regulates T cell activation by reducing the persistence of signaling microclusters by phosphorylating SLP76 at Ser376 (Di Bartolo et al. (2007) JEM 204:681-691) and Gads at Thr254, which leads to the recruitment of 14-3-3 proteins that bind to the phosphorylated SLP76 and Gads, releasing the SLP76-Gads-14-3-3 complex from LAT-containing microclusters (Lasserre et al. (2011) J Cell Biol 195(5):839-853). HPK1 can also become activated in response to prostaglandin E2, which is often secreted by tumors, contributing to the escape of tumor cells from the immune system.

[0005] HPKl is important in regulating the functions of various immune cells and it has been implicated in autoimmune diseases and anti-tumor immunity (Shui, J.W., et al., Nat Immunol, 2007. 8(1): p. 84-91; Wang, X., et al., J Biol Chem, 2012. 287(14): p. 11037-48).

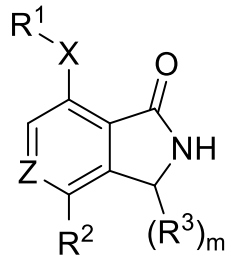
SUMMARY ~~OF THE INVENTION~~

[0006] It has now been found that compounds of this ~~invention~~present disclosure, and pharmaceutically acceptable compositions thereof, are effective as antagonists of HPK1. In certain ~~embodiments~~examples, the present disclosure ~~invention~~ provides for compounds of the formulae presented herein.

[0007] Compounds of the present disclosure~~invention~~, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with regulation of signaling pathways implicating HPK1 kinases. Such diseases, disorders, or conditions include those described herein.

[0008] Compounds provided by this present disclosure ~~invention~~ are also useful for the study of HPK1 enzymes in biological and pathological phenomena; the study of intracellular signal transduction pathways occurring in bodily tissues; and the comparative evaluation of new HPK1 inhibitors or other regulators of kinases, signaling pathways, and cytokine levels *in vitro* or *in vivo*.

[0008a] In an aspect of the present disclosure, there is provided a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

Z is CR or N;

X is a covalent bond, –O-, -S-, -NR-, -$S(O)_2$-, -$S(O)_2$NR-, -S(O)-, -S(O)NR-, -C(O)-, -C(O)O-, –C(O)NR-, -C(O)N(R)O-, -OC(O)-, -OC(O)NR-, -N(R)C(O)O-, -N(R)C(O)-, –N(R)$S(O)_2$-; or X is a C_{1-4} bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by –$C(R)_2$-, –N(R)-, -N(R)C(O)-, -C(O)N(R)-, -N(R)$S(O)_2$-, -$S(O)_2$N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)- or –$S(O)_2$-;

R^1 is selected from C_{1-6} aliphatic; phenyl; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and an 8-10 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with q instances of R^C;

R^2 is a 6-11 membered saturated, partially unsaturated, or unsaturated fused, bridged, or spiro bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with q instances of R^C;

each instance of R^3 is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each instance of R^C is independently oxo, halogen, –CN, –NO_2, –OR, -SR, -NR_2, -$S(O)_2$R, -$S(O)_2NR_2$, -S(O)R, -S(O)NR_2, -C(O)R, -C(O)OR, –C(O)NR_2, -C(O)N(R)OR, -OC(O)R, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR_2, -N(R)C(NR)NR_2, –N(R)NR_2, -N(R)$S(O)_2NR_2$, –N(R)$S(O)_2$R, –N=S(O)R_2, –S(NR)(O)R, –N(R)S(O)R, –N(R)CN, –P(O)(R)NR_2, –P(O)(R)OR or –P(O)R_2 ; or each instance of R^C is independently an optionally substituted group selected from C_{1-6} aliphatic; phenyl; naphthalenyl; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, phosphorous, silicon and sulfur; or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-8 membered

saturated or partially unsaturated bridged bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-11 membered saturated or partially unsaturated spirocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 6-11 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with r instances of R and s instances of R^D;

each instance of R^D is independently oxo, halogen, –CN, $–NO_2$, –OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-S(O)NR_2$, -C(O)R, -C(O)OR, $–C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $–N(R)NR_2$, $-N(R)S(O)_2NR_2$, $–N(R)S(O)_2R$, $–N=S(O)R_2$, –S(NR)(O)R, –N(R)S(O)R, –N(R)CN, $–P(O)(R)NR_2$, –P(O)(R)OR or $–P(O)R_2$;

each R is independently hydrogen, -CN, halogen, or an optionally substituted group selected from C_{1-6} aliphatic; phenyl; naphthalenyl; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-8 membered saturated or partially unsaturated bridged bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-10 membered saturated or partially unsaturated spirocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-11 membered saturated or partially unsaturated bicyclic carbocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or:

two R groups on the same nitrogen are taken together with the nitrogen to form an optionally substituted 4-7 membered monocyclic saturated, partially unsaturated, or heteroaryl ring having, in addition to the nitrogen, 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 7-12 membered saturated or

partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

m is 0, 1, or 2;

each q is independently 0, 1, 2, 3, or 4;

each r is independently 0, 1, 2, 3, or 4; and

each s is independently 0, 1, 2, 3, or 4.

[0008b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0008c] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or the pharmaceutical composition disclosed herein, for use as a medicament.

[0008d] In another aspect of the present disclosure, there is provided a method of inhibiting HPK1 in a biological sample comprising contacting the sample with the compound disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition disclosed herein.

[0008e] In a further aspect of the present disclosure, there is provided a use of a disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a HPK1-mediated disorder, disease, or condition.

[0008f] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for increasing the efficacy of vaccination in a patient, wherein the compound, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition is to be administered as an adjuvant.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

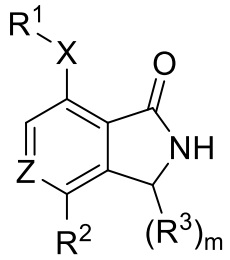
1. General Description of Certain Embodiments of the Invention:

[0009] In certain aspects, the present invention provides a compound of formula **I**:

CLAIMS

We claim:

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



I

or a pharmaceutically acceptable salt thereof, wherein:

Z is CR or N;

X is a covalent bond, –O-, -S-, -NR-, -$S(O)_2$-, -$S(O)_2$NR-, -S(O)-, -S(O)NR-, -C(O)-, -C(O)O-, –C(O)NR-, -C(O)N(R)O-, -OC(O)-, -OC(O)NR-, -N(R)C(O)O-, -N(R)C(O)-, –N(R)$S(O)_2$-; or X is a C_{1-4} bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by –$C(R)_2$-, –N(R)-, -N(R)C(O)-, -C(O)N(R)-, -N(R)$S(O)_2$-, -$S(O)_2$N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)- or –$S(O)_2$-;

R^1 is selected from C_{1-6} aliphatic; phenyl; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and an 8-10 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with q instances of R^C;

R^2 is a 6-11 membered saturated, partially unsaturated, or unsaturated fused, bridged, or spiro bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with q instances of R^C;

each instance of R^3 is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each instance of R^C is independently oxo, halogen, –CN, –NO_2, –OR, -SR, -NR_2, -$S(O)_2$R, -$S(O)_2NR_2$, -S(O)R, -S(O)NR_2, -C(O)R, -C(O)OR, –C(O)NR_2, -C(O)N(R)OR,

-OC(O)R, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR_2, -N(R)C(NR)NR_2, –N(R)NR_2, -N(R)S(O)$_2NR_2$, –N(R)S(O)$_2$R, –N=S(O)R_2, –S(NR)(O)R, –N(R)S(O)R, –N(R)CN, –P(O)(R)NR_2, –P(O)(R)OR or –P(O)R_2 ; or each instance of R^C is independently an optionally substituted group selected from C_{1-6} aliphatic; phenyl; naphthalenyl; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, phosphorous, silicon and sulfur; or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-8 membered saturated or partially unsaturated bridged bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-11 membered saturated or partially unsaturated spirocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 6-11 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with r instances of R and s instances of R^D;

each instance of R^D is independently oxo, halogen, –CN, –NO_2, –OR, -SR, -NR_2, -S(O)$_2$R, -S(O)$_2NR_2$, -S(O)R, -S(O)NR_2, -C(O)R, -C(O)OR, –C(O)NR_2, -C(O)N(R)OR, -OC(O)R, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR_2, -N(R)C(NR)NR_2, –N(R)NR_2, -N(R)S(O)$_2NR_2$, –N(R)S(O)$_2$R, –N=S(O)R_2, –S(NR)(O)R, –N(R)S(O)R, –N(R)CN, –P(O)(R)NR_2, –P(O)(R)OR or –P(O)R_2 ;

each R is independently hydrogen, -CN, halogen, or an optionally substituted group selected from C_{1-6} aliphatic; phenyl; naphthalenyl; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-8 membered saturated or partially unsaturated bridged bicyclic ring having 0-3 heteroatoms independently selected from

nitrogen, oxygen, and sulfur; a 6-10 membered saturated or partially unsaturated spirocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-11 membered saturated or partially unsaturated bicyclic carbocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or:

two R groups on the same nitrogen are taken together with the nitrogen to form an optionally substituted 4-7 membered monocyclic saturated, partially unsaturated, or heteroaryl ring having, in addition to the nitrogen, 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

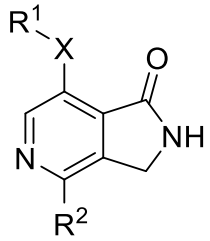
m is 0, 1, or 2;

each q is independently 0, 1, 2, 3, or 4;

each r is independently 0, 1, 2, 3, or 4; and

each s is independently 0, 1, 2, 3, or 4.

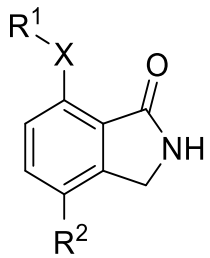
2. The compound of claim 1, wherein the compound is of formula **II**:



II

or a pharmaceutically acceptable salt thereof.

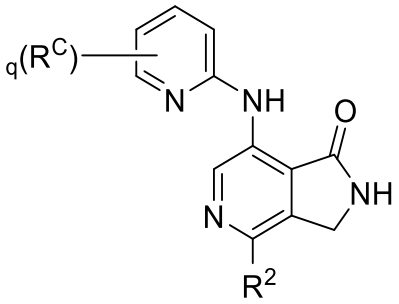
3. The compound of claim 1, wherein the compound is of formula **V**:



V

or a pharmaceutically acceptable salt thereof.

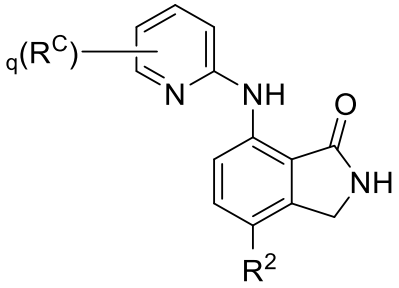
4. The compound of claim 2, wherein the compound is of formula **IV**:



IV

or a pharmaceutically acceptable salt thereof.

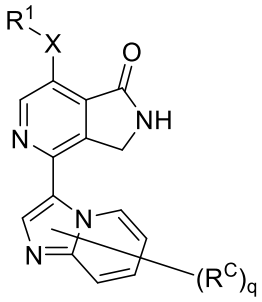
5. The compound of claim 3, wherein the compound is of formula **VII**:



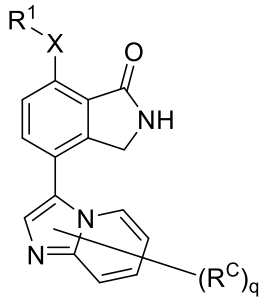
VII

or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1, wherein the compound is any one of formulae **XI-a** or **XI-b**:



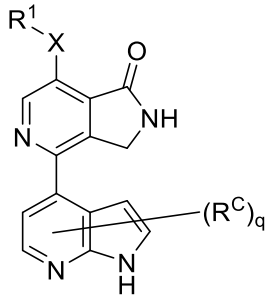
XI-a



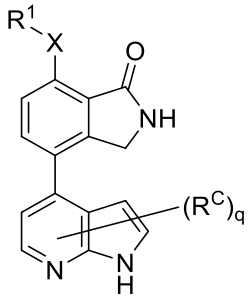
XI-b

or a pharmaceutically acceptable salt thereof.

7. The compound of claim 1, wherein the compound is any one of formulae **XIV-a** or **XIV-b**:



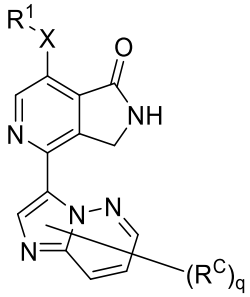
XIV-a



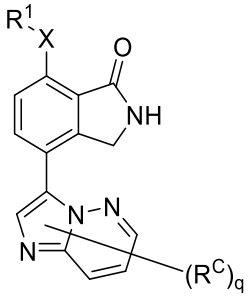
XIV-b

or a pharmaceutically acceptable salt thereof.

8. The compound of claim 1, wherein the compound is any one of formulae **XVII-a** or **XVII-b**:



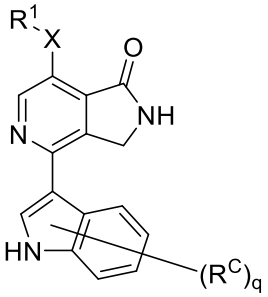
XVII-a



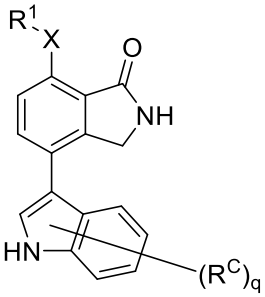
XVII-b

or a pharmaceutically acceptable salt thereof.

9. The compound of claim 1, wherein the compound is any one of formulae **XX-a** or **XX-b**:



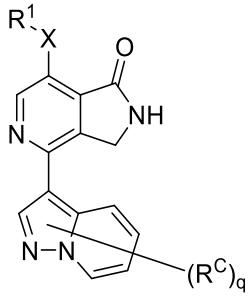
XX-a



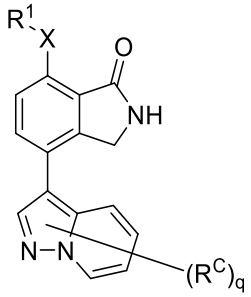
XX-b

or a pharmaceutically acceptable salt thereof.

10. The compound of claim 1, wherein the compound is any one of formulae **XXIII-a** or **XXIII-b**:



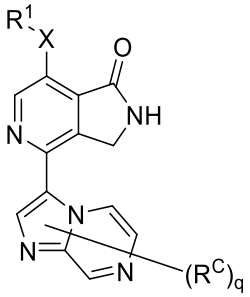
XXIII-a



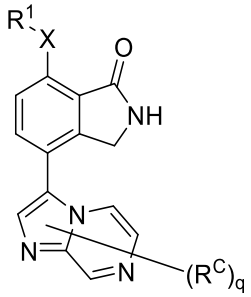
XXIII-b

or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1, wherein the compound is any one of formulae **XXVI-a** or **XXVI-b**:



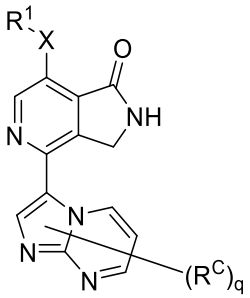
XXVI-a

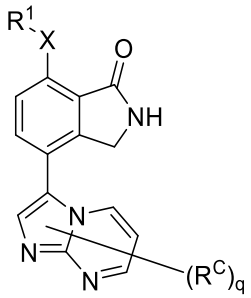


XXVI-b

or a pharmaceutically acceptable salt thereof.

12. The compound of claim 1, wherein the compound is any one of formulae **XXIX-a** or **XXIX-b**:





XXIX-a **XXIX-b**

or a pharmaceutically acceptable salt thereof.

13. The compound of claim 1-3 or 6-12, wherein X is -NR-.

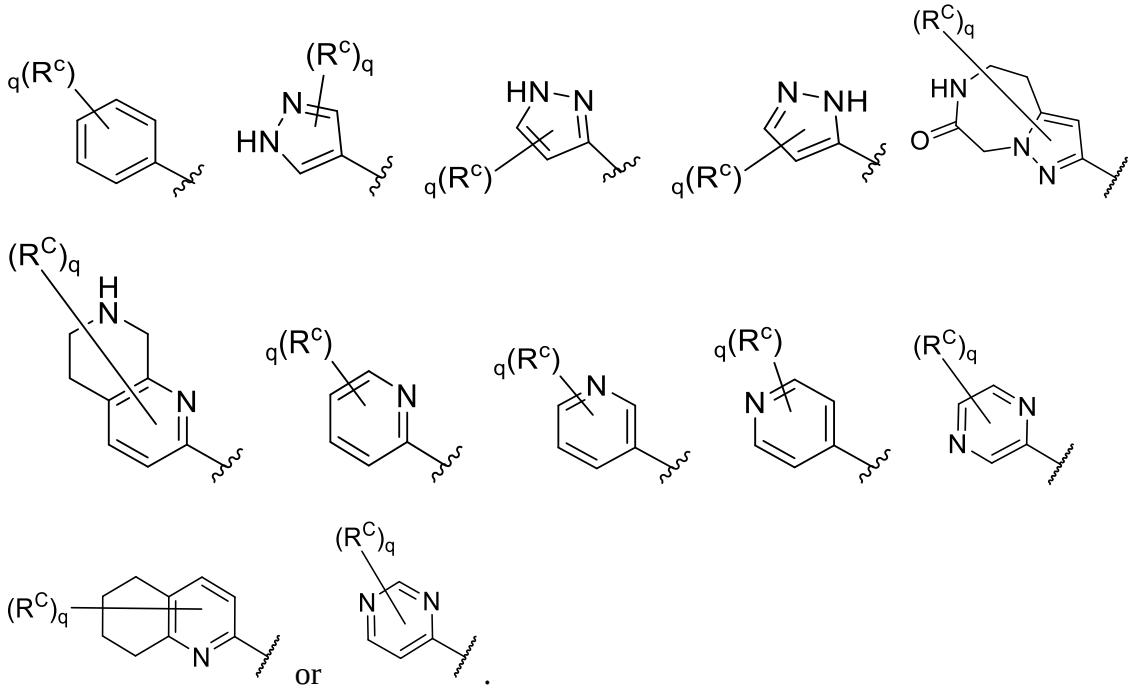
14. The compound of any one of claims 1-3 or 6-13, wherein R^1 is C_{1-6} aliphatic which is substituted with q instances of R^C; phenyl which is substituted with q instances of R^C; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring, which is substituted with q instances of R^C; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, which is substituted with q instances of R^C; or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, which is substituted with q instances of R^C.

15. The compound of any one of claims 1-3 or 6-14, wherein R^1 is phenyl or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, each of which is substituted with q instances of R^C.

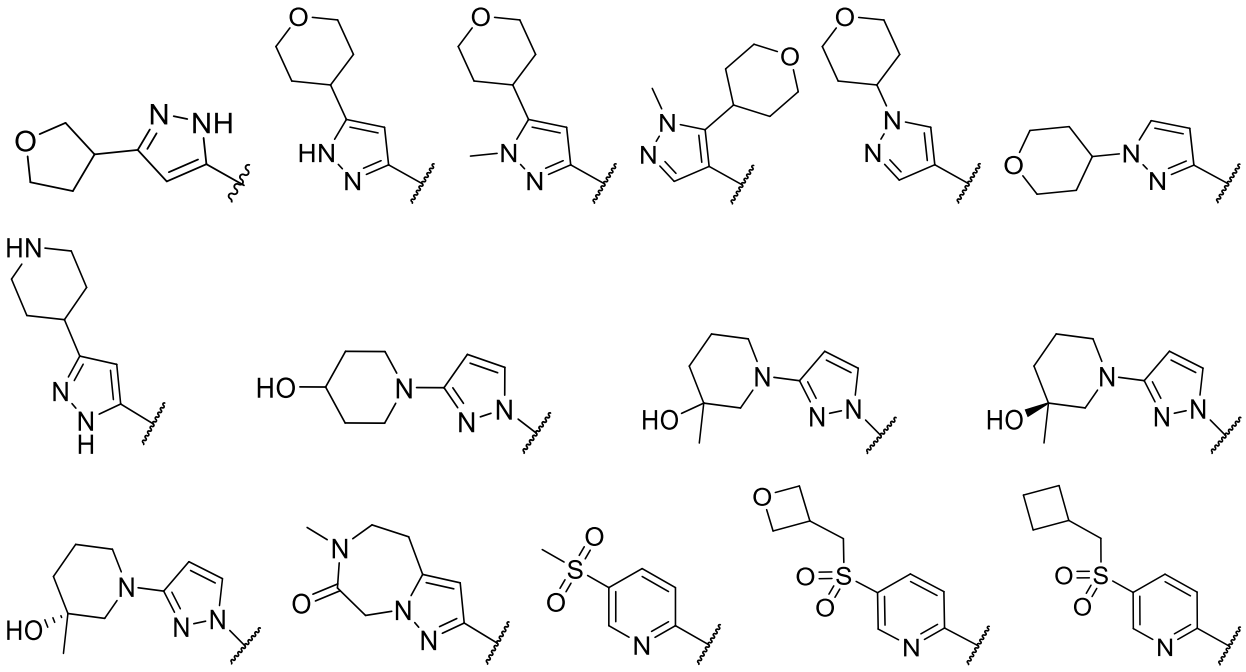
16. The compound of any one of claims 1-3 or 6-15, wherein R^1 is phenyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, isothiazolyl, isoxazolyl, morpholinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl;- 1,2,5oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, oxetanyl, pyrimidinyl, piperazinyl, piperidinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2*H*-pyrrolyl, pyrrolyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolyl, thienyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, oxetanyl, azetidinyl, or xanthenyl; each of which is substituted by q instances of R^C.

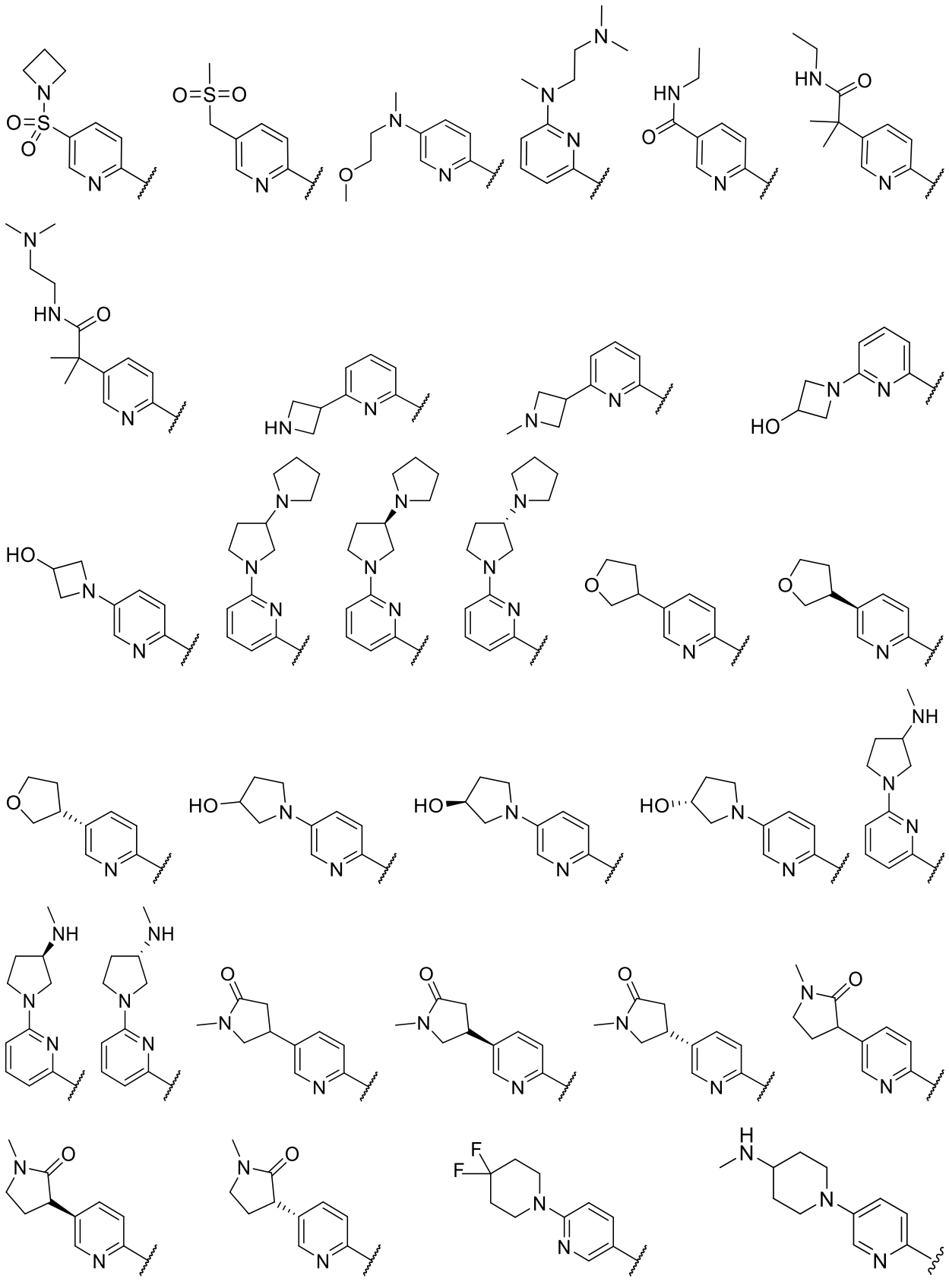
17. The compound of any one of claims 1-3 or 6-16, wherein R^1 is phenyl, pyrazolyl, pyridinyl, pyrazinyl, or pyrimidinyl; each of which is substituted by q instances of R^C.

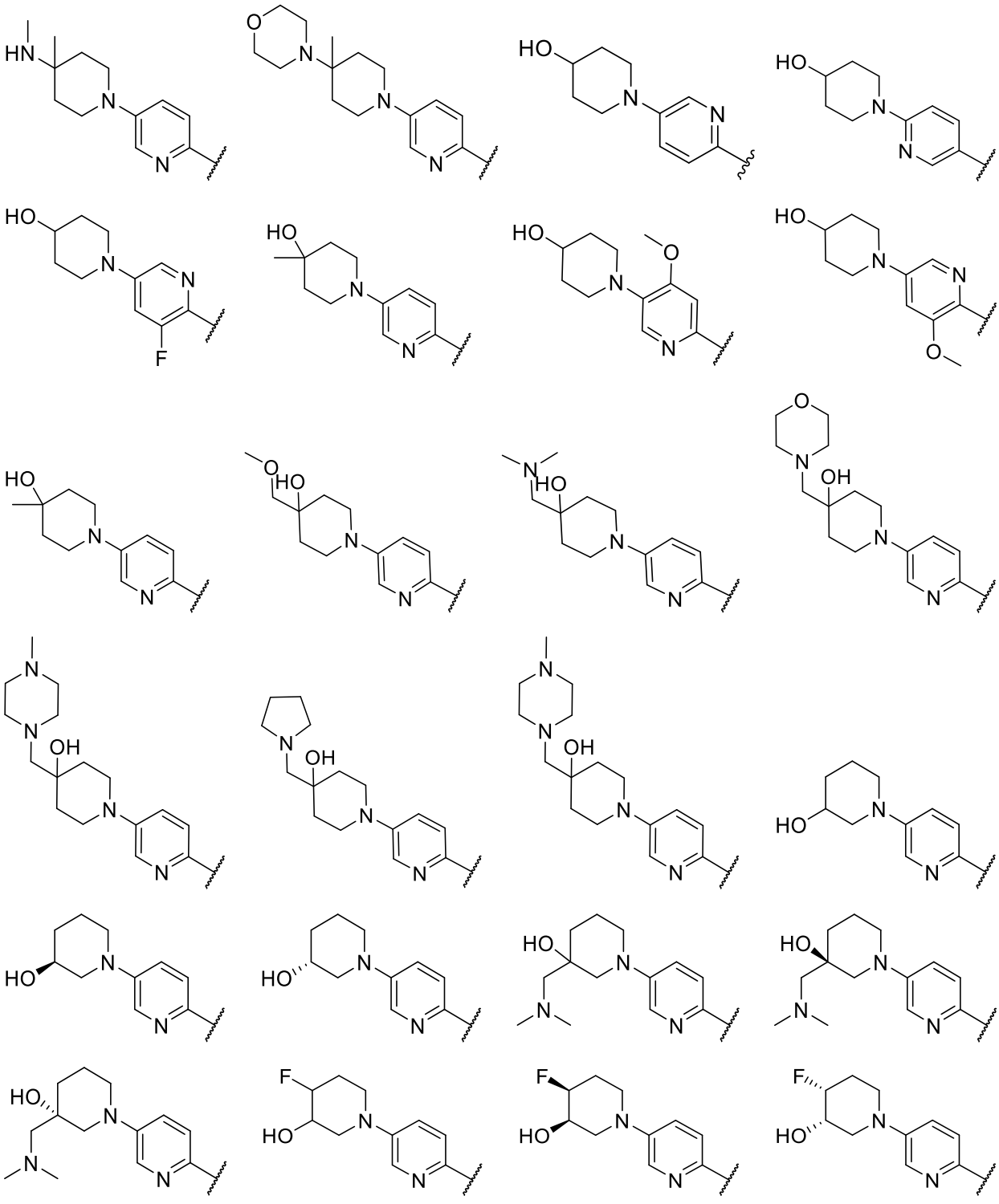
18. The compound of any one of claims 1-3 or 6-13, wherein R^1 is

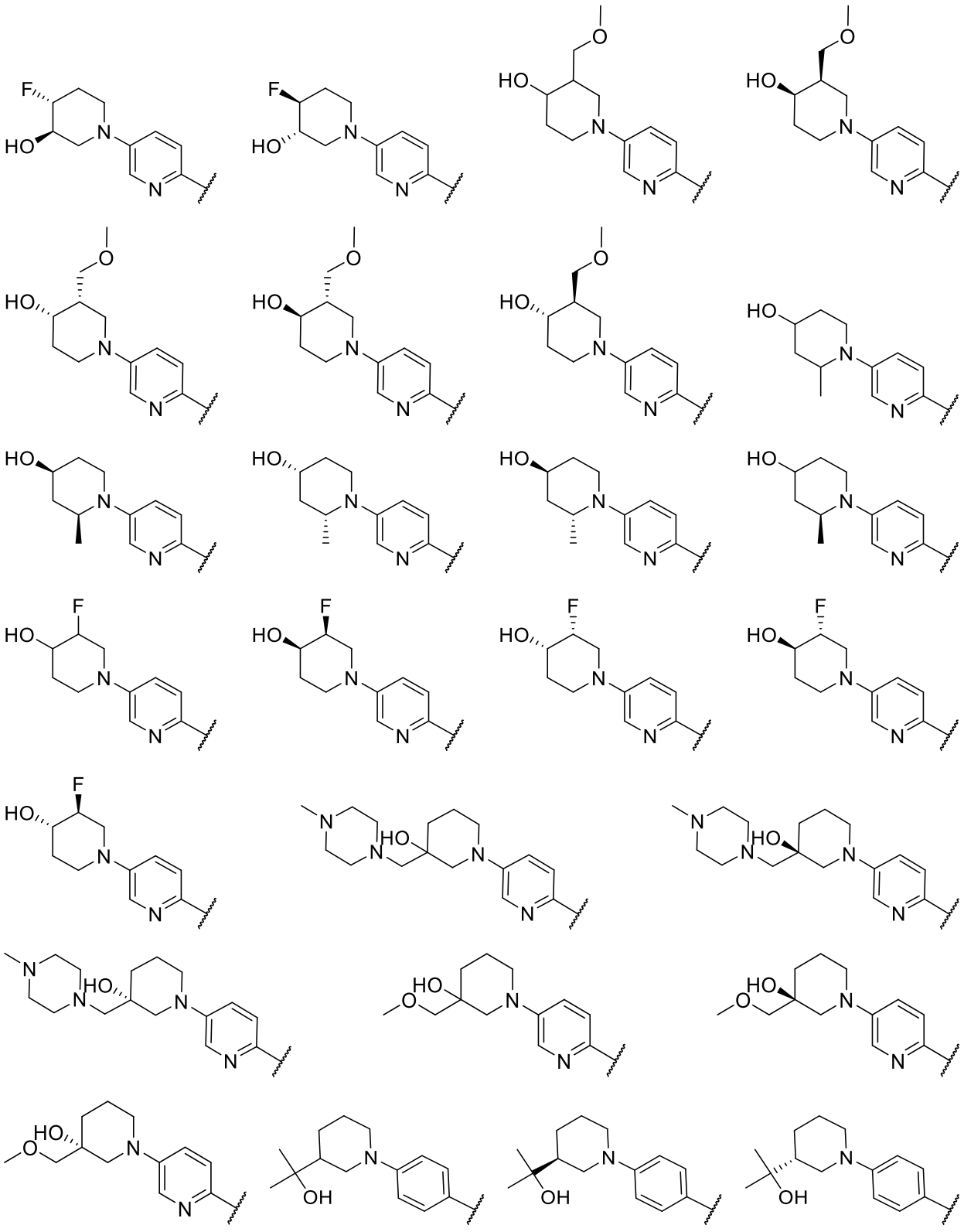


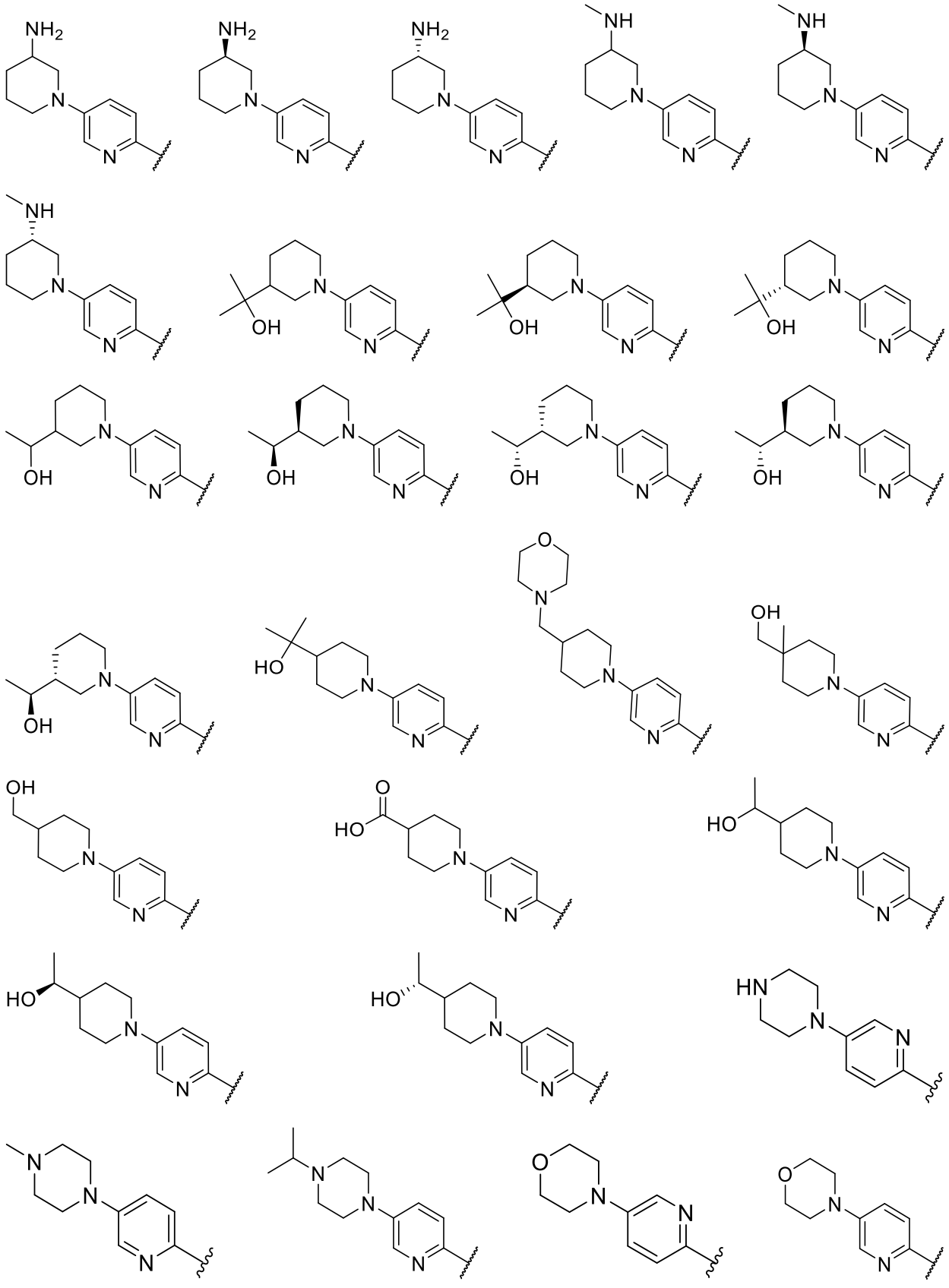
19. The compound of any one of claims 1-7 or 11-16, wherein R^1 is

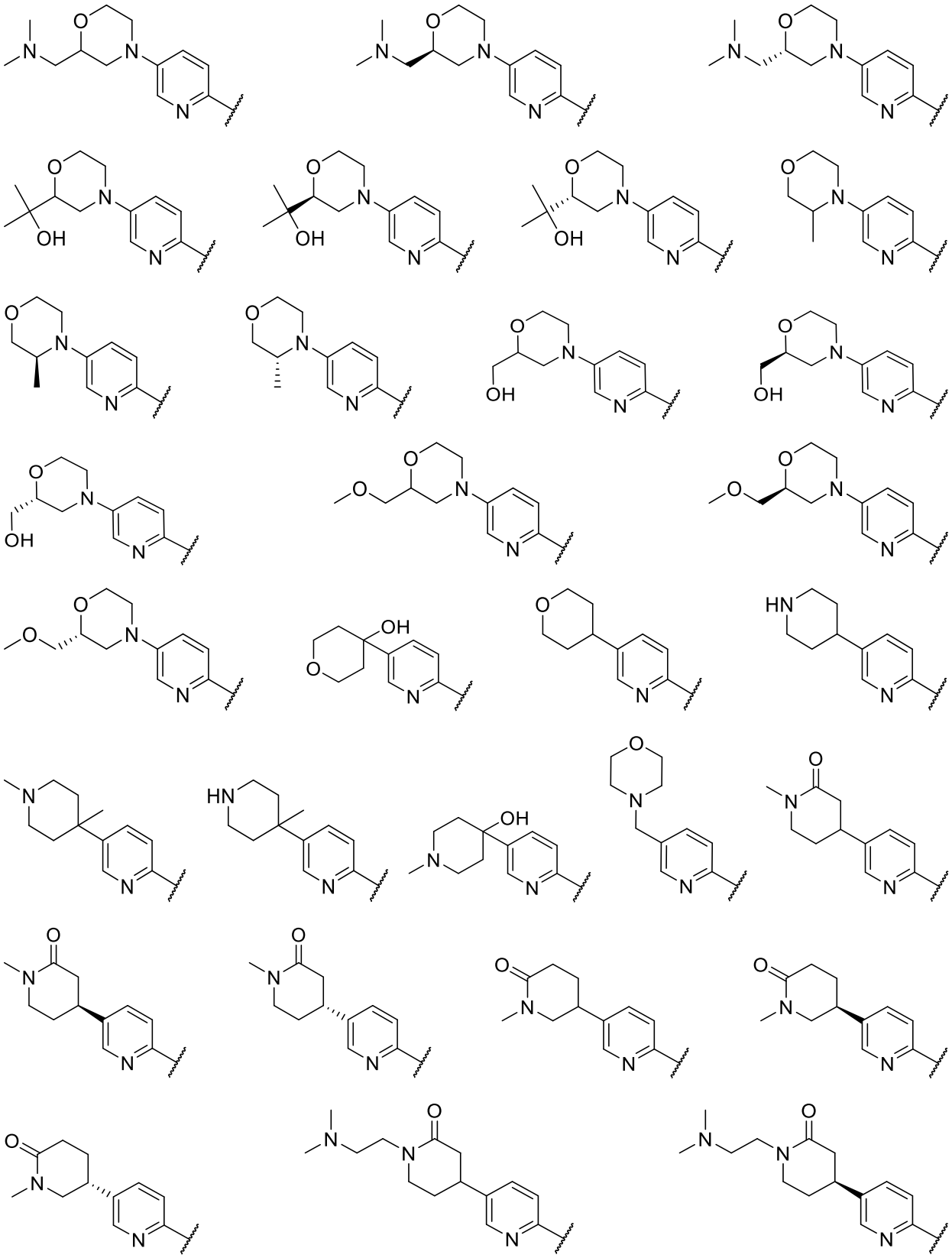


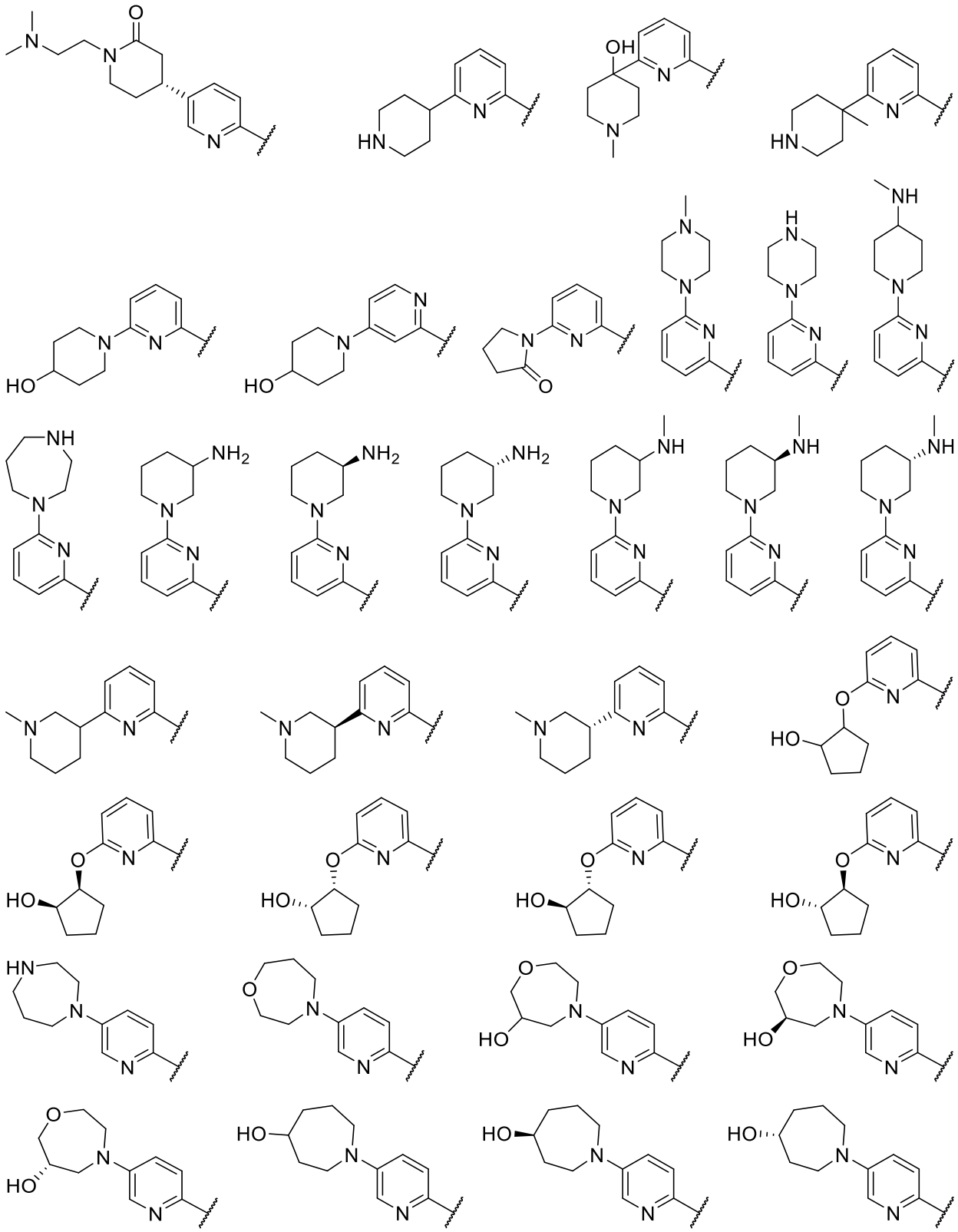


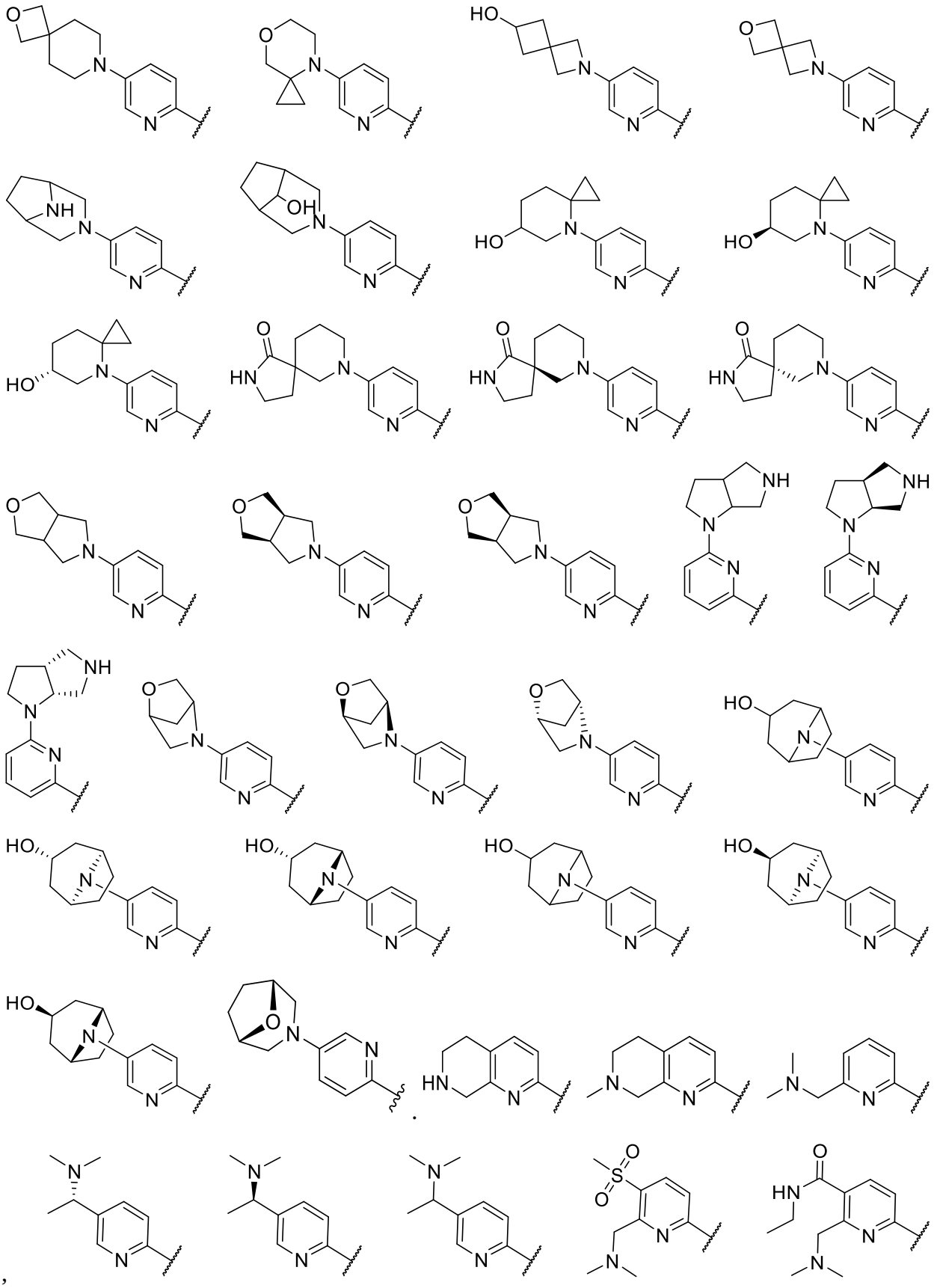


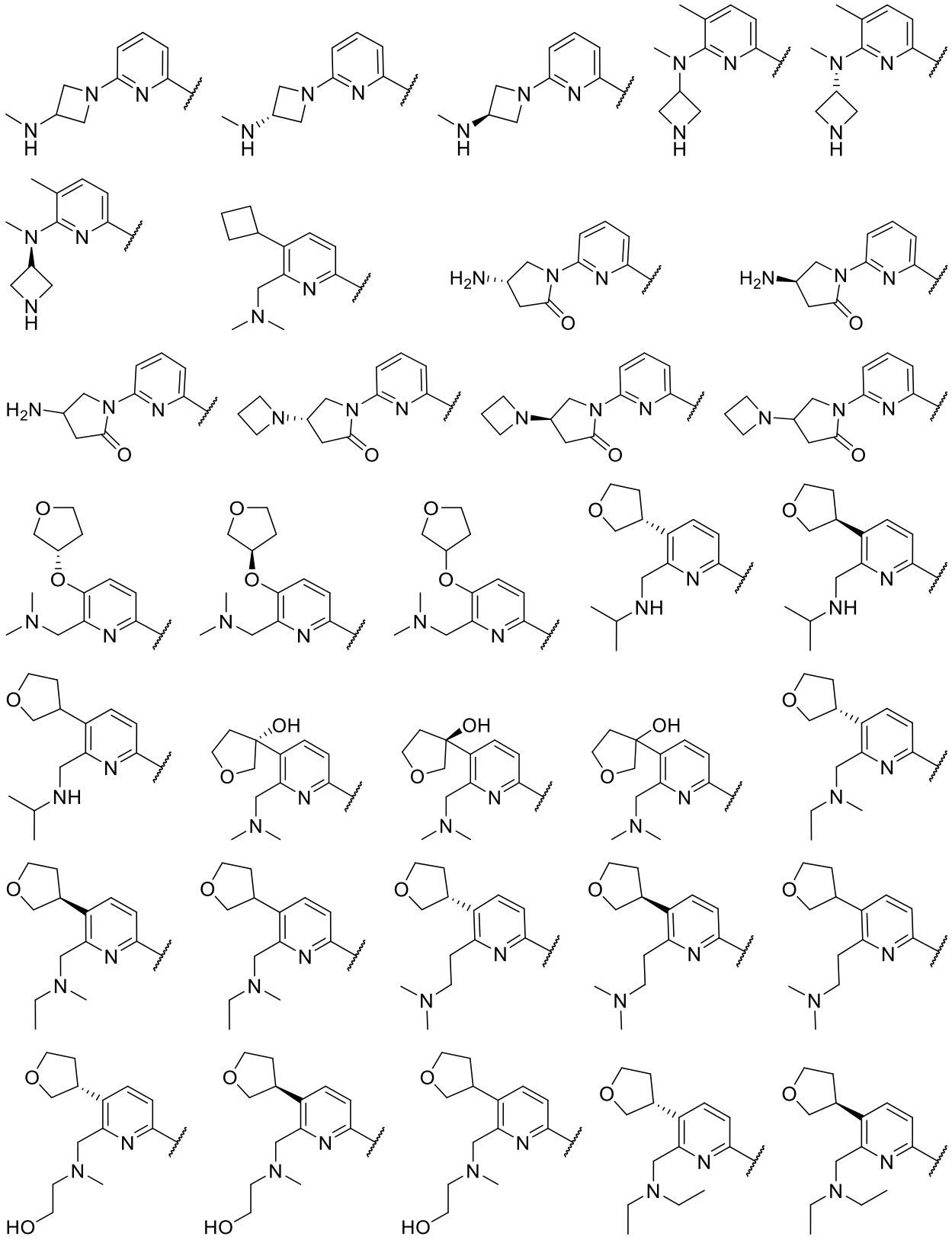


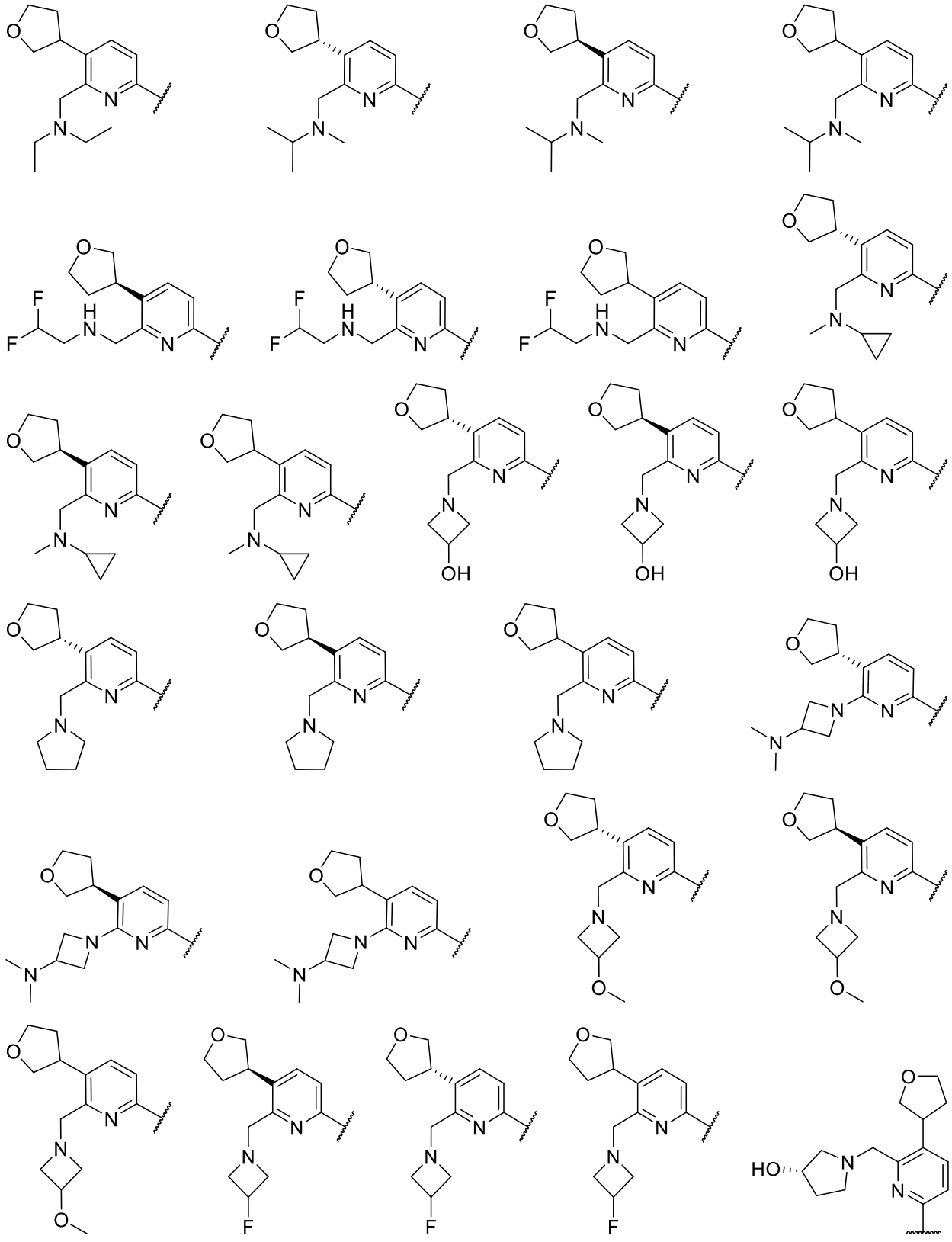


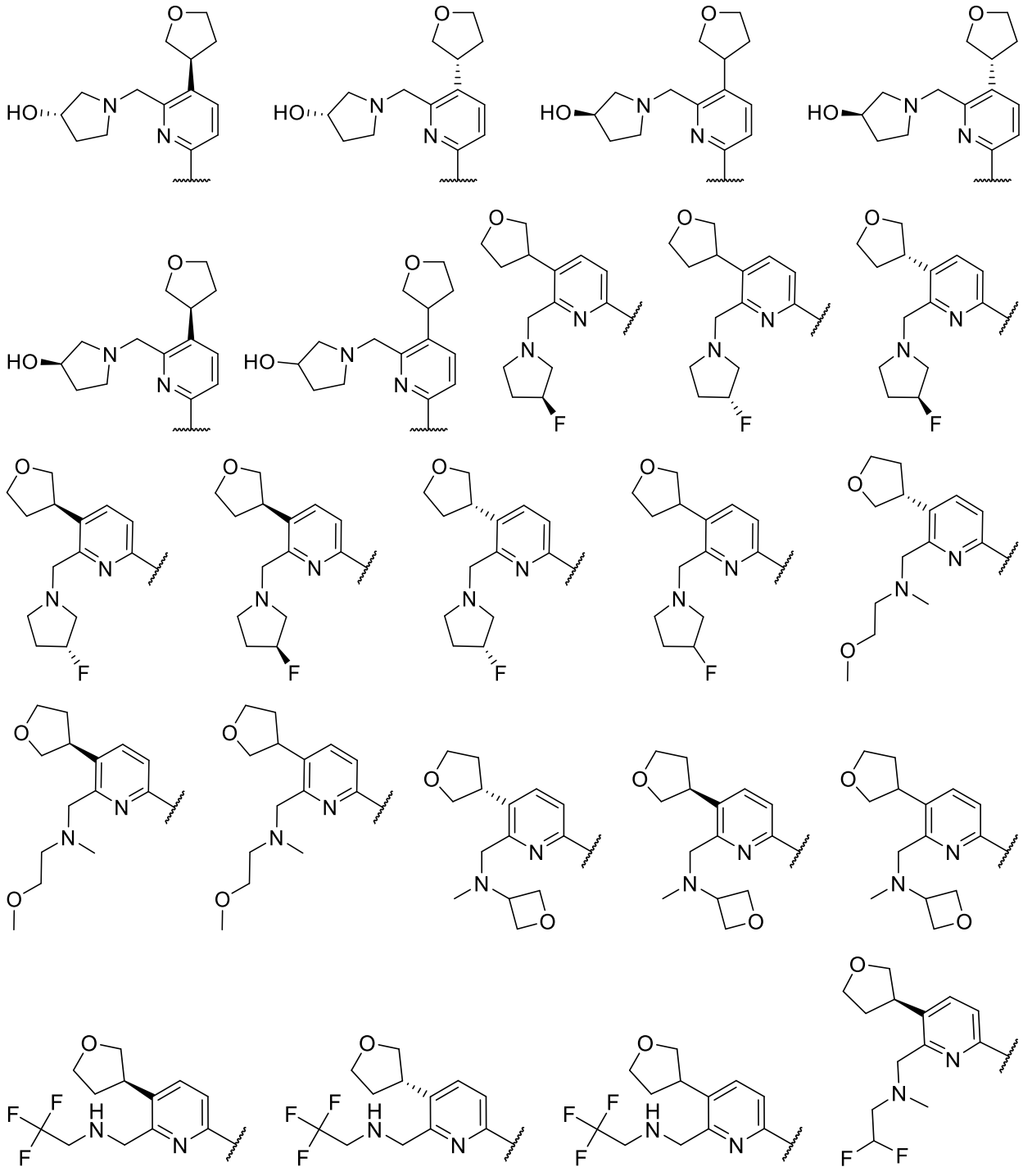


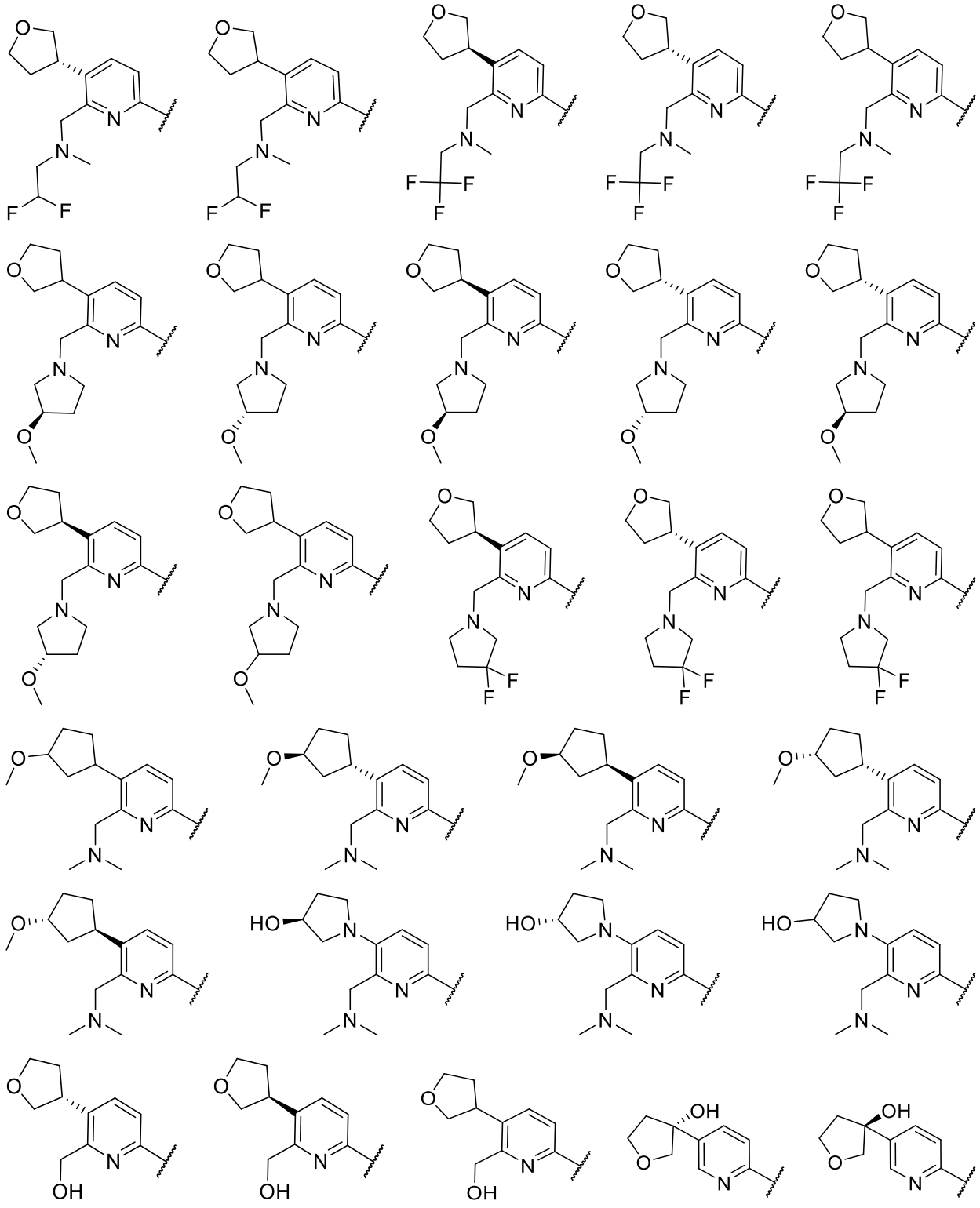


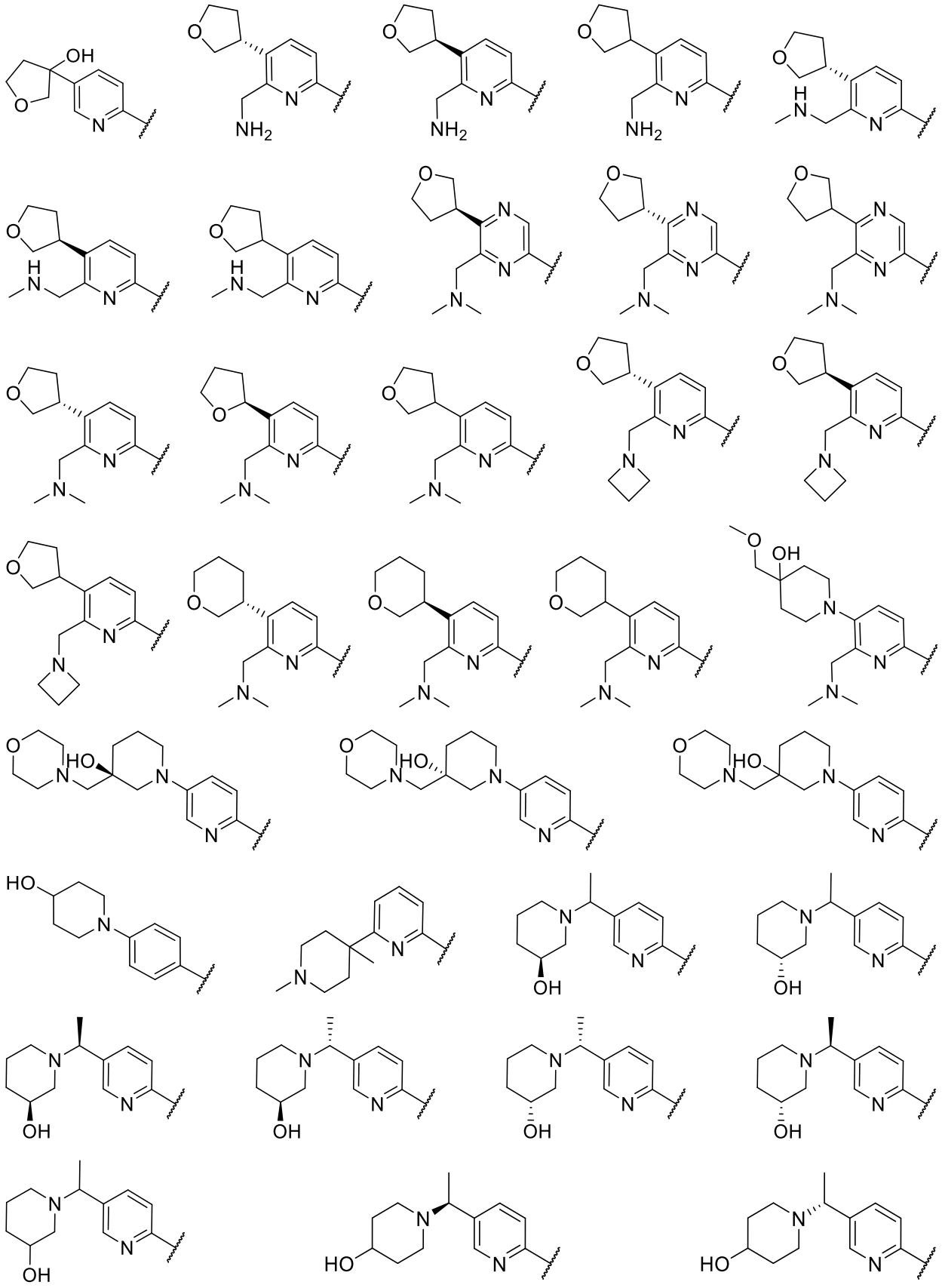


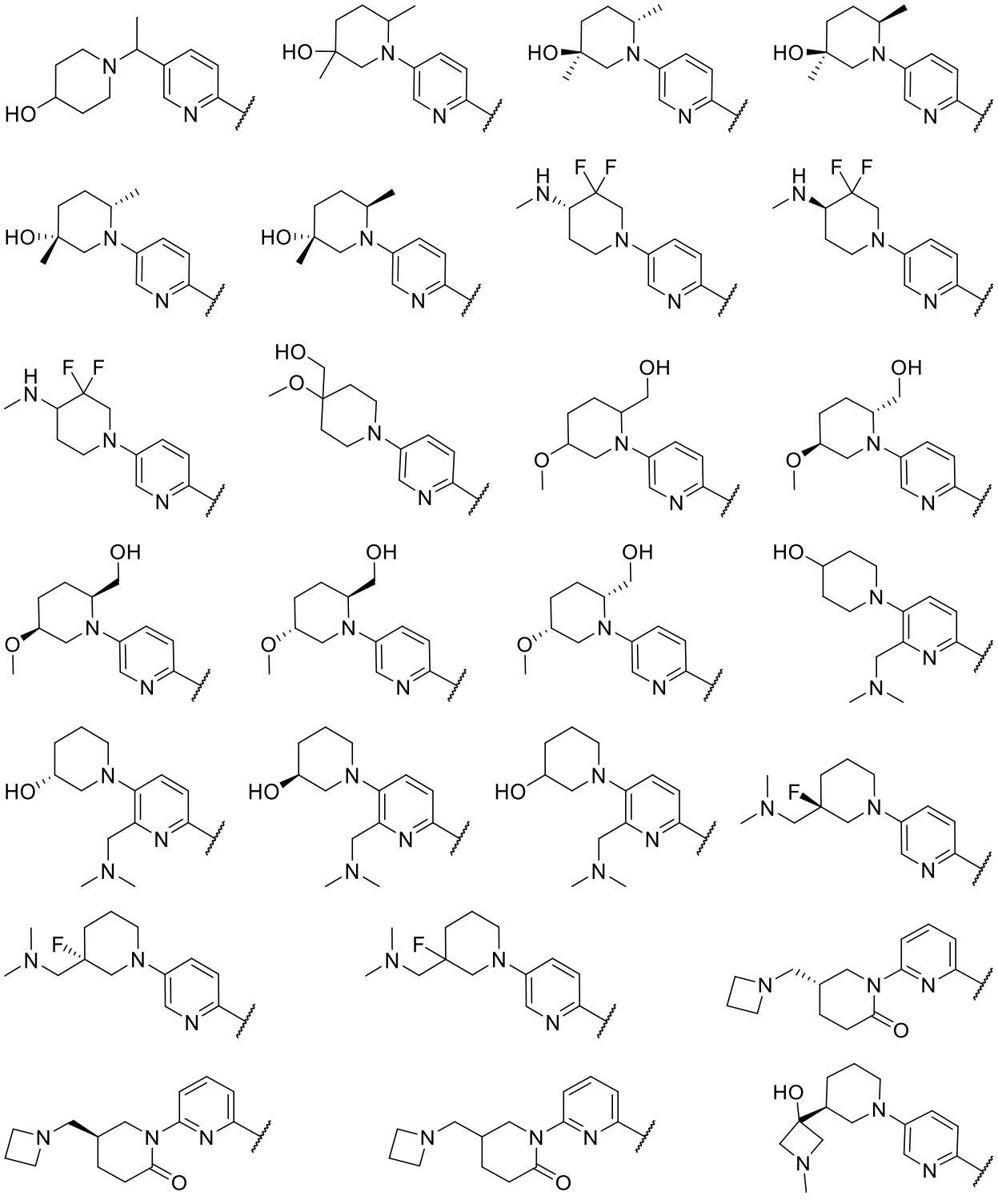


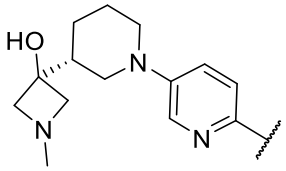
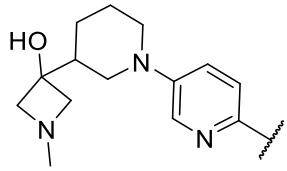
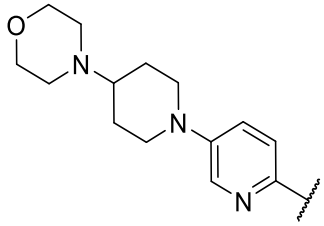
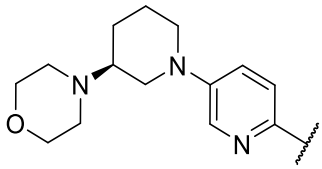
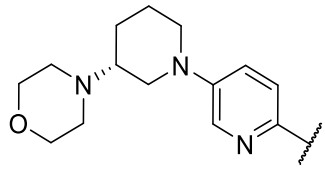
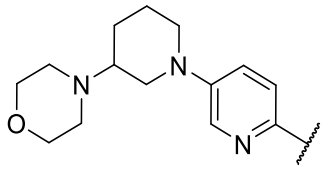
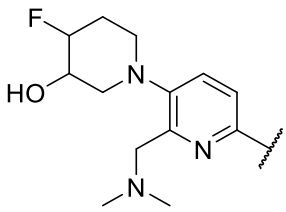
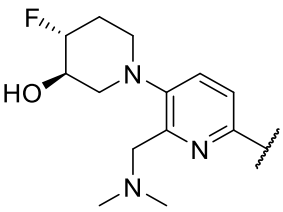
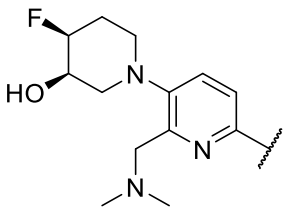
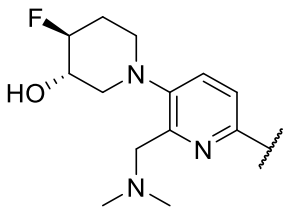
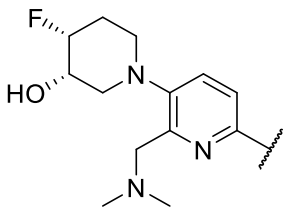
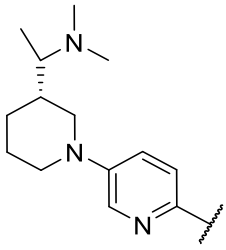
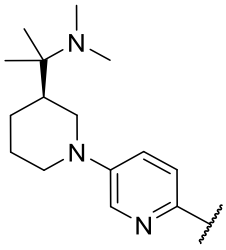
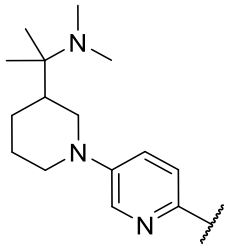
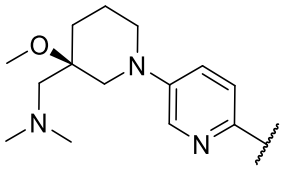
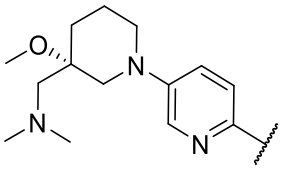
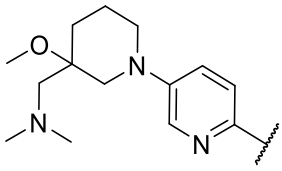
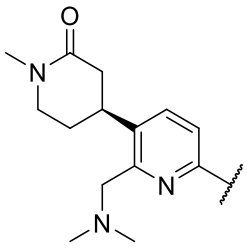
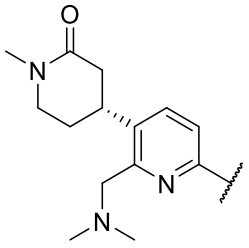
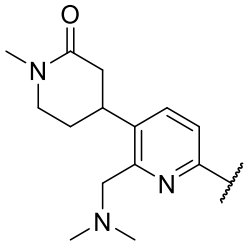
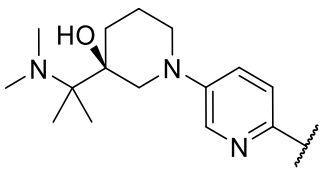
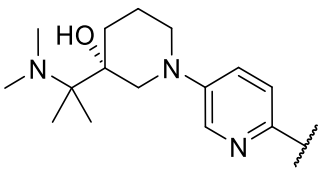
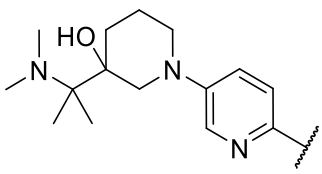
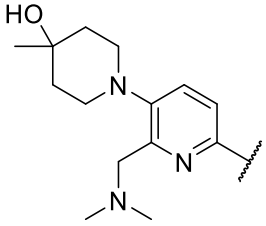
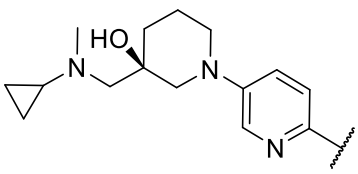


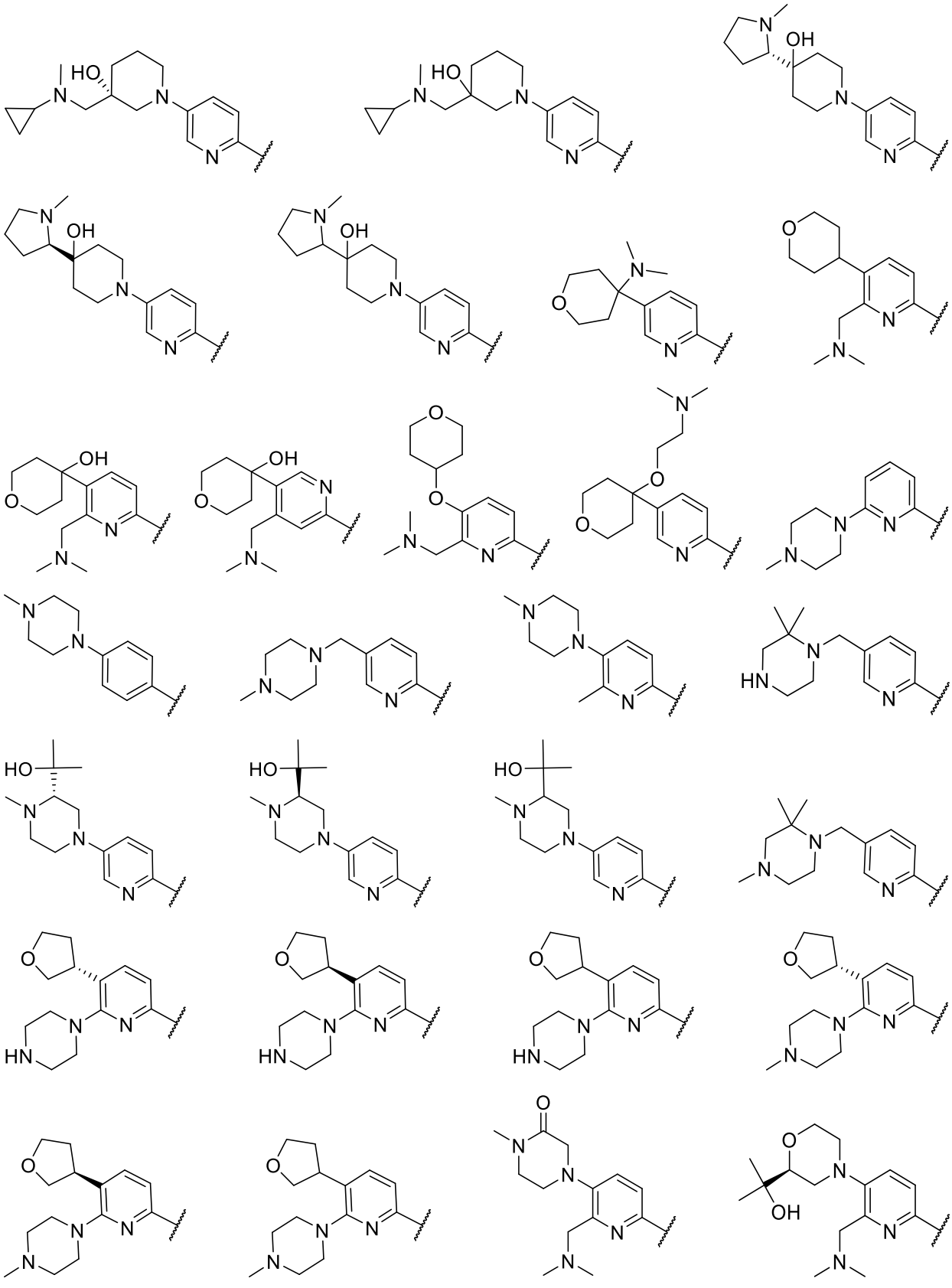


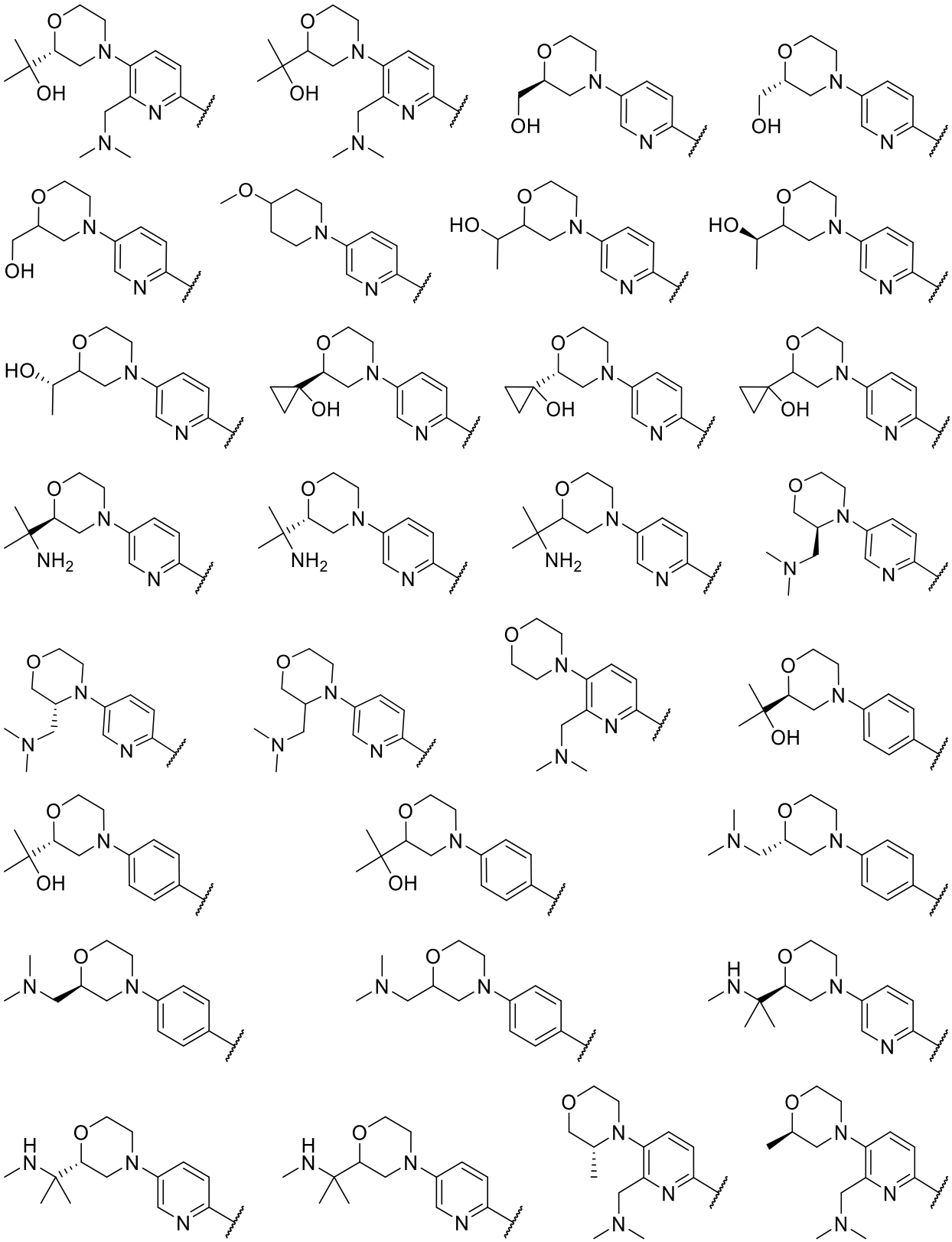


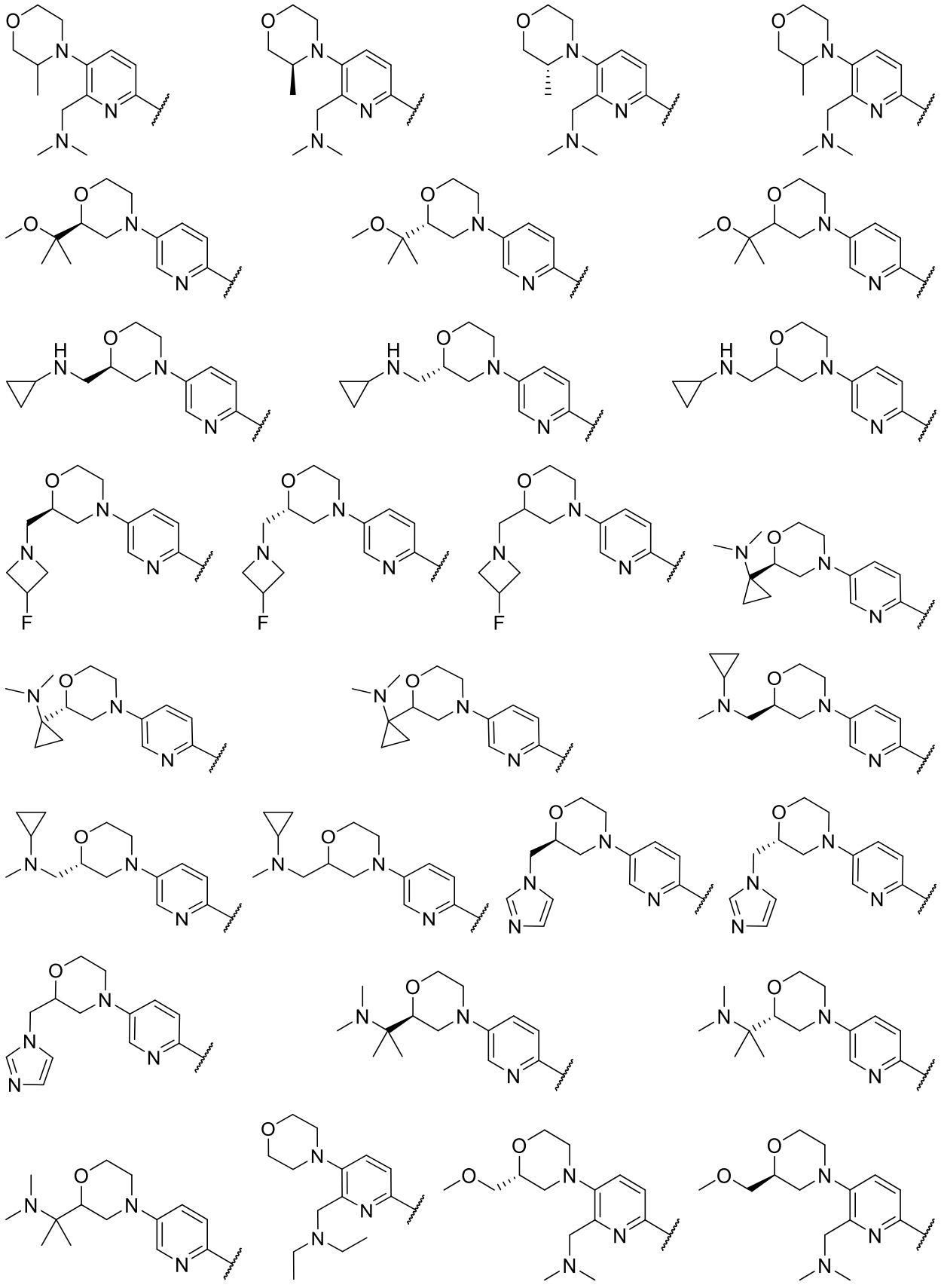


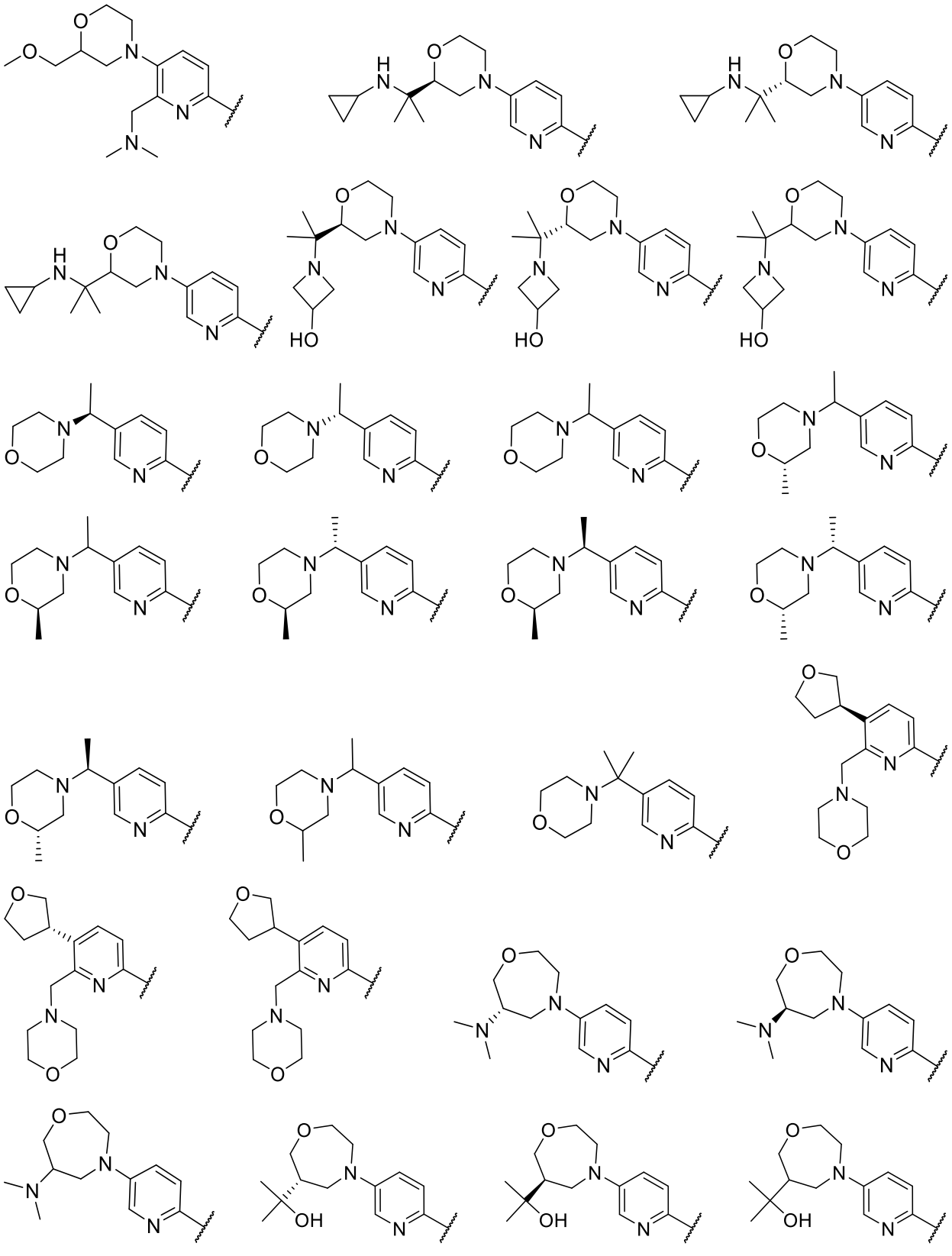


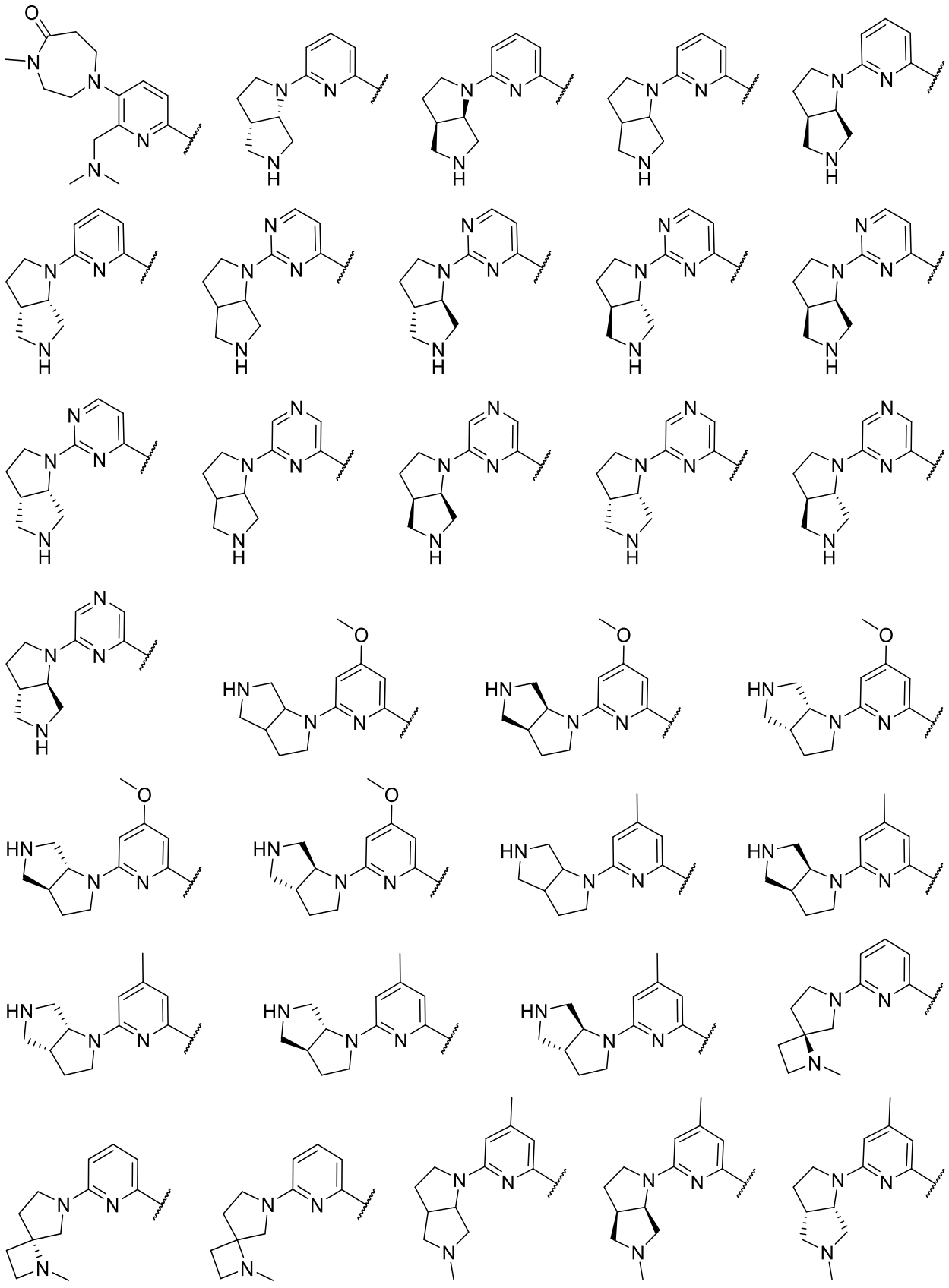


























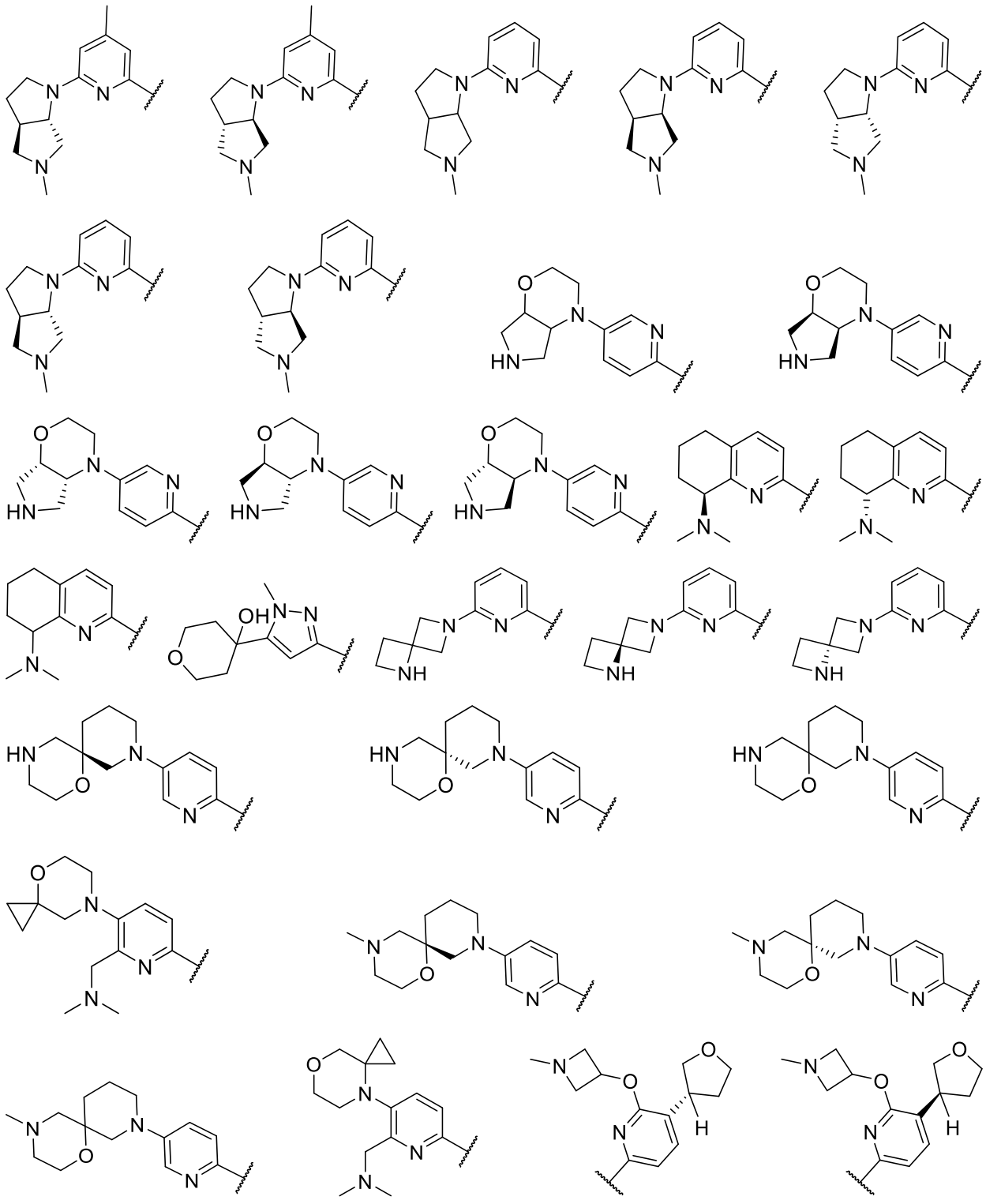


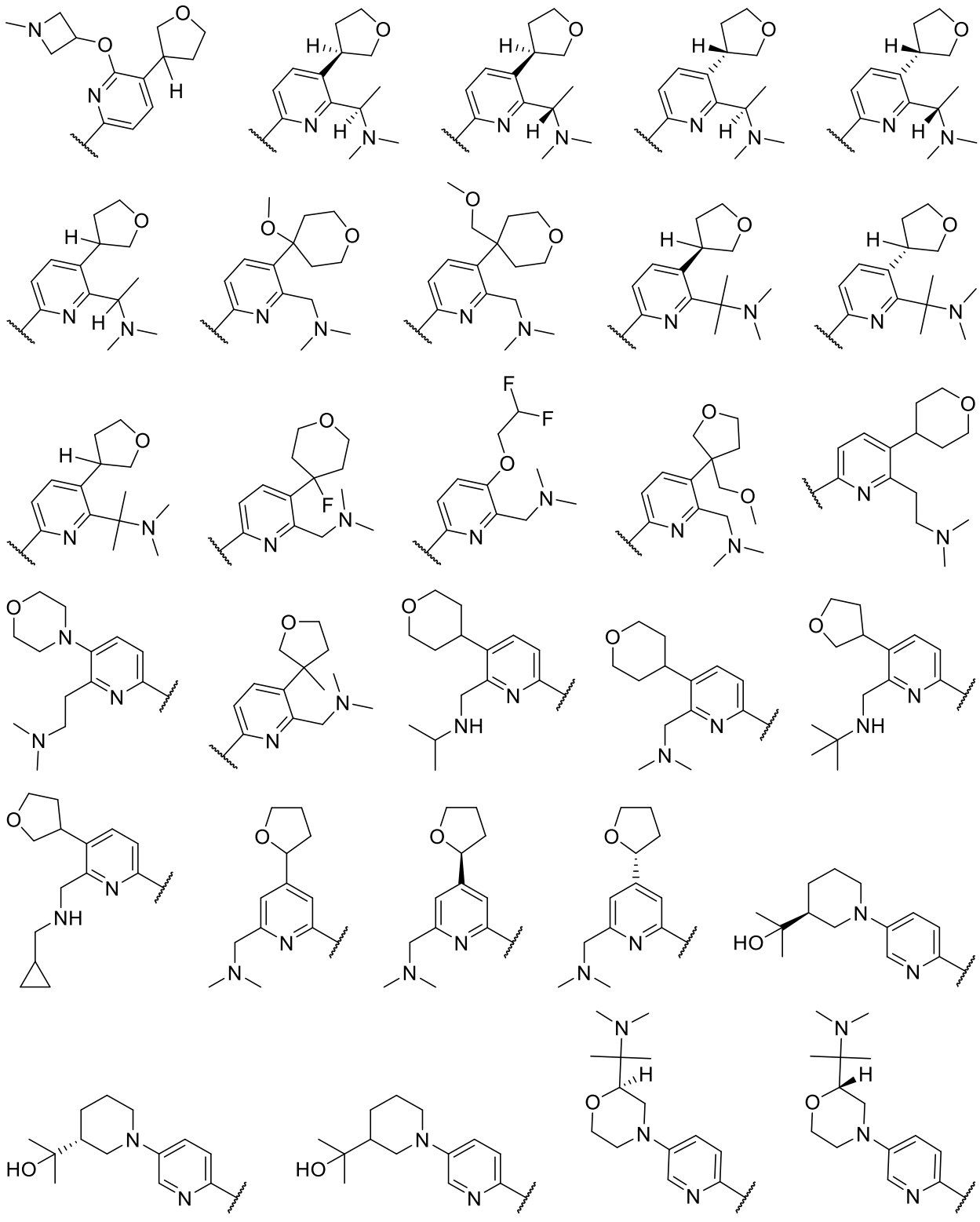


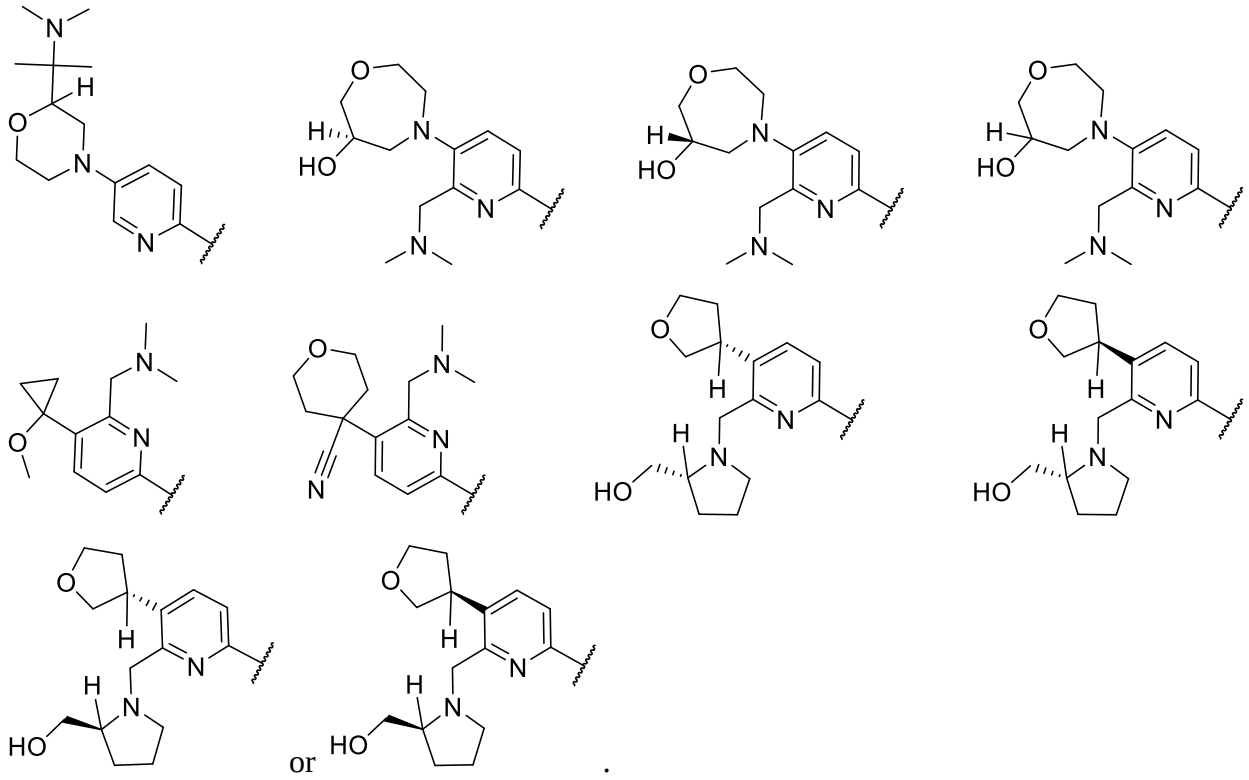








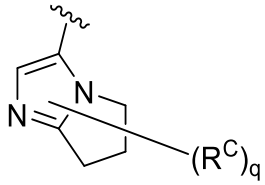
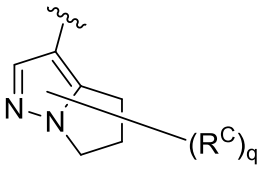


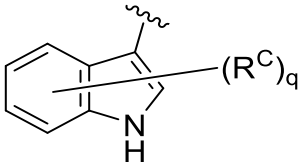
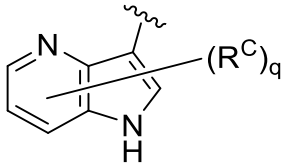
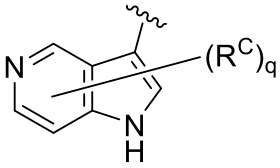
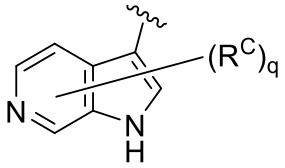


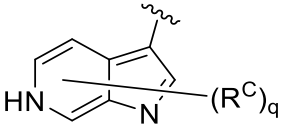
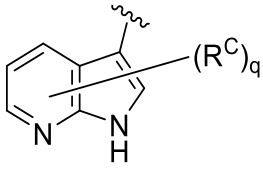
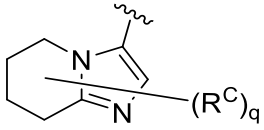
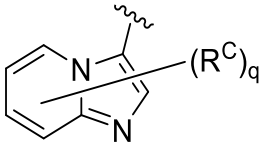
or .

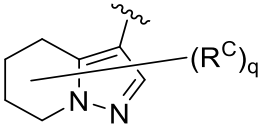
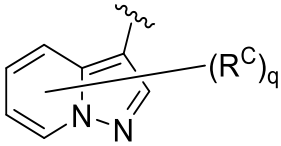
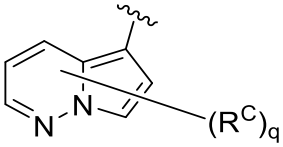
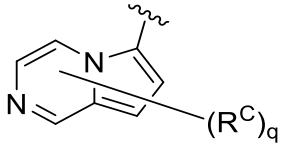
20. The compound of any one of claims 1-5, wherein R^2 is a 6-11 membered saturated, partially unsaturated, or unsatured fused, bridged, or spiro bicyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with q instances of R^C; wherein each instance of R^C is independently optionally substituted by r instances of R and s instances of R^D.

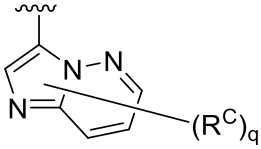
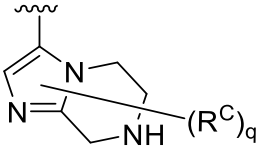
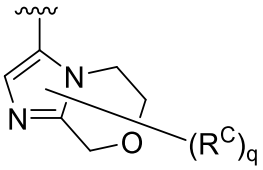
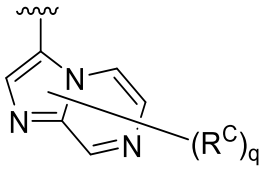
21. The compound of claim 20, wherein R^2 is a 7-10-membered fused bicyclic ring having 1-3 nitrogen atoms; each of which is substituted by each of which is substituted by q instances of R^C.

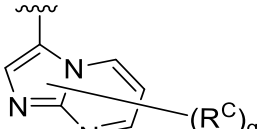
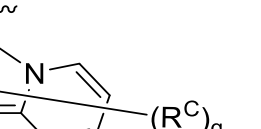
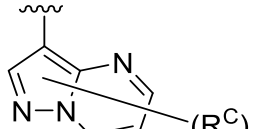
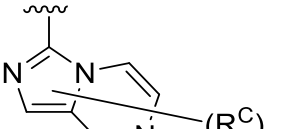
22. The compound of claim 20, wherein R^2 is  

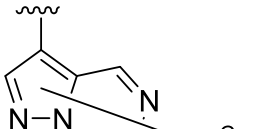
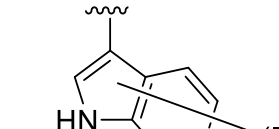
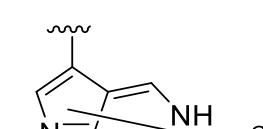
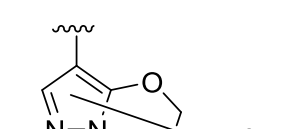
   

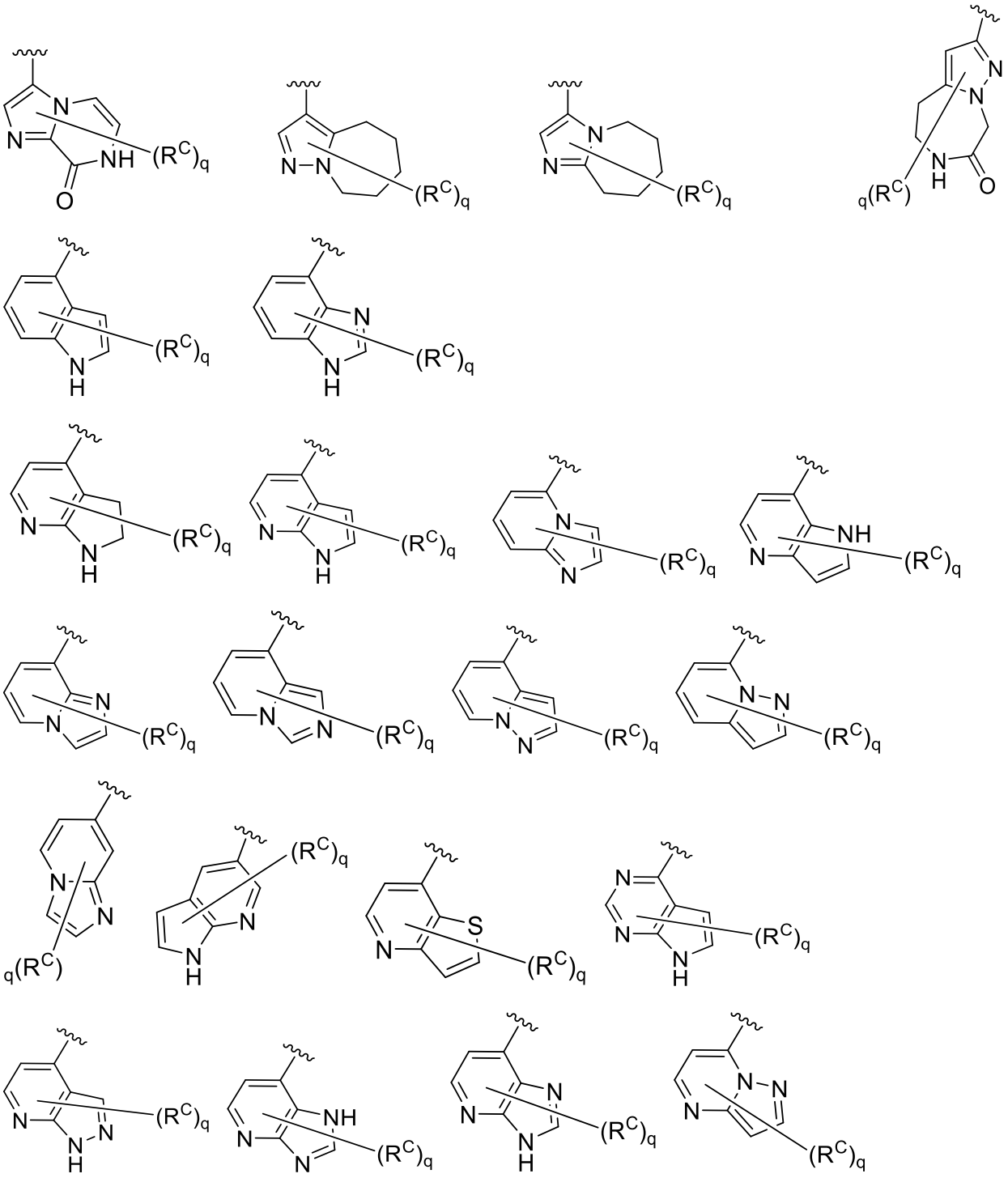
   

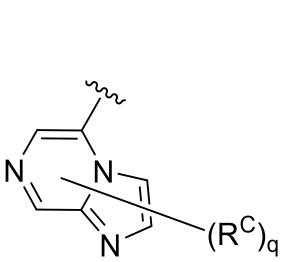
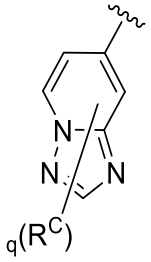
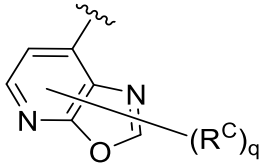
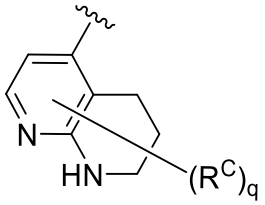
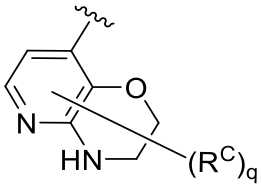
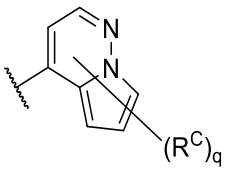
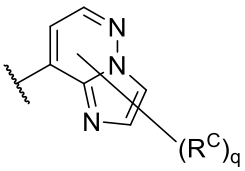
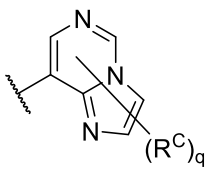
   

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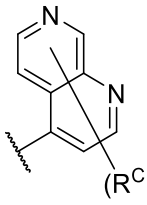
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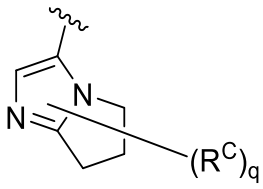
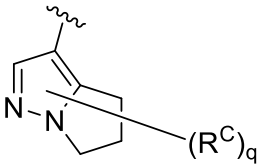
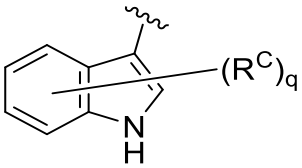
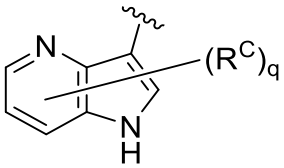
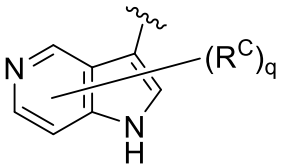
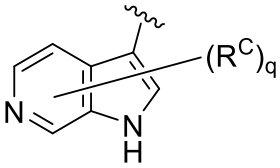
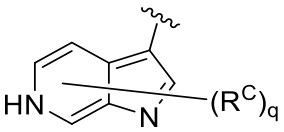
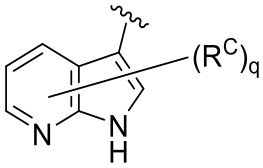
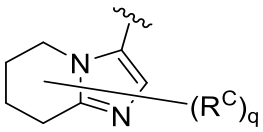
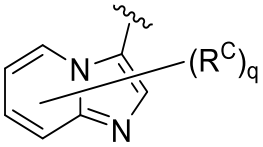
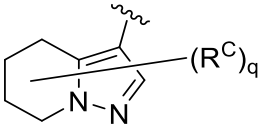
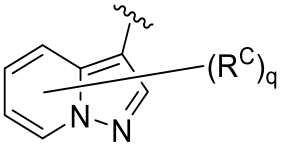
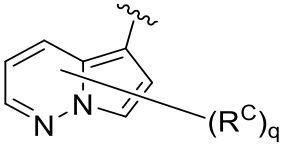
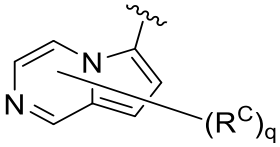
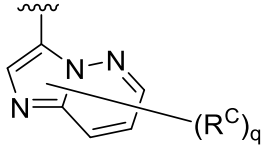
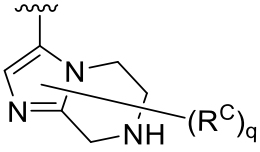
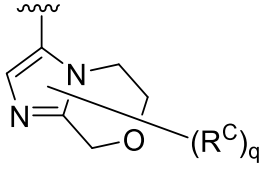
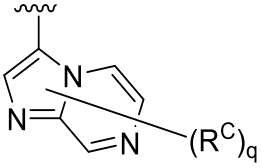
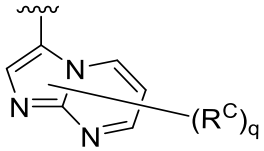
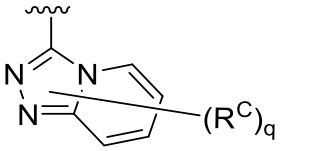
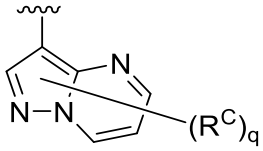
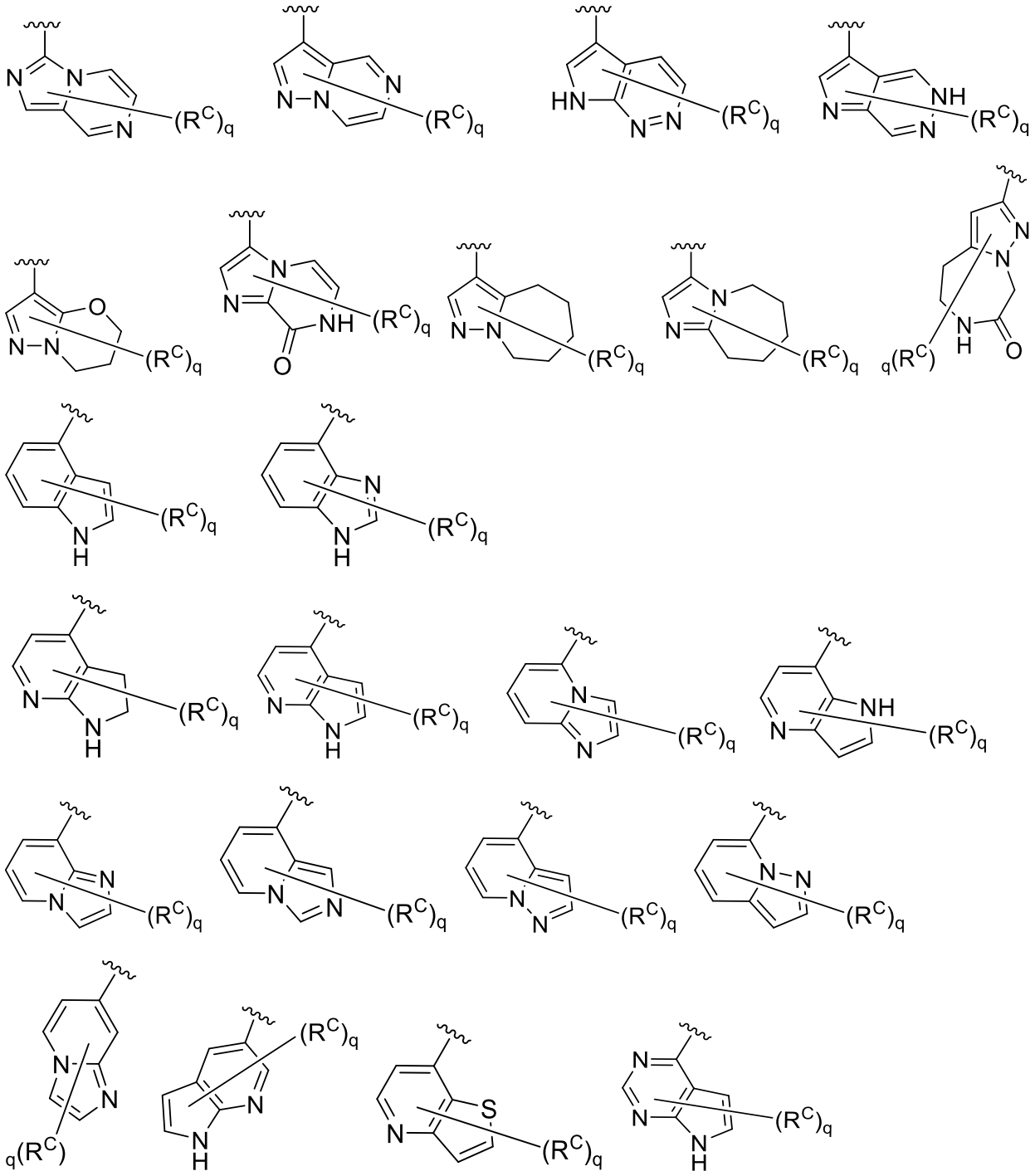
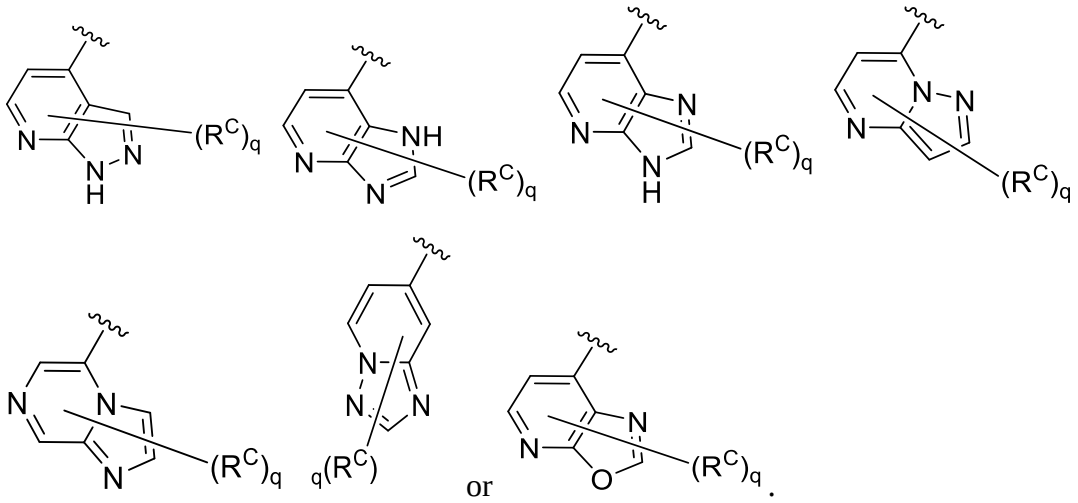
23. The compound of any one of claims 1-5, wherein R^2 is







or

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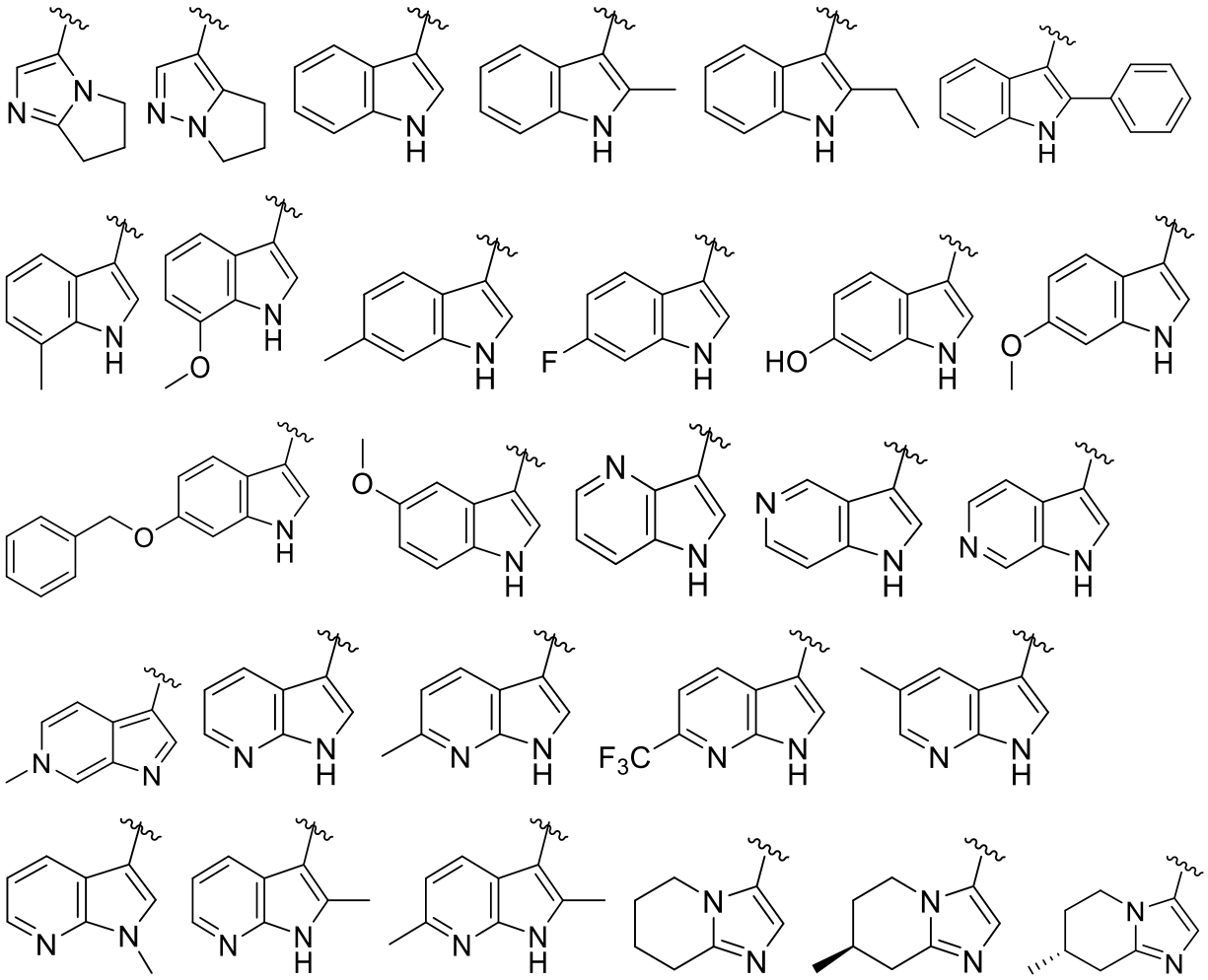
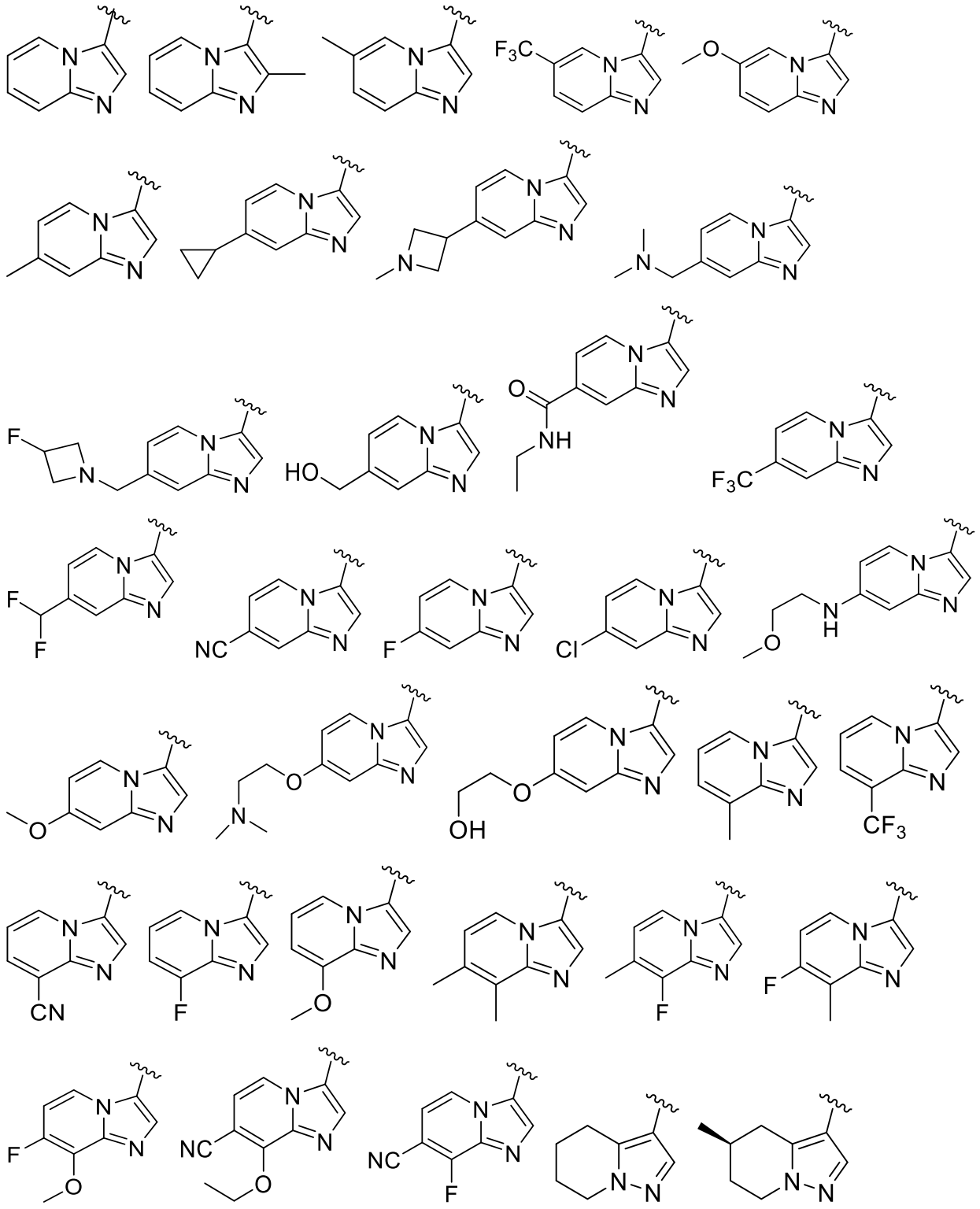
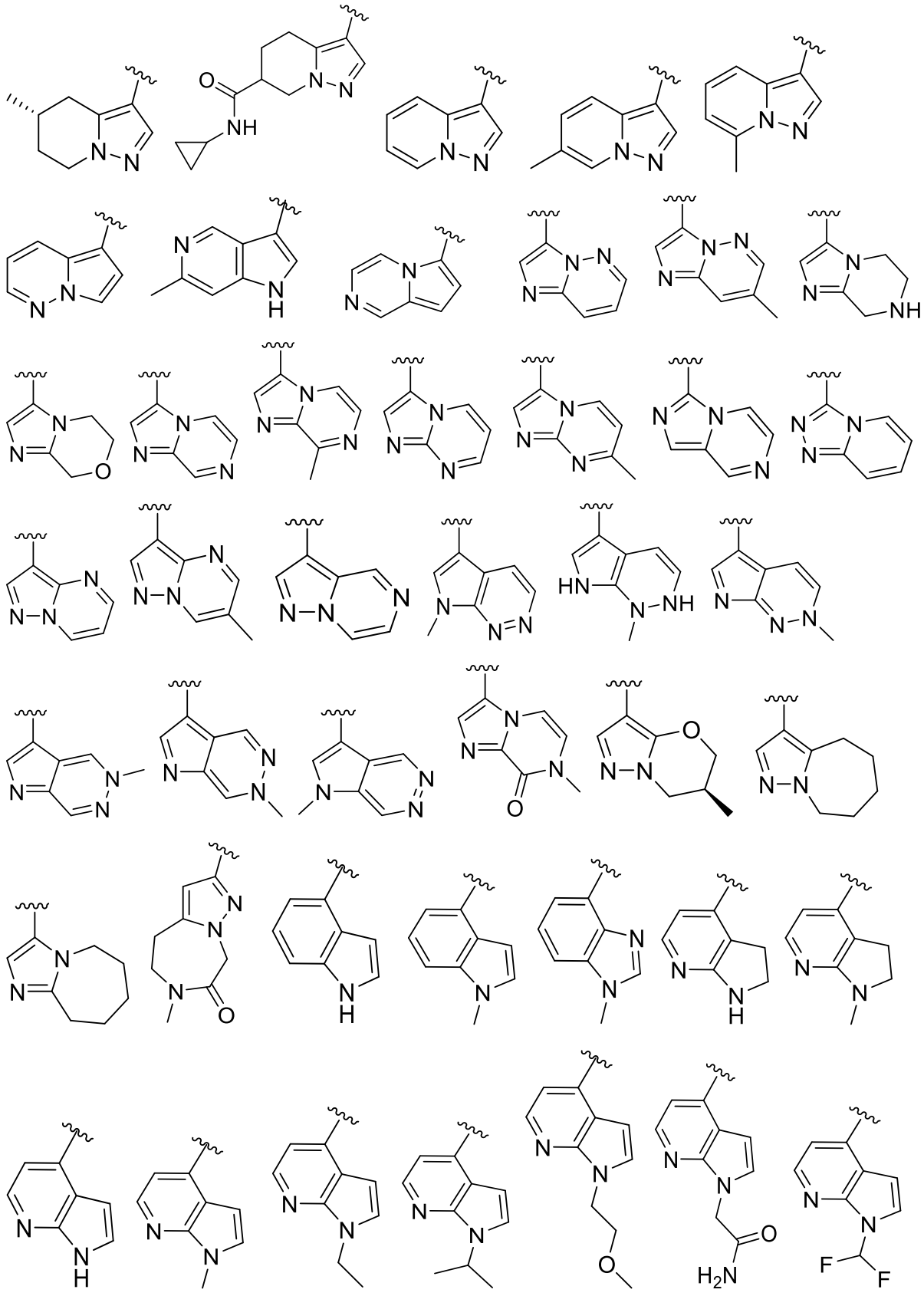
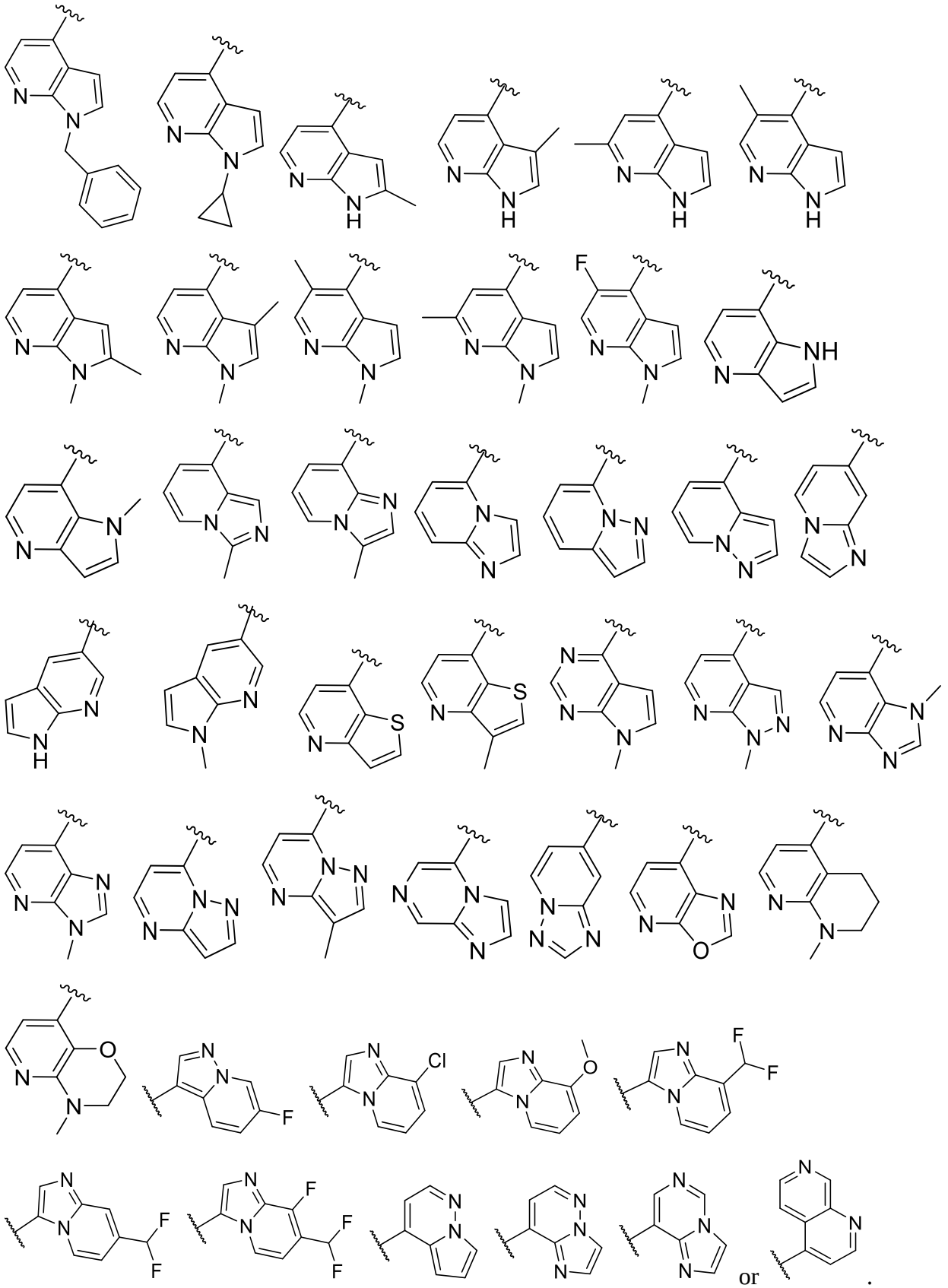
24. The compound of any one of claims 1-5 or 20, wherein R^2 is









or .

25. The compound of any one of claims 1-24, wherein the compound is selected from those depicted in **Table 1**, or a pharmaceutically acceptable salt thereof.

26. A pharmaceutical composition comprising a compound according to any one of claims 1-25, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

27. The compound of any one of claims 1-25, or the pharmaceutical composition of claim 26, for use as a medicament.

28. A method of inhibiting HPK1 in a biological sample comprising contacting the sample with the compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 26.

29. ~~A method of treating a HPK1-mediated disorder, disease, or condition in a patient comprising administering to said patient the~~ Use of a compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 26, in the manufacture of a medicament for treating a HPK1-mediated disorder, disease, or condition.

30. The ~~method~~ use of claim 29 wherein the disorder is a proliferative disorder.

31. The ~~method~~ use of claim 30 wherein the proliferative disorder is cancer.

32. The ~~method~~ use of claim 30 wherein the proliferative disorder is associated with one or more activating mutations in HPK1.

33. The ~~method~~ use of claim 29, wherein the disease is a chronic viral infection.

34. ~~A method of increasing the efficacy of vaccination in a patient comprising administering to said patient the~~Use of a compound of any one of claims 1-25, or a pharmaceutically

acceptable salt thereof, or the pharmaceutical composition of claim 26, in the manufacture of a medicament for increasing the efficacy of vaccination in a patient, wherein the compound, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition is to be administered as an adjuvant.