ROCK2 INHIBITORS AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Applications, U.S.S.N. 63/225,695, filed July 26, 2021; and U.S.S.N. 63/346,144, filed May 26, 2022, each of which is incorporated herein by reference in its entirety.

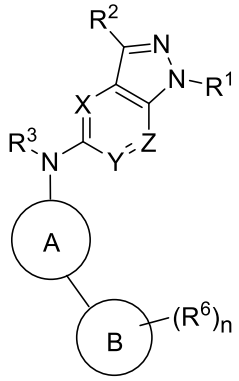
BACKGROUND

[0002] Rho-Kinase (ROCK) is a coiled-coil forming serine-threonine protein kinase family and exists in two isoforms, ROCK1 and ROCK2. ROCK has been identified as an effector molecule of RhoA, a small GTP-binding protein (G protein). Both proteins are ubiquitously expressed across tissues and play key roles in multiple cellular signalling pathways. Upon receptor activation RhoA activates ROCK that in turn controls several cellular functions including cell migration, cell adhesion, actin reorganisation, cytokinesis, and smooth muscle contraction. Accordingly, ROCK inhibitors have potential therapeutic applicability in a wide variety of pathological conditions.

SUMMARY OF THE DISCLOSURE

[0003] The present disclosure stems from the recognition that the unique structure and function of ROCK provides an opportunity for the design of ROCK2 inhibitors (*e.g.*, selective ROCK2 inhibitors) useful in the treatment of a wide variety of diseases. For example, ROCK is a critical mediator of both biomechanical (tissue stiffness) and biochemical (TGF-β mediated) pathways involved in the dysregulated activation of myofibroblasts, the cells thought to underlie the pathogenesis of fibrotic disease. Aberrant expression and activation of ROCK results in the sustained presence of activated myofibroblasts and excessive extracelluar matrix production, leading to tissue fibrosis. Recent studies show that selective inhibition of ROCK2 results in the inhibition of the production of pathogenic cytokine IL-17 in immune cells. As a result, selective inhibitors of ROCK2 may be effective in the treatment of fibrotic disease, among others. Thus, the disclosed compounds provide new compositions and methods for the treatment of diseases and disorders associated with ROCK2 (*e.g.*, associated with increased ROCK2 activity) (*e.g.*, fibrotic disorder, autoimmune disease, inflammatory condition, edema, ophthalmic disease, cardiovascular disease, central nervous system disorder, cancer).

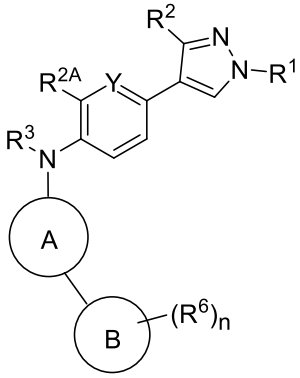
[0004] In one example, provided are compounds of Formula (**I**):



(**I**),

and pharmaceutically acceptable salts, co-crystals, tautomers, stereoisomers, solvates, hydrates, polymorphs, isotopically enriched compounds, and prodrugs thereof, wherein the moieties and variables included in Formula (**I**) are as described herein.

[0005] In another example, provided are compounds of Formula (**II**):



(**II**),

and pharmaceutically acceptable salts, co-crystals, tautomers, stereoisomers, solvates, hydrates, polymorphs, isotopically enriched compounds, and prodrugs thereof, wherein the moieties and variables included in Formula (**II**) are as described herein.

[0006] In another example, provided are pharmaceutical compositions comprising a provided compound and optionally a pharmaceutically acceptable excipient.

[0007] In another example, provided are methods of treating a disease or disorder associated with ROCK2 in a subject in need thereof, the method comprising administering to the subject an effective amount of a provided compound or pharmaceutical composition.

[0008] In another example, provided are methods of preventing a disease or disorder associated with ROCK2 in a subject in need thereof, the method comprising administering to the subject an effective amount of a provided compound or pharmaceutical composition.

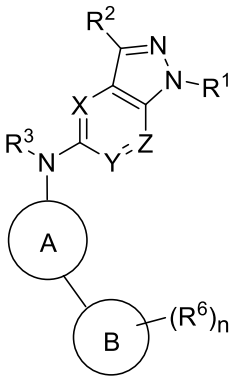
[0009] In certain examples, the disease or disorder associated with ROCK2 is edema (*e.g.*, lymphedema).

[0010] In another example, provided are methods of inhibiting the activity of ROCK2, the method comprising contacting ROCK2 with an effective amount of a provided compound or pharmaceutical composition.

[0011] In another example, the present disclosure provides methods of screening a library of compounds comprising performing an assay on a provided compound and an additional compound, wherein the additional compound is different from the provided compound.

[0012] In another example, provided are kits comprising a provided compound or pharmaceutical composition and instructions for using the provided compound or pharmaceutical composition.

[0012a] In one aspect, the disclosure provides a compound of Formula (**I**):



(**I**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof,

wherein:

R^1 is hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group;

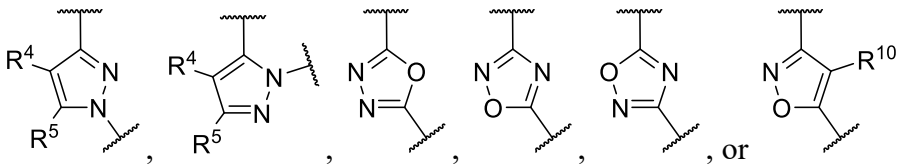
R^2 is hydrogen, halogen, -CN, substituted or unsubstituted alkyl, or substituted or unsubstituted carbocyclyl;

X is CR^7 or N;

Y is CR^8 or N;

Z is CR^9 or N;

R^3 is hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group;

A is , or ;

R^4 is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^5 is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or R^4 and R^5 together with the atoms to which they are attached form substituted or unsubstituted carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heteroaryl;

B is aryl or heteroaryl;

each R^6 is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroaliphatic, oxo, $–OR^A$, $–N_3$, $–N(R^A)_2$, $–SR^A$, –CN, –SCN, $–C(=NR^A)R^A$, $–C(=NR^A)OR^A$, $–C(=NR^A)N(R^A)_2$, $–C(=O)R^A$, $–C(=O)OR^A$, $–C(=O)N(R^A)_2$, $–NO_2$, $–NR^AC(=O)R^A$, $–NR^AC(=O)OR^A$, $–NR^AC(=O)N(R^A)_2$, $–NR^AC(=NR^A)N(R^A)_2$, $–OC(=O)R^A$, $–OC(=O)OR^A$, $–OC(=O)N(R^A)_2$, $–NR^AS(O)_2R^A$, $-OS(O)_2R^A$, or $-S(O)_2R^A$;

n is 1, 2, 3, 4, or 5;

each of R^7, R^8, and R^9 is independently hydrogen, halogen, -CN, or substituted or unsubstituted alkyl;

R^{10} is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

each occurrence of R^A is, independently, hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroaliphatic, substituted or unsubstituted carbocyclyl, substituted or unsubstituted carbocyclylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted hetaralkyl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two R^A groups are joined to form a substituted or unsubstituted heterocyclyl ring or a substituted or unsubstituted heteroaryl ring.

[0012b] In another aspect, the disclosure provides a pharmaceutical composition comprising a compound of the disclosure, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, and a pharmaceutically acceptable excipient.

[0012c] In yet another aspect, the disclosure provides use of a compound of the disclosure, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, or a pharmaceutical composition of the disclosure, in the manufacture of a medicament for treating a disease or disorder associated with ROCK2 in a subject in need thereof, wherein the disease or disorder associated with ROCK2 is a fibrotic disorder, autoimmune disease, inflammatory condition, edema, ophthalmic disease, cardiovascular disease, central nervous system disorder, or cancer.

[0012d] In yet another aspect, the disclosure provides use of a compound of the disclosure, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, or a pharmaceutical composition of the disclosure, in the manufacture of a medicament for preventing a disease or disorder associated with ROCK2 in a subject in need thereof, wherein the disease or disorder associated with ROCK2 is a fibrotic disorder, autoimmune disease, inflammatory condition, edema, ophthalmic disease, cardiovascular disease, central nervous system disorder, or cancer.

[0012e] In yet another aspect, the disclosure provides a compound of the disclosure, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, or a pharmaceutical composition of the disclosure, for use as a medicament.

[0012f] In yet another aspect, the disclosure provides an *in vitro* or *ex-vivo* method of inhibiting ROCK2 comprising contacting ROCK2 with an effective amount of a compound of the disclosure or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, or a pharmaceutical composition of the disclosure.

[0012g] In yet another aspect, the disclosure provides a method of screening a library of compounds comprising performing an assay on a compound of the disclosure, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, and an additional compound, wherein the additional compound is different from the compound of the disclosure, or pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof.

[0012h] In yet another aspect, the disclosure provides a kit comprising a compound of the disclosure, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, or a pharmaceutical composition of the disclosure and instructions for using the compound, or pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, or pharmaceutical composition.

[0013] The details of certain embodiments of the disclosure are set forth in the Detailed Description of Certain Embodiments, as described below. Other features, objects, and advantages of the disclosure will be apparent from the Definitions, Examples, and Claims.

DEFINITIONS

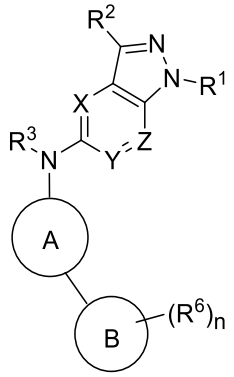
[0014] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0015] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, *e.g*., enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, E.L., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S.H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The invention additionally encompasses compounds as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

CLAIMS

What is claimed is:

1. A compound of Formula (**I**):



(**I**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof,

wherein:

R^1 is hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group;

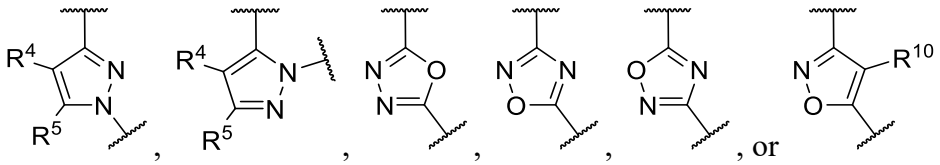
R^2 is hydrogen, halogen, -CN, substituted or unsubstituted alkyl, or substituted or unsubstituted carbocyclyl;

X is CR^7 or N;

Y is CR^8 or N;

Z is CR^9 or N;

R^3 is hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group;

A is ;

R^4 is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^5 is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or R^4 and R^5 together with the atoms to which they are attached form substituted or unsubstituted carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heteroaryl;

B is aryl or heteroaryl;

each R^6 is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroaliphatic, oxo, $–OR^A$, $–N_3$, $–N(R^A)_2$, $–SR^A$, –CN, –SCN, $–C(=NR^A)R^A$, $–C(=NR^A)OR^A$, $–C(=NR^A)N(R^A)_2$, $–C(=O)R^A$, $–C(=O)OR^A$, $–C(=O)N(R^A)_2$, $–NO_2$, $–NR^AC(=O)R^A$, $–NR^AC(=O)OR^A$, $–NR^AC(=O)N(R^A)_2$, $–NR^AC(=NR^A)N(R^A)_2$, $–OC(=O)R^A$, $–OC(=O)OR^A$, $–OC(=O)N(R^A)_2$, $–NR^AS(O)_2R^A$, $-OS(O)_2R^A$, or $-S(O)_2R^A$;

n is 1, 2, 3, 4, or 5;

each of R^7, R^8, and R^9 is independently hydrogen, halogen, -CN, or substituted or unsubstituted alkyl;

R^{10} is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

each occurrence of R^A is, independently, hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroaliphatic, substituted or unsubstituted carbocyclyl, substituted or unsubstituted carbocyclylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted hetaralkyl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two R^A groups are joined to form a substituted or unsubstituted heterocyclyl ring or a substituted or unsubstituted heteroaryl ring.

2. The compound of claim 1, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein R^1 is hydrogen or substituted or unsubstituted alkyl.

3. The compound of claim 1, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein R^1 is hydrogen.

4. The compound of any of claims 1-3, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein R^2 is hydrogen, halogen, or substituted or unsubstituted alkyl.

5. The compound of claim 4, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein R^2 is hydrogen or halogen.

6. The compound of claim 4, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein R^2 is hydrogen.

7. The compound of any of claims 1-6, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein R^3 is hydrogen or substituted or unsubstituted alkyl.

8. The compound of claim 7, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein R^3 is hydrogen.

9. The compound of any of claims 1-8, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein X is CR^7.

10. The compound of claim 9, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein:

R^7 is hydrogen or halogen, preferably hydrogen.

11. The compound of any of claims 1-10, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein Y is CR^8.

12. The compound of any of claims 1-11, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein Z is CR^9.

13. The compound of any of claims 1-8, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein:

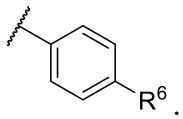
X is CR^7, wherein R^7 is hydrogen or halogen, preferably hydrogen;

Y is CR^8, wherein R^8 is hydrogen; and

Z is CR^9, wherein R^9 is hydrogen.

14. The compound of any of claims 1-13, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein B is aryl.

15. The compound of any of claims 1-13, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein B is heteroaryl.

16. The compound of claim 14, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein $-B(R^6)_n$ is 

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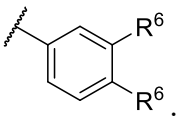
17. The compound of claim 14, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein B is phenyl.

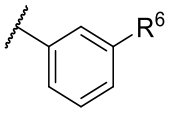
18. The compound of claim 15, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein B is pyridinyl.

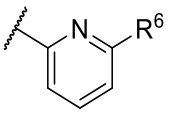
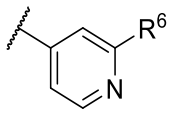
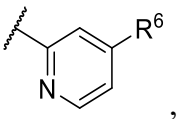
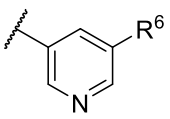
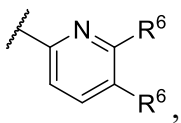
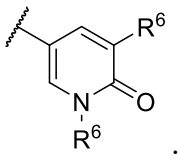
19. The compound of any of claims 1-15, 17, and 18, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein n is 1 or 2.

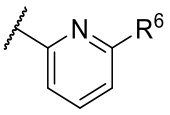
20. The compound of claim 19, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein n is 1.

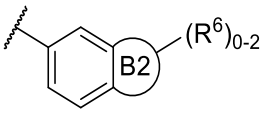
21. The compound of claim 19, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein n is 2.

22. The compound of claim 14, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein $-B(R^6)_n$ is .

23. The compound of claim 14, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein $-B(R^6)_n$ is .

24. The compound of any of claims 1-13, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein $-B(R^6)_n$ is , , , , , or .

25. The compound of any of claims 1-13, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein $-B(R^6)_n$ is .

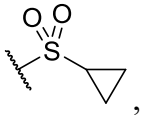
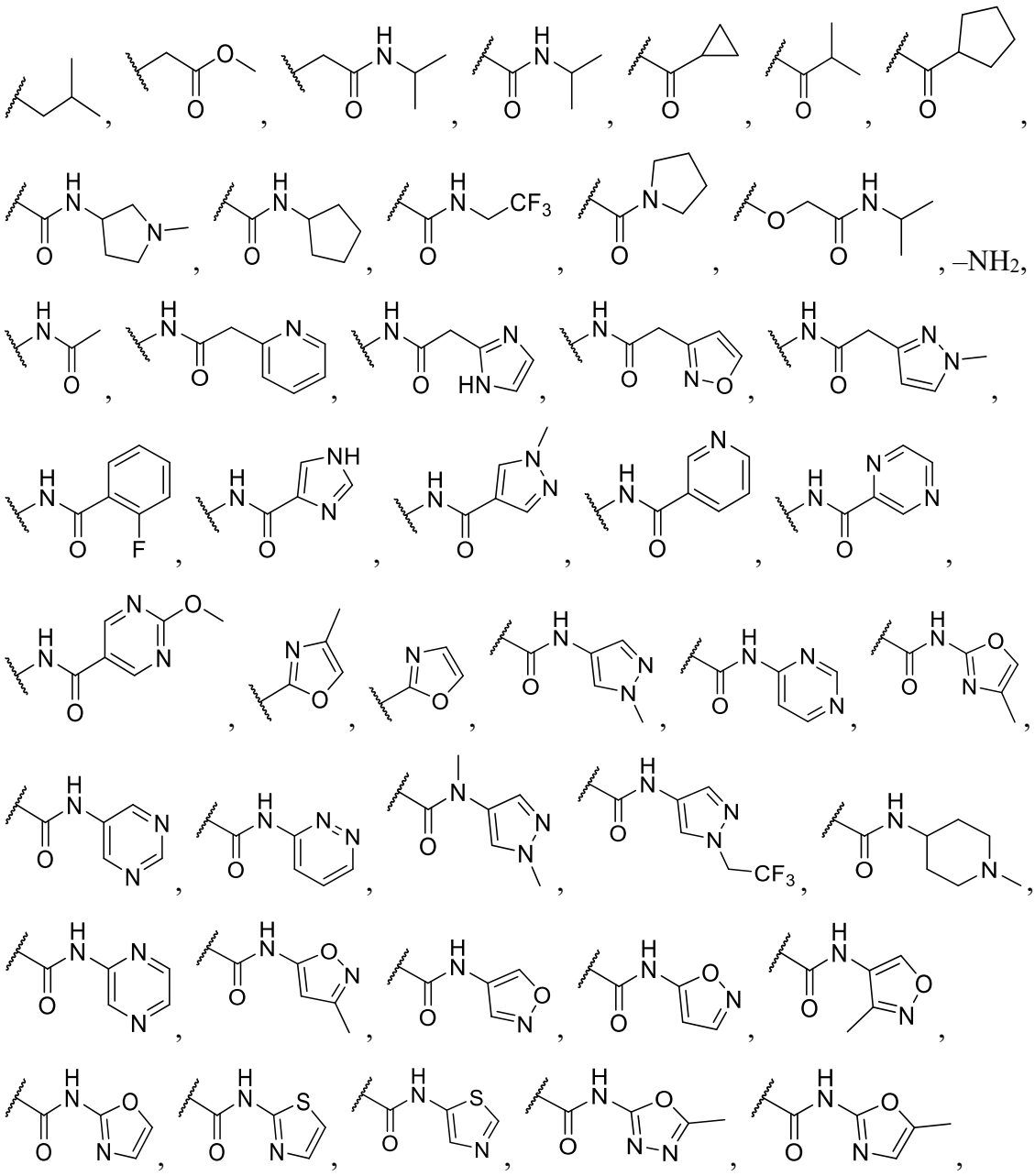
26. The compound of any of claims 1-13, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein $-B(R^6)_n$ is , wherein B2 is 5-6-membered, monocyclic, unsubstituted heteroaryl, or 5-6-membered, monocyclic, unsubstituted heterocyclyl, and R^6 is directly attached to B2.

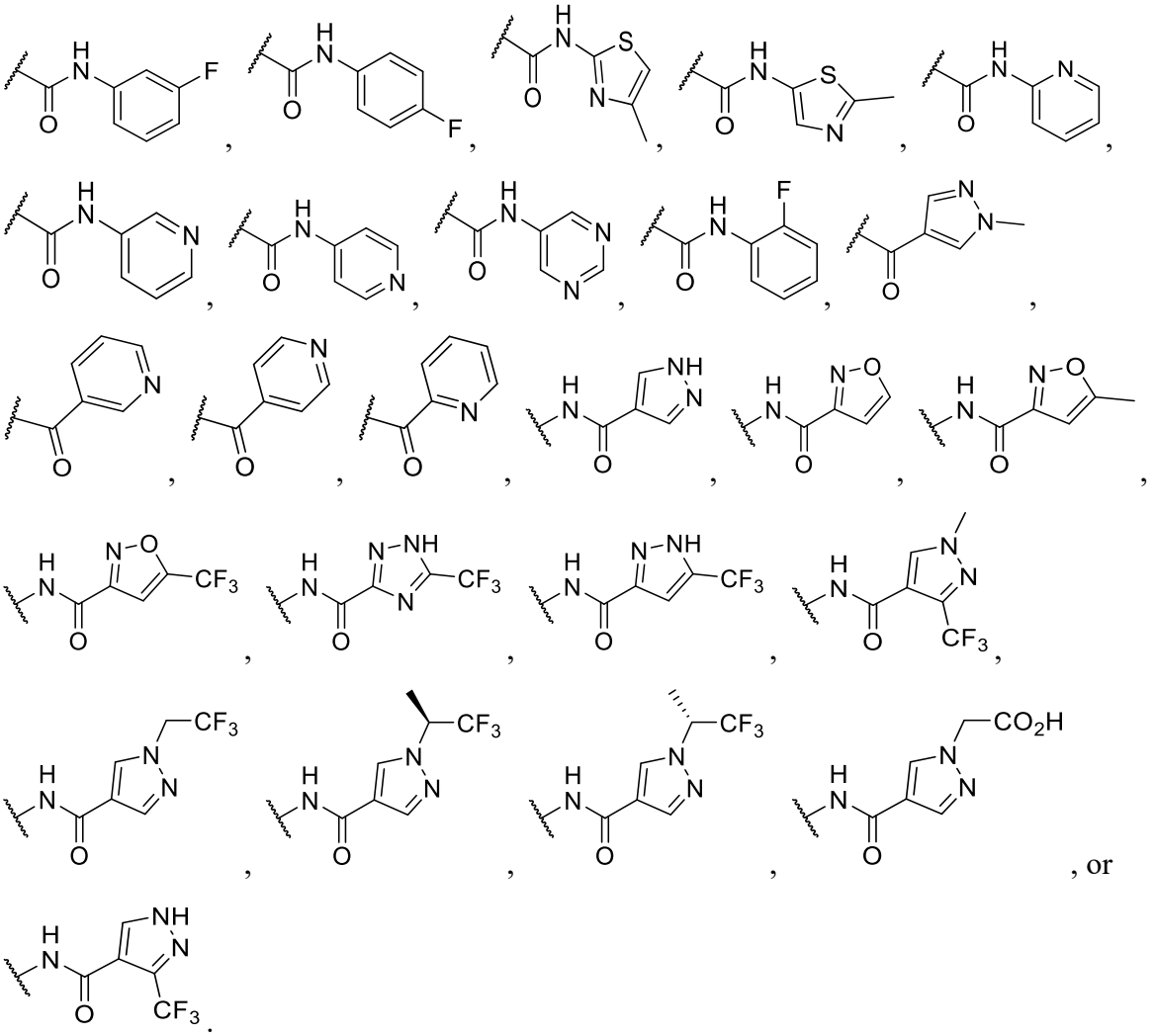
27. The compound of any of claims 1-26, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein each R^6 is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroaliphatic, oxo, $-OR^A$, $-N(R^A)_2$, $-CN$, $-C(=NR^A)R^A$, $-C(=NR^A)OR^A$, $-C(=NR^A)N(R^A)_2$, $-C(=O)R^A$, $-C(=O)OR^A$, $-C(=O)N(R^A)_2$, $-NR^AC(=O)R^A$, $-NR^AC(=O)OR^A$, $-NR^AC(=O)N(R^A)_2$, $-NR^AC(=NR^A)N(R^A)_2$, $-OC(=O)R^A$, $-OC(=O)OR^A$, $-OC(=O)N(R^A)_2$, $-NR^AS(O)_2R^A$, $-OS(O)_2R^A$, or $-S(O)_2R^A$.

28. The compound of any of claims 1-26, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein each R^6 is independently substituted or unsubstituted alkyl, substituted or unsubstituted heteroaryl, oxo, $-OR^A$, $-N(R^A)_2$, or $-NR^AC(=O)R^A$.

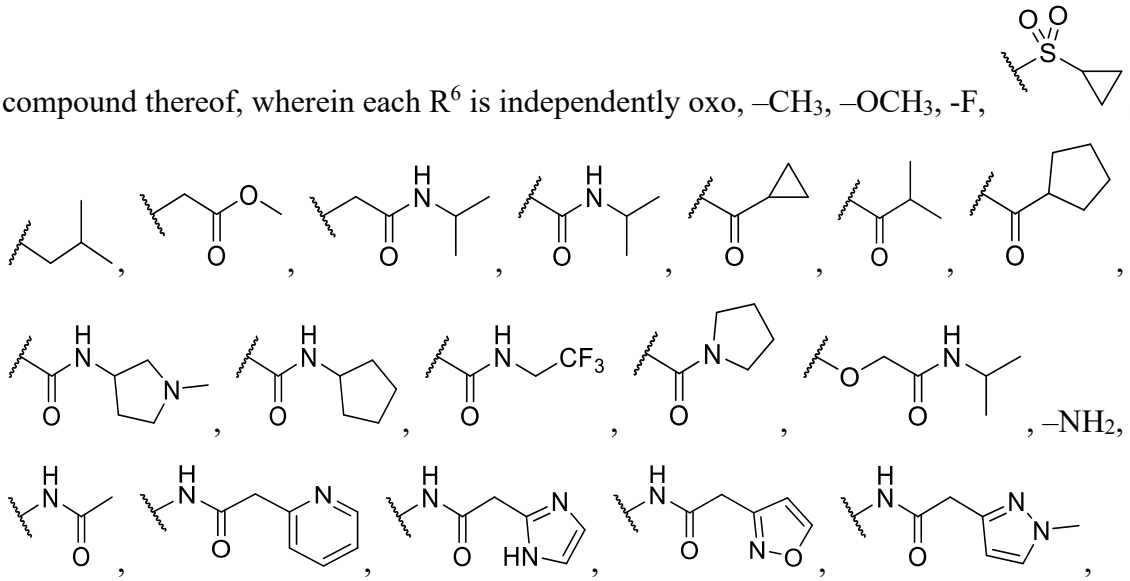
29. The compound of any of claims 1-26, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein each R^6 is independently substituted or unsubstituted alkyl, substituted or unsubstituted heteroaryl, oxo, $-OC_{1-4}$ alkyl, $-OCH_2C(=O)N(R^A)_2$, $-N(R^A)_2$, or $-NR^AC(=O)R^A$.

30. The compound of any of claims 1-26, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein each R^6 is independently C_{1-4} alkyl, substituted or unsubstituted heteroaryl, oxo, –OC_{1-4} alkyl, –$OCH_2C(=O)NHC_{1-4}$ alkyl, –NH_2, –NHC(=O)aryl, or –NHC(=O)heteroaryl, wherein each alkyl, aryl, and heteroaryl are substituted or unsubstituted.

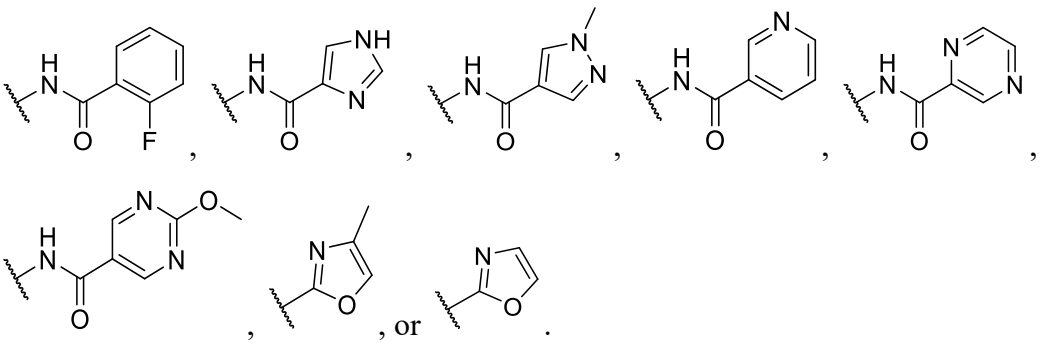
31. The compound of any of claims 1-26, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein each R^6 is independently oxo, –CH_3, –OCH_3, -F, , 

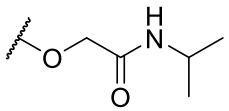
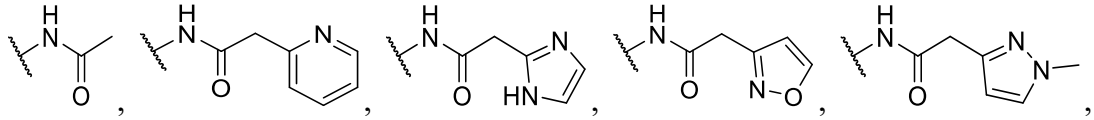


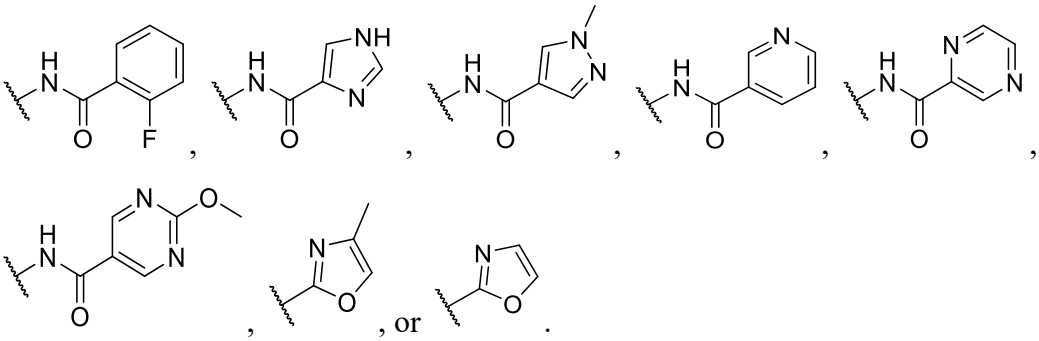
32. The compound of any of claims 1-26, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein each R^6 is independently oxo, $–CH_3$, $–OCH_3$, -F,

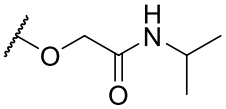
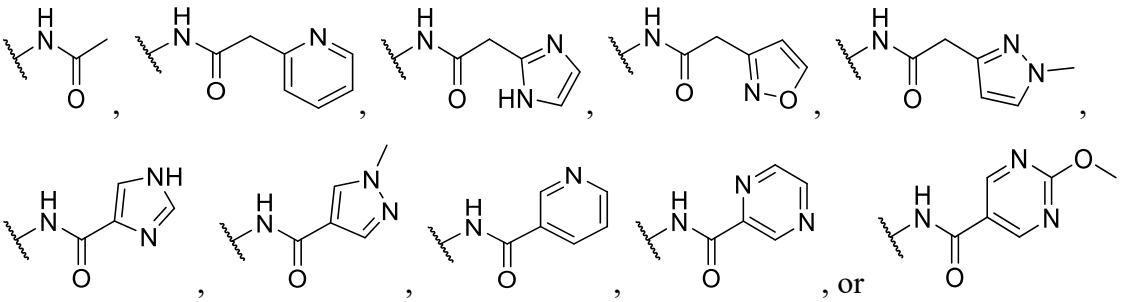


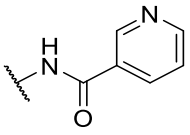
$–NH_2$,

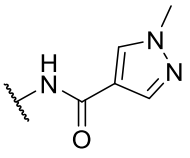


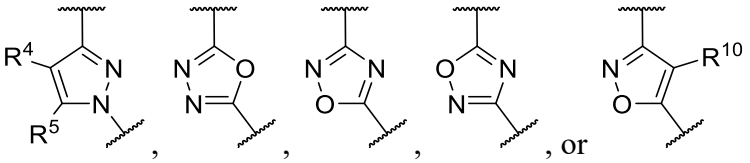
33. The compound of any of claims 1-26, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein each R^6 is independently oxo, $–CH_3$, $–OCH_3$, , $–NH_2$, 

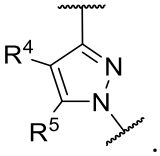


34. The compound of any of claims 1-26, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein each R^6 is independently $–OCH_3$, , $–NH_2$, 

35. The compound of any of claims 1-26, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein R^6 is .

36. The compound of any of claims 1-26, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein R^6 is .

37. The compound of any of claims 1-36, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein A is .

38. The compound of any of claims 1-37, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein A is .

39. The compound of any of claims 1-38, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein R^4 is hydrogen, halogen, or substituted or unsubstituted alkyl.

40. The compound of claim 39, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein R^4 is hydrogen.

41. The compound of claim 39, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein R^4 is substituted or unsubstituted alkyl.

42. The compound of any of claims 1-41, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein R^5 is hydrogen, halogen, or substituted or unsubstituted alkyl.

43. The compound of claim 42, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein R^5 is hydrogen.

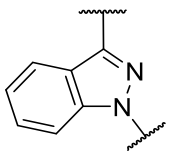
44. The compound of claim 42, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein R^5 is substituted or unsubstituted alkyl.

45. The compound of any of claims 1-38, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein:

R^4 is hydrogen or substituted or unsubstituted alkyl; and

R^5 is hydrogen or substituted or unsubstituted alkyl.

46. The compound of any of claims 1-38, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein R^4 and R^5 together with the atoms to which they are attached form a substituted or unsubstituted aryl ring.

47. The compound of any of claims 1-46, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein A is 

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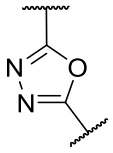
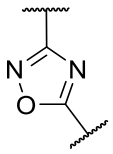
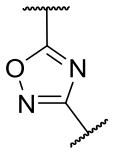
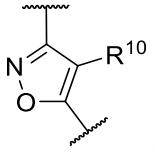
48. The compound of any of claims 1-37, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein A is .

49. The compound of any of claims 1-37, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein A is .

50. The compound of any of claims 1-37, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein A is .

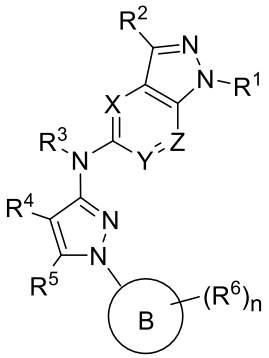
51. The compound of any of claims 1-37, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein A is .

52. The compound of any of claims 1-37 and 51, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein R^{10} is hydrogen, halogen, or substituted or unsubstituted alkyl.

53. The compound of claim 52, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, wherein R^{10} is hydrogen.

54. The compound of any of claims 1-53, wherein:

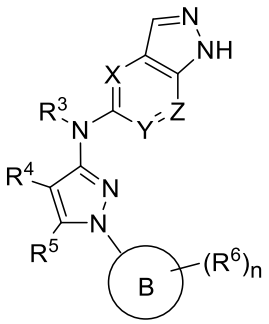
the compound is of Formula (**I-a**):



(**I-a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

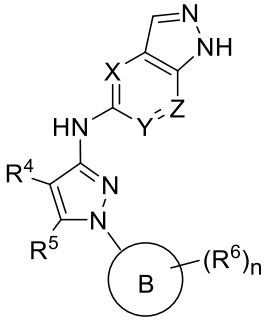
the compound is of Formula (**I-a-1**):



(**I-a-1**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

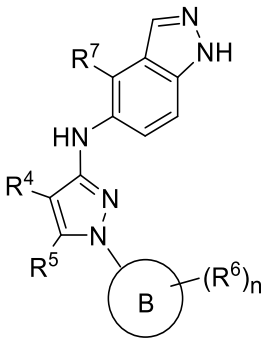
the compound is of Formula (**I-a-2**):



(**I-a-2**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

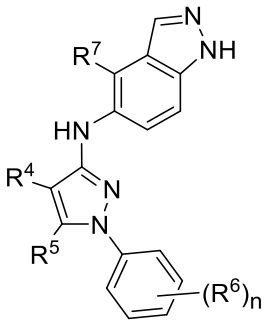
the compound is of Formula (**I-a-3**):



(**I-a-3**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

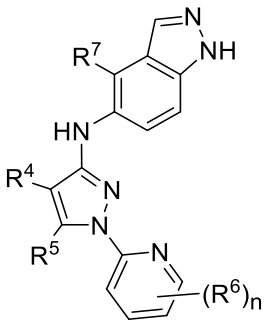
the compound is of Formula (**I-a-4**):



(**I-a-4**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

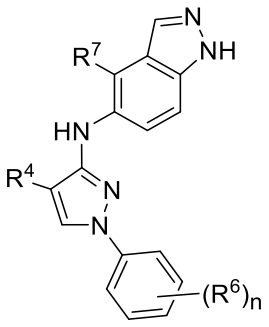
the compound is of Formula (**I-a-4a**):



(**I-a-4a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

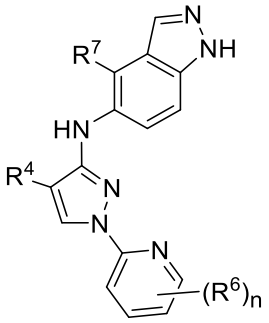
the compound is of Formula (**I-a-5**):



(**I-a-5**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

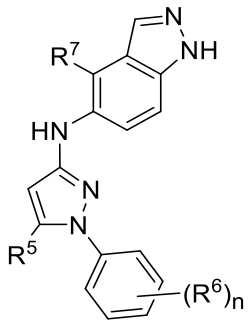
the compound is of Formula (**I-a-5a**):



(**I-a-5a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

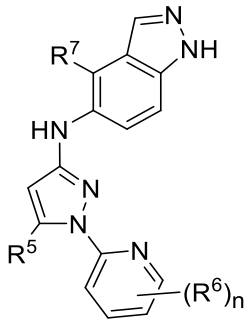
the compound is of Formula (**I-a-6**):



(**I-a-6**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

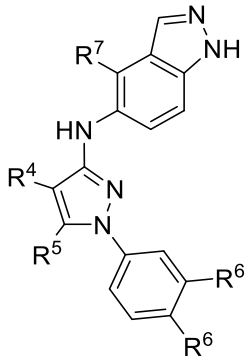
the compound is of Formula (**I-a-6a**):



(**I-a-6a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

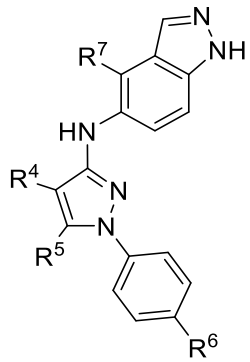
the compound is of Formula (**I-a-7**):



(**I-a-7**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

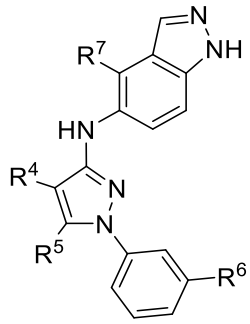
the compound is of Formula (**I-a-8**):



(**I-a-8**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

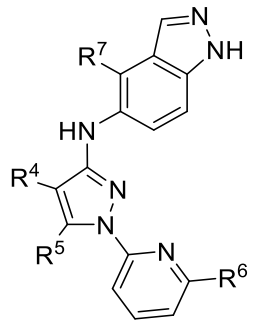
the compound is of Formula (**I-a-9**):



(**I-a-9**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

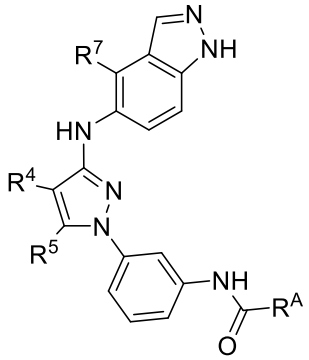
the compound is of Formula (**I-a-9a**):



(**I-a-9a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

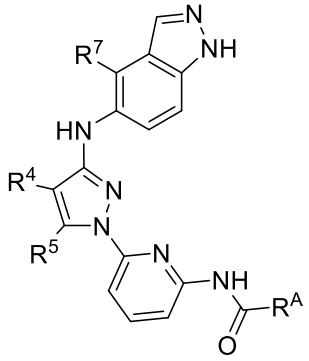
the compound is of Formula (**I-a-10**):



(**I-a-10**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof; or

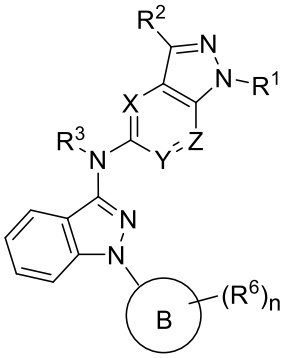
the compound is of Formula (**I-a-10a**):



(**I-a-10a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof.

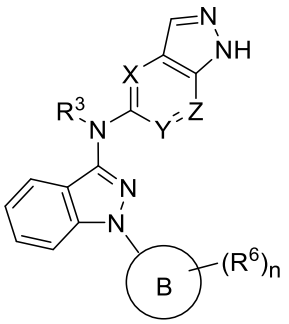
55. The compound of any of claims 1-53, wherein:
the compound is of Formula (**I-b**):



(**I-b**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

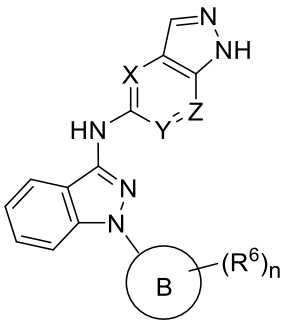
the compound is of Formula (**I-b-1**):



(**I-b-1**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

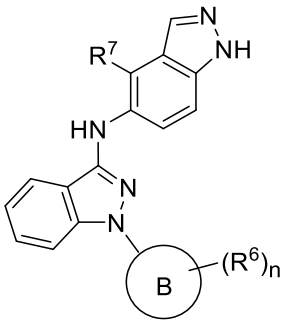
the compound is of Formula (**I-b-2**):



(**I-b-2**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

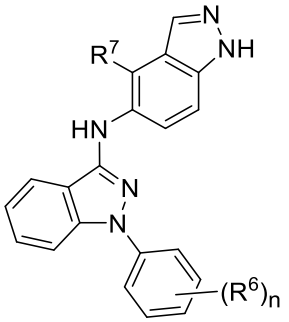
the compound is of Formula (**I-b-3**):



(**I-b-3**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

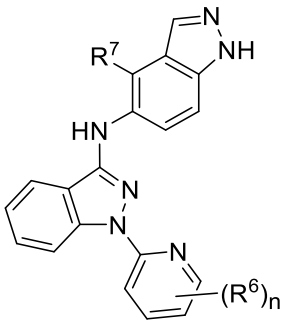
the compound is of Formula (**I-b-4**):



(**I-b-4**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

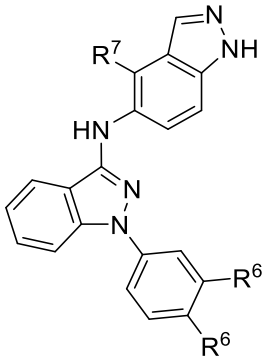
the compound is of Formula (**I-b-4a**):



(**I-b-4a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

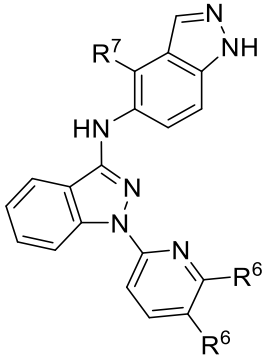
the compound is of Formula (**I-b-5**):



(**I-b-5**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

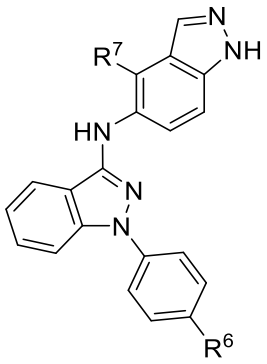
the compound is of Formula (**I-b-5a**):



(**I-b-5a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

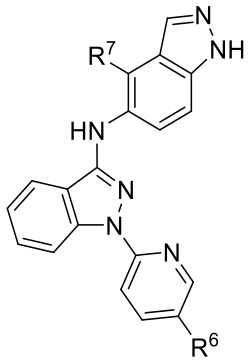
the compound is of Formula (**I-b-6**):



(**I-b-6**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

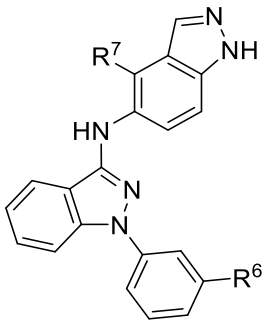
the compound is of Formula (**I-b-6a**):



(**I-b-6a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

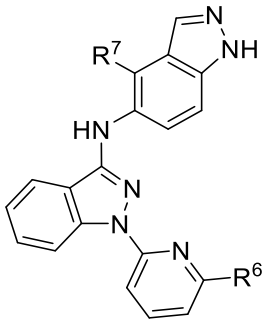
the compound is of Formula (**I-b-7**):



(**I-b-7**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

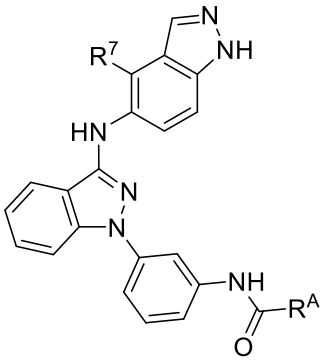
the compound is of Formula (**I-b-7a**):



(**I-b-7a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

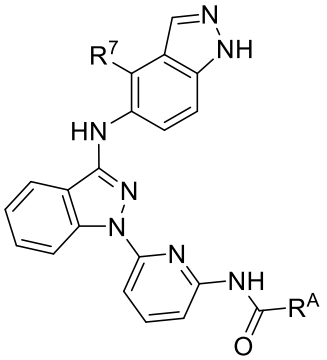
the compound is of Formula (**I-b-8**):



(**I-b-8**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof; or

the compound is of Formula (**I-b-8a**):

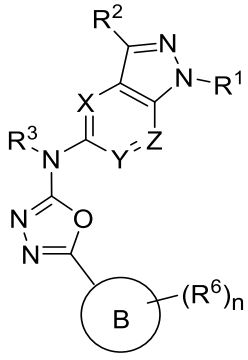


(**I-b-8a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof.

56. The compound of any of claims 1-53, wherein:

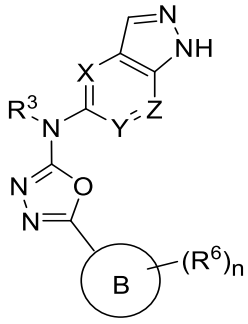
the compound is of Formula (**I-c**):



(**I-c**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

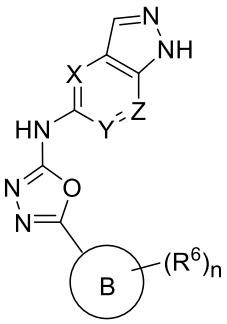
the compound is of Formula (**I-c-1**):



(**I-c-1**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

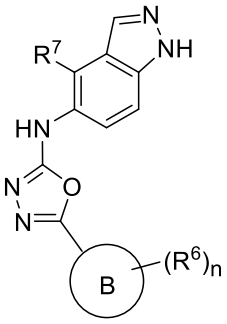
the compound is of Formula (**I-c-2**):



(**I-c-2**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

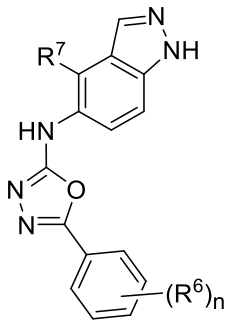
the compound is of Formula (**I-c-3**):



(**I-c-3**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

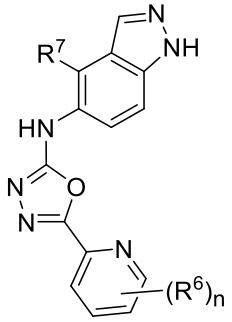
the compound is of Formula (**I-c-4**):



(**I-c-4**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

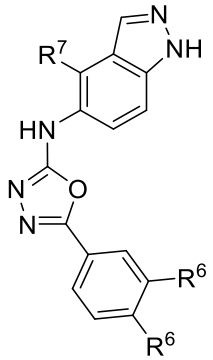
the compound is of Formula (**I-c-4a**):



(**I-c-4a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

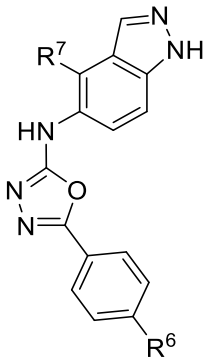
the compound is of Formula (**I-c-5**):



(**I-c-5**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

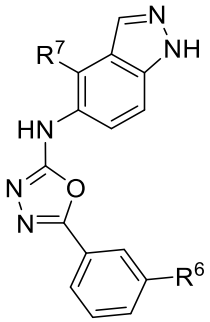
the compound is of Formula (**I-c-6**):



(**I-c-6**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

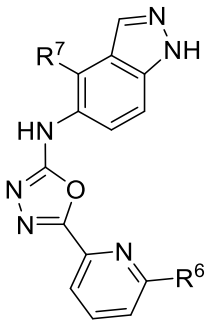
the compound is of Formula (**I-c-7**):



(**I-c-7**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

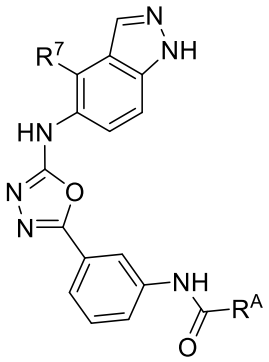
the compound is of Formula (**I-c-7a**):



(**I-c-7a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

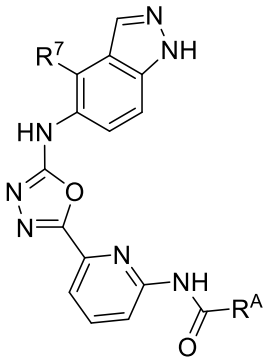
the compound is of Formula (**I-c-8**):



(**I-c-8**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof; or

the compound is of Formula (**I-c-8a**):

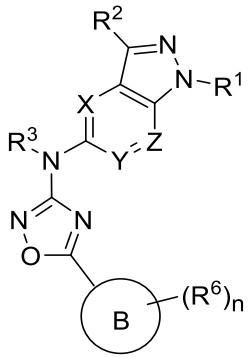


(**I-c-8a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof.

57. The compound of any of claims 1-53, wherein:

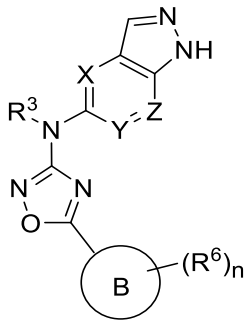
the compound is of Formula (**I-d**):



(**I-d**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

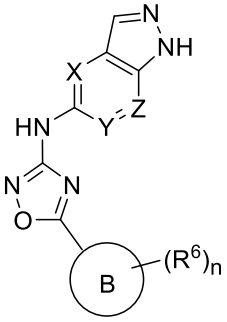
the compound is of Formula (**I-d-1**):



(**I-d-1**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

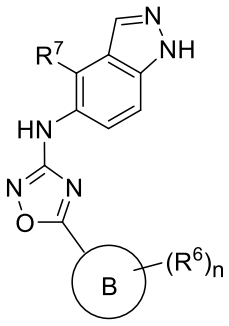
the compound is of Formula (**I-d-2**):



(**I-d-2**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

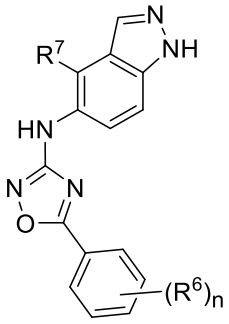
the compound is of Formula (**I-d-3**):



(**I-d-3**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

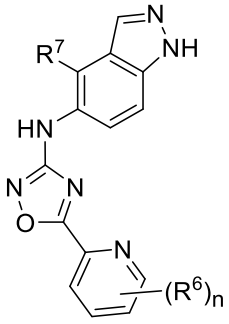
the compound is of Formula (**I-d-4**):



(**I-d-4**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

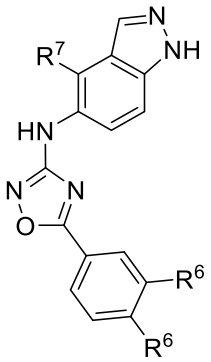
the compound is of Formula (**I-d-4a**):



(**I-d-4a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

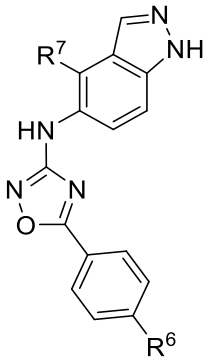
the compound is of Formula (**I-d-5**):



(**I-d-5**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

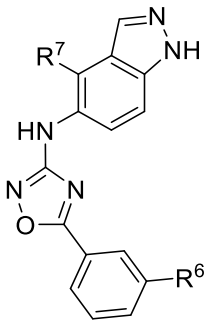
the compound is of Formula (**I-d-6**):



(**I-d-6**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

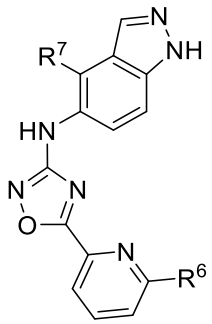
the compound is of Formula (**I-d-7**):



(**I-d-7**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

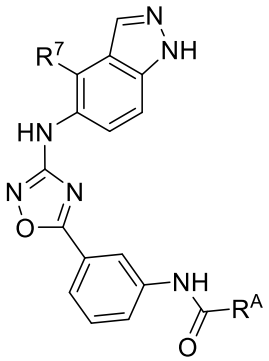
the compound is of Formula (**I-d-7a**):



(**I-d-7a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

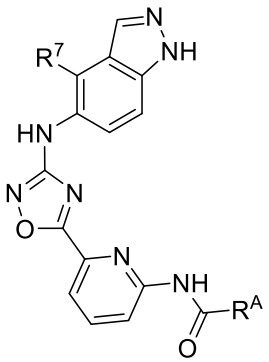
the compound is of Formula (**I-d-8**):



(**I-d-8**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof; or

the compound is of Formula (**I-d-8a**):

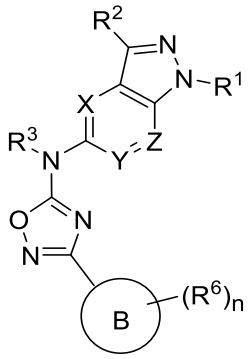


(**I-d-8a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof.

58. The compound of any of claims 1-53, wherein:

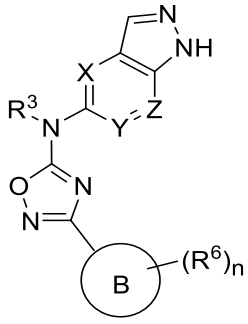
the compound is of Formula (**I-e**):



(**I-e**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

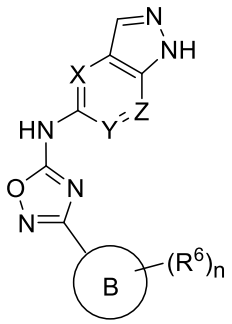
the compound is of Formula (**I-e-1**):



(**I-e-1**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

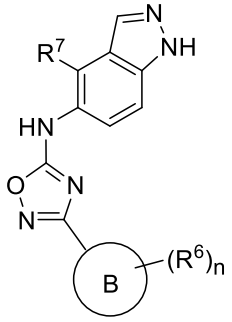
the compound is of Formula (**I-e-2**):



(**I-e-2**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

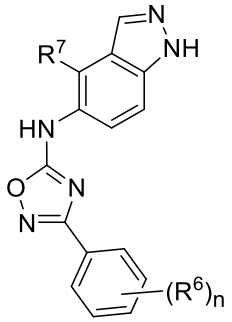
the compound is of Formula (**I-e-3**):



(**I-e-3**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

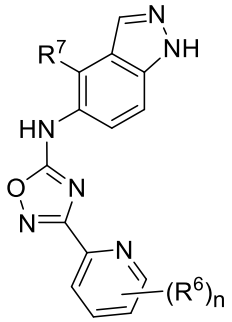
the compound is of Formula (**I-e-4**):



(**I-e-4**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

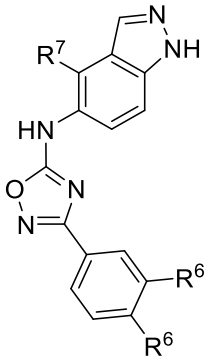
the compound is of Formula (**I-e-4a**):



(**I-e-4a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

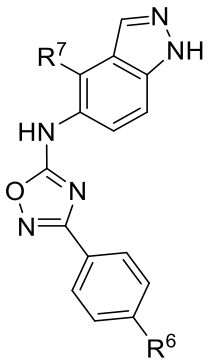
the compound is of Formula (**I-e-5**):



(**I-e-5**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

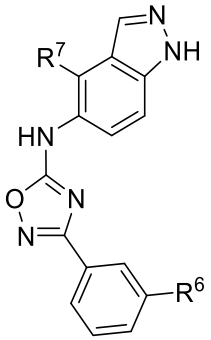
the compound is of Formula (**I-e-6**):



(**I-e-6**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

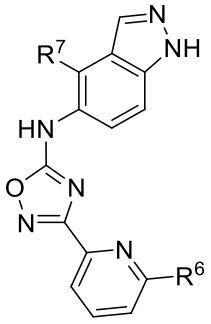
the compound is of Formula (**I-e-7**):



(**I-e-7**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

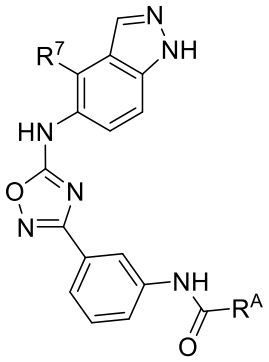
the compound is of Formula (**I-e-7a**):



(**I-e-7a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

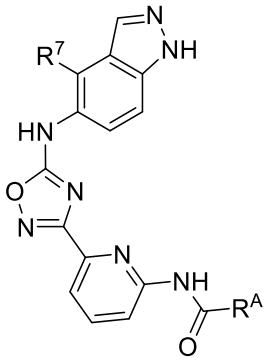
the compound is of Formula (**I-e-8**):



(**I-e-8**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof; or

the compound is of Formula (**I-e-8a**):

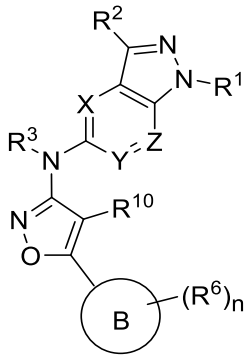


(**I-e-8a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof.

59. The compound of any of claims 1-53, wherein:

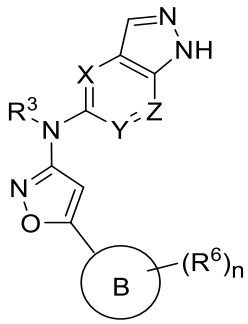
the compound is of Formula (**I-f**):



(**I-f**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

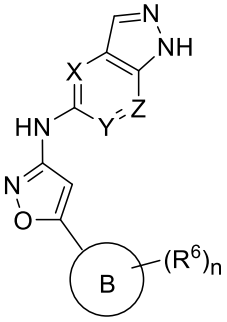
the compound is of Formula (**I-f-1**):



(**I-f-1**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

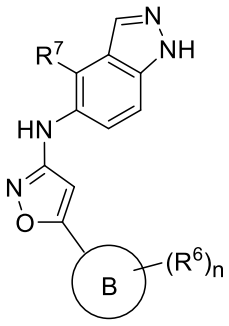
the compound is of Formula (**I-f-2**):



(**I-f-2**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

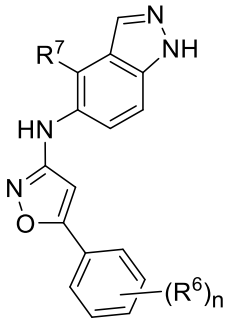
the compound is of Formula (**I-f-3**):



(**I-f-3**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

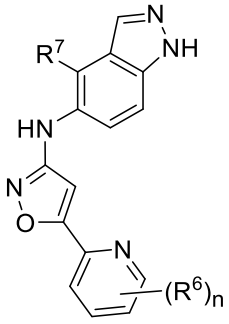
the compound is of Formula (**I-f-4**):



(**I-f-4**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

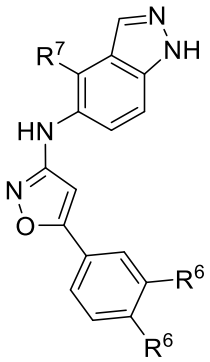
the compound is of Formula (**I-f-4a**):



(**I-f-4a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

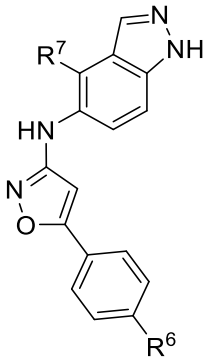
the compound is of Formula (**I-f-5**):



(**I-f-5**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

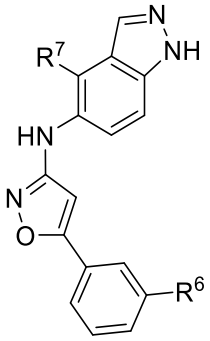
the compound is of Formula (**I-f-6**):



(**I-f-6**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

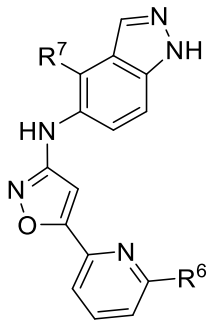
the compound is of Formula (**I-f-7**):



(**I-f-7**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

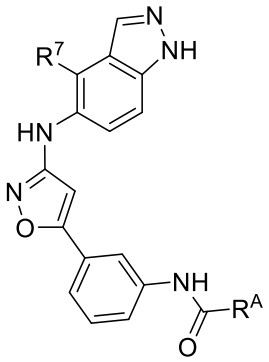
the compound is of Formula (**I-f-7a**):



(**I-f-7a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof;

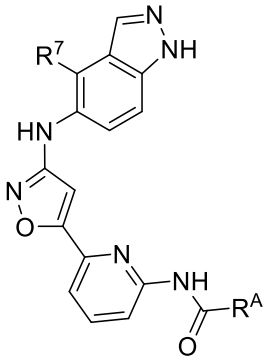
the compound is of Formula (**I-f-8**):



(**I-f-8**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof; or

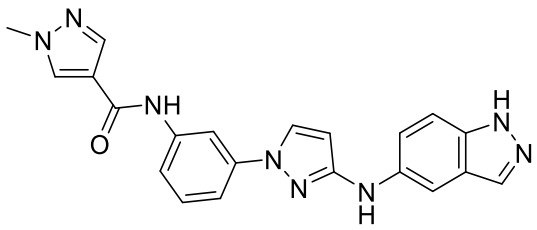
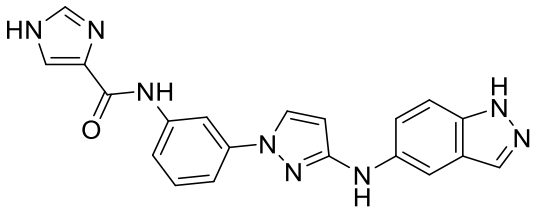
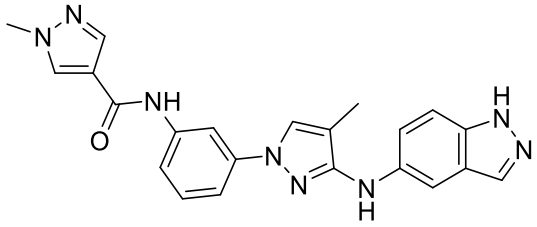
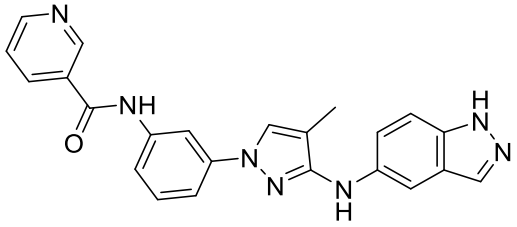
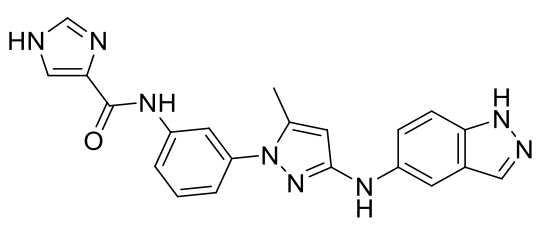
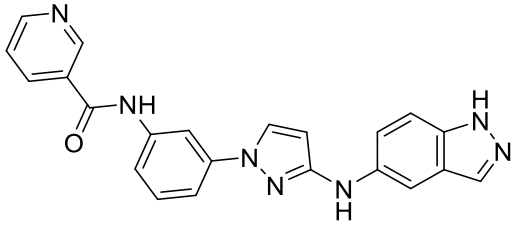
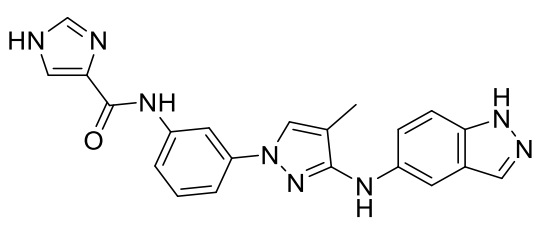
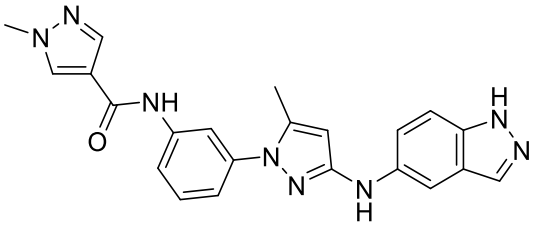
the compound is of Formula (**I-f-8a**):

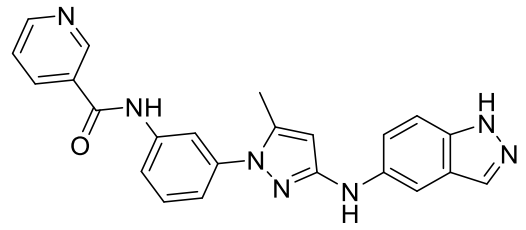
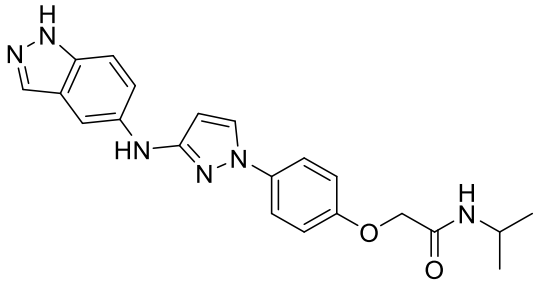
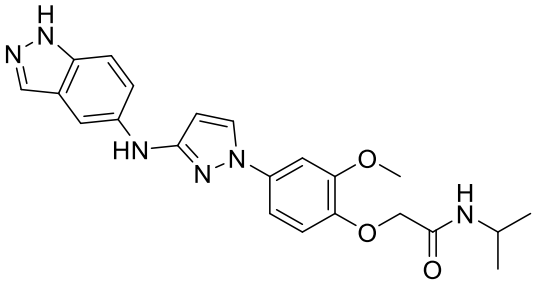
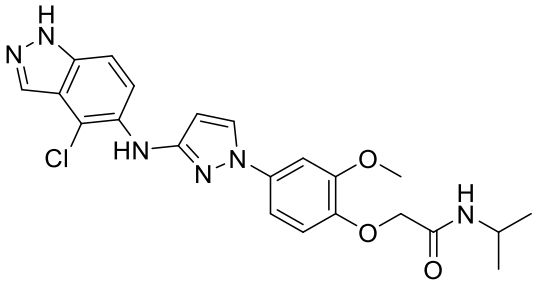
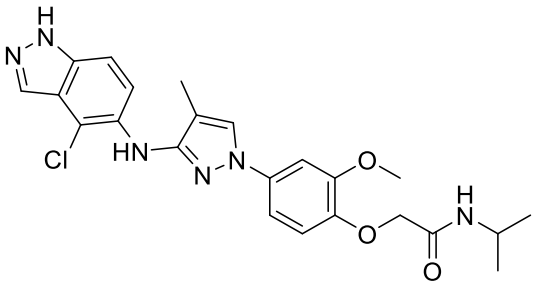
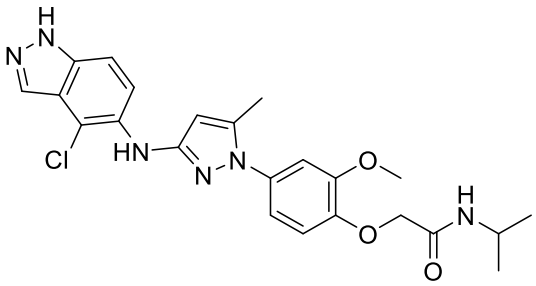
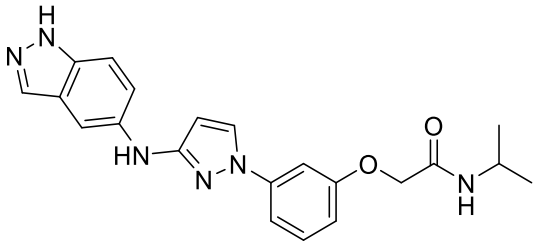
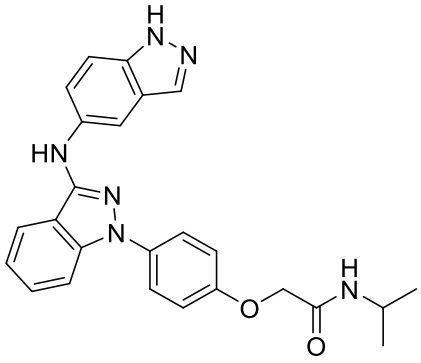
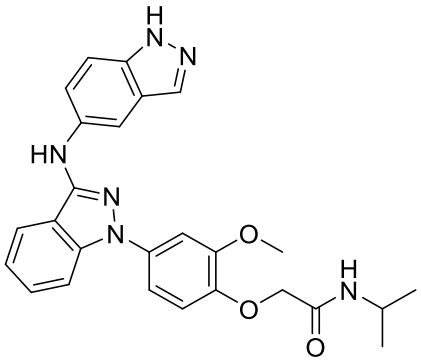
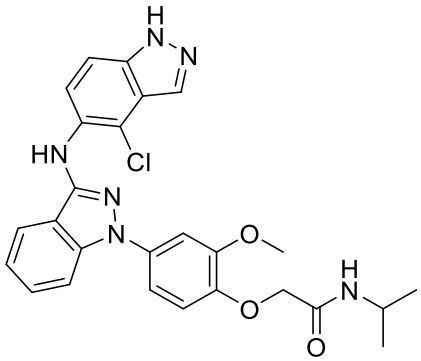


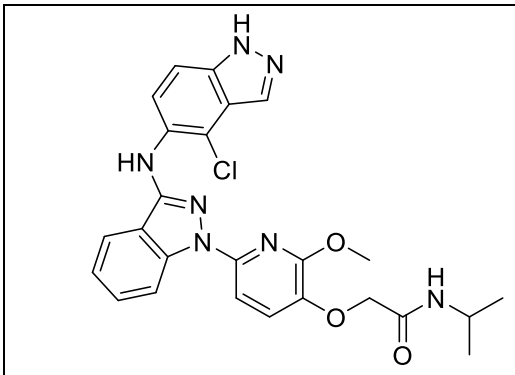
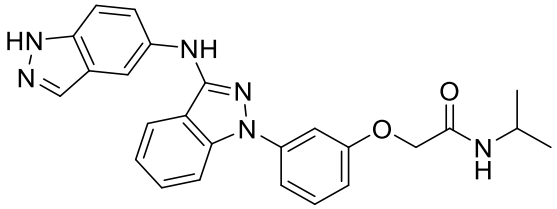
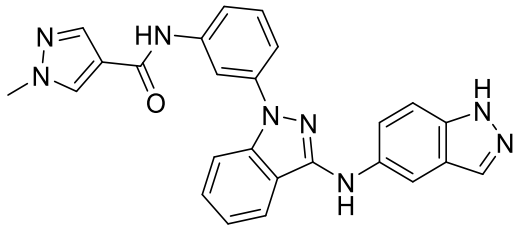
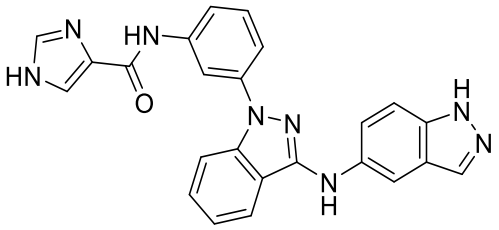
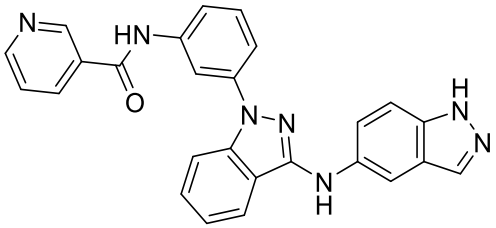
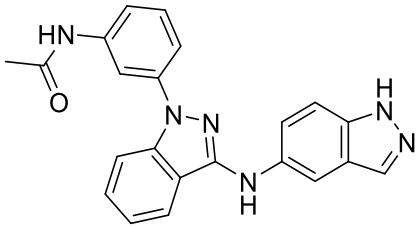
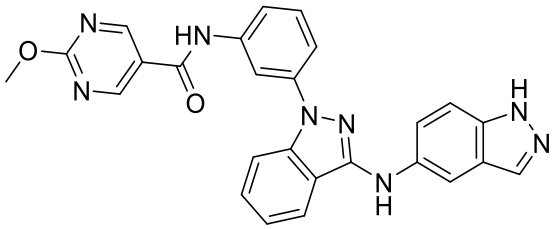
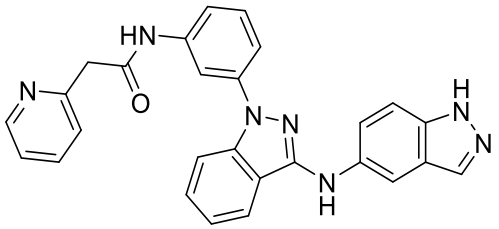
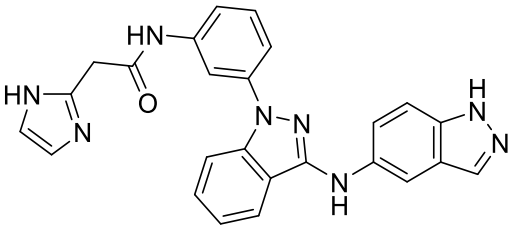
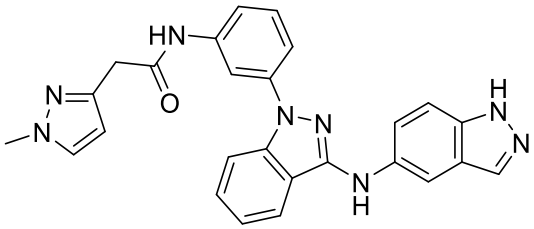
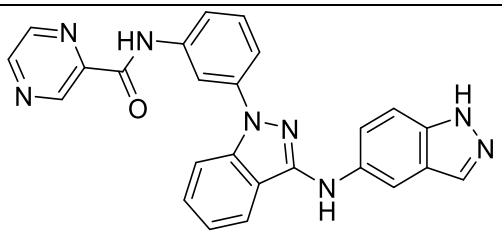
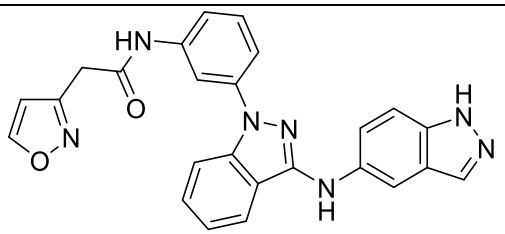
(**I-f-8a**),

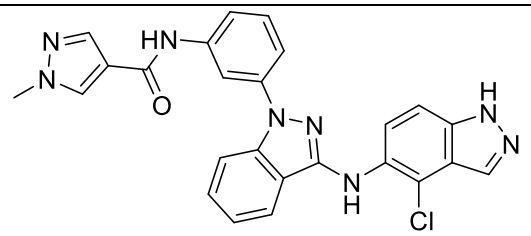
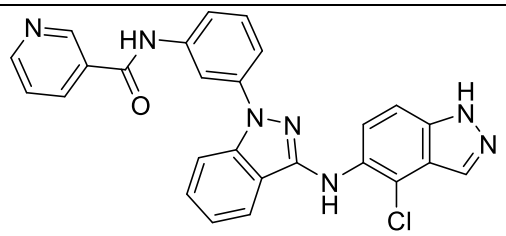
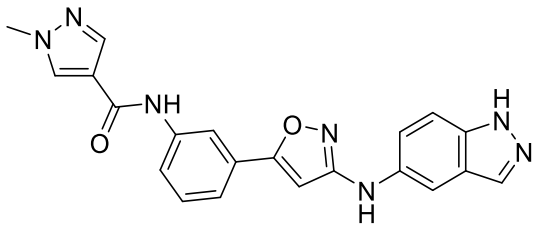
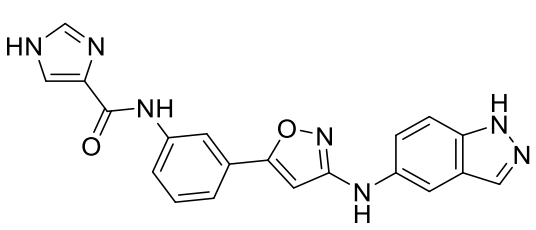
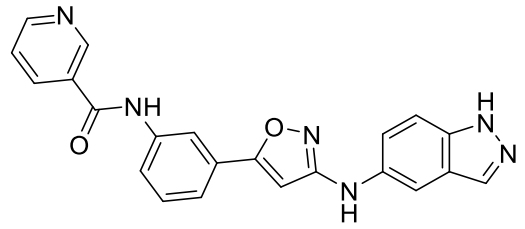
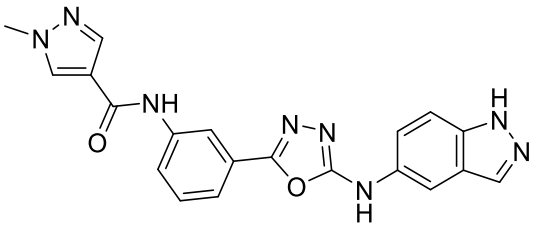
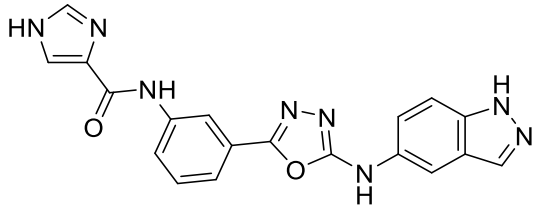
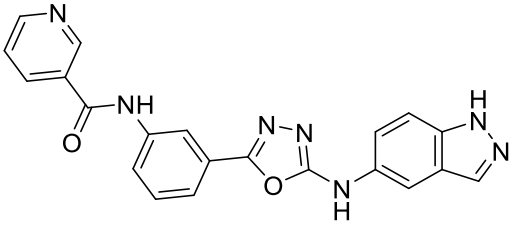
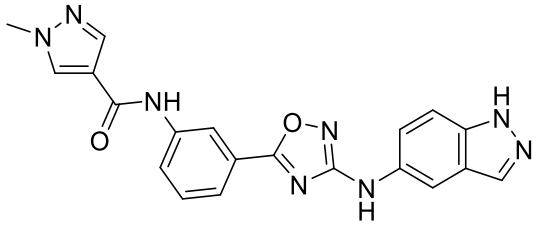
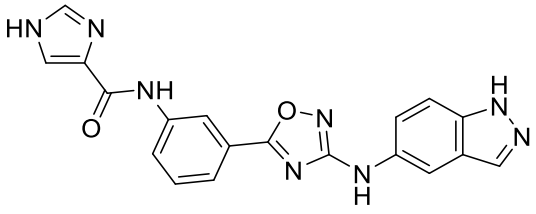
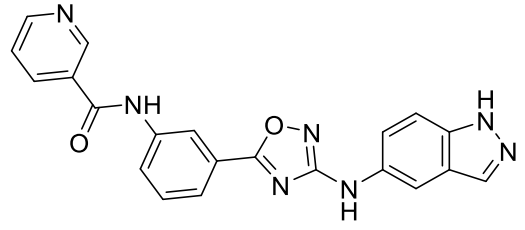
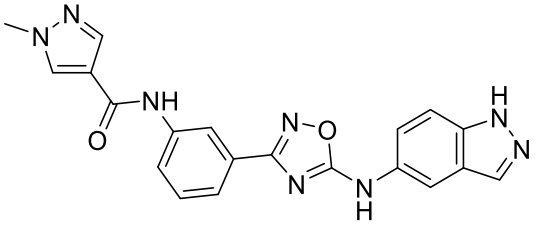
or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof.

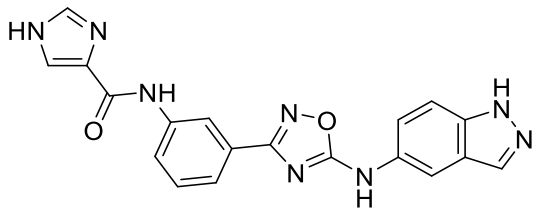
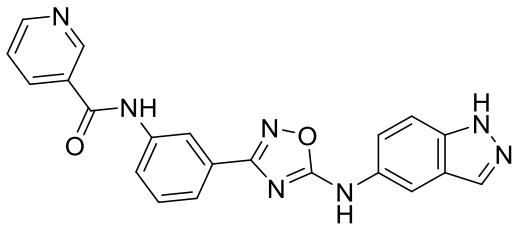
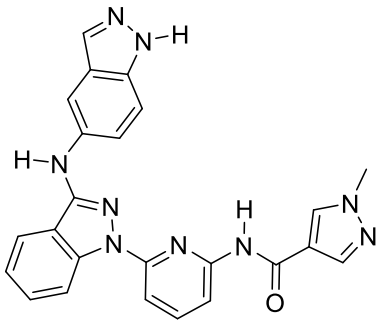
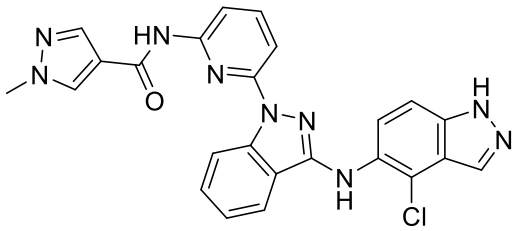
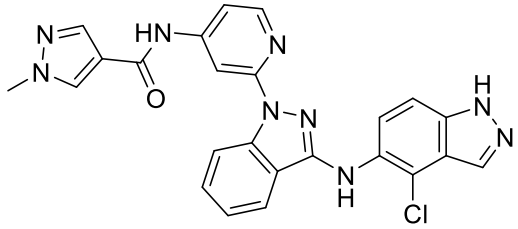
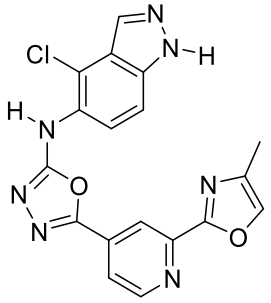
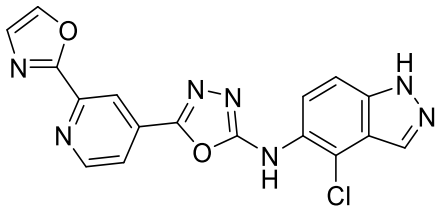
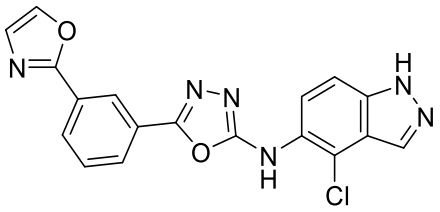
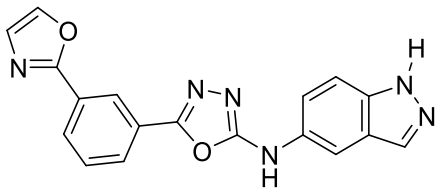
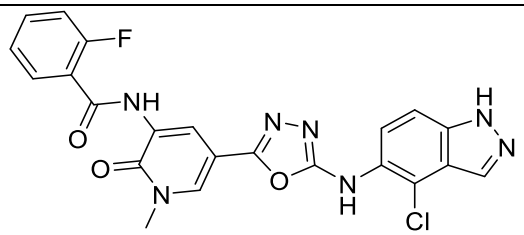
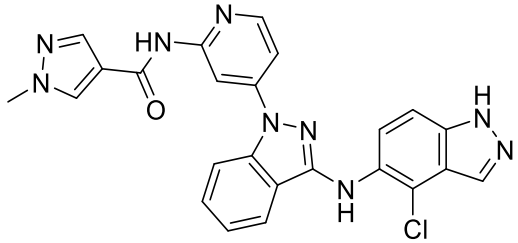
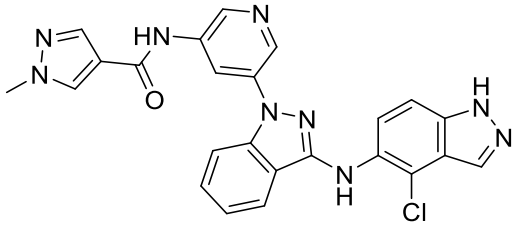
60. The compound of claim 1, wherein the compound is of the formula:

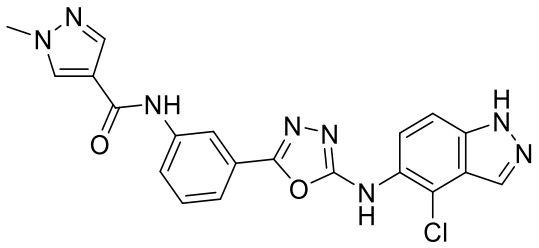
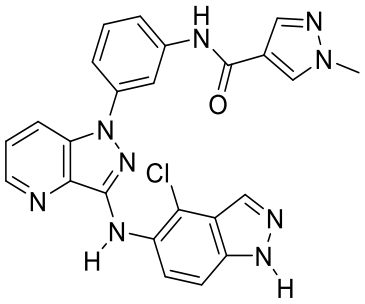
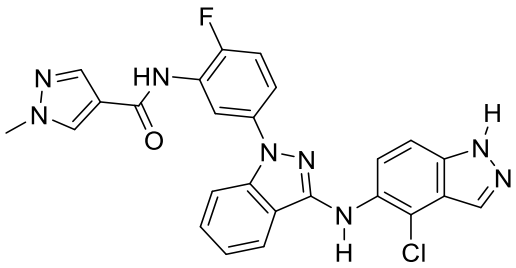
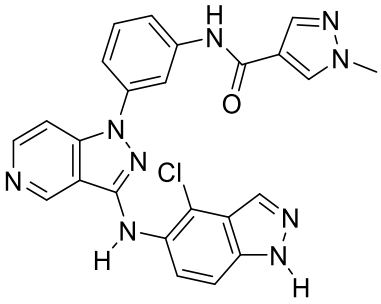
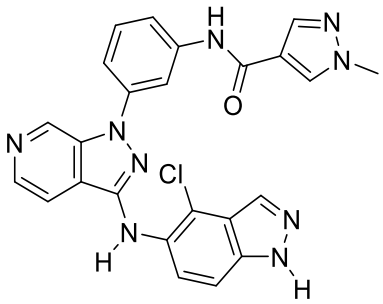
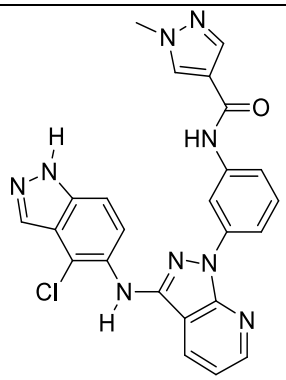
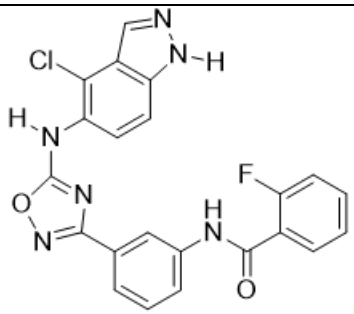
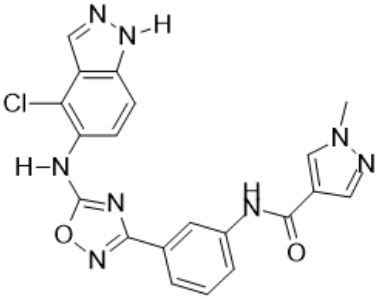
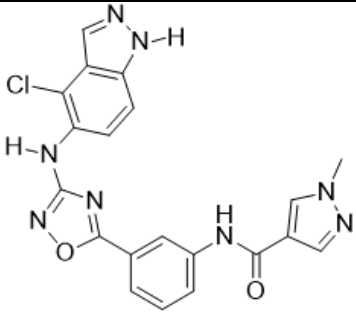
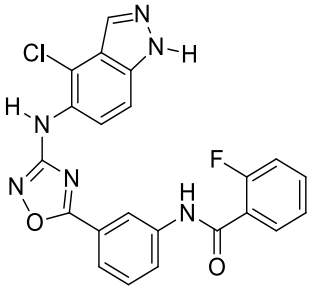
 1	 2
 3	 4
 5	 6
 7	 8

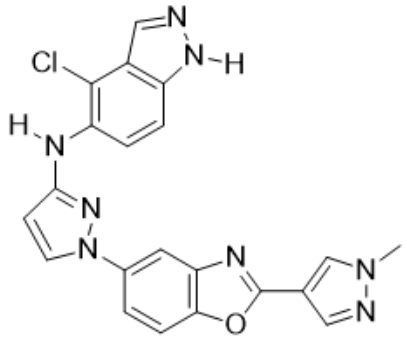
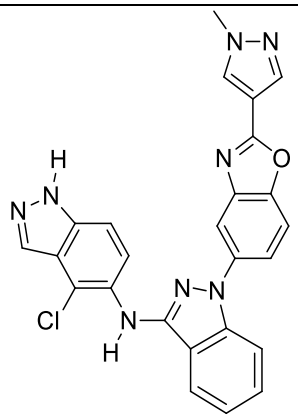
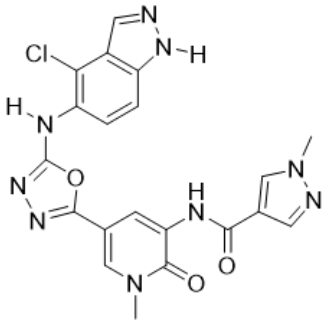
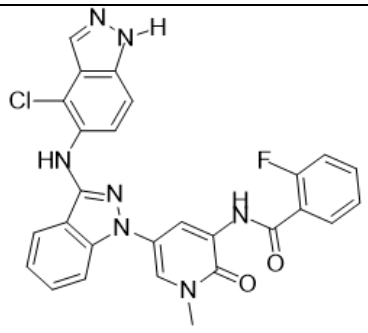
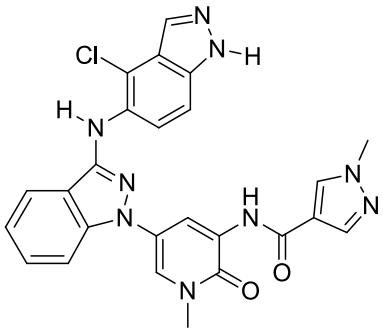
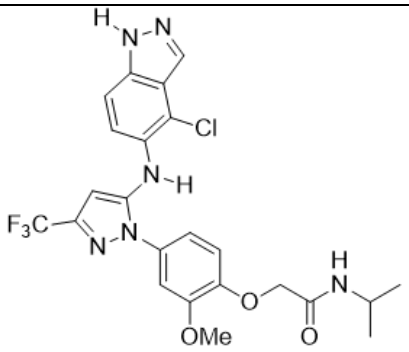
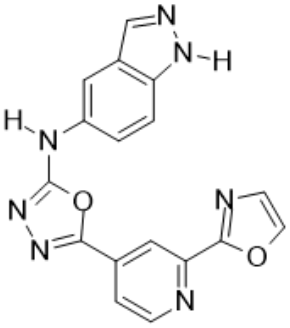
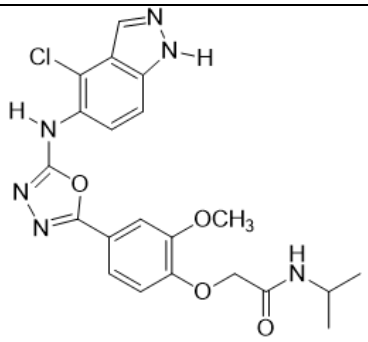
 9	 10
 11	 12
 13	 14
 15	 16
 17	 18

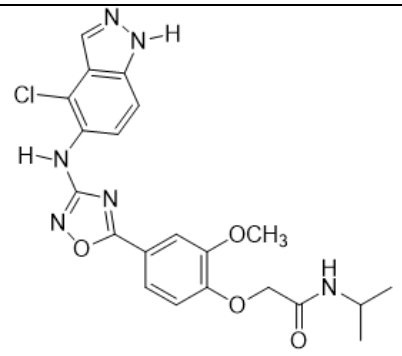
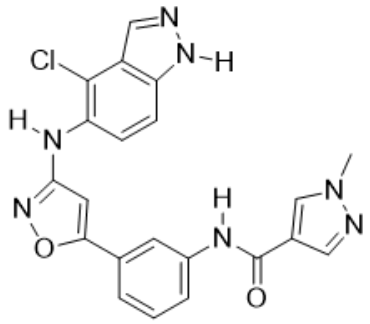
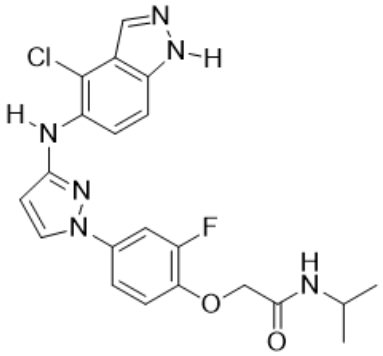
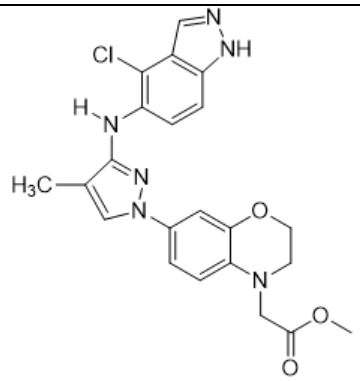
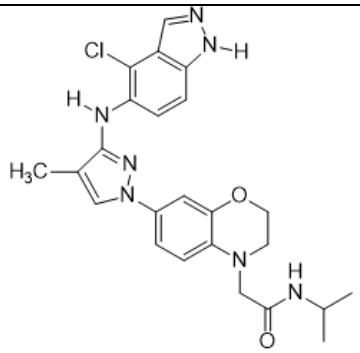
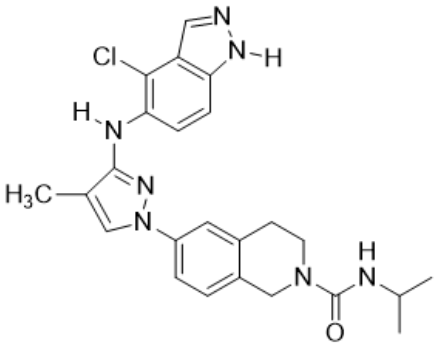
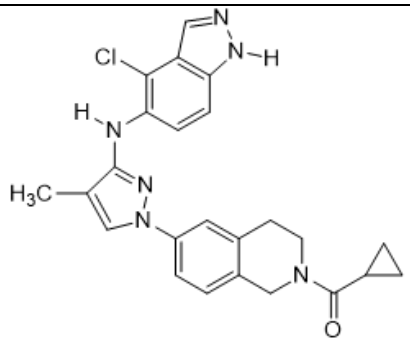
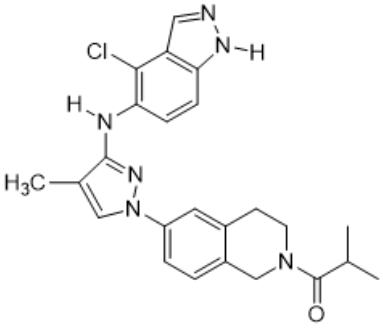
 19	 20
 21	 22
 23	 24
 25	 26
 27	 28
 29	 30

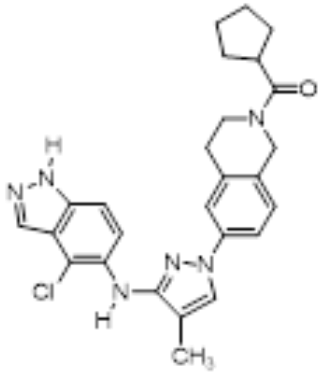
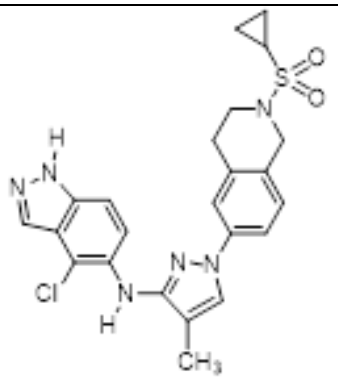
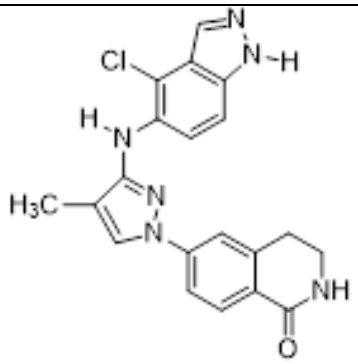
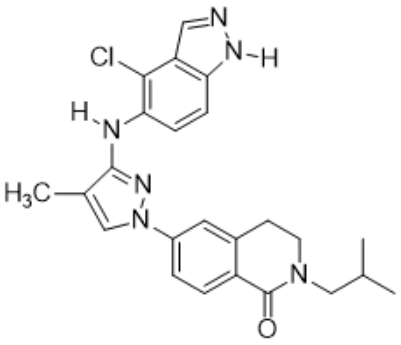
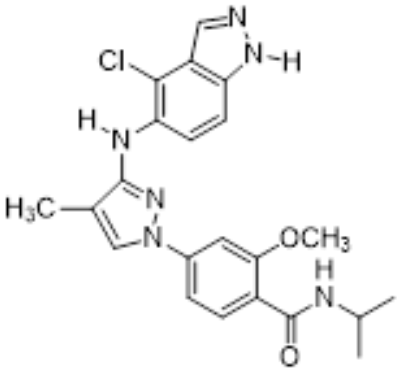
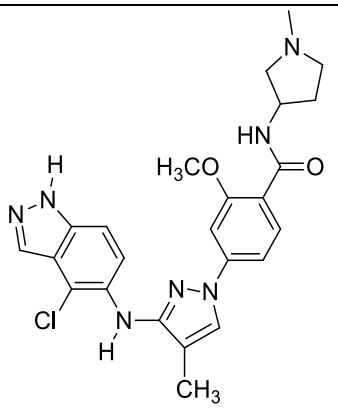
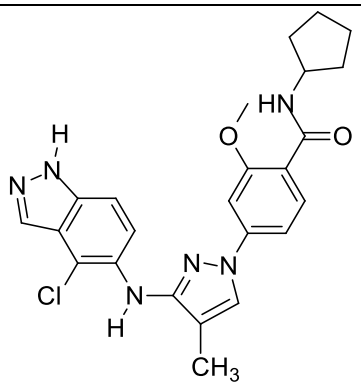
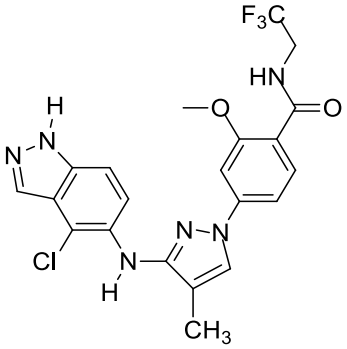
 31	 32
 33	 34
 35	 36
 37	 38
 39	 40
 41	 42

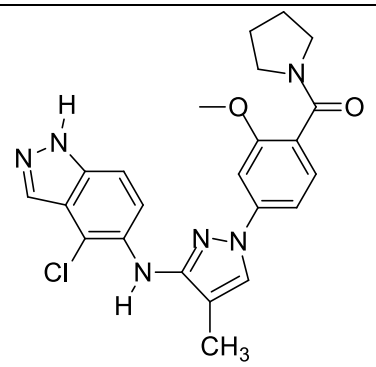
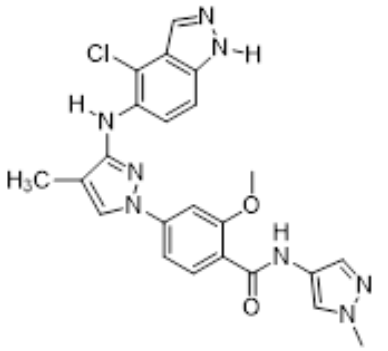
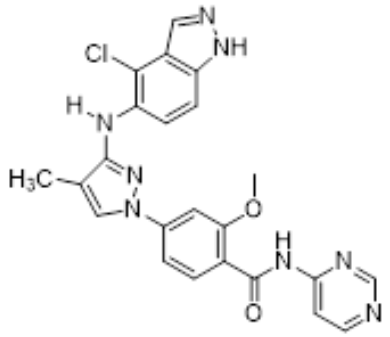
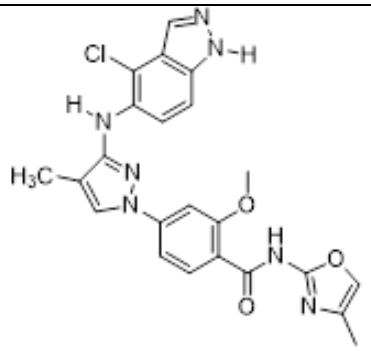
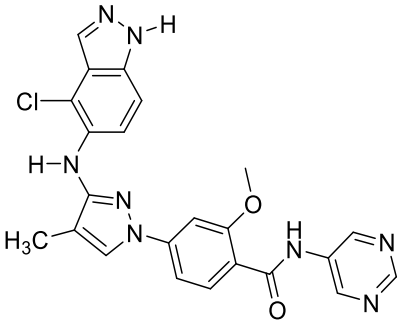
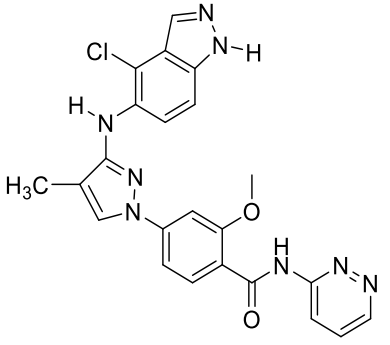
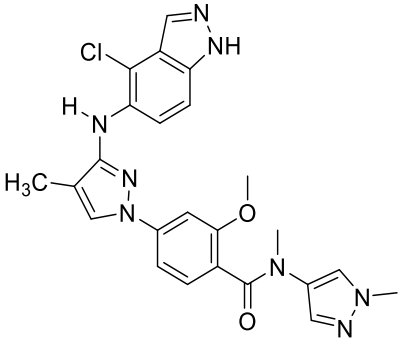
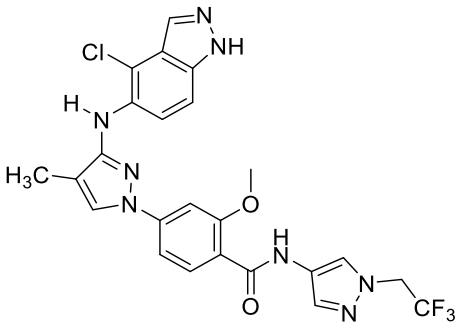
 43	 44
 45	 46
 47	 48
 49	 50
 51	 52
 53	 54

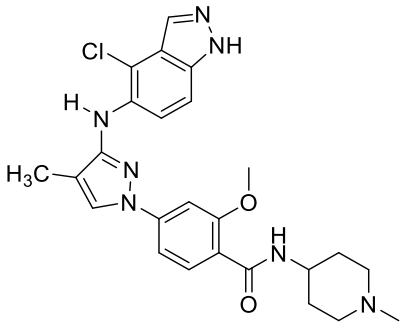
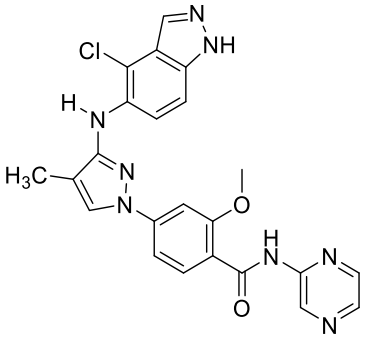
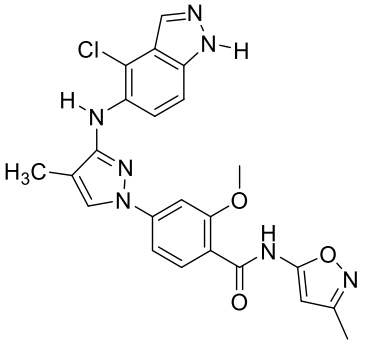
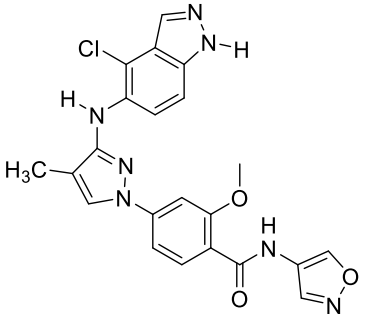
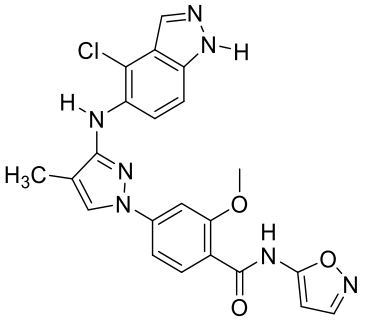
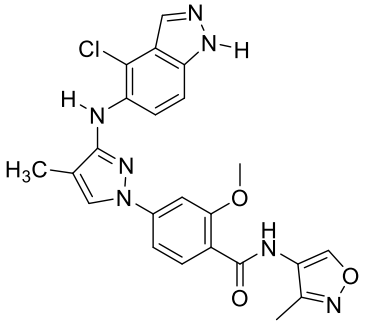
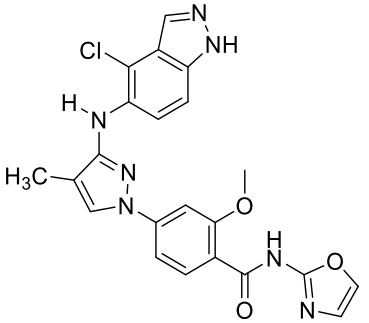
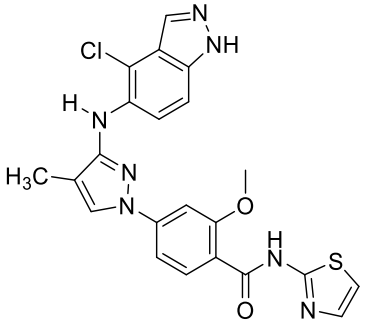
 55	 56
 57	 58
 59	 60
 61	 62
 63	 64

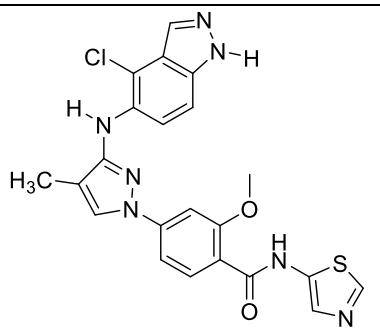
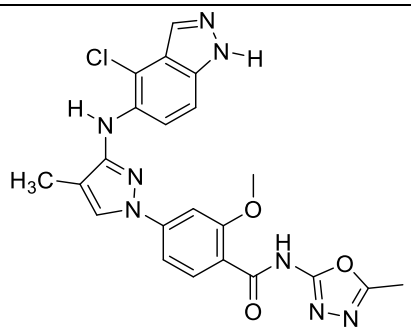
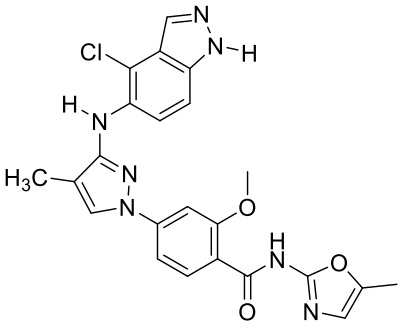
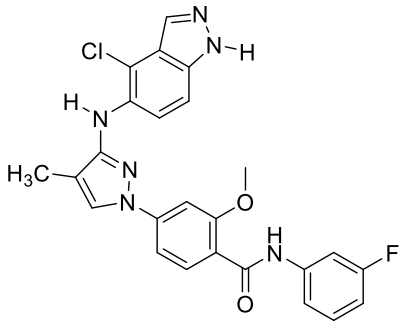
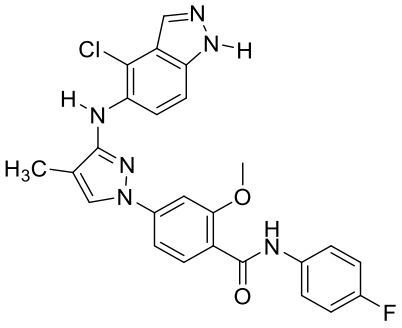
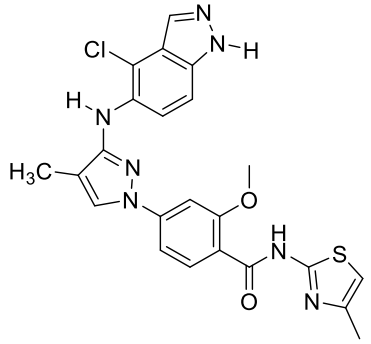
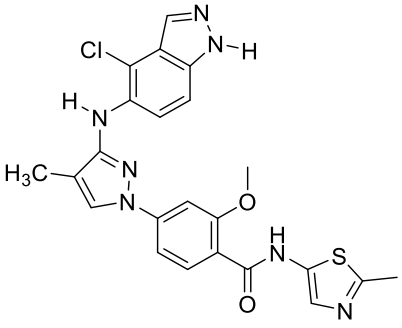
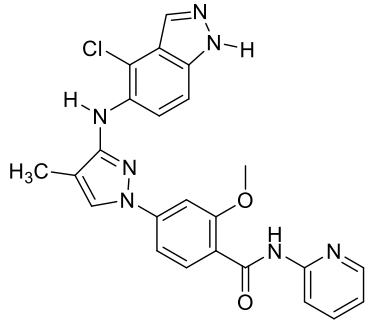
 65	 66
 67	 68
 69	 70
 71	 72

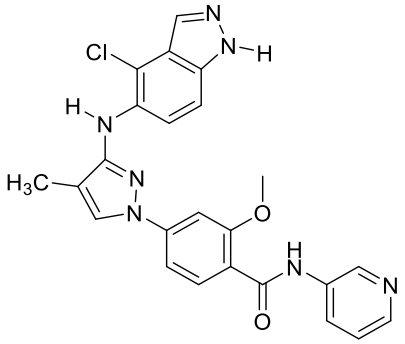
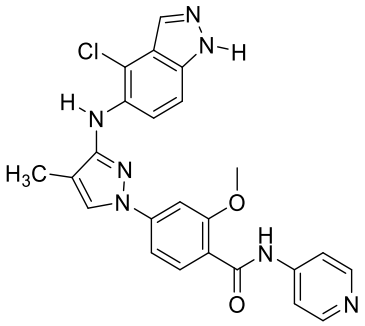
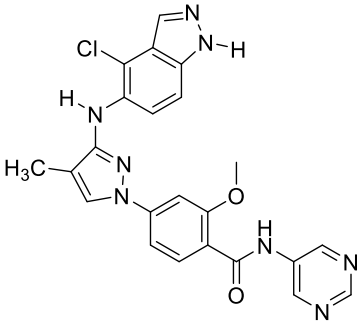
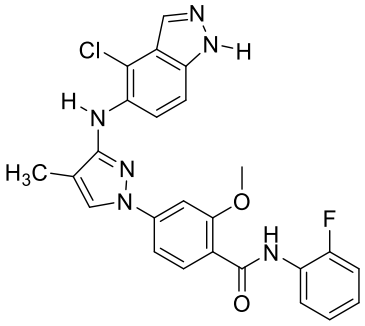
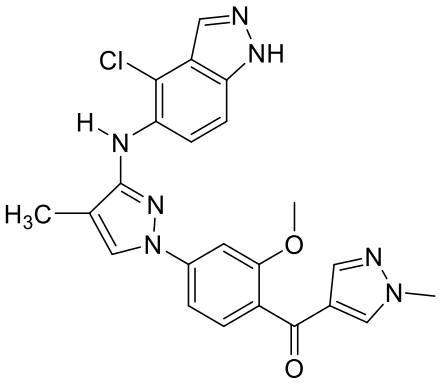
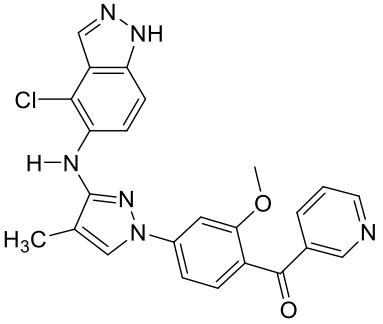
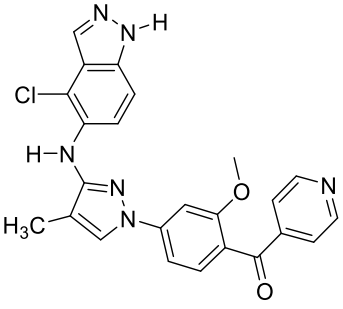
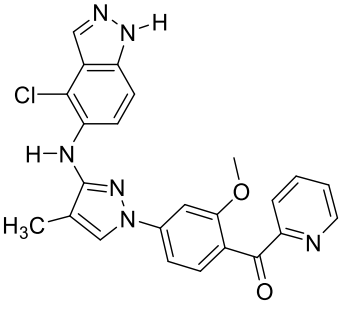
 73	 74
 75	 76
 77	 78
 79	 80

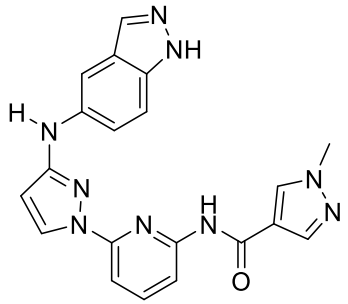
 81	 82
 83	 84
 85	 86
 87	 88

 89	 90
 91	 92
 93	 94
 95	 96

 97	 98
 99	 100
 101	 102
 103	 104

 105	 106
 107	 108
 109	 110
 111	 112

 113	 114
 115	 116
 117	 118
 119	 120



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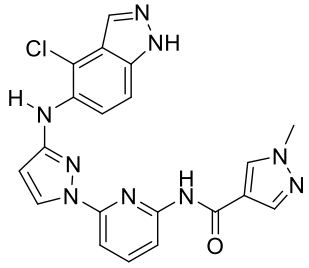

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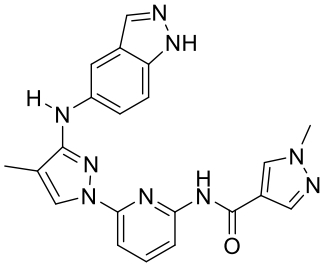

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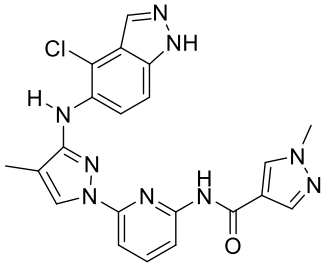

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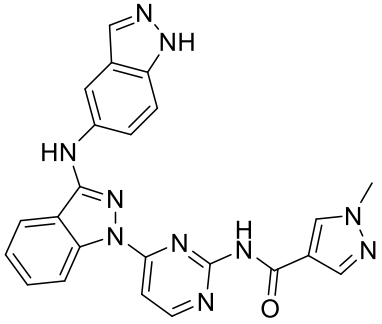

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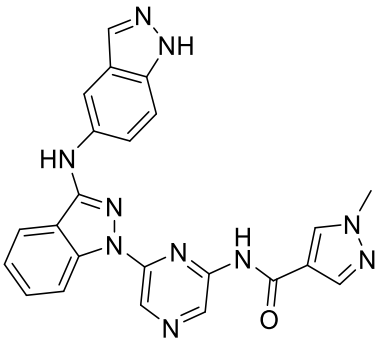

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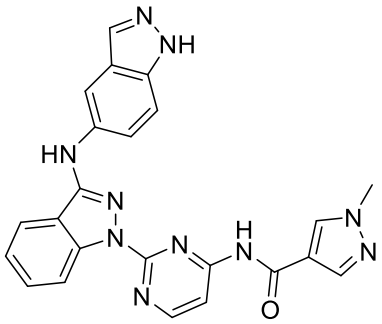

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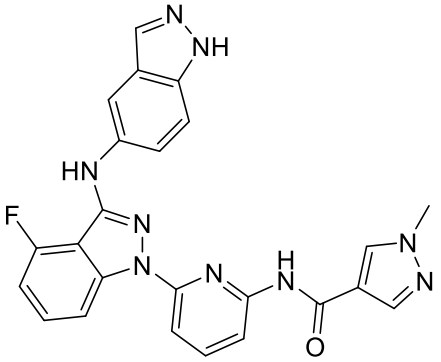

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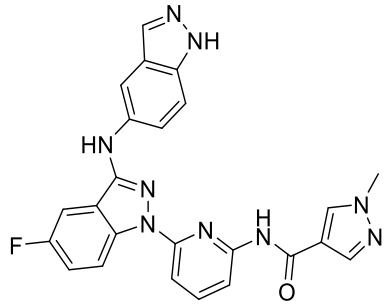
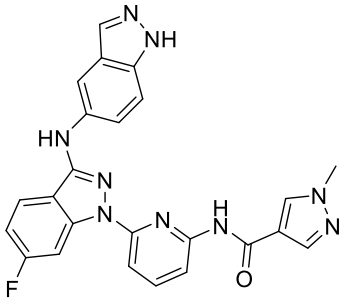
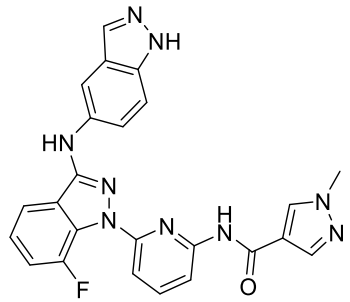
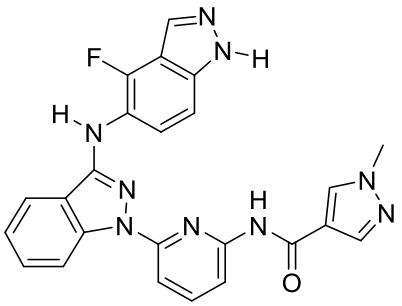
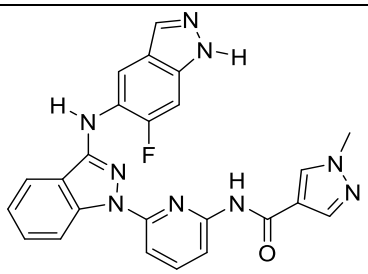
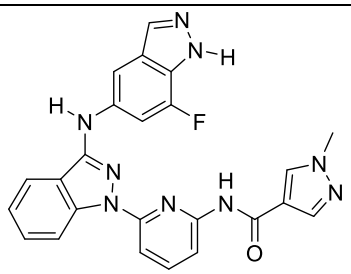
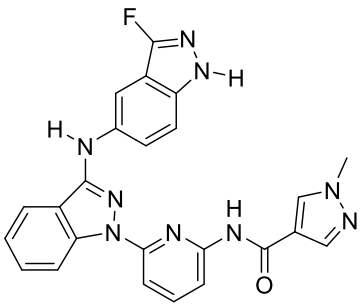
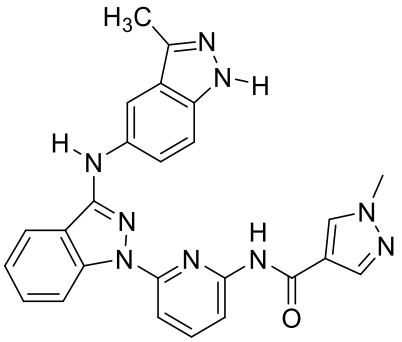
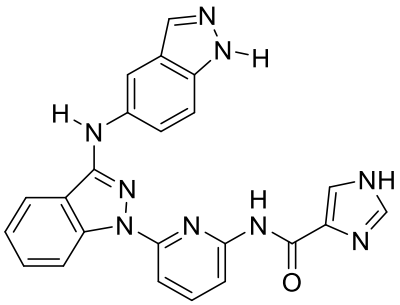
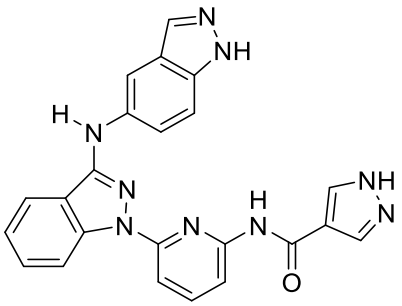
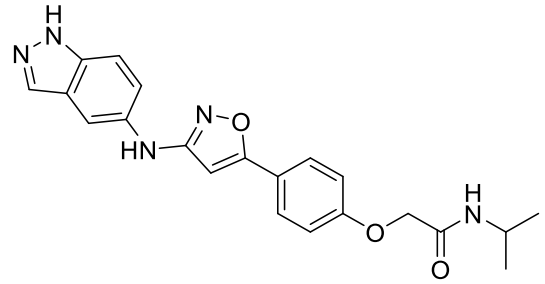
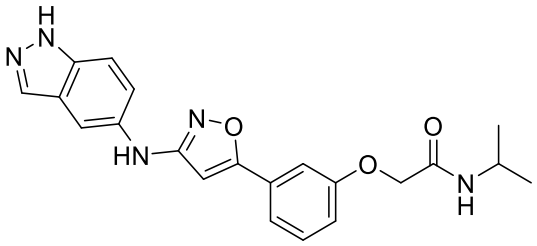
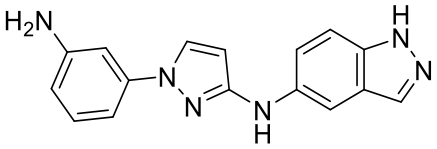
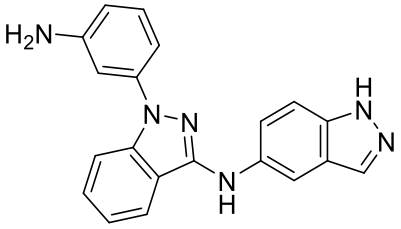
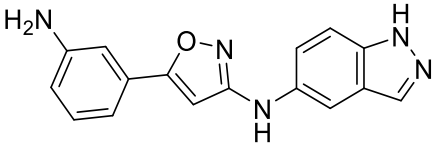
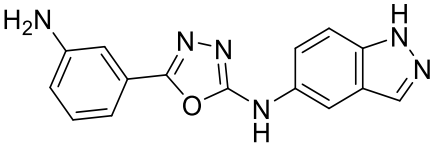
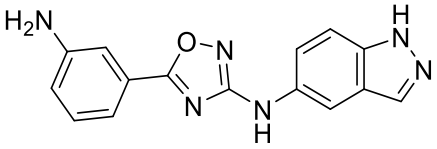
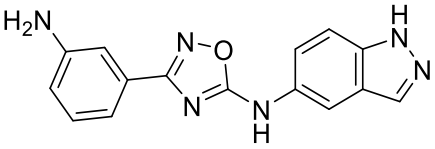
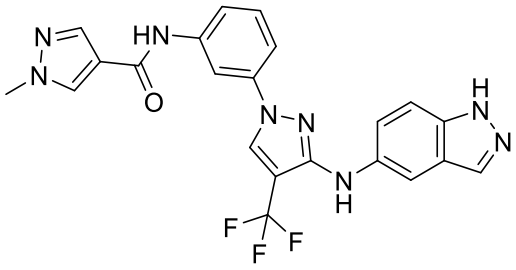
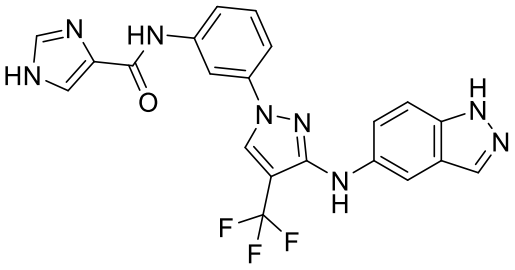
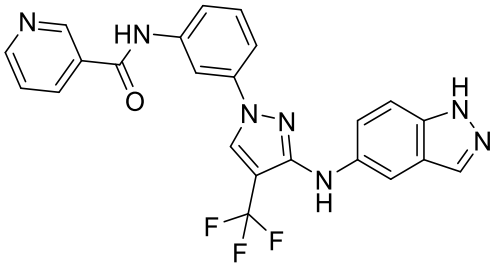
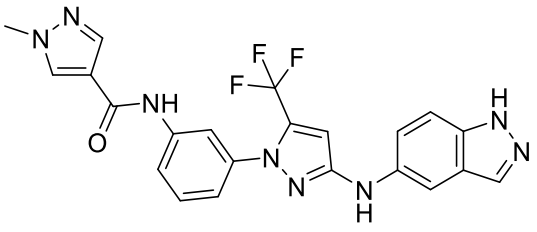
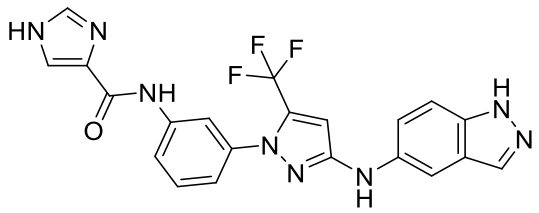
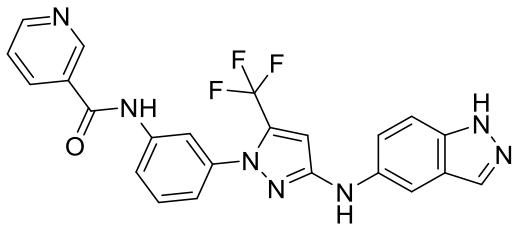
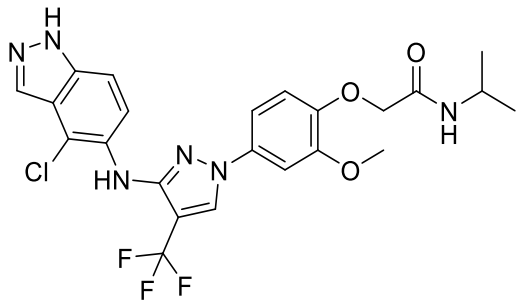
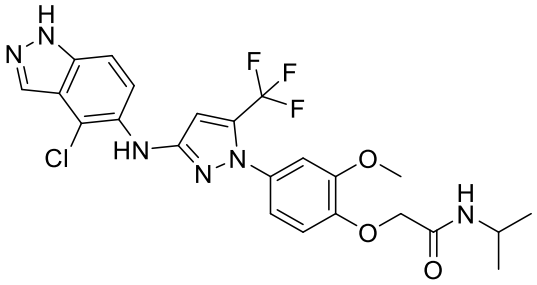
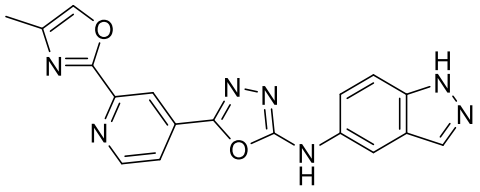
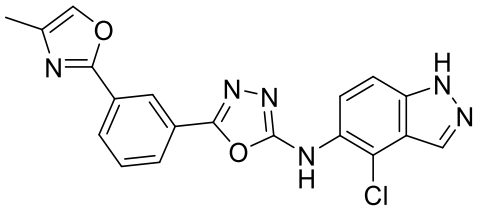
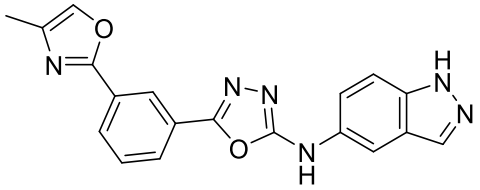
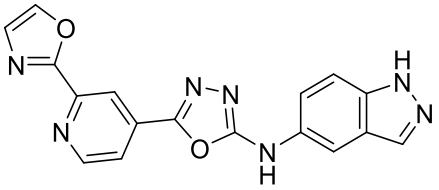
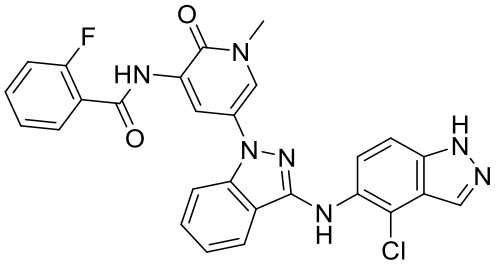
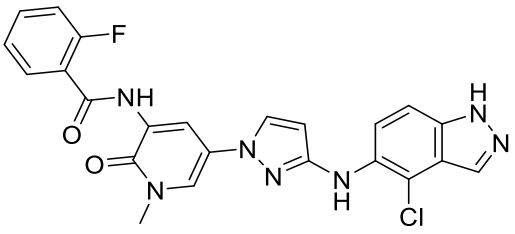
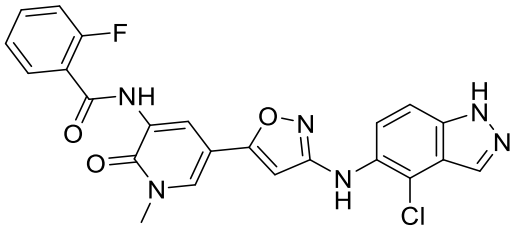
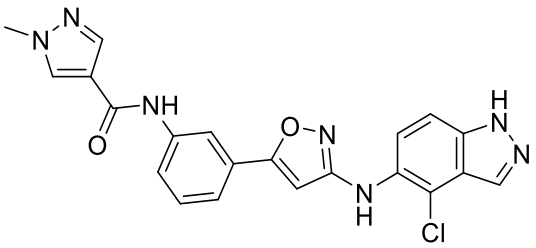
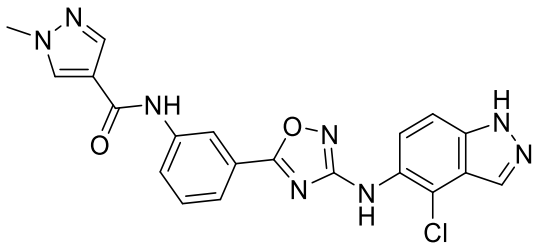
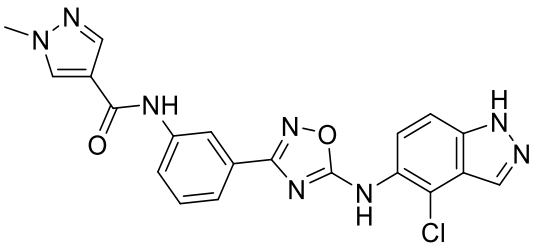
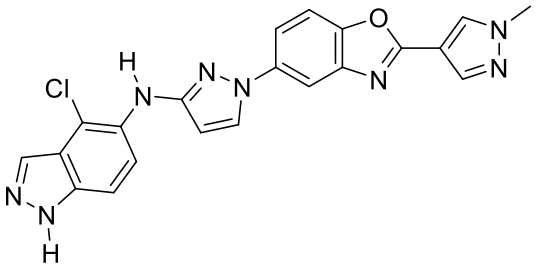
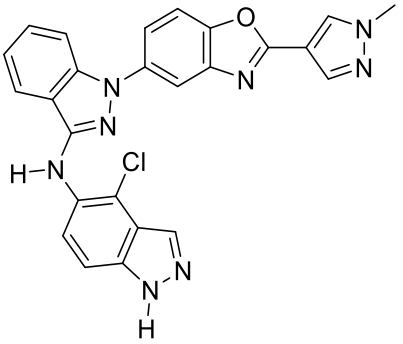
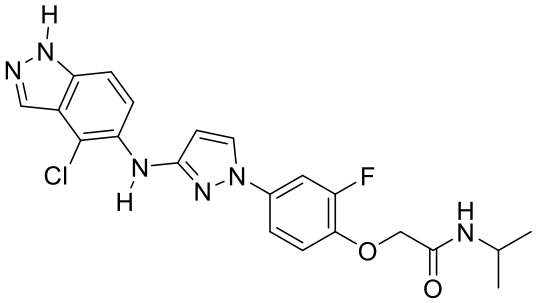
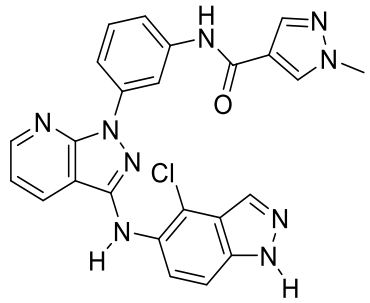
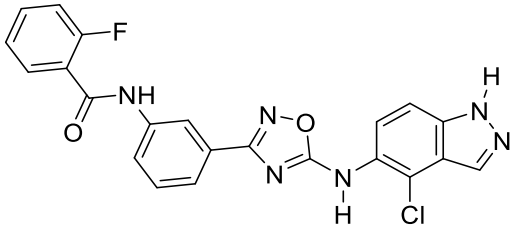
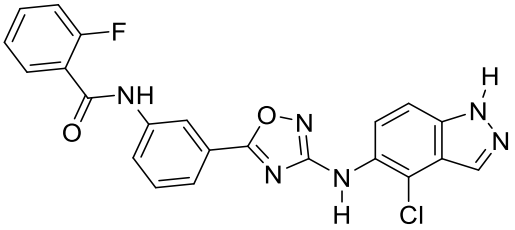
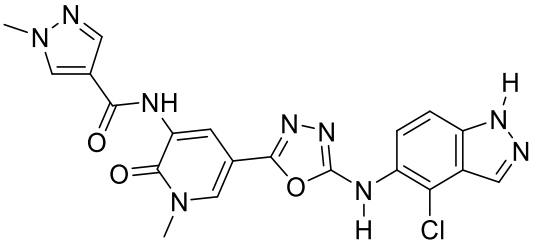
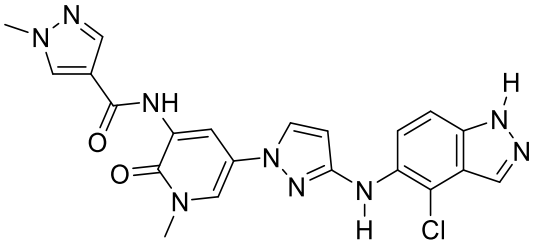
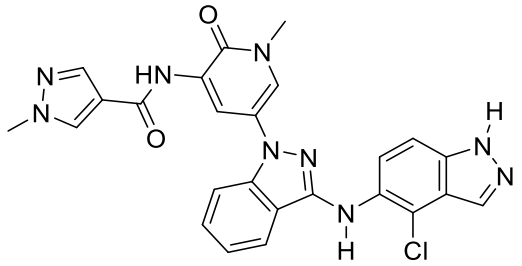
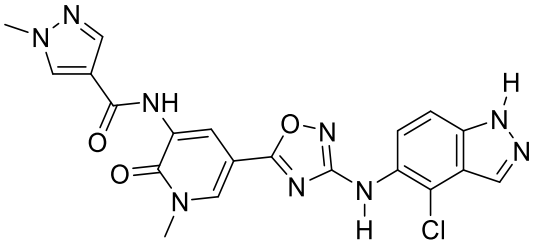
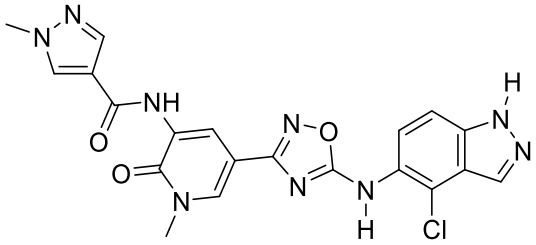
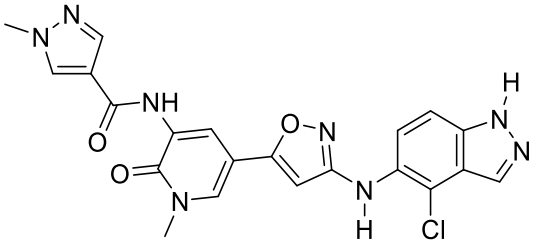
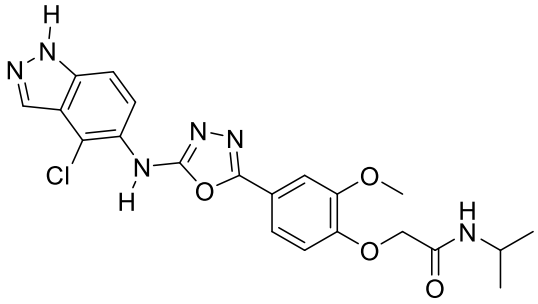
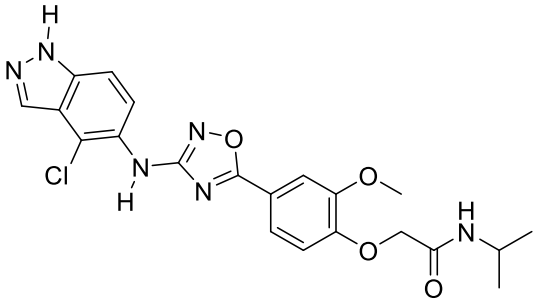
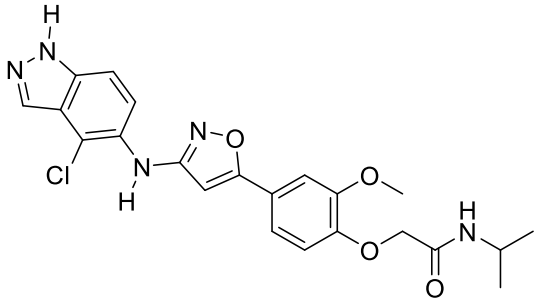
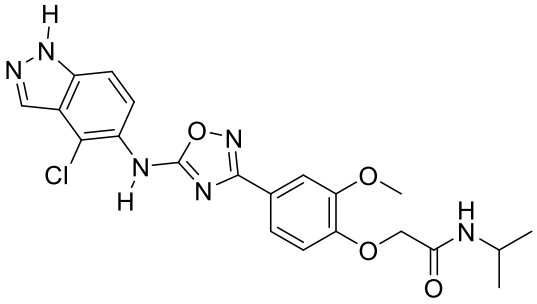
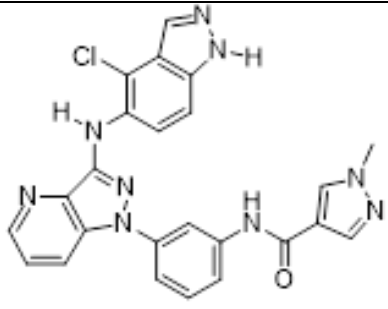
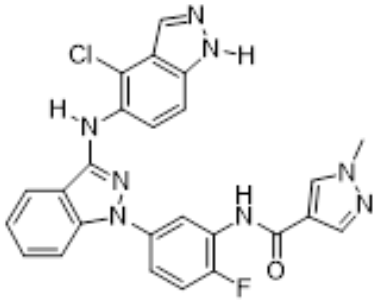
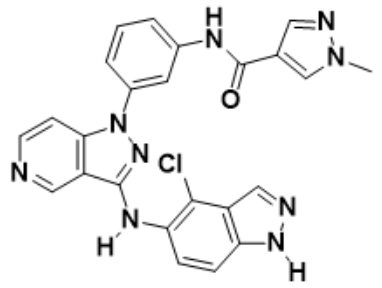
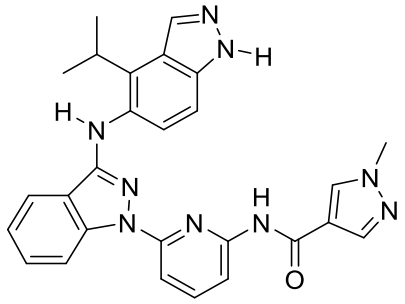
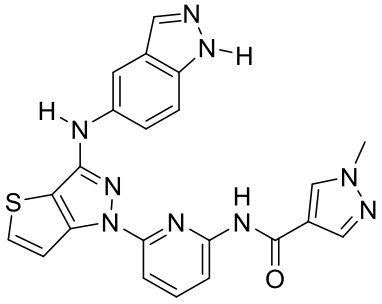
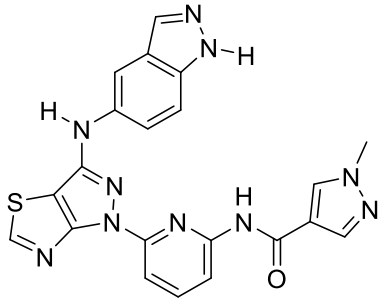
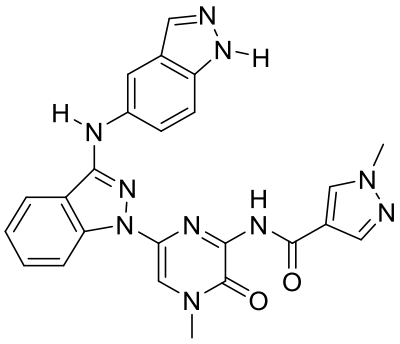
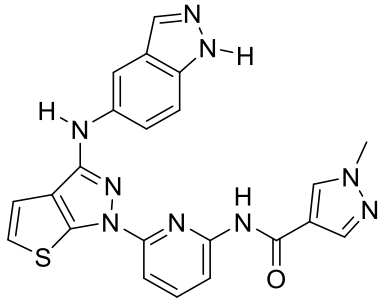
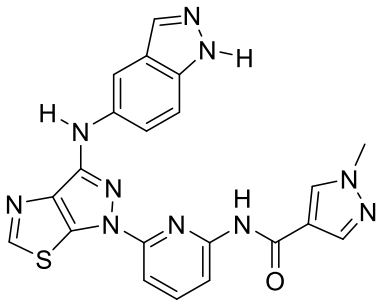
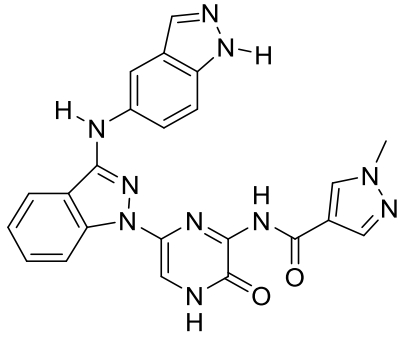
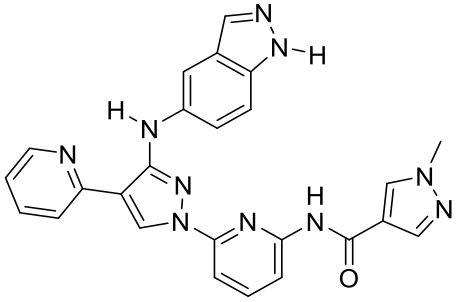
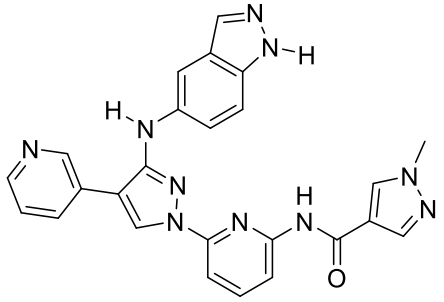
 139	 140
 141	 142
 143	 144
 145	 146
 147	 148

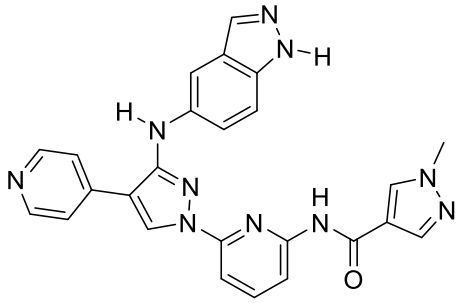
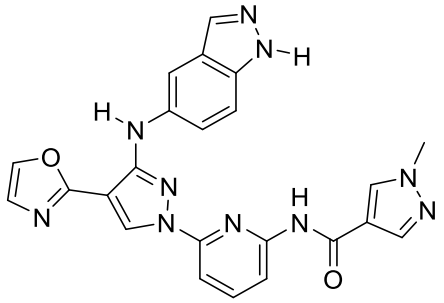
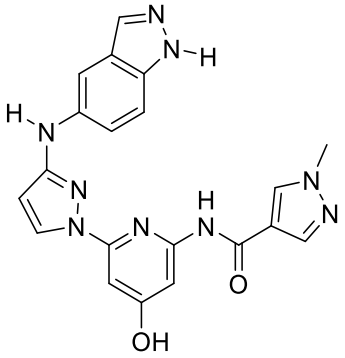
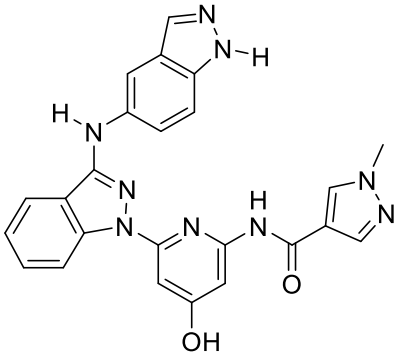
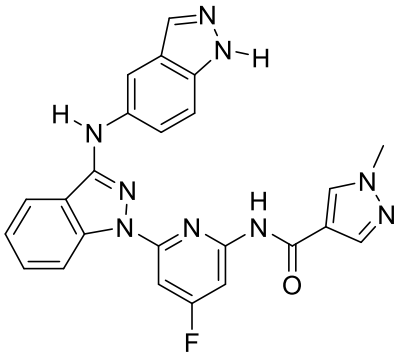
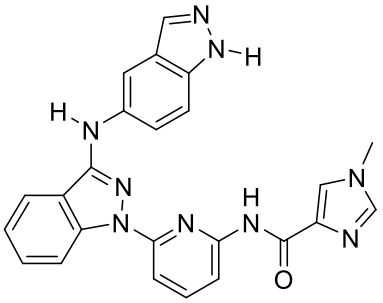
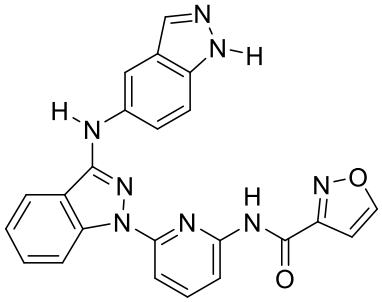
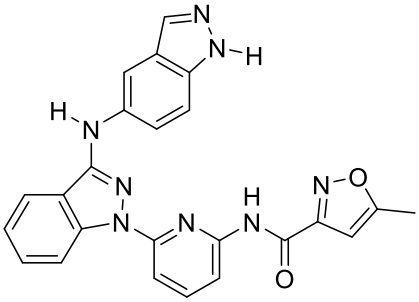
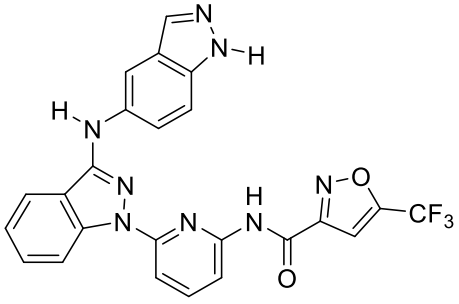
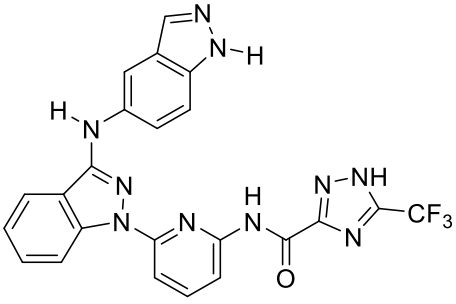
 149	 150
 151	 152
 153	 154
 155	 156
 157	 158
 159	 160

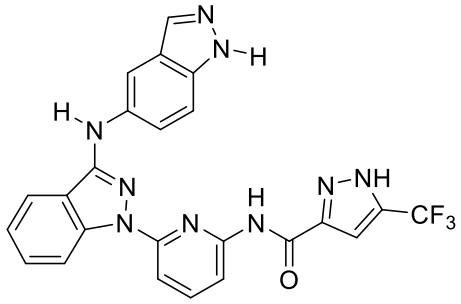
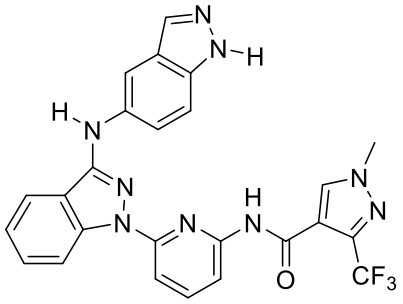
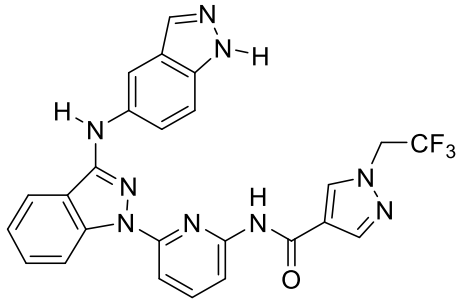
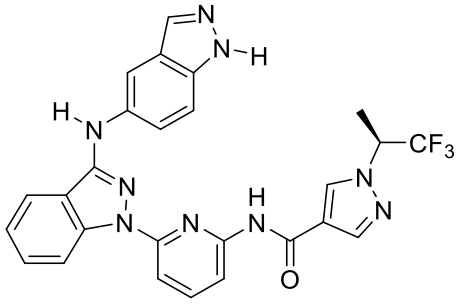
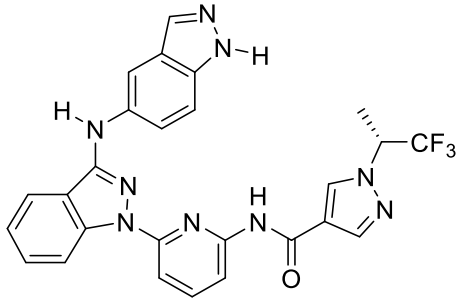
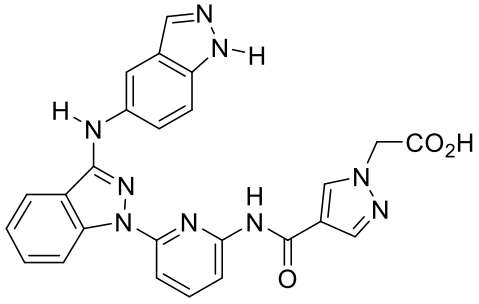
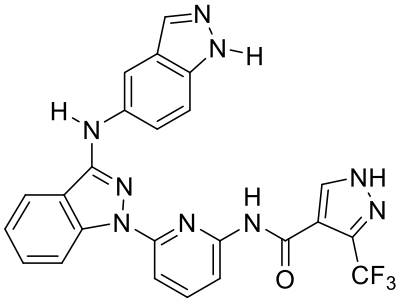
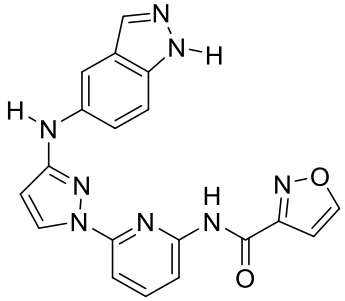
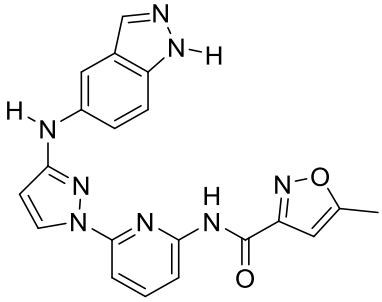
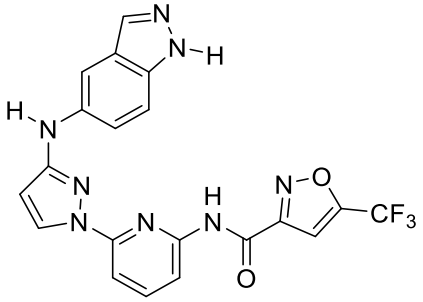
 161	 162
 163	 164
 165	 166
 167	 168
 169	 170
 171	 172

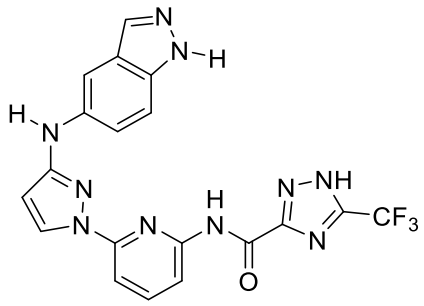
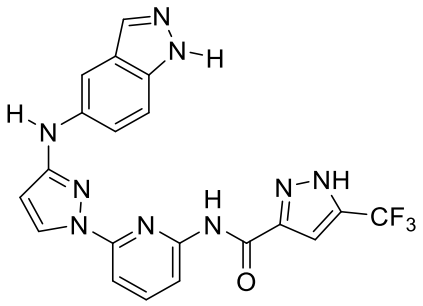
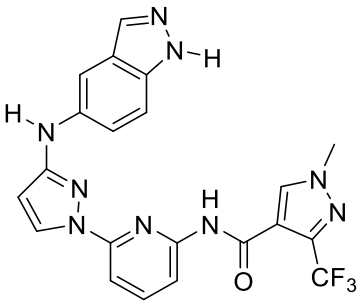
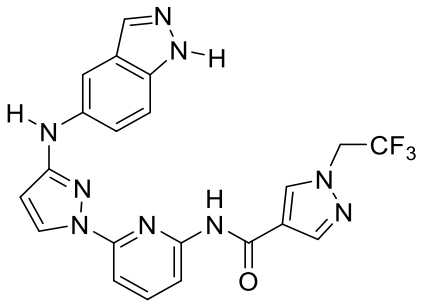
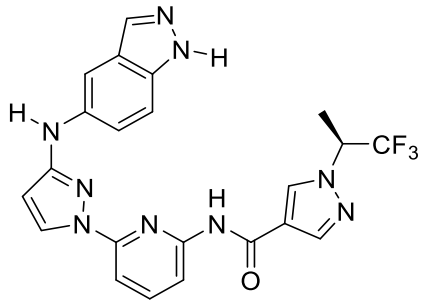
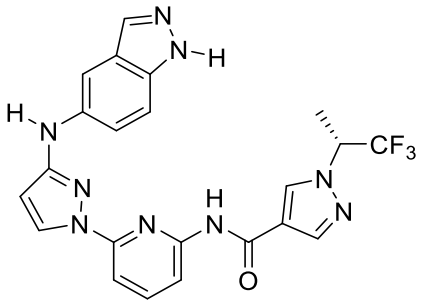
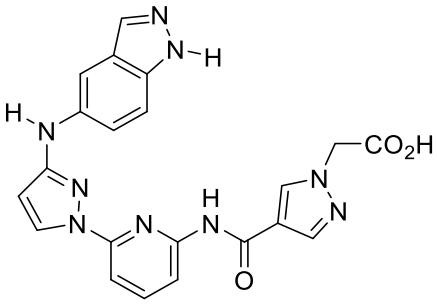
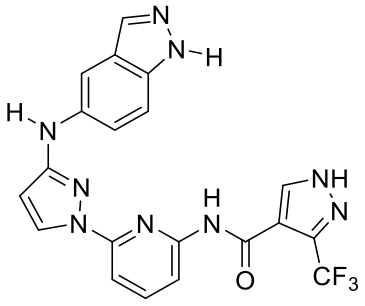
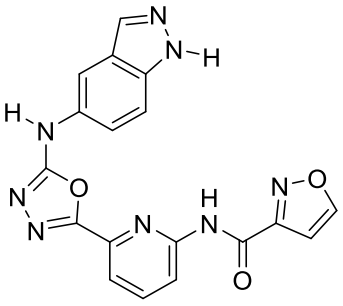
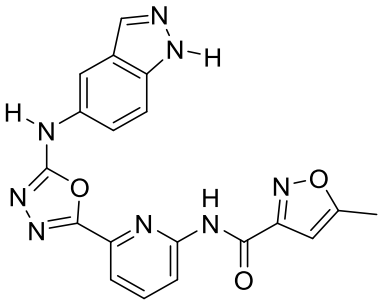
 173	 174
 175	 176
 177	 178
 179	 180
 181	 182

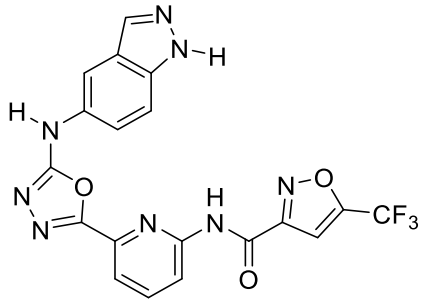
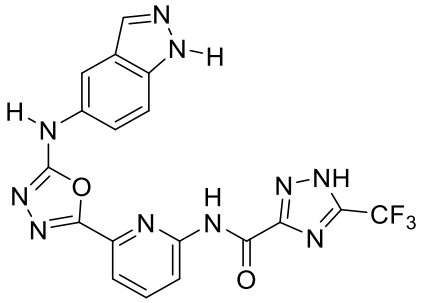
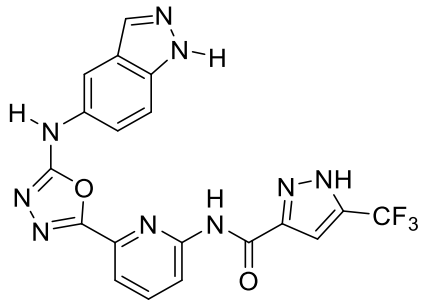
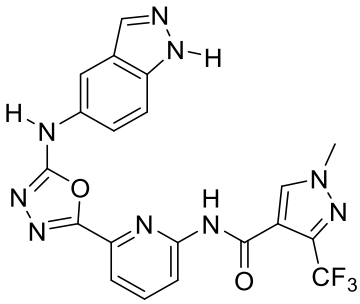
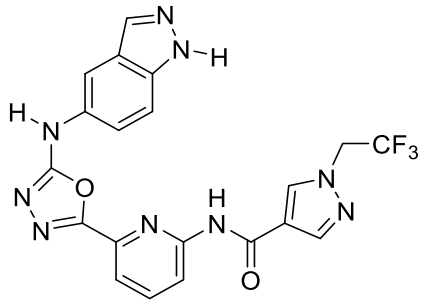
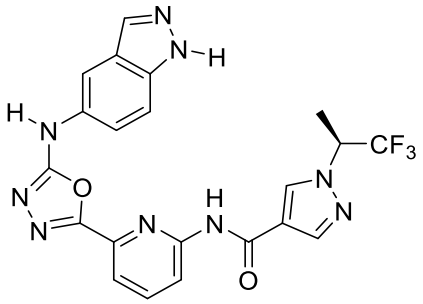
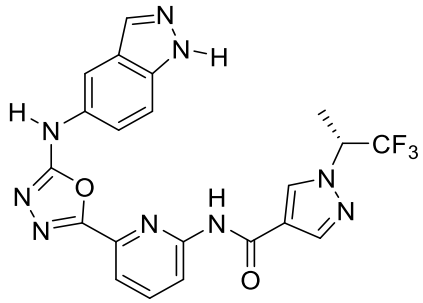
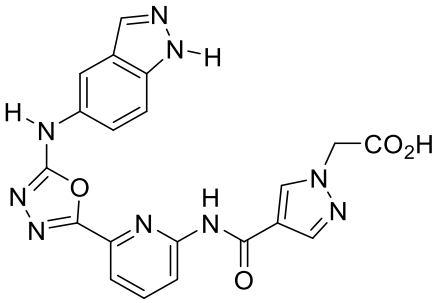
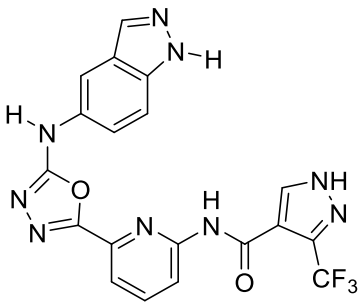
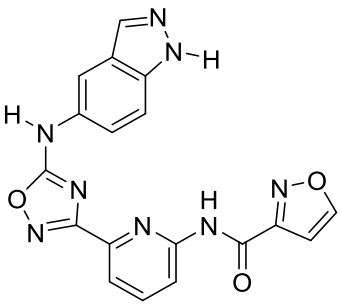
 183	 184
 185	 186
 187	 188
 189	 190
 191	 192

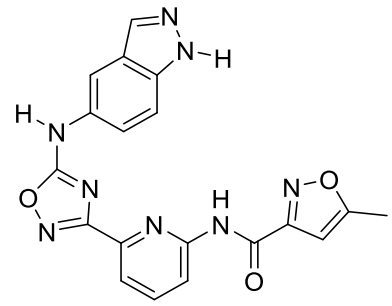
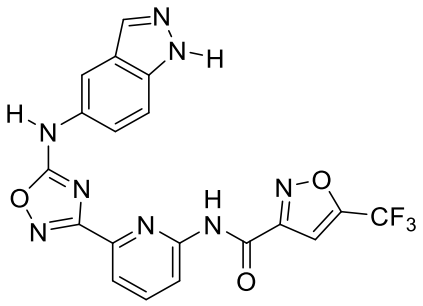
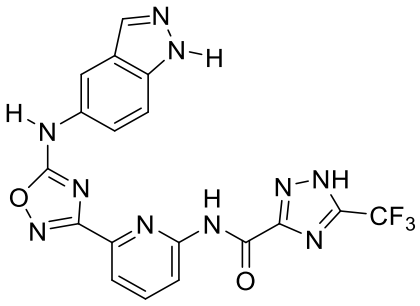
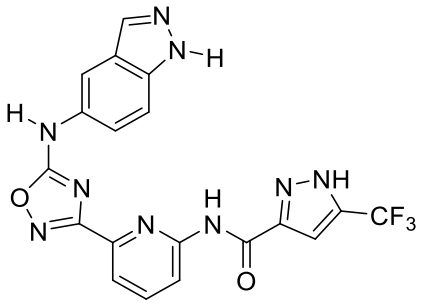
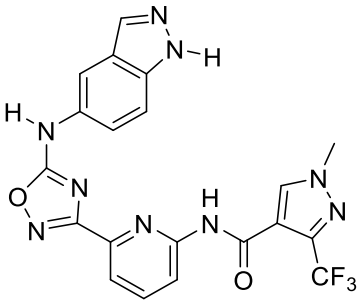
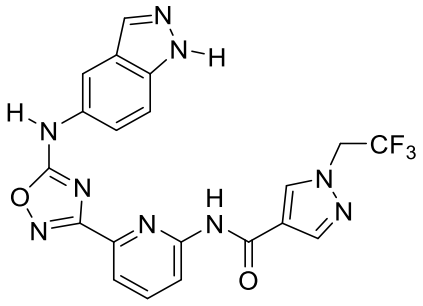
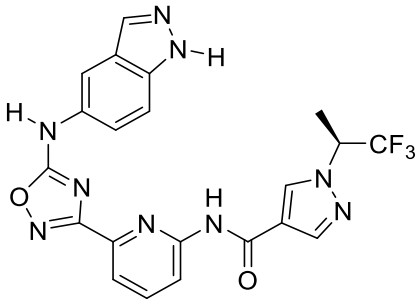
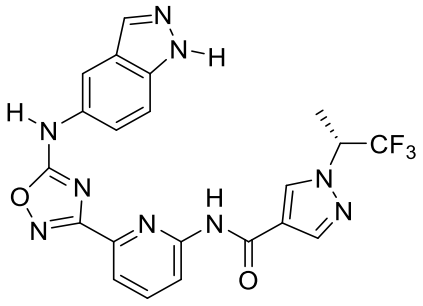
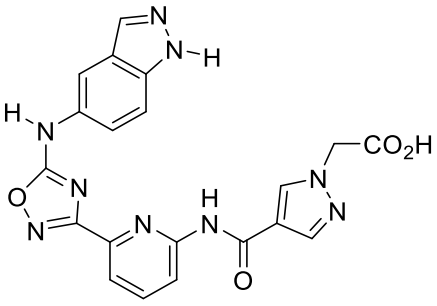
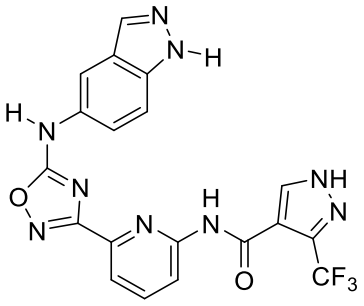
 193	 194
 195	 196
 197	 198
 199	 200
 201	 202

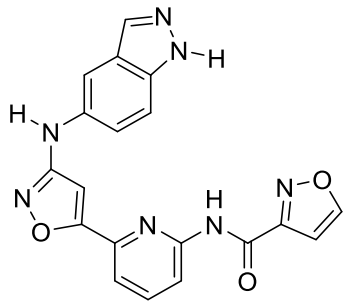
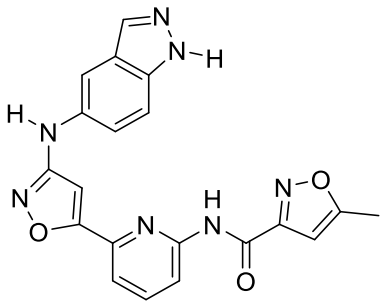
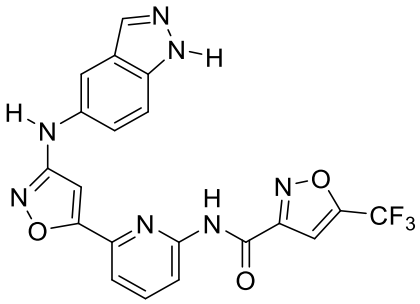
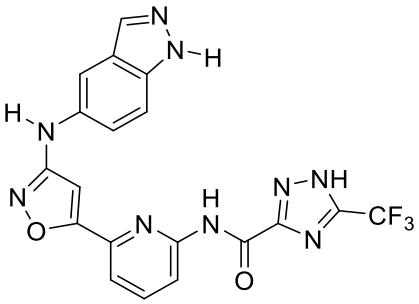
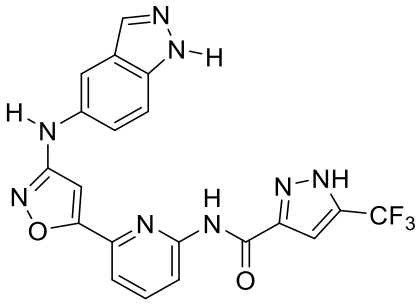
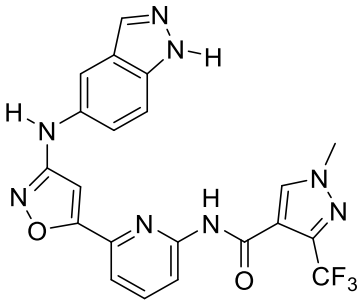
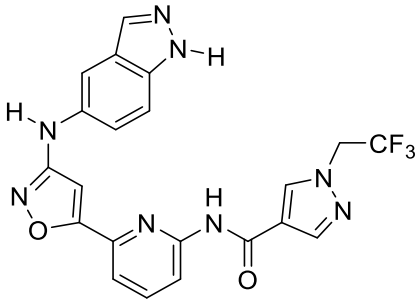
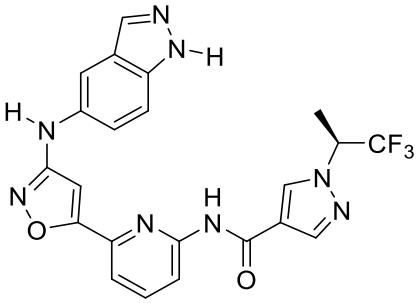
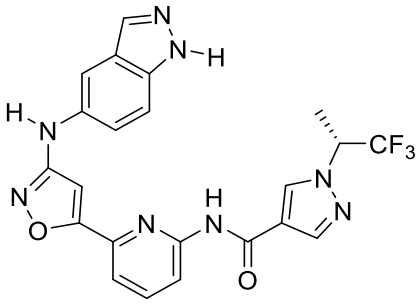
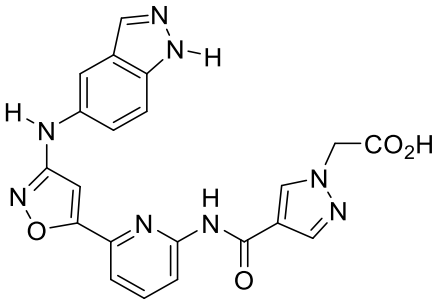
 203	 204
 205	 206
 207	 208
 209	 210
 211	 212

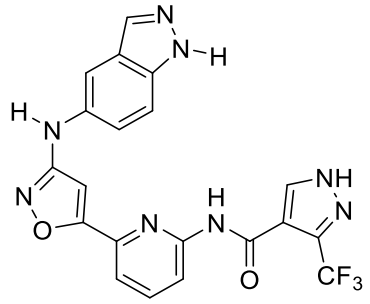
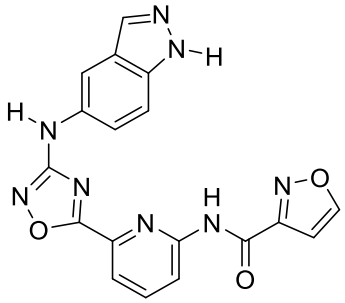
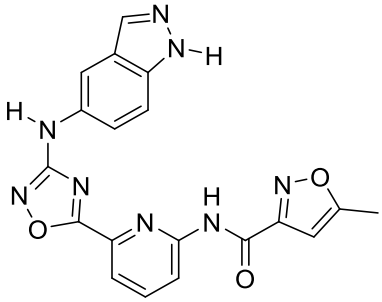
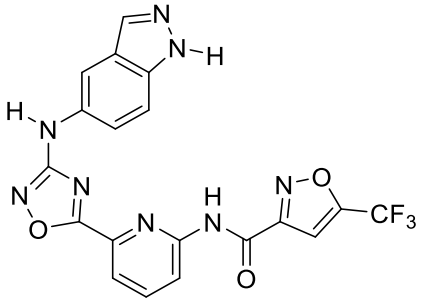
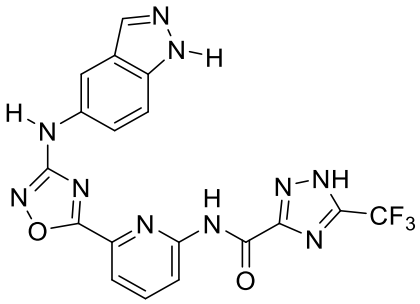
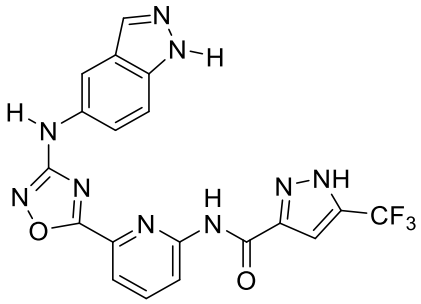
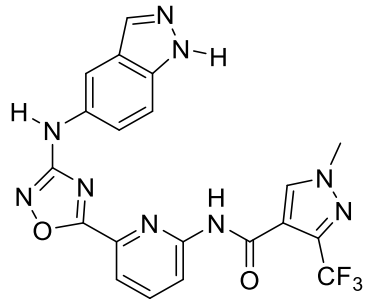
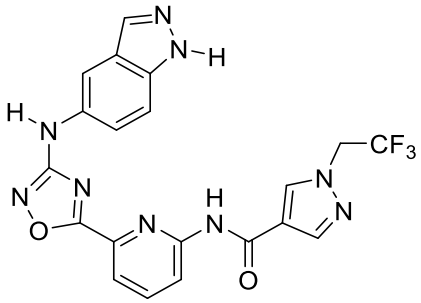
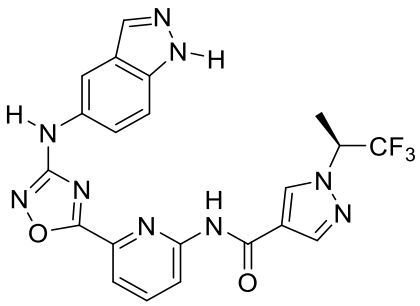
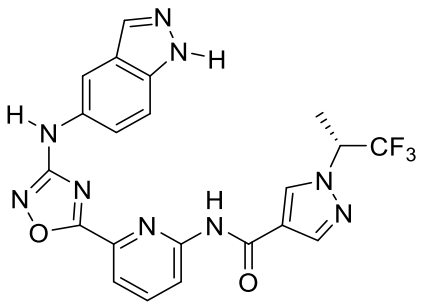
 213	 214
 215	 216
 217	 218
 219	 220
 221	 222

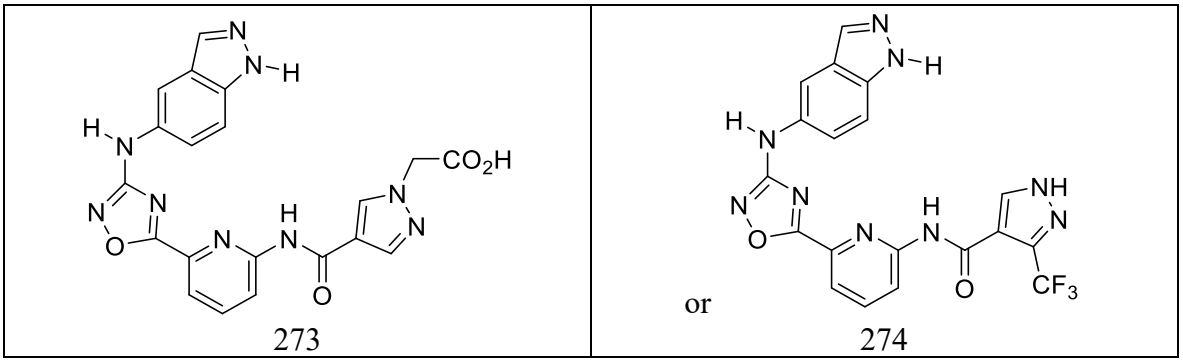
 223	 224
 225	 226
 227	 228
 229	 230
 231	 232

 233	 234
 235	 236
 237	 238
 239	 240
 241	 242

 243	 244
 245	 246
 247	 248
 249	 250
 251	 252

 253	 254
 255	 256
 257	 258
 259	 260
 261	 262

 263	 264
 265	 266
 267	 268
 269	 270
 271	 272



273 or 274

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof.

61. The compound of any of claims 1-60, or a pharmaceutically acceptable salt or tautomer thereof.

62. A pharmaceutical composition comprising a compound of any of claims 1-60, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, and a pharmaceutically acceptable excipient.

63. Use of a compound of any of claims 1-60, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, or a pharmaceutical composition of claim 62, in the manufacture of a medicament for treating a disease or disorder associated with ROCK2 in a subject in need thereof, wherein the disease or disorder associated with ROCK2 is a fibrotic disorder, autoimmune disease, inflammatory condition, edema, ophthalmic disease, cardiovascular disease, central nervous system disorder, or cancer.

64. Use of a compound of any of claims 1-60, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, or a pharmaceutical composition of claim 62, in the manufacture of a medicament for preventing a disease or disorder associated with ROCK2 in a subject in need thereof, wherein the disease or disorder associated with ROCK2 is a fibrotic disorder, autoimmune disease, inflammatory condition, edema, ophthalmic disease, cardiovascular disease, central nervous system disorder, or cancer.

65. A compound of any one of claims 1-60, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, or a pharmaceutical composition of claim 62, for use as a medicament.

66. The use of claim 63 or 64, wherein the disease or disorder associated with ROCK2 is a fibrotic disorder.

67. The use of claim 63 or 64, wherein the disease or disorder associated with ROCK2 is pulmonary fibrosis, cystic pulmonary fibrosis, idiopathic pulmonary fibrosis, radiation induced lung injury, liver fibrosis including cirrhosis, cardiac fibrosis including arterial fibrosis, endomyocardial fibrosis, old myocardial infarction, arterial stiffness, atherosclerosis, restenosis, arthrofibrosis, Crohn's disease, myelofibrosis, Peyronie's disease, nephrogenic systemic fibrosis, progressive massive fibrosis, retroperitoneal cavity fibrosis, scleroderma/systemic sclerosis, mediastinal fibrosis, keloids and hypertrophic scars, glial scarring, or renal fibrosis.

68. The use of claim 63 or 64, wherein the disease or disorder associated with ROCK2 is Huntington's disease, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Batten disease, dementia, spinal muscular atrophy, motor neurone disease, spinocerebellar ataxia, acute or chronic pain, dementia, neuronal degeneration, spinal cord injury, or cerebral vasospasm.

69. The use of claim 63 or 64, wherein the disease or disorder associated with ROCK2 is glaucoma.

70. The use of claim 63 or 64, wherein the disease or disorder associated with ROCK2 is asthma, cardiovascular inflammation, renal inflammation, or arteriosclerosis.

71. The use of claim 63 or 64, wherein the disease or disorder associated with ROCK2 is hypertension, atherosclerosis, angina, arterial obstruction, peripheral arterial disease, peripheral circulatory disorder, cerebral cavernous malformation, restenosis, cardiac hypertrophy, ocular hypertension, cerebral ischemia, cerebral vasospasm, acute respiratory distress syndrome (ARDS), or erectile dysfunction.

72. The use of claim 63 or 64, wherein the disease or disorder associated with ROCK2 is rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, psoriasis, Crohn's disease, atopic dermatitis, eczema, or graft-versus-host disease (GVHD).

73. The use of claim 63 or 64, wherein the disease or disorder associated with ROCK2 is cancer.

74. The use of claim 63 or 64, wherein the disease or disorder associated with ROCK2 is lymphedema.

75. The use of claim 74, wherein the lymphedema is caused at least by a parasitic disease.

76. The use of claim 63 or 64, wherein the disease or disorder associated with ROCK2 is angioedema, brain edema, CHAPLE syndrome, cardiac edema, hydrops fetalis, inflammatory edema, macular edema, myxedema, pulmonary edema, peripheral edema, periorbital edema, or cutaneous edema.

77. The use of claim 63 or 64, wherein the disease or disorder associated with ROCK2 is hereditary angioedema, cystoid macular edema, Irvine-Gass syndrome, diabetic macular edema, or pedal edema.

78. An *in vitro* or *ex-vivo* method of inhibiting ROCK2 comprising contacting ROCK2 with an effective amount of a compound of any of claims 1-60, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, or a pharmaceutical composition of claim 62.

79. A method of screening a library of compounds comprising performing an assay on a compound of any of claims 1-60, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, and an additional compound, wherein the additional compound is different from the compound of any of claims 1-60, or pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof.

80. A kit comprising a compound of any of claims 1-60, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, or a pharmaceutical composition of claim 62 and instructions for using the compound, or pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, or isotopically enriched compound thereof, or pharmaceutical composition.