SMALL MOLECULE MODULATORS OF GLUCOCEREBROSIDASE ACTIVITY AND USES THEREOF

RELATED APPLICATION

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application 63/255,272, filed October 13, 2021, the entirety of which is incorporated herein by reference.

BACKGROUND

[0002] Glucocerebrosidase (EC 3.2.1.45), also called β-glucocerebrosidase, β-glucosidase, D-glucosyl-N-acylsphingosine glucohydrolase, or GCase, is an enzyme having glucosylceramidase activity. Glucocerebrosidase is required to cleave the beta-glucosidic linkage of the chemical glucocerebroside, which is an intermediate in glycolipid metabolism. Glucocerebrosidase is localized in the lysosome and disabling mutations in the gene for glucocerebrosidase (GBA1) are associated with abnormal accumulation of lipids in lysosomes.

[0003] Genetic diseases caused by mutations in GBA1 include neurodegenerative diseases such as Gaucher's disease and Parkinson's disease. Current treatments for diseases such Type 1 Gaucher's disease are limited to enzyme replacement therapy (ERT) administered every two weeks. ERT is very expensive and not effective for neuronopathic forms of Gaucher's disease. Efforts to discover and employ small molecule compounds to activate Gcase have been met with limited success. Thus, there is a need for new compounds that effectively activate Gcase and are useful in the treatment of neurodegenerative diseases (e.g., Gaucher's disease and Parkinson's disease).

SUMMARY

[0004] The present disclosure provides compounds that are modulators of GCase. These compounds provide new compositions and methods for the treatment of diseases associated with GCase activity (*e.g.*, neurodegenerative diseases, such as Gaucher's disease and Parkinson's disease).

[0005] Provided are compounds of Formula (**I**):

substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^7 is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy;

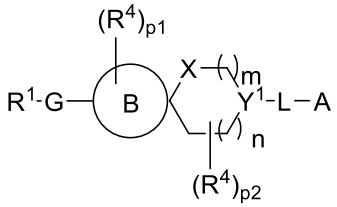
R^8 is substituted or unsubstituted alkyl;

each R^A is independently hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group;

m and n are each independently 0, 1, or 2; and

p1 and p2 are each independently 0, 1, 2, 3, 4, 5, or 6.

[0005a] In one aspect, the present disclosure provides a compound of Formula (**I**):



(**I**),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl, haloalkyl, or a nitrogen protecting group;

G is a bond, $-NR^A-$, $-C(=O)-$, $-SO_2-$, -O-, $-OC(R^5)(R^6)-$, or $-C(R^5)(R^6)-$;

B is heterocyclyl comprising at least one nitrogen atom in its ring, or cycloalkyl;

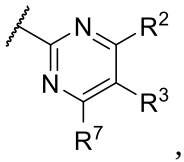
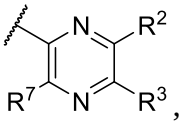
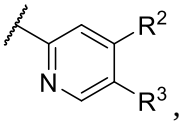
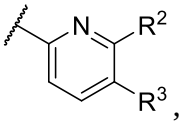
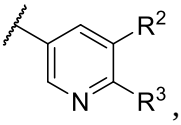
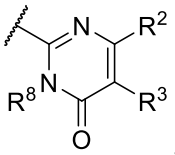
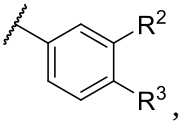
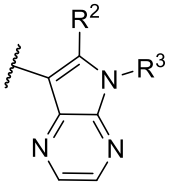
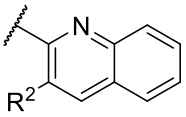
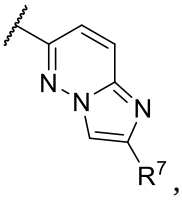
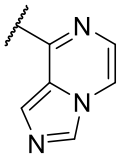
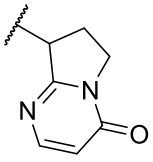
each occurrence of R^4 is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or two instances of R^4 on different carbons combine to form a bridged ring, or two instances of R^4 on the same carbon form with that carbon a carbonyl or a cycloalkyl;

X is $-C(R^4)_2-$, $-NR^A-$, or -O-;

Y^1 is N or CR^5;

each occurrence of R^5 and R^6 are each independently hydrogen, halogen, or substituted or unsubstituted alkyl;

L is a bond, $–SO_2–$, –C(=O)–, –C(=O)C(R^5)(R^6)-, $-NR^A-$, or -NHC(=O)-;

A is , , , , , , , , , , , , or substituted or unsubstituted 5-membered heteroaryl;

R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted aryl; or R^2 and R^3 are each independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^7 is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy;

R^8 is substituted or unsubstituted alkyl;

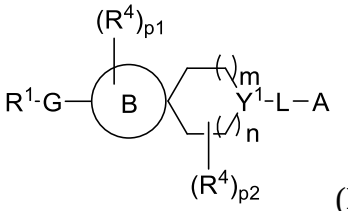
each R^A is independently hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group;

m is 0, 1, or 2;

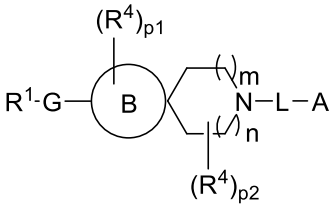
n is 1, 0, or 2; and

p1 and p2 are each independently 0, 1, 2, 3, 4, 5, or 6.

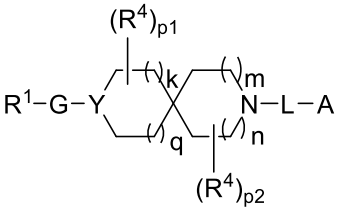
[0006] In certain examples, the compounds of Formula (**I**) are compounds of Formula (**I-1**), (**I-a**), (**I-b**), (**I-g**), (**I-g-13**), (**I-k**), (**I-k-3**), (**I-k-5**), (**I-l**), (**I-l-3**), (**I-l-5**), (**I-m**), (**I-m-3**), (**I-n**), (**I-n'**), (**I-o**), (**I-o'**), (**I-p**), (**I-p'**), (**I-x**), (**I-x-1**), (**I-y**), (**I-z**), (**I-aa**), (**I-bb**), (**I-cc**), (**I-dd**), (**I-ee**), (**I-ff**), or (**I-gg**):



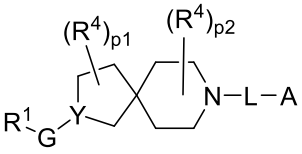
(**I-1**),



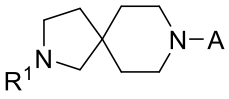
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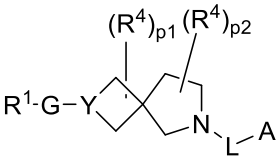
(**I-b**),



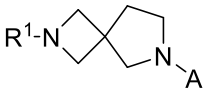
(**I-g**),



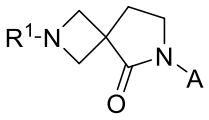
(**I-g-13**),



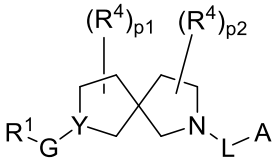
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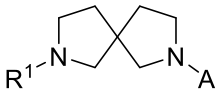
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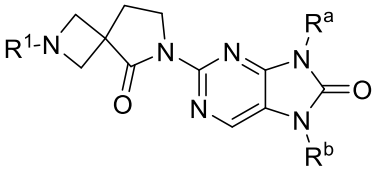
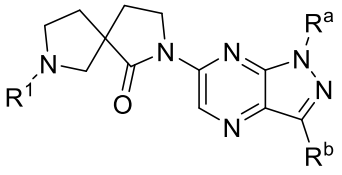
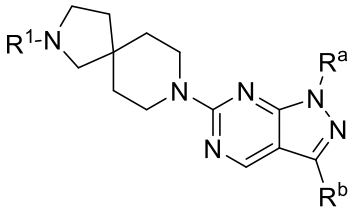
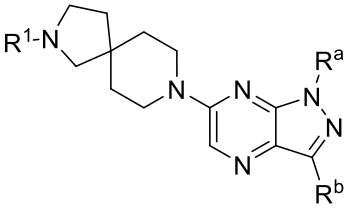
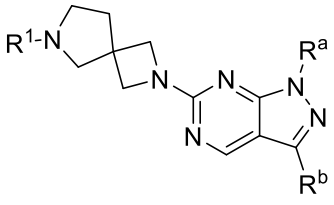
(**I-k-5**),



(**I-l**),



(**I-l-3**),


(**I-cc**),

(**I-dd**),

(**I-ee**),

(**I-ff**),

(**I-gg**),

or pharmaceutically acceptable salts thereof.

[0007] Provided are pharmaceutical compositions comprising a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient.

[0007a] In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0008] Provided are methods of treating a disease or disorder in a subject in need thereof, the method comprising administering a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (**I**) to the subject.

[0008a] In another aspect, the present disclosure provides use of a compound as described herein, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein in the manufacture of a medicament for treating a disease or disorder in a subject in need thereof.

[0008b] In another aspect, the present disclosure provides a compound as described herein, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein for use in therapy.

[0009] In certain examples, the disease or disorder is associated with glucocerebrosidase activity. In certain examples, the disease or disorder is a neurological disease or disorder. In certain examples, the neurological disease or disorder is Parkinson's disease or Gaucher's disease.

[0010] Provided are methods of activating glucocerebrosidase, the method comprising contacting glucocerebrosidase with an effective amount of a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (**I**) to the subject.

[0010a] In another aspect, the present disclosure provides a method of activating glucocerebrosidase, the method comprising contacting glucocerebrosidase *in vitro* with an effective amount of a compound as described herein, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein.

[0011] Provided are kits comprising a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof. In certain examples, the kits further comprise instructions for administration (*e.g*., human administration).

[0011a] In another aspect, the present disclosure provides a kit comprising a compound as described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein, and instructions for administering the compound or pharmaceutical composition to a subject in need thereof.

[0012] The details of certain examples 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

Chemical definitions

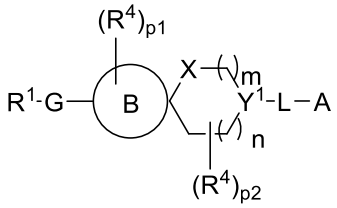
[0013] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups 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.

[0014] 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. While compounds may be depicted as racemic or as one or more diastereoisomers, enantiomers, or other isomers, all such racemic, diastereoisomer, enantiomer, or other isomer forms of that depicted are included in the present disclosure.

CLAIMS

What is claimed is:

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



(**I**),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl, haloalkyl, or a nitrogen protecting group;

G is a bond, -NR^A-, –C(=O)–, –SO_2–, -O-, -$OC(R^5)(R^6)$-, or -$C(R^5)(R^6)$-;

B is heterocyclyl comprising at least one nitrogen atom in its ring, or cycloalkyl;

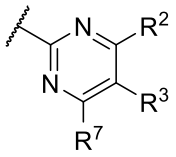
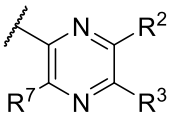
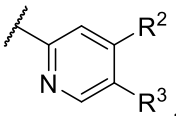
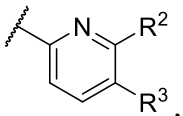
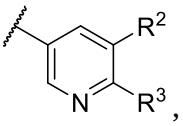
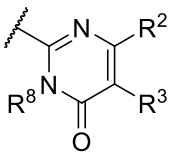
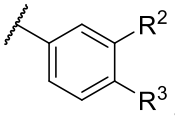
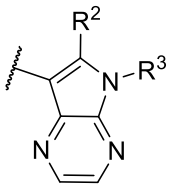
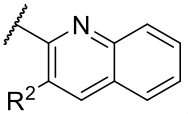
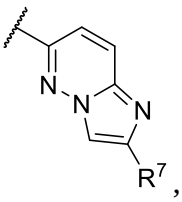
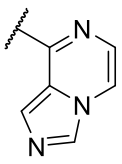
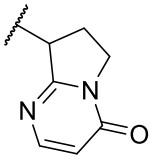
each occurrence of R^4 is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or two instances of R^4 on different carbons combine to form a bridged ring, or two instances of R^4 on the same carbon form with that carbon a carbonyl or a cycloalkyl;

X is -$C(R^4)_2$-, -NR^A-, or -O-;

Y^1 is N or CR^5;

each occurrence of R^5 and R^6 are each independently hydrogen, halogen, or substituted or unsubstituted alkyl;

L is a bond, –SO_2–, –C(=O)–, –C(=O)$C(R^5)(R^6)$-, -NR^A-, or -NHC(=O)-;

A is , , , , , , , , , , , , or substituted or unsubstituted 5-membered heteroaryl;

R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted aryl; or R^2 and R^3 are each independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^7 is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy;

R^8 is substituted or unsubstituted alkyl;

each R^A is independently hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group;

m is 0, 1, or 2;

n is 1, 0, or 2; and

p1 and p2 are each independently 0, 1, 2, 3, 4, 5, or 6.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is substituted or unsubstituted heteroaryl.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is substituted or unsubstituted pyridinyl or substituted or unsubstituted pyrimidinyl.

4. The compound of any of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is substituted pyridinyl or substituted pyrimidinyl.

5. The compound of any of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is pyridinyl substituted with at least one instance of halogen, unsubstituted alkyl, or haloalkyl; or pyrimidinyl substituted with at least one instance of halogen, unsubstituted alkyl, or haloalkyl.

6. The compound of any of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is pyridinyl substituted with at least one instance of haloalkyl.

7. The compound of any of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is pyrimidinyl substituted with at least one instance of unsubstituted alkyl or haloalkyl.

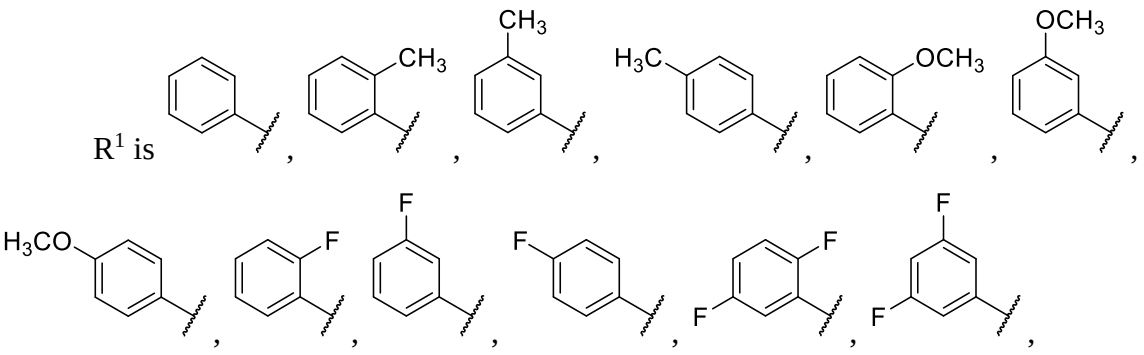
8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

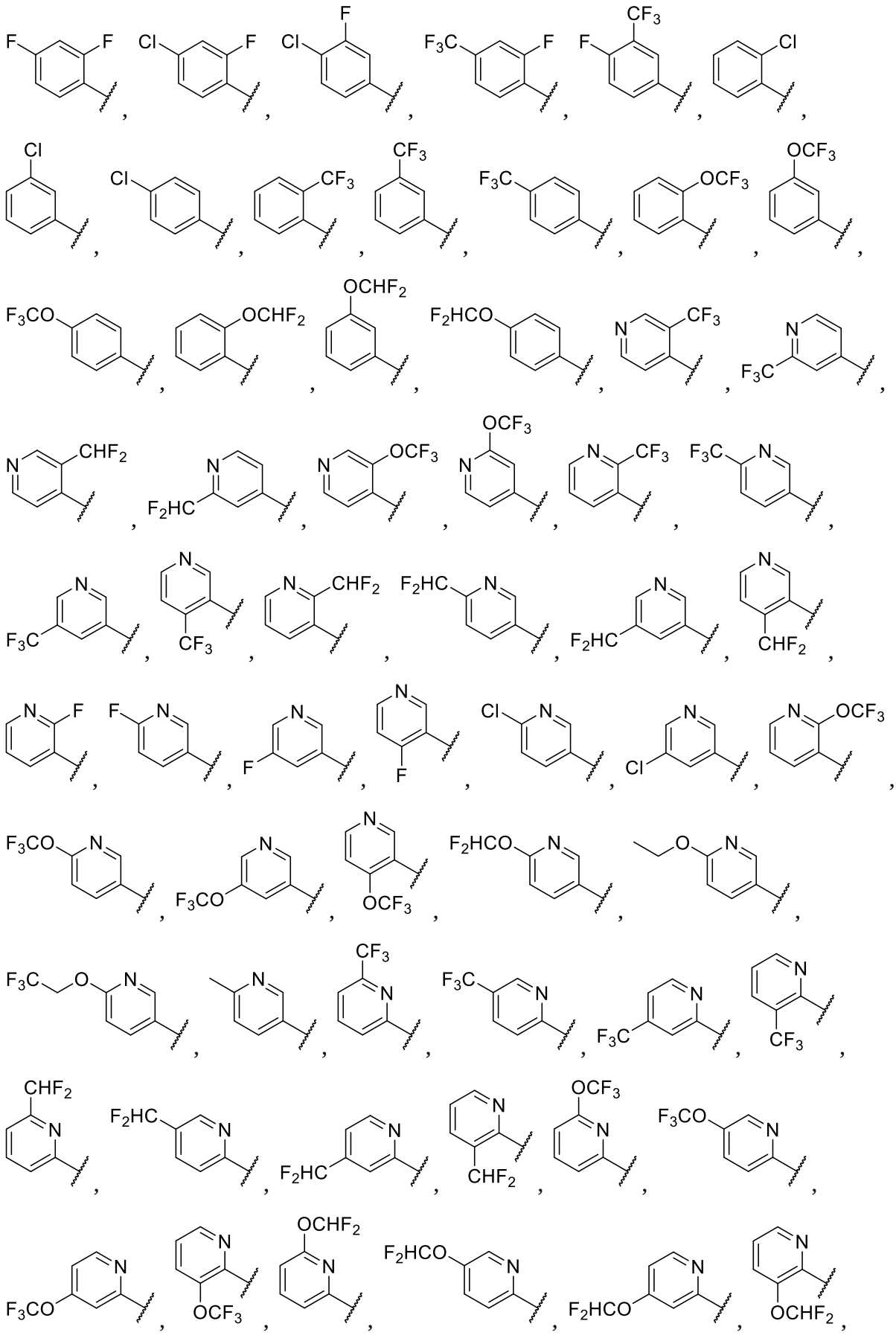
R^1 is substituted or unsubstituted phenyl.

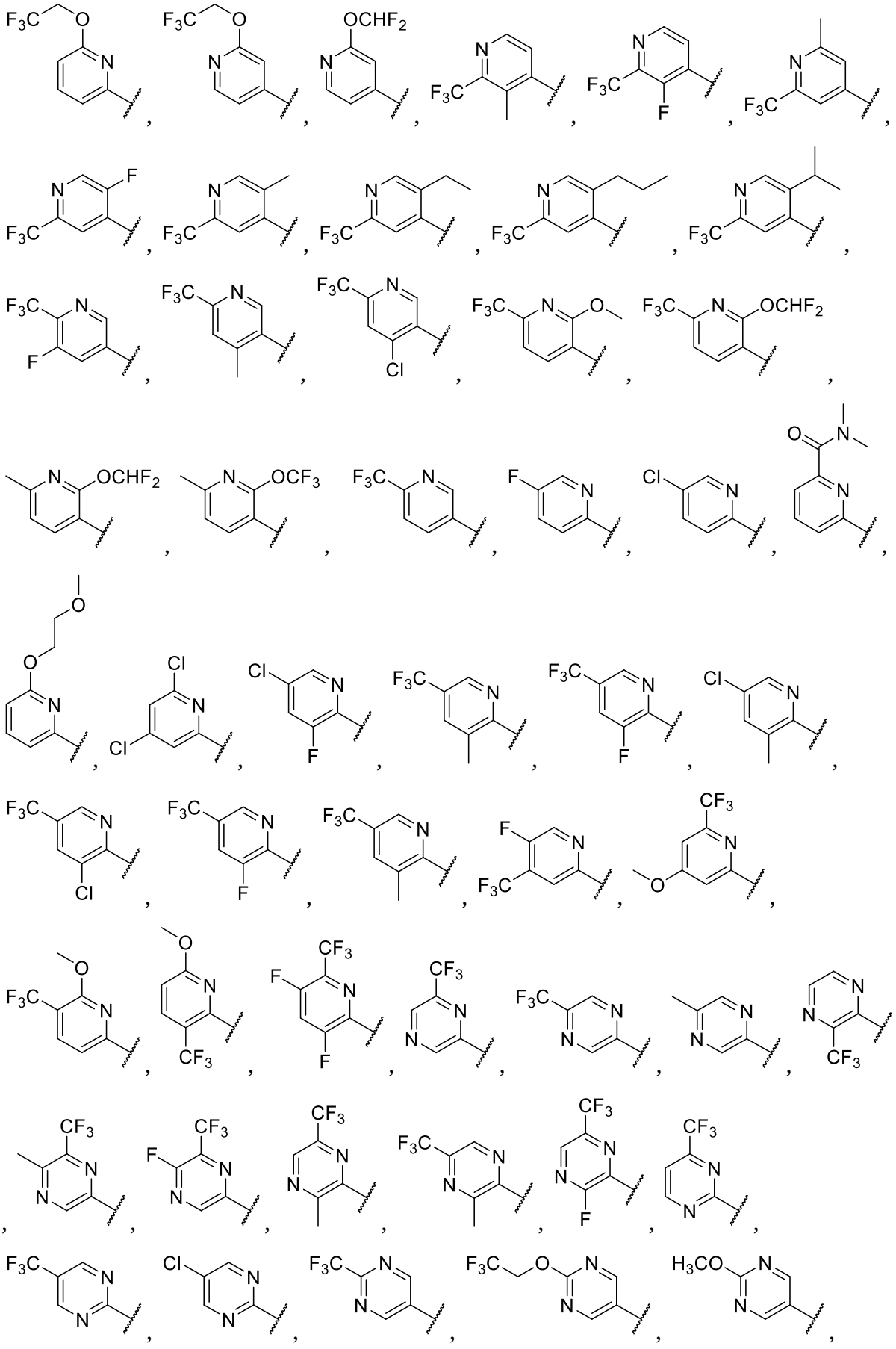
9. The compound of claim 1 or 7, or a pharmaceutically acceptable salt thereof, wherein:

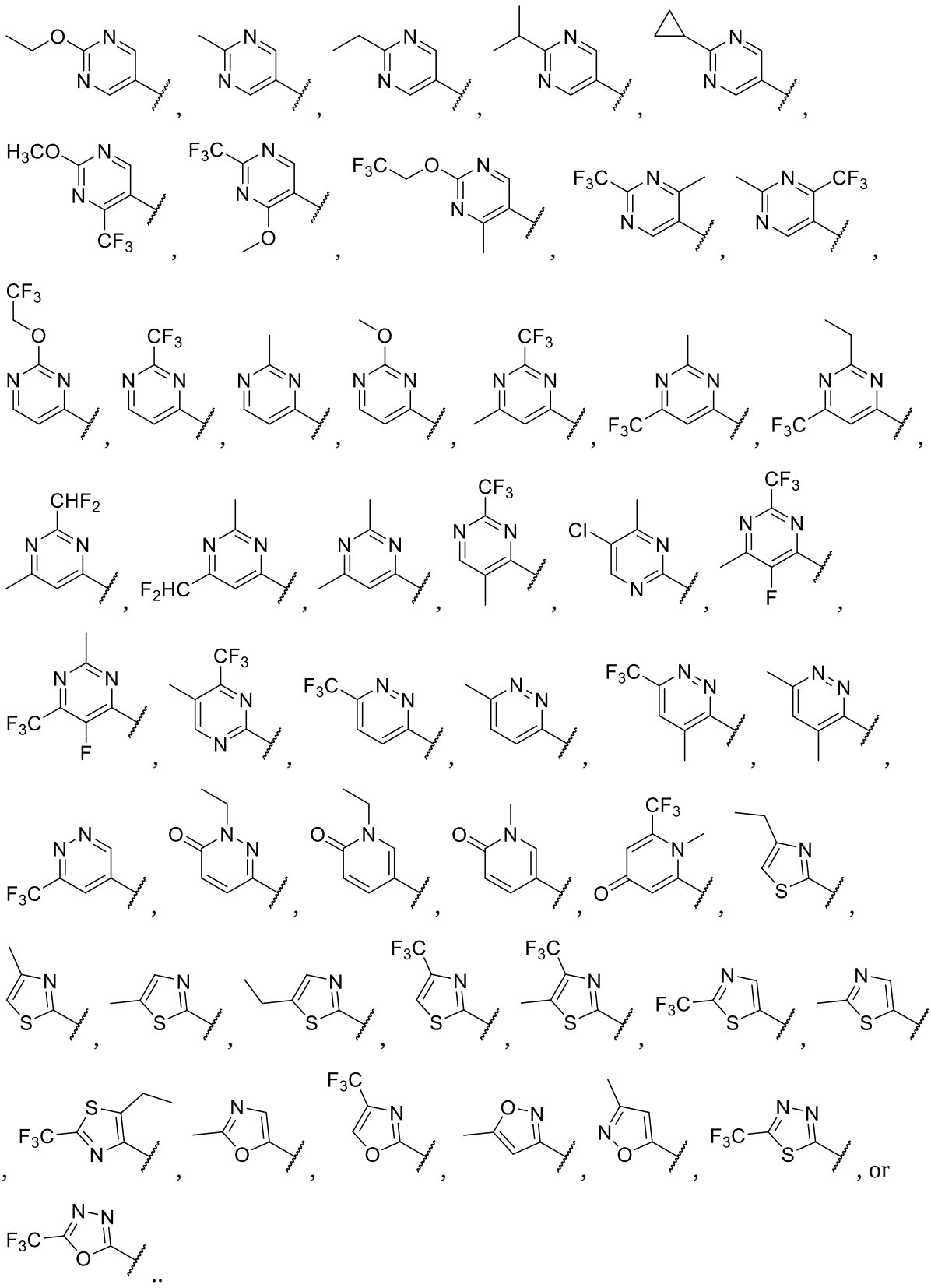
R^1 is unsubstituted phenyl or phenyl substituted with halogen or haloalkyl.

10. The compound of any of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein:

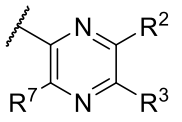
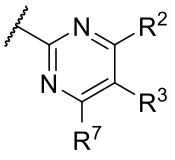
R^1 is 



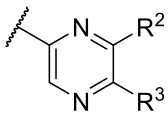
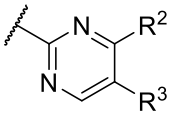




11. The compound of any of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein:

A is  or .

12. The compound of any of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein:

A is  or .

13. The compound of any of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein:

R^2 and R^3 are each independently hydrogen or substituted or unsubstituted heteroaryl; or R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl.

14. The compound of any of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein:

R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted heteroaryl.

15. The compound of any of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein:

R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted pyrazolyl.

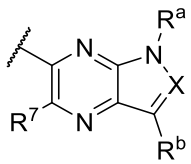
16. The compound of any of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein:

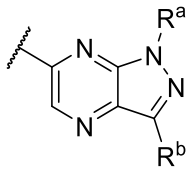
R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted heterocyclyl.

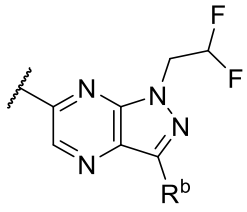
17. The compound of any of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein:

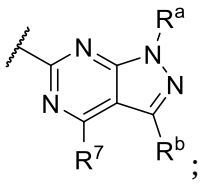
R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted dihydroimidazol-2-one.

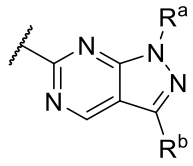
18. The compound of any of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein:

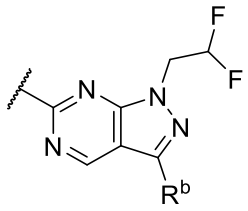
A is ; wherein R^7 is hydrogen, unsubstituted C_{1-4} alkyl, or unsubstituted C_{1-4} alkoxy; X is N or CR^a; each R^a is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heterocyclyl; and R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy;

A is ; wherein R^a is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl; and R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy;

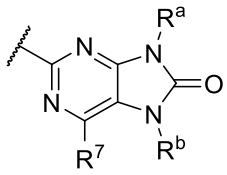
A is ; wherein R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy;

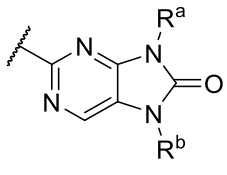
A is ; wherein R^7 is hydrogen, unsubstituted C_{1-4} alkyl, or unsubstituted C_{1-4} alkoxy; R^a is substituted or unsubstituted alkyl or substituted or unsubstituted heterocyclyl; and R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy;

A is  ; wherein R^a is substituted or unsubstituted alkyl or substituted or unsubstituted heterocyclyl; and R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy; or

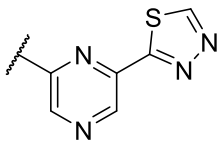
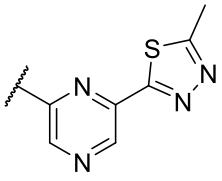
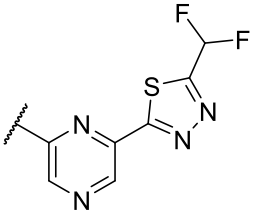
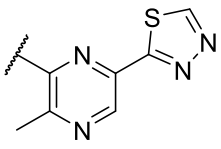
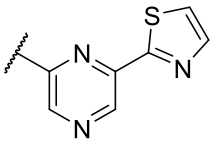
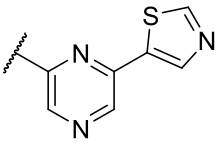
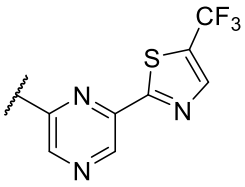
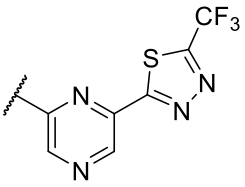
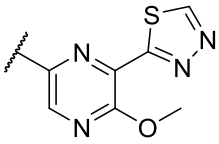
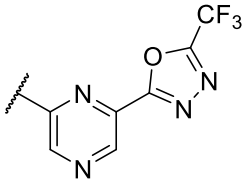
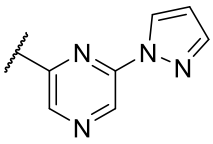
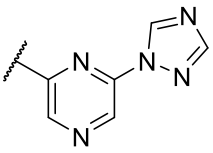
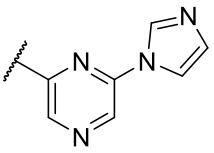
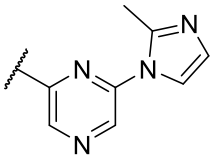
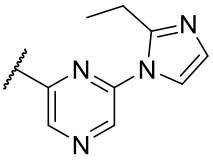
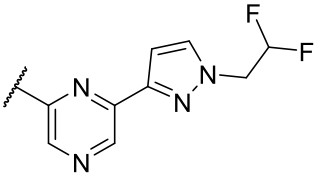
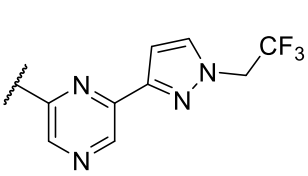
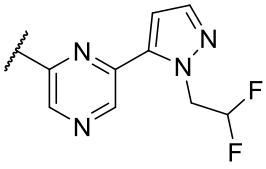
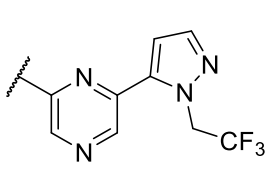
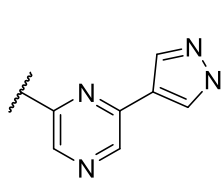
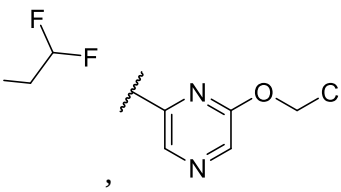
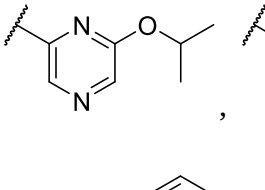
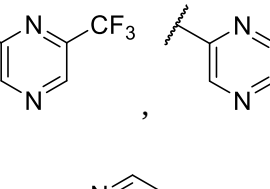
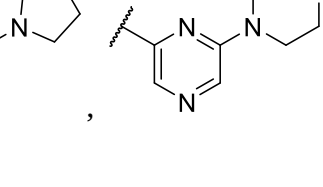
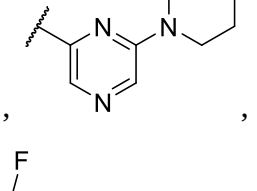
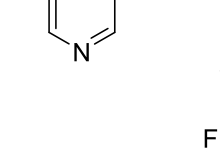
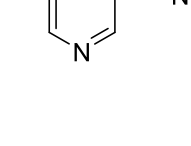
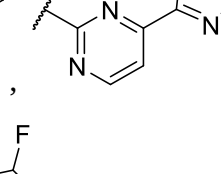
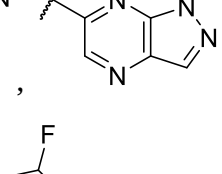
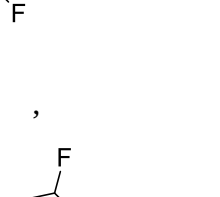
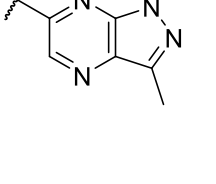
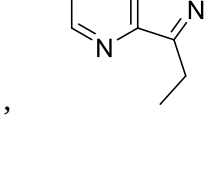
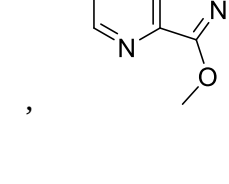
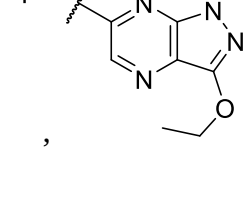
A is  ; wherein R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy.

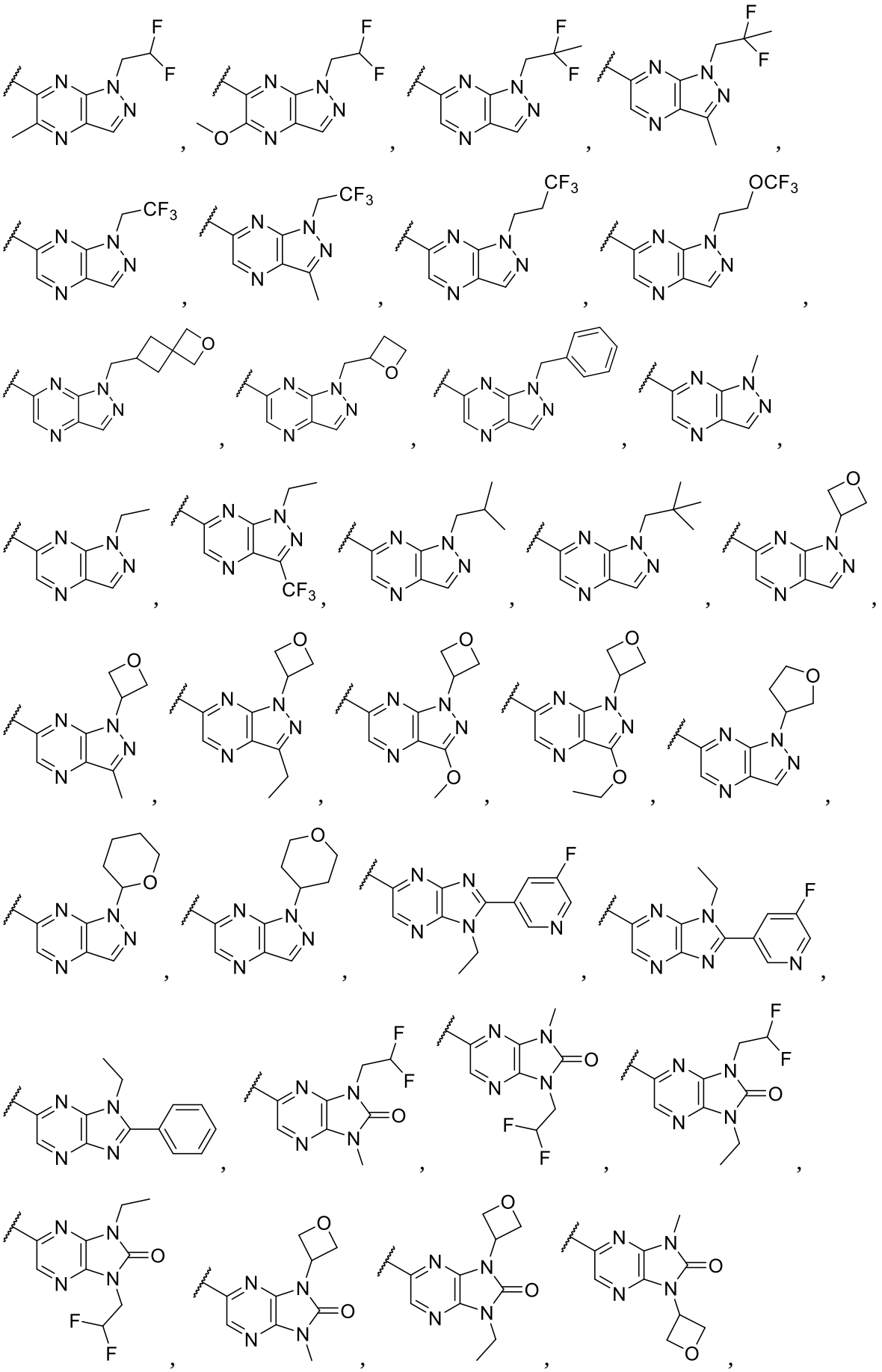
19. The compound of any of claims 1-13, 16, or 17, or a pharmaceutically acceptable salt thereof, wherein:

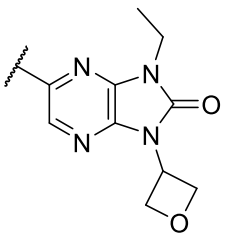
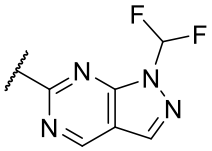
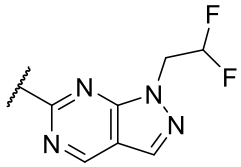
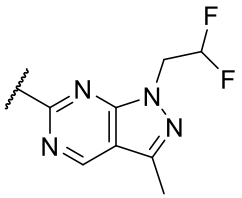
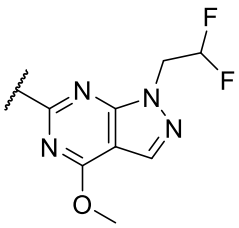
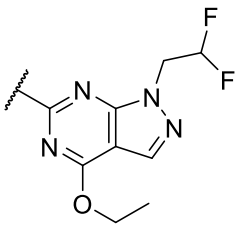
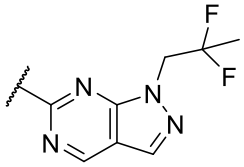
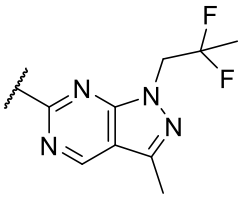
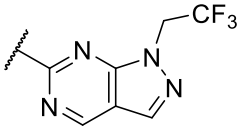
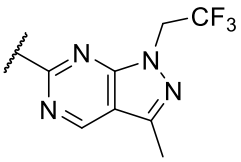
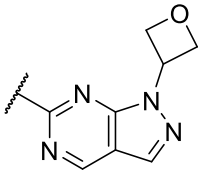
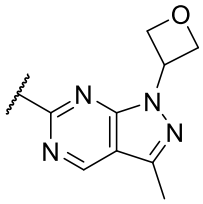
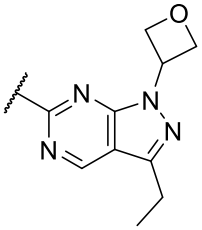
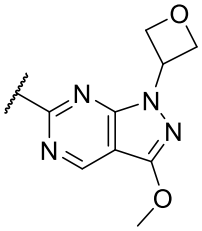
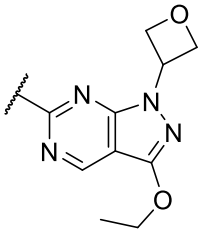
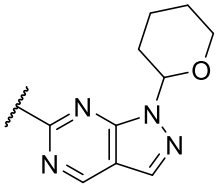
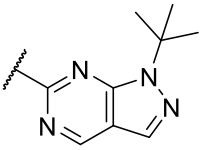
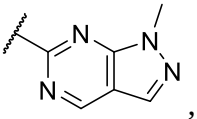
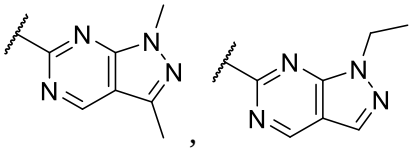
A is  ; wherein R^7 is hydrogen, unsubstituted C_{1-4} alkyl, or unsubstituted C_{1-4} alkoxy; R^a is substituted or unsubstituted alkyl or substituted or unsubstituted heterocyclyl; and R^b is substituted or unsubstituted alkyl or substituted or unsubstituted heterocyclyl; or

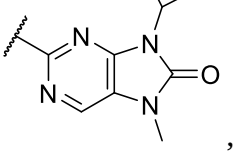
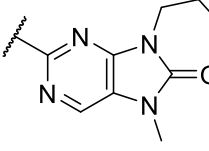
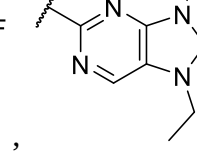
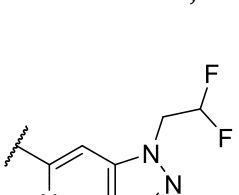
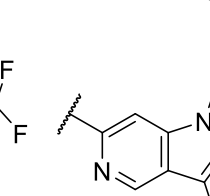
A is  ; wherein R^a is substituted or unsubstituted alkyl or substituted or unsubstituted heterocyclyl; and R^b is substituted or unsubstituted alkyl or substituted or unsubstituted heterocyclyl.

20. The compound of any of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein:

A is , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , ,




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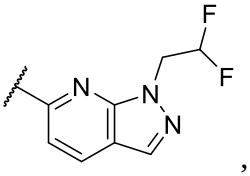
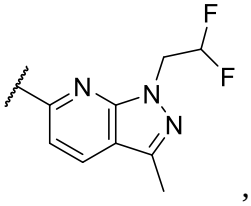
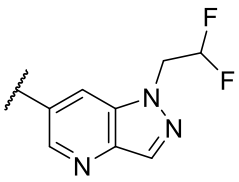
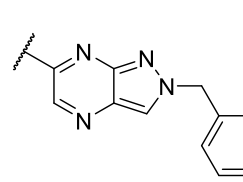
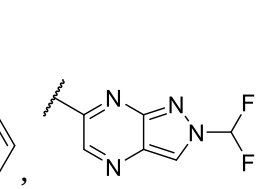
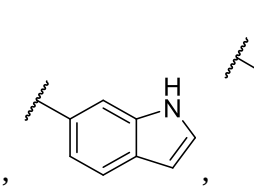
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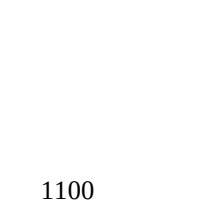
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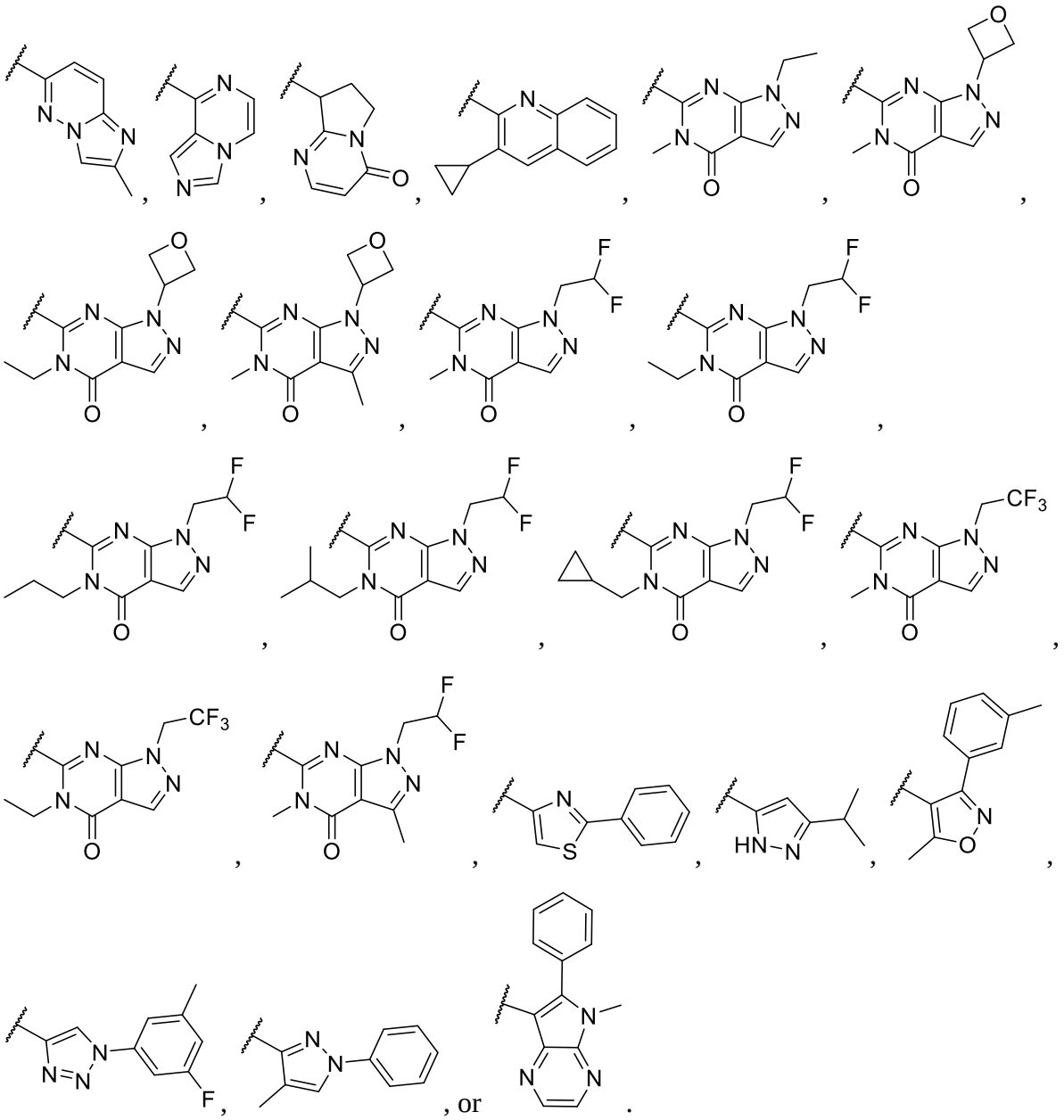
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21. The compound of any of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein:

G is a bond or -O-.

22. The compound of any of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is N.

23. The compound of any of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is CR^5.

24. The compound of any of claims 1-23, or a pharmaceutically acceptable salt thereof, wherein:

m is 1; and n is 1;

m is 0; and n is 0;

m is 2; and n is 0;

m is 1; and n is 0;

m is 0; and n is 1; or

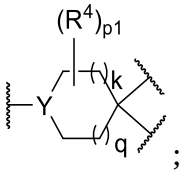
m is 0; and n is 2.

25. The compound of any of claims 1-24, or a pharmaceutically acceptable salt thereof, wherein:

L is a bond.

26. The compound of any of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein:

$-B(R^4)_{p1}-$ is



;

wherein:

Y is N or CR^5;

k and q are each independently 0, 1, or 2; and Y is bound to G of Formula (**I**).

27. The compound of claim 26, or a pharmaceutically acceptable salt thereof, wherein:

k is 0; and q is 2;

k is 1; and q is 1;

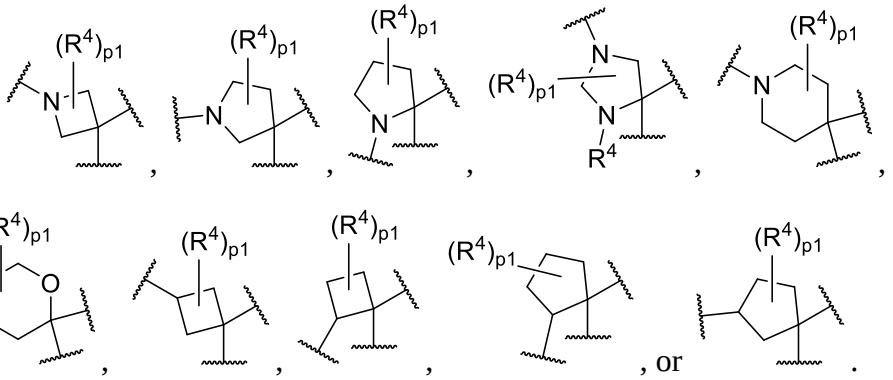
k is 0; and q is 0;

k is 2; and q is 0;

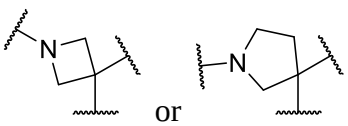
k is 1; and q is 0; or

k is 0; and q is 1.

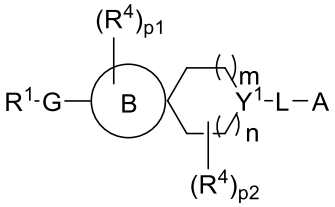
28. The compound of any of claims 1-27, or a pharmaceutically acceptable salt thereof, wherein:

-B(R^4)$_{p1}$- is .

29. The compound of any of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein:

-B(R^4)$_{p1}$- is  or .

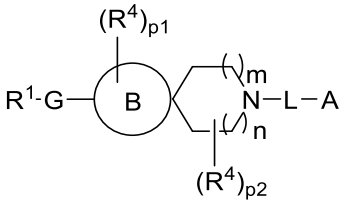
30. The compound of claim 1, wherein the compound is of Formula (**I-1**):



(**I-1**),

or a pharmaceutically acceptable salt thereof;

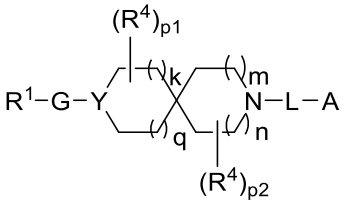
Formula (**I-a**):



(**I-a**),

or a pharmaceutically acceptable salt thereof;

Formula (**I-b**):



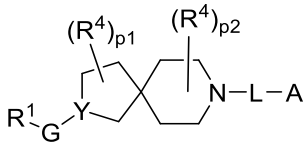
(**I-b**),

or a pharmaceutically acceptable salt thereof, wherein:

Y is N or CR^5; and

k and q are each independently 0, 1, or 2;

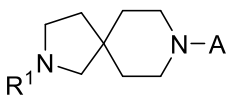
Formula (**I-g**):



(**I-g**),

or a pharmaceutically acceptable salt thereof;

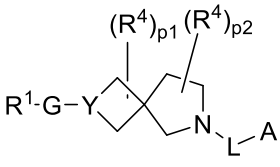
Formula (**I-g-13**):



(**I-g-13**),

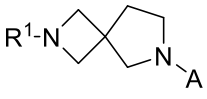
or a pharmaceutically acceptable salt thereof;

Formula (**I-k**):

 (**I-k**),

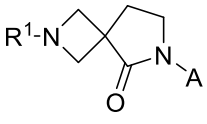
or a pharmaceutically acceptable salt thereof;

Formula (**I-k-3**):

 (**I-k-3**),

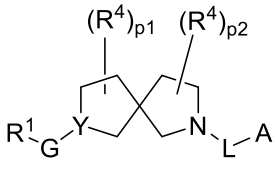
or a pharmaceutically acceptable salt thereof;

Formula (**I-k-5**):

 (**I-k-5**),

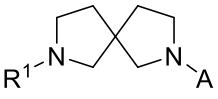
or a pharmaceutically acceptable salt thereof;

Formula (**I-l**):

 (**I-l**),

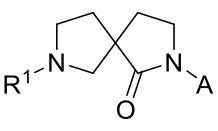
or a pharmaceutically acceptable salt thereof;

Formula (**I-l-3**):

 (**I-l-3**),

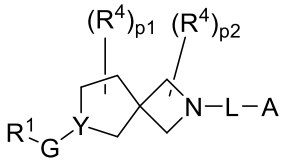
or a pharmaceutically acceptable salt thereof;

Formula (**I-l-5**):

 (**I-l-5**),

or a pharmaceutically acceptable salt thereof;

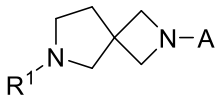
Formula (**I-m**):



(**I-m**),

or a pharmaceutically acceptable salt thereof; or

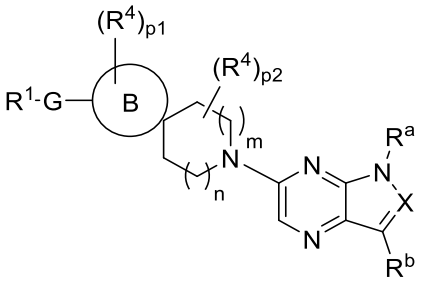
Formula (**I-m-3**):



(**I-m-3**),

or a pharmaceutically acceptable salt thereof.

31. The compound of claim 1, wherein the compound is of Formula (**I-n**):

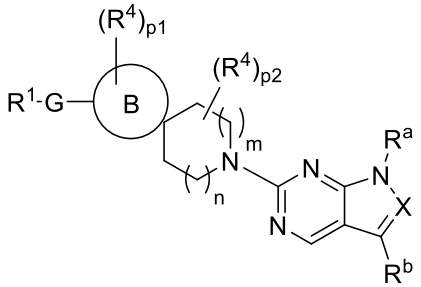


(**I-n**),

or a pharmaceutically acceptable salt thereof; wherein:

X is N or CR^a; each R^a is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted aryl; and R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy;

Formula (**I-n'**):

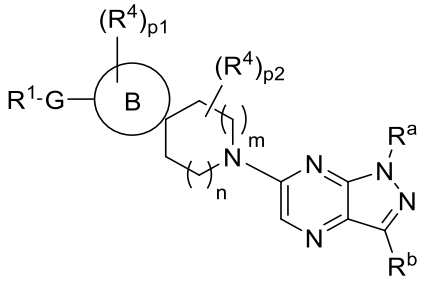


(**I-n'**),

or a pharmaceutically acceptable salt thereof; wherein:

X is N or CR^a; each R^a is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted aryl; and R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy;

Formula (**I-o**):

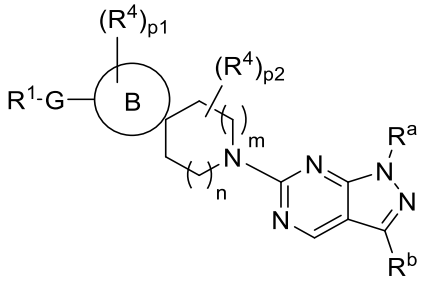


(**I-o**),

or a pharmaceutically acceptable salt thereof; wherein:

R^a is independently hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl; and R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy;

Formula (**I-o'**):

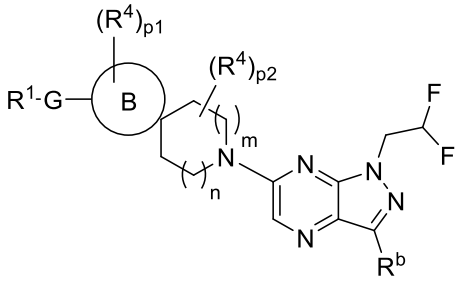


(**I-o'**),

or a pharmaceutically acceptable salt thereof; wherein:

R^a is independently hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl; and R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy;

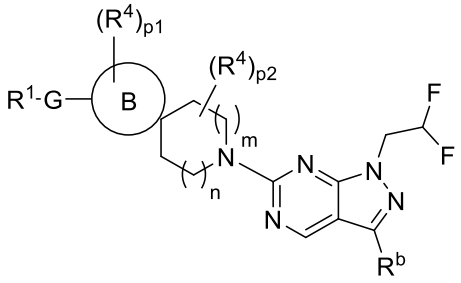
Formula (**I-p**):



(**I-p**),

or a pharmaceutically acceptable salt thereof; wherein R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy;

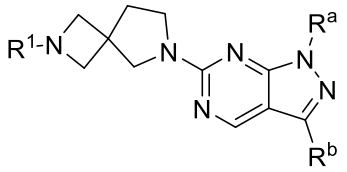
Formula (**I-p'**):



(**I-p'**),

or a pharmaceutically acceptable salt thereof; wherein R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy;

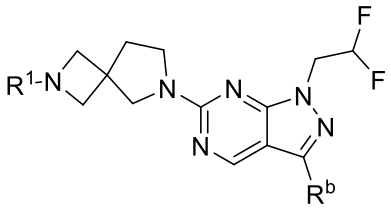
Formula (**I-x**):



(**I-x**),

or a pharmaceutically acceptable salt thereof; wherein R^a is substituted or unsubstituted alkyl or substituted or unsubstituted heterocyclyl; and R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy;

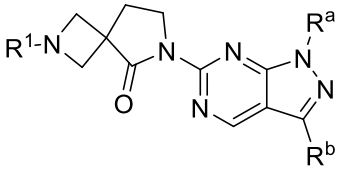
Formula (**I-x-1**):



(**I-x-1**),

or a pharmaceutically acceptable salt thereof; wherein R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy;

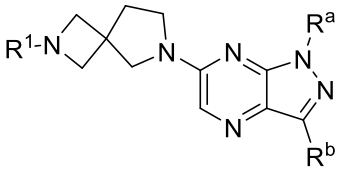
Formula (**I-y**):



(**I-y**),

or a pharmaceutically acceptable salt thereof; wherein R^a is substituted or unsubstituted alkyl or substituted or unsubstituted heterocyclyl; and R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy;

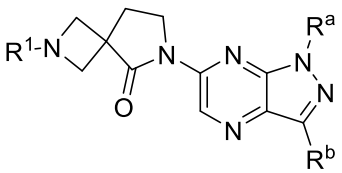
Formula (**I-z**):



(**I-z**),

or a pharmaceutically acceptable salt thereof; wherein R^a is substituted or unsubstituted alkyl or substituted or unsubstituted heterocyclyl; and R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy;

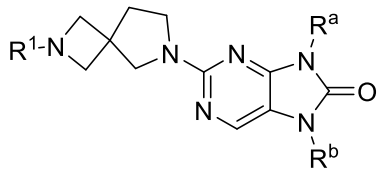
Formula (**I-aa**):



(**I-aa**),

or a pharmaceutically acceptable salt thereof; wherein R^a is substituted or unsubstituted alkyl or substituted or unsubstituted heterocyclyl; and R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy;

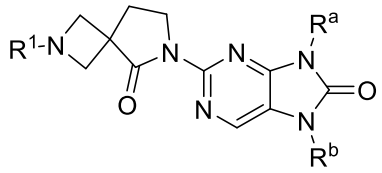
Formula (**I-bb**):



(**I-bb**),

or a pharmaceutically acceptable salt thereof; wherein R^a is substituted or unsubstituted alkyl or substituted or unsubstituted heterocyclyl; and R^b is substituted or unsubstituted alkyl or substituted or unsubstituted heterocyclyl;

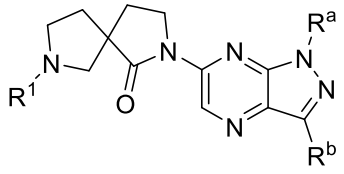
Formula (**I-cc**):



(**I-cc**),

or a pharmaceutically acceptable salt thereof; wherein R^a is substituted or unsubstituted alkyl or substituted or unsubstituted heterocyclyl; and R^b is substituted or unsubstituted alkyl or substituted or unsubstituted heterocyclyl;

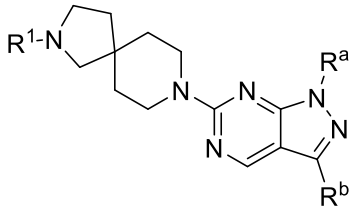
Formula (**I-dd**):



(**I-dd**),

or a pharmaceutically acceptable salt thereof; wherein R^a is substituted or unsubstituted alkyl or substituted or unsubstituted heterocyclyl; and R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy;

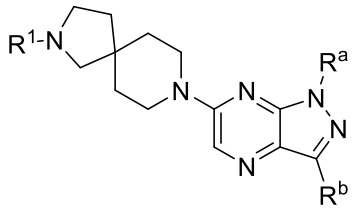
Formula (**I-ee**):



(**I-ee**),

or a pharmaceutically acceptable salt thereof; wherein R^a is substituted or unsubstituted alkyl or substituted or unsubstituted heterocyclyl; and R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy;

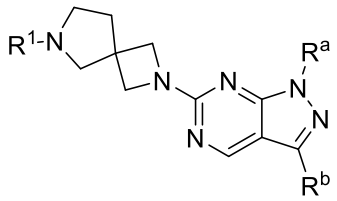
Formula (**I-ff**):



(**I-ff**),

or a pharmaceutically acceptable salt thereof; wherein R^a is substituted or unsubstituted alkyl or substituted or unsubstituted heterocyclyl; and R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy; or

Formula (**I-gg**):



(**I-gg**),

or a pharmaceutically acceptable salt thereof; wherein R^a is substituted or unsubstituted alkyl or substituted or unsubstituted heterocyclyl; and R^b is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy.

32. The compound of claim 1, wherein the compound is a compound of Table 1, or a pharmaceutically acceptable salt thereof.

33. A pharmaceutical composition comprising a compound of any of claims 1-32, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

34. A kit comprising a compound of any of claims 1-32, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 33, and instructions for administering the compound or pharmaceutical composition to a subject in need thereof.

35. Use of a compound of any of claims 1-32, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 33 in the manufacture of a medicament for treating a disease or disorder in a subject in need thereof.

36. The use of claim 35, wherein the disease or disorder is associated with glucocerebrosidase activity.

37. The use of claim 35 or 36, wherein the disease or disorder is a neurological disease or disorder.

38. The use of claim 37, wherein the neurological disease or disorder is Parkinson's disease or Gaucher's disease.

39. A compound of any of claims 1-32, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 33 for use in therapy.

40. A method of activating glucocerebrosidase, the method comprising contacting glucocerebrosidase *in vitro* with an effective amount of a compound of any of claims 1-32, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 33.