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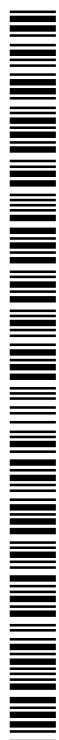
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(54) Title: EAAT2 ENHANCING MOLECULES

(57) Abstract: The present application provides pyridine, pyrimidine, and pyrazine derivatives that activate excitatory amino acid transporter 2 (EAAT2), and methods of using the derivatives for treating or preventing diseases, disorders, and conditions associated with glutamate excitotoxicity.



EAAT2 Enhancing Molecules

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Application 62/531,668, filed July 12, 2017, which is incorporated by reference herein in its entirety.

TECHNICAL FIELD

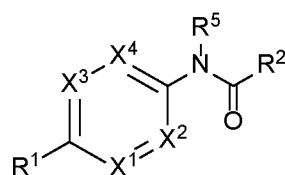
The present description relates to pyridine, pyrimidine, and pyrazine derivatives that activate excitatory amino acid transporter 2 (EAAT2), and methods of use thereof for treating or preventing diseases, disorders, and conditions associated with glutamate excitotoxicity.

BACKGROUND

Glutamate is a major neurotransmitter in the mammalian central nervous system (CNS) and essential for normal brain function including cognition, memory, and learning. However, the extracellular concentration of glutamate must remain below excitotoxic levels ($\sim 1 \mu\text{M}$) to avoid overstimulation of glutamate receptors, leading to neuronal damage or death (Sheldon and Robinson, *Neurochem. Int.* 2007, 51, 333). Excitotoxicity has been associated with multiple acute neurological conditions such as ischemic stroke, epilepsy, and trauma, chronic adult-onset neurodegenerative disorders such as Alzheimer's disease and amyotrophic lateral sclerosis (ALS) (Guo et al., *Hum. Mol. Genet.* 2003, 12, 2519; Tian et al., *J. Biol. Chem.* 2007, 282, 1727; Hazell, *Neurochem. Int.* 2007 50, 941; Seifert et al., *Brain. Res. Rev.* 2010, 63, 212; Tian et al., *J. Neurochem.* 2010, 113, 978), and depression. One potential approach to preventing excitotoxicity is to enhance glutamate reuptake. EAAT2 is the major glutamate transporter and functions to remove glutamate from synapses (Lin et al., *Am. J. Physiol. Gastrointest Liver Physiol.* 2009, 296, 129). An increase in EAAT2 protein expression and function can provide a means to prevent insufficient glutamate reuptake and consequently reduce neuronal damage.

SUMMARY

Provided herein is a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

X¹ is CH or N;

X² is CH or N;

X³ is CR³ or N;

5 X⁴ is CR⁴ or N;

wherein the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R¹ is selected from the group consisting of 6-10 membered aryl and 5-10 membered heteroaryl, each of which is optionally substituted by 1, 2, 3, or 4 independently selected R^A groups;

R² is selected from the group consisting of 6-10 membered aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, each of which is optionally substituted by 1, 2, 3, or 4 independently selected R^B groups;

R³, R⁴, and R⁵ are each independently selected from H and C₁₋₆ alkyl;

15 each R^A and R^B is independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cOR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, and C₁₋₄ haloalkyl are

20 optionally substituted with 1, 2, 3, or 4 independently selected R⁶ groups;

each R^a, R^b, R^c, and R^d is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₃₋₁₀ cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₃₋₁₀ cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, and 4-10 membered

25 heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 independently selected R⁶ groups;

each R^e is independently selected from H, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkylaminosulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, and di(C₁₋₆ alkyl)aminosulfonyl;

30 and

each R⁶ is independently selected from OH, NO₂, CN, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, cyano-C₁₋₃ alkyl, HO-C₁₋₃ alkyl, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, thio, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, carboxy, C₁₋₆ alkylcarbonyl, C₁₋₆

alkoxycarbonyl, C₁₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, di(C₁₋₆ alkyl)aminosulfonyl, aminosulfonylamino, C₁₋₆ alkylaminosulfonylamino, di(C₁₋₆ alkyl)aminosulfonylamino, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, and di(C₁₋₆ alkyl)aminocarbonylamino.

In some embodiments, R¹ is a 5-10 membered heteroaryl which is optionally substituted by 1, 2, 3, or 4 independently selected R^A groups. For example, R¹ is an unsubstituted 5-6 membered heteroaryl. In some embodiments,

5 R¹ is unsubstituted pyridyl.

In some embodiments, R² is selected from the group consisting of phenyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl, each of which is optionally substituted by 1, 2, 3, or 4 independently selected R^B groups. For example, R² is selected from the group consisting of phenyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl, each of which is
10 optionally substituted by 1 R^B group. In some embodiments, each R^B is independently selected from the group consisting of halo, C₁₋₆ alkyl, and OR^a. For example, each R^B is independently selected from the group consisting of F, Cl, C₁₋₃ alkyl, and C₁₋₃ alkoxy.

In some embodiments, R³ is H.

In some embodiments, R⁴ is H.

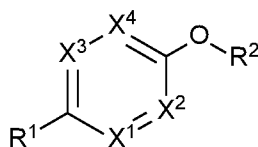
15 In some embodiments, R⁵ is H.

In some embodiments, the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring. In some embodiments, the ring comprising X¹, X², X³, and X⁴ forms a pyrazine ring. In some embodiments, the ring comprising X¹, X², X³, and X⁴ forms a pyrimidine ring.

In some embodiments, the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring, a
20 pyrazine ring, or a pyrimidine ring; R¹ is a 5-6 membered heteroaryl which is optionally substituted by 1 or 2 independently selected R^A groups; R² is selected from the group consisting of phenyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl, each of which is optionally substituted by 1, 2, 3, or 4 independently selected R^B groups; each R^B is independently selected from the group consisting of halo, C₁₋₆ alkyl, and OR^a; R³ is H; R⁴ is H;
25 and R⁵ is H.

In some embodiments, the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring, a pyrazine ring, or a pyrimidine ring; R¹ is an unsubstituted 5-6 membered heteroaryl; R² is selected from the group consisting of phenyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl, each of which is optionally substituted by 1 or 2 independently selected R^B
30 groups; each R^B is independently selected from the group consisting of halo, C₁₋₆ alkyl, and OCH₃; R³ is H; R⁴ is H; and R⁵ is H.

Also provided herein is a compound of Formula II:



II

or a pharmaceutically acceptable salt thereof, wherein:

X¹ is CH or N;

X² is CH or N;

X³ is CR³ or N;

X⁴ is CR⁴ or N;

wherein the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R¹ is selected from the group consisting of 6-10 membered aryl and 5-10 membered heteroaryl, each of which is optionally substituted by 1, 2, 3, or 4 independently selected R^A groups;

R² is $-(\text{CHR}^{\text{E}})_n\text{R}^5$;

R⁵ is selected from the group consisting of OR^C, NR^CR^D, C(O)NR^CR^D, C(O)OR^C, C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1, 2, 3, or 4 independently selected R^B groups;

R^E is selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ alkoxy, and amino, wherein said C₁₋₆ alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R⁶ groups;

R³ and R⁴ are independently selected from H and C₁₋₆ alkyl;

each R^A and R^B is independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cOR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, and C₁₋₄ haloalkyl are optionally substituted with 1, 2, 3, or 4 independently selected R⁶ groups;

R^C and R^D are independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₃₋₁₀ cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, 4-10 membered heterocycloalkyl-C₁₋₄ alkylene, 6-10 membered aryl-C₁₋₄ alkylene, 5-10 membered heteroaryl-C₁₋₄ alkylene; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₃₋₁₀ cycloalkyl, 6-10 membered aryl, 5-10

membered heteroaryl, 4-10 membered heterocycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, 4-10 membered heterocycloalkyl-C₁₋₄ alkylene, 6-10 membered aryl-C₁₋₄ alkylene, and 5-10 membered heteroaryl-C₁₋₄ alkylene are each optionally substituted with 1, 2, 3, or 4 independently selected R⁶ groups; or

alternatively, any R^C and R^D attached to the same N atom, together with the N atom to which they are attached, form a 4-6 membered heterocycloalkyl group or a 5-6 membered heteroaryl group, each optionally substituted with 1, 2, or 3 independently selected R⁶ groups;

each R^a, R^b, R^c, and R^d is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₃₋₁₀ cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₃₋₁₀ cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 independently selected R⁶ groups;

each R^e is independently selected from H, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkylaminosulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, and di(C₁₋₆ alkyl)aminosulfonyl;

each R⁶ is independently selected from OH, NO₂, CN, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, cyano-C₁₋₃ alkyl, HO-C₁₋₃ alkyl, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, thio, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, carboxy, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, di(C₁₋₆ alkyl)aminosulfonyl, aminosulfonylamino, C₁₋₆ alkylaminosulfonylamino, di(C₁₋₆ alkyl)aminosulfonylamino, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, and di(C₁₋₆ alkyl)aminocarbonylamino; and

n is 0, 1, 2, 3, 4, or 5.

In some embodiments, R¹ is a 5-10 membered heteroaryl which is optionally substituted by 1, 2, 3, or 4 independently selected R^A groups. For example, R¹ is an unsubstituted 5-6 membered heteroaryl. In some embodiments, R¹ is unsubstituted pyridyl.

In some embodiments, R² is selected from the group consisting of $-(CH_2)_nR^5$, $-(CH(CH_3))_nR^5$, and $-(CH_2CH(NH_2))_nR^5$.

In some embodiments, R³ is H.

In some embodiments, R⁴ is H.

In some embodiments, R⁵ is selected from the group consisting of OR^C, NR^CR^D, C(O)NR^CR^D, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, and 5-10 membered

heteroaryl, wherein the C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1, 2, 3, or 4 independently selected R^B groups. For example, R⁵ is selected from the group consisting of OR^C, NR^CR^D, C(O)NR^CR^D, phenyl, C₃₋₆ cycloalkyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the phenyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1 or 2 independently selected R^B groups. In some embodiments, R⁵ is selected from the group consisting of OCH₃, N(CH₃)₂, C(O)N(CH₃)₂, phenyl, C₃₋₆ cycloalkyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the phenyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1 or 2 independently selected R^B groups. In some embodiments, each R^B is independently selected from the group consisting of C₁₋₆ alkyl and NR^CR^D. For example, each R^B is independently selected from the group consisting of C₁₋₃ alkyl and N(C₁₋₃ alkyl)₂.

In some embodiments, n is 0, 1, or 2.

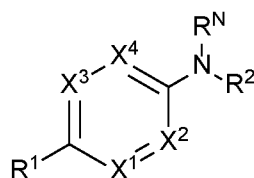
In some embodiments, the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring. In some embodiments, the ring comprising X¹, X², X³, and X⁴ forms a pyrazine ring. In some embodiments, the ring comprising X¹, X², X³, and X⁴ forms a pyrimidine ring.

In some embodiments, the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring, a pyrazine ring, or a pyrimidine ring; R¹ is a 5-6 membered heteroaryl which is optionally substituted by 1 or 2 independently selected R^A groups; R² is selected from the group consisting of $-(CH_2)_nR^5$, $-(CH(CH_3))_nR^5$, and $-(CH_2CH(NH_2))_nR^5$; R³ is H; R⁴ is H; R⁵ is selected from the group consisting of OR^C, NR^CR^D, C(O)NR^CR^D, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1, 2, 3, or 4 independently selected R^B groups; each R^B is independently selected from the group consisting of C₁₋₆ alkyl and NR^CR^D; and n is 0, 1, 2, 3, 4, or 5.

In some embodiments, the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring, a pyrazine ring, or a pyrimidine ring; R¹ is an unsubstituted 5-6 membered heteroaryl; R² is selected from the group consisting of $-(CH_2)_nR^5$, $-(CH(CH_3))_nR^5$, and $-(CH_2CH(NH_2))_nR^5$; R³ is H; R⁴ is H; R⁵ is selected from the group consisting of OR^C, NR^CR^D, C(O)NR^CR^D, phenyl, C₃₋₆ cycloalkyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the phenyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1 or 2 independently selected R^B groups; each R^B is independently selected from the group consisting of C₁₋₆ alkyl and NR^CR^D; and n is 0, 1, or 2.

In some embodiments, the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring, a pyrazine ring, or a pyrimidine ring; R^1 is unsubstituted pyridyl; R^2 is selected from the group consisting of $-(CH_2)_nR^5$, $-(CH(CH_3))_nR^5$, and $-(CH_2CH(NH_2))_nR^5$; R^3 is H; R^4 is H; R^5 is selected from the group consisting of OCH_3 , $N(CH_3)_2$, $C(O)N(CH_3)_2$, phenyl, C_{3-6} cycloalkyl, 4-
 5 6 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the phenyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1 or 2 independently selected R^B groups; each R^B is independently is selected from the group consisting of C_{1-3} alkyl and $N(C_{1-3} \text{ alkyl})_2$; and n is 0, 1, or 2.

Further provided herein is a compound of Formula III:



III

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is CH or N;

X^2 is CH or N;

X^3 is CR^3 or N;

X^4 is CR^4 or N;

wherein the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R^N is selected from the group consisting of H, C_{1-6} alkyl, and $C(O)R^{N1}$;

R^{N1} is a C_{6-10} aryl which is optionally substituted by 1, 2, 3, or 4 independently selected halo groups;

R^1 is selected from the group consisting of 6-10 membered aryl and 5-10 membered heteroaryl, each of which is optionally substituted by 1, 2, 3, or 4 independently selected R^A groups;

R^2 is $-(CHR^E)_nR^5$;

R^5 is selected from the group consisting of $NR^C R^D$, $C(O)NR^C R^D$, $C(O)OR^C$, C_{3-10} cycloalkyl, C_{6-10} aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the C_{3-10} cycloalkyl, C_{6-10} aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1, 2, 3, or 4 independently selected R^B groups;

R^E is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkoxy, and amino, wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^6 groups;

R³ and R⁴ are independently selected from H and C₁₋₆ alkyl;

each R^A and R^B is independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cOR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, and C₁₋₄ haloalkyl are optionally substituted with 1, 2, 3, or 4 independently selected R⁶ groups;

R^C and R^D are independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₃₋₁₀ cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, 4-10 membered heterocycloalkyl-C₁₋₄ alkylene, 6-10 membered aryl-C₁₋₄ alkylene, 5-10 membered heteroaryl-C₁₋₄ alkylene; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₃₋₁₀ cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, 4-10 membered heterocycloalkyl-C₁₋₄ alkylene, 6-10 membered aryl-C₁₋₄ alkylene, and 5-10 membered heteroaryl-C₁₋₄ alkylene are each optionally substituted with 1, 2, 3, or 4 independently selected R⁶ groups; or

alternatively, any R^C and R^D attached to the same N atom, together with the N atom to which they are attached, form a 4-6 membered heterocycloalkyl group or a 5-6 membered heteroaryl group, each optionally substituted with 1, 2, or 3 independently selected R⁶ groups;

each R^a, R^b, R^c, and R^d is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₃₋₁₀ cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₃₋₁₀ cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 independently selected R⁶ groups;

each R^e is independently selected from H, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkylaminosulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, and di(C₁₋₆ alkyl)aminosulfonyl;

each R⁶ is independently selected from OH, NO₂, CN, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, cyano-C₁₋₃ alkyl, HO-C₁₋₃ alkyl, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, thio, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, carboxy, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, di(C₁₋₆ alkyl)aminosulfonyl, aminosulfonylamino, C₁₋₆

alkylaminosulfonylamino, di(C₁₋₆ alkyl)aminosulfonylamino, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, and di(C₁₋₆ alkyl)aminocarbonylamino; and

n is 0, 1, 2, 3, 4, or 5.

In some embodiments, R^N is selected from the group consisting of H, C₁₋₃ alkyl, and C(O)-phenyl.

In some embodiments, R¹ is a 5-10 membered heteroaryl which is optionally substituted by 1, 2, 3, or 4 independently selected R^A groups. For example, R¹ is an unsubstituted 5-6 membered heteroaryl. In some embodiments, R¹ is unsubstituted pyridyl.

In some embodiments, R² is $-(CH_2)_nR^5$.

In some embodiments, R³ is H.

In some embodiments, R⁴ is H.

In some embodiments, R⁵ is selected from the group consisting of NR^CR^D, C₆₋₁₀ aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the C₆₋₁₀ aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1, 2, 3, or 4 independently selected R^B groups. For example, R⁵ is selected from the group consisting of NR^CR^D, phenyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl, wherein the phenyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl are each optionally substituted by 1 or 2 independently selected R^B groups. In some embodiments, R⁵ is selected from the group consisting of N(C₁₋₃ alkyl)₂, phenyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl. For example, R⁵ is selected from the group consisting of N(CH₃)₂, phenyl, oxazolyl, piperidinyl, and pyrrolidinyl.

In some embodiments, the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring. In some embodiments, the ring comprising X¹, X², X³, and X⁴ forms a pyrazine ring. In some embodiments, the ring comprising X¹, X², X³, and X⁴ forms a pyrimidine ring.

In some embodiments, the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring, a pyrazine ring, or a pyrimidine ring; R^N is selected from the group consisting of H, C₁₋₃ alkyl, and C(O)-phenyl; R¹ is a 5-6 membered heteroaryl which is optionally substituted by 1 or 2 independently selected R^A groups; R² is $-(CH_2)_nR^5$; R³ is H; R⁴ is H; R⁵ is selected from the group consisting of NR^CR^D, C₆₋₁₀ aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the C₆₋₁₀ aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1, 2, 3, or 4 independently selected R^B groups; and n is 1, 2, or 3.

In some embodiments, the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring, a pyrazine ring, or a pyrimidine ring; R^N is selected from the group consisting of H, C₁₋₃ alkyl, and

C(O)-phenyl; R¹ is an unsubstituted 5-6 membered heteroaryl; R² is $-(CH_2)_nR^5$; R³ is H; R⁴ is H; R⁵ is selected from the group consisting of NR^CR^D, phenyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl, wherein the phenyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl are each optionally substituted by 1 or 2 independently selected R^B groups; and n is 1, 2, or 3.

In some embodiments, the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring, a pyrazine ring, or a pyrimidine ring; R^N is selected from the group consisting of H, C₁₋₃ alkyl, and C(O)-phenyl; R¹ is unsubstituted pyridyl; R² is $-(CH_2)_nR^5$; R³ is H; R⁴ is H; R⁵ is selected from the group consisting of N(C₁₋₃ alkyl)₂, phenyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl; and n is 1, 2, or 3.

This disclosure also provides a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

Also provided herein is a method for treating or preventing glutamate excitotoxicity in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof.

Further provided herein is a method for increasing EAAT2 protein expression in a cell or a subject in need thereof, the method comprising contacting the cell or administering to the subject an effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof.

This disclosure provides a method for activating the NRF2 pathway in a cell or a subject in need thereof, the method comprising contacting the cell or administering to the subject an effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof.

Also provided herein a method for treating a disease or disorder selected from the group consisting of ischemic stroke, epilepsy, or a trauma, including blunt trauma, an abrasion, an avulsion, an incision, a laceration, a puncture, a penetration, a surgical trauma, iatrogenic trauma, a spinal cord injury, a traumatic brain injury, or any combination thereof; a chronic neurodegenerative disorder, including mild cognitive impairment, Parkinson's disease, Alzheimer's disease, multiple sclerosis, mesial temporal sclerosis, Huntington's disease, AIDS dementia complex, or amyotrophic lateral sclerosis (ALS); a psychotic disorder including schizophrenia, bipolar disorder, or autism; a pain disorder including migraine, temporomandibular disorders, neuropathic pain, visceral pain, or complex regional pain syndrome; an addiction including alcohol addiction, cocaine addiction, heroin addiction, methamphetamine addiction, or nicotine addiction; or a cancer, including glioblastoma; or a

mood disorder, including anxiety disorders, depressive disorders, borderline personality disorder, attention-deficit-hyperactivity disorder, suicidal behavior, eating disorders, posttraumatic stress disorder, gulf war illness, and obsessive-Compulsive Disorder in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound provided
 5 herein, or a pharmaceutically acceptable salt thereof.

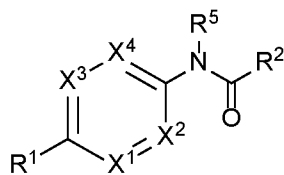
Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present invention; other, suitable methods and materials known in the art can also be used. The materials, methods, and
 10 examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

DETAILED DESCRIPTION

The compounds provided herein may be useful for activating EAAT2, and thus useful in methods of reducing extracellular glutamate levels, thereby reducing glutamate excitotoxicity in cells and tissues, making the compounds therapeutically useful in treating or preventing conditions associated with glutamate excitotoxicity, *e.g.*, acute neurological conditions such as ischemic stroke, epilepsy, and trauma, as well as chronic adult-onset neurodegenerative disorders
 20 such as Alzheimer's disease and amyotrophic lateral sclerosis (ALS). In some embodiments, the compounds provided herein may be therapeutically useful in treating or preventing depression.

Compounds of Formula I

The present application provides compounds of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

X¹ is CH or N;

X² is CH or N;

X³ is CR³ or N;

X⁴ is CR⁴ or N;

wherein the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R¹ is selected from the group consisting of 6-10 membered aryl and 5-10 membered heteroaryl, each of which is optionally substituted by 1, 2, 3, or 4 independently selected R^A groups;

R² is selected from the group consisting of 6-10 membered aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, each of which is optionally substituted by 1, 2, 3, or 4 independently selected R^B groups;

R³, R⁴, and R⁵ are each independently selected from H and C₁₋₆ alkyl;

each R^A and R^B is independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cOR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, and C₁₋₄ haloalkyl are optionally substituted with 1, 2, 3, or 4 independently selected R⁶ groups;

each R^a, R^b, R^c, and R^d is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₃₋₁₀ cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₃₋₁₀ cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 independently selected R⁶ groups;

each R^e is independently selected from H, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkylaminosulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, and di(C₁₋₆ alkyl)aminosulfonyl; and

each R⁶ is independently selected from OH, NO₂, CN, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, cyano-C₁₋₃ alkyl, HO-C₁₋₃ alkyl, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, thio, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, carboxy, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, di(C₁₋₆ alkyl)aminosulfonyl, aminosulfonylamino, C₁₋₆ alkylaminosulfonylamino, di(C₁₋₆ alkyl)aminosulfonylamino, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, and di(C₁₋₆ alkyl)aminocarbonylamino.

In some embodiments, R¹ is a C₆₋₁₀ aryl, which is optionally substituted by 1, 2, 3, or 4 independently selected R^A groups. In some embodiments, R¹ is phenyl, which is optionally substituted by 1 or 2 independently selected R^A groups. In some embodiments, R¹ is phenyl, which is optionally substituted by 1 or 2 independently selected halo groups. In some
5 embodiments, R¹ is 2-fluorophenyl.

In some embodiments, R¹ is a 5-10 membered heteroaryl which is optionally substituted by 1, 2, 3, or 4 independently selected R^A groups. In some embodiments, R¹ is a 5-6 membered heteroaryl which is optionally substituted by 1 or 2 independently selected R^A groups. In some
10 embodiments, R¹ is an unsubstituted 5-6 membered heteroaryl. In some embodiments, R¹ is unsubstituted pyridyl. In some embodiments, R¹ is 2-pyridyl or 3-pyridyl. In some embodiments, R¹ is 2-pyridyl. In some embodiments, R¹ is 3-pyridyl.

In some embodiments, R² is selected from the group consisting of phenyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl, each of which is optionally substituted by 1, 2, 3, or 4 independently selected R^B groups. In some embodiments, R² is selected from the group
15 consisting of phenyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl, each of which is optionally substituted by 1 R^B group. In some embodiments, R² is selected from the group consisting of phenyl, pyridyl, imidazolyl, thiazolyl, oxazolyl, pyrrolidinyl, and piperidinyl, wherein the phenyl, pyridyl, imidazolyl, thiazolyl, oxazolyl, pyrrolidinyl, and piperidinyl are each optionally substituted with 1 R^B group.

In some embodiments, each R^B is independently selected from the group consisting of
20 halo, C₁₋₆ alkyl, and OR^a. In some embodiments, each R^B is an independently selected halo group. In some embodiments, each R^B is an independently selected C₁₋₆ alkyl group. In some embodiments, each R^B is OR^a. In some embodiments, each R^B is an independently selected C₁₋₆ alkoxy group. In some embodiments, each R^B is independently selected from the group
25 consisting of C₁₋₃ alkyl, F, Cl, and C₁₋₃ alkoxy. In some embodiments, each R^B is independently selected from the group consisting of CH₃, F, Cl, and OCH₃. In some embodiments, each R^B is CH₃. In some embodiments, each R^B is F. In some embodiments, each R^B is Cl. In some
embodiments, each R^B is OCH₃.

In some embodiments, R³ is H.

30 In some embodiments, R⁴ is H.

In some embodiments, R⁵ is H.

In some embodiments, R³ and R⁴ are each H. In some embodiments, R³ and R⁵ are each H. In some embodiments, R⁴ and R⁵ are each H. In some embodiments, R³, R⁴, and R⁵ are each H.

In some embodiments, the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring.

In some embodiments, the ring comprising X¹, X², X³, and X⁴ forms a pyrazine ring.

In some embodiments, the ring comprising X¹, X², X³, and X⁴ forms a pyrimidine ring.

In some embodiments:

5 the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R¹ is a 5-6 membered heteroaryl which is optionally substituted by 1 or 2 independently selected R^A groups;

10 R² is selected from the group consisting of phenyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl, each of which is optionally substituted by 1, 2, 3, or 4 independently selected R^B groups;

each R^B is independently selected from the group consisting of halo, C₁₋₆ alkyl, and OR^a;

R³ is H;

R⁴ is H; and

15 R⁵ is H.

In some embodiments:

the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R¹ is an unsubstituted 5-6 membered heteroaryl;

20 R² is selected from the group consisting of phenyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl, each of which is optionally substituted by 1 or 2 independently selected R^B groups;

each R^B is independently selected from the group consisting of halo, C₁₋₆ alkyl, and OCH₃;

25 R³ is H;

R⁴ is H; and

R⁵ is H.

In some embodiments:

30 the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R¹ is pyridyl;

R² is selected from the group consisting of phenyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl, each of which is optionally substituted by 1 or 2 independently selected R^B groups;

each R^B is independently selected from the group consisting of halo, C_{1-6} alkyl, and OCH_3 ;

R^3 is H;

R^4 is H; and

R^5 is H.

In some embodiments:

the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R^1 is pyridyl;

R^2 is selected from the group consisting of phenyl, pyridyl, imidazolyl, thiazolyl, oxazolyl, pyrrolidinyl, and piperidinyl, wherein the phenyl, pyridyl, imidazolyl, thiazolyl, oxazolyl, pyrrolidinyl, and piperidinyl are each optionally substituted with 1 R^B group;

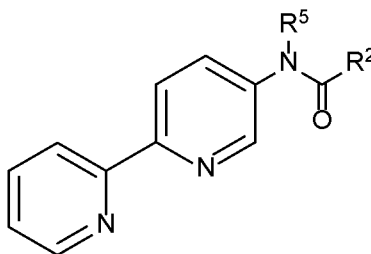
each R^B is independently selected from the group consisting of halo, C_{1-6} alkyl, and OCH_3 ;

R^3 is H;

R^4 is H; and

R^5 is H.

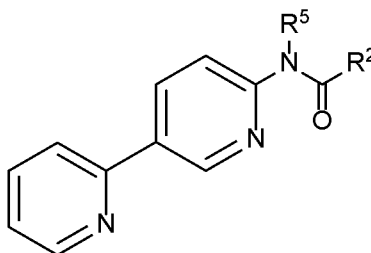
In some embodiments, the compound of Formula I is a compound of Formula Ia:



Ia

or a pharmaceutically acceptable salt thereof.

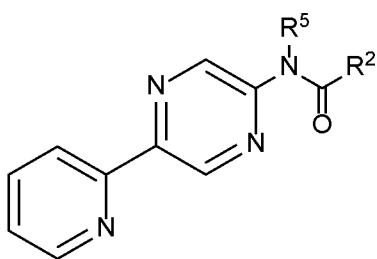
In some embodiments, the compound of Formula I is a compound of Formula Ib:



Ib

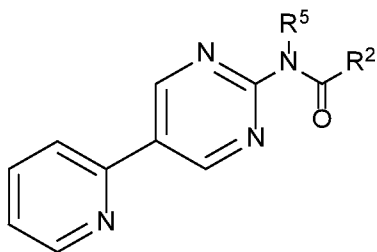
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula I is a compound of Formula Ic:

**Ic**

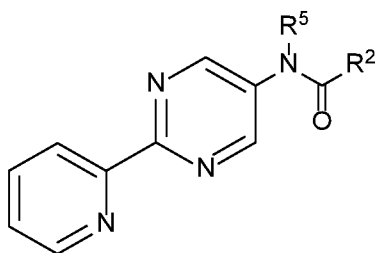
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula I is a compound of Formula Id:

**Id**

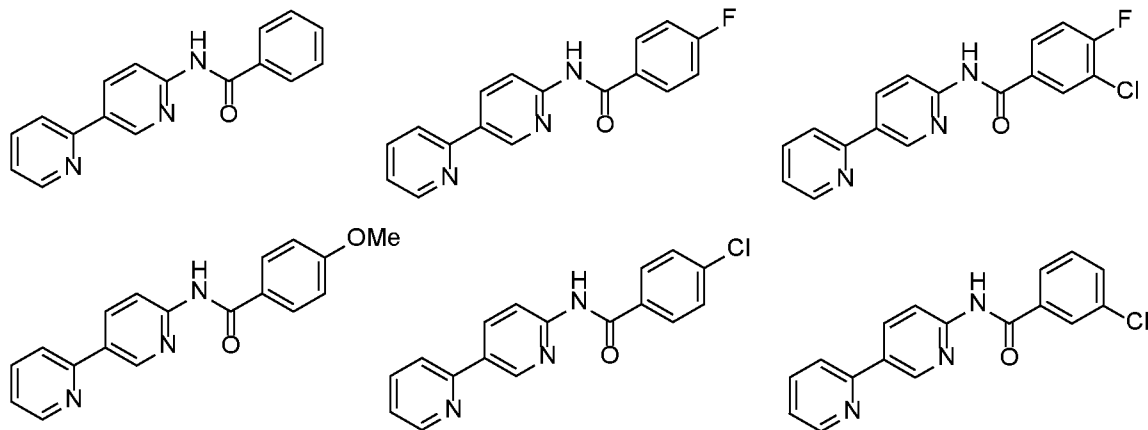
or a pharmaceutically acceptable salt thereof.

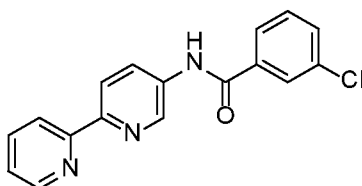
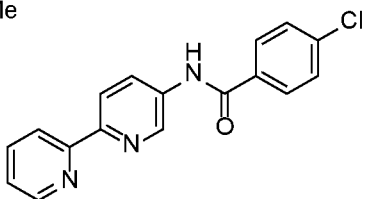
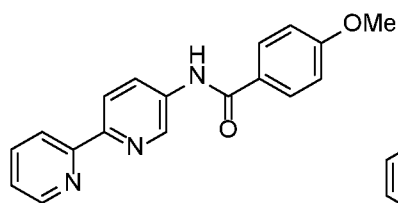
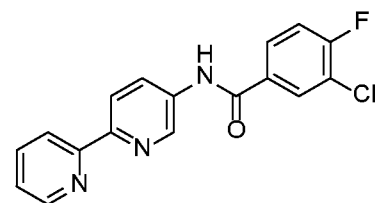
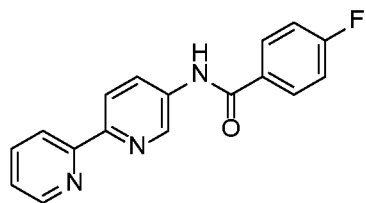
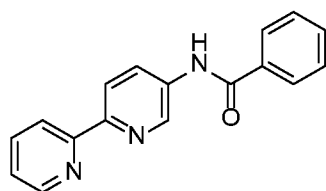
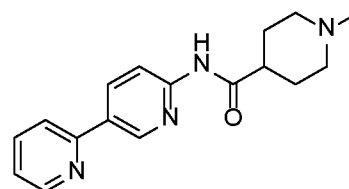
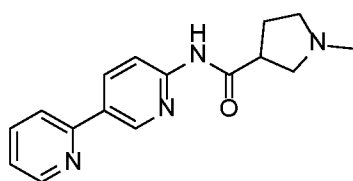
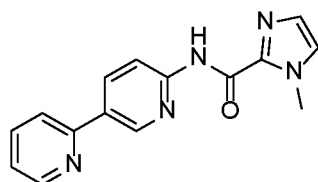
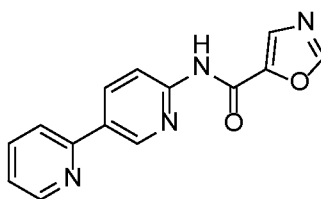
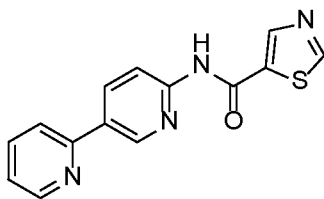
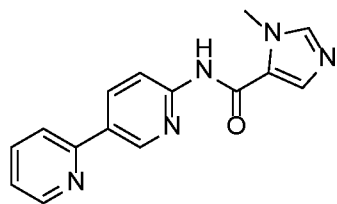
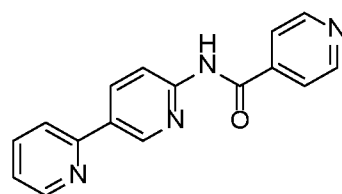
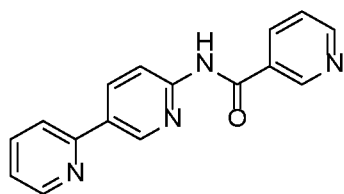
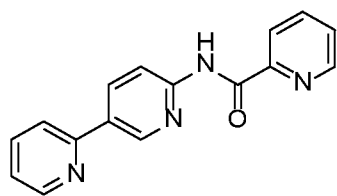
In some embodiments, the compound of Formula I is a compound of Formula Ie:

**Ie**

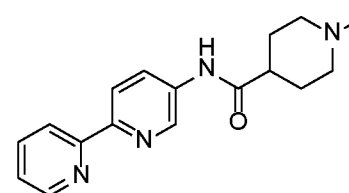
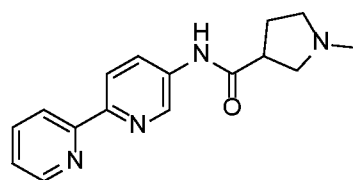
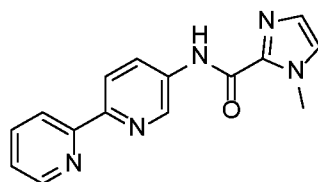
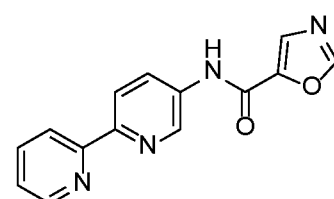
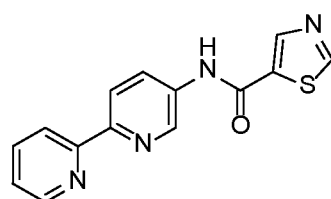
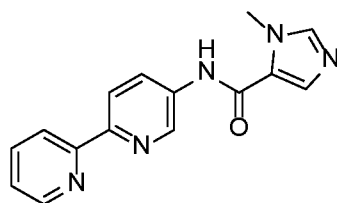
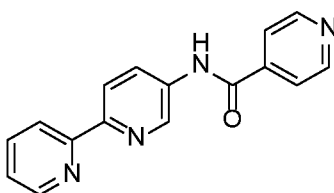
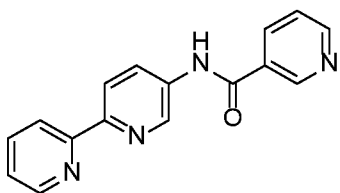
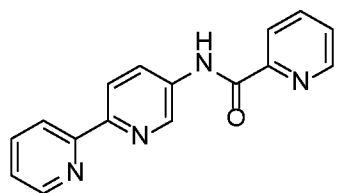
or a pharmaceutically acceptable salt thereof.

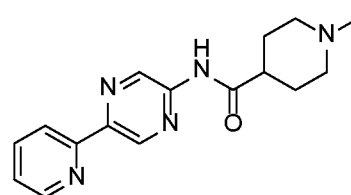
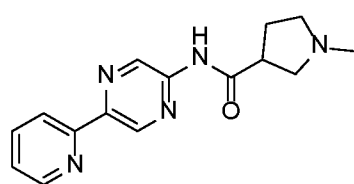
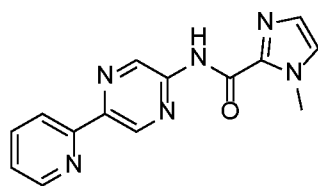
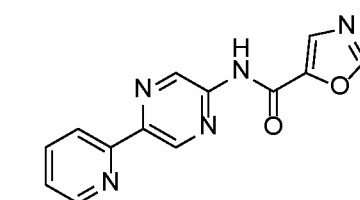
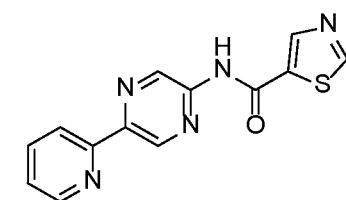
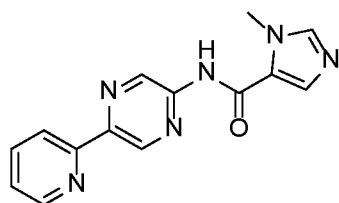
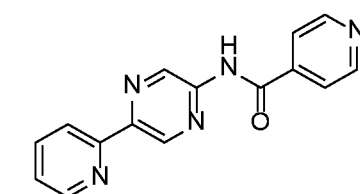
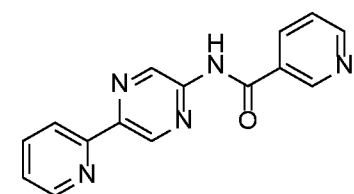
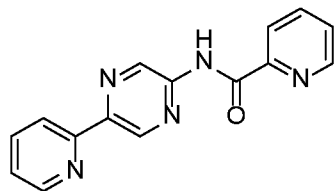
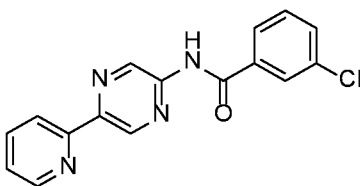
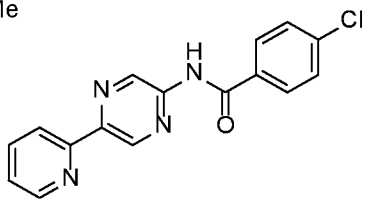
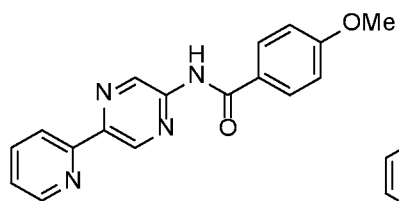
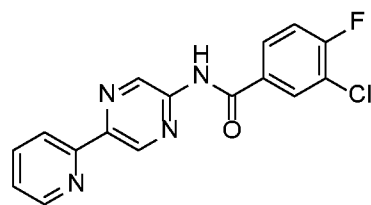
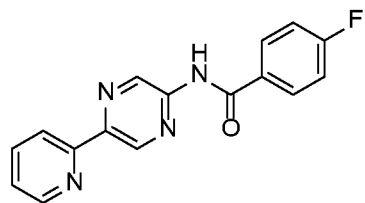
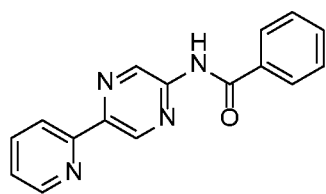
In some embodiments, the compound of Formula I is selected from the group consisting of:



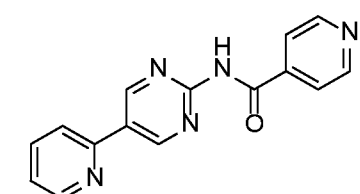
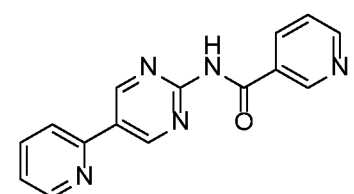
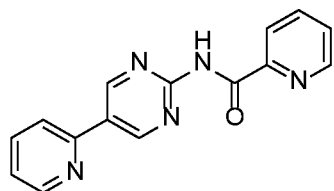
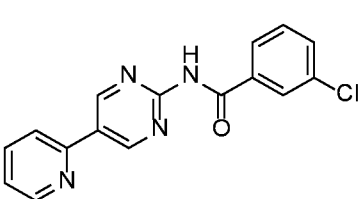
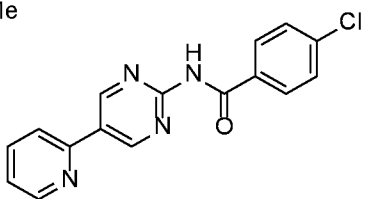
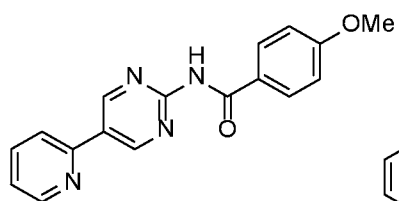
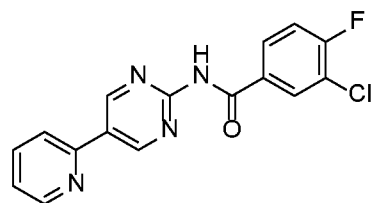
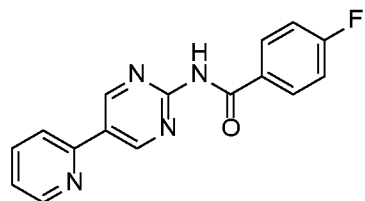
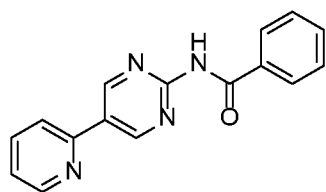


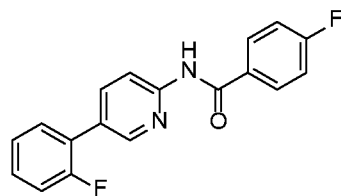
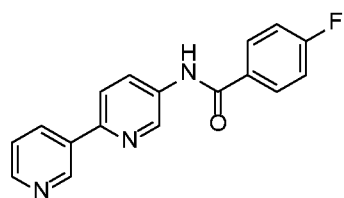
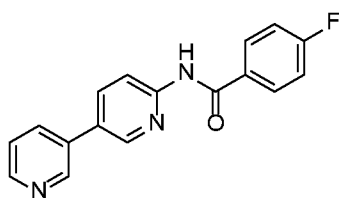
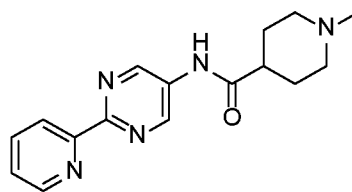
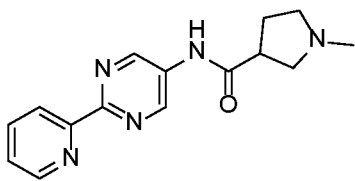
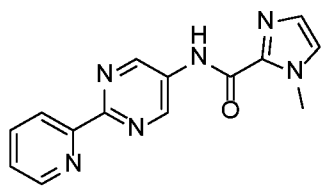
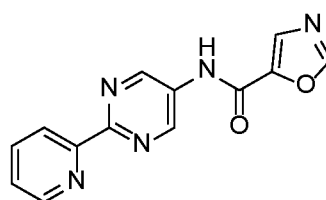
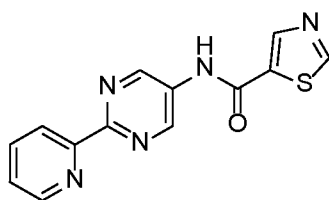
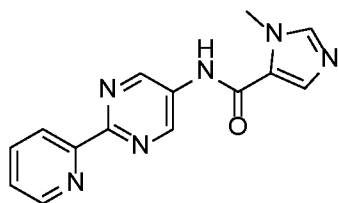
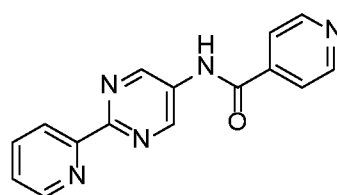
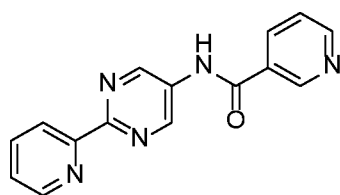
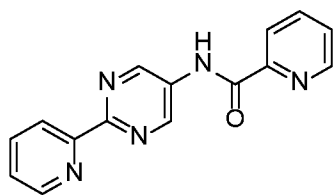
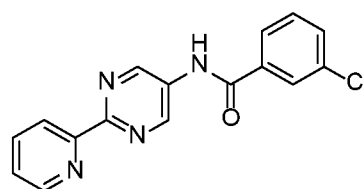
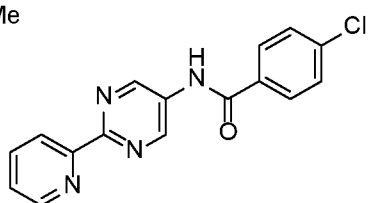
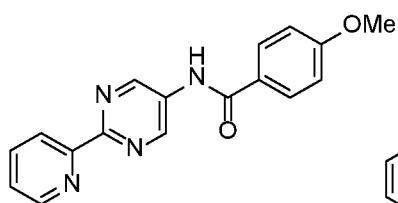
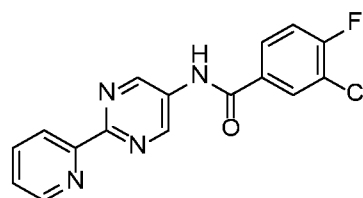
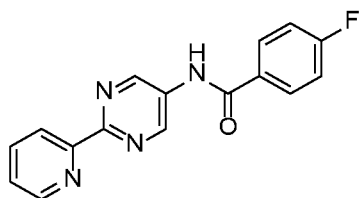
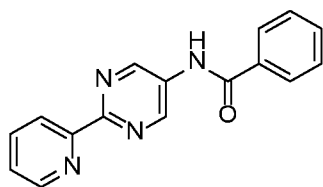
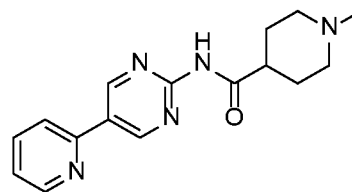
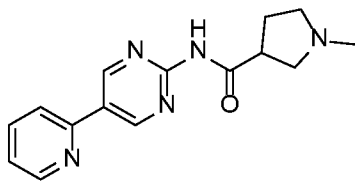
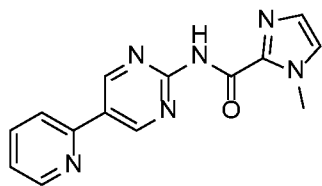
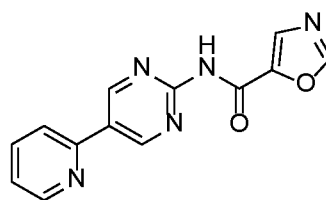
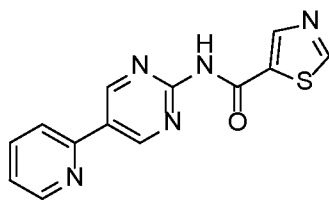
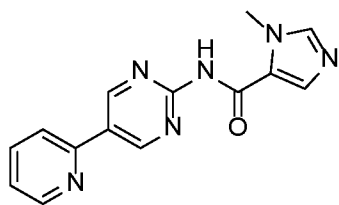
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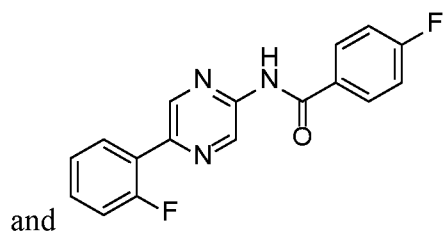
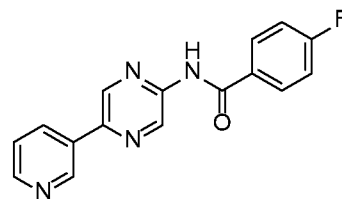
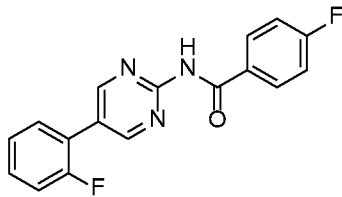
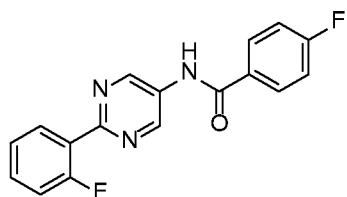
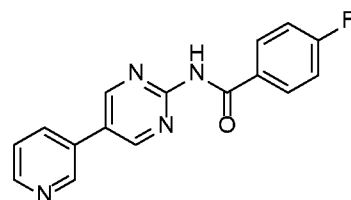
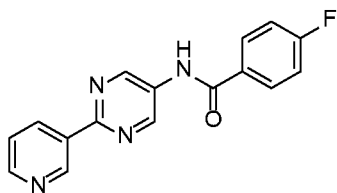
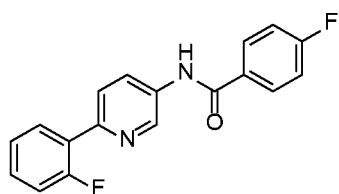




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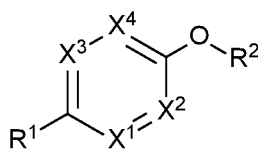


or a pharmaceutically acceptable salt thereof.

5

Compounds of Formula II

The present application further provides compounds of Formula II:



II

10 or a pharmaceutically acceptable salt thereof, wherein:

X^1 is CH or N;

X^2 is CH or N;

X^3 is CR^3 or N;

X^4 is CR^4 or N;

15

wherein the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R^1 is selected from the group consisting of 6-10 membered aryl and 5-10 membered heteroaryl, each of which is optionally substituted by 1, 2, 3, or 4 independently selected R^A groups;

20

R^2 is $-(CHR^E)_nR^5$;

R^5 is selected from the group consisting of OR^C , $NR^C R^D$, $C(O)NR^C R^D$, $C(O)OR^C$, C_{3-10} cycloalkyl, C_{6-10} aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the C_{3-10} cycloalkyl, C_{6-10} aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1, 2, 3, or 4 independently selected R^B groups;

5 R^E is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkoxy, and amino, wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^6 groups;

R^3 and R^4 are independently selected from H and C_{1-6} alkyl;

each R^A and R^B is independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^C R^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^C R^d$,
 10 $NR^C R^d$, $NR^C OR^d$, $NR^C C(O)R^b$, $NR^C C(O)OR^a$, $NR^C C(O)NR^C R^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^C R^d$,
 $NR^C C(=NR^e)NR^C R^d$, $NR^C S(O)R^b$, $NR^C S(O)_2 R^b$, $NR^C S(O)_2 NR^C R^d$, $S(O)R^b$, $S(O)NR^C R^d$, $S(O)_2 R^b$,
 and $S(O)_2 NR^C R^d$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{1-4} haloalkyl are optionally substituted with 1, 2, 3, or 4 independently selected R^6 groups;

R^C and R^D are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4}
 15 haloalkyl, C_{3-10} cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkylene, 4-10 membered heterocycloalkyl- C_{1-4} alkylene, 6-10 membered aryl- C_{1-4} alkylene, 5-10 membered heteroaryl- C_{1-4} alkylene; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{3-10} cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkylene, 4-10
 20 membered heterocycloalkyl- C_{1-4} alkylene, 6-10 membered aryl- C_{1-4} alkylene, and 5-10 membered heteroaryl- C_{1-4} alkylene are each optionally substituted with 1, 2, 3, or 4 independently selected R^6 groups; or

alternatively, any R^C and R^D attached to the same N atom, together with the N atom to which they are attached, form a 4-6 membered heterocycloalkyl group or a 5-6 membered
 25 heteroaryl group, each optionally substituted with 1, 2, or 3 independently selected R^6 groups;

each R^a , R^b , R^c , and R^d is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{3-10} cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{3-10} cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, and 4-10 membered
 30 heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 independently selected R^6 groups;

each R^e is independently selected from H, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, C_{1-6} alkylcarbonyl, C_{1-6} alkylaminosulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, aminosulfonyl, C_{1-6} alkylaminosulfonyl, and di(C_{1-6} alkyl)aminosulfonyl;

each R^6 is independently selected from OH, NO_2 , CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano- C_{1-3} alkyl, HO- C_{1-3} alkyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy carbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino; and

n is 0, 1, 2, 3, 4, or 5.

In some embodiments, R^1 is a 5-10 membered heteroaryl which is optionally substituted by 1, 2, 3, or 4 independently selected R^A groups. In some embodiments, R^1 is a 5-6 membered heteroaryl which is optionally substituted by 1 or 2 independently selected R^A groups. In some embodiments, R^1 is an unsubstituted 5-6 membered heteroaryl. In some embodiments, R^1 is unsubstituted pyridyl. In some embodiments, R^1 is 2-pyridyl.

In some embodiments, R^2 is selected from the group consisting of $-(\text{CH}_2)_nR^5$, $-(\text{CH}(\text{CH}_3))_nR^5$, and $-(\text{CH}_2\text{CH}(\text{NH}_2))_nR^5$. In some embodiments, R^2 is $-(\text{CH}_2)_nR^5$. In some embodiments, R^2 is $-(\text{CH}(\text{CH}_3))_nR^5$. In some embodiments, R^2 is $-(\text{CH}_2\text{CH}(\text{NH}_2))_nR^5$. In some embodiments, n is 0, 1 or 2. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2.

In some embodiments, R^3 is H.

In some embodiments, R^4 is H.

In some embodiments, R^3 and R^4 are each H.

In some embodiments, R^5 is selected from the group consisting of OR^C , NR^CR^D , $\text{C}(\text{O})\text{NR}^C\text{R}^D$, C_{6-10} aryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the C_{6-10} aryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1, 2, 3, or 4 independently selected R^B groups.

In some embodiments, R^5 is selected from the group consisting of OR^C , NR^CR^D , $\text{C}(\text{O})\text{NR}^C\text{R}^D$, phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the phenyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1 or 2 independently selected R^B groups.

In some embodiments, R^5 is selected from the group consisting of OCH_3 , $\text{N}(\text{CH}_3)_2$, $\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{NHCH}_3$, $\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $\text{C}(\text{O})\text{N}(\text{CH}_2\text{CH}_3)_2$, phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the phenyl, 4-6 membered

heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1 or 2 independently selected R^B groups.

In some embodiments, R^5 is selected from the group consisting of OCH_3 , $N(CH_3)_2$, $C(O)NH_2$, $C(O)NHCH_3$, $C(O)N(CH_3)_2$, $C(O)N(CH_2CH_3)_2$, phenyl, cyclopentyl, cyclohexyl, oxazolyl, pyridyl, thiazolyl, imidazolyl, pyrazolyl, piperidinyl, piperidinonyl, pyrrolidinyl, pyrrolidinonyl, benzoimidazolyl, and quinolinyl, wherein the phenyl, cyclopentyl, cyclohexyl, oxazolyl, pyridyl, thiazolyl, imidazolyl, pyrazolyl, piperidinyl, piperidinonyl, pyrrolidinyl, pyrrolidinonyl, benzoimidazolyl, and quinolinyl are each optionally substituted by 1 or 2 independently selected R^B groups.

In some embodiments, each R^B is independently selected from the group consisting of C_{1-6} alkyl and $NR^C R^D$. In some embodiments, each R^B is independently selected from the group consisting of C_{1-3} alkyl and $N(C_{1-3} \text{ alkyl})_2$. In some embodiments, each R^B is independently selected from the group consisting of CH_3 and $N(CH_3)_2$.

In some embodiments, the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring.

In some embodiments, the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyrazine ring.

In some embodiments, the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyrimidine ring.

In some embodiments:

the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R^1 is a 5-6 membered heteroaryl which is optionally substituted by 1 or 2 independently selected R^A groups;

R^2 is selected from the group consisting of $-(CH_2)_n R^5$, $-(CH(CH_3))_n R^5$, and $-(CH_2CH(NH_2))_n R^5$;

R^3 is H;

R^4 is H;

R^5 is selected from the group consisting of OR^C , $NR^C R^D$, $C(O)NR^C R^D$, C_{6-10} aryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the C_{6-10} aryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1, 2, 3, or 4 independently selected R^B groups;

each R^B is independently selected from the group consisting of C_{1-6} alkyl and $NR^C R^D$, and n is 0, 1, 2, 3, 4, or 5.

In some embodiments:

the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R^1 is an unsubstituted 5-6 membered heteroaryl;

R^2 is selected from the group consisting of $-(CH_2)_nR^5$, $-(CH(CH_3))_nR^5$, and $-(CH_2CH(NH_2))_nR^5$;

R^3 is H;

5 R^4 is H;

R^5 is selected from the group consisting of OR^C , $NR^C R^D$, $C(O)NR^C R^D$, phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the phenyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1 or 2 independently selected R^B groups;

10 each R^B is independently selected from the group consisting of C_{1-6} alkyl and $NR^C R^d$, and n is 0, 1, or 2.

In some embodiments:

the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

15 R^1 is pyridyl;

R^2 is selected from the group consisting of $-(CH_2)_nR^5$, $-(CH(CH_3))_nR^5$, and $-(CH_2CH(NH_2))_nR^5$;

R^3 is H;

R^4 is H;

20 R^5 is selected from the group consisting of OCH_3 , $N(CH_3)_2$, $C(O)N(CH_3)_2$, phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the phenyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1 or 2 independently selected R^B groups;

25 each R^B is independently is selected from the group consisting of C_{1-3} alkyl and $N(C_{1-3} alkyl)_2$; and

n is 0, 1, or 2.

In some embodiments:

the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

30 R^1 is pyridyl;

R^2 is selected from the group consisting of $-(CH_2)_nR^5$, $-(CH(CH_3))_nR^5$, and $-(CH_2CH(NH_2))_nR^5$;

R^3 is H;

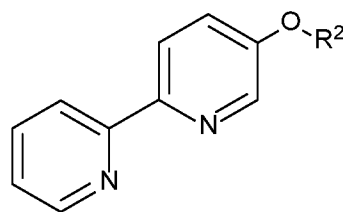
R^4 is H;

R^5 is selected from the group consisting of OCH_3 , $N(CH_3)_2$, $C(O)N(CH_3)_2$, phenyl, cyclopentyl, cyclohexyl, oxazolyl, pyridyl, thiazolyl, imidazolyl, piperidinyl, piperidinonyl, pyrrolidinyl, pyrrolidinonyl, and quinolinyl, wherein the phenyl, cyclopentyl, cyclohexyl, oxazolyl, pyridyl, thiazolyl, pyrazolyl, piperidinyl, piperidinonyl, pyrrolidinyl, pyrrolidinonyl, and quinolinyl are each optionally substituted by 1 or 2 independently selected R^B groups;

each R^B is independently is selected from the group consisting of C_{1-3} alkyl and $N(C_{1-3} \text{ alkyl})_2$; and

n is 0, 1, or 2.

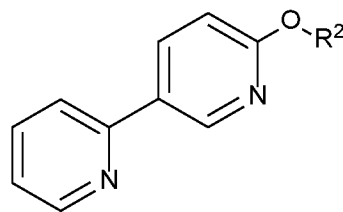
In some embodiments, the compound of Formula II is a compound of Formula IIa:



IIa

or a pharmaceutically acceptable salt thereof.

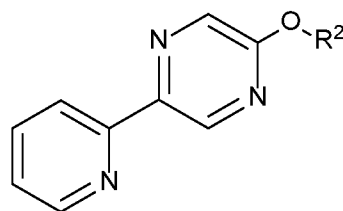
In some embodiments, the compound of Formula II is a compound of Formula IIb:



IIb

or a pharmaceutically acceptable salt thereof.

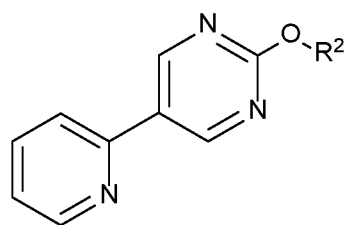
In some embodiments, the compound of Formula II is a compound of Formula IIc:



IIc

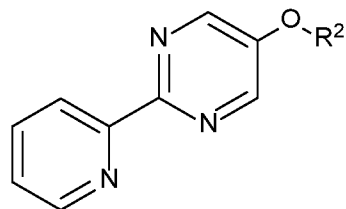
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula II is a compound of Formula IId:

**IIId**

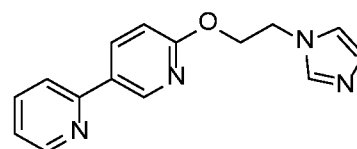
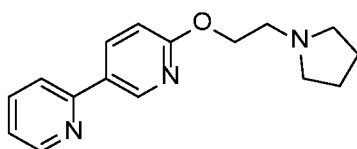
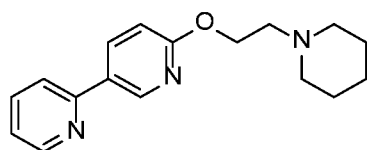
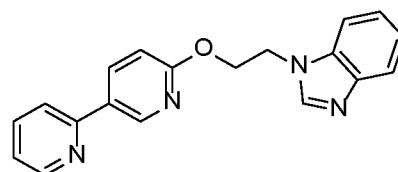
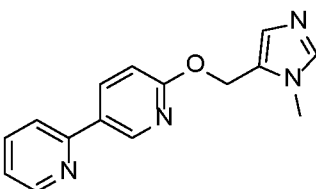
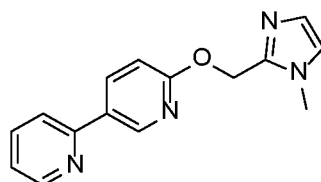
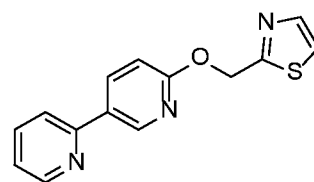
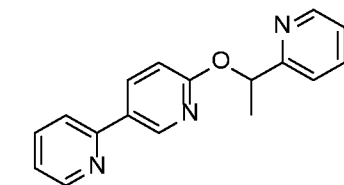
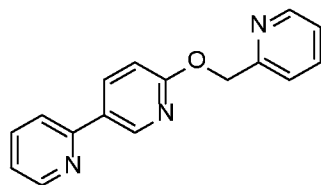
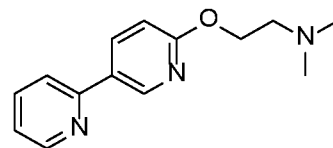
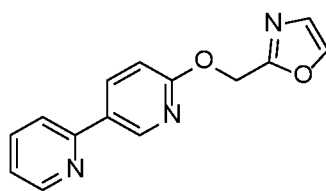
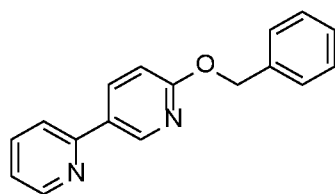
or a pharmaceutically acceptable salt thereof.

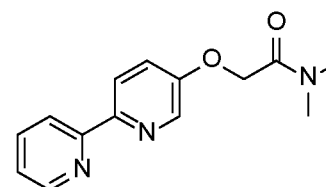
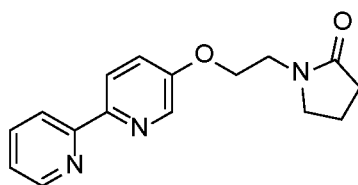
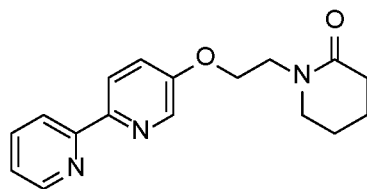
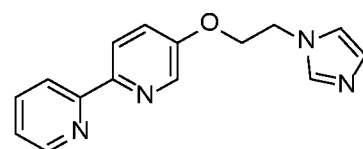
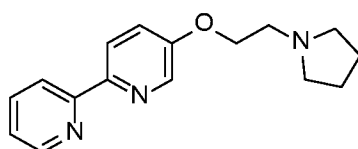
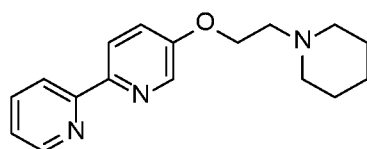
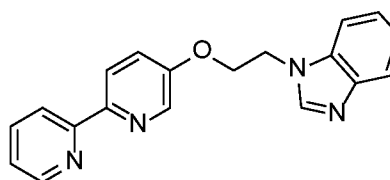
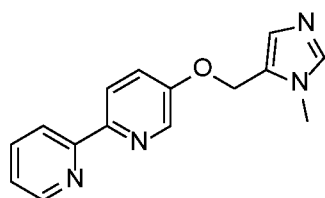
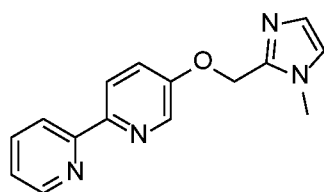
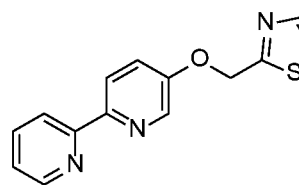
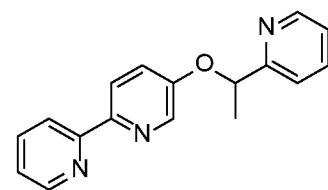
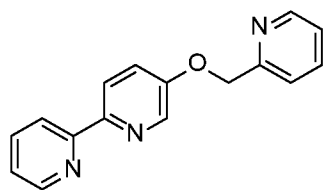
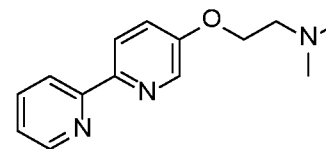
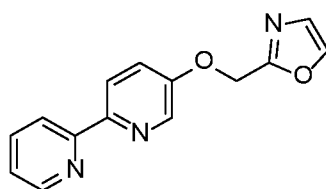
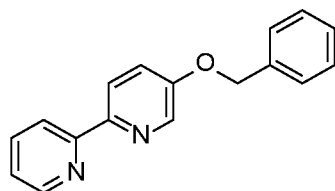
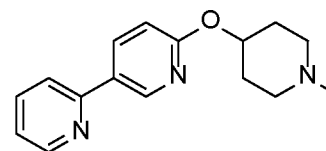
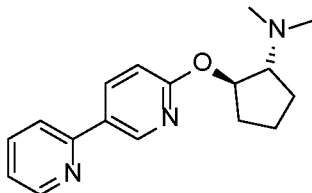
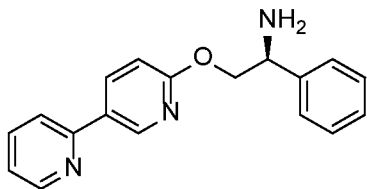
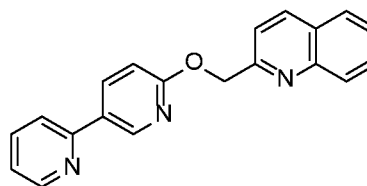
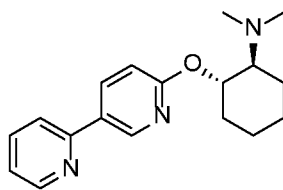
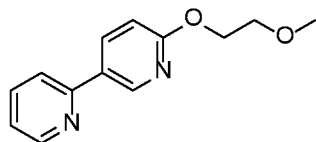
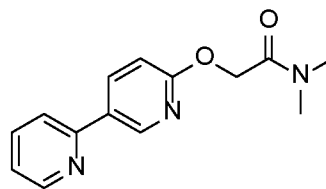
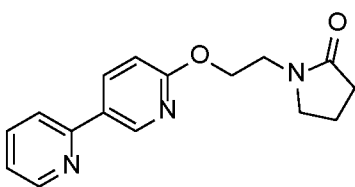
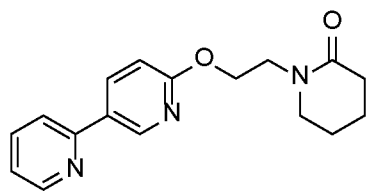
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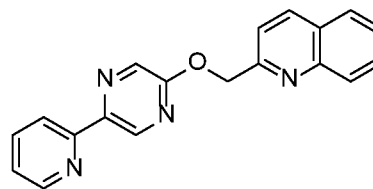
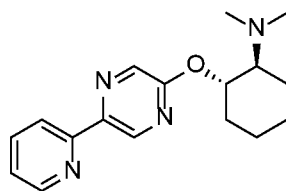
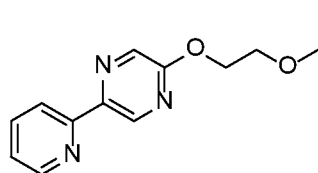
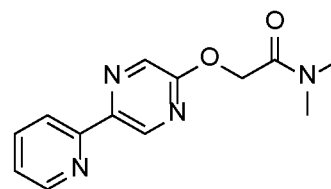
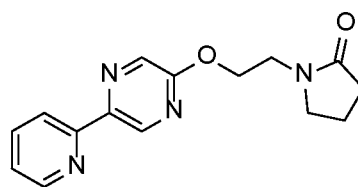
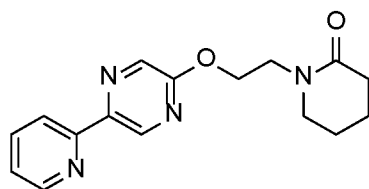
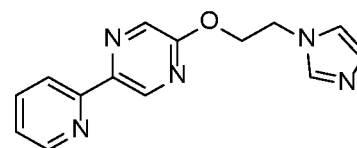
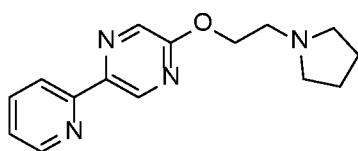
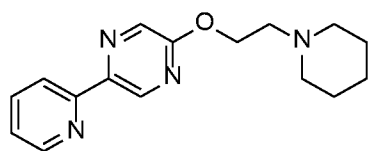
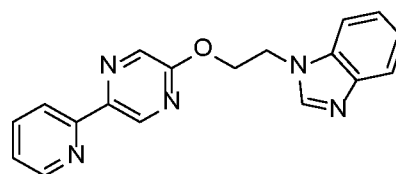
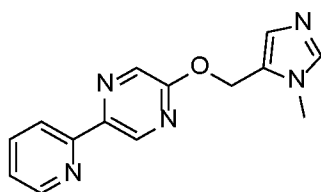
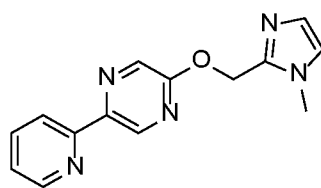
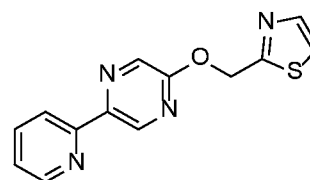
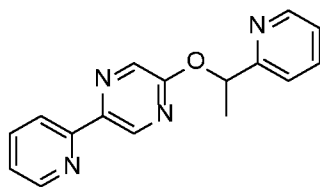
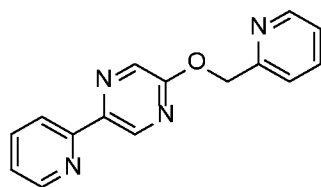
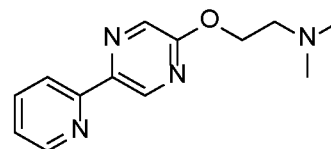
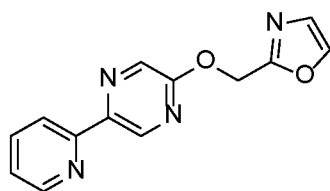
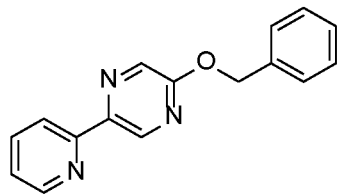
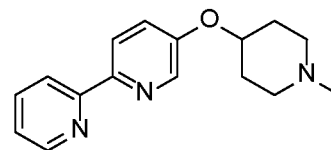
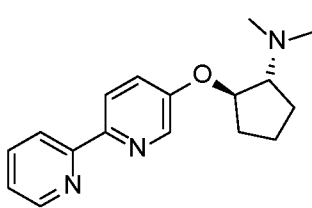
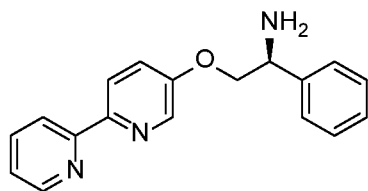
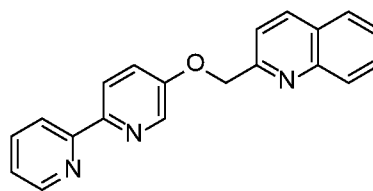
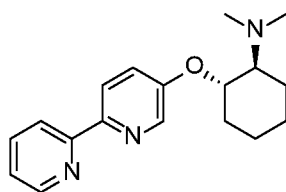
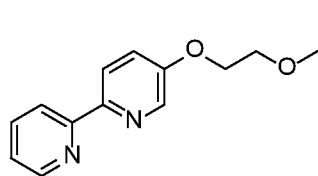
**IIe**

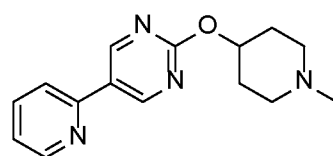
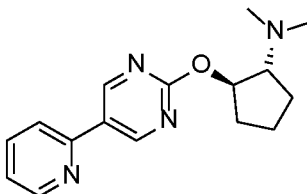
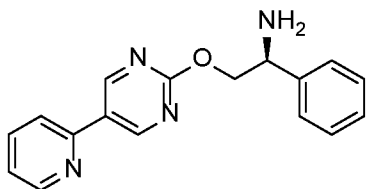
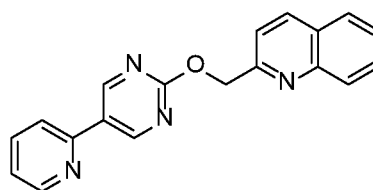
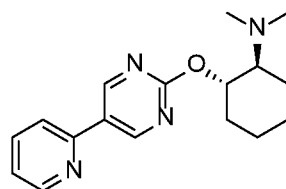
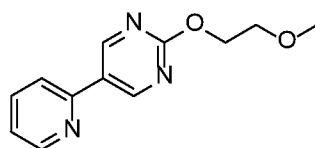
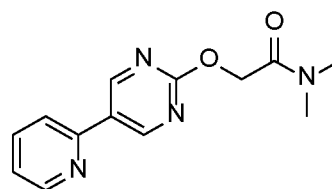
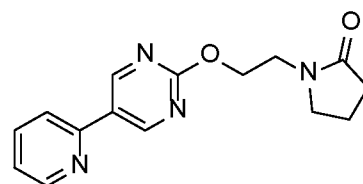
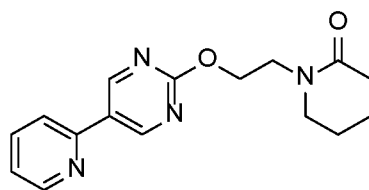
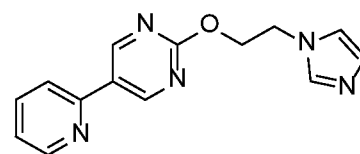
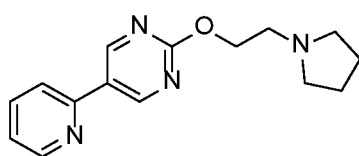
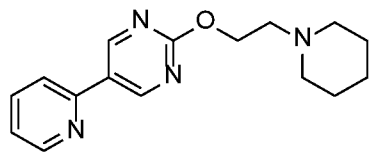
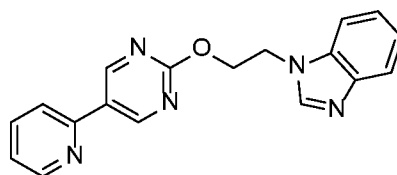
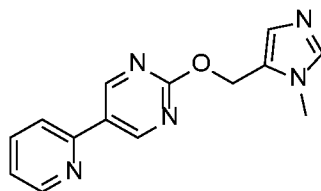
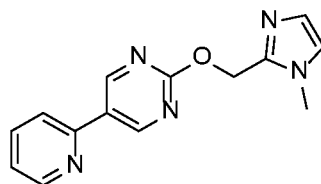
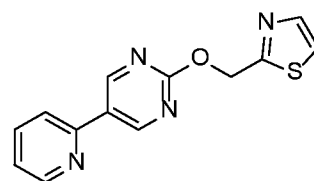
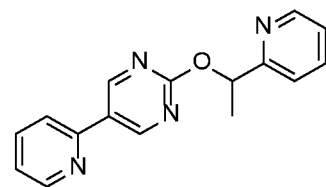
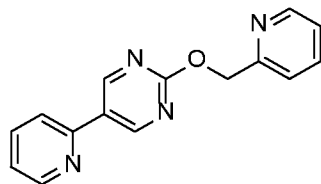
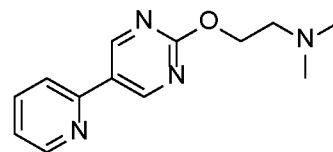
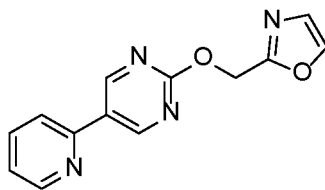
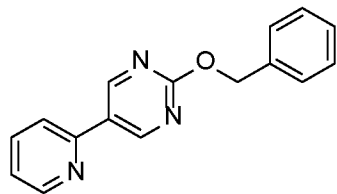
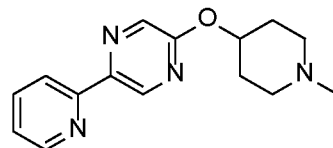
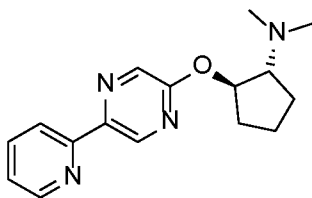
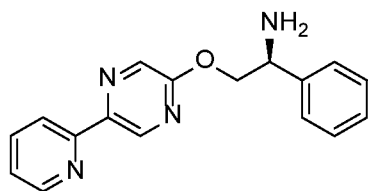
or a pharmaceutically acceptable salt thereof.

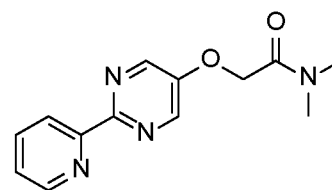
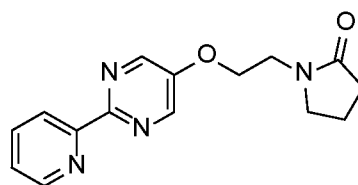
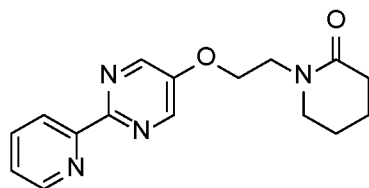
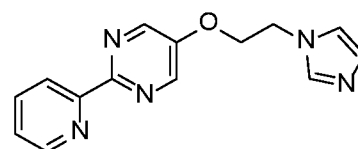
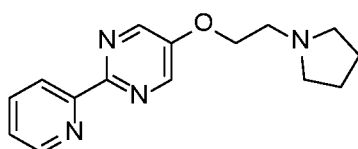
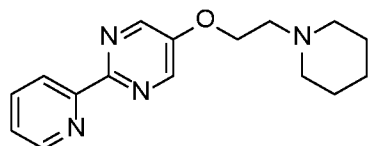
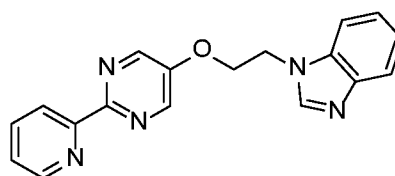
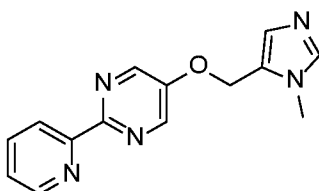
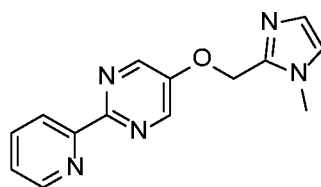
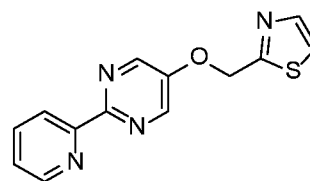
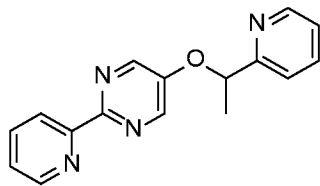
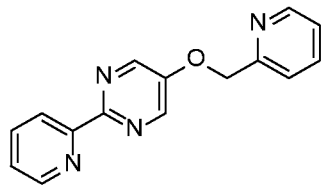
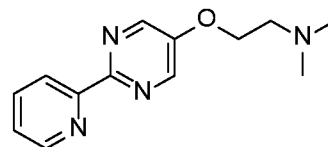
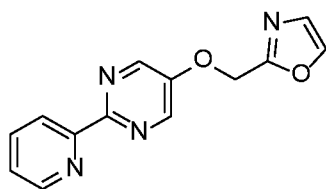
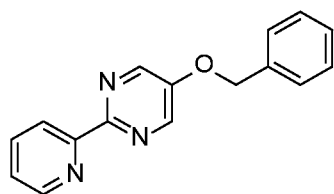
In some embodiments, the compound of Formula II is selected from the group consisting of:



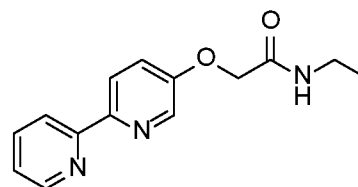
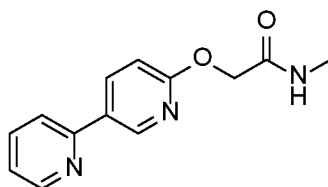
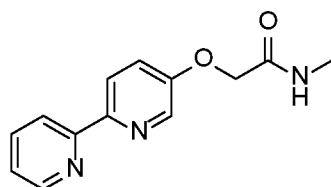
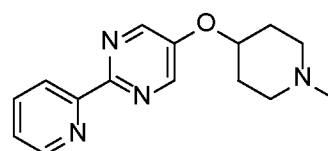
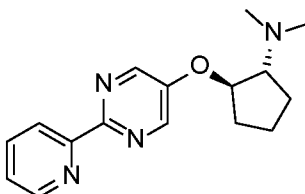
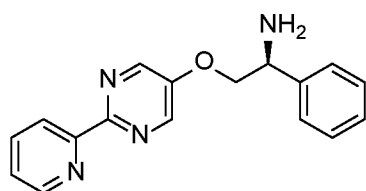
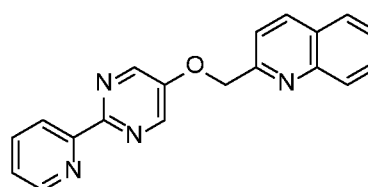
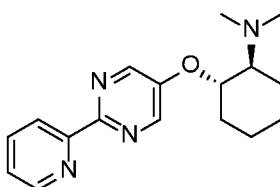
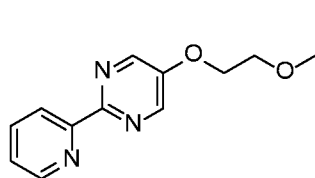


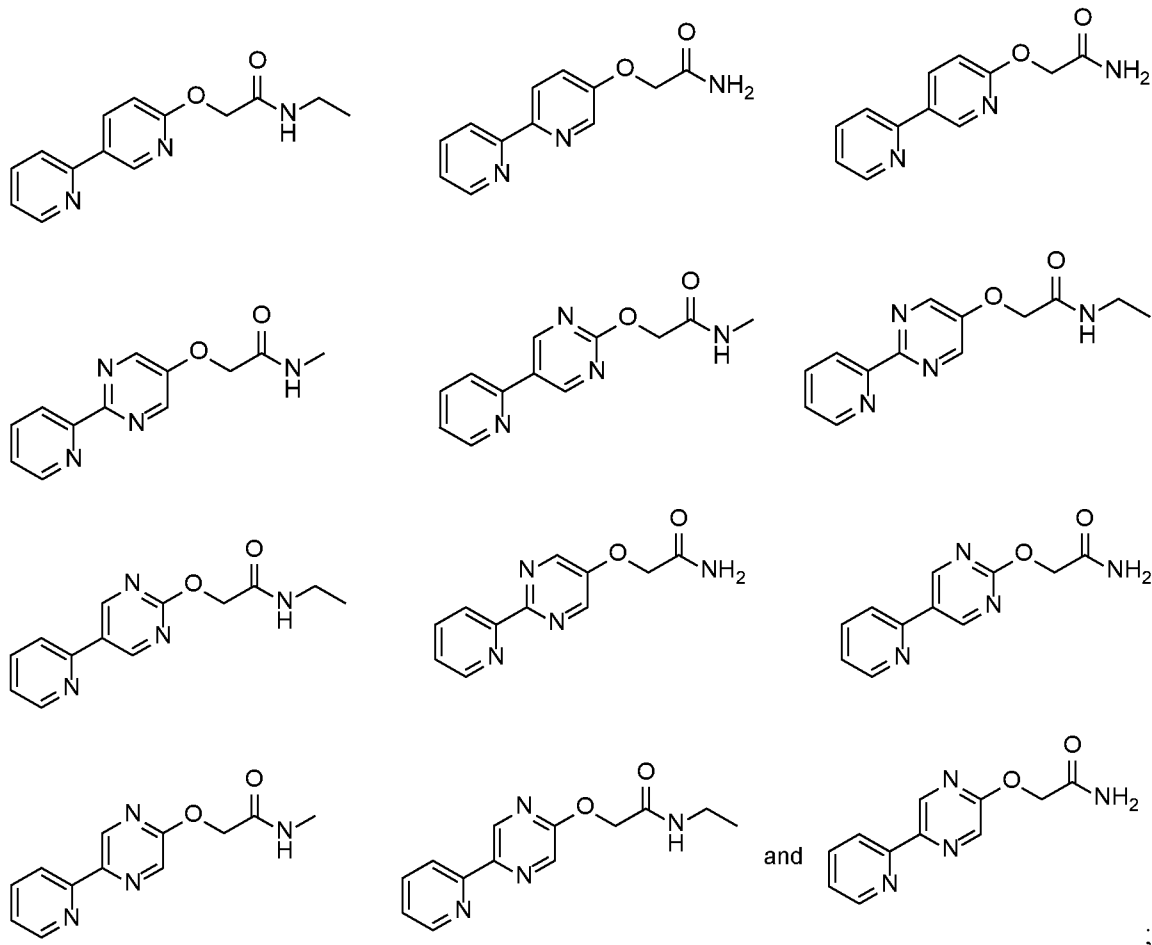






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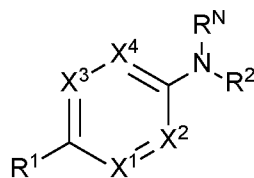




5 or a pharmaceutically acceptable salt thereof.

Compounds of Formula III

The present application further provides compounds of Formula III:



III

10 or a pharmaceutically acceptable salt thereof, wherein:

X^1 is CH or N;

X^2 is CH or N;

X^3 is CR^3 or N;

15 X^4 is CR^4 or N;

wherein the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R^N is selected from the group consisting of H, C_{1-6} alkyl, and $C(O)R^{N1}$;

R^{N1} is a C_{6-10} aryl which is optionally substituted by 1, 2, 3, or 4 independently selected halo groups;

R^1 is selected from the group consisting of 6-10 membered aryl and 5-10 membered heteroaryl, each of which is optionally substituted by 1, 2, 3, or 4 independently selected R^A groups;

R^2 is $-(CHR^E)_nR^5$;

R^5 is selected from the group consisting of $NR^C R^D$, $C(O)NR^C R^D$, $C(O)OR^C$, C_{3-10} cycloalkyl, C_{6-10} aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the C_{3-10} cycloalkyl, C_{6-10} aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1, 2, 3, or 4 independently selected R^B groups;

R^E is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkoxy, and amino, wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^6 groups;

R^3 and R^4 are independently selected from H and C_{1-6} alkyl;

each R^A and R^B is independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^c R^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^c R^d$, $NR^c R^d$, $NR^c OR^d$, $NR^c C(O)R^b$, $NR^c C(O)OR^a$, $NR^c C(O)NR^c R^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^c R^d$, $NR^c C(=NR^e)NR^c R^d$, $NR^c S(O)R^b$, $NR^c S(O)_2 R^b$, $NR^c S(O)_2 NR^c R^d$, $S(O)R^b$, $S(O)NR^c R^d$, $S(O)_2 R^b$, and $S(O)_2 NR^c R^d$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{1-4} haloalkyl are optionally substituted with 1, 2, 3, or 4 independently selected R^6 groups;

R^C and R^D are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{3-10} cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkylene, 4-10 membered heterocycloalkyl- C_{1-4} alkylene, 6-10 membered aryl- C_{1-4} alkylene, 5-10 membered heteroaryl- C_{1-4} alkylene; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{3-10} cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkylene, 4-10 membered heterocycloalkyl- C_{1-4} alkylene, 6-10 membered aryl- C_{1-4} alkylene, and 5-10 membered heteroaryl- C_{1-4} alkylene are each optionally substituted with 1, 2, 3, or 4 independently selected R^6 groups; or

alternatively, any R^C and R^D attached to the same N atom, together with the N atom to which they are attached, form a 4-6 membered heterocycloalkyl group or a 5-6 membered heteroaryl group, each optionally substituted with 1, 2, or 3 independently selected R^6 groups;

each R^a , R^b , R^c , and R^d is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{3-10} cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl,

C₃₋₁₀ cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 independently selected R⁶ groups;

each R^e is independently selected from H, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkylaminosulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, and di(C₁₋₆ alkyl)aminosulfonyl;

each R⁶ is independently selected from OH, NO₂, CN, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, cyano-C₁₋₃ alkyl, HO-C₁₋₃ alkyl, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, thio, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, carboxy, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, di(C₁₋₆ alkyl)aminosulfonyl, aminosulfonylamino, C₁₋₆ alkylaminosulfonylamino, di(C₁₋₆ alkyl)aminosulfonylamino, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, and di(C₁₋₆ alkyl)aminocarbonylamino; and

n is 0, 1, 2, 3, 4, or 5.

In some embodiments, R^N is selected from the group consisting of H, C₁₋₃ alkyl, and C(O)-phenyl. In some embodiments, R^N is selected from the group consisting of H, CH₃, and C(O)-phenyl. In some embodiments, R^N is H.

In some embodiments, R¹ is a 5-10 membered heteroaryl which is optionally substituted by 1, 2, 3, or 4 independently selected R^A groups. In some embodiments, R¹ is a 5-6 membered heteroaryl which is optionally substituted by 1 or 2 independently selected R^A groups. In some embodiments, R¹ is an unsubstituted 5-6 membered heteroaryl. In some embodiments, R¹ is unsubstituted pyridyl. In some embodiments, R¹ is 2-pyridyl.

In some embodiments, R² is -(CH₂)_nR⁵. In some embodiments, n is 1, 2, or 3. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3.

In some embodiments, R³ is H.

In some embodiments, R⁴ is H.

In some embodiments, R³ and R⁴ are each H.

In some embodiments, R⁵ is selected from the group consisting of NR^CR^D, C₆₋₁₀ aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the C₆₋₁₀ aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1, 2, 3, or 4 independently selected R^B groups. In some embodiments, R⁵ is selected from the group consisting of NR^CR^D, phenyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl, wherein the phenyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl are each

optionally substituted by 1 or 2 independently selected R^B groups. In some embodiments, R^5 is selected from the group consisting of $N(C_{1-3} \text{ alkyl})_2$, phenyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl. In some embodiments, R^5 is selected from the group consisting of $N(CH_3)_2$, phenyl, oxazolyl, piperidinyl, and pyrrolidinyl.

- 5 In some embodiments:
the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;
 R^N is selected from the group consisting of H, C_{1-3} alkyl, and C(O)-phenyl;
 R^1 is a 5-6 membered heteroaryl which is optionally substituted by 1 or 2 independently
10 selected R^A groups;
 R^2 is $-(CH_2)_nR^5$;
 R^3 is H;
 R^4 is H;
 R^5 is selected from the group consisting of $NR^C R^D$, C_{6-10} aryl, 4-10 membered
15 heterocycloalkyl, and 5-10 membered heteroaryl, wherein the C_{6-10} aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1, 2, 3, or 4 independently selected R^B groups; and
n is 1, 2, or 3.
In some embodiments:
20 the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;
 R^N is selected from the group consisting of H, C_{1-3} alkyl, and C(O)-phenyl;
 R^1 is an unsubstituted 5-6 membered heteroaryl;
 R^2 is $-(CH_2)_nR^5$;
25 R^3 is H;
 R^4 is H;
 R^5 is selected from the group consisting of $NR^C R^D$, phenyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl, wherein the phenyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl are each optionally substituted by 1 or 2
30 independently selected R^B groups; and
n is 1, 2, or 3.
In some embodiments:
the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R^N is selected from the group consisting of H, C_{1-3} alkyl, and C(O)-phenyl;

R^1 is pyridyl;

R^2 is $-(CH_2)_nR^5$;

R^3 is H;

R^4 is H;

R^5 is selected from the group consisting of $N(C_{1-3} \text{ alkyl})_2$, phenyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl; and

n is 1, 2, or 3.

In some embodiments:

the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R^N is selected from the group consisting of H, C_{1-3} alkyl, and C(O)-phenyl;

R^1 is pyridyl;

R^2 is $-(CH_2)_nR^5$;

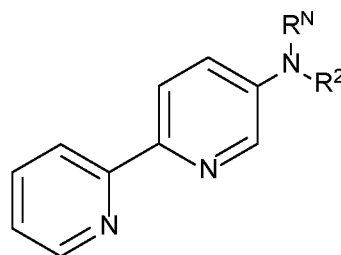
R^3 is H;

R^4 is H;

R^5 is selected from the group consisting of $N(CH_3)_2$, phenyl, oxazolyl, piperidinyl, and pyrrolidinyl; and

n is 1, 2, or 3.

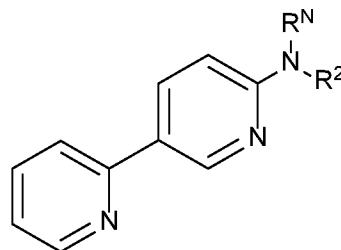
In some embodiments, the compound of Formula III is a compound of Formula IIIa:



IIIa

or a pharmaceutically acceptable salt thereof.

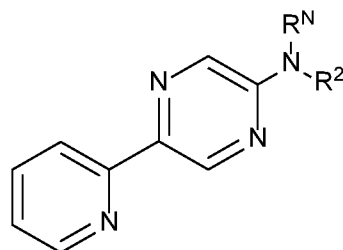
In some embodiments, the compound of Formula III is a compound of Formula IIIb:



IIIb

or a pharmaceutically acceptable salt thereof.

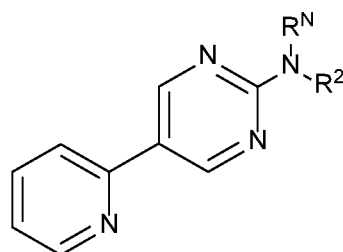
In some embodiments, the compound of Formula III is a compound of Formula IIIc:



IIIc

5 or a pharmaceutically acceptable salt thereof.

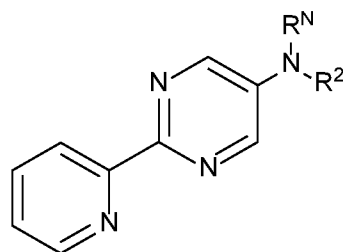
In some embodiments, the compound of Formula III is a compound of Formula IIId:



IIIId

or a pharmaceutically acceptable salt thereof.

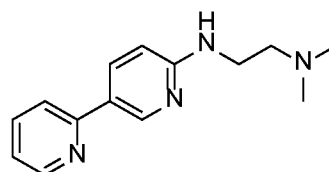
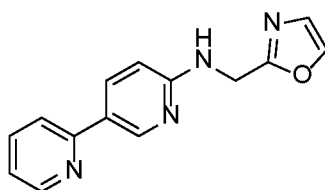
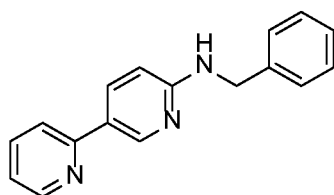
10 In some embodiments, the compound of Formula III is a compound of Formula IIIe:

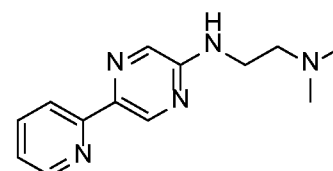
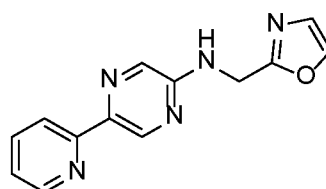
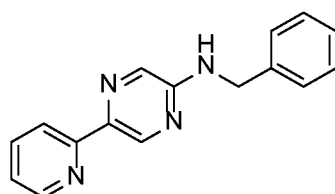
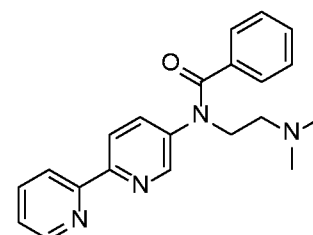
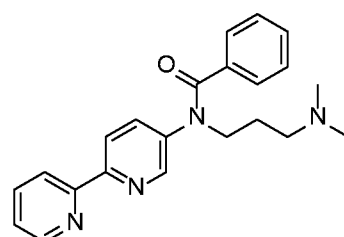
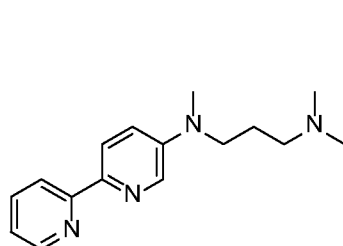
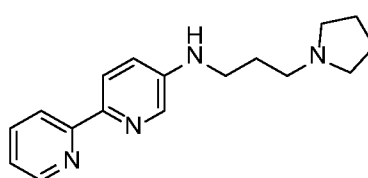
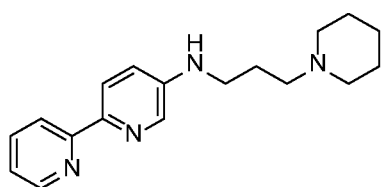
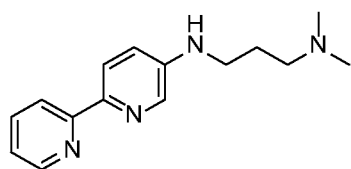
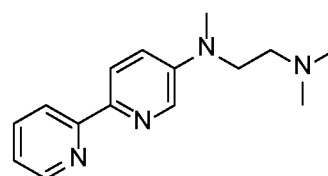
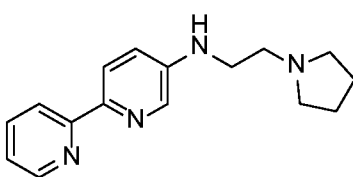
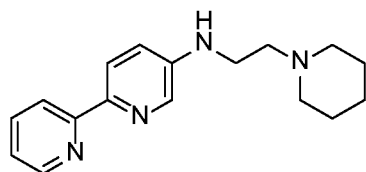
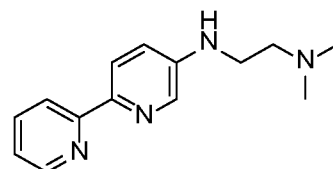
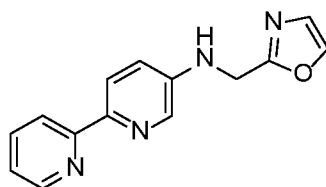
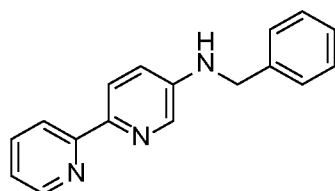
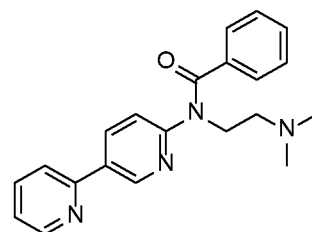
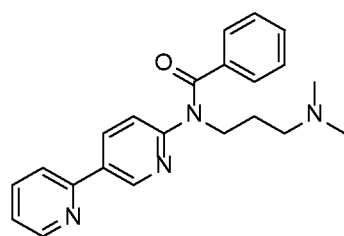
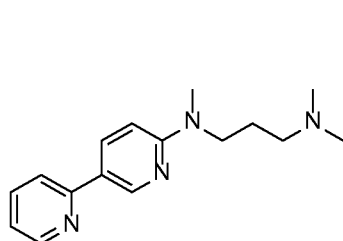
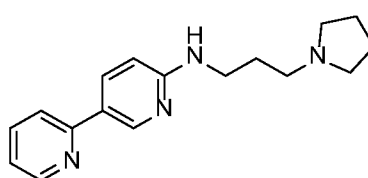
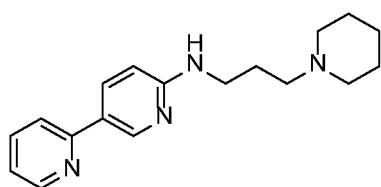
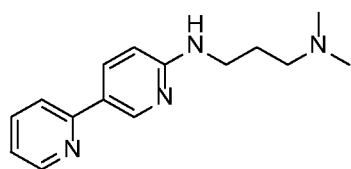
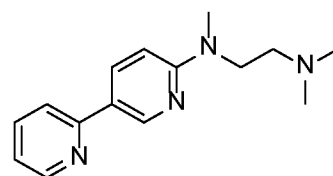
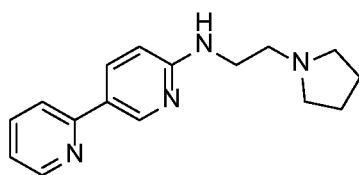
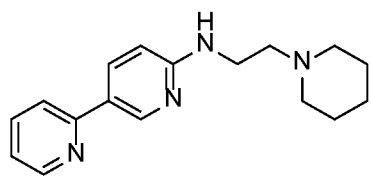


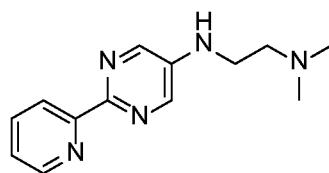
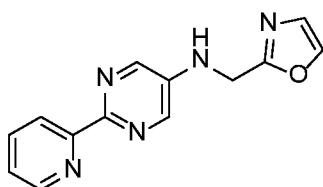
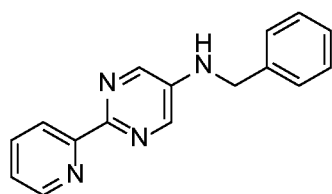
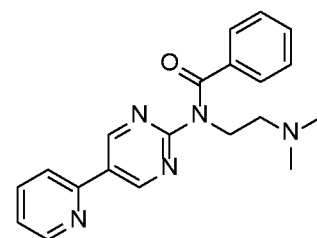
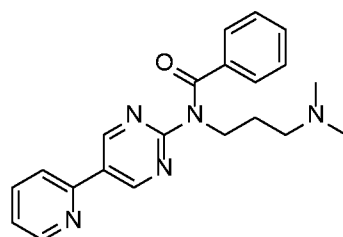
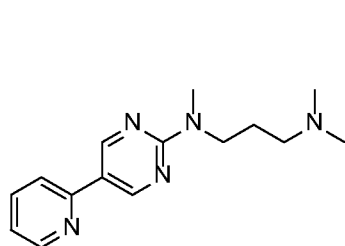
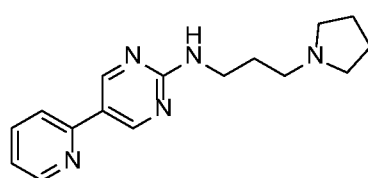
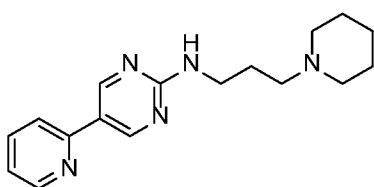
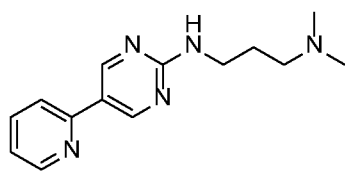
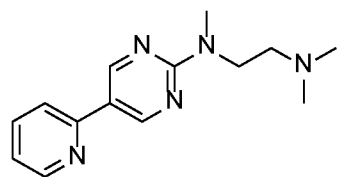
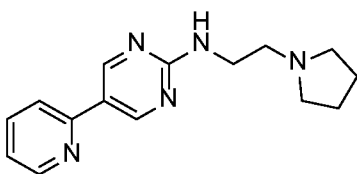
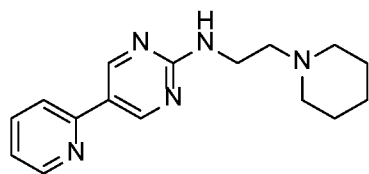
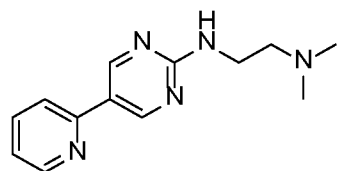
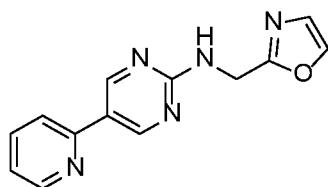
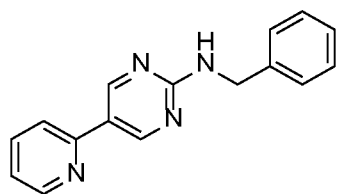
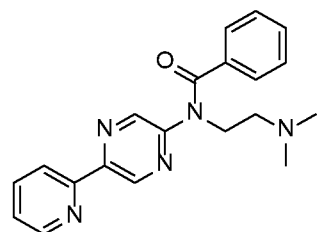
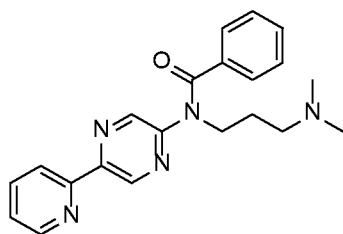
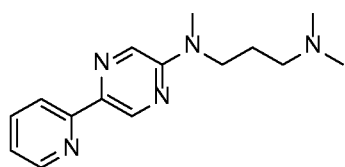
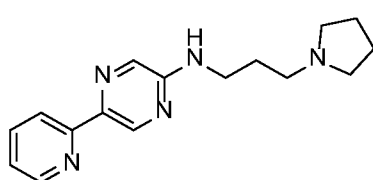
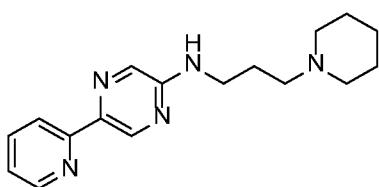
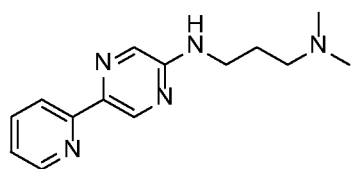
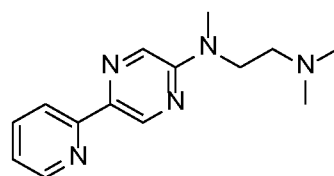
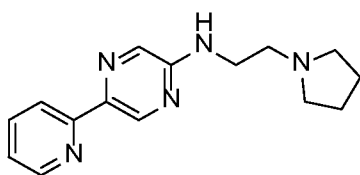
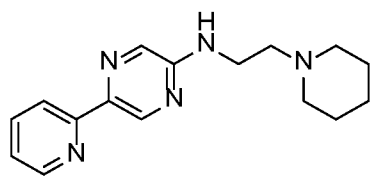
IIIe

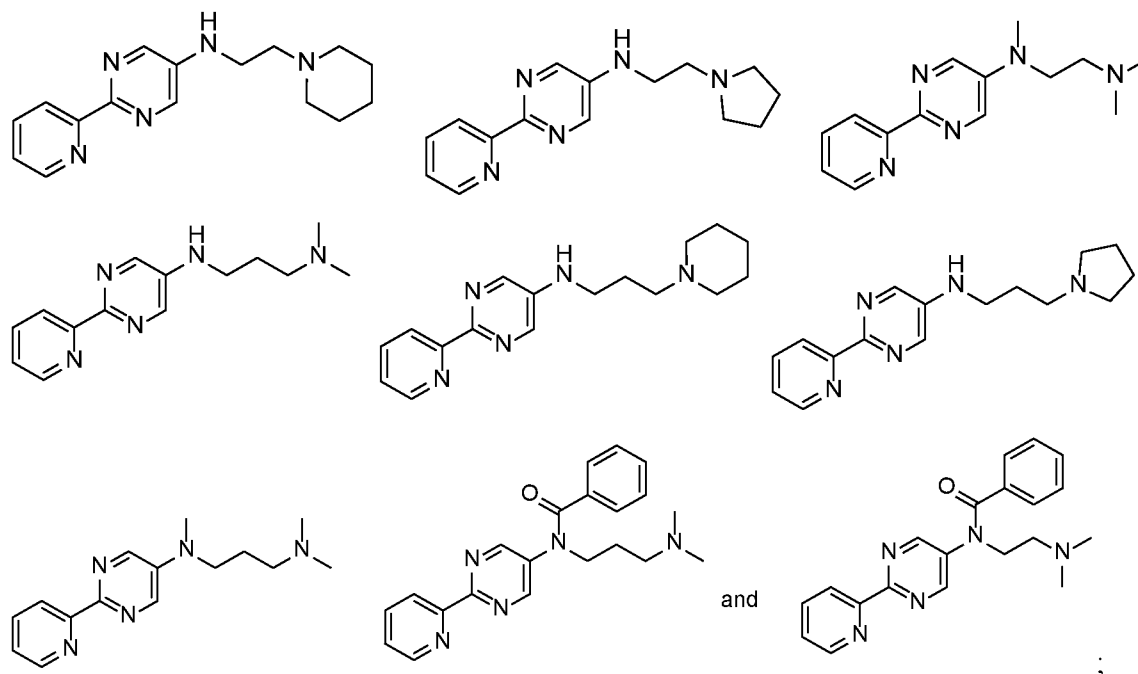
or a pharmaceutically acceptable salt thereof.

15 In some embodiments, the compound of Formula III is selected from the group consisting of:









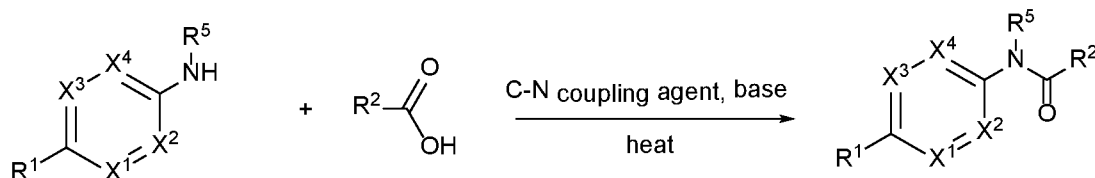
or a pharmaceutically acceptable salt thereof.

5

Synthesis

Compounds of Formula I can be prepared, for example, according to the procedure shown in Scheme 1. An amine-substituted pyridine, pyrimidine, or pyrazine (**i**) can be reacted with carboxylic acid (**ii**) in the presence of a C-N coupling agent and a base (*e.g.*, 1-
 10 [bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) and *N,N*-diisopropylethylamine (DIPEA)) to form the amide-substituted pyridine, pyrimidine, or pyrazine analog (**iii**).

Scheme 1A.

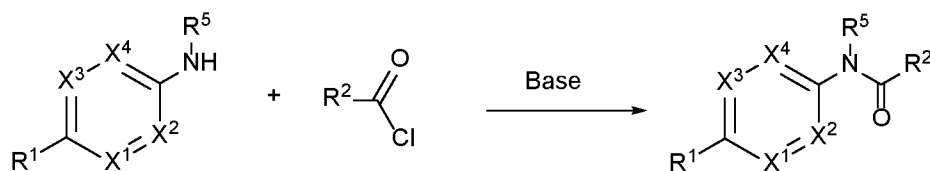


15

Compounds of Formula I can be prepared, for example, according to the procedure shown in Scheme 1B. An amine substituted pyridine, pyrimidine, or pyrazine (**i**) can be reacted with an appropriately substituted acid chloride (**ii**) in the presence of base (*e.g.*, a mixture of 4-dimethylaminopyridine and triethylamine) to form the amide-substituted pyridine, pyrimidine, or pyrazine analog (**iii**).

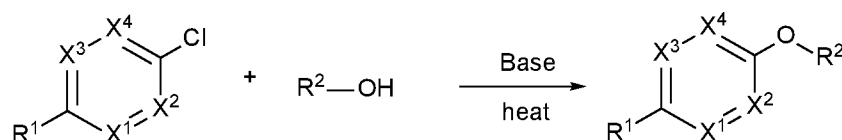
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Scheme 1B.



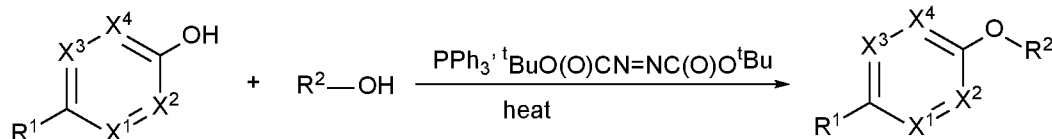
Compounds of Formula II can be prepared, for example, according to the procedure shown in Scheme 2A. A chloro substituted pyridine, pyrimidine, or pyrazine (i) can be reacted with an appropriately substituted alcohol (ii) in the presence of base (e.g., sodium *tert*-butoxide) to form the ether-substituted pyridine, pyrimidine, or pyrazine analog (iii).

Scheme 2A.



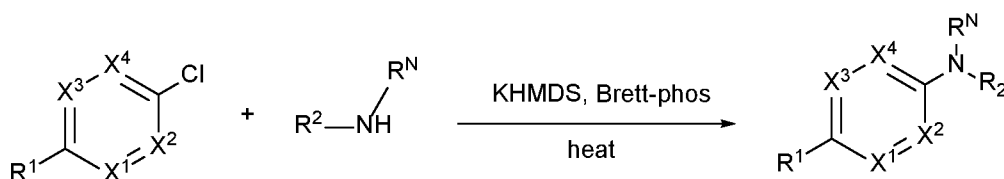
Compounds of Formula II can also be prepared, for example, according to the procedure shown in Scheme 2B. A hydroxy substituted pyridine, pyrimidine, or pyrazine (i) can be reacted with an appropriately substituted alcohol (ii) in the presence of triphenylphosphine (PPh₃) and ^tBuO(O)CN=NC(O)O^tBu to form the ether-substituted pyridine, pyrimidine, or pyrazine analog (iii).

Scheme 2B.



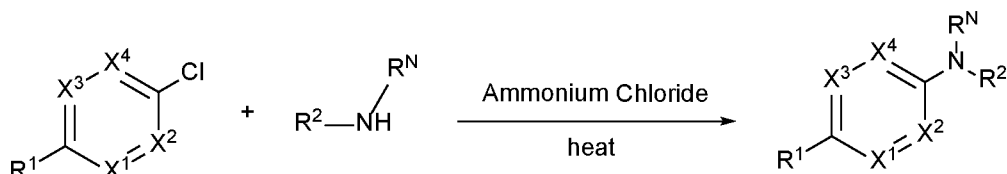
Compounds of Formula III can be prepared, for example, according to the procedure shown in Scheme 3A. A chloro-substituted pyridine, pyrimidine, or pyrazine (i) can be reacted with an appropriately substituted amine (ii) in the presence of KHMDS and Brett-phos to form the amine-substituted pyridine, pyrimidine, or pyrazine analog (iii).

Scheme 3A.



Compounds of Formula III can also be prepared, for example, according to the procedure shown in Scheme 3B. A chloro-substituted pyridine, pyrimidine, or pyrazine (i) can be reacted with an appropriately substituted amine (ii) in the presence of ammonium chloride to form the amine-substituted pyridine, pyrimidine, or pyrazine analog (iii).

Scheme 3B.



It will be appreciated by one skilled in the art that the processes described are not the exclusive means by which compounds provided herein may be synthesized and that a broad repertoire of synthetic organic reactions is available to be potentially employed in synthesizing compounds provided herein. The person skilled in the art knows how to select and implement appropriate synthetic routes. Suitable synthetic methods of starting materials, intermediates and products may be identified by reference to the literature, including reference sources such as: *Advances in Heterocyclic Chemistry*, Vols. 1-107 (Elsevier, 1963-2012); *Journal of Heterocyclic Chemistry* Vols. 1-49 (Journal of Heterocyclic Chemistry, 1964-2012); Carreira, *et al.* (Ed.) *Science of Synthesis*, Vols. 1-48 (2001-2010) and Knowledge Updates KU2010/1-4; 2011/1-4; 2012/1-2 (Thieme, 2001-2012); Katritzky, *et al.* (Ed.) *Comprehensive Organic Functional Group Transformations*, (Pergamon Press, 1996); Katritzky *et al.* (Ed.); *Comprehensive Organic Functional Group Transformations II* (Elsevier, 2nd Edition, 2004); Katritzky *et al.* (Ed.), *Comprehensive Heterocyclic Chemistry* (Pergamon Press, 1984); Katritzky *et al.*, *Comprehensive Heterocyclic Chemistry II*, (Pergamon Press, 1996); Smith *et al.*, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th Ed. (Wiley, 2007); Trost *et al.* (Ed.), *Comprehensive Organic Synthesis* (Pergamon Press, 1991).

The reactions for preparing compounds described herein can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, (e.g., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature). A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

Preparation of compounds described herein can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., Wiley & Sons, Inc., New York (1999).

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^1H or ^{13}C), infrared spectroscopy, spectrophotometry (e.g., UV-visible), mass spectrometry, or by chromatographic methods such as high performance liquid chromatography (HPLC), liquid chromatography-mass spectrometry (LCMS), or thin layer chromatography (TLC). Compounds can be purified by those skilled in the art by a variety of methods, including high performance liquid chromatography (HPLC) and normal phase silica chromatography.

At various places in the present specification, divalent linking substituents are described. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups.

The term “n-membered” where n is an integer typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, piperidinyl is an example of a 6-membered heterocycloalkyl ring, pyrazolyl is an example of a 5-membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring, and 1,2,3,4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

As used herein, the phrase “optionally substituted” means unsubstituted or substituted. As used herein, the term “substituted” means that a hydrogen atom is removed and replaced by a substituent. It is to be understood that substitution at a given atom is limited by valency.

Throughout the definitions, the term “C_{n-m}” indicates a range which includes the endpoints, wherein n and m are integers and indicate the number of carbons. Examples include C₁₋₄, C₁₋₆, and the like.

As used herein, the term “C_{n-m} alkyl”, employed alone or in combination with other terms, refers to a saturated hydrocarbon group that may be straight-chain or branched, having n to m carbons. Examples of alkyl moieties include, but are not limited to, chemical groups such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl, isobutyl, *sec*-butyl; higher homologs such as 2-methyl-1-butyl, *n*-pentyl, 3-pentyl, *n*-hexyl, 1,2,2-trimethylpropyl, and the like. In some embodiments, the alkyl group contains from 1 to 6 carbon atoms, from 1 to 4 carbon atoms, from 1 to 3 carbon atoms, or 1 to 2 carbon atoms.

As used herein, “C_{n-m} alkenyl” refers to an alkyl group having one or more double carbon-carbon bonds and having n to m carbons. Example alkenyl groups include, but are not limited to, ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, *sec*-butenyl, and the like. In some embodiments, the alkenyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms.

As used herein, “C_{n-m} alkynyl” refers to an alkyl group having one or more triple carbon-carbon bonds and having n to m carbons. Example alkynyl groups include, but are not limited to, ethynyl, propyn-1-yl, propyn-2-yl, and the like. In some embodiments, the alkynyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms.

5 As used herein, the term “C_{n-m} alkylene”, employed alone or in combination with other terms, refers to a divalent alkyl linking group having n to m carbons. Examples of alkylene groups include, but are not limited to, ethan-1,2-diyl, propan-1,3-diyl, propan-1,2-diyl, butan-1,4-diyl, butan-1,3-diyl, butan-1,2-diyl, 2-methyl-propan-1,3-diyl, and the like. In some
10 embodiments, the alkylene moiety contains 2 to 6, 2 to 4, 2 to 3, 1 to 6, 1 to 4, or 1 to 2 carbon atoms.

As used herein, the term “C_{n-m} alkoxy”, employed alone or in combination with other terms, refers to a group of formula -O-alkyl, wherein the alkyl group has n to m carbons. Example alkoxy groups include methoxy, ethoxy, propoxy (e.g., *n*-propoxy and isopropoxy), *tert*-butoxy, and the like. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3
15 carbon atoms.

As used herein, the term “C_{n-m} alkylamino” refers to a group of formula -NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “C_{n-m} alkoxycarbonyl” refers to a group of formula -C(O)O-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.
20

As used herein, the term “C_{n-m} alkylcarbonyl” refers to a group of formula -C(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

25 As used herein, the term “C_{n-m} alkylcarbonylamino” refers to a group of formula -NHC(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “C_{n-m} alkylsulfonylamino” refers to a group of formula -NHS(O)₂-alkyl, wherein the alkyl group has n to m carbon atoms. In some
30 embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “aminosulfonyl” refers to a group of formula -S(O)₂NH₂.

As used herein, the term “C_{n-m} alkylaminosulfonyl” refers to a group of formula -S(O)₂NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some
embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “di(C_{n-m} alkyl)aminosulfonyl” refers to a group of formula -S(O)₂N(alkyl)₂, wherein each alkyl group independently has n to m carbon atoms. In some embodiments, each alkyl group has, independently, 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “aminosulfonylamino” refers to a group of formula -NHS(O)₂NH₂.

As used herein, the term “C_{n-m} alkylaminosulfonylamino” refers to a group of formula -NHS(O)₂NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “di(C_{n-m} alkyl)aminosulfonylamino” refers to a group of formula -NHS(O)₂N(alkyl)₂, wherein each alkyl group independently has n to m carbon atoms. In some embodiments, each alkyl group has, independently, 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “aminocarbonylamino”, employed alone or in combination with other terms, refers to a group of formula -NHC(O)NH₂.

As used herein, the term “C_{n-m} alkylaminocarbonylamino” refers to a group of formula -NHC(O)NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “di(C_{n-m} alkyl)aminocarbonylamino” refers to a group of formula -NHC(O)N(alkyl)₂, wherein each alkyl group independently has n to m carbon atoms. In some embodiments, each alkyl group has, independently, 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “C_{n-m} alkylcarbonyl” refers to a group of formula -C(O)-NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “thio” refers to a group of formula -SH.

As used herein, the term “C_{n-m} alkylsulfinyl” refers to a group of formula -S(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “C_{n-m} alkylsulfonyl” refers to a group of formula -S(O)₂-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “amino” refers to a group of formula -NH₂.

As used herein, the term “aryl,” employed alone or in combination with other terms, refers to an aromatic hydrocarbon group, which may be monocyclic or polycyclic (e.g., having 2, 3 or 4 fused rings). The term “C_{n-m} aryl” refers to an aryl group having from n to m ring carbon

atoms. Aryl groups include, e.g., phenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl, and the like. In some embodiments, aryl groups have from 6 to about 20 carbon atoms, from 6 to about 15 carbon atoms, or from 6 to about 10 carbon atoms. In some embodiments, the aryl group is a substituted or unsubstituted phenyl.

5 As used herein, the term “carbamyl” to a group of formula $-C(O)NH_2$.

As used herein, the term “carbonyl”, employed alone or in combination with other terms, refers to a $-C(=O)-$ group, which may also be written as $C(O)$.

As used herein, the term “di(C_{n-m} -alkyl)amino” refers to a group of formula $-N(alkyl)_2$, wherein the two alkyl groups each has, independently, n to m carbon atoms. In some embodiments, each
10 alkyl group independently has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “di(C_{n-m} -alkyl)carbamyl” refers to a group of formula $-C(O)N(alkyl)_2$, wherein the two alkyl groups each has, independently, n to m carbon atoms. In some embodiments, each alkyl group independently has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “halo” refers to F, Cl, Br, or I. In some embodiments, a halo is
15 F, Cl, or Br. In some embodiments, a halo is F or Cl.

As used herein, “ C_{n-m} haloalkoxy” refers to a group of formula $-O$ -haloalkyl having n to m carbon atoms. An example haloalkoxy group is OCF_3 . In some embodiments, the haloalkoxy group is fluorinated only. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

20 As used herein, the term “ C_{n-m} haloalkyl”, employed alone or in combination with other terms, refers to an alkyl group having from one halogen atom to $2s+1$ halogen atoms which may be the same or different, where “s” is the number of carbon atoms in the alkyl group, wherein the alkyl group has n to m carbon atoms. In some embodiments, the haloalkyl group is fluorinated only. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

25 As used herein, “cycloalkyl” refers to non-aromatic cyclic hydrocarbons including cyclized alkyl and/or alkenyl groups. Cycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused rings) groups and spirocycles. Cycloalkyl groups can have 3, 4, 5, 6, 7, 8, 9, or 10 ring-forming carbons (C_{3-10}). Ring-forming carbon atoms of a cycloalkyl group can be optionally substituted by oxo or sulfido (e.g., $C(O)$ or $C(S)$). Cycloalkyl groups also include
30 cycloalkylidenes. Example cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, and the like. In some embodiments, cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl, or adamantyl. In some embodiments, the cycloalkyl has 6-10 ring-forming carbon atoms. In some embodiments, cycloalkyl is adamantyl.

Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo or thienyl derivatives of cyclopentane, cyclohexane, and the like. A cycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring.

As used herein, "heteroaryl" refers to a monocyclic or polycyclic aromatic heterocycle having at least one heteroatom ring member selected from sulfur, oxygen, and nitrogen. In some embodiments, the heteroaryl ring has 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, any ring-forming N in a heteroaryl moiety can be an N-oxide. In some embodiments, the heteroaryl has 5-10 ring atoms and 1, 2, 3 or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl has 5-6 ring atoms and 1 or 2 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl is a five-membered or six-membered heteroaryl ring. A five-membered heteroaryl ring is a heteroaryl with a ring having five ring atoms wherein one or more (e.g., 1, 2, or 3) ring atoms are independently selected from N, O, and S. Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4-oxadiazolyl. A six-membered heteroaryl ring is a heteroaryl with a ring having six ring atoms wherein one or more (e.g., 1, 2, or 3) ring atoms are independently selected from N, O, and S. Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

As used herein, "heterocycloalkyl" refers to non-aromatic monocyclic or polycyclic heterocycles having one or more ring-forming heteroatoms selected from O, N, or S. Included in heterocycloalkyl are monocyclic 4-, 5-, 6-, and 7-membered heterocycloalkyl groups. Heterocycloalkyl groups can also include spirocycles. Example heterocycloalkyl groups include pyrrolidin-2-one, 1,3-isoxazolidin-2-one, pyranal, tetrahydropuran, oxetanyl, azetidyl, morpholino, thiomorpholino, piperazinyl, tetrahydrofuranal, tetrahydrothienyl, piperidinyl, pyrrolidinyl, isoxazolidinyl, isothiazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, azepanyl, benzazapene, and the like. Ring-forming carbon atoms and heteroatoms of a heterocycloalkyl group can be optionally substituted by oxo or sulfido (e.g., C(O), S(O), C(S), or S(O)₂, etc.). The heterocycloalkyl group can be attached through a ring-forming carbon atom or a ring-forming heteroatom. In some embodiments, the heterocycloalkyl group contains 0 to 3 double bonds. In some embodiments, the heterocycloalkyl group contains

0 to 2 double bonds. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (*i.e.*, having a bond in common with) to the cycloalkyl ring, for example, benzo or thienyl derivatives of piperidine, morpholine, azepine, etc. A heterocycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including
5 a ring-forming atom of the fused aromatic ring. In some embodiments, the heterocycloalkyl has 4-10, 4-7 or 4-6 ring atoms with 1 or 2 heteroatoms independently selected from nitrogen, oxygen, or sulfur and having one or more oxidized ring members.

At certain places, the definitions or embodiments refer to specific rings (e.g., an azetidine ring, a pyridine ring, etc.). Unless otherwise indicated, these rings can be attached to any ring
10 member provided that the valency of the atom is not exceeded. For example, an azetidine ring may be attached at any position of the ring, whereas a pyridin-3-yl ring is attached at the 3-position.

The term “compound” as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted. Compounds herein identified by
15 name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified.

Compounds provided herein also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric
20 protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide - imidic acid pairs, lactam – lactim pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or
25 sterically locked into one form by appropriate substitution.

In some embodiments, the compounds described herein can contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, enantiomerically enriched mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures (e.g., including (*R*)- and (*S*)-enantiomers, diastereomers, (*D*)-isomers, (*L*)-isomers, (+)
30 (*dextrorotatory*) forms, (-) (*levorotatory*) forms, the racemic mixtures thereof, and other mixtures thereof). Additional asymmetric carbon atoms can be present in a substituent, such as an alkyl group. All such isomeric forms, as well as mixtures thereof, of these compounds are expressly included in the present description. The compounds described herein can also or further contain linkages wherein bond rotation is restricted about that particular linkage, e.g.

restriction resulting from the presence of a ring or double bond (e.g., carbon-carbon bonds, carbon-nitrogen bonds such as amide bonds). Accordingly, all *cis/trans* and *E/Z* isomers and rotational isomers are expressly included in the present description. Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms of that compound.

Optical isomers can be obtained in pure form by standard procedures known to those skilled in the art, and include, but are not limited to, diastereomeric salt formation, kinetic resolution, and asymmetric synthesis. See, for example, Jacques, et al., *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen, S.H., et al., *Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972), each of which is incorporated herein by reference in their entireties. It is also understood that the compounds described herein include all possible regioisomers, and mixtures thereof, which can be obtained in pure form by standard separation procedures known to those skilled in the art, and include, but are not limited to, column chromatography, thin-layer chromatography, and high-performance liquid chromatography.

Unless specifically defined, compounds provided herein can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. Unless otherwise stated, when an atom is designated as an isotope or radioisotope (e.g., deuterium, [^{11}C], [^{18}F]), the atom is understood to comprise the isotope or radioisotope in an amount at least greater than the natural abundance of the isotope or radioisotope. For example, when an atom is designated as “D” or “deuterium”, the position is understood to have deuterium at an abundance that is at least 3000 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 45% incorporation of deuterium).

All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (e.g. hydrates and solvates) or can be isolated.

In some embodiments, preparation of compounds can involve the addition of acids or bases to affect, for example, catalysis of a desired reaction or formation of salt forms such as acid addition salts.

Example acids can be inorganic or organic acids and include, but are not limited to, strong and weak acids. Some example acids include hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, *p*-toluenesulfonic acid, 4-nitrobenzoic acid, methanesulfonic acid, benzenesulfonic acid, trifluoroacetic acid, and nitric acid. Some weak acids include, but are not

limited to acetic acid, propionic acid, butanoic acid, benzoic acid, tartaric acid, pentanoic acid, hexanoic acid, heptanoic acid, octanoic acid, nonanoic acid, and decanoic acid.

Example bases include lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, and sodium bicarbonate. Some
5 example strong bases include, but are not limited to, hydroxide, alkoxides, metal amides, metal hydrides, metal dialkylamides and arylamines, wherein; alkoxides include lithium, sodium and potassium salts of methyl, ethyl and t-butyl oxides; metal amides include sodium amide, potassium amide and lithium amide; metal hydrides include sodium hydride, potassium hydride and lithium hydride; and metal dialkylamides include lithium, sodium, and potassium salts of
10 methyl, ethyl, n-propyl, *iso*-propyl, n-butyl, *tert*-butyl, trimethylsilyl and cyclohexyl substituted amides.

In some embodiments, the compounds provided herein, or salts thereof, are substantially isolated. By “substantially isolated” is meant that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial
15 separation can include, for example, a composition enriched in the compounds provided herein. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compounds provided herein, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

20 The expressions, “ambient temperature” and “room temperature” or “rt” as used herein, are understood in the art, and refer generally to a temperature, e.g. a reaction temperature, that is about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20 °C to about 30 °C.

The phrase “pharmaceutically acceptable” is employed herein to refer to those
25 compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The present application also includes pharmaceutically acceptable salts of the compounds
30 described herein. As used herein, “pharmaceutically acceptable salts” refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of

the present application include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present application can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by
5 reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (e.g., methanol, ethanol, iso-propanol, or butanol) or acetonitrile (MeCN) are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and
10 *Journal of Pharmaceutical Science*, 66, 2 (1977). Conventional methods for preparing salt forms are described, for example, in *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, Wiley-VCH, 2002.

Methods of Use

15 The present application further provides methods for the treatment of disorders associated with glutamate excitotoxicity in a subject in need thereof. A number of such disorders are known in the art, and can be readily identified by one of skill in the art. In some embodiments, the methods include a method for treating or preventing glutamate excitotoxicity in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of
20 a compound provided herein, or a pharmaceutically acceptable salt thereof. As used herein, the term "subject," refers to any animal, including mammals. For example, the term "subject" includes, but is not limited to, mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, primates, and humans. In some embodiments, the subject is a human.

In some embodiments, the methods described herein can include *in vitro* methods, e.g.,
25 contacting a sample (e.g., a cell or tissue) with a compound provided herein, or a pharmaceutically acceptable salt thereof.

In some embodiments, the disorder is an acute neurological condition such as ischemic stroke, epilepsy, hypoglycemia, hypoxia, or trauma (see *e.g.*, J. Neurosci. 2016 Oct 12;36(41):10529-10544; J. Clin. Invest. 2014 Mar;124(3):1255-67; and Neurochem. Int. 2006
30 Apr;48(5):394-403).

In some embodiments, the disorder is a chronic neurodegenerative disorder such as Parkinson's disease, Alzheimer's disease, multiple sclerosis, mesial temporal sclerosis, Huntington's disease, AIDS dementia complex, or amyotrophic lateral sclerosis (ALS) (see, e.g., Hu et al., "Glutamate receptors in preclinical research on Alzheimer's disease: Update on recent

advances.” Pharmacol Biochem Behav. 2011 Apr 22 [Epub ahead of print, doi:10.1016/j.pbb.2011.04.013]; Wang and Qin, Apoptosis. 15(11):1382-402 (2010); Kaul and Lipton, Curr HIV Res. 4(3):307-18 (2006); Kim et al., J Cell Physiol. 226(10):2484-93 (2011); Sheldon and Robinson, Neurochem Int. 51(6-7):333-55 (2007); Guo et al., Hum. Mol. Genet. 2003, 12, 2519; Tian et al., J. Biol. Chem. 282:1727 (2007); Hazell, Neurochem. Int. 50:941 (2007); Seifert et al., Brain. Res. Rev. 63:212 (2010); Tian et al., J. Neurochem. 113:978 (2010); Olney, “Neurotoxicity of excitatory amino acids.” In: McGeer E, Olney J, McGeer P, eds. Kainic Acid as a Tool in Neurobiology. New York: Raven Press; 1978:95–121; Olney, APMIS Suppl 40:103-112 (2010); J. Exp. Med. 2015 Mar 9;212(3):319-32; Neurobiol. Aging. 2015 Jul;36(7):2260-71; Neural. Plast. 2016;2016:8941327; PLoS One. 2008 Sep 5;3(9):e3149; J. Clin. Invest. 2014 Mar;124(3):1255-67; J. Neurochem. 2012 May;121(4):629-38; and Curr. HIV Res. 2012 Jul;10(5):392-406).

In some embodiments, the disorder is depression (see, e.g., Chen et al., Presynaptic glutamatergic dysfunction in bipolar disorder, Biol. Psychiatry, 67(11): 1007-1009 (2010)).

In some embodiments, glutamate excitotoxicity can be a result of an environmental toxin, e.g., Tributyltin (Nakatsu et al., Toxicol. Sci. (January 2006) 89 (1): 235-242), lead, and domoic acid.

In some embodiments, excessive glutamate is associated with chronic pain disorders including migraine, fibromyalgia, temporomandibular disorders, neuropathic pain, visceral pain, or complex regional pain syndrome (see, e.g., Chizh et al., Amino Acids, 23(1-3):169-76 (2002); Descalzi et al., Mol Neurobiol. 40(3):253-9. Epub 2009 Oct 11 (2009); Larsson, Mol Neurobiol. 40(3):260-88 (2009); Yogeswaari et al., Expert Opin Ther Targets. 13(8):925-43 (2009); Vargas, Curr Pain Headache Rep. 13(1):64-6 (2009); Adv. Pharmacol. 2016;75:245-71; J. Neurochem. 2014 Dec;131(6):712-30; Eurasian J Med. 2011 Dec;43(3):182-5; and J. Pharmacol. Sci. 2010;114(4):347-53).

Disruptions in glutamate homeostasis are associated with addictive disorders. As substance abuse develops into addiction, neurochemistry shifts from dopamine-based to predominantly glutamate-based. Thus, subjects suffering from drug addiction and dependence, including alcohol and cocaine addiction, can also be treated using the methods described herein. See, e.g., Tzschenke, Amino Acids 23(1-3):147-52 (2002); Reissner and Kalivas, Behav Pharmacol. 2010 Sep;21(5-6):514-22 (2010); Myers et al., Neuropsychopharmacology. 36(1):274-93 (2011); World J. Psychiatry. 2016 Mar 22;6(1):31-42; CNS Neurol. Disord. Drug Targets. 2015;14(6):745-56; Neuroscientist. 2014 Dec;20(6):610-22; and Behav. Pharmacol. 2010 Sep;21(5-6):514-22.

Glutamate has also been shown to play a role in some psychotic disorders, including schizophrenia, bipolar disorder, and autism (see *e.g.*, Curr Mol Pharmacol. 2013 Jul;6(2):66-73; Eur J Pharmacol. 2012 May 5;682(1-3):1-11; Iran J Child Neurol. 2015 Winter;9(1):99-102; J Biomed Sci. 2005 Dec;12(6):975-84. The methods and compounds described herein can be used to treat subjects with psychotic disorders such as schizophrenia, bipolar disorder, and autism.

Glutamate has also been shown to play a role in some cancers, including necrosis in glioblastoma, which is associated with poor prognosis. See, *e.g.*, Noch and Khalili, Cancer Biol Ther. 8(19):1791-7 (2009). Thus, the compounds and compositions described herein can be used to treat subjects with cancers, *e.g.*, brain cancers such as glioblastoma and glioma.

Glutamate has been shown to play a role in modulating various mood disorders, for example, major depressive disorder (Owen, Drugs today, 2012, 48(7):469-78), anxiety disorders (see *e.g.*, Neuropsychiatr Dis Treat. 2013;9:1101-12), depressive disorders (see *e.g.*, Expert Rev Clin Pharmacol. 2016 Oct 26; Biol Psychiatry. 2007 Jan 15;61(2):250-2; and Biol Psychiatry. 2007 Jan 15;61(2):137-8), borderline personality disorder (see *e.g.*, Neuropsychopharmacology. 2016 Jan;41(2):410-8), attention-deficit-hyperactivity disorder (see *e.g.*, Neuropsychopharmacology. 2016 Jan;41(2):410-8; and World J. Biol. Psychiatry. 2016 Dec 15:1-9), suicidal behavior (see *e.g.*, Prog. Neuropsychopharmacol Biol. Psychiatry. 2016 Oct 27), eating disorders (see *e.g.*, Curr. Pharm. Des. 2011;17(14):1396-409), posttraumatic stress disorder (see *e.g.*, Neurosci. Lett. 2016 Dec 1), gulf war illness (see *e.g.*, J. Neurochem. 2011 Oct;119(2):303-13), and obsessive-Compulsive Disorder (see *e.g.*, Pharmacol. Ther. 2011 Dec; 132(3): 314-332).

The presence of a disorder associated with glutamate excitotoxicity can be diagnosed or determined using methods known in the art, including spectroscopy at 0.5 T to observe the combined glutamate and glutamine (glx) peak (see, *e.g.*, Prost et al., Magn Reson Med 1997;37:615-618; Mark et al., American Journal of Neuroradiology 22:1813-1824 (2001)). Other known clinical diagnostic methods can also be used to diagnose the presence of a disorder known to be associated with glutamate excitotoxicity, *e.g.*, as described herein.

In some embodiments, glutamate excitotoxicity (and subsequent neurological damage) can be a result of an environmental toxin, *e.g.*, Tributyltin (Nakatsu et al., Toxicol. Sci. (January 2006) 89 (1): 235-242), lead, and domoic acid. Subjects who have been or will be exposed to such toxins can be considered to have a disorder associated with glutamate excitotoxicity and can be treated using the methods described herein. In some embodiments subjects who have been exposed to an environmental toxin known to cause or contribute to glutamate excitotoxicity can

be treated using the methods described herein before the onset of clinical (e.g., neurological) symptoms, to prevent or reduce the risk of a disorder associated with glutamate excitotoxicity.

In some embodiments, the present application provides a method for treating a disease or disorder selected from the group consisting of ischemic stroke, epilepsy, trauma, a chronic neurodegenerative disorder, a psychotic disorder, a pain disorder, an addiction, a cancer, a mood disorder, or depression in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof.

In some embodiments, the present application provides a method for treating a disease or disorder selected from the group consisting of ischemic stroke, epilepsy, trauma, a chronic neurodegenerative disorder, a psychotic disorder, a pain disorder, an addiction, a cancer, or depression in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof.

Example traumas include, but are not limited to, blunt trauma, an abrasion, an avulsion, an incision, a laceration, a puncture, a penetration, a surgical trauma, iatrogenic trauma, a spinal cord injury, a traumatic brain injury, or any combination thereof.

In some embodiments, the chronic neurodegenerative disorder is selected from the group consisting of mild cognitive impairment, Parkinson's disease, Alzheimer's disease, multiple sclerosis, mesial temporal sclerosis, Huntington's disease, AIDS dementia complex, and amyotrophic lateral sclerosis (ALS).

In some embodiments, the psychotic disorder is selected from the group consisting of schizophrenia, bipolar disorder, and autism.

In some embodiments, the pain disorder is selected from the group consisting of migraine, a temporomandibular disorder, neuropathic pain, visceral pain, or complex regional pain syndrome.

In some embodiments, the addiction is selected from the group consisting of alcohol addiction, cocaine addiction, heroin addiction, methamphetamine addiction, and nicotine addiction. In some embodiments, the addiction is selected from the group consisting of alcohol addiction and cocaine addiction.

In some embodiments, the cancer is selected from the group consisting of brain cancer, glioblastoma, and glioma. In some embodiments, the cancer is glioblastoma. In some embodiments, the cancer is glioma.

In some embodiments, the mood disorder is selected from the group consisting of an anxiety disorder, a depressive disorder, borderline personality disorder, attention-deficit-

hyperactivity disorder, suicidal behavior, an eating disorder, posttraumatic stress disorder, gulf war illness, and obsessive-Compulsive Disorder.

In some embodiments, the depression comprises major depressive disorder. In some embodiments, the depression is major depressive disorder.

5 In some embodiments, the present application provides a method for treating a disease or disorder selected from the group consisting of ischemic stroke, epilepsy, trauma, or a chronic neurodegenerative disorder, including mild cognitive impairment, Parkinson's disease, Alzheimer's disease, multiple sclerosis, mesial temporal sclerosis, Huntington's disease, AIDS dementia complex, or amyotrophic lateral sclerosis (ALS); a psychotic disorder including
10 schizophrenia, bipolar disorder, and autism, a pain disorder including migraine, temporomandibular disorders, neuropathic pain, visceral pain, or complex regional pain syndrome; an addiction including alcohol addiction, cocaine addiction, heroin addiction, methamphetamine addiction, and nicotine addiction; or a cancer, including glioblastoma; or depression in a subject in need thereof, the method comprising administering to the subject an
15 effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof.

The present application further provides a method for increasing EAAT2 protein expression in a cell or a subject in need thereof, the method comprising contacting the cell or administering to the subject an effective amount of a compound provided herein, or a
pharmaceutically acceptable salt thereof.

20 The present application further provides a method for activating the NRF2 pathway in a cell or a subject in need thereof, the method comprising contacting the cell or administering to the subject an effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof.

As used herein, the phrase "effective amount" refers to the amount of active compound or
25 pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician. An effective amount of a compound provided herein can range, for example, from about 0.01 mg/kg to about 1000 mg/kg, (e.g., from about 0.1 mg/kg to about 100 mg/kg, from about 1 mg/kg to about 100 mg/kg). Effective doses will also vary depending on route of
30 administration, as well as the possibility of co-usage with other agents.

As used herein, to "treat" means to ameliorate at least one symptom of the disorder associated with glutamate excitotoxicity. Often, glutamate excitotoxicity results in neuronal cell death; thus, a treatment can result in a reduction in the rate or amount of neuronal cell death.

Combination Therapies

In some embodiments, the methods provided herein further comprise administering one or more additional therapeutic agents to the subject. In some embodiments, each of the one or more additional therapeutic agents is independently selected from the group consisting of a
 5 steroid, an anti-allergic agent, an anesthetic (*e.g.*, for use in combination with a surgical procedure), an immunosuppressant, an anti-microbial agent, an anti-inflammatory agent, and a chemotherapeutic agent.

Example steroids include, but are not limited to, corticosteroids such as cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, and prednisone.

10 Example anesthetics include, but are not limited to local anesthetics such as lidocaine, procain, and ropivacaine.

Example immunosuppressants include, but are not limited to, azathioprine, chlorambucil, cyclophosphamide, cyclosporine, daclizumab, infliximab, methotrexate, and tacrolimus.

15 Example anti-microbial agents include, but are not limited to, aminoglycosides (*e.g.*, gentamicin, neomycin, and streptomycin), penicillins (*e.g.*, amoxicillin and ampicillin), and macrolides (*e.g.*, erythromycin).

Example anti-inflammatory agents include, but are not limited to, aspirin, choline salicylates, celecoxib, diclofenac potassium, diclofenac sodium, diclofenac sodium with misoprostol, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, meclofenamate
 20 sodium, mefenamic acid, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, rofecoxib, salsalate, sodium salicylate, sulindac, tolmetin sodium, and valdecoxib.

Example chemotherapeutics include, but are not limited to, proteasome inhibitors (*e.g.*, bortezomib), thalidomide, revlimid, and DNA-damaging agents such as melphalan, doxorubicin, cyclophosphamide, vincristine, etoposide, carmustine, and the like. For example, one or more of
 25 the following agents may be used in combination with the compounds provided herein and are presented as a non-limiting list: a cytostatic agent, cisplatin, taxol, etoposide, irinotecan, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, temozolomide, cyclophosphamide, gefitinib, erlotinib hydrochloride, imatinib mesylate, gemcitabine, uracil mustard, chlormethine, ifosfamide, chlorambucil, pipobroman, triethylenemelamine,
 30 triethylenethiophosphoramine, busulfan, lomustine, streptozocin, dacarbazine, floxuridine, cytarabine, 6-mercaptopurine, 6-thioguanine, fludarabine phosphate, oxaliplatin, folinic acid, pentostatin, vinblastine, vindesine, bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, mithramycin, deoxycoformycin, mitomycin-C, L-asparaginase, teniposide, 17 α -ethinylestradiol, diethylstilbestrol, testosterone, prednisone, fluoxymesterone,

dromostanolone propionate, testolactone, megestrol acetate, methyltestosterone, triamcinolone, chlorotrianisene, hydroxyprogesterone, aminoglutethimide, estramustine, medroxyprogesteroneacetate, leuprolide, flutamide, toremifene, goserelin, carboplatin, hydroxyurea, amsacrine, procarbazine, mitotane, mitoxantrone, levamisole, vinorelbine, 5 anastrozole, letrozole, capecitabine, reloxafine, hexamethylmelamine, bevacizumab, bexxar, velcade, zevalin, trisenox, xeloda, porfimer, erbitux, thiotepa, altretamine, trastuzumab, fulvestrant, exemestane, ifosfamide, rituximab, alemtuzumab, clofarabine, cladribine, aphidicolin, sunitinib, dasatinib, tezacitabine, triapine, trimidox, amidox, bendamustine, and ofatumumab.

Pharmaceutical Compositions

When employed as pharmaceuticals, the compounds provided herein and pharmaceutically acceptable salts thereof can be administered in the form of pharmaceutical compositions. These compositions can be prepared as described herein or elsewhere, and can be 15 administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral, or parenteral. Parenteral administration includes 20 intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, (e.g., intrathecal or intraventricular, administration). Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. In some embodiments, the compounds provided herein, or a pharmaceutically acceptable salt thereof, are suitable for parenteral administration. In some embodiments, the compounds 25 provided herein are suitable for intravenous administration. In some embodiments, the compounds provided herein are suitable for oral administration. In some embodiments, the compounds provided herein are suitable for topical administration.

Pharmaceutical compositions and formulations for topical administration may include, but are not limited to, transdermal patches, ointments, lotions, creams, gels, drops, suppositories, 30 sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. In some embodiments, the pharmaceutical compositions provided herein are suitable for parenteral administration. In some embodiments, the pharmaceutical compositions provided herein are suitable for intravenous administration. In some embodiments, the pharmaceutical compositions provided herein are

suitable for oral administration. In some embodiments, the pharmaceutical compositions provided herein are suitable for topical administration.

Also provided are pharmaceutical compositions which contain, as the active ingredient, a compound provided herein, or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers (*e.g.* excipients). In making the pharmaceutical compositions provided herein, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be, for example, in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

Some examples of suitable excipients include, without limitation, lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include, without limitation, lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; flavoring agents, or combinations thereof.

The active compound can be effective over a wide dosage range and is generally administered in an effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual subject, the severity of the subject's symptoms, and the like.

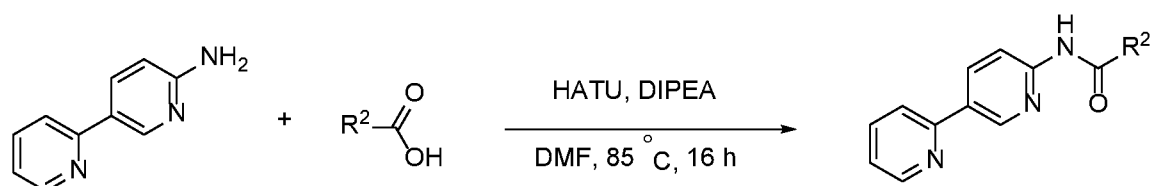
The compositions provided herein can be administered one from one or more times per day to one or more times per week; including once every other day. The skilled artisan will appreciate that certain factors can influence the dosage and timing required to effectively treat a subject, including, but not limited to, the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a compound described herein can include a single treatment or a series of treatments.

Dosage, toxicity and therapeutic efficacy of the compounds provided herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD₅₀/ED₅₀. Compounds exhibiting high therapeutic indices are preferred. While compounds that exhibit toxic side effects can be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

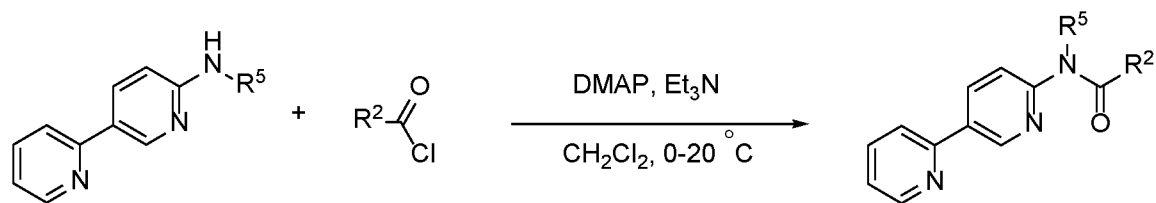
EXAMPLES

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same results.

Example 1. General Procedure for Synthesis of Amide Analogs



N,N-Diisopropylethylamine (DIPEA) (258 mg, 2.0 mmol) is slowly added dropwise to a solution of 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU) (456 mg, 1.2 mmol) in DMF (2.0 mL). The solution is stirred for 5 minutes and then added dropwise to a mixture of the appropriately substituted carboxylic acid (1.0 mmol) and 2,3'-bipyridin-6'-amine (171 mg, 1.0 mmol) in a reaction vial. The solution is then stirred at 85 °C for 16 hours. The reaction is monitored by TLC or LCMS. The residue is purified using a silica or basic alumina column chromatography and eluted with the appropriate solvent mixtures (*e.g.*, ethyl acetate-methanol-triethylamine, or cyclohexane-ethyl acetate) to give the desired compound.

Example 2. Alternative Procedure for Synthesis of Amide Analogs

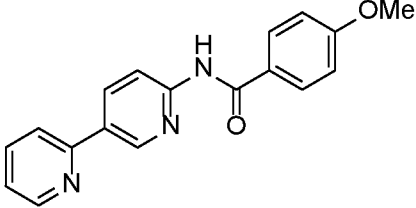
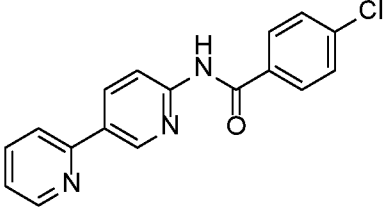
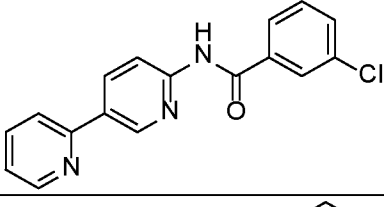
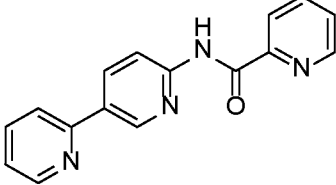
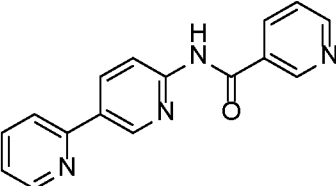
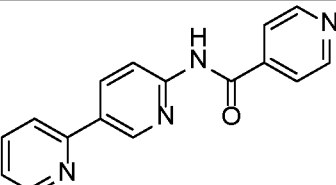
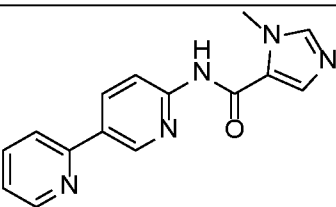
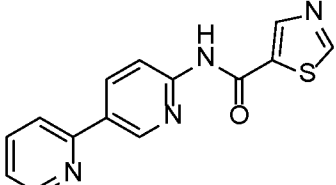
The appropriate amine product (0.17 mmol), DMAP (4.5 mg, 0.04 mmol) and triethylamine (41.8 μ L, 0.3 mmol) are dissolved in dichloromethane (1 mL) and cooled to 0 $^{\circ}$ C.

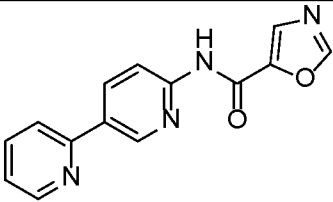
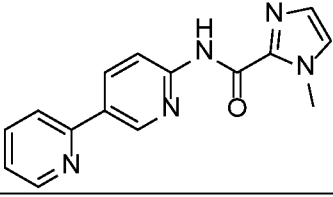
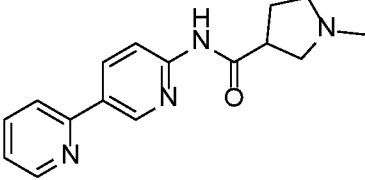
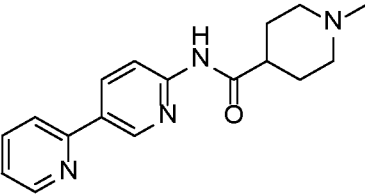
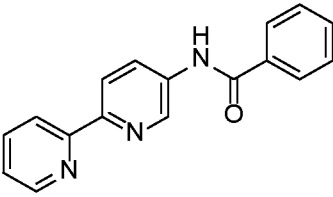
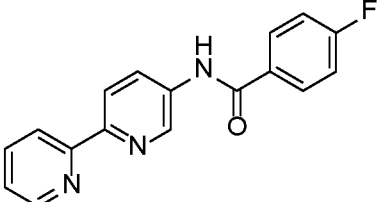
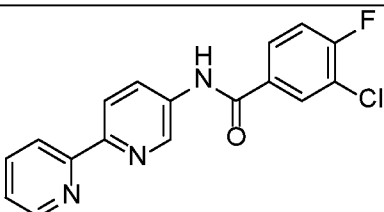
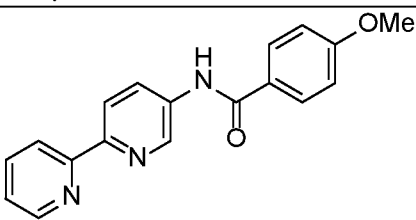
- 5 The appropriately substituted acid chloride (0.4 mmol) is added dropwise to the stirring solution. The reaction mixture is slowly warmed to room temperature and then stirred for 5 hours. To the reaction mixture is added dichloromethane (2 mL) and sat. aqueous NH_4Cl (1 mL) and the organic layer is extracted. The aqueous layer is then extracted with dichloromethane (2 x 2 mL) and the organic fractions are combined, dried over Na_2SO_4 , filtered, and evaporated under
- 10 reduced pressure. The residue is purified using a silica or basic alumina column chromatography and eluted with the appropriate solvent mixtures (*e.g.*, ethyl acetate-methanol-triethylamine, or cyclohexane-ethyl acetate) to give the desired compound.

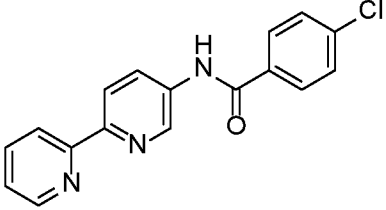
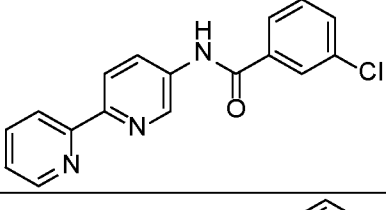
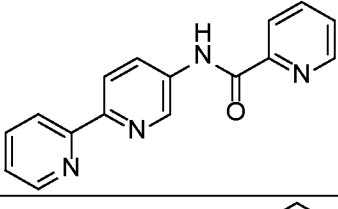
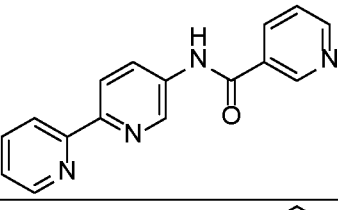
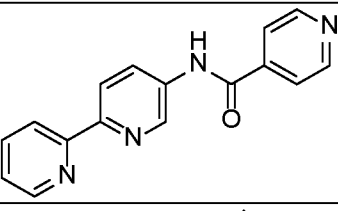
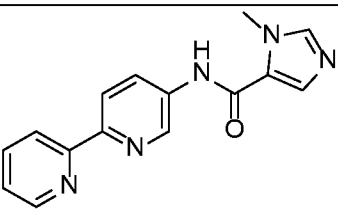
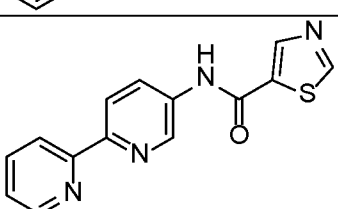
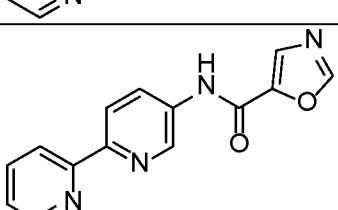
Examples 3-87.

- 15 The compounds of Examples 3-87 can be prepared according to the procedures described in Examples 1-2 using appropriately substituted starting materials.

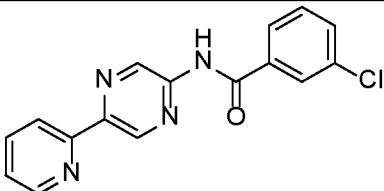
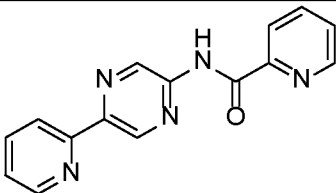
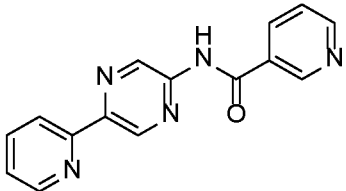
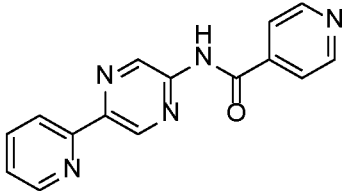
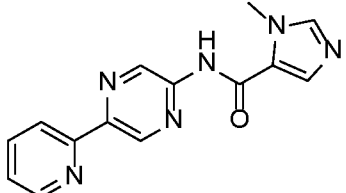
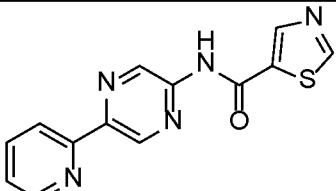
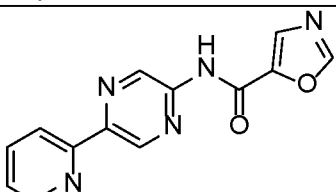
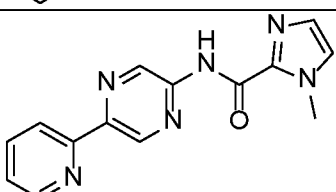
Example No.	Compound Structure	Compound Name
3		N-([2,3'-bipyridin]-6'-yl)benzamide
4		N-([2,3'-bipyridin]-6'-yl)-4-fluorobenzamide
5		N-([2,3'-bipyridin]-6'-yl)-3-chloro-4-fluorobenzamide

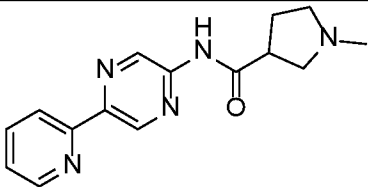
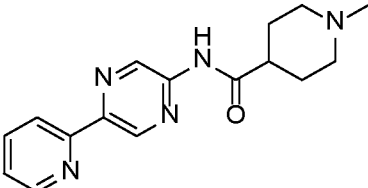
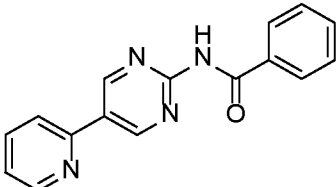
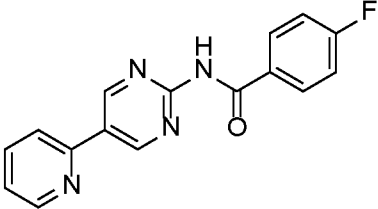
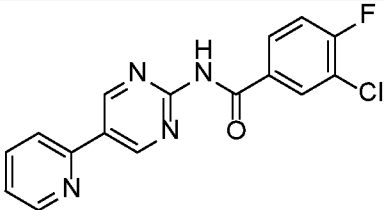
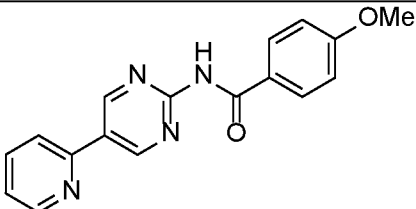
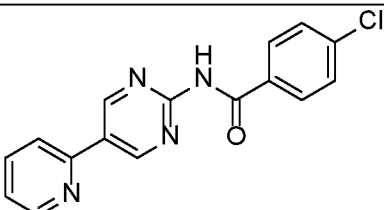
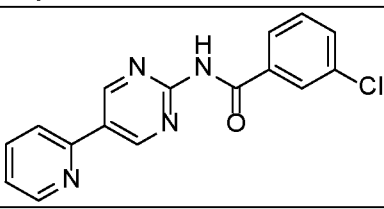
Example No.	Compound Structure	Compound Name
6		N-([2,3'-bipyridin]-6'-yl)-4-methoxybenzamide
7		N-([2,3'-bipyridin]-6'-yl)-4-chlorobenzamide
8		N-([2,3'-bipyridin]-6'-yl)-3-chlorobenzamide
9		N-([2,3'-bipyridin]-6'-yl)picolinamide
10		N-([2,3'-bipyridin]-6'-yl)nicotinamide
11		N-([2,3'-bipyridin]-6'-yl)isonicotinamide
12		N-([2,3'-bipyridin]-6'-yl)-1-methyl-1H-imidazole-5-carboxamide
13		N-([2,3'-bipyridin]-6'-yl)thiazole-5-carboxamide

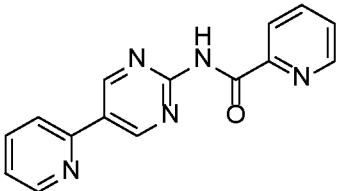
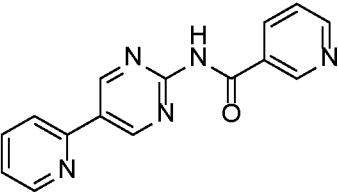
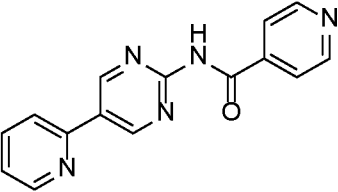
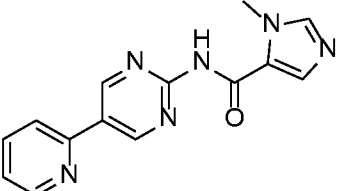
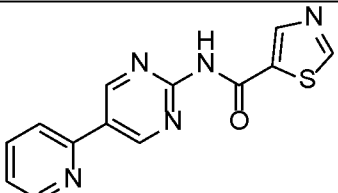
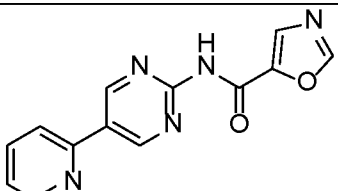
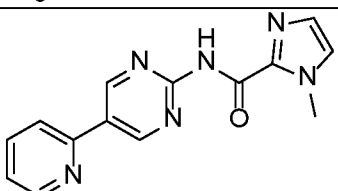
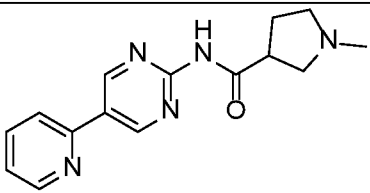
Example No.	Compound Structure	Compound Name
14		N-([2,3'-bipyridin]-6'-yl)oxazole-5-carboxamide
15		N-([2,3'-bipyridin]-6'-yl)-1-methyl-1H-imidazole-2-carboxamide
16		N-([2,3'-bipyridin]-6'-yl)-1-methylpyrrolidine-3-carboxamide
17		N-([2,3'-bipyridin]-6'-yl)-1-methylpiperidine-4-carboxamide
18		N-([2,2'-bipyridin]-5-yl)benzamide
19		N-([2,2'-bipyridin]-5-yl)-4-fluorobenzamide
20		N-([2,2'-bipyridin]-5-yl)-3-chloro-4-fluorobenzamide
21		N-([2,2'-bipyridin]-5-yl)-4-methoxybenzamide

Example No.	Compound Structure	Compound Name
22		N-([2,2'-bipyridin]-5-yl)-4-chlorobenzamide
23		N-([2,2'-bipyridin]-5-yl)-3-chlorobenzamide
24		N-([2,2'-bipyridin]-5-yl)picolinamide
25		N-([2,2'-bipyridin]-5-yl)nicotinamide
26		N-([2,2'-bipyridin]-5-yl)isonicotinamide
27		N-([2,2'-bipyridin]-5-yl)-1-methyl-1H-imidazole-5-carboxamide
28		N-([2,2'-bipyridin]-5-yl)thiazole-5-carboxamide
29		N-([2,2'-bipyridin]-5-yl)oxazole-5-carboxamide

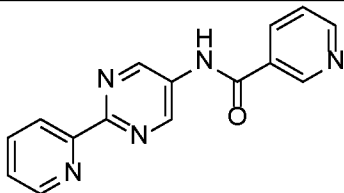
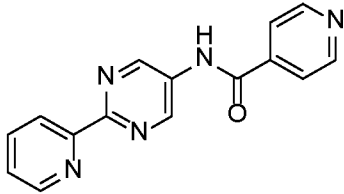
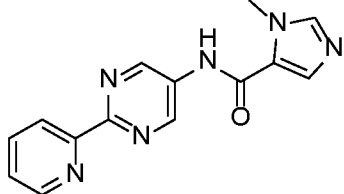
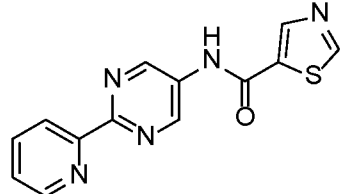
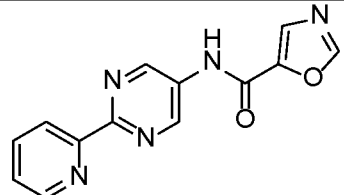
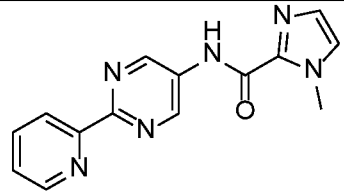
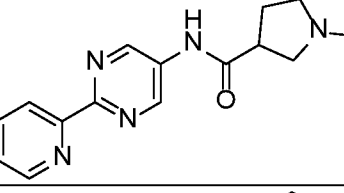
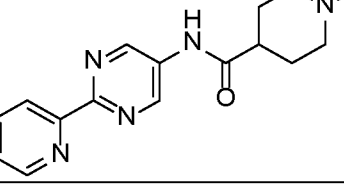
Example No.	Compound Structure	Compound Name
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31		N-([2,2'-bipyridin]-5-yl)-1-methylpyrrolidine-3-carboxamide
32		N-([2,2'-bipyridin]-5-yl)-1-methylpiperidine-4-carboxamide
33		N-(5-(pyridin-2-yl)pyrazin-2-yl)benzamide
34		4-fluoro-N-(5-(pyridin-2-yl)pyrazin-2-yl)benzamide
35		3-chloro-4-fluoro-N-(5-(pyridin-2-yl)pyrazin-2-yl)benzamide
36		4-methoxy-N-(5-(pyridin-2-yl)pyrazin-2-yl)benzamide
37		4-chloro-N-(5-(pyridin-2-yl)pyrazin-2-yl)benzamide

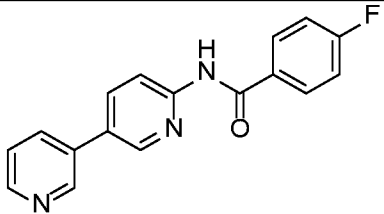
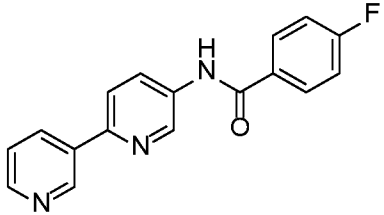
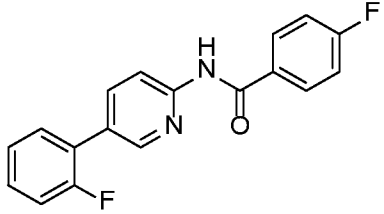
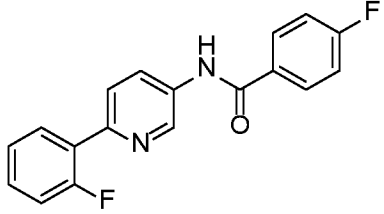
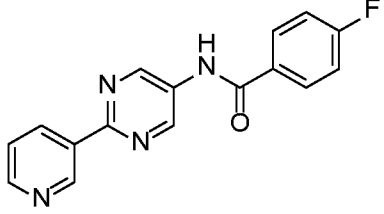
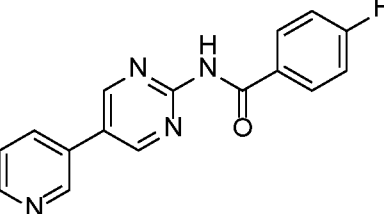
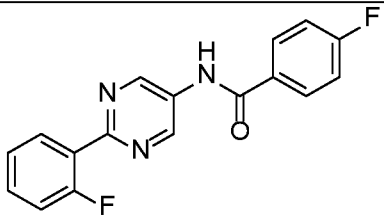
Example No.	Compound Structure	Compound Name
38		3-chloro-N-(5-(pyridin-2-yl)pyrazin-2-yl)benzamide
39		N-(5-(pyridin-2-yl)pyrazin-2-yl)picolinamide
40		N-(5-(pyridin-2-yl)pyrazin-2-yl)nicotinamide
41		N-(5-(pyridin-2-yl)pyrazin-2-yl)isonicotinamide
42		1-methyl-N-(5-(pyridin-2-yl)pyrazin-2-yl)-1H-imidazole-5-carboxamide
43		N-(5-(pyridin-2-yl)pyrazin-2-yl)thiazole-5-carboxamide
44		N-(5-(pyridin-2-yl)pyrazin-2-yl)oxazole-5-carboxamide
45		1-methyl-N-(5-(pyridin-2-yl)pyrazin-2-yl)-1H-imidazole-2-carboxamide

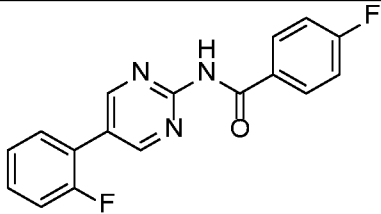
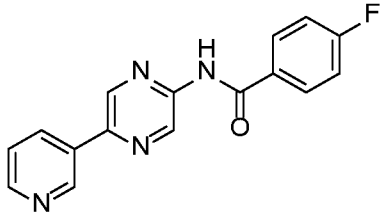
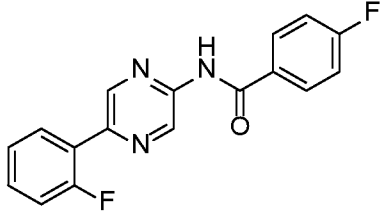
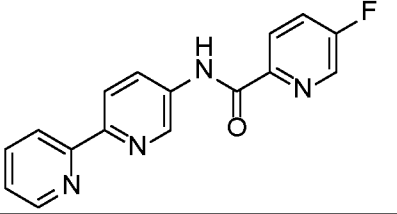
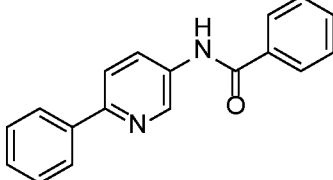
Example No.	Compound Structure	Compound Name
46		1-methyl-N-(5-(pyridin-2-yl)pyrazin-2-yl)pyrrolidine-3-carboxamide
47		1-methyl-N-(5-(pyridin-2-yl)pyrazin-2-yl)piperidine-4-carboxamide
48		N-(5-(pyridin-2-yl)pyrimidin-2-yl)benzamide
49		4-fluoro-N-(5-(pyridin-2-yl)pyrimidin-2-yl)benzamide
50		3-chloro-4-fluoro-N-(5-(pyridin-2-yl)pyrimidin-2-yl)benzamide
51		4-methoxy-N-(5-(pyridin-2-yl)pyrimidin-2-yl)benzamide
52		4-chloro-N-(5-(pyridin-2-yl)pyrimidin-2-yl)benzamide
53		3-chloro-N-(5-(pyridin-2-yl)pyrimidin-2-yl)benzamide

Example No.	Compound Structure	Compound Name
54		N-(5-(pyridin-2-yl)pyrimidin-2-yl)picolinamide
55		N-(5-(pyridin-2-yl)pyrimidin-2-yl)nicotinamide
56		N-(5-(pyridin-2-yl)pyrimidin-2-yl)isonicotinamide
57		1-methyl-N-(5-(pyridin-2-yl)pyrimidin-2-yl)-1H-imidazole-5-carboxamide
58		N-(5-(pyridin-2-yl)pyrimidin-2-yl)thiazole-5-carboxamide
59		N-(5-(pyridin-2-yl)pyrimidin-2-yl)oxazole-5-carboxamide
60		1-methyl-N-(5-(pyridin-2-yl)pyrimidin-2-yl)-1H-imidazole-2-carboxamide
61		1-methyl-N-(5-(pyridin-2-yl)pyrimidin-2-yl)pyrrolidine-3-carboxamide

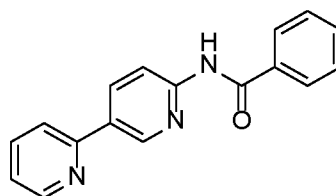
Example No.	Compound Structure	Compound Name
62		1-methyl-N-(5-(pyridin-2-yl)pyrimidin-2-yl)piperidine-4-carboxamide
63		N-(2-(pyridin-2-yl)pyrimidin-5-yl)benzamide
64		4-fluoro-N-(2-(pyridin-2-yl)pyrimidin-5-yl)benzamide
65		3-chloro-4-fluoro-N-(2-(pyridin-2-yl)pyrimidin-5-yl)benzamide
66		4-methoxy-N-(2-(pyridin-2-yl)pyrimidin-5-yl)benzamide
67		4-chloro-N-(2-(pyridin-2-yl)pyrimidin-5-yl)benzamide
68		3-chloro-N-(2-(pyridin-2-yl)pyrimidin-5-yl)benzamide
69		N-(2-(pyridin-2-yl)pyrimidin-5-yl)picolinamide

Example No.	Compound Structure	Compound Name
70		N-(2-(pyridin-2-yl)pyrimidin-5-yl)nicotinamide
71		N-(2-(pyridin-2-yl)pyrimidin-5-yl)isonicotinamide
72		1-methyl-N-(2-(pyridin-2-yl)pyrimidin-5-yl)-1H-imidazole-5-carboxamide
73		N-(2-(pyridin-2-yl)pyrimidin-5-yl)thiazole-5-carboxamide
74		N-(2-(pyridin-2-yl)pyrimidin-5-yl)oxazole-5-carboxamide
75		1-methyl-N-(2-(pyridin-2-yl)pyrimidin-5-yl)-1H-imidazole-2-carboxamide
76		1-methyl-N-(2-(pyridin-2-yl)pyrimidin-5-yl)pyrrolidine-3-carboxamide
77		1-methyl-N-(2-(pyridin-2-yl)pyrimidin-5-yl)piperidine-4-carboxamide

Example No.	Compound Structure	Compound Name
78		N-([3,3'-bipyridin]-6-yl)-4-fluorobenzamide
79		N-([2,3'-bipyridin]-5-yl)-4-fluorobenzamide
80		4-fluoro-N-(5-(2-fluorophenyl)pyridin-2-yl)benzamide
81		4-fluoro-N-(6-(2-fluorophenyl)pyridin-3-yl)benzamide
82		4-fluoro-N-(2-(pyridin-3-yl)pyrimidin-5-yl)benzamide
83		4-fluoro-N-(5-(pyridin-3-yl)pyrimidin-2-yl)benzamide
84		4-fluoro-N-(2-(2-fluorophenyl)pyrimidin-5-yl)benzamide

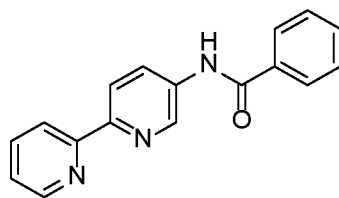
Example No.	Compound Structure	Compound Name
85		4-fluoro-N-(5-(2-fluorophenyl)pyrimidin-2-yl)benzamide
86		4-fluoro-N-(5-(pyridin-3-yl)pyrazin-2-yl)benzamide
87		4-fluoro-N-(5-(2-fluorophenyl)pyrazin-2-yl)benzamide
88		N-([2,2'-bipyridin]-5-yl)-6-fluoropicolinamide
89		N-(6-phenylpyridin-3-yl)benzamide

Example 3: *N-([2,3'-bipyridin]-6'-yl)benzamide*

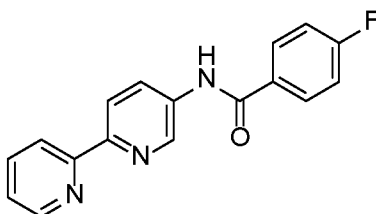


N-([2,3'-bipyridin]-6'-yl)benzamide was prepared using the general procedure described in

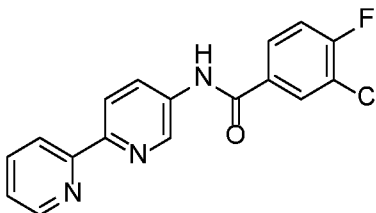
5 Example 1. ¹H NMR (CDCl₃, 400 MHz): δ_H 8.96 (s, 1H), 8.72-8.68 (m, 2H), 8.52 (d, 1H), 8.39 (d, 1H), 7.95-7.91 (m, 2H), 7.82-7.70 (m, 2H), 7.60-7.45 (m, 3H), MS (ESI): m/z 276 (M + H)⁺.

Example 18: *N*-([2,2'-bipyridin]-5-yl)benzamide

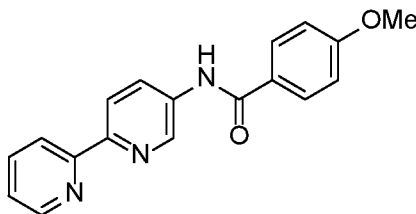
N-([2,2'-bipyridin]-5-yl)benzamide was prepared using the general procedure described in Example 1. ¹H NMR (CDCl₃, 400 MHz): δ_H 8.82 (d, 1H, J = 2.5 Hz), 8.69 (d, 1H, J = 4.75 Hz), 8.45-8.35 (m, 2H), 8.10 (d, 1H, J = 1.25 Hz), 7.93-7.90 (m, 2H), 7.59-7.47 (m, 3H), 7.32-7.30 (m, 1H), 7.19 (d, 1H, J = 1.75 Hz). MS (ESI): m/z 276 (M + H)⁺.

Example 19: *N*-([2,2'-bipyridin]-5-yl)-4-fluorobenzamide

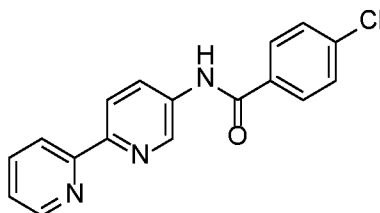
N-([2,2'-bipyridin]-5-yl)-4-fluorobenzamide was prepared using the general procedure described in Example 1. ¹H NMR (DMSO, 400 MHz): δ_H 10.8 (s, 1H), 9.15 (s, 1H), 8.72 (d, 1H, J = 4.5 Hz), 8.50-8.45 (m, 3H), 8.19-8.08 (m, 3H), 7.62 (d, 1H, J = 6.5 Hz), 7.40 (t, 2H, J = 6.5 Hz), MS (ESI): m/z 294 (M + H)⁺.

Example 20: *N*-([2,2'-bipyridin]-5-yl)-3-chloro-4-fluorobenzamide

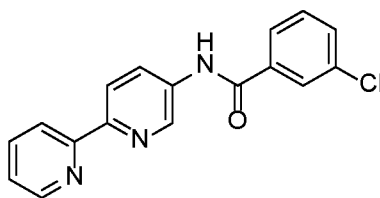
N-([2,2'-bipyridin]-5-yl)-3-chloro-4-fluorobenzamide was prepared using the general procedure described in Example 1. ¹H NMR (DMSO, 400 MHz): δ_H 11.1 (s, 1H), 9.20 (s, 1H), 8.75 (d, 1H, J = 4.5 Hz), 8.53-8.51 (m, 3H), 8.30 (d, 1H, J = 7.0 Hz), 8.26 (t, 1H, J = 7.5 Hz), 8.11-8.06 (m, 1H), 7.69 (t, 1H, J = 7.0 Hz), 7.62 (t, 1H, J = 9.0 Hz). MS (ESI): m/z 329 (M + H)⁺.

Example 21: *N-([2,2'-bipyridin]-5-yl)-4-methoxybenzamide*

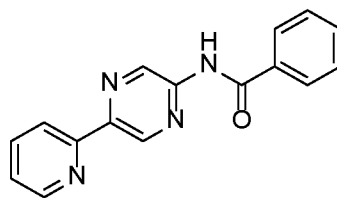
N-([2,2'-bipyridin]-5-yl)-4-methoxybenzamide was prepared using the general procedure described in Example 1. ¹H NMR (DMSO, 400 MHz): δ_{H} 10.75 (s, 1H), 9.23 (s, 1H), 8.76 (d, 1H, J = 4.5 Hz), 8.55-8.49 (m, 3H), 8.26 (t, 1H, J = 7.5 Hz), 8.07-8.03 (m, 2H), 7.69 (d, 1H, J = 6.5 Hz), 7.11-7.08 (m, 2H), 3.84 (s, 3H). MS (ESI): m/z 306 (M + H)⁺.

Example 22: *N-([2,2'-bipyridin]-5-yl)-4-chlorobenzamide*

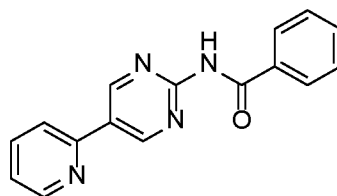
N-([2,2'-bipyridin]-5-yl)-4-chlorobenzamide was prepared using the general procedure described in Example 1. ¹H NMR (DMSO, 400 MHz): δ_{H} 10.79 (s, 1H), 9.10 (s, 1H), 8.69 (d, 1H, J = 4.5 Hz), 8.45-8.40 (m, 3H), 8.08-8.02 (m, 3H), 7.63 (d, 2H, J = 8.5 Hz), 7.53-7.52 (m, 1H). MS (ESI): m/z 311 (M + H)⁺.

Example 23: *N-([2,2'-bipyridin]-5-yl)-3-chlorobenzamide*

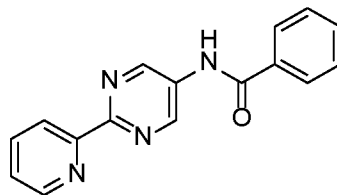
N-([2,2'-bipyridin]-5-yl)-3-chlorobenzamide was prepared using the general procedure described in Example 1. ¹H NMR (DMSO, 400 MHz): δ_{H} 10.9 (s, 1H), 9.16 (s, 1H), 8.74 (d, 1H, J = 4.4 Hz), 8.51 (s, 1H), 8.48 (s, 2H), 8.21 (t, 1H, J = 7.25 Hz), 8.08 (t, 1H, J = 2.0 Hz), 7.98 (d, 1H, J = 7.8 Hz), 7.70 (d, 1H, J = 9.0 Hz), 7.63-7.58 (m, 2H). MS (ESI): m/z 311 (M + H)⁺.

Example 33: *N*-(5-(pyridin-2-yl)pyrazin-2-yl)benzamide

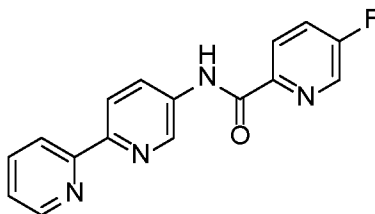
N-(5-(pyridin-2-yl)pyrazin-2-yl)benzamide was prepared using the general procedure described in Example 1. ^1H NMR (CDCl_3 , 400 MHz): δ_{H} 9.75 (d, 1H, $J = 1.50$ Hz), 9.35 (d, 1H, $J = 1.50$ Hz), 8.69 (d, 1H, $J = 4.0$ Hz), 8.61 (br s, 1H), 8.37 (d, 1H, $J = 8.0$ Hz), 7.97 (m, 2H), 7.84 (t, 1H, $J = 7.75$ Hz), 7.54 (m, 3H), 7.34 (t, 1H, $J = 6.25$ Hz). MS (ESI): m/z 277 ($\text{M} + \text{H}$) $^+$.

Example 48: *N*-(5-(pyridin-2-yl)pyrimidin-2-yl)benzamide

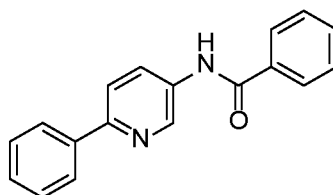
N-(5-(pyridin-2-yl)pyrimidin-2-yl)benzamide was prepared using the general procedure described in Example 1. ^1H NMR (CDCl_3 , 400 MHz): δ_{H} 9.28 (s, 2H), 8.73 (d, 1H, $J = 4.75$ Hz), 8.40 (d, 1H, $J = 8.0$ Hz), 7.98-7.97 (m, 2H), 7.82-7.79 (td, 1H, $J = 7.75$ Hz), 7.74-7.65 (m, 3H), 7.53-7.45 (m, 1H). MS (ESI): m/z 277 ($\text{M} + \text{H}$) $^+$.

Example 63: *N*-(2-(pyridin-2-yl)pyrimidin-5-yl)benzamide

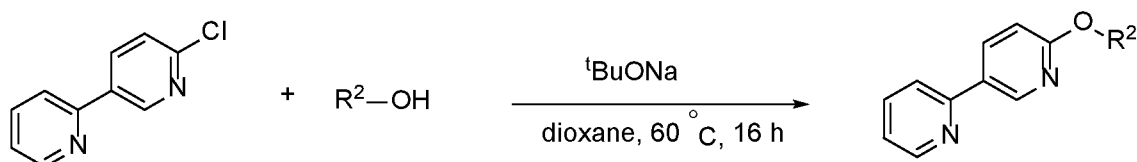
N-(2-(pyridin-2-yl)pyrimidin-5-yl)benzamide was prepared using the general procedure described in Example 1. ^1H NMR (CDCl_3 , 400 MHz): δ_{H} 9.33 (s, 2H), 8.78 (s, 1H), 8.52 (d, 1H, $J = 8.0$ Hz), 8.27 (br s, 1H), 7.97 (d, 2H, $J = 7.25$ Hz), 7.87 (t, 2H, $J = 7.0$ Hz), 7.63-7.65 (m, 1H), 7.54-7.39 (m, 4H). MS (ESI): m/z 277 ($\text{M} + \text{H}$) $^+$.

Example 88: *N*-([2,2'-bipyridin]-5-yl)-6-fluoropicolinamide

N-([2,2'-bipyridin]-5-yl)-6-fluoropicolinamide was prepared using the general procedure described in Example 1. ^1H NMR (CDCl_3 , 400 MHz): δ_{H} 11.0 (s, 1H), 9.17 (d, 1H, $J = 2.5$ Hz), 8.77 (d, 1H, $J = 2.5$ Hz), 8.67 (d, 1H, $J = 4.0$ Hz), 8.50 (dd, 1H, $J = 8.75$ Hz), 8.37 (dd, 2H, $J = 8.5$ Hz), 8.27 (q, 1H, $J = 8.5$ Hz, H_1), 7.96 (d, 2H, $J = 8.25$ Hz), 7.43-7.41 (m, 1H). MS (ESI): m/z 295 ($M + H$) $^+$.

Example 89: *N*-(6-phenylpyridin-3-yl)benzamide

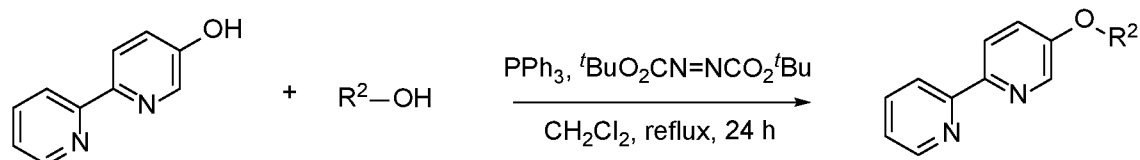
N-(6-phenylpyridin-3-yl)benzamide was prepared using the general procedure described in Example 1. ^1H NMR (CDCl_3 , 400 MHz): δ_{H} 8.73 (s, 1H), 8.41 (d, 1H, $J = 2.5$ Hz), 7.98 (d, 2H, $J = 1.5$ Hz), 7.95 (s, 1H), 7.91 (d, 2H, $J = 7.0$ Hz), 7.77 (d, 1H, $J = 8.5$ Hz), 7.61-7.38 (m, 6H). MS (ESI): m/z 275 ($M + H$) $^+$.

Example 90. General Procedure for Synthesis of Ether Analogs

To a solution of an appropriately substituted alcohol (1 mmol) and anhydrous 1,4-dioxane (1 mL) is added sodium *tert*-butoxide (106 mg, 1.1 mmol). The tube is flushed with argon, capped, and the mixture is stirred at room temperature for five minutes. A solution of 6'-chloro-2,2'-bipyridine (190 mg, 1 mmol) in anhydrous 1,4-dioxane (1 mL) is then added and the mixture is stirred at 60 °C for 16 hours. The mixture is partitioned between ethyl acetate (3 x 5 mL) and 5% aqueous NaH_2PO_4 (5 mL). The organic layer is evaporated and the residue is purified using silica or basic alumina column chromatography and eluted with the appropriate

solvent mixtures (*e.g.*, ethyl acetate-methanol-triethylamine, or cyclohexane-ethyl acetate) to give the desired compound.

Example 91. Alternative Procedure for Synthesis of Ether Analogs



2,2'-Bipyridin-5-ol (138 mg, 0.8 mmol), an appropriately substituted alcohol (0.8 mmol), di-tert-butyl azodicarboxylate, (219 mg, 0.95 mmol) and polymer-bound triphenylphosphine (314 mg, 1.2 mmol) are dissolved in dichloromethane (6 mL). The reaction mixture is heated to 40 °C for 24 hours. The reaction is then diluted with dichloromethane (15 mL), washed with saturated sodium bicarbonate solution and brine. The organic layer is dried with NaSO₄ and concentrated *in vacuo*. The residue is purified using a silica or basic alumina column chromatography and eluted with the appropriate solvent mixtures (*e.g.*, ethyl acetate-methanol-triethylamine, or cyclohexane-ethyl acetate) to give the desired compound.

10

Examples 92-211.

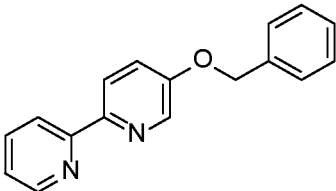
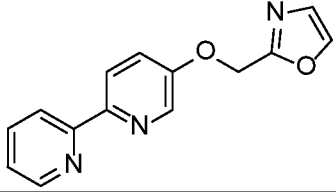
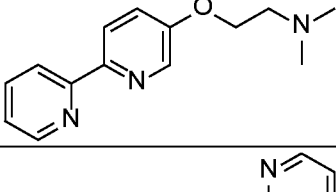
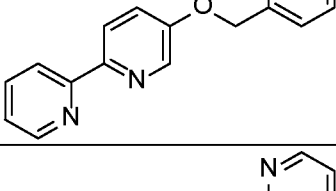
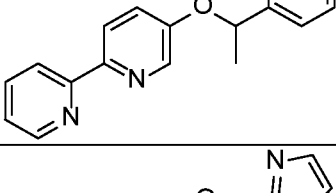
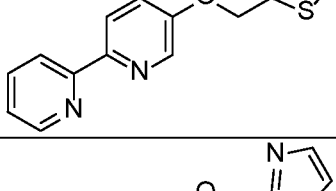
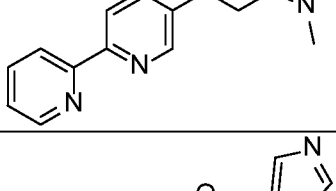
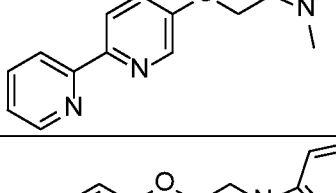
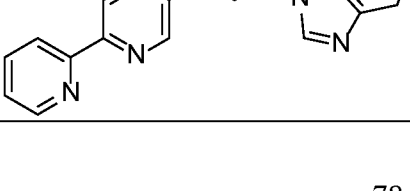
15

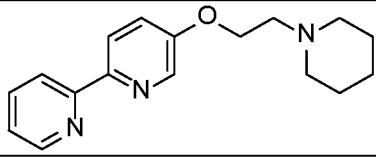
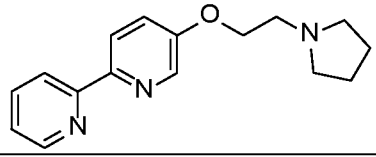
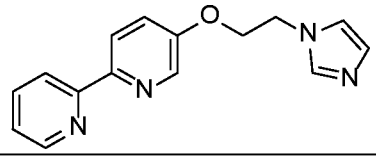
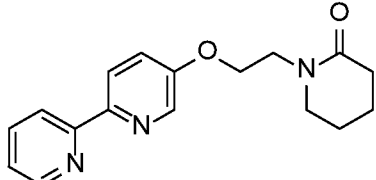
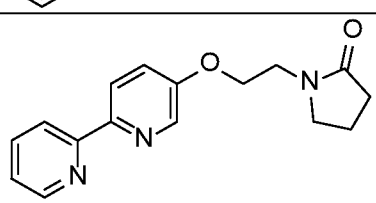
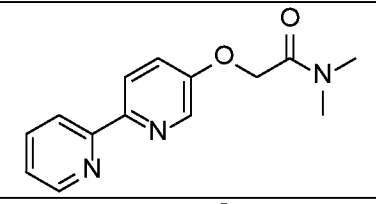
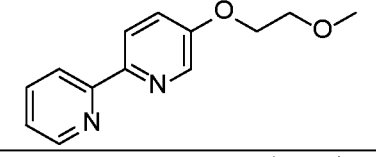
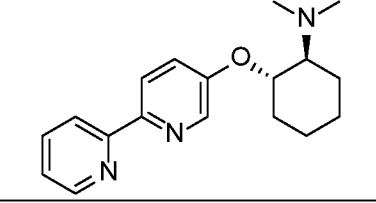
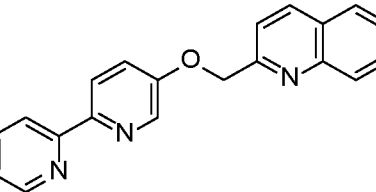
The compounds of Examples 92-211 can be prepared according to the procedures described in Examples 90-91 using appropriately substituted starting materials.

Example No.	Compound Structure	Compound Name
92		6'-(benzyloxy)-2,3'-bipyridine
93		2-(((2,3'-bipyridin]-6'-yloxy)methyl)oxazole
94		2-([2,3'-bipyridin]-6'-yloxy)-N,N-dimethylethan-1-amine

Example No.	Compound Structure	Compound Name
95		6'-(pyridin-2-ylmethoxy)-2,3'-bipyridine
96		6'-(1-(pyridin-2-yl)ethoxy)-2,3'-bipyridine
97		2-(((2,3'-bipyridin]-6'-yloxy)methyl)thiazole
98		6'-((1-methyl-1H-imidazol-2-yl)methoxy)-2,3'-bipyridine
99		6'-((1-methyl-1H-imidazol-5-yl)methoxy)-2,3'-bipyridine
100		1-(2-([2,3'-bipyridin]-6'-yloxy)ethyl)-1H-benzo[d]imidazole
101		6'-(2-(piperidin-1-yl)ethoxy)-2,3'-bipyridine
102		6'-(2-(pyrrolidin-1-yl)ethoxy)-2,3'-bipyridine
103		6'-(2-(1H-imidazol-1-yl)ethoxy)-2,3'-bipyridine

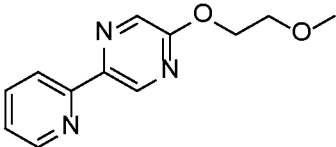
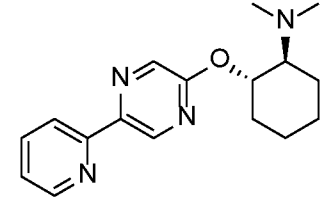
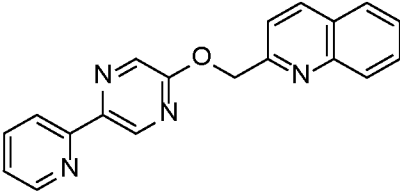
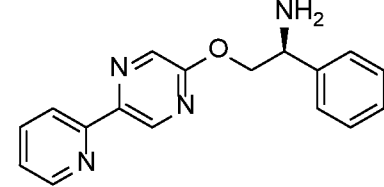
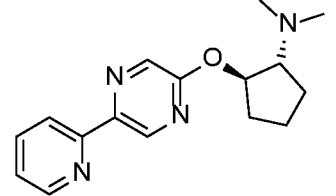
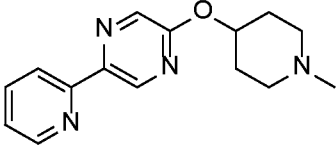
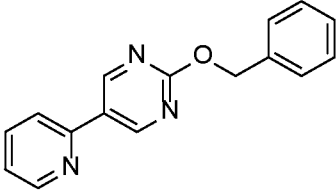
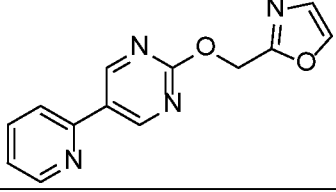
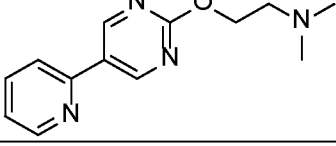
Example No.	Compound Structure	Compound Name
104		1-(2-([2,3'-bipyridin]-6'-yloxy)ethyl)piperidin-2-one
105		1-(2-([2,3'-bipyridin]-6'-yloxy)ethyl)pyrrolidin-2-one
106		2-([2,3'-bipyridin]-6'-yloxy)-N,N-dimethylacetamide
107		6'-(2-methoxyethoxy)-2,3'-bipyridine
108		(1S,2S)-2-([2,3'-bipyridin]-6'-yloxy)-N,N-dimethylcyclohexan-1-amine
109		2-(((2,3'-bipyridin]-6'-yloxy)methyl)quinolone
110		(S)-2-([2,3'-bipyridin]-6'-yloxy)-1-phenylethan-1-amine
111		(1R,2R)-2-([2,3'-bipyridin]-6'-yloxy)-N,N-dimethylcyclopentan-1-amine
112		6'-((1-methylpiperidin-4-yl)oxy)-2,3'-bipyridine

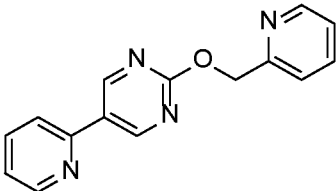
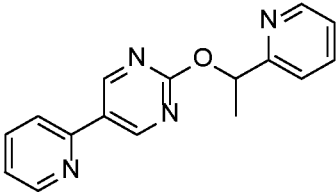
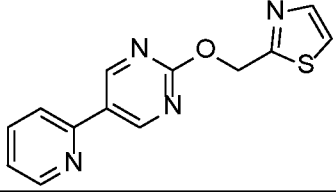
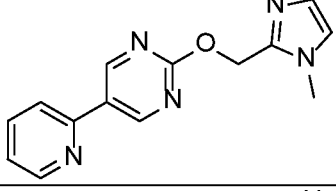
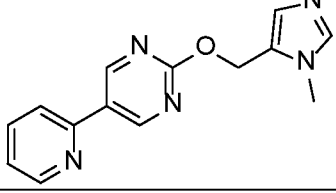
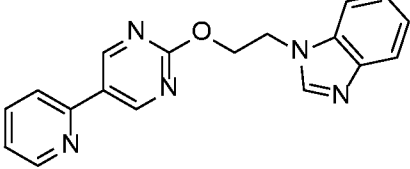
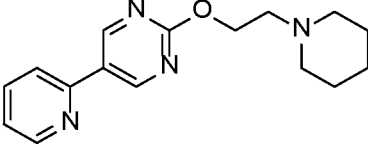
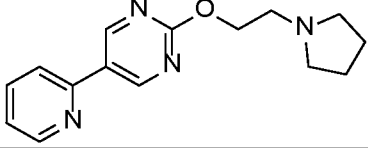
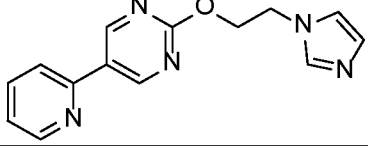
Example No.	Compound Structure	Compound Name
113		5-(benzyloxy)-2,2'-bipyridine
114		2-(((2,2'-bipyridin]-5-yloxy)methyl)oxazole
115		2-([2,2'-bipyridin]-5-yloxy)-N,N-dimethylethan-1-amine
116		5-(pyridin-2-ylmethoxy)-2,2'-bipyridine
117		5-(1-(pyridin-2-yl)ethoxy)-2,2'-bipyridine
118		2-(((2,2'-bipyridin]-5-yloxy)methyl)thiazole
119		5-((1-methyl-1H-imidazol-2-yl)methoxy)-2,2'-bipyridine
120		5-((1-methyl-1H-imidazol-5-yl)methoxy)-2,2'-bipyridine
121		1-(2-([2,2'-bipyridin]-5-yloxy)ethyl)-1H-benzo[d]imidazole

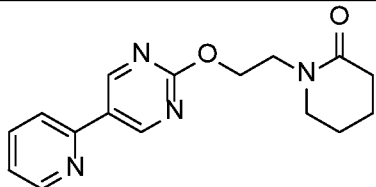
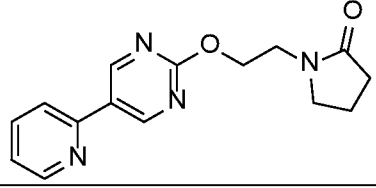
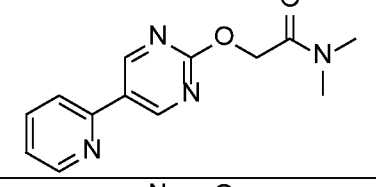
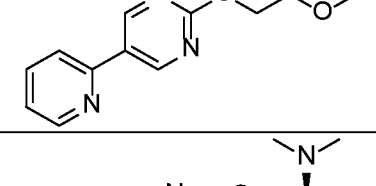
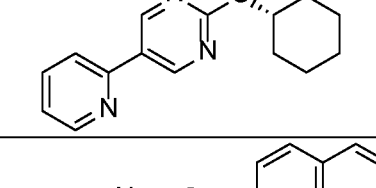
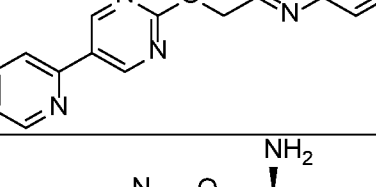
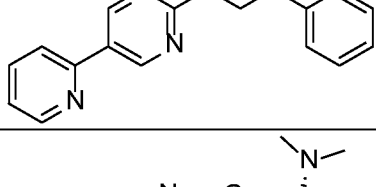
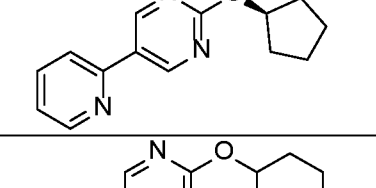
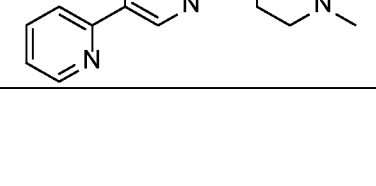
Example No.	Compound Structure	Compound Name
122		5-(2-(piperidin-1-yl)ethoxy)-2,2'-bipyridine
123		5-(2-(pyrrolidin-1-yl)ethoxy)-2,2'-bipyridine
124		5-(2-(1H-imidazol-1-yl)ethoxy)-2,2'-bipyridine
125		1-(2-([2,2'-bipyridin]-5-yloxy)ethyl)piperidin-2-one
126		1-(2-([2,2'-bipyridin]-5-yloxy)ethyl)pyrrolidin-2-one
127		2-([2,2'-bipyridin]-5-yloxy)-N,N-dimethylacetamide
128		5-(2-methoxyethoxy)-2,2'-bipyridine
129		(1S,2S)-2-([2,2'-bipyridin]-5-yloxy)-N,N-dimethylcyclohexan-1-amine
130		2-(((2,2'-bipyridin]-5-yloxy)methyl)quinolone

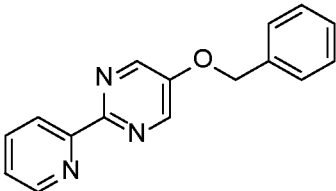
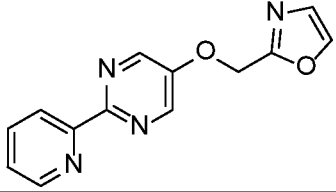
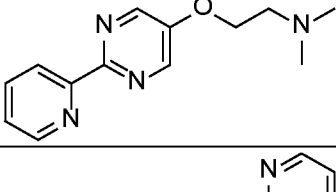
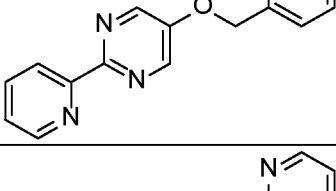
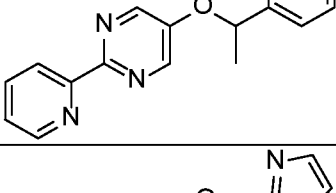
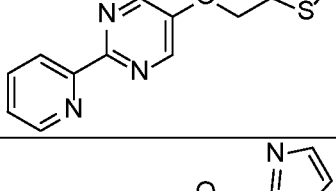
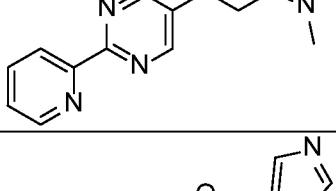
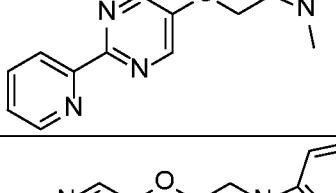
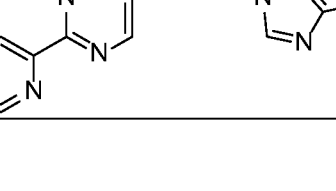
Example No.	Compound Structure	Compound Name
131		(S)-2-([2,2'-bipyridin]-5-yloxy)-1-phenylethan-1-amine
132		(1R,2R)-2-([2,2'-bipyridin]-5-yloxy)-N,N-dimethylcyclopentan-1-amine
133		5-((1-methylpiperidin-4-yl)oxy)-2,2'-bipyridine
134		2-(benzyloxy)-5-(pyridin-2-yl)pyrazine
135		2-(((5-(pyridin-2-yl)pyrazin-2-yl)oxy)methyl)oxazole
136		N,N-dimethyl-2-(((5-(pyridin-2-yl)pyrazin-2-yl)oxy)ethan-1-amine
137		2-(pyridin-2-yl)-5-(pyridin-2-ylmethoxy)pyrazine
138		2-(pyridin-2-yl)-5-(1-(pyridin-2-yl)ethoxy)pyrazine
139		2-(((5-(pyridin-2-yl)pyrazin-2-yl)oxy)methyl)thiazole

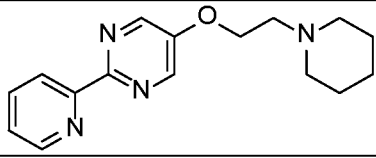
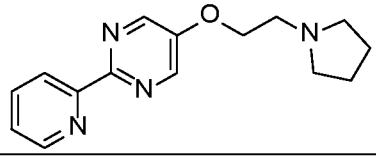
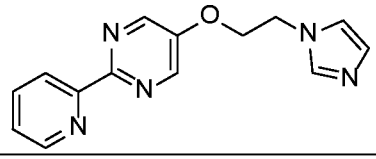
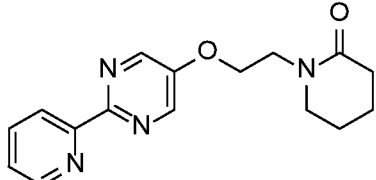
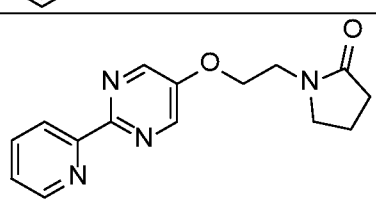
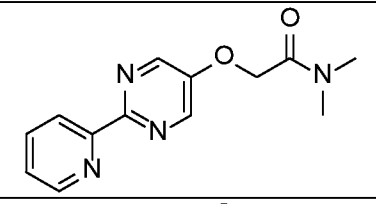
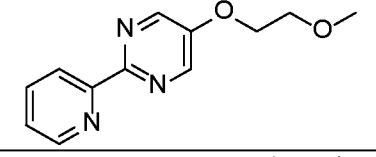
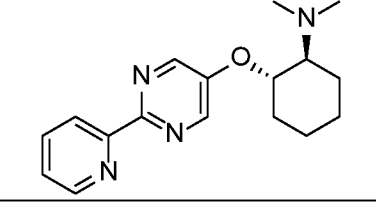
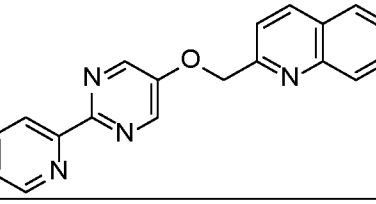
Example No.	Compound Structure	Compound Name
140		2-((1-methyl-1H-imidazol-2-yl)methoxy)-5-(pyridin-2-yl)pyrazine
141		2-((1-methyl-1H-imidazol-5-yl)methoxy)-5-(pyridin-2-yl)pyrazine
142		1-(2-((5-(pyridin-2-yl)pyrazin-2-yl)oxy)ethyl)-1H-benzo[d]imidazole
143		2-(2-(piperidin-1-yl)ethoxy)-5-(pyridin-2-yl)pyrazine
144		2-(pyridin-2-yl)-5-(2-(pyrrolidin-1-yl)ethoxy)pyrazine
145		2-(2-(1H-imidazol-1-yl)ethoxy)-5-(pyridin-2-yl)pyrazine
146		1-(2-((5-(pyridin-2-yl)pyrazin-2-yl)oxy)ethyl)piperidin-2-one
147		1-(2-((5-(pyridin-2-yl)pyrazin-2-yl)oxy)ethyl)pyrrolidin-2-one
148		N,N-dimethyl-2-((5-(pyridin-2-yl)pyrazin-2-yl)oxy)acetamide

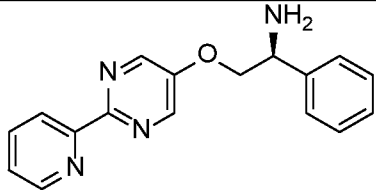
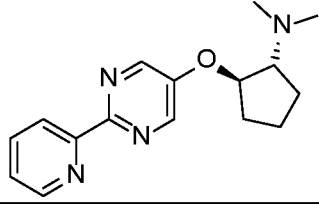
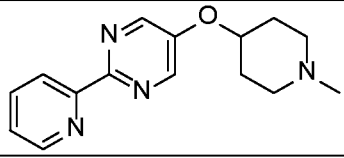
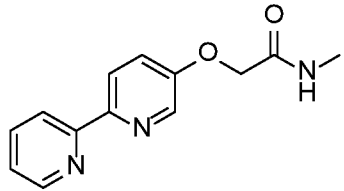
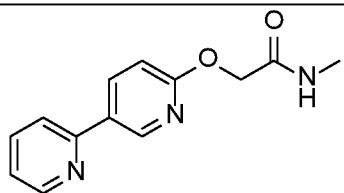
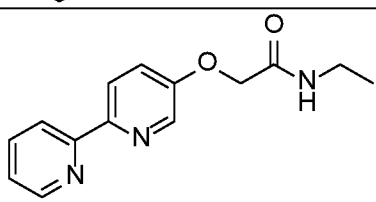
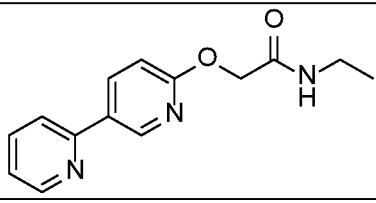
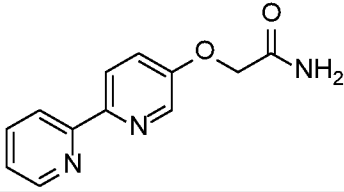
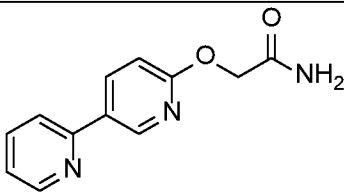
Example No.	Compound Structure	Compound Name
149		2-(2-methoxyethoxy)-5-(pyridin-2-yl)pyrazine
150		(1S,2S)-N,N-dimethyl-2-((5-(pyridin-2-yl)pyrazin-2-yl)oxy)cyclohexan-1-amine
151		2-(((5-(pyridin-2-yl)pyrazin-2-yl)oxy)methyl)quinolone
152		(S)-1-phenyl-2-((5-(pyridin-2-yl)pyrazin-2-yl)oxy)ethan-1-amine
153		(1R,2R)-N,N-dimethyl-2-((5-(pyridin-2-yl)pyrazin-2-yl)oxy)cyclopentan-1-amine
154		2-((1-methylpiperidin-4-yl)oxy)-5-(pyridin-2-yl)pyrazine
155		2-(benzyloxy)-5-(pyridin-2-yl)pyrimidine
156		2-(((5-(pyridin-2-yl)pyrimidin-2-yl)oxy)methyl)oxazole
157		N,N-dimethyl-2-((5-(pyridin-2-yl)pyrimidin-2-yl)oxy)ethan-1-amine

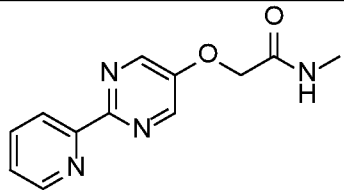
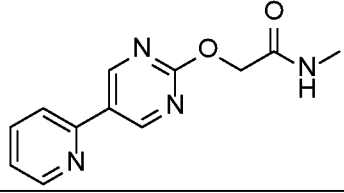
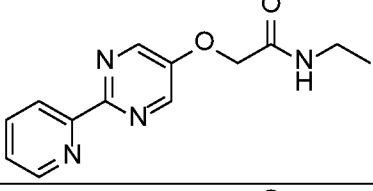
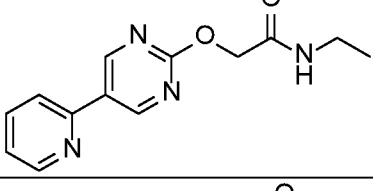
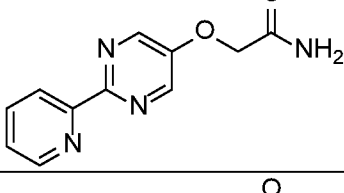
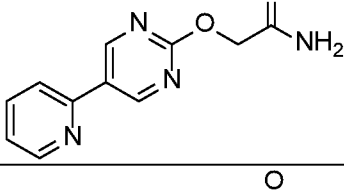
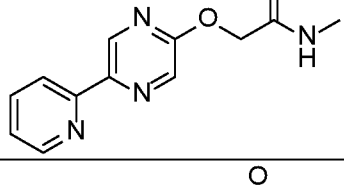
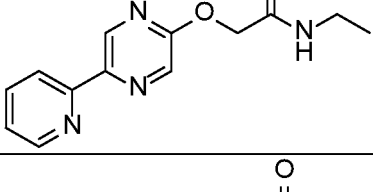
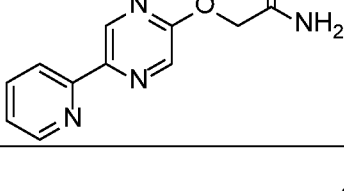
Example No.	Compound Structure	Compound Name
158		5-(pyridin-2-yl)-2-(pyridin-2-ylmethoxy)pyrimidine
159		5-(pyridin-2-yl)-2-(1-(pyridin-2-yl)ethoxy)pyrimidine
160		2-(((5-(pyridin-2-yl)pyrimidin-2-yl)oxy)methyl)thiazole
161		2-((1-methyl-1H-imidazol-2-yl)methoxy)-5-(pyridin-2-yl)pyrimidine
162		2-((1-methyl-1H-imidazol-5-yl)methoxy)-5-(pyridin-2-yl)pyrimidine
163		1-(2-(((5-(pyridin-2-yl)pyrimidin-2-yl)oxy)ethyl)-1H-benzo[d]imidazole
164		2-(2-(piperidin-1-yl)ethoxy)-5-(pyridin-2-yl)pyrimidine
165		5-(pyridin-2-yl)-2-(2-(pyrrolidin-1-yl)ethoxy)pyrimidine
166		2-(2-(1H-imidazol-1-yl)ethoxy)-5-(pyridin-2-yl)pyrimidine

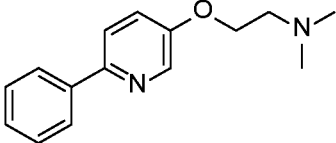
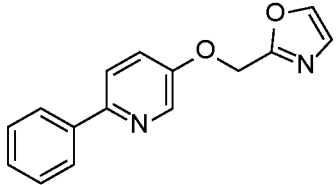
Example No.	Compound Structure	Compound Name
167		1-(2-((5-(pyridin-2-yl)pyrimidin-2-yl)oxy)ethyl)piperidin-2-one
168		1-(2-((5-(pyridin-2-yl)pyrimidin-2-yl)oxy)ethyl)pyrrolidin-2-one
169		N,N-dimethyl-2-((5-(pyridin-2-yl)pyrimidin-2-yl)oxy)acetamide
170		2-(2-methoxyethoxy)-5-(pyridin-2-yl)pyrimidine
171		(1S,2S)-N,N-dimethyl-2-((5-(pyridin-2-yl)pyrimidin-2-yl)oxy)cyclohexan-1-amine
172		2-(((5-(pyridin-2-yl)pyrimidin-2-yl)oxy)methyl)quinolone
173		(S)-1-phenyl-2-((5-(pyridin-2-yl)pyrimidin-2-yl)oxy)ethan-1-amine
174		(1R,2R)-N,N-dimethyl-2-((5-(pyridin-2-yl)pyrimidin-2-yl)oxy)cyclopentan-1-amine
175		2-((1-methylpiperidin-4-yl)oxy)-5-(pyridin-2-yl)pyrimidine

Example No.	Compound Structure	Compound Name
176		5-(benzyloxy)-2-(pyridin-2-yl)pyrimidine
177		2-(((2-(pyridin-2-yl)pyrimidin-5-yl)oxy)methyl)oxazole
178		N,N-dimethyl-2-(((2-(pyridin-2-yl)pyrimidin-5-yl)oxy)ethan-1-amine
179		2-(pyridin-2-yl)-5-(pyridin-2-ylmethoxy)pyrimidine
180		2-(pyridin-2-yl)-5-(1-(pyridin-2-yl)ethoxy)pyrimidine
181		2-(((2-(pyridin-2-yl)pyrimidin-5-yl)oxy)methyl)thiazole
182		5-((1-methyl-1H-imidazol-2-yl)methoxy)-2-(pyridin-2-yl)pyrimidine
183		5-((1-methyl-1H-imidazol-5-yl)methoxy)-2-(pyridin-2-yl)pyrimidine
184		1-(2-(((2-(pyridin-2-yl)pyrimidin-5-yl)oxy)ethyl)-1H-benzo[d]imidazole

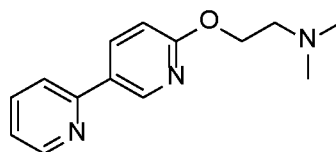
Example No.	Compound Structure	Compound Name
185		5-(2-(piperidin-1-yl)ethoxy)-2-(pyridin-2-yl)pyrimidine
186		2-(pyridin-2-yl)-5-(2-(pyrrolidin-1-yl)ethoxy)pyrimidine
187		5-(2-(1H-imidazol-1-yl)ethoxy)-2-(pyridin-2-yl)pyrimidine
188		1-(2-((2-(pyridin-2-yl)pyrimidin-5-yl)oxy)ethyl)piperidin-2-one
189		1-(2-((2-(pyridin-2-yl)pyrimidin-5-yl)oxy)ethyl)pyrrolidin-2-one
190		N,N-dimethyl-2-((2-(pyridin-2-yl)pyrimidin-5-yl)oxy)acetamide
191		5-(2-methoxyethoxy)-2-(pyridin-2-yl)pyrimidine
192		(1S,2S)-N,N-dimethyl-2-((2-(pyridin-2-yl)pyrimidin-5-yl)oxy)cyclohexan-1-amine
193		2-(((2-(pyridin-2-yl)pyrimidin-5-yl)oxy)methyl)quinolone

Example No.	Compound Structure	Compound Name
194		(S)-1-phenyl-2-((2-(pyridin-2-yl)pyrimidin-5-yl)oxy)ethan-1-amine
195		(1R,2R)-N,N-dimethyl-2-((2-(pyridin-2-yl)pyrimidin-5-yl)oxy)cyclopentan-1-amine
196		5-((1-methylpiperidin-4-yl)oxy)-2-(pyridin-2-yl)pyrimidine
197		2-([2,2'-bipyridin]-5-yloxy)-N-methylacetamide
198		2-([2,3'-bipyridin]-6'-yloxy)-N-methylacetamide
199		2-([2,2'-bipyridin]-5-yloxy)-N-ethylacetamide
200		2-([2,3'-bipyridin]-6'-yloxy)-N-ethylacetamide
201		2-([2,2'-bipyridin]-5-yloxy)acetamide
202		2-([2,3'-bipyridin]-6'-yloxy)acetamide

Example No.	Compound Structure	Compound Name
203		N-methyl-2-((2-(pyridin-2-yl)pyrimidin-5-yl)oxy)acetamide
204		N-methyl-2-((5-(pyridin-2-yl)pyrimidin-2-yl)oxy)acetamide
205		N-ethyl-2-((2-(pyridin-2-yl)pyrimidin-5-yl)oxy)acetamide
206		N-ethyl-2-((5-(pyridin-2-yl)pyrimidin-2-yl)oxy)acetamide
207		2-((2-(pyridin-2-yl)pyrimidin-5-yl)oxy)acetamide
208		2-((5-(pyridin-2-yl)pyrimidin-2-yl)oxy)acetamide
209		N-methyl-2-((5-(pyridin-2-yl)pyrazin-2-yl)oxy)acetamide
210		N-ethyl-2-((5-(pyridin-2-yl)pyrazin-2-yl)oxy)acetamide
211		2-((5-(pyridin-2-yl)pyrazin-2-yl)oxy)acetamide

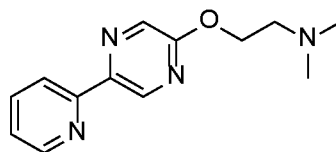
Example No.	Compound Structure	Compound Name
212		N,N-dimethyl-2-((6-phenylpyridin-3-yl)oxy)ethan-1-amine
213		2-(((6-phenylpyridin-3-yl)oxy)methyl)oxazole

Example 94: 2-([2,3'-bipyridin]-6'-yloxy)-N,N-dimethylethan-1-amine



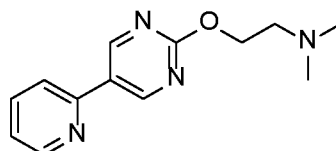
2-([2,3'-bipyridin]-6'-yloxy)-N,N-dimethylethan-1-amine was prepared using the general
 5 procedure described in Example 90. ¹H NMR (CDCl₃, 400 MHz): δ_H 8.73 (s, 1H), 8.65 (d, 1H),
 8.22 (d, 1H), 7.78-7.71 (m, 1H), 7.69-7.62 (m, 1H), 7.15-7.00 (m, 1H), 6.85 (d, 1H), 4.46 (m,
 2H), 2.76 (m, 2H), 2.38 (s, 6H). MS (ESI): m/z 244 (M + H)⁺.

Example 136: N,N-dimethyl-2-((5-(pyridin-2-yl)pyrazin-2-yl)oxy)ethan-1-amine



N,N-dimethyl-2-((5-(pyridin-2-yl)pyrazin-2-yl)oxy)ethan-1-amine was prepared using the
 general procedure described in Example 90. ¹H NMR (CDCl₃, 400 MHz): δ_H 9.11 (d, 1H, J =
 1.25 Hz), 8.65 (d, 1H, J = 4.25 Hz), 8.30 (d, 1H, J = 1.25 Hz), 8.21 (d, 1H, J = 8.0 Hz), 7.78 (t,
 1H, J = 7.75 Hz), 7.28-7.26 (m, 1H), 4.50 (t, 2H, J = 5.5 Hz), 2.75 (t, 2H, J = 5.5 Hz), 2.35 (s,
 15 6H). MS (ESI): m/z 245 (M + H)⁺.

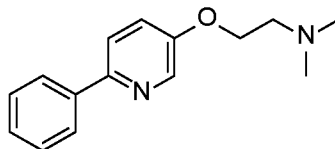
Example 157: N,N-dimethyl-2-((5-(pyridin-2-yl)pyrimidin-2-yl)oxy)ethan-1-amine



N,N-dimethyl-2-((5-(pyridin-2-yl)pyrimidin-2-yl)oxy)ethan-1-amine was prepared using the
 general procedure described in Example 90. ¹H NMR (CDCl₃, 400 MHz): δ_H 9.12 (s, 2H), 8.71-

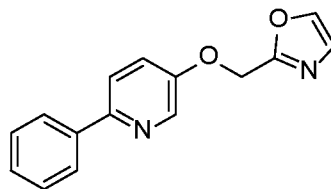
8.69 (m, 1H), 7.82-7.78 (m, 1H), 7.68 (d, 1H, J = 8.0 Hz), 7.32-7.25 (m, 1H), 4.91 (t, 2H, J = 5.0 Hz), 3.41 (t, 2H, J = 5.0 Hz), 2.84 (s, 6H). MS (ESI): m/z 245 (M + H)⁺.

Example 212: *N,N*-dimethyl-2-(((6-phenylpyridin-3-yl)oxy)ethan-1-amine



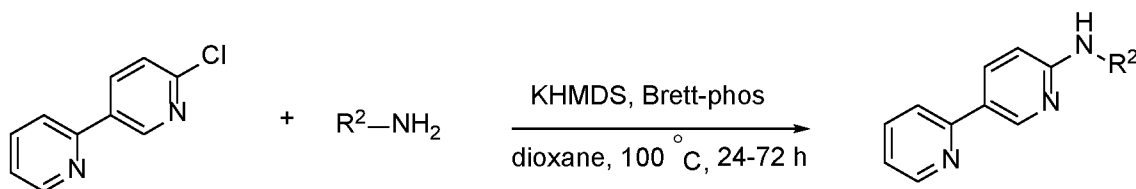
N,N-dimethyl-2-(((6-phenylpyridin-3-yl)oxy)ethan-1-amine was prepared using the general procedure described in Example 91. ¹H NMR (CDCl₃, 400 MHz): δ_H 8.40 (d, 1H, J = 3.0 Hz), 7.91 (d, 2H, J = 7.5 Hz), 7.63 (d, 1H, J = 8.5 Hz), 7.44-7.34 (m, 3H), 7.28-7.25 (m, 1H), 4.12 (t, 2H, J = 5.65 Hz), 2.75 (t, 2H, J = 5.65 Hz), 2.23 (s, 6H). MS (ESI): m/z 243 (M + H)⁺.

Example 213: 2-(((6-phenylpyridin-3-yl)oxy)methyl)oxazole



2-(((6-phenylpyridin-3-yl)oxy)methyl)oxazole was prepared using the general procedure described in Example 91. ¹H NMR (CDCl₃, 400 MHz): δ_H 8.65 (d, 1H, J = 3.0 Hz), 7.92 (d, 2H, J = 8.5 Hz), 7.71 (s, 1H), 7.68 (d, 1H, J = 8.8 Hz), 7.46-7.37 (m, 4H), 7.17 (s, 1H), 5.24 (s, 2H). MS (ESI): m/z 253 (M + H)⁺.

Example 214. General Procedure for Synthesis of Amine Analogs

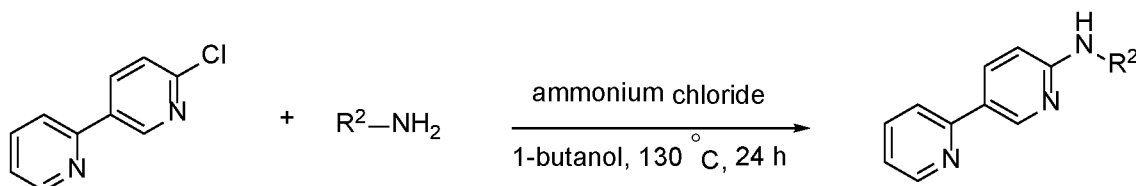


A mixture of 6'-chloro- 2,3'-bipyridine (95 mg, 0.5 mmol) an appropriately substituted amine (1 mmol) in anhydrous 1,4-dioxane (5 mL), and potassium bis(trimethylsilyl)amide (KHMDS, 263 mg, 1.3 mmol) is purged with argon for 10-15 minutes. 2-(Dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl (Brett-phos, 13.7 mg, 1.5 mol%) is added and the reaction mixture is stirred and heated at 100°C for 24-72 hours. The solution is cooled, saturated aqueous NaHCO₃ (10 mL) and dichloromethane (25 mL) are added, and the phases are separated. The aqueous phase is extracted with dichloromethane (2 x 25 mL).

The combined organics are dried with Na₂SO₄ and evaporated. The residue is purified using a silica or basic alumina column chromatography and eluted with the appropriate solvent mixtures (*e.g.*, ethyl acetate-methanol-triethylamine, or cyclohexane-ethyl acetate) to give the desired compound.

5

Example 215. Alternative Procedure for Synthesis of Amine Analogs



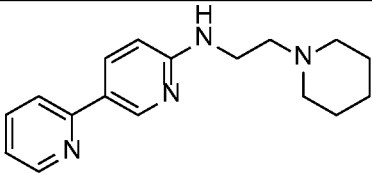
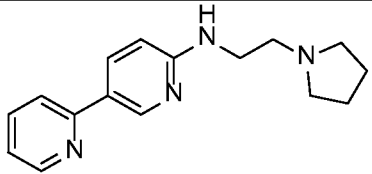
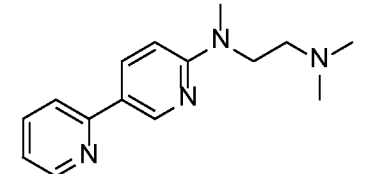
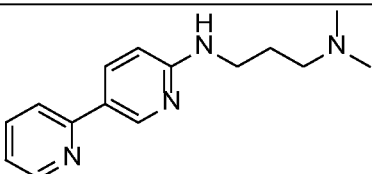
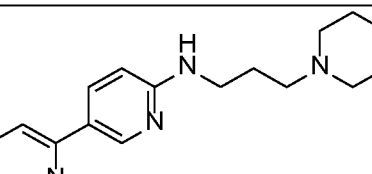
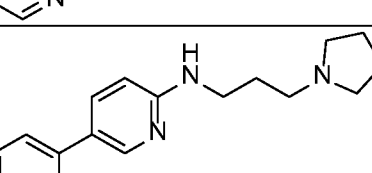
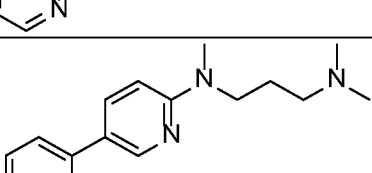
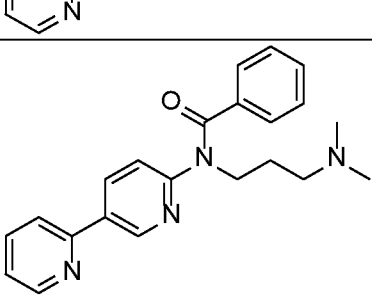
6'-chloro-2,3'-bipyridine (95 mg, 0.5 mmol), ammonium chloride (31.1 mg, 0.58 mmol) and an appropriately substituted amine (2.5 mmol) in 1-butanol (5 mL) are heated to 130 °C for 24 hours. The solvent is removed *in vacuo* and the residue is then partitioned between ethyl acetate and water (2:1, 15 mL). The aqueous layer is then extracted with EtOAc (2 x 5 mL) and the organic fractions combined and dried over Na₂SO₄. The reaction mixture is filtered and concentrated *in vacuo*. The residue is purified using a silica or basic alumina column chromatography and eluted with the appropriate solvent mixtures (*e.g.*, ethyl acetate-methanol-triethylamine, or cyclohexane-ethyl acetate) to give the desired compound.

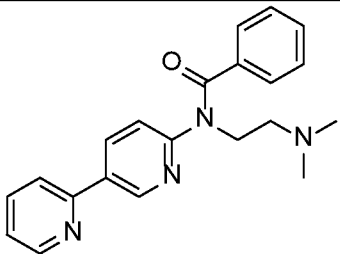
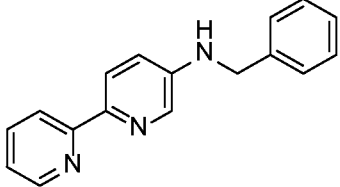
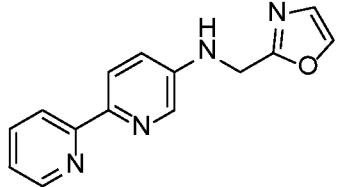
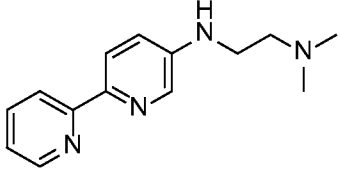
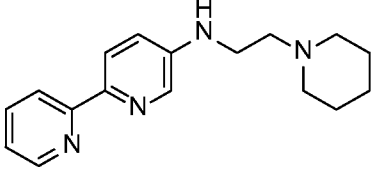
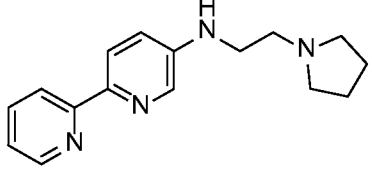
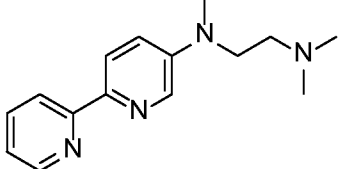
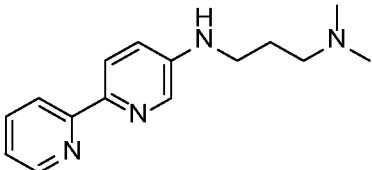
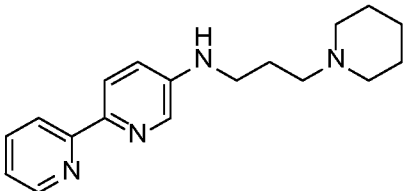
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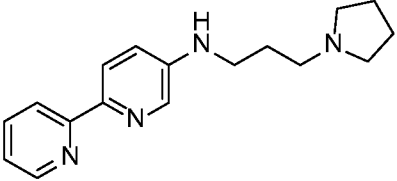
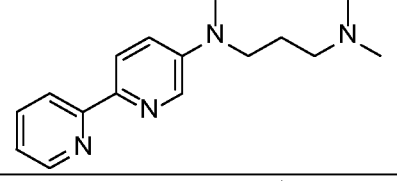
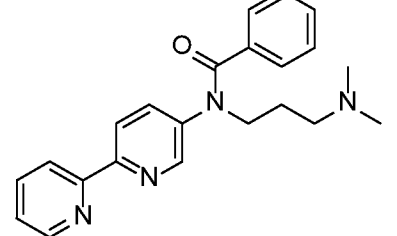
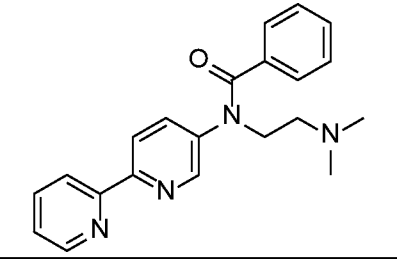
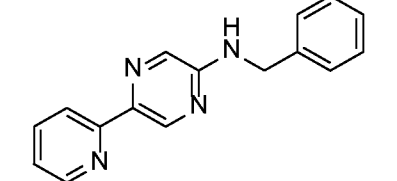
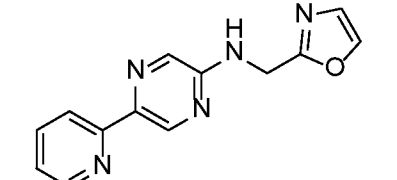
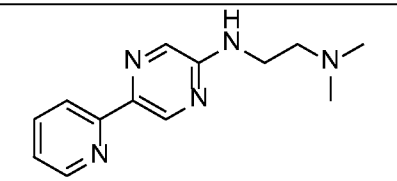
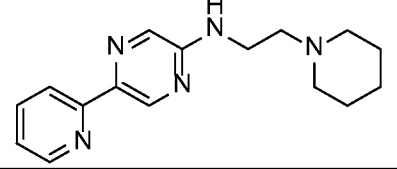
Examples 216-275.

The compounds of Examples 216-275 can be prepared according to the procedures described in Examples 214-215 using appropriately substituted starting materials.

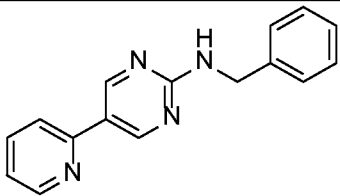
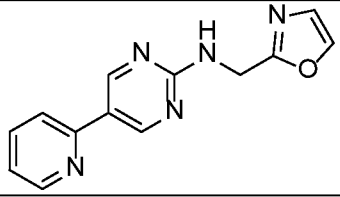
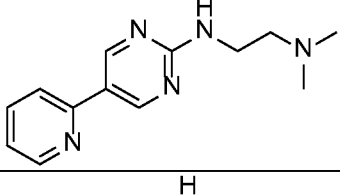
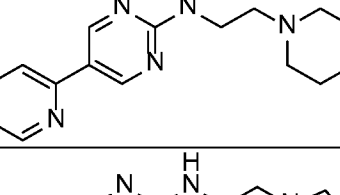
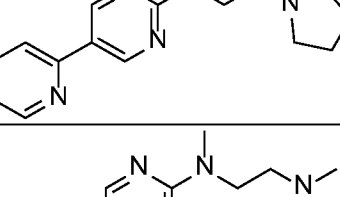
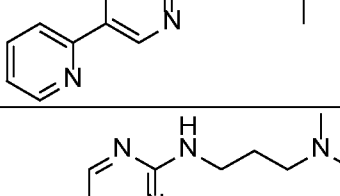
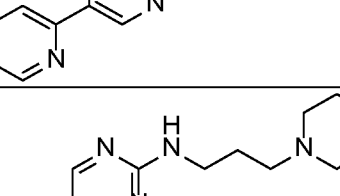
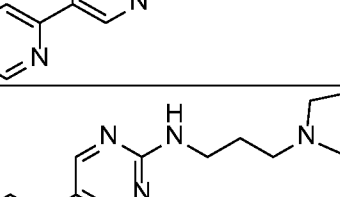
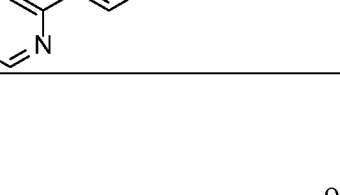
Example No.	Compound Structure	Compound Name
216		N-benzyl-[2,3'-bipyridin]-6'-amine
217		N-(oxazol-2-ylmethyl)-[2,3'-bipyridin]-6'-amine
218		N1-([2,3'-bipyridin]-6'-yl)-N2,N2-dimethylethane-1,2-diamine

Example No.	Compound Structure	Compound Name
219		N-(2-(piperidin-1-yl)ethyl)-[2,3'-bipyridin]-6'-amine
220		N-(2-(pyrrolidin-1-yl)ethyl)-[2,3'-bipyridin]-6'-amine
221		N1-([2,3'-bipyridin]-6'-yl)-N1,N2,N2-trimethylethane-1,2-diamine
222		N1-([2,3'-bipyridin]-6'-yl)-N3,N3-dimethylpropane-1,3-diamine
223		N-(3-(piperidin-1-yl)propyl)-[2,3'-bipyridin]-6'-amine
224		N-(3-(pyrrolidin-1-yl)propyl)-[2,3'-bipyridin]-6'-amine
225		N1-([2,3'-bipyridin]-6'-yl)-N1,N3,N3-trimethylpropane-1,3-diamine
226		N-([2,3'-bipyridin]-6'-yl)-N-(3-(dimethylamino)propyl)benzamide

Example No.	Compound Structure	Compound Name
227		N-([2,3'-bipyridin]-6'-yl)-N-(2-(dimethylamino)ethyl)benzamide
228		N-benzyl-[2,2'-bipyridin]-5-amine
229		N-(oxazol-2-ylmethyl)-[2,2'-bipyridin]-5-amine
230		N1-([2,2'-bipyridin]-5-yl)-N2,N2-dimethylethane-1,2-diamine
231		N-(2-(piperidin-1-yl)ethyl)-[2,2'-bipyridin]-5-amine
232		N-(2-(pyrrolidin-1-yl)ethyl)-[2,2'-bipyridin]-5-amine
233		N1-([2,2'-bipyridin]-5-yl)-N1,N2,N2-trimethylethane-1,2-diamine
234		N1-([2,2'-bipyridin]-5-yl)-N3,N3-dimethylpropane-1,3-diamine
235		N-(3-(piperidin-1-yl)propyl)-[2,2'-bipyridin]-5-amine

Example No.	Compound Structure	Compound Name
236		N-(3-(pyrrolidin-1-yl)propyl)-[2,2'-bipyridin]-5-amine
237		N1-([2,2'-bipyridin]-5-yl)-N1,N3,N3-trimethylpropane-1,3-diamine
238		N-([2,2'-bipyridin]-5-yl)-N-(3-(dimethylamino)propyl)benzamide
239		N-([2,2'-bipyridin]-5-yl)-N-(2-(dimethylamino)ethyl)benzamide
240		N-benzyl-5-(pyridin-2-yl)pyrazin-2-amine
241		N-(oxazol-2-ylmethyl)-5-(pyridin-2-yl)pyrazin-2-amine
242		N1,N1-dimethyl-N2-(5-(pyridin-2-yl)pyrazin-2-yl)ethane-1,2-diamine
243		N-(2-(piperidin-1-yl)ethyl)-5-(pyridin-2-yl)pyrazin-2-amine

Example No.	Compound Structure	Compound Name
244		5-(pyridin-2-yl)-N-(2-(pyrrolidin-1-yl)ethyl)pyrazin-2-amine
245		N1,N1,N2-trimethyl-N2-(5-(pyridin-2-yl)pyrazin-2-yl)ethane-1,2-diamine
246		N1,N1-dimethyl-N3-(5-(pyridin-2-yl)pyrazin-2-yl)propane-1,3-diamine
247		N-(3-(piperidin-1-yl)propyl)-5-(pyridin-2-yl)pyrazin-2-amine
248		5-(pyridin-2-yl)-N-(3-(pyrrolidin-1-yl)propyl)pyrazin-2-amine
249		N1,N1,N3-trimethyl-N3-(5-(pyridin-2-yl)pyrazin-2-yl)propane-1,3-diamine
250		N-(3-(dimethylamino)propyl)-N-(5-(pyridin-2-yl)pyrazin-2-yl)benzamide
251		N-(2-(dimethylamino)ethyl)-N-(5-(pyridin-2-yl)pyrazin-2-yl)benzamide

Example No.	Compound Structure	Compound Name
252		N-benzyl-5-(pyridin-2-yl)pyrimidin-2-amine
253		N-(oxazol-2-ylmethyl)-5-(pyridin-2-yl)pyrimidin-2-amine
254		N1,N1-dimethyl-N2-(5-(pyridin-2-yl)pyrimidin-2-yl)ethane-1,2-diamine
255		N-(2-(piperidin-1-yl)ethyl)-5-(pyridin-2-yl)pyrimidin-2-amine
256		5-(pyridin-2-yl)-N-(2-(pyrrolidin-1-yl)ethyl)pyrimidin-2-amine
257		N1,N1,N2-trimethyl-N2-(5-(pyridin-2-yl)pyrimidin-2-yl)ethane-1,2-diamine
258		N1,N1-dimethyl-N3-(5-(pyridin-2-yl)pyrimidin-2-yl)propane-1,3-diamine
259		N-(3-(piperidin-1-yl)propyl)-5-(pyridin-2-yl)pyrimidin-2-amine
260		5-(pyridin-2-yl)-N-(3-(pyrrolidin-1-yl)propyl)pyrimidin-2-amine

Example No.	Compound Structure	Compound Name
261		N1,N1,N3-trimethyl-N3-(5-(pyridin-2-yl)pyrimidin-2-yl)propane-1,3-diamine
262		N-(3-(dimethylamino)propyl)-N-(5-(pyridin-2-yl)pyrimidin-2-yl)benzamide
263		N-(2-(dimethylamino)ethyl)-N-(5-(pyridin-2-yl)pyrimidin-2-yl)benzamide
264		N-benzyl-2-(pyridin-2-yl)pyrimidin-5-amine
265		N-(oxazol-2-ylmethyl)-2-(pyridin-2-yl)pyrimidin-5-amine
266		N1,N1-dimethyl-N2-(2-(pyridin-2-yl)pyrimidin-5-yl)ethane-1,2-diamine
267		N-(2-(piperidin-1-yl)ethyl)-2-(pyridin-2-yl)pyrimidin-5-amine
268		2-(pyridin-2-yl)-N-(2-(pyrrolidin-1-yl)ethyl)pyrimidin-5-amine

Example No.	Compound Structure	Compound Name
269		N1,N1,N2-trimethyl-N2-(2-(pyridin-2-yl)pyrimidin-5-yl)ethane-1,2-diamine
270		N1,N1-dimethyl-N3-(2-(pyridin-2-yl)pyrimidin-5-yl)propane-1,3-diamine
271		N-(3-(piperidin-1-yl)propyl)-2-(pyridin-2-yl)pyrimidin-5-amine
272		2-(pyridin-2-yl)-N-(3-(pyrrolidin-1-yl)propyl)pyrimidin-5-amine
273		N1,N1,N3-trimethyl-N3-(2-(pyridin-2-yl)pyrimidin-5-yl)propane-1,3-diamine
274		N-(3-(dimethylamino)propyl)-N-(2-(pyridin-2-yl)pyrimidin-5-yl)benzamide
275		N-(2-(dimethylamino)ethyl)-N-(2-(pyridin-2-yl)pyrimidin-5-yl)benzamide

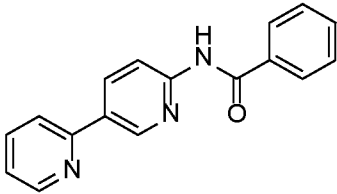
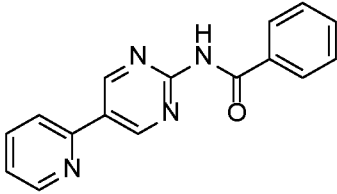
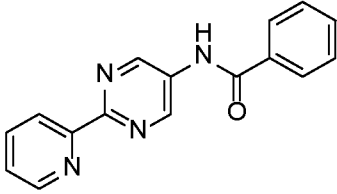
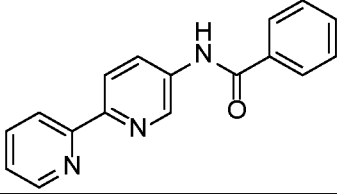
Example 276. Evaluation of the Biological Activity of Example Compounds

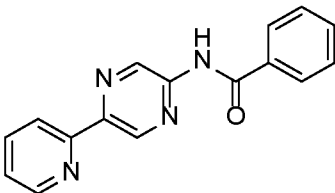
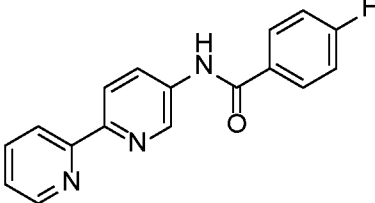
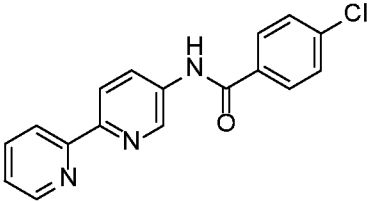
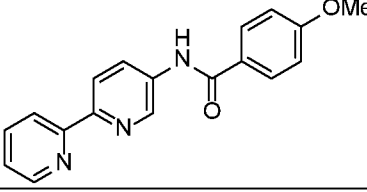
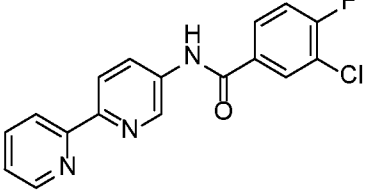
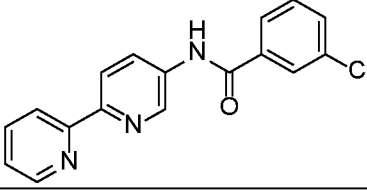
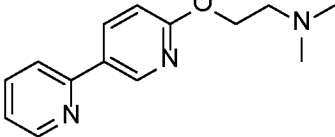
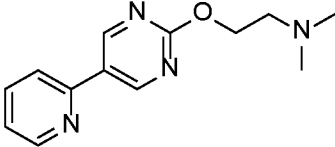
***In vitro* assay in primary astrocyte cultures.** Example compounds were initially evaluated in PA-EAAT2 cells, a primary astrocyte stably expressing human EAAT2 mRNAs (Kong et al., *J Clin Invest.* 124:1255-67). Cells were treated with the example compounds at 0.25 μ M, 0.5 μ M, 1 μ M, 2.5 μ M, 5 μ M, 10 μ M, and 25 μ M for 24 hr and then harvested for

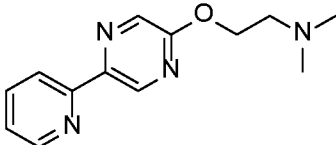
measuring EAAT2 protein levels by Western blot analysis. Table 1 shows the fold increases in EAAT2 protein levels relative to DMSO controls at indicated concentration that reaches maximum activity.

***In vivo* assay in wild-type mice.** Example compounds that were capable of increasing EAAT2 protein expression in cultured astrocytes were further evaluated in C57BL/6J mice. Mice were treated by oral gavage with the compound at 40 mg/kg. At 24 hr post-treatment, mice were euthanized and forebrains were harvested for the gliosome preparation (Dunkley et al., *Nat Protoc* 3, 1718-1728). Gliosomes are enriched with astrocytic processes, and majority of EAAT2 is localized in astrocytic processes (gliosomes). EAAT2 protein levels in gliosomes were determined by Western blot analysis. Table 1 shows the fold increases in EAAT2 protein levels relative to vehicle controls.

Table 1. Biological Activity of Example Compounds

Example	Compound Structure	<i>In vitro</i> - fold increase for EAAT2 in cultured astrocytes at indicated concentration (maximum activity)	<i>In vivo</i> - fold increase for EAAT2 in mouse forebrain at 24 hr post treatment (40 mg/kg by PO)
3		1.68 (5 μ M)	1.42
48		1.58 (2.5 μ M)	1.45
63		1.32 (5 μ M)	no increase
18		2.45 (1 μ M)	1.56

Example	Compound Structure	<i>In vitro</i> - fold increase for EAAT2 in cultured astrocytes at indicated concentration (maximum activity)	<i>In vivo</i> - fold increase for EAAT2 in mouse forebrain at 24 hr post treatment (40 mg/kg by PO)
33		no increase	no increase
19		1.97 (1 μ M)	1.41
22		1.64 (0.5 μ M)	1.20
21		1.73 (0.5 μ M)	1.34
20		no increase	no increase
23		1.84 (2.5 μ M)	1.45
94		1.51 (5 μ M)	1.49
157		1.54 (1 μ M)	1.37

Example	Compound Structure	<i>In vitro</i> - fold increase for EAAT2 in cultured astrocytes at indicated concentration (maximum activity)	<i>In vivo</i> - fold increase for EAAT2 in mouse forebrain at 24 hr post treatment (40 mg/kg by PO)
136		no increase	no increase

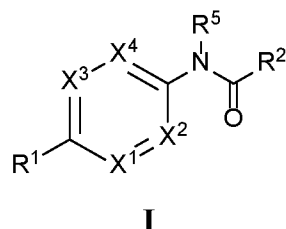
OTHER EMBODIMENTS

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims. It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment.

Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

WHAT IS CLAIMED IS:

1. A compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

X^1 is CH or N;

X^2 is CH or N;

X^3 is CR^3 or N;

X^4 is CR^4 or N;

wherein the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R^1 is selected from the group consisting of 6-10 membered aryl and 5-10 membered heteroaryl, each of which is optionally substituted by 1, 2, 3, or 4 independently selected R^A groups;

R^2 is selected from the group consisting of 6-10 membered aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, each of which is optionally substituted by 1, 2, 3, or 4 independently selected R^B groups;

R^3 , R^4 , and R^5 are each independently selected from H and C_{1-6} alkyl;

each R^A and R^B is independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d , NR^cOR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{1-4} haloalkyl are optionally substituted with 1, 2, 3, or 4 independently selected R^6 groups;

each R^a , R^b , R^c , and R^d is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{3-10} cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{3-10} cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 independently selected R^6 groups;

each R^e is independently selected from H, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkylaminosulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, and di(C₁₋₆ alkyl)aminosulfonyl; and

each R⁶ is independently selected from OH, NO₂, CN, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, cyano-C₁₋₃ alkyl, HO-C₁₋₃ alkyl, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, thio, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, carboxy, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, di(C₁₋₆ alkyl)aminosulfonyl, aminosulfonylamino, C₁₋₆ alkylaminosulfonylamino, di(C₁₋₆ alkyl)aminosulfonylamino, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, and di(C₁₋₆ alkyl)aminocarbonylamino.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is a 5-10 membered heteroaryl which is optionally substituted by 1, 2, 3, or 4 independently selected R^A groups.
3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is an unsubstituted 5-6 membered heteroaryl.
4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is unsubstituted pyridyl.
5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R² is selected from the group consisting of phenyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl, each of which is optionally substituted by 1, 2, 3, or 4 independently selected R^B groups.
6. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R² is selected from the group consisting of phenyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl, each of which is optionally substituted by 1 R^B group.

7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein each R^B is independently selected from the group consisting of halo, C_{1-6} alkyl, and OR^A .
8. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein each R^B is independently selected from the group consisting of F, Cl, C_{1-3} alkyl, and C_{1-3} alkoxy.
9. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein R^3 is H.
10. The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^4 is H.
11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^5 is H.
12. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring.
13. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyrazine ring.
14. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyrimidine ring.
15. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:
the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;
 R^1 is a 5-6 membered heteroaryl which is optionally substituted by 1 or 2 independently selected R^A groups;
 R^2 is selected from the group consisting of phenyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl, each of which is optionally substituted by 1, 2, 3, or 4 independently selected R^B groups;

each R^B is independently selected from the group consisting of halo, C_{1-6} alkyl, and OR^a ;

R^3 is H;

R^4 is H; and

R^5 is H.

16. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:
the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R^1 is an unsubstituted 5-6 membered heteroaryl;

R^2 is selected from the group consisting of phenyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl, each of which is optionally substituted by 1 or 2 independently selected R^B groups;

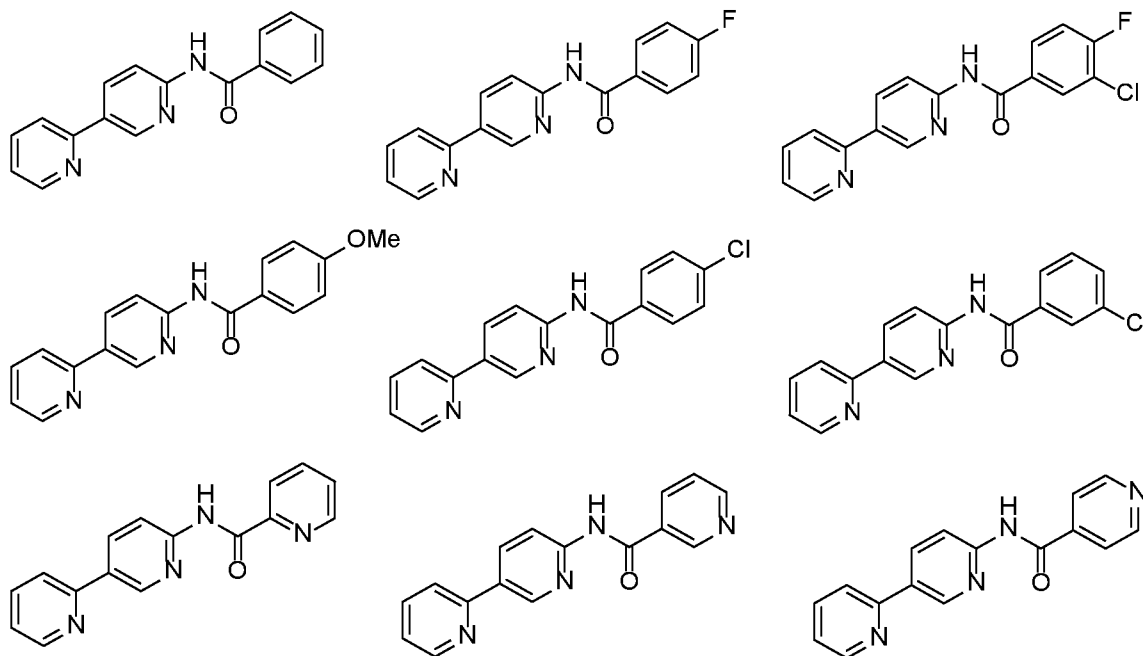
each R^B is independently selected from the group consisting of halo, C_{1-6} alkyl, and OCH_3 ;

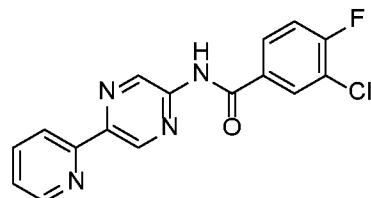
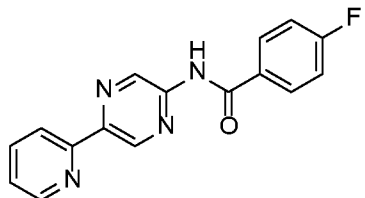
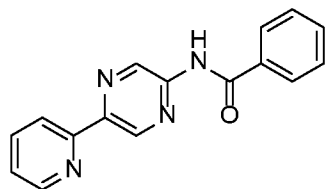
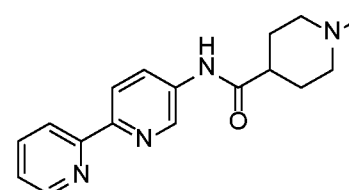
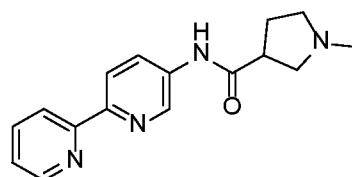
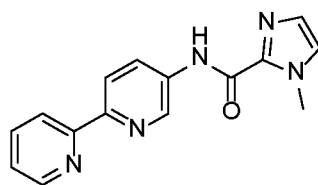
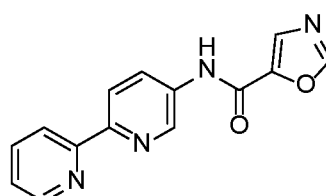
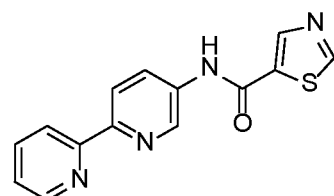
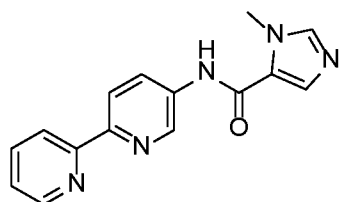
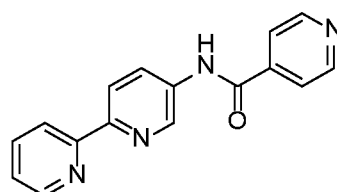
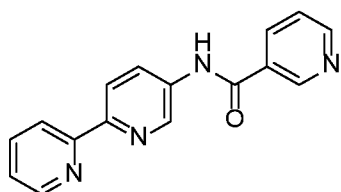
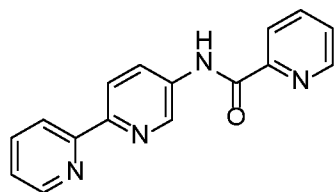
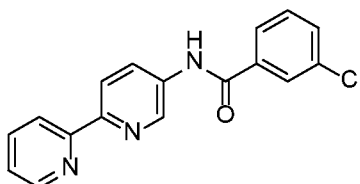
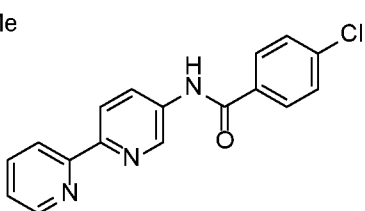
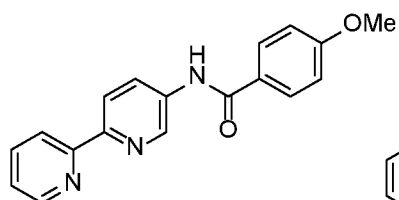
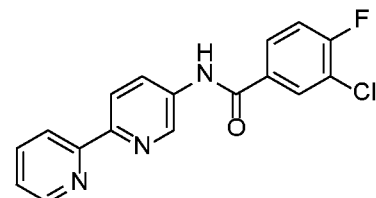
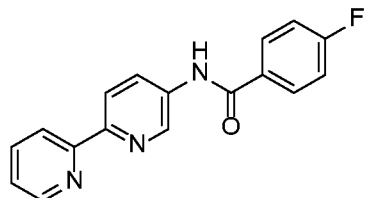
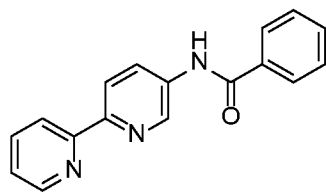
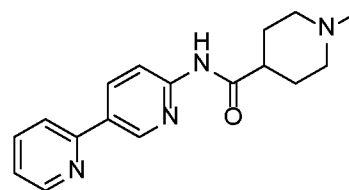
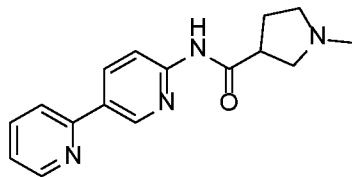
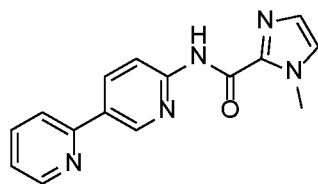
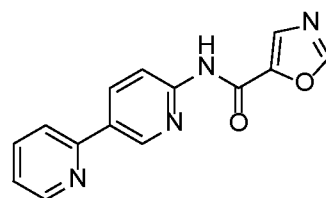
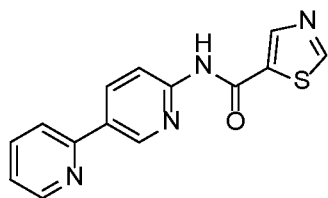
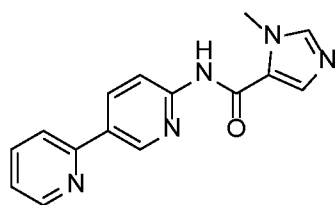
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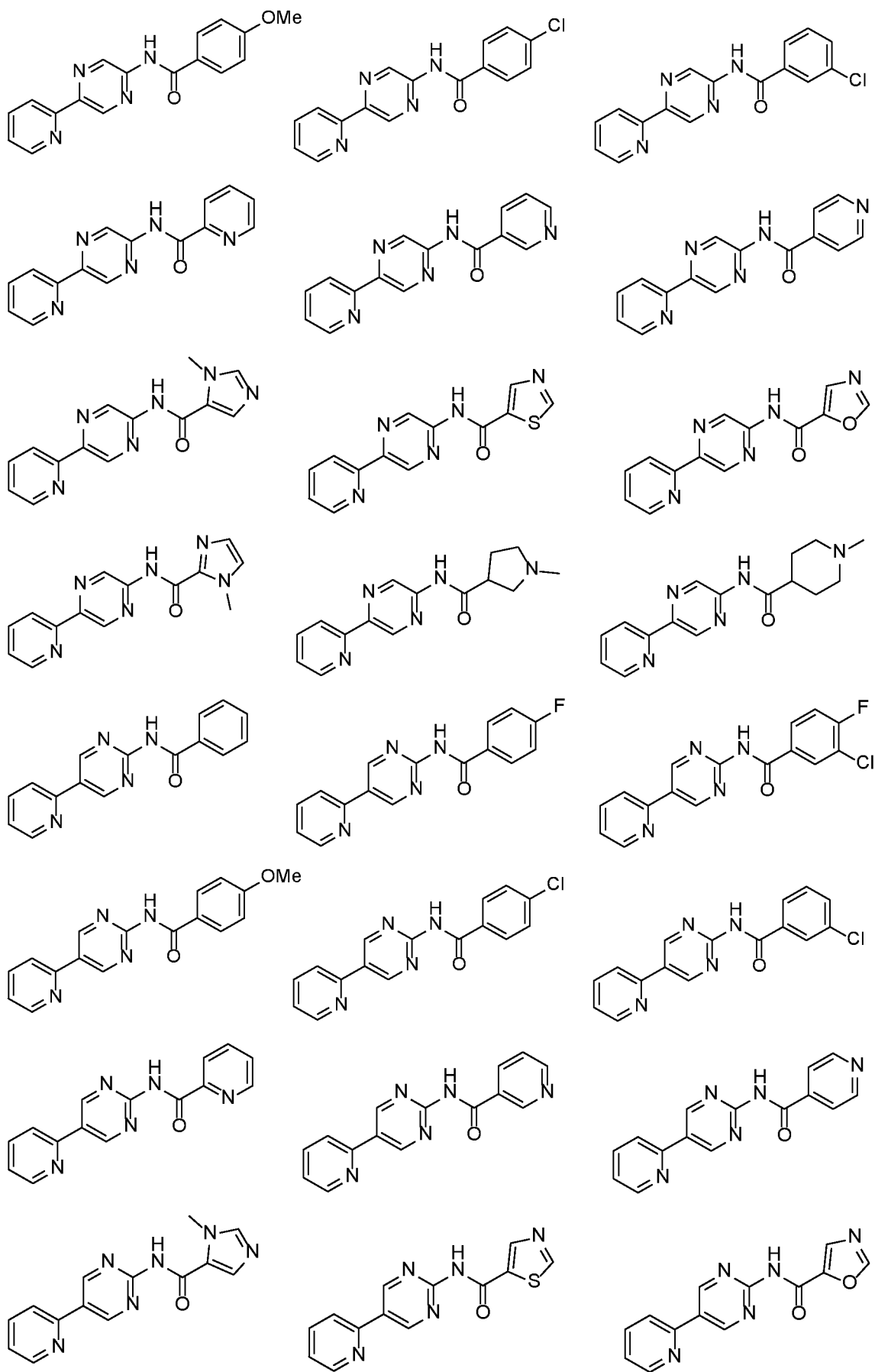
R^4 is H; and

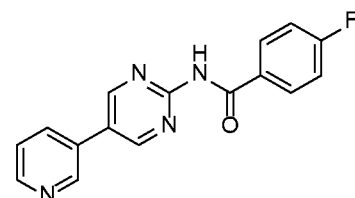
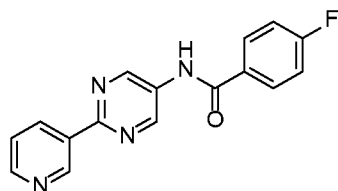
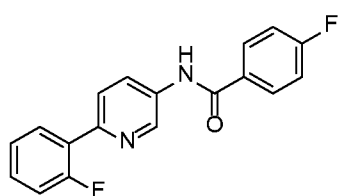
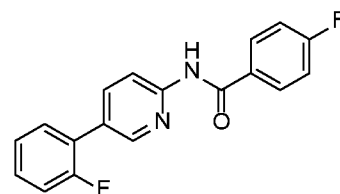
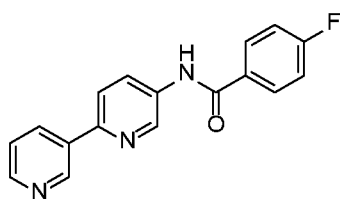
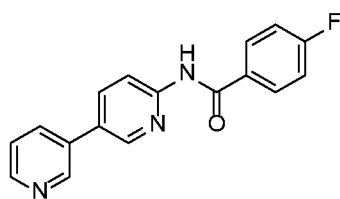
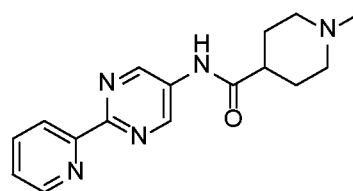
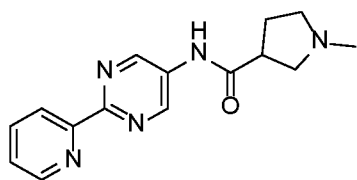
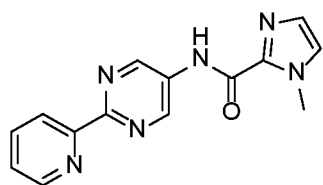
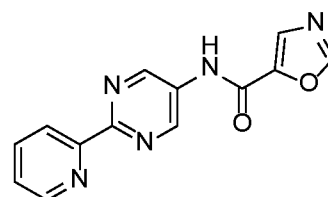
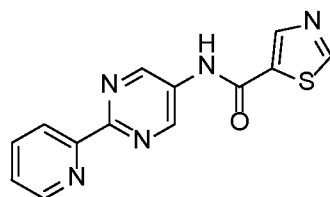
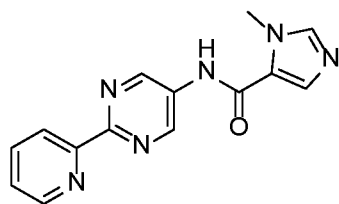
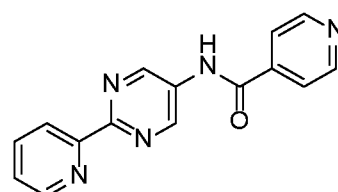
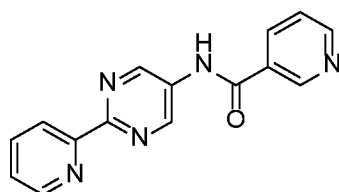
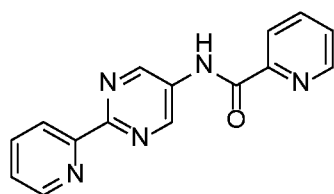
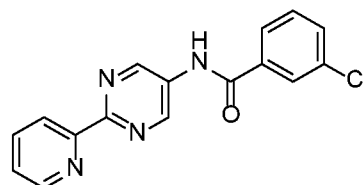
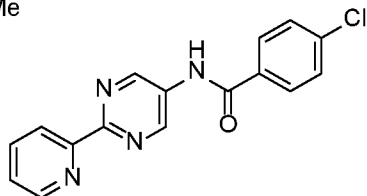
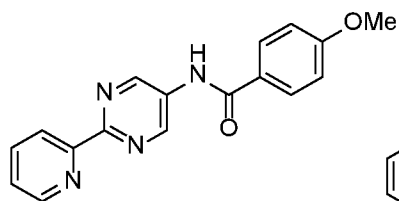
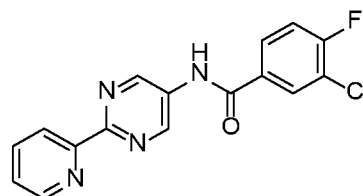
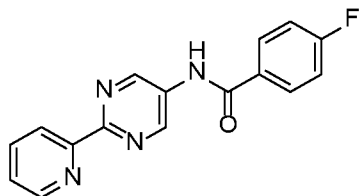
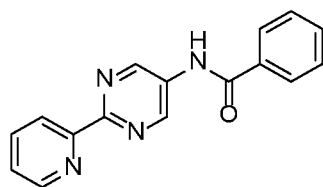
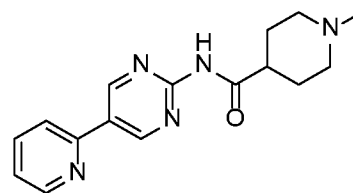
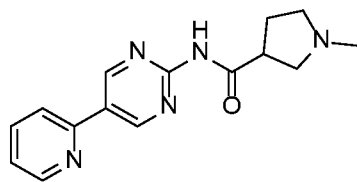
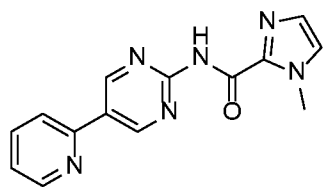
R^5 is H.

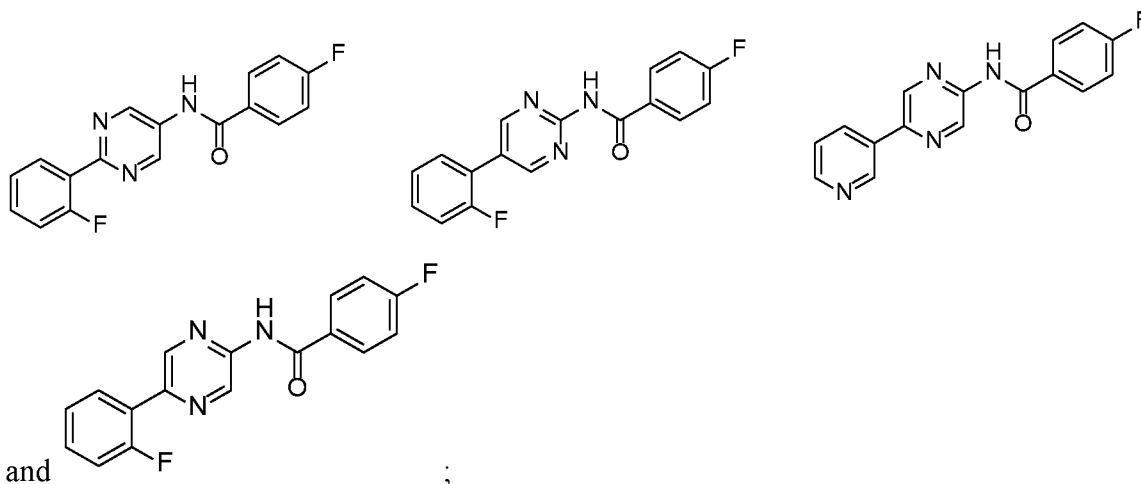
17. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula I is selected from the group consisting of:





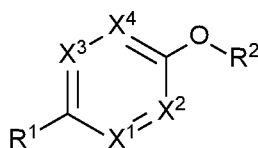






or a pharmaceutically acceptable salt thereof.

18. A compound of Formula II:



II

or a pharmaceutically acceptable salt thereof, wherein:

X¹ is CH or N;

X² is CH or N;

X³ is CR³ or N;

X⁴ is CR⁴ or N;

wherein the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R¹ is selected from the group consisting of 6-10 membered aryl and 5-10 membered heteroaryl, each of which is optionally substituted by 1, 2, 3, or 4 independently selected R^A groups;

R² is $-(\text{CHR}^{\text{E}})_n\text{R}^5$;

R⁵ is selected from the group consisting of OR^C, NR^CR^D, C(O)NR^CR^D, C(O)OR^C, C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1, 2, 3, or 4 independently selected R^B groups;

R^E is selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ alkoxy, and amino, wherein said C₁₋₆ alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R⁶ groups;

R³ and R⁴ are independently selected from H and C₁₋₆ alkyl;

each R^A and R^B is independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d , NR^cOR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{1-4} haloalkyl are optionally substituted with 1, 2, 3, or 4 independently selected R^6 groups;

R^C and R^D are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{3-10} cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkylene, 4-10 membered heterocycloalkyl- C_{1-4} alkylene, 6-10 membered aryl- C_{1-4} alkylene, 5-10 membered heteroaryl- C_{1-4} alkylene; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{3-10} cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkylene, 4-10 membered heterocycloalkyl- C_{1-4} alkylene, 6-10 membered aryl- C_{1-4} alkylene, and 5-10 membered heteroaryl- C_{1-4} alkylene are each optionally substituted with 1, 2, 3, or 4 independently selected R^6 groups; or

alternatively, any R^C and R^D attached to the same N atom, together with the N atom to which they are attached, form a 4-6 membered heterocycloalkyl group or a 5-6 membered heteroaryl group, each optionally substituted with 1, 2, or 3 independently selected R^6 groups;

each R^a , R^b , R^c , and R^d is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{3-10} cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{3-10} cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 independently selected R^6 groups;

each R^e is independently selected from H, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, C_{1-6} alkylcarbonyl, C_{1-6} alkylaminosulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, aminosulfonyl, C_{1-6} alkylaminosulfonyl, and di(C_{1-6} alkyl)aminosulfonyl;

each R^6 is independently selected from OH, NO_2 , CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano- C_{1-3} alkyl, HO- C_{1-3} alkyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6}

alkylaminosulfonylamino, di(C₁₋₆ alkyl)aminosulfonylamino, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, and di(C₁₋₆ alkyl)aminocarbonylamino; and
n is 0, 1, 2, 3, 4, or 5.

19. The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein R¹ is a 5-10 membered heteroaryl which is optionally substituted by 1, 2, 3, or 4 independently selected R^A groups.

20. The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein R¹ is an unsubstituted 5-6 membered heteroaryl.

21. The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein R¹ is unsubstituted pyridyl.

22. The compound of any one of claims 18 to 21, or a pharmaceutically acceptable salt thereof, wherein R² is selected from the group consisting of $-(CH_2)_nR^5$, $-(CH(CH_3))_nR^5$, and $-(CH_2CH(NH_2))_nR^5$.

23. The compound of any one of claims 18 to 22, or a pharmaceutically acceptable salt thereof, wherein R³ is H.

24. The compound of any one of claims 18 to 23, or a pharmaceutically acceptable salt thereof, wherein R⁴ is H.

25. The compound of any one of claims 18 to 24, or a pharmaceutically acceptable salt thereof, wherein R⁵ is selected from the group consisting of OR^C, NR^CR^D, C(O)NR^CR^D, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1, 2, 3, or 4 independently selected R^B groups.

26. The compound of any one of claims 18 to 24, or a pharmaceutically acceptable salt thereof, wherein R⁵ is selected from the group consisting of OR^C, NR^CR^D, C(O)NR^CR^D, phenyl, C₃₋₆ cycloalkyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the

phenyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1 or 2 independently selected R^B groups.

27. The compound of any one of claims 18 to 24, or a pharmaceutically acceptable salt thereof, wherein R⁵ is selected from the group consisting of OCH₃, N(CH₃)₂, C(O)N(CH₃)₂, phenyl, C₃₋₆ cycloalkyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the phenyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1 or 2 independently selected R^B groups.

28. The compound of any one of claims 18 to 27, or a pharmaceutically acceptable salt thereof, wherein each R^B is independently selected from the group consisting of C₁₋₆ alkyl and NR^cR^d.

29. The compound of any one of claims 18 to 27, or a pharmaceutically acceptable salt thereof, wherein each R^B is independently selected from the group consisting of C₁₋₃ alkyl and N(C₁₋₃ alkyl)₂.

30. The compound of any one of claims 18 to 29, or a pharmaceutically acceptable salt thereof, wherein n is 0, 1, or 2.

31. The compound of any one of claims 18 to 30, or a pharmaceutically acceptable salt thereof, wherein the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring.

32. The compound of any one of claims 18 to 30, or a pharmaceutically acceptable salt thereof, wherein the ring comprising X¹, X², X³, and X⁴ forms a pyrazine ring.

33. The compound of any one of claims 18 to 30, or a pharmaceutically acceptable salt thereof, wherein the ring comprising X¹, X², X³, and X⁴ forms a pyrimidine ring.

34. The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein:
the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R¹ is a 5-6 membered heteroaryl which is optionally substituted by 1 or 2 independently selected R^A groups;

R^2 is selected from the group consisting of $-(CH_2)_nR^5$, $-(CH(CH_3))_nR^5$, and $-(CH_2CH(NH_2))_nR^5$;

R^3 is H;

R^4 is H;

R^5 is selected from the group consisting of OR^C , $NR^C R^D$, $C(O)NR^C R^D$, C_{6-10} aryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the C_{6-10} aryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1, 2, 3, or 4 independently selected R^B groups;

each R^B is independently selected from the group consisting of C_{1-6} alkyl and $NR^C R^d$, and n is 0, 1, 2, 3, 4, or 5.

35. The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein: the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R^1 is an unsubstituted 5-6 membered heteroaryl;

R^2 is selected from the group consisting of $-(CH_2)_nR^5$, $-(CH(CH_3))_nR^5$, and $-(CH_2CH(NH_2))_nR^5$;

R^3 is H;

R^4 is H;

R^5 is selected from the group consisting of OR^C , $NR^C R^D$, $C(O)NR^C R^D$, phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the phenyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1 or 2 independently selected R^B groups;

each R^B is independently selected from the group consisting of C_{1-6} alkyl and $NR^C R^d$, and n is 0, 1, or 2.

36. The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein: the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R^1 is unsubstituted pyridyl;

R^2 is selected from the group consisting of $-(CH_2)_nR^5$, $-(CH(CH_3))_nR^5$, and $-(CH_2CH(NH_2))_nR^5$;

R^3 is H;

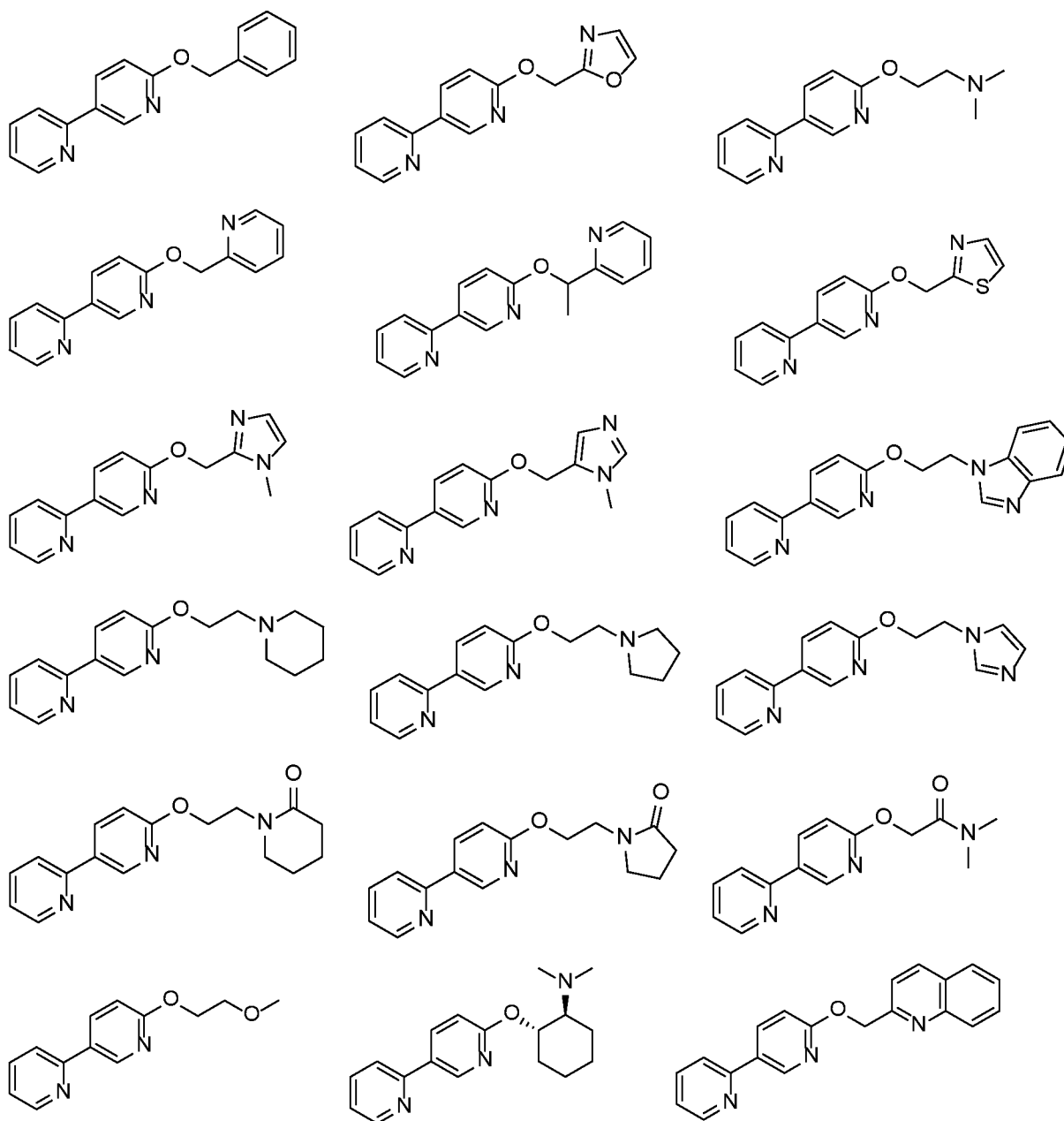
R^4 is H;

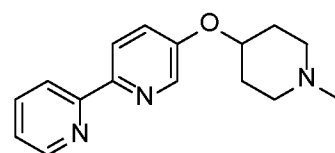
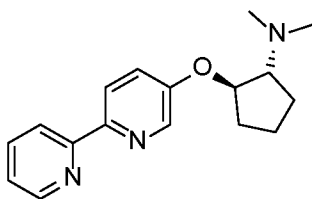
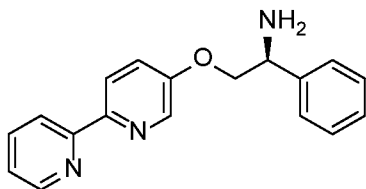
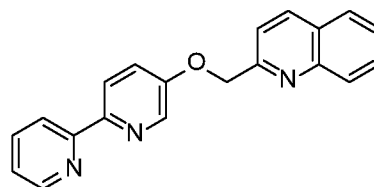
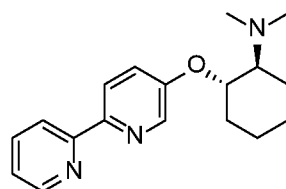
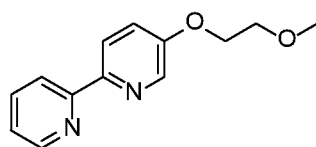
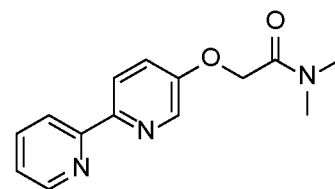
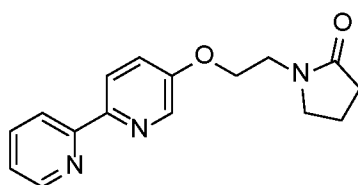
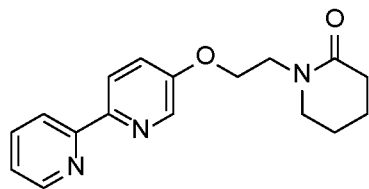
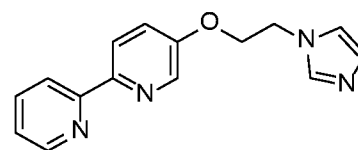
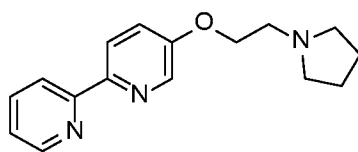
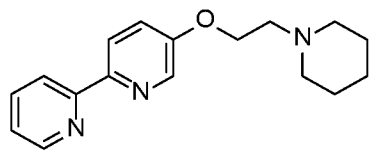
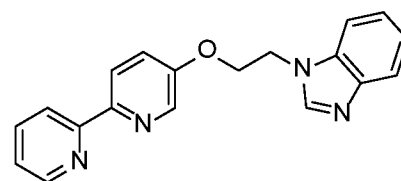
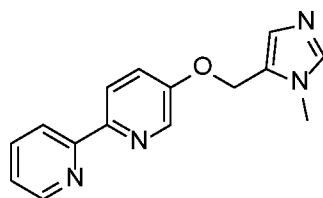
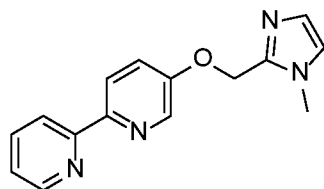
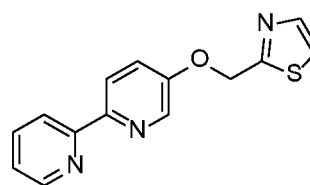
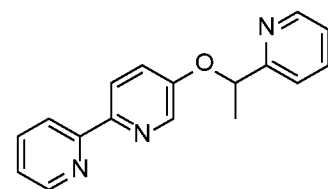
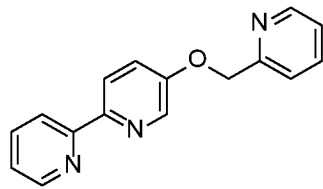
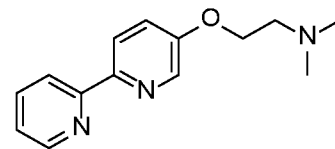
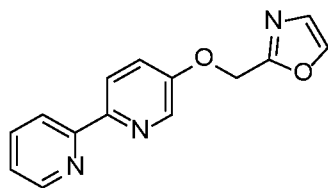
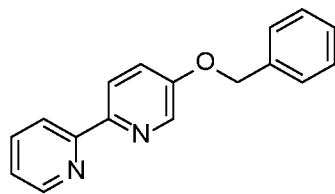
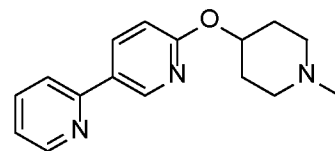
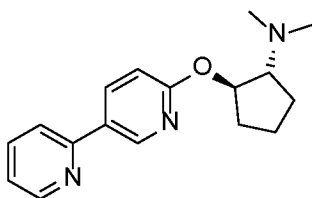
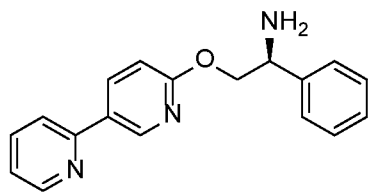
R^5 is selected from the group consisting of OCH_3 , $N(CH_3)_2$, $C(O)N(CH_3)_2$, phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the phenyl, 4-6 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1 or 2 independently selected R^B groups;

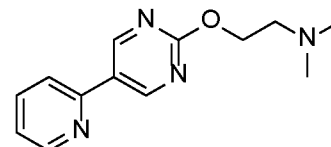
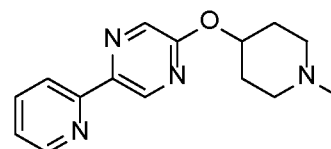
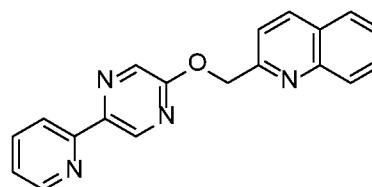
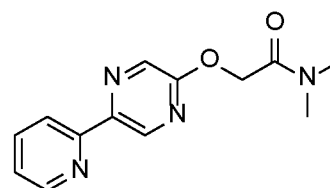
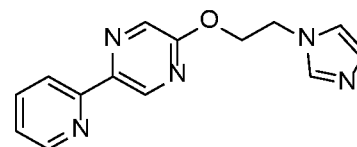
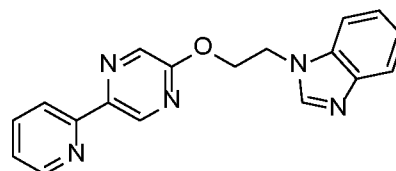
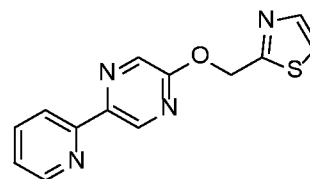
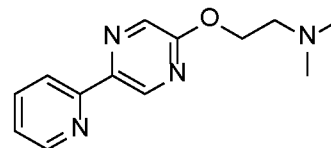
each R^B is independently is selected from the group consisting of C_{1-3} alkyl and $N(C_{1-3} \text{ alkyl})_2$; and

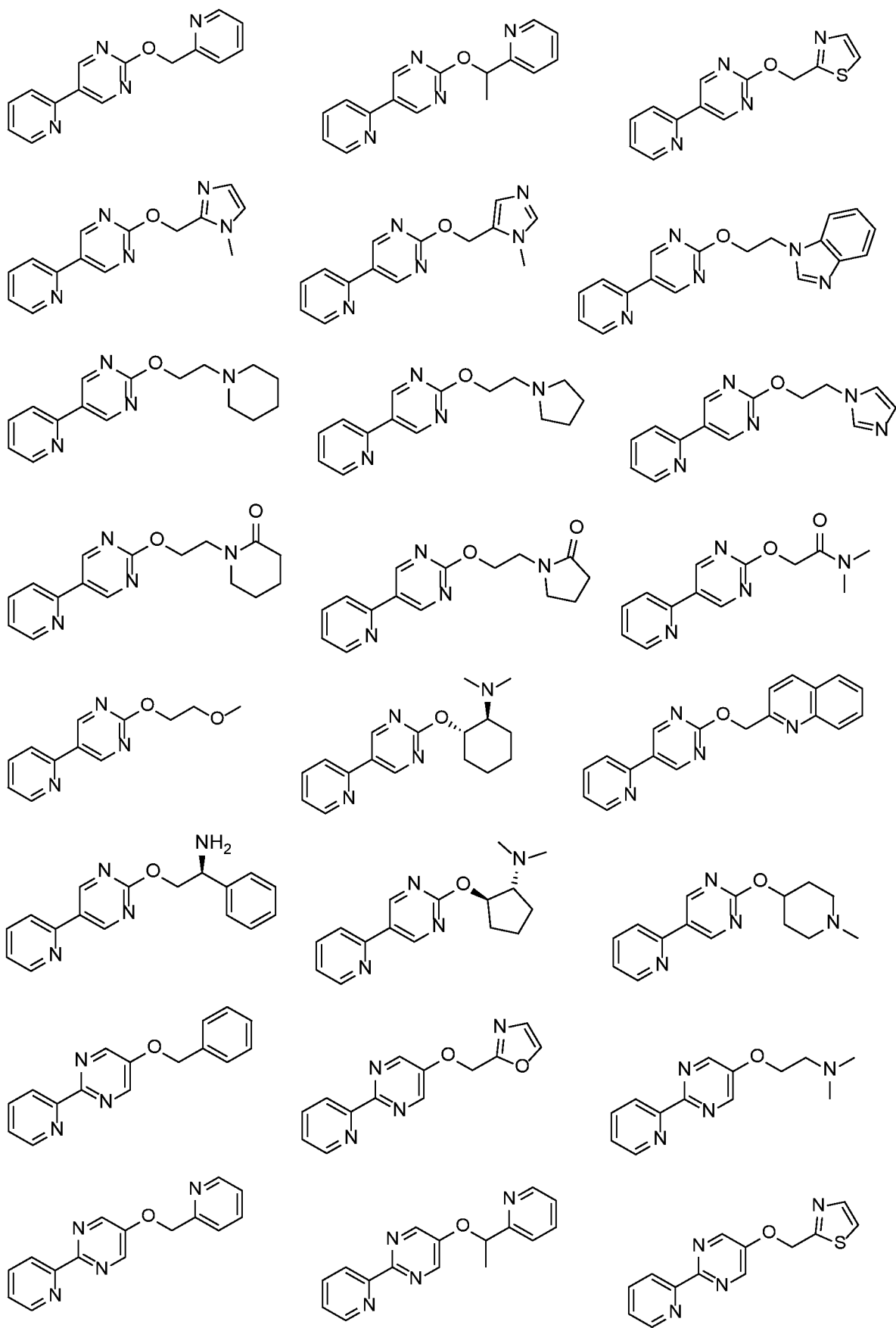
n is 0, 1, or 2.

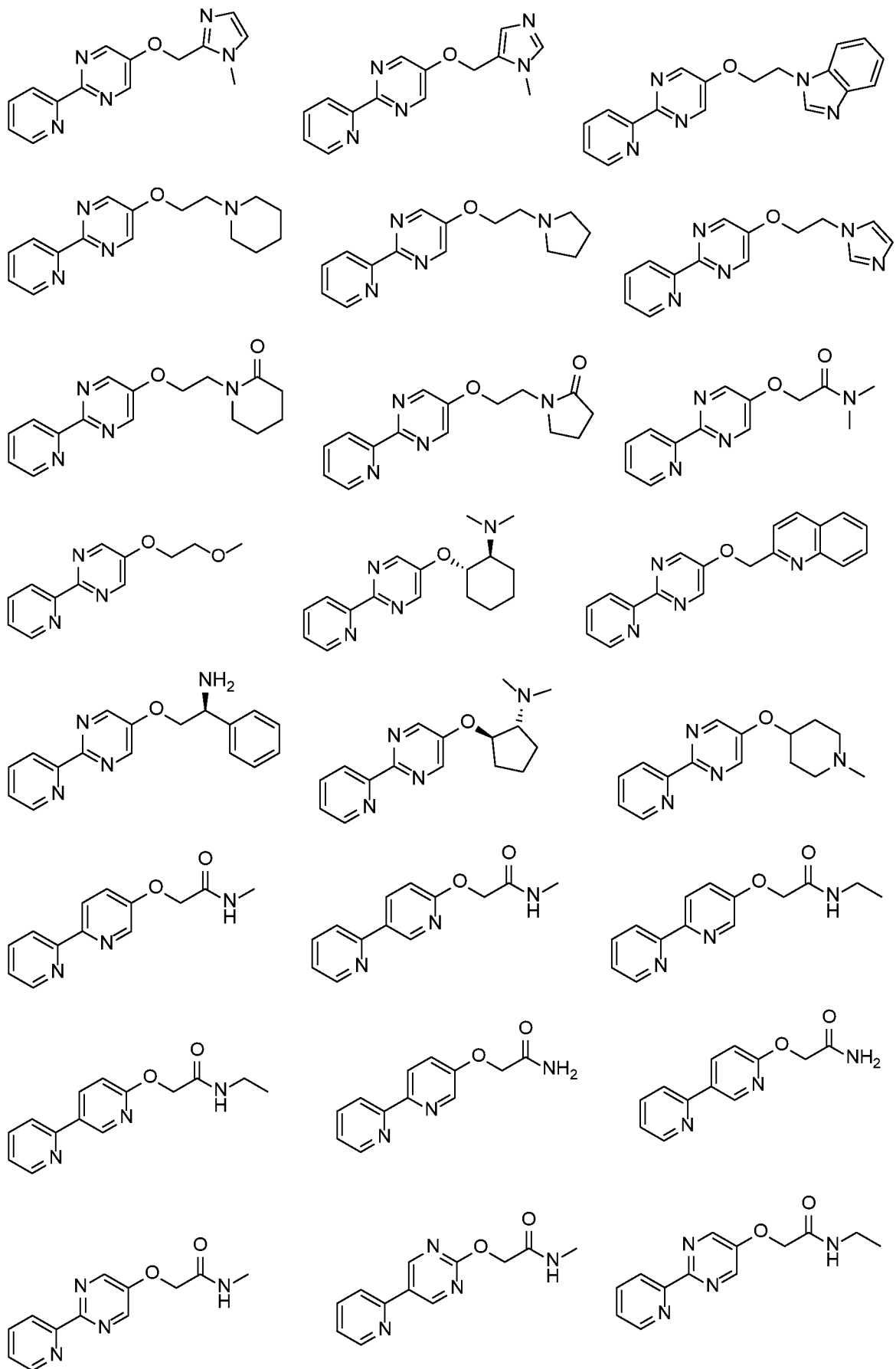
37. The compound of claim 24, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula II is selected from the group consisting of:

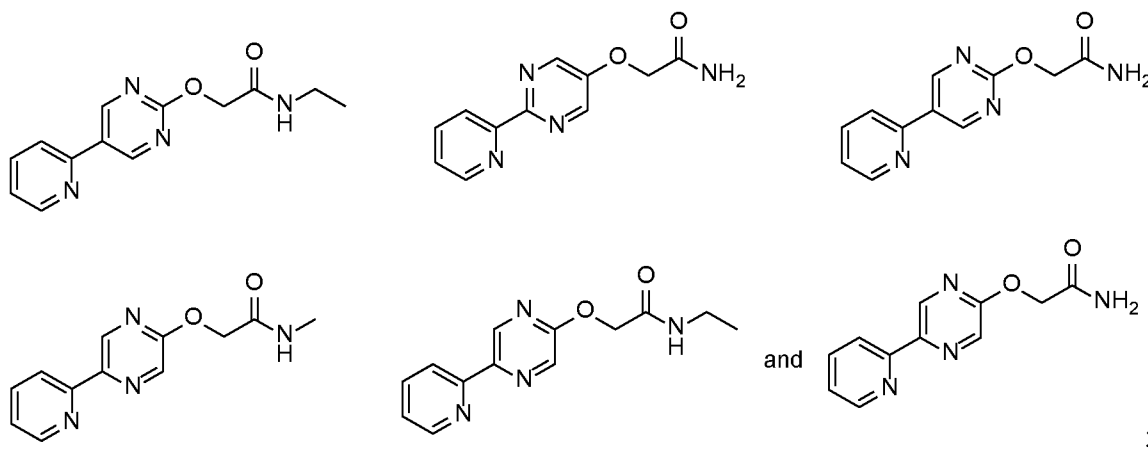






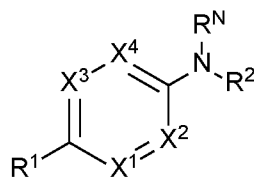






or a pharmaceutically acceptable salt thereof.

38. A compound of Formula III:



III

or a pharmaceutically acceptable salt thereof, wherein:

X¹ is CH or N;

X² is CH or N;

X³ is CR³ or N;

X⁴ is CR⁴ or N;

wherein the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R^N is selected from the group consisting of H, C₁₋₆ alkyl, and C(O)R^{N1};

R^{N1} is a C₆₋₁₀ aryl which is optionally substituted by 1, 2, 3, or 4 independently selected halo groups;

R¹ is selected from the group consisting of 6-10 membered aryl and 5-10 membered heteroaryl, each of which is optionally substituted by 1, 2, 3, or 4 independently selected R^A groups;

R² is -(CHR^E)_nR⁵;

R⁵ is selected from the group consisting of NR^CR^D, C(O)NR^CR^D, C(O)OR^C, C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1, 2, 3, or 4 independently selected R^B groups;

R^E is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkoxy, and amino, wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^6 groups;

R^3 and R^4 are independently selected from H and C_{1-6} alkyl;

each R^A and R^B is independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d , NR^cOR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{1-4} haloalkyl are optionally substituted with 1, 2, 3, or 4 independently selected R^6 groups;

R^C and R^D are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{3-10} cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkylene, 4-10 membered heterocycloalkyl- C_{1-4} alkylene, 6-10 membered aryl- C_{1-4} alkylene, 5-10 membered heteroaryl- C_{1-4} alkylene; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{3-10} cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkylene, 4-10 membered heterocycloalkyl- C_{1-4} alkylene, 6-10 membered aryl- C_{1-4} alkylene, and 5-10 membered heteroaryl- C_{1-4} alkylene are each optionally substituted with 1, 2, 3, or 4 independently selected R^6 groups; or

alternatively, any R^C and R^D attached to the same N atom, together with the N atom to which they are attached, form a 4-6 membered heterocycloalkyl group or a 5-6 membered heteroaryl group, each optionally substituted with 1, 2, or 3 independently selected R^6 groups;

each R^a , R^b , R^c , and R^d is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{3-10} cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{3-10} cycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 independently selected R^6 groups;

each R^e is independently selected from H, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, C_{1-6} alkylcarbonyl, C_{1-6} alkylaminosulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, aminosulfonyl, C_{1-6} alkylaminosulfonyl, and di(C_{1-6} alkyl)aminosulfonyl;

each R^6 is independently selected from OH, NO_2 , CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano- C_{1-3} alkyl, HO- C_{1-3} alkyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6}

alkoxycarbonyl, C₁₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, di(C₁₋₆ alkyl)aminosulfonyl, aminosulfonylamino, C₁₋₆ alkylaminosulfonylamino, di(C₁₋₆ alkyl)aminosulfonylamino, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, and di(C₁₋₆ alkyl)aminocarbonylamino; and

n is 0, 1, 2, 3, 4, or 5.

39. The compound of claim 38, or a pharmaceutically acceptable salt thereof, wherein R^N is selected from the group consisting of H, C₁₋₃ alkyl, and C(O)-phenyl.

40. The compound of claim 38 or 39, or a pharmaceutically acceptable salt thereof, wherein R¹ is a 5-10 membered heteroaryl which is optionally substituted by 1, 2, 3, or 4 independently selected R^A groups.

41. The compound of claim 38 or 39, or a pharmaceutically acceptable salt thereof, wherein R¹ is an unsubstituted 5-6 membered heteroaryl.

42. The compound of claim 38 or 39, or a pharmaceutically acceptable salt thereof, wherein R¹ is unsubstituted pyridyl.

43. The compound of any one of claims 38 to 42, or a pharmaceutically acceptable salt thereof, wherein R² is $-(CH_2)_nR^5$.

44. The compound of any one of claims 38 to 43, or a pharmaceutically acceptable salt thereof, wherein R³ is H.

45. The compound of any one of claims 38 to 44, or a pharmaceutically acceptable salt thereof, wherein R⁴ is H.

46. The compound of any one of claims 38 to 45, or a pharmaceutically acceptable salt thereof, wherein R⁵ is selected from the group consisting of NR^CR^D, C₆₋₁₀ aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the C₆₋₁₀ aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1, 2, 3, or 4 independently selected R^B groups.

47. The compound of any one of claims 38 to 45, or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from the group consisting of $NR^C R^D$, phenyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl, wherein the phenyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl are each optionally substituted by 1 or 2 independently selected R^B groups.

48. The compound of any one of claims 38 to 45, or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from the group consisting of $N(C_{1-3} \text{ alkyl})_2$, phenyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl.

49. The compound of any one of claims 38 to 45, or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from the group consisting of $N(CH_3)_2$, phenyl, oxazolyl, piperidinyl, and pyrrolidinyl.

50. The compound of any one of claims 38 to 49, or a pharmaceutically acceptable salt thereof, wherein the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring.

51. The compound of any one of claims 38 to 49, or a pharmaceutically acceptable salt thereof, wherein the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyrazine ring.

52. The compound of any one of claims 38 to 49, or a pharmaceutically acceptable salt thereof, wherein the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyrimidine ring.

53. The compound of claim 38, or a pharmaceutically acceptable salt thereof, wherein: the ring comprising X^1 , X^2 , X^3 , and X^4 forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R^N is selected from the group consisting of H, C_{1-3} alkyl, and $C(O)$ -phenyl;

R^1 is a 5-6 membered heteroaryl which is optionally substituted by 1 or 2 independently selected R^A groups;

R^2 is $-(CH_2)_n R^5$;

R^3 is H;

R^4 is H;

R^5 is selected from the group consisting of $NR^C R^D$, C_{6-10} aryl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein the C_{6-10} aryl, 4-10 membered

heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted by 1, 2, 3, or 4 independently selected R^B groups; and

n is 1, 2, or 3.

54. The compound of claim 38, or a pharmaceutically acceptable salt thereof, wherein: the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R^N is selected from the group consisting of H, C₁₋₃ alkyl, and C(O)-phenyl;

R¹ is an unsubstituted 5-6 membered heteroaryl;

R² is -(CH₂)_nR⁵;

R³ is H;

R⁴ is H;

R⁵ is selected from the group consisting of NR^CR^D, phenyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl, wherein the phenyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl are each optionally substituted by 1 or 2 independently selected R^B groups; and

n is 1, 2, or 3.

55. The compound of claim 38, or a pharmaceutically acceptable salt thereof, wherein: the ring comprising X¹, X², X³, and X⁴ forms a pyridine ring, a pyrazine ring, or a pyrimidine ring;

R^N is selected from the group consisting of H, C₁₋₃ alkyl, and C(O)-phenyl;

R¹ is unsubstituted pyridyl;

R² is -(CH₂)_nR⁵;

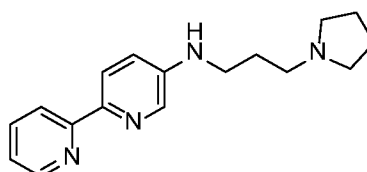
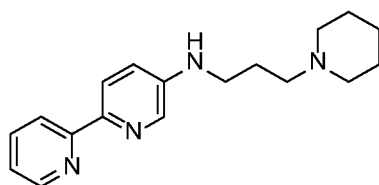
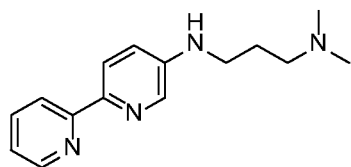
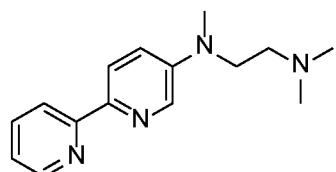
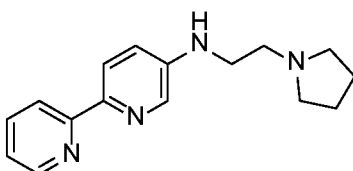
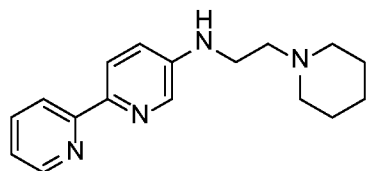
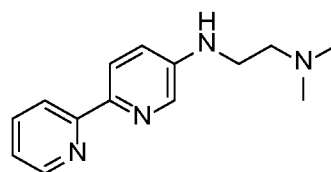
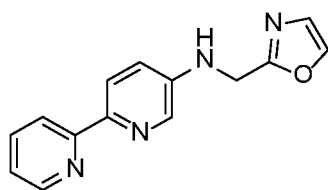
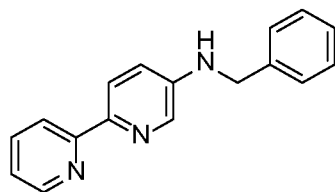
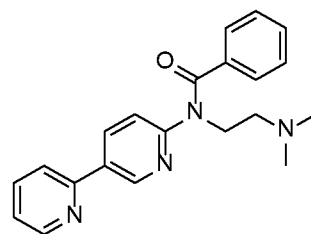
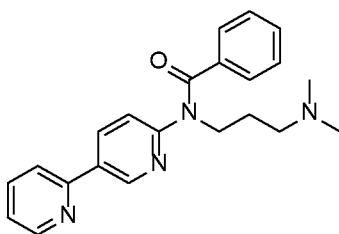
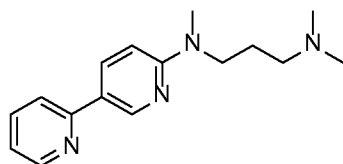
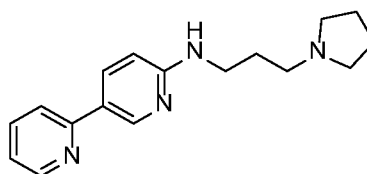
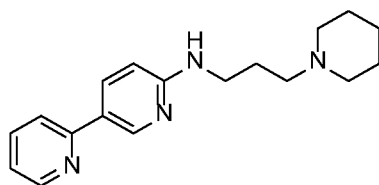
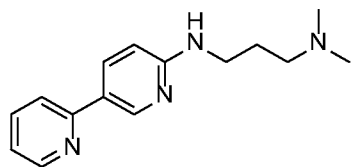
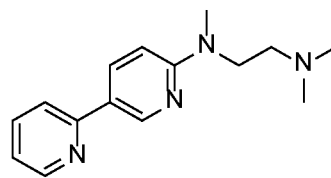
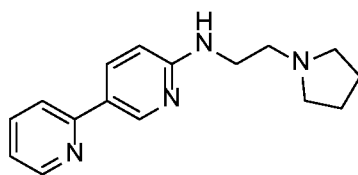
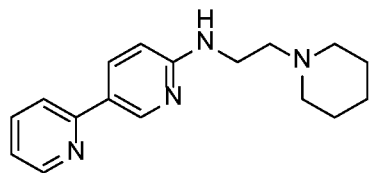
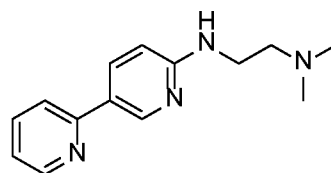
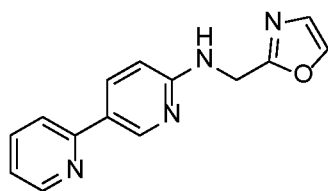
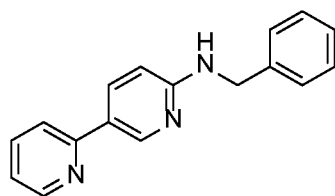
R³ is H;

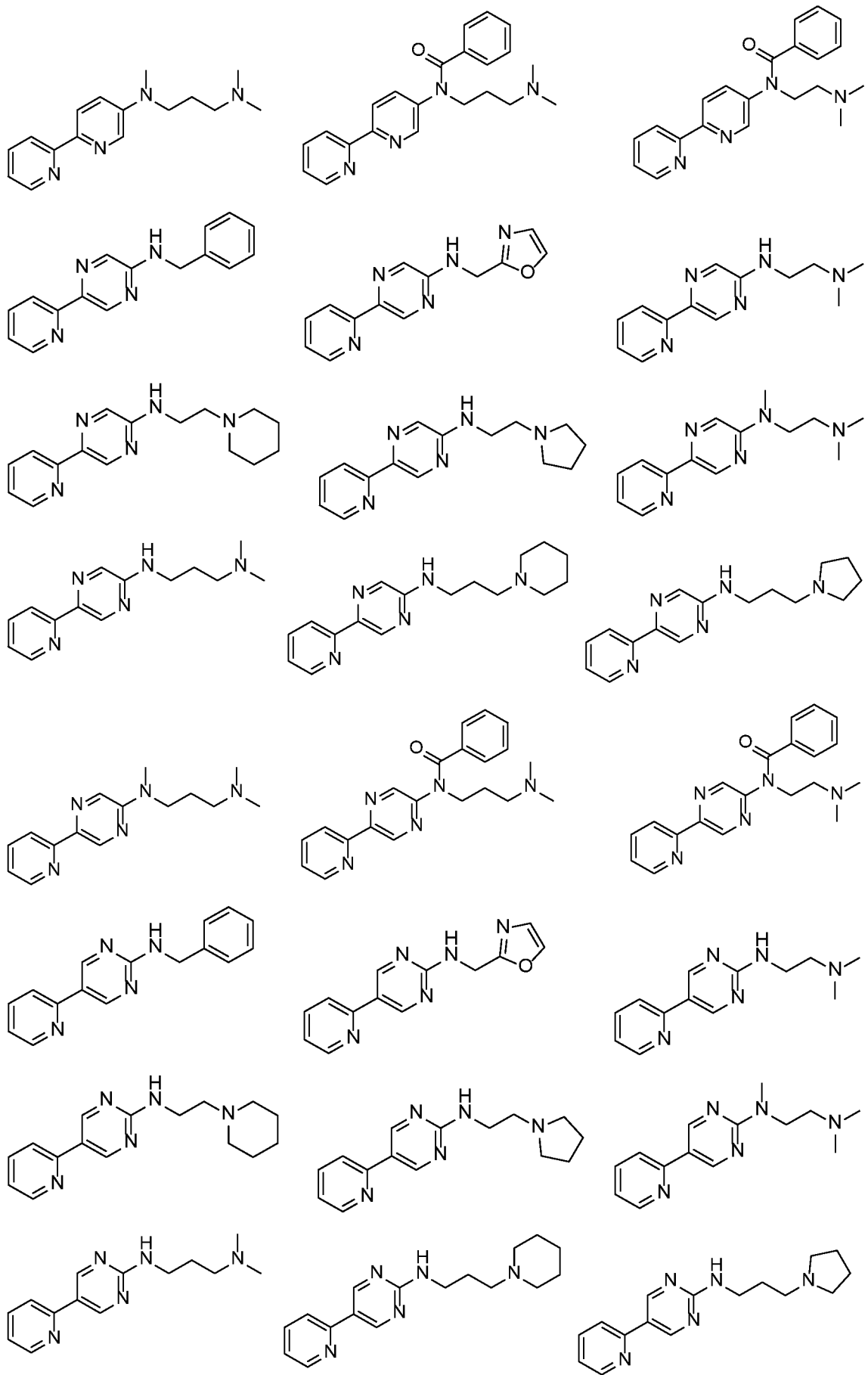
R⁴ is H;

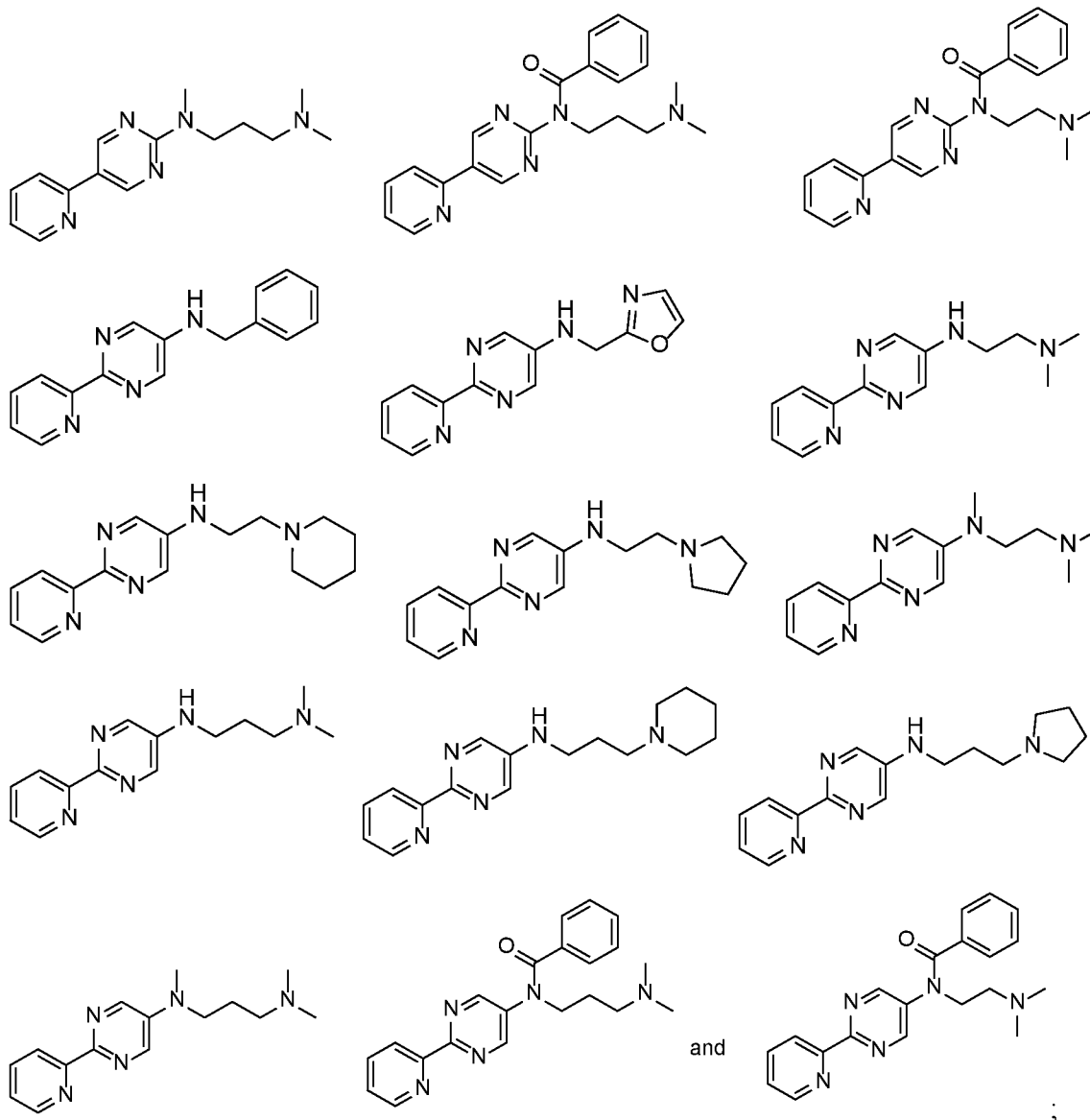
R⁵ is selected from the group consisting of N(C₁₋₃ alkyl)₂, phenyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl; and

n is 1, 2, or 3.

56. The compound of claim 38, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula III is selected from the group consisting of:







or a pharmaceutically acceptable salt thereof.

57. A pharmaceutical composition comprising a compound of any one of claims 1 to 56, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

58. A method for treating or preventing glutamate excitotoxicity in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of any one of claims 1 to 56, or a pharmaceutically acceptable salt thereof.

59. A method for increasing EAAT2 protein expression in a cell or a subject in need thereof, the method comprising contacting the cell or administering to the subject an effective amount of a compound of any one of claims 1 to 56, or a pharmaceutically acceptable salt thereof.

60. A method for activating the NRF2 pathway in a cell or a subject in need thereof, the method comprising contacting the cell or administering to the subject an effective amount of a compound of any one of claims 1 to 56, or a pharmaceutically acceptable salt thereof.

61. A method for treating a disease or disorder selected from the group consisting of ischemic stroke, epilepsy, or a trauma, including blunt trauma, an abrasion, an avulsion, an incision, a laceration, a puncture, a penetration, a surgical trauma, iatrogenic trauma, a spinal cord injury, a traumatic brain injury, or any combination thereof; a chronic neurodegenerative disorder, including mild cognitive impairment, Parkinson's disease, Alzheimer's disease, multiple sclerosis, mesial temporal sclerosis, Huntington's disease, AIDS dementia complex, or amyotrophic lateral sclerosis (ALS); a psychotic disorder including schizophrenia, bipolar disorder, or autism; a pain disorder including migraine, temporomandibular disorders, neuropathic pain, visceral pain, or complex regional pain syndrome; an addiction including alcohol addiction, cocaine addiction, heroin addiction, methamphetamine addiction, or nicotine addiction; or a cancer, including glioblastoma; or a mood disorder, including anxiety disorders, depressive disorders, borderline personality disorder, attention-deficit-hyperactivity disorder, suicidal behavior, eating disorders, posttraumatic stress disorder, gulf war illness, and obsessive-Compulsive Disorder in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of any one of claims 1 to 56, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US18/41844

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 7-14, 23-33, 37, 43-52 & 57-61
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US18/41844

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/497, 31/506; C07D 401/04, 401/14 (2018.01)

CPC - A61K 31/497, 31/506; C07D 401/04, 401/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2017/0172984 A1 (FROST BIOLOGIC, INC.) 22 June 2017; page 41, see compound 15, table 1	1
X	↖ PUBCHEM CID 100666531, pages 1-11, Create Date: 2015-12-11; page 3, see 2D structure	1-4, 5/1-4, 6/1-4, 15-17
X	↖ PUBCHEM CID 74237045, pages 1-11, Create Date: 2014-06-09; page 3, see 2D structure	18-19
X	↖ PUBCHEM CID 56672027, pages 1-14, Create Date: 2012-03-06; page 4, see 2D structure	18-21, 22/18-21, 34-36
X	↖ PUBCHEM CID 91068286, pages 1-10, Create Date: 2015-03-17; page 3, see 2D structure	38-39, 40/38-39, 41/38-39, 42/38-39, 53-55
A	↖ PUBCHEM CID 59932585, pages 1-12, Create Date: 2012-08-20; page 4, see 2D structure	56

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

31 August 2018 (31.08.2018)

Date of mailing of the international search report

18 SEP 2018

Name and mailing address of the ISA/

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Authorized officer

Shane Thomas

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