

COMPOUNDS AND USES THEREOF

Background

An incomplete understanding of the molecular perturbations that cause disease, as well as a limited arsenal of robust model systems, has contributed to a failure to generate successful disease-modifying therapies against common and progressive neurological disorders, such as Parkinson's Disease (PD) and Alzheimer's Disease (AD). Progress is being made on many fronts to find agents that can arrest the progress of these disorders. However, the present therapies for most, if not all, of these diseases provide very little relief. In particular, a need exists for better methods and compositions for the treatment of neurodegenerative diseases in order to improve the quality of the lives of those afflicted by such diseases.

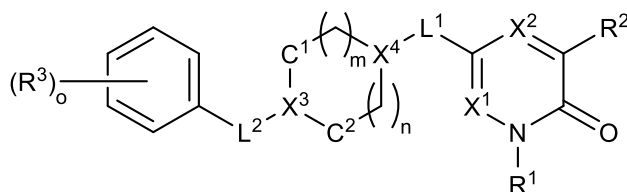
Further, cancers of the brain and nervous system are among the most difficult to treat. Prognosis for patients with these cancers depends on the type and location of the tumor as well as its stage of development. For many types of brain cancer, average life expectancy after symptom onset may be months or a year or two. Treatment consists primarily of surgical removal and radiation therapy. Chemotherapy is also used, but the range of suitable chemotherapeutic agents is limited. Using known chemotherapeutics along with surgery and radiation rarely extends survival much beyond that produced by surgery and radiation alone.

Accordingly, a need exists to develop therapies that can alter the course of diseases of the brain (including primary brain cancer) and neurodegenerative diseases.

Summary of the Invention

The [invention-disclosure](#) features compounds that modulate the activity of SCDs (e.g., SCD1 and/or SCD5), pharmaceutical compositions including such compounds, and methods of utilizing such compounds and compositions for modulating the activity of SCDs for the treatment of primary brain cancer and diseases and disorders related to toxicity caused by proteins such as toxicity related to misfolding and/or aggregation of proteins (e.g., a neurological disorder such as PD or AD).

[In one aspect, the invention-disclosure](#) features a compound of formula (I):

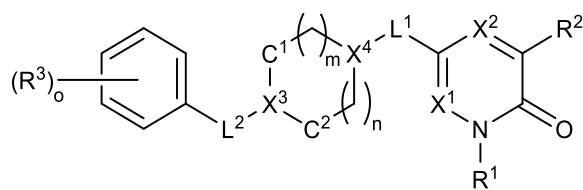


(I)

wherein: m is 0 or 1; n is 0, 1, or 2; o is 0, 1, 2, 3, 4, or 5; C^1 and C^2 optionally combine to form a bond; each of R^1 , R^2 , R^5 , and R^6 is, independently, H or optionally substituted C_{1-6} alkyl; R^3 is halo, cyano, C_{1-6} perfluoroalkyl, optionally substituted C_{1-6} alkoxy, or optionally substituted C_{1-6} alkyl; each of X^1 and X^2 is, independently, CH or N, wherein X^1 and X^2 are not both N; X^3 is CR^4 or N; or X^3 and C^1 or C^2 combine to form an optionally substituted alkene; X^4 is CH or N; wherein at least one of X^3 and X^4 is N; R^4 is H, OR^6 , optionally substituted C_{1-6} alkyl, or halo; L^1 is optionally substituted C_{5-10} heteroaryl or $-C(O)-X^5$; X^5 is NH, O, or optionally substituted C_{1-6} alkyl; and L^2 is O, NR^5 , optionally substituted C_{1-6} alkyl, optionally

substituted C₁₋₆ heteroalkyl, or absent; or X³ and L² combine to form an optionally substituted alkene, or a pharmaceutically acceptable salt thereof; wherein the compound does not have the structure of Compound 6, Compound 12, Compound 13, Compound 40, or Compound 106.

In one aspect, the disclosure features a compound of formula (I):



(I)

wherein:

m is 0 or 1;

n is 0, 1, or 2;

o is 0, 1, 2, 3, 4, or 5;

C¹ and C² optionally combine to form a bond;

each of R¹, R², R⁵, and R⁶ is, independently, H or optionally substituted C₁₋₆ alkyl;

R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted C₁₋₆ alkyl;

each of X¹ and X² is, independently, CH or N, wherein X¹ and X² are not both N;

X³ is CR⁴ or N; or X³ and C¹ or C² combine to form an optionally substituted alkene;

X⁴ is CH or N;

wherein at least one of X³ and X⁴ is N;

R⁴ is H, OR⁶, optionally substituted C₁₋₆ alkyl, or halo;

L¹ is -C(O)-X⁵- or optionally substituted C₅₋₁₀ heteroaryl;

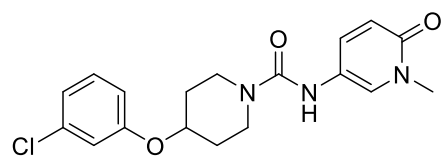
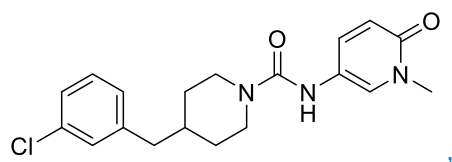
X⁵ is NH, O, or optionally substituted C₁₋₆ alkyl; and

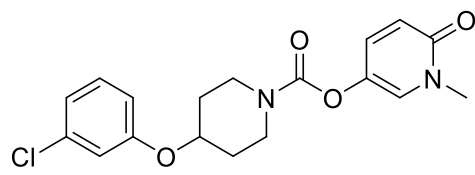
L² is O, NR⁵, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, or absent; or

X³ and L² combine to form an optionally substituted alkene,

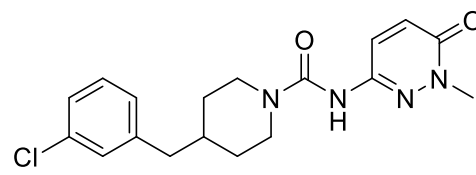
or a pharmaceutically acceptable salt thereof;

wherein the compound does not have the following structure

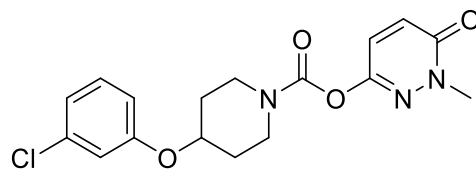




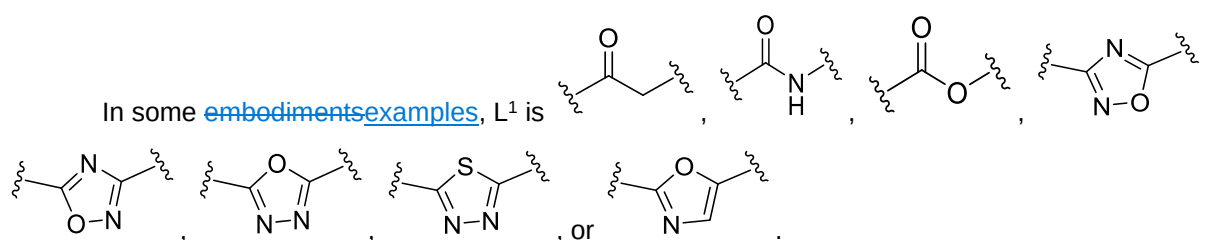
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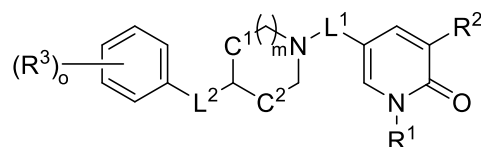


In some [examplesembodiments](#), L^2 is absent, NR^5 , optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, O, NH,

In some [examplesembodiments](#), m is 0 and n is 0; m is 0 and n is 1; m is 0 and n is 2; m is 1 and n is 0; m is 1 and n is 1; or m is 1 and n is 2.

In further [examplesembodiments](#), R^3 is halo (e.g., F, Cl, Br, or I), cyano, optionally substituted C_{1-6} alkyl, (e.g., methyl, ethyl), optionally substituted C_{1-6} alkoxy (e.g., methoxy), or C_{1-6} perfluoroalkyl (e.g., perfluoromethyl).

In certain [embodimentexamples](#), the compound has the structure of formula (II):



(II)

wherein: m is 0 or 1; o is 0, 1, 2, 3, 4, or 5; C^1 and C^2 optionally combine to form a bond; each of R^1 , R^2 , and R^5 is, independently, H or optionally substituted C_{1-6} alkyl; R^3 is halo, cyano, C_{1-6} perfluoroalkyl, optionally substituted C_{1-6} alkoxy, or optionally substituted C_{1-6} alkyl; L^1 is optionally substituted C_{5-10} heteroaryl or $-C(O)-X^5-$; X^5 is NH, O, or optionally substituted C_{1-6} alkyl; and L^2 is O, NR^5 , optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, or absent; or a pharmaceutically acceptable salt thereof; wherein the compound does not have the structure of Compound 6, Compound 12, or Compound 13.

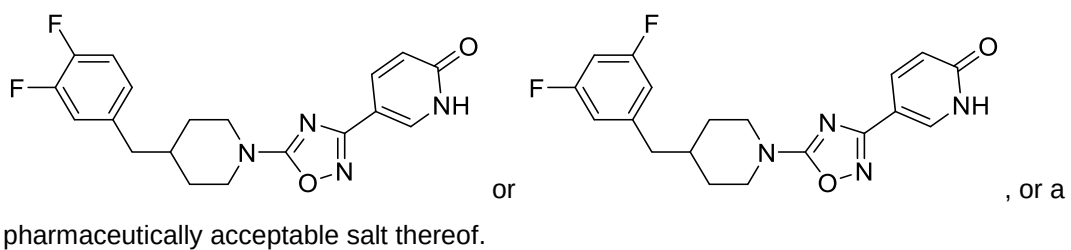
In some [embodimentexamples](#), R^2 is H. In some [embodimentexamples](#), R^1 is H. In some

[embodimentexamples](#), m is 1. In some [embodimentexamples](#), L^1 is

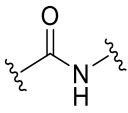
. In some [embodimentexamples](#), L^2 is optionally substituted C_{1-6} alkyl. In some [embodimentexamples](#), o is 2. In

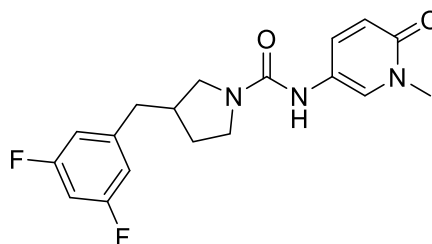
2a

some [embodiment examples](#), R³ is halo. In particular [embodiment examples](#), the compound is

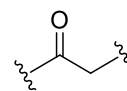


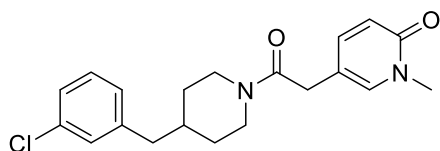
In some [embodimentexamples](#), R¹ is methyl. In some [embodimentexamples](#), m is 0. In some

[embodimentexample](#)s, L¹ is . In further [embodimentexample](#)s, L² is optionally substituted C₁₋₆ alkyl. In yet further [embodimentexamples](#), o is 2. In some [embodimentexample](#)s, R³ is halo. In particular

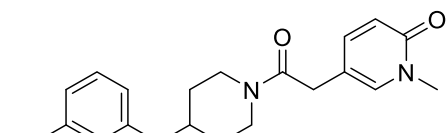


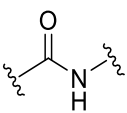
[embodimentexample](#)s, the compound is , or a pharmaceutically acceptable salt thereof.

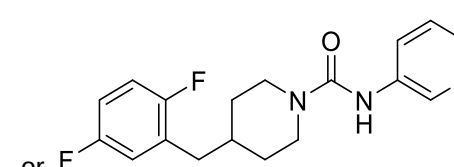
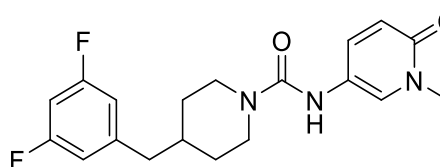
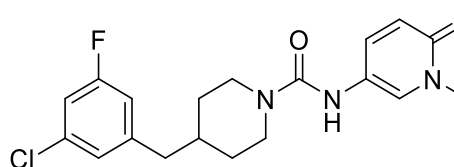
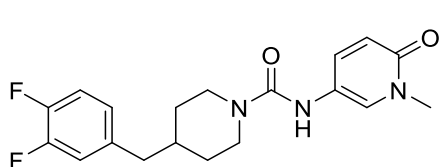
In other [embodimentexample](#)s, m is 1. In further [embodimentexample](#)s, L¹ is . In some [embodimentexamples](#), L² is optionally substituted C₁₋₆ alkyl. In some [embodimentexample](#)s, o is 1. In some [embodimentexamples](#), R³ is halo. In specific [embodimentexamples](#), the compound is



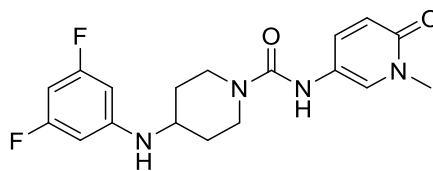
, or a pharmaceutically acceptable salt thereof. In further [embodimentexamples](#), L² is O. In some [embodimentexamples](#), o is 1. In some [embodimentexamples](#), R³

is halo. In particular [embodimentexamples](#), the compound is , or a pharmaceutically acceptable salt thereof.

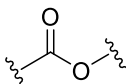
In yet other [embodimentexamples](#), L¹ is . In some [embodimentexample](#)s, L² is optionally substituted C₁₋₆ alkyl. In some [embodimentexamples](#), o is 1 or 2. In some [embodimentexamples](#), R³ is halo. In still other [embodimentexamples](#), the compound is



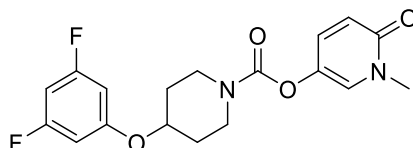
, or , or a pharmaceutically acceptable salt thereof. In other [embodimentexamples](#), L² is NH. In some [embodimentexample](#)s, o is 2. In some [embodimentexamples](#), R³ is halo. In particular



[embodimentexample](#)s, the compound is , or a pharmaceutically acceptable salt thereof. In still other [embodimentexample](#)s, L² is O. In further [embodimentexample](#)s, o is 1. In some [embodimentexample](#)s, R³ is halo.

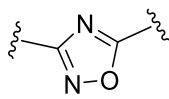


In further [embodimentexample](#)s, L¹ is . In some [embodimentexample](#)s, L² is O. In some [embodimentexample](#)s, o is 1 or 2. In some [embodimentexample](#)s, R³ is halo. In certain

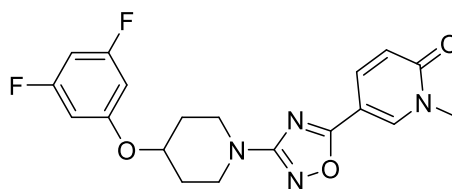


[embodimentexample](#)s, the compound is , or a pharmaceutically acceptable salt thereof.

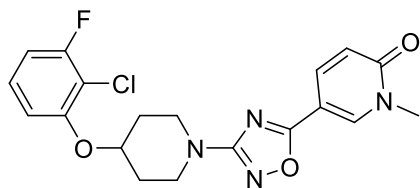
In yet further [embodimentexample](#)s, L¹ is optionally substituted C₅₋₁₀ heteroaryl. In some



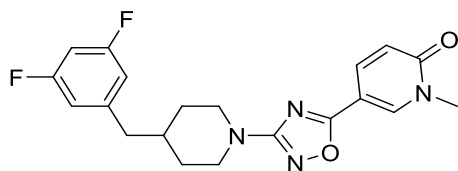
[embodimentexample](#)s, L¹ is . In some [embodimentexample](#)s, L² is O. In some [embodimentexample](#)s, o is 2. In some [embodimentexample](#)s, R³ is halo. In particular



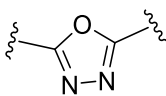
[embodimentexample](#)s, the compound is or



, or a pharmaceutically acceptable salt thereof. In other [embodimentexample](#)s, L² is optionally substituted C₁₋₆ alkyl. In some [embodimentexample](#)s, o is 2. In further [embodimentexample](#)s, R³ is halo. In certain [embodimentexample](#)s, the compound is

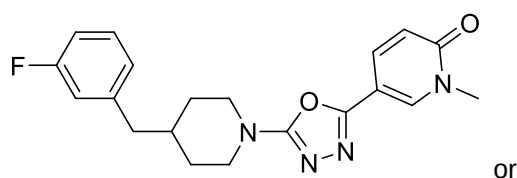
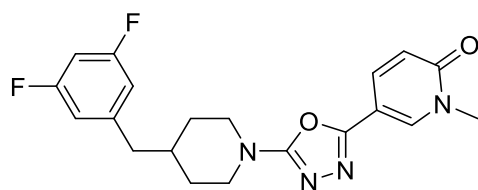


, or a pharmaceutically acceptable salt thereof.



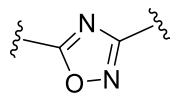
In further [embodimentexample](#)s, L¹ is . In some [embodimentexample](#)s, L² is optionally substituted C₁₋₆ alkyl. In some [embodimentexample](#)s, o is 1 or 2. In some [embodimentexample](#)s, R³ is halo. In particular

[embodimentexample](#)s, the compound is

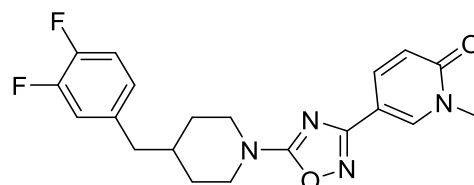


, or a pharmaceutically acceptable salt thereof.

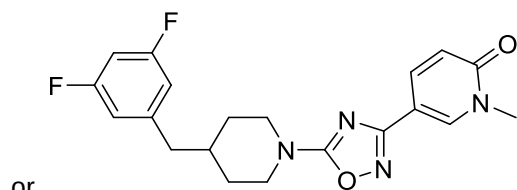
In still other [embodimentexample](#)s, L¹ is



. In some [embodimentexample](#)s, L² is optionally substituted C₁₋₆ alkyl. In some [embodimentexample](#)s, o is 2. In some [embodimentexample](#)s,



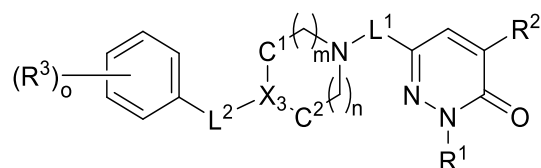
R³ is halo. In specific [embodimentexample](#)s, the compound is



or

, or a pharmaceutically acceptable salt thereof.

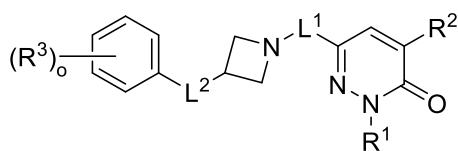
In further [embodimentexample](#)s, the compound has the structure of formula (III):



(III)

wherein: m is 0 or 1; n is 0, 1, or 2; o is 0, 1, 2, 3, 4, or 5; C¹ and C² optionally combine to form a bond; each of R¹, R², R⁵, and R⁶ is, independently, H or optionally substituted C₁₋₆ alkyl; R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted C₁₋₆ alkyl; X³ is CR⁴ or N; or X³ and C¹ or C² combine to form an optionally substituted alkene; R⁴ is H, OR⁶, optionally substituted C₁₋₆ alkyl, or halo; L¹ is optionally substituted C₅₋₁₀ heteroaryl or -C(O)-X⁵-; X⁵ is NH, O, or optionally substituted C₁₋₆ alkyl; and L² is O, NR⁵, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, or absent; or X³ and L² combine to form an optionally substituted alkene, or a pharmaceutically acceptable salt thereof; wherein the compound does not have the structure of Compound 40 or Compound 106.

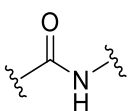
In some [embodimentexample](#)s, the compound has the structure of formula (III-A):

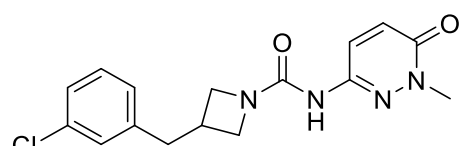


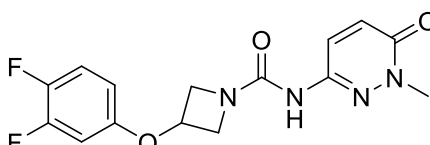
(III-A)

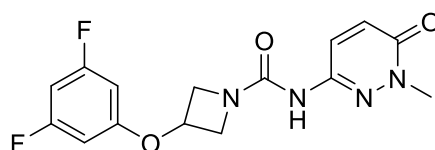
wherein: *o* is 0, 1, 2, 3, 4, or 5; each of R¹, R², and R⁵ is, independently, H or optionally substituted C₁₋₆ alkyl; R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted C₁₋₆ alkyl; L¹ is optionally substituted C₅₋₁₀ heteroaryl or -C(O)-X⁵-; X⁵ is NH, O, or optionally substituted C₁₋₆ alkyl; and L² is O, NR⁵, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, or absent; or a pharmaceutically acceptable salt thereof.

In some [embodimentexamples](#), R² is H. In some [embodimentexamples](#), R¹ is methyl. In some

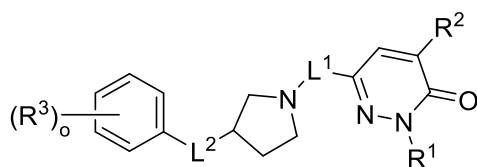
[embodimentexamples](#), L¹ is . In further [embodimentexamples](#), L² is optionally substituted C₁₋₆ alkyl. In further [embodimentexamples](#), *o* is 1. In yet further [embodimentexamples](#), R³ is halo. In

particular [embodimentexamples](#), the compound is , or a pharmaceutically acceptable salt thereof. In other [embodimentexamples](#), L² is O. In some [embodimentexamples](#), *o* is 2. In some [embodimentexamples](#), R³ is halo. In certain

[embodimentexamples](#), the compound is  or

, or a pharmaceutically acceptable salt thereof.

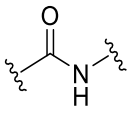
In further [embodimentexamples](#), the compound has the structure of formula (III-B):

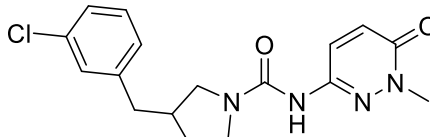


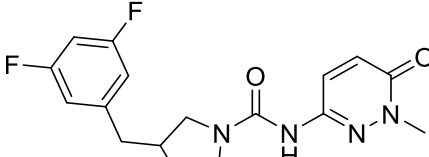
(III-B)

wherein: *o* is 0, 1, 2, 3, 4, or 5; each of R¹, R², and R⁵ is, independently, H or optionally substituted C₁₋₆ alkyl; R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted C₁₋₆ alkyl; L¹ is optionally substituted C₅₋₁₀ heteroaryl or -C(O)-X⁵-; X⁵ is NH, O, or optionally substituted C₁₋₆ alkyl; and L² is O, NR⁵, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, or absent; or a pharmaceutically acceptable salt thereof.

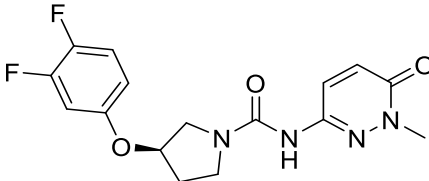
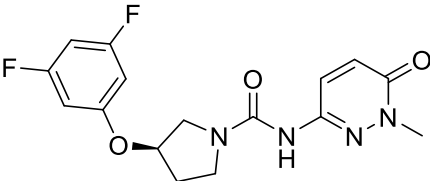
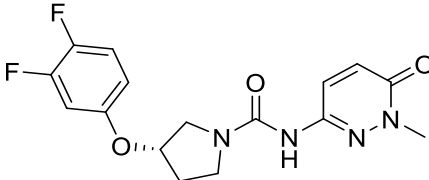
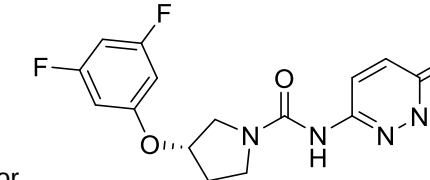
In some [embodimentexamples](#), R² is H. In some [embodimentexamples](#), R¹ is methyl. In some

[embodimentexamples](#), L¹ is . In further [embodimentexamples](#), L² is optionally substituted C₁₋₆ alkyl. In some [embodimentexamples](#), o is 1 or 2. In some [embodimentexamples](#), R³ is halo. In particular

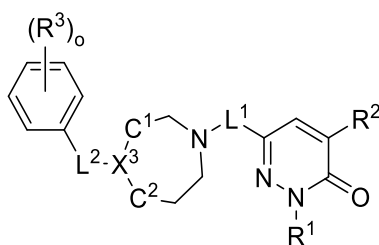
[embodimentexamples](#), the compound is  or

, or a pharmaceutically acceptable salt thereof. In further

[embodimentexamples](#), L² is O. In some [embodimentexamples](#), o is 2. In still other [embodimentexamples](#), R³ is halo. In some [embodimentexamples](#), the compound is

, , , or , or a pharmaceutically acceptable salt thereof.

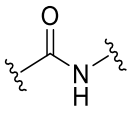
In yet other [embodimentexamples](#), the compound has the structure of formula (III-C):

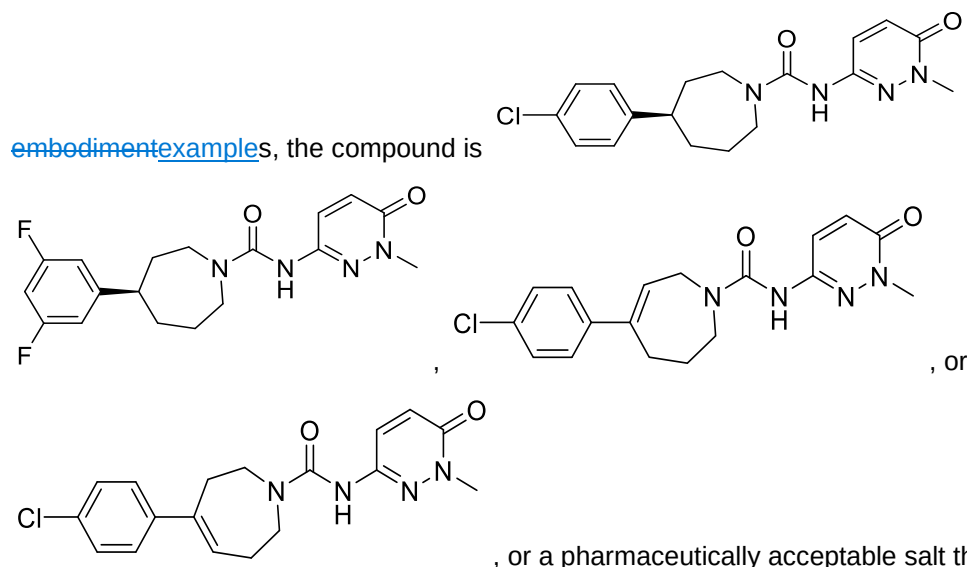


(III-C)

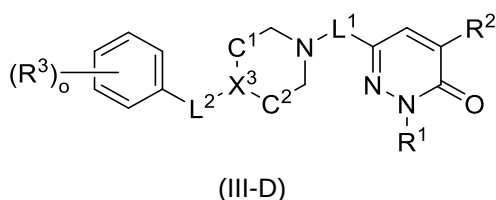
wherein: o is 0, 1, 2, 3, 4, or 5; C¹ and C² optionally combine to form a bond; each of R¹, R², R⁵, and R⁶ is, independently, H or optionally substituted C₁₋₆ alkyl; R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted C₁₋₆ alkyl; X³ is CR⁴ or N; or X³ and C¹ or C² combine to form an optionally substituted alkene; R⁴ is H, OR⁶, optionally substituted C₁₋₆ alkyl, or halo; L¹ is optionally substituted C₅₋₁₀ heteroaryl or -C(O)-X⁵; X⁵ is NH, O, or optionally substituted C₁₋₆ alkyl; and L² is O, NR⁵, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, or absent; or X³ and L² combine to form an optionally substituted alkene, or a pharmaceutically acceptable salt thereof.

In some [embodimentexamples](#), R² is H. In some [embodimentexamples](#), R¹ is methyl. In further

[embodimentexamples](#), L¹ is . In some [embodimentexamples](#), L² is absent. In some [embodimentexamples](#), o is 1 or 2. In further [embodimentexamples](#), R³ is halo. In specific

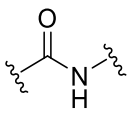


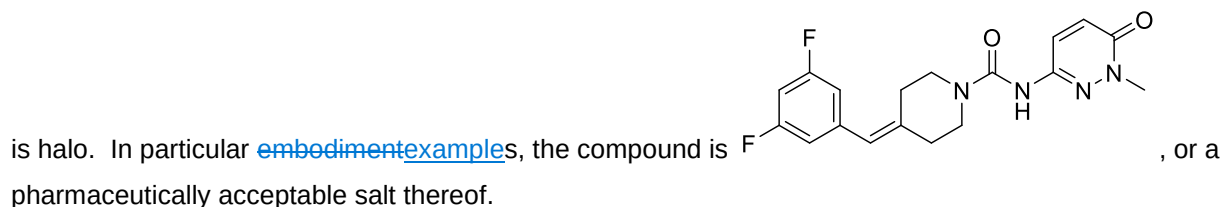
In further [embodimentexamples](#), the compound has the structure of formula (III-D):



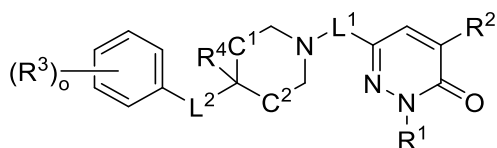
wherein: o is 0, 1, 2, 3, 4, or 5; C¹ and C² optionally combine to form a bond; each of R¹, R², R⁵, and R⁶ is, independently, H or optionally substituted C₁₋₆ alkyl; R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted C₁₋₆ alkyl; X³ is CR⁴ or N; or X³ and C¹ or C² combine to form an optionally substituted alkene; R⁴ is H, OR⁶, optionally substituted C₁₋₆ alkyl, or halo; L¹ is optionally substituted C₅₋₁₀ heteroaryl or -C(O)-X⁵-; X⁵ is NH, O, or optionally substituted C₁₋₆ alkyl; and L² is O, NR⁵, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, or absent; or X³ and L² combine to form an optionally substituted alkene, or a pharmaceutically acceptable salt thereof; wherein the compound does not have the structure of Compound 40 or Compound 106.

In some [embodimentexamples](#), R² is H. In certain [embodimentexamples](#), R¹ is methyl. In some

[embodimentexamples](#), L¹ is . In further [embodimentexamples](#), X³ and L² combine to form an optionally substituted alkene. In some [embodimentexamples](#), o is 2. In some [embodimentexamples](#), R³



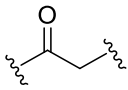
In some [embodimentexamples](#), the compound has the structure of formula (III-D-1):

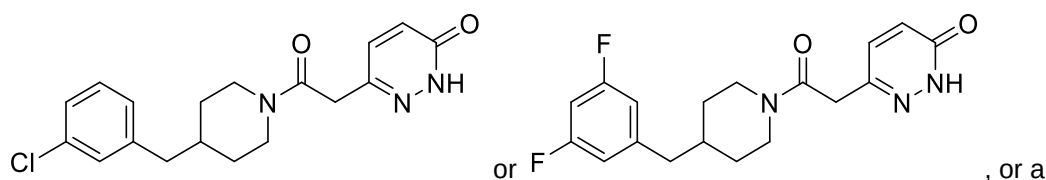


(III-D-1)

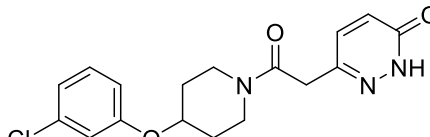
wherein: o is 0, 1, 2, 3, 4, or 5; C¹ and C² optionally combine to form a bond; each of R¹, R², R⁵, and R⁶ is, independently, H or optionally substituted C₁₋₆ alkyl; R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted C₁₋₆ alkyl; R⁴ is H, OR⁶, optionally substituted C₁₋₆ alkyl, or halo; L¹ is optionally substituted C₅₋₁₀ heteroaryl or –C(O)–X⁵–; X⁵ is NH, O, or optionally substituted C₁₋₆ alkyl; and L² is O, NR⁵, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, or absent; or a pharmaceutically acceptable salt thereof; wherein the compound does not have the structure of Compound 40 or Compound 106.

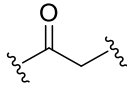
In some [embodimentexamples](#), R² is H. In some [embodimentexample](#)s, R¹ is H. In some

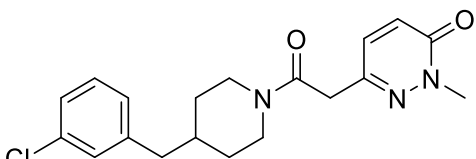
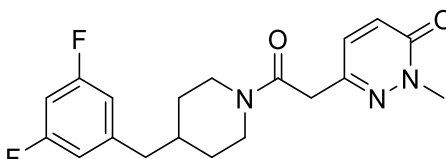
[embodimentexamples](#), L¹ is . In further [embodimentexamples](#), L² is optionally substituted C₁₋₆ alkyl. In some [embodimentexamples](#), o is 1 or 2. In some [embodimentexample](#)s, R³ is halo. In some [embodimentexamples](#), R⁴ is H. In certain [embodimentexamples](#), the compound is



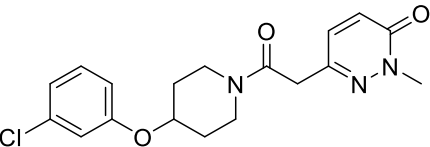
pharmaceutically acceptable salt thereof. In further [embodimentexamples](#), L² is O. In some [embodimentexamples](#), o is 1. In some [embodimentexample](#)s, R³ is halo. In some [embodimentexamples](#),

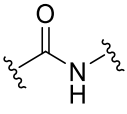
R⁴ is H. In some [embodimentexample](#)s, the compound is , or a pharmaceutically acceptable salt thereof.

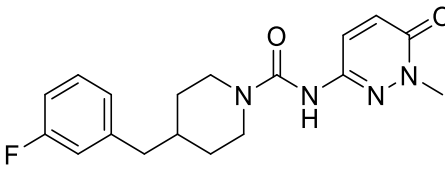
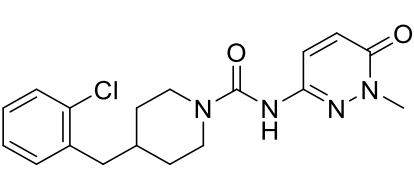
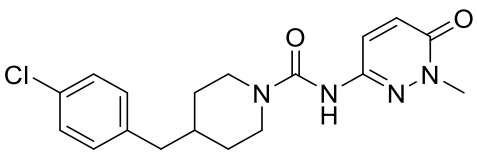
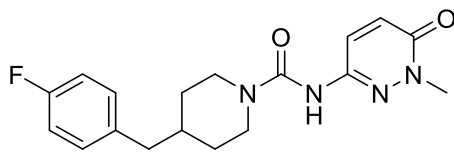
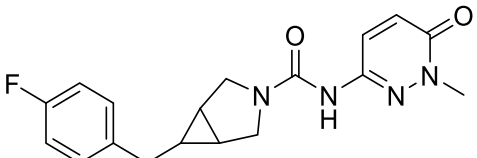
In further [embodimentexample](#)s, R¹ is methyl. In some [embodimentexamples](#), L¹ is . In some [embodimentexamples](#), L² is optionally substituted C₁₋₆ alkyl. In some [embodimentexamples](#), o is 1 or 2. In further [embodimentexamples](#), R³ is halo. In still further [embodimentexamples](#), R⁴ is H. In particular [embodimentexample](#)s,

the compound is  or , or a pharmaceutically acceptable salt thereof. In other [embodimentexamples](#), L² is O. In some [embodimentexamples](#), o is 1.

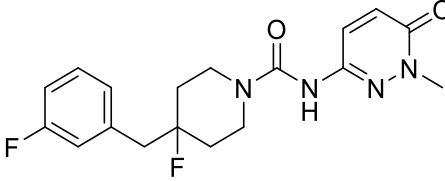
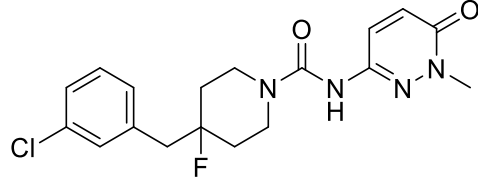
In some [embodimentexamples](#), R³ is halo. In some [embodimentexamples](#), R⁴ is H. In further

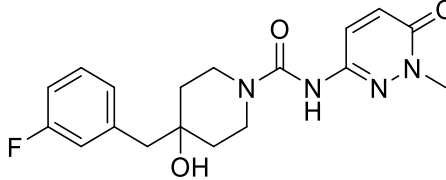
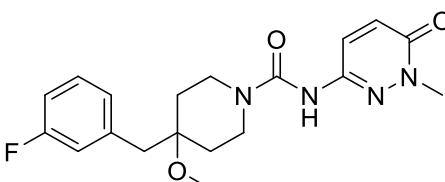
[embodimentexamples](#), the compound is , or a pharmaceutically acceptable salt thereof.

In yet other [embodimentexamples](#), L¹ is . In some [embodimentexamples](#), L² is optionally substituted C₁₋₆ alkyl. In some [embodimentexamples](#), o is 1. In some [embodimentexamples](#), R³ is halo. In some [embodimentexamples](#), R⁴ is H. In further [embodimentexamples](#), the compound is

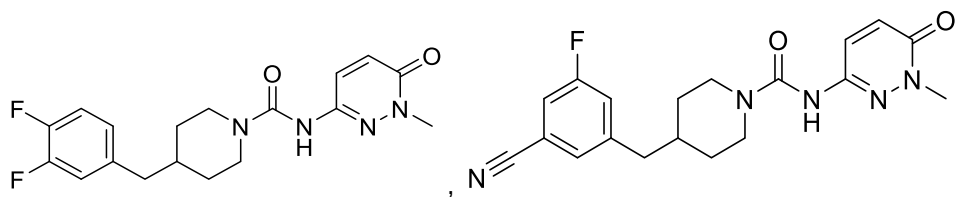
, , , , or , or a pharmaceutically acceptable salt thereof. In other

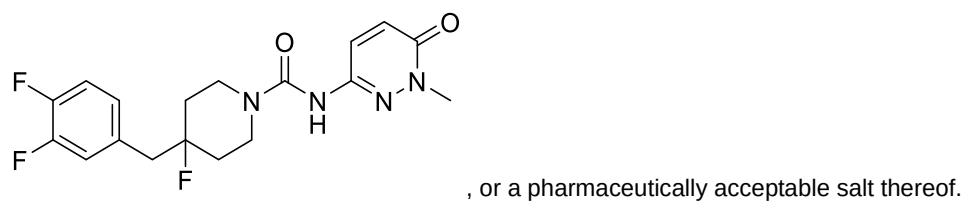
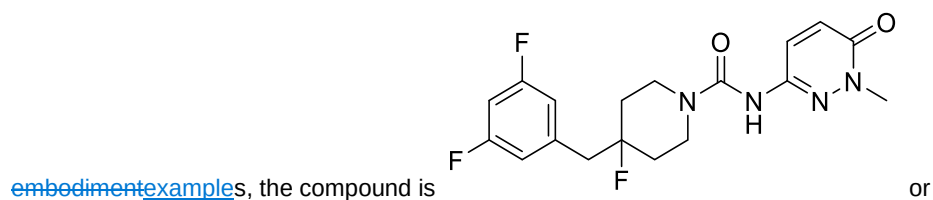
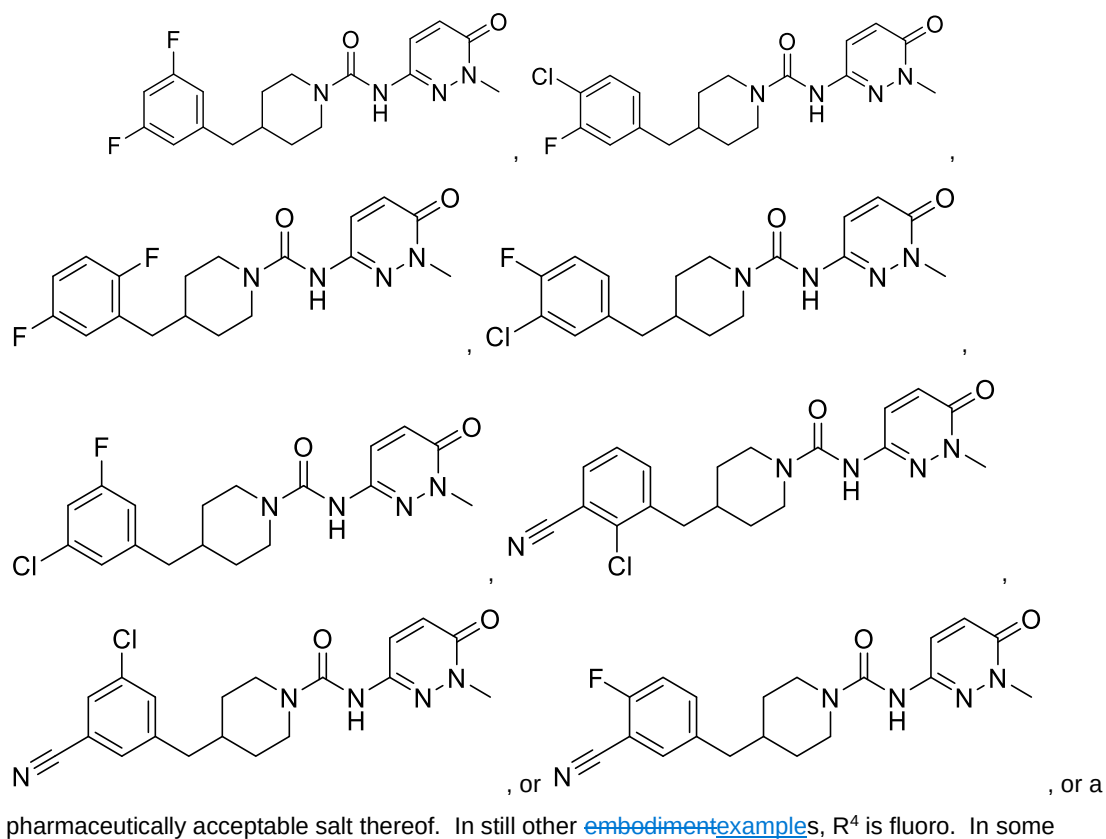
[embodimentexamples](#), R⁴ is fluoro. In certain [embodimentexamples](#), the compound is

, or , or a pharmaceutically acceptable salt thereof. In still further [embodimentexamples](#), R⁴ is OR⁶. In some

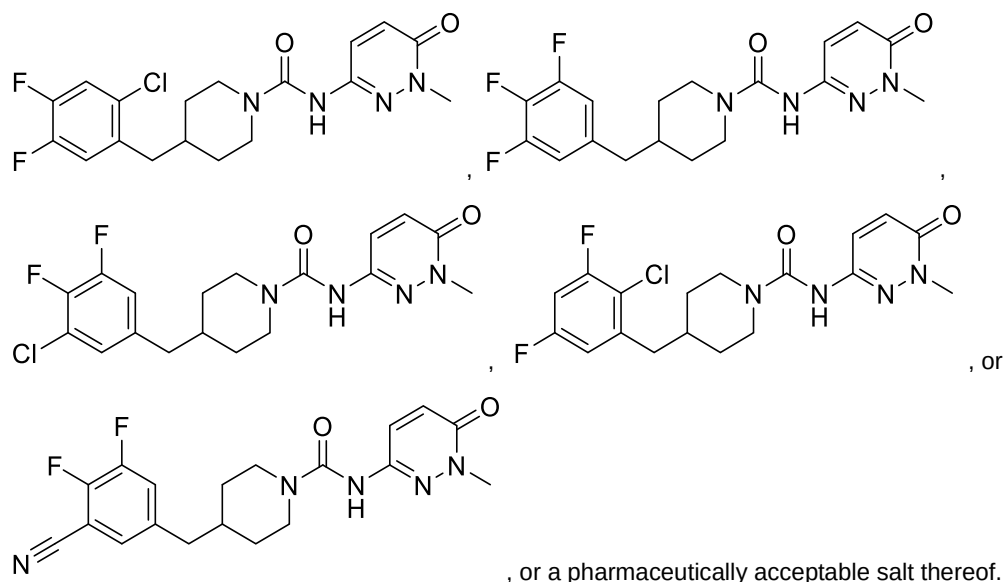
[embodimentexamples](#), the compound is  or , or a pharmaceutically acceptable salt thereof.

In other [embodiment examples](#), o is 2. In some [embodiment examples](#), R³ is, independently, halo or cyano. In some [embodiment examples](#), R⁴ is H. In certain [embodiment examples](#), the compound is

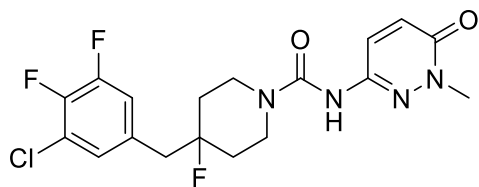




In further [embodimentexample](#), o is 3. In some [embodimentexample](#), each R³ is, independently, halo or cyano. In some [embodimentexamples](#), R⁴ is H. In particular [embodimentexample](#), the compound is

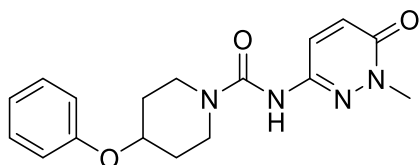


[embodimentexamples](#), R⁴ is fluoro. In some [embodimentexamples](#), the compound is



, or a pharmaceutically acceptable salt thereof.

In some [embodimentexamples](#), L² is O. In further [embodimentexamples](#), o is 0. In some [embodimentexamples](#), R⁴ is H. In some [embodimentexamples](#), the compound is

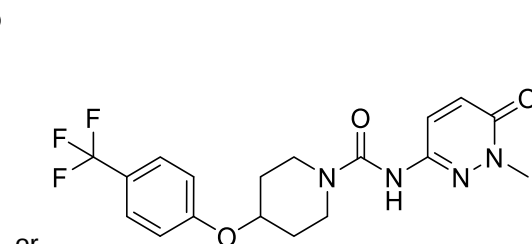
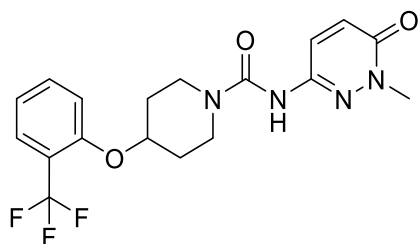
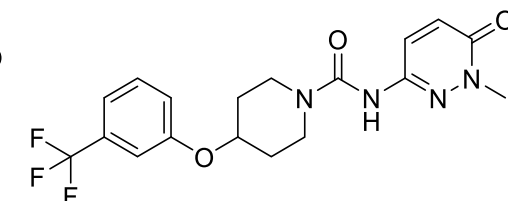
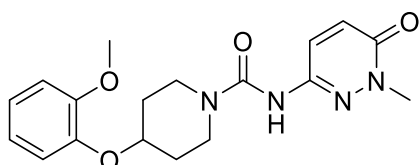
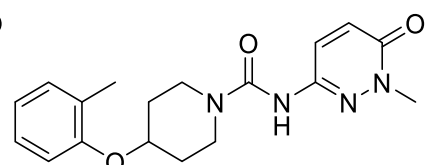
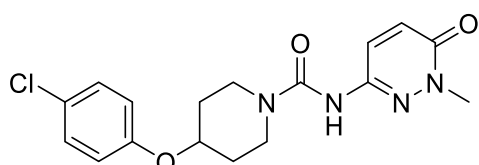
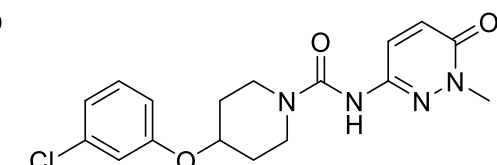
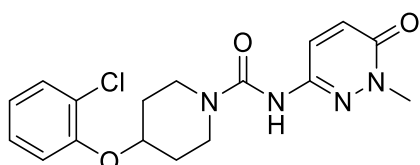


, or a pharmaceutically acceptable salt thereof. In other

[embodimentexamples](#), o is 1. In some [embodimentexamples](#), R³ is halo, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ alkoxy, or C₁₋₆ perfluoroalkyl. In further [embodimentexamples](#), R⁴ is H. In

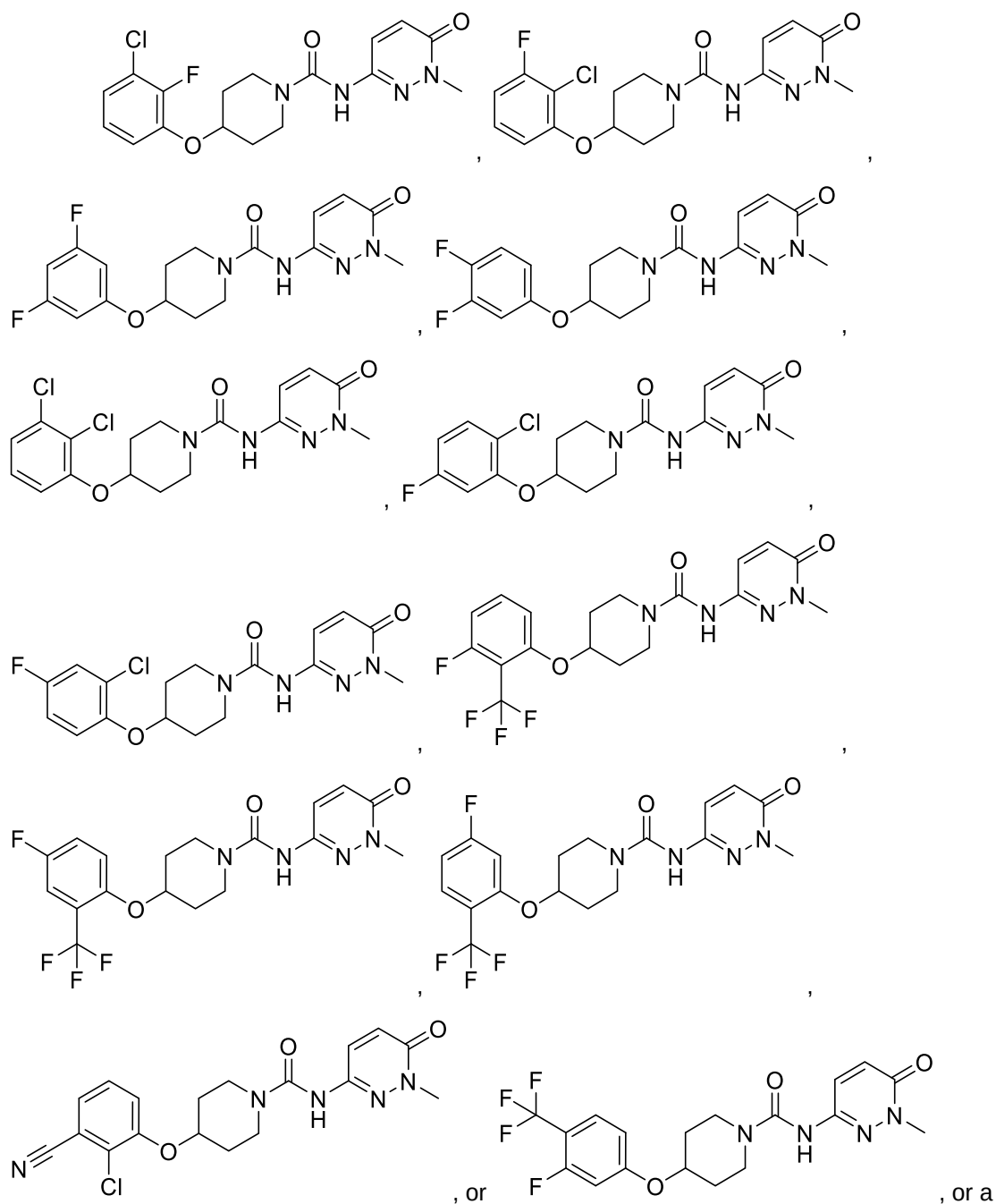
particular [embodimentexamples](#), the compound is

Chemical structure of a piperidine derivative. The piperidine ring is substituted with a 4-chlorophenoxymethyl group and a 1-methyl-2-pyridonecarboxamide group.



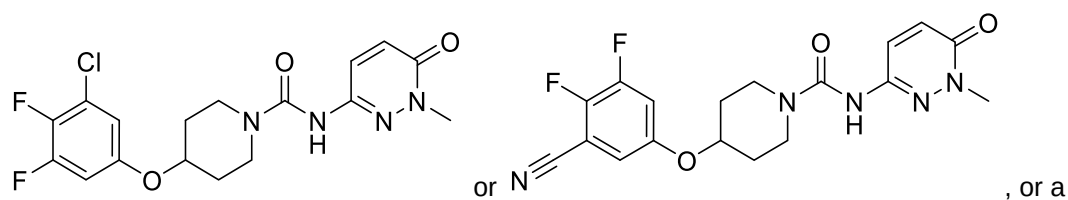
or , or a pharmaceutically acceptable salt thereof.

In still further [embodimentexamples](#), o is 2. In some [embodimentexamples](#), each R³ is, independently, halo, C₁₋₆ perfluoroalkyl, or cyano. In some [embodimentexamples](#), R⁴ is H. In specific [embodimentexamples](#), the compound is



pharmaceutically acceptable salt thereof.

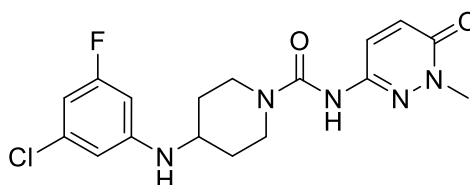
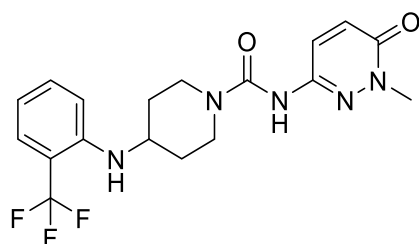
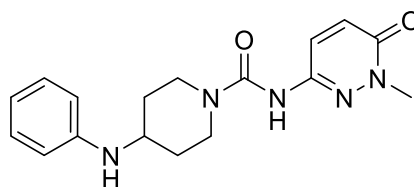
In some [embodimentexamples](#), o is 3. In certain [embodimentexamples](#), R³ is halo or cyano. In further [embodimentexamples](#), R⁴ is H. In particular [embodimentexamples](#), the compound is



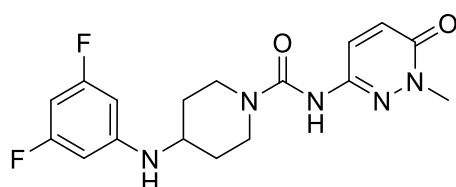
pharmaceutically acceptable salt thereof.

In still further [embodimentexamples](#), L² is NR⁵. In certain [embodimentexamples](#), L² is NH. In some [embodimentexamples](#), o is 0, 1, or 2. In some [embodimentexamples](#), R³ is halo or C₁₋₆ perfluoroalkyl. In some [embodimentexamples](#), R⁴ is H. In

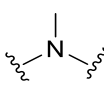
certain [embodimentexamples](#), the compound is

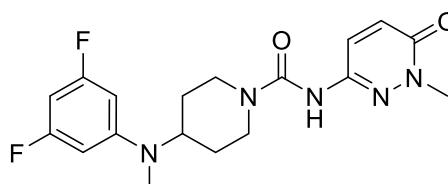


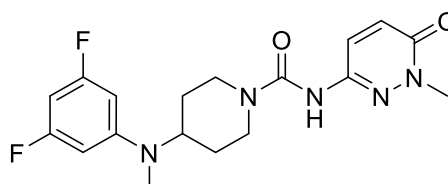
, or



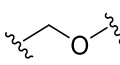
, or a pharmaceutically acceptable salt thereof. In other

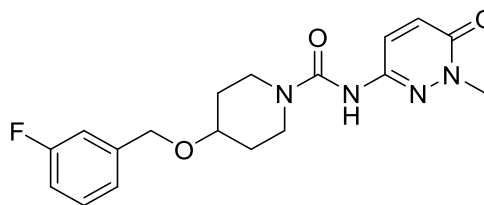
[embodimentexamples](#), L^2 is . In some [embodimentexamples](#), o is 2. In some [embodimentexamples](#), R^3 is halo. In further [embodimentexamples](#), R^4 is H. In some

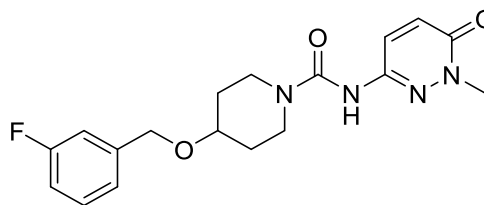


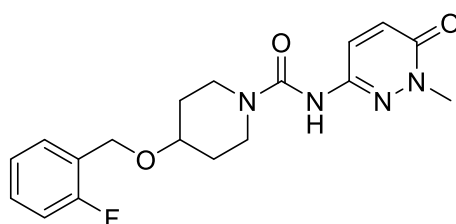
[embodimentexamples](#), the compound is , or a pharmaceutically acceptable salt thereof.

In other [embodimentexamples](#), L^2 is optionally substituted C_{1-6} heteroalkyl. In particular

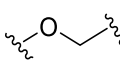
[embodimentexamples](#), L^2 is . In some [embodimentexamples](#), o is 1. In some [embodimentexamples](#), R^3 is halo. In some [embodimentexamples](#), R^4 is H. In further

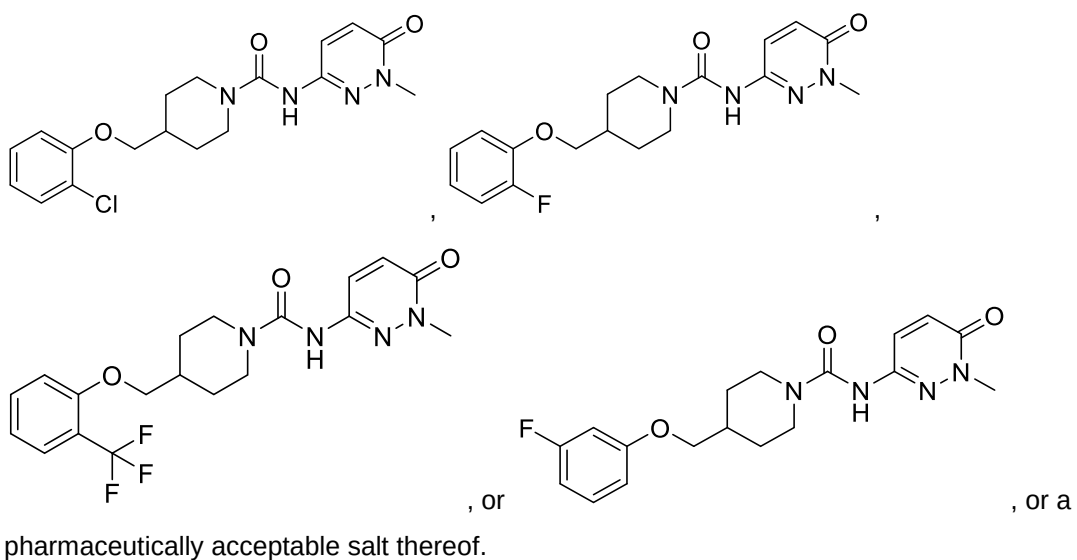


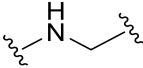
[embodimentexamples](#), the compound is  or

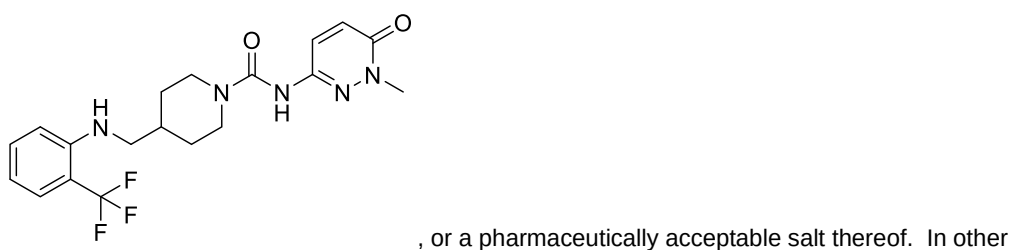
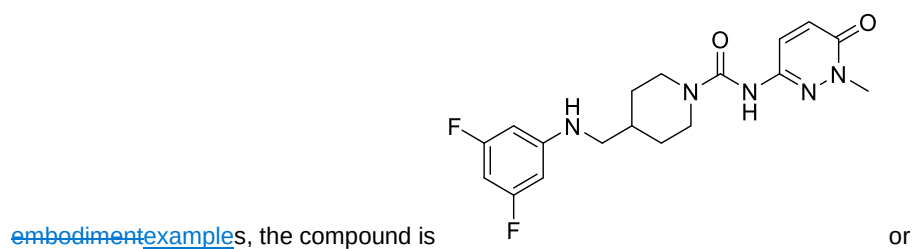


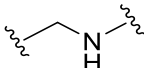
, or a pharmaceutically acceptable salt thereof. In further

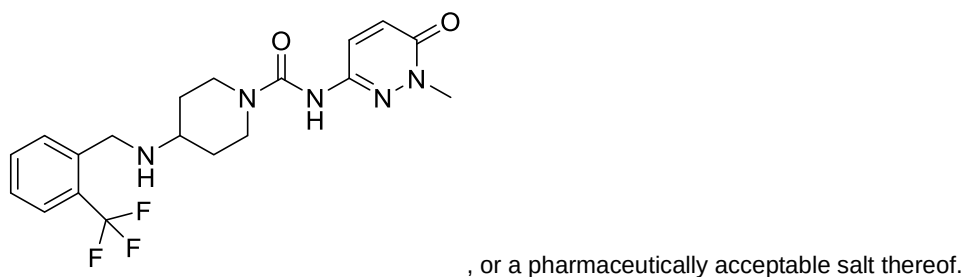
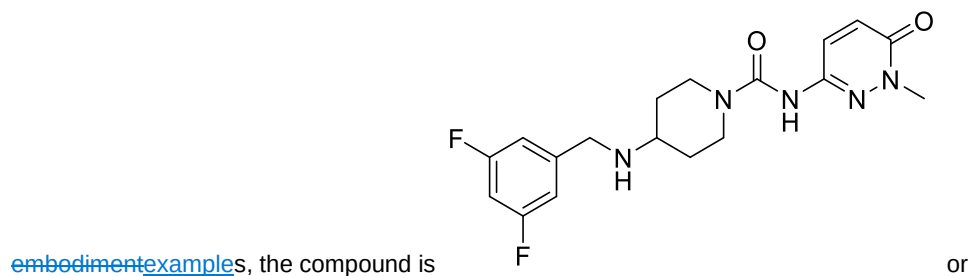
[embodimentexamples](#), L^2 is . In some [embodimentexamples](#), o is 1. In certain [embodimentexamples](#), R^3 is halo or C_{1-6} perfluoroalkyl. In some [embodimentexamples](#), R^4 is H. In particular [embodimentexamples](#), the compound is

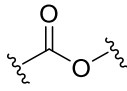


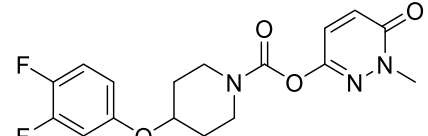
In yet further [embodimentexamples](#), L^2 is . In some [embodimentexample](#)s, o is 1 or 2. In some [embodimentexamples](#), R^3 is halo or C_{1-6} perfluoroalkyl. In further [embodimentexamples](#), R^4 is H. In particular

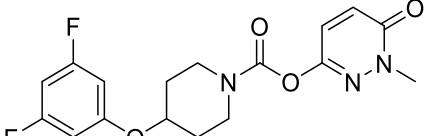


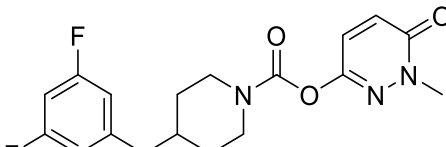
[embodimentexamples](#), L^2 is . In certain [embodimentexamples](#), o is 1 or 2. In further [embodimentexamples](#), R^3 is halo or C_{1-6} perfluoroalkyl. In some [embodimentexample](#)s, R^4 is H. In some



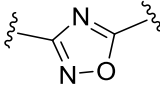
In still other [embodimentexamples](#), L¹ is . In some [embodimentexamples](#), L² is O. In some [embodimentexamples](#), o is 1 or 2. In some [embodimentexamples](#), R³ is halo. In further [embodimentexamples](#), R⁴ is

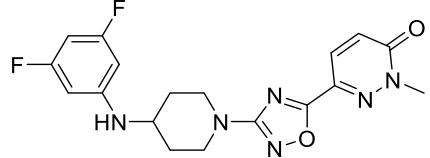
H. In particular [embodimentexamples](#), the compound is , or

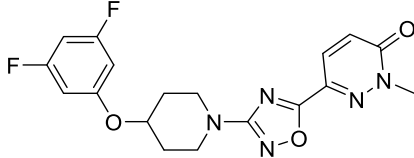
, or a pharmaceutically acceptable salt thereof. In further [embodimentexamples](#), L² is optionally substituted C₁₋₆ alkyl. In some [embodimentexamples](#), o is 2. In certain [embodimentexamples](#), R³ is halo. In some [embodimentexamples](#), R⁴ is H. In some [embodimentexamples](#), the

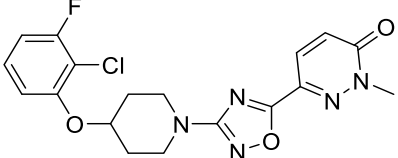
compound is , or a pharmaceutically acceptable salt thereof.

In further [embodimentexamples](#), L¹ is optionally substituted C₅₋₁₀ heteroaryl. In particular

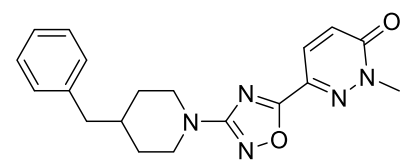
[embodimentexamples](#), L¹ is . In some [embodimentexamples](#), L² is NH. In some [embodimentexamples](#), o is 2. In some [embodimentexamples](#), R³ is halo. In further [embodimentexamples](#), R⁴ is H.

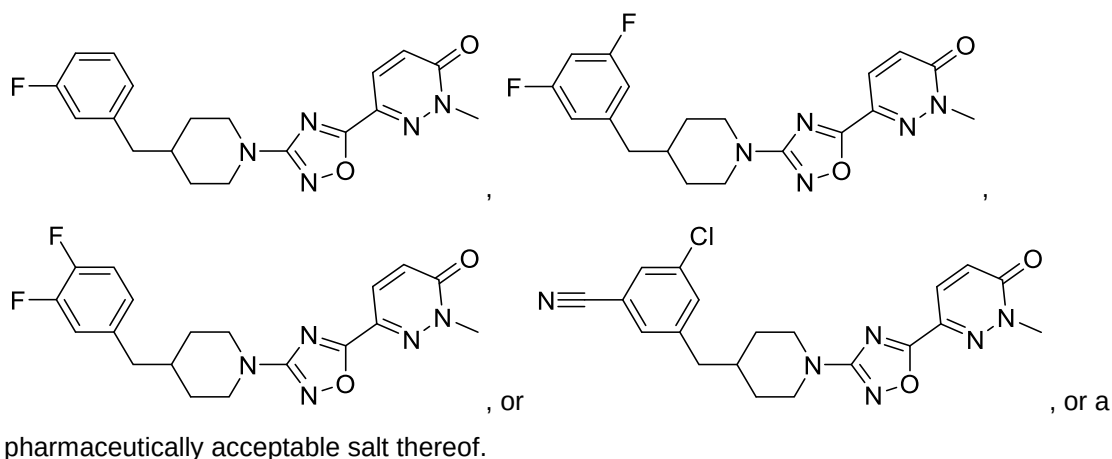
In particular [embodimentexample](#), the compound is , or a pharmaceutically acceptable salt thereof. In further [embodimentexamples](#), L² is O. In some [embodimentexamples](#), o is 2. In still further [embodimentexamples](#), R³ is halo. In some [embodimentexamples](#), R⁴ is H. In particular

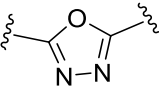
[embodimentexamples](#), the compound is  or

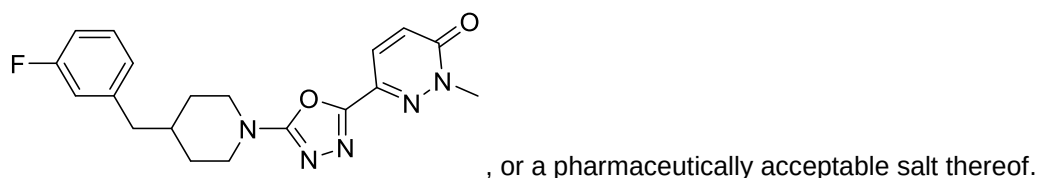
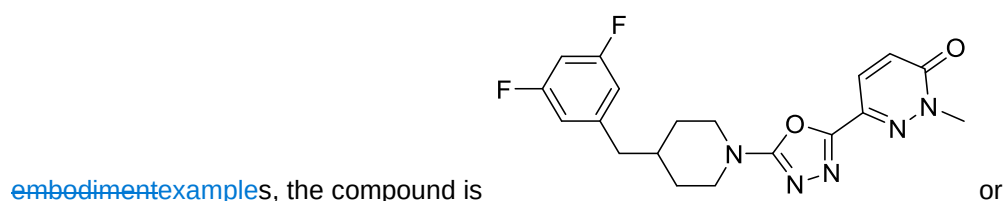
, or a pharmaceutically acceptable salt thereof.

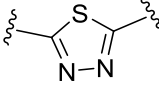
In still other [embodimentexamples](#), L² is optionally substituted C₁₋₆ alkyl. In some [embodimentexamples](#), o is 0, 1, or 2. In some [embodimentexamples](#), each R³ is, independently, halo or cyano. In some [embodimentexamples](#), R⁴ is H. In further [embodimentexamples](#), the compound is

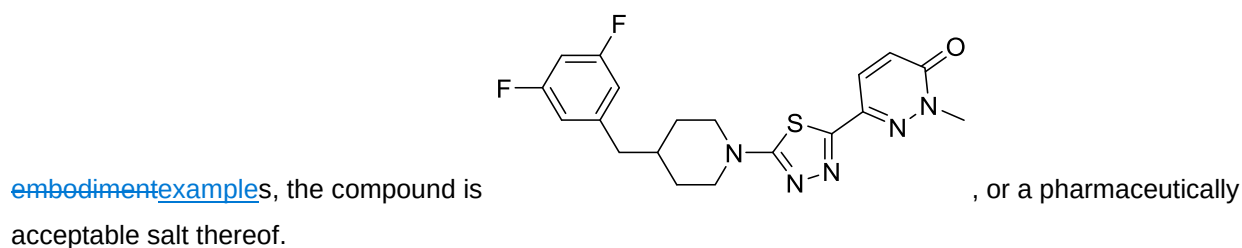
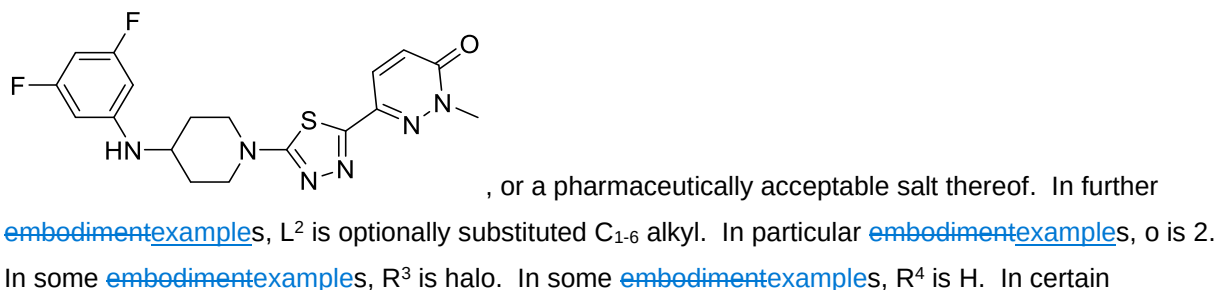


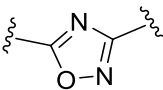


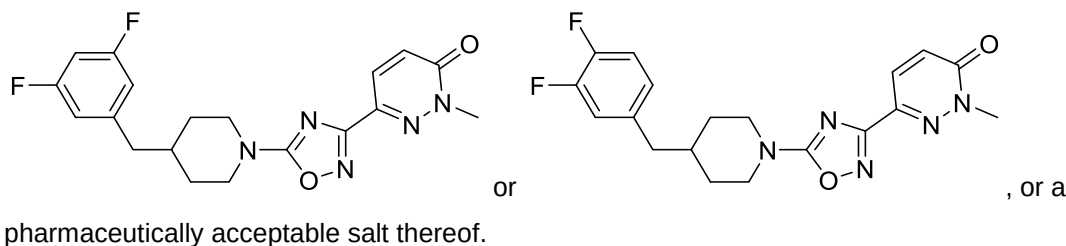
In further [embodimentexamples](#), L^1 is . In some [embodimentexamples](#), L^2 is optionally substituted C_{1-6} alkyl. In certain [embodimentexamples](#), o is 1 or 2. In some [embodimentexamples](#), R^3 is halo. In some [embodimentexamples](#), R^4 is H. In specific

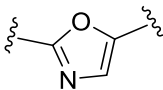


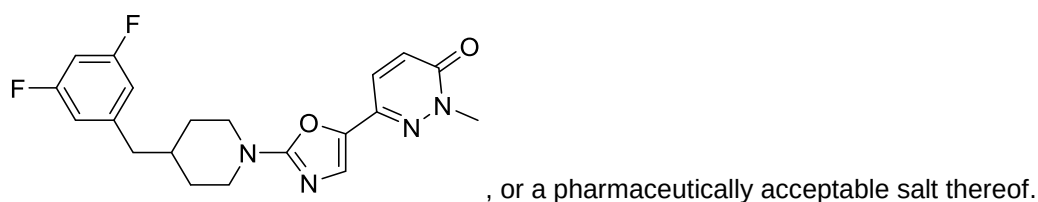
In yet other [embodimentexamples](#), L^1 is . In some [embodimentexamples](#), L^2 is NH. In further [embodimentexamples](#), o is 2. In some [embodimentexamples](#), R^3 is halo. In some [embodimentexamples](#), R^4 is H. In certain [embodimentexamples](#), the compound is

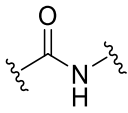


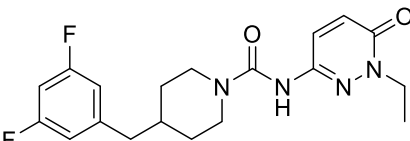
In still further [embodimentexamples](#), L¹ is . In some [embodimentexamples](#), L² is optionally substituted C₁₋₆ alkyl. In some [embodimentexamples](#), o is 2. In further [embodimentexamples](#), R³ is halo. In some [embodimentexamples](#), R⁴ is H. In further [embodimentexamples](#), the compound is

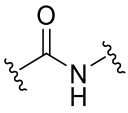


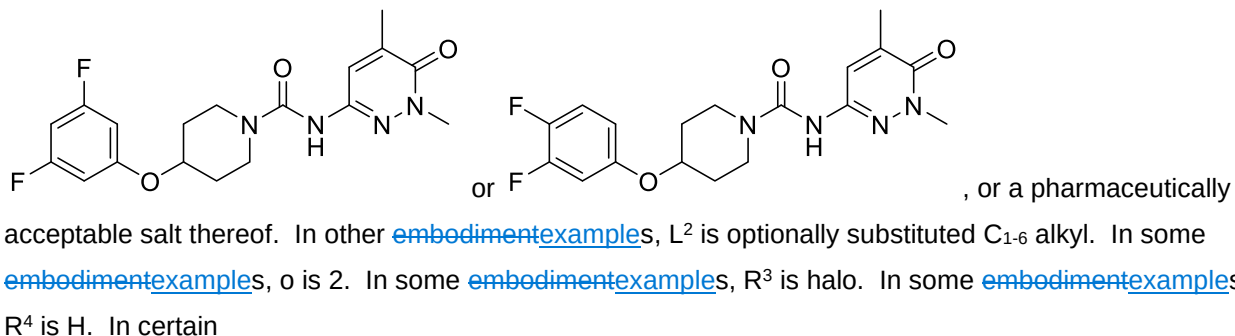
In other [embodimentexamples](#), L¹ is . In some [embodimentexamples](#), L² is optionally substituted C₁₋₆ alkyl. In some [embodimentexamples](#), o is 2. In some [embodimentexamples](#), R³ is halo. In some [embodimentexamples](#), R⁴ is H. In some [embodimentexamples](#), the compound is

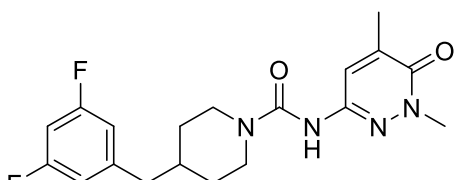


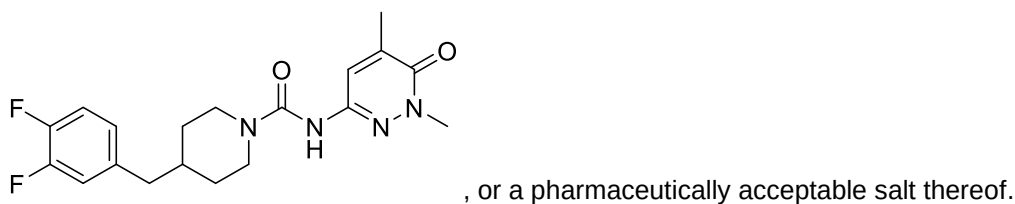
In still other [embodimentexamples](#), R¹ is ethyl. In some [embodimentexamples](#), L¹ is . In some [embodimentexamples](#), L² is optionally substituted C₁₋₆ alkyl. In further [embodimentexamples](#), o is 2. In some [embodimentexamples](#), R³ is halo. In some [embodimentexamples](#), R⁴ is H. In certain

[embodimentexamples](#), the compound is , or a pharmaceutically acceptable salt thereof. In specific [embodimentexamples](#), R² is methyl. In certain [embodimentexamples](#),

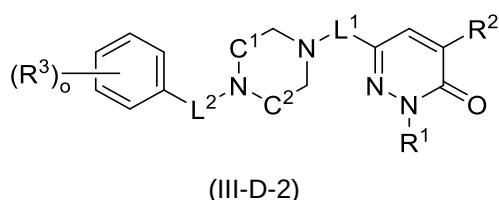
R¹ is methyl. In some [embodimentexamples](#), L¹ is . In some [embodimentexamples](#), L² is O. In further [embodimentexamples](#), o is 2. In some [embodimentexamples](#), R³ is halo. In some [embodimentexamples](#), R⁴ is H. In particular [embodimentexamples](#), the compound is



[embodiment examples](#), the compound is  or

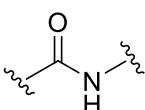


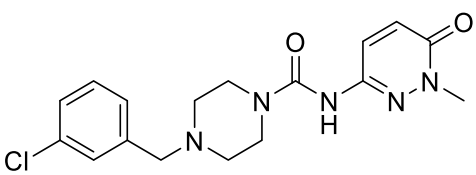
In other [embodiment examples](#), the compound has the structure of formula (III-D-2):



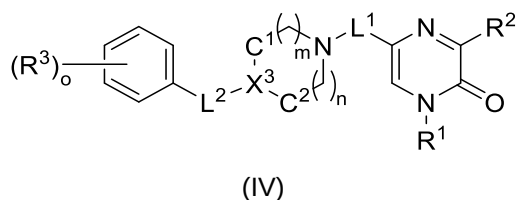
wherein: o is 0, 1, 2, 3, 4, or 5; C¹ and C² optionally combine to form a bond; each of R¹, R², and R⁵ is, independently, H or optionally substituted C₁₋₆ alkyl; R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted C₁₋₆ alkyl; L¹ is optionally substituted C₅₋₁₀ heteroaryl or –C(O)–X⁵–; X⁵ is NH, O, or optionally substituted C₁₋₆ alkyl; and L² is O, NR⁵, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, or absent; or a pharmaceutically acceptable salt thereof.

In some [embodiment examples](#), R¹ is methyl. In certain [embodiment examples](#), R² is H. In

particular [embodiment examples](#), L¹ is . In further [embodiment examples](#), L² is optionally substituted C₁₋₆ alkyl. In some [embodiment examples](#), o is 1. In some [embodiment examples](#), R³ is halo.

In certain [embodiment examples](#), the compound is  , or a pharmaceutically acceptable salt thereof.

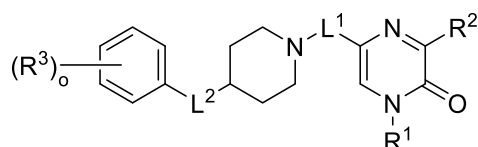
In yet other [embodiment examples](#), the compound has the structure of formula (IV):



wherein: m is 0 or 1; n is 0, 1, or 2; o is 0, 1, 2, 3, 4, or 5; C¹ and C² optionally combine to form a bond; each of R¹, R², R⁵, and R⁶ is, independently, H or optionally substituted C₁₋₆ alkyl; R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted C₁₋₆ alkyl; X³ is CR⁴ or N; or X³ and C¹ or C² combine to form an optionally substituted alkene; R⁴ is H, OR⁶, optionally substituted C₁₋₆ alkyl, or halo; L¹ is optionally substituted C₅₋₁₀ heteroaryl or –C(O)–X⁵–; X⁵ is NH, O, or optionally substituted C₁₋₆ alkyl; and L² is O, NR⁵, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆

heteroalkyl, or absent; or X^3 and L^2 combine to form an optionally substituted alkene, or a pharmaceutically acceptable salt thereof.

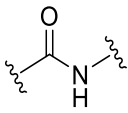
In further [embodimentexamples](#), the compound has the structure of formula (IV-A):

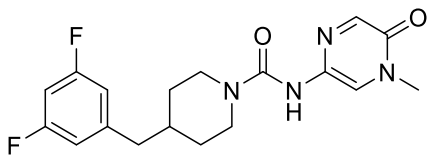


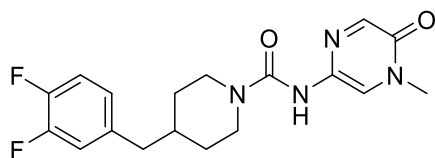
(IV-A)

wherein: o is 0, 1, 2, 3, 4, or 5; each of R^1 , R^2 , and R^5 is, independently, H or optionally substituted C_{1-6} alkyl; R^3 is halo, cyano, C_{1-6} perfluoroalkyl, optionally substituted C_{1-6} alkoxy, or optionally substituted C_{1-6} alkyl; L^1 is optionally substituted C_{5-10} heteroaryl or $-C(O)-X^5-$; X^5 is NH, O, or optionally substituted C_{1-6} alkyl; and L^2 is O, NR^5 , optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, or absent; or a pharmaceutically acceptable salt thereof.

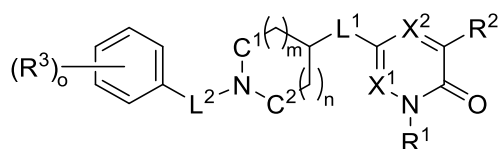
In some [embodimentexamples](#), R^2 is H. In further [embodimentexamples](#), R^1 is methyl. In some

[embodimentexamples](#), L^1 is . In certain [embodimentexamples](#), L^2 is optionally substituted C_{1-6} alkyl. In some [embodimentexamples](#), o is 2. In further [embodimentexamples](#), R^3 is halo. In some

[embodimentexamples](#), the compound is  or

, or a pharmaceutically acceptable salt thereof.

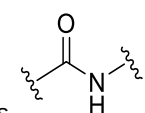
In some [embodimentexample](#)s, the compound has the structure of formula (V):



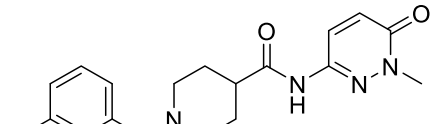
(V)

wherein: m is 0 or 1; n is 0, 1, or 2; o is 0, 1, 2, 3, 4, or 5; C^1 and C^2 optionally combine to form a bond; each of R^1 , R^2 , R^5 , and R^6 is, independently, H or optionally substituted C_{1-6} alkyl; R^3 is halo, cyano, C_{1-6} perfluoroalkyl, optionally substituted C_{1-6} alkoxy, or optionally substituted C_{1-6} alkyl; each of X^1 and X^2 is, independently, CH or N, wherein X^1 and X^2 are not both N; L^1 is optionally substituted C_{5-10} heteroaryl or $-C(O)-X^5-$; X^5 is NH, O, or optionally substituted C_{1-6} alkyl; and L^2 is O, NR^5 , optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, or absent; or a pharmaceutically acceptable salt thereof.

In certain [embodimentexample](#)s, X^1 is N and X^2 is CH. In further [embodimentexamples](#), R^2 is H. In some [embodimentexamples](#), R^1 is methyl. In some [embodimentexample](#)s, m is 1. In some [embodimentexample](#)s, n is 1.

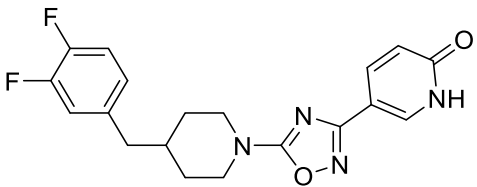
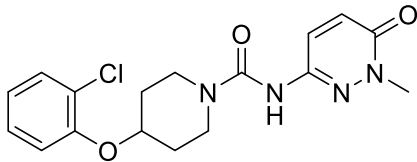
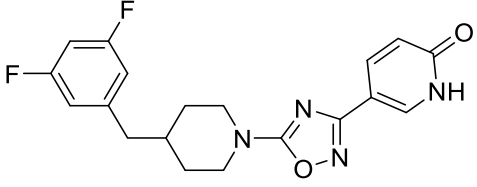
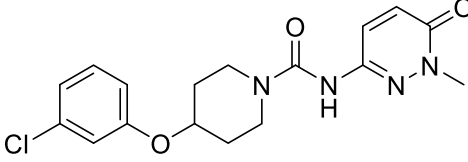
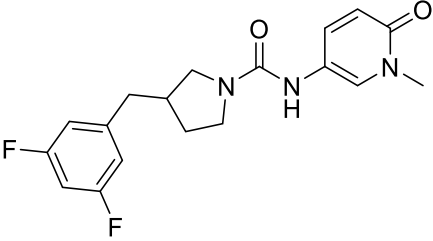
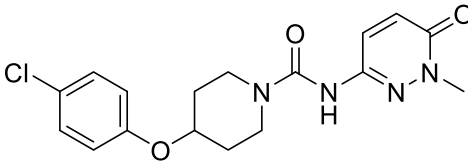
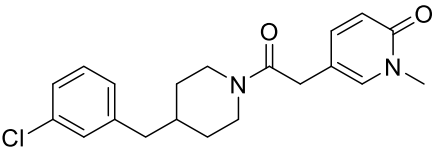
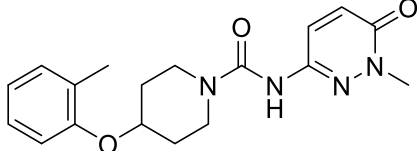
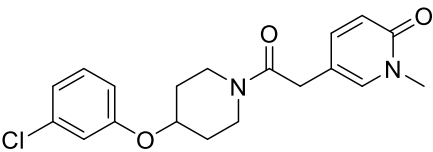
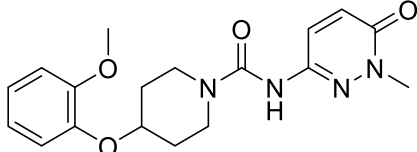
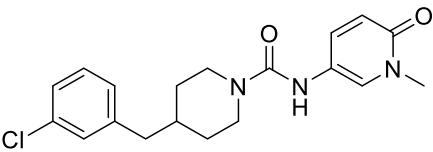
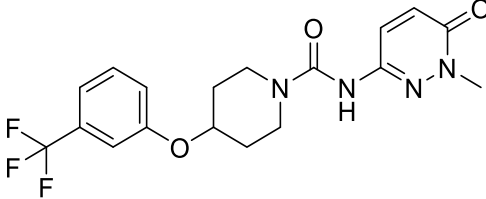
In still further [embodimentexamples](#), L^1 is . In particular [embodimentexamples](#), L^2 is optionally substituted C_{1-6} alkyl. In

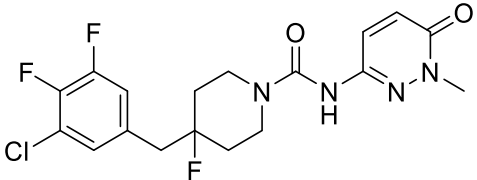
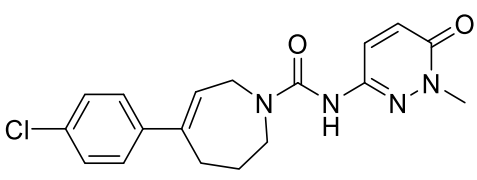
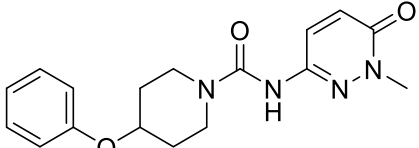
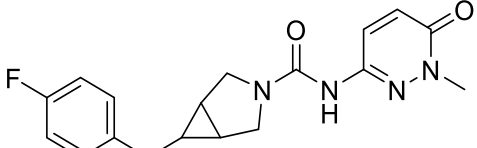
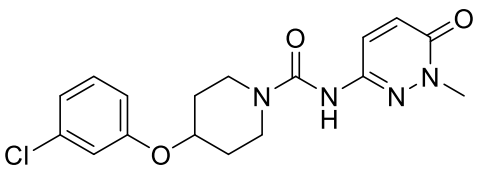
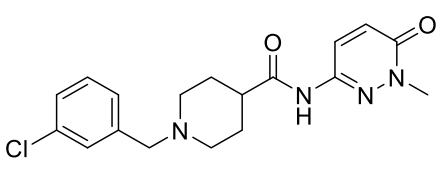
some [embodiment examples](#), o is 1. In some [embodiment examples](#), R³ is halo. In some

[embodiment examples](#), the compound is , or a pharmaceutically acceptable salt thereof.

In another [aspect example](#), the [invention disclosure](#) features a compound, or a pharmaceutically acceptable salt thereof, having the structure of any one of compounds 1-5, 7-11, 14-39, 41-105, 107-136 in Table 1.

Table 1. Compounds of the Invention

	Compound		Compound
1		69	
2		70	
3		71	
4		72	
5		73	
6		74	

66		134	
67		135	
68		136	

In another aspect, this disclosure provides a pharmaceutical composition comprising a compound of any of the foregoing compounds, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In some [embodimentexamples](#), the pharmaceutical composition includes a compound of one of formulas I-V and a pharmaceutically acceptable excipient.

[In another aspect, this disclosure provides a compound, or pharmaceutically acceptable salt thereof, as defined herein, for use as a medicament.](#)

~~In an aspect,~~ [this disclosure provides a method of treating a neurological disorder in a subject in need thereof, the method comprising administering an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof. In another aspect, this disclosure provides use of a compound, or pharmaceutically acceptable salt thereof as defined herein or a pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment of a neurological disorder.](#)

~~In an aspect,~~ [this disclosure provides a method of inhibiting toxicity in a cell related to a protein, the method comprising administering an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof. In another aspect, this disclosure provides a method of inhibiting toxicity in a cell in culture related to a protein, the method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, as defined herein.](#)

In some [embodimentexamples](#), the toxicity is α -synuclein-related toxicity. In some [embodimentexamples](#), the toxicity is ApoE4-related toxicity.

In some [embodimentexamples](#), the cell is a mammalian neural cell.

~~In an aspect,~~ [this disclosure provides a method of treating a stearyl-CoA desaturase \(SCD\)-associated disorder in a subject in need thereof, the method comprising administering an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof. In another aspect, this disclosure provides use of a compound, or pharmaceutically acceptable salt thereof as defined herein or a pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment of a stearyl-CoA desaturase \(SCD\) associated disorder.](#)

Non-limiting exemplary SCD-associated disorders include, but are not limited to metabolic disorders (e.g., diabetes (e.g., Type I diabetes and Type II diabetes), hyperglycemia, metabolic syndrome, obesity, lipid disorders, fatty liver, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), and hypertension), cancer, cardiovascular diseases, cerebrovascular diseases, kidney diseases, liver diseases, skin disorders (e.g., acne (e.g., acne vulgaris)), central nervous system (CNS) disorders, dementia, multiple sclerosis, schizophrenia, mild cognitive impairment, Alzheimer's Disease, cerebral amyloid angiopathy, and dementia associated with Down Syndrome.

In some [embodiment examples](#), the SCD-associated disorder is a SCD5-associated disorder.

~~In an aspect, this disclosure provides a method of inhibiting SCD5, the method comprising contacting a cell with an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof.~~

~~In an aspect, this disclosure provides a method of inhibiting SCD1, the method comprising contacting a cell with an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof.~~

~~In an aspect, this disclosure provides a method of treating a primary brain cancer in a subject in need thereof, the method comprising administering an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof. In another aspect, this disclosure provides use of a compound as defined herein or a pharmaceutical composition as defined herein in the manufacture of medicament for the treatment of primary brain cancer.~~

In some [embodimentexamples](#), the primary brain cancer is a glioma. In some [embodimentexamples](#), the glioma is an astrocytoma. In some [embodimentexamples](#), the astrocytoma is a glioblastoma.

In some [embodimentexamples](#), the cancer is determined or predicted to be resistant to one or more chemotherapeutic agents. In some [embodimentexamples](#), the cancer has failed to respond to one or more chemotherapeutic agents. In some [embodimentexamples](#), one or more therapeutic agents is selected from the group of temozolomide, carmustine, bevacizumab, lomustine, everolimus, vincristine, or procarbazine. In some [embodimentexamples](#), one or more therapeutic agents is temozolomide.

In some [embodimentexamples](#), the subject is further administered one or more additional therapeutic interventions. In some [embodimentexamples](#), one or more additional therapeutic interventions comprises surgery, radiation, and/or one or more additional chemotherapeutic agents. In some [embodimentexamples](#), one or more additional therapeutic interventions is one or more chemotherapeutic agents. In some [embodimentexamples](#), one or more chemotherapeutic agents is selected from the group of temozolomide, carmustine, bevacizumab, lomustine, everolimus, vincristine, or procarbazine. In some [embodimentexamples](#), one or more chemotherapeutic agents is temozolomide.

Chemical Terms

It is to be understood that the terminology employed herein is for the purpose of describing particular embodiments and is not intended to be limiting.

The term “acyl,” as used herein, represents a hydrogen or an alkyl group, as defined herein that is attached to a parent molecular group through a carbonyl group, as defined herein, and is exemplified by formyl (i.e., a carboxyaldehyde group), acetyl, trifluoroacetyl, propionyl, and butanoyl. Exemplary unsubstituted acyl groups include from 1 to 6, from 1 to 11, or from 1 to 21 carbons.

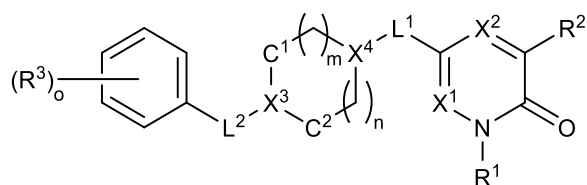
The term “alkyl,” as used herein, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of 1 to 20 carbon atoms (e.g., 1 to 16 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms). An alkylene is a divalent alkyl group.

The term “alkenyl,” as used herein, alone or in combination with other groups, refers to a straight-chain or branched hydrocarbon residue having a carbon-carbon double bond and having 2 to 20 carbon atoms (e.g., 2 to 16 carbon atoms, 2 to 10 carbon atoms, 2 to 6, or 2 carbon atoms).

The term "alkynyl," as used herein, alone or in combination with other groups, refers to a straight-chain or branched hydrocarbon residue having a carbon-carbon triple bond and having 2 to 20 carbon atoms (e.g., 2 to 16 carbon atoms, 2 to 10 carbon atoms, 2 to 6, or 2 carbon atoms).

Claims

1. A compound of formula (I):



(I)

wherein:

m is 0 or 1;

n is 0, 1, or 2;

o is 0, 1, 2, 3, 4, or 5;

C¹ and C² optionally combine to form a bond;

each of R¹, R², R⁵, and R⁶ is, independently, H or optionally substituted C₁-₆ alkyl;

R³ is halo, cyano, C₁-₆ perfluoroalkyl, optionally substituted C₁-₆ alkoxy, or optionally substituted C₁-₆ alkyl;

each of X¹ and X² is, independently, CH or N, wherein X¹ and X² are not both N;

X³ is CR⁴ or N; or X³ and C¹ or C² combine to form an optionally substituted alkene;

X⁴ is CH or N;

wherein at least one of X³ and X⁴ is N;

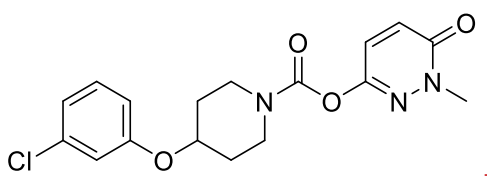
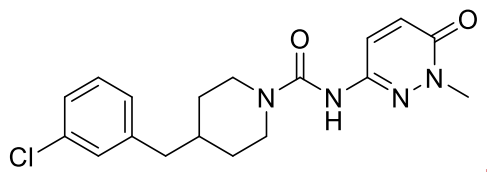
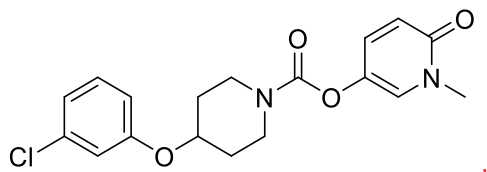
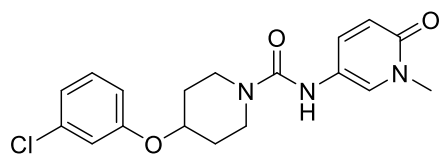
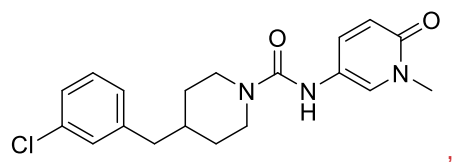
R⁴ is H, OR⁶, optionally substituted C₁-₆ alkyl, or halo;

L¹ is ~~—C(O)—X⁵—~~ or optionally substituted C₅-₁₀ heteroaryl ~~—C(O)—X⁵—~~;

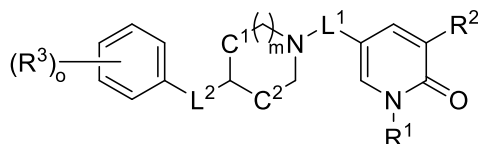
X⁵ is NH, O, or optionally substituted C₁-₆ alkyl; and

L² is O, NR⁵, optionally substituted C₁-₆ alkyl, optionally substituted C₁-₆ heteroalkyl, or absent; or X³ and L² combine to form an optionally substituted alkene, or a pharmaceutically acceptable salt thereof;

wherein the compound does not have the following structure ~~of Compound 6, Compound 12, Compound 13, Compound 40, or Compound 106.~~



2. The compound of claim 1, wherein the compound has the structure of formula (II):



(II)

wherein:

m is 0 or 1;

o is 0, 1, 2, 3, 4, or 5;

C¹ and C² optionally combine to form a bond;

each of R¹, R², and R⁵ is, independently, H or optionally substituted C₁₋₆ alkyl;

R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted

C₁₋₆ alkyl;

L¹ is ~~—C(O)—X⁵—~~ or optionally substituted C₅₋₁₀ heteroaryl ~~or —C(O)—X⁵—~~;

X⁵ is NH, O, or optionally substituted C₁₋₆ alkyl; and

L² is O, NR⁵, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, or absent;

or a pharmaceutically acceptable salt thereof;

wherein the compound does not have the structure of Compound 6, Compound 12, or Compound

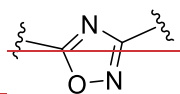
13.

~~3. The compound of claim 2, wherein R² is H.~~

~~4. The compound of claim 2 or 3, wherein R¹ is H.~~

~~5. The compound of any one of claims 2-4, wherein m is 1.~~

~~6. The compound of any one of claims 2-5, wherein L¹ is~~

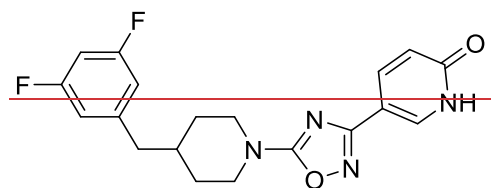
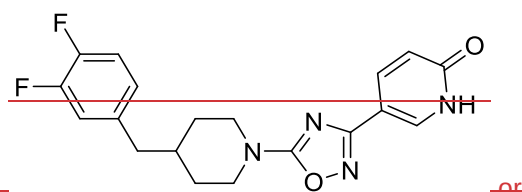


~~7. The compound of any one of claims 2-6, wherein L² is optionally substituted C₁₋₆ alkyl.~~

~~8. The compound of any one of claims 2-7, wherein o is 2.~~

~~9. The compound of any one of claims 2-8, wherein R³ is halo.~~

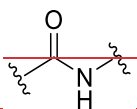
~~10. The compound of claim 1, wherein the compound is-~~



~~11. The compound of claim 2 or 3, wherein R¹ is methyl.~~

~~12. The compound of claim 11, wherein m is 0.~~

~~13. The compound of claim 11 or 12, wherein L¹ is-~~

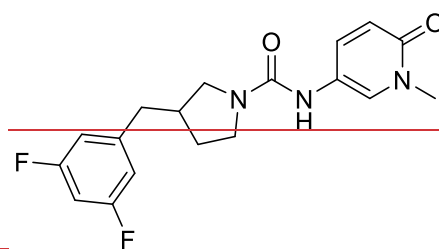


~~14. The compound of any one of claims 11-13, wherein L² is optionally substituted C₁₋₆ alkyl.~~

~~15. The compound of any one of claims 11-14, wherein o is 2.~~

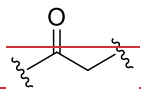
~~16. The compound of any one of claims 11-15, wherein R³ is halo.~~

~~17. The compound of claim 1, wherein the compound is-
pharmaceutically acceptable salt thereof.~~



~~18. The compound of claim 11, wherein m is 1.~~

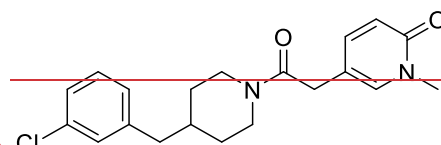
~~19. The compound of claim 18, wherein L¹ is-~~



~~20. The compound of claim 18 or 19, wherein L² is optionally substituted C₁₋₆ alkyl.~~

~~21. The compound of any one of claims 18-20, wherein o is 1.~~

~~22. The compound of any one of claims 18-21, wherein R³ is halo.~~

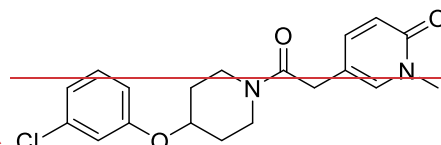


~~23. The compound of claim 1, wherein the compound is~~
~~pharmaceutically acceptable salt thereof.~~

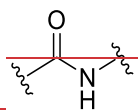
~~24. The compound of claim 18 or 19, wherein L² is O.~~

~~25. The compound of claim 24, wherein o is 1.~~

~~26. The compound of claim 24 or 25, wherein R³ is halo.~~



~~27. The compound of claim 1, wherein the compound is~~
~~pharmaceutically acceptable salt thereof.~~

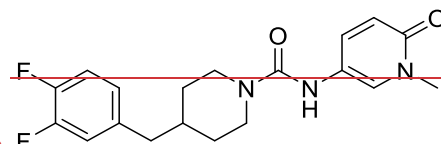


~~28. The compound of claim 18, wherein L¹ is~~

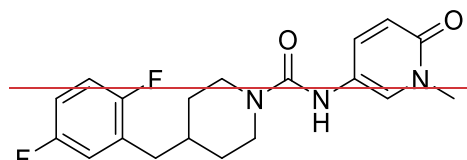
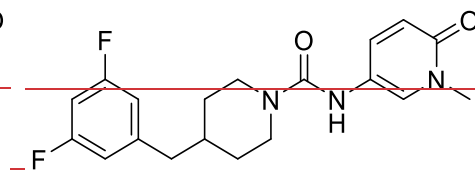
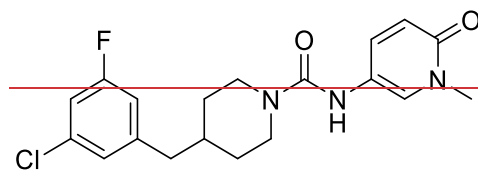
~~29. The compound of claim 18 or 28, wherein L² is optionally substituted C₁₋₆ alkyl.~~

~~30. The compound of claim 28 or 29, wherein o is 1 or 2.~~

~~31. The compound of any one of claims 28-30, wherein R³ is halo.~~



~~32. The compound of claim 1, wherein the compound is~~

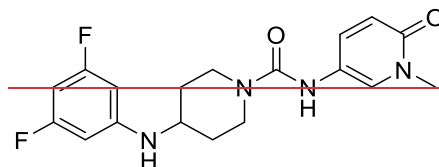


~~, or a pharmaceutically acceptable salt thereof.~~

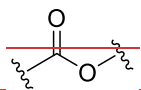
33. The compound of claim 18 or 28, wherein L^2 is NH or O.

34. The compound of claim 33, wherein α is 1 or 2.

35. The compound of claim 33 or 34, wherein R^3 is halo.



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

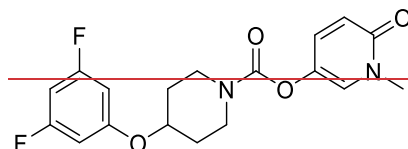


37. The compound of claim 18, wherein L^1 is

38. The compound of claim 18 or 37, wherein L^2 is O.

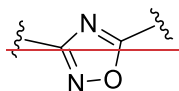
39. The compound of claim 37 or 38, wherein α is 1 or 2.

40. The compound of any one of claims 37-39, wherein R^3 is halo.



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

42. The compound of claim 18, wherein L^1 is optionally substituted C_{5-10} heteroaryl.



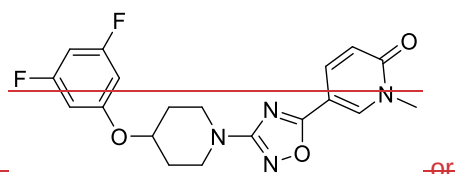
43. The compound of claim 42, wherein L^1 is

44. The compound of claim 42 or 43, wherein L^2 is O.

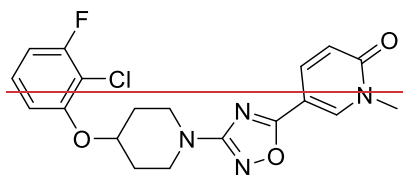
45. The compound of any one of claims 42-44, wherein α is 2.

46. The compound of any one of claims 42-45, wherein R^3 is halo.

47. ~~The compound of claim 1, wherein the compound is-~~



~~-or~~



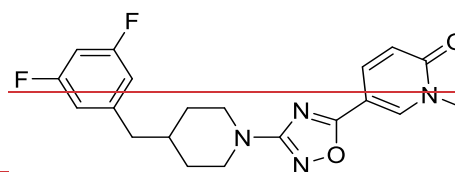
~~, or a pharmaceutically acceptable salt thereof.~~

48. ~~The compound of claim 42 or 43, wherein L² is optionally substituted C₁₋₆ alkyl.~~

49. ~~The compound of claim 48, wherein o is 2.~~

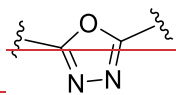
50. ~~The compound of claim 48 or 49, wherein R³ is halo.~~

51. ~~The compound of claim 1, wherein the compound is-
pharmaceutically acceptable salt thereof.~~



~~, or a~~

52. ~~The compound of claim 42, wherein L¹ is-~~

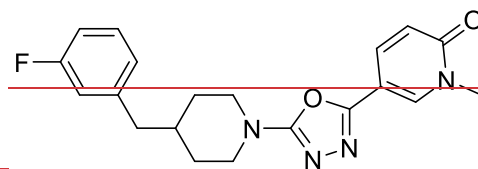


53. ~~The compound of claim 42 or 52, wherein L² is optionally substituted C₁₋₆ alkyl.~~

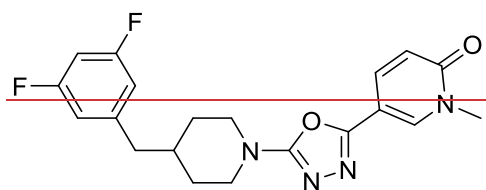
54. ~~The compound of claim 52 or 53, wherein o is 1 or 2.~~

55. ~~The compound of any one of claims 52-54, wherein R³ is halo.~~

56. ~~The compound of claim 1, wherein the compound is-~~

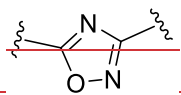


~~-or~~



~~, or a pharmaceutically acceptable salt thereof.~~

57. ~~The compound of claim 42, wherein L¹ is~~

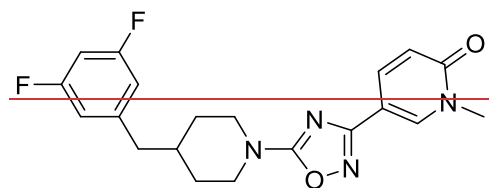
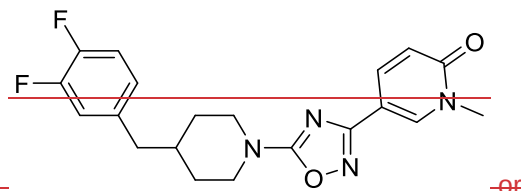


58. ~~The compound of claim 42 or 57, wherein L² is optionally substituted C₁₋₆ alkyl.~~

59. ~~The compound of claim 57 or 58, wherein o is 2.~~

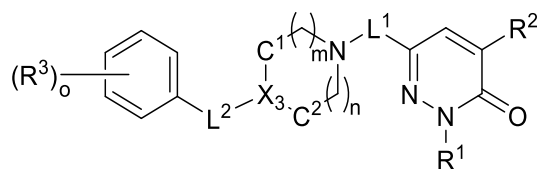
60. ~~The compound of any one of claims 57-59, wherein R³ is halo.~~

61. ~~The compound of claim 1, wherein the compound is~~



~~, or a pharmaceutically acceptable salt thereof.~~

362. The compound of claim 1, wherein the compound has the structure of formula (III):



(III)

wherein:

m is 0 or 1;

n is 0, 1, or 2;

o is 0, 1, 2, 3, 4, or 5;

C¹ and C² optionally combine to form a bond;

each of R¹, R², R⁵, and R⁶ is, independently, H or optionally substituted C₁₋₆ alkyl;

R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted C₁₋₆ alkyl;

X³ is CR⁴ or N; or X³ and C¹ or C² combine to form an optionally substituted alkene;

R⁴ is H, OR⁶, optionally substituted C₁₋₆ alkyl, or halo;

L¹ is ~~-C(O)-X⁵-~~ or optionally substituted C₅₋₁₀ heteroaryl ~~or -C(O)-X⁵-~~;

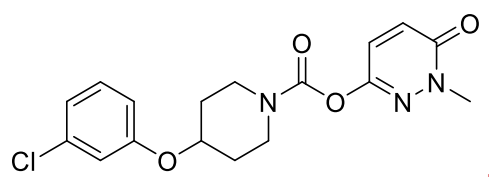
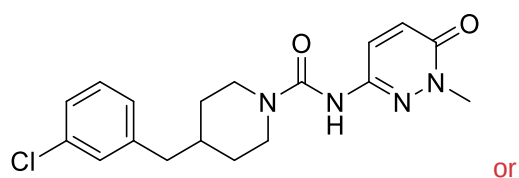
X⁵ is NH, O, or optionally substituted C₁₋₆ alkyl; and

L² is O, NR⁵, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, or absent; or

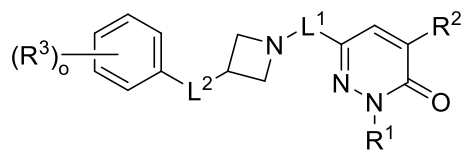
X³ and L² combine to form an optionally substituted alkene,

or a pharmaceutically acceptable salt thereof;

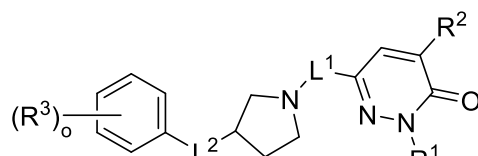
wherein the compound does not have the structure ~~of Compound 40 or Compound 106.~~



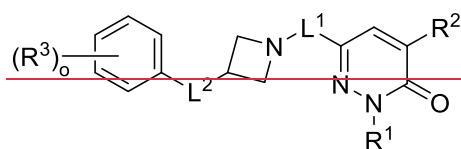
~~463.~~ The compound of claim ~~362~~, wherein the compound has the structure of formula (III-A) or (III-B):



(III-A)



(III-B)



(III-A)

wherein:

o is 0, 1, 2, 3, 4, or 5;

each of R^1 , R^2 , and R^5 is, independently, H or optionally substituted C_{1-6} alkyl;

R^3 is halo, cyano, C_{1-6} perfluoroalkyl, optionally substituted C_{1-6} alkoxy, or optionally substituted C_{1-6} alkyl;

L^1 is ~~$-C(O)-X^5-$~~ or optionally substituted C_{5-10} heteroaryl ~~or $-C(O)-X^5-$~~ ;

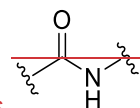
X^5 is NH, O, or optionally substituted C_{1-6} alkyl; and

L^2 is O, NR^5 , optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, or absent; or a pharmaceutically acceptable salt thereof.

~~64. The compound of claim 63, wherein R^2 is H.~~

~~65. The compound of claim 63 or 64, wherein R^1 is methyl.~~

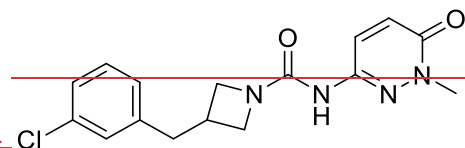
~~66. The compound of any one of claims 63-65, wherein L^1 is~~



~~67. The compound of any one of claims 63-66, wherein L^2 is optionally substituted C_{1-6} alkyl.~~

~~68. The compound of any one of claims 63-67, wherein o is 1.~~

~~69. The compound of any one of claims 63-68, wherein R^3 is halo.~~

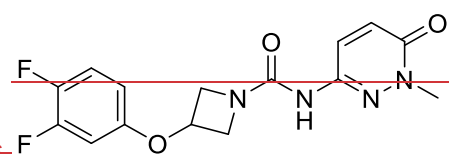


~~70. The compound of claim 63, wherein the compound is~~
~~, or a pharmaceutically acceptable salt thereof.~~

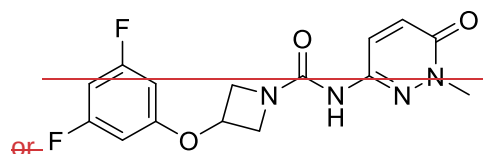
~~71. The compound of claim 63-66, wherein L² is O.~~

~~72. The compound of claim 71, wherein o is 2.~~

~~73. The compound of claim 71 or 72, wherein R³ is halo.~~

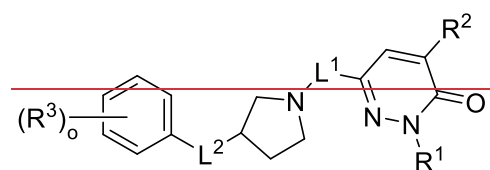


~~74. The compound of claim 63, wherein the compound is~~



~~, or a pharmaceutically acceptable salt thereof.~~

~~75. The compound of claim 62, wherein the compound has the structure of formula (III-B):~~



~~(III-B)~~

~~wherein:~~

~~o is 0, 1, 2, 3, 4, or 5;~~

~~each of R¹, R², and R⁵ is, independently, H or optionally substituted C₁₋₆ alkyl;~~

~~R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted C₁₋₆ alkyl;~~

~~L¹ is optionally substituted C₅₋₁₀ heteroaryl or C(O)-X⁵;~~

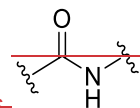
~~X⁵ is NH, O, or optionally substituted C₁₋₆ alkyl; and~~

~~L² is O, NR⁵, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, or absent;~~

~~or a pharmaceutically acceptable salt thereof.~~

~~76. The compound of claim 75, wherein R² is H.~~

~~77. The compound of claim 75 or 76, wherein R¹ is methyl.~~

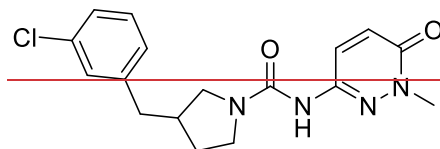


~~78. The compound of any one of claims 75-77, wherein L¹ is~~

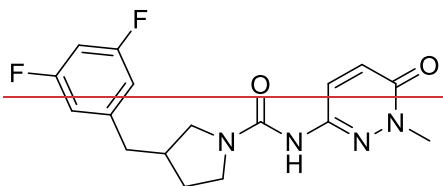
~~79. The compound of any one of claims 75-78, wherein L² is optionally substituted C₁₋₆ alkyl.~~

~~80. The compound of any one of claims 75-79, wherein o is 1 or 2.~~

~~81. The compound of any one of claims 75-80, wherein R³ is halo.~~



~~82. The compound of claim 75, wherein the compound is~~



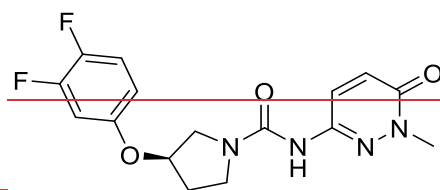
~~or~~

~~, or a pharmaceutically acceptable salt thereof.~~

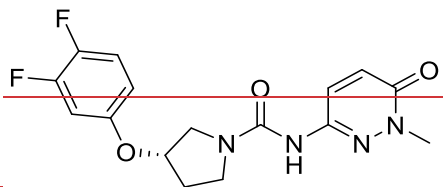
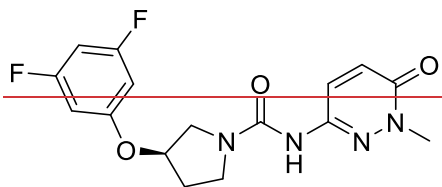
~~83. The compound of claim 75-78, wherein L² is O.~~

~~84. The compound of claim 83, wherein o is 2.~~

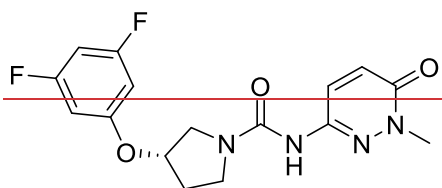
~~85. The compound of claim 83 or 84, wherein R³ is halo.~~



~~86. The compound of claim 75, wherein the compound is~~

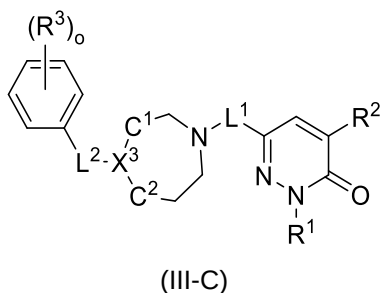


~~, or~~



~~, or a pharmaceutically acceptable salt thereof.~~

~~587.~~ The compound of claim ~~362~~, wherein the compound has the structure of formula (III-C):



wherein:

o is 0, 1, 2, 3, 4, or 5;

C¹ and C² optionally combine to form a bond;

each of R¹, R², R⁵, and R⁶ is, independently, H or optionally substituted C₁-₆ alkyl;

R³ is halo, cyano, C₁-₆ perfluoroalkyl, optionally substituted C₁-₆ alkoxy, or optionally substituted C₁-₆ alkyl;

X³ is CR⁴ or N; or X³ and C¹ or C² combine to form an optionally substituted alkene;

R⁴ is H, OR⁶, optionally substituted C₁-₆ alkyl, or halo;

L¹ is ~~-C(O)-X⁵-~~ or optionally substituted C₅-₁₀ heteroaryl ~~-C(O)-X⁵-~~;

X⁵ is NH, O, or optionally substituted C₁-₆ alkyl; and

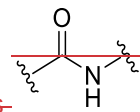
L² is O, NR⁵, optionally substituted C₁-₆ alkyl, optionally substituted C₁-₆ heteroalkyl, or absent; or

X³ and L² combine to form an optionally substituted alkene,
or a pharmaceutically acceptable salt thereof.

~~88. The compound of claim 87, wherein R² is H.~~

~~89. The compound of claim 87 or 88, wherein R³ is methyl.~~

~~90. The compound of any one of claims 87-89, wherein L¹ is~~

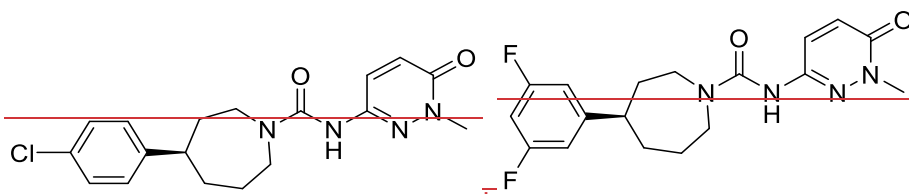


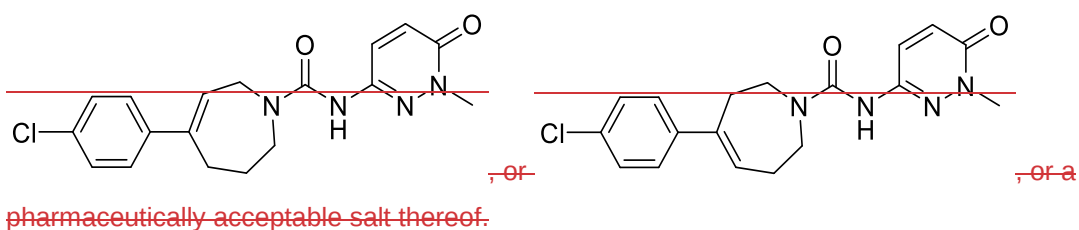
~~91. The compound of any one of claims 87-90, wherein L² is absent.~~

~~92. The compound of any one of claims 87-91, wherein o is 1 or 2.~~

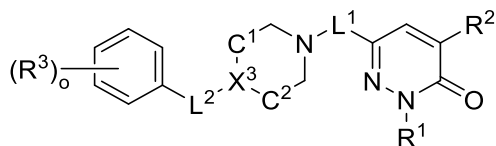
~~93. The compound of any one of claims 87-92, wherein R³ is halo.~~

~~94. The compound of claim 87, wherein the compound is~~





~~695.~~ The compound of claim ~~362~~, wherein the compound has the structure of formula (III-D):



(III-D)

wherein:

o is 0, 1, 2, 3, 4, or 5;

C^1 and C^2 optionally combine to form a bond;

each of R^1 , R^2 , R^5 , and R^6 is, independently, H or optionally substituted C_{1-6} alkyl;

R^3 is halo, cyano, C_{1-6} perfluoroalkyl, optionally substituted C_{1-6} alkoxy, or optionally substituted C_{1-6} alkyl;

X^3 is CR^4 or N; or X^3 and C^1 or C^2 combine to form an optionally substituted alkene;

R^4 is H, OR^6 , optionally substituted C_{1-6} alkyl, or halo;

L^1 is ~~$-C(O)-X^5-$~~ or optionally substituted C_{5-10} heteroaryl ~~or $-C(O)-X^5-$~~ ;

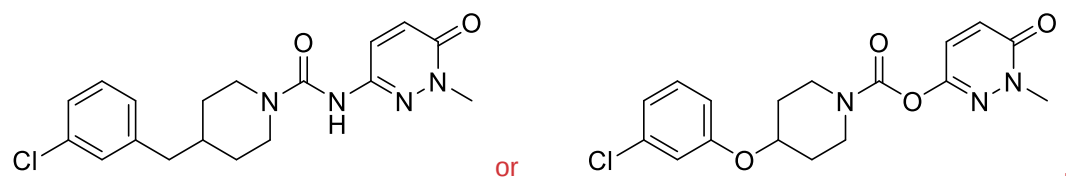
X^5 is NH, O, or optionally substituted C_{1-6} alkyl; and

L^2 is O, NR^5 , optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, or absent; or

X^3 and L^2 combine to form an optionally substituted alkene,

or a pharmaceutically acceptable salt thereof;

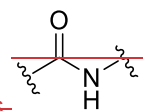
wherein the compound does not have the structure ~~of Compound 40 or Compound 106.~~



~~96.~~ The compound of claim 95, wherein R^2 is H.

~~97.~~ The compound of claim 95 or 96, wherein R^1 is methyl.

~~98.~~ The compound of any one of claims 95-97, wherein L^1 is-



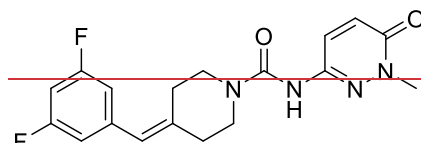
~~99.~~ The compound of any one of claims 95-98, wherein X^3 and L^2 combine to form an optionally substituted alkene.

~~100. The compound of any one of claims 95-99, wherein o is 2.~~

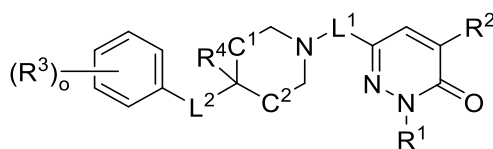
~~101. The compound of any one of claims 95-100, wherein R³ is halo.~~

5

~~102. The compound of claim 95, wherein the compound is
or a pharmaceutically acceptable salt thereof.~~



~~103.~~ The compound of claim ~~95~~, wherein the compound has the structure of formula (III-D-1):



10

(III-D-1)

wherein:

o is 0, 1, 2, 3, 4, or 5;

C¹ and C² optionally combine to form a bond;

15

each of R¹, R², R⁵, and R⁶ is, independently, H or optionally substituted C₁₋₆ alkyl;

R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted C₁₋₆ alkyl;

R⁴ is H, OR⁶, optionally substituted C₁₋₆ alkyl, or halo;

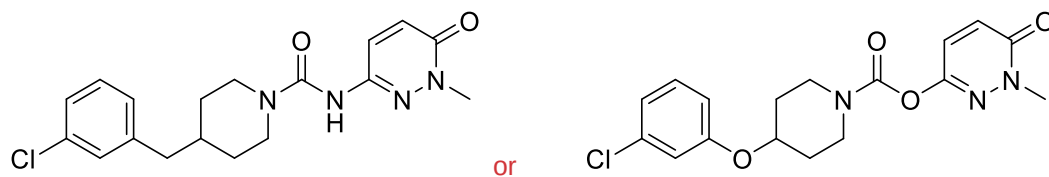
L¹ is ~~-C(O)-X⁵-~~ or optionally substituted C₅₋₁₀ heteroaryl ~~or -C(O)-X⁵-~~;

20

X⁵ is NH, O, or optionally substituted C₁₋₆ alkyl; and

L² is O, NR⁵, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, or absent;
or a pharmaceutically acceptable salt thereof;

wherein the compound does not have the structure ~~of Compound 40 or Compound 106.~~



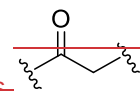
25

~~104. The compound of claim 103, wherein R² is H.~~

~~105. The compound of claim 103 or 104, wherein R¹ is H.~~

30

~~106. The compound of any one of claims 103-105, wherein L¹ is~~



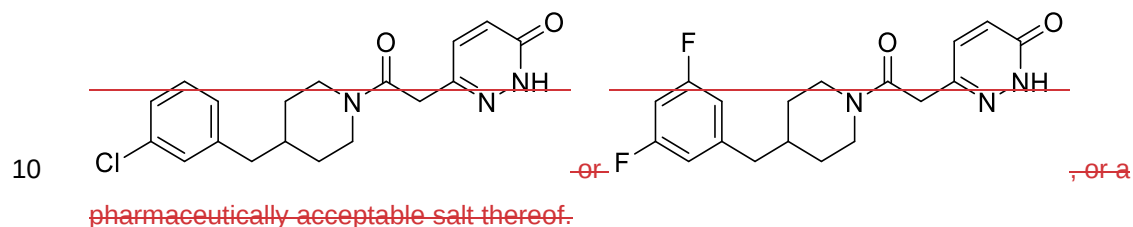
~~107. The compound of any one of claims 103-106, wherein L² is optionally substituted C₁₋₆ alkyl.~~

~~108. The compound of any one of claims 103-107, wherein o is 1 or 2.~~

5 ~~109. The compound of any one of claims 103-108, wherein R³ is halo.~~

~~110. The compound of any one of claims 103-109, wherein R⁴ is H.~~

~~111. The compound of claim 103, wherein the compound is~~



~~112. The compound of claim 103-106, wherein L² is O.~~

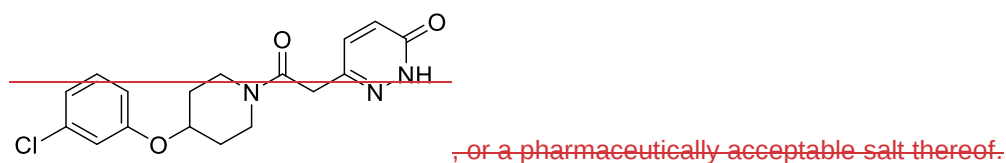
15 ~~113. The compound of claim 112, wherein o is 1.~~

~~114. The compound of claim 112 or 113, wherein R³ is halo.~~

~~115. The compound of any one of claims 112-114, wherein R⁴ is H.~~

20

~~116. The compound of claim 103, wherein the compound is~~



~~117. The compound of claim 103 or 104, wherein R¹ is methyl.~~

25



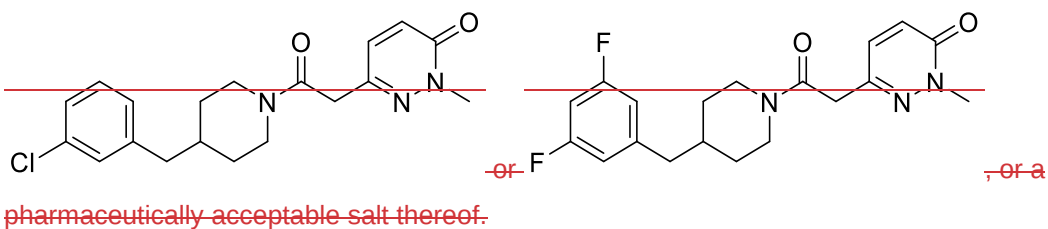
~~119. The compound of claim 117 or 118, wherein L² is optionally substituted C₁₋₆ alkyl.~~

30 ~~120. The compound of any one of claims 117-119, wherein o is 1 or 2.~~

~~121. The compound of any one of claims 117-120, wherein R³ is halo.~~

~~122. The compound of any one of claims 117-121, wherein R⁴ is H.~~

~~123. The compound of claim 103, wherein the compound is~~



5

~~124. The compound of claim 117 or 118, wherein L² is O.~~

~~125. The compound of claim 124, wherein o is 1.~~

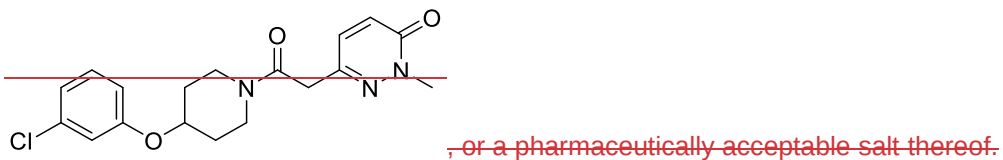
10

~~126. The compound of claim 124 or 125, wherein R³ is halo.~~

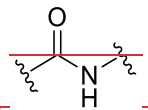
~~127. The compound of any one of claims 124-126, wherein R⁴ is H.~~

~~128. The compound of claim 103, wherein the compound is~~

15



~~129. The compound of claim 117, wherein L¹ is~~



20

~~130. The compound of claim 117 or 129, wherein L² is optionally substituted C₁₋₆ alkyl.~~

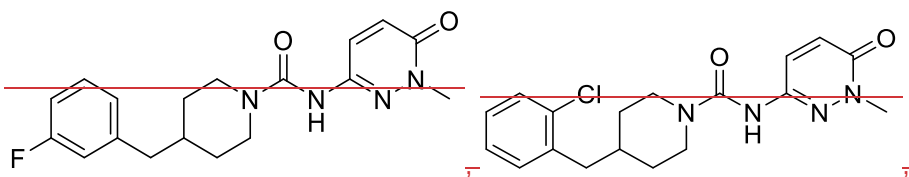
~~131. The compound of claim 129 or 130, wherein o is 1.~~

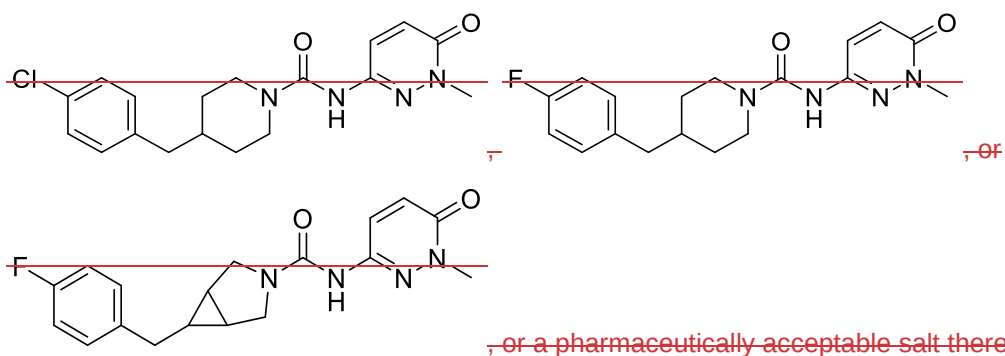
~~132. The compound of any one of claims 129-131, wherein R³ is halo.~~

25

~~133. The compound of any one of claims 129-132, wherein R⁴ is H.~~

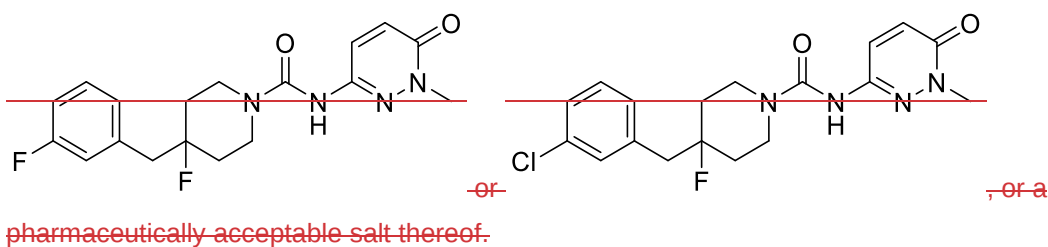
~~134. The compound of claim 103, wherein the compound is~~





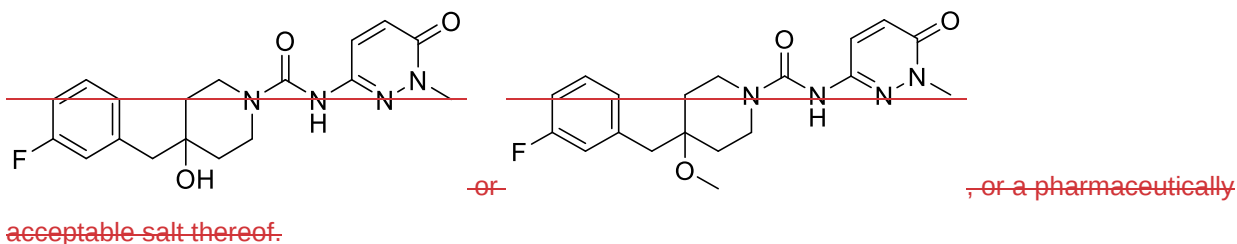
~~135. The compound of any one of claims 129-132, wherein R⁴ is fluoro.~~

~~136. The compound of claim 103, wherein the compound is~~



~~137. The compound of any one of claims 129-132, wherein R⁴ is OR⁶.~~

~~138. The compound of claim 103, wherein the compound is~~

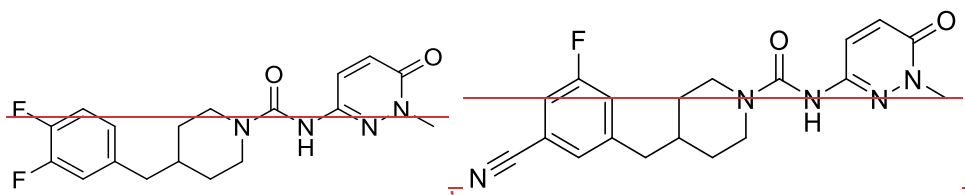


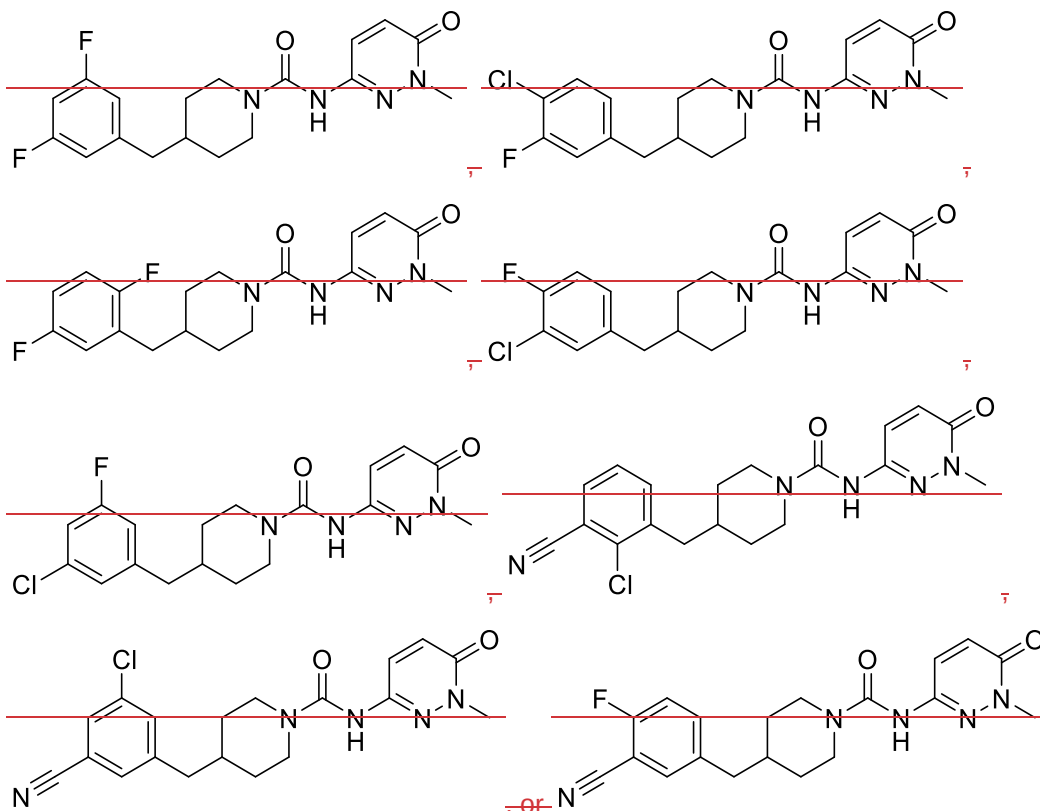
~~139. The compound of claim 129 or 130, wherein o is 2.~~

~~140. The compound of claim 139, wherein each R³ is, independently, halo or cyano.~~

~~141. The compound of claim 139 or 140, wherein R⁴ is H.~~

~~142. The compound of claim 103, wherein the compound is~~

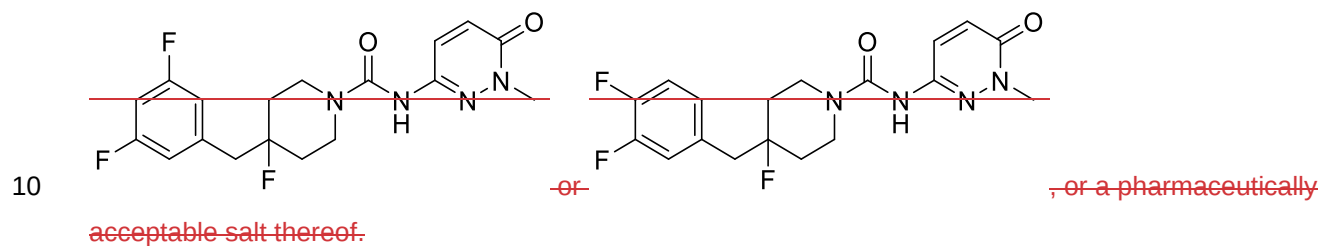




5 ~~pharmaceutically acceptable salt thereof.~~

~~143. The compound of claim 139 or 140, wherein R⁴ is fluoro.~~

~~144. The compound of claim 103, wherein the compound is~~



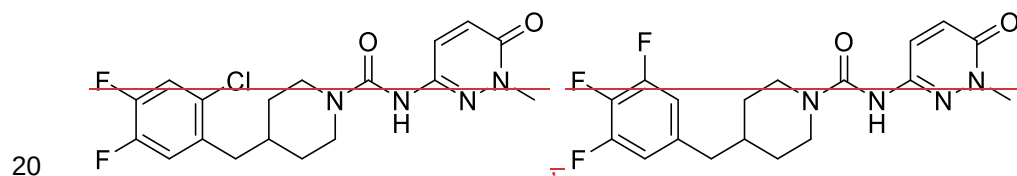
10 ~~or~~ ~~or a pharmaceutically acceptable salt thereof.~~

~~145. The compound of claim 129 or 130, wherein o is 3.~~

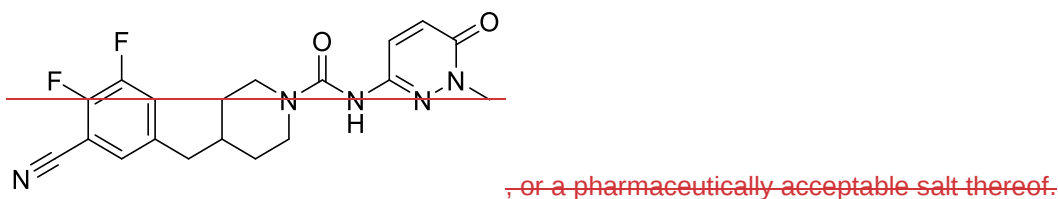
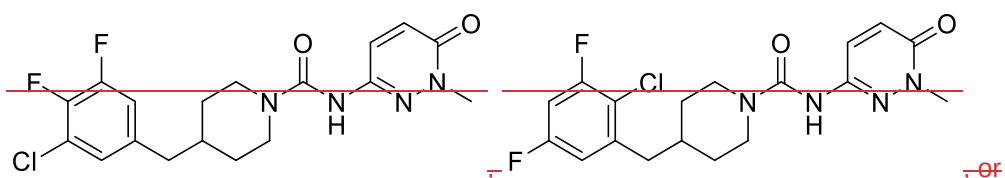
15 ~~146. The compound of claim 145, wherein each R³ is, independently, halo or cyano.~~

~~147. The compound of claim 145 or 146, wherein R⁴ is H.~~

~~148. The compound of claim 103, wherein the compound is~~

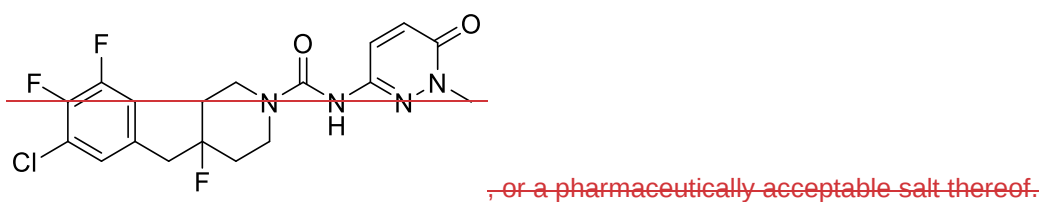


20 ~~or~~



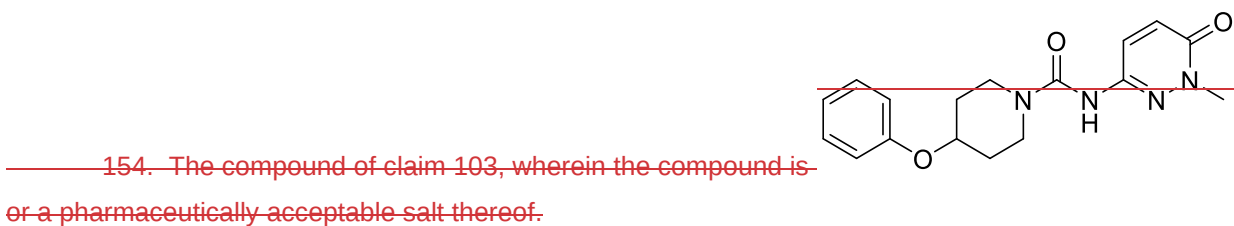
~~149. The compound of claim 145 or 146, wherein R⁴ is fluoro.~~

~~150. The compound of claim 103, wherein the compound is~~



~~152. The compound of claim 151, wherein o is O.~~

~~153. The compound of claim 151 or 152, wherein R⁴ is H.~~

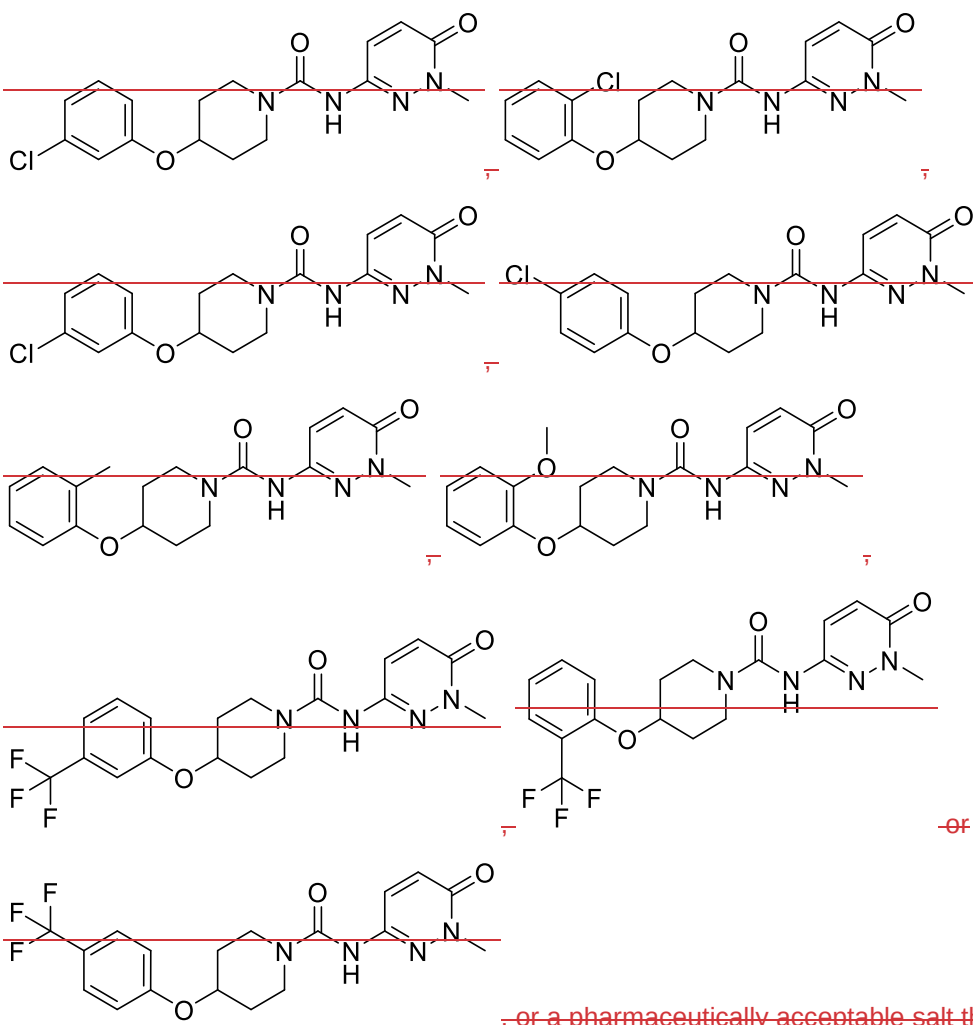


~~155. The compound of claim 151, wherein o is 1.~~

~~156. The compound of claim 155, wherein R³ is halo, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ alkoxy, or C₁₋₆ perfluoroalkyl.~~

~~157. The compound of claim 155 or 156, wherein R⁴ is H.~~

~~158. The compound of claim 103, wherein the compound is~~

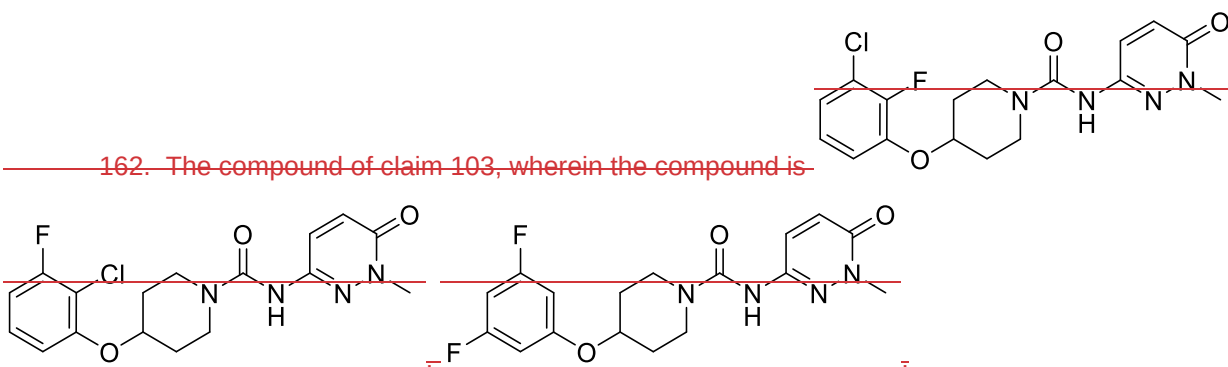


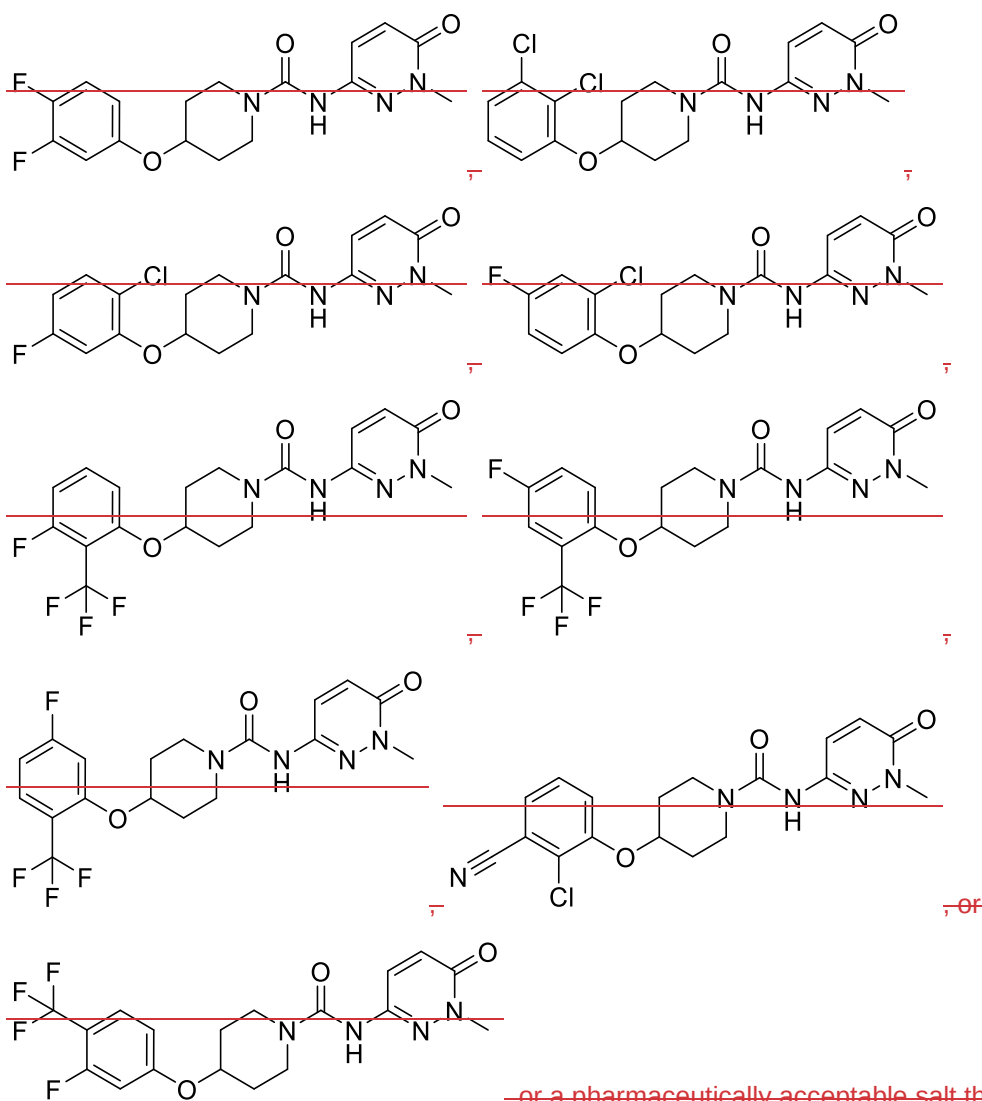
~~159. The compound of claim 151, wherein o is 2.~~

~~160. The compound of claim 159, wherein each R³ is, independently, halo, C₁₋₆ perfluoroalkyl, or cyano.~~

~~161. The compound of claim 159 or 160, wherein R⁴ is H.~~

~~162. The compound of claim 103, wherein the compound is~~





5 ~~, or a pharmaceutically acceptable salt thereof.~~

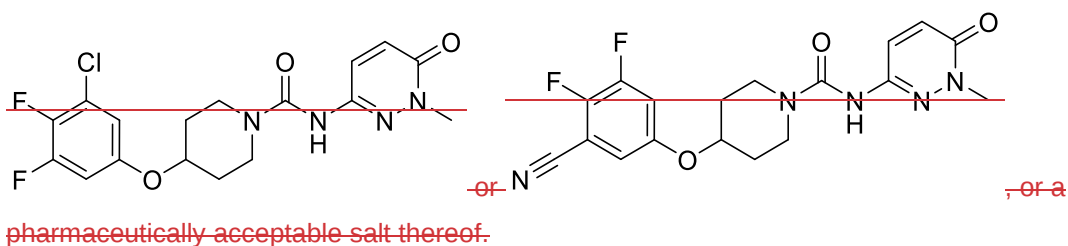
~~163. The compound of claim 151, wherein o is 3.~~

~~164. The compound of claim 163, wherein R³ is halo or cyano.~~

10

~~165. The compound of claim 163 or 164, wherein R⁴ is H.~~

~~166. The compound of claim 103, wherein the compound is~~



15

~~pharmaceutically acceptable salt thereof.~~

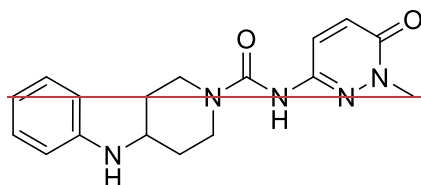
~~167. The compound of claim 117 or 129, wherein L² is NR⁵.~~

~~168. The compound of claim 167, wherein L² is NH.~~

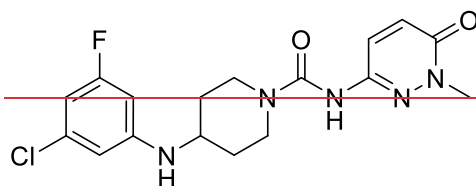
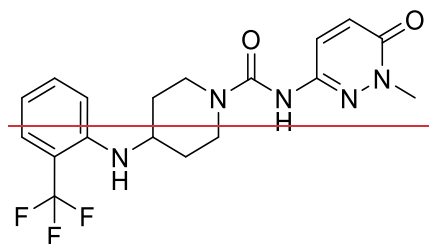
~~169. The compound of claim 167 or 168, wherein o is 0, 1, or 2.~~

~~170. The compound of any one of claims 167-169, wherein R³ is halo or C₁₋₆ perfluoroalkyl.~~

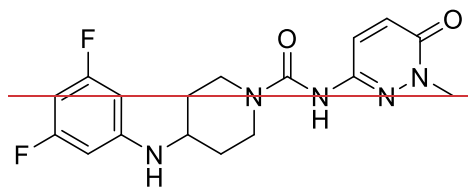
~~171. The compound of any one of claims 167-170, wherein R⁴ is H.~~



~~172. The compound of claim 103, wherein the compound is~~

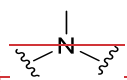


~~, or~~



~~, or a pharmaceutically acceptable salt thereof.~~

~~173. The compound of claim 167, wherein L² is~~

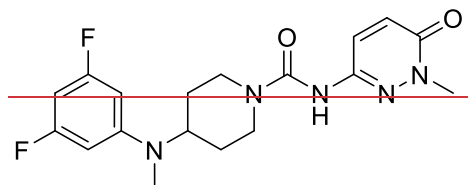


~~174. The compound of claim 173, wherein o is 2.~~

~~175. The compound of claim 173 or 174, wherein R³ is halo.~~

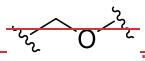
~~176. The compound of any one of claims 173-175, wherein R⁴ is H.~~

~~177. The compound of claim 103, wherein the compound is~~



~~, or a pharmaceutically acceptable salt thereof.~~

~~178. The compound of claim 117 or 129, wherein L² is optionally substituted C₁₋₆ heteroalkyl.~~

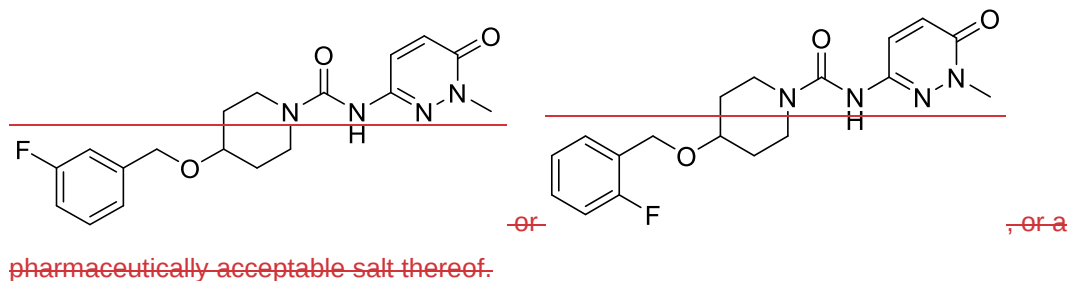
~~179. The compound of claim 178, wherein L² is~~ 

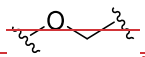
~~180. The compound of claim 178 or 179, wherein o is 1.~~

5 ~~181. The compound of any one of claims 178-180, wherein R³ is halo.~~

~~182. The compound of any one of claims 178-181, wherein R⁴ is H.~~

~~183. The compound of claim 103, wherein the compound is~~



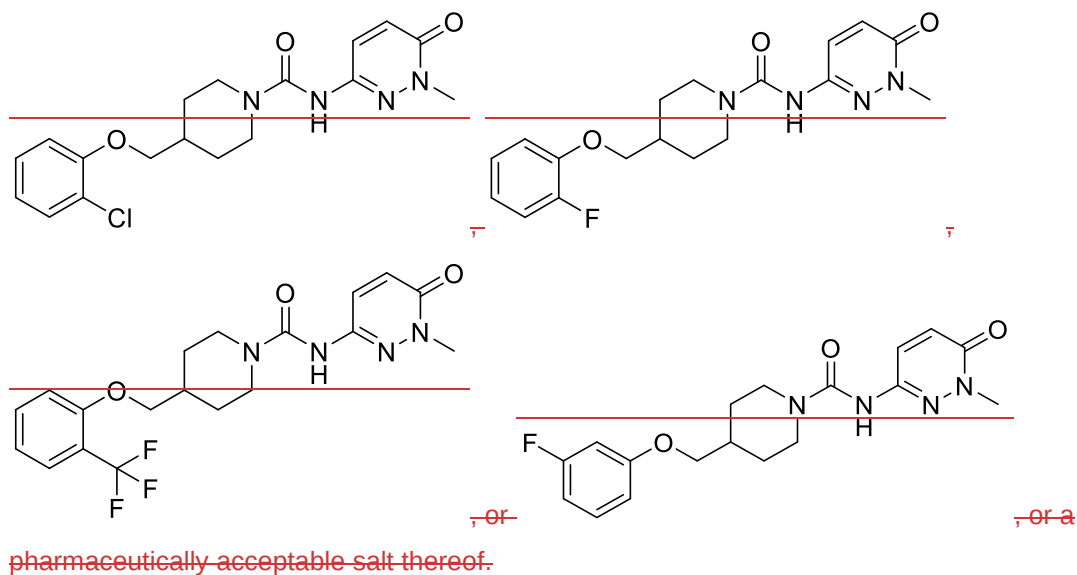
~~184. The compound of claim 178, wherein L² is~~ 

15 ~~185. The compound of claim 184, wherein o is 1.~~

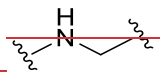
~~186. The compound of claim 184 or 185, wherein R³ is halo or C₁₋₆ perfluoroalkyl.~~

~~187. The compound of any one of claims 184-186, wherein R⁴ is H.~~

20 ~~188. The compound of claim 103, wherein the compound is~~



25

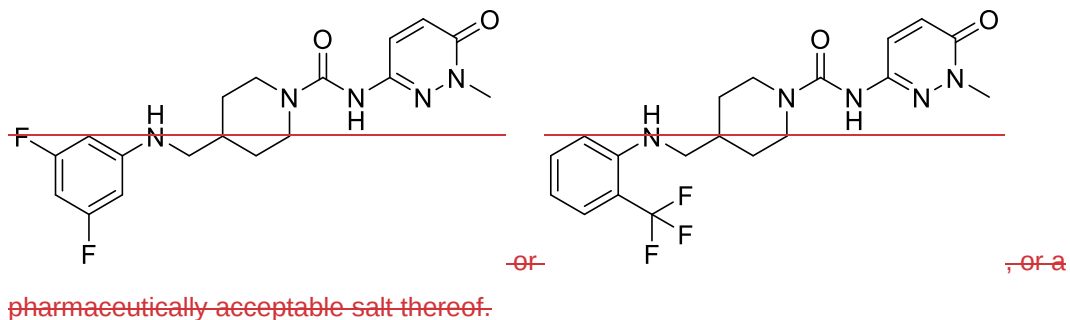
~~189. The compound of claim 178, wherein L² is~~ 

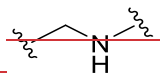
~~190. The compound of claim 189, wherein o is 1 or 2.~~

5 ~~191. The compound of claim 189 or 190, wherein R³ is halo or C₁₋₆ perfluoroalkyl.~~

~~192. The compound of any one of claims 189-191, wherein R⁴ is H.~~

~~193. The compound of claim 103, wherein the compound is~~



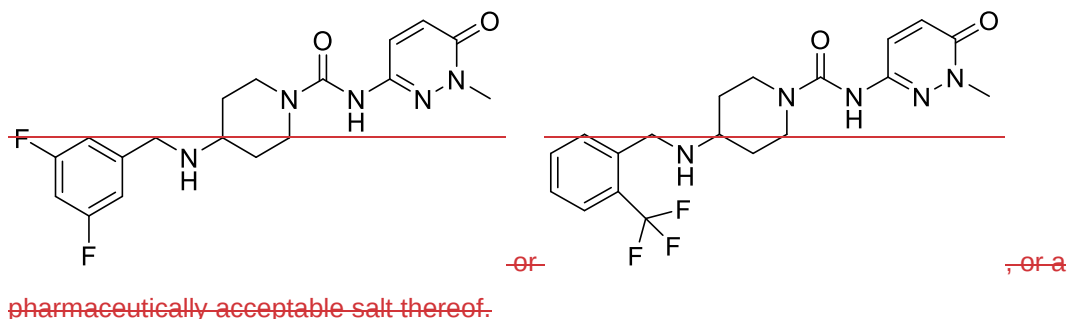
~~194. The compound of claim 178, wherein L² is~~ 

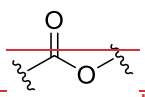
15 ~~195. The compound of claim 194, wherein o is 1 or 2.~~

~~196. The compound of claim 194 or 195, wherein R³ is halo or C₁₋₆ perfluoroalkyl.~~

~~197. The compound of any one of claims 194-196, wherein R⁴ is H.~~

20 ~~198. The compound of claim 103, wherein the compound is~~



~~199. The compound of claim 117, wherein L¹ is~~ 

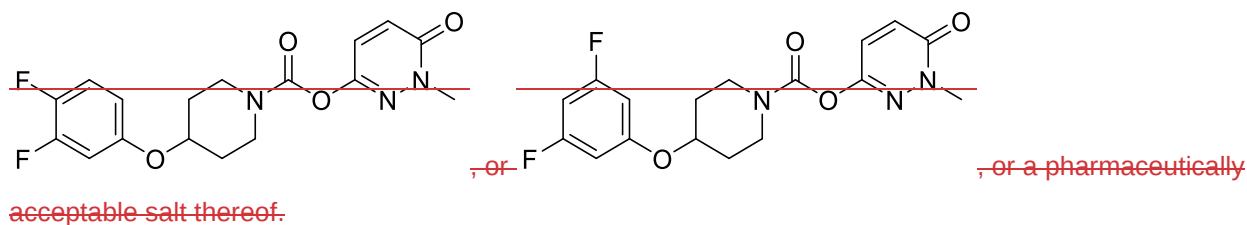
~~200. The compound of claim 117 or 199, wherein L² is O.~~

~~201. The compound of claim 200, wherein o is 1 or 2.~~

~~202. The compound of any one of claims 199-201, wherein R³ is halo.~~

5 ~~203. The compound of any one of claims 199-202, wherein R⁴ is H.~~

~~204. The compound of claim 103, wherein the compound is~~



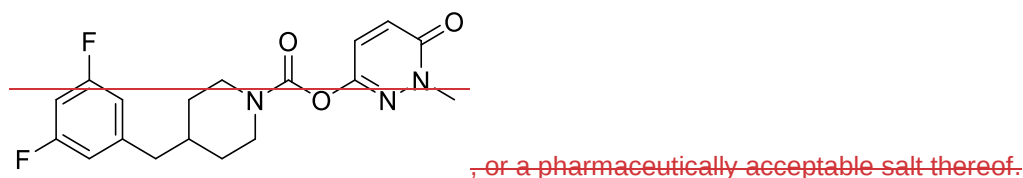
10 ~~205. The compound of claim 117 or 199, wherein L² is optionally substituted C₁₋₆ alkyl.~~

~~206. The compound of claim 205, wherein o is 2.~~

15 ~~207. The compound of claim 205 or 206, wherein R³ is halo.~~

~~208. The compound of any one of claims 205-207, wherein R⁴ is H.~~

~~209. The compound of claim 103, wherein the compound is~~



20 ~~210. The compound of claim 117, wherein L¹ is optionally substituted C₅₋₁₀ heteroaryl.~~



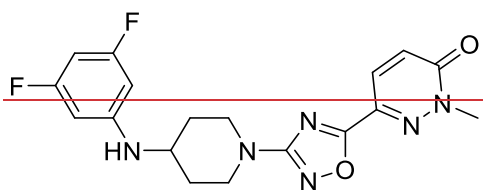
25 ~~212. The compound of claim 210 or 211, wherein L² is NH.~~

~~213. The compound of any one of claims 210-212, wherein o is 2.~~

~~214. The compound of any one of claims 210-213, wherein R³ is halo.~~

30 ~~215. The compound of any one of claims 210-214, wherein R⁴ is H.~~

~~216. The compound of claim 103, wherein the compound is~~



~~, or a pharmaceutically acceptable salt thereof.~~

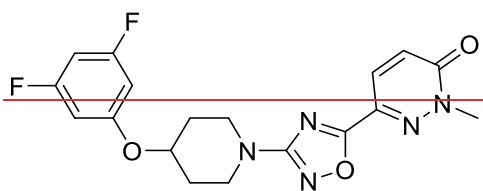
~~217. The compound of claim 210 or 211, wherein L² is O.~~

~~218. The compound of claim 217, wherein o is 2.~~

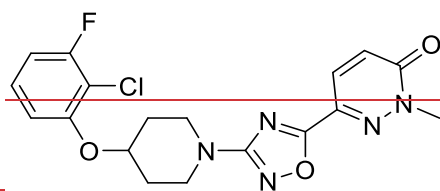
~~219. The compound of claim 217 or 218, wherein R³ is halo.~~

~~220. The compound of any one of claims 217-219, wherein R⁴ is H.~~

~~221. The compound of claim 103, wherein the compound is~~



~~-or-~~



~~, or a pharmaceutically~~

~~acceptable salt thereof.~~

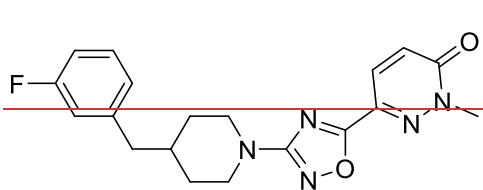
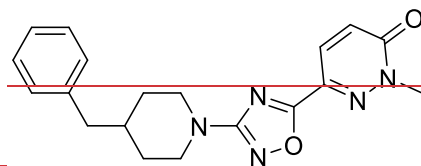
~~222. The compound of claim 210 or 211, wherein L² is optionally substituted C₁₋₆ alkyl.~~

~~223. The compound of claim 222, wherein o is 0, 1, or 2.~~

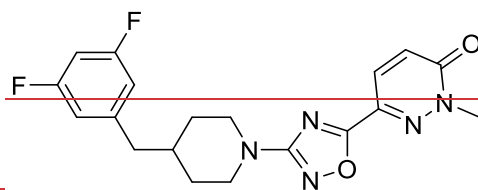
~~224. The compound of claim 222 or 223, wherein each R³ is, independently, halo or cyano.~~

~~225. The compound of any one of claims 222-224, wherein R⁴ is H.~~

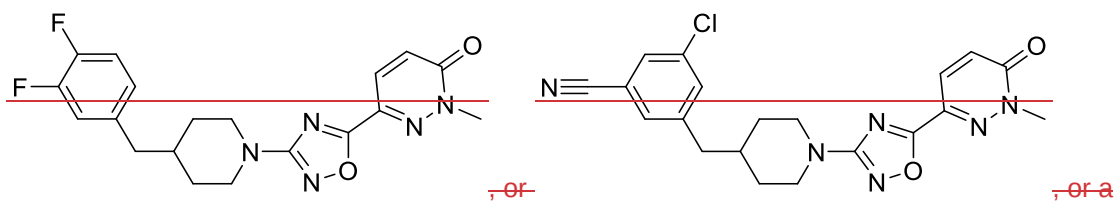
~~226. The compound of claim 103, wherein the compound is-~~



~~-~~

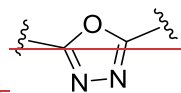


~~-~~



~~pharmaceutically acceptable salt thereof.~~

~~_____ 227. The compound of claim 210, wherein L¹ is-~~



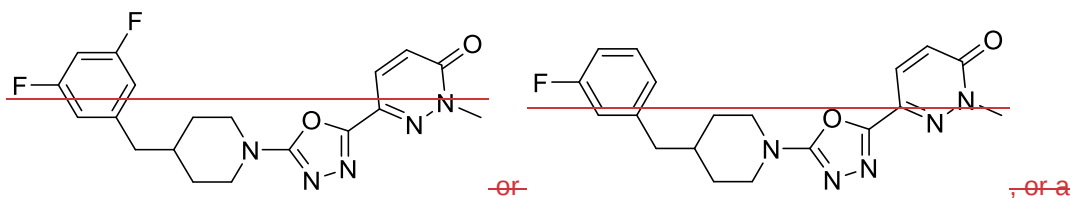
~~_____ 228. The compound of claim 210 or 227, wherein L² is optionally substituted C₁₋₆ alkyl.~~

~~_____ 229. The compound of claim 227 or 228, wherein o is 1 or 2.~~

~~_____ 230. The compound of any one of claims 227-229, wherein R³ is halo.~~

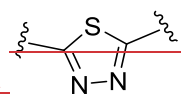
~~_____ 231. The compound of any one of claims 227-230, wherein R⁴ is H.~~

~~_____ 232. The compound of claim 103, wherein the compound is~~



~~pharmaceutically acceptable salt thereof.~~

~~_____ 233. The compound of claim 210, wherein L¹ is-~~



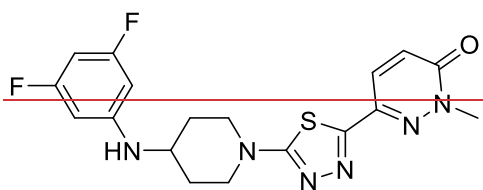
~~_____ 234. The compound of claim 210 or 233, wherein L² is NH.~~

~~_____ 235. The compound of claim 233 or 234, wherein o is 2.~~

~~_____ 236. The compound of any one of claims 233-235, wherein R³ is halo.~~

~~_____ 237. The compound of any one of claims 233-236, wherein R⁴ is H.~~

~~238. The compound of claim 103, wherein the compound is~~



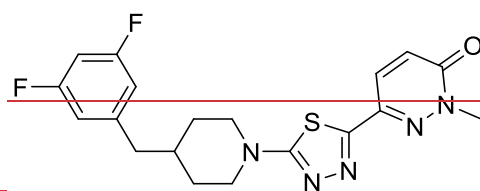
~~, or a pharmaceutically acceptable salt thereof.~~

~~239. The compound of claim 210 or 233, wherein L^2 is optionally substituted C_{1-6} -alkyl.~~

~~240. The compound of claim 239, wherein o is 2.~~

~~241. The compound of claim 239 or 240, wherein R^3 is halo.~~

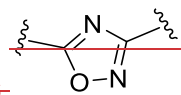
~~242. The compound of any one of claims 239-241, wherein R^4 is H.~~



~~243. The compound of claim 103, wherein the compound is
a pharmaceutically acceptable salt thereof.~~

~~, or~~

~~244. The compound of claim 210, wherein L^1 is~~



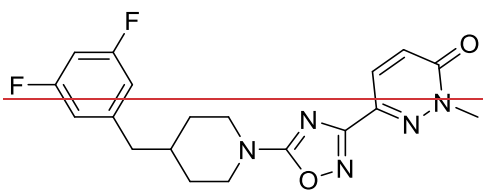
~~245. The compound of claim 210 or 244, wherein L^2 is optionally substituted C_{1-6} -alkyl.~~

~~246. The compound of claim 244 or 245, wherein o is 2.~~

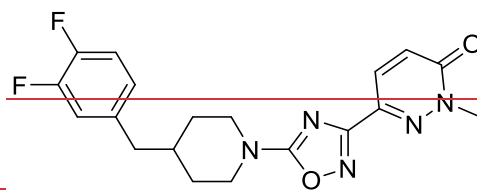
~~247. The compound of any one of claims 244-246, wherein R^3 is halo.~~

~~248. The compound of any one of claims 244-247, wherein R^4 is H.~~

~~249. The compound of claim 103, wherein the compound is~~



~~-or-~~

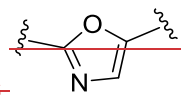


~~, or a~~

~~pharmaceutically acceptable salt thereof.~~

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~~250. The compound of claim 210, wherein L¹ is-~~



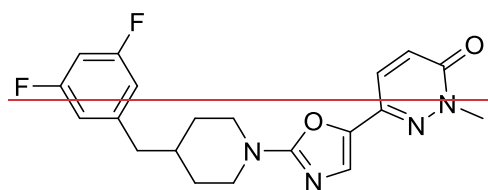
~~251. The compound of claim 210 or 250, wherein L² is optionally substituted C₁₋₆-alkyl.~~

~~252. The compound of claim 250 or 251, wherein o is 2.~~

~~253. The compound of any one of claims 250-252, wherein R³ is halo.~~

~~254. The compound of any one of claims 250-253, wherein R⁴ is H.~~

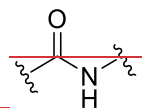
~~255. The compound of claim 103, wherein the compound is~~



~~, or a pharmaceutically acceptable salt thereof.~~

~~256. The compound of claim 103 or 104, wherein R¹ is ethyl.~~

~~257. The compound of claim 256, wherein L¹ is-~~



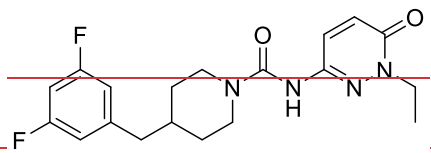
~~258. The compound of claim 256 or 257, wherein L² is optionally substituted C₁₋₆-alkyl.~~

~~259. The compound of any one of claims 256-258, wherein o is 2.~~

~~260. The compound of any one of claims 256-259, wherein R³ is halo.~~

~~261. The compound of any one of claims 256-260, wherein R⁴ is H.~~

~~262. The compound of claim 103, wherein the compound is~~

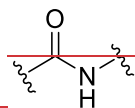


~~or a pharmaceutically acceptable salt thereof.~~

~~263. The compound of claim 103, wherein R² is methyl.~~

~~264. The compound of claim 103 or 263, wherein R¹ is methyl.~~

~~265. The compound of claim 263 or 264, wherein L¹ is~~



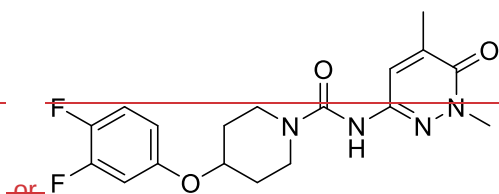
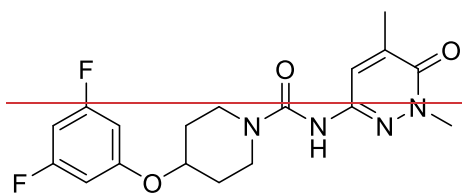
~~266. The compound of any one of claims 263-265, wherein L² is O.~~

~~267. The compound of any one of claims 263-266, wherein o is 2.~~

~~268. The compound of any one of claims 263-267, wherein R³ is halo.~~

~~269. The compound of any one of claims 263-268, wherein R⁴ is H.~~

~~270. The compound of claim 103, wherein the compound is~~



~~or~~ ~~or a pharmaceutically acceptable salt thereof.~~

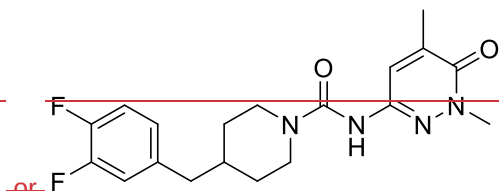
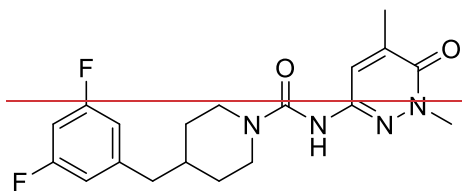
~~271. The compound of claim 263-265, wherein L² is optionally substituted C₁₋₆ alkyl.~~

~~272. The compound of claim 271, wherein o is 2.~~

~~273. The compound of claim 271 or 272, wherein R³ is halo.~~

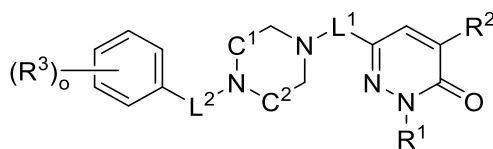
~~274. The compound of any one of claims 271-273, wherein R⁴ is H.~~

~~275. The compound of claim 103, wherein the compound is~~



~~or~~ ~~or a pharmaceutically acceptable salt thereof.~~

8276. The compound of claim 695, wherein the compound has the structure of formula (III-D-2):



(III-D-2)

wherein:

o is 0, 1, 2, 3, 4, or 5;

C¹ and C² optionally combine to form a bond;

each of R¹, R², and R⁵ is, independently, H or optionally substituted C₁₋₆ alkyl;

R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted

5 C₁₋₆ alkyl;

L¹ is ~~C(O)-X⁵-~~ or optionally substituted C₅₋₁₀ heteroaryl ~~or C(O)-X⁵-~~;

X⁵ is NH, O, or optionally substituted C₁₋₆ alkyl; and

L² is O, NR⁵, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, or absent;
or a pharmaceutically acceptable salt thereof.

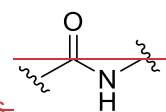
10

~~277. The compound of claim 276, wherein R¹ is methyl.~~

~~278. The compound of claim 276 or 277, wherein R² is H.~~

15

~~279. The compound of any one of claims 276-278, wherein L¹ is~~



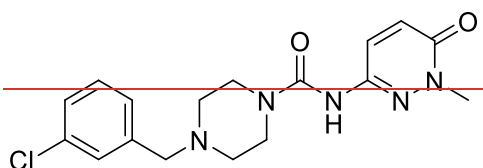
~~280. The compound of any one of claims 276-279, wherein L² is optionally substituted C₁₋₆ alkyl.~~

~~281. The compound of any one of claims 276-280, wherein o is 1.~~

20

~~282. The compound of any one of claims 276-281, wherein R³ is halo.~~

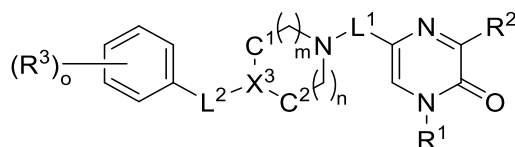
~~283. The compound of claim 276, wherein the compound is~~



~~, or a pharmaceutically acceptable salt thereof.~~

25

~~9284.~~ The compound of claim 1, wherein the compound has the structure of formula (IV):



(IV)

wherein:

30

m is 0 or 1;

n is 0, 1, or 2;

o is 0, 1, 2, 3, 4, or 5;

C¹ and C² optionally combine to form a bond;

each of R¹, R², R⁵, and R⁶ is, independently, H or optionally substituted C₁₋₆ alkyl;

R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted C₁₋₆ alkyl;

X³ is CR⁴ or N; or X³ and C¹ or C² combine to form an optionally substituted alkene;

R⁴ is H, OR⁶, optionally substituted C₁₋₆ alkyl, or halo;

L¹ is ~~-C(O)-X⁵- or~~ optionally substituted C₅₋₁₀ heteroaryl ~~or -C(O)-X⁵-~~;

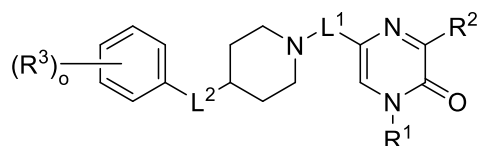
X⁵ is NH, O, or optionally substituted C₁₋₆ alkyl; and

L² is O, NR⁵, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, or absent; or

X³ and L² combine to form an optionally substituted alkene,

or a pharmaceutically acceptable salt thereof.

~~10285.~~ The compound of claim ~~9284~~, wherein the compound has the structure of formula (IV-A):



(IV-A)

wherein:

o is 0, 1, 2, 3, 4, or 5;

each of R¹, R², and R⁵ is, independently, H or optionally substituted C₁₋₆ alkyl;

R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted C₁₋₆ alkyl;

L¹ is ~~-C(O)-X⁵- or~~ optionally substituted C₅₋₁₀ heteroaryl ~~or -C(O)-X⁵-~~;

X⁵ is NH, O, or optionally substituted C₁₋₆ alkyl; and

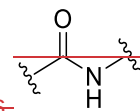
L² is O, NR⁵, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, or absent;

or a pharmaceutically acceptable salt thereof.

~~286. The compound of claim 284 or 285, wherein R² is H.~~

~~287. The compound of any one of claims 284-286, wherein R¹ is methyl.~~

~~288. The compound of any one of claims 284-287, wherein L¹ is~~

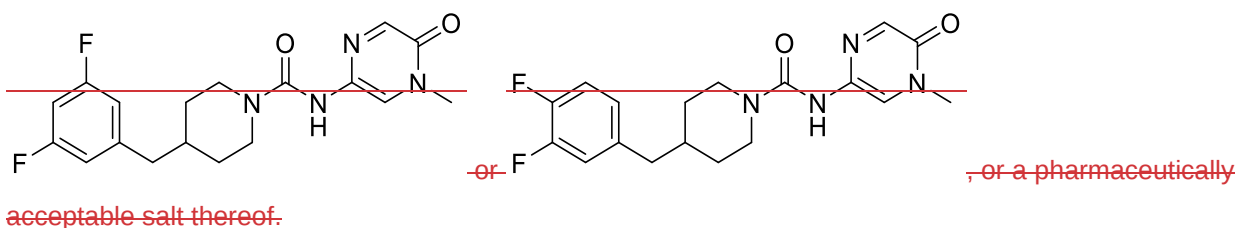


~~289. The compound of any one of claims 284-288, wherein L² is optionally substituted C₁₋₆ alkyl.~~

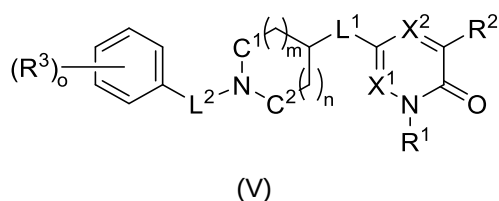
~~290. The compound of any one of claims 284-289, wherein o is 2.~~

~~291. The compound of any one of claims 284-290, wherein R³ is halo.~~

~~292. The compound of claim 284, wherein the compound is~~



5 11293. The compound of claim 1, wherein the compound has the structure of formula (V):



wherein:

m is 0 or 1;

10 n is 0, 1, or 2;

o is 0, 1, 2, 3, 4, or 5;

C¹ and C² optionally combine to form a bond;

each of R¹, R², R⁵, and R⁶ is, independently, H or optionally substituted C₁₋₆ alkyl;

15 R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted C₁₋₆ alkyl;

each of X¹ and X² is, independently, CH or N, wherein X¹ and X² are not both N;

L¹ is ~~-C(O)-X⁵-~~ or optionally substituted C₅₋₁₀ heteroaryl ~~or -C(O)-X⁵-~~;

X⁵ is NH, O, or optionally substituted C₁₋₆ alkyl; and

20 L² is O, NR⁵, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, or absent; or a pharmaceutically acceptable salt thereof.

~~294. The compound of claim 293, wherein X¹ is N and X² is CH.~~

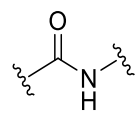
25 12295. The compound of any one of claims 1 to 11293 ~~or 294~~, wherein R² is H or methyl.

13296. The compound of any one of claims 1 to 11293-295, wherein R¹ is H, methyl or ethyl.

14297. The compound of any one of claims 1-3, 9 or 11293-296, wherein m is 1.

30 15298. The compound of any one of claims 1, 3, 9 or 11293-297, wherein n is 1.

16299. The compound of any one of claims 1 to 11293-298, wherein L¹ is



~~17300.~~ The compound of any one of claims ~~1 to 11~~~~293-299~~, wherein L² is O or optionally substituted C₁₋₆ alkyl.

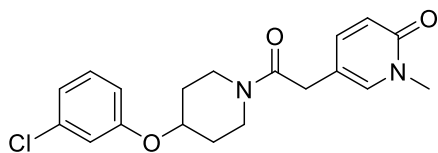
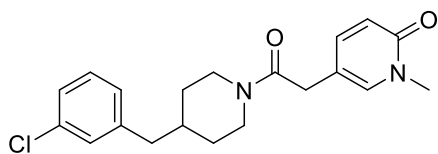
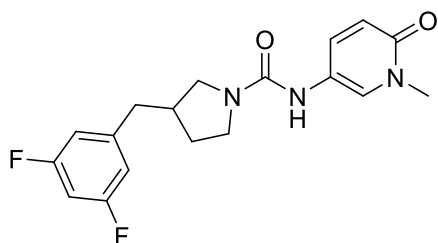
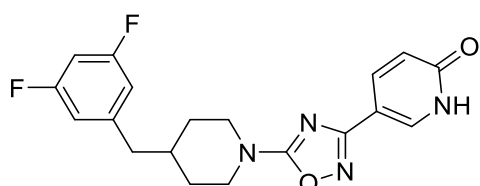
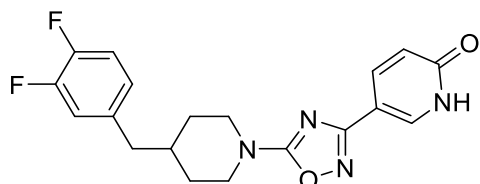
18. The compound of any one of claims 1 to 11, wherein o is 1 or 2.

19. The compound of any one of claims 1 to 11, wherein R³ is halo.

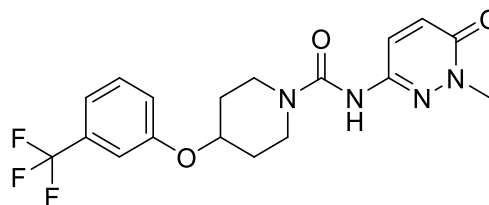
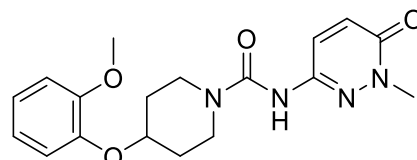
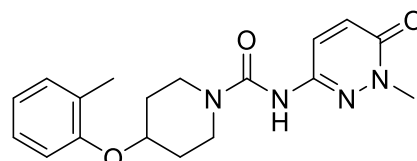
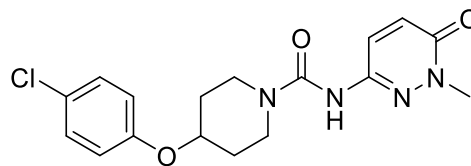
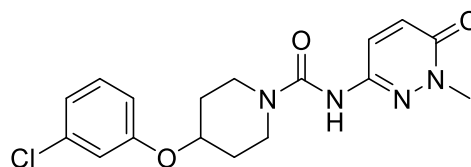
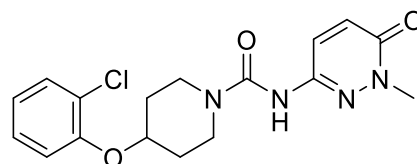
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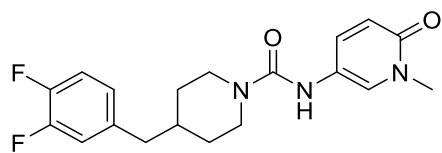
~~20301.~~ The compound of any one of claims ~~293-300~~, wherein o is 1. The compound of claim 1, wherein the compound is

Compound

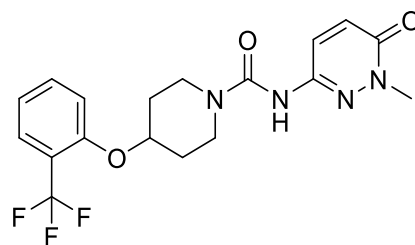


Compound

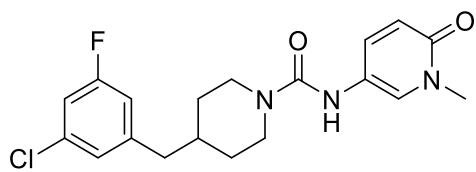




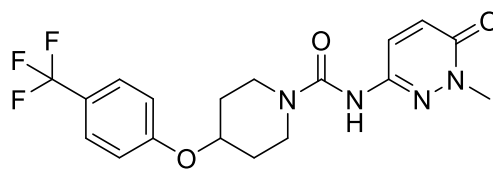
1



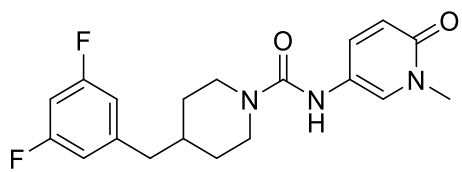
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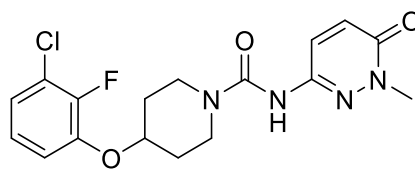
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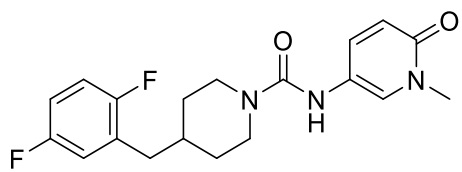
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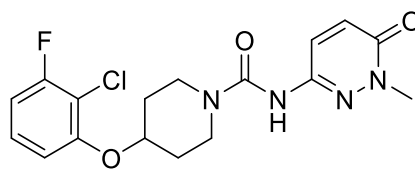
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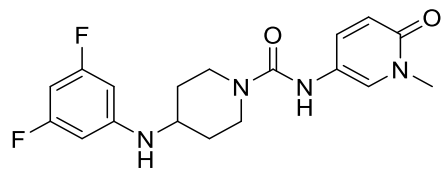
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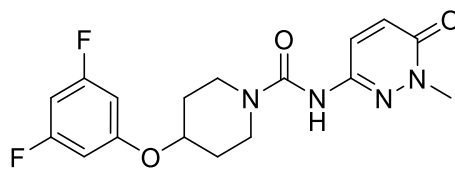
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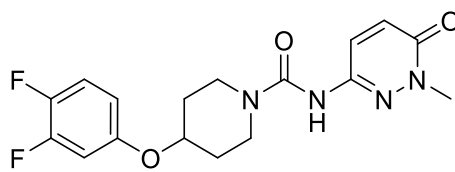
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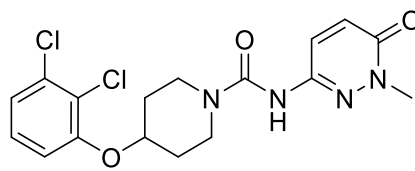
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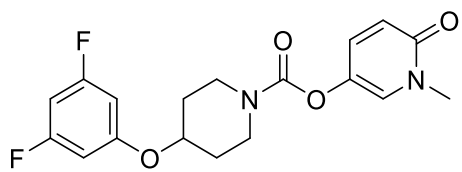
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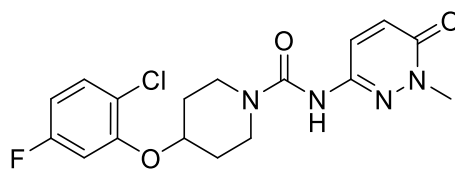
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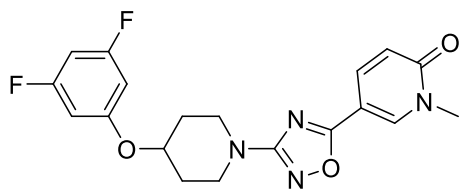
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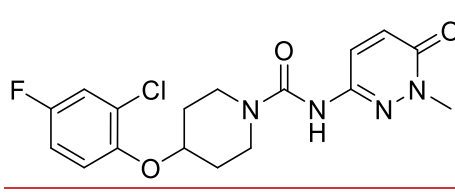
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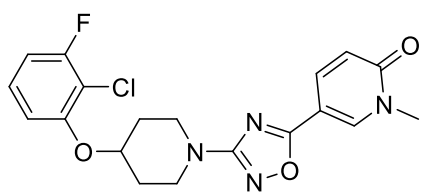
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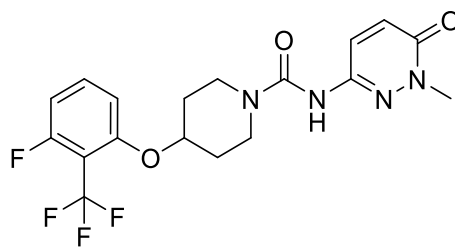
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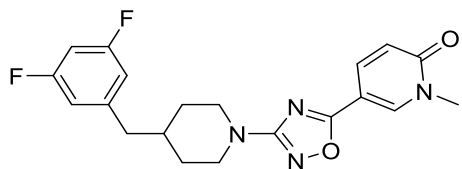
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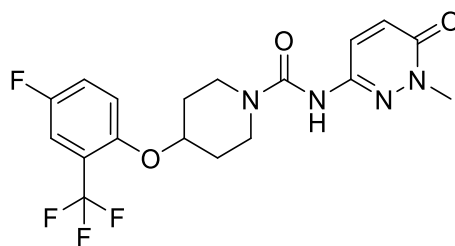
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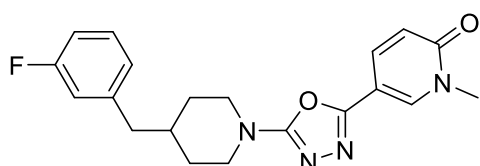
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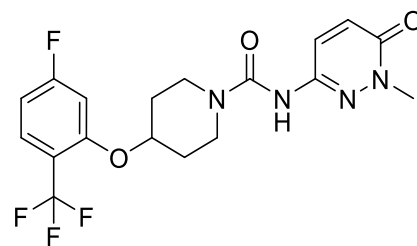
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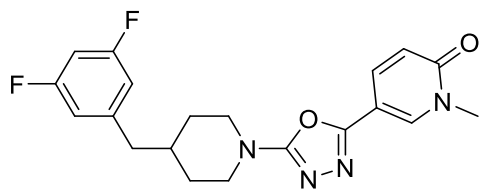
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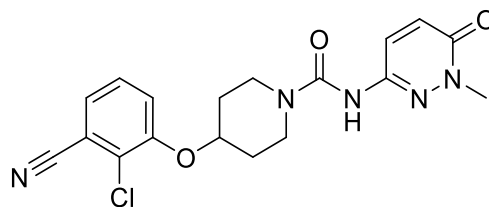
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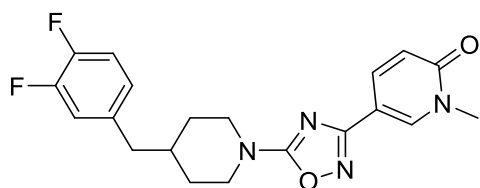
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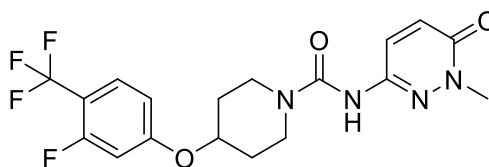
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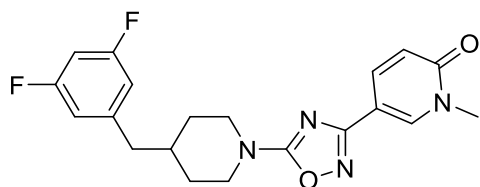
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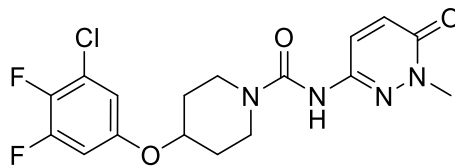
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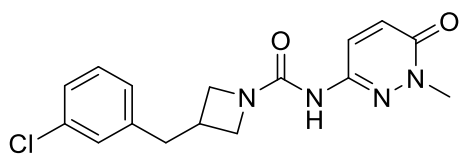
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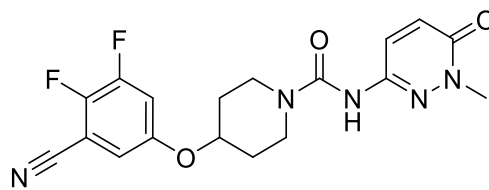
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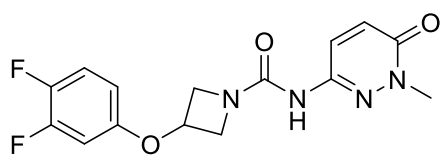
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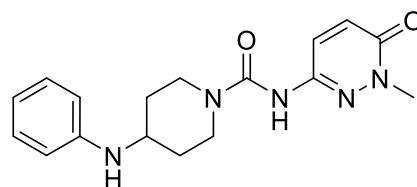
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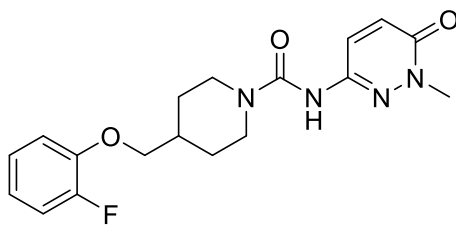
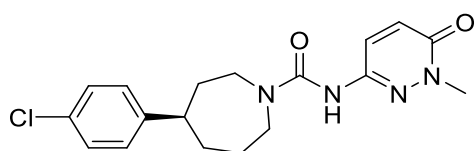
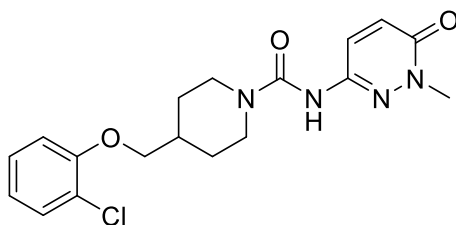
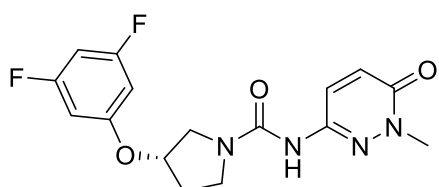
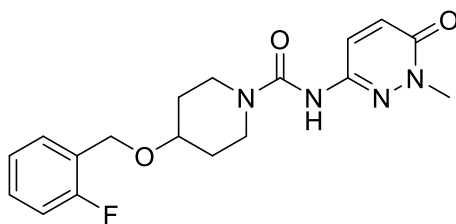
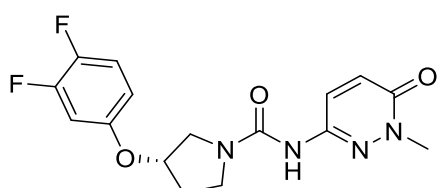
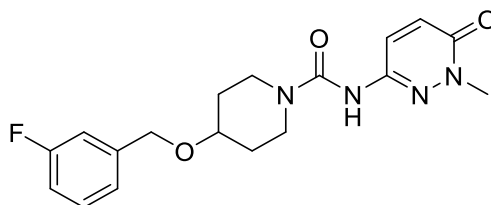
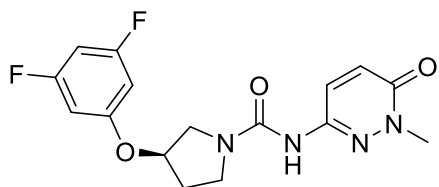
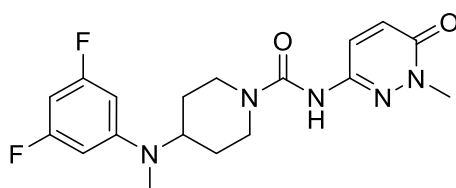
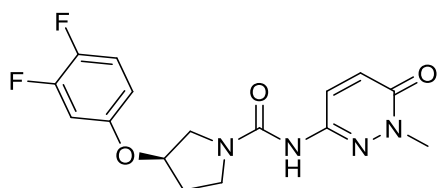
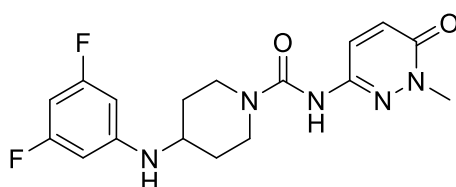
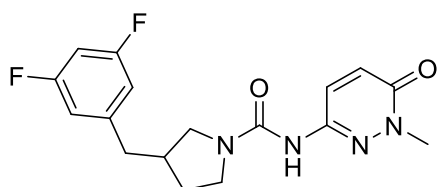
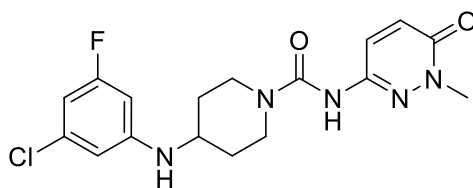
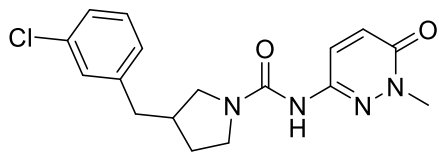
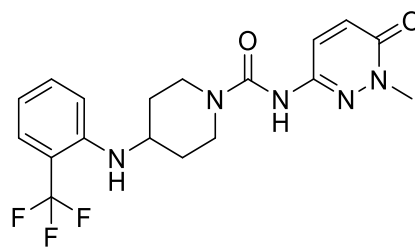
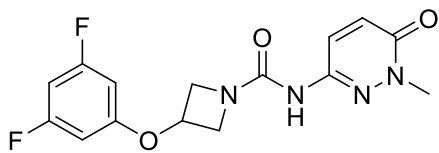
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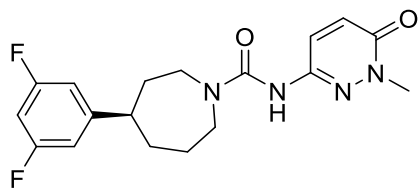


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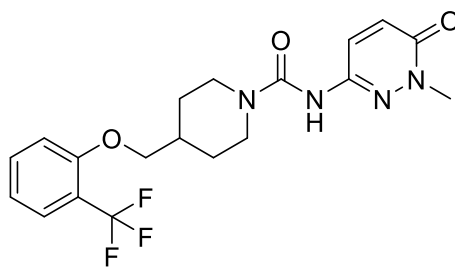


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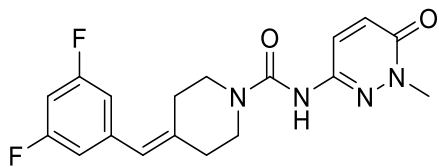




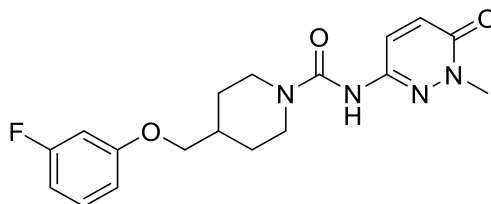
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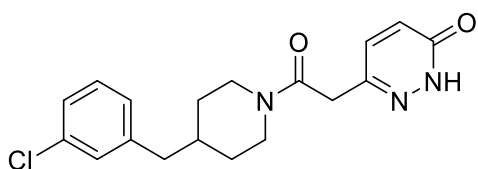
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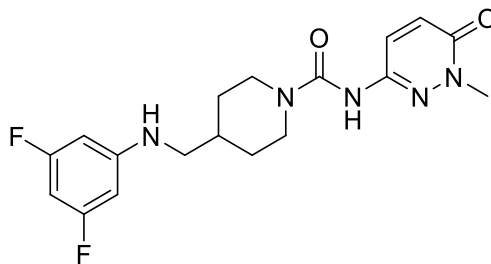
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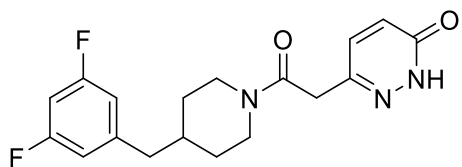
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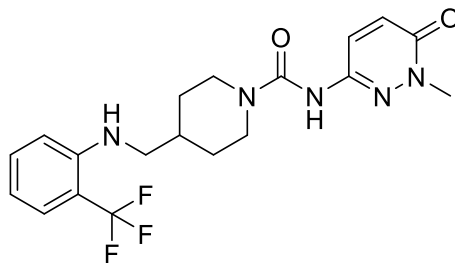
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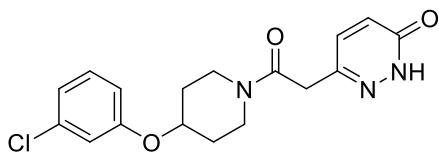
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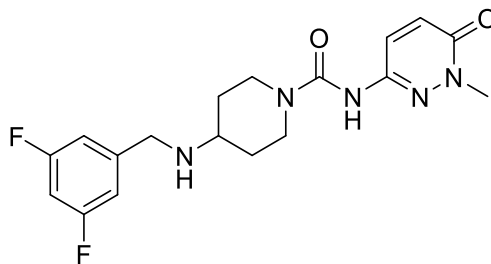
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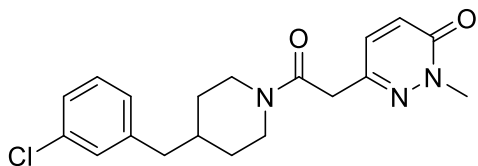
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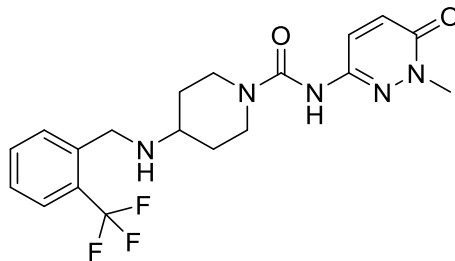
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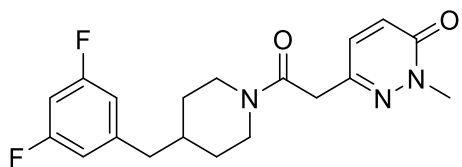
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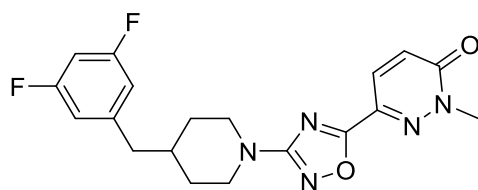
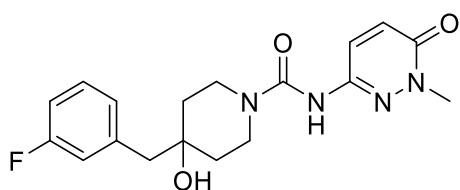
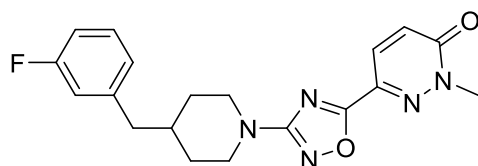
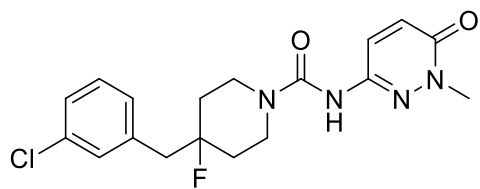
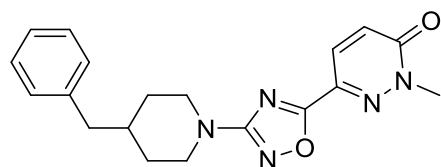
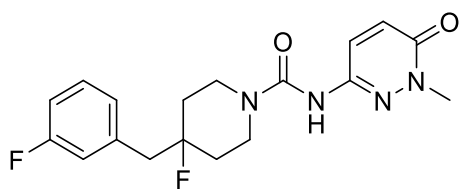
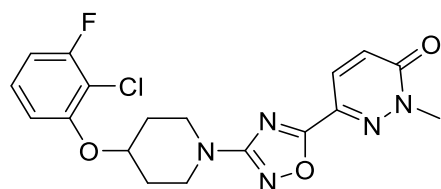
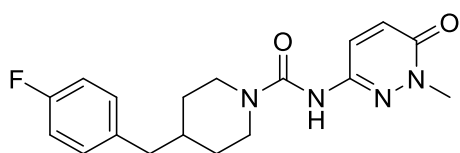
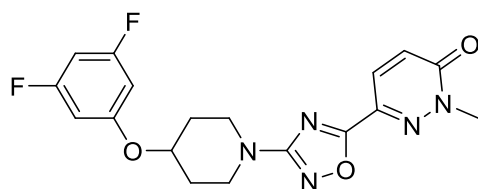
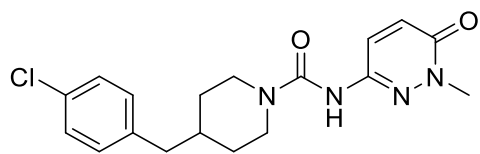
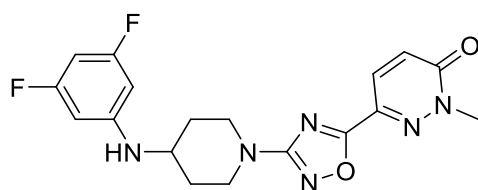
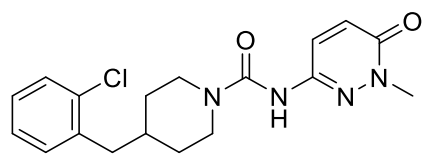
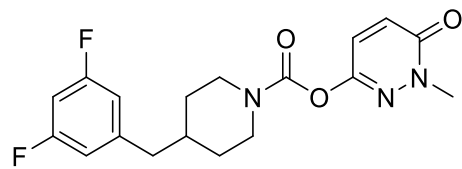
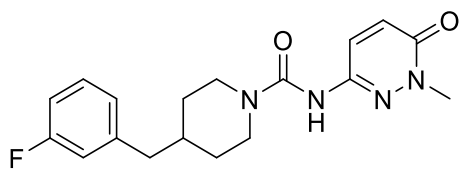
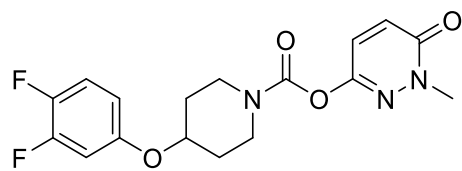
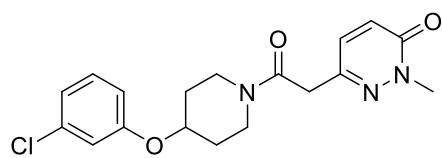
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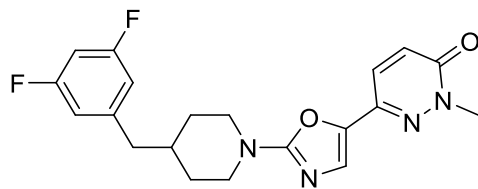
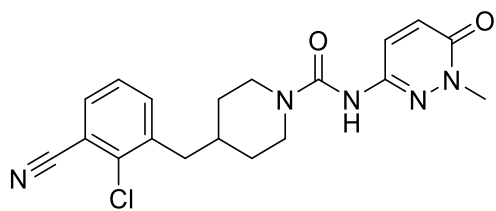
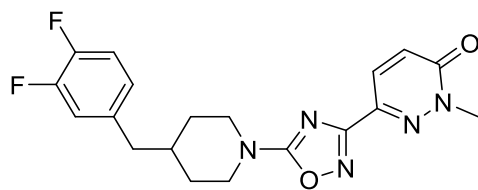
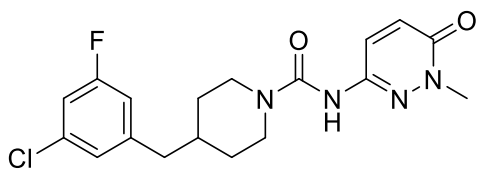
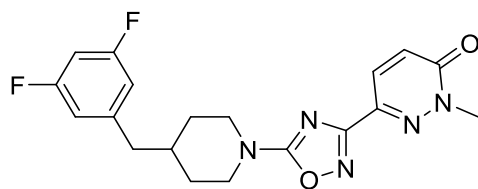
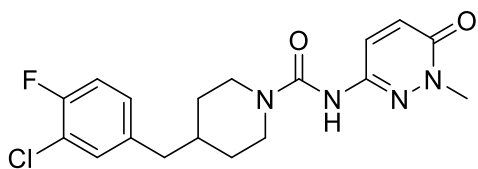
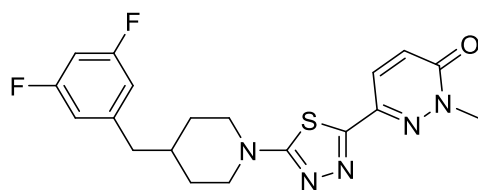
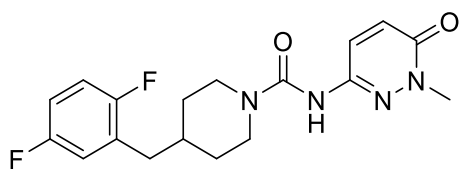
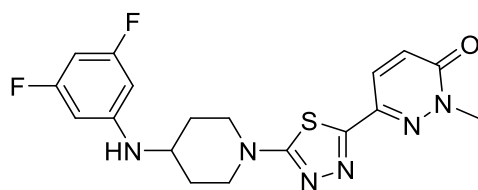
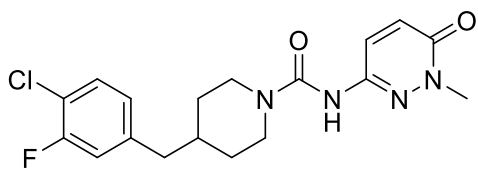
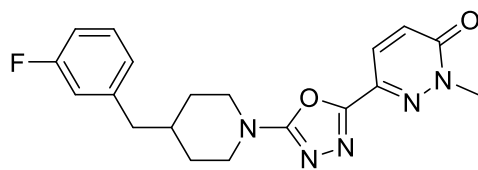
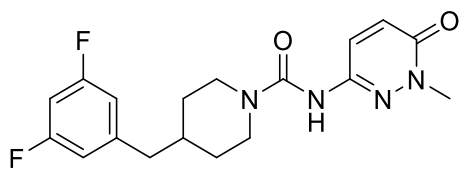
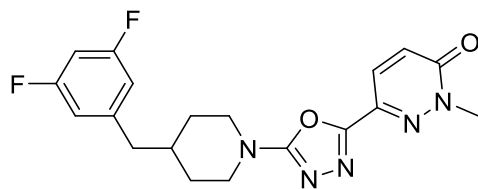
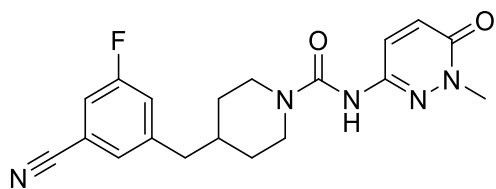
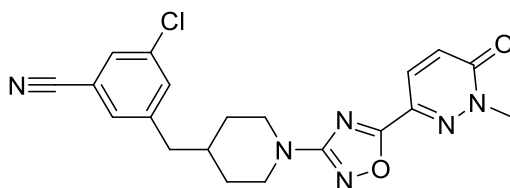
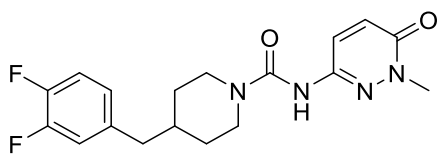
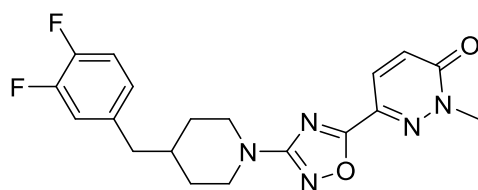
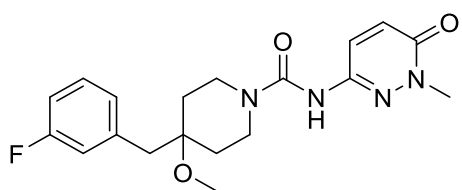


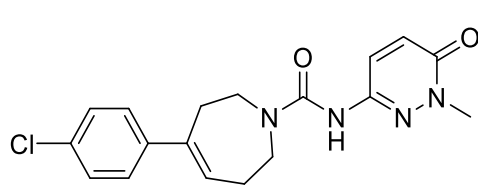
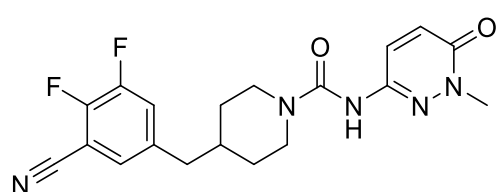
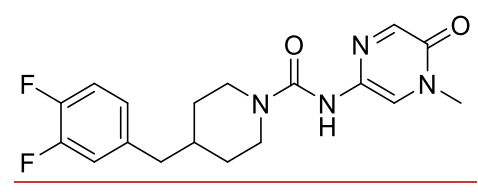
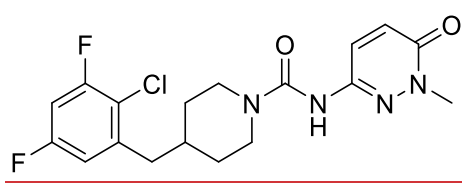
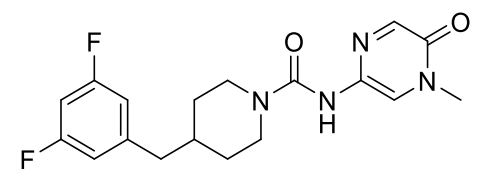
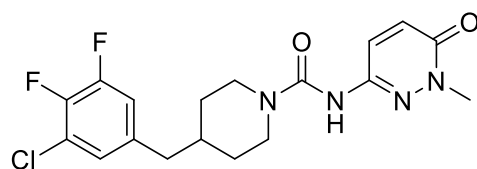
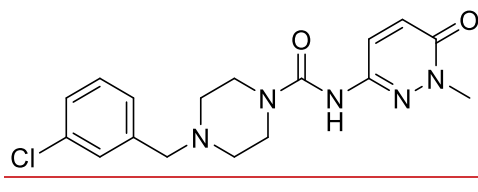
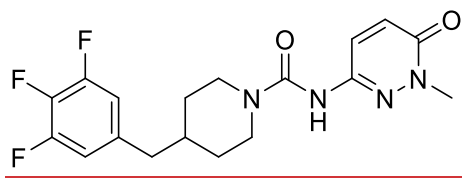
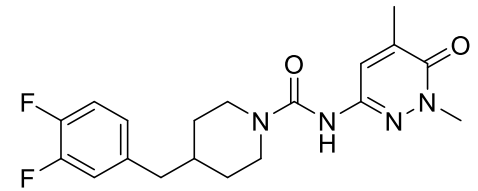
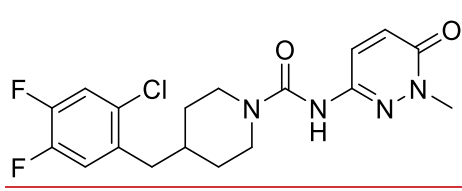
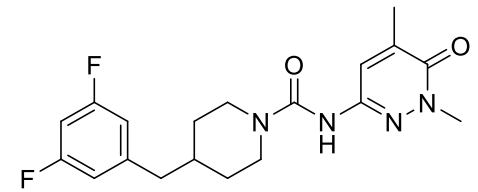
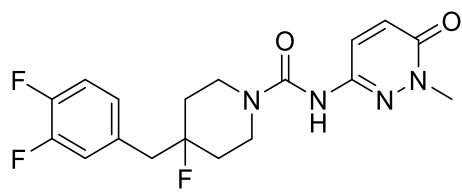
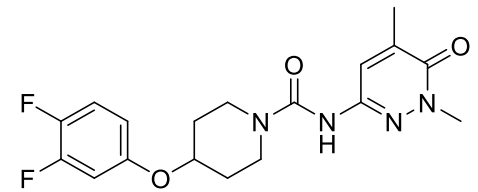
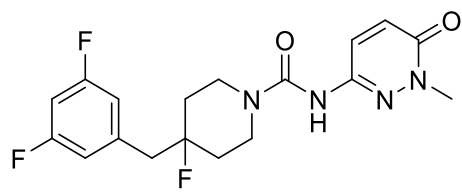
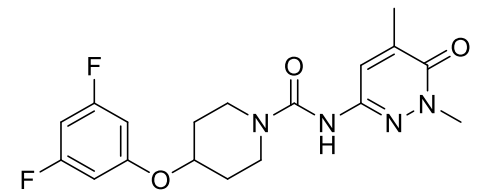
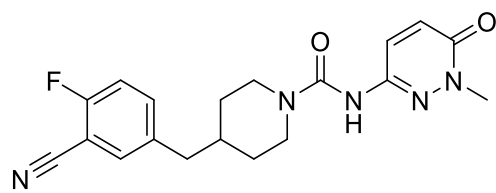
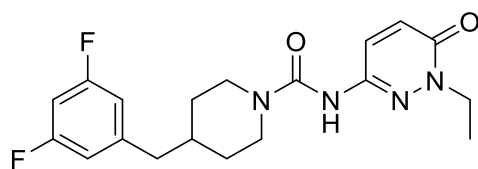
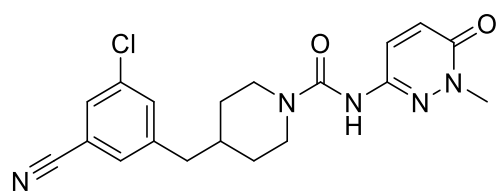
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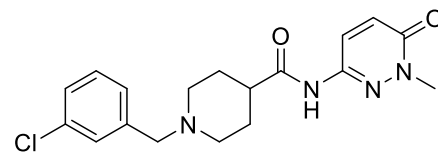
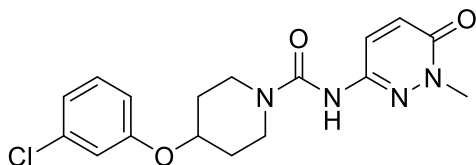
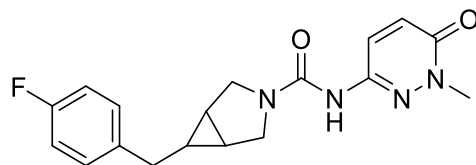
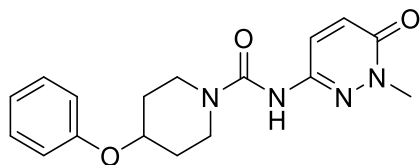
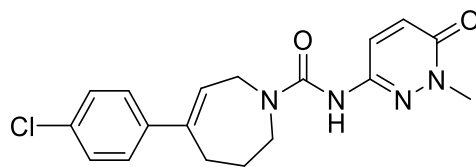
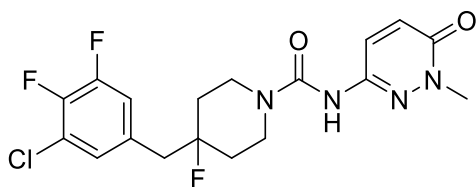


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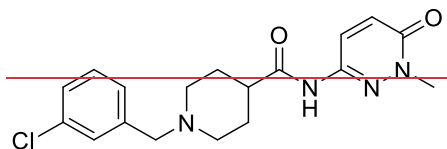




or a pharmaceutically acceptable salt thereof.

~~302. The compound of any one of claims 293-301, wherein R³ is halo.~~

5 ~~303. The compound of claim 293, wherein the compound is~~



~~, or a pharmaceutically acceptable salt thereof.~~

10 ~~21304.~~ A pharmaceutical composition comprising a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to ~~20303~~, and a pharmaceutically acceptable excipient.

~~22. A compound, or pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 20, for use as a medicament.~~

15 ~~23305. Use of a A method of treating a neurological disorder in a subject in need thereof, the method comprising administering an effective amount of a~~ compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to ~~20303~~ or a pharmaceutical composition of claim ~~21304~~ in the manufacture of a medicament for the treatment of a neurological disorder.

20 ~~24306.~~ A method of inhibiting toxicity in a cell in culture related to a protein, the method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to ~~20303~~.

25 ~~25307.~~ The method of claim ~~24306~~, wherein the toxicity is α -synuclein-related toxicity or apolipoprotein E4 (ApoE4)-related toxicity.

~~308. The method of claim 307, wherein the toxicity is apolipoprotein E4 (ApoE4)-related toxicity.~~

~~26309~~. The method of any one of claims ~~24-25306-308~~, wherein the cell is a mammalian neural cell.

~~27310~~. ~~Use A method of treating a stearyl-CoA desaturase (SCD)-associated disorder in a subject in need thereof, the method comprising administering an effective amount~~ of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to ~~20303~~ or a pharmaceutical composition of claim ~~30421~~ in the manufacture of a medicament for the treatment of a stearyl-CoA desaturase (SCD) associated disorder.

~~28~~. The use of claim 27, wherein the SCD-associated disorder is selected from the group consisting of metabolic disorders, cancer, cardiovascular diseases, cerebrovascular diseases, kidney diseases, liver diseases, skin disorders, central nervous system disorders, autoimmune diseases, and eye diseases.

~~29~~. The use of claim 28, wherein the SCD-associated disorder is selected from the group consisting of diabetes, metabolic syndrome, insulin resistance, obesity, a cardiovascular disorder, a CNS disorder, schizophrenia, and Alzheimer's disease.

~~30311~~. ~~Use A method of treating a primary brain cancer in a subject in need thereof, the method comprising administering an effective amount~~ of a compound, ~~or pharmaceutically acceptable salt thereof~~, of any one of claims 1-~~20303~~ or a pharmaceutical composition of claim ~~21304~~ in the manufacture of medicament for the treatment of primary brain cancer.

~~31312~~. ~~The use The method~~ of claim ~~30311~~, wherein the primary brain cancer is a glioma.

~~32313~~. ~~The use The method~~ of claim ~~31312~~, wherein the glioma is an astrocytoma.

~~33314~~. ~~The use The method~~ of claim ~~32313~~, wherein the astrocytoma is a glioblastoma.

~~34315~~. ~~The use The method~~ of any one of claims ~~30-33311-314~~, wherein the cancer is determined or predicted to be resistant to one or more chemotherapeutic agents.

~~35316~~. ~~The use The method~~ of any one of claims ~~30-34311-315~~, wherein the cancer has failed to respond to one or more chemotherapeutic agents.

~~36317~~. ~~The use The method~~ of claims ~~34-35315 or 316~~, wherein one or more therapeutic agents is selected from the group of temozolomide, carmustine, bevacizumab, lomustine, everolimus, vincristine, or procarbazine.

~~37318~~. ~~The use The method~~ of claim ~~36317~~, wherein one or more therapeutic agents is temozolomide.

38319. ~~The use~~ ~~The method~~ of any one of claims ~~30-37~~311-318, wherein the subject is to be further administered one or more additional therapeutic interventions.

5 39320. The ~~use method~~ of claim 38319, wherein one or more additional therapeutic interventions comprises surgery, radiation, and/or one or more additional chemotherapeutic agents.

10 ~~321. The method of claim 320, wherein one or more additional therapeutic interventions is one or more chemotherapeutic agents.~~

~~322. The method of claim 321, wherein one or more chemotherapeutic agents is selected from the group of temozolomide, carmustine, bevacizumab, lomustine, everolimus, vincristine, or procarbazine.~~

~~323. The method of claim 322, wherein one or more chemotherapeutic agents is temozolomide.~~

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