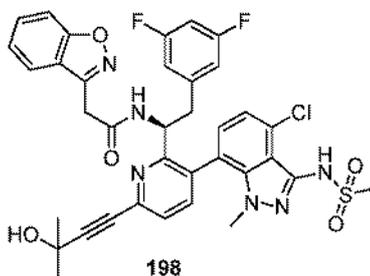


Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(4-ethylpiperazin-1-yl)acetamide (197):

**[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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

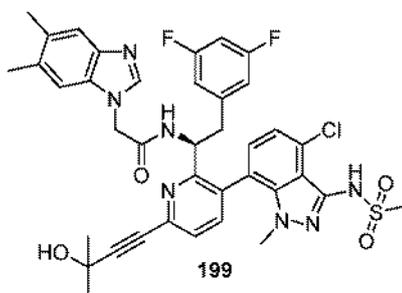
Example 198.



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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

Example 199.

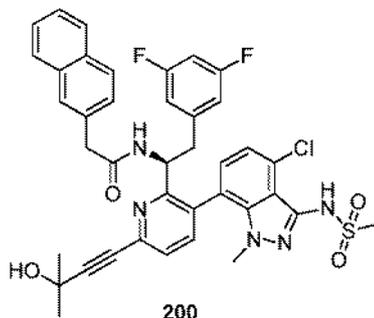


Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetamide (**199**):

**[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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

Example 200.

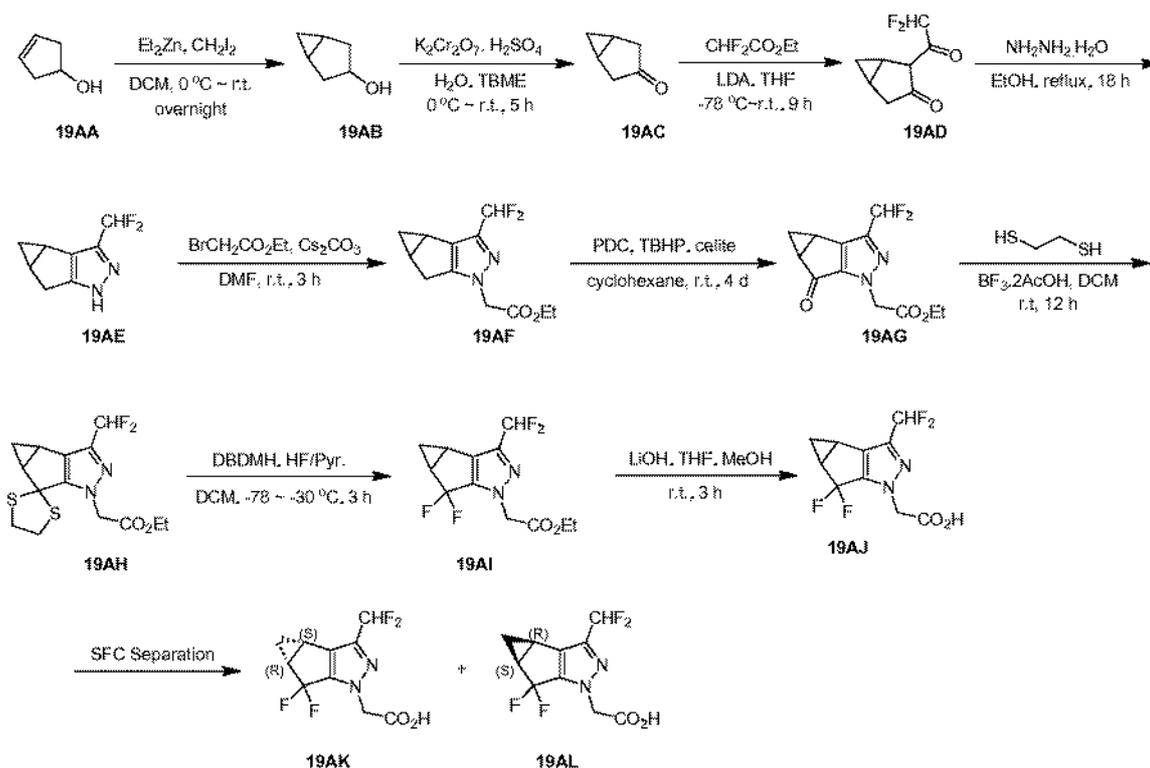


Synthesis of (S)-N-(1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(naphthalen-2-yl)acetamide (200):

[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. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) 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]<sup>+</sup>.

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]**  $\text{Et}_2\text{Zn}$  (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  $\text{N}_2$  at  $0\text{--}5^\circ\text{C}$ . The mixture was stirred at  $0\text{--}5^\circ\text{C}$  for 30 min, then  $\text{CH}_2\text{I}_2$  (636 g, 2.37 mol) in DCM (200 ml) was added drop-wise in 1 h at  $0\text{--}5^\circ\text{C}$ . The resulting mixture was stirred at room temperature overnight. The mixture was added slowly to ice-cold aq.  $\text{NH}_4\text{Cl}$  (1.5 L). The mixture was filtered. The aqueous phase was extracted with DCM (2L x 3). The combined organic layer was dried over  $\text{MgSO}_4$ , concentrated in vacuo to give crude residue, which was purified by distillation (20 mmHg,  $80^\circ\text{C}\text{--}82^\circ\text{C}$ ) to give compound **19AB**.  $^1\text{H NMR}$ : (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{K}_2\text{Cr}_2\text{O}_7$  (240 g, 0.82 mol) in  $\text{H}_2\text{O}$  (2 L),  $\text{H}_2\text{SO}_4$  (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  $0^\circ\text{C}$ , 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  $\text{MgSO}_4$ , filtered, concentrated in vacuo to give the crude product, which was purified by distillation (20 mmHg,  $60^\circ\text{C}\text{--}62^\circ\text{C}$ ) to give compound **19AC**.  $^1\text{H NMR}$  (400 MHz,

$\text{CDCl}_3$ )  $\delta$  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  $\text{N}_2$  over a period of 2 h. The resulting mixture was stirred 1 h at  $-78^\circ\text{C}$ . 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  $-78^\circ\text{C}$ . 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.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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]  $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$  (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  $[\text{M}+\text{H}]^+$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{Cs}_2\text{CO}_3$  (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  $\text{H}_2\text{O}$  (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  $\text{MgSO}_4$ , 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  $[\text{M}+\text{H}]^+$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{Na}_2\text{S}_2\text{O}_3$  (1000 ml) for 1 h. The organic layer was separated and treated with half saturated  $\text{FeSO}_4$  (300 ml), washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . 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  $[\text{M}+\text{H}]^+$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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.  $\text{BF}_3 \cdot 2\text{AcOH}$  (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  $\text{NaHCO}_3$  (1000 ml). The organic layer was separated, washed with brine (500 ml) and dried over  $\text{Na}_2\text{SO}_4$ . 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  $[\text{M}+\text{H}]^+$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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

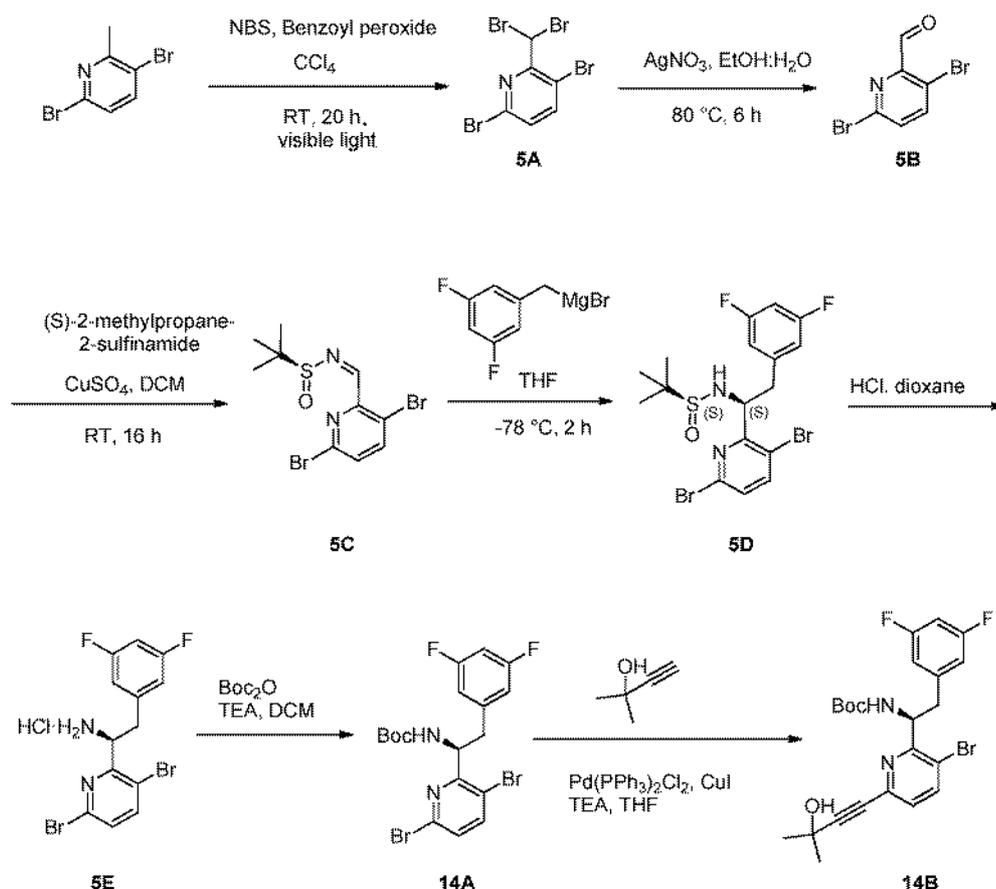
DCM (80 mL) was added drop-wise over a period of 15 min at -78 °C. The resulting mixture was stirred for 30 min at this temperature, then slowly warm to -30 °C and stirred for 1.5 h. The reaction mixture was slowly poured into aq. NaHCO<sub>3</sub> (500 mL) and extracted with EA (500 mLx3). The combined organic layer was washed with 10% aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (500 mL), brine (500 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. 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]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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<sub>2</sub>O (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<sub>2</sub>SO<sub>4</sub>, 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, 300x50mm I.D., mobile phase: CO<sub>2</sub> / isopropanol (0.1% NH<sub>3</sub>H<sub>2</sub>O), 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]<sup>+</sup>; <sup>1</sup>H NMR: (400 MHz, DMSO-d<sub>6</sub>) 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]<sup>+</sup>; <sup>1</sup>H NMR: (400 MHz, DMSO-d<sub>6</sub>) 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  $\text{CCl}_4$  (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  $\text{CCl}_4$  (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  $[\text{M}+\text{H}]^+$ .

#### Synthesis of 3,6-dibromopicolinaldehyde (5B):

[0866] To a solution of compound 5A (100.0 g, 244.67 mmol) in EtOH (1000 mL) at  $80^\circ\text{C}$ , 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]<sup>+</sup>

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]<sup>+</sup>

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<sub>4</sub>Cl (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<sub>2</sub>SO<sub>4</sub>. 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]<sup>+</sup>

Synthesis of (S)-1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethanamine hydrochloride(**5E**):

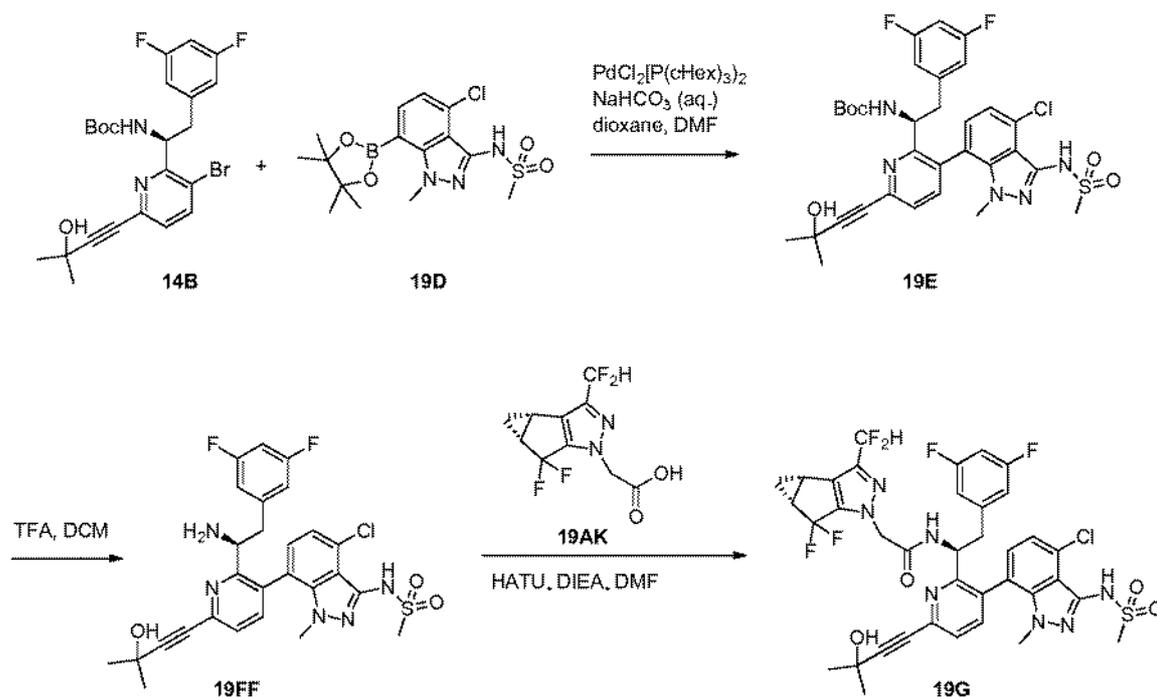
[0869] To a solution of compound **5D** (53 g, 107 mmol) in methanol (100 mL) was slowly added 4 N HCl in dioxane (30 mL) at room temperature. Upon completion of the reaction, the volatiles were removed in vacuo. The resulting solid was suspended in ether (200 mL) and collected by filtration to provide compound **5E**. MS (*m/z*) 393.17 [M+H]<sup>+</sup>

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)ethylcarbamate (14B):

**[0871]** A solution of compound **14A** (570 mg, 1.16 mmol), 3-methyl butynol (179  $\mu$ L, 1.74 mmol), CuI (6 mg, 0.03 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (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 °C 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<sub>4</sub>Cl, water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>. 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<sub>2</sub> 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]<sup>+</sup>.

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<sub>3</sub> (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]<sup>+</sup>.

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<sub>3</sub>. 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]<sup>+</sup>.

#### 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	<u>mg/tablet</u>
Compound X=	100.0
Lactose	77.5
Povidone	15.0
Croscarmellose sodium	12.0
Microcrystalline cellulose	92.5
Magnesium stearate	<u>3.0</u>
	300.0

<u>(ii) Tablet 2</u>	<u>mg/tablet</u>
Compound X=	20.0
Microcrystalline cellulose	410.0
Starch	50.0
Sodium starch glycolate	15.0
Magnesium stearate	<u>5.0</u>
	500.0
<u>(iii) Capsule</u>	<u>mg/capsule</u>
Compound X=	10.0
Colloidal silicon dioxide	1.5
Lactose	465.5
Pregelatinized starch	120.0
Magnesium stearate	<u>3.0</u>
	600.0
<u>(iv) Injection 1 (1 mg/ml)</u>	<u>mg/ml</u>
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
<u>(v) Injection 2 (10 mg/ml)</u>	<u>mg/ml</u>
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
<u>(vi) Aerosol</u>	<u>mg/can</u>
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

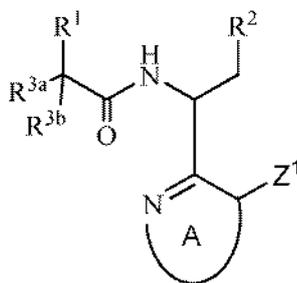
of the element and/or the effect a given amount of variation will have on the performance of the claimed subject matter, as well as other considerations known to those of skill in the art. As used herein, the use of differing amounts of significant digits for different numerical values is not meant to 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<sup>1</sup> group at the position shown, one Z<sup>2</sup> group, and optionally substituted with one or more (e.g., 1 or 2) Z<sup>3</sup> 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<sub>3</sub>-C<sub>7</sub>)carbocycle, wherein any phenyl, 5-membered monocyclic-heteroaryl, 6-membered monocyclic-heteroaryl or (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>3</sub>)alkyl and (C<sub>1</sub>-C<sub>3</sub>)haloalkyl, or  $R^{3a}$  is selected from H, (C<sub>1</sub>-C<sub>3</sub>)alkyl and (C<sub>1</sub>-C<sub>3</sub>)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<sub>3</sub>-C<sub>7</sub>)carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, -OR<sup>n1</sup>, -OC(O)R<sup>p1</sup>, -OC(O)NR<sup>q1</sup>R<sup>r1</sup>, -SR<sup>n1</sup>, -S(O)R<sup>p1</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p1</sup>, -S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>COR<sup>p1</sup>, -NR<sup>n1</sup>CO<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>CONR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>OR<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, NO<sub>2</sub>, -C(O)R<sup>n1</sup>, -C(O)OR<sup>n1</sup>, -C(O)NR<sup>q1</sup>R<sup>r1</sup> and -S(O)<sub>2</sub>NR<sup>n1</sup>COR<sup>p1</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)alkynyl, wherein any (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)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<sub>3</sub>-C<sub>7</sub>)carbocycle, phenyl, 5-6 membered monocyclic-heteroaryl, 3-7 membered heterocycle, halogen, -CN, -OR<sup>n2</sup>, -OC(O)R<sup>p2</sup>, -OC(O)NR<sup>q2</sup>R<sup>r2</sup>, -SR<sup>n2</sup>, -S(O)R<sup>p2</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p2</sup>, -S(O)<sub>2</sub>NR<sup>q2</sup>R<sup>r2</sup>, -NR<sup>q2</sup>R<sup>r2</sup>, -NR<sup>n2</sup>COR<sup>p2</sup>, -NR<sup>n2</sup>CO<sub>2</sub>R<sup>p2</sup>, -NR<sup>n2</sup>CONR<sup>q2</sup>R<sup>r2</sup>, -NR<sup>n2</sup>S(O)<sub>2</sub>R<sup>p2</sup>, -NR<sup>n2</sup>S(O)<sub>2</sub>OR<sup>p2</sup>, -NR<sup>n2</sup>S(O)<sub>2</sub>NR<sup>q2</sup>R<sup>r2</sup>, NO<sub>2</sub>, -C(O)R<sup>n2</sup>, -C(O)OR<sup>n2</sup>, -C(O)NR<sup>q2</sup>R<sup>r2</sup>, halophenyl, 5-6 membered haloheteroaryl, 3-7 membered haloheterocycle and (C<sub>1</sub>-C<sub>8</sub>)heteroalkyl;

each  $Z^{1d}$  is independently selected from (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl and (C<sub>1</sub>-C<sub>8</sub>)haloalkyl;

each  $R^{n1}$  is independently selected from H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, (C<sub>1</sub>-C<sub>8</sub>)haloalkyl and (C<sub>1</sub>-C<sub>8</sub>)heteroalkyl;

each  $R^{p2}$  is independently selected from (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, (C<sub>1</sub>-C<sub>8</sub>)haloalkyl and (C<sub>1</sub>-C<sub>8</sub>)heteroalkyl;

$R^{q2}$  and  $R^{r2}$  are each independently selected from H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered

haloheterocycle, (C<sub>1</sub>-C<sub>8</sub>)haloalkyl and (C<sub>1</sub>-C<sub>8</sub>)heteroalkyl, or R<sup>q2</sup> and R<sup>r2</sup> together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

Z<sup>2</sup> is selected from (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, -C(O)R<sup>n3</sup> and -C(O)NR<sup>q3</sup>R<sup>r3</sup>, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl and 3-12 membered C-linked-heterocycle of Z<sup>2</sup> is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z<sup>2b</sup> or Z<sup>2c</sup> groups, and wherein any (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)alkynyl of Z<sup>2</sup> is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) Z<sup>2c</sup> groups;

each Z<sup>2a</sup> is independently selected from (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, -OR<sup>n4</sup>, -OC(O)R<sup>p4</sup>, -OC(O)NR<sup>q4</sup>R<sup>r4</sup>, -SR<sup>n4</sup>, -S(O)R<sup>p4</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p4</sup>, -S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>COR<sup>p4</sup>, -NR<sup>n4</sup>CO<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>CONR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>OR<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, NO<sub>2</sub>, -C(O)R<sup>n4</sup>, -C(O)OR<sup>n4</sup> and -C(O)NR<sup>q4</sup>R<sup>r4</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z<sup>2a</sup> is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z<sup>2b</sup> or Z<sup>2c</sup> groups;

each Z<sup>2b</sup> is independently selected from (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl and (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

each Z<sup>2c</sup> is independently selected from halogen, -CN, -OR<sup>n4</sup>, -OC(O)R<sup>p4</sup>, -OC(O)NR<sup>q4</sup>R<sup>r4</sup>, -SR<sup>n4</sup>, -S(O)R<sup>p4</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p4</sup>, -S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>COR<sup>p4</sup>, -NR<sup>n4</sup>CO<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>CONR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>OR<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, NO<sub>2</sub>, -C(O)R<sup>n4</sup>, -C(O)OR<sup>n4</sup> and -C(O)NR<sup>q4</sup>R<sup>r4</sup>;

each R<sup>n3</sup> is independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl of R<sup>n3</sup> is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z<sup>2b</sup> or Z<sup>2c</sup> groups, and wherein any (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl of R<sup>n3</sup> is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z<sup>2a</sup> groups;

R<sup>q3</sup> and R<sup>r3</sup> are each independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl of R<sup>q3</sup> or R<sup>r3</sup> is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z<sup>2b</sup> or Z<sup>2c</sup> groups, and wherein any (C<sub>1</sub>-C<sub>4</sub>)alkyl and (C<sub>2</sub>-C<sub>4</sub>)alkenyl of R<sup>q3</sup> or R<sup>r3</sup> 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<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl and (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $R^{p4}$  is independently selected from (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>2</sub>-C<sub>4</sub>)alkynyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl and (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

$R^{q4}$  and  $R^{r4}$  are each independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>2</sub>-C<sub>4</sub>)alkynyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl and (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $Z^3$  is independently selected from halogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, -OH, -CN, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl and (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

each  $Z^4$  is independently selected from (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, halogen, -CN, -OR<sup>n5</sup>, -OC(O)R<sup>p5</sup>, -OC(O)NR<sup>q5</sup>R<sup>r5</sup>, -SR<sup>n5</sup>, -S(O)R<sup>p5</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p5</sup>, -S(O)<sub>2</sub>NR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>n5</sup>COR<sup>p5</sup>, -NR<sup>n5</sup>CO<sub>2</sub>R<sup>p5</sup>, -NR<sup>n5</sup>CONR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>n5</sup>S(O)<sub>2</sub>R<sup>p5</sup>, -NR<sup>n5</sup>S(O)<sub>2</sub>OR<sup>p5</sup>, -NR<sup>n5</sup>S(O)<sub>2</sub>NR<sup>q5</sup>R<sup>r5</sup>, NO<sub>2</sub>, -C(O)R<sup>n5</sup>, -C(O)OR<sup>n5</sup> and -C(O)NR<sup>q5</sup>R<sup>r5</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)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<sup>n6</sup>, -OC(O)R<sup>p6</sup>, -OC(O)NR<sup>q6</sup>R<sup>r6</sup>, -SR<sup>n6</sup>, -S(O)R<sup>p6</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p6</sup>, -S(O)<sub>2</sub>NR<sup>q6</sup>R<sup>r6</sup>, -NR<sup>q6</sup>R<sup>r6</sup>, -NR<sup>n6</sup>COR<sup>p6</sup>, -NR<sup>n6</sup>CO<sub>2</sub>R<sup>p6</sup>, -NR<sup>n6</sup>CONR<sup>q6</sup>R<sup>r6</sup>, -NR<sup>n6</sup>S(O)<sub>2</sub>R<sup>p6</sup>, -NR<sup>n6</sup>S(O)<sub>2</sub>OR<sup>p6</sup>, -NR<sup>n6</sup>S(O)<sub>2</sub>NR<sup>q6</sup>R<sup>r6</sup>, NO<sub>2</sub>, -C(O)R<sup>n6</sup>, -C(O)OR<sup>n6</sup> and -C(O)NR<sup>q6</sup>R<sup>r6</sup>;

each  $Z^{4b}$  is independently selected from (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl (C<sub>2</sub>-C<sub>4</sub>)alkynyl and (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

each  $R^{n5}$  is independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

each  $R^{p5}$  is independently selected from (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

$R^{q5}$  and  $R^{r5}$  are each independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

each  $R^{n6}$  is independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

each  $R^{p6}$  is independently selected from (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

$R^{q6}$  and  $R^{r6}$  are each independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

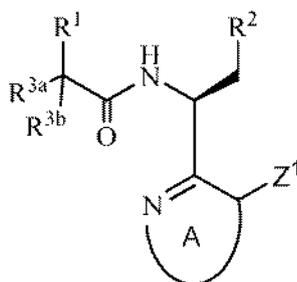
each  $Z^5$  is independently selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, -CN and -OR<sup>n7</sup>,

wherein any (C<sub>1</sub>-C<sub>6</sub>)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<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>3</sub>)haloalkyl and (C<sub>3</sub>-C<sub>7</sub>)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.

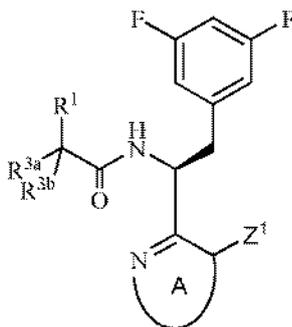
Embodiment I-5. The compound of any one of Embodiments I-1 to I-3 wherein  $R^2$  is phenyl optionally substituted with one or more  $Z^5$  groups.

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.

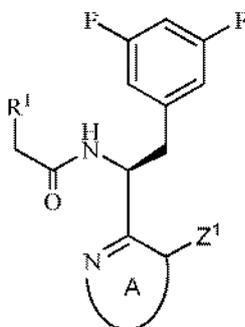
Embodiment I-9. The compound of Embodiment I-1 which is a compound of formula Ig:



Ig

or a pharmaceutically acceptable salt thereof.

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



Ie

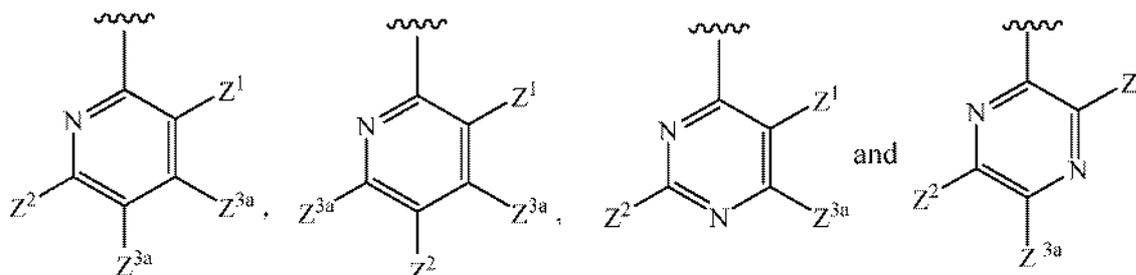
or a pharmaceutically acceptable salt thereof.

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.

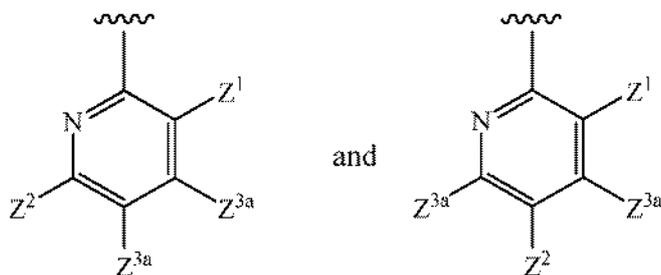
Embodiment I-13. The compound of any one of Embodiments I-1 to I-12 wherein A is substituted with one  $Z^1$  group at the position shown and one  $Z^2$  group.

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



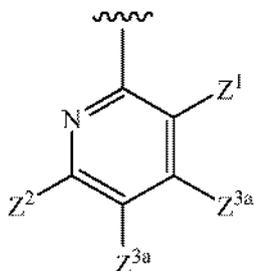
wherein each  $Z^{3a}$  is independently selected from H and  $Z^3$ .

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



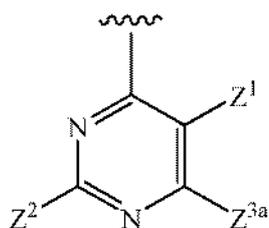
wherein each  $Z^{3a}$  is independently selected from H and  $Z^3$ .

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



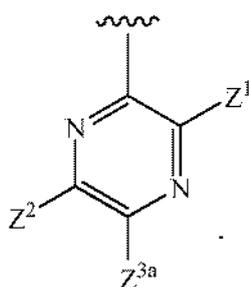
wherein each  $Z^{3a}$  is independently selected from H and  $Z^3$ .

Embodiment I-17. The compound of any one of Embodiments I-1 to I-10 wherein A- $Z^1$  is:



wherein Z<sup>3a</sup> is selected from H and Z<sup>3</sup>.

Embodiment I-18. The compound of any one of Embodiments I-1 to I-10 wherein A-Z<sup>1</sup> is:



wherein Z<sup>3a</sup> is selected from H and Z<sup>3</sup>.

Embodiment I-19. The compound of any one of Embodiments I-14 to I-18 wherein each Z<sup>3a</sup> is H.

Embodiment I-20. The compound of any one of Embodiments I-1 to I-19 wherein Z<sup>1</sup> 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<sup>1</sup> is optionally substituted with one or more Z<sup>1a</sup> or Z<sup>1b</sup> groups.

Embodiment I-21. The compound of any one of Embodiments I-1 to I-19 wherein Z<sup>1</sup> 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<sup>1</sup> is optionally substituted with one or more Z<sup>1a</sup> or Z<sup>1b</sup> groups.

Embodiment I-22. The compound of any one of Embodiments I-1 to I-19 wherein Z<sup>1</sup> 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-oxoisindolinyl, 4-oxo-3,4-dihydroquinazolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, 1H-2-oxo-pyridinyl and 2,4-dioxo-1,2,3,4-tetrahydroquinazolinyl, wherein any phenyl, 1H-pyrrolo[2,3-b]pyridinyl, 1-oxoisindolinyl, 4-oxo-3,4-dihydroquinazolinyl, 3-oxospiro[cyclopropane-1,1'-isoindolin]-yl, 1H-2-oxo-pyridinyl and 2,4-dioxo-1,2,3,4-tetrahydroquinazolinyl of  $Z^1$  is optionally substituted with one or more  $Z^{1a}$  or  $Z^{1b}$  groups.

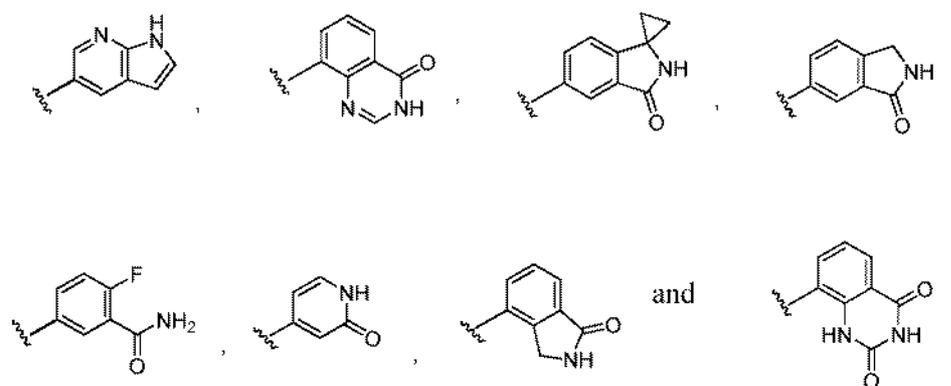
Embodiment I-26. The compound of any one of Embodiments I-1 to I-19 wherein  $Z^1$  is selected from phenyl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1-oxoisindolin-5-yl, 1-oxoisindolin-4-yl, 4-oxo-3,4-dihydroquinazolin-8-yl, 3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl, 1H-2-oxo-pyridin-4-yl and 2,4-dioxo-1,2,3,4-tetrahydroquinazolin-8-yl,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



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.

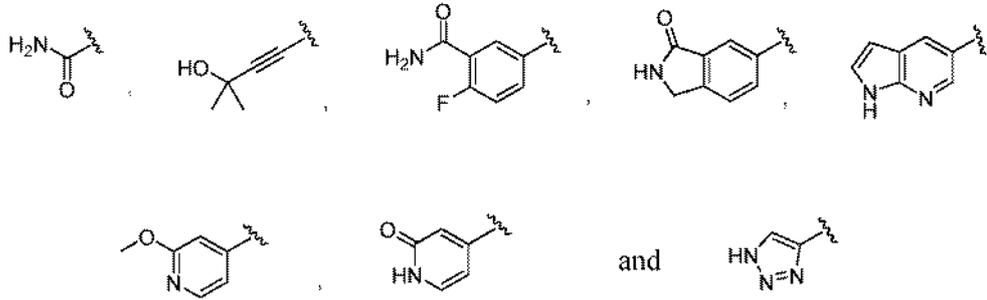
Embodiment I-36. The compound of any one of Embodiments I-1 to I-35 wherein  $Z^2$  is optionally substituted with one or more  $Z^{2c}$  groups.

Embodiment I-37. The compound of any one of Embodiments I-1 to I-36 wherein  $R^{q3}$  and  $R^{r3}$  are each H.

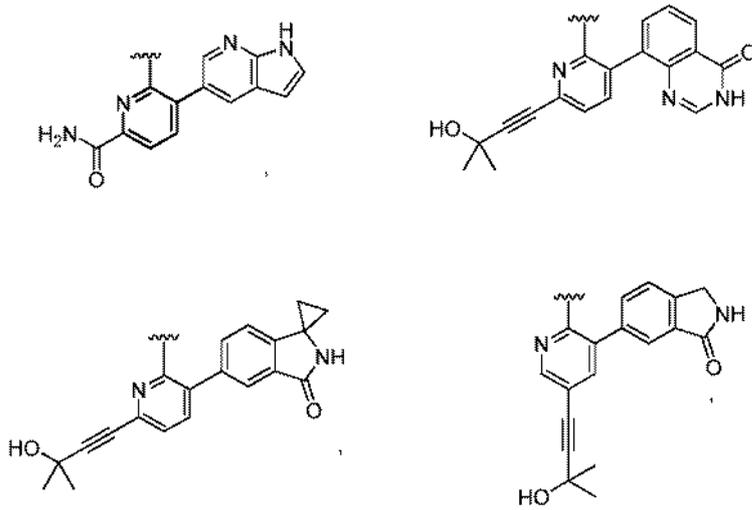
Embodiment I-38. The compound of any one of Embodiments I-1 to I-37 wherein each  $Z^{2c}$  is independently selected from halogen,  $-OR^{n4}$  and  $-C(O)NR^{q4}R^{r4}$ .

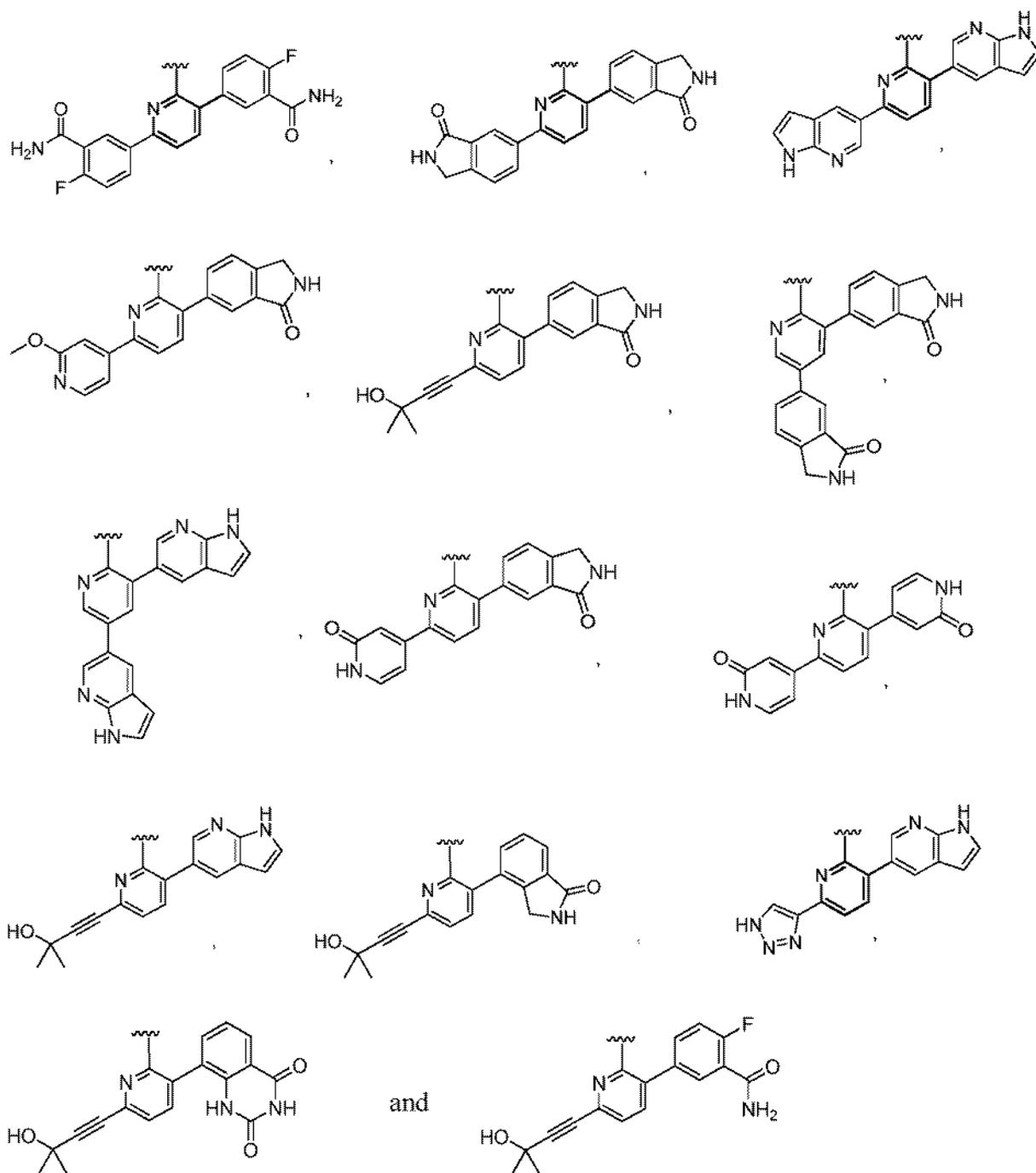
Embodiment I-39. The compound of any one of Embodiments I-1 to I-38 wherein  $R^{n4}$  is H or methyl, and  $R^{q4}$  and  $R^{r4}$  are each H.

Embodiment I-40. The compound of any one of Embodiments I-1 to I-30 wherein  $Z^2$  is selected from:



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





Embodiment I-42. The compound of any one of Embodiments I-1 to I-41 wherein R<sup>1</sup> is a 5-12 membered heteroaryl, wherein any 5-12 membered heteroaryl of R<sup>1</sup> is optionally substituted with one or more Z<sup>4</sup> groups.

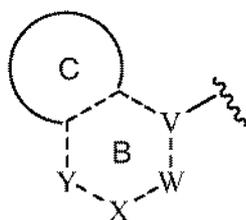
Embodiment I-43. The compound of any one of Embodiments I-1 to I-41 wherein R<sup>1</sup> is a 8-12 membered bicyclic-heteroaryl or 8-12 membered tricyclic-heteroaryl, wherein any 8-12

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;

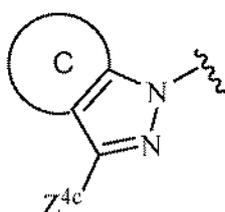
X is CZ<sup>4c</sup>, NZ<sup>4c</sup> or N;

Y is CZ<sup>4c</sup>, 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<sup>4c</sup> is independently selected from H or Z<sup>4</sup>.

Embodiment I-47. The compound of any one of Embodiments I-1 to I-41 wherein R<sup>1</sup> has the following formula II d:



II d

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<sup>4</sup> groups; and

each Z<sup>4c</sup> is independently selected from H or Z<sup>4</sup>.

Embodiment I-48. The compound of any one of Embodiments I-1 to I-41 wherein R<sup>1</sup> 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<sup>1</sup> is optionally substituted with one or more Z<sup>4</sup> groups.

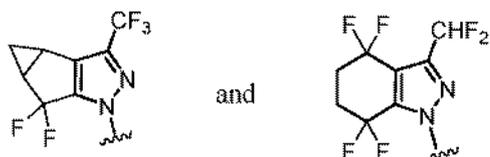
Embodiment I-49. The compound of any one of Embodiments I-1 to I-41 wherein R<sup>1</sup> is selected from 3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl and 4,5,6,7-tetrahydro-indazol-1-yl, wherein any 3b,4,4a,5-tetrahydro-1H-

cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl and 4,5,6,7-tetrahydro-indazol-1-yl of R<sup>1</sup> is optionally substituted with one or more Z<sup>4</sup> groups.

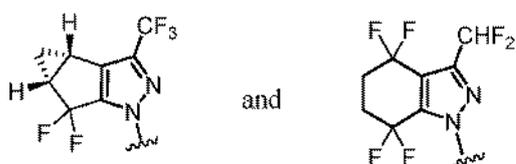
Embodiment I-50. The compound of any one of Embodiments I-1 to I-49 wherein each Z<sup>4</sup> is independently selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl and halogen, wherein any (C<sub>1</sub>-C<sub>6</sub>)alkyl of Z<sup>4</sup> is optionally substituted with one or more halogen.

Embodiment I-51. The compound of any one of Embodiments I-1 to I-49 wherein each Z<sup>4</sup> is independently selected from fluoro, trifluoromethyl and difluoromethyl.

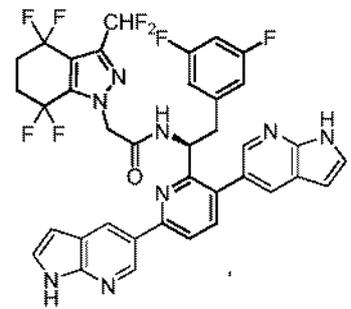
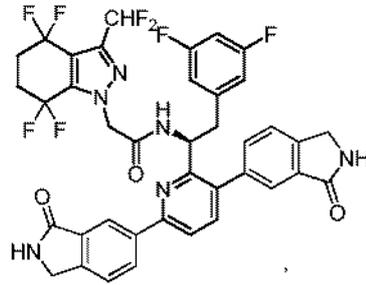
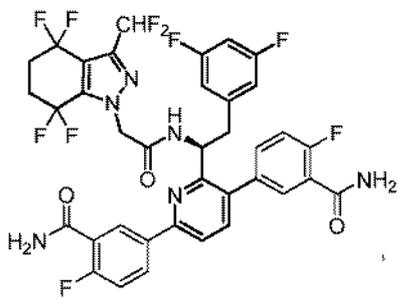
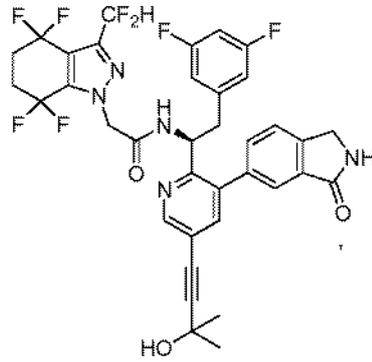
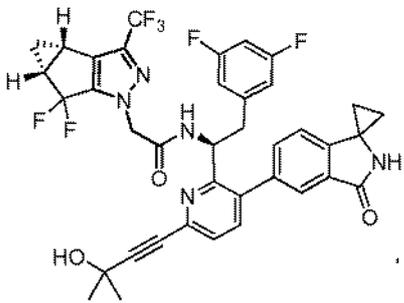
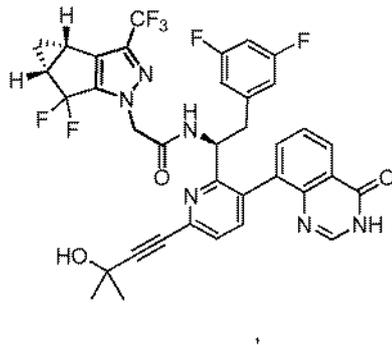
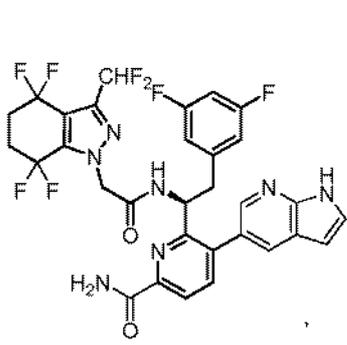
Embodiment I-52. The compound of any one of Embodiments I-1 to I-41 wherein R<sup>1</sup> is selected from:

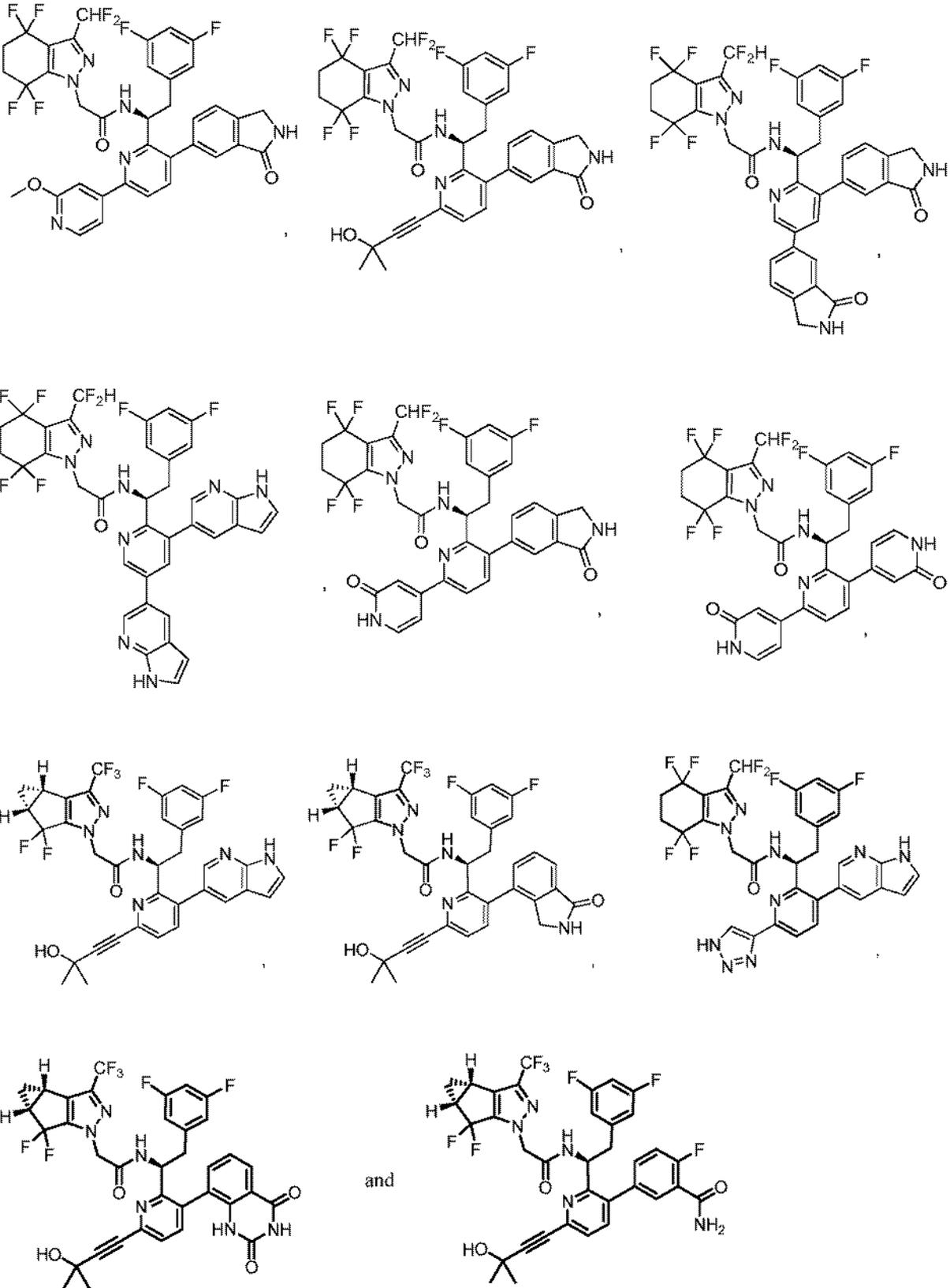


Embodiment I-53. The compound of any one of Embodiments I-1 to I-41 wherein R<sup>1</sup> is selected from:



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





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.

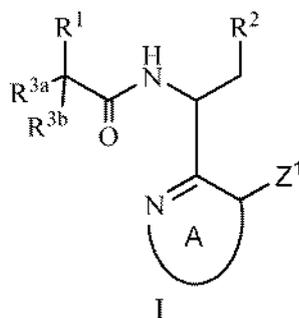
Embodiment I-60. A compound of formula I as described in any one of Embodiments I-1 to I-54 or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of a *Retroviridae* virus infection or an HIV virus infection.

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:



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<sup>n1</sup>, -OC(O)R<sup>p1</sup>, -OC(O)NR<sup>q1</sup>R<sup>r1</sup>, -SR<sup>n1</sup>, -S(O)R<sup>p1</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p1</sup>, -S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>COR<sup>p1</sup>, -NR<sup>n1</sup>CO<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>CONR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>OR<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, NO<sub>2</sub>, -C(O)R<sup>n1</sup>, -C(O)OR<sup>n1</sup>, -C(O)NR<sup>q1</sup>R<sup>r1</sup> and -S(O)<sub>2</sub>NR<sup>n1</sup>COR<sup>p1</sup>, 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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)alkynyl, wherein any (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)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<sub>3</sub>-C<sub>7</sub>)carbocycle, phenyl, 5-6 membered monocyclic-heteroaryl, 3-7 membered heterocycle, halogen, -CN, -OR<sup>n2</sup>, -OC(O)R<sup>p2</sup>, -OC(O)NR<sup>q2</sup>R<sup>r2</sup>, -SR<sup>n2</sup>, -S(O)R<sup>p2</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p2</sup>, -S(O)<sub>2</sub>NR<sup>q2</sup>R<sup>r2</sup>, -NR<sup>q2</sup>R<sup>r2</sup>, -NR<sup>n2</sup>COR<sup>p2</sup>, -NR<sup>n2</sup>CO<sub>2</sub>R<sup>p2</sup>, -NR<sup>n2</sup>CONR<sup>q2</sup>R<sup>r2</sup>, -NR<sup>n2</sup>S(O)<sub>2</sub>R<sup>p2</sup>, -NR<sup>n2</sup>S(O)<sub>2</sub>OR<sup>p2</sup>, -NR<sup>n2</sup>S(O)<sub>2</sub>NR<sup>q2</sup>R<sup>r2</sup>, NO<sub>2</sub>, -C(O)R<sup>n2</sup>, -C(O)OR<sup>n2</sup>, -C(O)NR<sup>q2</sup>R<sup>r2</sup>, halophenyl, 5-6 membered haloheteroaryl, 3-7 membered haloheterocycle and (C<sub>1</sub>-C<sub>8</sub>)heteroalkyl;

each  $Z^{1d}$  is independently selected from (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl and (C<sub>1</sub>-C<sub>8</sub>)haloalkyl;

each R<sup>n1</sup> is independently selected from H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R<sup>n1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)alkynyl of R<sup>n1</sup> is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5)  $Z^{1c}$  groups;

each R<sup>p1</sup> is independently selected from (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R<sup>p1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)alkynyl of R<sup>p1</sup> is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5)  $Z^{1c}$  groups;

R<sup>q1</sup> and R<sup>r1</sup> are each independently selected from H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R<sup>q1</sup> or R<sup>r1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)alkynyl of R<sup>q1</sup> or R<sup>r1</sup> is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5)  $Z^{1c}$  groups, or R<sup>q1</sup> and R<sup>r1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, (C<sub>1</sub>-C<sub>8</sub>)haloalkyl and (C<sub>1</sub>-C<sub>8</sub>)heteroalkyl;

each  $R^{p2}$  is independently selected from (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, (C<sub>1</sub>-C<sub>8</sub>)haloalkyl and (C<sub>1</sub>-C<sub>8</sub>)heteroalkyl;

$R^{q2}$  and  $R^{r2}$  are each independently selected from H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, (C<sub>1</sub>-C<sub>8</sub>)haloalkyl and (C<sub>1</sub>-C<sub>8</sub>)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<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, -C(O)R<sup>n3</sup> and -C(O)NR<sup>q3</sup>R<sup>r3</sup>, 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<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)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<sub>3</sub>-C<sub>7</sub>)carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, -OR<sup>n4</sup>, -OC(O)R<sup>p4</sup>, -OC(O)NR<sup>q4</sup>R<sup>r4</sup>, -SR<sup>n4</sup>, -S(O)R<sup>p4</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p4</sup>, -S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>COR<sup>p4</sup>, -NR<sup>n4</sup>CO<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>CONR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>OR<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, NO<sub>2</sub>, -C(O)R<sup>n4</sup>, -C(O)OR<sup>n4</sup> and -C(O)NR<sup>q4</sup>R<sup>r4</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl and (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

each  $Z^{2c}$  is independently selected from halogen, -CN, -OR<sup>n4</sup>, -OC(O)R<sup>p4</sup>, -OC(O)NR<sup>q4</sup>R<sup>r4</sup>, -SR<sup>n4</sup>, -S(O)R<sup>p4</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p4</sup>, -S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>COR<sup>p4</sup>, -NR<sup>n4</sup>CO<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>CONR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>OR<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, NO<sub>2</sub>, -C(O)R<sup>n4</sup>, -C(O)OR<sup>n4</sup> and -C(O)NR<sup>q4</sup>R<sup>r4</sup>;

each  $R^{n3}$  is independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl and (C<sub>2</sub>-C<sub>4</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl and (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $R^{p4}$  is independently selected from (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>2</sub>-C<sub>4</sub>)alkynyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl and (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

$R^{q4}$  and  $R^{r4}$  are each independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>2</sub>-C<sub>4</sub>)alkynyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl and (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $Z^3$  is independently selected from halogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, -OH, -CN, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl and (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

each  $Z^4$  is independently selected from (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, halogen, -CN, -OR<sup>n5</sup>, -OC(O)R<sup>p5</sup>, -OC(O)NR<sup>q5</sup>R<sup>r5</sup>, -SR<sup>n5</sup>, -S(O)R<sup>p5</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p5</sup>, -S(O)<sub>2</sub>NR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>n5</sup>COR<sup>p5</sup>, -NR<sup>n5</sup>CO<sub>2</sub>R<sup>p5</sup>, -NR<sup>n5</sup>CONR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>n5</sup>S(O)<sub>2</sub>R<sup>p5</sup>, -NR<sup>n5</sup>S(O)<sub>2</sub>OR<sup>p5</sup>, -NR<sup>n5</sup>S(O)<sub>2</sub>NR<sup>q5</sup>R<sup>r5</sup>, NO<sub>2</sub>, -C(O)R<sup>n5</sup>, -C(O)OR<sup>n5</sup> and -C(O)NR<sup>q5</sup>R<sup>r5</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)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<sup>n6</sup>, -OC(O)R<sup>p6</sup>, -OC(O)NR<sup>q6</sup>R<sup>r6</sup>, -SR<sup>n6</sup>, -S(O)R<sup>p6</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p6</sup>, -S(O)<sub>2</sub>NR<sup>q6</sup>R<sup>r6</sup>, -NR<sup>q6</sup>R<sup>r6</sup>, -NR<sup>n6</sup>COR<sup>p6</sup>,

$-\text{NR}^{\text{n}6}\text{CO}_2\text{R}^{\text{p}6}$ ,  $-\text{NR}^{\text{n}6}\text{CONR}^{\text{q}6}\text{R}^{\text{r}6}$ ,  $-\text{NR}^{\text{n}6}\text{S}(\text{O})_2\text{R}^{\text{p}6}$ ,  $-\text{NR}^{\text{n}6}\text{S}(\text{O})_2\text{OR}^{\text{p}6}$ ,  $-\text{NR}^{\text{n}6}\text{S}(\text{O})_2\text{NR}^{\text{q}6}\text{R}^{\text{r}6}$ ,  $\text{NO}_2$ ,  $-\text{C}(\text{O})\text{R}^{\text{n}6}$ ,  $-\text{C}(\text{O})\text{OR}^{\text{n}6}$  and  $-\text{C}(\text{O})\text{NR}^{\text{q}6}\text{R}^{\text{r}6}$ ;

each  $\text{Z}^{\text{4b}}$  is independently selected from (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl (C<sub>2</sub>-C<sub>4</sub>)alkynyl and (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

each  $\text{R}^{\text{n}5}$  is independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

each  $\text{R}^{\text{p}5}$  is independently selected from (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

$\text{R}^{\text{q}5}$  and  $\text{R}^{\text{r}5}$  are each independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

each  $\text{R}^{\text{n}6}$  is independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

each  $\text{R}^{\text{p}6}$  is independently selected from (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

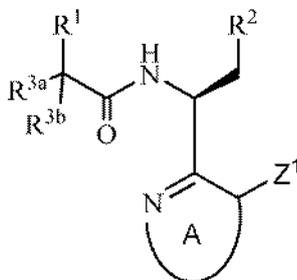
$\text{R}^{\text{q}6}$  and  $\text{R}^{\text{r}6}$  are each independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

each  $\text{Z}^5$  is independently selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, -CN and -OR<sup>n7</sup>, wherein any (C<sub>1</sub>-C<sub>6</sub>)alkyl of  $\text{Z}^5$  is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen; and

each  $\text{R}^{\text{n}7}$  is independently selected from H, (C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>3</sub>)haloalkyl and (C<sub>3</sub>-C<sub>7</sub>)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.

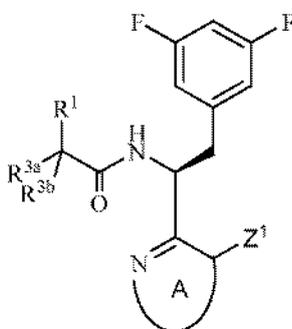
Embodiment II-5. The compound of any one of Embodiments II-1 to II-3 wherein  $R^2$  is phenyl optionally substituted with one or more  $Z^5$  groups.

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.

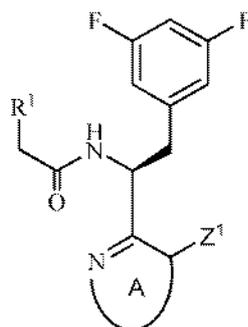
Embodiment II-9. The compound of Embodiment II-1 which is a compound of formula Ig:



Ig

or a pharmaceutically acceptable salt thereof.

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



Ie

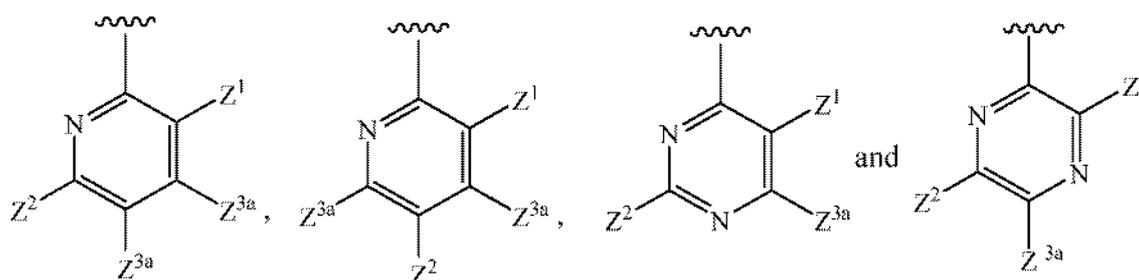
or a pharmaceutically acceptable salt thereof.

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.

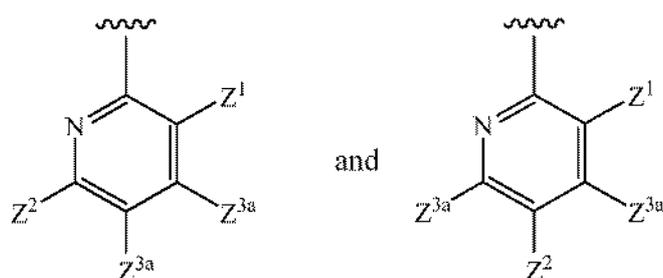
Embodiment II-13. The compound of any one of Embodiments II-1 to II-12 wherein A is substituted with one  $Z^1$  group at the position shown and one  $Z^2$  group.

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



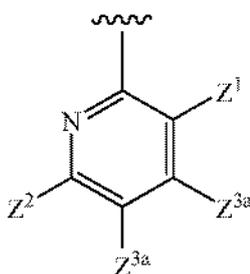
wherein each  $Z^{3a}$  is independently selected from H and  $Z^3$ .

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



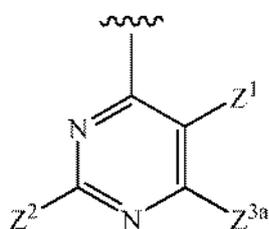
wherein each  $Z^{3a}$  is independently selected from H and  $Z^3$ .

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



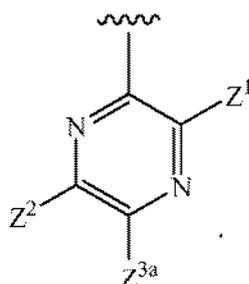
wherein each  $Z^{3a}$  is independently selected from H and  $Z^3$ .

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

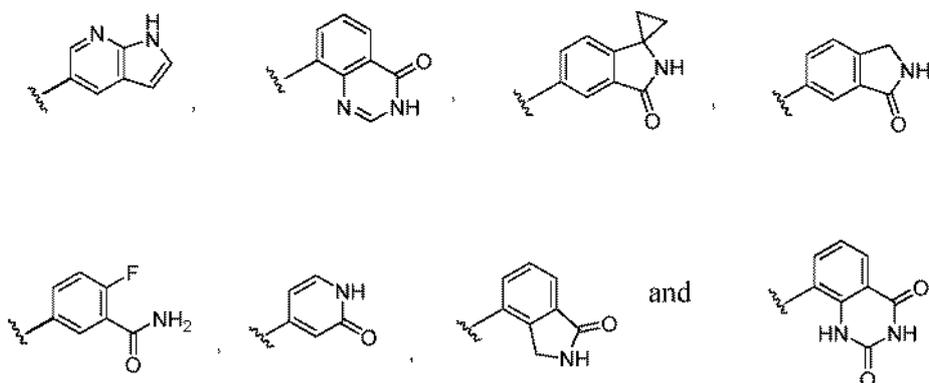
Embodiment II-30. The compound of any one of Embodiments II-1 to II-27 wherein each  $Z^{1b}$  is independently selected from  $(C_1-C_8)$ alkyl.

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  $(C_1-C_8)$ alkyl.

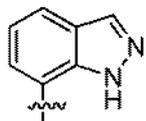
Embodiment II-32. The compound of any one of Embodiments II-1 to II-27 wherein each  $Z^{1a}$  is independently selected from halogen and  $-C(O)NR^{q1}R^{r1}$ .

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.

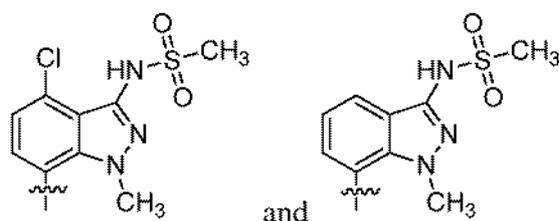
Embodiment II-34. The compound of any one of Embodiments II-1 to II-19 wherein  $Z^1$  is selected from:



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



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



Embodiment II-37. The compound of any one of Embodiments II-1 to II-36 wherein  $Z^2$  is selected from  $(C_2-C_8)$ alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle and  $-C(O)NR^{q3}R^{r3}$ , wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl and 3-12 membered C-linked-heterocycle of  $Z^2$  is optionally

substituted with one or more  $Z^{2b}$  or  $Z^{2c}$  groups, and wherein any  $(C_2-C_8)$ alkynyl of  $Z^2$  is optionally substituted with one or more  $Z^{2c}$  groups.

Embodiment II-38. The compound of any one of Embodiments II-1 to II-36 wherein  $Z^2$  is selected from  $(C_2-C_8)$ alkynyl, phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heterocycle and  $-C(O)NR^{q3}R^{r3}$ , wherein any phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl and 8-10 membered C-linked-bicyclic-heterocycle of  $Z^2$  is optionally substituted with one or more  $Z^{2b}$  or  $Z^{2c}$  groups, and wherein any  $(C_2-C_8)$ alkynyl of  $Z^2$  is optionally substituted with one or more  $Z^{2c}$  groups.

Embodiment II-39. The compound of any one of Embodiments II-1 to II-36 wherein  $Z^2$  is selected from  $(C_2-C_8)$ alkynyl, phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heterocycle and  $-C(O)NR^{q3}R^{r3}$ , wherein the 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl and 8-10 membered C-linked-bicyclic-heterocycle have 1-9 carbon atoms and 1-4 heteroatoms in the ring system, and wherein any phenyl, 5-6 membered C-linked-monocyclic-heteroaryl, 8-10 membered C-linked-bicyclic-heteroaryl, 8-10 membered and C-linked-bicyclic-heterocycle of  $Z^2$  is optionally substituted with one or more  $Z^{2b}$  or  $Z^{2c}$  groups, and wherein any  $(C_2-C_8)$ alkynyl of  $Z^2$  is optionally substituted with one or more  $Z^{2c}$  groups.

Embodiment II-40. The compound of any one of Embodiments II-1 to II-36 wherein  $Z^2$  is selected from 4-methylpentynyl, phenyl, pyridinyl, 1H-2-oxo-pyridinyl, triazolyl, 1-oxoisoindolinyl, 1H-pyrrolo[2,3-b]pyridinyl and  $-C(O)NR^{q3}R^{r3}$ , wherein any phenyl, pyridinyl, 2-oxopyridinyl, triazolyl, 1-oxoisoindolinyl and 1H-pyrrolo[2,3-b]pyridinyl of  $Z^2$  is optionally substituted with one or more  $Z^{2b}$  or  $Z^{2c}$  groups, and wherein any 4-methylpentynyl of  $Z^2$  is optionally substituted with one or more  $Z^{2c}$  groups.

Embodiment II-41. The compound of any one of Embodiments II-1 to II-36 wherein  $Z^2$  is selected from 4-methylpentyn-1-yl, phenyl, pyridin-4-yl, 1H-2-oxo-pyridin-2-yl, triazol-4-yl, 1-oxoisoindolin-6-yl, 1H-pyrrolo[2,3-b]pyridine-5-yl and  $-C(O)NR^{q3}R^{r3}$ , wherein any phenyl, pyridin-4-yl, 2-hydroxypyridin-2-yl, triazol-4-yl, 1-oxoisoindolin-6-yl and 1H-pyrrolo[2,3-b]pyridine-5-yl of  $Z^2$  is optionally substituted with one or more  $Z^{2b}$  or  $Z^{2c}$  groups, and wherein any 4-methylpentyn-1-yl of  $Z^2$  is optionally substituted with one or more  $Z^{2c}$  groups.

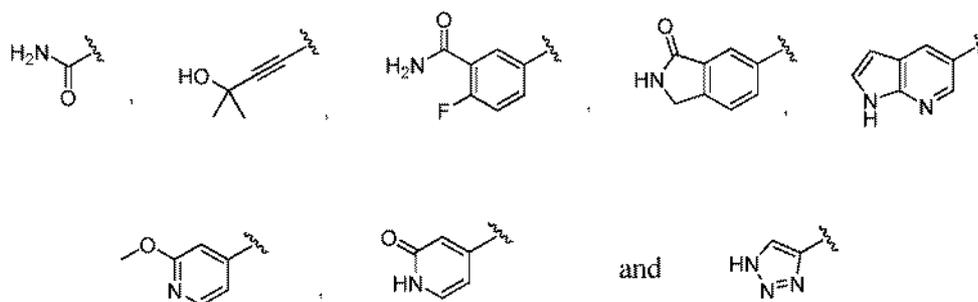
Embodiment II-42. The compound of any one of Embodiments II-1 to II-41 wherein  $Z^2$  is optionally substituted with one or more  $Z^{2c}$  groups.

Embodiment II-43. The compound of any one of Embodiments II-1 to II-42 wherein  $R^{q3}$  and  $R^{r3}$  are each H.

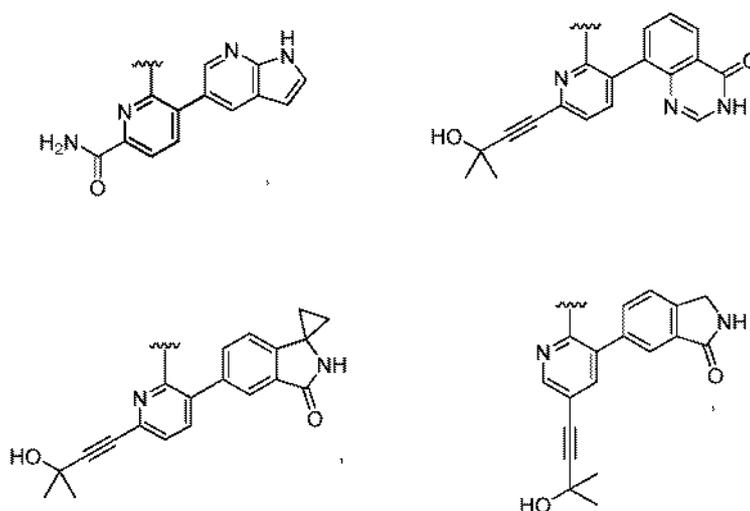
Embodiment II-44. The compound of any one of Embodiments II-1 to II-43 wherein each  $Z^{2c}$  is independently selected from halogen,  $-OR^{n4}$  and  $-C(O)NR^{q4}R^{r4}$ .

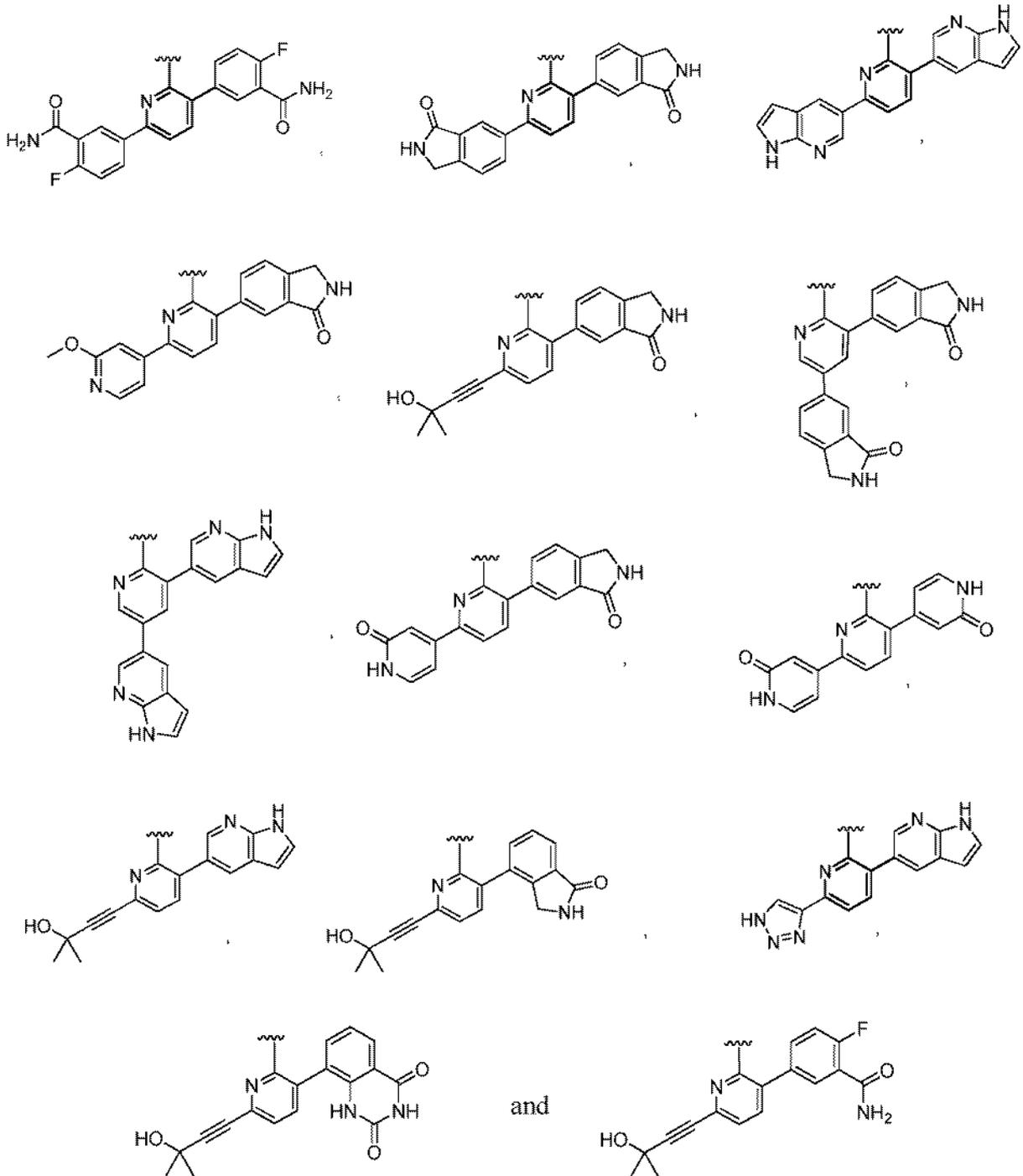
Embodiment II-45. The compound of any one of Embodiments II-1 to II-44 wherein  $R^{n4}$  is H or methyl, and  $R^{q4}$  and  $R^{r4}$  are each H.

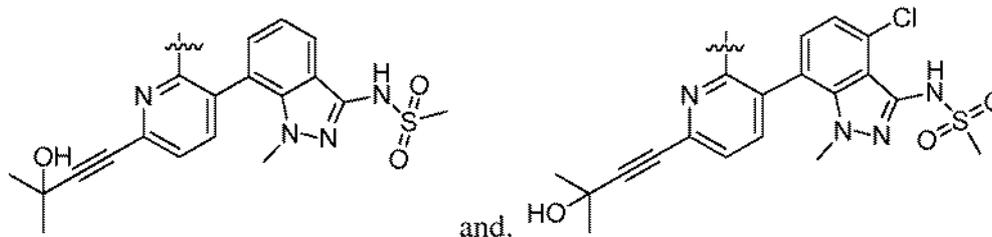
Embodiment II-46. The compound of any one of Embodiments II-1 to II-36 wherein  $Z^2$  is selected from:



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







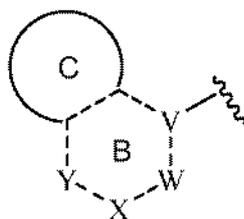
Embodiment II-49. The compound of any one of Embodiments II-1 to II-48 wherein  $R^1$  is a 5-12 membered heteroaryl, wherein any 5-12 membered heteroaryl of  $R^1$  is optionally substituted with one or more  $Z^4$  groups.

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;

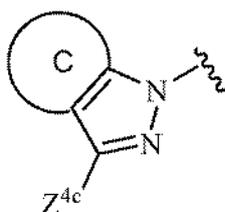
X is  $CZ^{4c}$ ,  $NZ^{4c}$  or N;

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 IIId:



IIId

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  $Z^4$ .

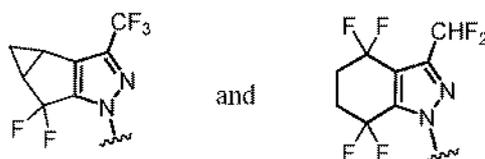
Embodiment II-55. The compound of any one of Embodiments II-1 to II-48 wherein  $R^1$  is selected from 3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazolyl and 4,5,6,7-tetrahydro-indazolyl, wherein any 3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazolyl and 4,5,6,7-tetrahydro-indazolyl 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.

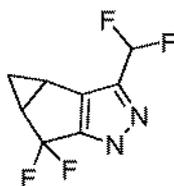
Embodiment II-57. The compound of any one of Embodiments II-1 to II-56 wherein each  $Z^4$  is independently selected from  $(C_1-C_6)$ alkyl and halogen, wherein any  $(C_1-C_6)$ alkyl of  $Z^4$  is optionally substituted with one or more halogen.

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.

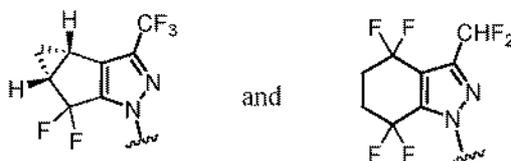
Embodiment II-59. The compound of any one of Embodiments II-1 to II-48 wherein  $R^1$  is selected from:



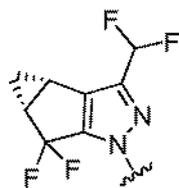
Embodiment II-60. The compound of any one of Embodiments II-1 to II-48 wherein  $R^1$  is



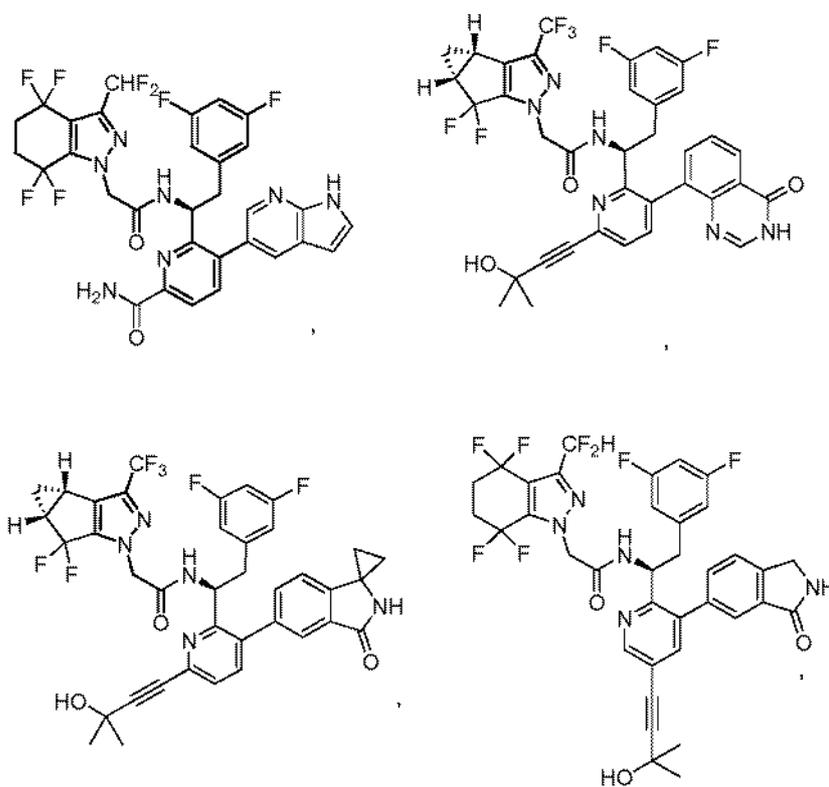
Embodiment II-61. The compound of any one of Embodiments II-1 to II-48 wherein R<sup>1</sup> is selected from:

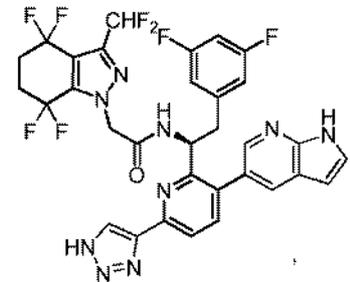
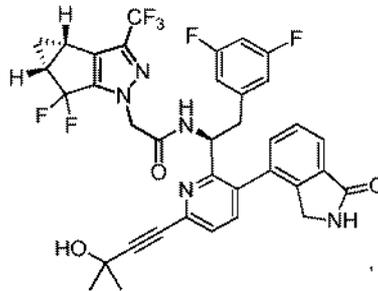
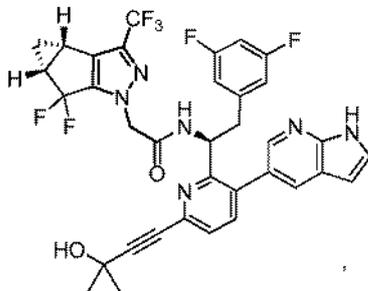
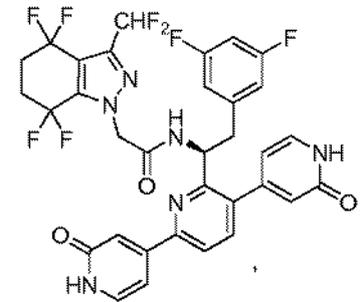
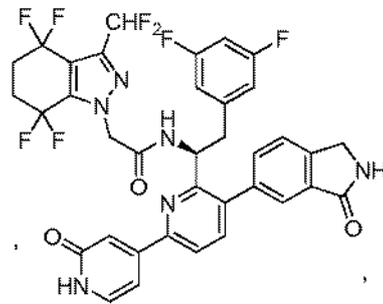
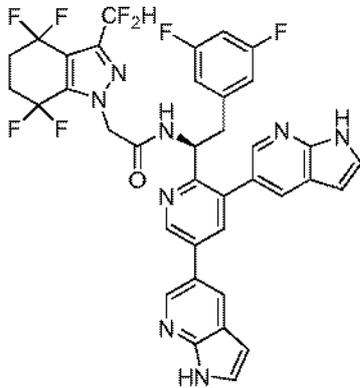
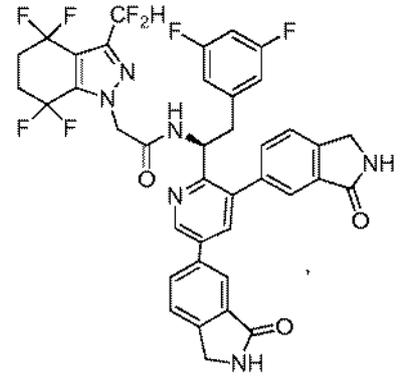
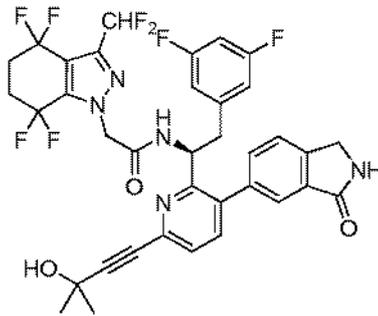
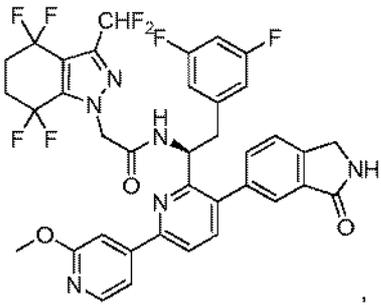
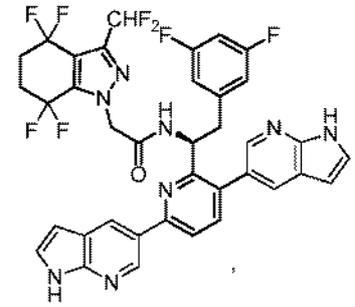
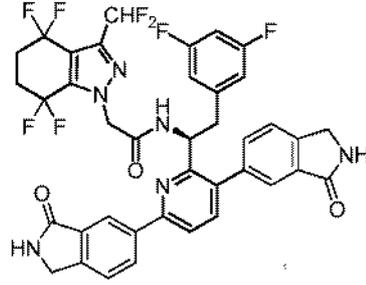
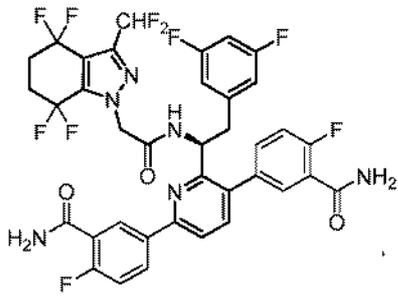


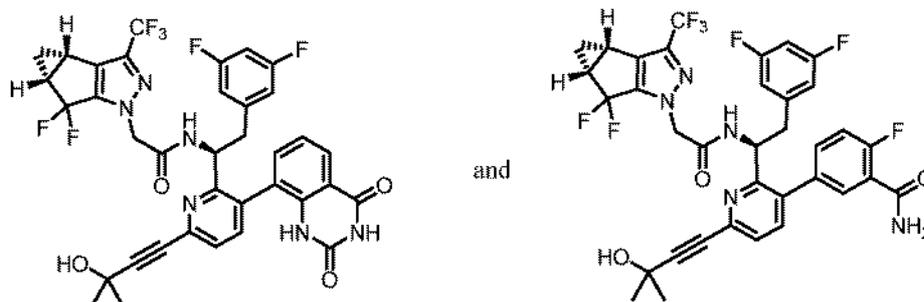
Embodiment II-62. The compound of any one of Embodiments II-1 to II-48 wherein R<sup>1</sup> is



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

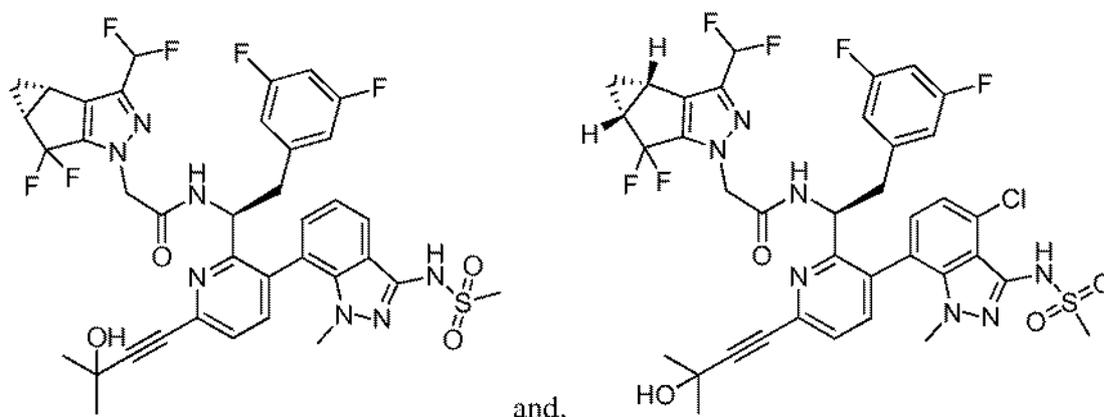






and pharmaceutically acceptable salts thereof.

Embodiment II-64. The compound of Embodiment II-1 selected from:



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.

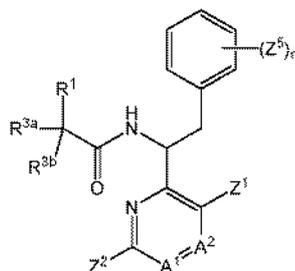
Embodiment II-71. The use of a compound as described in any one of Embodiments II-1 to II-44 or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a *Retroviridae* virus infection or an HIV virus infection in a mammal.

Embodiment II-72. A compound or method as described herein.

## CLAIMS

What is claimed is:

I. A compound of formula III d:



III d

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<sub>1</sub>-C<sub>3</sub>)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<sub>3</sub>-C<sub>7</sub>)carbocycle, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, -OR<sup>n1</sup>, -OC(O)R<sup>p1</sup>, -OC(O)NR<sup>q1</sup>R<sup>r1</sup>, -SR<sup>n1</sup>, -S(O)R<sup>p1</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p1</sup>, -S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>COR<sup>p1</sup>, -NR<sup>n1</sup>CO<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>CONR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>OR<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -C(O)R<sup>n1</sup>, -C(O)OR<sup>n1</sup>, -C(O)NR<sup>q1</sup>R<sup>r1</sup> and -S(O)<sub>2</sub>NR<sup>n1</sup>COR<sup>p1</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)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<sub>2</sub>, -C(O)NR<sup>q2</sup>R<sup>r2</sup>, or (C<sub>1</sub>-C<sub>8</sub>)heteroalkyl;

each  $Z^{1d}$  is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl or (C<sub>1</sub>-C<sub>8</sub>)haloalkyl;

each  $R^{n1}$  is independently H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)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<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)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<sup>q3</sup>R<sup>r3</sup>, 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<sub>2</sub>-C<sub>8</sub>)alkenyl or (C<sub>2</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl;

each  $R^{q3}$  and  $R^{r3}$  is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

each  $Z^{2b}$  is independently oxo, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl or (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;  
 each  $Z^{2c}$  is independently oxo, halogen, -CN, -OR<sup>n4</sup>, -OC(O)R<sup>p4</sup>, -OC(O)NR<sup>q4</sup>R<sup>r4</sup>, -SR<sup>n4</sup>, -S(O)R<sup>p4</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p4</sup>, -S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>COR<sup>p4</sup>, -NR<sup>n4</sup>CO<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>CONR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>OR<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NO<sub>2</sub>, -C(O)R<sup>n4</sup>, -C(O)OR<sup>n4</sup>, or -C(O)NR<sup>q4</sup>R<sup>r4</sup>;

each R<sup>n4</sup> is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each R<sup>p4</sup> is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each R<sup>q4</sup> and R<sup>r4</sup> is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each Z<sup>3</sup> is independently a (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each Z<sup>4</sup> is independently oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, halogen, -CN, -OR<sup>n5</sup>, -NR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>n5</sup>COR<sup>p5</sup>, -NR<sup>n5</sup>CO<sub>2</sub>R<sup>p5</sup>, -C(O)R<sup>n5</sup>, -C(O)OR<sup>n5</sup>, or -C(O)NR<sup>q5</sup>R<sup>r5</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle or (C<sub>1</sub>-C<sub>8</sub>)alkyl of Z<sup>4</sup> is optionally substituted with 1, 2, 3, 4 or 5 Z<sup>4a</sup> groups, wherein the Z<sup>4a</sup> groups are the same or different;

each Z<sup>4a</sup> is independently halogen, -CN, or -OR<sup>n6</sup>;

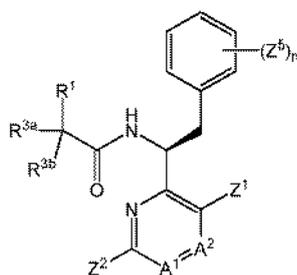
each R<sup>n5</sup>, R<sup>p5</sup>, R<sup>q5</sup>, R<sup>r5</sup>, and R<sup>n6</sup> is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

each Z<sup>5</sup> is independently halogen, which may be same or different; and

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof.

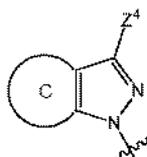
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, which is a compound of formula IIIe:



IIIe

or a pharmaceutically acceptable salt thereof.

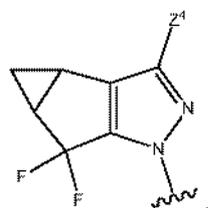
3. The compound of any one of claims 1-2, or a pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is



wherein

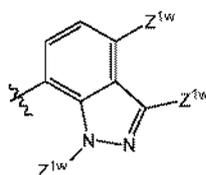
C together with the two carbon atoms to which it is attached forms a 3-7 membered monocyclic-carbocycle or 5-9 membered bicyclic-carbocycle, wherein any 3-7 membered monocyclic-carbocycle or 5-9 membered bicyclic-carbocycle of C is optionally substituted with 1, 2, 3, 4 or 5  $Z^4$  groups, wherein the  $Z^4$  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  $-NR^{n1}CO_2R^{p1}$ ;

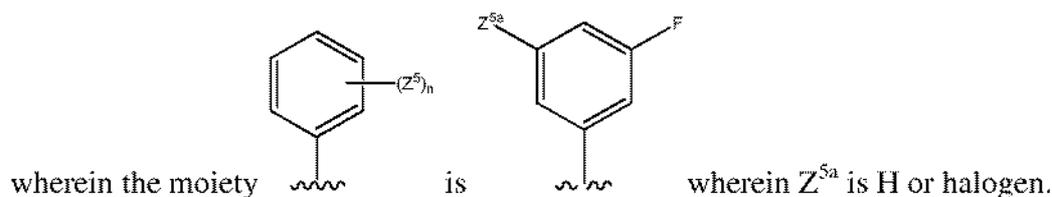
each  $Z^{1b}$  is independently  $(C_1-C_8\text{alkyl})$ , wherein the  $(C_1-C_8\text{alkyl})$  is optionally substituted with 1, 2, or 3 halogen, which are the same or different; and

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,

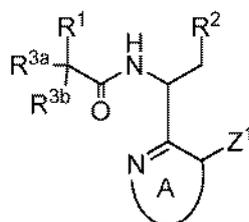


10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein  $A^1$  is CH.

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<sup>n1</sup>, -OC(O)R<sup>p1</sup>, -OC(O)NR<sup>q1</sup>R<sup>r1</sup>, -SR<sup>n1</sup>, -S(O)R<sup>p1</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p1</sup>, -S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>COR<sup>p1</sup>, -NR<sup>n1</sup>CO<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>CONR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>OR<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -C(O)R<sup>n1</sup>, -C(O)OR<sup>n1</sup>, -C(O)NR<sup>q1</sup>R<sup>r1</sup> and -S(O)<sub>2</sub>NR<sup>n1</sup>COR<sup>p1</sup>, 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<sub>2</sub>, -C(O)NR<sup>q2</sup>R<sup>r2</sup>, 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<sub>1</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)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<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)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<sup>q3</sup>R<sup>r3</sup>, 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<sub>2</sub>-C<sub>8</sub>)alkenyl or (C<sub>2</sub>-C<sub>8</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl;

each  $R^{q3}$  and  $R^{r3}$  is independently H or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

each  $Z^{2b}$  is independently oxo, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, or (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

each  $Z^{2c}$  is independently oxo, halogen, -CN, -OR<sup>n4</sup>, -OC(O)R<sup>p4</sup>, -OC(O)NR<sup>q4</sup>R<sup>r4</sup>, -SR<sup>n4</sup>, -S(O)R<sup>p4</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p4</sup>, -S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>COR<sup>p4</sup>, -NR<sup>n4</sup>CO<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>CONR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>OR<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NO<sub>2</sub>, -C(O)R<sup>n4</sup>, -C(O)OR<sup>n4</sup>, or -C(O)NR<sup>q4</sup>R<sup>r4</sup>;

each  $R^{n4}$  is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $R^{p4}$  is independently (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $R^{q4}$  and  $R^{r4}$  is independently H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, or (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $Z^3$  is independently a (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl or halogen;

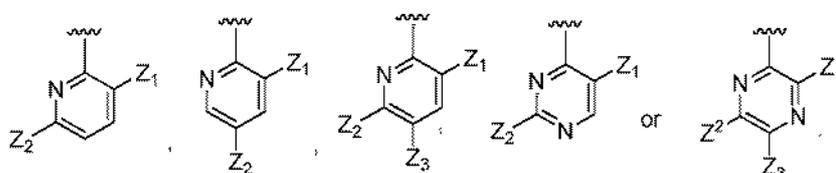
each  $Z^4$  is independently oxo,  $(C_1-C_8)$ alkyl,  $(C_3-C_7)$ carbocycle, halogen,  $-CN$ ,  $-OR^{n5}$ ,  $-NR^{q5}R^{r5}$ ,  $-NR^{n5}COR^{p5}$ ,  $-NR^{n5}CO_2R^{p5}$ ,  $-C(O)R^{n5}$ ,  $-C(O)OR^{n5}$ , or  $-C(O)NR^{q5}R^{r5}$ , wherein any  $(C_3-C_7)$ carbocycle or  $(C_1-C_8)$ alkyl of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

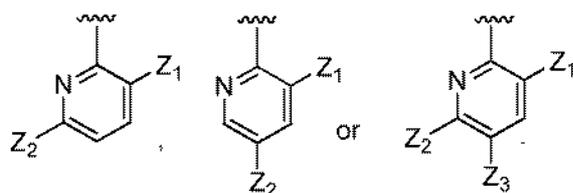
each  $R^{n5}$ ,  $R^{p5}$ ,  $R^{q5}$ ,  $R^{r5}$ , and  $R^{n6}$  is independently H or  $(C_1-C_4)$ alkyl;

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.

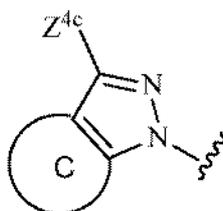
18. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein  $R^{3a}$  is methyl and  $R^{3b}$  is H.

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



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 II d:



II d

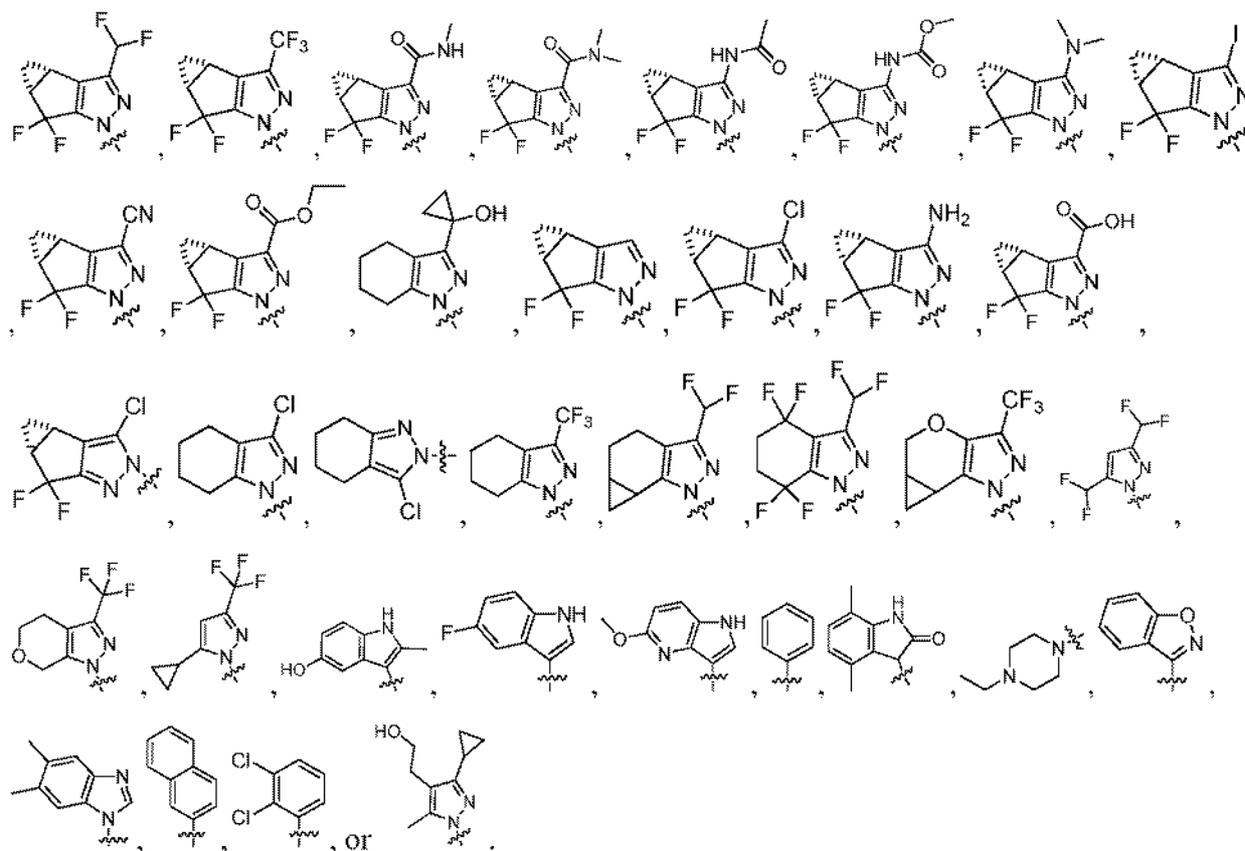
wherein:

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

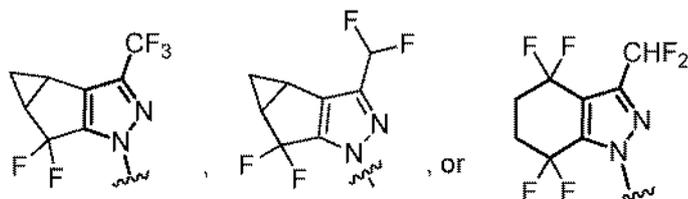
each  $Z^{4c}$  is independently selected from H or  $Z^4$ , wherein the  $Z^4$  groups are the same or different.

26. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein each  $Z^4$  is independently (C<sub>1</sub>-C<sub>4</sub>)alkyl or halogen, wherein any (C<sub>1</sub>-C<sub>4</sub>)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-

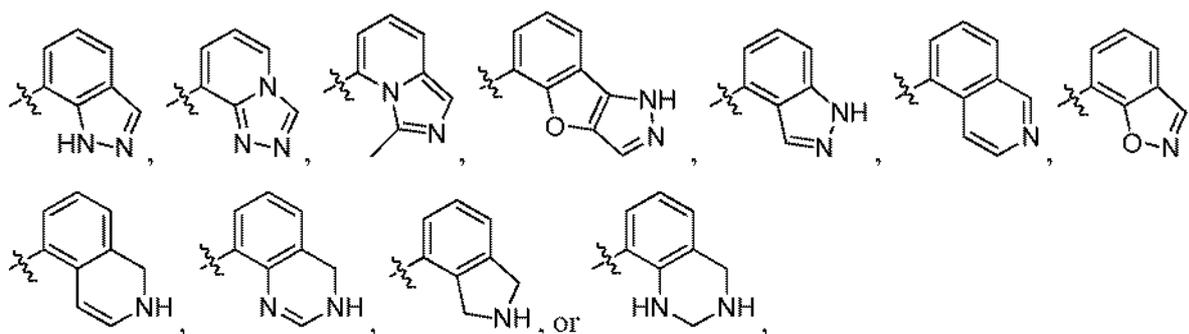
heterocycle, wherein any 8-10 membered bicyclic-heteroaryl or 8-10 membered bicyclic-heterocycle has 3-9 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any 8-10 membered bicyclic-heteroaryl or 8-10 membered bicyclic-heterocycle of  $Z^1$  is optionally substituted with 1, 2, 3, 4, or 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<sub>3</sub>-C<sub>7</sub>)carbocycle, halogen, -CN, -O-(C<sub>1</sub>-C<sub>8</sub>)alkyl, -NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>COR<sup>p1</sup>, -NR<sup>n1</sup>CO<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>CONR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, or -C(O)NR<sup>q1</sup>R<sup>r1</sup>.

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.

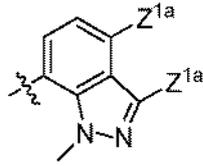
33. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt thereof, wherein  $Z^1$  is substituted with 2  $Z^{1a}$  groups, wherein each  $Z^{1a}$  is independently -NR<sup>n1</sup>S(O)<sub>2</sub>R<sup>p1</sup>, -NR<sup>n1</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, or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

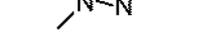
34. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein  $Z^1$  is



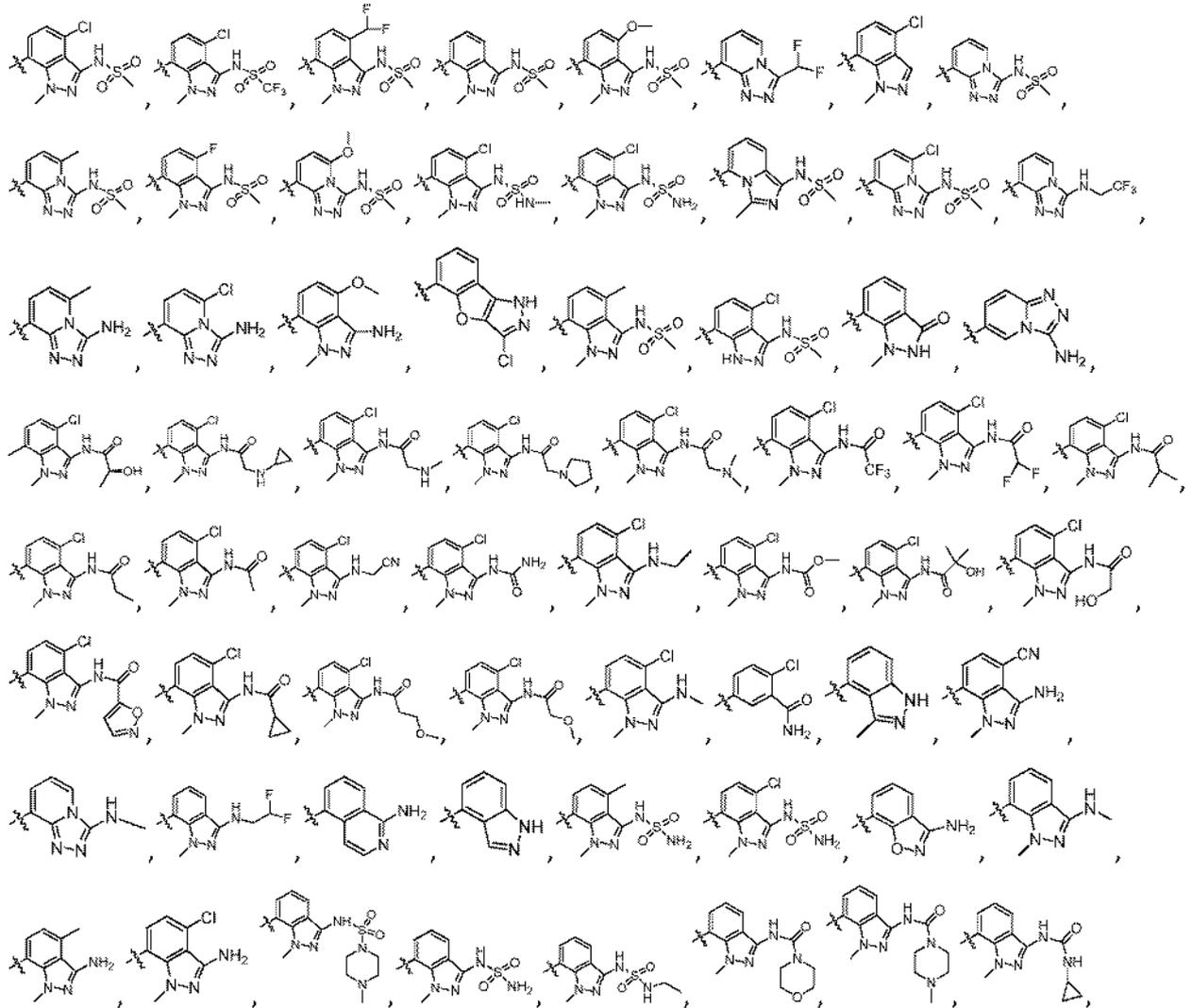
optionally substituted with 1, 2, 3, 4 or 5  $Z^{1a}$  or  $Z^{1b}$ .

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

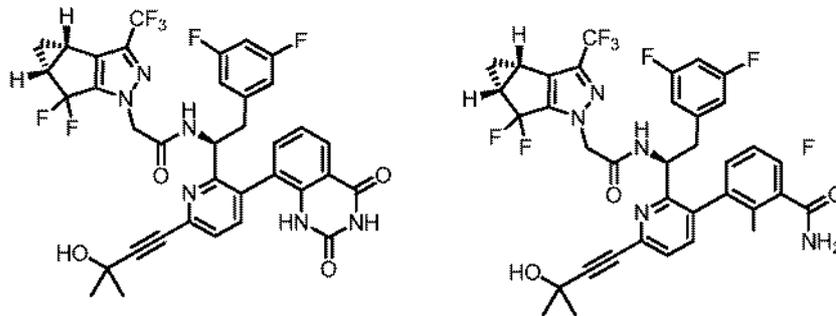
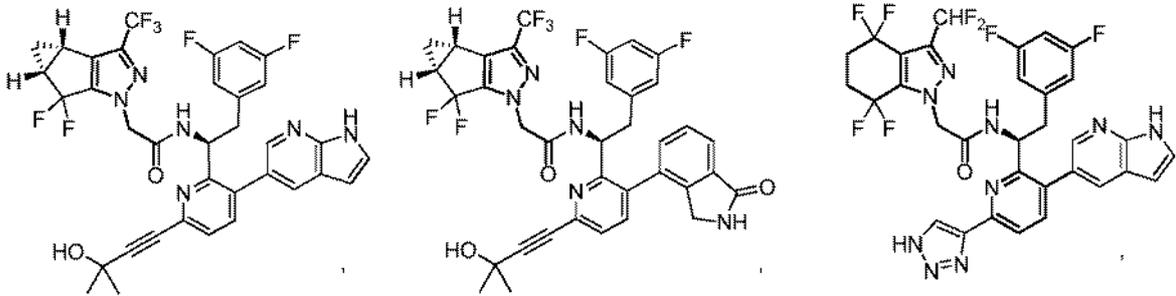
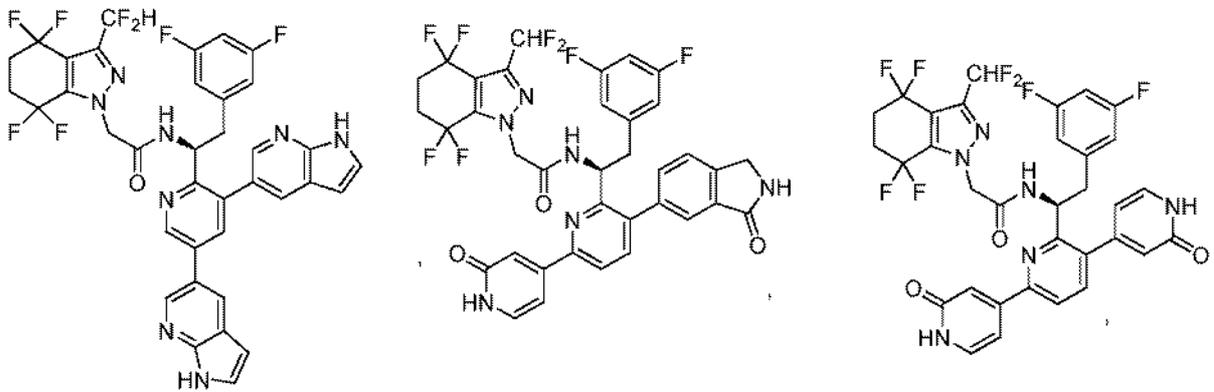
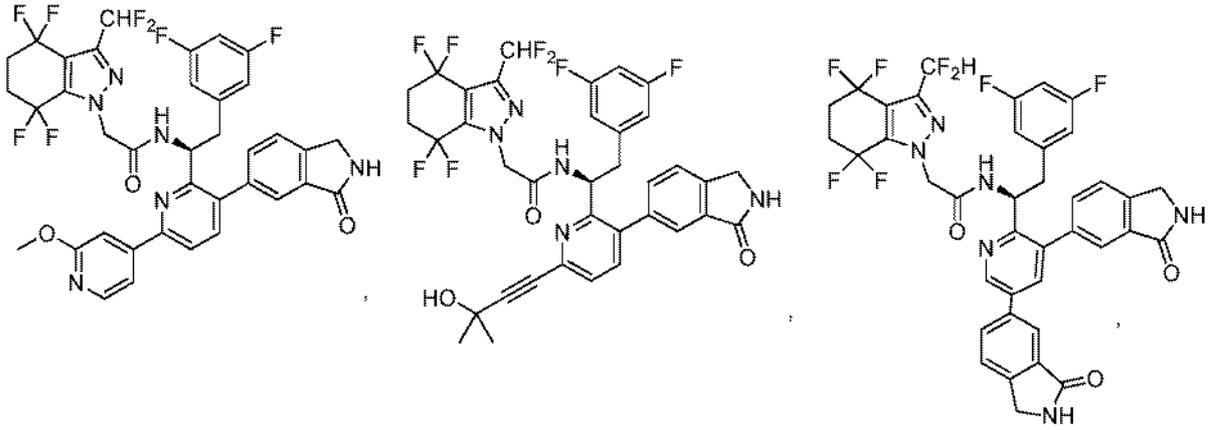


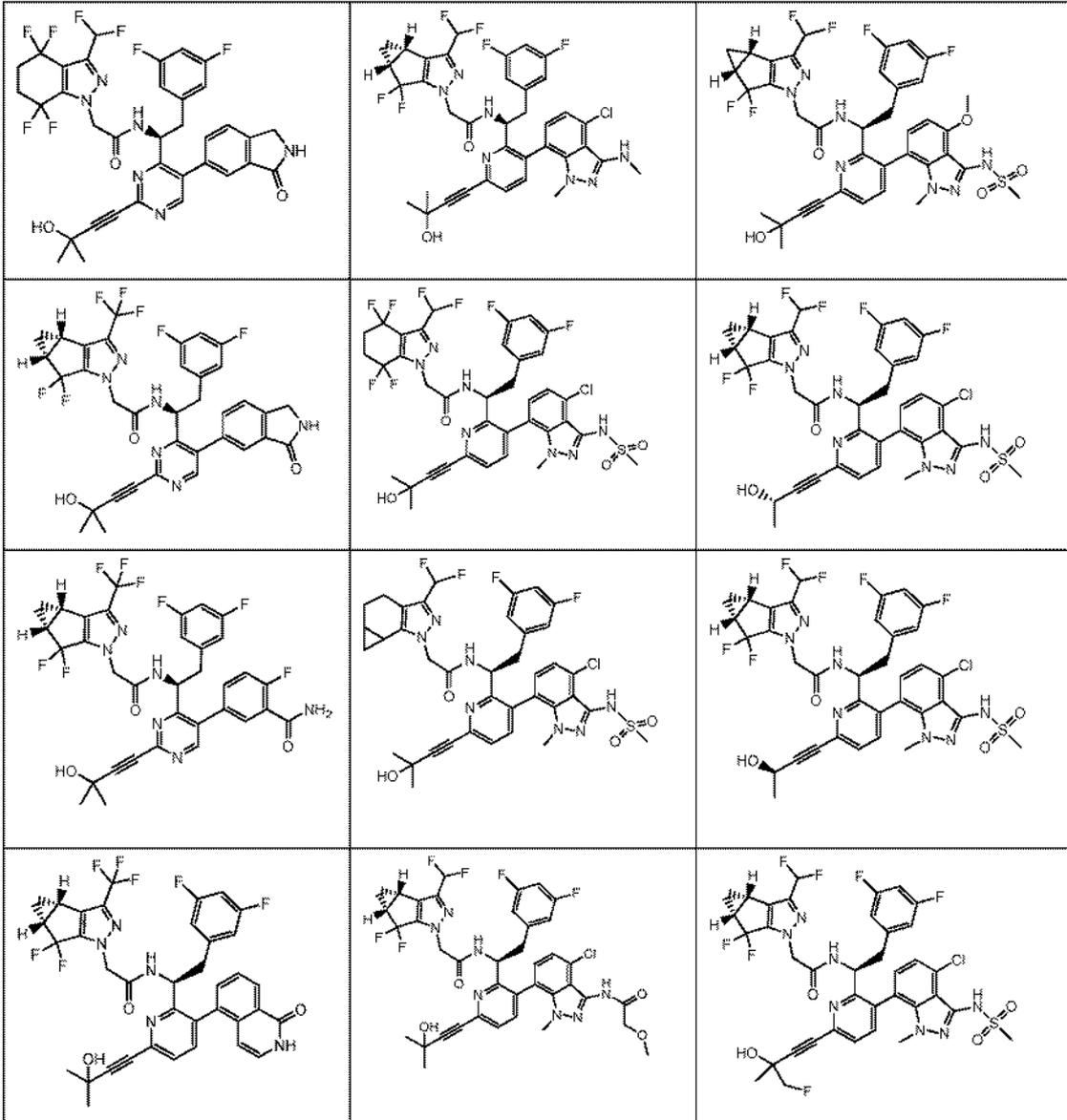
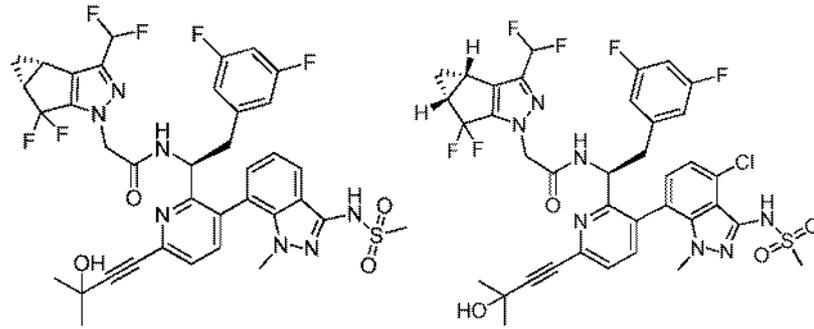
wherein  $Z^1$  is , wherein each  $Z^{1a}$  is independently halogen,  $-NR^{n1}S(O)_2R^{p1}$  or  $-NR^{n1}S(O)_2NR^{q1}R^{r1}$ .

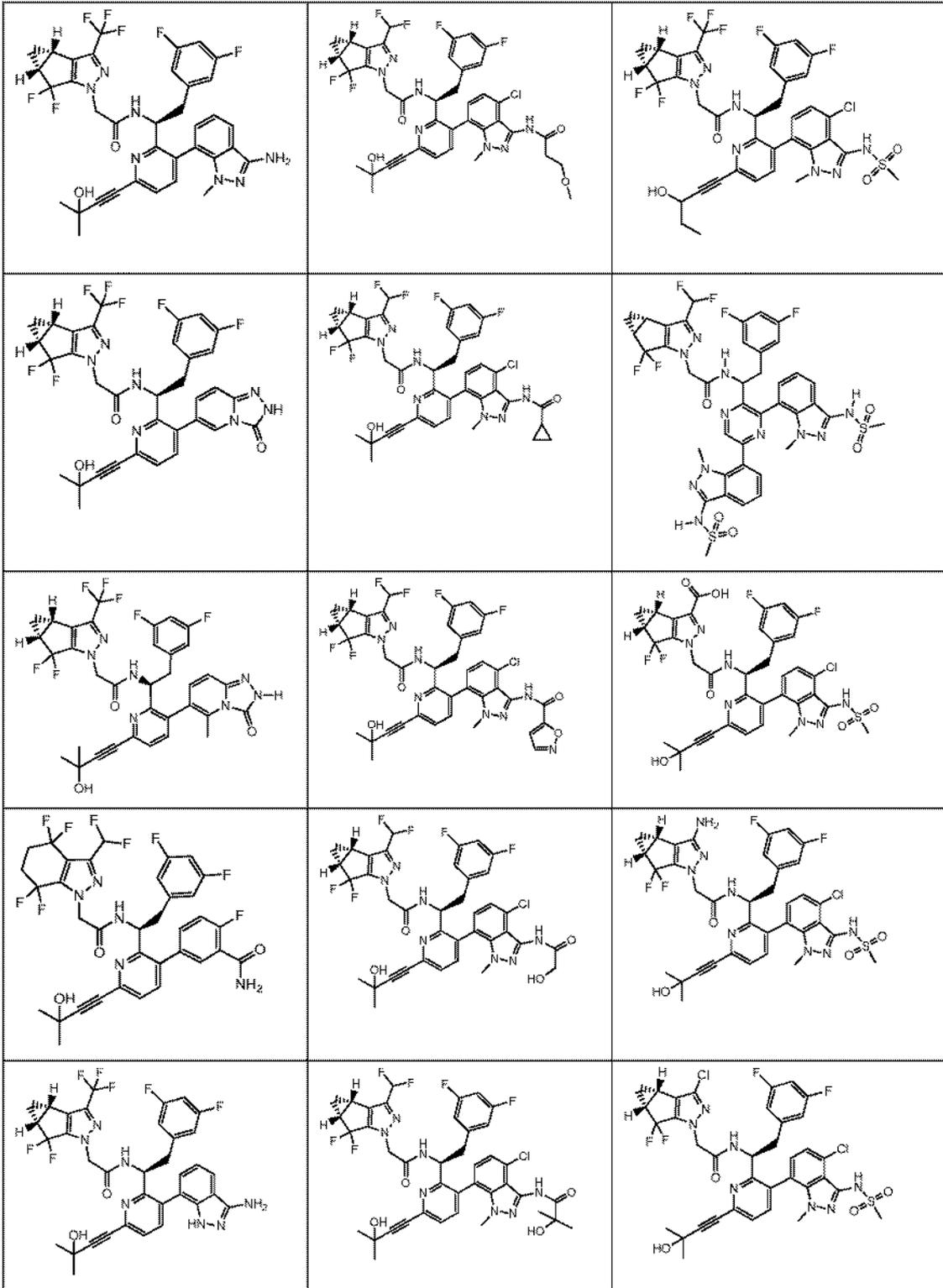
36. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein  $Z^1$  optionally substituted with 1, 2, 3, 4, or 5  $Z^{1a}$  or  $Z^{1b}$  groups is

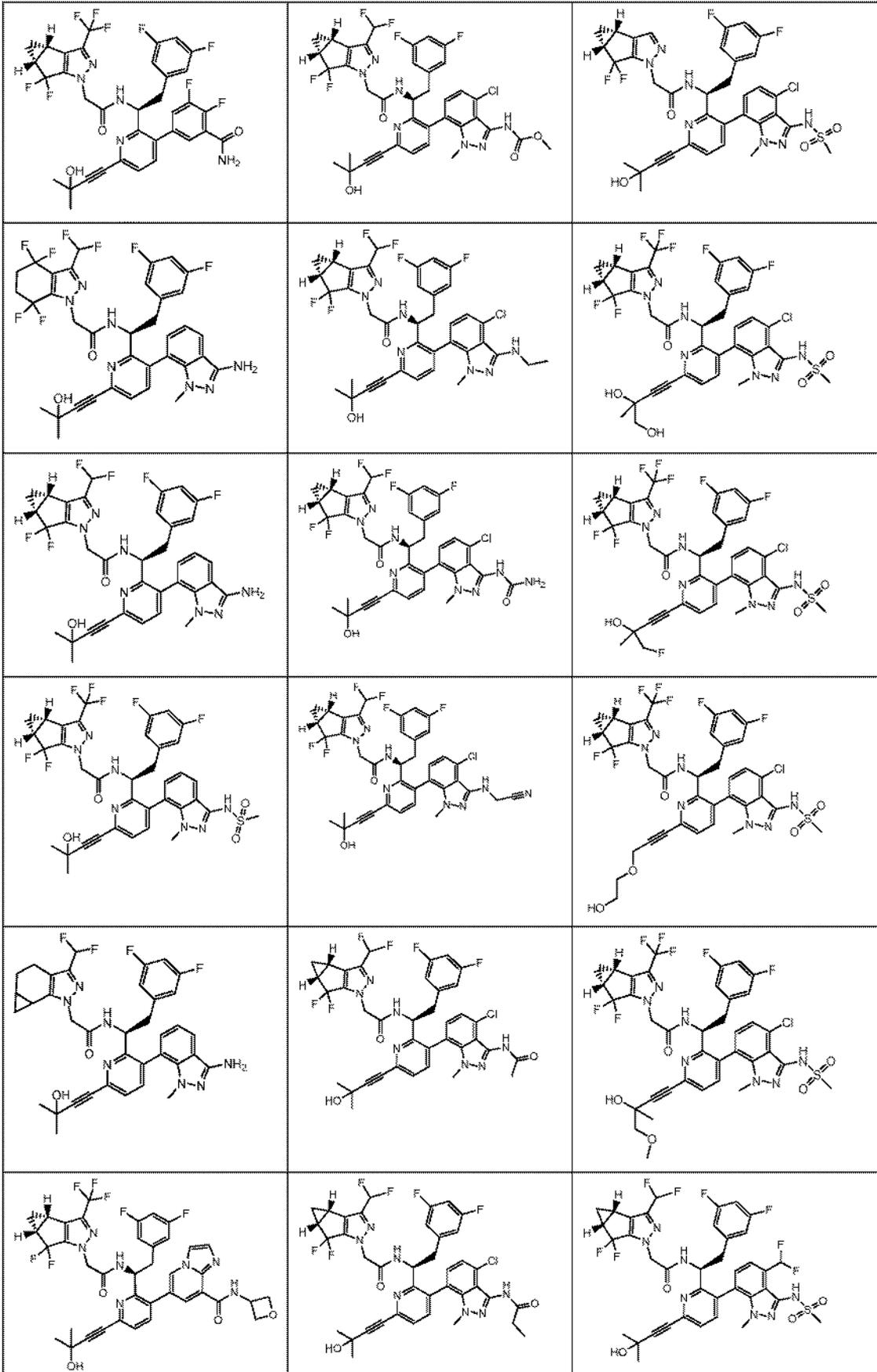


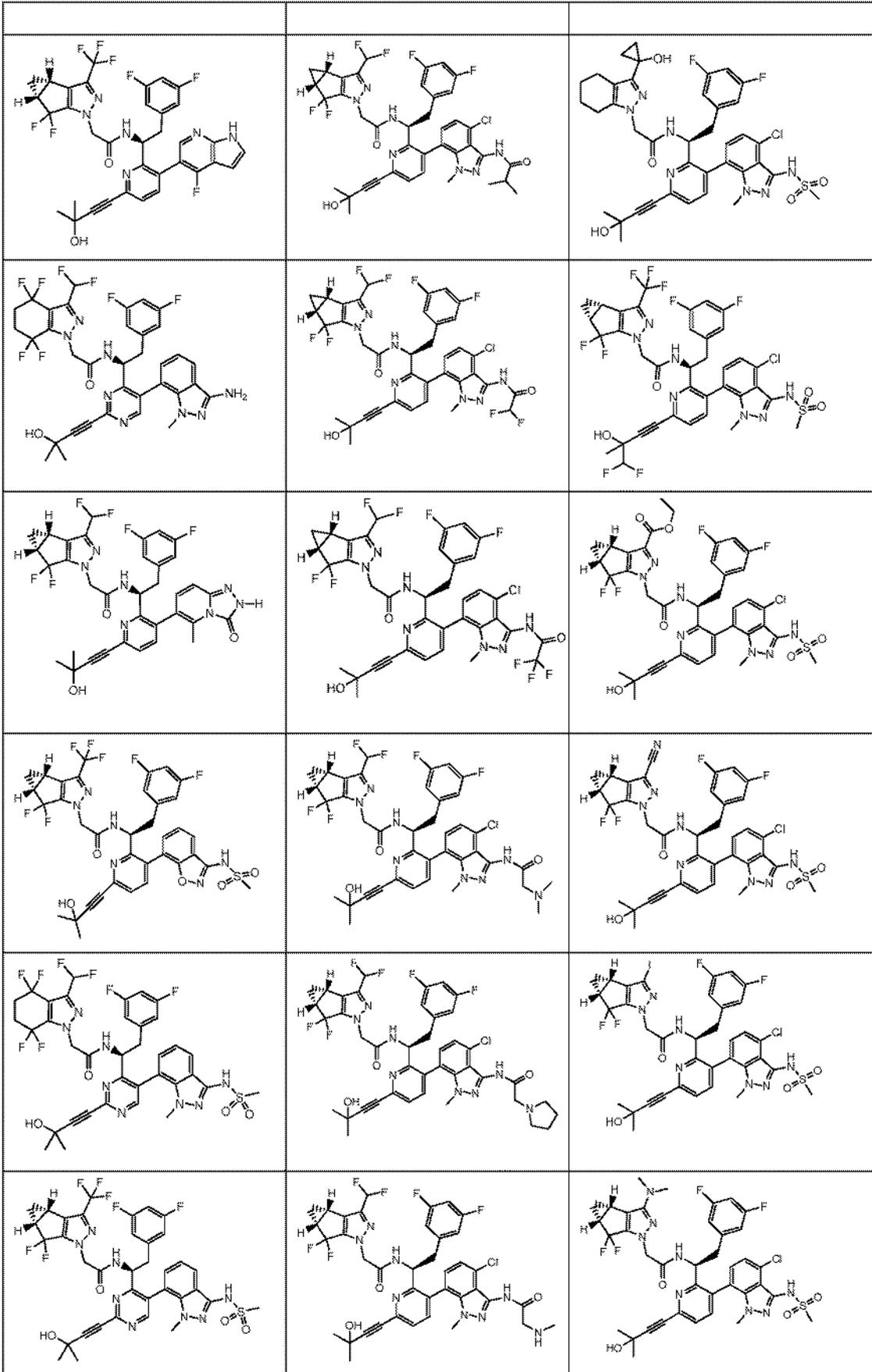


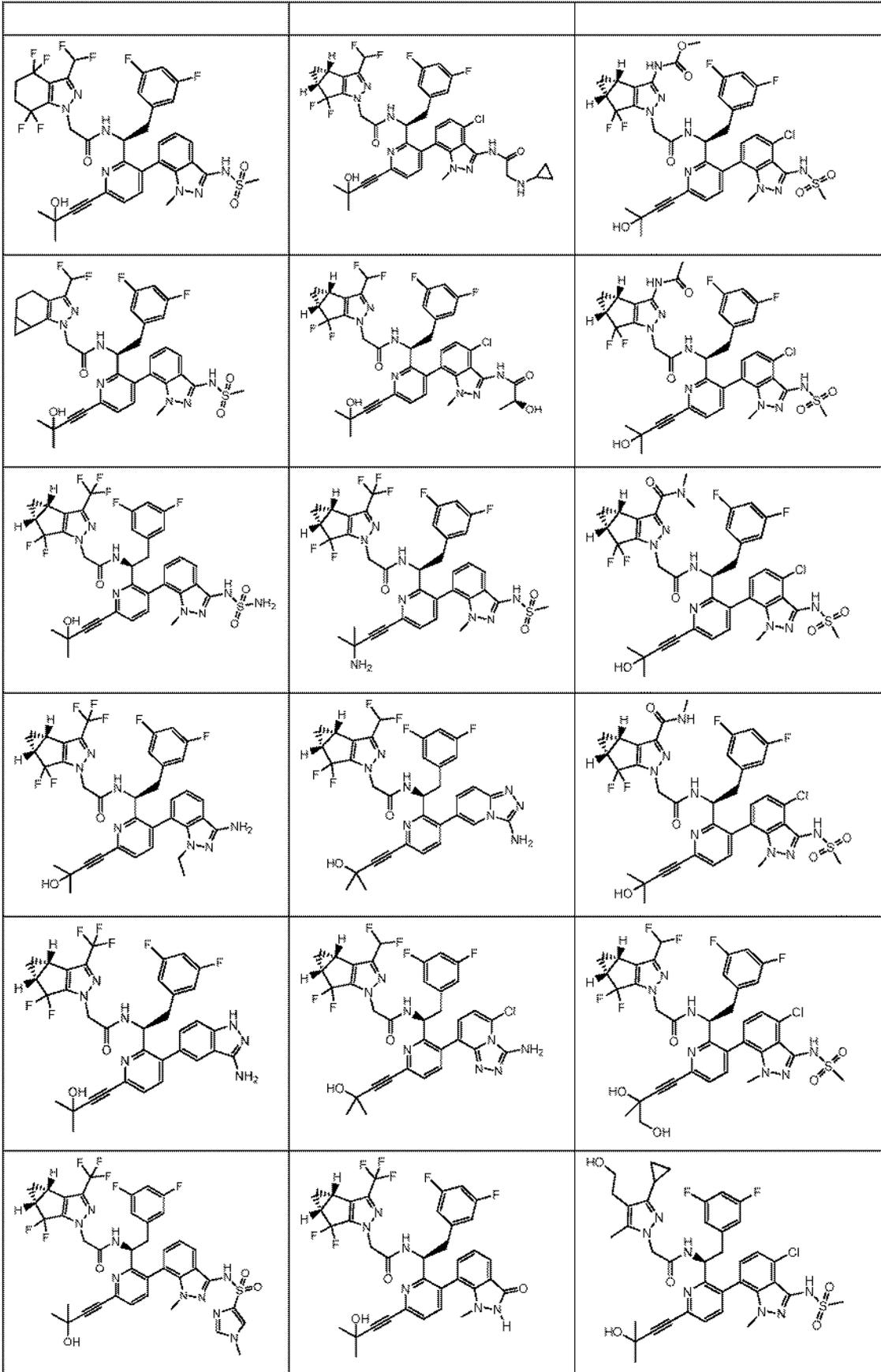


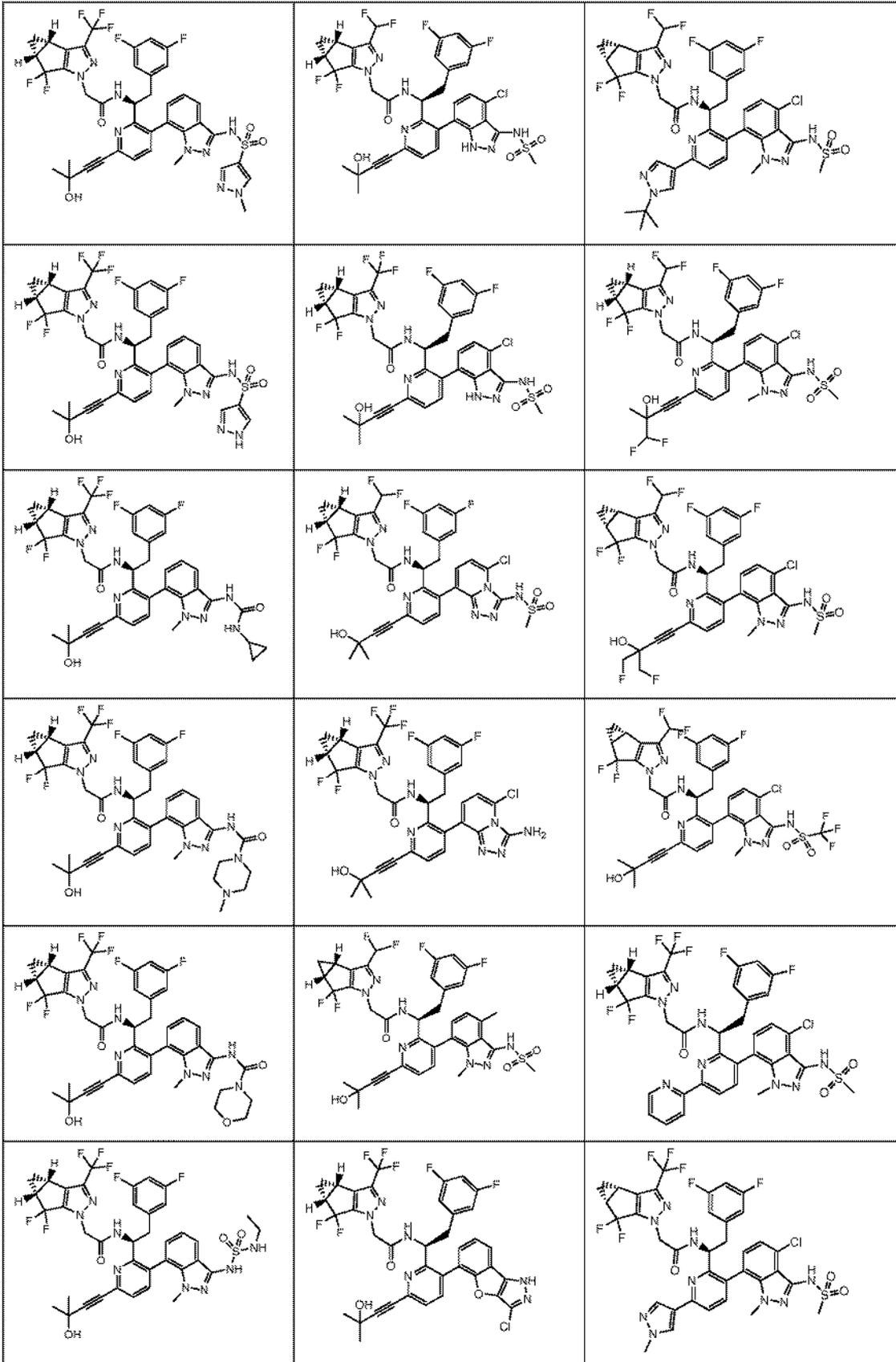


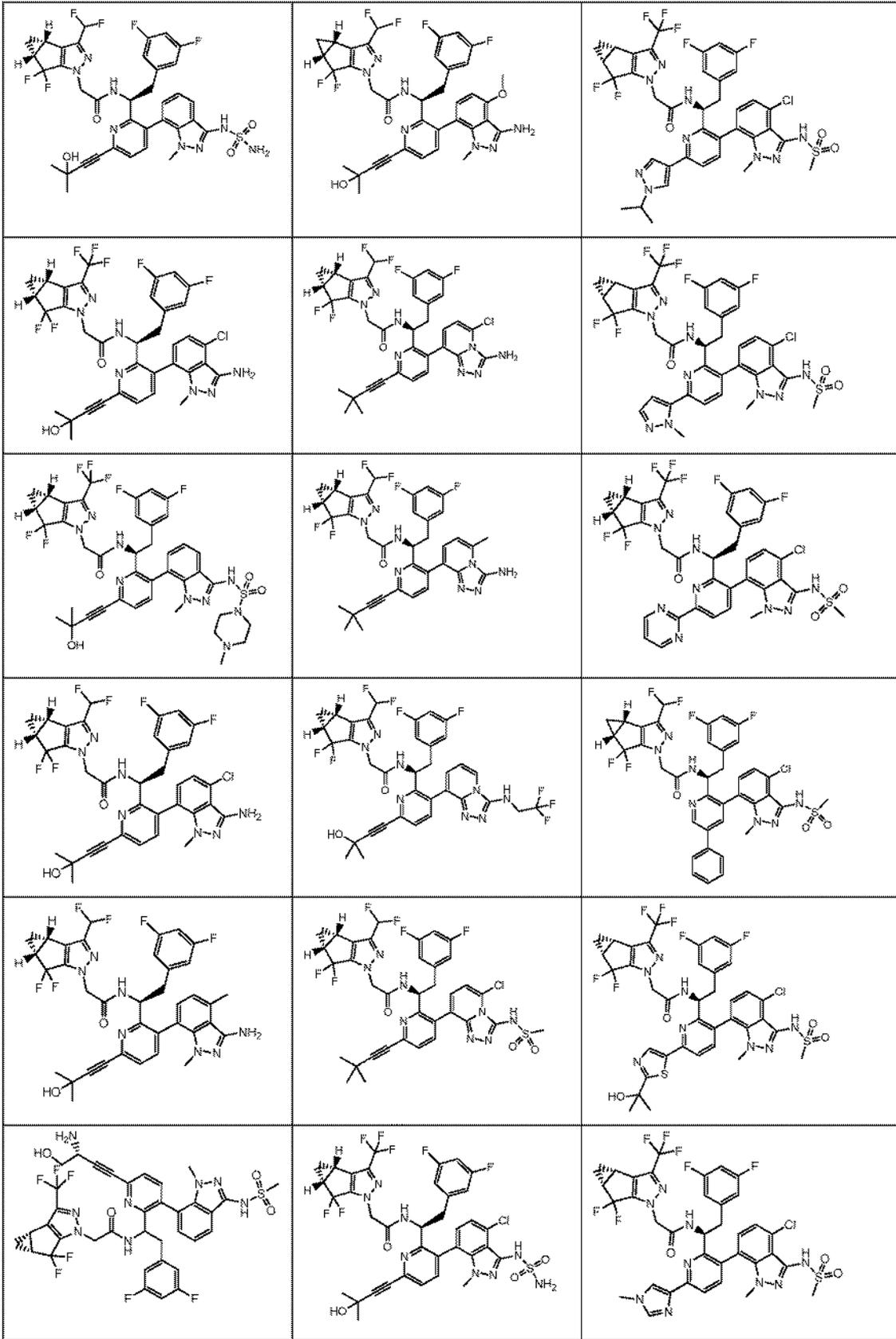


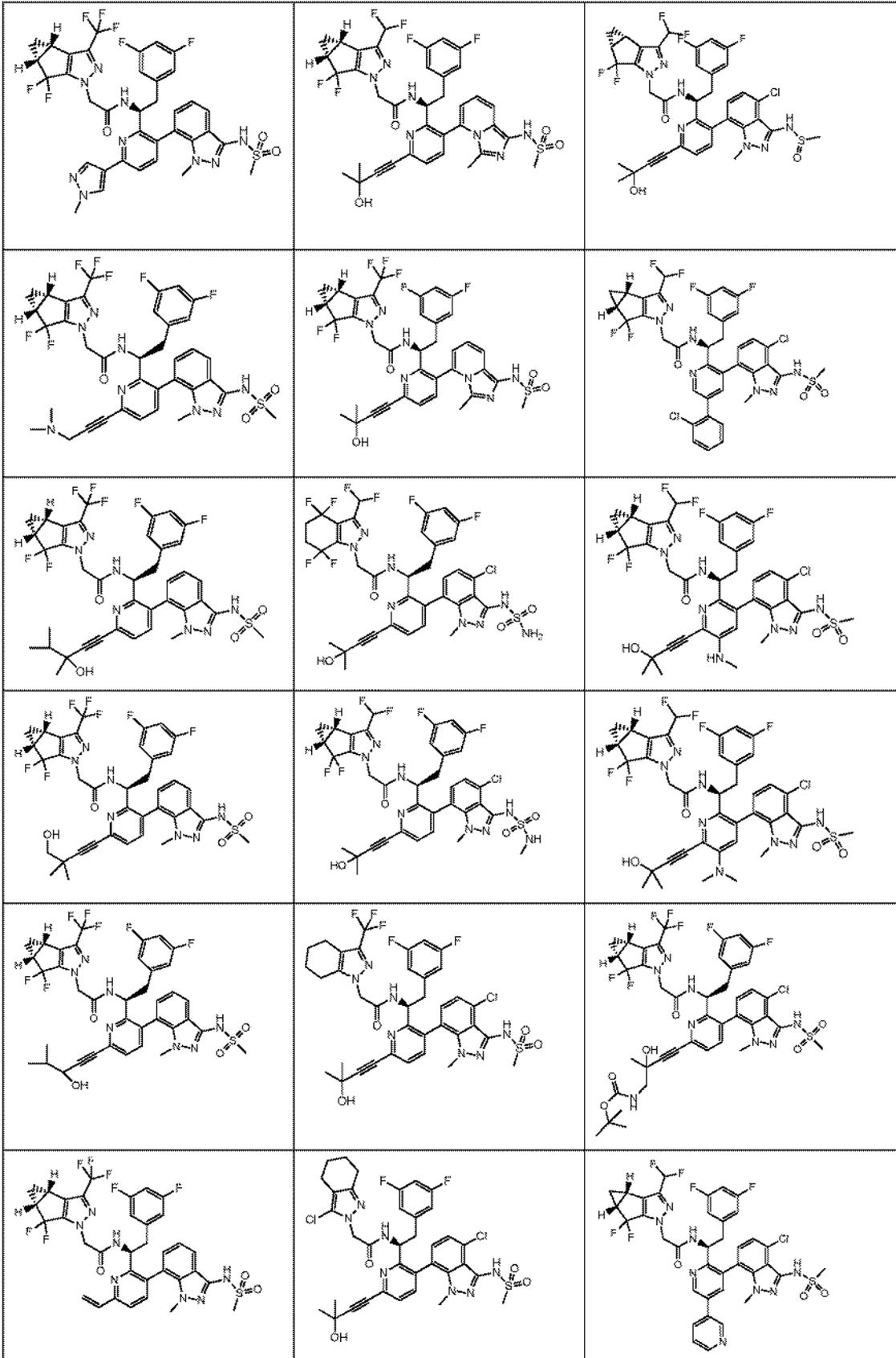


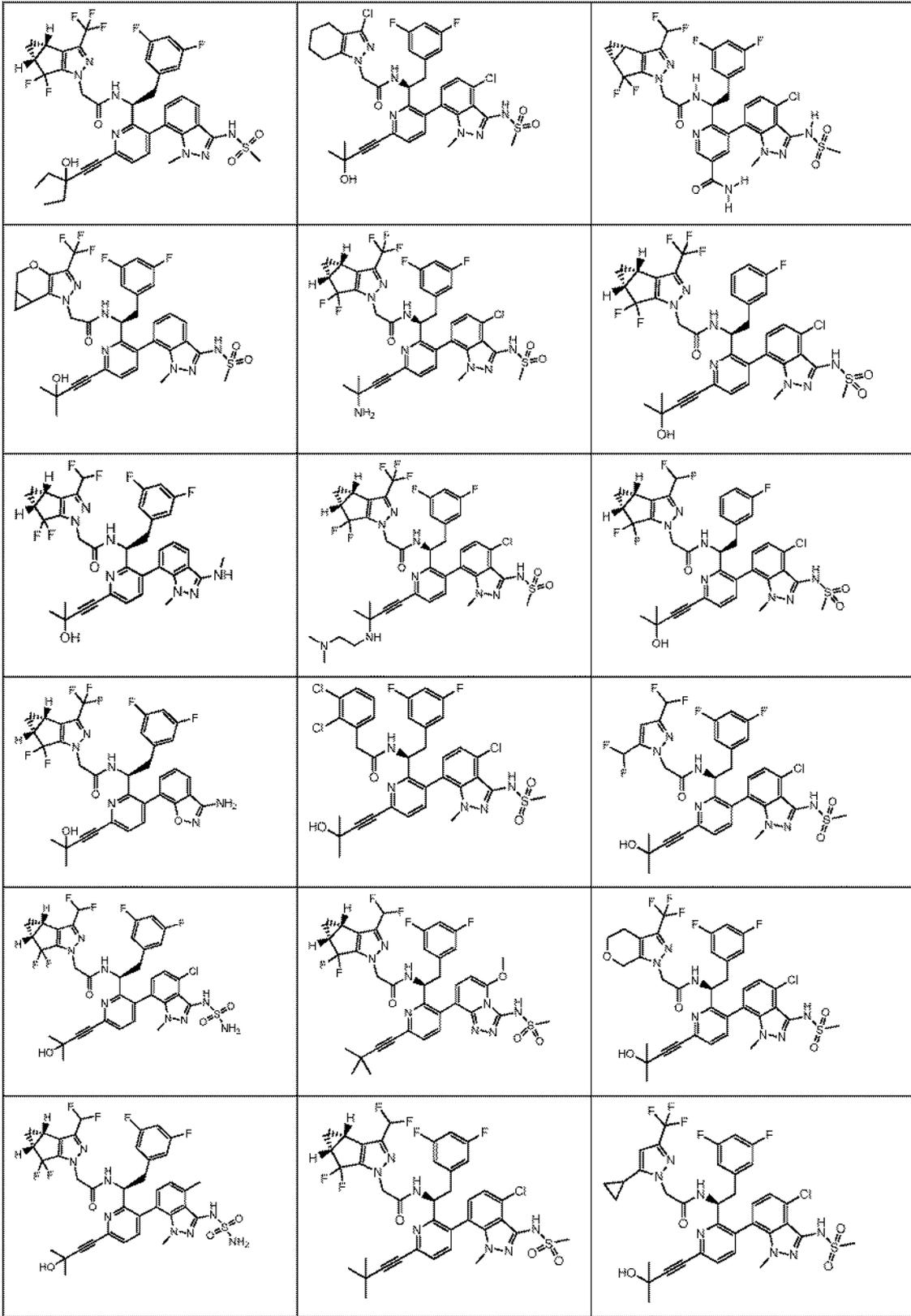


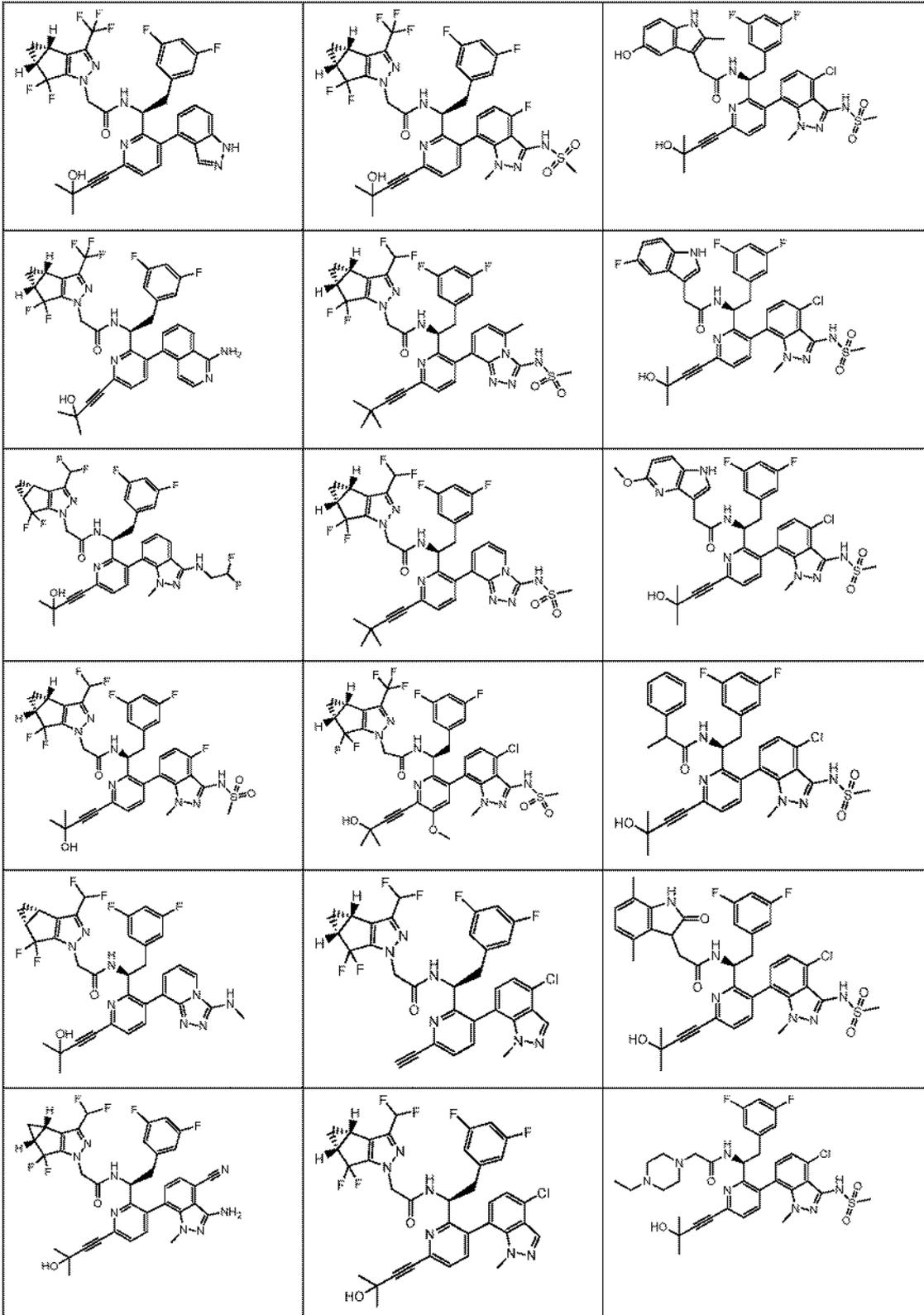


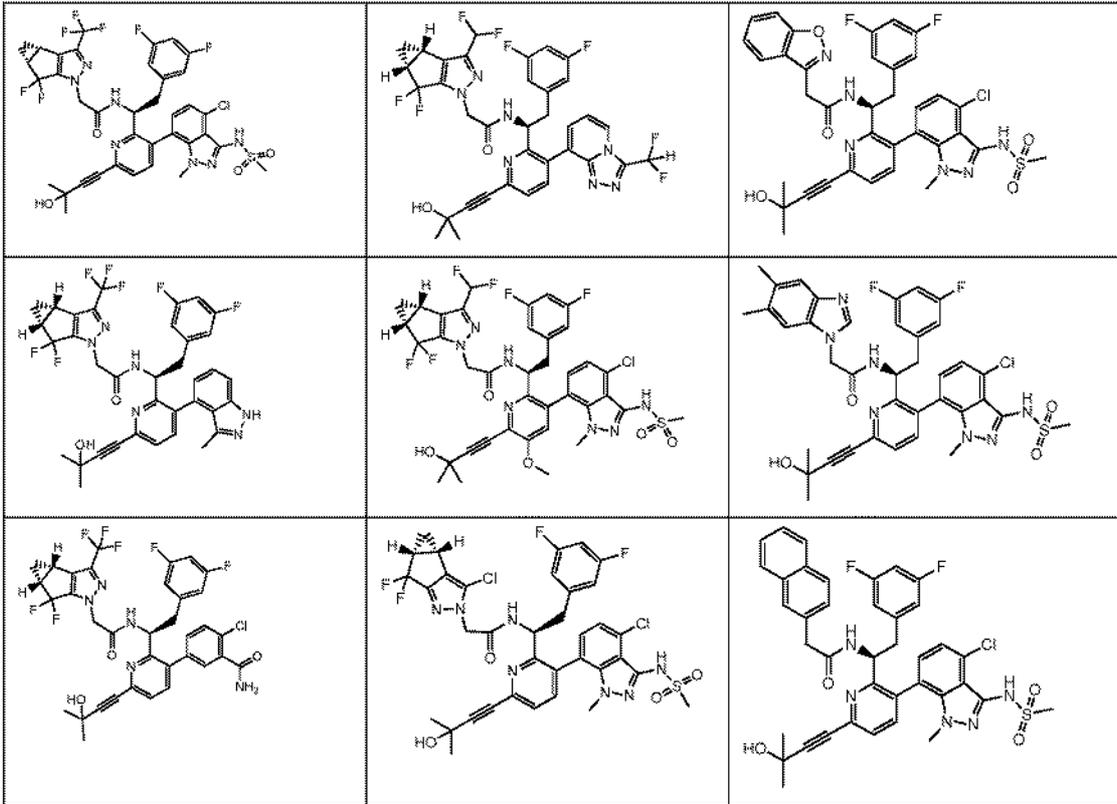




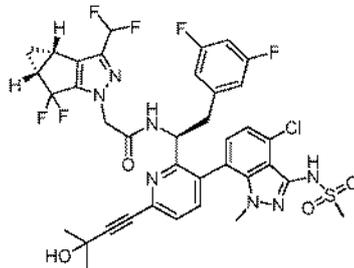






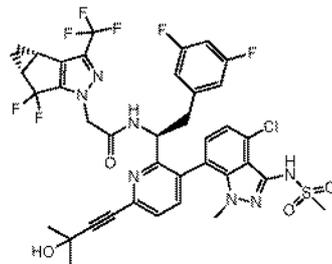


38. A compound of formula:



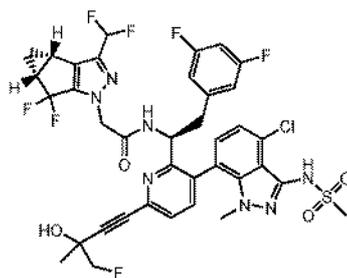
or a pharmaceutically acceptable salt thereof.

39. A compound of formula:



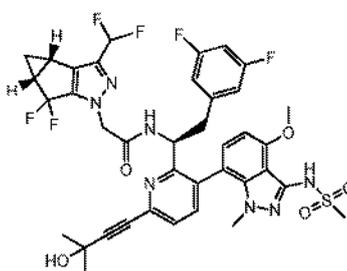
or a pharmaceutically acceptable salt thereof.

40. A compound of formula:



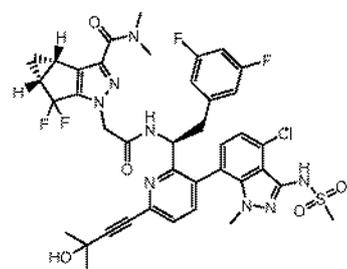
or a pharmaceutically acceptable salt thereof.

41. A compound of formula:



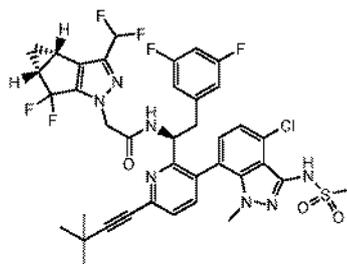
or a pharmaceutically acceptable salt thereof.

42. A compound of formula:



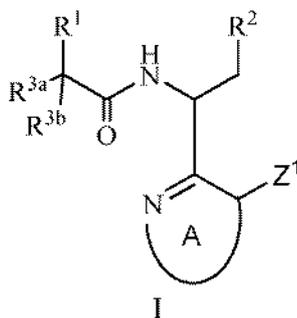
or a pharmaceutically acceptable salt thereof.

43. A compound of formula:



or a pharmaceutically acceptable salt thereof.

44. A compound of formula I:



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<sup>nl</sup>, -OC(O)R<sup>p1</sup>, -OC(O)NR<sup>q1</sup>R<sup>r1</sup>, -SR<sup>nl</sup>, -S(O)R<sup>p1</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p1</sup>, -S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>nl</sup>COR<sup>p1</sup>, -NR<sup>nl</sup>CO<sub>2</sub>R<sup>p1</sup>, -NR<sup>nl</sup>CONR<sup>q1</sup>R<sup>r1</sup>, -NR<sup>nl</sup>S(O)<sub>2</sub>R<sup>p1</sup>, -NR<sup>nl</sup>S(O)<sub>2</sub>OR<sup>p1</sup>, -NR<sup>nl</sup>S(O)<sub>2</sub>NR<sup>q1</sup>R<sup>r1</sup>, NO<sub>2</sub>, -C(O)R<sup>nl</sup>, -C(O)OR<sup>nl</sup>, -C(O)NR<sup>q1</sup>R<sup>r1</sup> and -S(O)<sub>2</sub>NR<sup>nl</sup>COR<sup>p1</sup>, 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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)alkynyl, wherein any (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)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<sub>3</sub>-C<sub>7</sub>)carbocycle, phenyl, 5-6 membered monocyclic-heteroaryl, 3-7 membered heterocycle, halogen, -CN, -OR<sup>n2</sup>, -OC(O)R<sup>p2</sup>, -OC(O)NR<sup>q2</sup>R<sup>r2</sup>, -SR<sup>n2</sup>, -S(O)R<sup>p2</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p2</sup>, -S(O)<sub>2</sub>NR<sup>q2</sup>R<sup>r2</sup>, -NR<sup>q2</sup>R<sup>r2</sup>, -NR<sup>n2</sup>COR<sup>p2</sup>, -NR<sup>n2</sup>CO<sub>2</sub>R<sup>p2</sup>, -NR<sup>n2</sup>CONR<sup>q2</sup>R<sup>r2</sup>, -NR<sup>n2</sup>S(O)<sub>2</sub>R<sup>p2</sup>, -NR<sup>n2</sup>S(O)<sub>2</sub>OR<sup>p2</sup>, -NR<sup>n2</sup>S(O)<sub>2</sub>NR<sup>q2</sup>R<sup>r2</sup>, NO<sub>2</sub>, -C(O)R<sup>n2</sup>, -C(O)OR<sup>n2</sup>, -C(O)NR<sup>q2</sup>R<sup>r2</sup>, halophenyl, 5-6 membered haloheteroaryl, 3-7 membered haloheterocycle and (C<sub>1</sub>-C<sub>8</sub>)heteroalkyl;

each  $Z^{1d}$  is independently selected from (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl and (C<sub>1</sub>-C<sub>8</sub>)haloalkyl;

each R<sup>n1</sup> is independently selected from H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R<sup>n1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)alkynyl of R<sup>n1</sup> is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5)  $Z^{1c}$  groups;

each R<sup>p1</sup> is independently selected from (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R<sup>p1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)alkynyl of R<sup>p1</sup> is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5)  $Z^{1c}$  groups;

R<sup>q1</sup> and R<sup>r1</sup> are each independently selected from H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R<sup>q1</sup> or R<sup>r1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)alkynyl of R<sup>q1</sup> or R<sup>r1</sup> is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5)  $Z^{1c}$  groups, or R<sup>q1</sup> and R<sup>r1</sup> 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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, (C<sub>1</sub>-C<sub>8</sub>)haloalkyl and (C<sub>1</sub>-C<sub>8</sub>)heteroalkyl;

each  $R^{p2}$  is independently selected from (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, (C<sub>1</sub>-C<sub>8</sub>)haloalkyl and (C<sub>1</sub>-C<sub>8</sub>)heteroalkyl;

$R^{q2}$  and  $R^{r2}$  are each independently selected from H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, (C<sub>1</sub>-C<sub>8</sub>)haloalkyl and (C<sub>1</sub>-C<sub>8</sub>)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<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, -C(O)R<sup>n3</sup> and -C(O)NR<sup>q3</sup>R<sup>r3</sup>, 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<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)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<sub>3</sub>-C<sub>7</sub>)carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, -OR<sup>n4</sup>, -OC(O)R<sup>p4</sup>, -OC(O)NR<sup>q4</sup>R<sup>r4</sup>, -SR<sup>n4</sup>, -S(O)R<sup>p4</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p4</sup>, -S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>COR<sup>p4</sup>, -NR<sup>n4</sup>CO<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>CONR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>OR<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, NO<sub>2</sub>, -C(O)R<sup>n4</sup>, -C(O)OR<sup>n4</sup> and -C(O)NR<sup>q4</sup>R<sup>r4</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl and (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

each  $Z^{2c}$  is independently selected from halogen, -CN, -OR<sup>n4</sup>, -OC(O)R<sup>p4</sup>, -OC(O)NR<sup>q4</sup>R<sup>r4</sup>, -SR<sup>n4</sup>, -S(O)R<sup>p4</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p4</sup>, -S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>COR<sup>p4</sup>, -NR<sup>n4</sup>CO<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>CONR<sup>q4</sup>R<sup>r4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>R<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>OR<sup>p4</sup>, -NR<sup>n4</sup>S(O)<sub>2</sub>NR<sup>q4</sup>R<sup>r4</sup>, NO<sub>2</sub>, -C(O)R<sup>n4</sup>, -C(O)OR<sup>n4</sup> and -C(O)NR<sup>q4</sup>R<sup>r4</sup>;

each  $R^{n3}$  is independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl and (C<sub>2</sub>-C<sub>4</sub>)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<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl and (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $R^{p4}$  is independently selected from (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>2</sub>-C<sub>4</sub>)alkynyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl and (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

$R^{q4}$  and  $R^{r4}$  are each independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>2</sub>-C<sub>4</sub>)alkynyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl and (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl;

each  $Z^3$  is independently selected from halogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, -OH, -CN, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl and (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

each  $Z^4$  is independently selected from (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)carbocycle, halogen, -CN, -OR<sup>n5</sup>, -OC(O)R<sup>p5</sup>, -OC(O)NR<sup>q5</sup>R<sup>r5</sup>, -SR<sup>n5</sup>, -S(O)R<sup>p5</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p5</sup>, -S(O)<sub>2</sub>NR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>n5</sup>COR<sup>p5</sup>, -NR<sup>n5</sup>CO<sub>2</sub>R<sup>p5</sup>, -NR<sup>n5</sup>CONR<sup>q5</sup>R<sup>r5</sup>, -NR<sup>n5</sup>S(O)<sub>2</sub>R<sup>p5</sup>, -NR<sup>n5</sup>S(O)<sub>2</sub>OR<sup>p5</sup>, -NR<sup>n5</sup>S(O)<sub>2</sub>NR<sup>q5</sup>R<sup>r5</sup>, NO<sub>2</sub>, -C(O)R<sup>n5</sup>, -C(O)OR<sup>n5</sup> and -C(O)NR<sup>q5</sup>R<sup>r5</sup>, wherein any (C<sub>3</sub>-C<sub>7</sub>)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<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl and (C<sub>2</sub>-C<sub>8</sub>)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<sup>n6</sup>, -OC(O)R<sup>p6</sup>, -OC(O)NR<sup>q6</sup>R<sup>r6</sup>, -SR<sup>n6</sup>, -S(O)R<sup>p6</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>p6</sup>, -S(O)<sub>2</sub>NR<sup>q6</sup>R<sup>r6</sup>, -NR<sup>q6</sup>R<sup>r6</sup>, -NR<sup>n6</sup>COR<sup>p6</sup>,

$-\text{NR}^{\text{n}6}\text{CO}_2\text{R}^{\text{p}6}$ ,  $-\text{NR}^{\text{n}6}\text{CONR}^{\text{q}6}\text{R}^{\text{r}6}$ ,  $-\text{NR}^{\text{n}6}\text{S}(\text{O})_2\text{R}^{\text{p}6}$ ,  $-\text{NR}^{\text{n}6}\text{S}(\text{O})_2\text{OR}^{\text{p}6}$ ,  $-\text{NR}^{\text{n}6}\text{S}(\text{O})_2\text{NR}^{\text{q}6}\text{R}^{\text{r}6}$ ,  $\text{NO}_2$ ,  $-\text{C}(\text{O})\text{R}^{\text{n}6}$ ,  $-\text{C}(\text{O})\text{OR}^{\text{n}6}$  and  $-\text{C}(\text{O})\text{NR}^{\text{q}6}\text{R}^{\text{r}6}$ ;

each  $\text{Z}^{\text{4b}}$  is independently selected from (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl (C<sub>2</sub>-C<sub>4</sub>)alkynyl and (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

each  $\text{R}^{\text{n}5}$  is independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

each  $\text{R}^{\text{p}5}$  is independently selected from (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

$\text{R}^{\text{q}5}$  and  $\text{R}^{\text{r}5}$  are each independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

each  $\text{R}^{\text{n}6}$  is independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

each  $\text{R}^{\text{p}6}$  is independently selected from (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

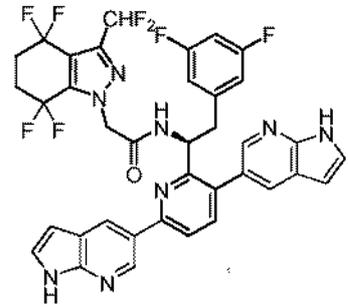
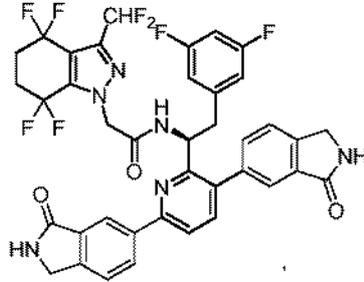
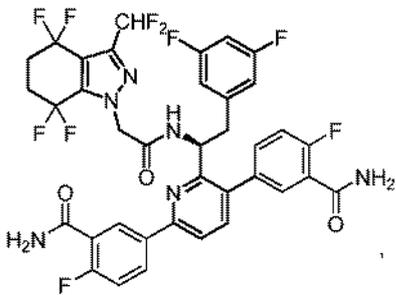
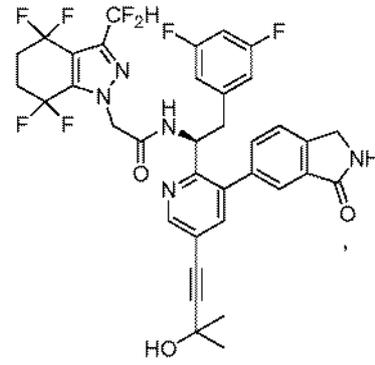
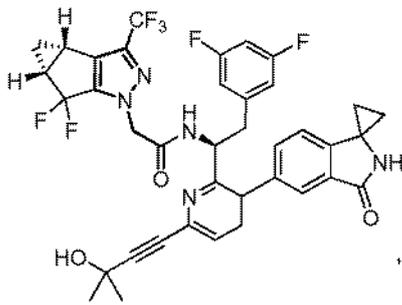
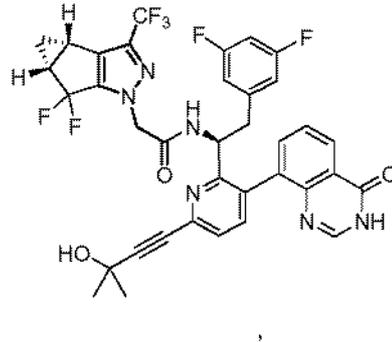
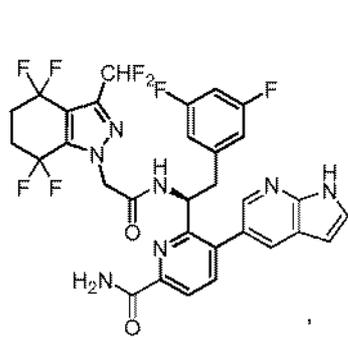
$\text{R}^{\text{q}6}$  and  $\text{R}^{\text{r}6}$  are each independently selected from H, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl;

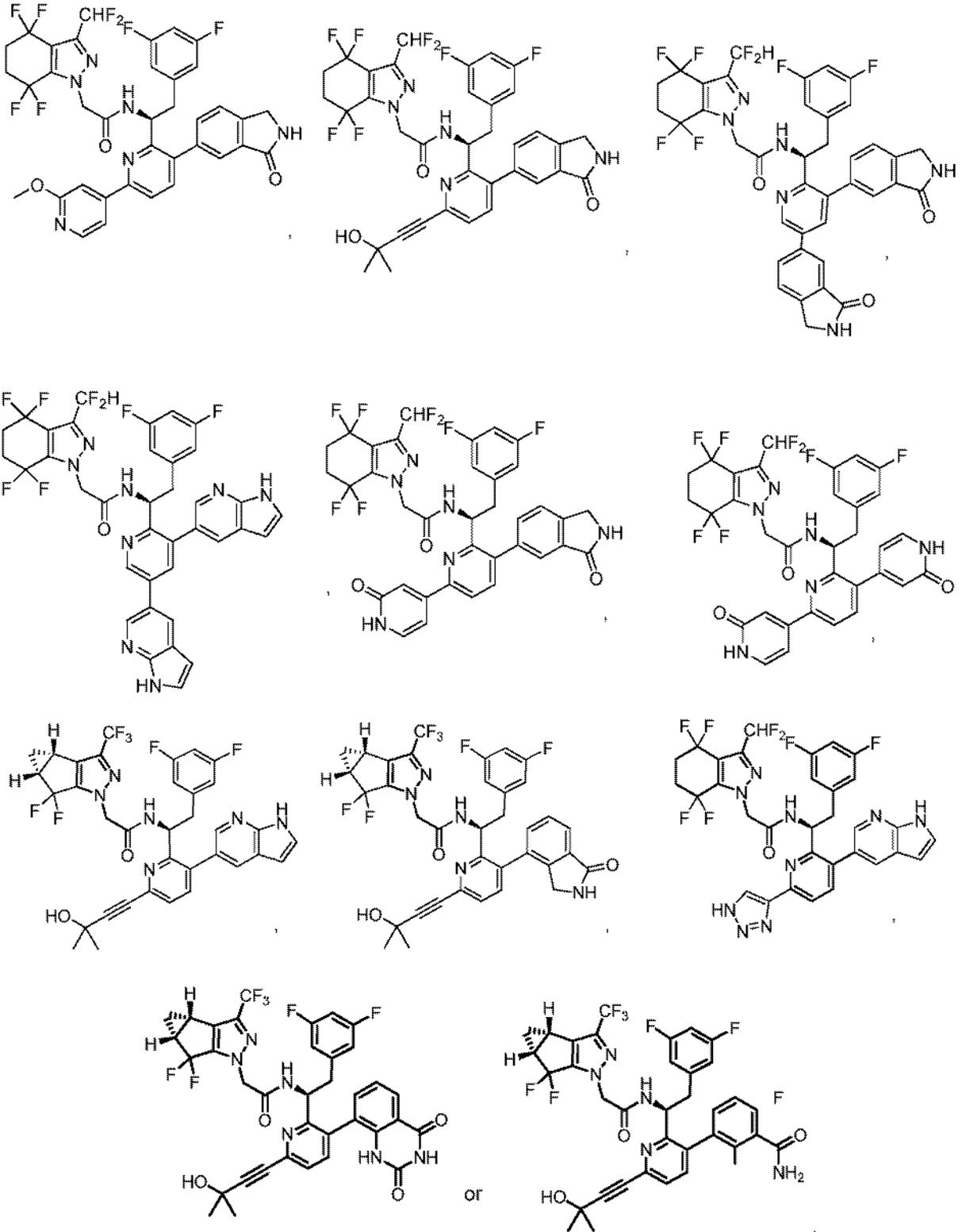
each  $\text{Z}^5$  is independently selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, -CN and -OR<sup>n7</sup>, wherein any (C<sub>1</sub>-C<sub>6</sub>)alkyl of  $\text{Z}^5$  is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen; and

each  $\text{R}^{\text{n}7}$  is independently selected from H, (C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>3</sub>)haloalkyl and (C<sub>3</sub>-C<sub>7</sub>)carbocycle;

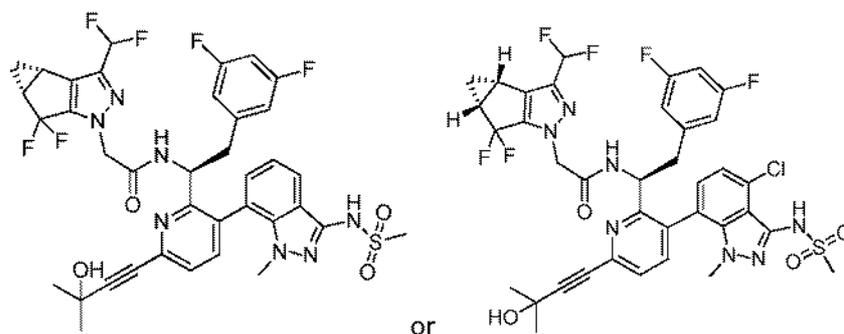
or a pharmaceutically acceptable salt thereof.

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





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



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 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.

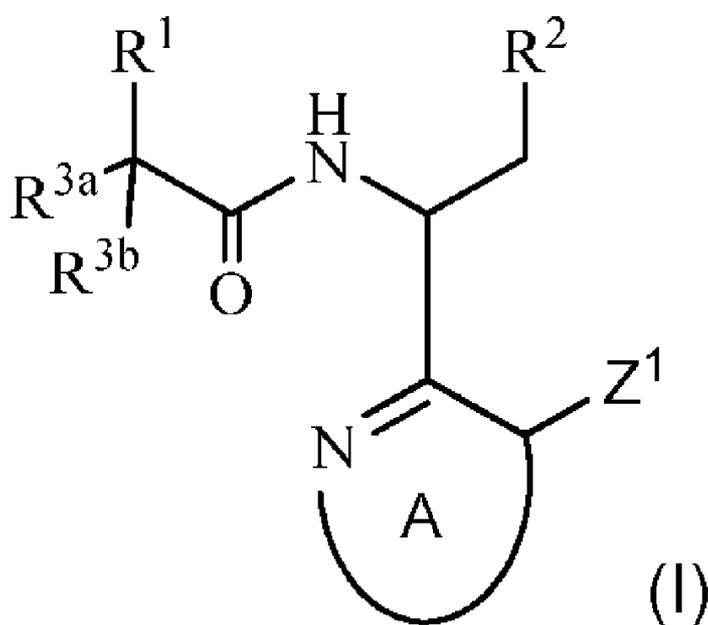
51. A compound of any of claims 1-46, or a pharmaceutically acceptable salt thereof, for use in medical therapy.
52. A compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of an HIV virus infection.
53. The use of a compound 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.

Dated this the 21<sup>st</sup> day of August 2015.

ABSTRACT

## "AMIDE COMPOUNDS FOR THE TREATMENT OF HIV"

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.



# 4D-QSAR Models of HOE/BAY-793 Analogues as HIV-1 Protease Inhibitors

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## Abstract

HIV-1 protease is a homodimer composed of monomer subunits, each containing 99 amino acids with a single catalytic Asp residue. Four-dimensional quantitative structure-activity relationship (4D-QSAR) analysis was applied to a series of 32 C<sub>2</sub>-symmetric diol inhibitors of HIV-1 protease. The 4D-QSAR approach can be applied to both receptor-dependent (RD) and receptor-independent (RI) problems. In the first scheme, the geometry of the receptor (molecular target, usually an enzyme) is available. By contrast, in the second scheme, the geometry of the receptor is not available or is not included in the data necessary to the analysis. Twenty-eight compounds belong to the training set, and four to the test set, which was used for external validation. These compounds are analogues of inhibitor HOE/BAY-793, important for its outstanding potency *in vitro* and, especially, in HIV-1 infected cell culture. Five thousand conformations of each analogue were sampled by molecular dynamic simulation for 50 ps at a constant temperature of 300 K. For each of the three trial alignments, each conformation was placed in a 2 Å grid cell lattice. Optimized 4D-QSAR models were constructed by genetic algorithm (GA) optimization and partial least squares (PLS) fitting, and evaluated by the leave-one-out cross-validation method. The models developed in this analysis suggest that alignment 3 yields the best results, both statistically and qualitatively. The 4D-QSAR models developed in this study suggest novel molecular regions to be explored in the search for better anti-HIV agents to inhibit HIV-1 protease.

## 1 Introduction

The Acquired Immune Deficiency Syndrome (AIDS) is still one of the most serious problems faced by humanity today. The human immunodeficiency virus (HIV) has been identified as the etiologic agent of this disease, that causes a large number of deaths, and has a great and limiting

influence in the quality of live and the economic development of many countries [1]. The HIV-1 protease was identified as one of the major targets for intervention in HIV infection. Navia and co-workers, from Merck laboratories, was the first group to obtain the crystal structure of HIV-1 protease [2], and subsequently, Kent and co-workers reported a more accurate structure [3]. The active HIV-1 protease is a homodimer, in which each monomer subunit is composed by 99 amino acids with a single catalytic Asp-residue at the active center, located on a single protein chain. HIV-1 protease is enzymatically active only as a C<sub>2</sub> symmetric dimer [4]. More than 140 structures of HIV-1 proteases, their mutants, and complexes with various inhibitors have been reported so far [1]. A significant clinical outcome is the emergence of viral strains that exhibit resistance to multiple HIV-1 protease inhibitors. Loss of sensitivity to protease inhibitors occurs because the resistant viral strains encode protease molecules containing specific

**Abbreviations:** 4D-QSAR: Four-Dimensional Quantitative Structure-Activity Relationship; AIDS: Acquired Immune Deficiency Syndrome; GA: Genetic Algorithm; HIV: Human Immunodeficiency Virus; HOE/BAY-793: N-(1-benzyl-2,3-dihydroxy-4-[3-methyl-2-[2-(2-methyl-propane-2-sulfonylmethyl)-3-naphthalen-1-yl-propionylamino]-butyrylamino]-5-phenyl-pentyl)-3-methyl-2-[2-(2-methyl-propane-2-sulfonylmethyl)-3-naphthalen-1-yl-propionylamino]-butyramide; IC<sub>50</sub>: Inhibitory Concentration 50%; MD: molecular dynamic; PLS: Partial Least Squares; RD: Receptor-Dependent; RI: Receptor-Independent; SAR: Structure-Activity Relationship

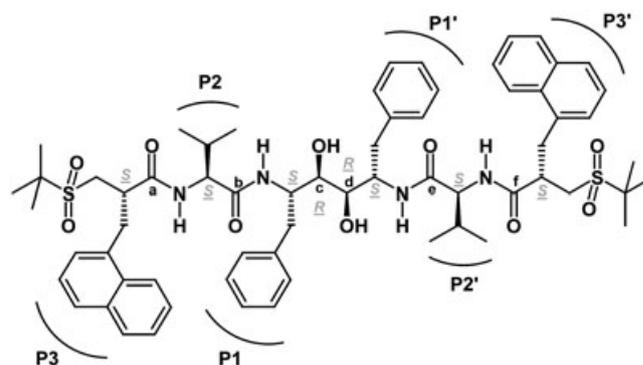
amino acid mutations that lower the affinity with the inhibitors, yet maintain sufficient affinity with the substrate [5].

Proteases play an essential role in many biological processes: they catalyze the hydrolysis of peptide bonds with high sequence selectivity and catalytic efficiency. The two different catalytic mechanisms divide the proteases into two broad classes of enzymes: the first uses an activated water molecule to attack the amide bond carbonyl of the substrate's scissile bond; and the second uses a nucleophilic atom of an amino acid side chain to initiate amide hydrolysis. The activation by a water molecule is achieved either by a zinc cation (zinc-metalloproteinases) or by two aspartyl- $\beta$ -carboxyl groups at the active site (aspartate-proteases). The activation by a nucleophilic atom (e.g. hydroxyl or thiol group) is achieved by another amino acid side chain, and then the activated nucleophile attacks the carbonyl of the scissile amide bond to form an ester or a thioester-acyl intermediate. Eventually, a water molecule, corresponding to the hydrolysis products, hydrolyzes this acyl-enzyme intermediate [6, 7].

Although there are six HIV-1 protease inhibitors (Saquinavir, Amprenavir, Nelfinavir, Indinavir, Ritonavir, and Lopinavir) currently approved by the U.S. Food and Drug Administration (FDA), their effectiveness has been hampered by the emergence of drug-resistant and cross-resistant mutants. Therefore, a definitive cure for AIDS has yet to be found [8]. The development of a new generation of protease inhibitors that effectively addresses the issue of resistance requires a better understanding of the interactions between protease and substrate or inhibitor.

Budt and coworkers [9] described a series of compounds with  $C_2$  symmetry and a vicinal diol group as central unit, with the ability to bind to the HIV-1 protease active site. These compounds are improved analogues of inhibitor HOE/BAY-793 (*N*-(1-benzyl-2,3-dihydroxy-4-(3-methyl-2-[2-(2-methyl-propane-2-sulfonylmethyl)-3-naphthalen-1-yl-propionylamino]-butyrylamino)-5-phenyl-pentyl)-3-methyl-2-[2-(2-methyl-propane-2-sulfonylmethyl)-3-naphthalen-1-yl-propionylamino]-butyramide, compound **32**, Figure 1), presenting outstanding potency, especially in HIV-1 infected cell cultures. Structure-activity relationship (SAR) studies showed that all three side chains (P1-P3/P1'-P3', Figure 1) need to be lipophilic in both enzyme and in vitro virus inhibition, and, in some cases, when the enzyme tolerates hydrophilic substituents, drastic reductions in anti-HIV activity (cell culture assay) are observed, most likely due to insufficient cell penetration [9].

Quantitative structure-activity relationship (QSAR) studies may be useful in the search for molecule sites capable of being transformed into better specific ligands [10, 11]. This methodology is mostly used to correlate properties (e.g. biological activities) with structures, but it can also be applied to predict the activity value of non-synthesized compounds, structurally related to training sets. It is a mathematical model of correlation statistically validated



**Figure 1.** Ordered atom letter codes (a, b, c, d, e, and f) used in the 4D-QSAR analysis defining the three trial alignments: (1) a-c-e, (2) b-d-e, and (3) f-d-a. Compound **32** ( $pIC_{50}=9.52$ ) is used to define the atom letter code. The chirality (*R* or *S*) is defined in gray.

between the chemical structure and their activity profile. With the advent of molecular modeling, three-dimensional (3D) descriptors replaced the didactical physicochemical and bidimensional descriptors [12, 13].

In those studies, methods that can incorporate molecular flexibility, such as the 4D-QSAR methods, proposed by Hopfinger and co-workers [12–19], proved advantageous because they allowed the identification of the conformation that maximized the activity from 3D-QSAR models. Therefore, the main purpose of this study is to use the 4D-QSAR method to map the interaction sites of the series of inhibitors developed by Budt and co-workers [9], and to propose structural changes to make them more potent and, thereby, better anti-HIV agents.

## 2 Methods

### 2.1 Biological Data

The 4D-QSAR models were developed using 28 compounds (**1–15**, **17–18**, **20–24**, **26–30**, and **32**), the training set, and externally validated using four compounds (**16**, **19**, **25**, and **31**), the test set, selected from a series of HIV-1 protease inhibitors developed by Budt and co-workers [9]. The biological activities of these compounds were reported as the concentration capable of inhibiting 50% of the enzyme activity ( $IC_{50}$ ), using the HIV-1 protease expressed and purified from *Escherichia coli* strain K12 [9]. In addition, all pharmacological data were obtained from the same laboratory, eliminating the potential noise that might have been introduced by the pooling of data sets from different sources. The  $IC_{50}$  (nM) values were converted into molar units, and, then, expressed in negative logarithmic units ( $pIC_{50}$ ). The range of  $pIC_{50}$  values for the training and test set spans at least three orders of magnitude (6.44 to 9.52), and the biological activity values shows a regular distribution over the whole range.

The 32 compounds (training and test set) are listed in the Table 1 and compound **32**, used as a reference in this work, corresponds to HOE/BAY-793. Since the inhibitors of this series are structurally related, the compounds of the training and test set were assigned as follows: the 32 compounds were assembled in four sub-groups according their increasing values of  $pIC_{50}$  (Group I:  $pIC_{50}=6.01-7.00$ , Group II:  $pIC_{50}=7.01-8.00$ , Group III:  $pIC_{50}=8.01-9.00$ , and Group IV:  $pIC_{50}=9.01-10.00$ ), and one compound from each group was randomly selected as a test set compound. As a result, the remaining 28 compounds comprise the training set. Using this approach we have test set compounds spread over the whole range of the activity values, and at least one test set compound from each range of biological activity. Compound **32** (HOE/BAY-793), included in Group IV, was not considered in the random selection, since it was selected as the reference compound in the training set.

## 2.2 Minimization of the Crystallographic Structure Complex of HOE/BAY-793 and HIV-1 Protease

Hydrogen atoms were added to the crystallographic structure of HOE/BAY-793 and HIV-1 protease complex obtained from the Protein Data Bank (PDB code: 1VIJ) [20]. Energy minimization, using steepest descent and conjugate gradient algorithms, were carried out until a gradient of  $0.1 \text{ kcal} \cdot \text{mol}^{-1} \cdot \text{Å}^{-1}$  was reached. Four steps were used successively: (a) minimization of the hydrogen atoms; (b) minimization of the side-chains, keeping the backbone fixed; (c) minimization of the backbone, keeping the side-chain fixed; and (d) minimization of the entire enzyme. All minimization steps were performed in the CVFF force field of the INSIGHTII software [21], applying a distance-dependent dielectric function,  $\epsilon_r = D^*r_{ij}$ , which was set to  $3^*r_{ij}$  in order to try to model the solvent effect in the absence of explicit solvent. In this expression,  $r_{ij}$  is the distance between atoms  $i$  and  $j$ , and  $D$  is the scale factor of the dielectric function.

## 2.3 Minimization of the HIV-1 Protease Complexes with the 32 Compounds

The HOE/BAY-793 (Figure 1) crystallographic conformation was retrieved from the Protein Data Bank (PDB code: 1VIJ) [20] and used for modeling the 32 compounds of the training and test sets. Three-dimensional models of each of the 32 compounds reported in Table 1 were constructed inside the active site of HIV-1 protease, using Builder module of INSIGHTII software [21]. Subsequently, we performed geometry optimizations of the all enzyme-ligand complexes, keeping the backbone fixed, and using steepest descent and conjugate gradient algorithms until a gradient of  $0.01 \text{ kcal} \cdot \text{mol}^{-1} \cdot \text{Å}^{-1}$  was reached. All minimization steps were performed in the CVFF force field of the INSIGHTII software [21], applying a distance-dependent dielectric function ( $\epsilon_r$ ), which was set to  $3^*r_{ij}$ . In order to

obtain the partial atomic charges, the resultant geometry of each compound was submitted to the AM1 semi-empirical calculation using the AMPAC/MOPAC module from the INSIGHTII software [21].

## 2.4 Molecular Dynamic Simulation

The AM1 optimized structures were the initial structures in each molecular dynamic simulation (MDS). The MDS resulting structures, were, then, used to construct the conformational ensemble profile (CEP) of each ligand. The MDS was performed using the 4D-QSAR program [22] and the Molsim 3.0 software [23] with an extended MM2 force field [24]. The temperature for the MDS was set at 300 K, close to the temperature assays, with a simulation sampling time of 50 ps, and intervals of 0.001 ps. Applying this scheme, it was obtained a total sampling of 50000 conformations of each compound. The MDS calculations were carried out applying a distance-dependent dielectric function,  $\epsilon_r = D^*r_{ij}$ , which was set to  $3^*r_{ij}$  in order to try to model the solvent effect in the absence of explicit solvent. In addition, the carbon atoms of the carbonyl groups (Figure 1, atoms a-b-e-f), common to all compounds, were fixed (frozen) to prevent a large conformational change of the ligands in the absence of the protein structure.

## 2.5 Alignment Definition

The alignment is one of the most important steps in 3D-QSAR methodologies (e.g. CoMFA and 4D-QSAR). In this work, we will assume that all molecules bind to the enzyme in a similar mode, since the compounds are structural analogs. Three-ordered atom trial alignments were selected in this study. In general, the alignments are chosen to span the common framework of the molecules in the training and test sets. Alignments using atoms from the right, left, and middle of the common framework and alignments that use atoms that span the common framework should be used to ensure a complete alignment analysis [25]. The three-ordered atom alignment definitions are (1) a-c-e, (2) b-d-e, and (3) f-d-a (Figure 1), using compound **32** (HOE/BAY-793) as a reference. The CEP for each compound was obtained after the MDS step was overlaid onto a cubic lattice of a selected grid cell size, according to each selected alignment. The cubic lattice serves to record the distribution of spatial occupancy of each atom of each ligand in the training. We defined two cubic grid cell sizes: (a) the 2.0 Å grid cell was used to test all alignments and select the best one; and (b) the 1.0 Å grid cell was used for derived models from the best alignment selected.

## 2.6 Interaction Pharmacophore Elements

The atoms of each compound were classified in seven types of interaction pharmacophore elements (IPE), corresponding to atom types, which may occupy the grid cells, according

**Table 1.** Structures of the 32 HIV-1 protease inhibitors [9]. Training set compound numbers are in bold and test set compound numbers are in *italic*.

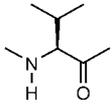
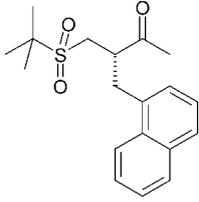
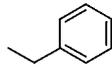
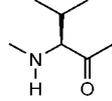
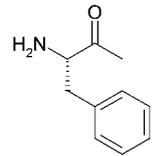
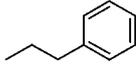
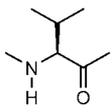
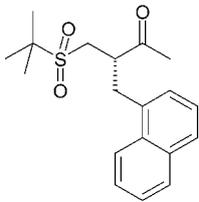
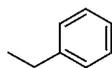
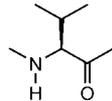
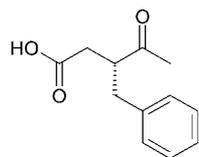
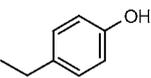
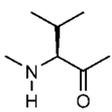
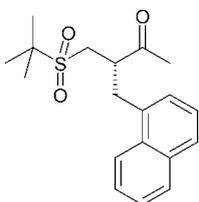
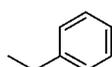
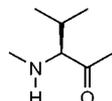
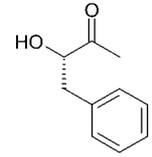
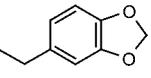
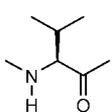
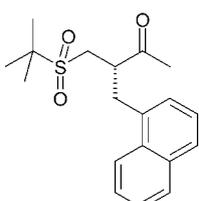
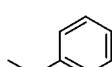
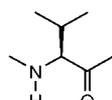
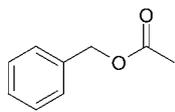
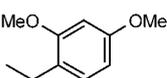
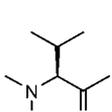
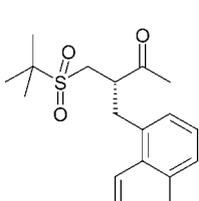
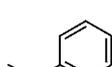
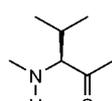
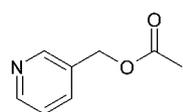
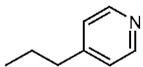
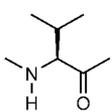
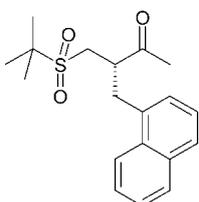
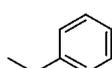
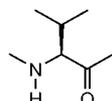
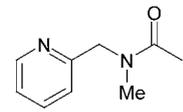
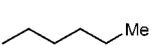
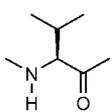
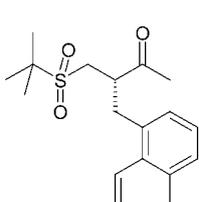
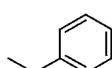
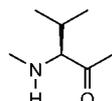
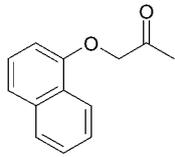
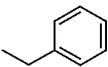
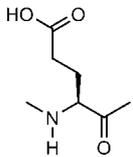
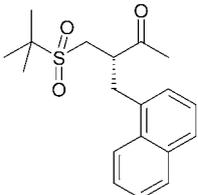
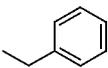
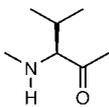
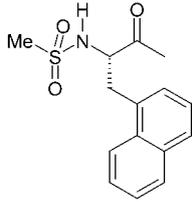
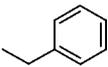
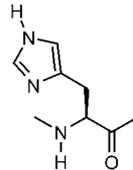
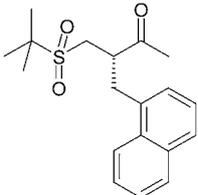
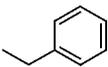
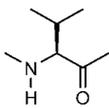
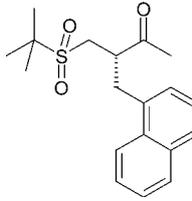
No.	P1/P1'	P2/P2'	P3/P3'	No.	P1/P1'	P2/P2'	P3/P3'
<b>1</b>				<b>17</b>			
<b>2</b>				<b>18</b>			
<b>3</b>				<b>19</b>			
<b>4</b>				<b>20</b>			
<b>5</b>				<b>21</b>			
<b>6</b>				<b>22</b>			
<b>7</b>				<b>23</b>			

Table 1. (cont.)

No.	P1/P1'	P2/P2'	P3/P3'	No.	P1/P1'	P2/P2'	P3/P3'
8				24			
9				25			
10				26			
11				27			
12				28			
13				29			
14				30			

**Table 1.** (cont.)

No.	P1/P1'	P2/P2'	P3/P3'	No.	P1/P1'	P2/P2'	P3/P3'
15				31			
16				32			

the 4D-QSAR methodology [12]. These IPEs correspond to the interactions that may occur in the active site, and are related to the pharmacophore groups. In this work, we have selected the following trial set of interaction pharmacophore elements: i) any atom type (any); ii) nonpolar atom (np); iii) atom of polar-positive charge density (p+); iv) atom of polar-negative charge density (p-); v) hydrogen bond acceptor atom (hba); vi) hydrogen bond donor atom (hbd); and vi) atoms in aromatic systems (ar). The occupancy of the grid cells by each IPE type is recorded over the conformational assembly profile, and forms the set of grid cell occupancy descriptors (GCOD), to be utilized as the pool of trial descriptors in the model building and optimization process [12].

### 2.7 4D-QSAR Model Calculation: Data Reduction and GA-PLS Approach

Partial least-squares (PLS) regression analysis was performed as a data (QSAR descriptors) reduction fit between the observed dependent variable measures and the corresponding set of GCOD values. After this, we performed two variable selections: in the first, GCODs that showed variance (self-variance) values of up to zero were eliminated; and in the second, the variables where GCODs were different from zero in three or less than three molecules were excluded. These procedures were used to prune the complete trial set of generated GCODs by identifying and selecting only the most highly weighted GCODs.

The GCODs with the highest weight on each data bank from the data reduction were optimized using a combined genetic algorithm (GA) and partial least-squares (PLS) approach [26], implemented in the 4D-QSAR program [22]. Their optimizations were initiated using 10000 randomly generated models, each having initially four variables.

Mutation probability over the crossover optimization cycle was set at 100%. The smoothing factor, the variable that specifies the number of descriptors in the QSAR models, was varied in order to determine equations with no more than six terms. Each alignment was evaluated using the procedure described above.

The best models resultant of the 4D-QSAR study were based on different criteria: i) the leave-one-out (LOO) cross-validated correlation coefficient, or  $q^2$ , currently used as the preferred parameter of model fitness [27]; ii) number of significant and independent 4D-QSAR models; iii) indices of model significance including statistical measures such as  $r^2$ , standard error (SE), and lack-of-fit (LOF) [26], and real prediction using the test set compounds (external validation).

### 2.8 Bioactive Conformation Selection

The 4D-QSAR method is able to predicted the "active" conformation of each compound in a training set, therefore, this conformation and the corresponding alignment can be used as the input for other 3D-QSAR methods (e.g. CoMFA) [12]. In the 4D-QSAR method, the "active" conformation can be postulated as the lowest-energy conformer state from the set sampled for each compound, which predicted the maximum activity using the optimum 4D-QSAR model [12]. This is achieved by first identifying all conformer states sampled for each compound, that are within  $\Delta E$  of the global minimum energy conformation of the CEP [12]. Only thermodynamically accessible conformations were considered, and, then, we determined which of these possible conformations had the highest activity as predicted by the model [12]. In this work we have tried a  $\Delta E = 2.0$  kcal/mol as a cutoff value.

**Table A.** Cross-correlation coefficients of the residuals of the fit for the top-ten models obtained in the 4D-QSAR analysis using alignment 3 and cubic grid cells of 1.0 Å.

	Mod 1	Mod 2	Mod 3	Mod 4	Mod 5	Mod 6	Mod 7	Mod 8	Mod 9	Mod 10
<b>Mod 1</b>	1.000									
<b>Mod 2</b>	0.562	1.000								
<b>Mod 3</b>	0.998	0.562	1.000							
<b>Mod 4</b>	0.710	0.755	0.708	1.000						
<b>Mod 5</b>	0.724	0.882	0.723	0.826	1.000					
<b>Mod 6</b>	0.816	0.848	0.814	0.837	0.961	1.000				
<b>Mod 7</b>	0.672	0.673	0.660	0.682	0.765	0.771	1.000			
<b>Mod 8</b>	0.807	0.844	0.808	0.830	0.959	0.996	0.759	1.000		
<b>Mod 9</b>	0.850	0.418	0.846	0.594	0.616	0.690	0.618	0.690	1.000	
<b>Mod 10</b>	0.705	0.785	0.695	0.756	0.862	0.874	0.895	0.874	0.647	1.000

### 3 Results

#### 3.1 Alignments 1, 2 and 3 Using Grid Cells of 2.0 Å

As shown in Figure 1, three-ordered atoms alignments were applied in the 4D-QSAR study: (1) a-c-e, (2) b-d-e, and (3) f-d-a. Considering local lattices represented by cubic grid cell of 2.0 Å, alignment 1 and 2 exhibited the poorest performance ( $q^2 < 0.5$ ) and an excessive number of terms (9–15 descriptors) in each equation (model). Evaluating the statistical quality of the models in terms of  $q^2$  and number of terms, we selected alignment 3 as the best alignment, which used a grid cell of 2.0 Å (Figure 1). In this alignment, we started using a grid cell of 1.0 Å in order to derive 4D-QSAR models, and no significant increase in predictive ability was observed after the seventh GCOD. Thus, from this point forward, only the results obtained from alignment 3 using cubic grid cells of 1.0 Å are discussed.

#### 3.2 Best Models from Alignment 3 Using Grid Cells of 1.0 Å

The best models from alignment 3 had good predictive abilities ( $q^2 = 0.75–0.89$ ) and squared coefficient of linear correlation ( $r^2$ ) between 0.84–0.90. The cross-correlation matrix of the residuals of fit of the top-ten models after the GA-PLS optimization step is given in Table A (Supplementary Material). A coefficient of linear correlation ( $r$ ) greater than 0.7 indicates that two models are highly correlated and may be considered to represent the training set in the same manner [12]. The matrix in Table A (Supplementary Material) indicates that there are at least three unique models among the top-ten models for alignment 3: Models 1, 2, and 7, which are given as Eqs. 1, 2, and 3, respectively.

##### Model 1

$$pIC_{50} = 8.88 - 64.25 (-6,5,0,any) - 4.42 (-1,3,14, any) + 34.01 (-3,6,0,any) - 21.03 (3,4,5,np) + 2.21 (4,3,1,any) + 53.48 (6,8,14,np)$$

$$n = 28 \quad r^2 = 0.90 \quad SE = 0.08 \quad q^2 = 0.86 \quad LOF = 0.36 \quad (1)$$

##### Model 2

$$pIC_{50} = 9.03 - 68.32 (-6,5,0,any) - 4.63 (-1,3,14,any) + 38.23 (-3,6,0,any) - 21.80 (3,4,5,np) - 1.88 (-2,3,17,any) + 3.90 (3,6,17,ar)$$

$$n = 28 \quad r^2 = 0.89 \quad SE = 0.09 \quad q^2 = 0.85 \quad LOF = 0.38 \quad (2)$$

##### Model 7

$$pIC_{50} = 8.84 - 52.40 (-6,5,0,any) + 22.57 (-1,-2,1,any) - 3.80 (-1,3,14,any) + 12.73 (-3,4,-1,np) - 54.80 (3,6,4,any)$$

$$n = 28 \quad r^2 = 0.85 \quad SE = 0.13 \quad q^2 = 0.83 \quad LOF = 0.42 \quad (3)$$

The GCODs (-3,6,0,any), (-3,4,-1,np), (-1,-2,1,any), (3,6,17,ar), (4,3,1,any), and (6,8,14,np), presenting positive coefficients (Eqs. 1–3), correspond to favorable interactions between the molecule substituent and amino acid residues in the active site of HIV-1 protease. Therefore, substituents in these positions increase the potency of the compounds. The GCODs (-6,5,0,any), (-2,3,17,any), (-1,3,14,any), (3,4,5,np), and (3,6,4,any), presenting negative coefficients (Eqs. 1–3), correspond to unfavorable interactions between the molecule substituent and amino acid residues in the active site of HIV-1 protease. Therefore, substituents in these positions decrease the potency. The most important GCODs should be (-6,5,0,any) and (-1,3,14,any) since they were most frequently selected by the GA analysis and present in the three best models (Models 1, 2, and 7). The second most important GCODs should be (-3,6,0,any) and (3,4,5,np), present in two of the three best models (Models 1 and 2). Therefore, the occupation of these GCODs is fundamental for the activity.

In order to gain a better understanding of the behavior of the data fitted to the models, the cross-correlation matrix among the different GCODs in Models 1, 2, and 7 are given in Table B (Supplementary Material). There are correlation ( $r > 0.7$ ) between three pairs of GCODs: (-6,5,0,any) and (-3,6,0,any) ( $r = 0.770$ ); (-3,4,-1,np) and (-3,6,0,any) ( $r = 0.838$ ); and (3,6,4,any) and (3,4,5,np) ( $r = 0.936$ ). The only pair of correlated GCODs that occurs in the same model (Models 1 and 2) is the first one. Interrelated

**Table B.** Cross-correlation coefficients of the GCODs of Models 1, 2, and 7 obtained in the 4D-QSAR analysis using alignment 3 and cubic grid cells of 1.0 Å.

	(-6,5,0, any)	(-1,3,14, any)	(-3,6,0, any)	(3,4,5, np)	(4,3,1, any)	(6,8,14,1 np)	(-1,-2,1, any)	(-3,4,-1, np)	(3,6,4, any)	(-2,3,17, any)	(3,6,17, ar)
(-6,5,0,any)	1.000										
(-1,3,14,any)	-0.120	1.000									
(-3,6,0,any)	0.770	-0.085	1.000								
(3,4,5,np)	0.141	0.100	0.194	1.000							
(4,3,1,any)	0.212	0.020	0.322	-0.132	1.000						
(6,8,14,np)	-0.011	-0.138	0.009	-0.027	0.212	1.000					
(-1,-2,1,any)	-0.044	0.035	-0.016	0.437	0.455	0.160	1.000				
(-3,4,-1,np)	0.612	-0.152	0.838	0.100	0.381	0.012	0.066	1.000			
(3,6,4,any)	0.078	0.204	0.093	0.936	-0.133	-0.063	0.509	0.052	1.000		
(-2,3,17,any)	-0.005	-0.118	-0.054	0.022	-0.005	-0.124	-0.119	-0.104	-0.039	1.000	
(3,6,17,ar)	0.166	-0.218	-0.002	-0.033	-0.060	-0.109	0.085	0.080	-0.060	0.213	1.000

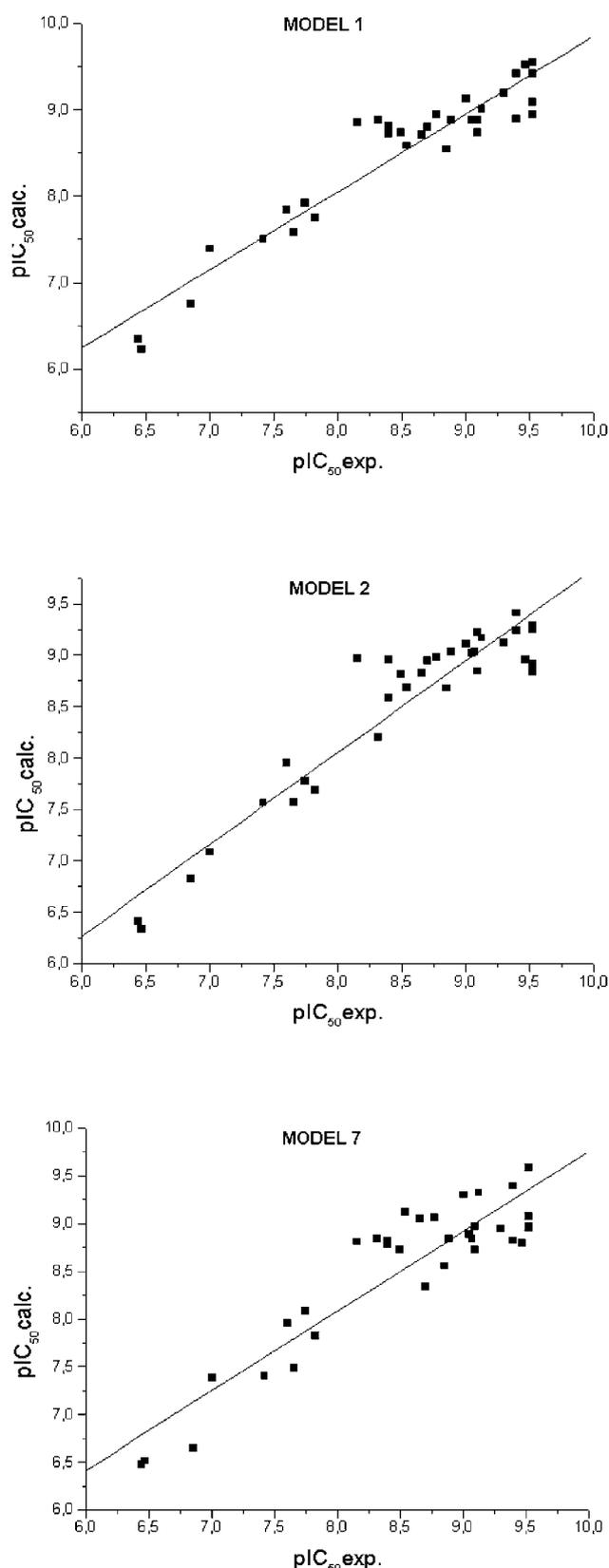
**Table 2.** Observed and predicted pIC<sub>50</sub> values and residual values for the training (bold) and test (italic) set compounds using Models 1, 2 and 7 (alignment 3 and cubic grid cells of 1.0 Å).

No.	pIC <sub>50</sub> Observed	Model 1		Model 2		Model 7	
		Predicted	Residual	Predicted	Residual	Predicted	Residual
<b>1</b>	8.66	8.71	0.052	8.82	0.168	9.05	0.395
<b>2</b>	6.44	6.34	-0.096	6.40	-0.035	6.47	0.024
<b>3</b>	8.54	8.58	0.044	8.68	0.147	9.12	0.585
<b>4</b>	9.40	8.89	-0.506	9.41	0.013	9.39	-0.005
<b>5</b>	7.75	7.92	0.178	7.78	0.035	8.08	0.341
<b>6</b>	6.85	6.75	-0.098	6.82	-0.028	6.64	-0.211
<b>7</b>	9.00	9.12	0.129	9.11	0.113	9.30	0.300
<b>8</b>	9.52	9.54	0.018	8.84	-0.683	8.96	-0.556
<b>9</b>	9.30	9.18	-0.114	9.11	-0.183	8.94	-0.358
<b>10</b>	8.77	8.94	0.172	8.97	0.204	9.06	0.294
<b>11</b>	9.52	9.41	-0.109	8.91	-0.606	9.58	0.060
<b>12</b>	9.40	9.41	0.016	9.24	-0.156	8.82	-0.576
<b>13</b>	7.00	7.38	0.388	7.08	0.083	7.38	0.380
<b>14</b>	9.52	9.08	-0.440	9.28	-0.239	9.07	-0.452
<b>15</b>	9.13	9.01	-0.110	9.17	0.045	9.32	0.197
<i>16</i>	6.47	6.23	-0.235	6.33	-0.137	6.51	0.043
<i>17</i>	9.07	8.87	-0.192	9.03	-0.040	8.84	-0.229
<i>18</i>	8.85	8.54	-0.311	8.67	-0.175	8.55	-0.301
<i>19</i>	7.66	7.57	-0.083	7.56	-0.092	7.48	-0.174
<i>20</i>	8.70	8.80	0.104	8.94	0.247	8.33	-0.361
<i>21</i>	8.89	8.87	-0.008	9.03	0.145	8.84	-0.045
<i>22</i>	7.82	7.75	-0.069	7.69	-0.132	7.82	0.000
<i>23</i>	7.42	7.49	0.075	7.56	0.143	7.40	-0.011
<i>24</i>	9.05	8.87	-0.167	9.01	-0.026	8.88	-0.159
<i>25</i>	8.50	8.73	0.242	8.81	0.316	8.72	0.225
<i>26</i>	9.47	9.52	0.051	8.96	-0.509	8.79	-0.673
<i>27</i>	9.10	8.73	-0.359	8.84	-0.255	8.72	-0.376
<i>28</i>	8.16	8.84	0.693	8.96	0.812	8.81	0.656
<i>29</i>	8.40	8.71	0.320	8.58	0.183	8.82	0.424
<i>30</i>	8.40	8.80	0.409	8.95	0.559	8.78	0.383
<i>31</i>	9.10	8.87	-0.218	9.22	0.124	8.96	-0.128
<i>32</i>	9.52	8.94	-0.576	9.25	-0.267	8.95	-0.566

independent variables occur in both the same model and in different models, which is not surprising because many models (Table A, Supplementary Material) are highly correlated with one another. This behavior was also observed in a different data set [13].

### 3.3 Outliers

The calculated pIC<sub>50</sub> values for the training (28 compounds) and test set (four compounds) were computed using Eqs. 1, 2, and 3. The residual values were calculated as the observed



**Figure 2.** Plot of  $pIC_{50}$  calculated versus  $pIC_{50}$  experimental from the 32 compounds in the Models 1, 2 and 7 (alignment 3 and cubic grid cells of 1.0 Å).

less calculated activity (Table 2). The observed and calculated  $pIC_{50}$  values are plotted in Figure 2 for training and test sets.

To establish outlier compounds, the standard deviations (SD) of the residuals from the training set (28 compounds) were computed. Outliers are defined as compounds whose residuals are more than twice the SD of the residual of fit. Analyses of the data showed that Model 1 (Eq. 1) has two outliers (compounds **28** and **32**), Model 2 (Eq. 2) has also two outliers (compounds **8** and **28**), and Model 7 (Eq. 3) does not have any outlier at all.

The template structure used in this 4D-QSAR study, HOE/BAY-793 (compound **32**), is an outlier compound according Model 1. Since there is no reasonable explanation this behavior, Model 1 was excluded and only Models 2 and 7 were discussed.

## 4 Discussion

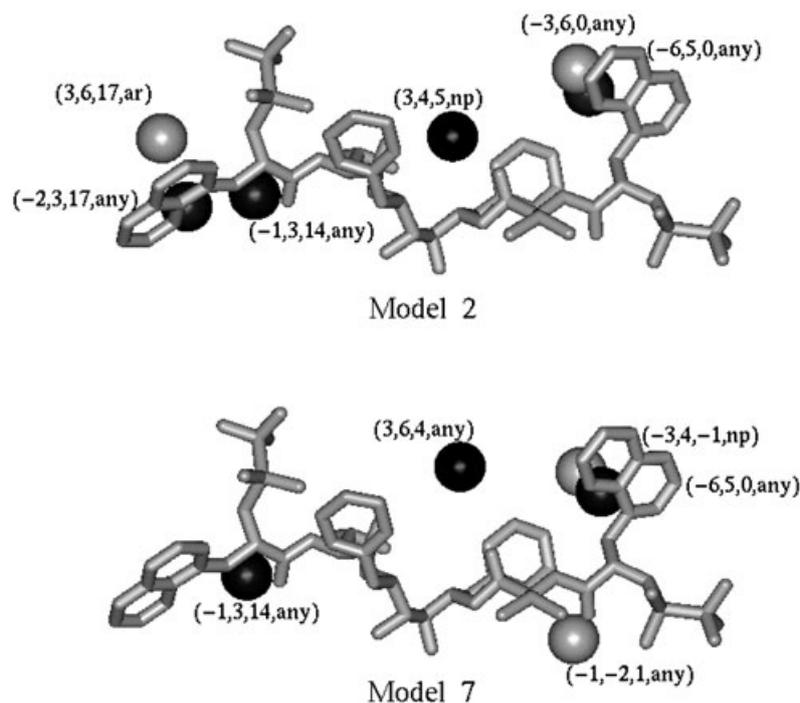
### 4.1 Interpretation of Models 2 and 7

A graphic representation of the 3D-pharmacophore embedded in 4D-QSAR Models 2 and 7 is shown in Figure 3 using compound **32** as a reference. Light and dark spheres represent GCODs with positive and negative coefficients, respectively, in accordance with Eqs. 2 (Model 2) and 3 (Model 7). Each GCOD is labeled as “x, y, z, IPE” which represent the Cartesian coordinates position of the selected grid cell (x, y, z) and the respective atom type (IPE).

GCODs (3,4,5,np) and (3,6,4,any), which are highly interrelated ( $r=0.936$ ), are located near the P1 site of Models 2 and 7, respectively (Figure 3). They are located at almost the same region of space. The only difference between them is that the first GCOD represents the non-polar atom type closest to the P1 site, while the second represents the other any atom types. These grid cells show the highest frequency of occupation for compounds **2**, **5**, and **6**, which belong to compounds **1-7** and **32**. They differ only in the P1/P1' substituent (Table 1). Since the coefficients of these GCODs are negative, the P1/P1' substituents of compounds **2**, **5**, and **6** are detrimental to the activity. This decrease in potency suggests a steric limitation in this region of the receptor for nonpolar substituents greater than benzyl group and a favorable region of the receptor for a hydrogen-bonding interaction.

In fact, the P1/P1' side chains are more important for activity in cell culture than for enzyme inhibition as demonstrated by compound **1** which, though lacking the P1/P1' side chain, is highly active on the enzyme ( $IC_{50}=2.2$  nM) and almost inactive in cell culture ( $EC_{50}=10.000$  nM) [9].

GCOD (-1,3,14,any) is located close to the P3 site of Models 2 and 7 (Figure 3). This grid cell represents a non-specific atom type (IPE) and shows the highest frequency of occupation, again for compounds **2**, **5** and **6**. Since the



**Figure 3.** Models 2 and 7 obtained by 4D-QSAR (alignment 3 and cubic grid cells of 1.0 Å) using compound **32** as a reference. Light spheres indicate activity-enhancing pharmacophore sites and dark spheres indicate activity-decreasing pharmacophore sites. The hydrogen atoms are omitted for clarity. GCODs are labeled as (x, y, z, IPE) which means the Cartesian coordinates position of the selected grid cell (x, y, z) and the respective atom type (Interaction Pharmacophore Element, IPE).

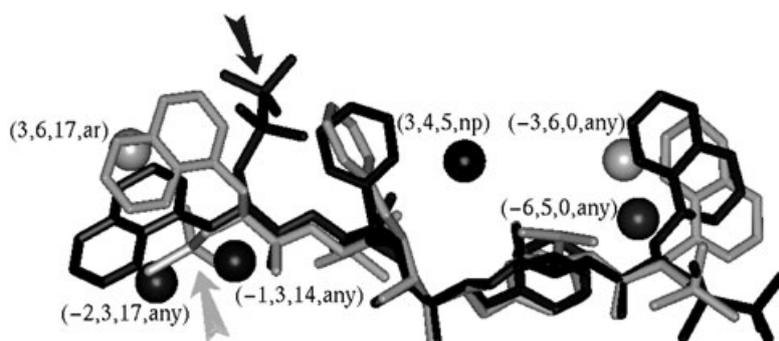
coefficient of this GCOD is negative, the P3/P3' substituents of compounds **2**, **5**, and **6** are detrimental to the activity. However, these substituents are not directly responsible for the decrease in potency because we could observe a spatial interference, i.e., intramolecular interactions, between the P1 and the P3 substituents. Compounds **5** and **6** have one intramolecular hydrogen bond between the oxygen atom of the *tert*-butyl-sulfonyl (*t*-Bu-SO<sub>2</sub>) group (P3) and the amino group of phenylalanine (P1), while compound **2** has two (P3/P1 and P3'/P1'). Additionally, compound **2** has a  $\pi$ -stacking interaction between the phenyl group (P1) and the naphthyl (P3) aromatic ring.

GCOD (-6,5,0,any) is located close to the naphthyl group in the P3' site of Models 2 and 7 (Figure 3), and represents a non-specific atom type (IPE). GCODs (-3,6,0,any) and (-3,4,-1,np) are also located near the naphthyl group in the P3' site of Models 2 and 7, respectively (Figure 3), where the first GCOD represents an unspecific atom type IPE while the second represents a nonpolar atom type. All of them are interrelated to some extent (Table B, Supplementary Material). The grid cell (-6,5,0,any), however, has a negative coefficient which decreases the potency of the compounds, while the GCODs (-3,6,0,any) and GCOD (-3,4,-1,np) have positive coefficients, increasing their potency. Therefore, we have always a pair of grid cells with opposite effects in P3' site, indicating that small movements in the naphthyl ring will be able to increase or decrease the potency. The P3' substituent might be directly responsible for this behavior;

e.g. compound **23**, which has the highest frequency of occupation of GCODs (-6,5,0,any) and (-3,6,0,any). On the other hand, P1' and P2' might be indirectly responsible for this behavior, since the highest frequency of grid cell (-6,5,0,any) occupation was found for compounds **6**, **13**, and **16** and also for compounds **6** and **12** in the case of grid cell (-3,6,0,any). This indirect influence between the P1'/P3' sites was also observed in the previous discussion of GCOD (-1,3,14,any) at P3 site. Overall, the potency of the compounds depends on the size and type of the substituents at these positions (P1', P2' and P3'), indicating that substituents other than P3' may have influence at P3' site. In other words, they might be responsible for favorable or unfavorable steric interactions in this region of the receptor.

GCOD (3,6,17,ar) is located near the proximal ring of the naphthyl group in P3 site of Model 2, and corresponds to an aromatic type (IPE). This grid cell shows the highest frequency of occupation for compounds **4** and **31**, suggesting a hydrophobic region in the receptor close to this ring. Because the coefficient of this grid cell is positive, potential inhibitors would benefit from the exploitation of this region with others types of aromatic groups. In addition, the region involving GCOD (-1,-2,1,any), located next to the naphthyl ring in P3' site of Model 7, and also with a positive regression coefficient, confirms the importance of this site for the increase of the potency of these compounds.

GCOD (-2,3,17,any) is located near the sulfonyl group in the P3 site of Model 2, and represents a non-specific atom



**Figure 4.** Superimposition of compounds **31** (gray) and **32** (black). The gray and black arrows indicate the methyl-sulfonyl and *tert*-butyl-sulfonyl groups, respectively. Light spheres indicate activity-enhancing pharmacophore sites and dark spheres indicate activity-decreasing pharmacophore sites. The hydrogen atoms are omitted for clarity. GCODs are labeled as (x, y, z, IPE) which means the Cartesian coordinates position of the selected grid cell (x, y, z) and the respective atom type (Interaction Pharmacophore Element, IPE).

type (IPE). In all compounds in which this grid cell shows the highest frequency of occupation, e.g. **1**, **5**, **7**, **10**, **12**, **29**, and **31**, there is a *t*-Bu-SO<sub>2</sub> substituent located in the P3/P3' position. This is detrimental to their potency, since this GCOD has a negative regression coefficient. This occurs because these compounds adopt a conformation modulated by intramolecular interactions between groups of the P1 and P3 sites, as described earlier, modifying the preferential orientation of the sulfonyl group.

It is important to have in mind that not all compounds having the *t*-Bu-SO<sub>2</sub> group are occupying this grid cell and that analogues having other substituents do not occupy this grid cell. Anyway, GCOD (-2,3,17,any) has no great weight in the potency of the compounds as the magnitude of its regression coefficient is just 1.88 (Eq. 2). In order to illustrate the occupancy of this GCOD, Figure 4 shows a superimposition between compounds **31** (pIC<sub>50</sub> = 9.09) and **32** (pIC<sub>50</sub> = 9.52), which differ only at the P3/P3' site. Compound **31** has the highest frequency of occupation for GCOD (-2,3,17,any) while compound **32** does not have any frequency of occupation at all.

#### 4.2 External Validation of Models 2 and 7

The test data set (compounds **16**, **19**, **25**, and **31**) was used in order to evaluate the predictive ability of the Models 2 and 7, since it was not included in the development of the 4D-QSAR models. The observed and predicted pIC<sub>50</sub> values and the residues of the fit for the test set are shown in Table 2. It is interesting to see how well the experimentally observed activity agrees with the predicted one. Considering only the test set compounds, the standard deviation (SD) of the residuals computed by Eq. 2 is equal to 0.21 while for Eq. 3, the SD is equal to 0.18.

#### 4.3 Postulated 4D-QSAR Bioactive Conformation

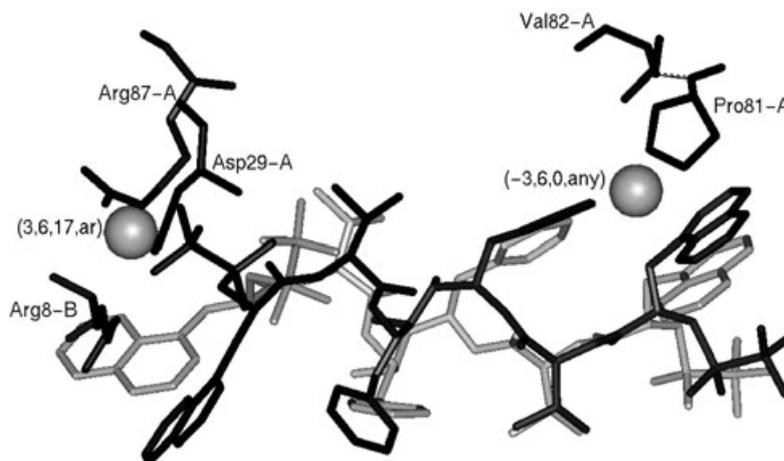
The 4D-QSAR methodology postulates as the "active" conformation the lowest-energy conformer state from the

set sampled for each compound, which maximize the predicted activity value using the best 4D-QSAR model [12]. In this work, ΔE was set at 2.0 kcal/mol. Therefore, the bioactive conformation of compound **32** was selected from Models 2 and 7 (a unique conformation), and it was assumed to be the bioactive conformation for this compound in this series of inhibitors. In addition, the postulated bioactive conformation of **32** was docked (Figures 5 and 6) into the region occupied by the crystallographic structure of **32** (HOE/BAY-793) complexed with HIV-1 protease [20].

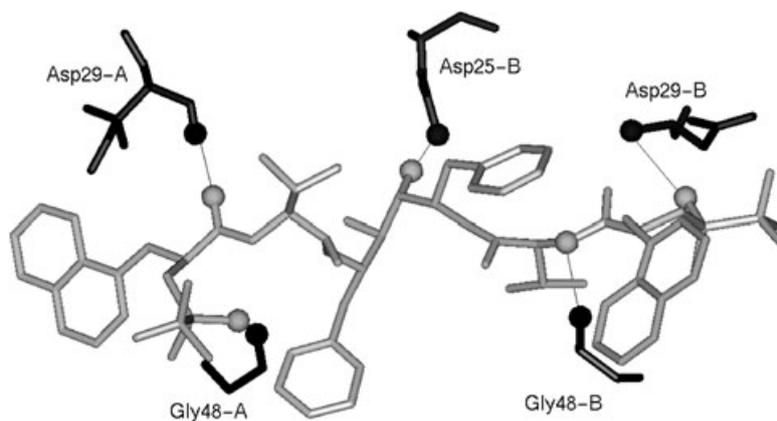
We superimposed the bioactive conformation of compound **32** and its complexed crystallographic structure [20], as shown in Figure 5, considering the four carbon atoms from the carbonyl groups (Figure 1). We observed a very similar orientation for the P1', P2' and P3' substituents. However, on the P1, P2 and P3 sites, it showed a different orientation. The root-mean-square (RMS) deviation was equal to 0.083 Å.

Figure 5 shows the GCODs of Model 2 with a frequency of occupation higher than zero for compound **32**. Therefore, we can see only GCODs (3,6,17,ar) and (-3,6,0,any), both with positive coefficients, corresponding to substituents of P3 and P3', respectively. The amino acid residues, which define the binding pocket of compound **32** into the HIV-1 protease active site around these two GCODs, were designated in Figure 5. Substituents of compound **32** occupying GCOD (3,6,17,ar) are proximal to three polar residues, namely, the side chains of Arg87, Asp29, and Arg87, and those occupying GCOD (-3,6,0,any) are proximal to two apolar residues, namely, the side chains of Pro81 and Val82. Therefore, future inhibitor design studies should focus on the length and volume of the substituents (P3/P3') in the aromatic region related to GCOD (3,6,17,ar), in order to avoid repulsive steric interactions or steric hindrance predicted by GCOD (-3,6,0,any), close to the side chain of Pro81 and Val82.

In addition, in Figure 6, the five hydrogen bond interactions observed after the docking of the bioactive conformation of compound **32** into the active site of HIV-1



**Figure 5.** The bioactive conformation of compound **32** (gray) postulated by the best 4D-QSAR models (Model 2 and 7) superimposed to the crystallographic structure of HOE/BAY-793 (black) into the active site of HIV-1 protease (PDB code: 1VIJ) [20]. The spheres represent the GCODs of compound **32** according to Model 2 and the only protein residues shown (black) are those in around these GCODs. Light spheres indicate activity-enhancing pharmacophore sites. The hydrogen atoms are omitted for clarity. GCODs are labeled as (x, y, z, IPE) which means the Cartesian coordinates position of the selected grid cell (x, y, z) and the respective atom type (Interaction Pharmacophore Element, IPE).



**Figure 6.** Representation of postulated bioactive conformation the compound **32** (gray) after docking into the active site of the crystal structure of HIV-1 protease (PDB code: 1VIJ) [20] showing the protein residues (black) participating in hydrogen bonding with **32**. The spheres represent heteroatoms involved in hydrogen bonding. The hydrogen atoms are omitted for clarity.

protease are shown. Considering the direction from P3 to P3' of **32** (Figures 1 and 6), the hydrogen bonds are between the P3 terminal *t*-Bu-SO<sub>2</sub> group and the backbone-NH group of Gly48 (1.82 Å); the P3 amide-carbonyl group and the backbone-NH group of Asp29 (2.31 Å); the P1' hydroxyl group and the carboxyl group of Asp25' (2.39 Å); the P2' amide-NH group and the backbone-carbonyl group of Gly48' (2.23 Å), and the P3' terminal *t*-Bu-SO<sub>2</sub> group and the backbone-NH group of Asp29' (2.04 Å).

In resemblance, the crystallographic conformation of **32** [20] shows seven hydrogen bond interactions in the active site of HIV-1 protease: two with Gly48 (P3-SO<sub>2</sub> and P2-NH groups), one with Asp29 (P3-carbonyl group), one with Gly27 (P1-hydroxyl group), one with Asp25' (P1-hydroxyl group), and two with Asp25 (P1'-hydroxyl group). It is

interesting to note that, although the best superimposition between the postulated bioactive conformation of **32** and its crystallographic bounded conformation to be observed for residues of P' side (Figure 5), the hydrogen bonding pattern of the docked postulated bioactive conformation is similar to that of the crystallographic structure at P side and not at P' side.

## 5 Concluding Remarks

In the present study, we built and evaluated 4D-QSAR models for HIV-1 protease inhibitors, based on a series of HOE/BAY-793 analogues, a diaminiol inhibitor. The models, generated from the best alignment (alignment 3)

selected from the three trial alignments, reflect a mutual superposition of the ligands along with their relative orientation towards the binding pocket. It should be pointed out that the starting structure of each ligand was constructed and minimized inside the active site of the HIV-1 crystallographic structure [20], replacing the bounded structure of the reference compound (HOE/BAY-793, compound **32**). In this way, information about the geometry of the binding pocket was indirectly included in the models developed by the 4D-QSAR approach.

In the best 4D-QSAR models, namely Models 2 and 7, from alignment 3 using a grid cell of 1.0 Å, we observed a decrease in the potency related to GCODs (3,4,5np) and (3,6,4,any), suggesting a receptor steric limitation around the P1/P1' sites for nonpolar substituents greater than benzyl groups but, at the same time, a receptor favorable region for hydrogen-bonding interactions.

In the P3/P3' sites, we observed an increase in the potency related to GCODs (3,6,17,ar), (-3,6,0,any), and (-3,4,-1,np) and, at the same time, a decrease in the potency related to GCOD (-6,5,0,any), all of them related to the naphthyl group, thus indicating that small movements in this aromatic ring may increase or decrease the potency. Compounds **29** (no substituent,  $pIC_{50} = 8.39$ ) and **25** (benzyl,  $pIC_{50} = 8.49$ ), which differ only at the  $\alpha$ -substituent at the P3/P3' site, are almost equipotent, while compound **32** is one logarithm unity more potent (naphthyl,  $pIC_{50} = 9.52$ ). A decrease in potency related to the GCOD (-2,3,17,any), which corresponds to the t-Bu-SO<sub>2</sub> group, was also observed in the P3/P3' site.

In addition, we noted a preferential orientation for P3/P3' substituents (e.g. naphthyl and t-Bu-SO<sub>2</sub> groups), modulated by intramolecular interactions between groups at the P1 and P3 (P1' and P3') sites; e.g., compound **2** has two intramolecular hydrogen bond interactions (P1/P3 and P1'/P3') and a  $\pi$ -stacking interaction between the aromatic rings of the P1 and P3 sites.

Unfortunately, since we could not find any correlation between the P2/P2' sites and the GCODs from Models 2 and 7, they could not be explored in our 4D-QSAR analysis. However, P2' (and P1') may be indirectly responsible for the opposite effects of the pair of GCODs at P3' site, since the highest frequency of occupation of grid cell (-6,5,0,any) was found for compounds **6**, **13**, and **16** and also for compounds **6** and **12** in the case of GCOD (-3,6,0,any).

Moreover, the lowest-energy conformer state which maximize the predicted activity value using the best 4D-QSAR models (Models 2 and 7) was docked into the active site of the HIV-1 protease, and it is clear that the postulated bioactive conformation of **32** is well accommodated and shares a similar binding mode when compared to the crystallographic structure of the HIV-1 protease complex (PDB code: 1VIJ).

Finally, these studies showed that molecular modification at the P1/P1' and P3/P3' sites on the core structure of compound **32** may lead to an increase in the potency,

generating more powerful inhibitors. Concerning the P1/P1' position, polar and hydrophilic groups should be preferred for two reasons: because they are not very bulky; and because GCOD (3,4,5,np), detrimental to the potency, showed the highest frequency of occupation for hydrophobic substituent. Therefore, we propose the application of the Eqs. 2 and 3 for compounds with modification in the P1/P1' site by hydrophobic substituents no greater than benzyl groups (e.g. phenyl, 1-naphthyl and 2-naphthyl) or by hydrophilic substituents.

## Acknowledgement

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## Design, synthesis and anti-HIV-1 evaluation of hydrazide-based peptidomimetics as selective gelatinase inhibitors

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### ABSTRACT

As our ongoing work on research of gelatinase inhibitors, an array of hydrazide-containing peptidomimetic derivatives bearing quinoxalinone as well as spiro-heterocyclic backbones were designed, synthesized, and assayed for their *in vitro* enzymatic inhibitory effects. The results demonstrated that both the quinoxalinone (series I and II) and 1,4-dithia-7-azaspiro[4.4]nonane-based hydrazide peptidomimetics (series III) displayed remarkably selectivity towards gelatinase A as compared to APN, with IC<sub>50</sub> values in the micromole range. Structure–activity relationships were herein briefly discussed. Given evidences have validated that gelatinase inhibition may be contributable to the therapy of HIV-1 infection, all the target compounds were also submitted to the preliminary *in vitro* anti-HIV-1 evaluation. It resulted that gelatinase inhibition really has positive correlation with anti-HIV-1 activity, especially compounds **4m** and **7h**, which gave enhanced gelatinase inhibition in comparison with the positive control LY52, and also decent anti-HIV-1 potencies. The FlexX docking results provided a straightforward insight into the binding pattern between inhibitors and gelatinase, as well as the selective inhibition towards gelatinase over APN. Collectively, our research encouraged potent gelatinase inhibitors might be used in the development of anti-HIV-1 agents. And else, compounds **4m** and **7h** might be promising candidates to be considered for further chemical optimization.

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### 1. Introduction

Matrix metalloproteinases (MMPs) are a category of zinc-dependent extracellular endopeptidases which primarily participate in the proteolytic degradation of major components of extracellular matrix (ECM). Evidence has revealed that among the more than 20 identified subtypes of MMPs, MMP-2 and MMP-9 (also called as gelatinase A and B) have been proved to have high correlation with a variety of neoplasms-associated events. These two MMP isoforms are found to be overexpressed abundantly in multifarious tumor cells and involve various tumor stages mainly by degrading of ECM components.<sup>1,2</sup> Accordingly, our previous

concerns about the specific gelatinase inhibition led to a series of gelatinase inhibitors derived from the quinoxalinone as well as sulfonyl 1,4-dithia-7-azaspiro[4.4]nonane chemical entities, as shown in Figure 1, that might be useful in the effective interference with tumor progressions.<sup>3–5</sup>

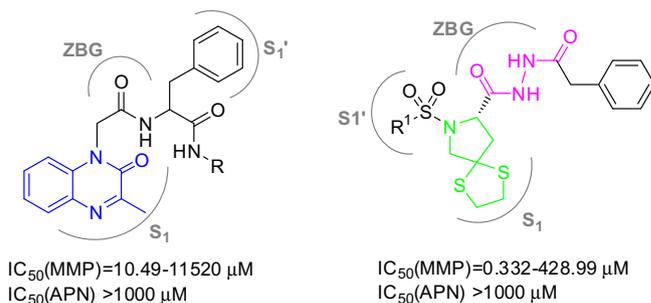
Recently, correlation between the dysregulation of gelatinase and pathogenesis of human immunodeficiency virus-1 (HIV-1) infection has aroused many researchers' interests.<sup>6,7</sup> In this regard, a spectrum of anti-HIV drugs with varieties of mechanism of action, e.g., protease inhibitors indinavir and saquinavir,<sup>8–10</sup> CCR5 receptor antagonist Maraviroc,<sup>11</sup> and nucleoside analog reverse transcriptase inhibitor azidothymidine (AZT) etc.,<sup>12</sup> have been submitted to the assessment whether they could exert their favorable potency at decreasing the high expressing levels of gelatinase. However, in turn, whether the gelatinase inhibition might lead to beneficial anti-HIV-1 effect has not been fully investigated. On these grounds, the purpose of this study was to unearth a new series of gelatinase inhibitors based on our previous findings and

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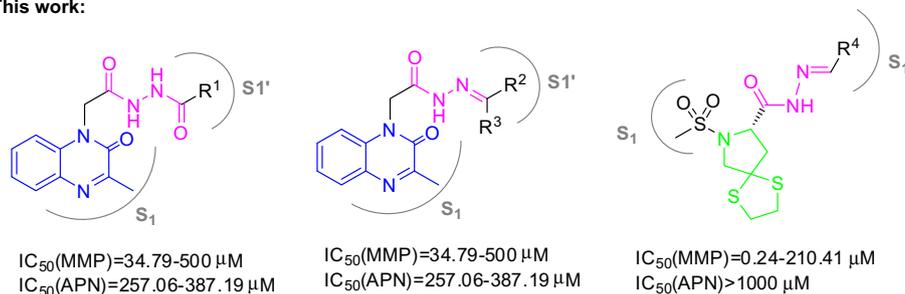
E-mail addresses: [zhengyt@mail.kiz.ac.cn](mailto:zhengyt@mail.kiz.ac.cn) (Y.-T. Zheng), [tjulx2004@sdu.edu.cn](mailto:tjulx2004@sdu.edu.cn) (X. Li).

† These authors contributed equally to this work.

## Our previous work:



## This work:



**Figure 1.** Design concept and enzyme inhibitory comparison of new hydrazide-based peptidomimetic derivatives with our previously reported peptidomimetic counterparts.

determine whether they might have HIV-1 therapeutic potentials through inhibiting the gelatinase-related activities.

In this work, two validated skeletal scaffolds by our previous efforts were still utilized as chemical prototypes to design novel gelatinase inhibitors. From the molecular modeling results between the inhibitors and gelatinase,<sup>3,4</sup> we noticed that although both the coplanar quinoxalinone motif and the relatively flexible spiro-heterocyclic 1,4-dithia-7-azaspiro[4,4]nonane scaffold could penetrate into the relatively broad  $S_1$  binding subdomain of gelatinase, the spiro-heterocyclic ring seems to fit into this pocket more easily, owing to its better dimensional topology. Based on this information and also as a continuation of our long-standing interest in engaging in gelatinase inhibitor-oriented medicinal chemistry,<sup>3,4,13,14</sup> we therefore extended the research scopes of the quinoxalinone and sulfonyl 1,4-dithia-7-azaspiro[4,4]nonane chemotypes by introducing hydrazide functionality into these two entities, and comparing their binding affinities for gelatinase.

Hydrazide-type framework was chosen to make structural optimizations could be due to, at least in part, the following aspects:<sup>15,16</sup> (i) the beneficial coordination ability along with pharmaco-modulation properties described by Ledour et al.<sup>17</sup> has endowed hydrazide frame with a zinc-binding group (ZBG)-like function, thus leading to an effective coordination with the catalytic zinc ion of gelatinase; (ii) the electron donor (NH) and/or acceptor (C=O) of the hydrazide frame can ensure effective H-bonding interactions with the target enzyme, which are especially conducive to the binding affinity; (iii) as a common organic synthon or building block, hydrazide can easily achieve molecular diversity by reacting with a variety of chemical substances, such as carboxylic acid, aldehyde, anhydride, acyl chloride and ester under mild conditions; (iv) given imino (NH) is the bioisostere of methylene ( $\text{CH}_2$ ), hydrazide can behave as a surrogate of aza-substituted amino acid. It is therefore gifted hydrazide group with drug-like property that might be very valuable in designing pharmacologically useful biomolecules; (v) the stereochemical nature of hydrazide, characterized by a keto-enol tautomerism with two isomers (*E*- and *Z*-form, see Fig. 2), may properly orient and anchor the conjugated hydrophobic substituent R into the key binding

pocket,  $S_1'$  groove, via a favorable and stable configuration, as displayed in Figure 1.

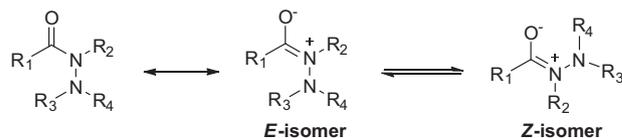
As far as the hydrophobic substituents ( $R^1$ – $R^4$ ) are concerned, according to our previous SAR findings,<sup>3,4</sup> the aromatic side chains are more preferable than aliphatic counterparts in terms of gaining a satisfactory gelatinase inhibition. Based on this, varied aromatic substituents were introduced in order to perform the SAR exploration. Furthermore, the incorporated acylamide linkage and acylhydrazone bond can not only construct a peptidomimetic pattern, the carbonyl O and NH also act as potent H-bonding acceptor/donor to interact with the active amino acids in the enzyme.

Herein, the design, synthesis, docking studies, and SAR investigations of the hydrazide-derived peptidomimetics were presented. Meanwhile, their gelatinase inhibitory activities as well as the preliminary anti-HIV potencies were also explored and described. All in all, we anticipated the present exploration on the relevance of gelatinase inhibition and anti-HIV property might provide a clue for further development of diversified compounds with HIV therapeutic potentials.

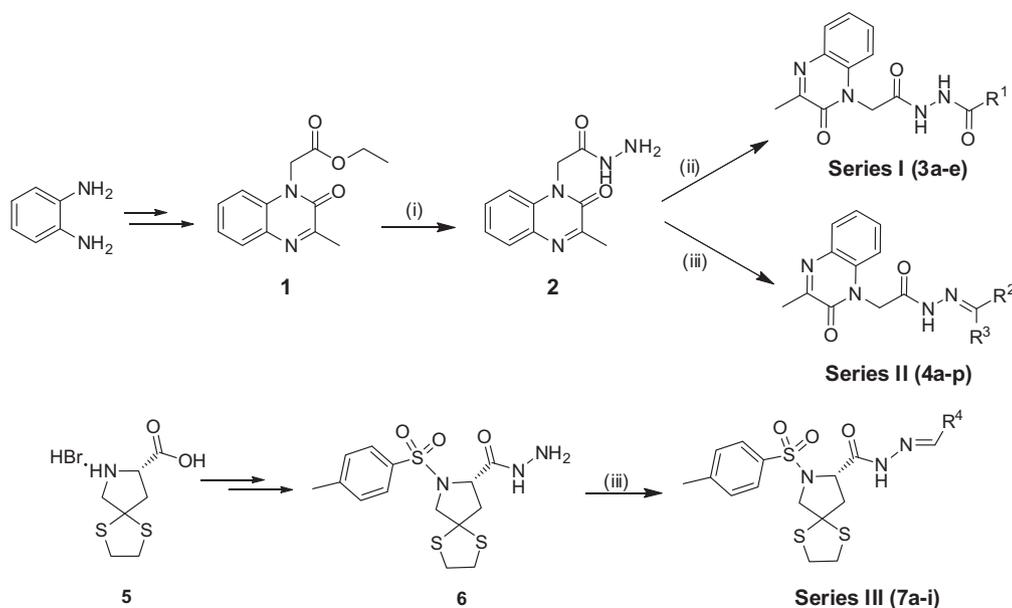
## 2. Results and discussion

### 2.1. Synthesis

The hydrazide-based peptidomimetics **3**, **4** and **7** were prepared following the procedures summarized in Scheme 1, and the structures of target compounds were analytically confirmed by ESI-MS,  $^1\text{H}$  NMR, and elementary analysis. In our synthesis, in the case of



**Figure 2.** Hydrazide can undergo two conformations (*E*- & *Z*-isomers) to reach a stable configuration.



**Scheme 1.** Reagents and conditions: (i) 80% hydrazine hydrate, ethanol; (ii)  $R^1COCl$ ,  $Na_2CO_3$ , THF; (iii) substituted benzaldehydes or acetophenones, anhydrous methanol, reflux for about 6 h.

series I & II compounds, the intermediate ethyl 2-(3-methyl-2-oxoquinoxalin-1(2*H*)-yl)acetate **1** was easily prepared from the commercially available 1,2-phenylenediamine according to our previously reported procedure.<sup>4</sup> Subsequent hydrazinolysis was accomplished using 80% hydrazine hydrate in anhydrous ethanol, followed by nucleophilic substitution with varied acyl chlorides in the presence of weak base  $K_2CO_3$  to afford desired compounds **3a–e** (series I), which can be purified by recrystallization. In addition, the hydrazine intermediate (**2**) can also be submitted to the nucleophilic addition–condensation reaction with various substituted benzaldehydes or acetophenones to generate the quinoxalinone acylhydrazone derivatives **4a–p** (series II).

As to series III, the key hydrazide intermediate (**6**) can be obtained from the commercially available (*S*)-1,4-dithia-7-azaspiro[4.4]nonane-8-carboxylic acid (**5**) via the sequential sequences of sulfonation, esterification, ammonolysis and hydrazinolysis as has been described in our previous steps.<sup>3</sup> This intermediate (**6**) was subsequently subjected to the similar procedure with compound **4** to afford the desired acylhydrazone derivatives **7a–i** (series III).

## 2.2. Biological evaluation and discussion

### 2.2.1. Enzymatic inhibition

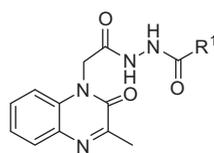
It has been validated that one of the restrictions of MMP inhibitors in clinical application comes from their relatively low selectivity, not only towards different MMP isoforms, but towards other types of zinc-related proteinases which might possess various physiologic or pathologic effects.<sup>18</sup> In our *in vitro* enzymatic inhibition assay, gelatinase and another kind of zinc-related metalloproteinase aminopeptidase N (APN, also known as CD13), which are all closely related to varied stages of tumor progressions, were initially chosen to investigate the selective potencies of target compounds. Moreover, LY52, a fully evaluated gelatinase inhibitor in our lab, was still utilized as a positive control as described in our previous work,<sup>3,4</sup> and the results have been listed in Table 1.

We initially compared the enzyme inhibitory activities of the peptidomimetic derivatives with quinoxalinone backbone (series I and II). Overall, although both the gelatinase and APN inhibition of these two series did not surpass the control LY52, almost all of them displayed selective inhibition against gelatinase over APN,

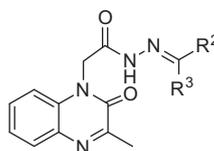
except compounds **3a**, **4m**, and **4p**, which actually presented reversed subtype selectivity. As far as series III which possess spiro-heterocyclic 1,4-dithia-7-azaspiro[4.4]nonane scaffold was concerned, more remarkable selectivity has been achieved, which at least partially validated our strategy for exploring selective gelatinase inhibitors. This selective inhibition, to some extent, might ascribe to the structural differences of two metalloproteinases, leading to different matching requirements for their respective inhibitors. In specific, gelatinase is an endopeptidase that cleaves the peptide from specific amino residues, while APN is an exopeptidase that catalyzes the removal of N-terminus of the amino acids. Additionally, the 3-D structures of these two enzymes hinted that the active binding domain of gelatinase, especially referring to the  $S_1'$  region, seems to be deeper than that of APN. The structural characteristics may partly be explained for the better APN inhibition of entries **4m** and **4p**, in which the relatively bulky substituents are more likely to extend into the broader binding area of APN. Based on this selectivity, the following SARs were mainly focused on the gelatinase inhibition.

For series I, we only prepared a limited series of quinoxalinone peptidomimetics since they only gave moderate to weak bioactivities. The preliminary SAR information can be seen as follows: (i) the benzyl motif (**3c**) caused a slightly increased activity as compared with the phenyl counterpart (**3b**), and (ii) the 2,6-di-chloro substitution (**3e**) furnished moderated but reduced gelatinase inhibition compared to the mono-chloro substituted counterpart (**3d**).

For series II, there were only two compounds, **4a** and **4m**, gave comparable gelatinase inhibition compared to LY52. The most likely reason for this is that the introduced substituents have suitable space sizes and orientations to guide the compounds to accommodate the active binding cavity of biotarget. In addition, compound **4m** exhibited slightly improved potency when compared to **4a**, this is likely that the phenolic hydroxyl group can provide more effective hydrogen-bonding interaction with target protein, which is favorable to increase the binding affinity. Furthermore, among these inhibitors, compound **3a** with the only aliphatic methyl substitution was, unsurprisingly, inactive, which is consistent with our previous SAR results.<sup>3,4</sup> Accordingly, compounds with other aliphatic side chains were not studied any more in this assay.

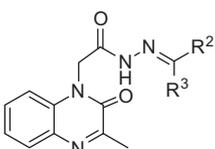
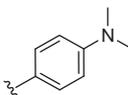
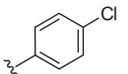
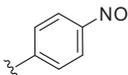
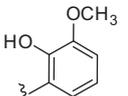
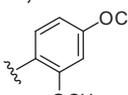
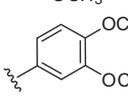
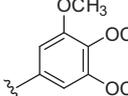
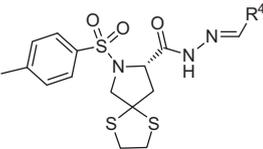
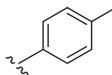
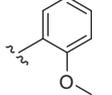
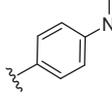
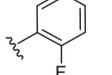
**Table 1**  
The enzymatic inhibition, cytotoxicity (CC<sub>50</sub>), anti-HIV-1 activity on wild-type strain HIV-1<sub>IIIIB</sub> (EC<sub>50</sub>), and therapeutic index (TI) of tested compounds (series I, II and III)**Series I (3a-e)**

Compds	R <sup>1</sup>	Gelatinase/IC <sub>50</sub> <sup>a</sup> (μM)	APN/IC <sub>50</sub> <sup>a</sup> (μM)	Cytotoxicity CC <sub>50</sub> (μM)	CPE EC <sub>50</sub> (μM)	TI
<b>2</b>	—	98.02 ± 3.5	257.06 ± 7.8	>861.70	>861.70	—
<b>3a</b>	CH <sub>3</sub>	>500	327.61 ± 11.2*	>729.63	>729.63	—
<b>3b</b>		187.41 ± 21.58****	387.19 ± 10.6	>595.03	272.97	>2.2
<b>3c</b>		159.39 ± 7.60***	333.41 ± 7.1	>571.20	296.42	>1.9
<b>3d</b>		34.79 ± 6.3*	271.53 ± 6.92	>540.42	168.69	>3.2
<b>3e</b>		58.22 ± 13.3	298.80 ± 8.4**	153.08	51.60	2.97
LY52 <sup>5</sup>	—	5.64 ± 0.6***	116.7 ± 1.7**	>454.37	32.99	>13.8
AZI	—	—	—	4676.07 ± 379.89	0.00794 ± 0.0014	588,644

**Series II (4a-p)**

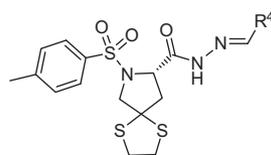
Compds	R <sup>2</sup>	R <sup>3</sup>	Gelatinase/IC <sub>50</sub> <sup>a</sup> (μM)	APN/IC <sub>50</sub> <sup>a</sup> (μM)	Cytotoxicity CC <sub>50</sub> (μM)	CPE EC <sub>50</sub> (μM)	TI
<b>4a</b>		CH <sub>3</sub>	9.39 ± 0.7*	99.87 ± 11.1	490.96	54.89	8.9
<b>4b</b>		CH <sub>3</sub>	13.22 ± 6.59**	125.09 ± 6.0	>543.33	>543.33	—
<b>4c</b>		CH <sub>3</sub>	90.81 ± 8.63****	388.65 ± 5.9	>527.52	144.73	>3.6
<b>4d</b>		CH <sub>3</sub>	112.26 ± 11.24***	439.24 ± 20.3*	>543.33	>543.33	—
<b>4e</b>		CH <sub>3</sub>	566.89 ± 23.17	NA	>543.33	>543.33	—
<b>4f</b>		H	17.17 ± 0.22**	103.34 ± 13.6	>644.93	301.44	>2.1
<b>4g</b>		H	67.01 ± 3.53*	341.22 ± 9.2	>624.75	120.64	>5.2
<b>4h</b>		H	36.04 ± 0.42	222.68 ± 7.8	>598.55	82.81	>7.2
<b>4i</b>		H	38.65 ± 2.75****	306.58 ± 2.4	262.05	51.30	5.1

Table 1 (continued)

Compds	R <sup>2</sup>	R <sup>3</sup>	Gelatinase/IC <sub>50</sub> <sup>a</sup> (μM)	APN/IC <sub>50</sub> <sup>a</sup> (μM)	Cytotoxicity CC <sub>50</sub> (μM)	CPE EC <sub>50</sub> (μM)	TI
 <b>Series II (4a-p)</b>							
4j		H	64.30 ± 7.07***	330.77 ± 15.2	355.18	158.93	2.2
4k		H	81.01 ± 1.42****	449.26 ± 12.9	>564.83	32.25	>17.5
4l		H	246.26 ± 12.64***	644.48 ± 20.4	>547.78	70.83	>7.7
4m		H	7.17 ± 0.95**	80.95 ± 0.3**	114.99	2.79	41.3
4n		H	74.91 ± 1.78****	242.54 ± 4.9*	>526.11	125.58	>4.2
4o		H	28.76 ± 0.83****	480.93 ± 20.1*	>526.11	80.97	>6.5
4p		H	223.37 ± 12.77****	57.55 ± 8.3**	>487.61	83.02	>5.9
 <b>Series III (7a-i)</b>							
Compds	R <sup>4</sup>	Gelatinase/IC <sub>50</sub> <sup>a</sup> (μM)	APN/IC <sub>50</sub> <sup>a</sup> (μM)	Cytotoxicity CC <sub>50</sub> (μM)	CPE EC <sub>50</sub> (μM)	TI	
6	—	430.27 ± 1.57*	NA <sup>b</sup>	>519.40	238.61	>2.2	
7a		36.79 ± 2.58****	NA <sup>b</sup>	>420.96	40.45	>10.4	
7b		28.52 ± 7.60***	NA <sup>b</sup>	387.76	51.13	7.6	
7c		5.52 ± 0.053*	NA <sup>b</sup>	>396.73	37.69	>10.5	
7d		1.89 ± 6.59**	NA <sup>b</sup>	280.14	38.78	7.2	

(continued on next page)

Table 1 (continued)



Series III (7a-i)

Compds	R <sup>4</sup>	Gelatinase/IC <sub>50</sub> <sup>a</sup> (μM)	APN/IC <sub>50</sub> <sup>a</sup> (μM)	Cytotoxicity CC <sub>50</sub> (μM)	CPE EC <sub>50</sub> (μM)	TI
7e		0.64 ± 0.063****	NA <sup>b</sup>	>404.00	30.30	>13.3
7f		0.41 ± 0.17***	NA <sup>b</sup>	176.59	28.03	6.3
7g		0.24 ± 0.095*	NA <sup>b</sup>	64.95	33.73	1.9
7h		1.05 ± 0.79*	NA <sup>b</sup>	>395.19	16.04	>24.6
7i		210.41 ± 0.55**	NA <sup>b</sup>	327.41	38.49	8.5

<sup>a</sup> Values are means ± standard errors of three experiments. *p* values <0.05, 0.01, 0.005 and 0.0001 are indicated by \*, \*\*, \*\*\*, and \*\*\*\*, respectively, compared to the control group (LY52).

<sup>b</sup> Not activity (in the inhibitory assays, IC<sub>50</sub> values >1000 μM).

We then devoted our attention to the aromatic congeners. It resulted the furan ring was better than the phenyl counterpart (entries **4f** vs **4g**). This result might be owing to the stabilization of the interactions between the inhibitor and enzyme, by an electronegative O atom, which can more easily form H-bond with the target enzyme. The benzyl moiety (**4h**) caused an elevated potency as compared with the phenyl counterpart (**4g**), with approximately 2-fold increased activity. However, due to the lack of effective hydrogen donor or acceptor, **4h** gave more than 2-fold impaired activity in comparison with the O-containing furan counterpart (**4f**).

Comparing compounds **4a** versus **4g**, **4b** versus **4k** and **4c** versus **4l**, it revealed that installation of methyl group at R<sup>3</sup> induced more robust inhibition than their H analogues. Compounds **4i–l** with mono-substitution at the *para*-position on the benzene ring, varying from electron-sufficient to electron-deficient groups, were synthesized to examine how electronic environment affect bioactivity of inhibitors. The results showed that, the electron-sufficient substituents, to some extent, were positively related to the potency. For instance, the introduction of methyl group (**4i**) offered the highest activity; the dimethylamino group (**4j**) was in the next place, followed by the chloro group (**4k**) and, the nitro group (**4l**) displayed the least activity. This rule was also applied to the congeners **4b** and **4c**, viz. compound **4c** with strong electron-attractive nitro group gave much weak potency than that of the *para*-chloro counterpart **4b**. Additionally, compounds **4b**, **4d** and **4e** with halogen-substitution at different positions on the aromatic ring, were utilized to test the influence of the substituent position. As a consequence, the best position was *para*-position (**4b**), followed by *ortho*-position (**4d**), and the worst one is *meta*-position (**4e**) which leads to a markedly detrimental activity, reducing affinity by about 43-fold (Table 1, entries **4b** vs **4e**).

To better understand how the number and disposition of substituents on the quinoxaline core affects the bioactivity, compounds **4n–p** were prepared by introducing the methoxyl group, since an electron-donating substituent is believed to be beneficial to the gelatinase inhibition based on the aforementioned SAR results. Not surprisingly, tri-methoxyl substitution manifested decreased potency in comparison with the 2,5- or 3,4-di-substituted analogues (entries **4p** vs **4n** and **4o**), validating there is a space requirement to hold suitable substituents. Besides, introduction of a phenolic hydroxyl group (**4m**) caused a significantly enhanced potency and selectivity against gelatinase, implying the hydroxyl group is positively related with the bioactivity by forming effective hydrogen bond with the residues in target enzyme.

As far as series III was concerned, they obviously provided dramatically decent enzyme activity and selective inhibition. This promoted enzymatic inhibitory was caused by the existence of sulfonamide group as well as the spiro-heterocyclic 1,4-dithia-7-azaspiro[4.4]nonane motif. The sulfonamide functionality has been proved to be a facilitator for gelatinase inhibition,<sup>19</sup> and the spiro-heterocyclic 1,4-dithia-7-azaspiro[4.4]nonane core is more flexible than the relatively rigid bicyclic quinoxaline framework to adjust the conformation to match the binding area.

Besides, the unsubstituted hydrazide **6** was also used in the enzyme inhibitory evaluation to check whether the free hydrazo group has an impact on the bioactivity. It turned out that the derivation of hydrazo group produced significantly higher gelatinase binding affinity. Although the amino group, acting as a potential H-bond donor, is commonly regarded as the favorable contributor to the bioactivity, the outstretched side chains might furnish strengthened chelation effect with catalytic zinc ion of gelatinase, making the corresponding inhibitors more adaptive to active binding domain.

In brief, we found that the size and disposition of the substituents on the phenyl ring are important determinants of the potency and selectivity for this series. First, comparing compounds **7a–c** with mono-substitution at the *para*-position, it expounded that larger size and stronger electrophilic induction effect of a substituent tend to acquire an increased binding affinity. The activities were decreased in the sequence of  $N(CH_3)_2 > OCH_3 > CH_3$ , and **7c** is equipotent to the control. Likewise, the same situation can also apply to compounds **7d–g** with mono-substitution at the *ortho*-position. The inhibitory ability of all members (**7d–g**) was tremendously better than the control, and the activities were decreased in the order of  $NO_2 > Br > Cl > F$ , indicating that appending a large electron-withdrawing substituent, as nitro group, to the *ortho*-position of the phenyl in **7d–g** contributed to an increase in potency. However, the conversion of nitro group from *ortho*- to *meta*-position led to moderate drop in bioactivity (**7g** vs **7h**). Similar with the SAR results in series II members, the introduction of bulky trisubstituted group (**7i**) would generate deleterious impact on activity, highlighting the weight of preferable substituents to the biotarget.

### 2.2.2. Cytotoxicity and anti-HIV-1 activity

To examine whether there is a certain correlation between gelatinase inhibition and anti-HIV-1 efficacy, all newly synthesized compounds were subsequently submitted to the preliminary in vitro anti-HIV-1 evaluation. To this end, the cytotoxicity of these compounds on T cell line C8166 was firstly assessed by MTT colorimetric assay, and 50% cytotoxicity concentration ( $CC_{50}$ ) was calculated.<sup>20,21</sup> If the  $CC_{50}$  value is greater than 200, the resulting compound is considered to possess relatively low toxicity. Subsequently, the cytopathic effect (CPE) was examined on laboratory adaptive strain HIV-1<sub>IIIIB</sub> by detecting the inhibition of syncytia formation, and 50% effective concentration ( $EC_{50}$ ) was calculated. The therapeutic index (TI) is given by the  $CC_{50}/EC_{50}$  ratio, and the corresponding compound will be considered to have some activity if the TI value is greater than 10. For comparison, zidovudine (AZT), the first anti-HIV drug approved by FDA, was utilized as reference compound.

The results unfolded that nearly all of the tested analogues demonstrated weak cytotoxicity towards normal C8166 cells, except for compounds **4l** and **7g** which were found to exhibit moderate cytotoxicity, with  $EC_{50}$  values of 42.10 and 32.87  $\mu M$ , respectively. It is more notable that even though all the analogues showed significantly lowered anti-HIV-1 activities compared to the control AZT, there is a certain connection between the gelatinase inhibition and anti-HIV-1 activity. For instances, those who are highly active against gelatinase inhibition (e.g., **4m**, **7a**, **7c**, **7e**, **7h**) also gave relatively better anti-HIV-1 activities. The interrelationship between them will be completely investigated in our lab.

The congeners **4m**, **7a–c**, **7e**, **7f**, **7h** and **7i** that have were further chosen to evaluate the inhibitory effects on HIV-1<sub>IIIIB</sub>, replica-

tion by p24 antigen level in acute infection using capture ELISA method.<sup>22</sup> In our assay, the laboratory adaptive strain HIV-1<sub>IIIIB</sub>, HIV-1 reverse transcriptase (RT) resistant strains, including nucleosides HIV-1<sub>A17</sub> and non-nucleoside HIV-1<sub>74V</sub>, were employed, and 50% effective concentrations ( $EC_{50}$ ) were calculated, which have been listed in Table 2. The results unravel that albeit compounds **4m** and **7h** stand out from these anti-HIV-1 evaluations, they possess obviously lower anti-HIV-1 activities than the positive controls, AZT and EFV. Further structural optimization should be deliberately carried out in order to achieve significantly improvement in terms of both efficacy and drug resistance.

### 2.3. Binding mode investigation

To better understand the SARs and also gain insight into the binding pattern of target compounds, two potent compounds which have displayed decent gelatinase inhibition and anti-HIV potencies, the quinoxalinone-derived **4m** and spiro-heterocyclic-based **7h**, were selected for molecular docking study via the FlexX flexible-Dock method by utilizing SYBYL 7.0 program. The preferred pharmacophore binding mode of two compounds in the active site of gelatinase A (PDB entry: 1HOV) is proposed based on the computational-docking results.

The possible binding modes provided by docking experiments revealed that both the two compounds could be embedded in the active binding domains ( $S_1$  and  $S_1'$  pockets) of gelatinase A, so that they exhibited leading enzymatic potencies amongst their respective series. More specifically, for the quinoxalinone compound **4m**, the coplanar quinoxalinone backbones, as expected, occupied the  $S_1$  pocket with their preponderant conformations, while the phenyl hydrazide portion extended into relatively long-narrow  $S_1'$  pocket, as illustrated in Figure 3A. As to the spiro-heterocyclic compound **7h**, it adopted a diametrically opposed binding situation as compared to our previously reported analogues. The methyl sulfonamide inserted into the broad  $S_1$  area, whereas the phenyl hydrazide fragment can adjust its flexibility to orient and take possession of another binding pocket, the  $S_1'$  sub-domain, as displayed in Figure 3B. In addition, Figure 3C and D manifested the hydrogen-bonding interactions of these two compounds with gelatinase. Specifically, the amide NH and phenolic hydroxyl group of **4m**, acting as H-bond donors, can bind with Glu121 and Ala86, with the distances of 2.06, 1.96 and 2.10 Å, respectively. By contrast, compound **7h** forms H-bond contacts with Leu83, Ala84 and Glu121, with distances of 2.24, 2.64 and 2.06 Å, respectively.

Compound **7h** was further utilized as a tool to examine the selectivity against the other zinc-related metallo-enzyme, APN. The interaction of **7h** with the active sites of APN (PDB ID: 2DQM) was thereby docked and compared, which have been diagrammed in Figure 4. It unfolded that this compound could not well-orienting occupy two active subdomains of APN (also named as  $S_1'$  and  $S_1$  regions), resulting in loss of activity, which is consistent with the enzyme evaluation results.

Finally, from the proposed binding styles with biotargets, both compounds (**4m** and **7h**) did not generate effective chelations with the catalytic zinc(II) ion, this may be why all the synthesized compounds did not offer satisfactory enzymatic potencies. Therefore, further chemical modifications should be deliberately manipulated so as to exploit more potent inhibitors.

### 3. Conclusion

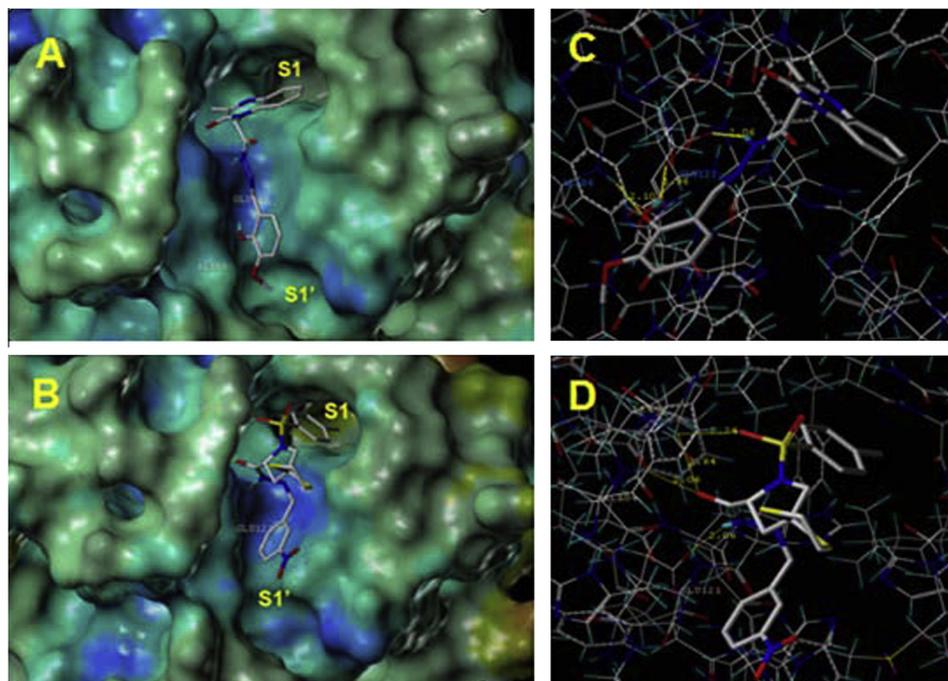
In summary, we have presented the design and synthesis of new series of quinoxalinone and spiro-heterocyclic-derived hydrazide peptidomimetic derivatives which showed high selective inhibition towards gelatinase over APN on the basis of our previous

**Table 2**

The inhibitory effects on HIV-1 virus (HIV-1<sub>IIIIB</sub>, HIV-1<sub>A17</sub> and HIV-1<sub>74V</sub>) replication

Comps	HIV-1 <sub>IIIIB</sub> ( $EC_{50}$ , $\mu M$ ) <sup>a</sup>	HIV-1 <sub>A17</sub> ( $EC_{50}$ , $\mu M$ ) <sup>a</sup>	HIV-1 <sub>74V</sub> ( $EC_{50}$ , $\mu M$ ) <sup>a</sup>
<b>4m</b>	6.05 ± 1.97	2.46 ± 1.71	3.48 ± 0.73
<b>7a</b>	39.28 ± 1.59*	>200	>200
<b>7b</b>	69.60 ± 6.35*	11.41 ± 4.52	29.99 ± 1.44*
<b>7c</b>	75.58 ± 10.92	73.98 ± 6.68*	56.32 ± 15.25
<b>7e</b>	148.98 ± 6.43*	18.15 ± 0.98*	93.59 ± 43.94
<b>7f</b>	33.36 ± 4.21**	18.32 ± 5.17	30.62 ± 7.83
<b>7h</b>	3.89 ± 0.34*	9.94 ± 1.70	5.07 ± 0.67
<b>7i</b>	65.14 ± 19.85	38.71 ± 0.21**	96.03 ± 1.35**
AZT	0.00436 ± 0.0024	—	0.00152 ± 0.0011
EFV	—	183.63 ± 16.41 nM	—

<sup>a</sup> Values are means ± standard errors of three experiments. *p* values <0.05 and 0.01 are indicated by \*\* and \*\*\*, respectively, compared to the control group (AZT or EFV).



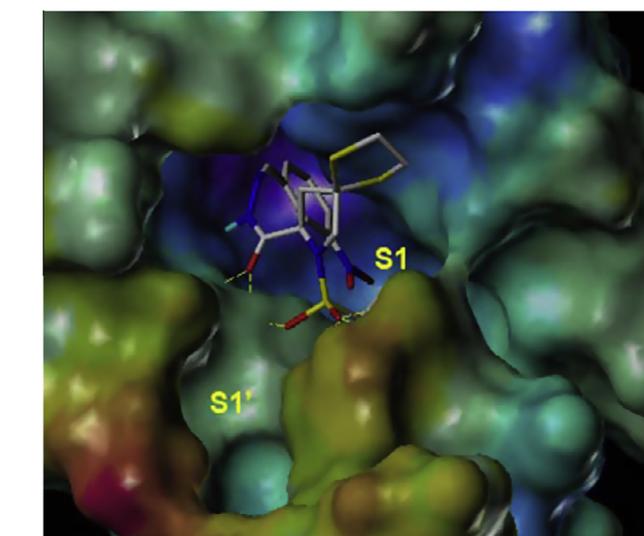
**Figure 3.** The preferred binding modes (A and B) and hydrogen bonding interactions (C and D) of two potent inhibitors **4m** & **7h** with gelatinase A (PDB code: 1HOV).

work. Detailed SAR discussions indicated that introduction of aromatic substituents was better than the aliphatic counterpart, and variation of size and positions of substituents also had impact on their potency. At the same time, our research also provided evidences that gelatinase inhibition has certain positive correlation with anti-HIV-1 activity. We hope our SAR and docking studies will provide effective clues for further gelatinase inhibitor and anti-HIV-1 drug development.

## 4. Experimental section

### 4.1. Chemistry

Unless specified otherwise, all the starting materials, reagents and solvents were commercially available. All reactions except those in aqueous media were carried out by standard techniques



**Figure 4.** FlexX docking results of compound **7h** with APN (PDB code: 2DQM), showing the inappropriate occupation of the active binding pocket.

for the exclusion of moisture. All reactions were monitored by thin-layer chromatography on 0.25-mm silica gel plates commercially available from YanTai MuPing Corporation and visualized with UV light (254 nm), or iodine vapor. Yields were recorded via purification. Melting points were determined using X-6 digital display binocular microscope (uncorrected).  $^1\text{H}$  NMR spectra were determined on a Bruker Advance DRX-400 spectrometer using TMS as an internal standard,  $\delta$  in parts per million and  $J$  in hertz (Hz). Electrospray ionization mass spectrometry (ESI-MS) was performed on an API-4000 triple-stage quadrupole instrument. Elemental analyses were carried out on a Perkin-Elmer C, H, N elemental analyzer.

#### 4.1.1. Preparation of 2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetohydrazide (**2**)

Compound **1** (2.46 g, 10 mmol) was dissolved in anhydrous EtOH (50 mL). To this solution was added 80% hydrazine hydrate (5.01 g, 10 mmol) dropwise at ambient temperature. After finishing dropping, the mixture was refluxed for 10 h until completion monitored by TLC. The solvent was then removed in vacuo and extracted with EtOAc ( $3 \times 100$  mL). The organic layer was combined and concentrated, the obtained crude product was further purified by recrystallization in EtOAc to give 2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetohydrazide **2** as white solid (2.0 g, 86.4%). Mp 221–224 °C; ESI-MS  $m/z$ : 233.14  $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ , ppm):  $\delta$  2.45 (s, 3H,  $\text{CH}_3$ ), 4.28 (d,  $J = 1.8$  Hz, 2H,  $\text{NH}_2$ ), 4.86 (s, 2H,  $\text{NCH}_2\text{C}=\text{O}$ ), 7.30 (d,  $J = 8.4$  Hz, 1H, ArH), 7.35 (t,  $J = 7.8$  Hz, 1H, ArH), 7.54 (t,  $J = 7.2$  Hz, 1H, ArH), 7.76 (d,  $J = 7.8$  Hz, 1H, ArH), 9.36 (s, 1H,  $\text{C}=\text{ONH}$ ); Anal. Calcd for  $\text{C}_{11}\text{H}_{12}\text{N}_4\text{O}_2$ : C, 56.89; H, 5.21; N, 24.12; Found: C, 56.68; H, 5.26; N, 24.13.

#### 4.1.2. General procedures for the preparation of quinoxalinone hydrazide peptidomimetics (**3a–e**), taking *N*-(2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetyl)propionohydrazide (**3a**) as an example

To a solution of compound **2** (230 mg, 1 mmol) in anhydrous THF (20 mL), was added anhydrous  $\text{Na}_2\text{CO}_3$  (120 g, 1 mmol) and acetyl chloride (71  $\mu\text{L}$ , 1 mmol) successively in an ice-salt bath.

The reaction mixture was allowed to warm to room temperature and stirred for about 12 h until completion monitored by TLC. The solvent was evaporated in vacuo and the crude product was washed with a small amount of distilled water. The obtained solid was recrystallized with 95% ethanol to provide the final pure product as white solid (192 mg, 53.6%). Mp 210–212 °C; ESI-MS *m/z*: 289.16 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, ppm): δ 1.92–2.00 (m, 3H, CH<sub>3</sub>), 2.46 (s, 3H, CH<sub>3</sub>), 2.26 (m, 2H, CH<sub>2</sub>), 5.28 (s, 2H, NCH<sub>2</sub>C=O), 7.30–7.38 (m, 2H, ArH), 7.50–7.56 (m, 1H, ArH), 7.78 (d, *J* = 8.4 Hz, 1H, ArH), 10.44 (s, 1H, C=ONH), 10.63 (s, 1H, NHC=O); Anal. Calcd for C<sub>14</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub>: C, 58.32; H, 5.59; N, 19.43; Found: C, 58.58; H, 5.61; N, 19.33.

The other analogues **3b–e** were synthesized following the general procedures as described above.

**4.1.2.1. *N*-(2-(3-Methyl-2-oxoquinoxalin-1(2H)-yl)acetyl)benzohydrazide (3b).** White solid, yield: 81.2%, mp 275–277 °C; ESI-MS *m/z*: 337.43 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, ppm): δ 2.47 (s, 3H, CH<sub>3</sub>), 5.06 (s, 2H, NCH<sub>2</sub>C=O), 7.31–7.43 (m, 3H, ArH), 7.74 (d, *J* = 7.8 Hz, 1H, ArH), 7.86–7.95 (m, 5H, ArH), 10.42 (s, 1H, C=ONH), 10.49 (s, 1H, NHC=O); Anal. Calcd for C<sub>18</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub>: C, 64.28; H, 4.79; N, 16.66; Found: C, 64.13; H, 4.81; N, 16.68.

**4.1.2.2. 2-(3-Methyl-2-oxoquinoxalin-1(2H)-yl)-*N*-(2-phenylacetyl)acetohydrazide (3c).** White solid, yield: 47.6%, mp 276–277 °C; ESI-MS *m/z*: 351.22 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, ppm): δ 2.45 (s, 3H, CH<sub>3</sub>), 3.46 (s, 2H, C=OCH<sub>2</sub>Ar), 4.98 (s, 2H, NCH<sub>2</sub>C=O), 7.21–7.32 (m, 5H, ArH), 7.33–7.36 (m, 2H, ArH), 7.54 (t, *J* = 7.2 Hz, 1H, ArH), 7.76 (d, *J* = 7.8 Hz, 1H, ArH), 10.18 (s, 1H, C=ONH), 10.31 (s, 1H, NHC=O); Anal. Calcd for C<sub>19</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>: C, 65.13; H, 5.18; N, 15.99; Found: C, 65.30; H, 5.21; N, 15.65.

**4.1.2.3. 4-Chloro-*N*-(2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetyl)benzohydrazide (3d).** Off-white solid, yield: 77.1%, mp 252–253 °C; ESI-MS *m/z*: 371.66 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, ppm): δ 2.47 (s, 3H, CH<sub>3</sub>), 5.49 (s, 2H, NCH<sub>2</sub>C=O), 7.36 (t, *J* = 7.8 Hz, 1H, ArH), 7.42–7.46 (m, 1H, ArH), 7.52–7.56 (m, 1H, ArH), 7.61–7.64 (m, 2H, ArH), 7.79 (dd, *J*<sub>1</sub> = 1.2 Hz, *J*<sub>2</sub> = 7.8 Hz, 1H, ArH), 7.83 (d, *J* = 8.4 Hz, 2H, ArH), 10.55 (s, 1H, C=ONH), 10.76 (s, 1H, NHC=O); Anal. Calcd for C<sub>18</sub>H<sub>15</sub>ClN<sub>4</sub>O<sub>3</sub>: C, 58.31; H, 4.08; N, 15.11; Found: C, 58.35; H, 4.11; N, 15.02.

**4.1.2.4. 2,6-Dichloro-*N*-(2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetyl)benzohydrazide (3e).** Solid, yield: 57.1%, mp 294–296 °C; ESI-MS *m/z*: 405.89 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, ppm): δ 2.43 (s, 3H, CH<sub>3</sub>), 5.05 (s, 2H, NCH<sub>2</sub>C=O), 7.36–7.38 (m, 2H, ArH), 7.46 (d, *J* = 8.4 Hz, 1H, ArH), 7.52–7.58 (m, 2H, ArH), 7.72 (d, *J* = 1.8 Hz, 1H, ArH), 7.78 (dd, *J* = 1.8, 8.4 Hz, 1H, ArH), 10.50 (s, 1H, C=ONH), 10.59 (s, 1H, NHC=O); Anal. Calcd for C<sub>18</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>3</sub>: C, 53.35; H, 3.48; N, 13.83; Found: C, 53.44; H, 3.38; N, 13.79.

### 4.1.3. General procedures for the preparation of quinoxalinone hydrazide peptidomimetics (4a–p)

Compound **2** (1 mmol) was dissolved in anhydrous methanol (20 mL). To this solution was added substituted benzaldehydes or acetophenones (1.2 mmol) dropwise at ambient temperature. After finishing dropping, the mixture was refluxed for 6 h until completion monitored by TLC. The obtained solid was collected after filtration, and then washed with a small amount of methanol and distilled water. The solid was further purified by recrystallization in 75% EtOH and dried in vacuum drying chamber to give the desired products.

**4.1.3.1. (*E*)-2-(3-Methyl-2-oxoquinoxalin-1(2H)-yl)-*N*-(1-phenylethylidene)acetohydrazide (4a).** White solid, yield: 77.9%, mp 238–240 °C; ESI-MS *m/z*: 335.63 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, ppm)

δ: 2.32 (s, 3H, CH<sub>3</sub>), 2.48 (s, 3H, CH<sub>3</sub>), 5.49 (s, 2H, NCH<sub>2</sub>C=O), 7.35–7.57 (m, 6H, ArH), 7.79 (d, *J* = 7.8 Hz, 1H, ArH), 7.88–7.89 (m, 2H, ArH), 11.11 (s, 1H, CH=N); Anal. Calcd for C<sub>19</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>: C, 68.25; H, 5.43; N, 16.76; Found: C, 68.23; H, 5.48; N, 16.79.

**4.1.3.2. (*E*)-*N*-(1-(4-Chlorophenyl)ethylidene)-2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetohydrazide (4b).** White solid, yield: 70.1%, mp 250–251 °C; ESI-MS *m/z*: 369.77 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, ppm): δ: 2.31 (s, 3H, CH<sub>3</sub>), 2.48 (s, 3H, CH<sub>3</sub>), 5.49 (s, 2H, NCH<sub>2</sub>C=O), 7.36 (t, *J* = 7.8 Hz, 1H, ArH), 7.42–7.46 (m, 1H, ArH), 7.52–7.57 (m, 1H, ArH), 7.61–7.64 (m, 2H, ArH), 7.79 (dd, *J* = 1.2, 7.8 Hz, 1H, ArH), 7.83 (d, *J* = 8.4 Hz, 2H, ArH), 11.16 (s, 1H, CONHN); Anal. Calcd for C<sub>19</sub>H<sub>17</sub>ClN<sub>4</sub>O<sub>2</sub>: C, 61.87; H, 4.65; N, 15.19; Found: C, 61.93; H, 4.60; N, 15.17.

**4.1.3.3. (*E*)-2-(3-Methyl-2-oxoquinoxalin-1(2H)-yl)-*N*-(1-(4-nitrophenyl)ethylidene)acetohydrazide (4c).** White solid, yield: 48.1%, mp 287–289 °C; ESI-MS *m/z*: 380.48 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, ppm): δ: 2.38 (s, 3H, CH<sub>3</sub>), 2.48 (s, 3H, CH<sub>3</sub>), 5.53 (s, 2H, NCH<sub>2</sub>C=O), 7.35–7.57 (m, 3H, ArH), 7.80 (d, *J* = 8.4 Hz, 1H, ArH), 8.14 (d, *J* = 9 Hz, 2H, ArH), 8.27 (d, *J* = 9 Hz, 2H, ArH), 11.34 (s, 1H, CONH); Anal. Calcd for C<sub>19</sub>H<sub>17</sub>N<sub>5</sub>O<sub>4</sub>: C, 60.15; H, 4.52; N, 18.46; Found: C, 60.11; H, 4.58; N, 18.47.

**4.1.3.4. (*E*)-*N*-(1-(2-Chlorophenyl)ethylidene)-2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetohydrazide (4d).** White solid, yield: 67.5%, mp 235–236 °C; ESI-MS *m/z*: 369.57 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, ppm): δ: 2.33 (s, 3H, CH<sub>3</sub>), 2.51 (s, 3H, CH<sub>3</sub>), 5.50 (s, 2H, NCH<sub>2</sub>C=O), 7.43–7.47 (m, 2H, ArH), 7.56–7.57 (d, *J* = 7.8 Hz, 1H, ArH), 7.61–7.63 (m, 2H, ArH), 7.78–7.79 (d, *J* = 2.8 Hz, 1H, ArH), 8.01–8.04 (d, *J* = 8.4 Hz, 2H, ArH), 11.14 (s, 1H, CONH); Anal. Calcd for C<sub>19</sub>H<sub>17</sub>ClN<sub>4</sub>O<sub>2</sub>: C, 61.87; H, 4.65; N, 15.19; Found: C, 61.89; H, 4.61; N, 15.20.

**4.1.3.5. (*E*)-*N*-(1-(3-Chlorophenyl)ethylidene)-2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetohydrazide (4e).** White solid, yield: 77.9%, mp 229–231 °C; ESI-MS *m/z*: 369.44 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, ppm): δ: 2.31 (s, 3H, CH<sub>3</sub>), 2.48 (s, 3H, CH<sub>3</sub>), 5.49 (s, 2H, NCH<sub>2</sub>C=O), 7.36 (t, *J* = 7.8 Hz, 1H, ArH), 7.42–7.46 (m, 1H, ArH), 7.52–7.57 (m, 1H, ArH), 7.61–7.64 (m, 2H, ArH), 7.79 (dd, *J* = 1.2, 7.8 Hz, 1H, ArH), 7.83 (d, *J* = 8.4 Hz, 2H, ArH), 11.16 (s, 1H, CONH); Anal. Calcd for C<sub>19</sub>H<sub>17</sub>ClN<sub>4</sub>O<sub>2</sub>: C, 61.87; H, 4.65; N, 15.19; Found: C, 61.89; H, 4.61; N, 15.20.

**4.1.3.6. (*E*)-*N*-(Furan-2-ylmethylene)-2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetohydrazide (4f).** Light yellow solid, yield: 51.3%, mp 248–250 °C; ESI-MS *m/z*: 311.38 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, ppm): δ: 2.47 (s, 3H, CH<sub>3</sub>), 5.37 (s, 2H, NCH<sub>2</sub>C=O), 6.62–6.66 (m, 1H, ArH), 6.95 (m, 1H, ArH), 7.34–7.58 (m, 3H, ArH), 7.78–7.86 (m, 2H, ArH), 7.97 (s, 1H, N=CH), 11.77 (s, 1H, CONH); Anal. Calcd for C<sub>16</sub>H<sub>14</sub>N<sub>4</sub>O<sub>3</sub>: C, 61.93; H, 4.55; N, 18.06; Found: C, 61.90; H, 4.56; N, 18.08.

**4.1.3.7. (*E*)-*N*-(Benzylidene)-2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetohydrazide (4g).** Off-white solid, yield: 47.5%, mp 272–273 °C; ESI-MS *m/z*: 321.56 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, ppm): δ: 2.47 (s, 3H, CH<sub>3</sub>), 5.46 (s, 2H, NCH<sub>2</sub>C=O), 7.15–7.16 (d, 1H, *J* = 4.0 Hz, ArH), 7.19–7.21 (d, 1H, *J* = 8.0 Hz, ArH), 7.35–7.47 (m, 3H, ArH), 7.71–7.74 (m, 2H, ArH), 7.80–7.83 (m, 2H, ArH), 8.08 (s, 1H, N=CH), 10.49 (s, 1H, CONH); Anal. Calcd for C<sub>18</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub>: C, 67.49; H, 5.03; N, 17.49; Found: C, 67.52; H, 5.06; N, 17.46.

**4.1.3.8. (*E*)-2-(3-Methyl-2-oxoquinoxalin-1(2H)-yl)-*N*-(2-phenylethylidene)acetohydrazide (4h).** White solid, yield: 67.4%, mp 227–228 °C; ESI-MS *m/z*: 335.55 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, ppm): δ: 2.42 (3H, s, CH<sub>3</sub>), 3.48 (2H, d, *J* = 7.8 Hz,

$N=CCH_2Ar$ ), 4.95 (2H, s,  $NCH_2C=O$ ), 6.62–6.66 (1H, m, ArH), 6.95 (1H, t,  $J_1 = 8.0$  Hz,  $J_2 = 8.0$  Hz,  $N=CH$ ), 7.34–7.58 (3H, m, ArH), 7.78–7.86 (2H, m, ArH), 7.97 (1H, d,  $J = 6.0$  Hz, ArH), 11.77 (1H, s, CONH); Anal. Calcd for  $C_{19}H_{18}N_4O_2$ : C, 68.25; H, 5.43; N, 16.76; Found: C, 68.27; H, 5.44; N, 16.78.

**4.1.3.9. (E)-2-(3-Methyl-2-oxoquinoxalin-1(2H)-yl)-N'-(4-methylbenzylidene)acetohydrazide (4i).** White solid, yield: 66.7%, mp 286–287 °C; ESI-MS  $m/z$ : 335.55  $[M+H]^+$ ;  $^1H$  NMR (DMSO- $d_6$ , ppm)  $\delta$ : 2.35 (s, 3H,  $CH_3$ ), 2.48 (s, 3H,  $CH_3$ ), 5.45 (s, 2H,  $NCH_2C=O$ ), 7.25–7.60 (m, 5H, ArH), 7.65 (d,  $J = 7.8$  Hz, 2H, ArH), 7.79 (d,  $J = 7.8$  Hz, 1H, ArH), 8.05 (s, 1H,  $N=CH$ ), 11.78 (s, 1H, CONHN=C); Anal. Calcd for  $C_{19}H_{18}N_4O_2$ : C, 68.25; H, 5.43; N, 16.76; Found: C, 68.22; H, 5.46; N, 16.75.

**4.1.3.10. (E)-N'-(4-(Dimethylamino)benzylidene)-2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetohydrazide (4j).** Pale brown solid, yield: 63.2%, mp 282–283 °C; ESI-MS  $m/z$ : 364.72  $[M+H]^+$ ;  $^1H$  NMR (DMSO- $d_6$ , ppm)  $\delta$ : 2.48 (s, 3H,  $CH_3$ ), 2.96 (s, 3H,  $NCH_3$ ), 2.97 (s, 3H,  $NCH_3$ ), 5.41 (s, 2H,  $NCH_2C=O$ ), 6.74 (t,  $J_1 = J_2 = 8.4$  Hz, 2H, ArH), 7.34–7.37 (m, 2H, ArH), 7.50–7.56 (m, 3H, ArH), 7.79 (d,  $J = 7.8$  Hz, 1H, ArH), 7.94 (d,  $J = 4.2$  Hz, 1H, ArH), 8.42 (1H, s,  $N=CH$ ), 11.53 (1H, s, CONHN=C); Anal. Calcd for  $C_{20}H_{21}N_5O_2$ : C, 66.10; H, 5.82; N, 19.27; Found: C, 66.12; H, 5.86; N, 19.22.

**4.1.3.11. (E)-N'-(4-Chlorobenzylidene)-2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetohydrazide (4k).** Pale yellow solid, yield: 66.8%, mp 266–267 °C; ESI-MS  $m/z$ : 355.66  $[M+H]^+$ ;  $^1H$  NMR (DMSO- $d_6$ , ppm)  $\delta$ : 2.48 (s, 3H,  $CH_3$ ), 5.48 (s, 2H,  $NCH_2C=O$ ), 7.11–7.14 (1H, dd,  $J_1 = 8.0$  Hz,  $J_2 = 4.0$  Hz, 1H, ArH), 7.35–7.39 (m, 2H, ArH), 7.52–7.57 (m, 2H, ArH), 7.77–7.79 (d,  $J = 7.8$  Hz, 2H, ArH), 8.09 (d,  $J = 7.8$  Hz, 1H, ArH), 8.45 (s, 1H,  $N=CH$ ), 12.03 (s, 1H, O=CNHN=C); Anal. Calcd for  $C_{18}H_{15}ClN_4O_2$ : C, 60.94; H, 4.26; N, 15.79; Found: C, 60.92; H, 4.27; N, 15.81.

**4.1.3.12. (E)-2-(3-Methyl-2-oxoquinoxalin-1(2H)-yl)-N'-(4-nitrobenzylidene)acetohydrazide (4l).** Yellow solid, yield: 70.1%, mp 280–281 °C; ESI-MS  $m/z$ : 355.66  $[M+H]^+$ ;  $^1H$  NMR (DMSO- $d_6$ , ppm)  $\delta$ : 2.48 (s, 3H,  $CH_3$ ), 5.14 (s, 2H,  $NCH_2C=O$ ), 7.11–7.13 (1H, dd,  $J_1 = 4.0$  Hz,  $J_2 = 4.0$  Hz, 1H, ArH), 7.35–7.39 (m, 1H, ArH), 7.53–7.58 (m, 1H, ArH), 7.80–7.83 (m, 1H, ArH), 8.08–8.10 (m, 2H, ArH), 8.30–8.32 (m, 2H, ArH), 8.38 (s, 1H,  $N=CH$ ), 12.11 (s, 1H, O=CNHN=C); Anal. Calcd for  $C_{18}H_{15}N_5O_4$ : C, 59.18; H, 4.14; N, 19.17; Found: C, 59.22; H, 4.11; N, 19.16.

**4.1.3.13. (E)-N'-(2-Hydroxy-3-methoxybenzylidene)-2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetohydrazide (4m).** Light yellow solid, yield: 49.5%, mp 253–254 °C; ESI-MS  $m/z$ : 367.71  $[M+H]^+$ ;  $^1H$  NMR (DMSO- $d_6$ , ppm)  $\delta$ : 2.47 (s, 3H,  $CH_3$ ), 3.84 (s, 3H,  $OCH_3$ ), 5.43 (s, 2H,  $NCH_2C=O$ ), 6.82–6.87 (dd, 1H,  $J_1 = J_2 = 8.0$  Hz, ArH), 7.02–7.05 (d, 1H,  $J = 12.0$  Hz, ArH), 7.11–7.19 (m, 3H, ArH), 7.74–7.76 (d, 1H,  $J = 8.0$  Hz, ArH), 7.79–7.80 (d, 1H,  $J = 4.0$  Hz, ArH), 8.42 (s, 1H,  $N=CH$ ), 9.37 (s, 1H, ArOH), 11.76 (s, 1H, O=CNHN=C); Anal. Calcd for  $C_{19}H_{18}N_4O_4$ : C, 62.29; H, 4.95; N, 15.29; Found: C, 62.27; H, 4.92; N, 15.32.

**4.1.3.14. (E)-N'-(2,4-Dimethoxybenzylidene)-2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetohydrazide (4n).** Off-white solid, yield: 69.1%, mp 242–244 °C; ESI-MS  $m/z$ : 381.56  $[M+H]^+$ ;  $^1H$  NMR (DMSO- $d_6$ , ppm)  $\delta$ : 2.47 (s, 3H,  $CH_3$ ), 3.81–3.86 (m, 6H,  $2 \times OCH_3$ ), 5.41 (s, 2H,  $NCH_2C=O$ ), 6.57 (s, 1H, ArH), 6.62–6.65 (d, 1H,  $J = 12.0$  Hz, ArH), 7.06–7.11 (m, 2H, ArH), 7.22–7.25 (dd, 1H,  $J_1 = 4.0$  Hz,  $J_2 = 8.0$  Hz, ArH), 7.75–7.76 (d, 1H,  $J = 4.0$  Hz, ArH), 7.82–7.84 (d, 1H,  $J = 8.0$  Hz, ArH), 8.32 (s, 1H,  $N=CH$ ), 11.63 (s, 1H, O=CNHN=C); Anal. Calcd for  $C_{20}H_{20}N_4O_4$ : C, 63.15; H, 5.30; N, 14.73; Found: C, 63.13; H, 5.29; N, 14.76.

**4.1.3.15. (E)-N'-(3,4-Dimethoxybenzylidene)-2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetohydrazide (4o).** White solid, yield: 55.5%, mp 241–243 °C; ESI-MS  $m/z$ : 381.73  $[M+H]^+$ ;  $^1H$  NMR (DMSO- $d_6$ , ppm)  $\delta$ : 2.48 (s, 3H,  $CH_3$ ), 3.81 (s, 3H,  $OCH_3$ ), 3.86 (s, 3H,  $OCH_3$ ), 5.46 (s, 2H,  $NCH_2C=O$ ), 7.01–7.03 (d, 1H,  $J = 8.0$  Hz, ArH), 7.20–7.22 (dd, 1H,  $J_1 = J_2 = 4.0$  Hz, ArH), 7.29–7.33 (m, 2H, ArH), 7.55–7.58 (d, 1H,  $J = 12.0$  Hz, ArH), 7.79 (d,  $J = 7.2$  Hz, 1H, ArH), 8.00 (s, 1H, ArH), 8.35 (s, 1H,  $N=CH$ ), 11.74 (s, 1H, O=CNHN=C); Anal. Calcd for  $C_{20}H_{20}N_4O_4$ : C, 63.15; H, 5.30; N, 14.73; Found: C, 63.16; H, 5.28; N, 14.75.

**4.1.3.16. (E)-2-(3-Methyl-2-oxoquinoxalin-1(2H)-yl)-N'-(3,4,5-trimethoxybenzylidene)acetohydrazide (4p).** Off-white solid, yield: 57.8%, mp 251–252 °C; ESI-MS  $m/z$ : 411.57  $[M+H]^+$ ;  $^1H$  NMR (DMSO- $d_6$ , ppm)  $\delta$ : 2.47 (s, 3H,  $CH_3$ ), 3.71 (s, 3H,  $OCH_3$ ), 3.81–3.83 (m, 6H,  $2 \times OCH_3$ ), 5.47 (s, 2H,  $NCH_2C=O$ ), 7.09 (s, 2H, ArH), 7.35–7.57 (m, 3H, ArH), 7.79 (d,  $J = 7.8$  Hz, 1H, ArH), 7.99 (s, 1H,  $N=CHAr$ ), 11.87 (s, 1H, CONHN=C); Anal. Calcd for  $C_{21}H_{22}N_4O_5$ : C, 61.45; H, 5.40; N, 13.65; Found: C, 61.46; H, 5.41; N, 13.62.

#### 4.1.4. General procedures for the preparation of spiro-heterocyclic 1,4-dithia-7-azaspiro[4.4]nonane hydrazide peptidomimetics (7a–i)

A similar procedure with that of compounds in series II was employed for the series III products **7a–i**, by using the (*S*)-7-tosyl-1,4-dithia-7-azaspiro[4.4]nonane-8-carbohydrazide (compound **6**) as the starting material. Besides, the synthetic procedure and spectroscopic data of compound **6** have been reported in our previously work.<sup>3</sup>

**4.1.4.1. (S,E)-N'-(4-Methylbenzylidene)-7-tosyl-1,4-dithia-7-azaspiro[4.4]nonane-8-carbohydrazide (7a).** Solid, yield: 66.8%, mp 195–197 °C; ESI-MS  $m/z$ : 476.53  $[M+H]^+$ ;  $^1H$  NMR ( $CDCl_3$ , ppm)  $\delta$ : 9.85 (s, 1H,  $N=CH-Ph$ ), 8.14 (s, 1H,  $O=C-NH-N=C$ ), 7.75 (d,  $J = 8.3$  Hz, 2H, ArH), 7.69 (d,  $J = 8.1$  Hz, 2H, ArH), 7.40 (d,  $J = 8.0$  Hz, 2H, ArH), 7.21 (d,  $J = 8.0$  Hz, 2H, ArH), 4.23 (dd,  $J_1 = 9.5$  Hz,  $J_2 = 3.7$  Hz, 1H,  $SO_2-NCH-C=O$ ), 3.95 (d,  $J = 10.0$  Hz, 1H,  $SO_2-NCH_2$ ), 3.55 (d,  $J = 10.8$  Hz, 1H,  $SO_2-NCH_2$ ), 3.31 (dd,  $J_1 = 10.9$  Hz,  $J_2 = 4.7$  Hz, 2H,  $-SCH_2$ ), 3.25 (dd,  $J_1 = 7.4$  Hz,  $J_2 = 3.2$  Hz, 2H,  $-CH_2S$ ), 2.79 (dd,  $J_1 = 13.4$  Hz,  $J_2 = 4.0$  Hz, 1H,  $-S-C-CH_2$ ), 2.48 (s, 3H,  $-CH_3Ar$ ), 2.42–2.45 (t,  $J = 5.5$  Hz, 1H,  $-S-C-CH_2$ ), 2.39 (s, 3H,  $PhCH_3$ ); Anal. Calcd for  $C_{22}H_{25}N_3O_3S_3$ : C, 55.55; H, 5.30; N, 8.83; Found: C, 55.56; H, 5.31; N, 8.85.

**4.1.4.2. (S,E)-N'-(2-Methoxybenzylidene)-7-tosyl-1,4-dithia-7-azaspiro[4.4]nonane-8-carbohydrazide (7b).** Solid, yield: 50.2%, mp 140–142 °C; ESI-MS  $m/z$ : 498.33  $[M+Li]^+$ ;  $^1H$  NMR ( $CDCl_3$ , ppm)  $\delta$ : 9.95 (s, 1H,  $N=CHPh$ ), 8.57 (s, 1H,  $O=C-NH-N=C$ ), 8.11–8.13 (d,  $J = 8.0$  Hz, 1H, ArH), 7.75–7.77 (d,  $J = 8.0$  Hz, 2H, ArH), 7.40–7.42 (d,  $J = 8.0$  Hz, 2H, ArH), 7.38 (s, 1H, ArH), 6.96–6.99 (t,  $J_1 = 4.0$  Hz,  $J_2 = 8.0$  Hz, 1H), 6.90–6.92 (d,  $J = 8.4$  Hz, 1H, ArH), 4.25 (dd,  $J_1 = 9.4$  Hz,  $J_2 = 3.9$  Hz, 1H,  $SO_2-N-CH-C=O$ ), 3.95 (d,  $J = 10.9$  Hz, 1H,  $SO_2-N-CH_2$ ), 3.90 (s, 3H,  $PhOCH_3$ ), 3.56–3.59 (d,  $J = 10.9$  Hz, 1H,  $SO_2-N-CH_2$ ), 3.29 (dd,  $J_1 = 12.0$  Hz,  $J_2 = 5.9$  Hz, 2H,  $C-S-CH_2$ ), 3.24 (d,  $J = 7.5$  Hz, 2H,  $CH_2-S-C$ ), 2.79 (dd,  $J_1 = 13.6$  Hz,  $J_2 = 3.7$  Hz, 1H,  $-C-CH_2-CHC=O$ ), 2.46 (s, 3H,  $-CH_3Ph$ ), 2.41 (dd,  $J_1 = 8.9$  Hz,  $J_2 = 4.8$  Hz, 1H,  $-C-CH_2-CHC=O$ ); Anal. Calcd for  $C_{22}H_{25}N_3O_4S_3$ : C, 53.74; H, 5.13; N, 8.55; Found: C, 53.76; H, 5.11; N, 8.56.

**4.1.4.3. (S,E)-N'-(4-(Dimethylamino)benzylidene)-7-tosyl-1,4-dithia-7-azaspiro[4.4]nonane-8-carbohydrazide (7c).** Solid, yield: 55.1%, mp 161–162 °C; ESI-MS  $m/z$ : 505.63  $[M+H]^+$ , 527.82  $[M+Na]^+$ ;  $^1H$  NMR ( $CDCl_3$ , ppm)  $\delta$ : 11.31 (d,  $J = 3.1$  Hz, 1H,  $N=CH-Ph$ ), 8.10 (s, 1H,  $O=C-NH-N=C$ ), 7.78 (dd,  $J_1 = 12.6$  Hz,

$J_2 = 8.2$  Hz, 2H, ArH), 7.51 (dd,  $J_1 = 12.6$  Hz,  $J_2 = 8.8$  Hz, 2H, ArH), 7.43 (dd,  $J_1 = 12.7$  Hz,  $J_2 = 8.0$  Hz, 2H, ArH), 6.81 (d,  $J = 8.7$  Hz, 1H, ArH), 6.76 (d,  $J = 8.9$  Hz, 1H, ArH), 4.17–4.09 (m, 1H,  $-NCH-C=ONH$ ), 3.84–3.66 (m, 2H,  $SO_2-N-CH_2C$ ), 3.28–3.24 (m, 2H,  $-S-CH_2$ ), 3.22 (dd,  $J_1 = 9.0$  Hz,  $J_2 = 5.1$  Hz, 2H,  $-S-CH_2$ ), 3.00 (s, 3H,  $PhNCH_3$ ), 2.98 (s, 3H,  $PhNCH_3$ ), 2.69–2.54 (m, 2H,  $-C-CH_2CC=O$ ), 2.42 (d,  $J = 7.7$  Hz, 3H,  $-CH_3Ph$ ); Anal. Calcd for  $C_{23}H_{28}N_4O_3S_3$ : C, 54.74; H, 5.59; N, 11.10; Found: C, 54.75; H, 5.61; N, 11.09.

**4.1.4.4. (S,E)-N'-(2-Fluorobenzylidene)-7-tosyl-1,4-dithia-7-azaspiro[4.4]nonane-8-carbohydrazide (7d).** Solid, yield: 46.8%, mp 107–108 °C; ESI-MS  $m/z$ : 480.77 [M+H]<sup>+</sup>, 518.17 [M+K]<sup>+</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, ppm):  $\delta$  9.99 (s, 1H, N=CH-Ph), 8.42 (s, 1H, O=C-NH-N=C), 8.15 (t,  $J_1 = 7.7$  Hz,  $J_2 = 1.5$  Hz, 1H, ArH), 7.76 (d,  $J = 8.2$  Hz, 2H, ArH), 7.40 (d,  $J = 7.6$  Hz, 2H, ArH), 7.36 (d,  $J = 1.7$  Hz, 1H, ArH), 7.18 (t,  $J = 7.6$  Hz, 1H, ArH), 7.08 (t,  $J = 7.8$  Hz, 1H, ArH), 4.26 (dd,  $J_1 = 9.5$  Hz,  $J_2 = 3.7$  Hz, 1H,  $-NCH-C=ONH$ ), 3.95 (d,  $J = 10.4$  Hz, 1H,  $SO_2-N-CH_2C$ ), 3.57 (d,  $J = 10.8$  Hz, 1H,  $SO_2-N-CH_2C$ ), 3.34–3.28 (m, 2H,  $-S-CH_2$ ), 3.25 (dd,  $J_1 = 7.5$  Hz,  $J_2 = 3.1$  Hz, 2H,  $-S-CH_2$ ), 2.79 (dd,  $J_1 = 13.7$  Hz,  $J_2 = 3.7$  Hz, 1H,  $-C-CH_2CC=O$ ), 2.47 (s, 3H,  $-CH_3Ph$ ), 2.41 (dd,  $J_1 = 14.6$  Hz,  $J_2 = 8.7$  Hz, 1H,  $-C-CH_2CC=O$ ); Anal. Calcd for  $C_{21}H_{22}FN_3O_3S_3$ : C, 52.59; H, 4.62; N, 8.76; Found: C, 52.60; H, 4.61; N, 8.77.

**4.1.4.5. (S,E)-N'-(2-Chlorobenzylidene)-7-tosyl-1,4-dithia-7-azaspiro[4.4]nonane-8-carbohydrazide (7e).** Solid, yield: 42.7%, mp 119–120 °C; ESI-MS  $m/z$ : 496.17 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, ppm):  $\delta$  10.03 (d,  $J = 2.8$  Hz, 1H, N=CH-Ph), 8.57 (s, 1H, O=C-NH-N=C), 8.21 (d,  $J = 7.5$  Hz, 1H, ArH), 7.76 (d,  $J = 8.2$  Hz, 2H, ArH), 7.40 (d,  $J = 8.1$  Hz, 2H, ArH), 7.36 (d,  $J = 8.1$  Hz, 1H, ArH), 7.32 (d,  $J = 5.5$  Hz, 1H, ArH), 7.29 (d,  $J = 8.0$  Hz, 1H, ArH), 4.27 (dd,  $J_1 = 9.4$  Hz,  $J_2 = 3.7$  Hz, 1H,  $-NCH-C=ONH$ ), 3.96 (d,  $J = 10.8$  Hz, 1H,  $SO_2-N-CH_2C$ ), 3.59 (d,  $J = 10.9$  Hz, 1H,  $SO_2-N-CH_2C$ ), 3.34–3.27 (m, 2H,  $-S-CH_2$ ), 3.25 (dd,  $J_1 = 6.6$  Hz,  $J_2 = 3.2$  Hz, 2H,  $-S-CH_2$ ), 2.79 (dd,  $J_1 = 13.7$  Hz,  $J_2 = 3.9$  Hz, 1H,  $-C-CH_2CC=O$ ), 2.47 (s, 3H,  $-CH_3Ph$ ), 2.42 (t,  $J = 11.6$  Hz, 1H,  $-C-CH_2CC=O$ ); Anal. Calcd for  $C_{21}H_{22}ClN_3O_3S_3$ : C, 50.85; H, 4.47; N, 8.47; Found: C, 50.88; H, 4.45; N, 8.43.

**4.1.4.6. (S,E)-N'-(2-Bromobenzylidene)-7-tosyl-1,4-dithia-7-azaspiro[4.4]nonane-8-carbohydrazide (7f).** Solid, yield: 49.6%, mp 152–153 °C; ESI-MS  $m/z$ : 540.05 [M+H]<sup>+</sup>, 545.97 [M+Li]<sup>+</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, ppm):  $\delta$  10.07 (s, 1H, N=CH-Ph), 8.54 (s, 1H, O=C-NH-N=C), 8.19 (dd,  $J_1 = 7.7$  Hz,  $J_2 = 1.6$  Hz, 1H, ArH), 7.77 (d,  $J = 8.2$  Hz, 2H, ArH), 7.56 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 0.9$  Hz, 1H, ArH), 7.39 (t,  $J = 8.3$  Hz, 2H, ArH), 7.33 (t,  $J = 7.2$  Hz, 1H, ArH), 7.23 (dd,  $J_1 = 7.5$  Hz,  $J_2 = 1.7$  Hz, 1H, ArH), 4.27 (dd,  $J_1 = 9.3$  Hz,  $J_2 = 4.0$  Hz, 1H,  $-NCH-C=ONH$ ), 3.97 (d,  $J = 10.8$  Hz, 1H,  $SO_2-N-CH_2C$ ), 3.60 (d,  $J = 10.9$  Hz, 1H,  $SO_2-N-CH_2C$ ), 3.35–3.27 (m, 2H,  $-S-CH_2$ ), 3.24 (dd,  $J_1 = 7.7$  Hz,  $J_2 = 3.4$  Hz, 2H,  $-S-CH_2$ ), 2.79 (dd,  $J_1 = 13.8$  Hz,  $J_2 = 4.3$  Hz, 1H,  $-C-CH_2CC=O$ ), 2.47 (s, 3H,  $-CH_3Ph$ ), 2.41 (dd,  $J_1 = 8.1$  Hz,  $J_2 = 5.6$  Hz, 1H,  $-C-CH_2CC=O$ ); Anal. Calcd for  $C_{21}H_{22}BrN_3O_3S_3$ : C, 46.66; H, 4.10; N, 7.77; Found: C, 46.67; H, 4.12; N, 7.74.

**4.1.4.7. (S,E)-N'-(2-Nitrobenzylidene)-7-tosyl-1,4-dithia-7-azaspiro[4.4]nonane-8-carbohydrazide (7g).** Solid, yield: 55.2%, mp 103–104 °C; ESI-MS  $m/z$ : 507.71 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, ppm):  $\delta$  10.22 (s, 1H, N=CH-Ph), 8.77 (s, 1H, O=C-NH-N=C), 8.31 (d,  $J = 7.6$  Hz, 1H, ArH), 8.07 (d,  $J = 8.8$  Hz, 2H, ArH), 7.77 (d,  $J = 8.1$  Hz, 1H, ArH), 7.67 (t,  $J = 7.6$  Hz, 1H, ArH), 7.56 (t,  $J = 7.2$  Hz, 1H, ArH), 7.40 (d,  $J = 8.1$  Hz, 2H, ArH), 4.29 (dd,  $J_1 = 9.3$  Hz,  $J_2 = 4.1$  Hz, 1H,  $-NCH-C=ONH$ ), 3.97 (d,  $J = 10.9$  Hz, 1H,  $SO_2-N-CH_2C$ ), 3.59 (d,  $J = 10.9$  Hz, 1H,  $SO_2-N-CH_2C$ ), 3.35–3.28 (m, 2H,  $-S-CH_2$ ), 3.25 (dd,  $J_1 = 7.8$  Hz,  $J_2 = 3.9$  Hz, 2H,  $-S-CH_2$ ), 2.77 (dd,  $J_1 = 13.6$  Hz,  $J_2 = 3.9$  Hz, 1H,  $-C-CH_2CC=O$ ),

2.47 (s, 3H,  $-CH_3Ph$ ), 2.40 (d,  $J = 6.1$  Hz, 2H,  $-C-CH_2CC=O$ ); Anal. Calcd for  $C_{21}H_{22}N_4O_5S_3$ : C, 49.79; H, 4.38; N, 11.06; Found: C, 49.80; H, 4.36; N, 11.05.

**4.1.4.8. (S,E)-N'-(3-Nitrobenzylidene)-7-tosyl-1,4-dithia-7-azaspiro[4.4]nonane-8-carbohydrazide (7h).** Solid, yield: 46.6%, mp 182–183 °C; ESI-MS  $m/z$ : 507.66 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, ppm):  $\delta$  10.19 (s, 1H, N=CH-Ph), 8.58 (s, 1H, O=C-NH-N=C), 8.36 (s, 1H, ArH), 8.26 (dd,  $J_1 = 2.2$  Hz,  $J_2 = 0.9$  Hz, 1H, ArH), 8.18 (d,  $J = 7.8$  Hz, 1H, ArH), 7.76 (d,  $J = 8.2$  Hz, 2H, ArH), 7.60 (t,  $J_1 = 10.1$  Hz,  $J_2 = 5.9$  Hz, 1H, ArH), 7.42 (d,  $J = 8.1$  Hz, 2H, ArH), 4.24 (dd,  $J_1 = 9.4$  Hz,  $J_2 = 3.7$  Hz, 1H,  $-NCH-C=ONH$ ), 3.96 (d,  $J = 10.8$  Hz, 1H,  $SO_2-N-CH_2C$ ), 3.55 (d,  $J = 10.8$  Hz, 1H,  $SO_2-N-CH_2C$ ), 3.37–3.29 (m, 2H,  $-S-CH_2$ ), 3.26 (dd,  $J_1 = 7.1$  Hz,  $J_2 = 3.5$  Hz, 2H,  $-S-CH_2$ ), 2.80 (dd,  $J_1 = 13.8$  Hz,  $J_2 = 3.1$  Hz, 1H,  $-C-CH_2CC=O$ ), 2.49 (s, 3H,  $-CH_3Ph$ ), 2.39 (dd,  $J_1 = 13.8$  Hz,  $J_2 = 9.5$  Hz, 1H,  $-C-CH_2CC=O$ ); Anal. Calcd for  $C_{21}H_{22}N_4O_5S_3$ : C, 49.79; H, 4.38; N, 11.06; Found: C, 49.78; H, 4.37; N, 11.07.

**4.1.4.9. (S,E)-7-Tosyl-N'-(3,4,5-trimethoxybenzylidene)-1,4-dithia-7-azaspiro[4.4]nonane-8-carbohydrazide (7i).** White solid, yield: 51.9%, mp 122–123 °C; ESI-MS  $m/z$ : 552.65 [M+H]<sup>+</sup>, 574.32 [M+Na]<sup>+</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, ppm):  $\delta$  10.00 (s, 1H, N=CH-Ph), 8.15 (s, 1H, O=C-NH-N=C), 7.76 (d,  $J = 8.2$  Hz, 2H, ArH), 7.40 (d,  $J = 8.0$  Hz, 2H, ArH), 7.02 (s, 2H, ArH), 4.24 (dd,  $J_1 = 9.3$  Hz,  $J_2 = 3.9$  Hz, 1H,  $-NCH-C=ONH$ ), 3.94 (dd,  $J_1 = 10.4$  Hz,  $J_2 = 7.5$  Hz, 1H,  $SO_2-N-CH_2C$ ), 3.88 (d,  $J = 2.1$  Hz, 9H,  $3 \times OCH_3$ ), 3.57 (d,  $J = 10.9$  Hz, 1H,  $SO_2-N-CH_2C$ ), 3.29 (ddd,  $J_1 = 5.9$  Hz,  $J_2 = 5.3$  Hz,  $J_3 = 3.6$  Hz, 2H,  $-S-CH_2$ ), 3.23 (dd,  $J_1 = 11.9$  Hz,  $J_2 = 5.2$  Hz, 2H,  $-S-CH_2$ ), 2.80 (dd,  $J_1 = 13.7$  Hz,  $J_2 = 3.8$  Hz, 1H,  $-C-CH_2CC=O$ ), 2.47 (s, 3H,  $-CH_3Ph$ ), 2.40 (t,  $J = 11.5$  Hz, 1H,  $-C-CH_2CC=O$ ); Anal. Calcd for  $C_{24}H_{29}N_3O_6S_3$ : C, 52.25; H, 5.30; N, 7.62; Found: C, 52.24; H, 5.31; N, 7.67.

## 4.2. Biological evaluation procedures

### 4.2.1. Chemicals, reagents, cells and viruses

The controls, AZT and EFV, were purchased from USP and dissolved in serum-free RPMI-1640 medium *N*-2-(2-Hydroxyethyl) piperazine-*N'*-2-ethanesulfonic acid (HEPES), and LY52 was prepared in our lab. MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide], DMF, penicillin, streptomycin sulfate, glutamine, gelatinase A (MMP-2) and CD13 (APN) Elisa kits were commercially available from Sigma, and 2-mercaptoethanol (2-ME) was purchased from Bio-Rad. RPMI-1640 and fetal bovine serum (FBS) were purchased from Gibco company. C8166 cell line and HIV-1<sub>IIIB</sub> strain were kindly donated by Medical Research Council, AIDS Regent Project. HIV-1<sub>74V</sub> and HIV-1<sub>A17</sub> strains were kindly donated by NIH. The cells were maintained at 37 °C in 5% CO<sub>2</sub> in RPMI-1640 medium supplemented with 10% heat-inactivating FBS. HIV-1<sub>IIIB</sub> was prepared from the supernatants of H9/HIV-1<sub>IIIB</sub> cells. Virus stocks were stored in small aliquots at –70 °C.

### 4.2.2. Enzymatic inhibitory assay

Gelatinase and APN inhibitory assays were performed as described by our previously work.<sup>3,4</sup> The gelatinase A, substrate and inhibitor were dissolved in sodium borate (pH 8.5, 50 mmol/L) and incubated for 30 min at 37 °C, and then 0.03% trinitrobenzenesulfonic acid (TNBS, Sigma) was added and incubated for additional 20 min, the resulting solution was detected under 450 nm wavelength to gain absorption.

The IC<sub>50</sub> values against APN were determined using *l*-Leu-p-nitroanilide as substrate and microsomal aminopeptidase from Porcine Kidney Microsomes (Sigma) as the enzyme in 50 nM PBS, pH 7.2 at 37 °C. The hydrolysis of the substrate was monitored

by following the change in the absorbance measured at 405 nm with the UV–VIS spectrophotometer Pharmacia LKB, Biochrom 4060. All solutions of inhibitors were prepared in the assay buffer, and pH was adjusted to 7.5 by the addition of 0.1 M HCl or 0.1 M NaOH. All inhibitors were preincubated with APN for 30 min at room temperature. The assay mixture which contained the inhibitor solution (concentration dependent on the inhibitor), the enzyme solution (4 µg/ml final concentration), and the assay buffer, was adjusted to 200 µl.

#### 4.2.3. Cytotoxicity assay

The cellular toxicity of tested compounds on C8166 was assessed by MTT colorimetric assay. Briefly, 100 µl of  $4 \times 10^5$  cells were plated into 96-well plates, 100 µl of various concentrations of compounds was added and incubated at 37 °C in a humidified atmosphere of 5% CO<sub>2</sub> for 72 h. 20 µl MTT reagent was added and incubated for 4 h, discard 100 µl supernatant, 100 µl 50% DMF-15% SDS was added. After the formazan was dissolved completely, the plates were analyzed by a Bio-Tek ELx 800 ELISA reader at 570 nm/630 nm. 50% cytotoxicity concentration (CC<sub>50</sub>) was calculated.

#### 4.2.4. Inhibition of syncytia formation

The inhibitory effect of samples on acute HIV-1<sub>IIIB</sub> infection was measured by the syncytia formation assay. In the presence or absence of various concentrations of samples,  $4 \times 10^5$  C8166 cells were infected with HIV-1 at a multiplicity of infection (MOI) of 0.07, and cultured in 96-well plates at 37 °C in 5% CO<sub>2</sub> for 3 days. AZT was used as a positive control. After post-infection for 3 days, cytopathic effect (CPE) was measured by counting the number of syncytia in each well of 96-well plates under an inverted microscope (100×). The inhibitory percentage of syncytia formation was calculated by the percentage of syncytia number in treated sample compared to that in infected control. 50% effective concentration (EC<sub>50</sub>) was calculated.

#### 4.2.5. Inhibition of HIV-1 p24 antigen level in acute infection

The in vitro inhibitory effect of compounds on HIV-1 replication was detected by quantification of p24 expression using capture ELISA method. Briefly, C8166 cells were infected with HIV-1 in the absence or presence of various concentrations of tested compounds at 37 °C for 2 h (HIV-1<sub>IIIB</sub>) or 4 h (HIV-1<sub>A17</sub> and HIV-1<sub>74V</sub>) to allow for viral absorption. It was then washed three times with PBS. The cells were plated at  $4 \times 10^4$  cells/well with or without various concentrations of compounds and incubated at 37 °C in a humidified atmosphere of 5% CO<sub>2</sub> for 72 h. HIV-1 p24 expression in cell-free supernatants was assayed by ELISA. The inhibitory percentage of p24 antigen production was calculated by the OD<sub>490/630</sub> value of sample-treated culture compared to that in infected control culture. 50% effective concentrations (EC<sub>50</sub>) were calculated.

#### 4.2.6. Formula

According to the recognized method described by Reed & Muench, 50% cytotoxic concentration (CC<sub>50</sub>) and 50% effective concentration (EC<sub>50</sub>) was determined from dose–response curve. Therapeutic index (TI) of anti-HIV activity is CC<sub>50</sub>/EC<sub>50</sub>.

- (1) Cell viability (%) =  $(OD_{\text{test}} - OD_{\text{blk}})/(OD_{\text{ctrl}} - OD_{\text{blk}}) \times 100$
- (2) CPE inhibition (%) =  $(1 - CPE_{\text{test}}/CPE_{\text{ctrl}}) \times 100$
- (3) p24 inhibition (%) =  $100 - (OD_{\text{test}} - OD_{\text{blk}})/(OD_{\text{ctrl}} - OD_{\text{blk}}) \times 100$

### 4.3. Computational-docking procedures

The docking study was performed using Sybyl/FlexX module and described as follows. The selected compounds **4m** and **7h** were optimized using the Powell Energetic Gradient method built in the Sketch/Build Edit model, with the Tripos force field with convergence criterion set at 0.005 kcal/mol Å, and assigned with Gasteiger–Hückel mode. When it comes to the docking assay of gelatinase A, residues in a radius of 4.0 Å around the self-contained ligand SC-74020 were considered as the active site, including the zinc166 (II) ion. As to APN, the residues in a radius of 7.0 Å around bestatin (the provided ligand of APN in the co-crystal structure, PDB code: 2DQM) were regarded as the active binding sites, other docking parameters implied in the program were kept default.

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## Novel Indolyl Aryl Sulfones Active against HIV-1 Carrying NNRTI Resistance Mutations: Synthesis and SAR Studies

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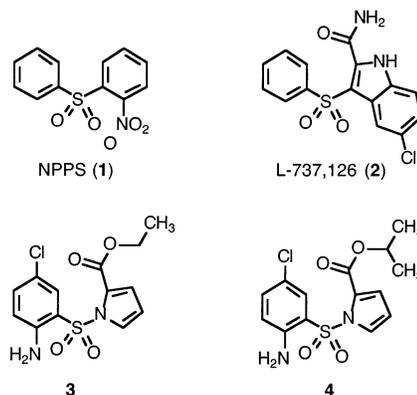
The potent anti-HIV-1 activities of L-737,126 (**2**) and PAS sulfones prompted us to design and test against HIV-1 in acutely infected MT-4 cells a number of novel 1- and 3-benzenesulfonylindoles. Indoles belonging to the 1-benzenesulfonyl series were found poorly or totally inactive. On the contrary, some of the 3-benzenesulfonyl derivatives turned out to be as potent as **2**, being endowed with potencies in the low nanomolar concentration range. In particular, (2-methylphenyl)sulfonyl (**72**) and (3-methylphenyl)sulfonyl (**73**) derivatives showed EC<sub>50</sub> values of 1 nM. Introduction of two methyl groups at positions 3 and 5 of the phenyl ring of **2** furnished derivatives (**80** and **83**) which showed very potent and selective anti-HIV-1 activity not only against the wt strain, but also against mutants carrying NNRTI-resistant mutations at positions 103 and 181 of the reverse transcriptase gene.

### Introduction

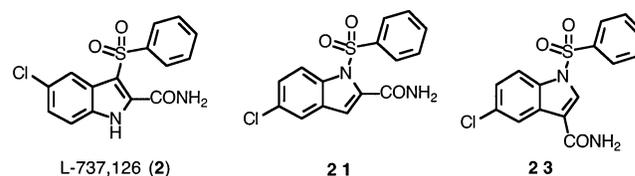
Current drugs effective against the HIV-1 reverse transcriptase (RT) are classified according to their structure as nucleoside (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs).<sup>1</sup> NRTIs, such as AZT, ddC, ddI, and 3TC, interfere with the enzyme activity following metabolic activation to the triphosphate forms and incorporation into the growing DNA strand, which causes premature chain termination. On the contrary, NNRTIs do not require preliminary phosphorylation and are less toxic than nucleoside analogues because they do not affect the activity of cellular polymerases. However, NNRTIs give rise to the rapid emergence of drug-resistant strains which are cross-resistant to other inhibitors within the class. Development of new NNRTIs effective against current clinical resistant strains is, therefore, highly pursued.

Following the discovery of the nitrophenyl phenyl sulfone (NNPS, **1**),<sup>2</sup> new derivatives (such as L-737,126, **2**) have been described which were characterized by the substitution of the nitrophenyl moiety with a 5-chloro-1*H*-indol-3-yl-2-carboxamide<sup>3</sup> (Chart 1). Although L-737,126 turned out to be one of the most potent and selective NNRTIs ever known, its poor solubility hindered further development. Compounds more potent than NNPS have also been obtained following the replacement of the benzene ring with pyrrole<sup>4,5</sup> (e.g., the 1*H*-pyrrol-1-yl aryl sulfones (PASSs) **3** and **4**). In this case, the presence of a *p*-chloroanilino moiety was determinant for their potency and selectivity.

### Chart 1



### Chart 2



To our knowledge, no attempts have been published reporting SAR investigations on indolyl sulfones. Therefore, we designed, synthesized, and evaluated in vitro the anti-HIV-1 activity of novel indolyl aryl sulfones (IASs). The aim was to investigate the effect of the following structural changes: (i) the shift of the benzene sulfonyl moiety from position 3 to position 1 of the indole ring; (ii) the modification of the carboxamide side chain and its shift from position 2 to position 3 (Chart 2); (iii) the introduction of different substituents on the phenyl ring; (iv) the replacement of phenyl ring with a *p*-chloroanilino pharmacophore. The most potent derivatives were also tested for activity against HIV-1 strains

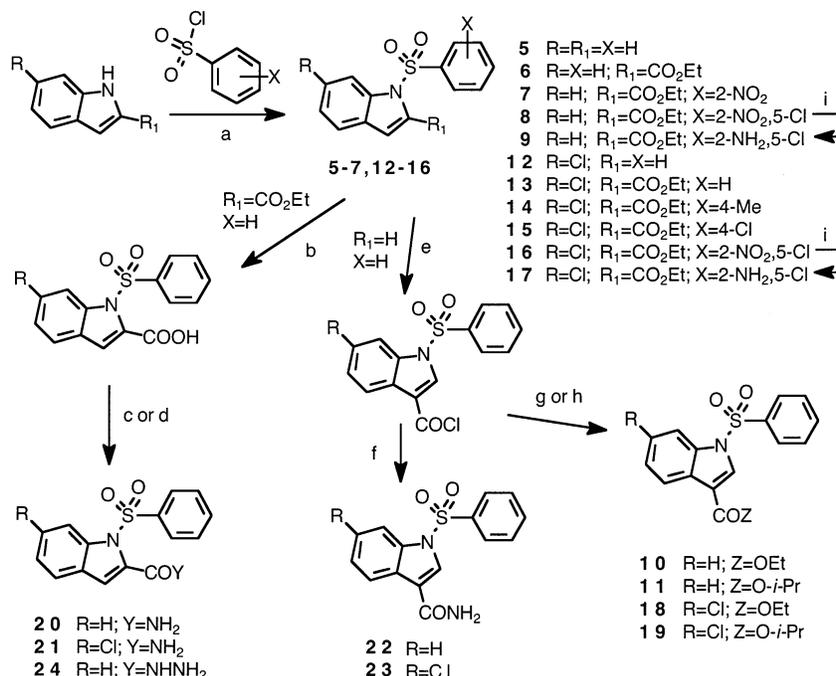
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Scheme 1<sup>a</sup>

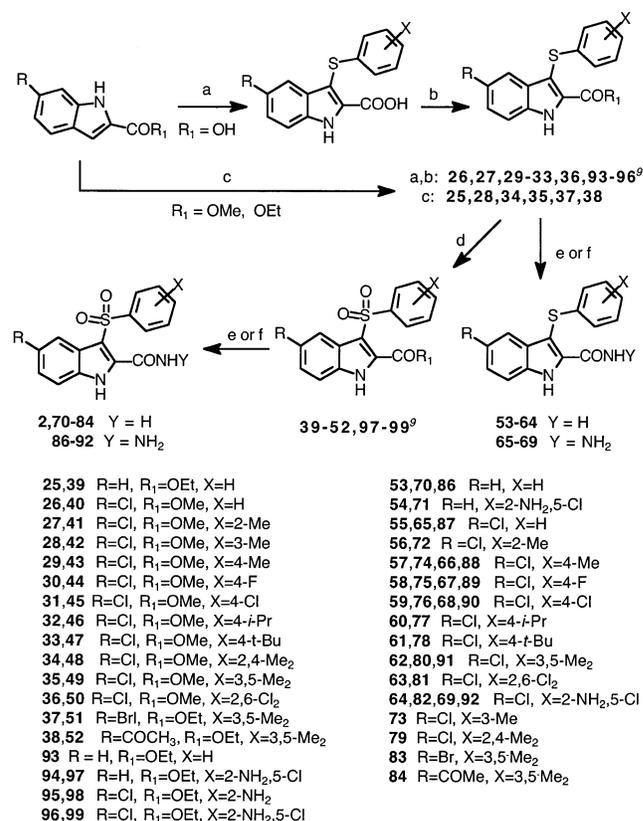
<sup>a</sup> Reagents and reaction conditions: a: *t*-BuOK, 18-crown-6, THF, r.t., 3.5 h; b: KOH, EtOH-THF 1:1, r.t., 4 h; c: CDI, THF, r.t., 2 h, then NH<sub>3</sub>(g), r.t., 1 h; d: CDI, THF, r.t., 2 h, then NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O, r.t., 1 h; e: (COCl)<sub>2</sub>, AlCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to r.t., 2 h; f: NH<sub>3</sub>(g), DMF, r.t., 1 h; g: EtOH, NaHCO<sub>3</sub>, r.t., overnight; h: *i*-PrOH, NaHCO<sub>3</sub>, r.t., overnight; i: Fe, MeCOOH, 60 °C, 2 h.

carrying some of the most clinically relevant mutations conferring resistance to NNRTIs.

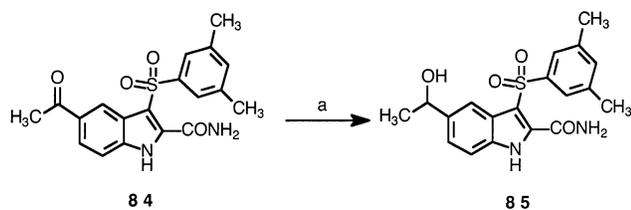
## Chemistry

The synthesis of 1-arylsulfonyl-1*H*-indole derivatives is depicted in Scheme 1. Compounds **5-7** and **12-16** were prepared by reaction of indole or ethyl indole-2-carboxylate with appropriate arylsulfonyl chlorides in the presence of potassium *tert*-butoxide and 18-crown-6. Amino derivative **17** was obtained by iron powder reduction of **16** in glacial acetic acid. Reaction of 1-phenylsulfonyl-1*H*-indole (**5**) or its 5-chloro derivative **12** with oxalyl chloride in the presence of anhydrous aluminum trichloride<sup>6</sup> afforded the corresponding 3-carbonyl chlorides, which were transformed into **10, 18**, and **11, 19** by reaction with ethanol or 2-propanol, respectively, in the presence of sodium hydrogen carbonate, or into amides **22** and **23** by reaction with ammonia. Alkaline hydrolysis of the esters **6** or **13** furnished the corresponding acids which were transformed into amides **20** and **21** by reaction with 1,1'-carbonyldiimidazole and subsequent displacement of the related imidazolides with gaseous ammonia. The hydrazide **24** was prepared similarly by using hydrazine hydrate.

The synthesis of 3-arylthio-1*H*-indole and the corresponding 3-arylsulfonyl derivatives is depicted in Scheme 2. The required 3-arylthio-1*H*-indole-2-carboxylates were prepared by reaction of proper arylthiodisulfides with 1*H*-indole-2-carboxylic acids in the presence of sodium hydride according to the Atkinson method<sup>7</sup> and subsequent esterification of the 3-arylthio-1*H*-indole-2-carboxylic acids with (trimethylsilyl)diazomethane. Esters **26, 27, 29-33**, and **36** were prepared according to this procedure. The intermediates 3-arylthio-1*H*-indole-2-carboxylic acids were purified with some difficulty by

Scheme 2<sup>a</sup>

<sup>a</sup> Reagents and reaction conditions: a: ArS-SAr, NaH, DMF, 50 °C, overnight, N<sub>2</sub> stream; b: (trimethylsilyl)diazomethane, CH<sub>2</sub>-Cl<sub>2</sub>, r.t., 90 min; c: *N*-(ArS)succinimide, BF<sub>3</sub>·Et<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, r.t., 2 h, then 45 °C, 2 h, Ar stream; d: MCPBA, CHCl<sub>3</sub>, r.t., 1 h; e: 30% NH<sub>4</sub>OH, NH<sub>4</sub>Cl, sealed tube, 100 °C, overnight; f: NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O, EtOH, 60 °C, 1.5 h.

Scheme 3<sup>a</sup>

<sup>a</sup> Reagents and reaction conditions. a: NaBH<sub>4</sub>, THF–H<sub>2</sub>O, 60 °C, 2 h.

**Table 1.** Cytotoxicities and Anti-HIV-1 Activities of Derivatives **5–24**<sup>a</sup>

compd	CC <sub>50</sub> <sup>b</sup>	EC <sub>50</sub> <sup>c</sup>	SI <sup>d</sup>
<b>5</b>	15012	>150	-
<b>6</b>	>200	>200	-
<b>7</b>	>200	>200	-
<b>8</b>	>100	>100	-
<b>9</b>	50 ± 6	1.8 ± 0.22	28
<b>10</b>	32 ± 2.5	>32	-
<b>11</b>	54 ± 5	>54	-
<b>12</b>	75 ± 6.2	>75	-
<b>13</b>	>200	>200	-
<b>14</b>	>200	>200	-
<b>15</b>	>200	>200	-
<b>16</b>	31 ± 2	>31	-
<b>17</b>	39 ± 4	8.30 ± 72	4.7
<b>18</b>	42 ± 3.5	>42	-
<b>19</b>	>200	>200	13.3
<b>20</b>	>200	15 ± 1.2	-
<b>21</b>	>200	66 ± 5	>3
<b>22</b>	32 ± 3.1	>32	-
<b>23</b>	200	>200	-
<b>24</b>	>200	>200	-
<b>2</b>	45 ± 5	0.001 ± 0.0002	45 000

<sup>a</sup> Data represent mean values ± SE for three separate experiments. <sup>b</sup> Compound concentration (μM) required to reduce the viability of mock-infected cells by 50% as determined by the MTT method. <sup>c</sup> Compound concentration (μM) required to achieve 50% protection of MT-4 cells from HIV-1 induced cytopathogenicity as determined by the MTT method. <sup>d</sup> Selectivity index: CC<sub>50</sub>/EC<sub>50</sub> ratio.

crystallization. Moreover, as already reported,<sup>7</sup> this procedure furnished poor yields when the preparation of carboxylic esters was attempted. For this reason, an alternative synthetic method was adopted. Compounds **25**, **28**, **34**, **35**, **37**, and **38** were prepared by reaction of methyl or ethyl 1*H*-indole-2-carboxylates with *N*-(aryltio)succinimides in the presence of boron trifluoride diethyl etherate.<sup>8</sup> Oxidation of 3-aryltio-1*H*-indole-2-carboxylates to the related sulfones was performed with 3-chloroperoxybenzoic acid (MCPBA). Esters **25–52**, **94**,<sup>9</sup> **96**,<sup>9</sup> **98**,<sup>9</sup> and **99**<sup>9</sup> were transformed into amides **2**, **53–64**, **70–84** and hydrazides **65–69**, **86–92** by heating at 100 °C with 30% ammonium hydroxide in a sealed tube or by treatment with hydrazine hydrate at 60 °C, respectively. Sodium borohydride reduction of ketone **84** furnished the related alcohol **85** (Scheme 3).

## Results and Discussion

Table 1 reports the results obtained with compounds synthesized to investigate the effect, on the antiretroviral activity, of the shift of the benzenesulfonyl moiety from position 3 (the prototype is L-737,126, **2**) to position 1 of the indole ring. These derivatives are also characterized by the presence of carboxyethyl or carboxamide groups either at positions 2 or 3 of the indole.

**Table 2.** Cytotoxicities and Anti-HIV-1 Activities of Sulfides **25**, **93–96**, and Sulfones **39**, **97–99**<sup>a</sup>

compd	CC <sub>50</sub> <sup>b</sup>	EC <sub>50</sub> <sup>c</sup>	SI <sup>d</sup>
<b>25</b>	1.4 ± 0.5	1.4 ± 0.4	-
<b>93</b> <sup>e</sup>	>200	>200	-
<b>94</b> <sup>e</sup>	≥200	≥200	-
<b>95</b> <sup>e</sup>	>200	2.3 ± 0.28	>87
<b>96</b> <sup>e</sup>	>200	2.5 ± 0.22	>80
<b>39</b>	157 ± 12	3.7 ± 0.3	42
<b>97</b> <sup>e</sup>	>200	2.5 ± 0.23	>91
<b>98</b> <sup>e</sup>	>200	>200	-
<b>99</b> <sup>e</sup>	>200	1.9 ± 0.5	105
<b>2</b>	45 ± 5	0.001 ± 0.0002	45 000

<sup>a</sup> Data represent mean values ± SE for three separate experiments. <sup>b</sup> Compound concentration (μM) required to reduce the viability of mock-infected cells by 50% as determined by the MTT method. <sup>c</sup> Compound concentration (μM) required to achieve 50% protection of MT-4 cells from HIV-1 induced cytopathogenicity as determined by the MTT method. <sup>d</sup> Selectivity index: CC<sub>50</sub>/EC<sub>50</sub> ratio. <sup>e</sup> Literature<sup>13</sup>

With the exception of **9** (EC<sub>50</sub> = 1.8 μM) and **17** (EC<sub>50</sub> = 8.3 μM), which are 1-benzenesulfonyl-2-carboxyethyl derivatives, and of **20** (EC<sub>50</sub> = 15 μM) and **21** (EC<sub>50</sub> = 66 μM), which are 1-benzenesulfonyl-2-carboxamide derivatives, the other 1-benzenesulfonyl indoles were totally devoid of anti-HIV-1 activity. Noteworthy, **9** and **17** were both characterized by a *p*-chloroanilino pharmacophore, which appears to be determinant for the antiretroviral activity (compare **9** and **17** with **6** and **13**, respectively). As far as 1-benzenesulfonyl-2-carboxamide derivatives are concerned, the shift of the carboxamide function to position 3 of the indole (**22**, **23**), or its substitution with a 2-carboxyhydrazide group (**24**), led to loss of activity. Noteworthy, an about 4-fold reduction of antiretroviral activity correlated with the introduction of a chlorine atom at position 5 of the indole ring, no matter whether a carboxyethyl or a carboxamide group was present at position 2 (compare **9** and **20** with **17** and **21**, respectively).

Tables 2–4 summarize the anti-HIV-1 activity of arylthio and 3-benzenesulfonyl indoles carrying different substituents on the phenyl ring and/or at position 2 of the indole moiety. With some exceptions, compounds carrying carboxyethyl groups at position 2 of the indole proved weakly active (Table 2). Noteworthy, three of them (**39**, **97**, **99**) were the counterparts of the 1-arylsulfonylindoles **6**, **9**, **17**, respectively. Although structure–activity relationships were not immediately obvious, the 2-carboxyethyl sulfone derivatives **39**, **97**, **99** proved equally or even more potent than sulfur counterparts **25**, **94**, **96** with sole exception of the 2-aminobenzene derivative **95** (compare **98** and **95**).

Substitution of the ester function with an amide function led to a very significant increase of both potency and selectivity (Table 3). Among the monosubstituted sulfones, the introduction of a methyl group at position ortho (**72**), meta (**73**), or para (**74**) of the phenyl ring led to derivatives as potent as the reference compound **2**. When electron-withdrawing (**75**, **76**) or bulky (**77**, **78**) substituents were introduced, a 10- to 100-fold reduction of potency was observed. The positive biological effect of the presence of methyl groups in the phenyl ring was confirmed in the disubstituted series, where 2,4-Me<sub>2</sub> and 3,5-Me<sub>2</sub> derivatives proved fairly potent (**79**, **80**, **83–85**), although in some cases also cytotoxic. Unlike what

**Table 3.** Cytotoxicities and Anti-HIV-1 Activities of Derivatives **53–64** and **70–85**<sup>a</sup>

compd	CC <sub>50</sub> <sup>b</sup>	EC <sub>50</sub> <sup>c</sup>	SI <sup>d</sup>
<b>53</b>	14 ± 2	1.4 ± 0.95	10
<b>54</b>	20 ± 2.8	9 ± 1.2	2.2
<b>55</b>	9 ± 1.5	0.02 ± 0.005	450
<b>56</b>	26 ± 2.5	0.3 ± 0.1	87
<b>57</b>	0.45 ± 0.3	>0.45	-
<b>58</b>	13 ± 2	1.4 ± 0.5	9
<b>59</b>	13 ± 1.6	3.1 ± 0.4	4
<b>60</b>	52 ± 4.2	1.9 ± 0.17	27
<b>61</b>	45 ± 3	8 ± 0.6	6
<b>62</b>	0.7 ± 0.1	0.006 ± 0.0005	117
<b>63</b>	61 ± ± ± 7	1.2 ± 0.6	51
<b>64</b>	33 ± 2.7	1.6 ± 0.2	20
<b>70</b>	>200	0.18 ± 0.05	>1,111
<b>71</b>	3.5 ± 0.18	0.3 ± 0.06	11.7
<b>72</b>	>200	0.001 ± 0.0001	>200 000
<b>73</b>	>200	0.001 ± 0.0002	>200 000
<b>74</b>	>200	0.003 ± 0.0003	>66 667
<b>75</b>	17 ± 2.1	0.014 ± 0.002	1214
<b>76</b>	>200	0.011 ± 0.0009	>18 182
<b>77</b>	>200	0.08 ± 0.006	>2500
<b>78</b>	26 ± 2	0.13 ± 0.02	200
<b>79</b>	37 ± 3.2	0.004 ± 0.0004	9250
<b>80</b>	15 ± 1.2	0.004 ± 0.0003	3750
<b>81</b>	40 ± 5.2	0.1 ± 0.018	400
<b>82</b>	4.6 ± 0.33	0.04 ± 0.005	115
<b>83</b>	18 ± 0.9	0.002 ± 0.0001	9000
<b>84</b>	>200	0.015 ± 0.002	>13 333
<b>85</b>	>200	0.025 ± 0.002	>8000
<b>2</b>	45 ± 5	0.001 ± 0.0002	45 000

<sup>a</sup> Data represent mean values ± SE for three separate experiments. <sup>b</sup> Compound concentration (μM) required to reduce the viability of mock-infected cells by 50% as determined by the MTT method. <sup>c</sup> Compound concentration (μM) required to achieve 50% protection of MT-4 cells from HIV-1 induced cytopathogenicity as determined by the MTT method. <sup>d</sup> Selectivity index: CC<sub>50</sub>/EC<sub>50</sub> ratio.

was observed in the PAS series,<sup>5</sup> replacement of the phenyl ring with a *p*-chloroanilino pharmacophore led to loss of activity (compare **2** with **82**). As a rule, the 2-carboxyamido sulfone derivatives (**70–85**) turned out to be less cytotoxic and more potent than sulfur counterparts (**53–64**) (compare **55**, **56**, **57**, **62** with **2**, **72**, **74**, **80**, respectively).

To improve the solubility of IAS derivatives, the carboxyamido group was replaced with a carboxyhydrazide chain (Table 4). Unfortunately, this attempt gave compounds considerably less potent than the amide counterparts. Again, sulfone derivatives were less cytotoxic and more potent than sulfur counterparts.

The most potent derivatives were then tested against a panel of HIV-1 strains carrying clinically relevant NNRTI resistance mutations (Table 5) in comparison with Efavirenz, the most potent clinically used NNRTI.<sup>10</sup> The lead compound **2** and its monomethyl-substituted derivatives (**72**, **73**, **74**) were found inhibitory to the Y181C mutant at submicromolar concentrations, whereas they proved inefficient inhibitors of both the K103N-Y181C double mutant and the EFV<sup>R</sup> (K103R-V179D-P225H) triple mutant, which is highly resistant to Efavirenz. Interestingly, the potency of monomethyl derivatives against the mutant strains was found to progressively increase as the methyl group was shifted from position 4 (**74**) (in the case of K103N-Y181C and K103R-V179D-P225H), or from position 2 (**72**) (in the case of Y181C), to position 3 (**73**) of the phenyl ring. Among disubstituted derivatives, the 2,4-Me<sub>2</sub> derivative (**79**) confirmed the same low inhibitory potency of the

**Table 4.** Cytotoxicities and Anti-HIV-1 Activities of Derivatives **65–69** and **86–92**<sup>a</sup>

compd	CC <sub>50</sub> <sup>b</sup>	EC <sub>50</sub> <sup>c</sup>	SI <sup>d</sup>
<b>65</b>	44 ± 3.2	0.5 ± 0.06	88
<b>66</b>	129 ± 2.5	1.5 ± 0.02	86
<b>67</b>	66 ± 7	5 ± 0.6	13
<b>68</b>	30 ± 3.3	10 ± 1.7	3
<b>69</b>	13 ± 2.1	>13	-
<b>86</b>	133 ± 17	0.5 ± 0.06	266
<b>87</b>	>200	0.01 ± 0.004	>20 000
<b>88</b>	>200	0.05 ± 0.006	>4000
<b>89</b>	44 ± 5.2	0.3 ± 0.025	147
<b>90</b>	>200	0.2 ± 0.015	>1000
<b>91</b>	>200	0.1 ± 0.005	>2000
<b>92</b>	19 ± 2.2	0.3 ± 0.02	63
<b>2</b>	45 ± 5	0.001 ± 0.0002	45 000

<sup>a</sup> Data represent mean values ± SE for three separate experiments. <sup>b</sup> Compound concentration (μM) required to reduce the viability of mock-infected cells by 50% as determined by the MTT method. <sup>c</sup> Compound concentration (μM) required to achieve 50% protection of MT-4 cells from HIV-1 induced cytopathogenicity as determined by the MTT method. <sup>d</sup> Selectivity index: CC<sub>50</sub>/EC<sub>50</sub> ratio.

2-methyl derivative (**72**) against all resistant strains. On the contrary, the 3,5-Me<sub>2</sub> derivative (**80**) proved highly potent against Y181C, K103N-Y181C, and K103R-V179D-P225H mutants. Interestingly, the activity of **80** against the two HIV-1 strains carrying mutations at the 103 position of the RT gene was 10-fold superior to that of **2**. Finally, it is worth noting that, when compared to Efavirenz, **80** turned out to be a 4-fold less efficient inhibitor of the double mutant K103N-Y181C, but a 22-fold better inhibitor of the triple mutant K103R-V179D-P225H.

HIV-1 bearing the K103N mutation are known to be the most frequently emerging variants in patients subjected to HAART based on Nevirapine and Efavirenz as single NNRTIs. Therefore, it was interesting to determine whether the high level resistance of the double mutant K103N-Y181C to the more active indoles was due primarily to the K103N mutation or to the concomitant effect of the two mutations on the RT non-nucleoside binding site. Hence, compounds **80**, **2** and Efavirenz were assayed in MT-4 cells against an HIV-1 strain containing a single K103N mutation. The EC<sub>50</sub>s were in each case greater than 1.0 μM, suggesting that the high level resistance of the double mutant has to be related to the presence of K103N mutation.

Compounds **74**, **80**, and **2** were then tested against recombinant RTs (rRT) from wt, K103N, and Y181C mutant HIV-1. Consistently with the results obtained in cell-based assays, all compounds inhibited both the wt and Y181C enzymes, but not the rRT carrying the K103 mutation. This confirmed that title compounds target the HIV-1 reverse transcriptase (Table 6).

## Conclusions

This study clearly demonstrated that the position of both benzenesulfonyl and carboxyamido moieties on the indole ring were crucial for the anti-HIV-1 activity. In terms of chemical features we found that the best results were obtained with 3-benzenesulfonylindoles carrying a 2-carboxyamido function (Table 3). Related esters (Table 2) and hydrazides (Table 4) were always less potent, whereas the corresponding carboxylic acids were totally inactive (data not shown). The modest anti-

**Table 5.** Anti-HIV-1 Activities of Derivatives 72–74, 79 and 80 against Some Clinically Relevant HIV-1 Resistant Strains<sup>a</sup>

compd	wt <sub>IIB</sub> , EC <sub>50</sub> <sup>b</sup>	wt <sub>IIB</sub> , EC <sub>90</sub> <sup>c</sup>	Y181C, EC <sub>50</sub> <sup>b</sup>	K103N-Y181C, EC <sub>50</sub> <sup>b</sup>	EFV <sup>R</sup> , EC <sub>90</sub> <sup>d</sup>
<b>72</b>	0.001 ± 0.0001	0.005 ± 0.0003	0.16 ± 0.04	10 ± 2	2.6 ± 1
<b>73</b>	0.001 ± 0.0002	0.005 ± 0.0006	0.006 ± 0.001	7 ± 1.5	0.26 ± 0.05
<b>74</b>	0.003 ± 0.0003	0.01 ± 0.005	0.02 ± 0.004	>100	93 ± 12
<b>79</b>	0.004 ± 0.0004	0.01 ± 0.01	0.15 ± 0.08	10 ± 1.8	5.3 ± 1.2
<b>80</b>	0.004 ± 0.0003	0.002 ± 0.0003	0.03 ± 0.008	0.65 ± 0.1	0.08 ± 0.01
<b>2</b>	0.001 ± 0.0002	0.007 ± 0.0007	0.02 ± 0.005	8 ± 1.7	0.9 ± 0.15
EFV <sup>e</sup>	0.004 ± 0.0003	0.008 ± 0.001	0.025 ± 0.005	0.15 ± 0.05	1.8 ± 0.5

<sup>a</sup> Data represent mean values ± SE for three separate experiments. <sup>b</sup> Compound concentration (μM) required to achieve 50% protection of MT-4 cells from the indicated strain HIV-1 induced cytopathogenicity as determined by the MTT method. <sup>c</sup> Compound concentration (μM) required to reduce the amount of p24 by 90% in WT<sub>IIB</sub> infected C8166 cells. <sup>d</sup> Compound concentration (μM) required to reduce the amount of p24 by 90% in C8166 cells infected with an efavirenz resistant strain carrying mutations K103R, V179D, and P225H. <sup>e</sup> EFV, Efavirenz.

**Table 6.** Activities of Derivatives 74, 80, 2 and Efavirenz against wt and Mutant Recombinant RTs<sup>a</sup>

compd	wt <sub>IIB</sub> , IC <sub>50</sub> <sup>b</sup>	K103N, IC <sub>50</sub> <sup>b</sup>	Y181C, IC <sub>50</sub> <sup>b</sup>
<b>74</b>	0.072 ± 0.0055	>5	0.11 ± 0.010
<b>80</b>	0.031 ± 0.0061	>5	0.13 ± 0.024
<b>2</b>	0.025 ± 0.0032	>5	0.16 ± 0.051
EFV <sup>c</sup>	0.033 ± 0.0023	3.4 ± 0.3	0.085 ± 0.01

<sup>a</sup> Data represent mean values ± SE for two separate experiments. <sup>b</sup> Compound concentration (μM) required to inhibit the HIV-1 rRT activities by 50%. <sup>c</sup> EFV, Efavirenz.

HIV-1 activity of 1-benzenesulfonyl indoles, which has been previously reported by us on structurally similar derivatives,<sup>5</sup> may be due to the fact that they interact with the RT non-nucleoside binding site (NNBS) differently from 3-benzenesulfonyl indoles.

A second interesting aspect of this study is that both potency and spectrum of 3-benzenesulfonyl-2-carboxy-amido indoles vary depending on the number and position of the substituents on the phenyl ring. Numerous phenyl-substituted IASs proved as potent as the parent compound **2** against HIV-1 wt (**72–74**, **79**, **80**, and **83**) and some of them also showed comparable/slightly lower activity against the Y181C (**73**, **74**, and **80**) and K103N-Y181C (**72**, **73**, **79**, and **80**) strains carrying clinically relevant NNRTI resistance mutations and the K103R-V179D-P225H (**72**, **73**, and **80**) strain highly resistant to Efavirenz. However, it is the 3,5-Me<sub>2</sub> substitution that comes up as the major determinant for the broad spectrum activity against resistant mutants. In fact, derivative **80** turned out as active as **2** and Efavirenz against wt and Y181C, 10- and 20-fold more potent than **2** and Efavirenz, respectively, against K103R-V179D-P225H and, finally, about 10-fold more potent than **2** and only 4-fold less potent than Efavirenz against K103N-Y181C mutant.

Assays against both wt and mutant enzymes confirm that, like Efavirenz, title compounds target the HIV-1 RT. Why in enzyme assays the potency of all the compounds tested is up to 15-fold lower than in cell-based assays is not immediately obvious. Nevertheless, time of addition studies carried out with **80** (data not shown) indicate that, like Efavirenz, it must be added to acutely infected cell cultures within 6 h post infections in order to prevent the HIV-1 multiplication. In addition, **80** is not inhibitory to the HIV-2 multiplication in C8166 cells and lacks activity in enzyme assays with HIV-1 recombinant integrase (data not shown). Taken together, the above results suggest that IASs target the RT of susceptible viruses. Although title compounds potently inhibit wt and mutant HIV-1 carrying the Y181C mutation, but not the variants carrying other

clinically relevant NNRTI mutations such as K103N and K103N-Y181C, the results presented herein offer a great stimulus for further improvement of the activity spectrum of novel analogues of **2**.

## Experimental Section

**Chemistry.** Melting points (mp) were determined on a Büchi 510 apparatus and are uncorrected. Infrared spectra (IR) were run on Perkin-Elmer 1310 and SpectrumOne spectrophotometers. Band position and absorption ranges are given in cm<sup>-1</sup>. Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra were recorded on Bruker AM-200 (200 MHz) and Bruker Avance 400 MHz FT spectrometers in the indicated solvent. Chemical shifts are expressed in δ units (ppm) from tetramethylsilane. Column chromatography columns were packed with alumina Merck (70–230 mesh) and silica gel Merck (70–230 mesh). Aluminum oxide TLC cards (Fluka) (aluminum oxide precoated aluminum cards with fluorescent indicator at 254 nm) and silica gel TLC cards (Fluka) (silica gel precoated aluminum cards with fluorescent indicator at 254 nm) were used for thin-layer chromatography (TLC). Developed plates were visualized by Spectroline ENF 260C/F UV apparatus. Organic solutions were dried over anhydrous sodium sulfate. Concentration and evaporation of the solvent after reaction or extraction was carried out on a rotary evaporator Büchi Rotavapor operating at reduced pressure. Elemental analyses were performed by laboratories of Dr. M. Zancato, Dipartimento di Scienze Farmaceutiche, University of Padova (Italy). Analytical results were within ±0.4% of the theoretical values.

**General Procedure for the Preparation of the 1-Arylsulfonyl-1H-indoles 5–8 and 1-Arylsulfonyl-5-chloro-1H-indoles 12–16. Example. 1-Phenylsulfonyl-1H-indole (5).** To a stirred mixture of potassium *tert*-butoxide (2.58 g, 0.023 mol) and 18-crown-6 (0.45 g, 0.0017 mol) in anhydrous THF (25 mL) was added dropwise a solution of indole (2.00 g, 0.017 mol) in the same solvent (25 mL). After cooling at 0 °C for 15 min, a solution of benzenesulfonyl chloride (3.01 g, 0.017 mol) in anhydrous THF (25 mL) was added dropwise. Reaction was stirred at room temperature for 3.5 h, then concentrated to a small volume and extracted with ethyl acetate. Organic extracts were washed with brine and dried. Removal of the solvent gave a residue which was purified on silica gel column chromatography (chloroform) to afford **5**, yield 90%, mp 78–79 °C (from ligroin), lit.<sup>12</sup> mp 77–79 °C. Thus, compounds **6–8** and **12–16** were prepared.

**Ethyl 1-phenylsulfonyl-1H-indole-2-carboxylate (6),** yield 96%, mp 89–90 °C (from ligroin), lit.<sup>12</sup> mp 89–91 °C.

**Ethyl 1-[(2-nitrophenyl)sulfonyl]-1H-indole-2-carboxylate (7),** yield 30%, mp 140–142 °C (from toluene/cyclohexane), <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.23 (t, *J* = 7.1 Hz, 3H), 4.22 (q, *J* = 7.1 Hz, 2H), 7.30–7.42 (m, 2H), 7.49 (m, 1H), 7.62–7.80 (m, 3H), 7.82–7.95 (m, 2H), 8.10 ppm (d, *J* = 8.5 Hz, 1H). IR (Nujol): ν 1725 cm<sup>-1</sup>. Anal. (C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>O<sub>6</sub>S (374.36)) C, H, N, S.

**Ethyl 1-[(5-chloro-2-nitrophenyl)sulfonyl]-1H-indole-2-carboxylate (8),** and **Ethyl 1-[(2-amino-5-chlorophenyl)sulfonyl]-1H-indole-2-carboxylate (9)** were prepared by us previously.<sup>5</sup>

**5-Chloro-1-phenylsulfonyl-1H-indole (12)**, yield 73%, mp 73–74 °C (from ligroin), lit.<sup>14</sup> mp 47–48 °C.

**Ethyl 5-chloro-1-phenylsulfonyl-1H-indole-2-carboxylate (13)** yield 84%, mp 104–105 °C (from cyclohexane), lit.<sup>8</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.38 (t, *J* = 7.1 Hz, 3H), 4.39 (q, *J* = 7.1 Hz, 2H), 7.06 (s, 1H), 7.36 (dd, *J* = 2.1 and 9.1 Hz, 1H), 7.42–7.63 (m, 4H), 7.95–8.07 (m, 3H). IR (Nujol): ν 1730 cm<sup>-1</sup>. Anal. (C<sub>17</sub>H<sub>14</sub>ClNO<sub>4</sub>S (363.81)) C, H, N, Cl, S.

**Ethyl 1-[(4-methylphenyl)sulfonyl]-1H-indole-2-carboxylate (14)**, yield 58%, mp 84–86 °C (from cyclohexane). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.40 (t, *J* = 7.1 Hz, 3H), 2.38 (s, 3H), 4.41 (q, *J* = 7.1 Hz, 2H), 7.06 (s, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.37 (dd, *J* = 2.0 and 9.0 Hz, 1H), 7.52 (d, *J* = 2.0 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 2H), 8.04 ppm (d, *J* = 9.0 Hz, 1H), IR (Nujol): ν 1730 cm<sup>-1</sup>. Anal. (C<sub>18</sub>H<sub>16</sub>ClNO<sub>4</sub>S (377.84)) C, H, N, Cl, S.

**Ethyl 1-[(4-methylphenyl)sulfonyl]-1H-indole-2-carboxylate (15)**, yield 62%, mp 86–88 °C (from cyclohexane). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.40 (t, *J* = 7.1 Hz, 3H), 4.40 (q, *J* = 7.1 Hz, 2H), 7.10 (s, 1H), 7.39 (dd, *J* = 2.0 and 9.0 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.97 (d, *J* = 8.7 Hz, 2H), 8.04 ppm (d, *J* = 9.0 Hz, 1H). IR (Nujol): ν 1730 cm<sup>-1</sup>. Anal. (C<sub>17</sub>H<sub>13</sub>Cl<sub>2</sub>NO<sub>4</sub>S (398.26)) C, H, N, Cl, S.

**Ethyl 1-[(5-chloro-2-nitrophenyl)sulfonyl]-5-chloro-1H-indole-2-carboxylate (16)**, yield 28%, mp 161 °C (from toluene/cyclohexane). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.31 (t, *J* = 7.2 Hz, 3H), 4.34 (q, *J* = 7.2 Hz, 2H), 7.49 (dd, *J* = 2.1 and 9.1 Hz, 1H), 7.66–7.72 (m, 1H), 7.75 (d, *J* = 2.1 Hz, 1H), 7.86–7.92 (m, 2H), 7.95 ppm (d, *J* = 9.1 Hz, 1H), IR (Nujol): ν 1710 cm<sup>-1</sup>. Anal. (C<sub>17</sub>H<sub>12</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>6</sub>S (441.98)) C, H, N, Cl, S.

**Ethyl 1-[(2-amino-5-chlorophenyl)sulfonyl]-5-chloro-1H-indole-2-carboxylate (17)** was prepared by iron powder reduction of **16** in glacial acetic acid as previously reported by us,<sup>5</sup> yield 88%, mp 105–106 °C (from cyclohexane). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.39 (t, *J* = 7.0 Hz, 3H), 4.38 (q, *J* = 7.0 Hz, 2H), 5.30 (broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 6.61 (d, *J* = 8.8 Hz, 1H), 7.14 (s, 1H), 7.22 (dd, *J* = 2.4 and 8.8 Hz, 1H), 7.37 (dd, *J* = 2.1 and 9.2 Hz, 1H), 7.56 (d, *J* = 2.1 Hz, 1H), 7.72 (d, *J* = 2.4 Hz, 1H), 7.83 ppm (d, *J* = 9.2 Hz, 1H), IR (Nujol): ν 1710, 3370, 3480 cm<sup>-1</sup>. Anal. (C<sub>17</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S (412.00)) C, H, N, Cl, S.

**Synthesis of the 1-(Phenylsulfonyl)-1H-indole-3-carboxylic Esters 10, 11, 18, and 19. Example. Ethyl 1-(Phenylsulfonyl)-1H-indole-3-carboxylate (10).** 1-(Phenylsulfonyl)-1H-indole-3-carboxyl chloride was prepared by reaction with 1-phenylsulfonyl-1H-indole (**5**) with oxalyl chloride in the presence of anhydrous aluminum trichloride as reported by Ketcha and Gribble.<sup>6</sup> A suspension of 1-(phenylsulfonyl)-1H-indole-3-carboxyl chloride (1.0 g, 0.0031 mol), sodium hydrogen carbonate (0.62 g, 0.0031 mol), and absolute ethanol (150 mL) was stirred at room-temperature overnight. After concentration to a small volume, the residue was extracted with ethyl acetate and washed with brine. Evaporation of the solvent gave a residue which was purified on silica gel column chromatography (dichloromethane:petroleum ether 1:1) to afford **10**, yield 78%, mp 113–114 °C (from ligroin), lit.<sup>13</sup> mp 118.5–119.5 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.42 (t, *J* = 7.1 Hz, 3H), 4.41 (q, *J* = 7.1 Hz, 2H), 7.27–7.40 (m, 2H), 7.40–7.64 (m, 3H), 7.88–8.02 (m, 3H), 8.16 (m, 1H), 8.28 ppm (s, 1H). IR (Nujol): ν 1710 cm<sup>-1</sup>. Thus, compounds **11**, **18**, and **19** were prepared.

**Isopropyl 1-(phenylsulfonyl)-1H-indole-3-carboxylate (11)**, yield 86%, mp 90–92 °C (from ligroin). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.40 (d, *J* = 6.2 Hz, 6H), 5.28 (sp, *J* = 6.2 Hz, 1H), 7.28–7.42 (m, 2H), 7.42–7.66 (m, 3H), 7.95 (m, 3H), 8.13 (m, 1H), 8.27 ppm (s, 1H). IR (Nujol): ν 1680 cm<sup>-1</sup>. Anal. (C<sub>18</sub>H<sub>17</sub>NO<sub>4</sub>S (343.39)) C, H, N, S.

**Ethyl 5-chloro-1-(phenylsulfonyl)-1H-indole-3-carboxylate (18)**, yield 97%, mp 145–146 °C (from cyclohexane). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.42 (t, *J* = 7.1 Hz, 3H), 4.39 (q, *J* = 7.1 Hz, 2H), 7.32 (dd, *J* = 2.0 and 8.7 Hz, 1H), 7.42–7.67 (m, 3H), 7.83–7.98 (m, 3H), 8.11 (d, *J* = 2.0 Hz, 1H), 8.28 ppm (s, 1H). IR (Nujol): ν 1705 cm<sup>-1</sup>. Anal. (C<sub>17</sub>H<sub>14</sub>ClNO<sub>4</sub>S (363.81)) C, H, N, S, Cl.

**Isopropyl 5-chloro-1-(phenylsulfonyl)-1H-indole-3-carboxylate (19)**, yield 54%, mp 121–122 °C (from ligroin). <sup>1</sup>H

NMR (CDCl<sub>3</sub>): δ 1.40 (d, *J* = 6.2 Hz, 6H), 5.27 (sp, *J* = 6.2 Hz, 1H), 7.32 (dd, *J* = 2.0 and 8.9 Hz, 1H), 7.43–7.68 (m, 3H), 7.83–7.98 (m, 3H), 5.56 (d, *J* = 2.0 Hz, 1H), 8.26 ppm (s, 1H). IR (Nujol): ν 1715 cm<sup>-1</sup>. Anal. (C<sub>18</sub>H<sub>16</sub>ClNO<sub>4</sub>S (377.84)) C, H, N, S, Cl.

**1-(Phenylsulfonyl)-1H-indole-2-carboxamide (20).** A mixture of **6** (3.29 g, 0.01 mol), 2 N KOH (20 mL, 2.24 g KOH, 0.04 mol), THF (20 mL), and ethanol (20 mL) was stirred at room temperature for 4 h, then it was quenched on crushed ice and made acidic with 37% HCl. Ethyl acetate was added, and the organic layer was separated, washed with brine, and dried. Removal of the solvent furnished the crude acid (2.1 g, 0.007 mol, 70%) which was dissolved in anhydrous THF (50 mL) and treated portionwise with 1,1'-carbonyldiimidazole (1.62 g, 0.1 mol). After stirring at room temperature for 2 h, gaseous ammonia was bubbled through at 0 °C for 1 h. Water and ethyl acetate were added while shaking. The organic layer was separated, washed with brine, and dried. Removal of the solvent furnished a crude product which was purified on alumina column chromatography (chloroform-ethanol 95:5) to afford **20**, yield 95%, mp 205–206 °C (from toluene). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 7.03 (s, 1H), 7.21–7.47 (m, 2H), 7.53–7.81 (m, 5H, 4H disappeared on treatment with D<sub>2</sub>O), 7.97 (d, *J* = 8.2 Hz, 1H), 8.08–8.20 (m, 2H), 8.30 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1660, 3100, 3420 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>S (300.33)) C, H, N, S.

**5-Chloro-1-(phenylsulfonyl)-1H-indole-2-carboxamide (21)** was prepared as **20** starting from **13**, yield 50%, mp 193–194 °C (from ligroin). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 6.99 (s, 1H), 7.42 (dd, *J* = 2.0 and 9.0 Hz, 1H), 7.56–7.78 (m, 4H), 7.84 (broad s, 1H, disappeared on treatment with D<sub>2</sub>O), 7.99 (d, *J* = 9.0 Hz, 1H), 8.11–8.22 (m, 2H), 8.34 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1660, 3160, 3420 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>11</sub>ClN<sub>2</sub>O<sub>3</sub>S (334.77)) C, H, N, S, Cl.

**1-(Phenylsulfonyl)-1H-indole-2-carboxyhydrazide (24)** was prepared as **20** by reaction with hydrazine hydrate, yield 52%, mp 148–150 °C (from aqueous ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 4.63 (broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 6.98 (s, 1H), 7.28 (m, 1H), 7.40 (dt, *J* = 1.2 and 7.5 Hz, 1H), 7.54–7.78 (m, 4H), 7.97 (d, *J* = 8.1 Hz, 1H), 8.13–8.23 (m, 2H), 10.02 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1670, 3340 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>S (315.34)) C, H, N, S.

**1-(Phenylsulfonyl)-1H-indole-3-carboxamide (22).** Gaseous ammonia was bubbled at 0 °C through a solution of 1-(phenylsulfonyl)-1H-indole-3-carboxyl chloride<sup>6</sup> (1.0 g, 0.0031 mol) in DMF (20 mL) for 1 h. Reaction was quenched on crushed ice and extracted with ethyl acetate. Organic layer was washed with brine and dried. Removal of the solvent gave a crude product which was purified on silica gel column chromatography (ethyl acetate) to afford **22**, yield 21%, mp 233–235 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 7.24–7.44 (m, 3H, 2H disappeared on treatment with D<sub>2</sub>O), 7.57–7.80 (m, 3H), 7.87–8.09 (m, 4H, 3H disappeared on treatment with D<sub>2</sub>O), 8.18 (m, 1H), 8.59 ppm (s, 1H). IR (Nujol): ν 1640, 3330, 3440 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>S (300.33)) C, H, N, S.

**5-Chloro-1-(phenylsulfonyl)-1H-indole-3-carboxamide (23).** This compound was prepared as reported for **22** starting from 5-chloro-1-(phenylsulfonyl)-1H-indole-3-carboxyl chloride, yield 30%, mp 245–247 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 7.37–7.49 (dd, *J* = 2.0 and 8.9 Hz, 1H, and broad s, 1H, disappeared on treatment with D<sub>2</sub>O, overlapped signals), 7.60–7.83 (m, 3H), 7.91–8.10 (m, 4H, after treatment with D<sub>2</sub>O showed 3H), 8.19 (d, *J* = 2.0 Hz, 1H), 8.69 ppm (s, 1H). IR (Nujol): ν 1635, 3180, 3300, 3430 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>11</sub>ClN<sub>2</sub>O<sub>3</sub>S (334.77)) C, H, N, S, Cl.

**General Procedure for the Synthesis of the 3-Arylthio-1H-indole-2-carboxylates 25, 28, 34, 35, 37 and 38. Example. Ethyl 3-(phenylthio)-1H-indole-2-carboxylate (25).** Boron trifluoride diethyl etherate (0.135 g, 0.12 mL, 0.001 mol) was added to a mixture of ethyl 1H-indole-2-carboxylate (0.59 g, 0.003 mol), *N*-(phenylthio)succinimide<sup>11</sup> (0.68 g, 0.0033 mol), and anhydrous dichloromethane (20 mL) under dry argon

atmosphere. After stirring at room temperature for 2 h, boron trifluoride ethyl dietherate (0.27 g, 0.24 mL, 0.002 mol) was added, and then the reaction was heated at 45 °C for 2 h. After cooling, the reaction was diluted chloroform and brine while shaking. The organic layer was separated, washed with saturated solution of sodium hydrogen carbonate and then with brine, and dried. The solvent was evaporated to give a residue which was purified on silica gel column chromatography (chloroform–ethanol 95:5) to give **25**, yield 72%, mp 133–134 °C (from cyclohexane). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.30 (t, *J* = 7.2 Hz, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 7.00–7.20 (m, 5H), 7.26–7.50 (m, 3H), 7.59 (m, 1H), 9.52 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1680, 3300 cm<sup>-1</sup>. Anal. (C<sub>17</sub>H<sub>15</sub>NO<sub>2</sub>S (297.08)) C, H, N, S. Thus, compounds **28**, **34**, **35**, **37**, and **38** were prepared.

**Methyl 5-chloro-3-[(3-methylphenyl)thio]-1H-indole-2-carboxylate (28)**, methyl 5-chloro-1H-indole-2-carboxylate was used, yield 80%, mp 179–180 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.20 (s, 3H), 3.38 (s, 3H), 6.80 (m, 1H), 6.90–7.10 (m, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.38–7.48 (m, 2H), 7.55 (dd, *J* = 1.2 and 8.3 Hz, 1H), 12.58 ppm (broad, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1660, 3370 cm<sup>-1</sup>. Anal. (C<sub>17</sub>H<sub>14</sub>ClNO<sub>2</sub>S (331.82)) C, H, N, S, Cl.

**Methyl 5-chloro-3-[(2,4-dimethylphenyl)thio]-1H-indole-2-carboxylate (34)**, methyl 5-chloro-1H-indole-2-carboxylate was used, yield 60%, mp 191–193 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.19 (s, 3H), 2.35 (s, 3H), 3.87 (s, 3H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.81 (m, 1H), 7.04 (m, 1H), 7.23 (d, *J* = 2.0 Hz, 1H), 7.31 (dd, *J* = 2.1 and 8.7 Hz, 1H), 7.53 (d, *J* = 8.7 Hz, 1H), 12.52 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1670 and 3270 cm<sup>-1</sup>. Anal. (C<sub>18</sub>H<sub>16</sub>-ClNO<sub>2</sub>S (345.84)) C, H, N, S, Cl.

**Methyl 5-chloro-3-[(3,5-dimethylphenyl)thio]-1H-indole-2-carboxylate (35)**, methyl 5-chloro-1H-indole-2-carboxylate was used, yield 77%, mp 174–175 °C (from cyclohexane). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.19 (s, 6H), 3.95 (s, 3H), 6.73–6.82 (m, 3H), 7.28–7.41 (m, 2H), 7.58 (m, 1H), 9.30 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1675, 3280 cm<sup>-1</sup>. IR (Nujol): ν 1670 and 3270 cm<sup>-1</sup>. Anal. (C<sub>18</sub>H<sub>16</sub>ClNO<sub>2</sub>S (345.84)) C, H, N, S, Cl.

**Ethyl 5-bromo-3-[(3,5-dimethylphenyl)thio]-1H-indole-2-carboxylate (37)**, ethyl 5-bromo-1H-indole-2-carboxylate was used, yield 93%, mp 162–165 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.25 (t, *J* = 7.1 Hz, 3H), 2.14 (s, 6H), 4.29 (q, *J* = 7.1 Hz, 2H), 6.72 (m, 2H), 6.76 (m, 1H), 7.43 (dd, *J* = 1.8 and 8.8 Hz, 1H), 7.51 and 7.53 (two d, *J* = 1.8 and 8.8 Hz, overlapped signals, 2H), 12.65 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1670, 3270 cm<sup>-1</sup>. Anal. (C<sub>19</sub>H<sub>18</sub>BrNO<sub>2</sub>S (404.32)) C, H, N, S, Br.

**Ethyl 5-acetyl-3-[(3,5-dimethylphenyl)thio]-1H-indole-2-carboxylate (38)**, ethyl 5-acetyl-1H-indole-2-carboxylate was used, yield 70%, mp 164–166 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.25 (t, *J* = 7.1 Hz, 3H), 2.14 (s, 6H), 2.48 (s, 3H), 4.35 (q, *J* = 7.1 Hz, 2H), 6.80 (m, 3H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.90 (m, 1H), 8.02 (m, 1H), 8.02 (m, 1H), 12.80 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1670, 3270 cm<sup>-1</sup>. Anal. (C<sub>21</sub>H<sub>21</sub>NO<sub>3</sub>S (367.46)) C, H, N, S.

**General Procedure for the Synthesis of the 3-Arylthio-1H-indole-2-carboxylates 26, 27, 29–33 and 36. Example. Methyl 5-chloro-3-(phenylthio)-1H-indole-2-carboxylate (26).** 5-Chloro-1H-indole-2-carboxylic acid (2.93 g, 0.015 mol) was added by portions to a mixture of sodium hydride (60% dispersion in mineral oil, 1.80 g, 0.045 mol) in anhydrous DMF (35 mL) under a nitrogen stream at 0 °C. After 15 min, 1,1'-diphenyl disulfide (4.37 g, 0.020 mol) was added portionwise, and then the reaction was heated at 50 °C overnight under a nitrogen atmosphere. After cooling, the mixture was poured on crushed ice, made acidic with 2 N HCl, and extracted with ethyl acetate. The organic layer was separated, washed with brine, and dried. Removal of the solvent gave a residue which was triturated with cyclohexane, filtered, and then crystallized by the same solvent to give satisfactory pure 5-chloro-3-(phenylthio)-1H-indole-2-carboxylic acid (2.27 g, 45%). The acid

was dissolved in dichloromethane (120 mL) and methanol (30 mL) and treated with trimethylsilyldiazomethane (10.5 mL of a 2 N solution in hexane, 0.015 mol) while stirring at room temperature for 90 min. After concentration to a small volume, the residue was extracted with ethyl acetate, washed with 0.1 N acetic acid and then with brine, and dried. Removal of the solvent gave the crude product which was purified by passing through a silica gel column chromatography to furnish **26**, 1.95 g, yield 91%, (overall yield 41%), mp 195–195 °C (from toluene/cyclohexane). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.93 (s, 3H), 7.03–7.12 (m, 5H), 7.30 (dd, *J* = 1.9 and 8.7 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.56 (m, 1H), 9.30 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1675, 3270 cm<sup>-1</sup>. Anal. (C<sub>16</sub>H<sub>12</sub>ClNO<sub>2</sub>S (317.78)) C, H, N, S, Cl. Thus, compounds **27**, **29–33**, and **36** were prepared.

**Methyl 5-chloro-3-[(2-methylphenyl)thio]-1H-indole-2-carboxylate (27)**, overall yield 47%, mp 188–190 °C (from toluene/cyclohexane). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.48 (s, 3H), 3.91 (s, 3H), 6.78 (dd, *J* = 1.2 and 7.8 Hz, 1H), 6.93 (m, 1H), 7.04 (dt, *J* = 1.3 and 7.1 Hz, 1H), 7.16 (d, *J* = 7.1 Hz, 1H), 7.29 (dd, *J* = 1.8 and 8.8 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 1.8 Hz, 1H), 9.26 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1670, 3300 cm<sup>-1</sup>. Anal. (C<sub>17</sub>H<sub>14</sub>ClNO<sub>2</sub>S (331.82)) C, H, N, S, Cl.

**Methyl 5-chloro-3-[(4-methylphenyl)thio]-1H-indole-2-carboxylate (29)**, overall yield 52%, mp 220–222 °C (from toluene). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.28 (s, 3H), 3.94 (s, 3H), 7.02 and 7.10 (two d, *J* = 8.3 Hz, 4H), 7.30 (dd, *J* = 1.8 and 8.8 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 9.21 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1680 and 3270 cm<sup>-1</sup>. Anal. (C<sub>17</sub>H<sub>14</sub>ClNO<sub>2</sub>S (331.82)) C, H, N, S, Cl.

**Methyl 5-chloro-3-[(4-fluorophenyl)thio]-1H-indole-2-carboxylate (30)**, overall yield 54%, mp 176–177 °C (from toluene/cyclohexane). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.96 (s, 3H), 6.84–6.98 (m, 2H), 7.12–7.42 (m, 4H), 7.56 (d, *J* = 1.6 Hz, 1H), 9.38 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1680, 3290 cm<sup>-1</sup>. Anal. (C<sub>16</sub>H<sub>11</sub>ClFNO<sub>2</sub>S (335.78)) C, H, N, S, Cl, F.

**Methyl 5-chloro-3-[(4-chlorophenyl)thio]-1H-indole-2-carboxylate (31)**, overall yield 60%, mp 203–204 °C (from toluene/cyclohexane). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 3.87 (s, 3H), 7.09 and 7.30 (two d, *J* = 8.5 Hz, 4H), 7.33–7.43 (m, 2H), 7.57 (d, *J* = 8.6 Hz, 1H), 12.77 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1675, 3270 cm<sup>-1</sup>. IR (Nujol): ν 1680, 3290 cm<sup>-1</sup>. Anal. (C<sub>16</sub>H<sub>11</sub>Cl<sub>2</sub>NO<sub>2</sub>S (352.23)) C, H, N, S, Cl.

**Methyl 5-chloro-3-[(4-isopropylphenyl)thio]-1H-indole-2-carboxylate (32)**, overall yield 41%, mp 172–173 °C (from cyclohexane). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.12 (d, *J* = 7.0 Hz, 6H), 2.83 (sp, *J* = 7.0 Hz, 1H), 3.93 (s, 3H), 7.06 and 7.13 (two d, *J* = 8.3 Hz, 4H), 7.28–7.38 (m, 2H), 7.51 (m, 1H), 9.23 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1680, and 3280 cm<sup>-1</sup>. Anal. (C<sub>19</sub>H<sub>18</sub>ClNO<sub>2</sub>S (359.87)) C, H, N, S, Cl.

**Methyl 5-chloro-3-[(4-tert-butylphenyl)thio]-1H-indole-2-carboxylate (33)**, overall yield 58%, mp 237–238 °C (from toluene/cyclohexane). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.26 (s, 9H), 3.93 (s, 3H), 7.22 and 7.13 (two d, *J* = 8.7 Hz, 4H), 7.27 (dd, *J* = 1.9 and 8.5 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 1.9 Hz, 1H), 9.21 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1675 and 3280 cm<sup>-1</sup>. Anal. (C<sub>20</sub>H<sub>20</sub>Cl<sub>2</sub>NO<sub>2</sub>S (373.89)) C, H, N, S, Cl.

**Methyl 5-chloro-3-[(2,6-dichlorophenyl)thio]-1H-indole-2-carboxylate (36)**, overall yield 55%, mp 241–243 °C (from toluene). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 3.89 (s, 3H), 6.92 (dd, *J* = 0.6 and 2.0 Hz, 1H), 7.26 (dd, *J* = 2.0 and 8.8 Hz, 1H), 7.40 (dd, *J* = 6.8 and 9.1 Hz, 1H), 7.48 (dd, *J* = 0.6 and 8.8 Hz, 1H), 7.52–7.60 (m, 2H), 12.43 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1680, 3280 cm<sup>-1</sup>. Anal. (C<sub>16</sub>H<sub>10</sub>Cl<sub>3</sub>NO<sub>2</sub>S (386.67)) C, H, N, S, Cl.

**General Procedure for Oxidation of the 3-Arylthio-1H-indole-2-carboxylates 25–38 to Sulfones 39–52. Example. Ethyl 3-(phenylsulfonyl)-1H-indole-2-carboxylate**

(39). 3-Chloroperoxybenzoic acid (1.32 g, 0.00766 mol) was added to an ice-cooled solution of ethyl 3-(phenylthio)-2-carboxylate (25) (0.78 g, 0.00264 mol) in chloroform (42 mL). Reaction was stirred at room temperature for 1.5 h, poured on crushed ice, and extracted with chloroform. The organic solution was shaken with saturated solution of sodium hydrogen carbonate and then with brine. After concentration to a small volume, the solution was passed through a silica gel column chromatography (ethyl acetate) to afford 39, yield 75%, mp 148–149 °C (from toluene/cyclohexane). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.30 (t, *J* = 7.0 Hz, 3H), 4.36 (q, *J* = 7.0 Hz, 2H), 7.28–7.47 (m, 2H), 7.52–7.70 (m, 4H), 7.95–8.07 (m, 2H), 8.24 (m, 1H), 13.03 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). Anal. (C<sub>17</sub>H<sub>15</sub>NO<sub>4</sub>S (329.37)) C, H, N, S. Thus, compounds 40–52 were prepared.

**Methyl 5-chloro-3-(phenylsulfonyl)-1*H*-indole-2-carboxylate (40)**, yield 48%, mp 254–255 °C (from toluene). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 3.88 (s, 3H), 7.44 (dd, *J* = 1.6 and 8.9 Hz, 1H), 7.53–7.71 (m, 4H), 7.97–8.07 (m, 2H), 8.26 (d, *J* = 1.6 Hz, 1H), 13.39 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1715, 3250 cm<sup>-1</sup>. Anal. (C<sub>16</sub>H<sub>12</sub>ClNO<sub>4</sub>S (349.78)) C, H, N, S, Cl.

**Methyl 5-chloro-3-[(2-methylphenyl)sulfonyl]-1*H*-indole-2-carboxylate (41)**, yield 33%, mp 275–276 °C (from toluene). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.30 (s, 3H), 3.78 (s, 3H), 7.35 (d, *J* = 6.9 Hz, 1H), 7.42–7.66 (m, 3H), 7.70 (d, *J* = 8.8 Hz, 1H), 8.17 (dd, 1H), 8.32 (m, 1H), 13.49 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1710, 3220 cm<sup>-1</sup>. Anal. (C<sub>17</sub>H<sub>14</sub>ClNO<sub>4</sub>S (363.81)) C, H, N, S, Cl.

**Methyl 5-chloro-3-[(3-methylphenyl)sulfonyl]-1*H*-indole-2-carboxylate (42)**, yield 81%, mp 181–182 °C (from toluene). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.38 (s, 3H), 3.88 (s, 3H), 7.08–7.30 (m, 1H), 7.40–7.55 (m, 2H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.91 (m, 2H), 8.26 (d, *J* = 1.8 Hz, 1H), 13.33 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1735, 3700 cm<sup>-1</sup>. Anal. (C<sub>17</sub>H<sub>14</sub>ClNO<sub>4</sub>S (363.81)) C, H, N, S, Cl.

**Methyl 5-chloro-3-[(4-methylphenyl)sulfonyl]-1*H*-indole-2-carboxylate (43)**, yield 50%, mp 229–231 °C (from toluene). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.36 (s, 3H), 3.91 (s, 3H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.45 (dd, *J* = 1.8 and 8.8 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 8.27 (d, *J* = 1.8 Hz, 1H), 13.4 ppm (very broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1715 and 3260 cm<sup>-1</sup>. Anal. (C<sub>17</sub>H<sub>14</sub>ClNO<sub>4</sub>S (363.81)) C, H, N, S, Cl.

**Methyl 5-chloro-3-[(4-fluorophenyl)sulfonyl]-1*H*-indole-2-carboxylate (44)**, yield 74%, mp 211–213 °C (from toluene). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 3.90 (s, 3H), 7.36–7.51 (m, 3H), 7.51 (d, *J* = 8.9 Hz, 1H), 8.03–8.16 (m, 2H), 8.26 (m, 1H), 13.44 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1735, 3390 cm<sup>-1</sup>. Anal. (C<sub>16</sub>H<sub>11</sub>ClFNO<sub>4</sub>S (367.77)) C, H, N, S, Cl, F.

**Methyl 5-chloro-3-[(4-chlororophenyl)sulfonyl]-1*H*-indole-2-carboxylate (45)**, yield 54%, mp 218–219 °C (from toluene/cyclohexane). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 3.90 (s, 3H), 7.46 (dd, *J* = 2.0 and 8.8 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 1H), 8.03 (d, *J* = 8.6 Hz, 2H), 8.26 (d, *J* = 2.0 Hz, 1H), 13.49 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). Anal. (C<sub>16</sub>H<sub>11</sub>Cl<sub>2</sub>NO<sub>4</sub>S (384.23)) C, H, N, S, Cl.

**Methyl 5-chloro-3-[(4-isopropylphenyl)sulfonyl]-1*H*-indole-2-carboxylate (46)**, yield 100%, mp 204–206 °C (from toluene). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.18 (d, *J* = 7.0 Hz, 6H), 2.94 (sp, *J* = 7.0 Hz, 1H), 3.90 (s, 3H), 7.40–7.52 (m, 3H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 2H), 8.23 (d, *J* = 1.4 Hz, 1H), 13.33 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1735 and 3240 cm<sup>-1</sup>. Anal. (C<sub>19</sub>H<sub>18</sub>ClNO<sub>4</sub>S (391.86)) C, H, N, S, Cl.

**Methyl 5-chloro-3-[(4-*tert*-butylphenyl)sulfonyl]-1*H*-indole-2-carboxylate (47)**, yield 96%, mp 240–241 °C (from toluene). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.26 (s, 9H), 3.91 (s, 3H), 7.43 (dd, *J* = 1.9 and 8.6 Hz, 1H), 7.54–7.67 (m, 3H), 7.96 (d, *J* = 8.5 Hz, 2H), 8.23 (d, *J* = 1.9 Hz, 1H), 13.28 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1740 and 3260 cm<sup>-1</sup>. Anal. (C<sub>20</sub>H<sub>20</sub>ClNO<sub>4</sub>S (405.89)) C, H, N, S, Cl.

**Methyl 5-chloro-3-[(2,4-dimethylphenyl)sulfonyl]-1*H*-indole-2-carboxylate (48)**, yield 58%, mp 241–242 °C (from toluene). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.22 (s, 3H), 2.33 (s, 3H), 3.75 (s, 3H), 7.11 (m, 1H), 7.28 (m, 1H), 7.45 (dd, *J* = 1.7 and 8.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 8.28 (d, *J* = 1.7 Hz, 1H), 13.36 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1700 and 3235 cm<sup>-1</sup>. Anal. (C<sub>18</sub>H<sub>16</sub>ClNO<sub>4</sub>S (377.84)) C, H, N, S, Cl.

**Methyl 5-chloro-3-[(3,5-dimethylphenyl)sulfonyl]-1*H*-indole-2-carboxylate (49)**, yield 74%, mp 234–236 °C (from toluene/cyclohexane). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.33 (s, 6H), 3.88 (s, 3H), 7.28 (m, 1H), 7.43 (dd, *J* = 2.0 and 8.6 Hz, 1H), 7.55–7.67 (m, 3H), 8.24 (d, *J* = 2.0 Hz, 1H), 13.33 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1740, 3200 cm<sup>-1</sup>. Anal. (C<sub>18</sub>H<sub>16</sub>ClNO<sub>4</sub>S (377.84)) C, H, N, S, Cl.

**Methyl 5-chloro-3-[(2,6-dichlorophenyl)sulfonyl]-1*H*-indole-2-carboxylate (50)**, yield 100%, mp 273–276 °C (from toluene). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 3.72 (s, 3H), 7.46 (dd, *J* = 2.1 and 8.9 Hz, 1H), 7.53–7.68 (m, 4H), 8.28 (m, 1H), 12.42 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1670, 3240 cm<sup>-1</sup>. Anal. (C<sub>16</sub>H<sub>10</sub>Cl<sub>2</sub>NO<sub>4</sub>S (418.67)) C, H, N, S, Cl.

**Ethyl 5-bromo-3-[(3,5-dimethylphenyl)sulfonyl]-1*H*-indole-2-carboxylate (51)**, yield 77%, mp >300 °C (from aqueous ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.28 (t, *J* = 7.1 Hz, 3H), 2.32 (s, 6H), 4.35 (q, *J* = 7.1 Hz, 2H), 7.28 (m, 1H), 7.55 (d, *J* = 1.2 Hz, 2H), 7.60 (m, 2H), 8.38 ppm (t, *J* = 1.2 Hz, 1H). IR (Nujol): ν 1690, 3260 cm<sup>-1</sup>. Anal. (C<sub>19</sub>H<sub>18</sub>BrNO<sub>4</sub>S (436.32)) C, H, N, S, Br.

**Ethyl 5-acetyl-3-[(3,5-dimethylphenyl)sulfonyl]-1*H*-indole-2-carboxylate (52)**, yield 62%, mp 193–195 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.31 (t, *J* = 7.1 Hz, 3H), 2.32 (s, 6H), 2.68 (s, 3H), 4.38 (q, *J* = 7.1 Hz, 2H), 7.28 (m, 1H), 7.60–7.71 (m, 3H), 8.01 (dd, *J* = 1.7 and 8.8 Hz, 1H), 8.89 (m, 1H), 12.7 ppm (very broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1665, 1700, 3280 cm<sup>-1</sup>. Anal. (C<sub>21</sub>H<sub>21</sub>NO<sub>5</sub>S (399.46)) C, H, N, S.

**General Procedure for the Synthesis of Amides 2, 53–64, and 70–84. Example. 3-(Phenylthio)-1*H*-indole-2-carboxamide (53).** Ethyl 3-(phenylthio)-1*H*-indole-2-carboxylate (25) (0.50 g, 0.0017 mol) was heated with 30% ammonium hydroxide (25 mL) and ammonium chloride (40 mg) in a sealed tube at 100 °C overnight. After cooling, the reaction mixture was poured on ice water, stirred for 15 min, and extracted with ethyl acetate. The organic layer was washed with brine and dried and the solvent evaporated to afford a residue which was purified on silica gel column chromatography (chloroform–ethanol 95:5) to give 53, yield 69%, mp 197 °C (from toluene). <sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>): δ 7.00–7.38 (m, 8H, 7H, after treatment with D<sub>2</sub>O), 7.51–7.73 (m, 2H), 8.02 (broad s, 1H, disappeared on treatment with D<sub>2</sub>O), 11.58 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1730, 3280, 3400 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>S (368.33)) C, H, N, S. Thus, compounds 2, 54–64 and 70–84 were prepared.

**3-[(2-Amino-5-chlorophenyl)thio]-1*H*-indole-2-carboxamide (54)**, yield 64%, mp 200–202 °C (from toluene/cyclohexane). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 5.63 (broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 6.65–6.78 (m, 2H), 6.94 (dd, *J* = 2.3 and 8.6 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.43–7.65 (m, 2H), 7.83 and 7.99 (two broad s, 2H, disappeared on treatment with D<sub>2</sub>O) 12.21 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1655, 3280, 3380 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>12</sub>ClN<sub>3</sub>O<sub>2</sub>S (317.79)) C, H, N, S.

**5-Chloro-3-(phenylthio)-1*H*-indole-2-carboxamide (55)**, yield 51%, mp 212–213 °C (from toluene/cyclohexane), lit.<sup>8</sup> mp 213–215 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 7.05–7.35 (m, 6H), 7.44 (d, *J* = 1.9 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.77 and 8.05 (two broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 12.53 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1635, 3120, 3385 cm<sup>-1</sup>.

**5-Chloro-3-[(2-methylphenyl)thio]-1*H*-indole-2-carboxamide (56)**, yield 94%, mp 222–224 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.47 (s, 3H), 6.47 (d, *J* = 7.8 Hz, 1H),

6.89–7.12 (m, 2H), 7.18–7.41 (m, 2H), 7.60 (d,  $J = 8.7$  Hz, 1H), 7.70 and 7.96 (two broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 8.79 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1645, 3260, 3300, 3420 cm<sup>-1</sup>. Anal. (C<sub>16</sub>H<sub>13</sub>ClN<sub>2</sub>OS (316.80)) C, H, N, S, Cl.

**5-Chloro-3-[(4-methylphenyl)thio]-1H-indole-2-carboxamide (57)**, yield 69%, mp 232–235 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  2.21 (s, 3H), 6.99 and 7.08 (two d,  $J = 8.4$  Hz, 4H), 7.30 (dd,  $J = 1.8$  and 8.7 Hz, 1H), 7.44 (d,  $J = 1.8$  Hz, 1H), 7.54 (d,  $J = 8.7$  Hz, 1H), 7.79 and 8.09 (two broad s, disappeared on treatment with D<sub>2</sub>O), 12.51 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1650, 3200, 3300, and 3440 cm<sup>-1</sup>. Anal. (C<sub>16</sub>H<sub>13</sub>ClN<sub>2</sub>OS (316.80)) C, H, N, S, Cl.

**5-Chloro-3-[(4-fluorophenyl)thio]-1H-indole-2-carboxamide (58)**, yield 52%, mp 210–212 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  7.12 (s, 2H), 7.16 (s, 2H), 7.31 (dd,  $J = 1.9$  and 8.6 Hz, 1H), 7.46 (d,  $J = 1.9$  Hz, 1H), 7.55 (d,  $J = 8.6$  Hz, 1H), 7.81 and 8.10 (two broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 12.55 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1675, 3120, 3360, and 3440 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>10</sub>ClFN<sub>2</sub>OS (320.76)) C, H, N, S, Cl, F.

**5-Chloro-3-[(4-chlorophenyl)thio]-1H-indole-2-carboxamide (59)**, yield 57%, mp 232–233 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  7.06 (d,  $J = 8.5$  Hz, 2H), 7.24–7.38 (m, 3H), 7.43 (m, 1H), 7.55 (d,  $J = 8.7$  Hz, 1H), 7.75 and 8.08 (two broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 12.58 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1660, 3200, 3320, and 3460 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>10</sub>Cl<sub>2</sub>N<sub>2</sub>OS (337.22)) C, H, N, S, Cl.

**5-Chloro-3-[(4-isopropylphenyl)thio]-1H-indole-2-carboxamide (60)**, yield 75%, mp 195 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.12 (d,  $J = 6.7$  Hz, 6H), 2.79 (sp,  $J = 6.7$  Hz, 1H), 7.02 and 7.14 (two d,  $J = 8.2$  Hz, 4H), 7.29 (dd,  $J = 1.6$  and 8.7 Hz, 1H), 7.46 (d,  $J = 1.6$  Hz, 1H), 7.55 (d,  $J = 8.7$  Hz, 1H), 7.79 and 8.02 (two broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 12.48 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1640, 3280, and 3370 cm<sup>-1</sup>. Anal. (C<sub>18</sub>H<sub>17</sub>ClN<sub>2</sub>OS (344.85)) C, H, N, S, Cl.

**5-Chloro-3-[(4-*tert*-butylphenyl)thio]-1H-indole-2-carboxamide (61)**, yield 100%, mp 234–235 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.20 (s, 9H), 7.01 (d,  $J = 8.5$  Hz, 2H), 7.22–7.34 (m, 3H), 7.47 (d,  $J = 1.9$  Hz, 1H), 7.55 (d,  $J = 8.7$  Hz, 1H), 7.78 and 8.00 (two broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 12.46 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1630–50, 3160, 3280, 3420 cm<sup>-1</sup>. Anal. (C<sub>19</sub>H<sub>19</sub>ClN<sub>2</sub>OS (358.82)) C, H, N, S, Cl.

**5-Chloro-3-[(3,5-dimethylphenyl)thio]-1H-indole-2-carboxamide (62)**, yield 91%, mp 201–203 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  2.14 (s, 6H), 6.69 (m, 2H), 6.79 (m, 1H), 7.30 (dd,  $J = 1.6$  and 8.6 Hz, 1H), 7.44 (d,  $J = 1.6$  Hz, 1H), 7.55 (d,  $J = 8.6$  Hz, 1H), 7.73 and 8.01 (two broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 12.46 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1650, 3260, and 3440 cm<sup>-1</sup>. Anal. (C<sub>17</sub>H<sub>15</sub>ClN<sub>2</sub>OS (330.83)) C, H, N, S, Cl.

**5-Chloro-3-[(2,6-dichlorophenyl)thio]-1H-indole-2-carboxamide (63)**, yield 97%, mp 242–245 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  7.12 (dd,  $J = 0.6$  and 2.0 Hz, 1H), 7.20 (dd,  $J = 2.0$  and 8.7 Hz, 1H), 7.38 (dd,  $J = 7.0$  and 8.9 Hz, 1H), 7.46 (dd,  $J = 0.6$  and 8.7 Hz, 1H), 7.52–7.59 (two d,  $J = 7.0$  and 8.9 Hz, 2H), 7.74 and 8.03 (two broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 12.25 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1630, 3180, and 3380 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>9</sub>Cl<sub>3</sub>N<sub>2</sub>OS (371.66)) C, H, N, S, Cl.

**5-Chloro-3-[(2-amino-5-chlorophenyl)thio]-1H-indole-2-carboxamide (64)**, yield 85%, mp 233–235 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  5.70 (broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 6.71 (d,  $J = 8.6$  Hz, 1H), 6.76 (d,  $J = 2.4$  Hz, 1H), 6.97 (dd,  $J = 2.4$  and 8.6 Hz, 1H), 7.29 (dd,  $J = 1.9$  and 8.7 Hz, 1H), 7.52 (d,  $J = 8.7$  Hz, 1H), 7.56 (d,  $J = 1.9$  Hz, 1H), 7.88 and 8.10 (two broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 12.40 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1670, 3100, 3310, 3370, and 3420 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>11</sub>Cl<sub>2</sub>N<sub>3</sub>OS (352.24)) C, H, N, S, Cl.

**3-(Phenylsulfonyl)-1H-indole-2-carboxamide (70)**, yield 40%, mp 226–227 °C (from ethanol). <sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>):  $\delta$  7.24–7.72 (m, 8H, 7H, 6H, after treatment with D<sub>2</sub>O), 7.96–8.12 (m, 2H), 8.24 (m, 1H), 9.11 (broad s, 1H, disappeared on treatment with D<sub>2</sub>O), 11.88 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1660, 3170, 3270, 3370 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>S (300.05)) C, H, N, S.

**3-[(2-Amino-5-chlorophenyl)sulfonyl]-1H-indole-2-carboxamide (71)**, yield 40%, mp 238–239 °C (from aqueous ethanol). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  4.99 (broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 6.12 (broad s, 1H, disappeared on treatment with D<sub>2</sub>O), 6.58 (d,  $J = 8.8$  Hz, 1H), 7.15–7.55 (m, 4H), 7.76 (d,  $J = 2.3$  Hz, 1H), 8.02 (d,  $J = 7.9$  Hz, 1H), 9.15 (broad s, 1H, disappeared on treatment with D<sub>2</sub>O), 10.19 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1645, 3225, and 3380 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>12</sub>ClN<sub>3</sub>O<sub>3</sub>S (349.79)) C, H, N, S, Cl.

**5-Chloro-3-[(2-methylphenyl)sulfonyl]-1H-indole-2-carboxamide (72)**, yield 82%, mp 260–261 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  2.39 (s, 3H), 7.27–7.64 (m, 5H), 7.81 (d,  $J = 1.7$  Hz, 1H), 8.03 (dd,  $J = 1.1$  and 7.9 Hz, 1H), 8.23 and 8.29 (two partially overlapped broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 13.11 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1670, 3290, 3220, 3410 cm<sup>-1</sup>. Anal. (C<sub>16</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>3</sub>S (348.80)) C, H, N, S, Cl.

**5-Chloro-3-[(3-methylphenyl)sulfonyl]-1H-indole-2-carboxamide (73)**, yield 87%, mp 265–268 °C (from aqueous ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  2.36 (s, 3H), 7.34 (m, 1H), 7.40–7.58 (m, 3H), 7.77–7.88 (m, 2H), 7.95 (m, 1H), 8.24 and 8.47 (two broad s, 1H, disappeared on treatment with D<sub>2</sub>O), 13.02 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1650, 3180, 3380 cm<sup>-1</sup>. Anal. (C<sub>16</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>3</sub>S (348.80)) C, H, N, S, Cl.

**5-Chloro-3-[(4-methylphenyl)sulfonyl]-1H-indole-2-carboxamide (74)**, yield 90%, mp >300 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  2.33 (s, 3H), 7.28–7.46 (m, 3H), 7.54 (d,  $J = 8.7$  Hz, 1H), 7.86–7.99 (m, 3H), 8.27 and 8.51 (two broad s, disappeared on treatment with D<sub>2</sub>O), 13.08 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1660, 3200, and 3380 cm<sup>-1</sup>. Anal. (C<sub>16</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>3</sub>S (348.80)) C, H, N, S, Cl.

**5-Chloro-3-[(4-fluorophenyl)sulfonyl]-1H-indole-2-carboxamide (75)**, yield 94%, mp 229–230 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  7.29–7.58 (m, 4H), 7.95 (m, 1H), 8.07–8.21 (m, 2H), 8.24 and 8.47 (two broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 13.11 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1650, 3150, 3230 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>10</sub>ClFN<sub>2</sub>O<sub>3</sub>S (352.76)) C, H, N, S, Cl, F.

**5-Chloro-3-[(4-chlorophenyl)sulfonyl]-1H-indole-2-carboxamide (76)**, yield 90%, mp >300 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  7.36 (m, 1H), 7.55 (d,  $J = 8.6$  Hz, 1H), 7.68 (d,  $J = 8.2$  Hz, 2H), 7.94 (m, 1H), 8.07 (d,  $J = 8.2$  Hz, 2H), 8.23 and 8.45 (two broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 13.15 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1650, 3150, 3230, and 3440 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>10</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub>S (369.22)) C, H, N, S, Cl.

**5-Chloro-3-[(4-isopropylphenyl)sulfonyl]-1H-indole-2-carboxamide (77)**, yield 79%, mp 272–275 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.15 (d,  $J = 6.8$  Hz, 6H), 2.92 (sp,  $J = 6.8$  Hz, 1H), 7.35 (dd,  $J = 1.9$  and 8.6 Hz, 1H), 7.46 (d,  $J = 8.4$  Hz, 2H), 7.55 (d,  $J = 8.6$  Hz, 1H), 7.90 and 8.02 (m, 3H), 8.24 and 8.50 (two broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 13.03 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1660, 3140, and 3380 cm<sup>-1</sup>. Anal. (C<sub>18</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>3</sub>S (376.66)) C, H, N, S, Cl.

**5-Chloro-3-[(4-*tert*-butylphenyl)sulfonyl]-1H-indole-2-carboxamide (78)**, yield 100%, mp 276–277 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.25 (s, 9H), 7.44 (dd,  $J = 1.9$  and 8.7 Hz, 1H), 7.54 (d,  $J = 8.7$  Hz, 1H), 7.61 and 7.94 (two d,  $J = 8.6$  Hz, 4H), 7.98 (d,  $J = 1.9$  Hz, 1H), 8.22 and 8.48 (two broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 12.99 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1660, 3180, 3280, and 3430 cm<sup>-1</sup>. Anal. (C<sub>19</sub>H<sub>19</sub>ClN<sub>2</sub>O<sub>3</sub>S (390.88)) C, H, N, S, Cl.

**5-Chloro-3-[(2,4-dimethylphenyl)sulfonyl]-1H-indole-2-carboxamide (79)**, yield 89%, mp 217–220 °C (from aqueous ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.32 (s, 6H), 7.16 (s, 1H), 7.22–7.40 (m, 2H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.80 (s, 1H), 9.94 (d, *J* = 8.1 Hz, 1H), 8.26 and 8.32 (two broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 13.07 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1660, 3180, 3280 and 3420 cm<sup>-1</sup>. Anal. (C<sub>17</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>3</sub>S (362.83)) C, H, N, S, Cl.

**5-Chloro-3-[(3,5-dimethylphenyl)sulfonyl]-1H-indole-2-carboxamide (80)**, yield 85%, mp 274–277 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.31 (s, 6H), 7.26 (m, 1H), 7.34 (dd, *J* = 1.6 and 8.7 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.63 (m, 2H), 7.96 (d, *J* = 1.6 Hz, 1H), 8.21 and 8.46 (two broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 13.02 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1680, 3220, and 3340 cm<sup>-1</sup>. Anal. (C<sub>17</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>3</sub>S (362.83)) C, H, N, S, Cl.

**5-Chloro-3-[(2,6-dichlorophenyl)sulfonyl]-1H-indole-2-carboxamide (81)**, yield 100%, mp 288–290 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 7.37 (dd, *J* = 2.1 and 8.8 Hz, 1H), 7.54–7.66 (m, 4H), 7.94 (dd, *J* = 0.4 and 2.1 Hz, 1H), 8.14 (broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 13.16 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1670, 3160, 3300, and 3440 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>9</sub>Cl<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S (403.66)) C, H, N, S, Cl.

**5-Chloro-3-[(2-amino-5-chlorophenyl)sulfonyl]-1H-indole-2-carboxamide (82)**, yield 87%, mp 225–227 °C (from aqueous ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 6.54 (broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 6.73 (d, *J* = 8.9 Hz, 1H), 7.20–7.39 (m, 2H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.64 (m, 1H), 7.80 (d, *J* = 2.3 Hz, 1H), 8.27 and 8.48 (two broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 13.00 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1660, 3280, 3360, cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>11</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>3</sub>S (384.24)) C, H, N, S, Cl.

**5-Bromo-3-[(3,5-dimethylphenyl)sulfonyl]-1H-indole-2-carboxamide (83)**, yield 42%, mp > 300 °C (from aqueous DMF). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.31 (s, 6H), 7.26 (m, 1H), 7.46 (m, 2H), 7.62 (m, 2H), 8.10 (m, 1H), 8.31 and 8.46 (two broad s, 1H, disappeared on treatment with D<sub>2</sub>O), 13.05 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1680, 3210, 3360 cm<sup>-1</sup>. Anal. (C<sub>17</sub>H<sub>13</sub>BrN<sub>2</sub>O<sub>3</sub>S (407.28)) C, H, N, S, Br.

**5-Acetyl-3-[(3,5-dimethylphenyl)sulfonyl]-1H-indole-2-carboxamide (84)**, yield 54%, mp > 300 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.30 (s, 6H), 2.64 (s, 3H), 7.26 (m, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.49 (m, 2H), 7.91 (dd, *J* = 1.7 and 8.7 Hz, 1H), 8.31 and 8.50 (two broad s, 1H, disappeared on treatment with D<sub>2</sub>O), 8.60 (d, *J* = 1.7 Hz, 1H), 13.1 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1670, 3150, 3250, 3350 cm<sup>-1</sup>. Anal. (C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>S (370.42)) C, H, N, S.

**5-Chloro-3-(phenylsulfonyl)-1H-indole-2-carboxamide (2)**, yield 65%, mp 254–255 °C (from toluene), lit.<sup>8</sup> mp 255–257 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 7.35 (m, 1H), 7.48–7.62 (m, 4H), 7.94–8.12 (m, 3H), 8.25 and 8.49 (two broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 12.80 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1660, 3220, 3380 cm<sup>-1</sup>.

**General Procedure for the Synthesis of Hydrazides 65–69 and 86–92. Example. 5-Chloro-3-(phenylthio)-1H-indole-2-carboxamide (65).** A mixture of methyl 5-chloro-3-(phenylthio)-1H-indole-2-carboxylate (**26**) (0.54 g, 0.0017 mol), hydrazine hydrate (4 mL), and ethanol (4 mL) was heated at 60 °C for 1.5 h. After quenching on crushed ice, the solid which formed was filtered, washed with water, and dried to afford **65**, yield 80%, mp 231 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 4.73 (broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 6.98–7.34 (m, 6H), 7.39 (m, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 4.38 (broad s, 1H, disappeared on treatment with D<sub>2</sub>O), 12.55 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1630, 3210 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>12</sub>ClN<sub>3</sub>O<sub>3</sub>S (317.79)) C, H, N, S, Cl. Thus, compounds **66–69** and **86–92** were prepared.

**5-Chloro-3-[(4-methylphenyl)thio]-1H-indole-2-carboxamide (66)**, yield 90%, mp 249–250 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.21 (s, 3H), 4.74 (broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 6.96 and 7.07 (two d, *J* = 8.2 Hz, 4H), 7.28 (dd, 1H, *J* = 1.9 and 8.2 Hz), 7.39 (d, *J* = 1.9 Hz, 1H), 7.53 (d, *J* = 8.7 Hz, 1H), 4.37 (broad s, 1H, disappeared on treatment with D<sub>2</sub>O), 12.52 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1630, 3300 and 3380 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>14</sub>ClN<sub>3</sub>O<sub>3</sub>S (331.81)) C, H, N, S, Cl.

**5-Chloro-3-[(4-fluorophenyl)thio]-1H-indole-2-carboxamide (67)**, yield 90%, mp 235–236 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 4.74 (broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 7.10 (s, 2H), 7.13 (s, 2H), 7.28 (dd, *J* = 2.0 and 8.7 Hz, 1H), 7.41 (d, *J* = 2.0 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 9.43 (broad s, 1H, disappeared on treatment with D<sub>2</sub>O), 12.55 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1635, 3240 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>11</sub>ClF<sub>2</sub>N<sub>3</sub>O<sub>3</sub>S (335.78)) C, H, N, S, Cl, F.

**5-Chloro-3-[(4-chlorophenyl)thio]-1H-indole-2-carboxamide (68)**, yield 100%, mp 247–248 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 4.74 (broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 7.03 (d, *J* = 8.5 Hz, 2H), 7.25–7.36 (m, 3H), 7.39 (m, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 9.42 (broad s, 1H, disappeared on treatment with D<sub>2</sub>O), 12.60 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1630, 3240 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>11</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>3</sub>S (352.23)) C, H, N, S, Cl.

**5-Chloro-3-[(2-amino-5-chlorophenyl)thio]-1H-indole-2-carboxamide (69)**, yield 87%, mp 265–268 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 4.78 (broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 5.74 (broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 6.71 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 2.2 Hz, 1H), 6.97 (dd, *J* = 2.2 and 8.4 Hz, 1H), 7.27 (dd, *J* = 1.9 and 8.7 Hz, 1H), 7.45–7.56 (m, 2H), 9.57 (broad s, 1H, disappeared on treatment with D<sub>2</sub>O), 12.38 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1630, 3250, 3300, 3420 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>12</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>3</sub>S (367.25)) C, H, N, S, Cl.

**3-(Phenylsulfonyl)-1H-indole-2-carboxamide (86)**, yield 100%, mp 225–227 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 4.79 (broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 7.18–7.38 (m, 2H), 7.43–7.69 (m, 4H), 7.70–8.12 (m, 3H), 10.06 (broad s, 1H, disappeared on treatment with D<sub>2</sub>O), 12.81 ppm (s, 1H). Anal. (C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>S (301.34)) C, H, N, S.

**5-Chloro-3-(phenylsulfonyl)-1H-indole-2-carboxamide (87)**, yield 100%, mp > 300 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 4.77 (broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 7.34 (m, 1H), 7.50–7.67 (m, 4H), 7.93 (m, 1H), 8.02–8.14 (m, 2H), 10.11 (broad s, 1H, disappeared on treatment with D<sub>2</sub>O), 13.29 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1635, 3180, 3280 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>12</sub>ClN<sub>3</sub>O<sub>3</sub>S (349.79)) C, H, N, S, Cl.

**5-Chloro-3-[(4-methylphenyl)sulfonyl]-1H-indole-2-carboxamide (88)**, yield 100%, mp > 300 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.34 (s, 3H), 4.81 (broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 7.30–7.43 (m, 3H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.78–8.02 (m, 3H), 10.08 (broad s, 1H, disappeared on treatment with D<sub>2</sub>O), 13.07 ppm (very broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1640, 3310 and 3390 cm<sup>-1</sup>. Anal. (C<sub>16</sub>H<sub>14</sub>ClN<sub>3</sub>O<sub>3</sub>S (363.81)) C, H, N, S, Cl.

**5-Chloro-3-[(4-fluorophenyl)sulfonyl]-1H-indole-2-carboxamide (89)**, yield 90%, mp 252–253 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 4.81 (broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 7.28–7.58 (m, 4H), 7.94 (m, 1H), 8.12–8.24 (m, 2H), 10.10 (broad s, 1H, disappeared on treatment with D<sub>2</sub>O), 13.13 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol): ν 1640, 3190, 3280 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>11</sub>ClF<sub>2</sub>N<sub>3</sub>O<sub>3</sub>S (367.78)) C, H, N, S, Cl, F.

**5-Chloro-3-[(4-chlorophenyl)sulfonyl]-1H-indole-2-carboxamide (90)**, yield 100%, mp 247–248 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 4.80 (broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 7.35 (dd, *J* = 1.6 and 8.7 Hz, 1H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.93 (d, *J* = 1.6 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 2H), 10.07 (broad s, 1H,

disappeared on treatment with D<sub>2</sub>O) 13.15 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1640, 3180, 3300 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>11</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>3</sub>S (384.23)) C, H, N, S, Cl.

**5-Chloro-3-[(3,5-dimethylphenyl)sulfonyl]-1H-indole-2-carboxyhydrazide (91)**, yield 82%, mp >300 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  2.27 (s, 6H), 4.80 (very broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 7.20 (s, 1H), 7.28 (dd, *J* = 2.0 and 8.7 Hz, 1H), 7.48 (d, *J* = 8.7 Hz, 1H), 7.65 (s, 2H), 7.89 (d, *J* = 2.0 Hz, 1H), 10.05 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). Anal. (C<sub>17</sub>H<sub>16</sub>ClN<sub>3</sub>O<sub>3</sub>S (377.84)) C, H, N, S, Cl.

**5-Chloro-3-[(2-amino-5-chlorophenyl)sulfonyl]-1H-indole-2-carboxyhydrazide (92)**, yield 92%, mp 218–220 °C (from aqueous ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  4.82 (broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 6.63 (broad s, 2H, disappeared on treatment with D<sub>2</sub>O), 6.74 (d, *J* = 8.9 Hz, 1H), 7.23–7.38 (m, 2H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.61 (d, *J* = 1.6 Hz, 1H), 7.84 (d, *J* = 2.4 Hz, 1H), 10.20 (broad s, 1H, disappeared on treatment with D<sub>2</sub>O), 13.04 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1640, 3300, 3450 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>12</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>3</sub>S (399.35)) C, H, N, S, Cl.

**5-(1-Hydroxyethyl)-3-(3,5-dimethylphenylsulfonyl)-1H-indole-2-carboxamide (85)** Sodium borohydride (0.03 g, 0.0008 mol) was added to a mixture of 5-acetyl-3-(3,5-dimethylphenylsulfonyl)-1H-indole-2-carboxamide (**84**) (0.30 g, 0.0008 mol) in THF (8.5 mL) containing 0.1 mL of water, and then the reaction was refluxed for 1 h. After cooling, water was added while stirring for a few minutes, and then the mixture was extracted with ethyl acetate. The organic extracts were washed with brine, dried, and evaporated to dryness to give **85**, yield 83%, mp 260–262 °C (from ethanol). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.36 (d, *J* = 6.4 Hz, 3H), 4.80 (m, 1H, showed q, *J* = 6.4 Hz after treatment with D<sub>2</sub>O), 5.21 (d, *J* = 4.1 Hz, disappeared on treatment with D<sub>2</sub>O), 7.19 (m, 1H), 7.25 (dd, *J* = 1.5 and 8.7 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.54 (m, 2H), 7.91 (m, 1H), 8.16 and 8.54 (two broad s, 1H, disappeared on treatment with D<sub>2</sub>O), 12.7 ppm (broad s, 1H, disappeared on treatment with D<sub>2</sub>O). IR (Nujol):  $\nu$  1660, 3160, 3250, 3350, 3530 cm<sup>-1</sup>. Anal. (C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub>S (372.43)) C, H, N, S.

**N-(3,5-Dimethylphenylthio)succinimide.** 3,5-Dimethylthiophenol (2.76 g, 0.02 mol) was added by a syringe to an ice-cooled mixture of *N*-chlorosuccinimide (3.34 g, 0.025 mol) and anhydrous dichloromethane (30 mL) under argon atmosphere. After 1 h, *N*-chlorosuccinimide (0.4 g, 0.003 mol) was added, and then the reaction was stirred for 2.5 h. Triethylamine (3.9 mL, 0.028 mol) was added while stirring for 15 min, and then dichloromethane and 1 N HCl were added. After shaking, the organic layer was dried, concentrated to a small volume, and passed through a Celite column. After evaporation of the solvent, the residue was triturated with diethyl ether to give 3.0 g (64%) of title compound, mp 131–134 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.29 (s, 6H), 2.83 (s, 4H), 6.98 (s, 1H), 7.25 ppm (s, 2H).

**N-(3-Methylphenylthio)succinimide** was prepared as *N*-(3,5-dimethylphenylthio)succinimide by using 3-methylthiophenol, yield 48%, mp 98–100 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.29 (s, 6H), 2.83 (s, 4H), 6.98 (s, 1H), 7.25 ppm (s, 3H).

**Antiviral Assay Procedures. Compounds.** Compounds were solubilized in DMSO at 200 mM and then diluted in culture medium.

**Cells and Viruses.** MT-4, C8166, and H9/IIIB cells were grown at 37 °C in a 5% CO<sub>2</sub> atmosphere in RPMI 1640 medium and supplemented with 10% fetal calf serum (FCS), 100 IU/mL penicillin G, and 100 μg/mL streptomycin. Cell cultures were checked periodically for the absence of mycoplasma contamination with a MycoTect Kit (Gibco). Human immunodeficiency viruses type-1 (HIV-1, IIIB strain) was obtained from supernatants of persistently infected H9/IIIB cells. The HIV-1 stock solutions had titers of 4.5 × 10<sup>6</sup> 50% cell culture infectious dose (CCID<sub>50</sub>)/mL. The K103R-V179D-P225H mutant was derived from an IIIB strain passaged in C8166 cells in the presence of Efavirenz (up to 2 μM). The Y181C mutant (NIH N119) derives from an AZT-sensitive clinical isolate passaged initially in CEM, and then in MT-4 cells, in the

presence of nevirapine (10 μM). The K103N-Y181C (NIH A17) derives from the IIIB strain passaged in H9 cells in the presence of BI-RG 587 (1 μM). K103R-V179D-P225H, Y181C and K103N-Y181C stock solutions had titers of 3.0 × 10<sup>5</sup> CCID<sub>50</sub>/mL, 1.3 × 10<sup>6</sup> CCID<sub>50</sub>/mL and 2.5 × 10<sup>5</sup> CCID<sub>50</sub>/mL, respectively.

**HIV Titration.** Titration of HIV was performed in C8166 cells by the standard limiting dilution method (dilution 1:2, four replica wells per dilution) in 96-well plates. The infectious virus titer was determined by light microscope scoring of syncytia after 4 days of incubation. Virus titers were expressed as CCID<sub>50</sub>/mL.

**Anti-HIV Assays.** The activity of test compounds against multiplication of wt HIV-1, Y181C, and K103N-Y181C in acutely infected cells was based on inhibition of virus-induced cytopathicity in MT-4 cells. The activity of the compounds against the K103R multiplication in acutely infected cells was based on inhibition of p24 antigen in C8166 cells. Briefly, 50 μL of culture medium containing 1 × 10<sup>4</sup> cells were added to each well of flat-bottom microtiter trays containing 50 μL of culture medium with or without various concentrations of test compounds. Then 20 μL of HIV suspensions (containing the appropriate amount of CCID<sub>50</sub> to cause complete cytopathicity at day 4) were added. After incubation at 37 °C, cell viability was determined by the 3-(4,5-dimethylthiazol-1-yl)-2,5-diphenyltetrazolium bromide (MTT) method.<sup>15</sup> Alternatively, p24 levels were determined by an immunoenzymatic kit (Abbott). The cytotoxicity of test compounds was evaluated in parallel with their antiviral activity and was based on the viability of mock-infected cells, as monitored by the MTT method.

**RT Assays.** Assays were performed as previously described.<sup>16</sup> Briefly, purified rRTs were assayed for their RNA-dependent DNA polymerase activity in a 50 μL volume containing 50 mM Tris-HCl (pH 7.8), 80 mM KCl, 6mM MgCl<sub>2</sub>, 1 mM DTT, 0.1 mg mL<sup>-1</sup> BSA, 0.5 OD<sub>260</sub> unit mL<sup>-1</sup> template: primer [poly(rC)-oligo(dG)<sub>12–18</sub>], and 10 mM [<sup>3</sup>H]dGTP (1 Ci mmol<sup>-1</sup>). After incubation for 30 min at 37 °C, the samples were spotted on glass fiber filters (Whatman GF/A), and the acid-insoluble radioactivity was determined.

**Statistical Analysis.** Means ± SE for triplicate (cell-based assays) or duplicate (enzyme assays) determinations are reported. The statistical significance of differences was determined by a nonparametric Mann–Whitney test. *P* < 0.05 was the criterion for significance.

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