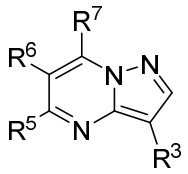
differentiation, secretion of hormones, activation of transcription factors, muscle contraction, glucose metabolism, control of protein synthesis, and regulation of the cell cycle.

[0005] Many diseases are associated with abnormal cellular responses triggered by kinase-mediated events. These diseases include, but are not limited to, autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies and asthma, Alzheimer's disease, and hormone-related diseases. Accordingly, there remains a need to find protein kinase inhibitors useful as therapeutic agents.

SUMMARY

[0006] It has now been found that compounds of this present disclosure, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of TYK2 kinase.

[0006a] In a first aspect of the present disclosure, there is provided a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

R^3 is $–C(O)NH_2$; $–C(O)NHR^{3A}$; or $-C(O)N(R^{3A})_2$;

R^5 is $-L^1-R^{5A}$;

R^6 is hydrogen, R^A, or R^B;

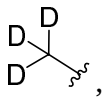
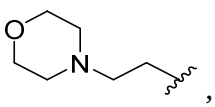
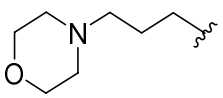
or R^5 and R^6 are taken together with their intervening atoms to form a 4-7 membered partially unsaturated, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted by R^{5A} and n instances of R^C;

R^7 is $-NH_2$, or $–NHR^{7A}$;

L^1 is -N(R)-;

R^{3A} is R^B, and is substituted by q instances of R^C, provide that R^{3A} is not phenyl;

R^{7A} is selected from the group consisting of hydrogen, C_{1-6} aliphatic,

, , , and ;

R^{5A} is R^A or R^B, and is substituted by r instances of R^C;

each instance of R^A is independently 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, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, or $–N(R)S(O)_2R$;

each instance of R^B is independently C_{1-6} aliphatic; phenyl; 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 3-7 membered saturated or partially unsaturated carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^C 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, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, or $–N(R)S(O)_2R$ or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

wherein each hydrogen bound to carbon can be optionally and independently replaced by deuterium; and

each instance of n, q, and r is independently 0, 1, 2, 3, or 4.

[0006b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[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 TYK2 kinases. Such diseases, disorders, or conditions include those described herein.

[0007a] In yet another aspect of the present disclosure, there is provided a use of a pharmaceutical composition as disclosed herein, or a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating an TYK2-mediated disorder, disease, or condition.

[0007b] In a further aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, for use as a medicament.

[0008] Compounds provided by this present disclosure are also useful for the study of TYK2 enzymes in biological and pathological phenomena; the study of intracellular signal transduction pathways occurring in bodily tissues; and the comparative evaluation of new TYK2 inhibitors or other regulators of kinases, signaling pathways, and cytokine levels *in vitro* or *in vivo*.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Certain Embodiments of the Invention:

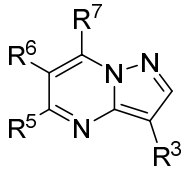
[0009] Compounds of the present invention, and compositions thereof, are useful as inhibitors of TYK2 protein kinase.

[0010] The pseudokinase binding pocket of TYK2 contains a plurality of hydration sites, each of which is occupied by a single molecule of water. Each of these water molecules has a stability rating associated with it. As used herein, the term “stability rating” refers to a numerical calculation which incorporates the enthalpy, entropy, and free energy values associated with each

CLAIMS

We claim:

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



I

or a pharmaceutically acceptable salt thereof, wherein:

R^3 is $–C(O)NH_2$; $–C(O)NHR^{3A}$; or $-C(O)N(R^{3A})_2$;

R^5 is $-L^1-R^{5A}$;

R^6 is hydrogen, R^A, or R^B;

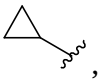
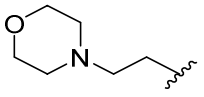
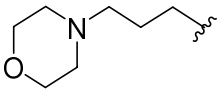
or R^5 and R^6 are taken together with their intervening atoms to form a 4-7 membered partially unsaturated, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted by R^{5A} and n instances of R^C;

R^7 is $-NH_2$, or $–NHR^{7A}$;

L^1 is -N(R)-;

R^{3A} is R^B, and is substituted by q instances of R^C, provide that R^{3A} is not phenyl;

R^{7A} is selected from the group consisting of hydrogen, C_{1-6} aliphatic,

, , , and ;

R^{5A} is R^A or R^B, and is substituted by r instances of R^C;

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

each instance of R^B is independently C_{1-6} aliphatic; phenyl; 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 3-7 membered saturated or partially unsaturated

carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^C 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, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, or $–N(R)S(O)_2R$ or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

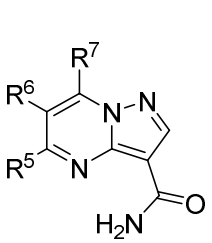
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

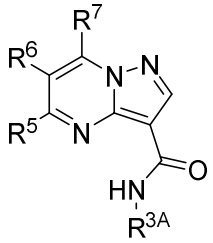
wherein each hydrogen bound to carbon can be optionally and independently replaced by deuterium; and

each instance of n, q, and r is independently 0, 1, 2, 3, or 4.

2. The compound of claim 1 of one of formulas **II** or **III**:



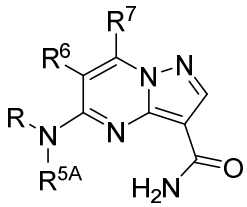
II



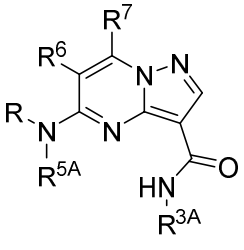
III

or a pharmaceutically acceptable salt thereof.

3. The compound of any one of claims 1 or 2 of formula **V** or **VI**:



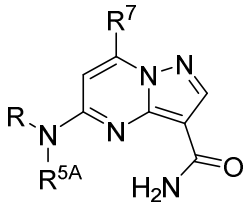
V



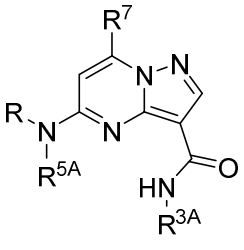
VI

or a pharmaceutically acceptable salt thereof.

4. The compound of any one of claims 1-3 of formula **V-a** or **VI-a**:



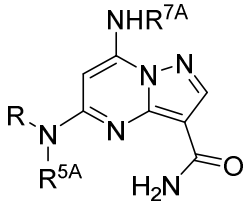
V-a



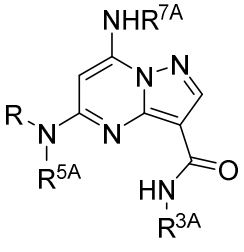
VI-a

or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 1-5 of one of formulas V-c or VI-c:



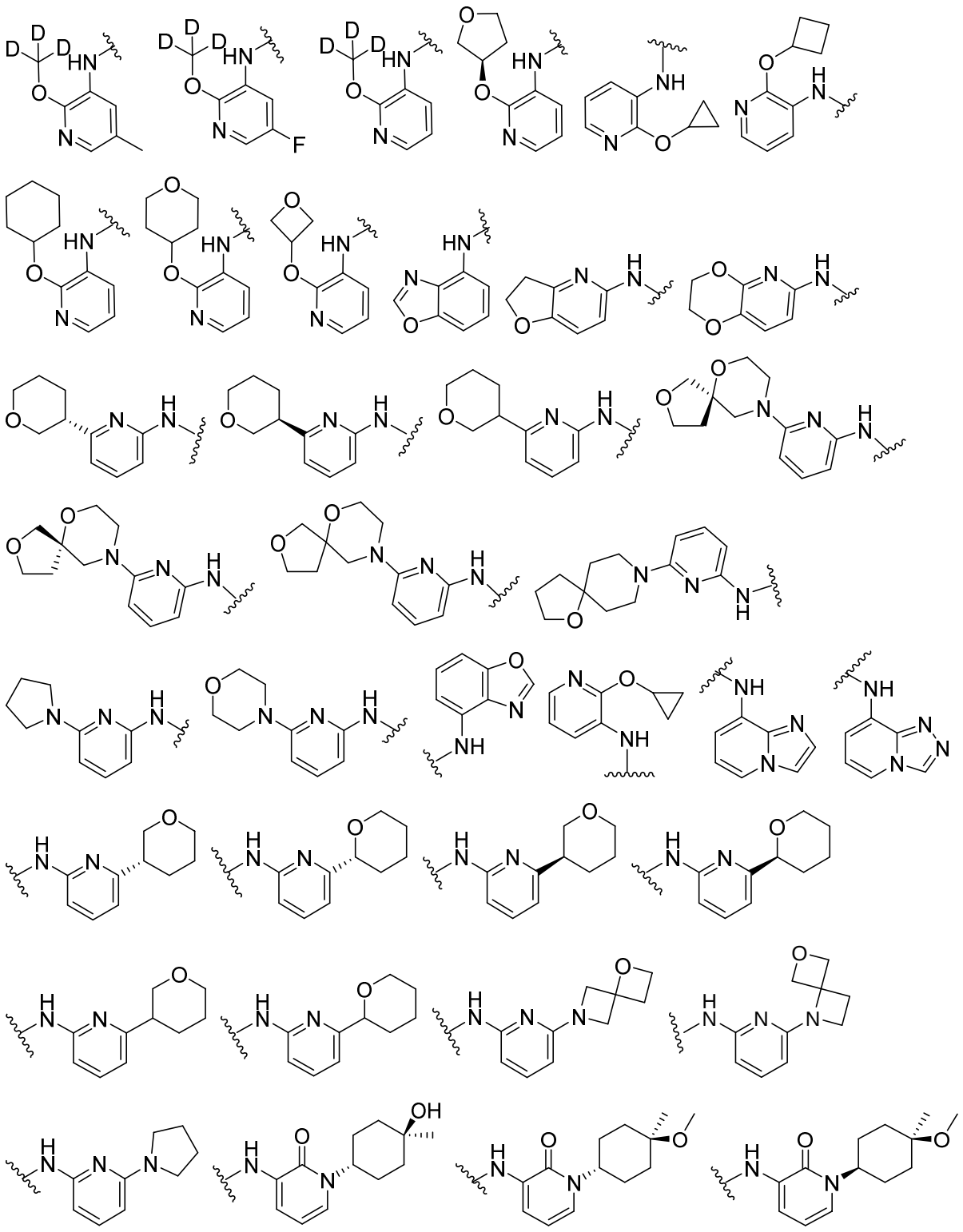
V-c

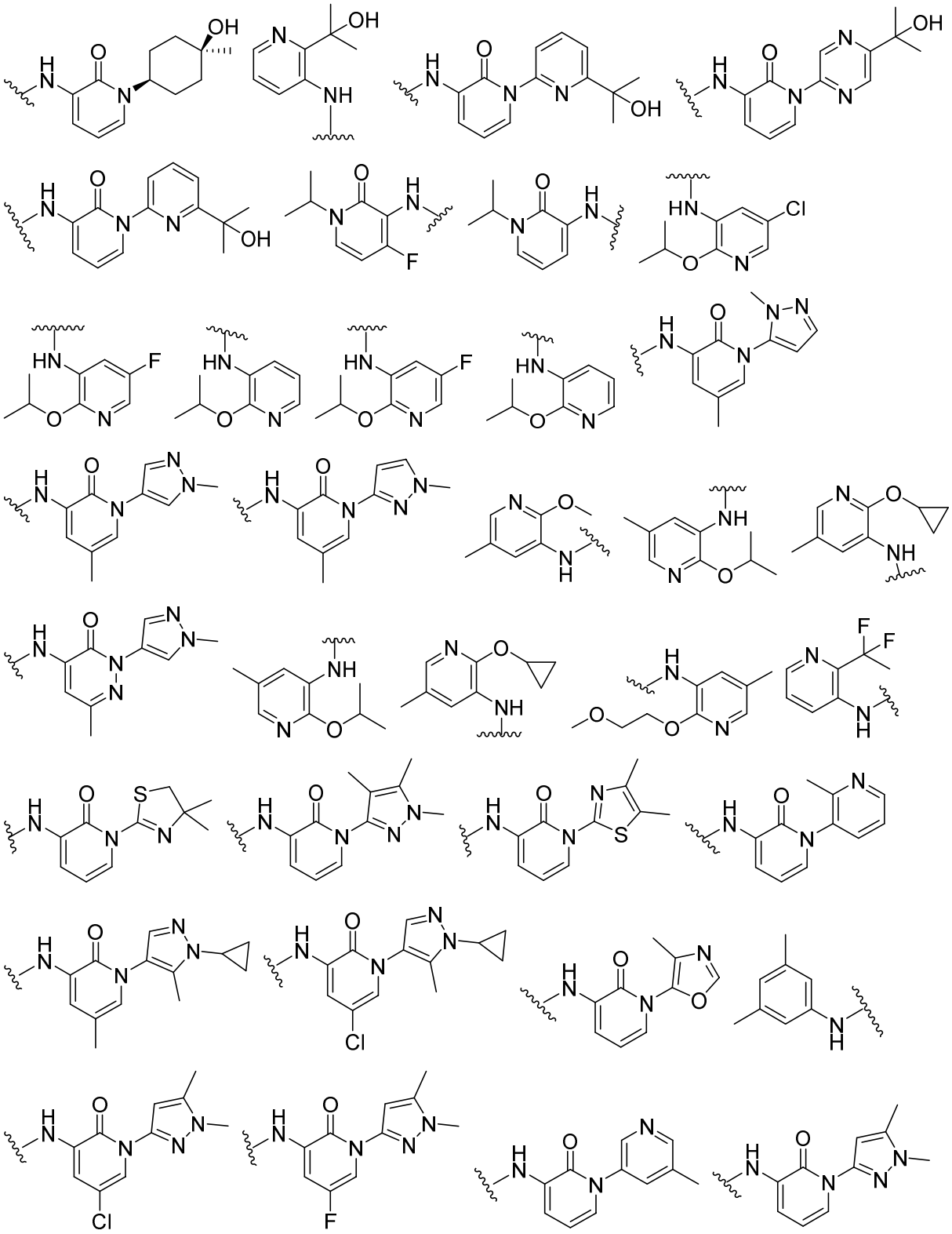


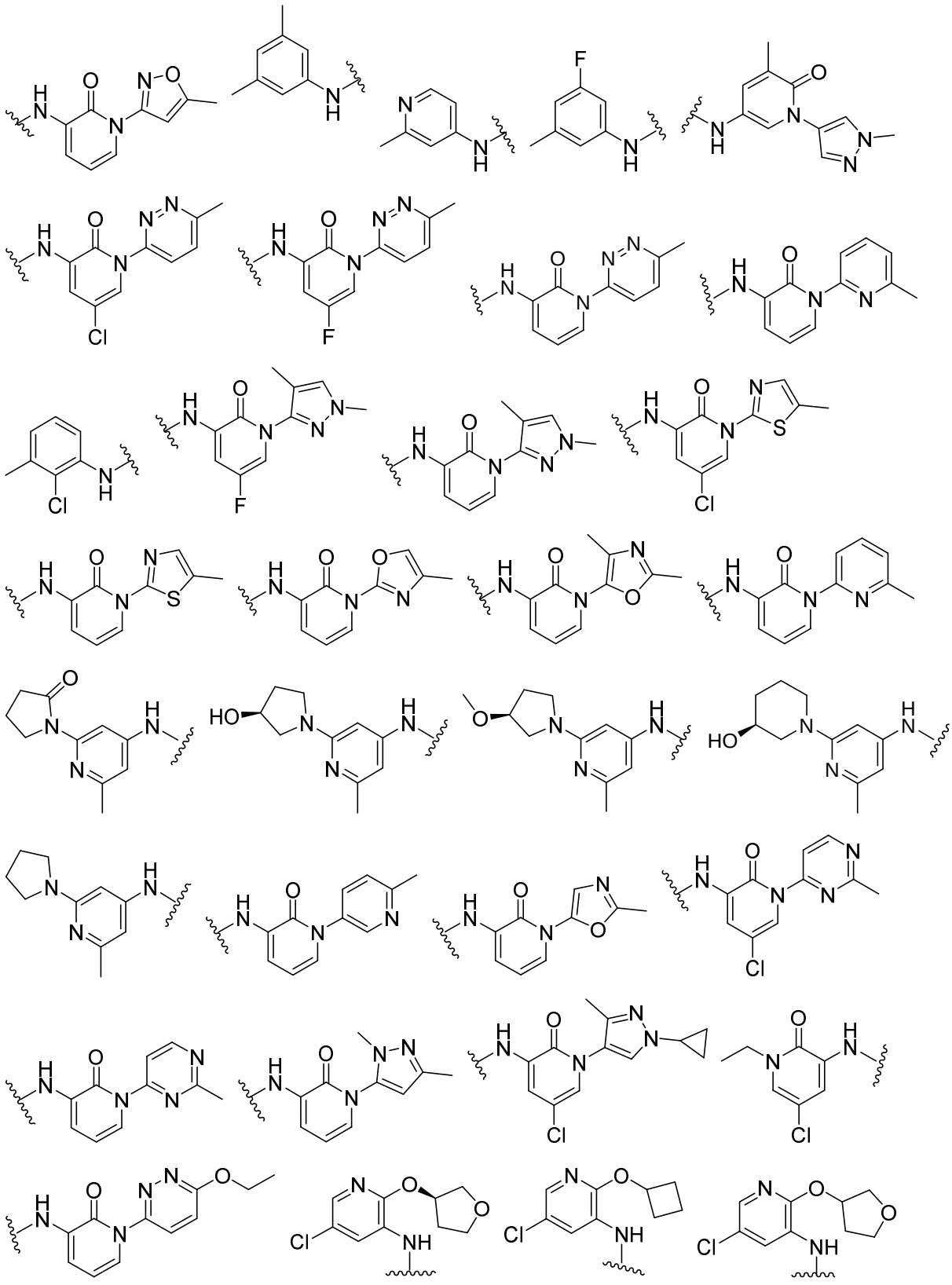
VI-c

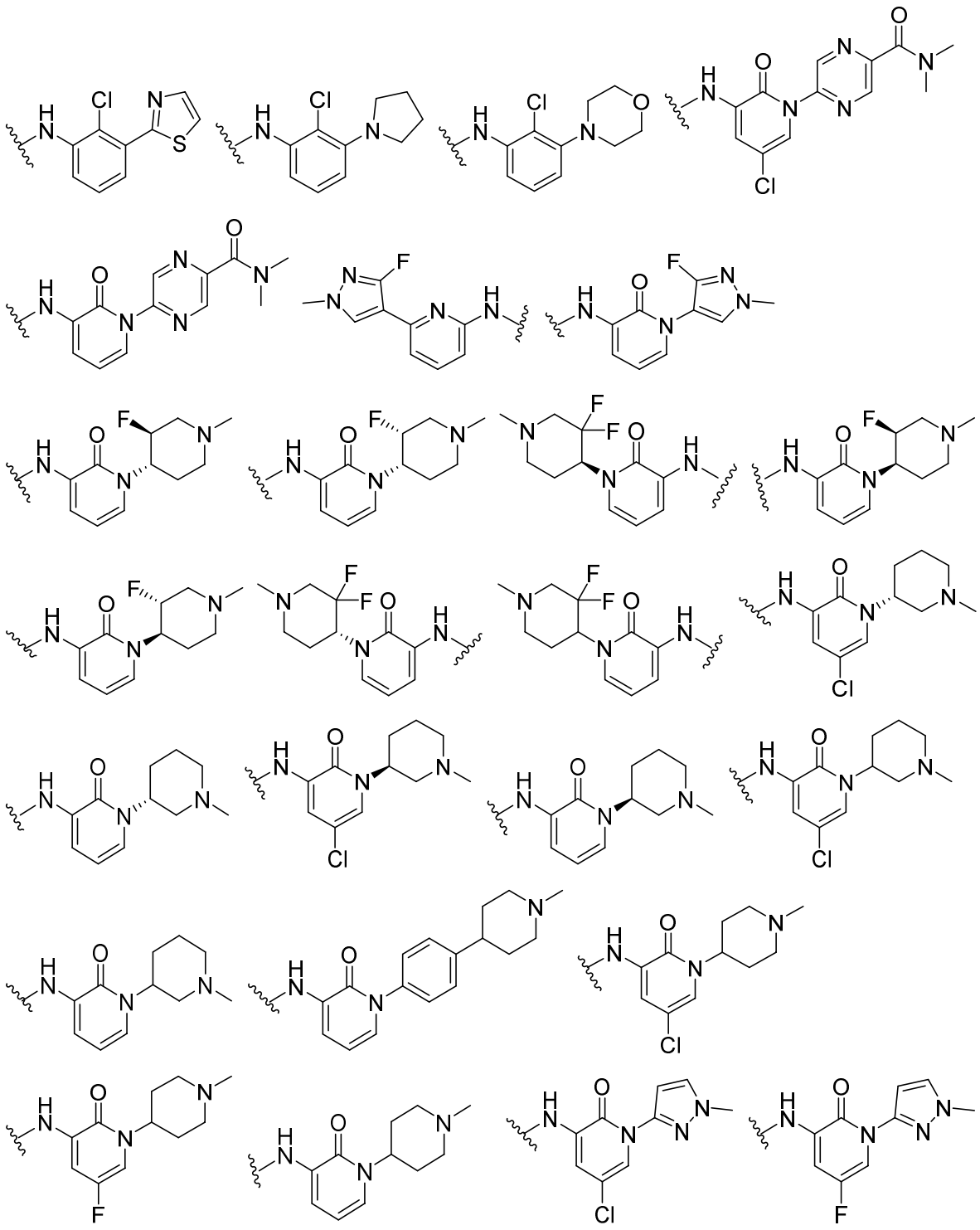
or a pharmaceutically acceptable salt thereof.

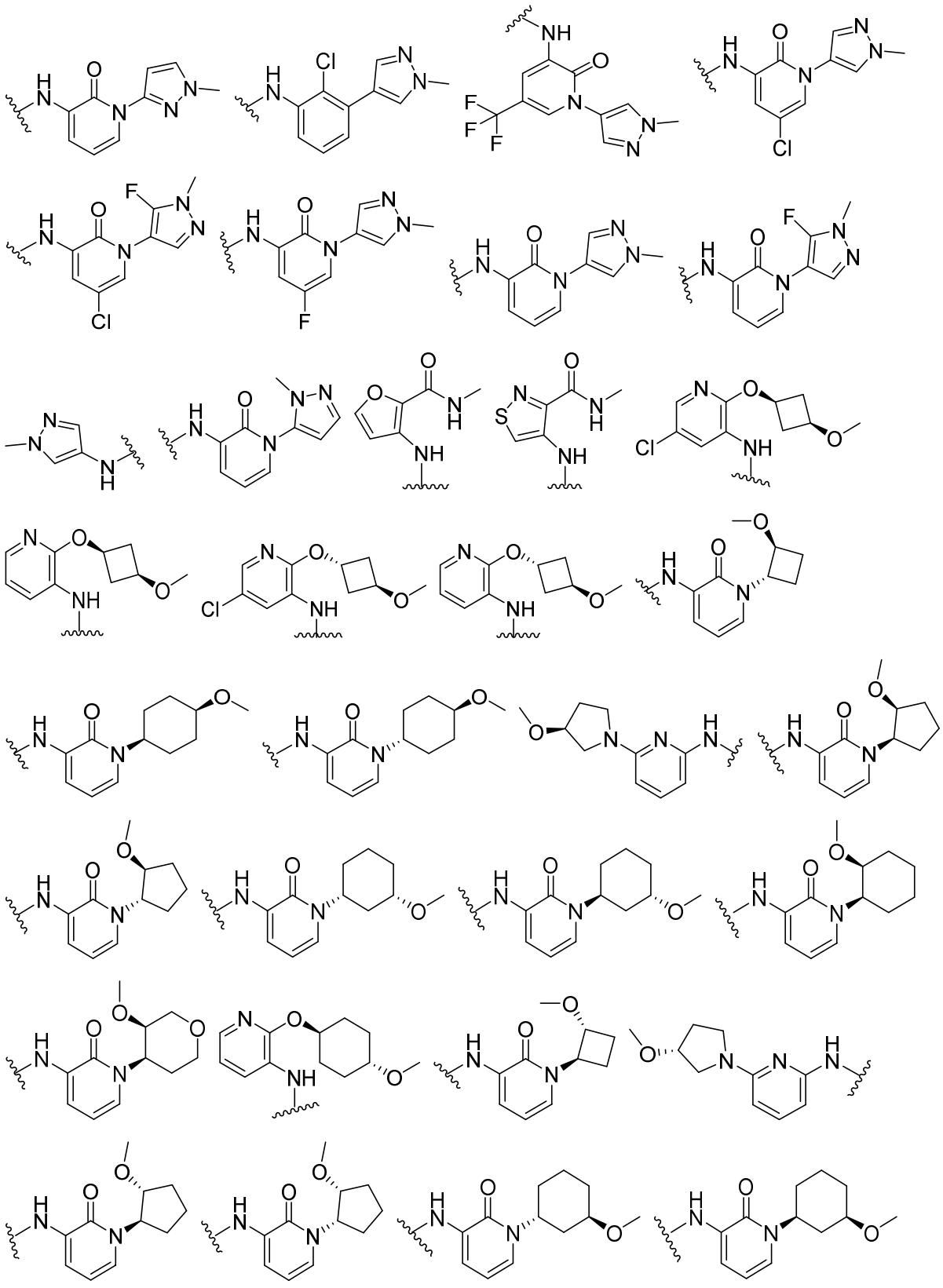
6. The compound of any one of claims 1-5 wherein R^5 is

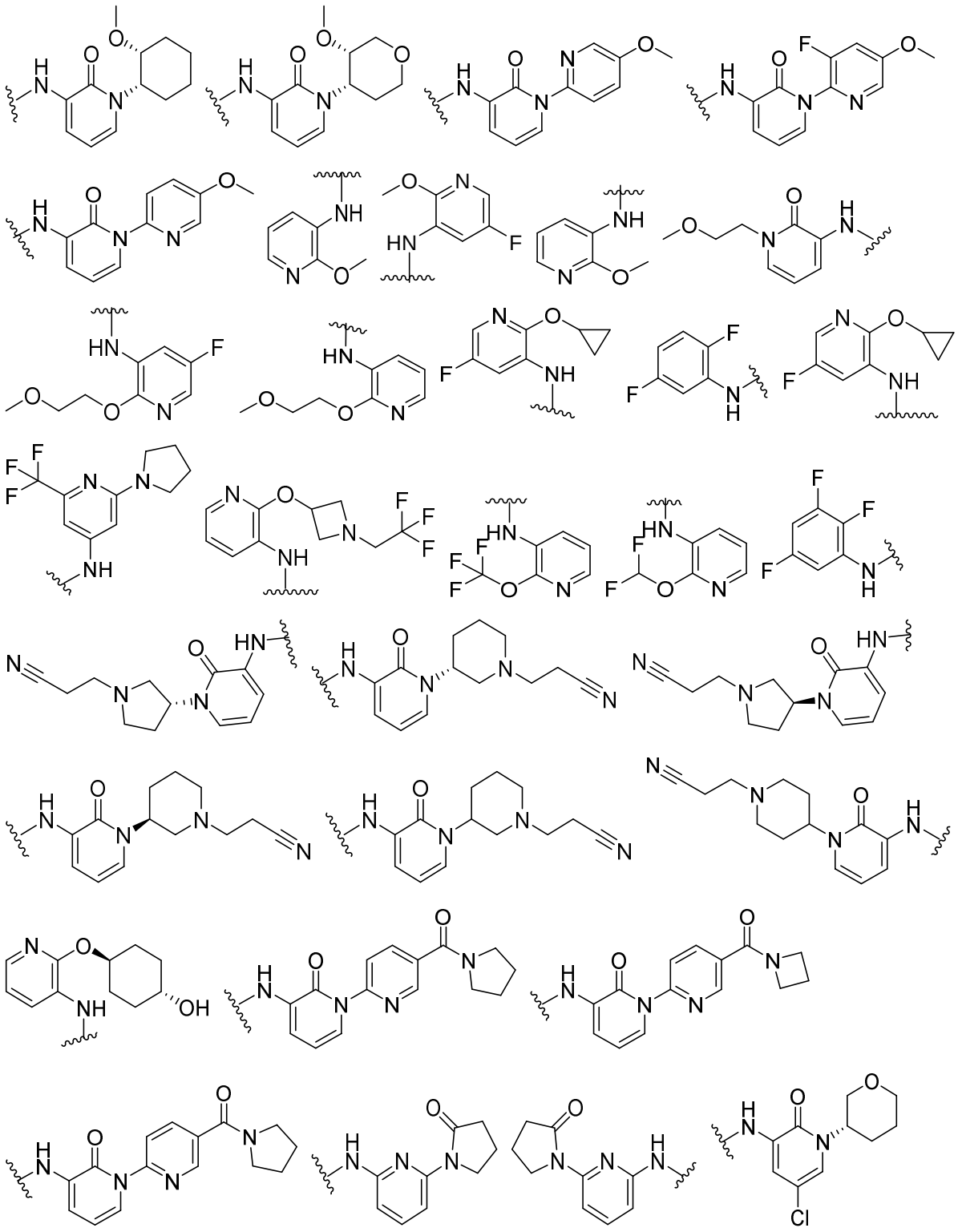


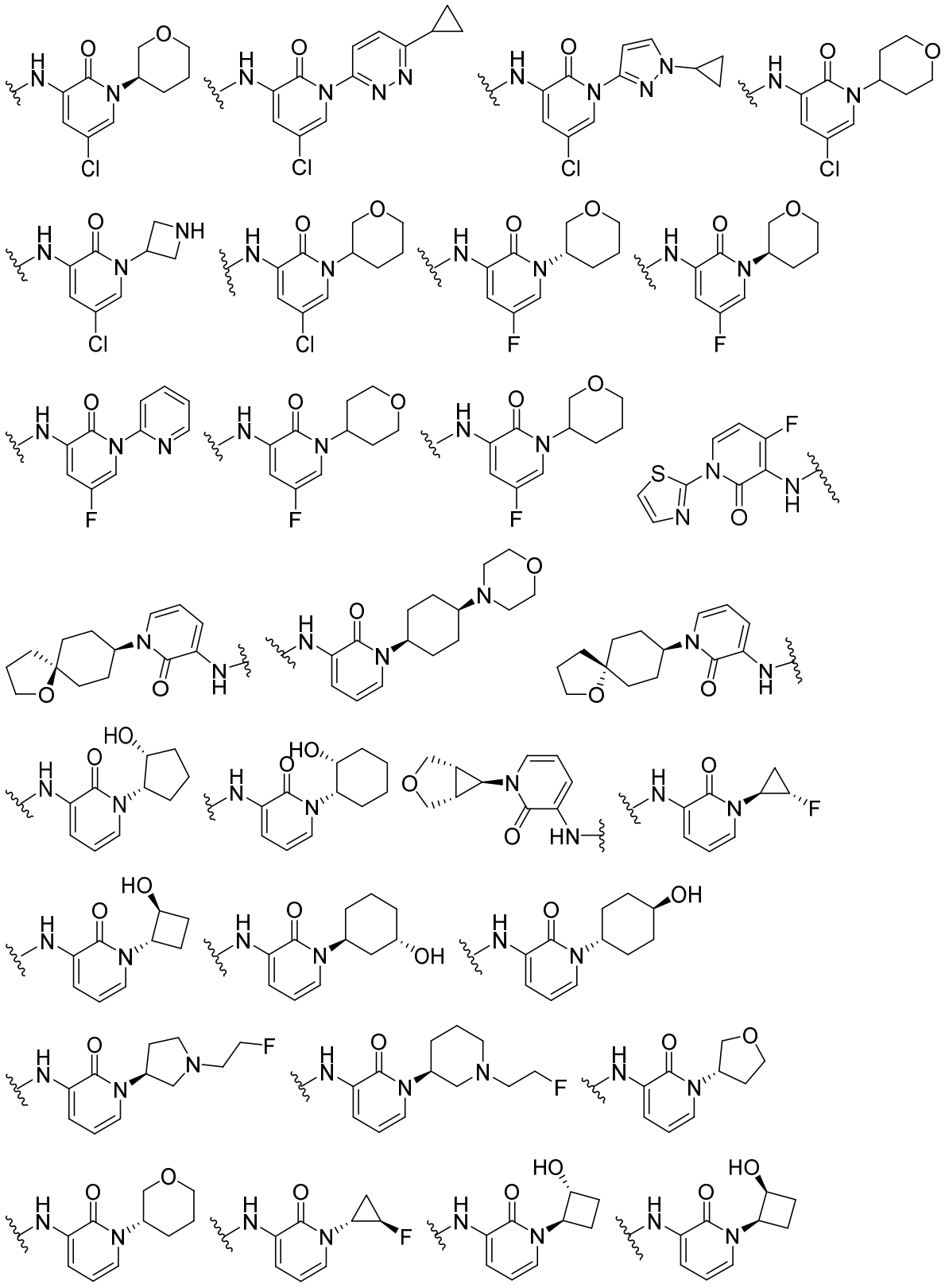


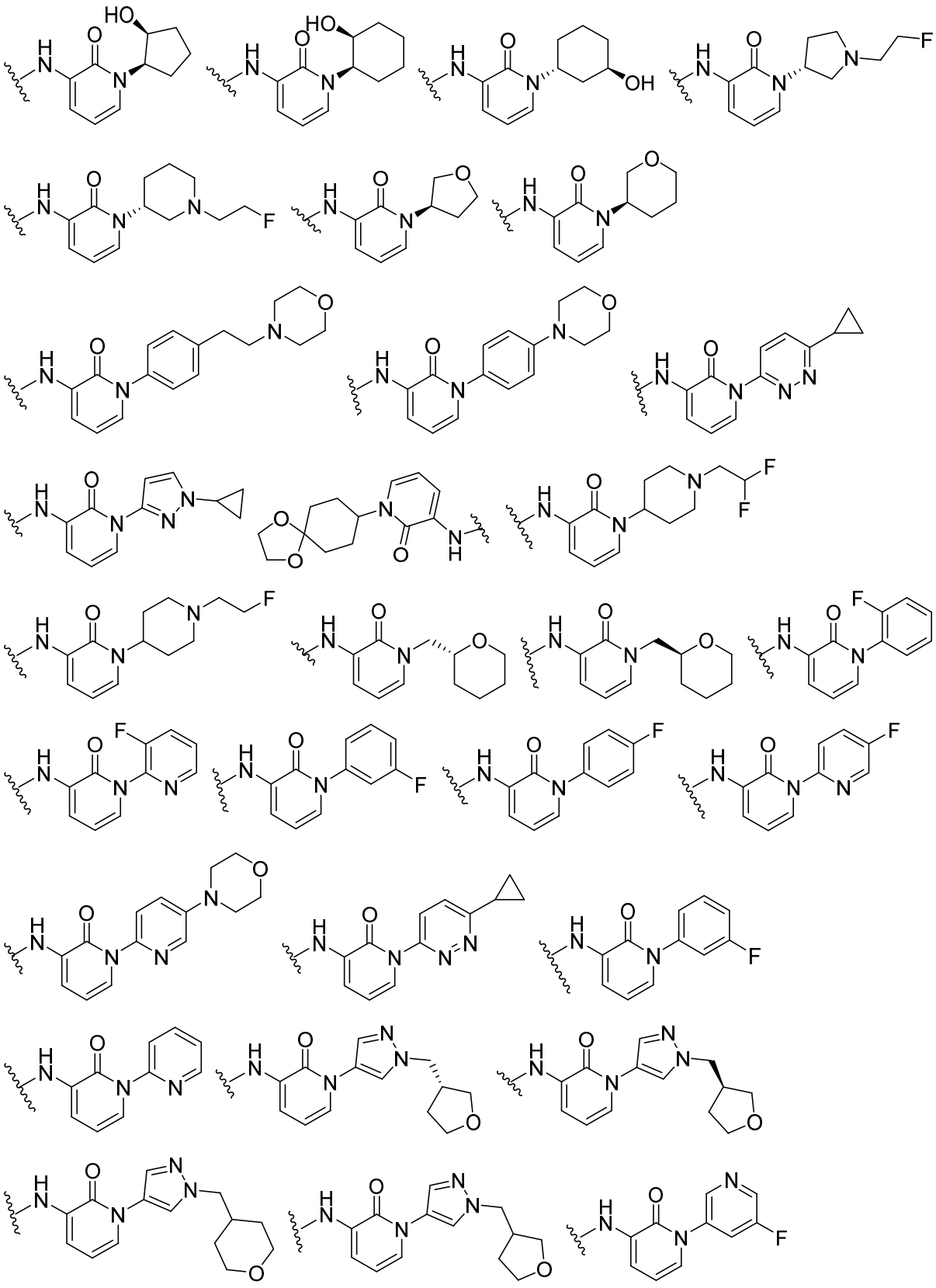


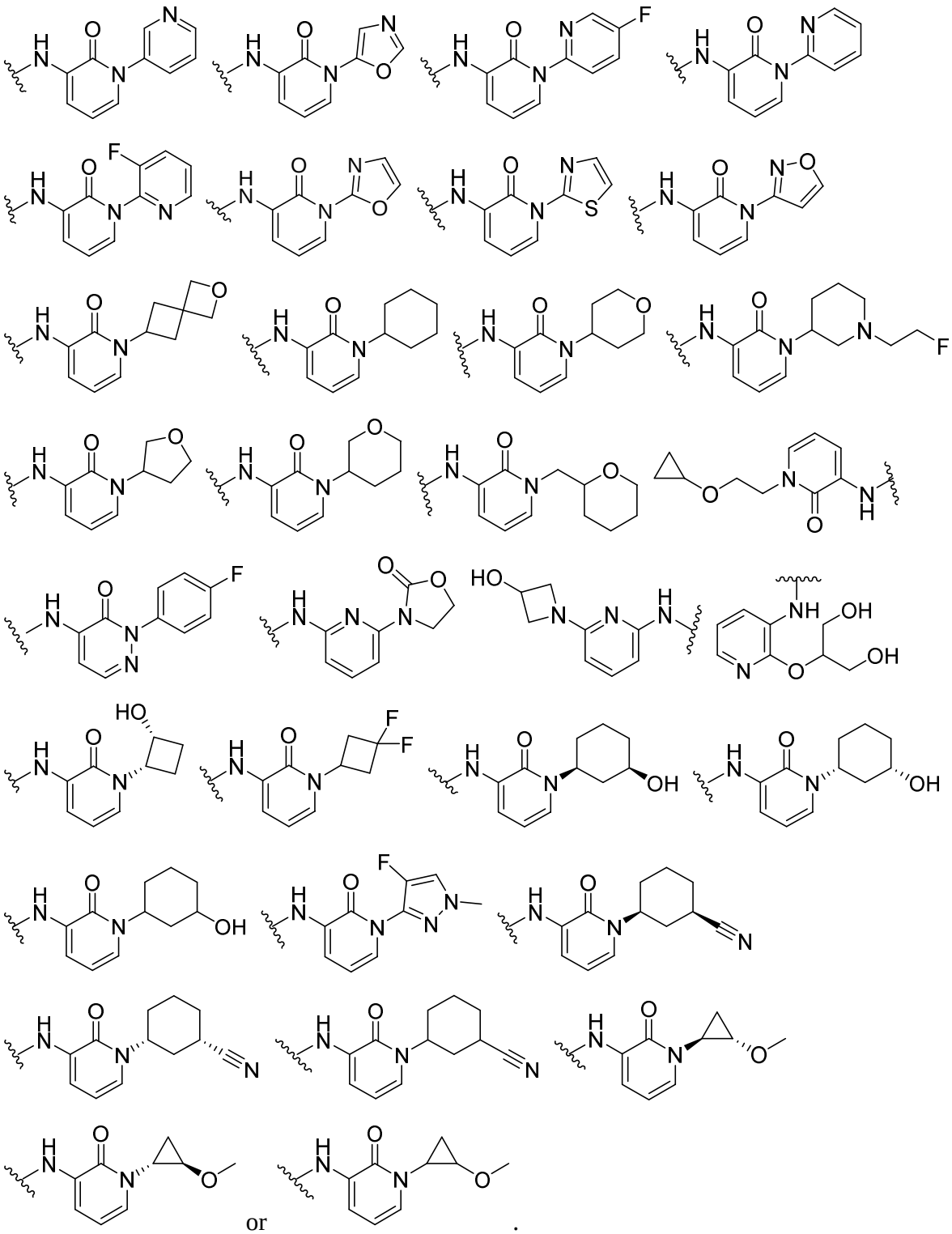






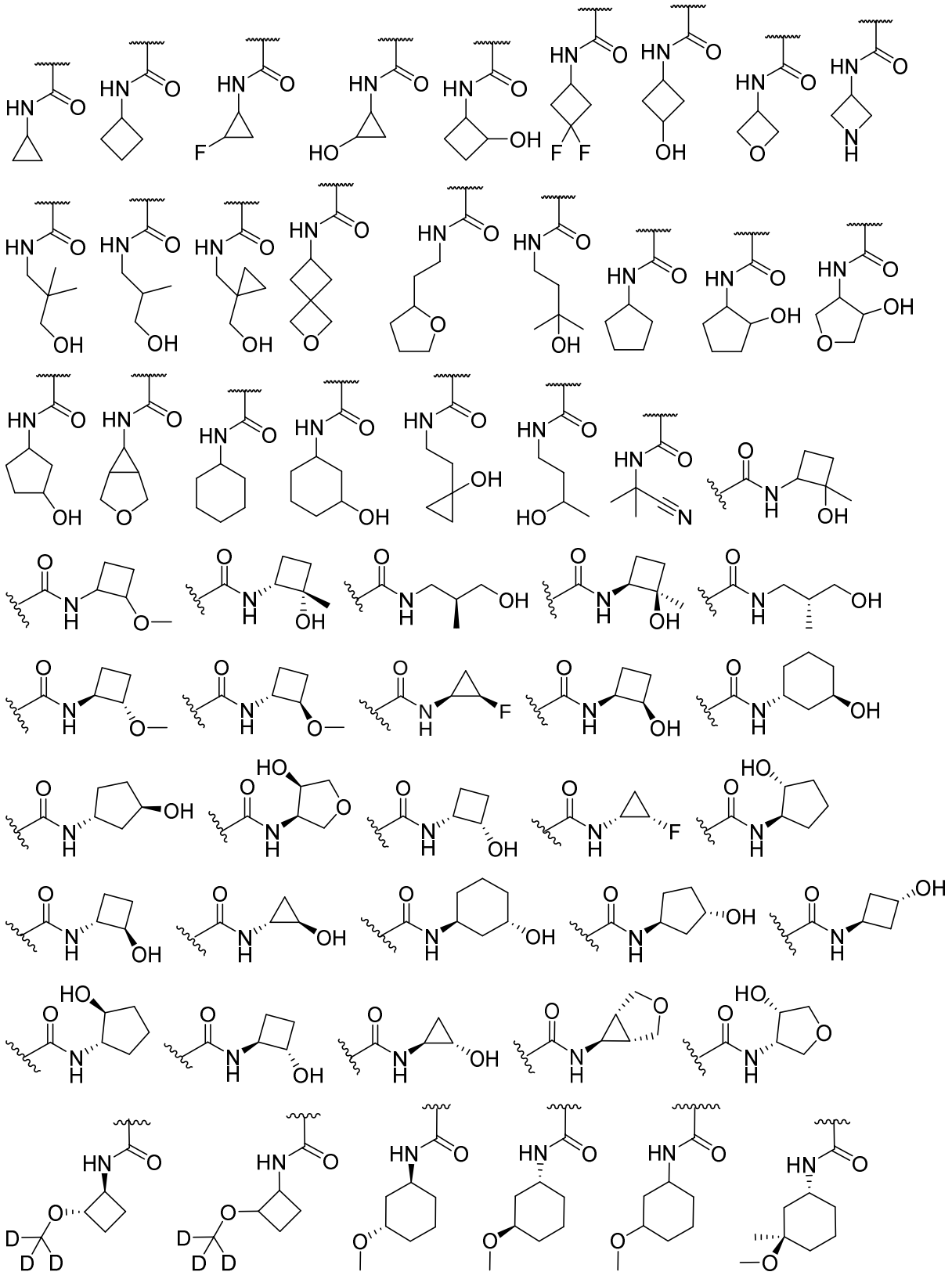


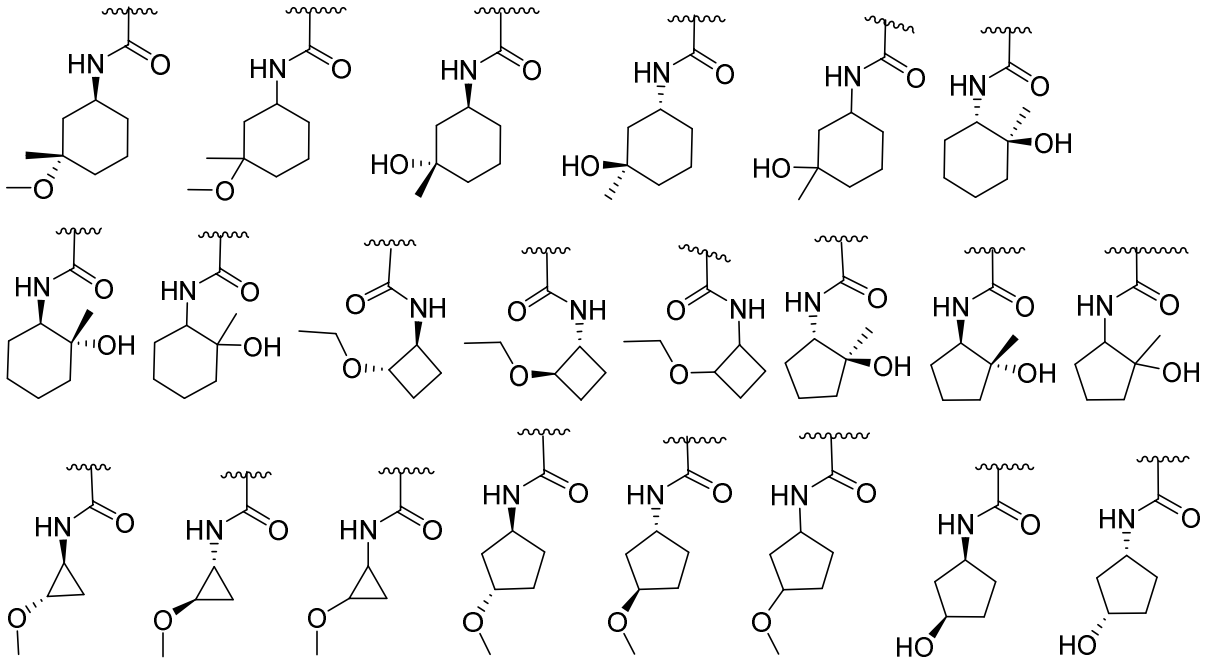


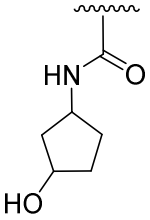


or .

7. The compound of any one of claims 1-5 wherein R^3 is





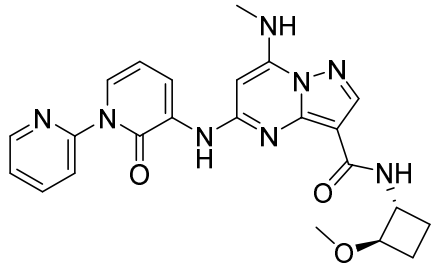
or .

8. The compound of any one of claims 1-7 wherein R^{7A} is C_{1-6} aliphatic.

9. The compound of any one of claims 1-8 wherein R^{7A} is methyl.

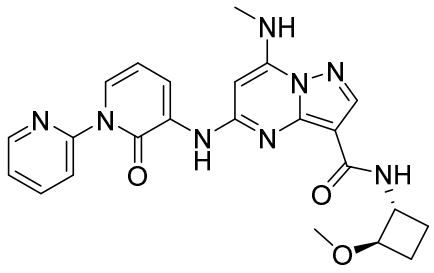
10. The compound of any one of claims 1-9, selected from those depicted in Table 1 of the specification, or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1, which is:

I-908 

or a pharmaceutically acceptable salt thereof.

12. The compound of claim 1, which is:

I-908 .

13. A pharmaceutical composition comprising a compound according to any one of claims 1-12, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

14. Use of a pharmaceutical composition of claim 13, or a compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating an TYK2-mediated disorder, disease, or condition.

15. The use of claim 14 wherein the disorder is selected from an autoimmune disorder, an inflammatory disorder, a proliferative disorder, an endocrine disorder, a neurological disorder, or a disorder associated with transplantation.

16. The use of claim 15 wherein the disorder is selected from psoriasis, psoriatic arthritis, Crohn’s disease, ulcerative colitis, Hidradenitis suppurativa, Vitiligo, and inflammatory bowel disease.

17. The use of claim 14 wherein the disorder is psoriasis.

18. The use of claim 14 wherein the disorder is psoriatic arthritis.

19. The use of claim 14 wherein the disorder is Crohn’s disease.

20. The use of claim 14 wherein the disorder is ulcerative colitis.

21. The use of claim 14 wherein the disorder is Hidradenitis suppurativa.

22. The use of claim 14 wherein the disorder is Vitiligo.

23. A compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 13, for use as a medicament.