

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.

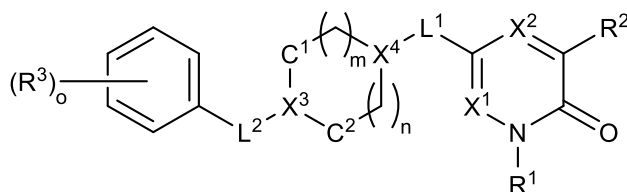
Further, cancers of the brain and nervous system are among the most difficult to treat. Prognosis for patients with these cancers depends on the type and location of the tumor as well as its stage of development. For many types of brain cancer, average life expectancy after symptom onset may be months 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

The 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).

The disclosure features a compound of formula (I):

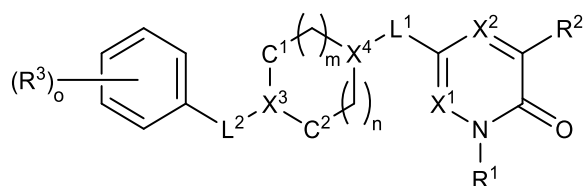


(I)

wherein: m is 0 or 1; n is 0, 1, or 2; o is 0, 1, 2, 3, 4, or 5; 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;

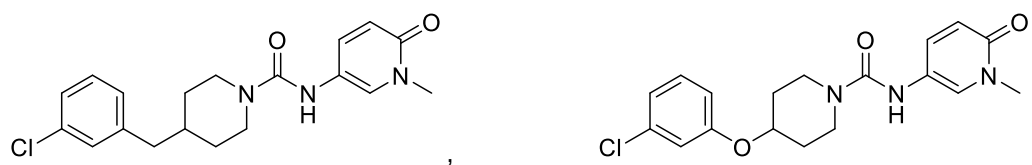
L¹ is -C(O)-X⁵- or optionally substituted C₅₋₁₀ heteroaryl;

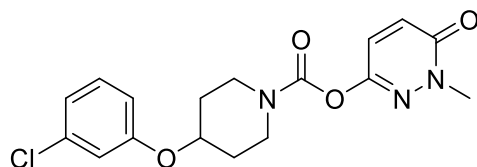
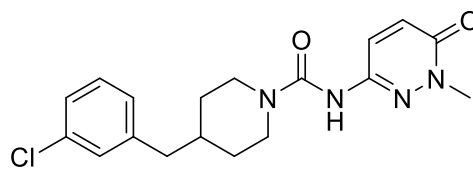
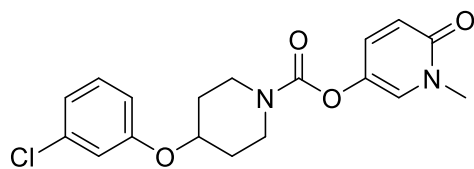
X⁵ is NH, O, or optionally substituted C₁₋₆ alkyl; and

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,

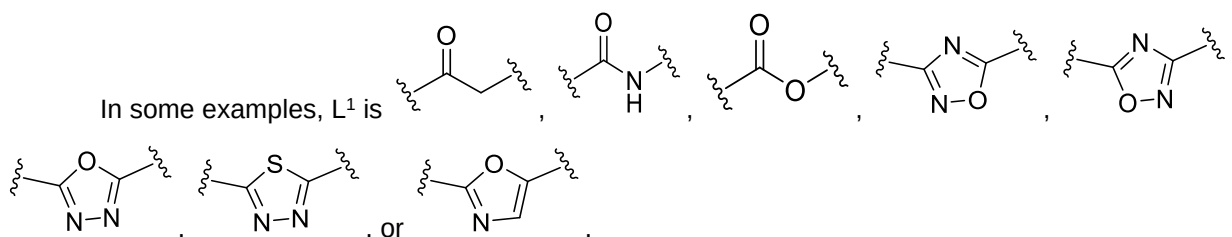
or a pharmaceutically acceptable salt thereof;

wherein the compound does not have the following structure

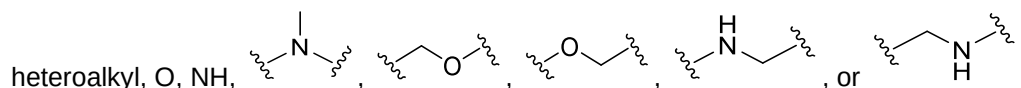




In some examples, L^1 is



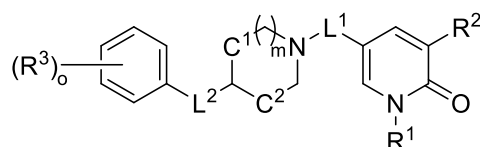
In some examples, L^2 is absent, NR^5 , optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6}



In some examples, 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 examples, 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).

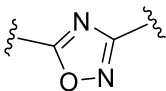
In certain examples, the compound has the structure of formula (II):

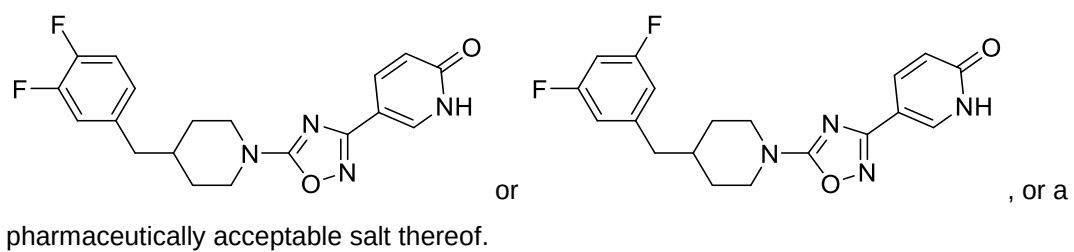


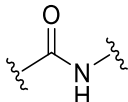
(II)

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.

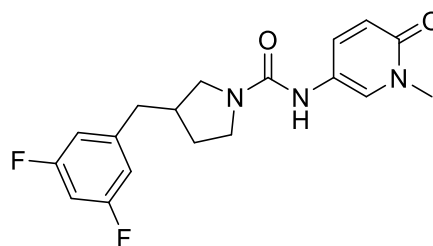
In some examples, R^2 is H. In some examples, R^1 is H. In some examples, m is 1. In some

examples, L^1 is . In some examples, L^2 is optionally substituted C_{1-6} alkyl. In some examples, o is 2. In some examples, R^3 is halo. In particular examples, the compound is

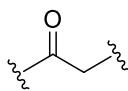


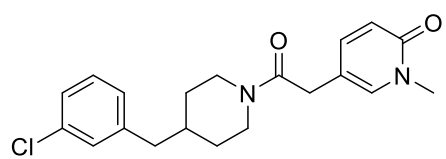
In some examples, R^1 is methyl. In some examples, m is 0. In some examples, L^1 is . In further examples, L^2 is optionally substituted C_{1-6} alkyl. In yet further examples, o is 2. In some

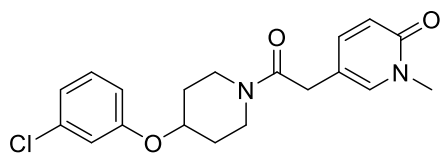
examples, R^3 is halo. In particular examples, the compound is

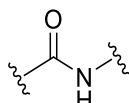


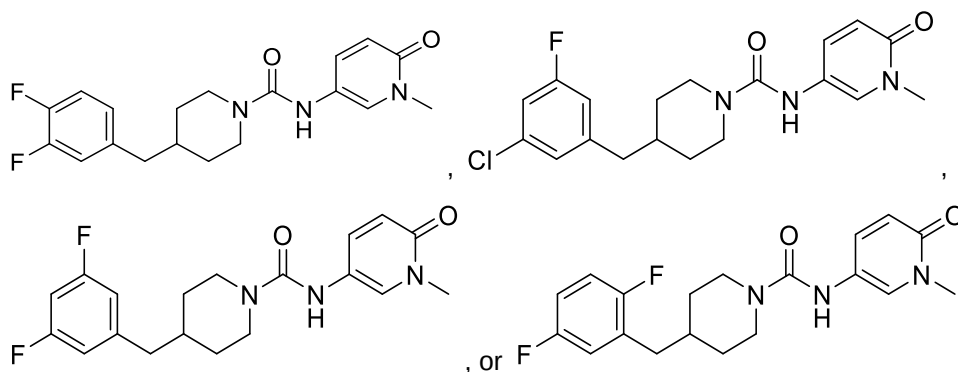
, or a

pharmaceutically acceptable salt thereof. In other examples, m is 1. In further examples, L^1 is . In some examples, L^2 is optionally substituted C_{1-6} alkyl. In some examples, o is 1. In some examples, R^3 is halo. In specific

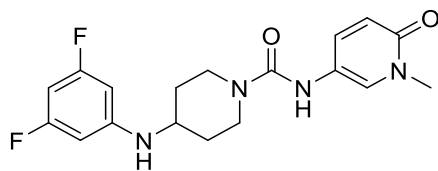
examples, the compound is , or a pharmaceutically acceptable salt thereof. In further examples, L^2 is O. In some examples, o is 1. In some examples, R^3 is halo. In

particular examples, the compound is , or a pharmaceutically acceptable salt thereof.

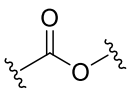
In yet other examples, L^1 is . In some examples, L^2 is optionally substituted C_{1-6} alkyl. In some examples, o is 1 or 2. In some examples, R^3 is halo. In still other examples, the compound is

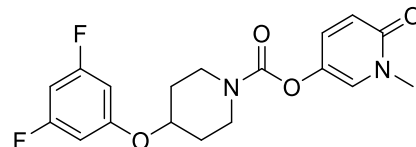


, or , or a pharmaceutically acceptable salt thereof. In other examples, L^2 is NH. In some examples, o is 2. In some examples, R^3 is halo. In particular



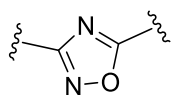
examples, the compound is , or a pharmaceutically acceptable salt thereof. In still other examples, L^2 is O. In further examples, o is 1. In some examples, R^3 is halo.

In further examples, L^1 is . In some examples, L^2 is O. In some examples, o is 1 or 2.

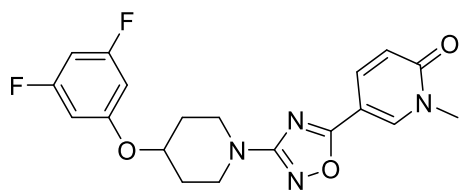


In some examples, R^3 is halo. In certain examples, the compound is , or a pharmaceutically acceptable salt thereof.

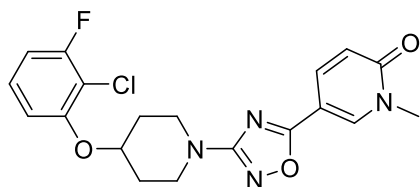
In yet further examples, L^1 is optionally substituted C_{5-10} heteroaryl. In some examples, L^1 is



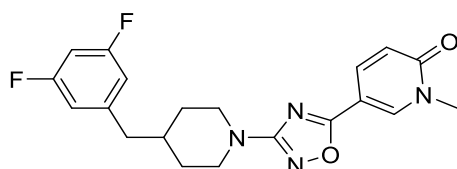
. In some examples, L^2 is O. In some examples, o is 2. In some examples, R^3 is halo. In



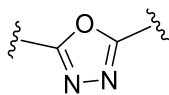
particular examples, the compound is or



, or a pharmaceutically acceptable salt thereof. In other examples, L^2 is optionally substituted C_{1-6} alkyl. In some examples, o is 2. In further examples, R^3 is halo. In certain

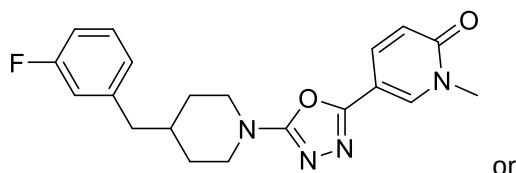


examples, the compound is , or a pharmaceutically acceptable salt thereof.

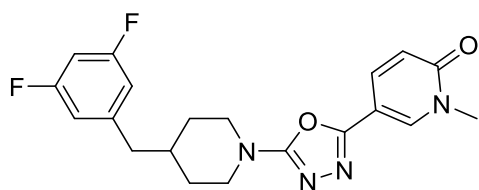


In further examples, L^1 is . In some examples, L^2 is optionally substituted C_{1-6} alkyl. In some examples, o is 1 or 2. In some examples, R^3 is halo. In particular

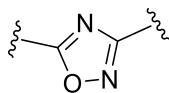
examples, the compound is



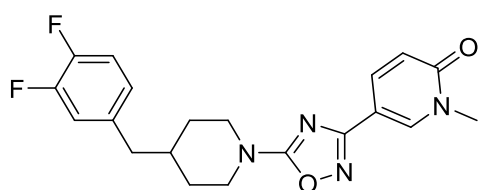
or



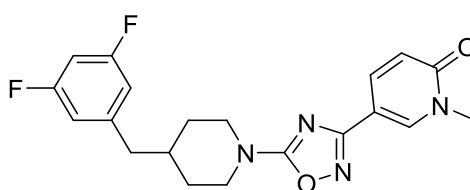
, or a pharmaceutically acceptable salt thereof.



In still other examples, L^1 is . In some examples, L^2 is optionally substituted C_{1-6} alkyl. In some examples, o is 2. In some examples, R^3 is halo. In specific examples, the compound is



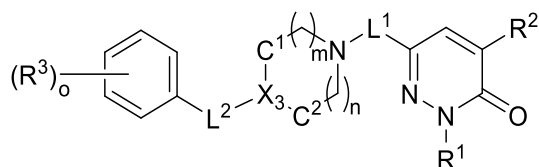
or



, or a

pharmaceutically acceptable salt thereof.

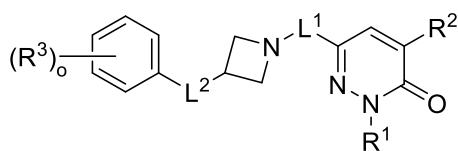
In further examples, the compound has the structure of formula (III):



(III)

wherein: m is 0 or 1; n is 0, 1, or 2; o is 0, 1, 2, 3, 4, or 5; 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 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.

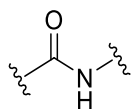
In some examples, the compound has the structure of formula (III-A):



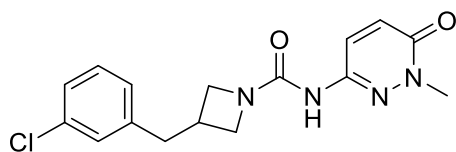
(III-A)

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.

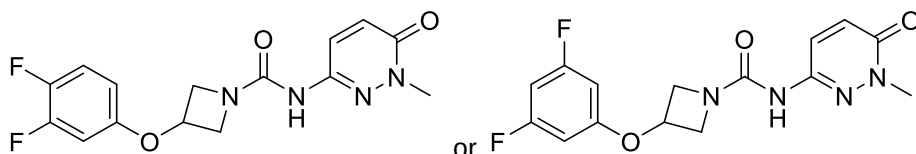
In some examples, R² is H. In some examples, R¹ is methyl. In some examples, L¹ is



. In further examples, L² is optionally substituted C₁₋₆ alkyl. In further examples, *o* is 1. In yet further examples, R³ is halo. In particular examples, the compound is

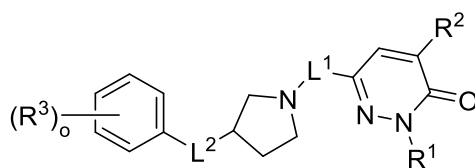


, or a pharmaceutically acceptable salt thereof. In other examples, L² is O. In some examples, *o* is 2. In some examples, R³ is halo. In certain examples, the compound is



, or a pharmaceutically acceptable salt thereof.

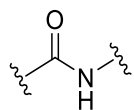
In further examples, the compound has the structure of formula (III-B):



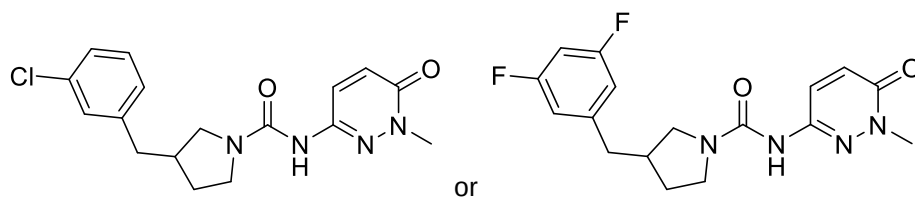
(III-B)

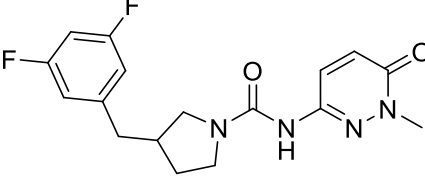
wherein: *o* is 0, 1, 2, 3, 4, or 5; each of R¹, R², and R⁵ is, independently, H or optionally substituted C₁₋₆ alkyl; R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted C₁₋₆ alkyl; L¹ is optionally substituted C₅₋₁₀ heteroaryl or –C(O)–X⁵–; X⁵ is NH,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

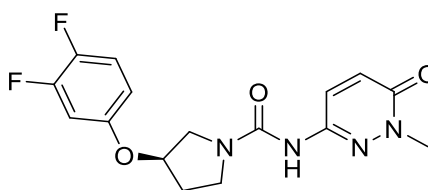
In some examples, R² is H. In some examples, R¹ is methyl. In some examples, L¹ is



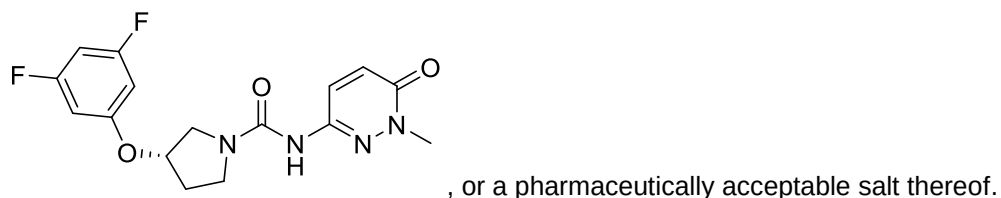
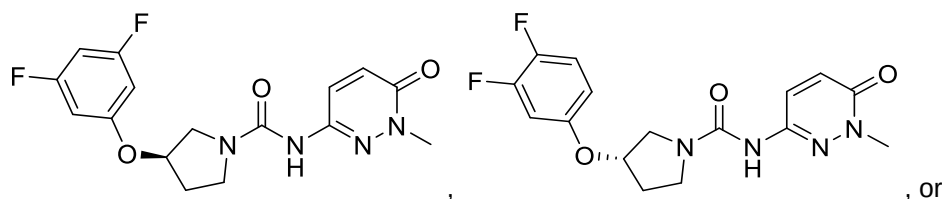
. In further examples, L² is optionally substituted C₁₋₆ alkyl. In some examples, o is 1 or 2. In some examples, R³ is halo. In particular examples, the compound is



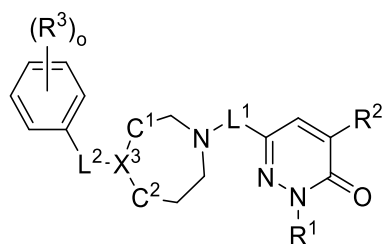
or , or a pharmaceutically acceptable salt thereof. In further examples, L² is O. In some examples, o is 2. In still other examples,



R³ is halo. In some examples, the compound is



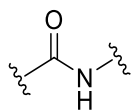
In yet other examples, the compound has the structure of formula (III-C):



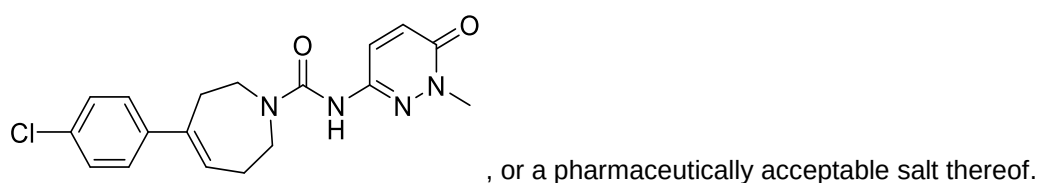
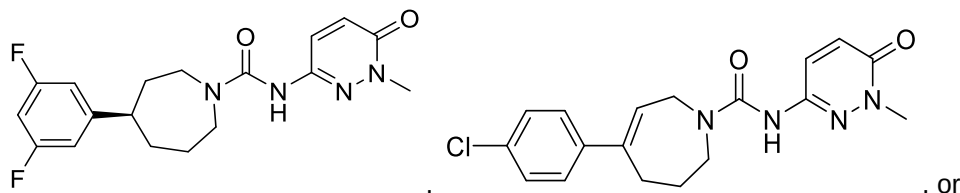
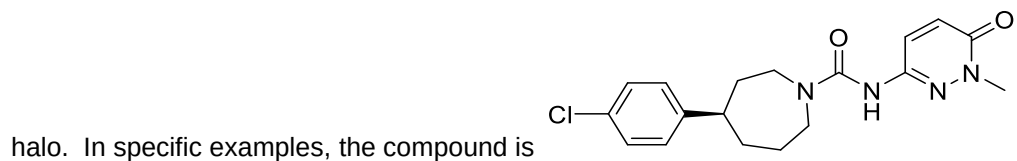
(III-C)

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.

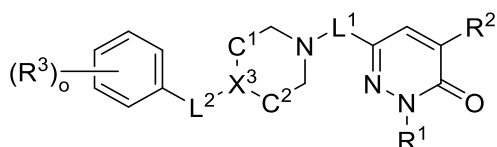
In some examples, R^2 is H. In some examples, R^1 is methyl. In further examples, L^1 is



. In some examples, L^2 is absent. In some examples, o is 1 or 2. In further examples, R^3 is



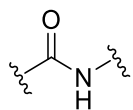
In further examples, the compound has the structure of formula (III-D):



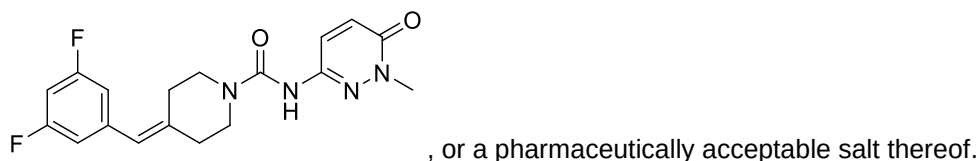
(III-D)

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 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.

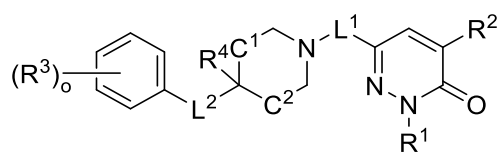
In some examples, R^2 is H. In certain examples, R^1 is methyl. In some examples, L^1 is



. In further examples, X^3 and L^2 combine to form an optionally substituted alkene. In some examples, o is 2. In some examples, R^3 is halo. In particular examples, the compound is

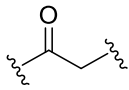


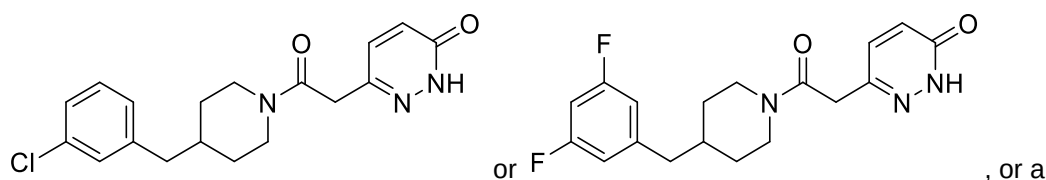
In some examples, the compound has the structure of formula (III-D-1):



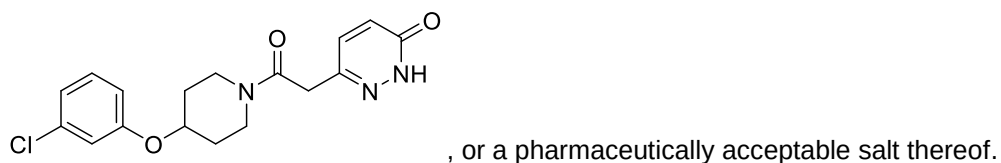
(III-D-1)

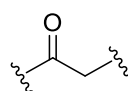
wherein: *o* is 0, 1, 2, 3, 4, or 5; C¹ and C² optionally combine to form a bond; each of R¹, R², R⁵, and R⁶ is, independently, H or optionally substituted C₁-₆ alkyl; R³ is halo, cyano, C₁-₆ perfluoroalkyl, optionally substituted C₁-₆ alkoxy, or optionally substituted C₁-₆ alkyl; R⁴ is H, OR⁶, optionally 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.

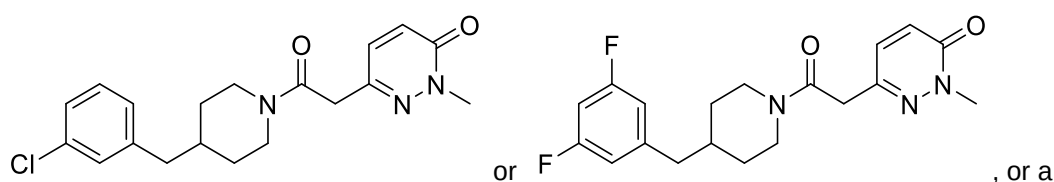
In some examples, R² is H. In some examples, R¹ is H. In some examples, L¹ is . In further examples, L² is optionally substituted C₁-₆ alkyl. In some examples, *o* is 1 or 2. In some examples, R³ is halo. In some examples, R⁴ is H. In certain examples, the compound is



, or a pharmaceutically acceptable salt thereof. In further examples, L² is O. In some examples, *o* is 1. In some examples, R³ is halo. In some examples, R⁴ is H. In some examples, the compound is

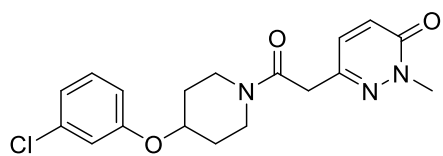


In further examples, R¹ is methyl. In some examples, L¹ is . In some examples, L² is optionally substituted C₁-₆ alkyl. In some examples, *o* is 1 or 2. In further examples, R³ is halo. In still further examples, R⁴ is H. In particular examples, the compound is

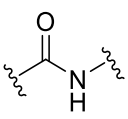


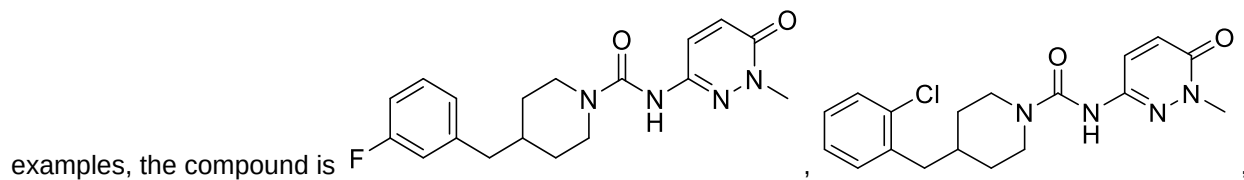
, or a pharmaceutically acceptable salt thereof. In other examples, L² is O. In some examples, *o* is 1.

In some examples, R^3 is halo. In some examples, R^4 is H. In further examples, the compound is

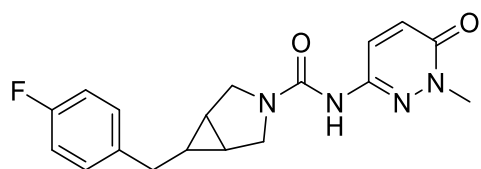
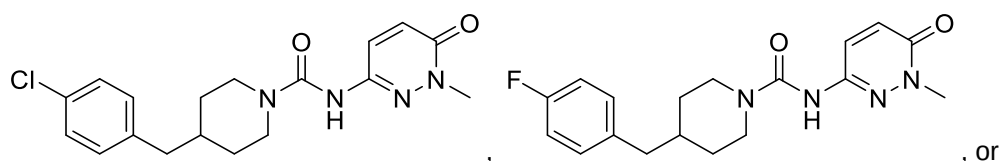


, or a pharmaceutically acceptable salt thereof.

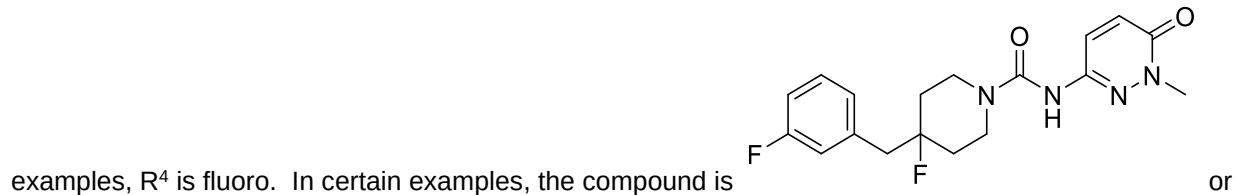
In yet other examples, L^1 is . In some examples, L^2 is optionally substituted C_{1-6} alkyl. In some examples, o is 1. In some examples, R^3 is halo. In some examples, R^4 is H. In further



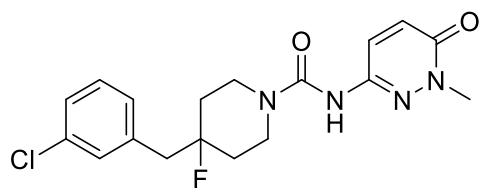
examples, the compound is



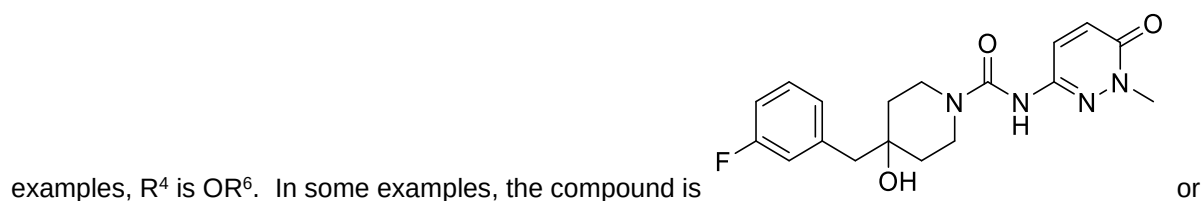
, or a pharmaceutically acceptable salt thereof. In other



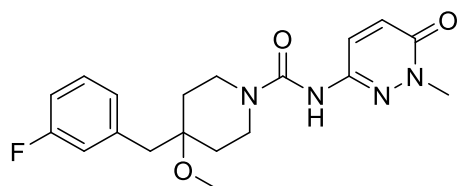
examples, R^4 is fluoro. In certain examples, the compound is



, or a pharmaceutically acceptable salt thereof. In still further

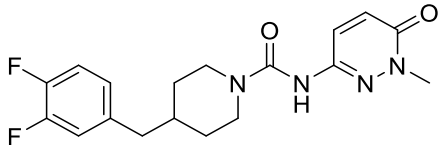


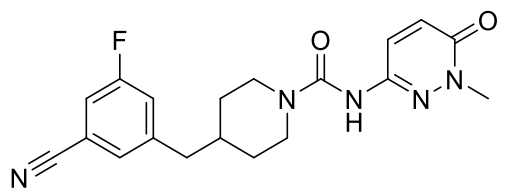
examples, R^4 is OR^6 . In some examples, the compound is

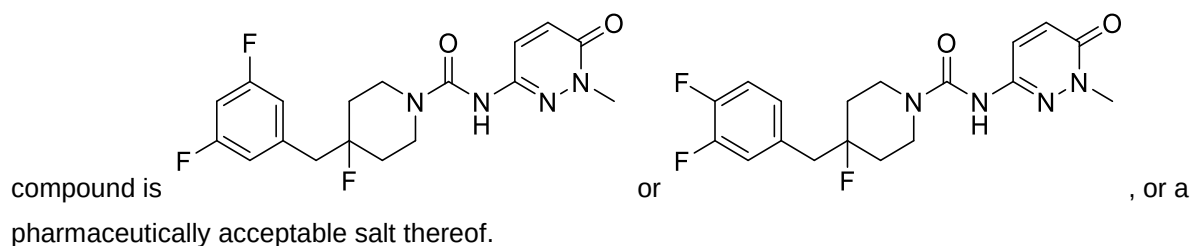
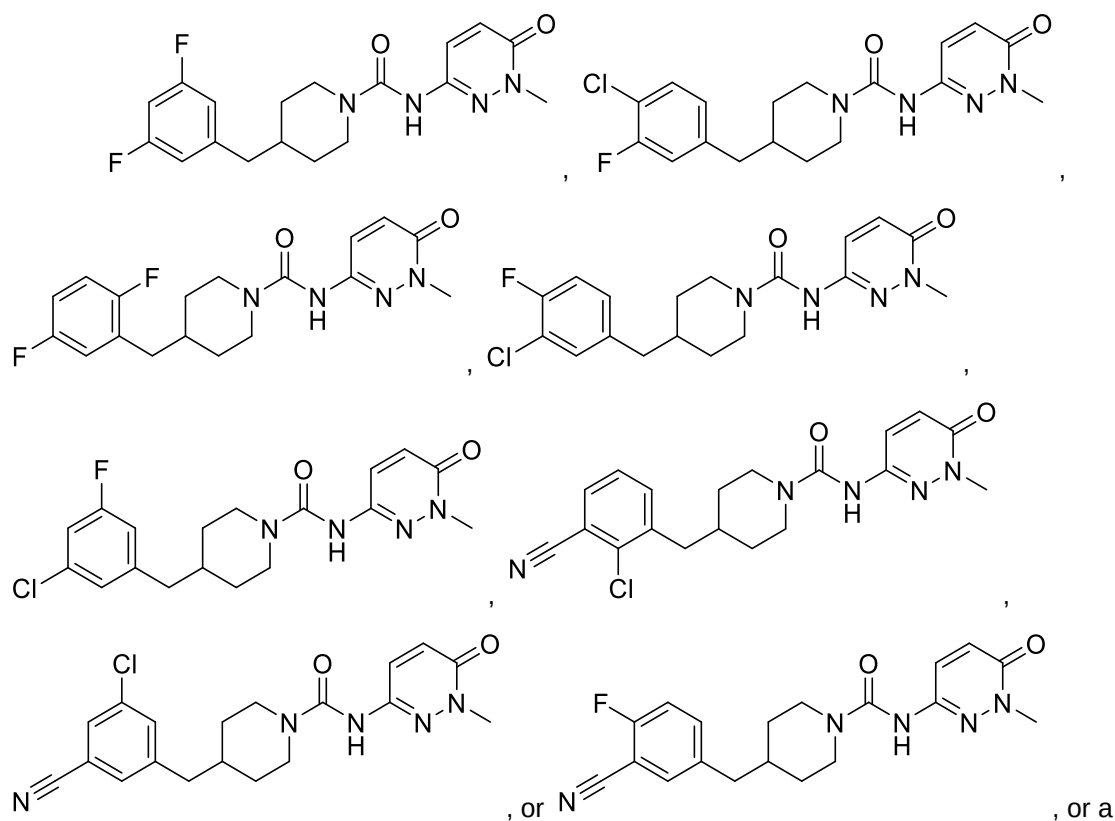


, or a pharmaceutically acceptable salt thereof.

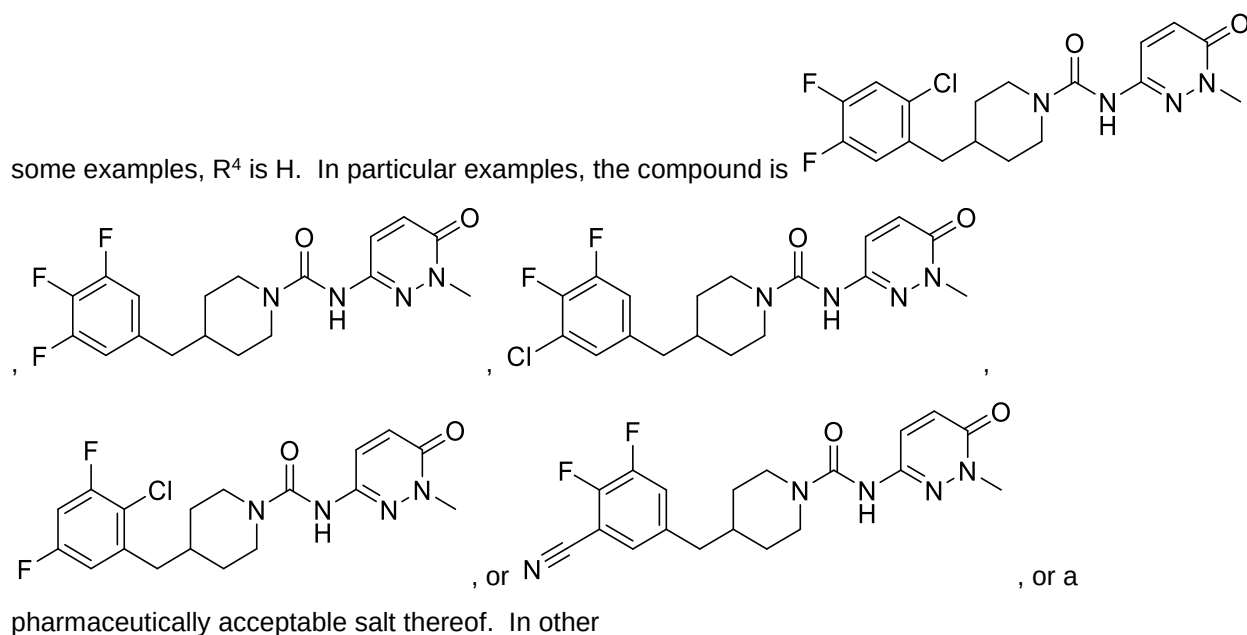
In other examples, o is 2. In some examples, R^3 is, independently, halo or cyano. In some

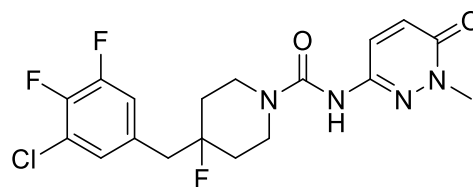
examples, R^4 is H. In certain examples, the compound is  ,





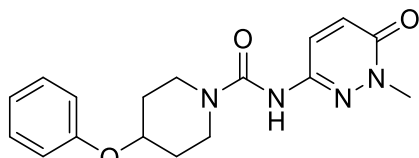
In further examples, o is 3. In some examples, each R³ is, independently, halo or cyano. In



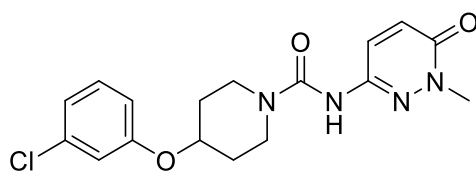


examples, R^4 is fluoro. In some examples, the compound is a pharmaceutically acceptable salt thereof.

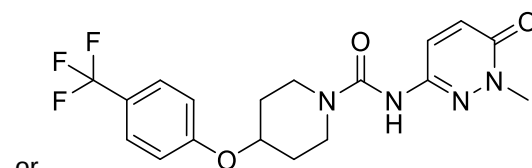
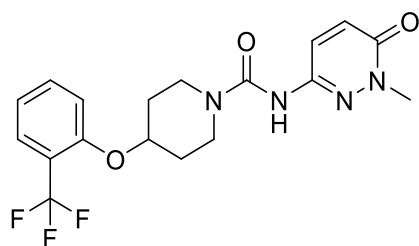
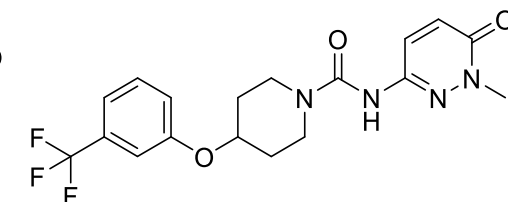
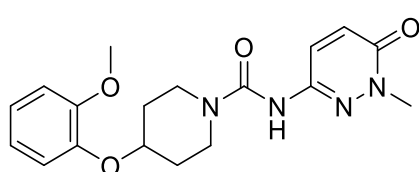
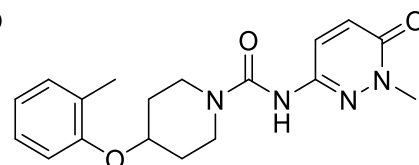
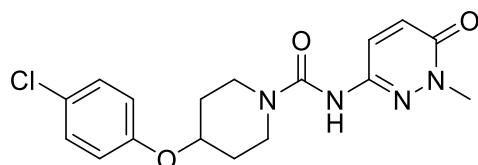
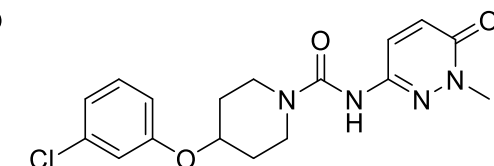
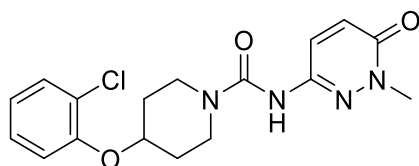
In some examples, L^2 is O. In further examples, o is 0. In some examples, R^4 is H. In some



examples, the compound is , or a pharmaceutically acceptable salt thereof. In other examples, o is 1. In some examples, R^3 is halo, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxy, or C_{1-6} perfluoroalkyl. In further examples, R^4 is H. In particular

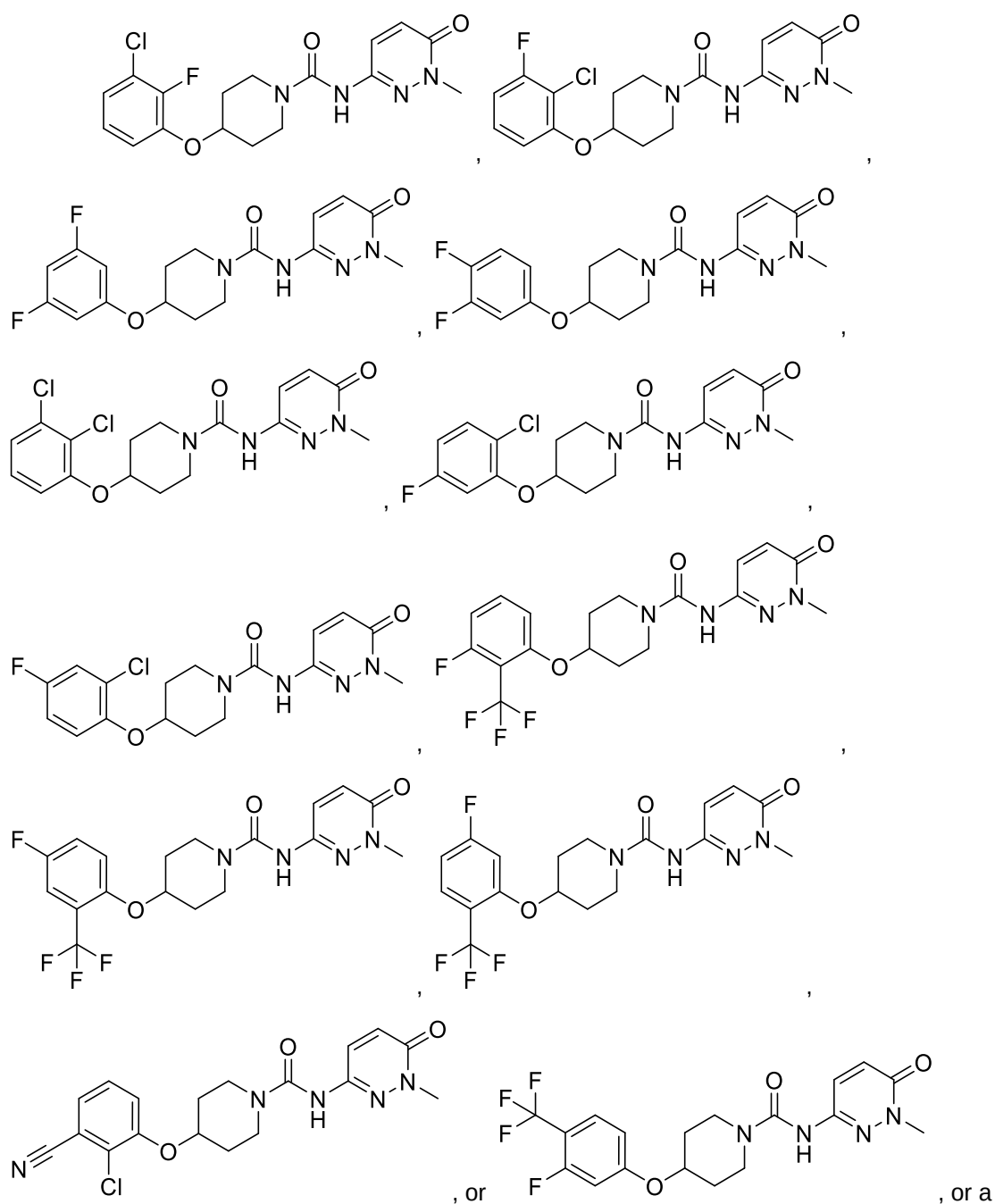


examples, the compound is ,



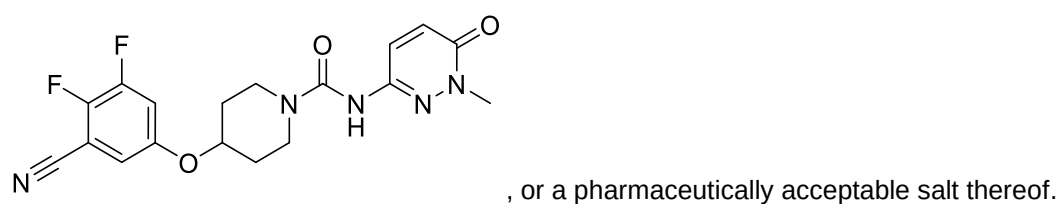
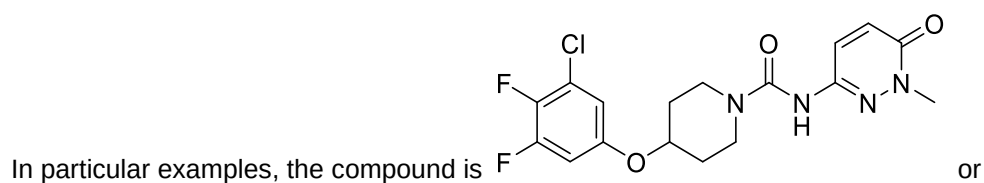
or , or a pharmaceutically acceptable salt thereof.

In still further examples, o is 2. In some examples, each R^3 is, independently, halo, C_{1-6} perfluoroalkyl, or cyano. In some examples, R^4 is H. In specific examples, the compound is

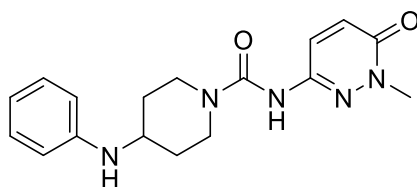


pharmaceutically acceptable salt thereof.

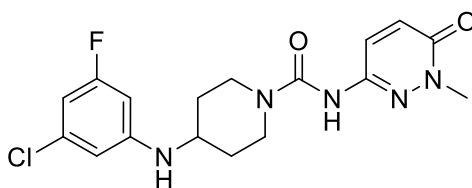
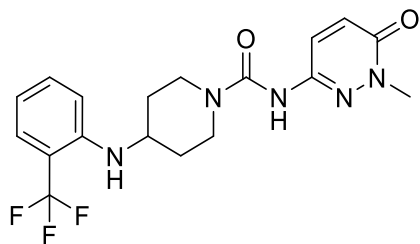
In some examples, o is 3. In certain examples, R³ is halo or cyano. In further examples, R⁴ is H.



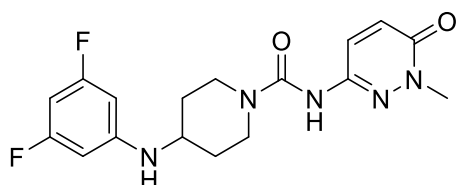
In still further examples, L² is NR⁵. In certain examples, L² is NH. In some examples, o is 0, 1, or 2. In some examples, R³ is halo or C₁₋₆ perfluoroalkyl. In some examples, R⁴ is H. In



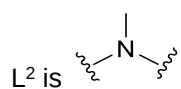
certain examples, the compound is



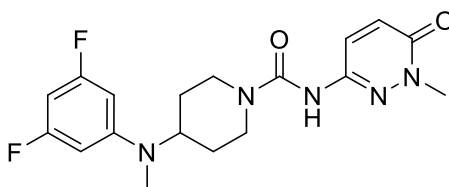
, or



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



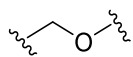
L^2 is . In some examples, o is 2. In some examples, R^3 is halo. In further examples, R^4 is H. In



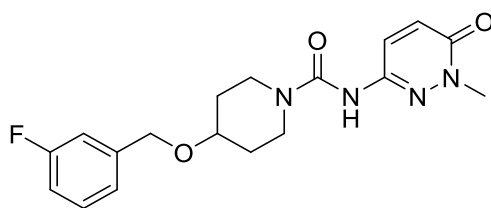
some examples, the compound is
acceptable salt thereof.

, or a pharmaceutically

In other examples, L^2 is optionally substituted C_{1-6} heteroalkyl. In particular examples, L^2 is

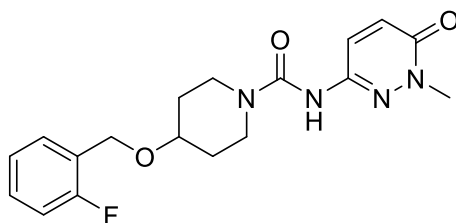


. In some examples, o is 1. In some examples, R^3 is halo. In some examples, R^4 is H. In

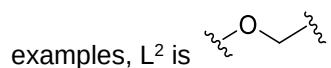


further examples, the compound is

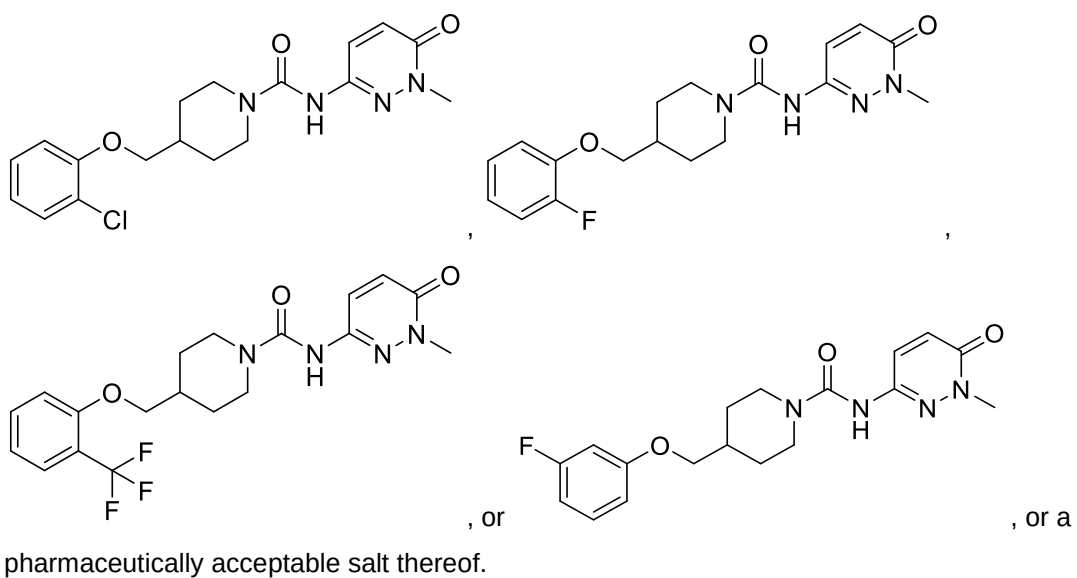
or

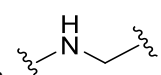


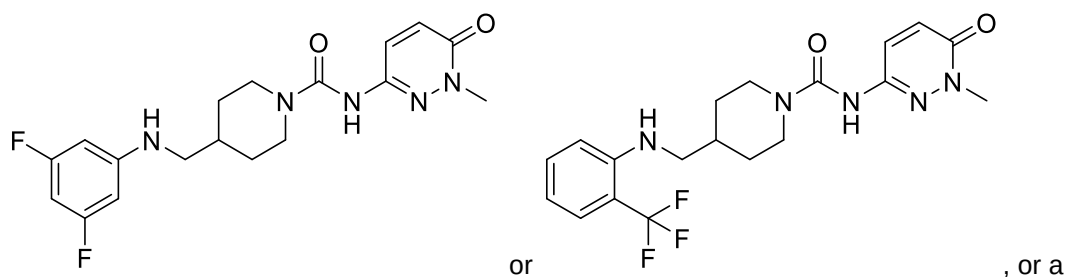
, or a pharmaceutically acceptable salt thereof. In further

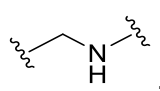


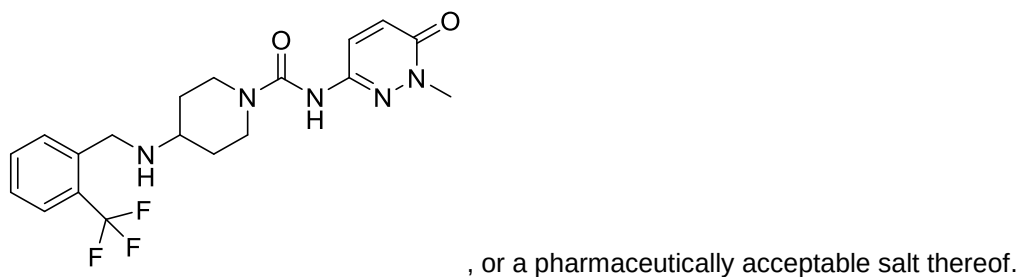
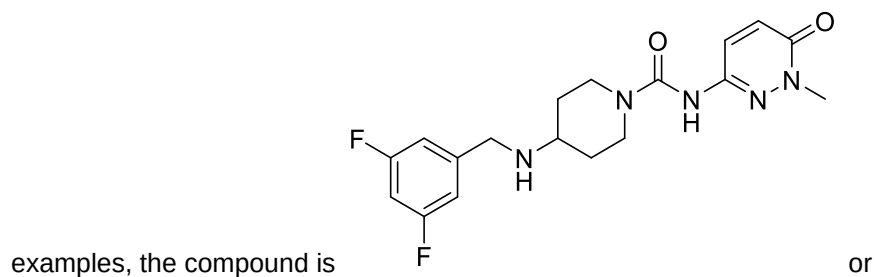
examples, L^2 is . In some examples, o is 1. In certain examples, R^3 is halo or C_{1-6} perfluoroalkyl. In some examples, R^4 is H. In particular examples, the compound is

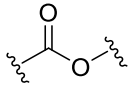


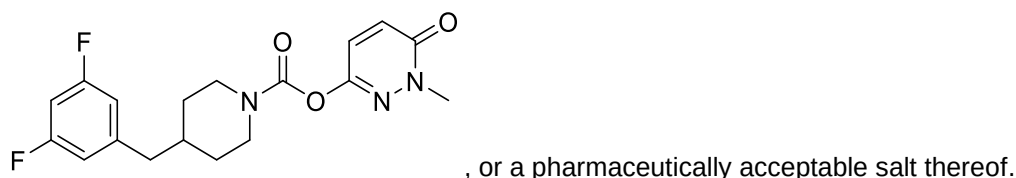
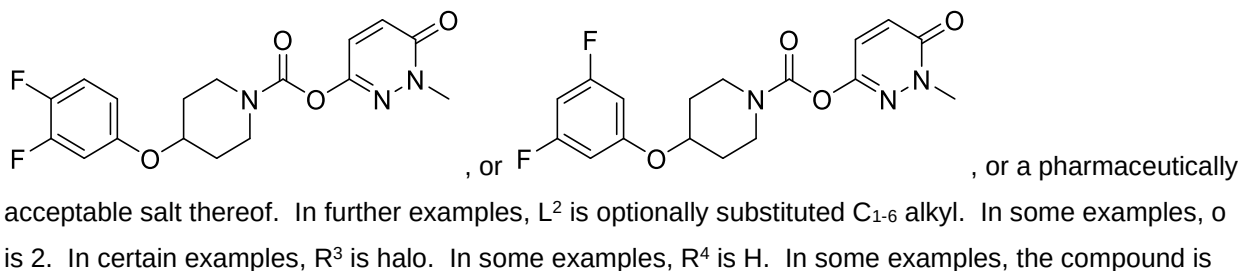
In yet further examples, L^2 is . In some examples, o is 1 or 2. In some examples, R^3 is halo or C_{1-6} perfluoroalkyl. In further examples, R^4 is H. In particular examples, the compound is

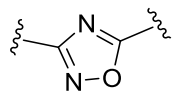


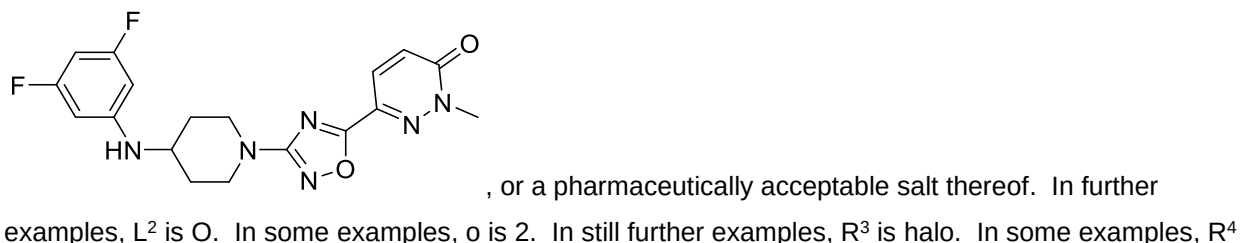
pharmaceutically acceptable salt thereof. In other examples, L^2 is . In certain examples, o is 1 or 2. In further examples, R^3 is halo or C_{1-6} perfluoroalkyl. In some examples, R^4 is H. In some

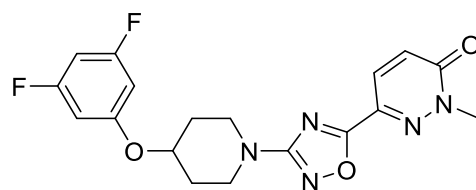


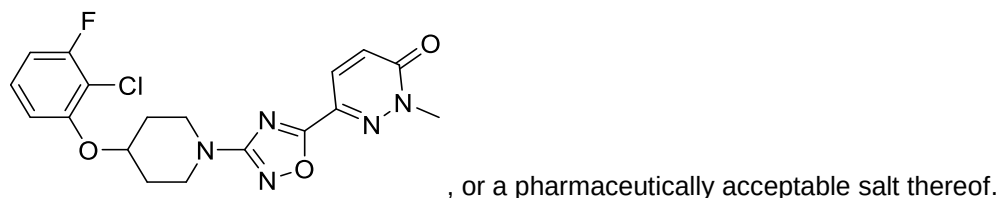
In still other examples, L¹ is . In some examples, L² is O. In some examples, o is 1 or 2. In some examples, R³ is halo. In further examples, R⁴ is H. In particular examples, the compound is



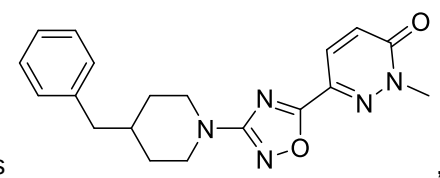
In further examples, L¹ is optionally substituted C₅₋₁₀ heteroaryl. In particular examples, L¹ is . In some examples, L² is NH. In some examples, o is 2. In some examples, R³ is halo. In further examples, R⁴ is H. In particular examples, the compound is

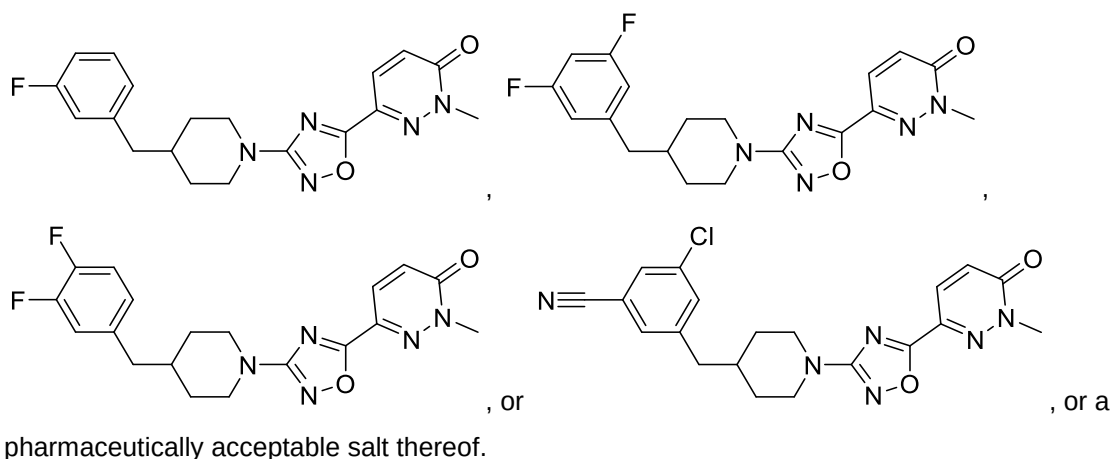


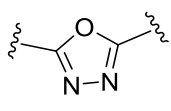
is H. In particular examples, the compound is  or

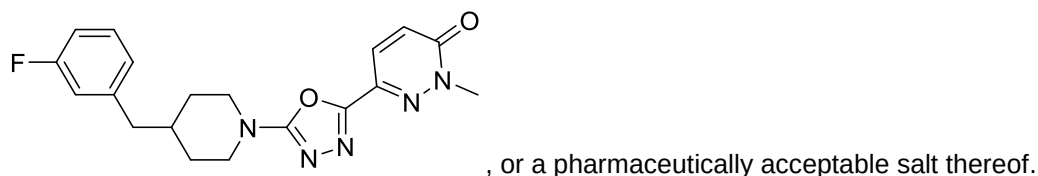
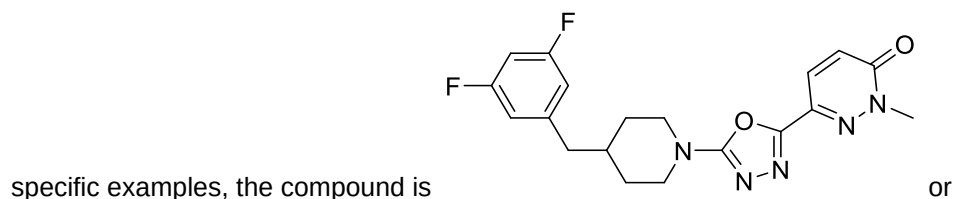


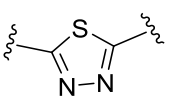
In still other examples, L² is optionally substituted C₁₋₆ alkyl. In some examples, o is 0, 1, or 2. In some examples, each R³ is, independently, halo or cyano. In some examples, R⁴ is H. In further

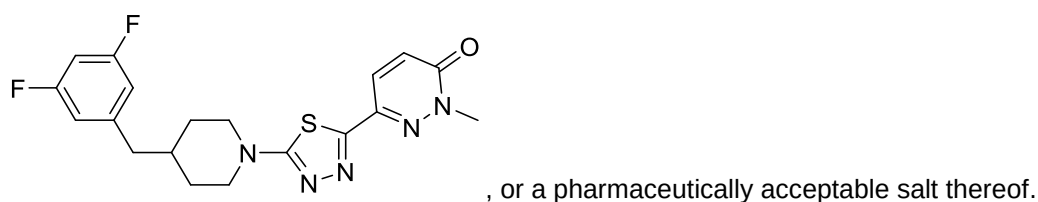
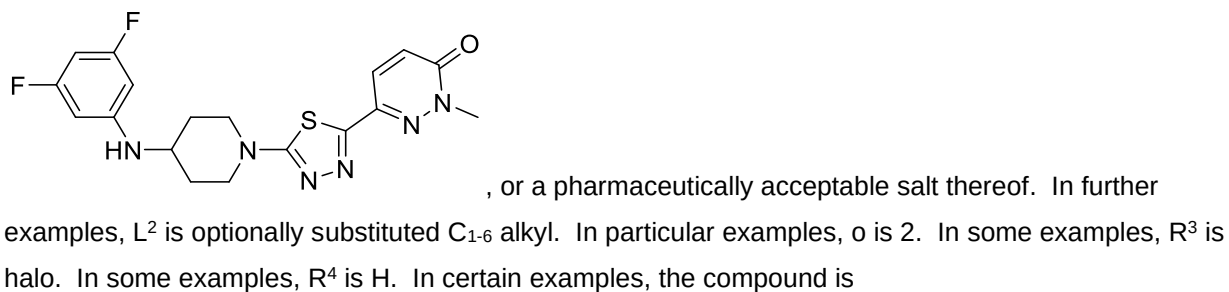
examples, the compound is ,

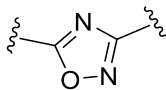


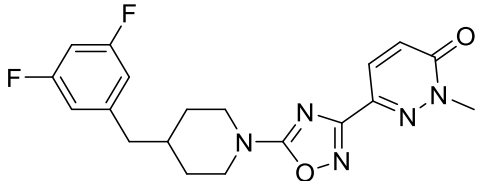
In further examples, L¹ is . In some examples, L² is optionally substituted C₁₋₆ alkyl. In certain examples, o is 1 or 2. In some examples, R³ is halo. In some examples, R⁴ is H. In

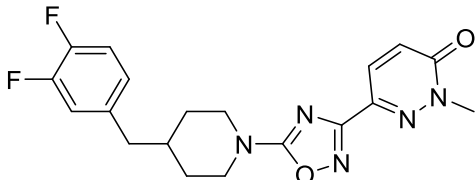


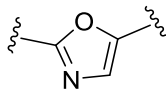
In yet other examples, L¹ is . In some examples, L² is NH. In further examples, o is 2. In some examples, R³ is halo. In some examples, R⁴ is H. In certain examples, the compound is

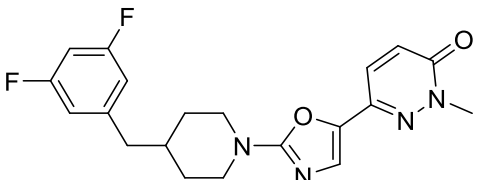


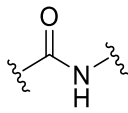
In still further examples, L^1 is . In some examples, L^2 is optionally substituted C_{1-6} alkyl. In some examples, o is 2. In further examples, R^3 is halo. In some examples, R^4 is H. In further

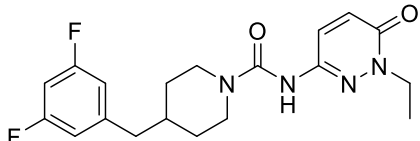
examples, the compound is  or

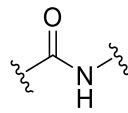
, or a pharmaceutically acceptable salt thereof.

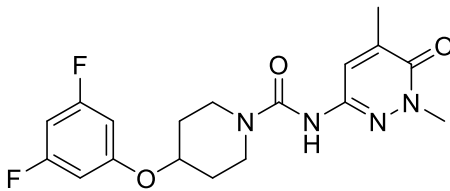
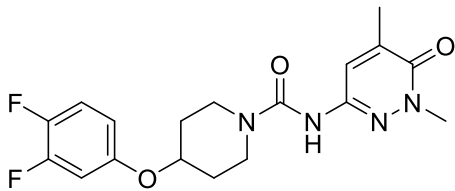
In other examples, L^1 is . In some examples, L^2 is optionally substituted C_{1-6} alkyl. In some examples, o is 2. In some examples, R^3 is halo. In some examples, R^4 is H. In some examples,

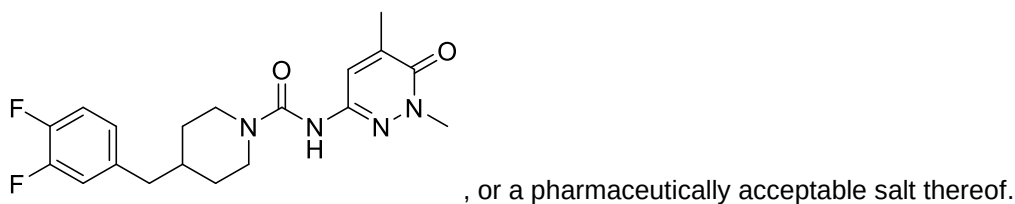
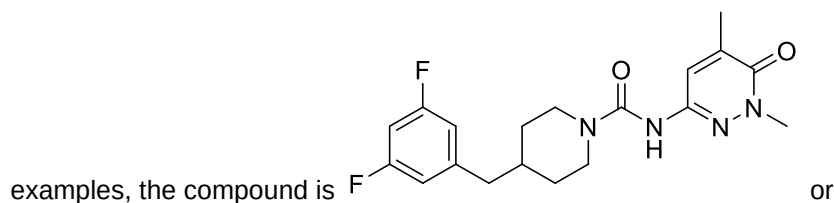
the compound is , or a pharmaceutically acceptable salt thereof.

In still other examples, R^1 is ethyl. In some examples, L^1 is . In some examples, L^2 is optionally substituted C_{1-6} alkyl. In further examples, o is 2. In some examples, R^3 is halo. In some

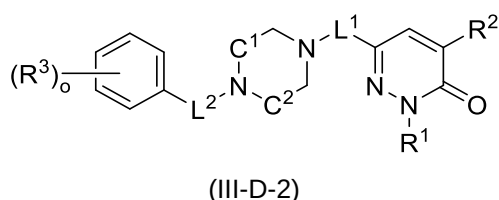
examples, R^4 is H. In certain examples, the compound is , or a pharmaceutically acceptable salt thereof. In specific examples, R^2 is methyl. In certain examples, R^1 is

methyl. In some examples, L^1 is . In some examples, L^2 is O. In further examples, o is 2. In some examples, R^3 is halo. In some examples, R^4 is H. In particular examples, the compound is

 or , or a pharmaceutically acceptable salt thereof. In other examples, L^2 is optionally substituted C_{1-6} alkyl. In some examples, o is 2. In some examples, R^3 is halo. In some examples, R^4 is H. In certain

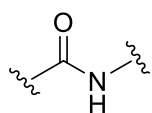


In other examples, the compound has the structure of formula (III-D-2):

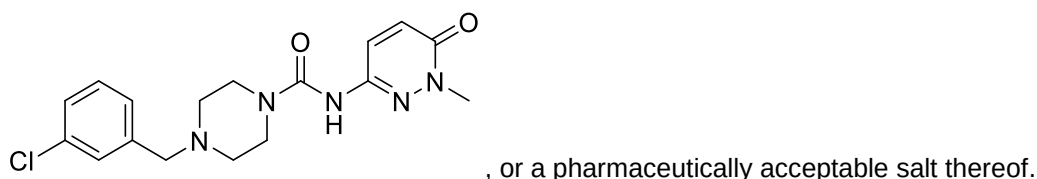


wherein: o is 0, 1, 2, 3, 4, or 5; C¹ and C² optionally combine to form a bond; each of R¹, R², and R⁵ is, independently, H or optionally substituted C₁₋₆ alkyl; R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted C₁₋₆ alkyl; L¹ is optionally substituted 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.

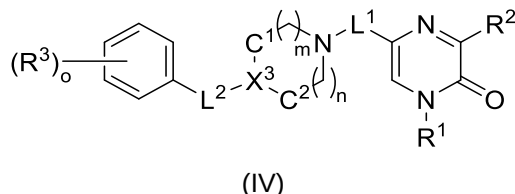
In some examples, R¹ is methyl. In certain examples, R² is H. In particular examples, L¹ is



. In further examples, L² is optionally substituted C₁₋₆ alkyl. In some examples, o is 1. In some examples, R³ is halo. In certain examples, the compound is



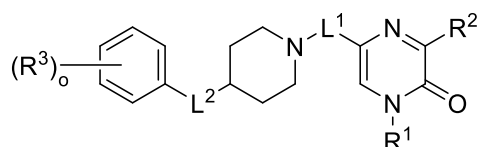
In yet other examples, the compound has the structure of formula (IV):



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.

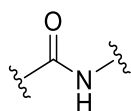
In further examples, the compound has the structure of formula (IV-A):



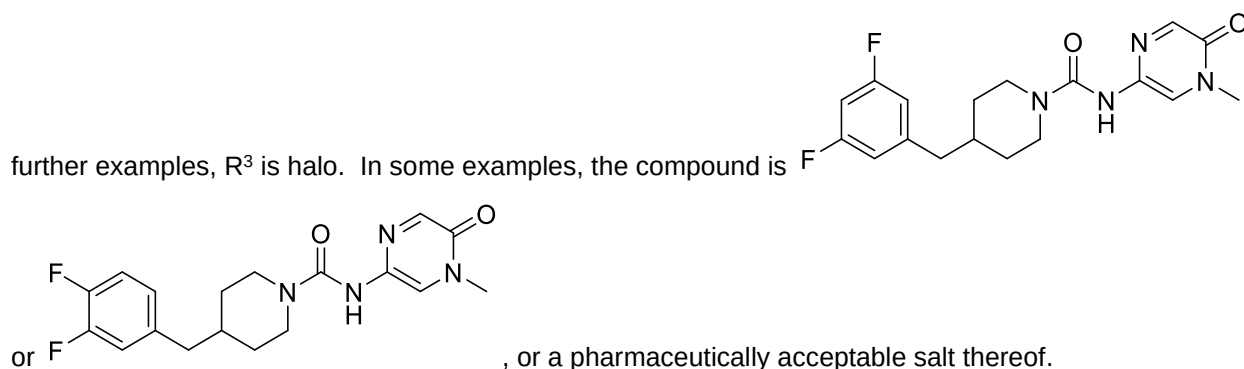
(IV-A)

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.

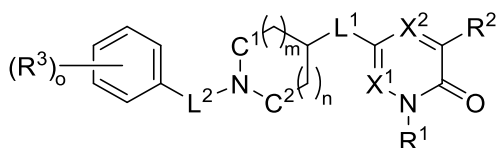
In some examples, R^2 is H. In further examples, R^1 is methyl. In some examples, L^1 is



. In certain examples, L^2 is optionally substituted C_{1-6} alkyl. In some examples, o is 2. In



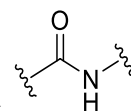
In some examples, the compound has the structure of formula (V):



(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.

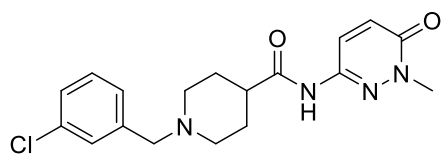
In certain examples, X^1 is N and X^2 is CH. In further examples, R^2 is H. In some examples, R^1 is



methyl. In some examples, m is 1. In some examples, n is 1. In still further examples, L^1 is

In particular examples, L^2 is optionally substituted C_{1-6} alkyl. In

some examples, o is 1. In some examples, R³ is halo. In some examples, the compound is

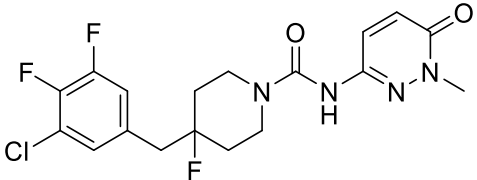
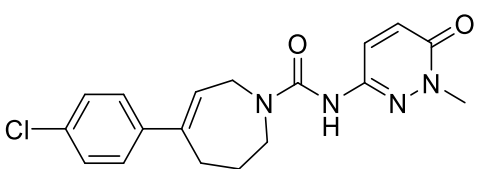
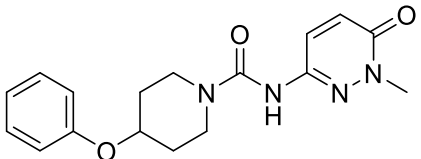
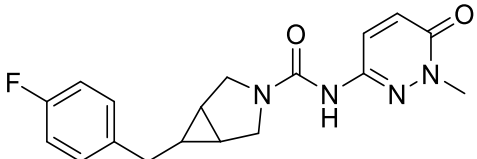
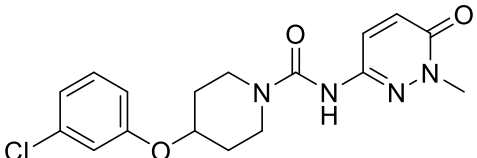
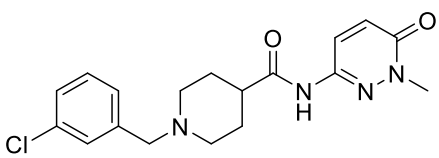


, or a pharmaceutically acceptable salt thereof.

In another example, the 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 examples, 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.

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.

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 examples, the toxicity is α -synuclein-related toxicity. In some examples, the toxicity is ApoE4-related toxicity.

In some examples, the cell is a mammalian neural cell.

This disclosure provides a method of treating a stearoyl-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 stearoyl-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 examples, the SCD-associated disorder is a SCD5-associated disorder.

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.

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.

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 examples, the primary brain cancer is a glioma. In some examples, the glioma is an astrocytoma. In some examples, the astrocytoma is a glioblastoma.

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

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

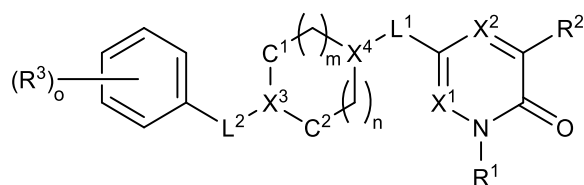
The term “alkyl,” as used herein, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of 1 to 20 carbon atoms (e.g., 1 to 16 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms). An alkylene is a divalent alkyl group.

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;

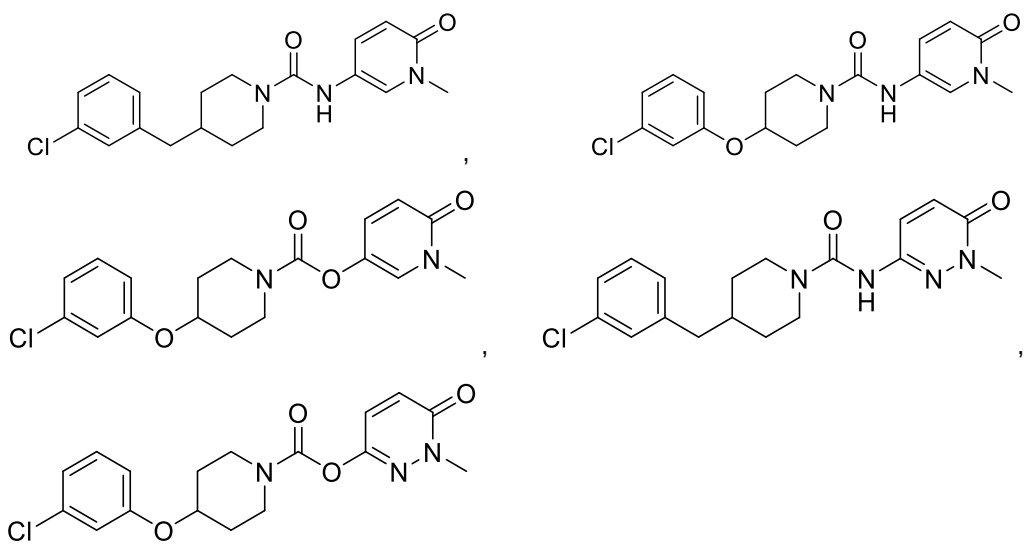
L¹ is -C(O)-X⁵- or optionally substituted C₅-₁₀ heteroaryl;

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

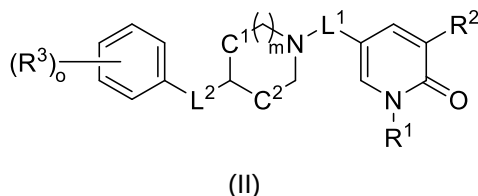
L² is O, NR⁵, optionally substituted C₁-₆ alkyl, optionally substituted C₁-₆ heteroalkyl, or absent; or X³ and L² combine to form an optionally substituted alkene,

or a pharmaceutically acceptable salt thereof;

wherein the compound does not have the following structure



2. The compound of claim 1, wherein the compound has the structure of formula (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;

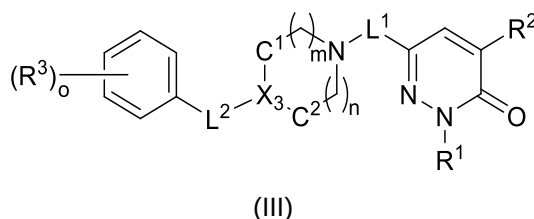
X⁵ is NH, O, or optionally substituted C₁-₆ alkyl; and

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 1, wherein the compound has the structure of formula (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;

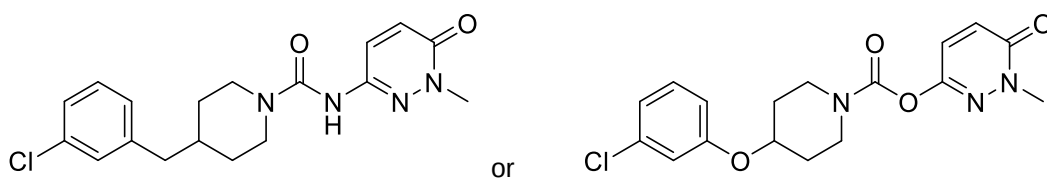
X⁵ is NH, O, or optionally substituted C₁-₆ alkyl; and

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

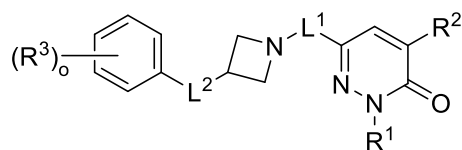
X³ and L² combine to form an optionally substituted alkene,

or a pharmaceutically acceptable salt thereof;

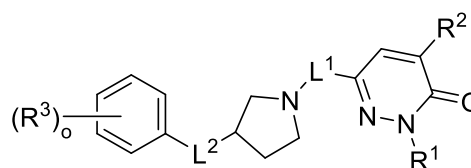
wherein the compound does not have the structure



4. The compound of claim 3, wherein the compound has the structure of formula (III-A) or (III-B):



(III-A)



(III-B)

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;

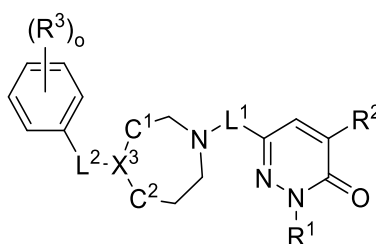
R^3 is halo, cyano, C_{1-6} perfluoroalkyl, optionally substituted C_{1-6} alkoxy, or optionally substituted C_{1-6} alkyl;

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

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.

5. The compound of claim 3, wherein the compound has the structure of formula (III-C):



(III-C)

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;

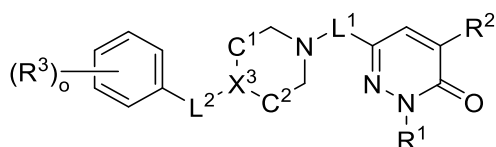
L^1 is $-C(O)-X^5-$ or optionally substituted C_{5-10} heteroaryl;

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.

6. The compound of claim 3, wherein the compound has the structure of formula (III-D):



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

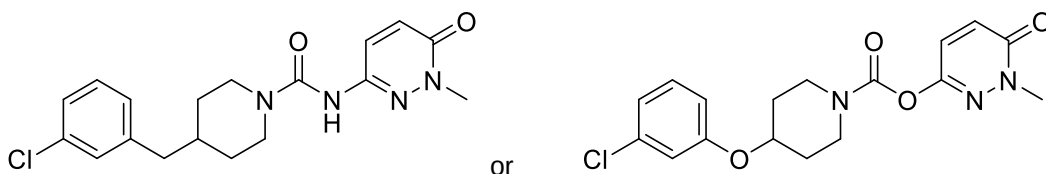
X⁵ is NH, O, or optionally substituted C₁₋₆ alkyl; and

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

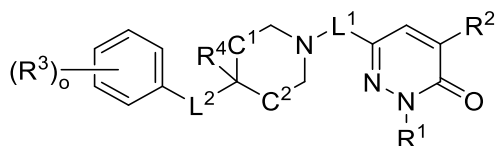
X³ and L² combine to form an optionally substituted alkene,

or a pharmaceutically acceptable salt thereof;

wherein the compound does not have the structure



7. The compound of claim 6, wherein 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;

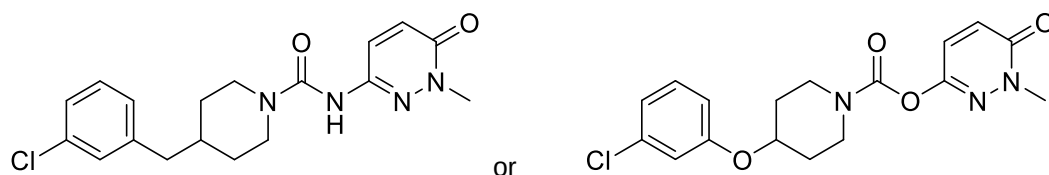
R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted C₁₋₆ alkyl;

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

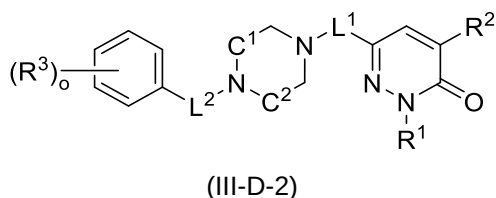
L¹ is -C(O)-X⁵- or optionally substituted C₅₋₁₀ heteroaryl;

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 a pharmaceutically acceptable salt thereof;
wherein the compound does not have the structure



5 8. The compound of claim 6, wherein the compound has the structure of formula (III-D-2):



wherein:

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

10 C¹ and C² optionally combine to form a bond;

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

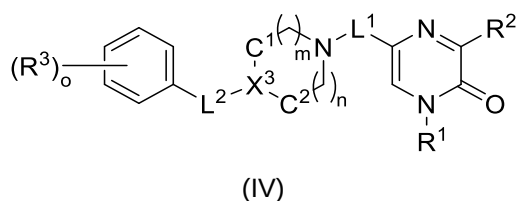
R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted C₁₋₆ alkyl;

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

15 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.

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



wherein:

m is 0 or 1;

n is 0, 1, or 2;

25 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;

30 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;

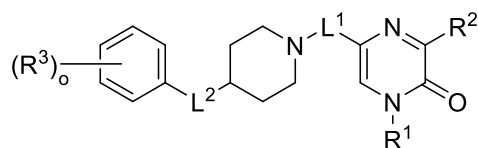
X⁵ is NH, O, or optionally substituted C₁₋₆ alkyl; and

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.

5

10. The compound of claim 9, wherein the compound has the structure of formula (IV-A):



(IV-A)

wherein:

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

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

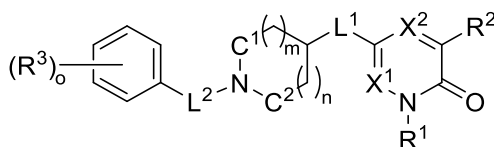
R³ is halo, cyano, C₁₋₆ perfluoroalkyl, optionally substituted C₁₋₆ alkoxy, or optionally substituted C₁₋₆ alkyl;

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

15 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.

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



(V)

wherein:

m is 0 or 1;

n is 0, 1, or 2;

25 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;

30 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;

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.

35

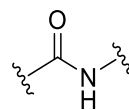
12. The compound of any one of claims 1 to 11, wherein R² is H or methyl.

13. The compound of any one of claims 1 to 11, wherein R¹ is H, methyl or ethyl.

14. The compound of any one of claims 1-3, 9 or 11, wherein m is 1.

5 15. The compound of any one of claims 1, 3, 9 or 11, wherein n is 1.

16. The compound of any one of claims 1 to 11, wherein L¹ is



17. The compound of any one of claims 1 to 11, wherein L² is O or optionally substituted C₁₋₆

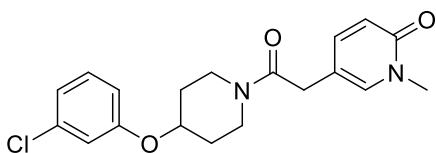
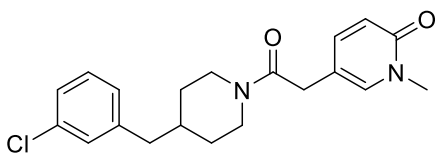
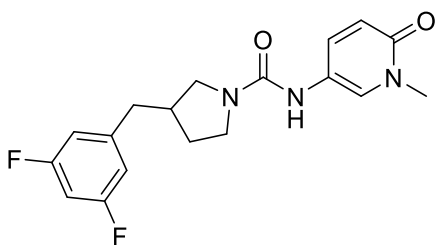
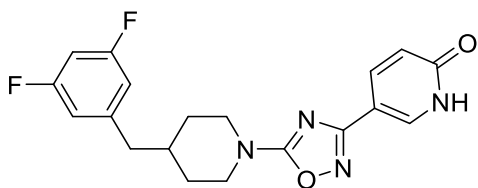
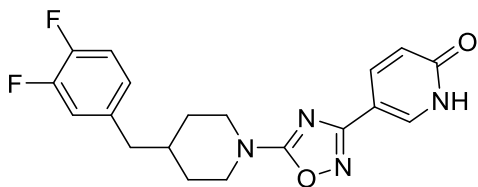
10 alkyl.

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

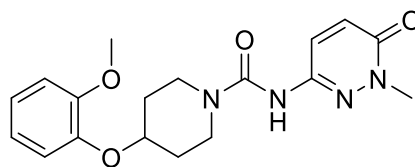
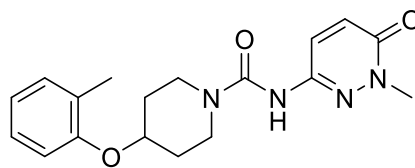
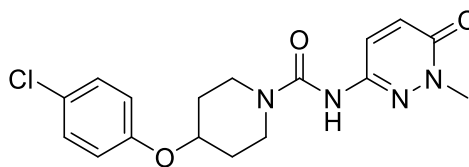
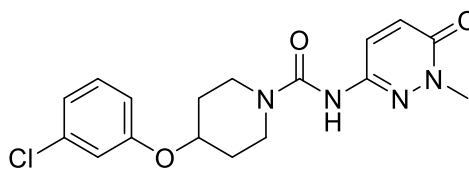
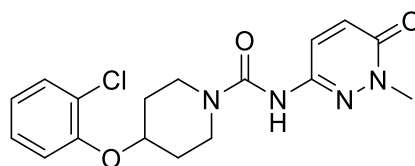
19. The compound of any one of claims 1 to 11, wherein R³ is halo.

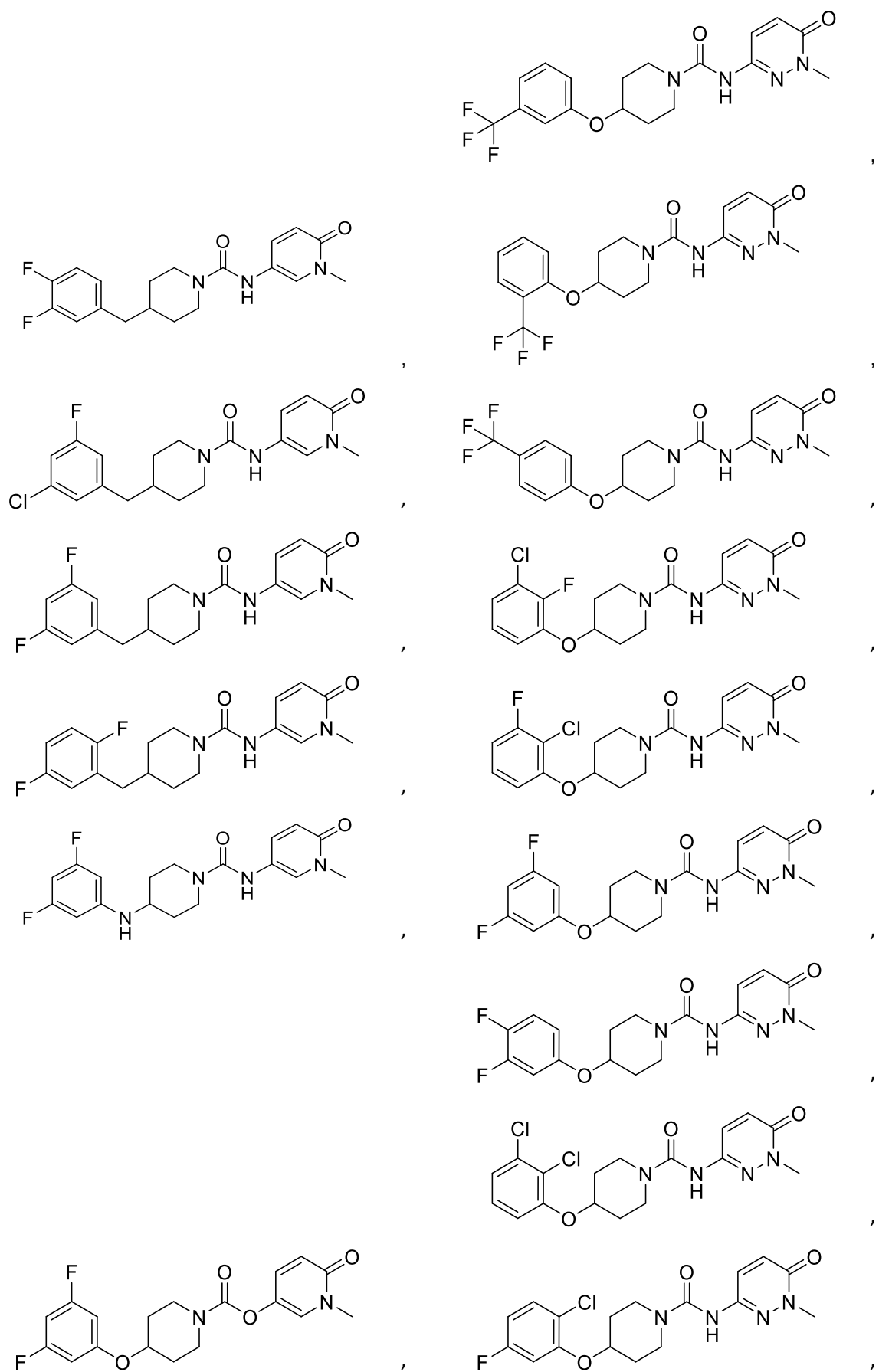
15 20. The compound of claim 1, wherein the compound is

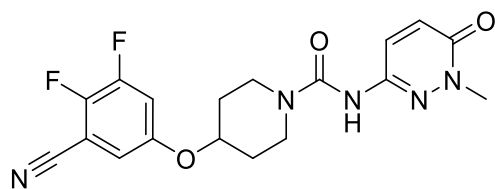
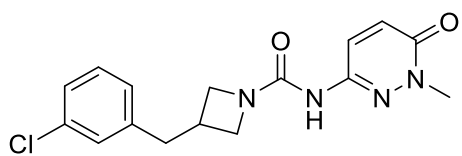
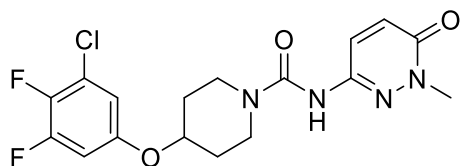
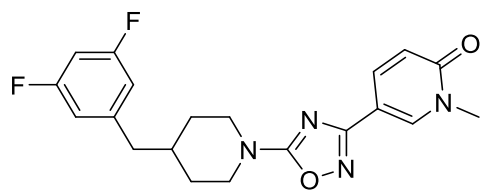
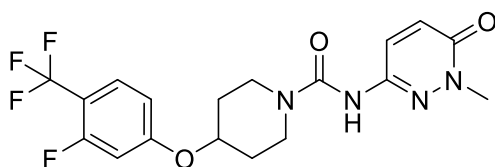
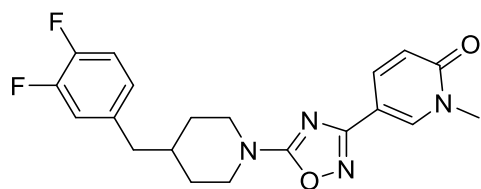
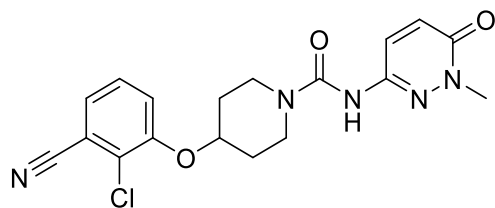
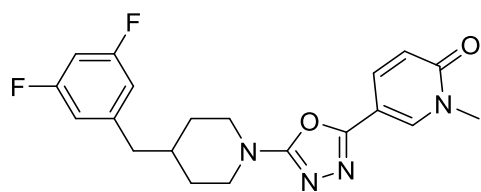
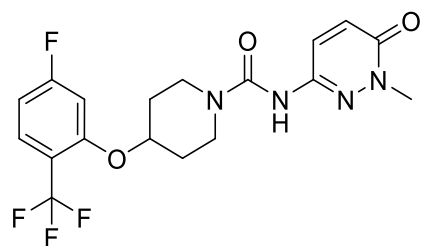
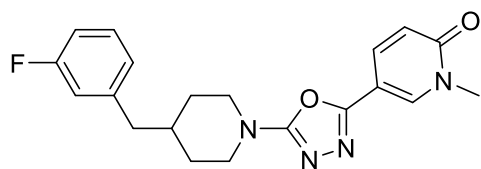
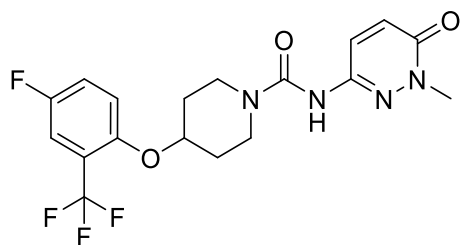
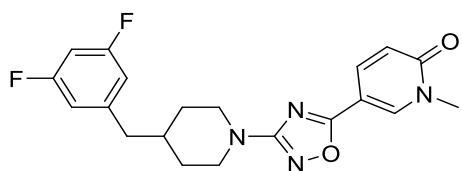
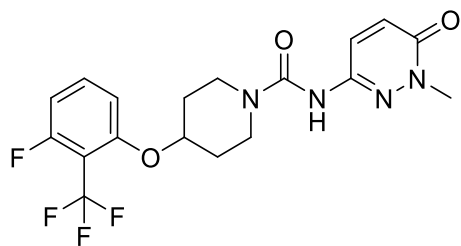
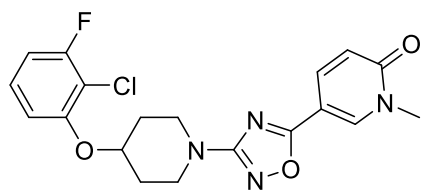
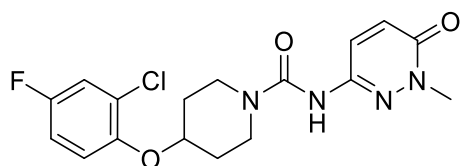
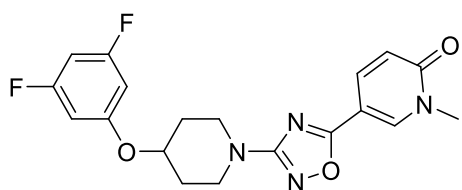
Compound

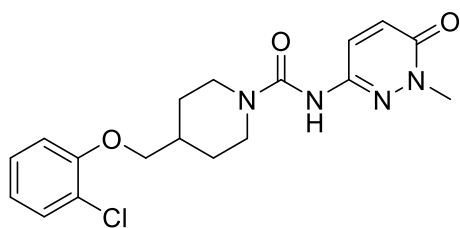
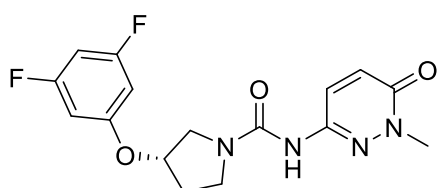
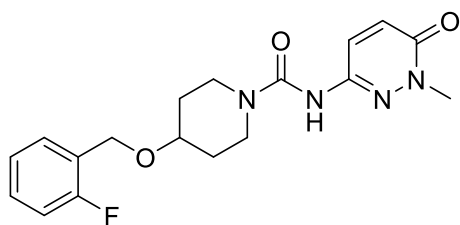
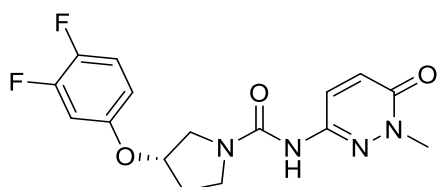
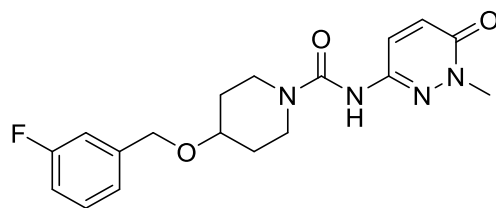
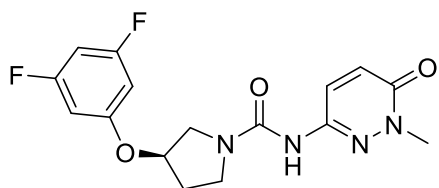
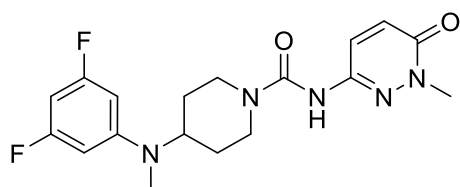
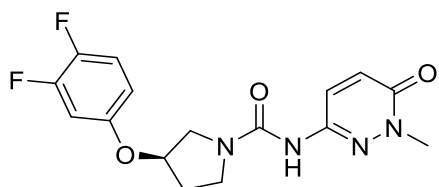
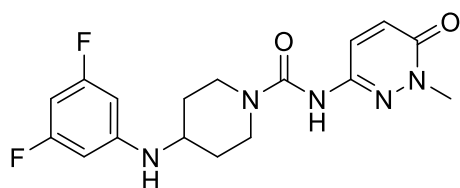
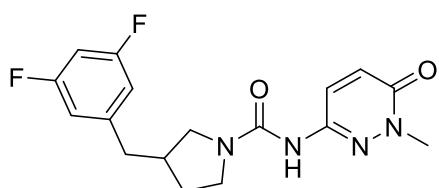
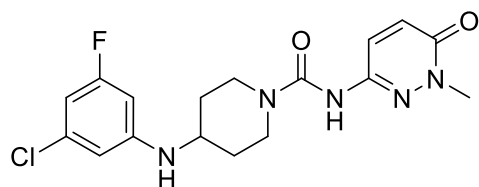
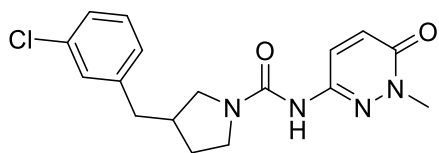
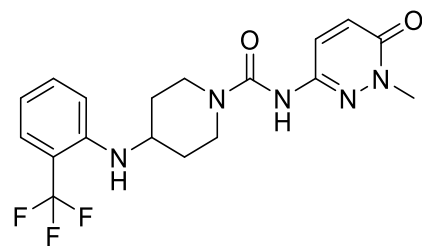
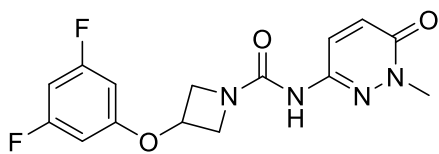
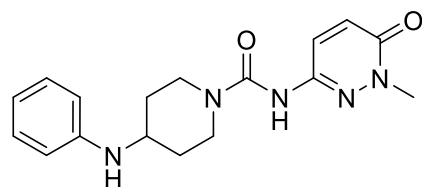
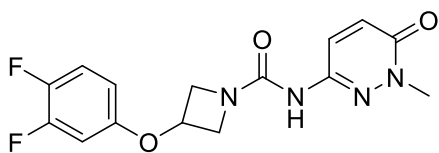


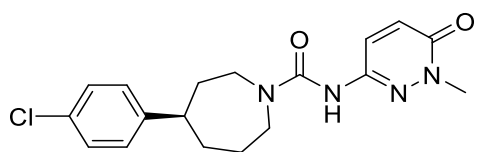
Compound



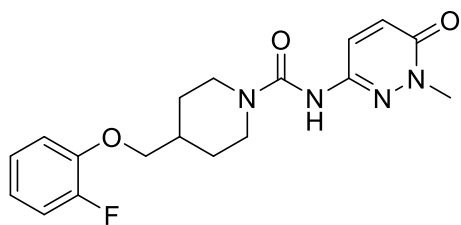




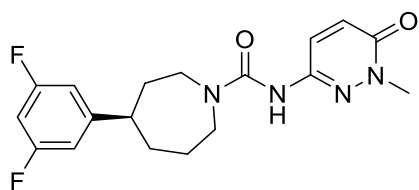




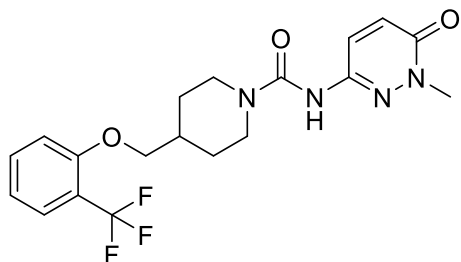
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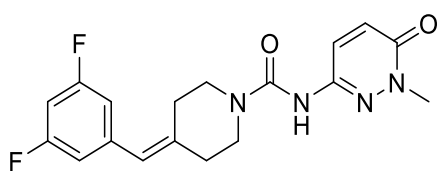
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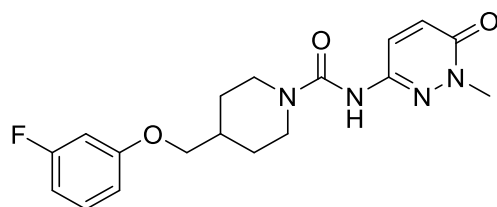
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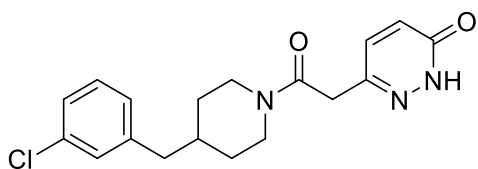
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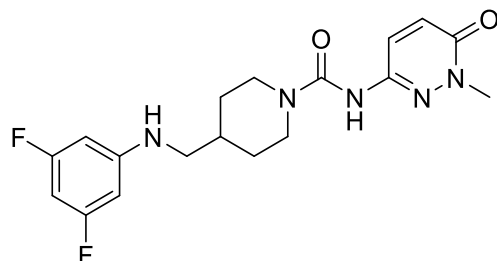
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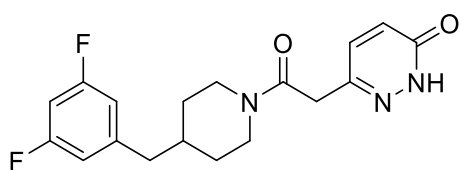
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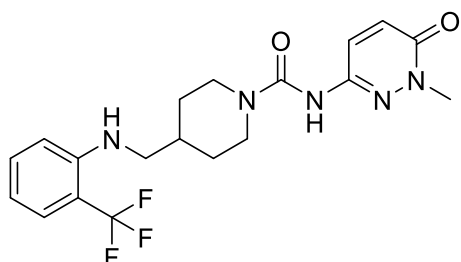
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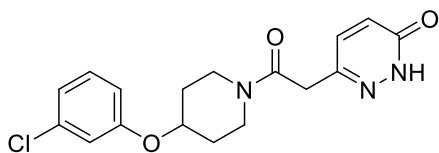
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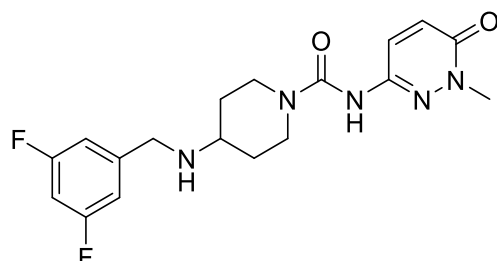
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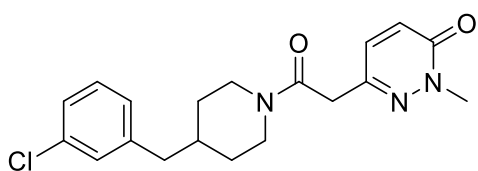
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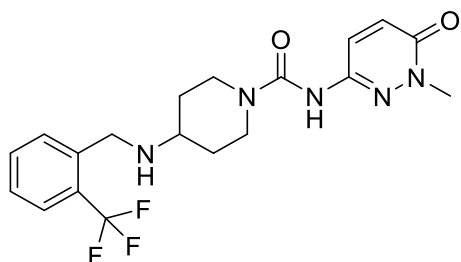
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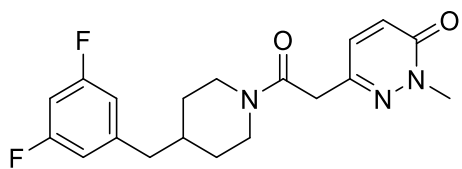
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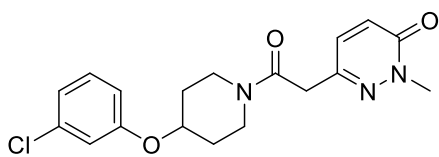
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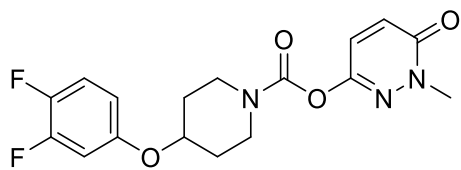
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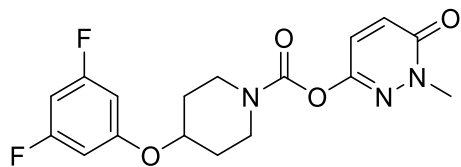
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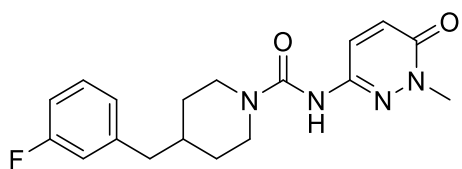
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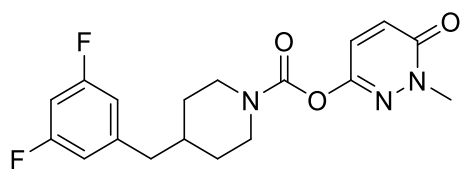
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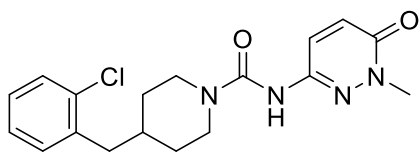
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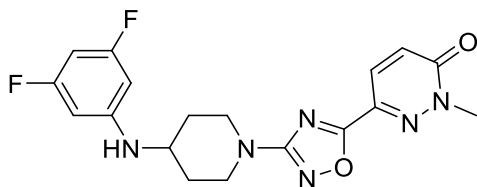
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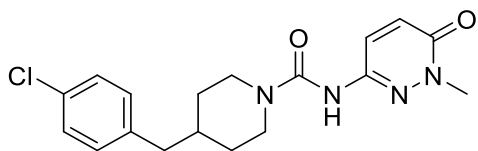
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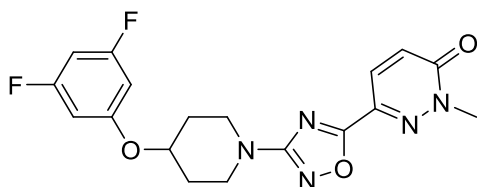
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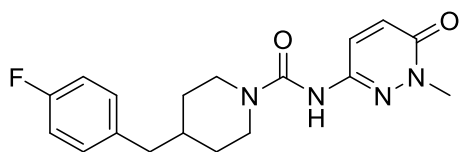
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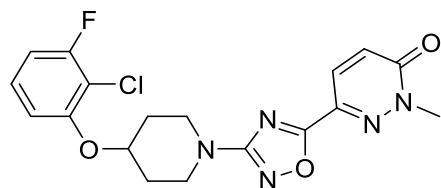
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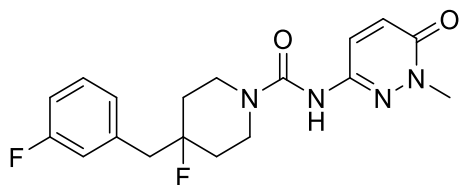
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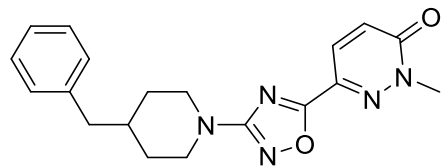
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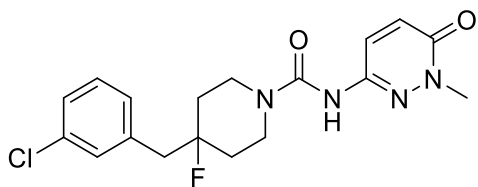
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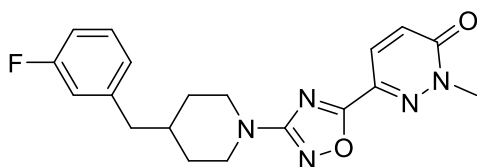
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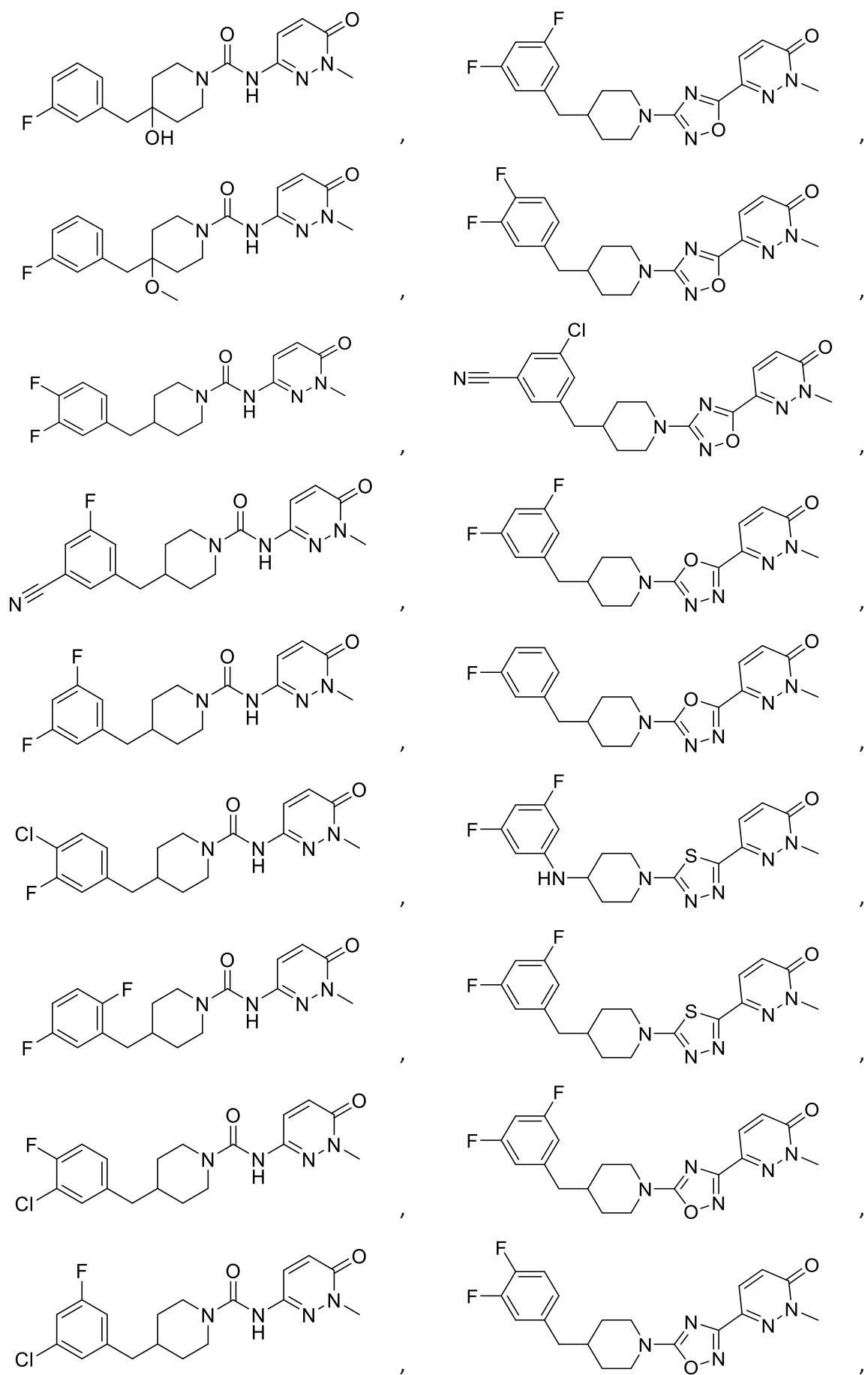
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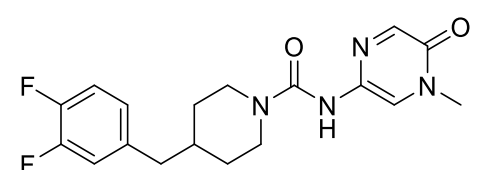
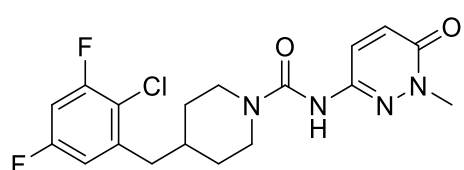
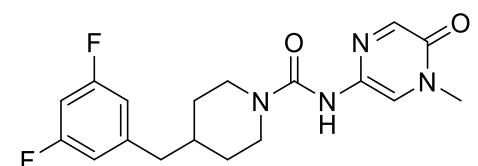
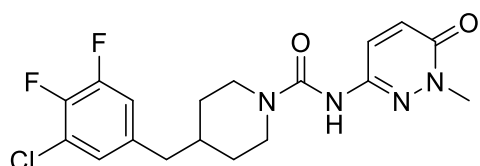
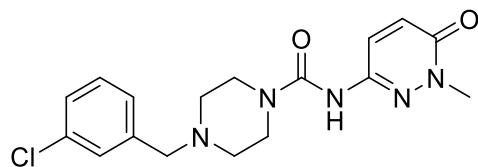
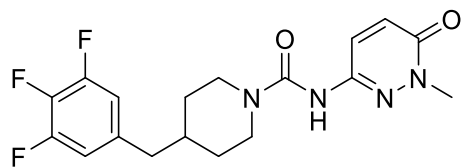
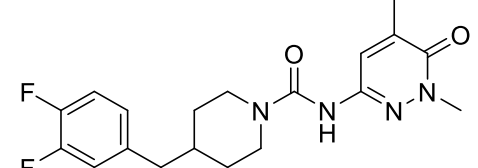
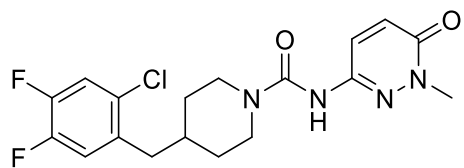
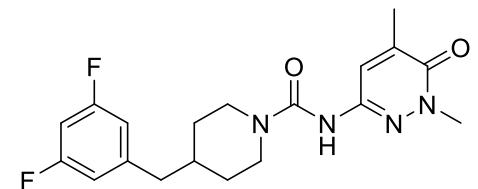
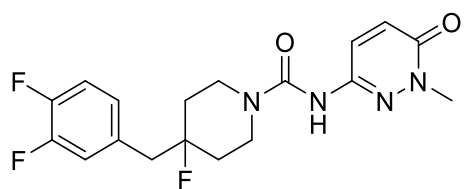
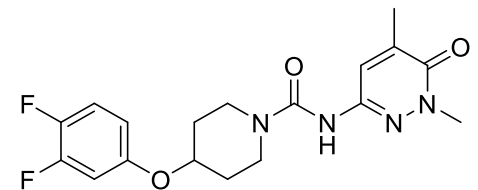
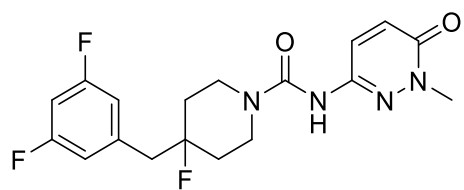
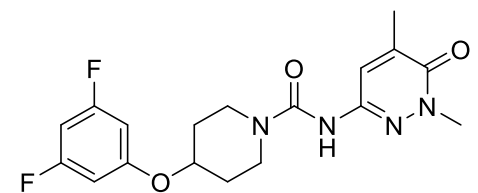
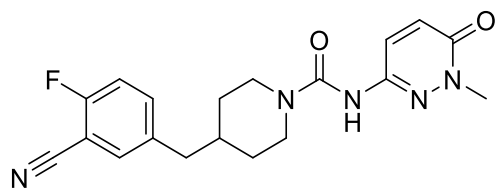
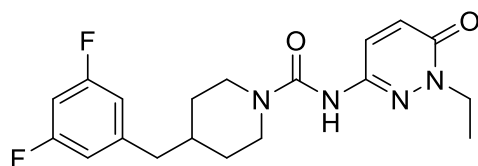
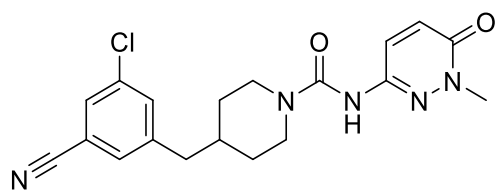
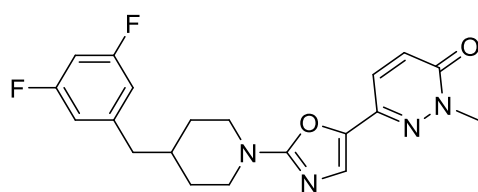
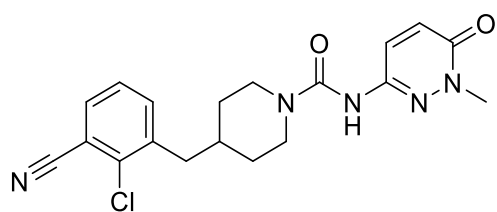


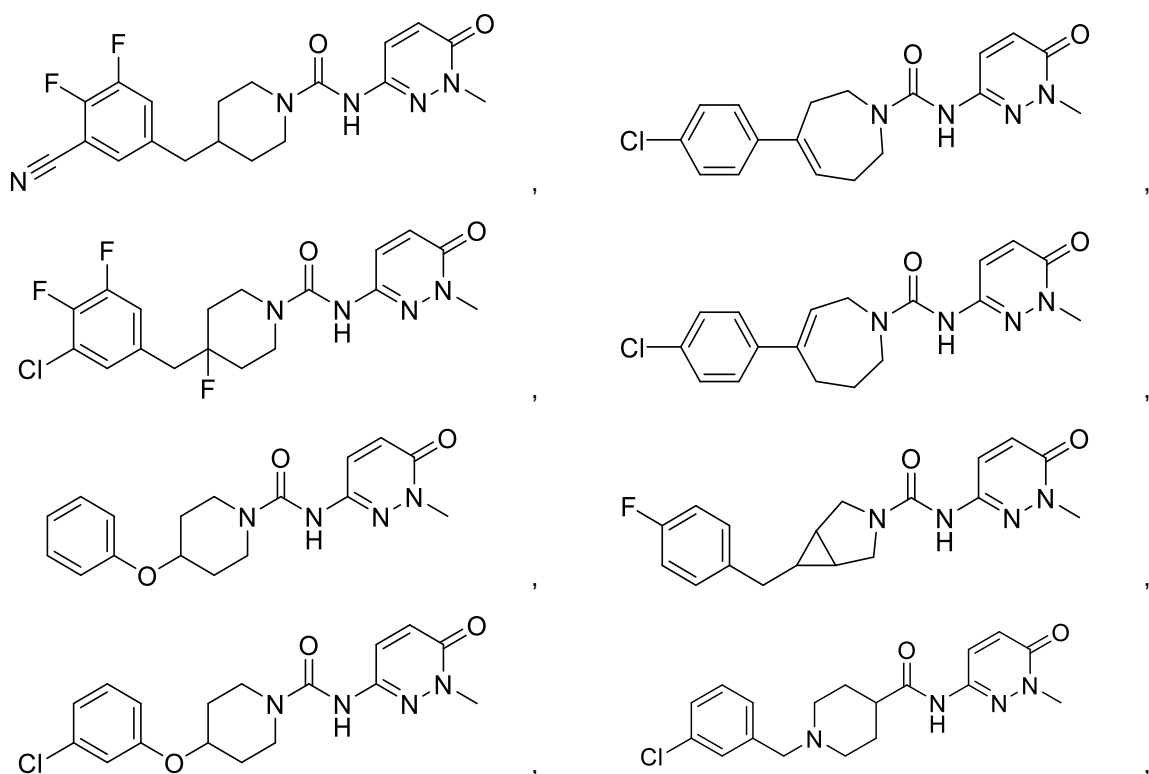
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or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition comprising a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 20, and a pharmaceutically acceptable excipient.

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

23. Use of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 20 or a pharmaceutical composition of claim 21 in the manufacture of a medicament for the treatment of a neurological disorder.

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24. 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 20.

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25. The method of claim 24, wherein the toxicity is α -synuclein-related toxicity or apolipoprotein E4 (ApoE4)-related toxicity.

20

26. The method of any one of claims 24-25, wherein the cell is a mammalian neural cell.

27. Use of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 20 or a pharmaceutical composition of claim 21 in the manufacture of a medicament for the treatment of a stearoyl-CoA desaturase (SCD) associated disorder.

25

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.

5

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.

10 30. Use of a compound of any one of claims 1-20 or a pharmaceutical composition of claim 21 in the manufacture of medicament for the treatment of primary brain cancer.

31. The use of claim 30, wherein the primary brain cancer is a glioma.

15 32. The use of claim 31, wherein the glioma is an astrocytoma.

33. The use of claim 32, wherein the astrocytoma is a glioblastoma.

20 34. The use of any one of claims 30-33, wherein the cancer is determined or predicted to be resistant to one or more chemotherapeutic agents.

35. The use of any one of claims 30-34, wherein the cancer has failed to respond to one or more chemotherapeutic agents.

25 36. The use of claims 34-35, wherein one or more therapeutic agents is selected from the group of temozolomide, carmustine, bevacizumab, lomustine, everolimus, vincristine, or procarbazine.

37. The use of claim 36, wherein one or more therapeutic agents is temozolomide.

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

39. The use of claim 38, wherein one or more additional therapeutic interventions comprises surgery, radiation, and/or one or more additional chemotherapeutic agents.

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