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).

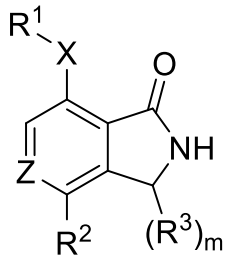
## SUMMARY

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

**[0007]** Compounds of the present disclosure, 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 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

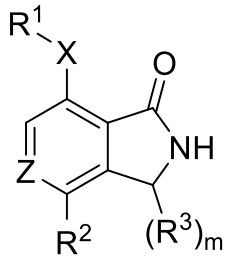
### *1. General Description of Certain Embodiments of the Invention:*

**[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;

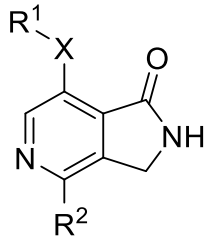
m is 0, 1, or 2;

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.

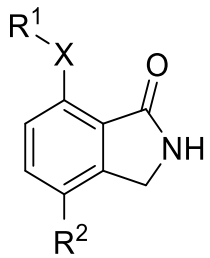
2. The compound of claim 1, wherein the compound is of formula **II**:




**II**

or a pharmaceutically acceptable salt thereof.

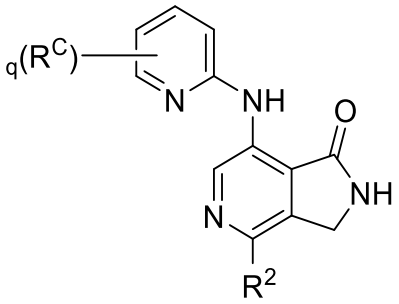
3. The compound of claim 1, wherein the compound is of formula **V**:




**V**

or a pharmaceutically acceptable salt thereof.

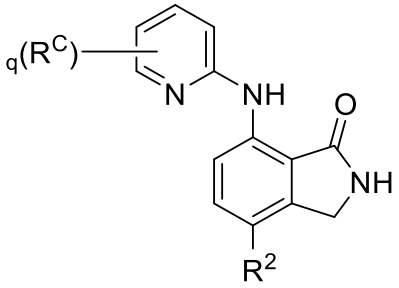
4. The compound of claim 2, wherein the compound is of formula **IV**:



**IV**

or a pharmaceutically acceptable salt thereof.

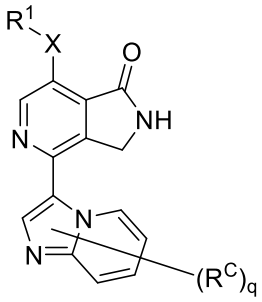
5. The compound of claim 3, wherein the compound is of formula **VII**:



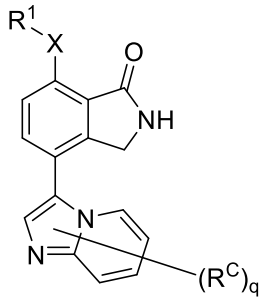
**VII**

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**:



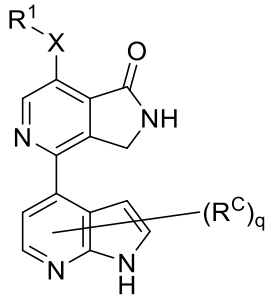
**XI-a**



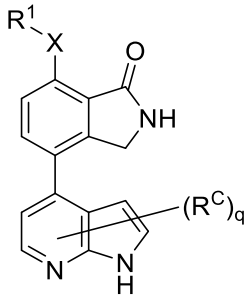
**XI-b**

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**:



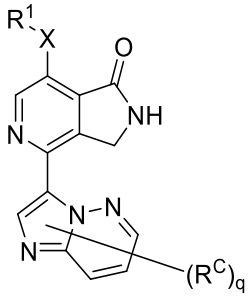
**XIV-a**



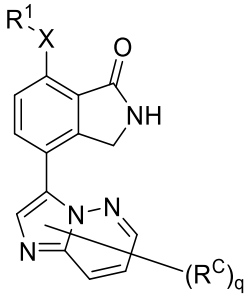
**XIV-b**

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**:



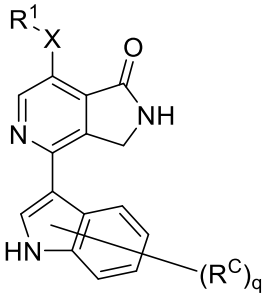
**XVII-a**



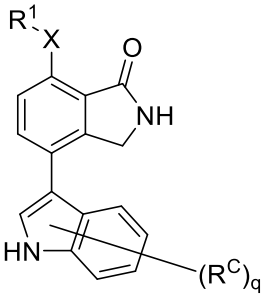
**XVII-b**

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**:



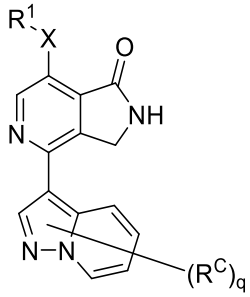
**XX-a**



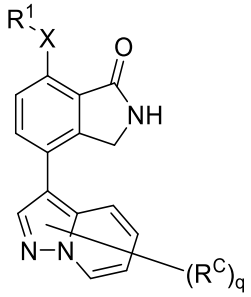
**XX-b**

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**:



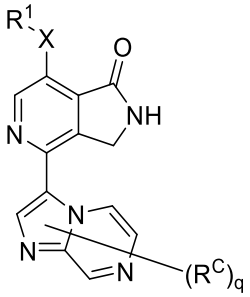
**XXIII-a**



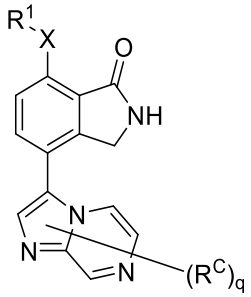
**XXIII-b**

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**:



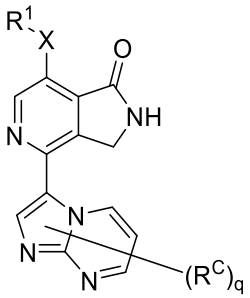
**XXVI-a**

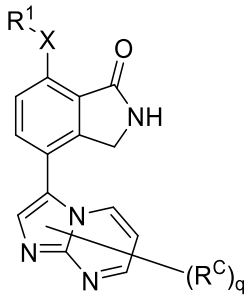


**XXVI-b**

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-.

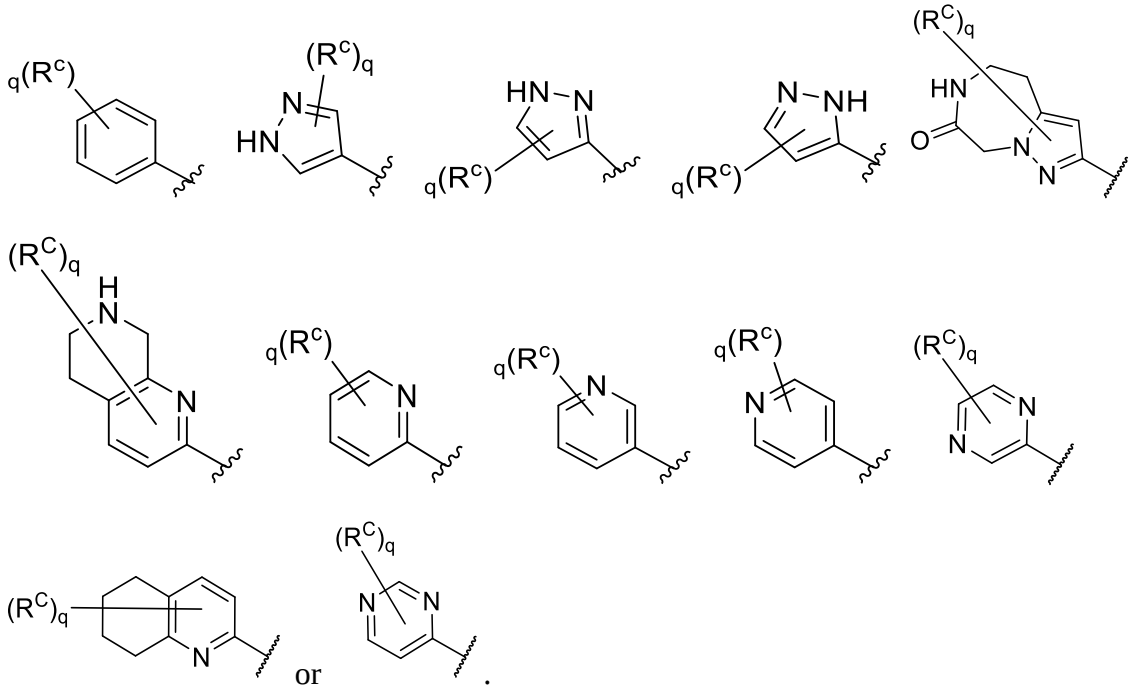
14. The compound of any one of claims 1-3 or 6-13, wherein $R^1$ is $C_{1-6}$ aliphatic which is substituted with q instances of $R^C$; phenyl which is substituted with q instances of $R^C$; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring, which is substituted with q instances 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 $R^C$.

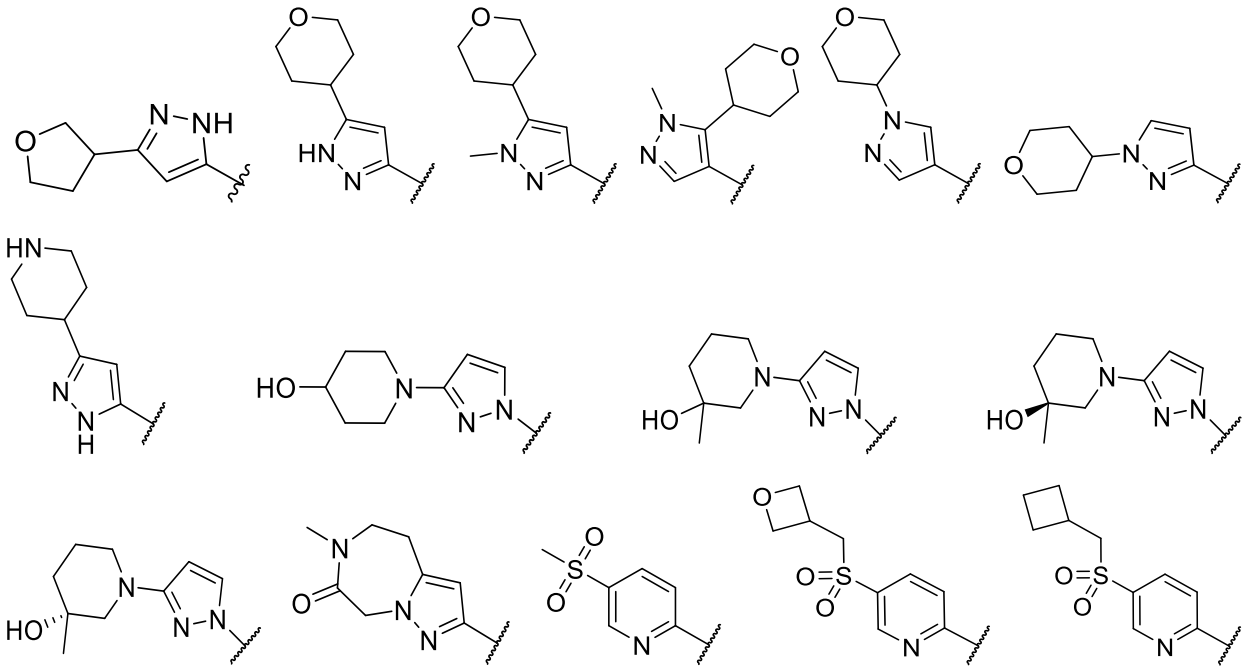
16. The compound of any one of claims 1-3 or 6-15, wherein $R^1$ is phenyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, isothiazolyl, isoxazolyl, morpholinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl;- 1,2,5oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, 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 $R^C$.

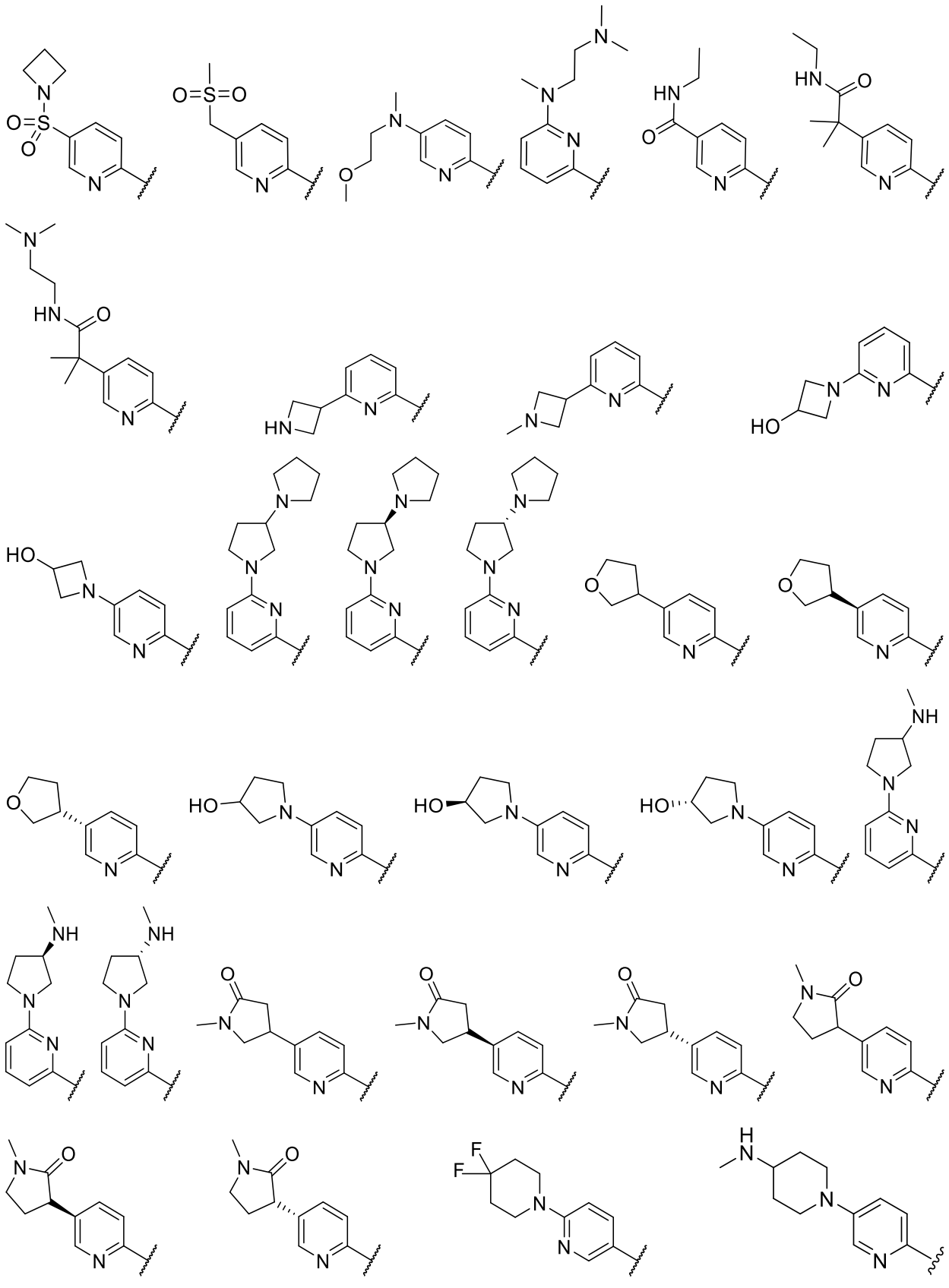
17. The compound of any one of claims 1-3 or 6-16, wherein $R^1$ is phenyl, pyrazolyl, pyridinyl, pyrazinyl, or pyrimidinyl; each of which is substituted by q instances of $R^C$.

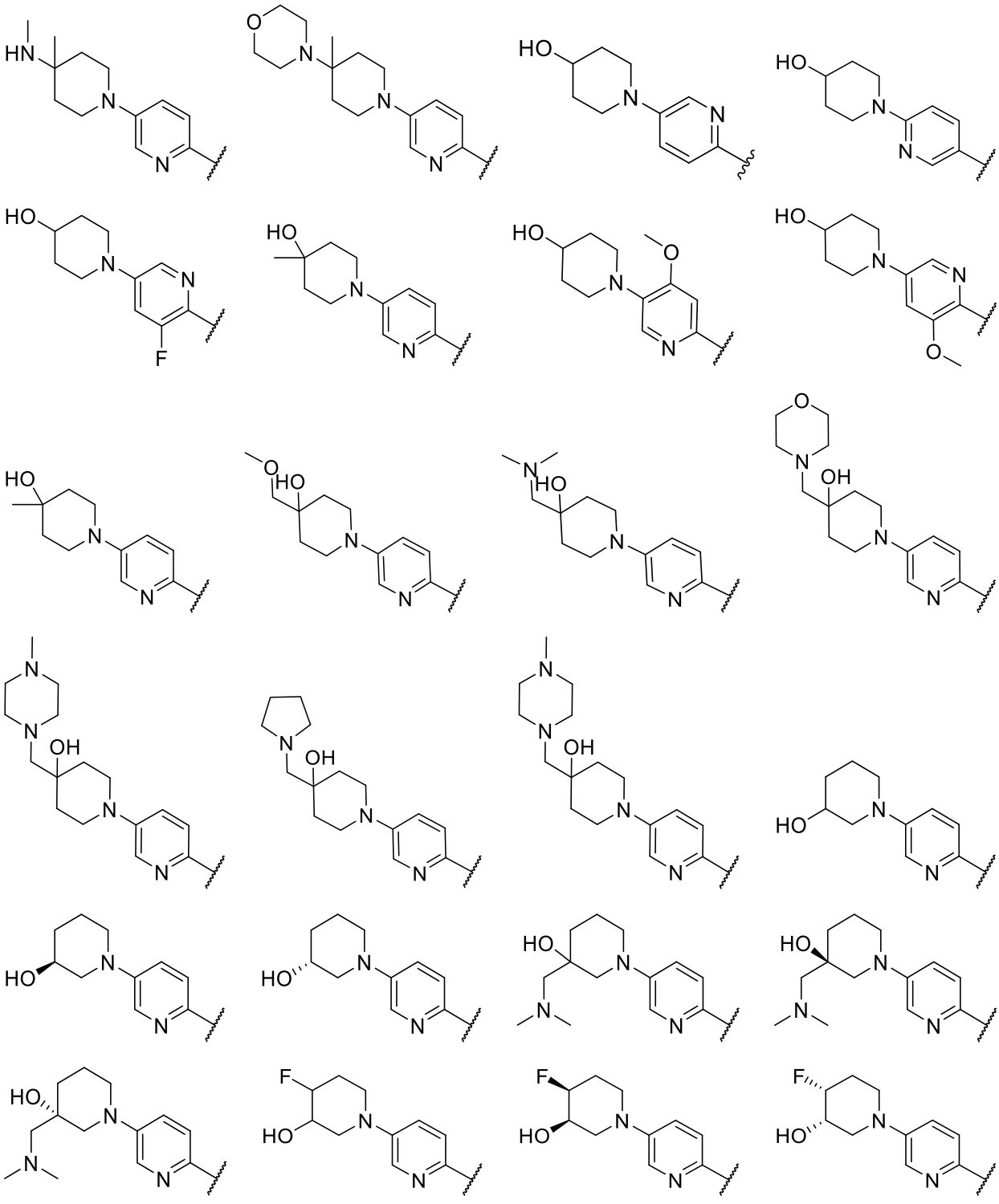
18. The compound of any one of claims 1-3 or 6-13, wherein $R^1$ is

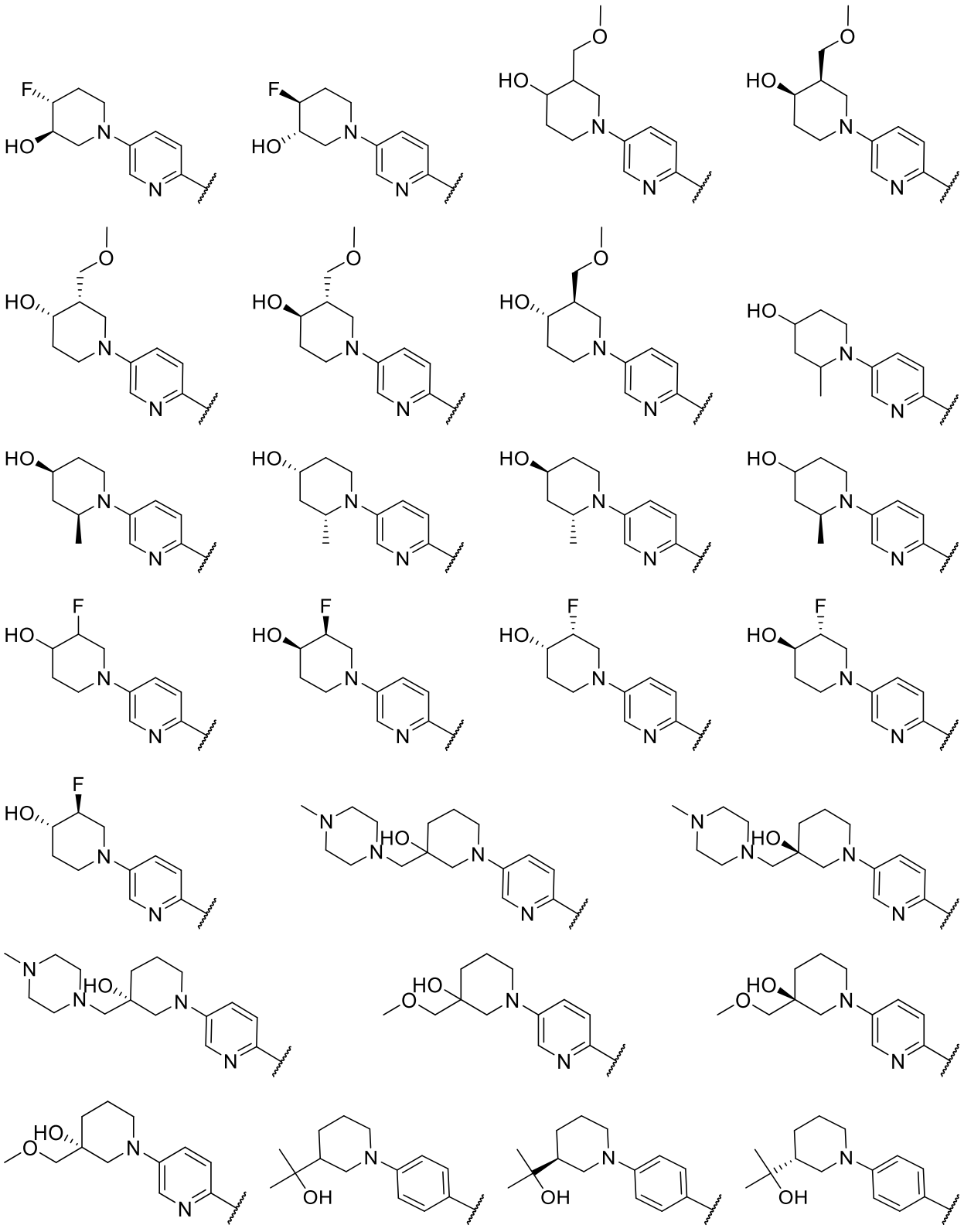


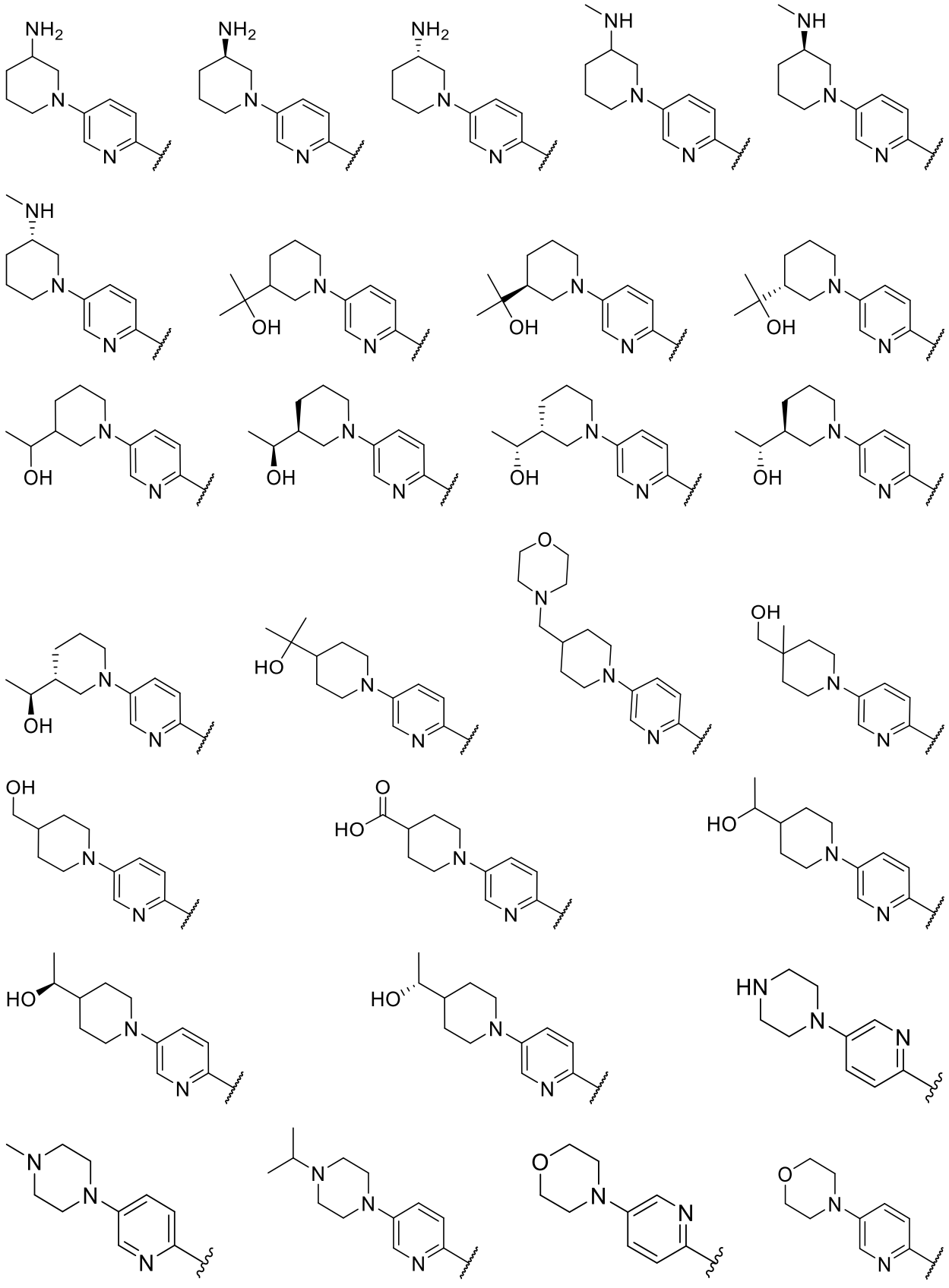
19. The compound of any one of claims 1-7 or 11-16, wherein $R^1$ is

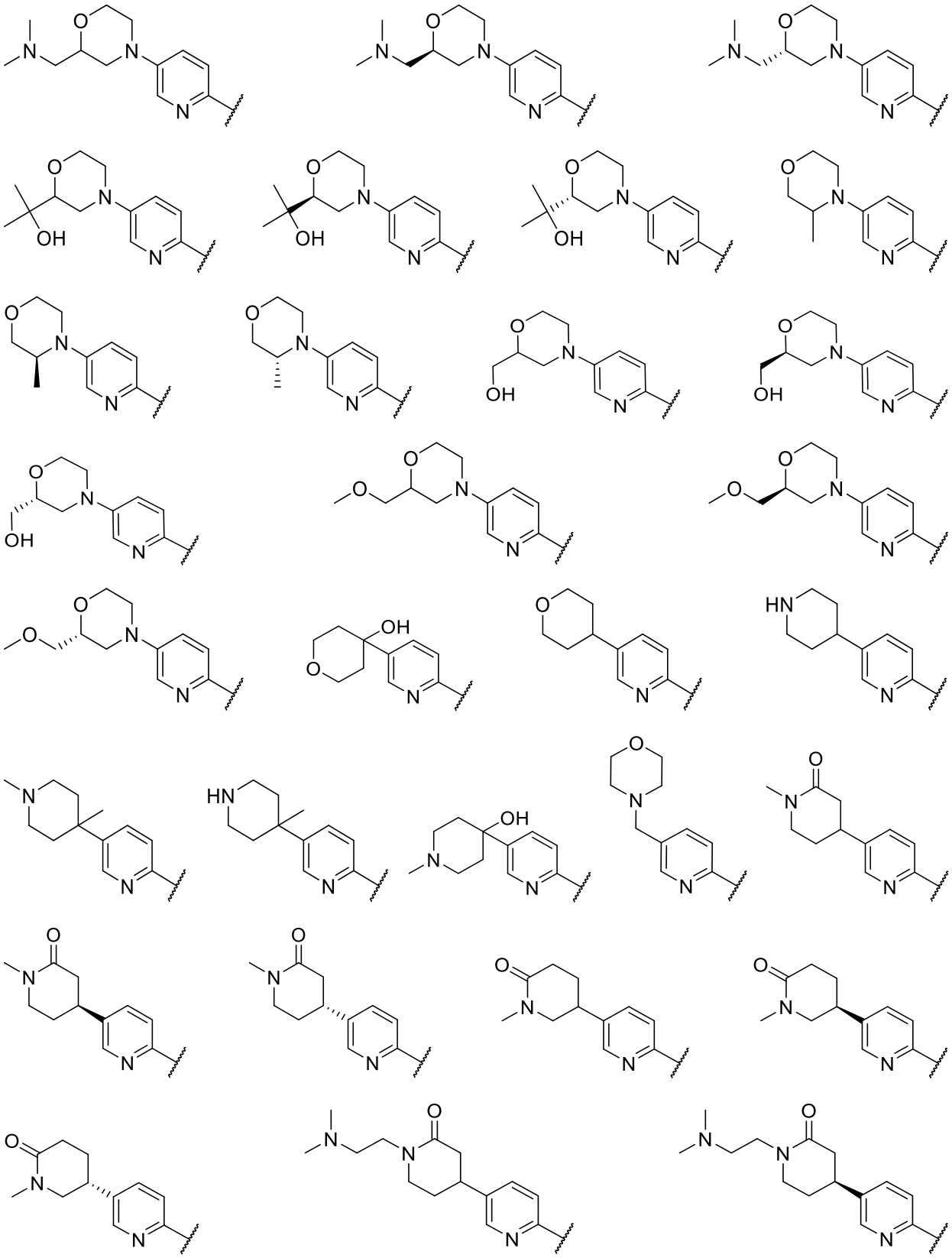


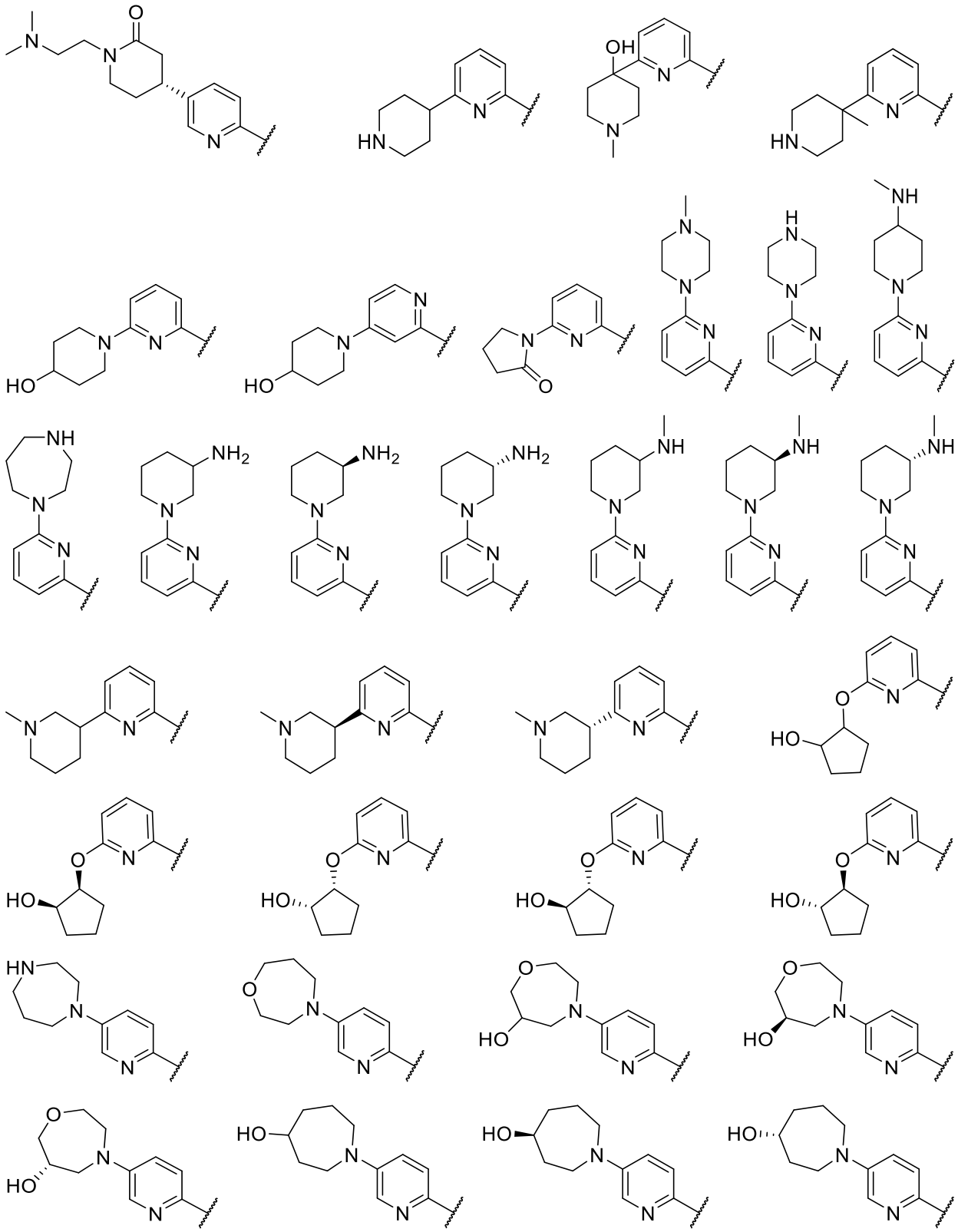


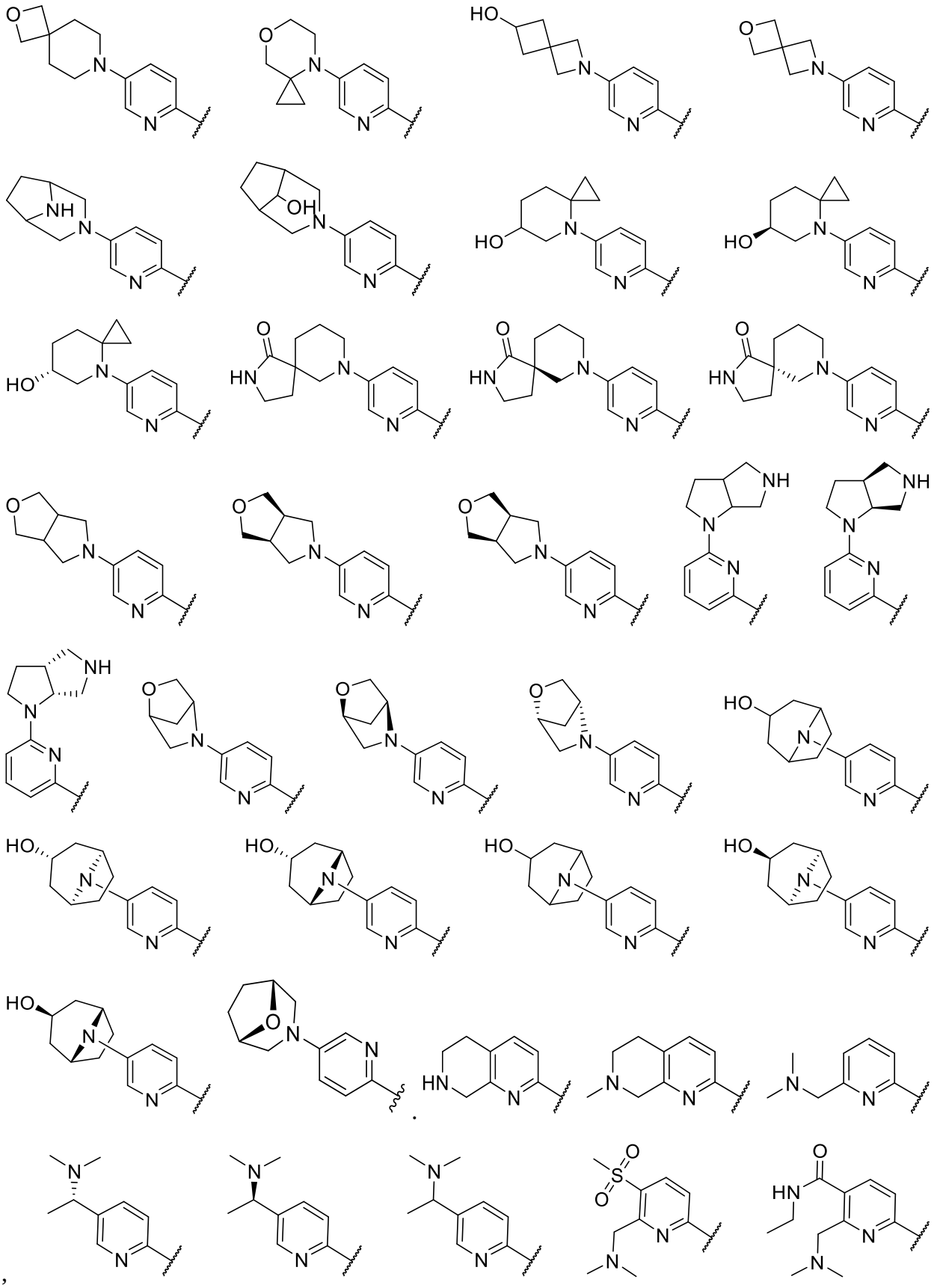


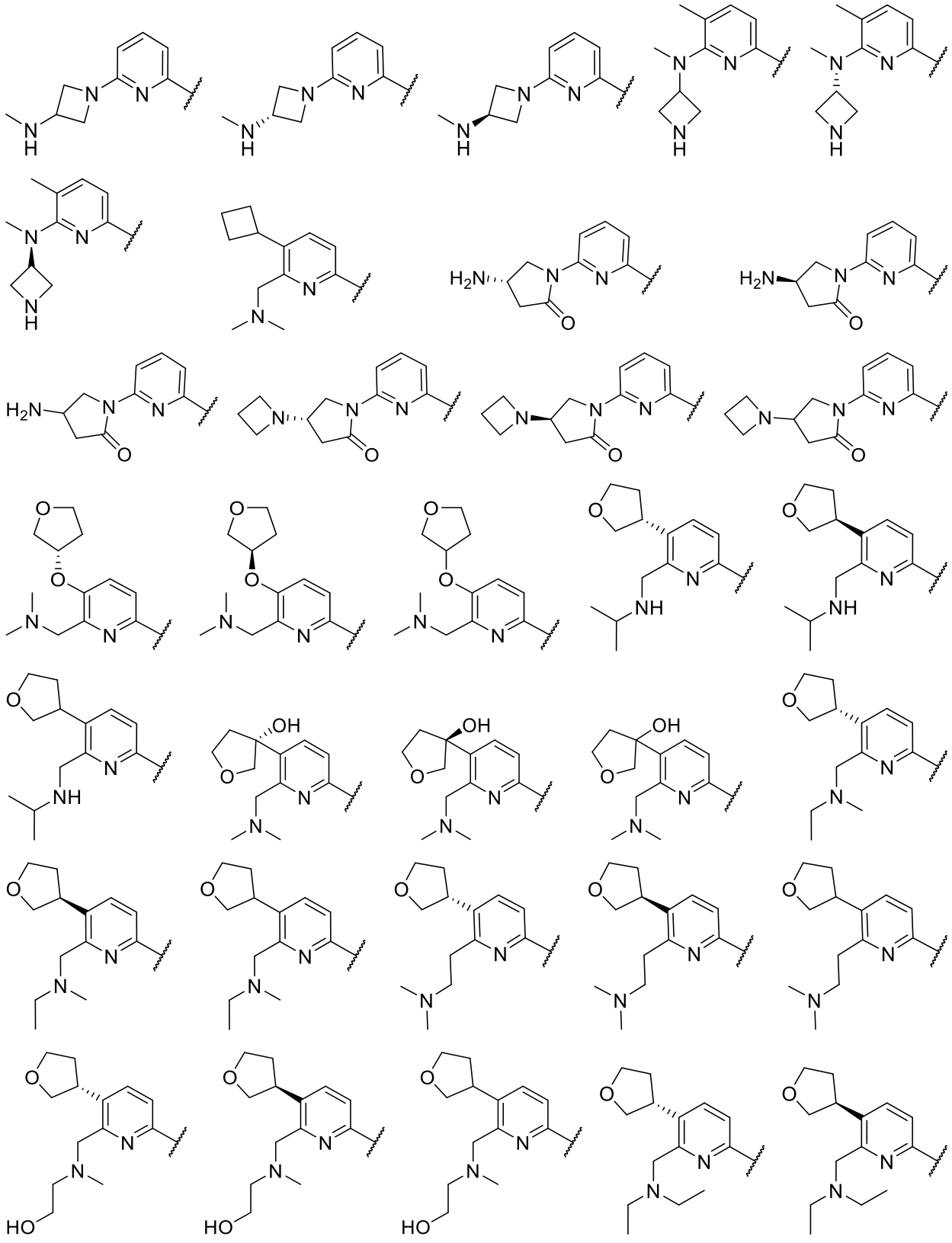


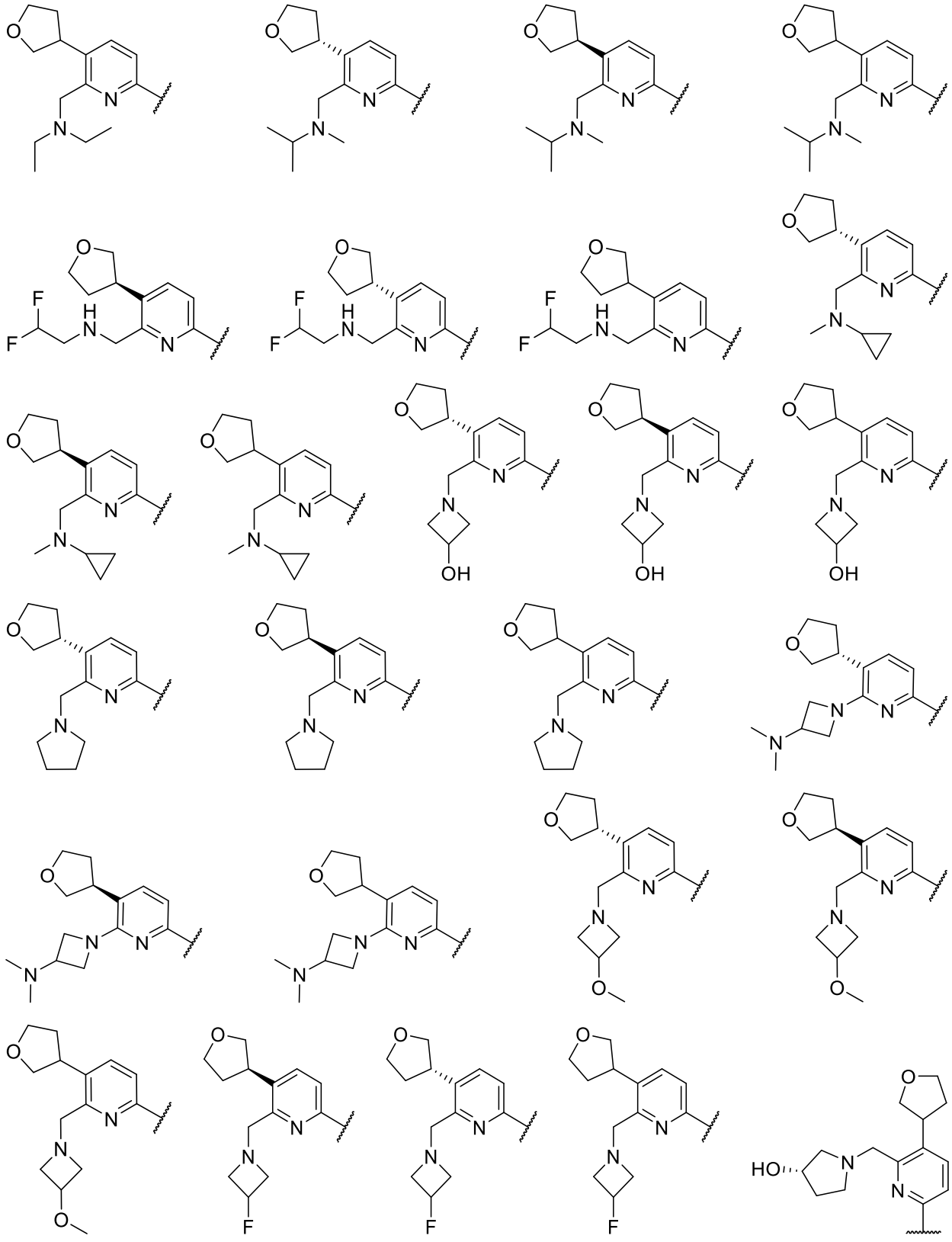


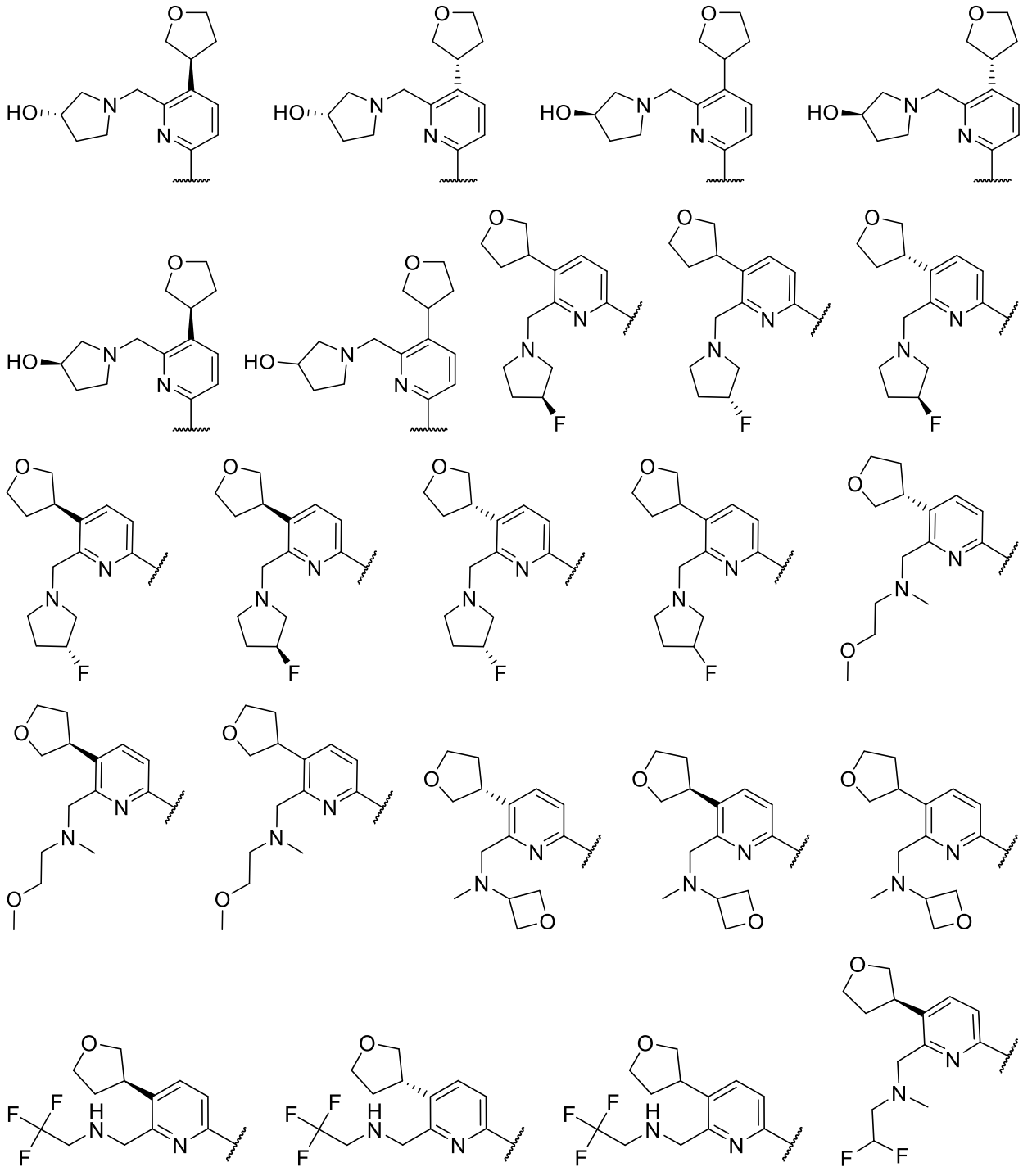


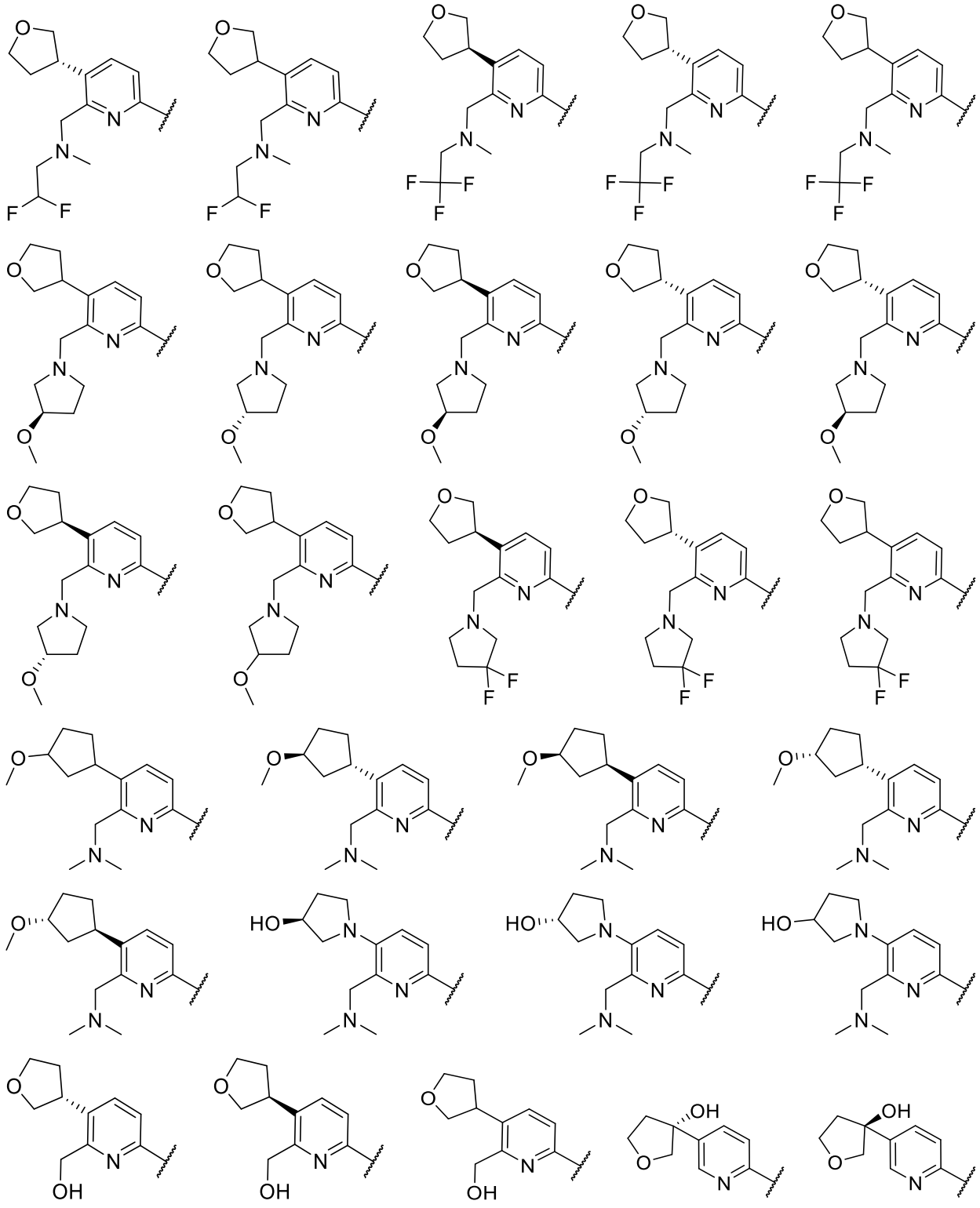


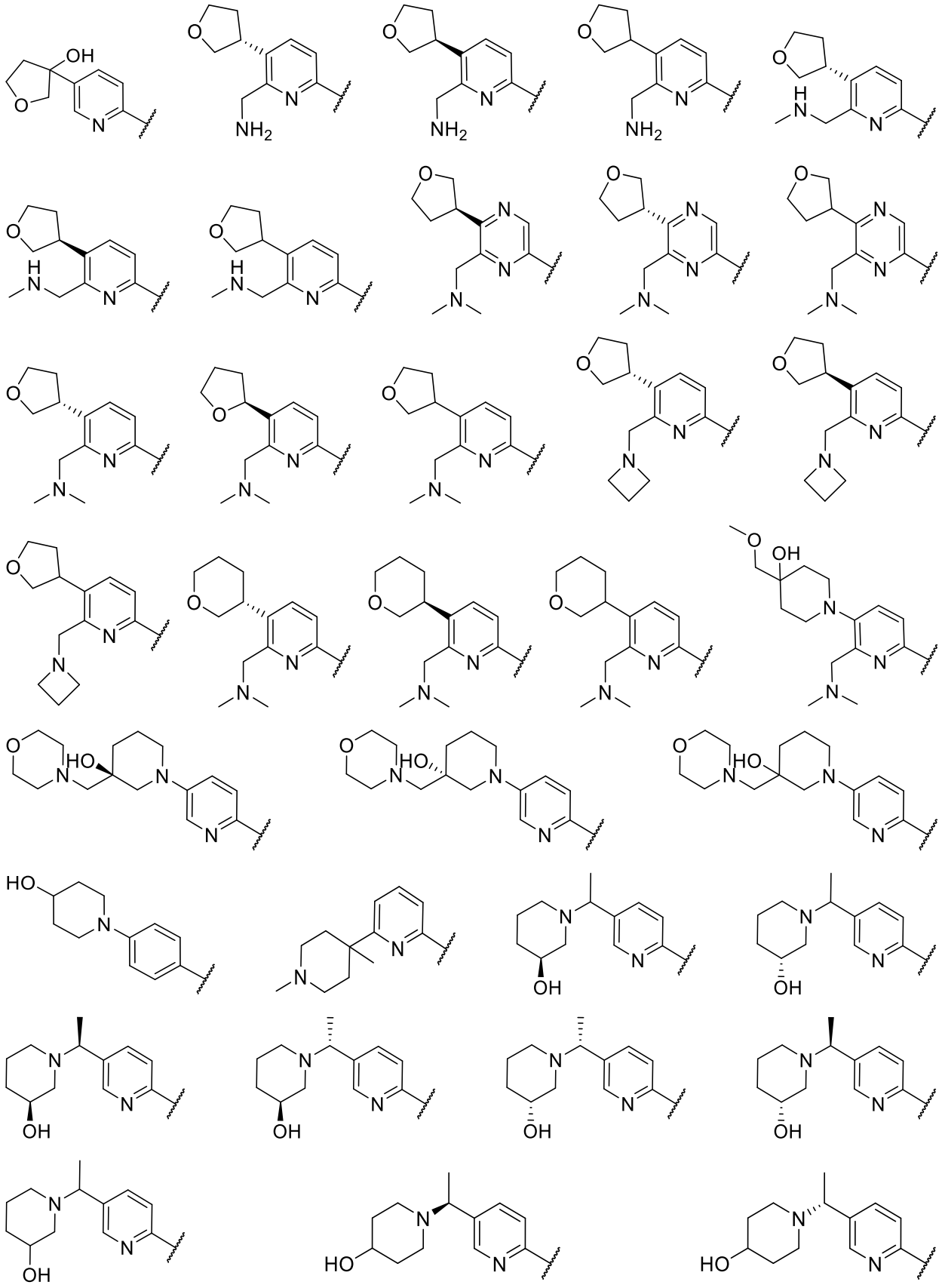


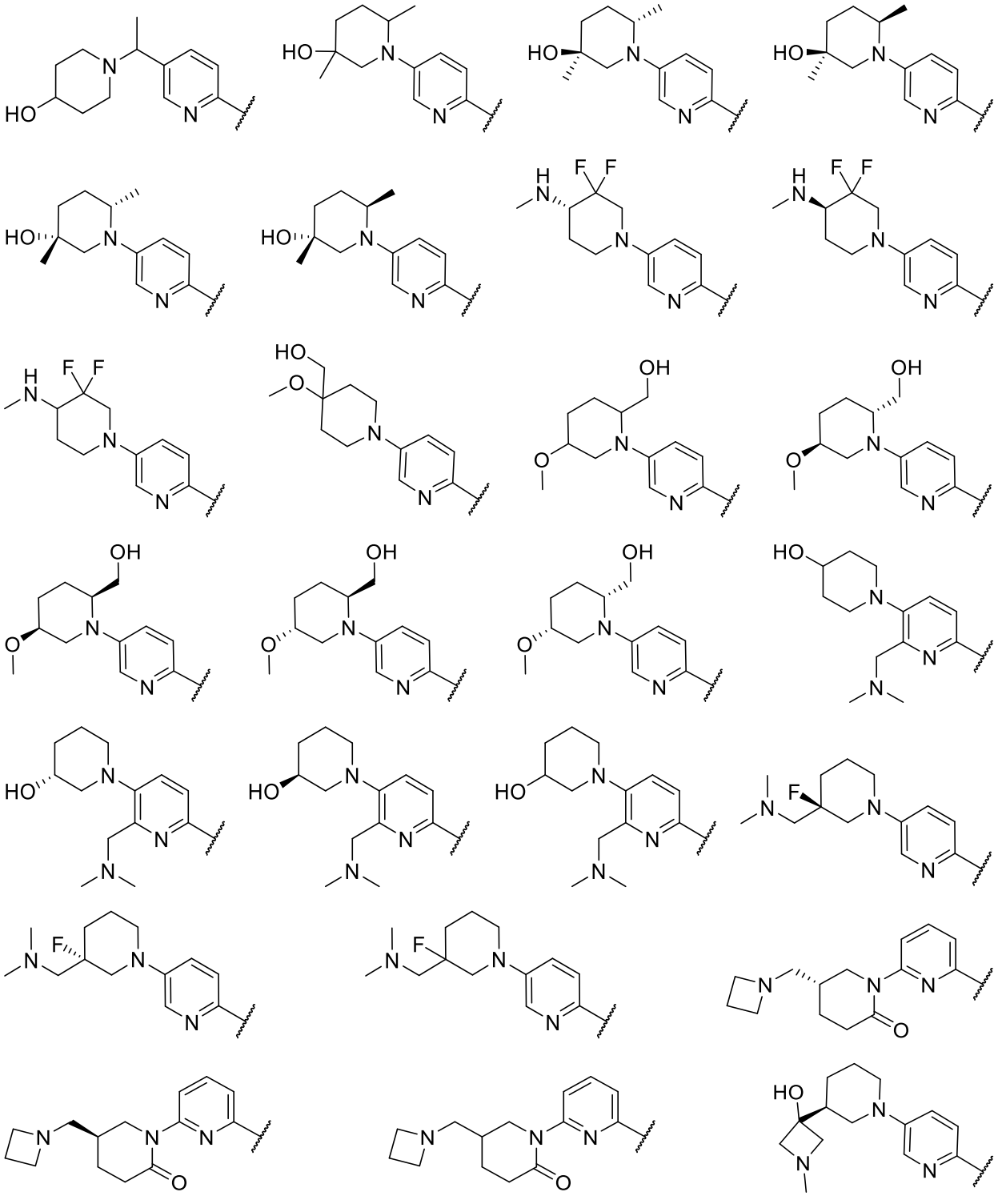


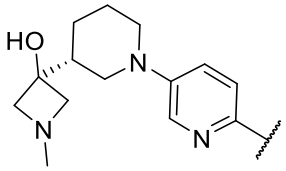
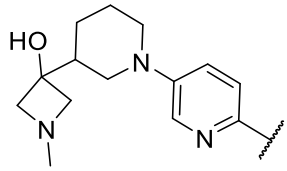
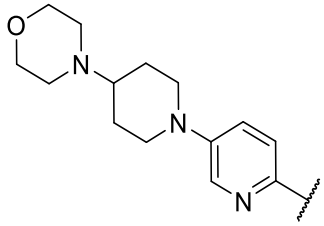
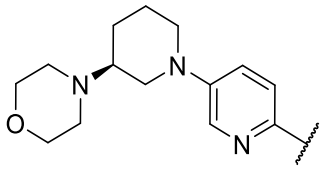
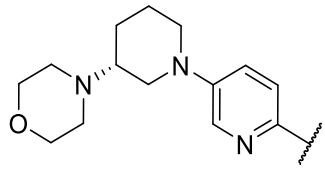
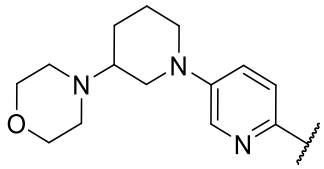
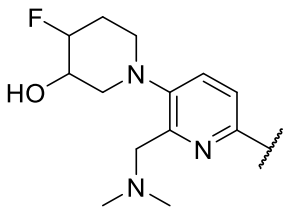
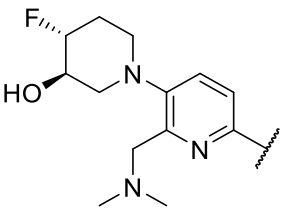
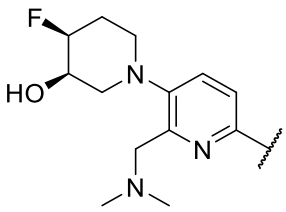
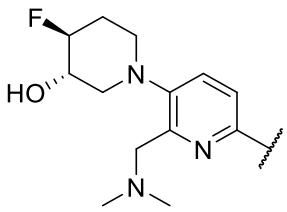
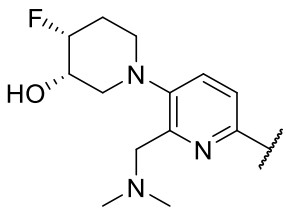
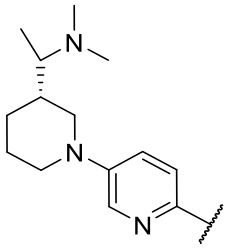
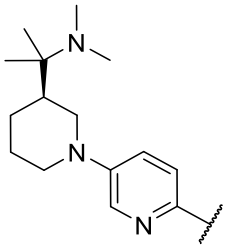
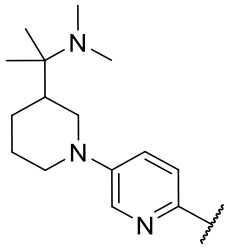
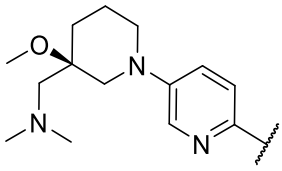
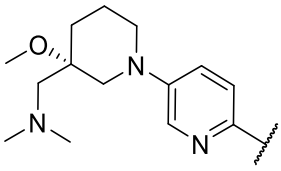
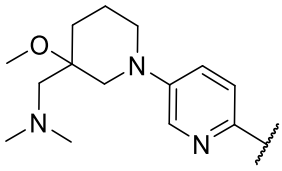
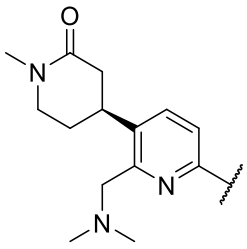
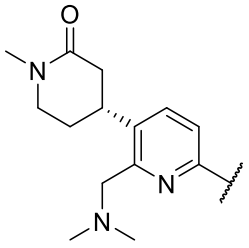
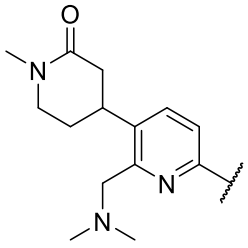
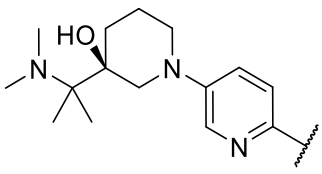
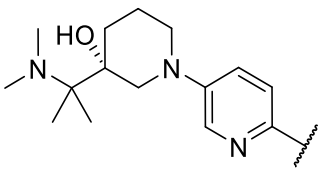
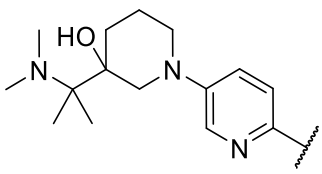
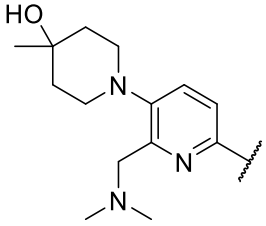
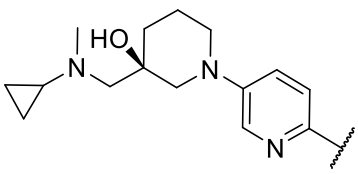


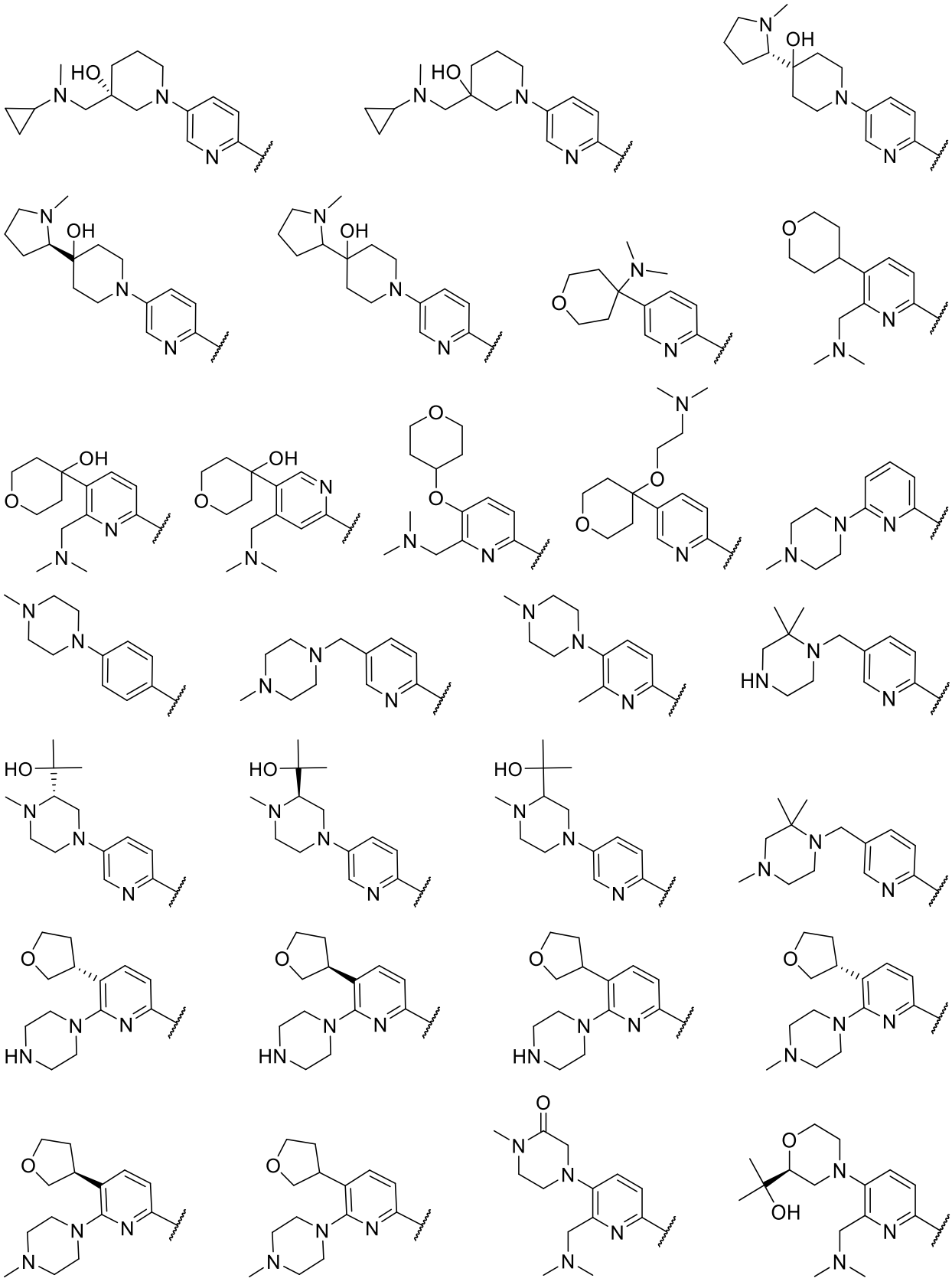


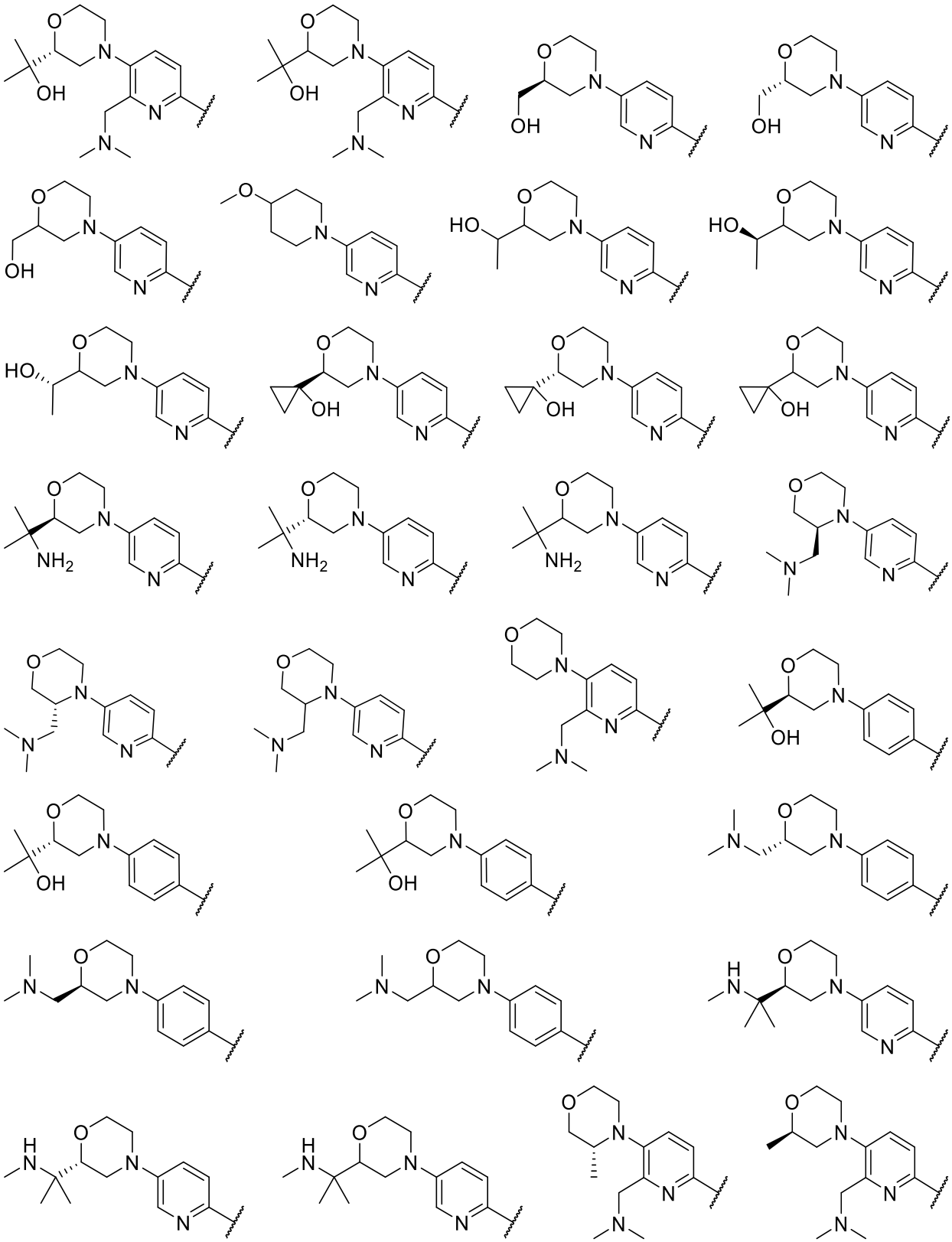


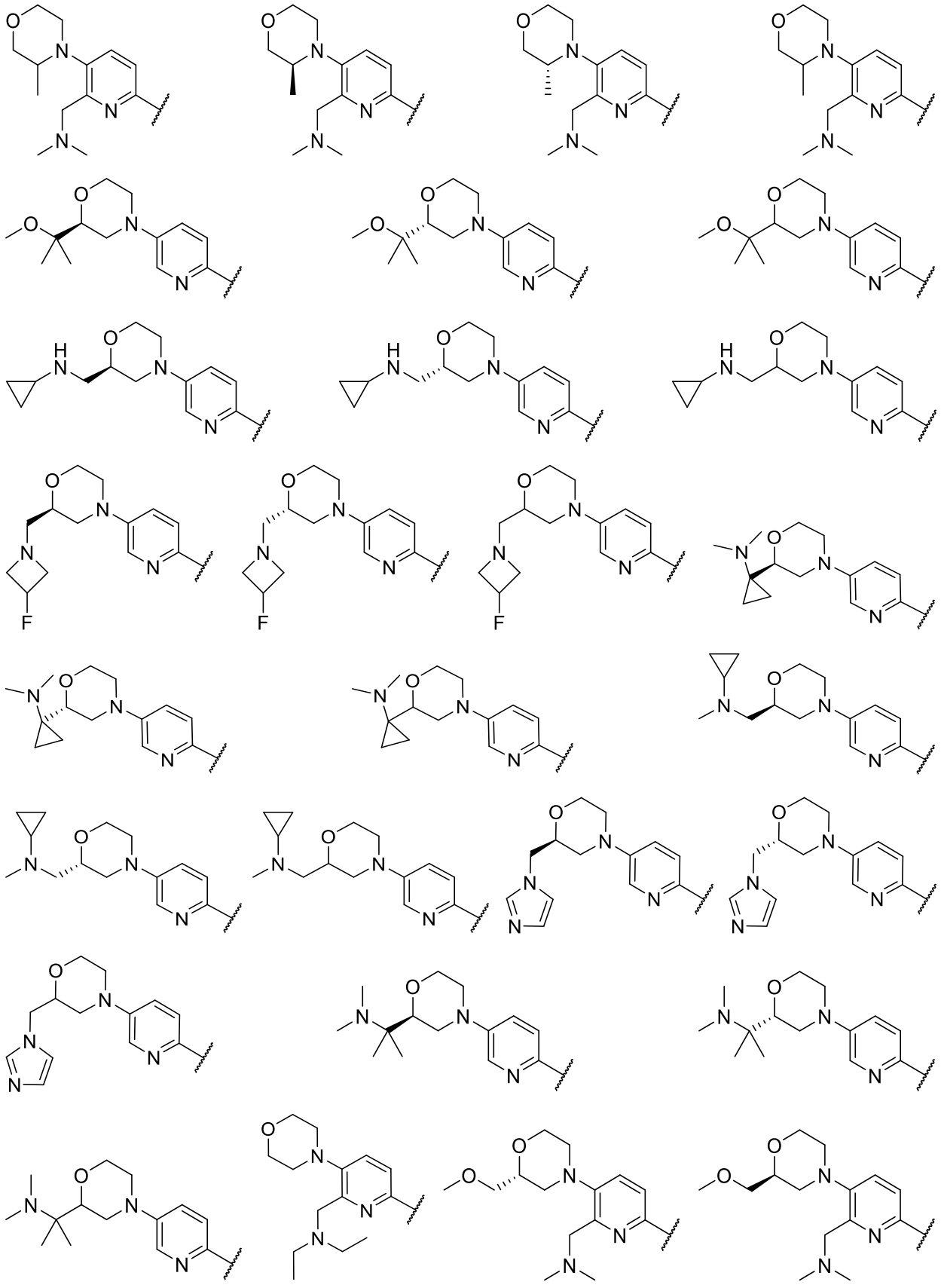


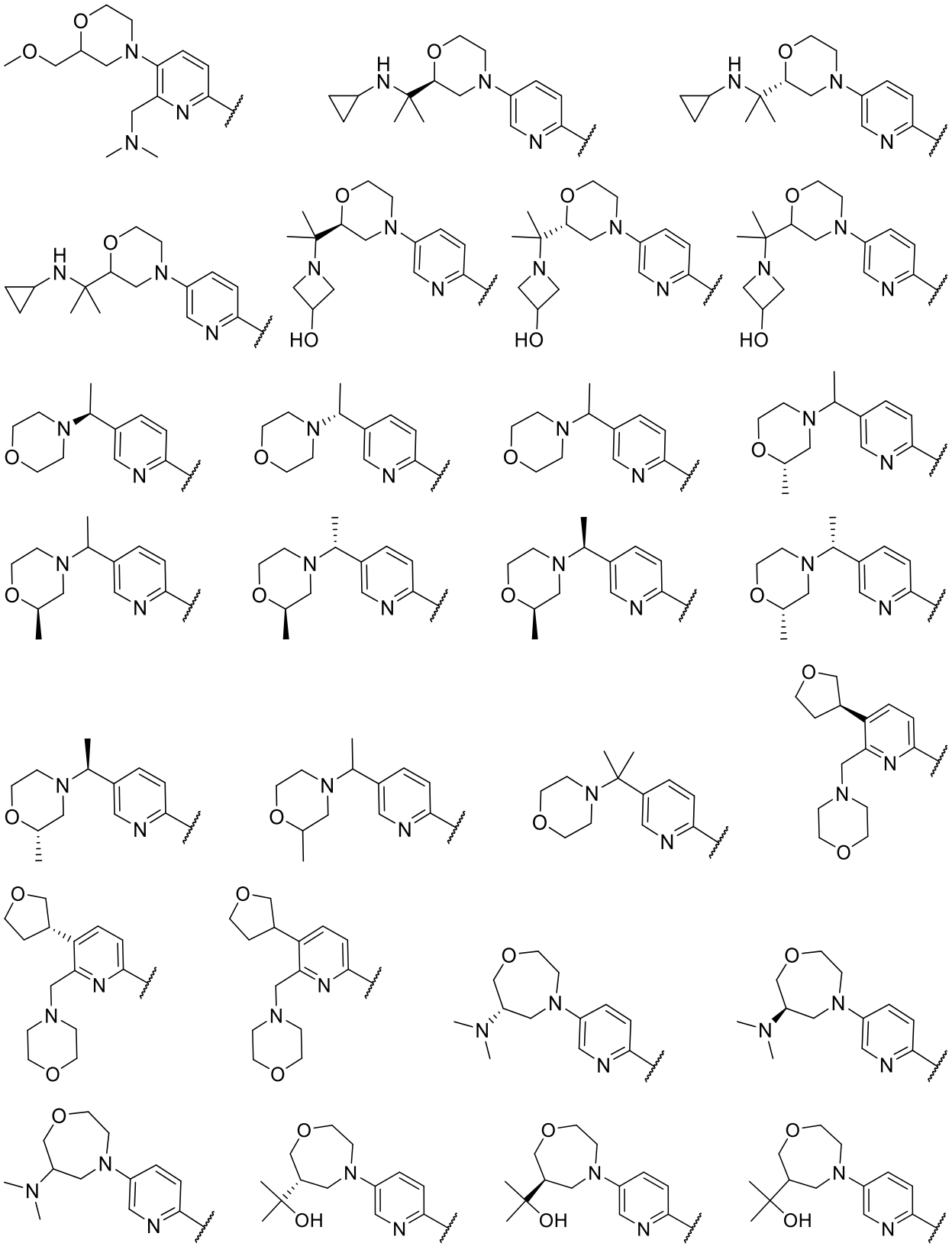


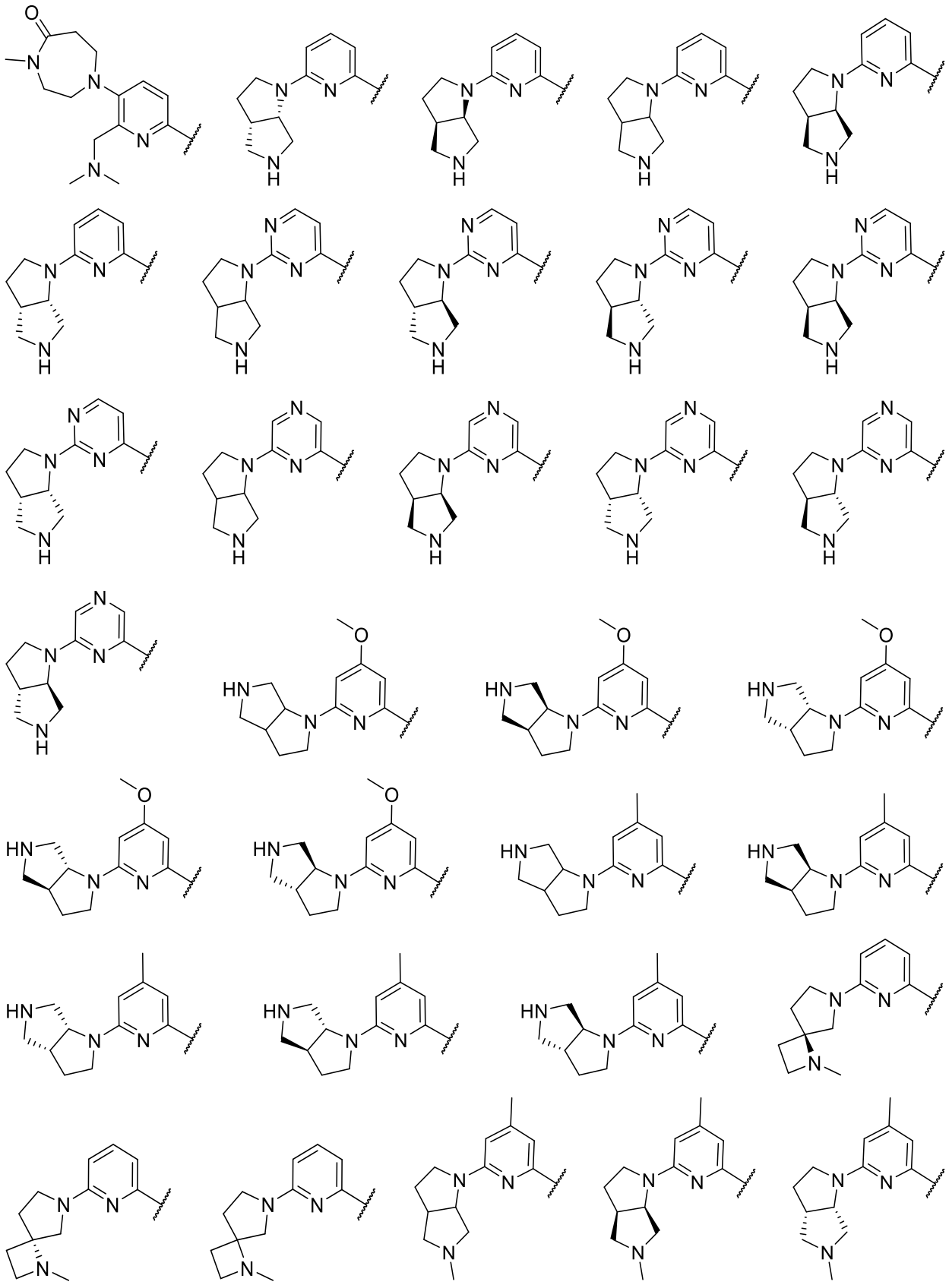


























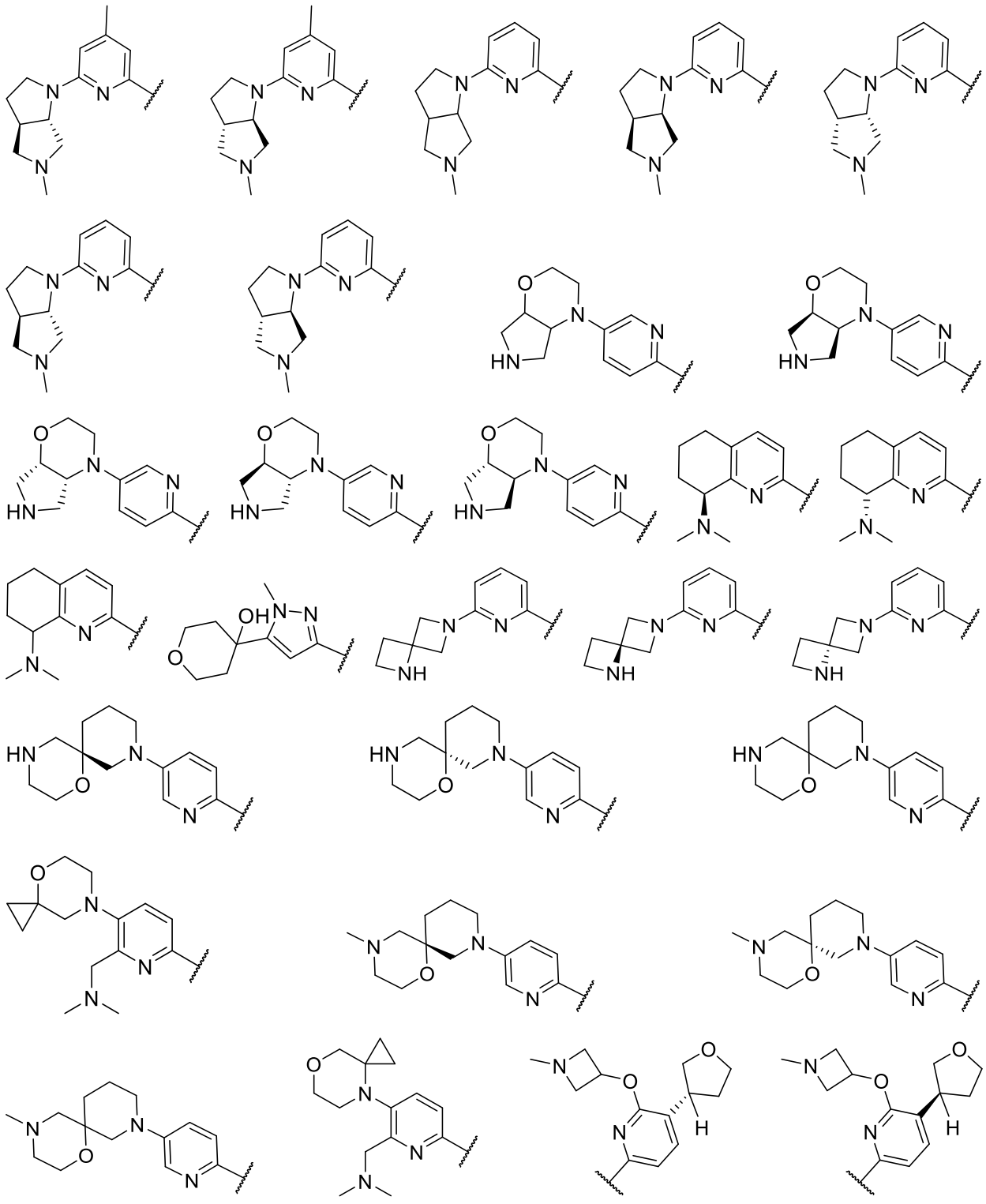


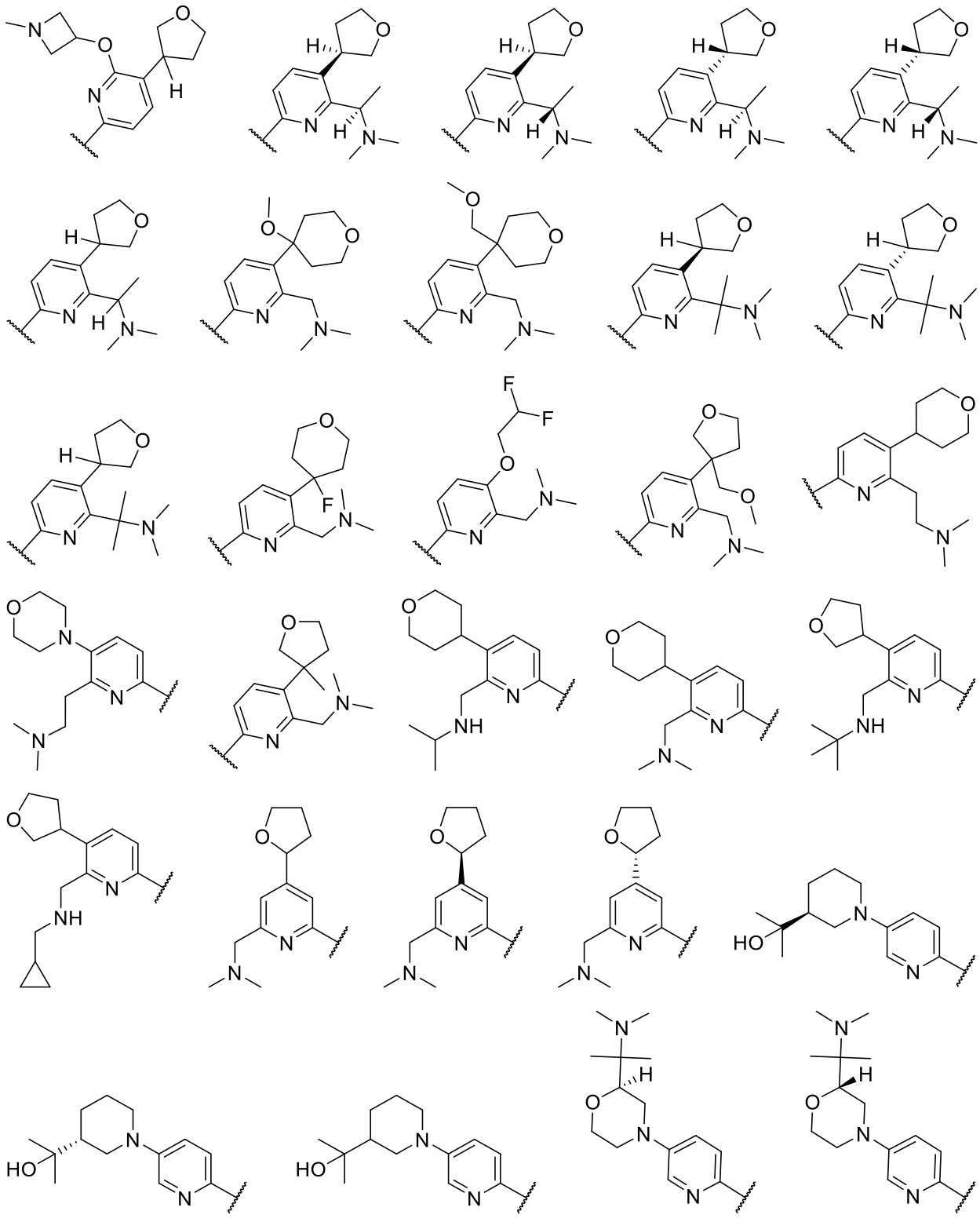


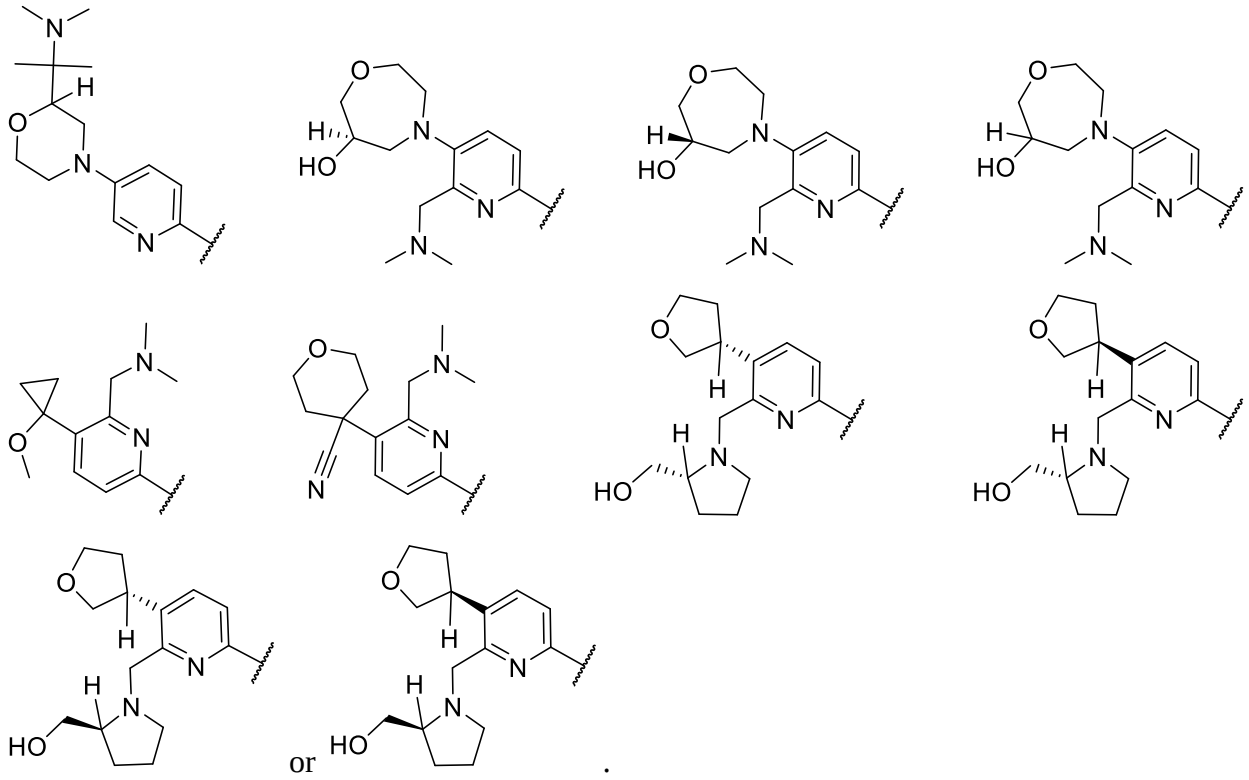








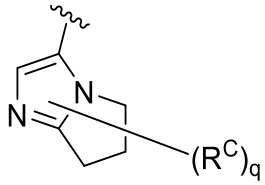
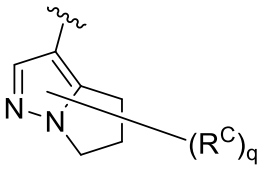


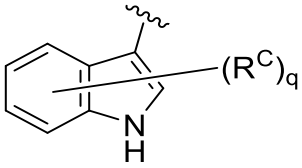
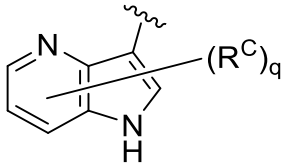
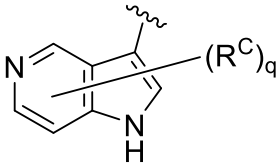
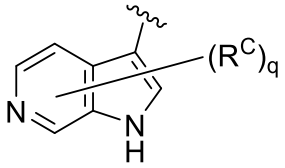


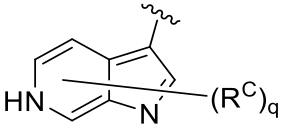
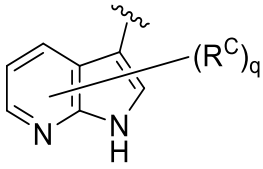
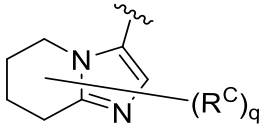
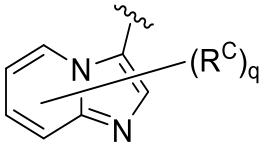
or .

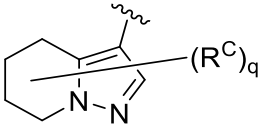
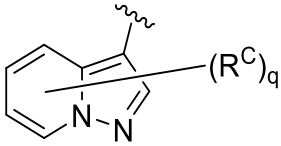
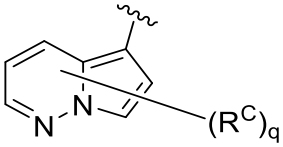
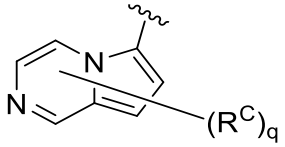
20. The compound of any one of claims 1-5, wherein $R^2$ is a 6-11 membered saturated, partially unsaturated, or unsatured fused, bridged, or spiro bicyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with q instances of $R^C$; wherein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

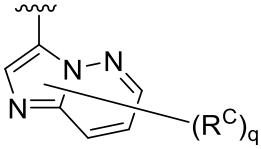
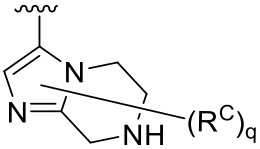
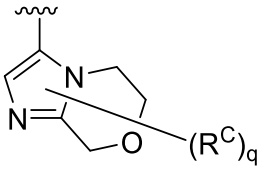
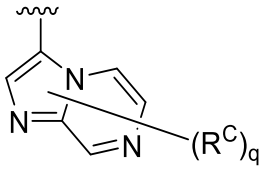
21. The compound of claim 20, wherein $R^2$ is a 7-10-membered fused bicyclic ring having 1-3 nitrogen atoms; each of which is substituted by each of which is substituted by q instances of $R^C$.

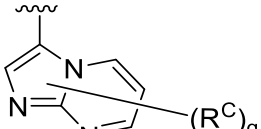
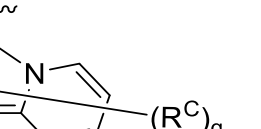
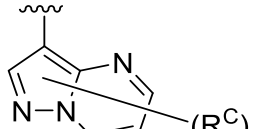
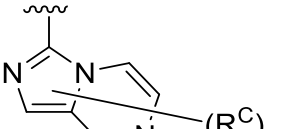
22. The compound of claim 20, wherein $R^2$ is  

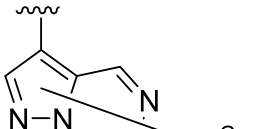
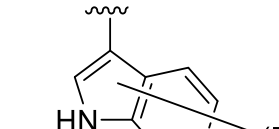
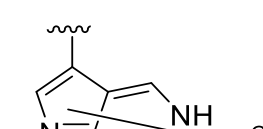
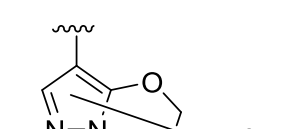
   

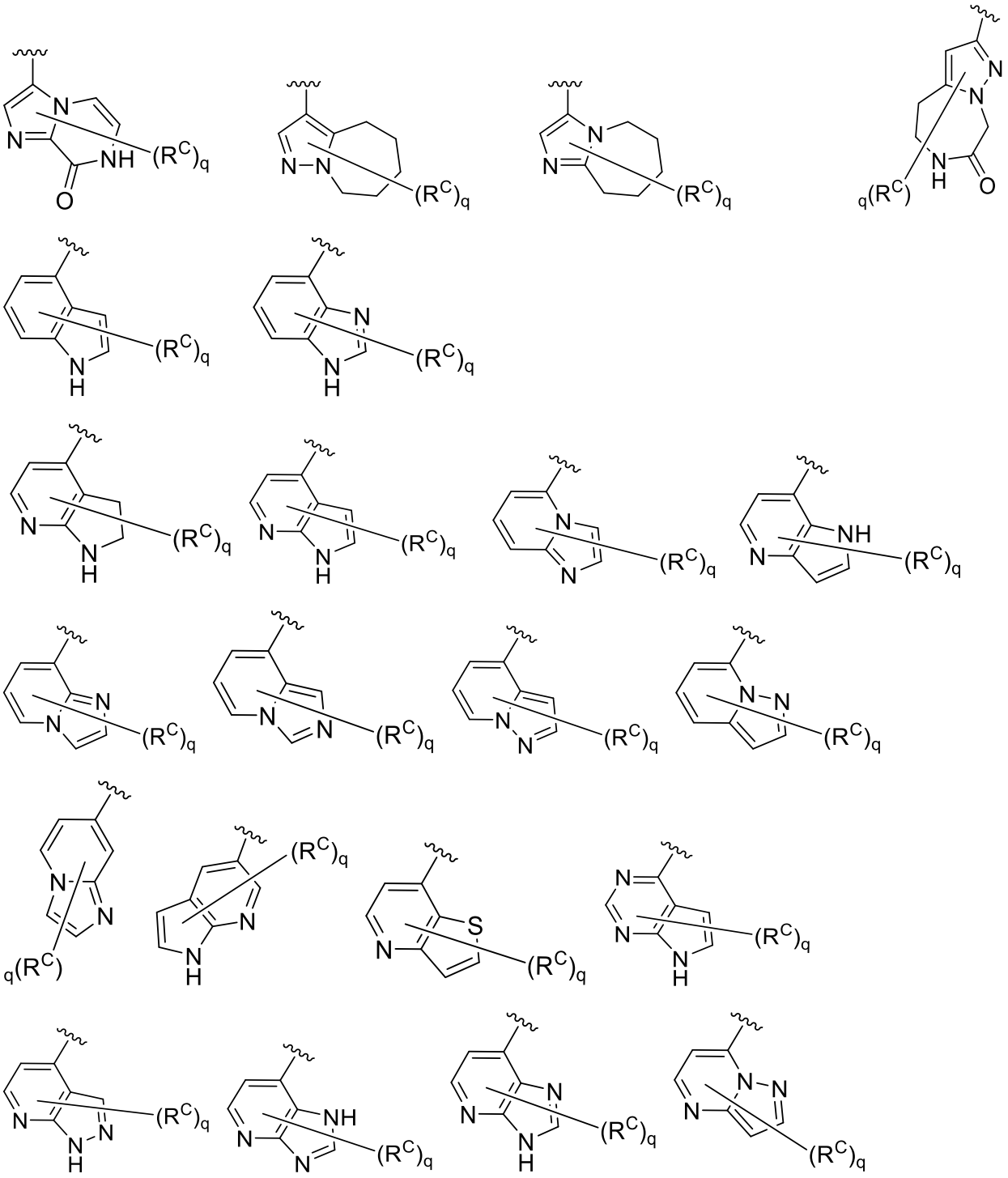
   

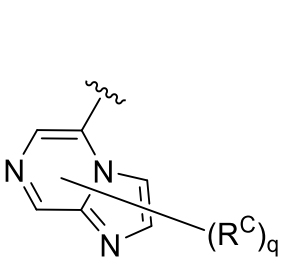
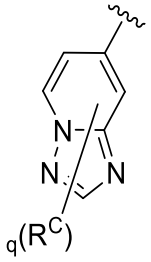
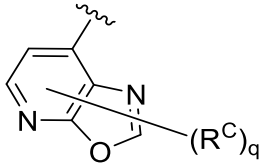
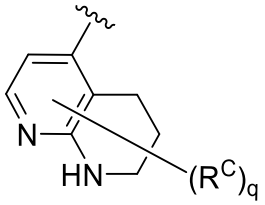
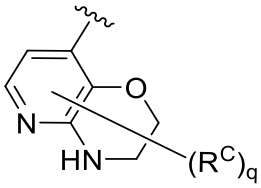
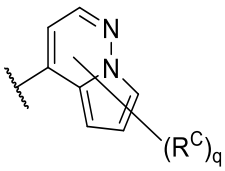
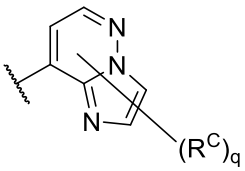
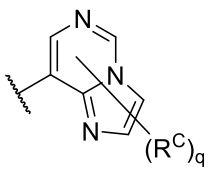
   

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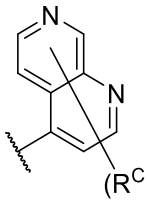
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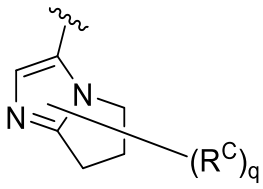
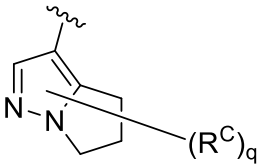
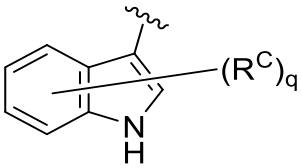
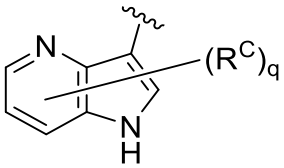
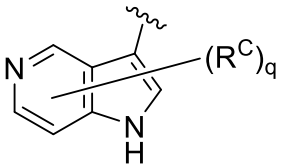
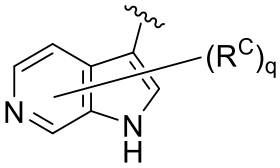
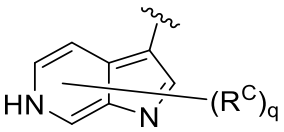
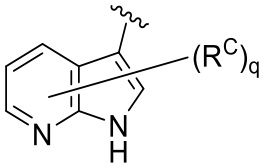
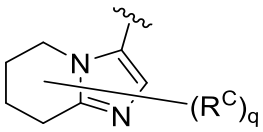
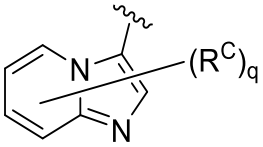
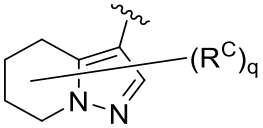
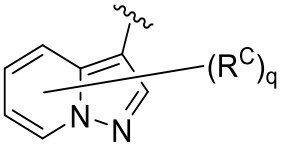
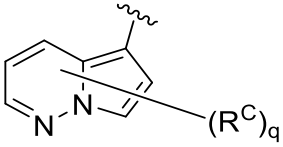
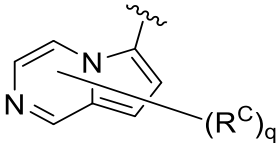
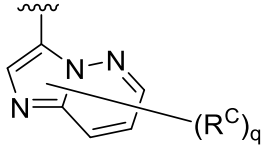
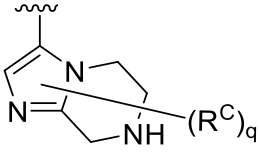
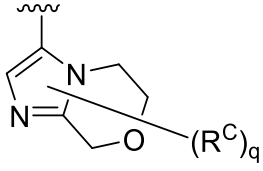
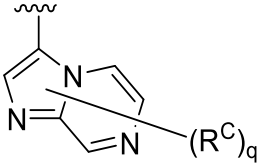
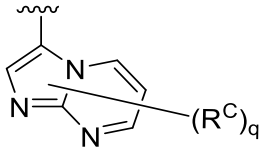
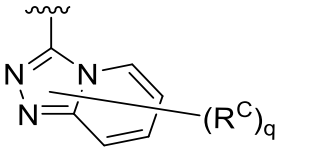
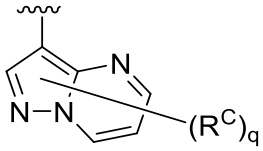
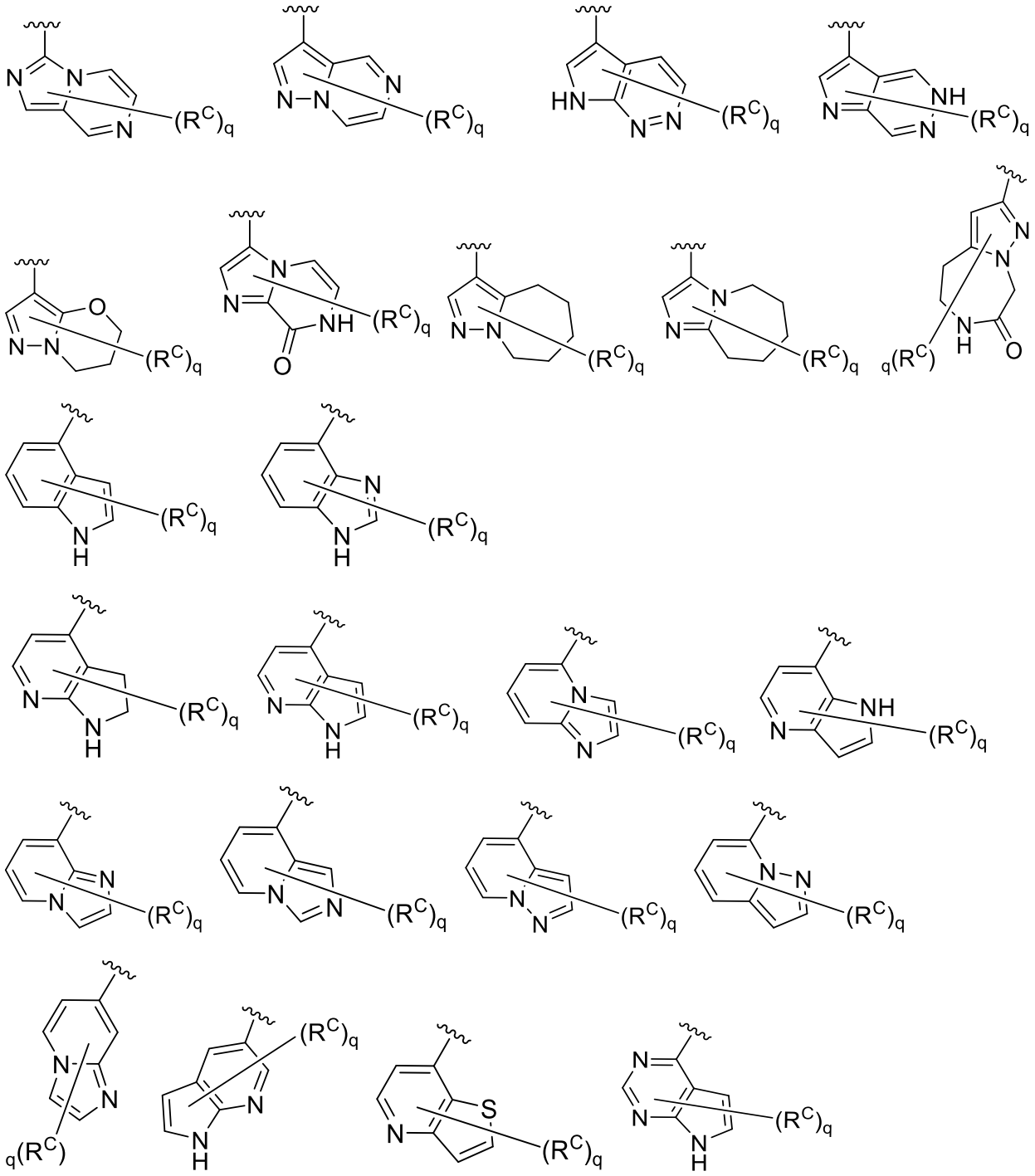
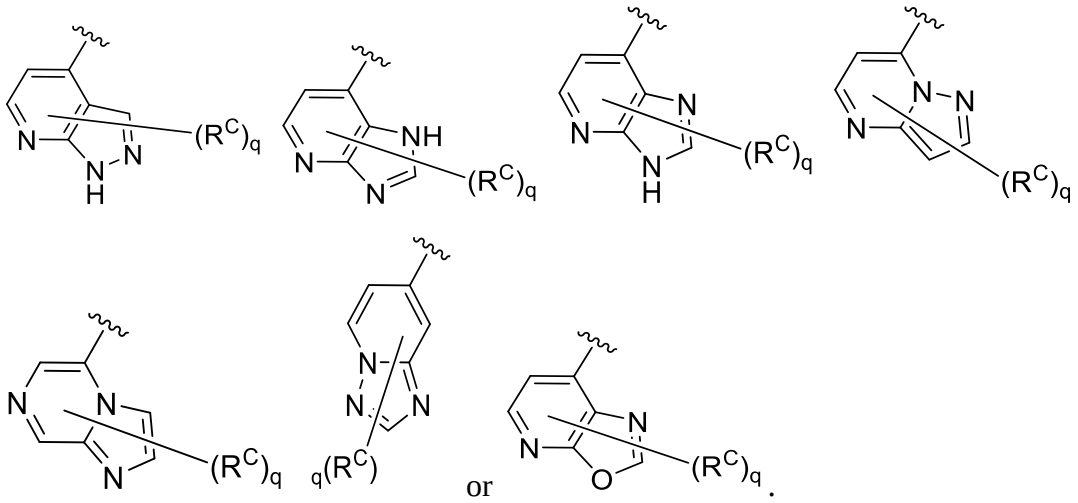
23. The compound of any one of claims 1-5, wherein $R^2$ is







or



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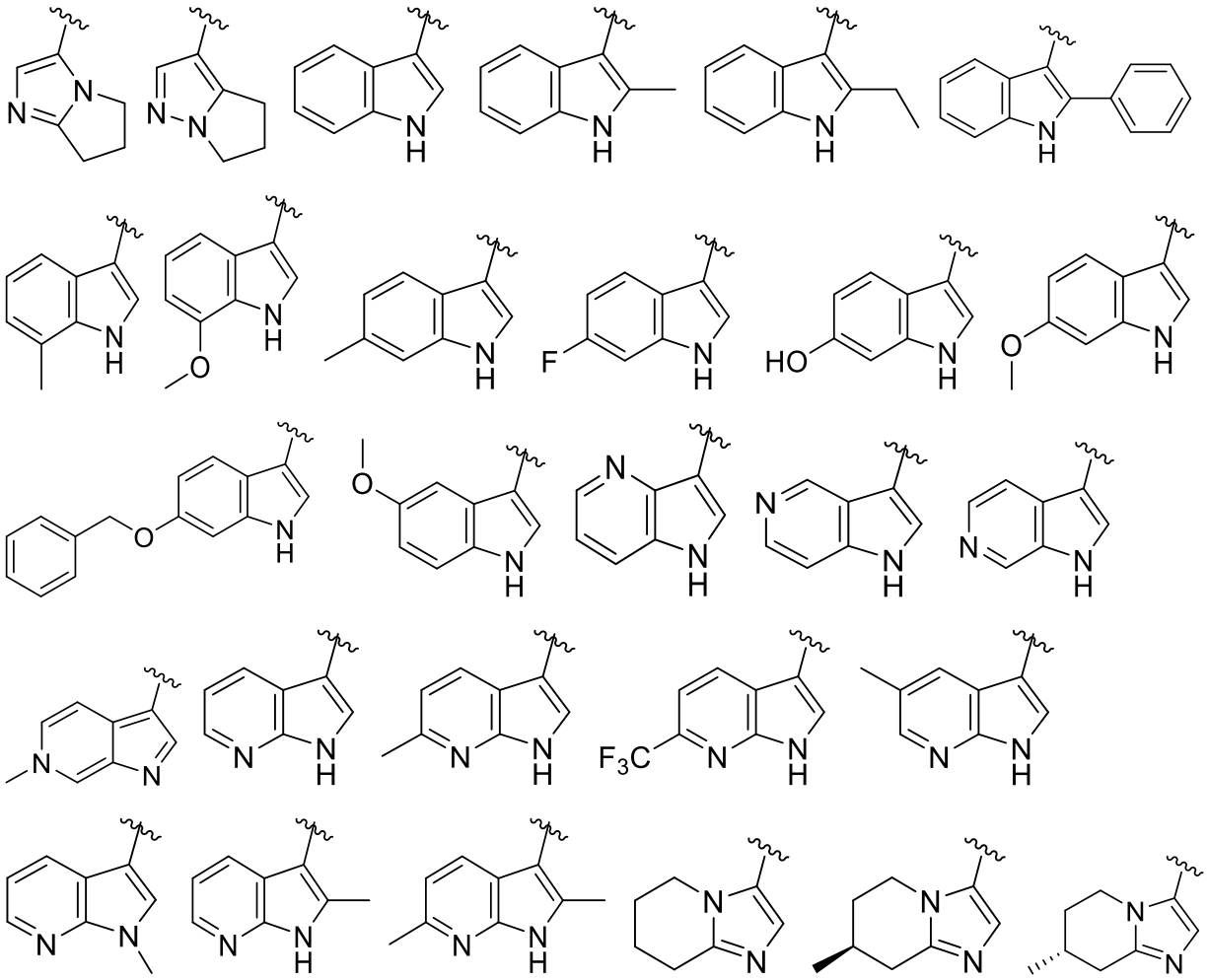
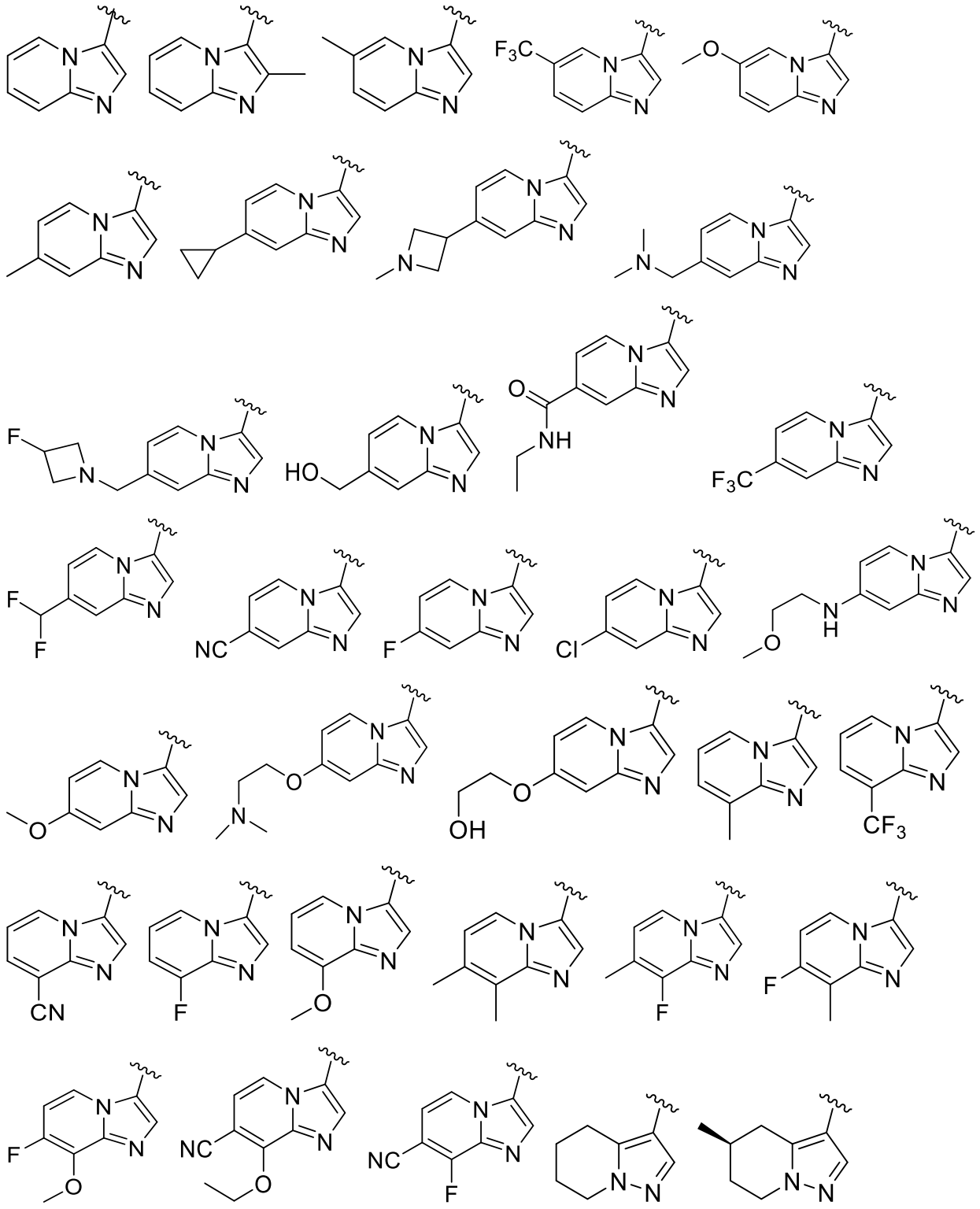
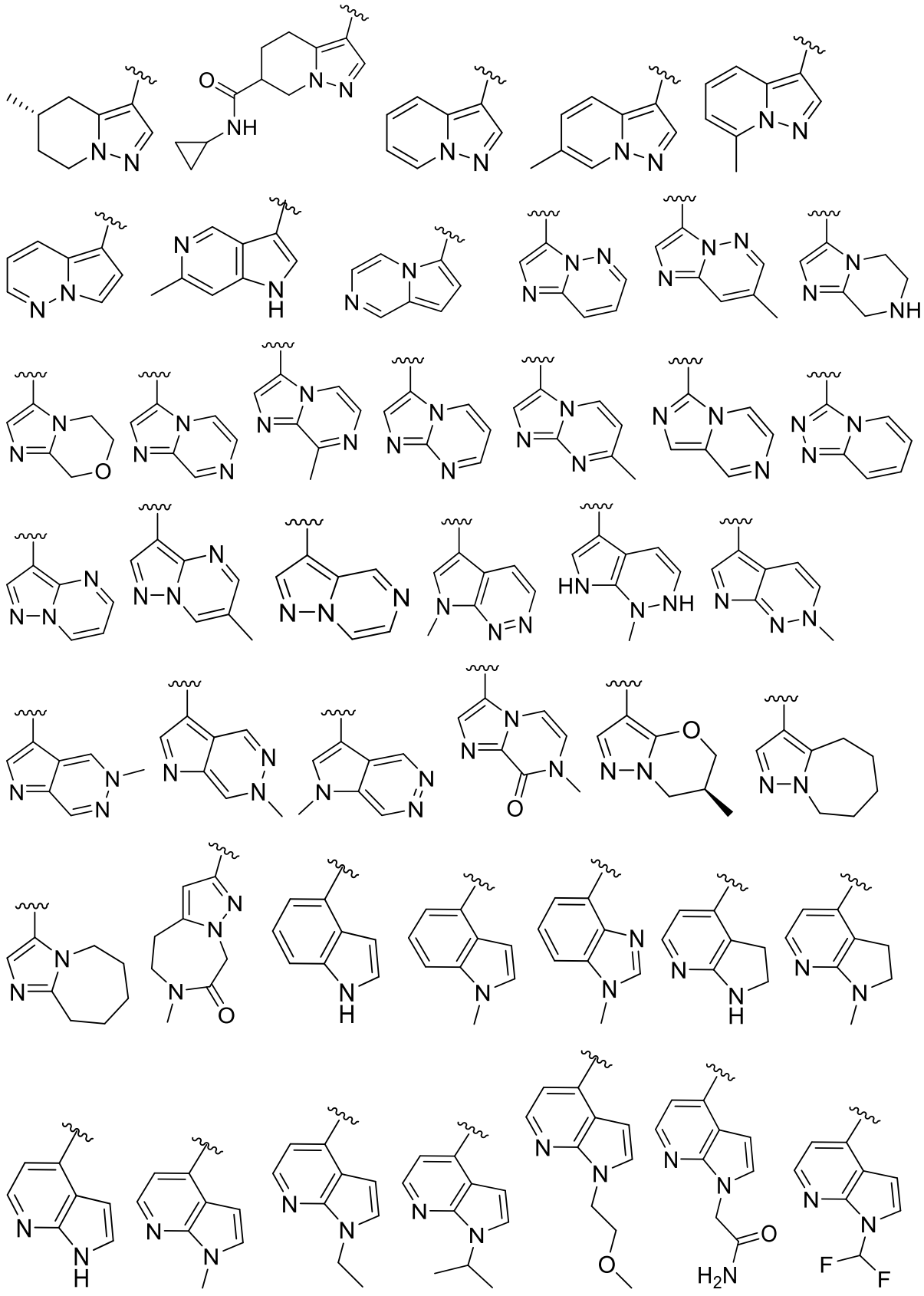
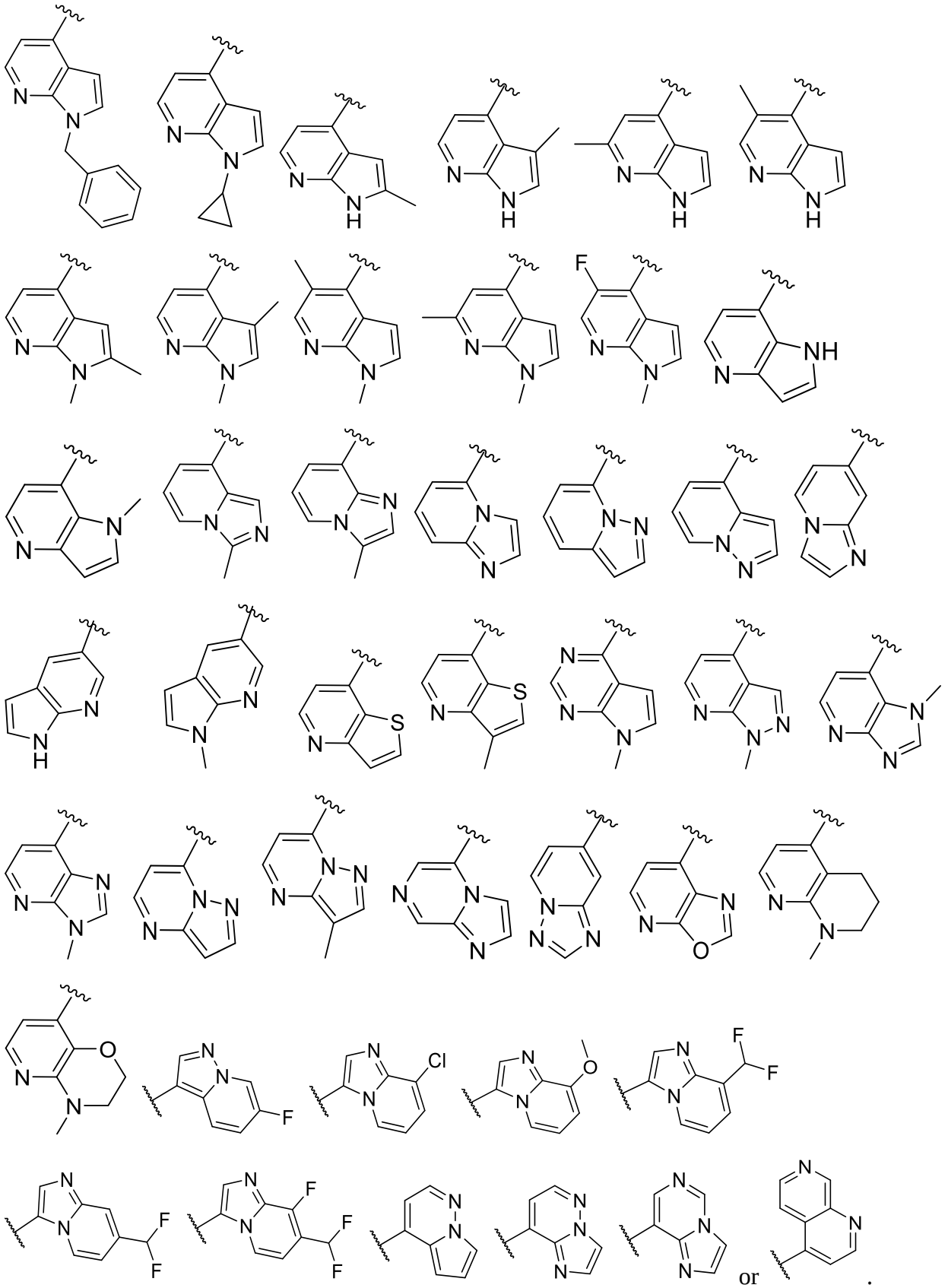
24. The compound of any one of claims 1-5 or 20, wherein $R^2$ is









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. 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 use of claim 29 wherein the disorder is a proliferative disorder.

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

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

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

34. 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.