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.

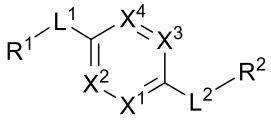
Further, cancers of the brain and nervous system are among the most difficult to treat. Prognosis for patients with these cancers depends on the type and location of the tumor as well as its stage of development. For many types of brain cancer, average life expectancy after symptom onset may be months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

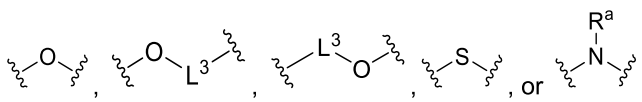
In an example, this disclosure features a compound having the structure of **Formula I**:



Formula I,

where

R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heteroaryl, or optionally substituted C_2-C_9 heterocyclyl;

L^1 is optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_2-C_6 alkenylene, optionally substituted C_2-C_6 alkynylene, optionally substituted C_3-C_6 carbocyclylene, 

;

R^a is H or optionally substituted C_1-C_6 alkyl;

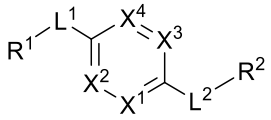
L^3 is optionally substituted C_2-C_9 heterocyclylene;

each of X^1, X^2, X^3, and X^4 is, independently, N or CH;

L^2 is optionally substituted C_1-C_6 alkylene or optionally substituted C_1-C_6 heteroalkylene; and

R^2 is optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl, or a pharmaceutically acceptable salt thereof.

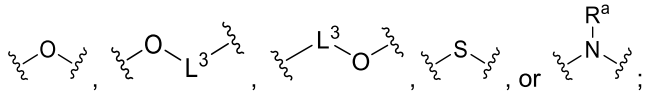
In an aspect, there is provided the use of a compoundhaving the structure of **Formula I**:



Formula I,

wherein

R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heteroaryl, or optionally substituted C_2-C_9 heterocyclyl;

L^1 is optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_2-C_6 alkenylene, optionally substituted C_2-C_6 alkynylene, optionally substituted C_3-C_6 carbocyclylene,  ;

R^a is H or optionally substituted C_1-C_6 alkyl;

L^3 is optionally substituted C_2-C_9 heterocyclylene;

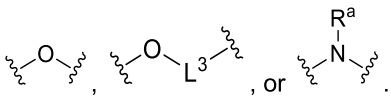
each of X^1, X^2, X^3, and X^4 is, independently, N or CH;

L^2 is optionally substituted C_1-C_6 alkylene or optionally substituted C_1-C_6 heteroalkylene; and

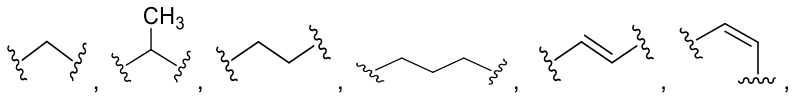
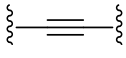
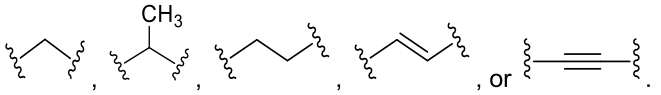
R^2 is optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl,

or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for the treatment of a primary brain cancer in a subject in need thereof.

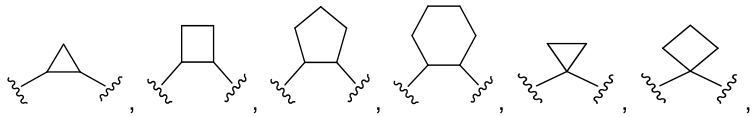
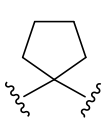
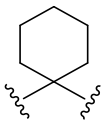
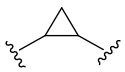
In some examples, L^1 is optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_2-C_6 alkenylene, optionally substituted C_2-C_6 alkynylene, optionally substituted C_3-C_6 carbocyclylene,  .

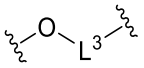
In some examples, L^1 is optionally substituted C_1-C_6 alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene.

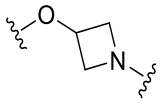
In some examples, L^1 is  , or  . In some embodiments, L^1 is  , or .

In some examples, L^1 is  .

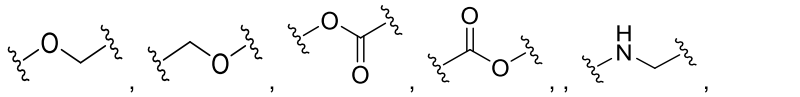
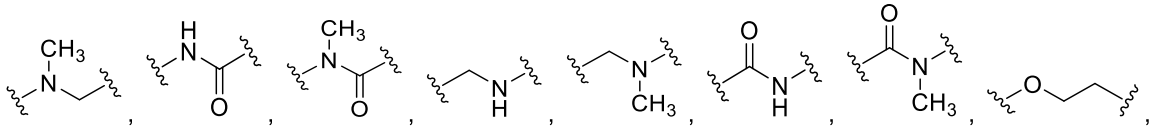
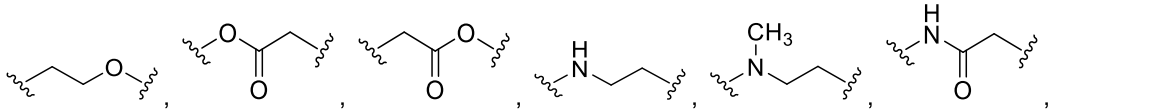
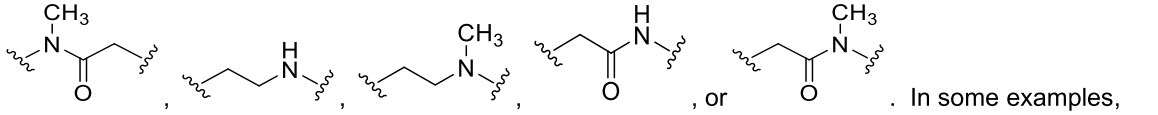
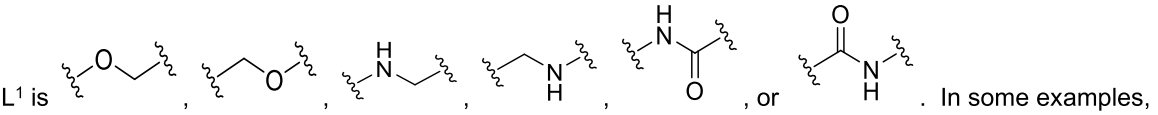
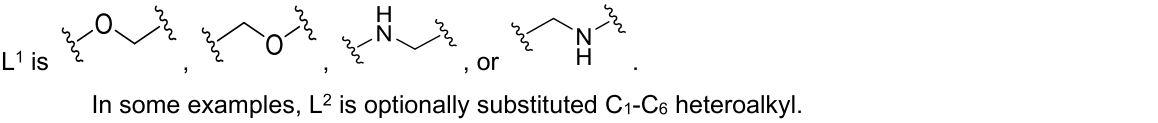
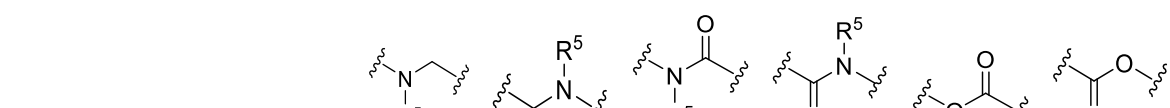
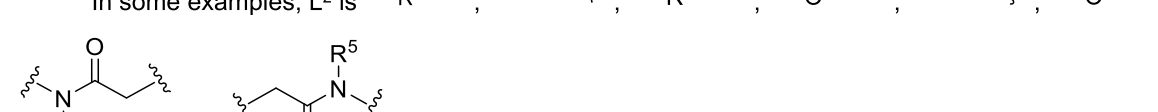
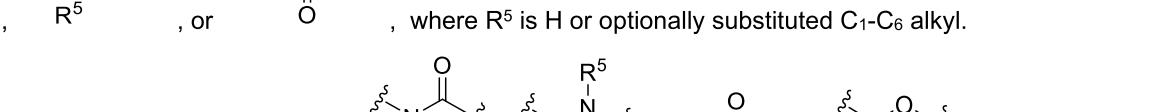
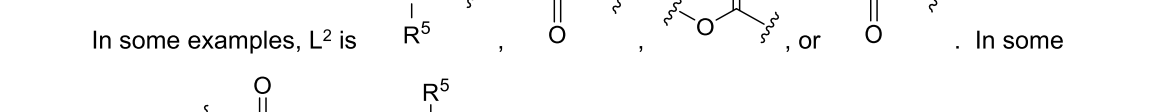
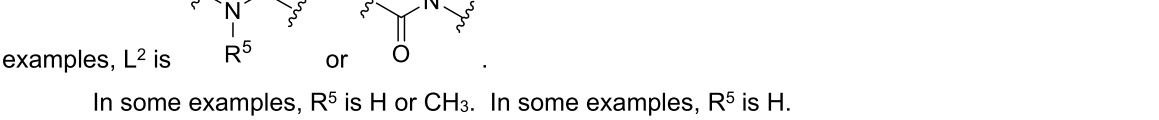
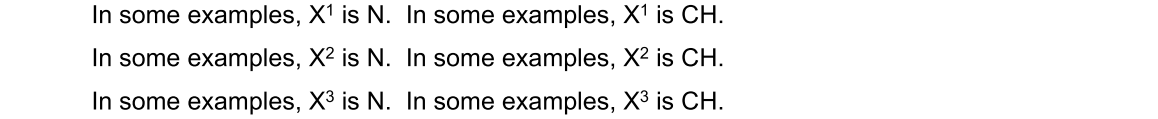
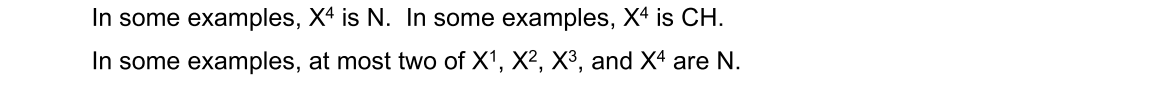
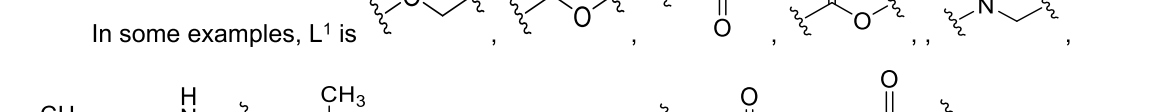
In some examples, L^1 is optionally substituted C_3-C_6 carbocyclylene.

In some examples, L^1 is  ,  , or  . In some examples, L^1 is  or  .

In some examples, L^1 is  . In some examples, L^1 is  . In some examples, L^1 is  .

In some examples, L^1 is  or  . In some examples, L^1 is  .

In some examples, L^1 is optionally substituted C_1-C_6 heteroalkylene.

In some examples, L^1 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ,  , or . In some examples, L^1 is  ,  , , , , or . In some examples, L^1 is , , , or .

In some examples, L^2 is optionally substituted C_1-C_6 heteroalkyl.

In some examples, L^2 is , , , or , where R^5 is H or optionally substituted C_1-C_6 alkyl.

In some examples, L^2 is , , or . In some examples, L^2 is , , or .

In some examples, R^5 is H or CH_3. In some examples, R^5 is H.

In some examples, X^1 is N. In some examples, X^1 is CH.

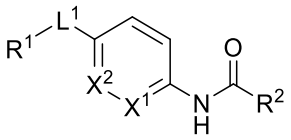
In some examples, X^2 is N. In some examples, X^2 is CH.

In some examples, X^3 is N. In some examples, X^3 is CH.

In some examples, X^4 is N. In some examples, X^4 is CH.

In some examples, at most two of X^1, X^2, X^3, and X^4 are N.

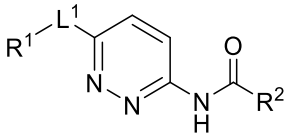
In some examples, the compound has the structure of **Formula Ia**:



Formula Ia,

or a pharmaceutically acceptable salt thereof.

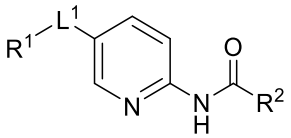
In some examples, the compound has the structure of **Formula Ib**:



Formula Ib,

or a pharmaceutically acceptable salt thereof.

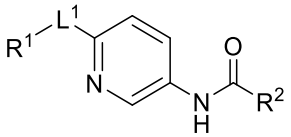
In some examples, the compound has the structure of **Formula Ic**:



Formula Ic,

or a pharmaceutically acceptable salt thereof.

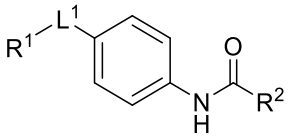
In some examples, the compound has the structure of **Formula Id**:



Formula Id,

or a pharmaceutically acceptable salt thereof.

In some examples, the compound has the structure of **Formula Ie**:



Formula Ie,

or a pharmaceutically acceptable salt thereof.

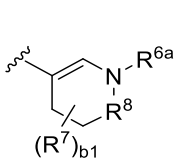
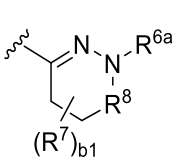
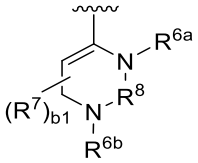
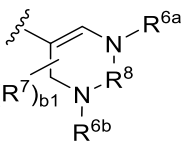
In some examples, R^2 is optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl.

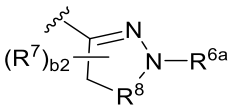
In some examples, R^2 is optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl.

In some examples, R^2 is optionally substituted C_2-C_9 heterocyclyl or optionally substituted C_2-C_9 heteroaryl.

In some examples, R^2 is optionally substituted C_2-C_9 heterocyclyl.

In some examples, R^2 is optionally substituted C_2-C_5 heterocyclyl.

In some examples, R^2 is  ,  ,  , 

, or  ,

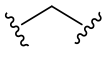
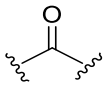
where b1 is 0, 1, 2, 3, or 4;

b2 is 0, 1, or 2;

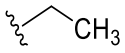
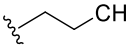
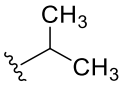
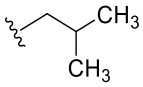
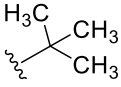
R^{6a} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 carbocyclyl;

R^{6b} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 carbocyclyl;

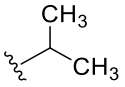
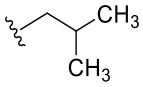
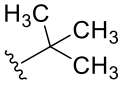
each R^7 is, independently, halo or optionally substituted C_1-C_6 alkyl; and

R^8 is  or  .

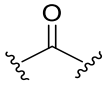
In some examples, R^{6a} is H or optionally substituted C_1-C_6 alkyl.

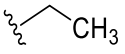
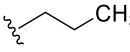
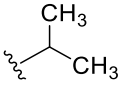
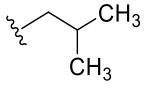
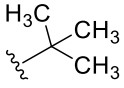
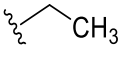
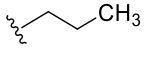
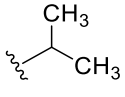
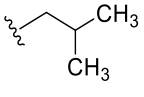
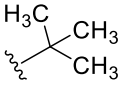
In some examples, R^{6a} is H,  ,  ,  ,  ,  , or  . In some examples, R^{6a} is H or  .

In some examples, R^{6b} is H or optionally substituted C_1-C_6 alkyl.

In some examples, R^{6b} is H, , , ,  ,  , or  .

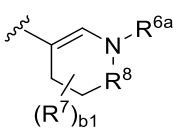
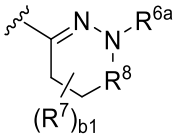
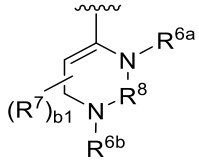
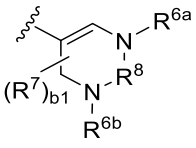
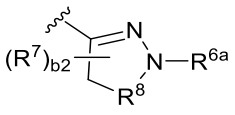
In some examples, R^{6b} is H or  .

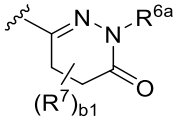
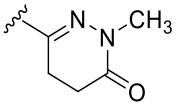
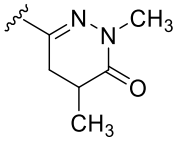
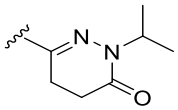
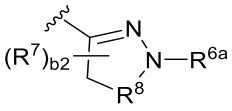
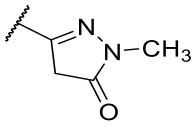
In some examples, R^8 is  .

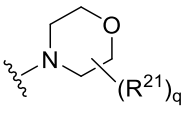
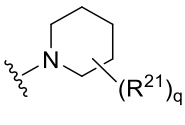
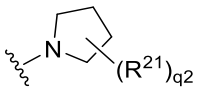
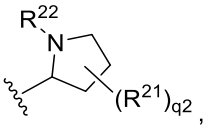
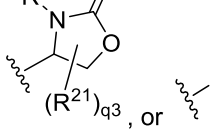
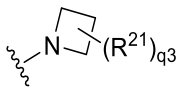
In some examples, each R^7 is, independently, F, Cl, Br, I,  ,  ,  ,  ,  , or  . In some examples, each R^7 is, independently,  ,  ,  ,  ,  , or  .

In some examples, b1 is 0 or 1. In some examples, b1 is 0. In some examples, b1 is 1.

In some examples, b2 is 0 or 1. In some examples, b2 is 0. In some examples, b2 is 1.

In some examples, R^2 is  . In some examples, R^2 is  . In some examples,  ,  . In some examples, R^2 is  .

In some examples, R^2 is  . In some examples, R^2 is  ,  , or  . In some examples, R^2 is  . In some examples, R^2 is  .

In some examples, R^2 is  ,  ,  ,  ,  , or  ,

where

q1 is 0, 1, 2, 3, 4, 5, or 6;

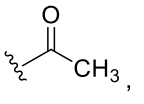
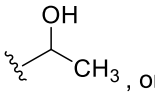
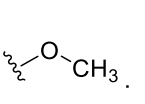
q2 is 0, 1, 2, 3, or 4;

q3 is 0, 1, or 2;

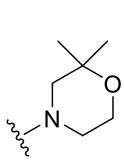
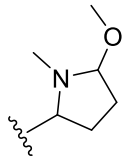
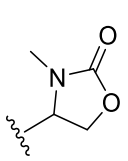
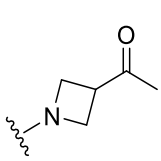
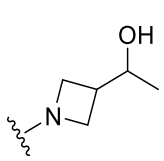
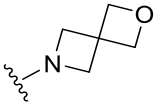
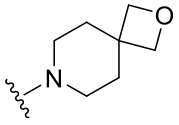
each R^{21} is, independently, hydroxyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl; or two of the R^{21} groups, taken together with the carbon atom to which each is

attached, combine to form an optionally substituted C_3-C_{10} carbocyclyl or optionally substituted C_2-C_9 heterocyclyl; and

R^{22} is H or optionally substituted C_1-C_6 alkyl.

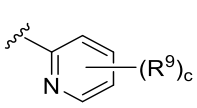
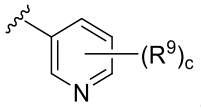
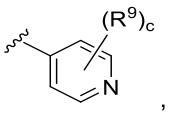
In some examples, each R^{21} is, independently,  ,  , or  .

In some examples, R^{22} is H or  .

In some examples, R^2 is  ,  ,  ,  ,  ,  , or  .

In some examples, R^2 is optionally substituted C_2-C_9 heteroaryl.

In some examples, R^2 is optionally substituted C_2-C_5 heteroaryl.

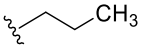
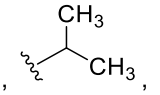
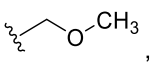
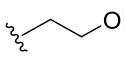
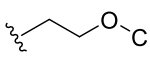
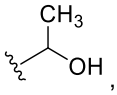
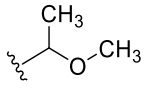
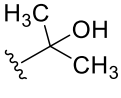
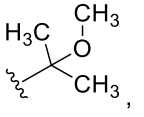
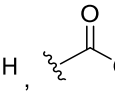
In some examples, R^2 is  ,  , or  ,

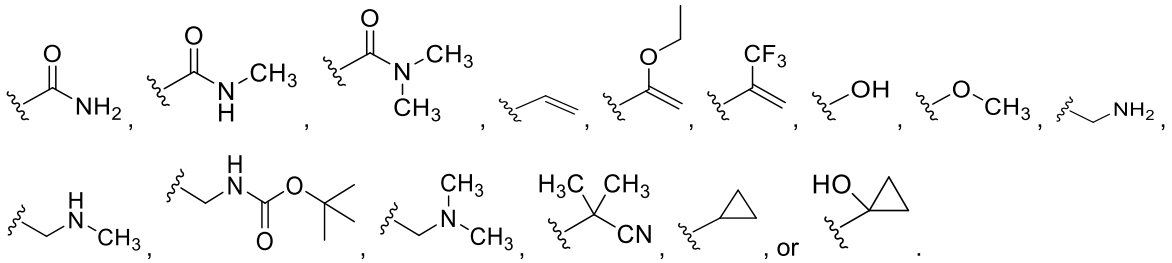
where

c is 0, 1, 2, 3, or 4; and

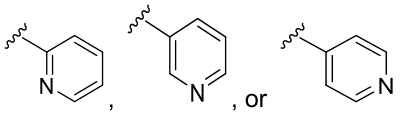
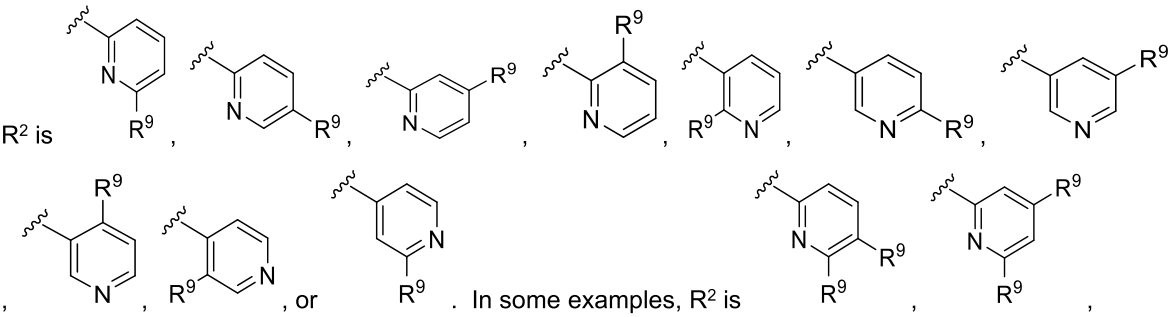
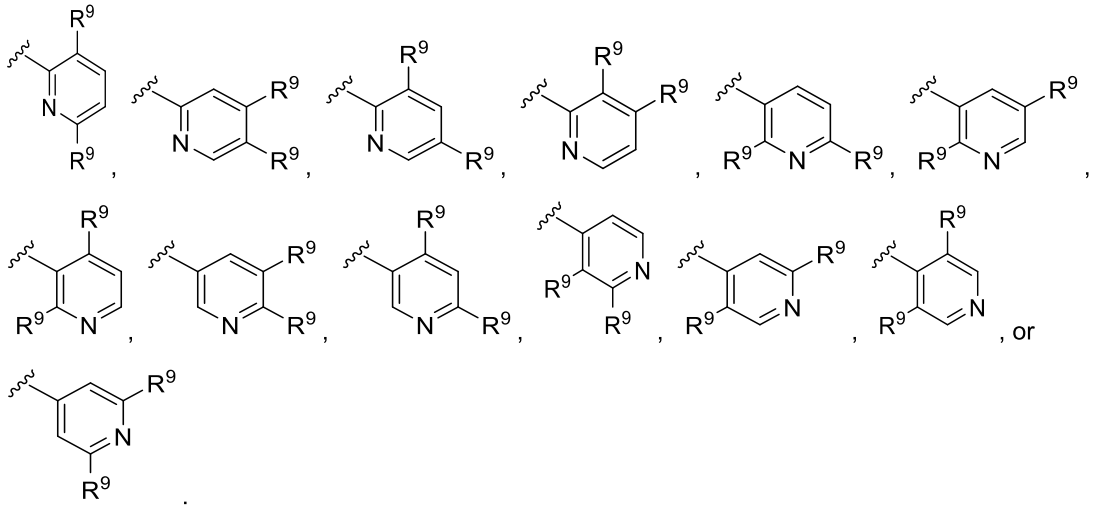
each R^9 is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2.

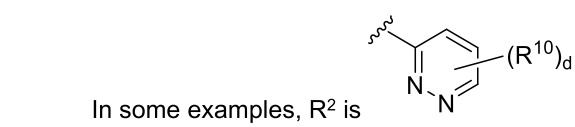
In some examples, each R^9 is, independently, halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, OH, or NH_2.

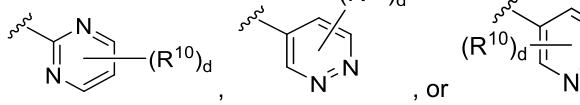
In some examples, each R^9 is, independently, F, Cl, Br, I, CN,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .



In some examples, c is 0, 1, or 2. In some examples, c is 0. In some examples, c is 1. In some examples, c is 2.

In some examples, R^2 is  . In some examples, R^2 is  . In some examples, R^2 is  .

In some examples, R^2 is  .

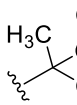
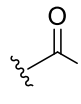
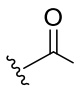
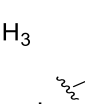
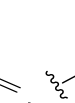
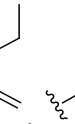
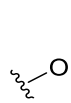
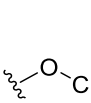
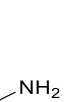
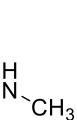
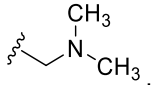
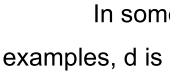
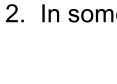
In some examples, R^2 is  .

where

d is 0, 1, 2, or 3; and

each R^{10} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2.

In some examples, each R^{10} is, independently, halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, OH, or NH_2.

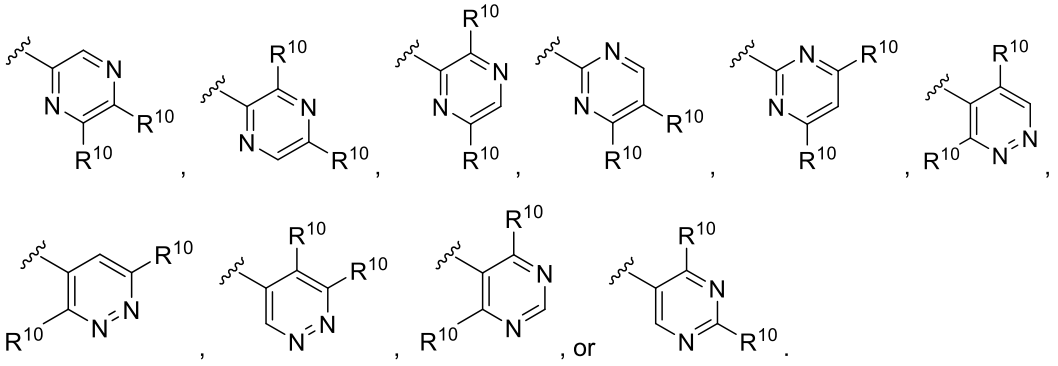
In some examples, each R^{10} is , independently, F, Cl, Br, I, CN,  , , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , , ,  ,  ,  ,  , or .

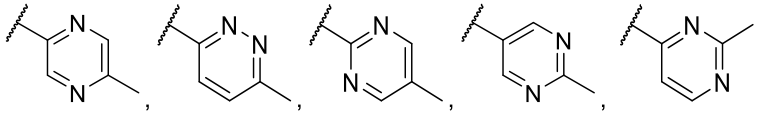
In some examples, d is 0, 1, or 2. In some examples, d is 0. In some examples, d is 1. In some examples, d is 2.

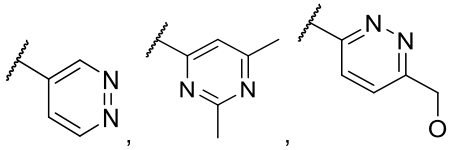
In some examples, R^2 is , , , , , or .

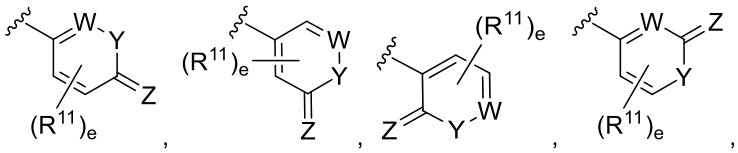
In some examples, R^2 is , , , , , , , , , , , , , , , , or . In some examples, R^2 is ,

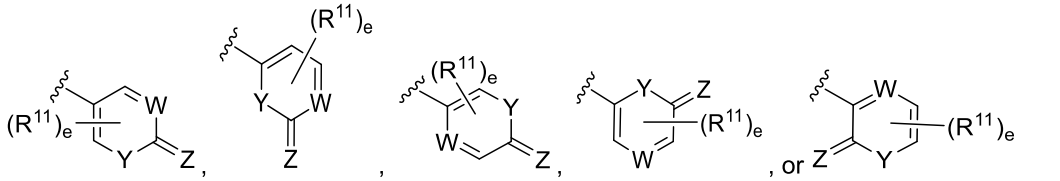
, , , , ,



In some examples, R^2 



In some examples, R^2 



where

e is 0, 1, or 2;

each R^{11} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2.

W is CH or N;

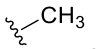
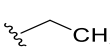
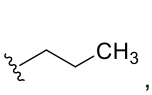
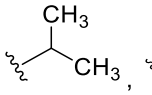
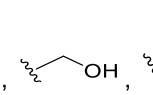
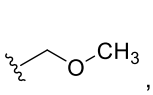
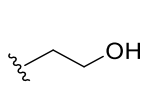
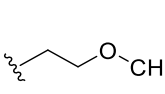
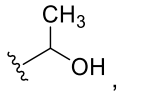
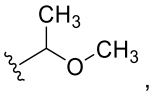
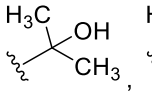
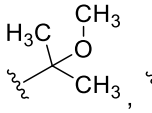
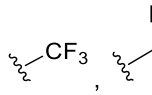
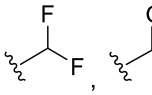
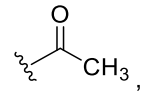
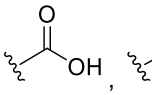
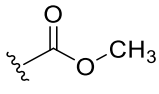
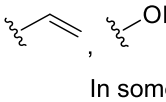
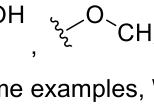
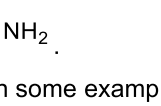
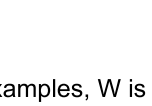
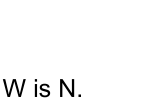
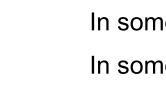
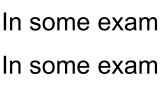
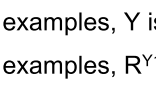
Y is O, S, or NR^{Y1};

R^{Y1} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, or optionally substituted C_2-C_9 heterocyclyl;

Z is O, S, or NR^{Z1}; and

R^{Z1} is H or optionally substituted C_1-C_6 alkyl.

In some examples, each R^{11} is, independently, halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, OH, or NH_2.

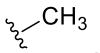
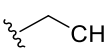
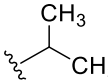
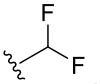
In some examples, each R^{11} is, independently, F, Cl, Br, I, CN,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ,  ,  , ,  ,  ,  , , ,  ,  ,  , .

In some examples, W is CH. In some examples, W is N.

In some examples, Y is NR^{Y1}.

In some examples, R^{Y1} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_{10} carbocyclyl.

In some examples, R^{Y1} is H. In some examples, R^{Y1} is optionally substituted C_1-C_6 alkyl.

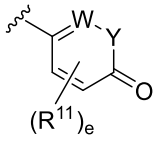
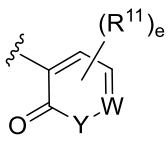
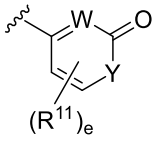
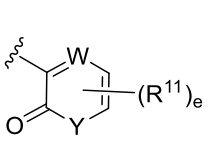
In some examples, R^{Y1} is  ,  ,  , or  .

In some examples, R^{Y1} is optionally substituted C_3-C_{10} carbocyclyl.

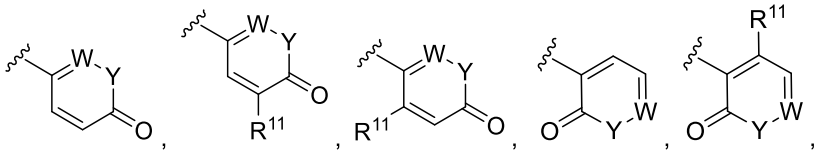
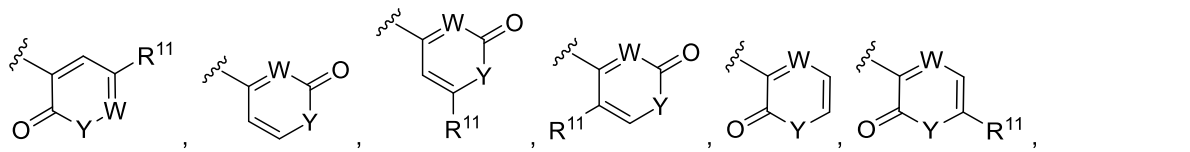
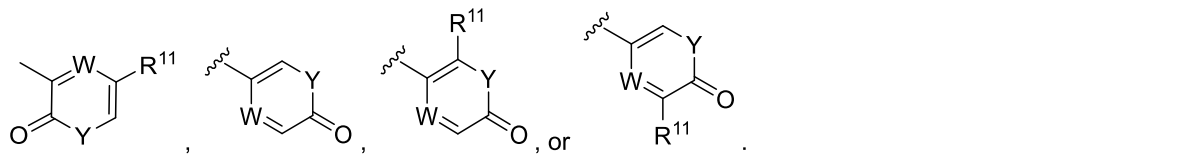
In some examples, R^{Y1} is optionally substituted C_3-C_6 carbocyclyl.

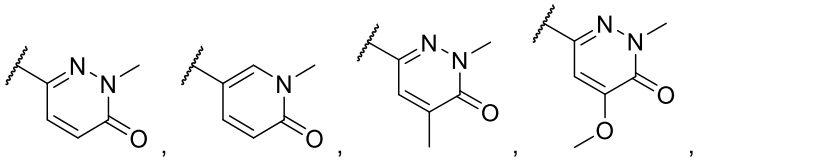
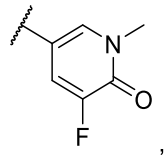
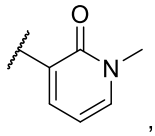
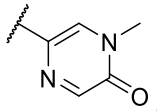
In some examples, R^{Y1} is  or  .

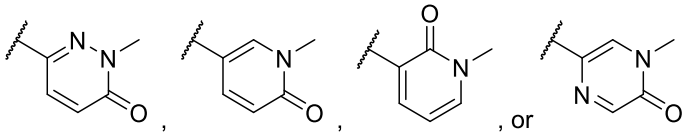
In some examples, Z is O.

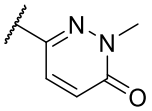
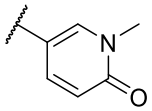
In some examples, R^2 is  ,  ,  ,  , or .

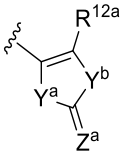
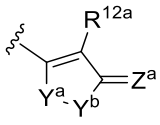
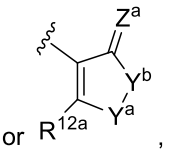
In some examples, e is 0 or 1. In some examples, e is 0. In some examples, e is 1.

In some examples, R^2 is  ,  ,  , or .

In some examples, R^2 is  ,  ,  , or  .

In some examples, R^2 is  , , or .

In some examples, R^2  or  .

In some examples, R^2 is  ,  , or 

where

R^{12a} is H, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2;

each of Y^a and Y^b is, independently, O, S, or NR^{Y2};

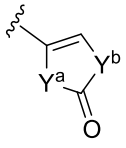
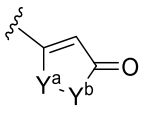
R^{Y2} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, or optionally substituted C_2-C_9 heterocyclyl;

Z^a is O, S, or NR^{Z2}; and

R^{Z2} is H or optionally substituted C_1-C_6 alkyl.

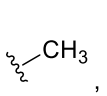
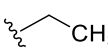
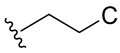
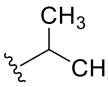
In some examples, R^{12a} is H.

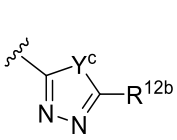
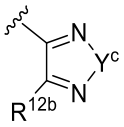
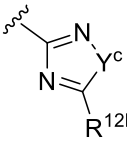
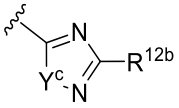
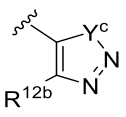
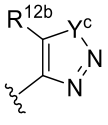
In some examples, Z^a is O.

In some examples, R^2 is  or  .

In some examples, each of Y^a and Y^b is NR^{Y2}.

In some examples, R^{Y2} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_{10} carbocyclyl.

In some examples, R^{Y2} is H,  ,  ,  ,  ,  ,  , or  .

In some examples, R^2 is  ,  ,  ,  ,  ,  ,

where

R^{12b} is H, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2; and

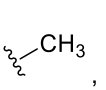
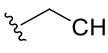
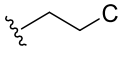
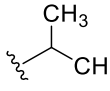
Y^c is O, S, or NR^{Y3};

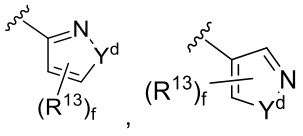
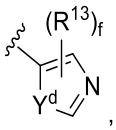
R^{Y3} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, or optionally substituted C_2-C_9 heterocyclyl.

In some examples, R^{12b} is H.

In some examples, Y^c is NR^{Y3}.

In some examples, R^{Y3} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_{10} carbocyclyl.

In some examples, R^{Y3} is H,  ,  ,  ,  ,  ,  , or  .

In some examples, R^2 is  , , , , , or  ,

where

f is 0, 1, or 2;

each R^{13} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2; and

Y^d is O, S, or NR^{Y4};

R^{Y4} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, or optionally substituted C_2-C_9 heterocyclyl.

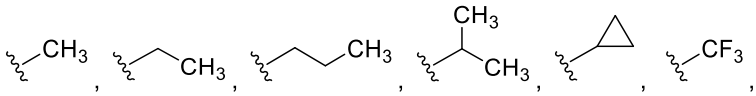
In some examples, each R^{13} is, independently, halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, OH, or NH_2.

In some examples, each R^{13} is, independently, halo, CN, or optionally substituted C_1-C_6 alkyl.

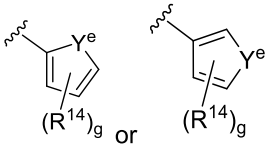
In some examples, f is 0 or 1. In some examples, f is 0. In some examples, f is 1.

In some examples, Y^d is NR^{Y4}.

In some examples, R^{Y4} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_{10} carbocyclyl.

In some examples, R^{Y4} is H,  , or  .

In some examples, Y^d is O.

In some examples, R^2 is  or ,

where

g is 0, 1, 2, 3, or 4;

each R^{14} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2;

Y^e is O, S, or NR^{Y5}; and

R^{Y5} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, or optionally substituted C_2-C_9 heterocyclyl.

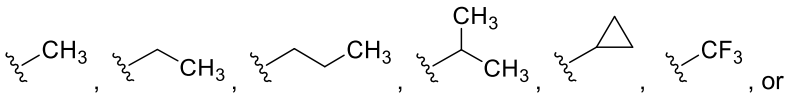
In some examples, R^{14} is halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, OH, or NH_2.

In some examples, R^{14} is halo, CN, or optionally substituted C_1-C_6 alkyl.

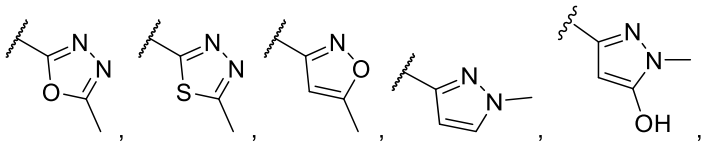
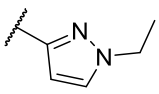
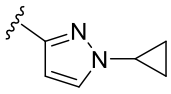
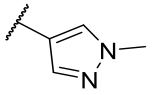
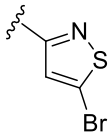
In some examples, g is 0, 1, or 2. In some examples, g is 0. In some examples, g is 1. In some examples, g is 2.

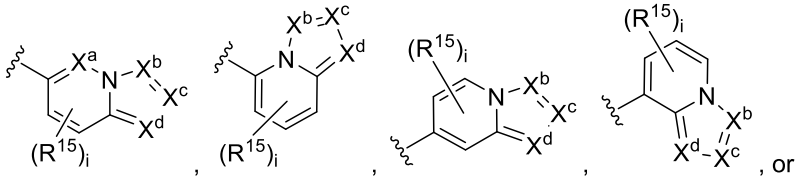
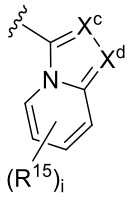
In some examples, Y^e is NR^{Y5}.

In some examples, R^{Y5} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_{10} carbocyclyl.

In some examples, R^{Y5} is  , or  .

In some examples, Y^e is O. In some examples, Y^e is S.

In some examples, R^2 is  ,  ,  ,  , or  .

In some examples, R^2 is  , or  ,

where

each of X^a, X^b, X^c, and X^d is, independently, N or CR^{17};

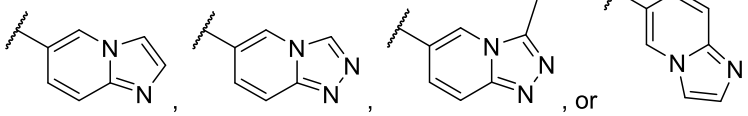
each R^{17} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2;

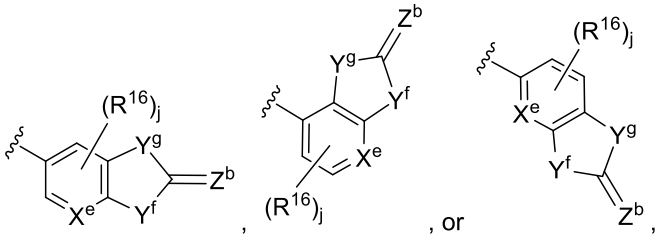
i is 0, 1, 2, or 3; and

each R^{15} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2.

In some examples, each R^{15} is, independently, halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, SH, OH, or NH_2.

In some examples, i is 0 or 1. In some examples, i is 0. In some examples, i is 1.

In some examples, R^2 is  .

In some examples, R^2 is  , where

X^e is N or CR^{18};

R^{18} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2;

j is 0, 1, or 2;

each R^{16} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2;

each of Y^f and Y^g is, independently, O, S, or NR^{Y6};

R^{Y6} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, or optionally substituted C_2-C_9 heterocyclyl;

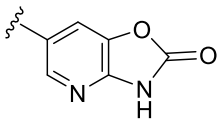
Z^b is O, S, or NR^{Z3}; and

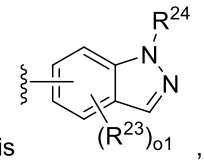
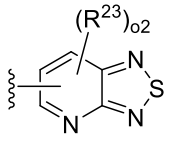
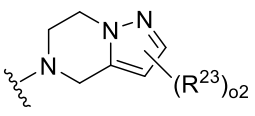
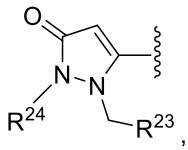
R^{Z3} is H or optionally substituted C_1-C_6 alkyl.

In some examples, each R^{16} is, independently, halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, SH, OH, or NH_2.

In some examples, j is 0 or 1. In some examples, j is 0. In some examples, j is 1.

In some examples, Z is O.

In some examples, R^2 is  .

In some examples, R^2 is  ,  ,  , or  ,

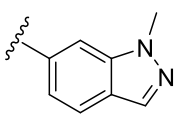
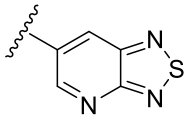
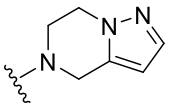
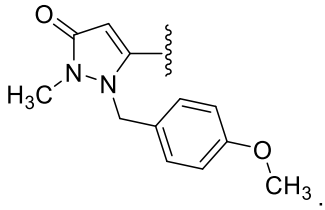
where

o1 is 0, 1, 2, or 3;

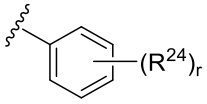
o2 is 0, 1, or 2;

each R^{23} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2; and

R^{24} is H or optionally substituted C_1-C_6 alkyl.

In some examples, R^2 is  ,  ,  , or  .

In some examples, R^2 is optionally substituted C_6-C_{10} aryl.

In some examples, R^2 is  ,

where

r is 0, 1, 2, 3, or 4; and

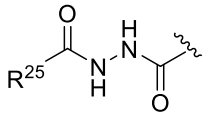
each R^{24} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted sulfone, SH, OH, or NH_2.

In some examples, each R^{24} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2.

In some examples, each R^{24} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, SH, OH, or NH_2.

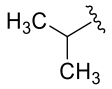
In some examples, r is 0, 1, or 2. In some examples, r is 0. In some examples, r is 1. In some examples, r is 2.

In some examples, R^2 is optionally substituted C_1-C_6 heteroalkyl.

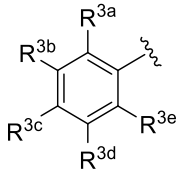
In some examples, R^2 is  , where R^{25} is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl.

In some examples, R^{25} is  .

In some examples, R^1 is optionally substituted C_1-C_6 alkyl.

In some examples, R^1 is  .

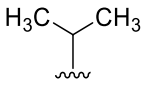
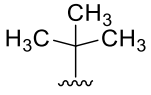
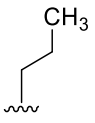
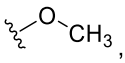
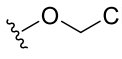
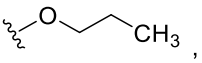
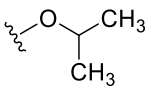
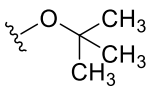
In some examples, R^1 is optionally substituted C_6-C_{10} aryl.

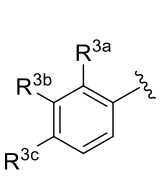
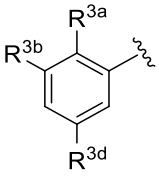
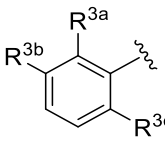
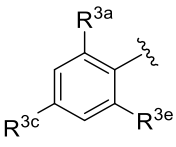
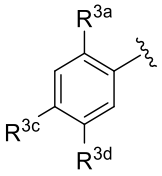
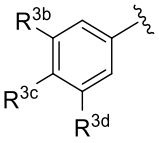
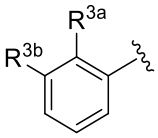
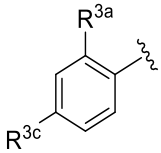
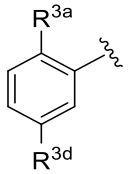
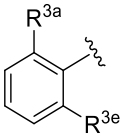
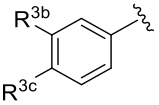
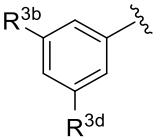
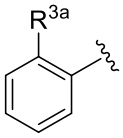
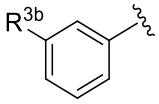
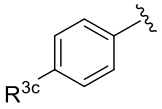
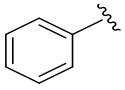
In some examples, R^1 is  ,

where

each of R^{3a}, R^{3b}, R^{3c}, R^{3d}, and R^{3e} is, independently, H, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2; or R^{3a} and R^{3b}, R^{3b} and R^{3c}, R^{3c} and R^{3d}, or R^{3d} and R^{3e}, together with the atoms to which each is attached, combine to form optionally substituted C_3-C_{10} carbocyclyl or optionally substituted C_2-C_9 heterocyclyl.

In some examples, each of R^{3a}, R^{3b}, R^{3c}, R^{3d}, and R^{3e} is, independently, H, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, SH, OH, or NH_2.

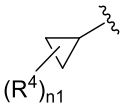
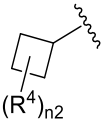
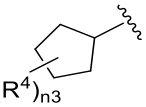
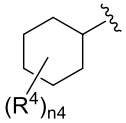
In some examples, each of R^{3a}, R^{3b}, R^{3c}, R^{3d}, and R^{3e} is, independently, H, F, Cl, Br, I, CN,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

In some examples, R^1 is  ,  ,  ,  ,  , or  . In some examples, R^1 is  ,  ,  ,  ,  , or  . In some examples, R^1 is  ,  , or  . In some examples, R^1 is  .

In some examples, R^1 is phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 3,4-di-fluoro-phenyl, 3,4-dichloro-phenyl, 3,5-di-fluoro-phenyl, 3,5-dichloro-phenyl, 3-chloro-4-fluoro-phenyl, 4-chloro-3-fluoro-phenyl, 3-chloro-4-nitrile-phenyl, 3-nitrile-4-fluoro-phenyl, 3-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 3-bromo-phenyl, 3-cyclopropyl-phenyl, 3-cyano-5-fluoro-phenyl, 3-chloro-5-fluoro-phenyl, 3-chloro-5-cyano-phenyl, 3-chloro-5-methoxy-phenyl, or 1,3-dihydroisobenzofuran.

In some examples, R^1 is optionally substituted C_3-C_{10} carbocyclyl.

In some examples, R^1 is optionally substituted C_3-C_{10} cycloalkyl.

In some examples, R^1 is  ,  ,  , or  ,

where

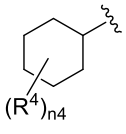
n1 is 0, 1, 2, or 3;

n2 is 0, 1, 2, 3, or 4;

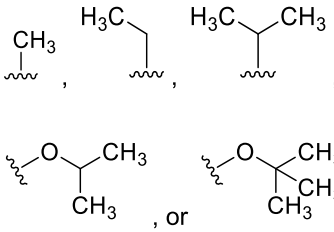
n3 is 0, 1, 2, 3, 4, or 5;

n4 is 0, 1, 2, 3, 4, 5, or 6; and

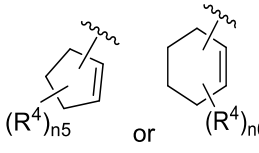
each R^4 is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2.

In some examples, R^1 is  .

In some examples, each R^4 is, independently, halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, SH, OH, or NH_2.

In some examples, each R^4 is, independently, F, Cl, Br, I, CN,  , , or .

In some examples, R^1 is optionally substituted cycloalkenyl.

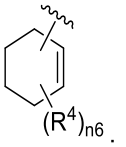
In some examples, R^1 is  ,

where

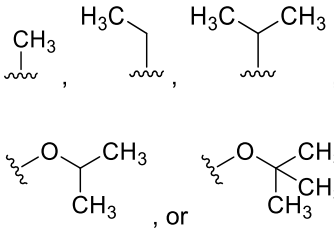
n5 is 0, 1, 2, 3, or 4;

n6 is 0, 1, 2, 3, 4, or 5; and

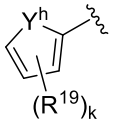
each R^4 is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2.

In some examples, R^1 is  .

In some examples, each R^4 is, independently, halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, SH, OH, or NH_2.

In some examples, each R^4 is, independently, F, Cl, Br, I, CN,  , , or .

In some examples, R^1 is optionally substituted C_2-C_6 heteroaryl.

In some examples, R^1 is  ,

where k is 0, 1, 2, or 3;

each R^{19} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2;

Y^h is O, S, or NR^{Y7}; and

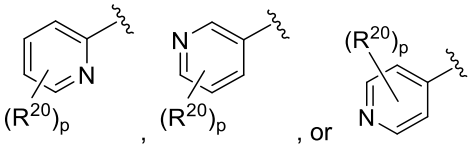
R^{Y7} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, or optionally substituted C_2-C_9 heterocyclyl.

In some examples, each R^{19} is, independently, halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, SH, OH, or NH_2.

In some examples, each R^{19} is, independently, F, Cl, Br, I, CN, or  .

In some examples, Y^h is S.

In some examples, k is 0 or 1. In some examples, k is 0. In some examples, k is 1.

In some examples, R^1 is  ,

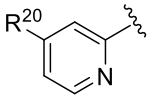
where p is 0, 1, 2, 3, or 4; and

each R^{20} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2.

In some examples, each R^{20} is, independently, halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, SH, OH, or NH_2.

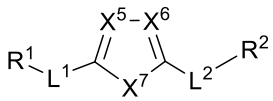
In some examples, each R^{20} is, independently, F, Cl, Br, I, CN, or  .

In some examples, p is 0 or 1. In some examples, p is 0. In some examples, p is 1.

In some examples, R^1 is  .

In some examples, R^1 is 5-chloropyridin-3-yl, 5-trifluoromethyl-pyridin-3-yl, 4-trifluoromethyl-pyridin-2-yl, 5-fluoropyridin-3-yl, or 5-fluoropyridin-3-yl.

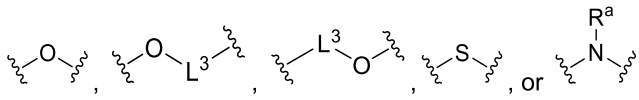
In an example, the disclosure features a compound having the structure of **Formula II**:



Formula II,

where

R^1 is optionally substituted C_6-C_{10} aryl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heteroaryl, or optionally substituted C_2-C_9 heterocyclyl;

L^1 is optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_2-C_6 alkenylene, optionally substituted C_2-C_6 alkynylene, optionally substituted C_3-C_6 carbocyclylene,  ;

R^a is H or optionally substituted C_1-C_6 alkyl;

L^3 is optionally substituted C_2-C_9 heterocyclylene;

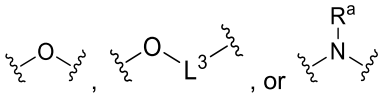
each of X^5 and X^6 is, independently, N or CH;

X^7 is O, S, or NR^b;

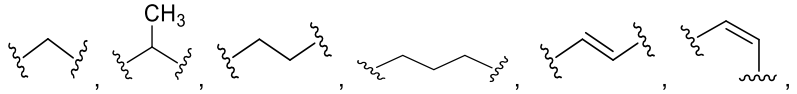
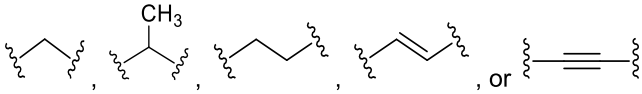
R^b is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, or optionally substituted C_2-C_9 heterocyclyl;

L^2 is optionally substituted C_1-C_6 alkylene or optionally substituted C_1-C_6 heteroalkylene; and

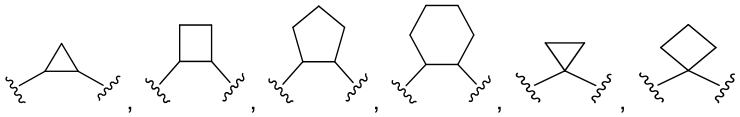
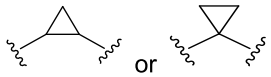
R^2 is optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl, or a pharmaceutically acceptable salt thereof.

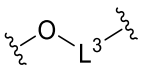
In some examples, L^1 is optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_2-C_6 alkenylene, optionally substituted C_2-C_6 alkynylene, optionally substituted C_3-C_6 carbocyclylene,  .

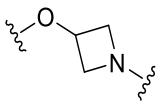
In some examples, L^1 is optionally substituted C_1-C_6 alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene.

In some examples, L^1 is  . In some examples, L^1 is  . In some examples, L^1 is  .

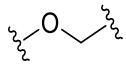
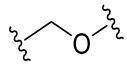
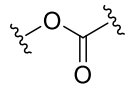
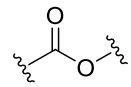
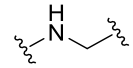
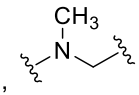
In some examples, L^1 is optionally substituted C_3-C_6 carbocyclylene.

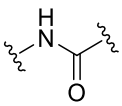
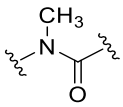
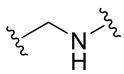
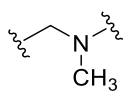
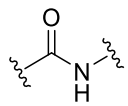
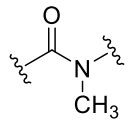
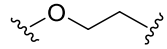
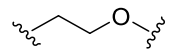
In some examples, L^1 is  . In some examples, L^1 is  or .

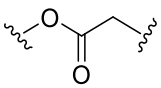
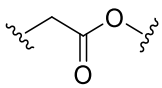
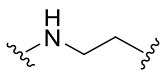
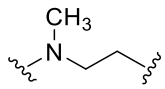
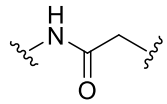
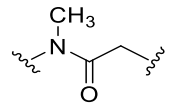
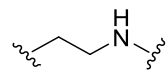
In some examples, L^1 is . In some examples, L^1 is  . In some examples, L^1 is  .

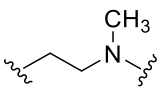
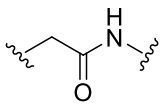
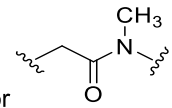
In some examples, L^1 is  or  . In some examples, L^1 is  .

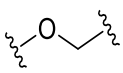
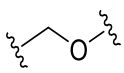
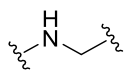
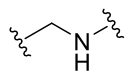
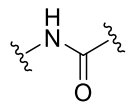
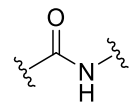
In some examples, L^1 is optionally substituted C_1-C_6 heteroalkylene.

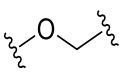
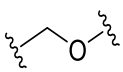
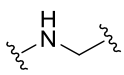
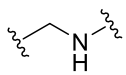
In some examples, L^1 is  ,  ,  ,  , ,  ,  ,

 ,  ,  ,  ,  ,  ,  ,  ,

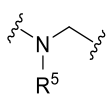
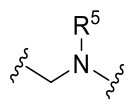
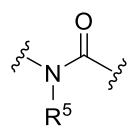
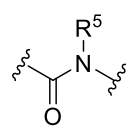
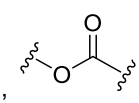
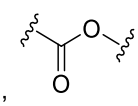
 ,  ,  ,  ,  ,  ,  ,

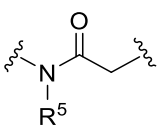
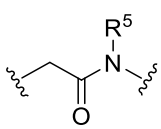
 ,  , or  . In some examples,

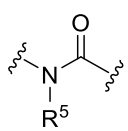
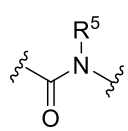
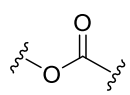
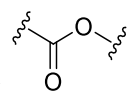
L^1 is  ,  ,  ,  ,  , or  . In some examples, L^1 is

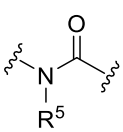
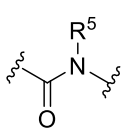
 ,  ,  , or  .

In some examples, L^2 is optionally substituted C_1-C_6 heteroalkyl.

In some examples, L^2 is  ,  ,  ,  ,  ,  ,

 , or  , where R^5 is H or optionally substituted C_1-C_6 alkyl.

In some examples, L^2 is  ,  ,  , or  . In some examples, L^2 is

 or  .

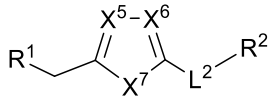
In some examples, R^5 is H or CH_3. In some examples, R^5 is H.

In some examples, X^5 is CH. In some examples, X^5 is N.

In some examples, X^6 is CH. In some examples, X^6 is N.

In some examples, X^7 is S.

In some examples, the compound has the structure of **Formula IIa**:



Formula IIa,

or a pharmaceutically acceptable salt thereof.

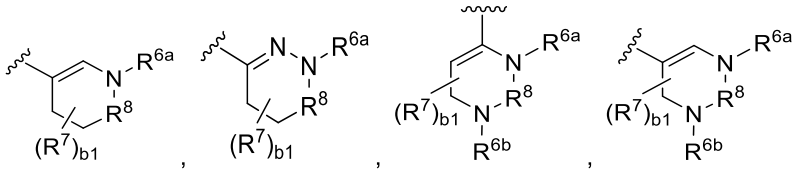
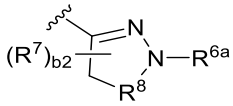
In some examples, R^2 is optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl.

In some examples, R^2 is optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl.

In some examples, R^2 is optionally substituted C_2-C_9 heterocyclyl or optionally substituted C_2-C_9 heteroaryl.

In some examples, R^2 is optionally substituted C_2-C_9 heterocyclyl.

In some examples, R^2 is optionally substituted C_2-C_5 heterocyclyl.

In some examples, R^2 is  , , , , or  ,

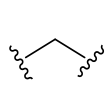
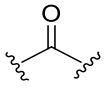
where b1 is 0, 1, 2, 3, or 4;

b2 is 0, 1, or 2;

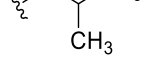
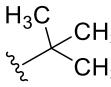
R^{6a} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 carbocyclyl;

R^{6b} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 carbocyclyl;

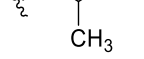
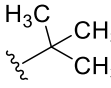
each R^7 is, independently, halo or optionally substituted C_1-C_6 alkyl; and

R^8 is  or  .

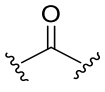
In some examples, R^{6a} is H or optionally substituted C_1-C_6 alkyl.

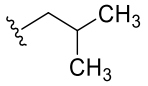
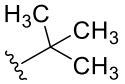
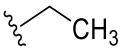
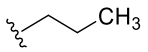
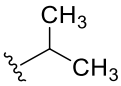
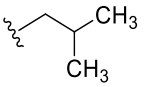
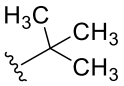
In some examples, R^{6a} is H,  ,  ,  ,  ,  , or  . In some examples, R^{6a} is H or  .

In some examples, R^{6b} is H or optionally substituted C_1-C_6 alkyl.

In some examples, R^{6b} is H,  ,  ,  ,  ,  , or  .

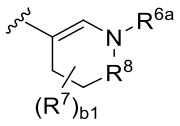
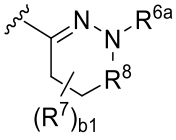
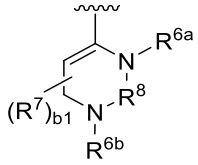
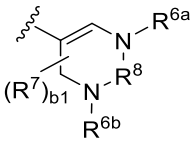
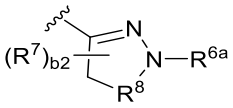
In some examples, R^{6b} is H or  .

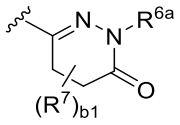
In some examples, R^8 is  .

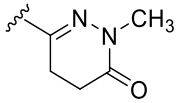
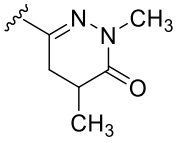
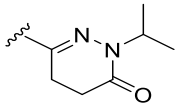
In some examples, each R^7 is, independently, F, Cl, Br, I,  ,  ,  ,  ,  , or  . In some examples, each R^7 is, independently,  ,  ,  ,  ,  , or  .

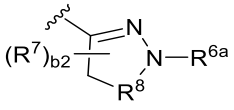
In some examples, b1 is 0 or 1. In some examples, b1 is 0. In some examples, b1 is 1.

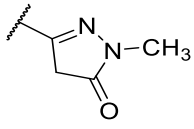
In some examples, b2 is 0 or 1. In some examples, b2 is 0. In some examples, b2 is 1.

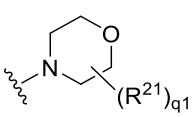
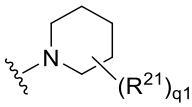
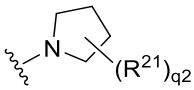
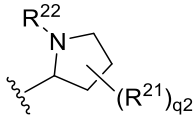
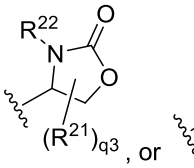
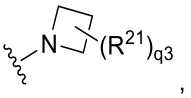
In some examples, R^2 is  . In some examples, R^2 is  . In some examples,  ,  . In some examples, R^2 is  .

In some examples, R^2 is  .

In some examples, R^2 is  ,  , or  .

In some examples, R^2 is  .

In some examples, R^2 is  .

In some examples, R^2 is  ,  ,  ,  ,  , or  ,

where

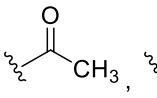
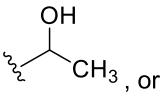
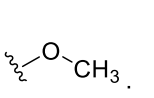
q1 is 0, 1, 2, 3, 4, 5, or 6;

q2 is 0, 1, 2, 3, or 4;

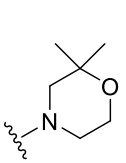
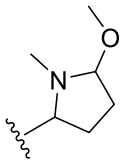
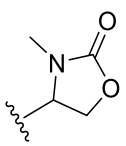
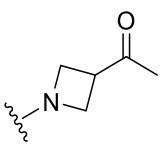
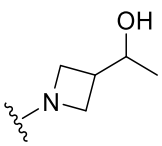
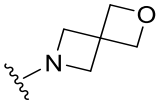
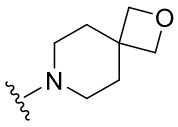
q3 is 0, 1, or 2;

each R^{21} is, independently, hydroxyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl; or two of the R^{21} groups, taken together with the carbon atom to which each is attached, combine to form an optionally substituted C_3-C_{10} carbocyclyl or optionally substituted C_2-C_9 heterocyclyl; and

R^{22} is H or optionally substituted C_1-C_6 alkyl.

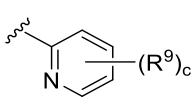
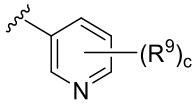
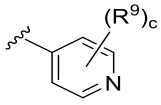
In some examples, each R^{21} is, independently,  ,  , or  .

In some examples, R^{22} is H or  .

In some examples, R^2 is  ,  ,  ,  ,  ,  , or  .

In some examples, R^2 is optionally substituted C_2-C_9 heteroaryl.

In some examples, R^2 is optionally substituted C_2-C_5 heteroaryl.

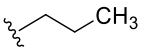
In some examples, R^2 is  ,  , or  ,

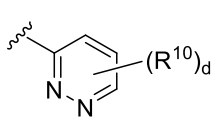
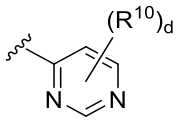
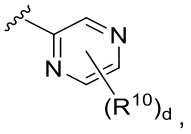
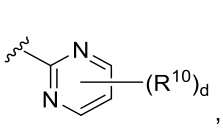
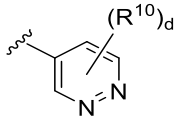
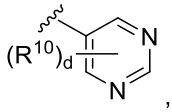
where

c is 0, 1, 2, 3, or 4; and

each R^9 is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2.

In some examples, each R^9 is, independently, halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, OH, or NH_2.

In some examples, each R^9 is, independently, F, Cl, Br, I, CN,  ,  , 

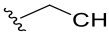
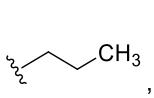
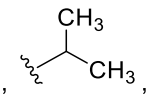
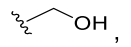
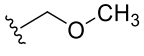
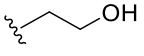
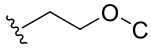
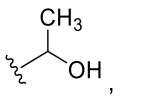
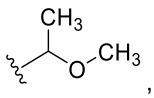
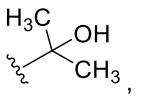
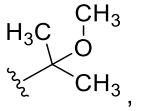
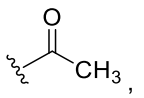
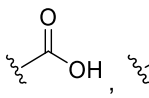
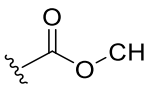
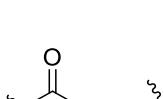
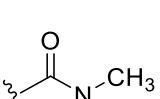
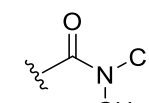
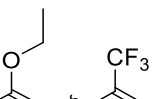
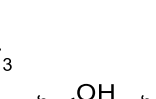
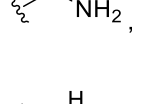
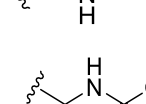
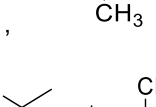
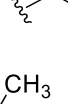
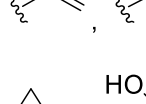
In some examples, R^2 is  ,  ,  ,  ,  , or  ,

where

d is 0, 1, 2, or 3; and

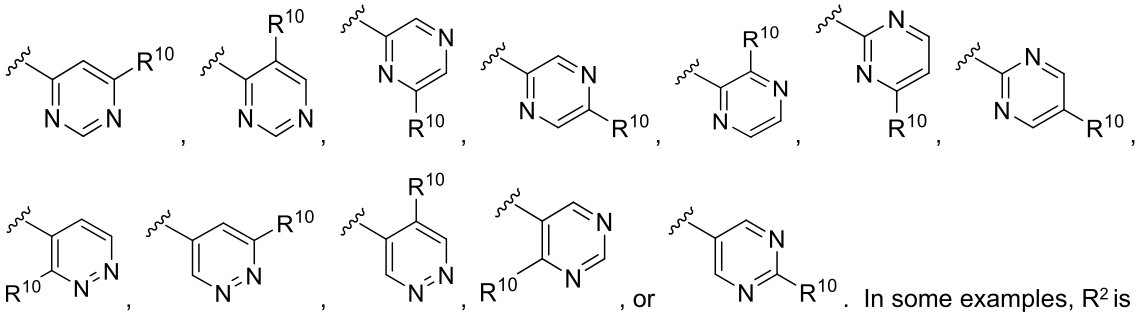
each R^{10} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2.

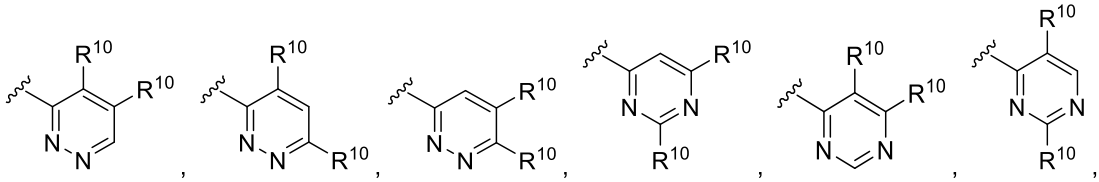
In some examples, each R^{10} is, independently, halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, OH, or NH_2.

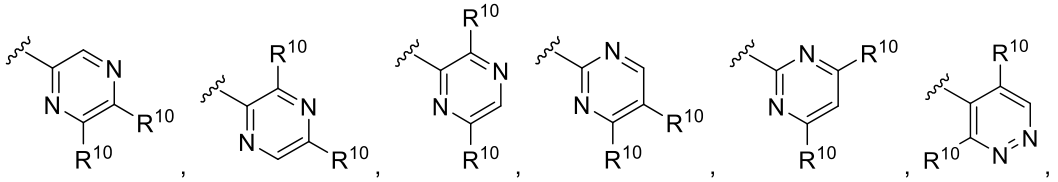
In some examples, each R^{10} is , independently, F, Cl, Br, I, CN,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ,  ,  ,  ,  ,  ,  ,  ,  , ,  ,  , ,  ,  ,  ,  ,  ,  ,  , , , , , , , , , , , , , , , , , .

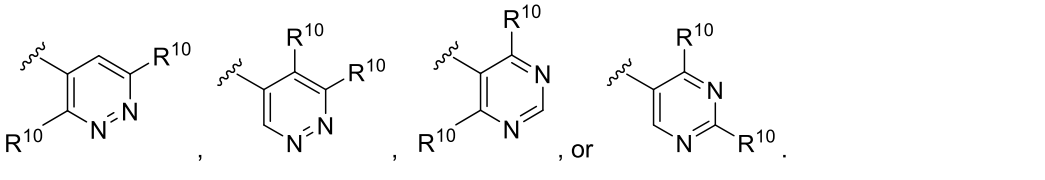
In some examples, d is 0, 1, or 2. In some examples, d is 0. In some examples, d is 1. In some examples, d is 2.

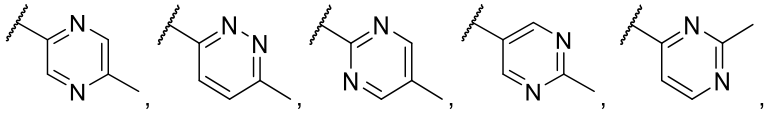
In some examples, R^2 is , , , , , or . In some examples, R^2 is , , , , ,

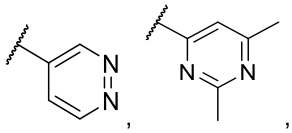

. In some examples, R^2 is

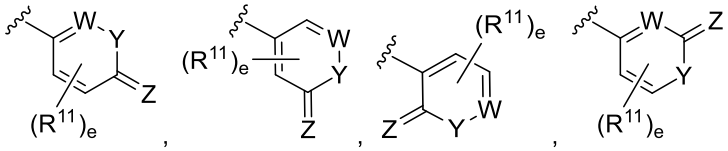


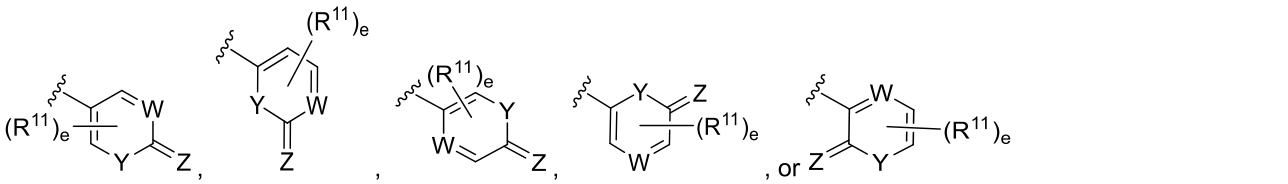



.

In some examples, R^2 



In some examples, R^2 



where

e is 0, 1, or 2;

each R^{11} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6

heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2.

W is CH or N;

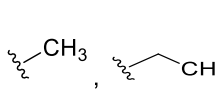
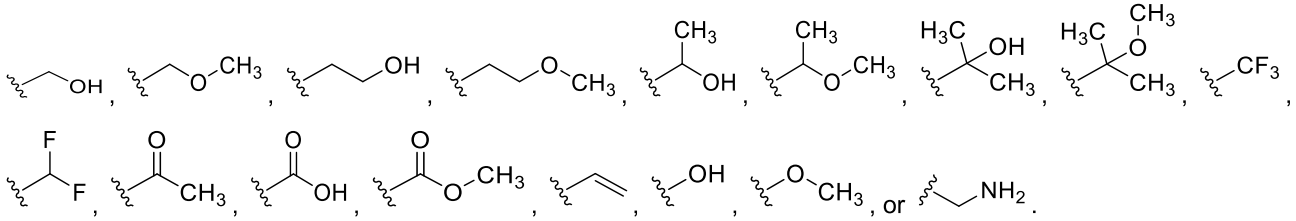
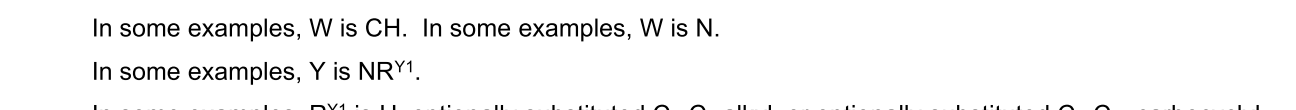
Y is O, S, or NR^{Y1};

R^{Y1} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, or optionally substituted C_2-C_9 heterocyclyl;

Z is O, S, or NR^{Z1}; and

R^{Z1} is H or optionally substituted C_1-C_6 alkyl.

In some examples, each R^{11} is, independently, halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, OH, or NH_2.

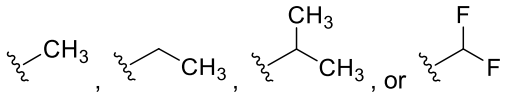
In some examples, each R^{11} is, independently, F, Cl, Br, I, CN,  ,  , ,  , or .

In some examples, W is CH. In some examples, W is N.

In some examples, Y is NR^{Y1}.

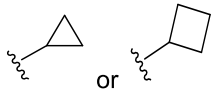
In some examples, R^{Y1} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_{10} carbocyclyl.

In some examples, R^{Y1} is H. In some examples, R^{Y1} is optionally substituted C_1-C_6 alkyl.

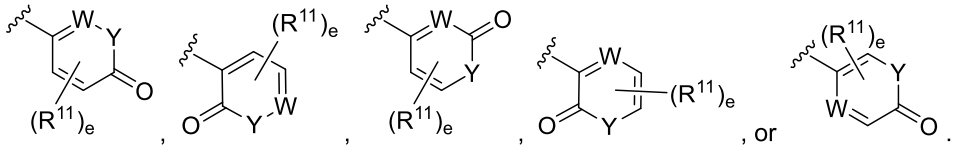
In some examples, R^{Y1} is  .

In some examples, R^{Y1} is optionally substituted C_3-C_{10} carbocyclyl.

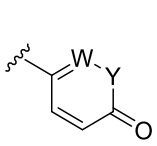
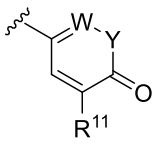
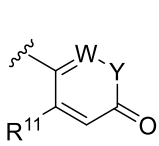
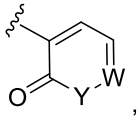
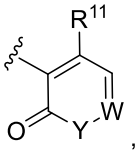
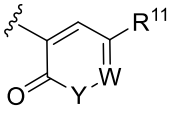
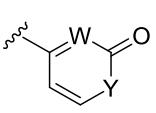
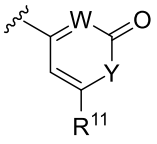
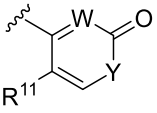
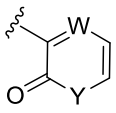
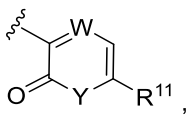
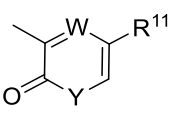
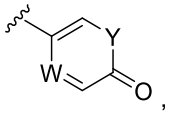
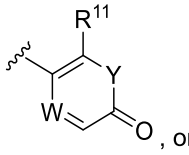
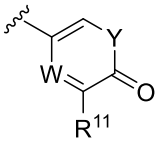
In some examples, R^{Y1} is optionally substituted C_3-C_6 carbocyclyl.

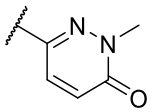
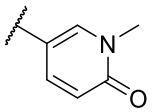
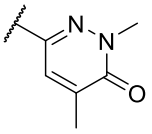
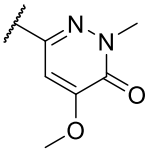
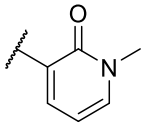
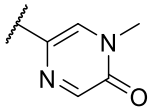
In some examples, R^{Y1} is  .

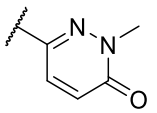
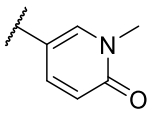
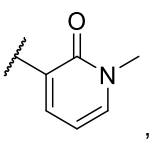
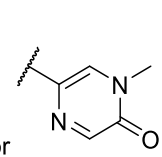
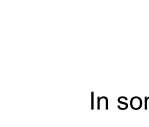
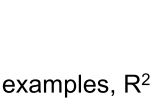
In some examples, Z is O.

In some examples, R^2 is  .

In some examples, e is 0 or 1. In some examples, e is 0. In some examples, e is 1.

In some examples, R^2 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

In some examples, R^2 is  ,  ,  ,  ,  ,  ,  , or .

In some examples, R^2 is  ,  ,  ,  , ,  ,  , or .

In some examples, R^2 is , , , , , , , or .

In some examples, R^2 is , , , or .

In some examples, R^2 or .

In some examples, R^2 is , , or ,

where

R^{12a} is H, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2;

each of Y^a and Y^b is, independently, O, S, or NR^{Y2};

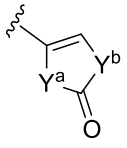
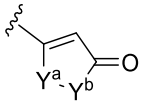
R^{Y2} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, or optionally substituted C_2-C_9 heterocyclyl;

Z^a is O, S, or NR^{Z2}; and

R^{Z2} is H or optionally substituted C_1-C_6 alkyl.

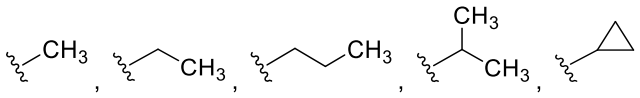
In some examples, R^{12a} is H.

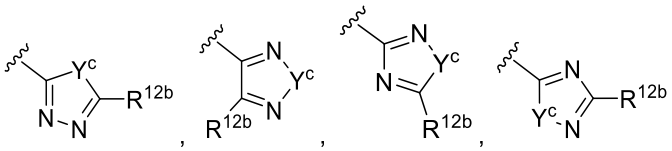
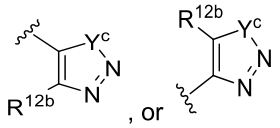
In some examples, Z^a is O.

In some examples, R^2 is  or  .

In some examples, each of Y^a and Y^b is NR^{Y2}.

In some examples, R^{Y2} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_{10} carbocyclyl.

In some examples, R^{Y2} is H,  ,  , or  .

In some examples, R^2 is  , , or  ,

where

R^{12b} is H, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2; and

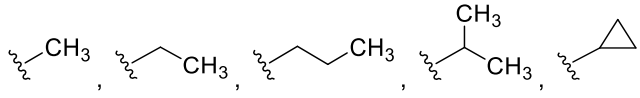
Y^c is O, S, or NR^{Y3};

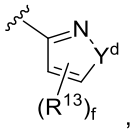
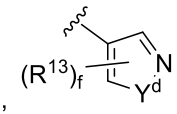
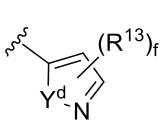
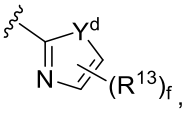
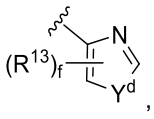
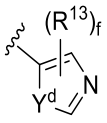
R^{Y3} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, or optionally substituted C_2-C_9 heterocyclyl.

In some examples, R^{12b} is H.

In some examples, Y^c is NR^{Y3}.

In some examples, R^{Y3} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_{10} carbocyclyl.

In some examples, R^{Y3} is H,  ,  , or  .

In some examples, R^2 is  ,  ,  ,  ,  , or  ,

where

f is 0, 1, or 2;

each R^{13} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2; and

Y^d is O, S, or NR^{Y4};

R^{Y4} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, or optionally substituted C_2-C_9 heterocyclyl.

In some examples, each R^{13} is, independently, halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, OH, or NH_2.

In some examples, each R^{13} is, independently, halo, CN, or optionally substituted C_1-C_6 alkyl.

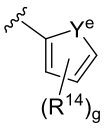
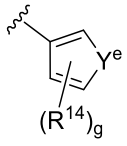
In some examples, f is 0 or 1. In some examples, f is 0. In some examples, f is 1.

In some examples, Y^d is NR^{Y4}.

In some examples, R^{Y4} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_{10} carbocyclyl.

In some examples, R^{Y4} is H,  ,  ,  ,  ,  ,  , or  .

In some examples, Y^d is O.

In some examples, R^2 is  or  ,

where

g is 0, 1, 2, 3, or 4;

each R^{14} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2;

Y^e is O, S, or NR^{Y5}; and

R^{Y5} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, or optionally substituted C_2-C_9 heterocyclyl.

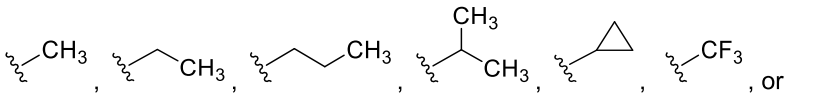
In some examples, R^{14} is halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, OH, or NH_2.

In some examples, R^{14} is halo, CN, or optionally substituted C_1-C_6 alkyl.

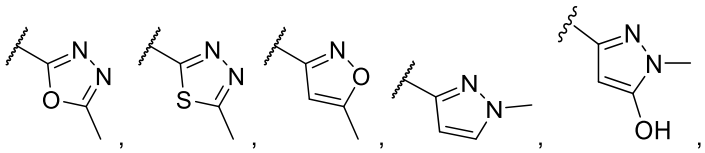
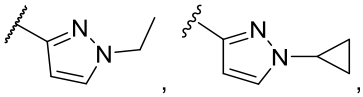
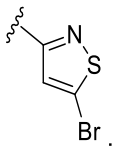
In some examples, g is 0, 1, or 2. In some examples, g is 0. In some examples, g is 1. In some examples, g is 2.

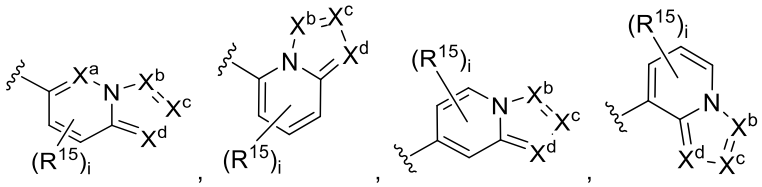
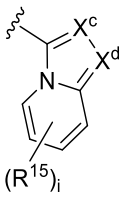
In some examples, Y^e is NR^{Y5}.

In some examples, R^{Y5} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_{10} carbocyclyl.

In some examples, R^{Y5} is  , or  .

In some examples, Y^e is O. In some examples, Y^e is S.

In some examples, R^2 is  ,  , or  .

In some examples, R^2 is  , or  ,

where

each of X^a, X^b, X^c, and X^d is, independently, N or CR^{17};

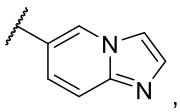
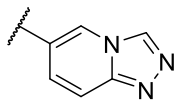
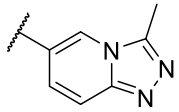
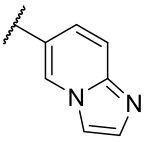
each R^{17} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2;

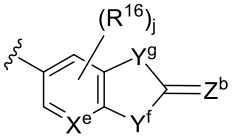
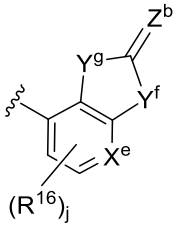
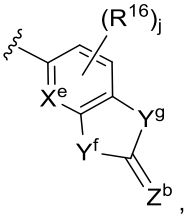
i is 0, 1, 2, or 3; and

each R^{15} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2.

In some examples, each R^{15} is, independently, halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, SH, OH, or NH_2.

In some examples, i is 0 or 1. In some examples, i is 0. In some examples, i is 1.

In some examples, R^2 is  ,  ,  , or  .

In some examples, R^2 is  ,  , or  ,

where

X^e is N or CR^{18};

R^{18} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2;

j is 0, 1, or 2;

each R^{16} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2;

each of Y^f and Y^g is, independently, O, S, or NR^{Y6};

R^{Y6} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, or optionally substituted C_2-C_9 heterocyclyl;

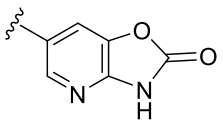
Z^b is O, S, or NR^{Z3}; and

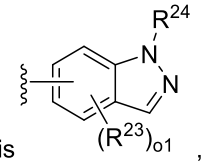
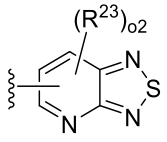
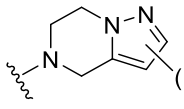
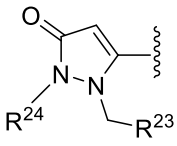
R^{Z3} is H or optionally substituted C_1-C_6 alkyl.

In some examples, each R^{16} is, independently, halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, SH, OH, or NH_2.

In some examples, j is 0 or 1. In some examples, j is 0. In some examples, j is 1.

In some examples, Z is O.

In some examples, R^2 is  .

In some examples, R^2 is  ,  ,  , or  ,

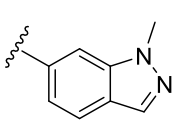
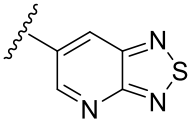
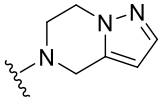
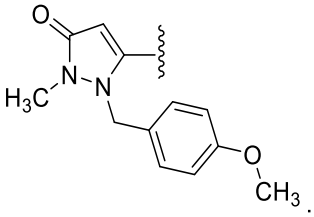
where

o1 is 0, 1, 2, or 3;

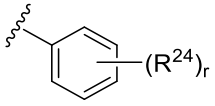
o2 is 0, 1, or 2;

each R^{23} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2; and

R^{24} is H or optionally substituted C_1-C_6 alkyl.

In some examples, R^2 is  ,  ,  , or  .

In some examples, R^2 is optionally substituted C_6-C_{10} aryl.

In some examples, R^2 is  ,

where

r is 0, 1, 2, 3, or 4; and

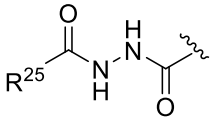
each R^{24} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted sulfone, SH, OH, or NH_2.

In some examples, each R^{24} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2.

In some examples, each R^{24} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, SH, OH, or NH_2.

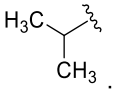
In some examples, r is 0, 1, or 2. In some examples, r is 0. In some examples, r is 1. In some examples, r is 2.

In some examples, R^2 is optionally substituted C_1-C_6 heteroalkyl.

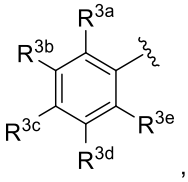
In some examples, R^2 is  , where R^{25} is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl.

In some examples, R^{25} is  .

In some examples, R^1 is optionally substituted C_1-C_6 alkyl.

In some examples, R^1 is  .

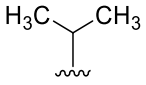
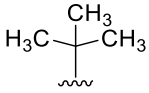
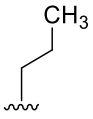
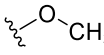
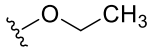
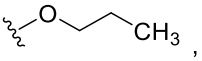
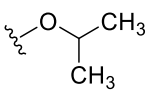
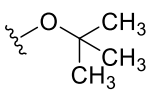
In some examples, R^1 is optionally substituted C_6-C_{10} aryl.

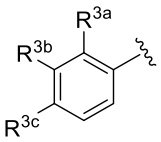
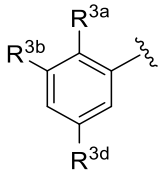
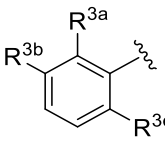
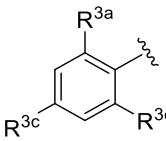
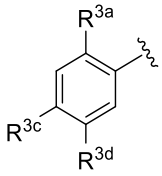
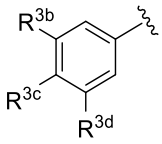
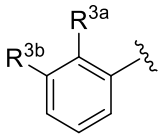
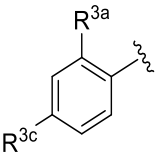
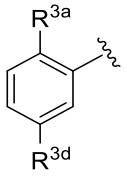
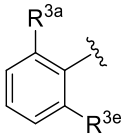
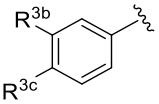
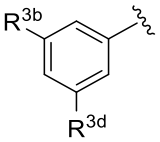
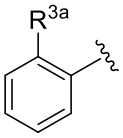
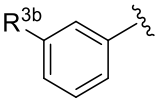
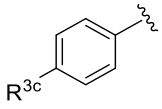
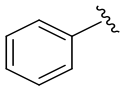
In some examples, R^1 is  ,

where

each of R^{3a}, R^{3b}, R^{3c}, R^{3d}, and R^{3e} is, independently, H, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2; or R^{3a} and R^{3b}, R^{3b} and R^{3c}, R^{3c} and R^{3d}, or R^{3d} and R^{3e}, together with the atoms to which each is attached, combine to form optionally substituted C_3-C_{10} carbocyclyl or optionally substituted C_2-C_9 heterocyclyl.

In some examples, each of R^{3a}, R^{3b}, R^{3c}, R^{3d}, and R^{3e} is, independently, H, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, SH, OH, or NH_2.

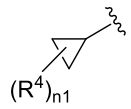
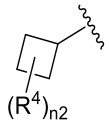
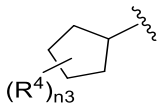
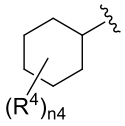
In some examples, each of R^{3a}, R^{3b}, R^{3c}, R^{3d}, and R^{3e} is, independently, H, F, Cl, Br, I, CN,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

In some examples, R^1 is  ,  ,  ,  ,  , or  . In some examples, R^1 is  ,  ,  ,  ,  , or  . In some examples, R^1 is  ,  , or  . In some examples, R^1 is  .

In some examples, R^1 is phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 3,4-di-fluoro-phenyl, 3,4-dichloro-phenyl, 3,5-di-fluoro-phenyl, 3,5-dichloro-phenyl, 3-chloro-4-fluoro-phenyl, 4-chloro-3-fluoro-phenyl, 3-chloro-4-nitrile-phenyl, 3-nitrile-4-fluoro-phenyl, 3-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 3-bromo-phenyl, 3-cyclopropyl-phenyl, 3-cyano-5-fluoro-phenyl, 3-chloro-5-fluoro-phenyl, 3-chloro-5-cyano-phenyl, 3-chloro-5-methoxy-phenyl, or 1,3-dihydroisobenzofuran.

In some examples, R^1 is optionally substituted C_3-C_{10} carbocyclyl.

In some examples, R^1 is optionally substituted C_3-C_{10} cycloalkyl.

In some examples, R^1 is  ,  ,  , or  ,

where

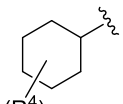
n1 is 0, 1, 2, or 3;

n2 is 0, 1, 2, 3, or 4;

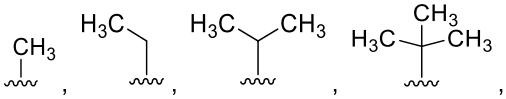
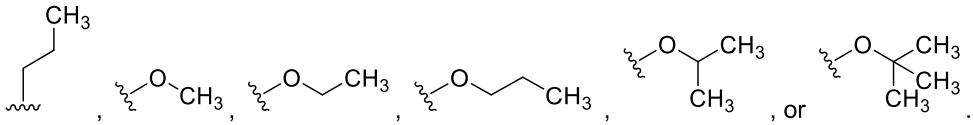
n3 is 0, 1, 2, 3, 4, or 5;

n4 is 0, 1, 2, 3, 4, 5, or 6; and

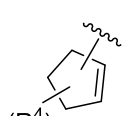
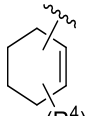
each R^4 is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2.

In some examples, R^1 is  .

In some examples, each R^4 is, independently, halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, SH, OH, or NH_2.

In some examples, each R^4 is, independently, F, Cl, Br, I, CN,  ,  , or .

In some examples, R^1 is optionally substituted cycloalkenyl.

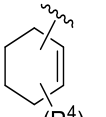
In some examples, R^1 is  or  ,

where

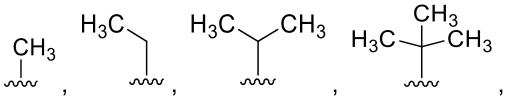
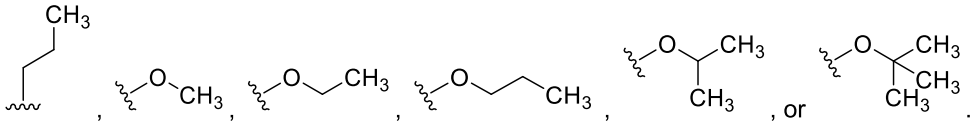
n5 is 0, 1, 2, 3, or 4;

n6 is 0, 1, 2, 3, 4, or 5; and

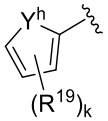
each R^4 is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2.

In some examples, R^1 is  .

In some examples, each R^4 is, independently, halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, SH, OH, or NH_2.

In some examples, each R^4 is, independently, F, Cl, Br, I, CN,  ,  , or .

In some examples, R^1 is optionally substituted C_2-C_6 heteroaryl.

In some examples, R^1 is  ,

where k is 0, 1, 2, or 3;

each R^{19} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2;

Y^h is O, S, or NR^{Y7}; and

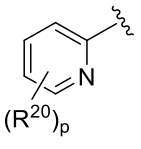
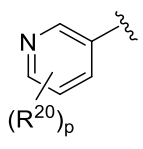
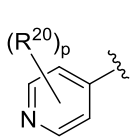
R^{Y7} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, or optionally substituted C_2-C_9 heterocyclyl.

In some examples, each R^{19} is, independently, halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, SH, OH, or NH_2.

In some examples, each R^{19} is, independently, F, Cl, Br, I, CN, or  .

In some examples, Y^h is S.

In some examples, k is 0 or 1. In some examples, k is 0. In some examples, k is 1.

In some examples, R^1 is  ,  , or  ,

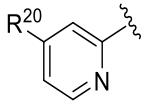
where p is 0, 1, 2, 3, or 4; and

each R^{20} is, independently, halo, CN, NO_2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, SH, OH, or NH_2.

In some examples, each R^{20} is, independently, halo, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkene, optionally substituted C_1-C_6 heteroalkyl, SH, OH, or NH_2.

In some examples, each R^{20} is, independently, F, Cl, Br, I, CN, or  .

In some examples, p is 0 or 1. In some examples, p is 0. In some examples, p is 1.

In some examples, R^1 is  .

In some examples, R^1 is 5-chloropyridin-3-yl, 5-trifluoromethyl-pyridin-3-yl, 4-trifluoromethyl-pyridin-2-yl, 5-fluoropyridin-3-yl, or 5-fluoropyridin-3-yl.

In another example, this disclosure features a compound, or pharmaceutically acceptable salt thereof, having the structure of any one of compounds 1-683 in Table 1 and Table 2. In some examples, the compound is any one of compounds 1-475 in Table 1. In some examples, the compound is any one of compounds 476-683 in Table 2.

In some examples, the compound is any one of compounds 40, 41, 46, 48, 53, 56, 57, 59, 66, 74-76, 79, 89, 91, 94, 95, 99, 111-114, 116, 119, 121, 122, 125, 128, 131, 132, 134, 137, 140, 142, 144, 146, 148, 149, 150, 202, 207, 216, 236, 239, 242-244, 248, 290, 292, 311, 315, 316, 321, 328-331, 366, 371, and 375 in Table 1. In some examples, the compound is any one of compounds 56, 76, 91, 94, 111, 112, 114, 116, 119, 122, 125, 131, 132, 137, 144, 148, 150, 236, 242-244, 290, 315, 316, 321, and 375 in Table 1. In some examples, the compound is any one of compounds 484, 494-497, 500-503, 506, 526, 528, 532, 540, 542, 543, 547, 555, 556, 559, 562, 567, 571, 572, 575, 580, 603, 616, 626, 627, 642-644, 657, 661, 668, 676, and 679 in Table 2. In some

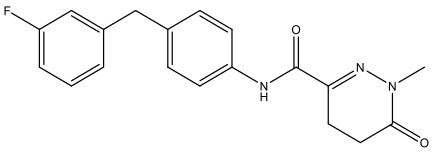
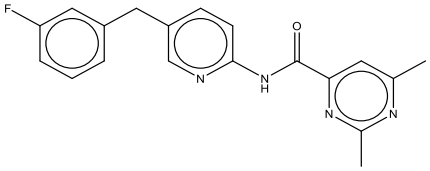
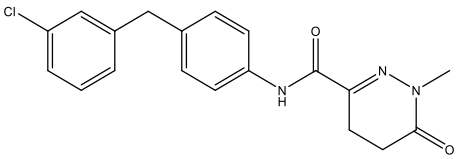
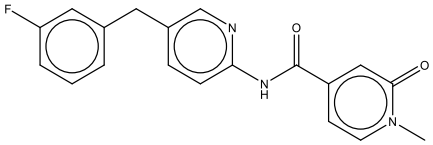
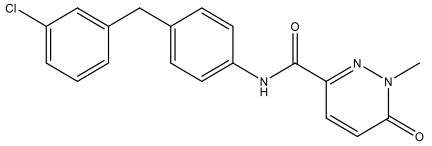
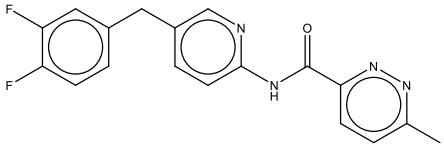
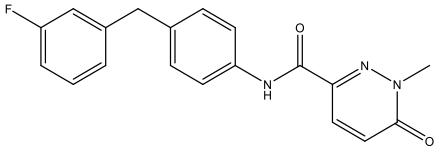
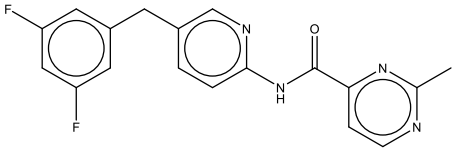
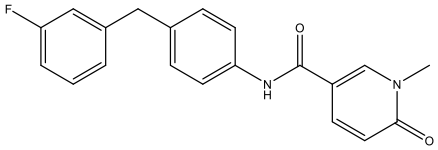
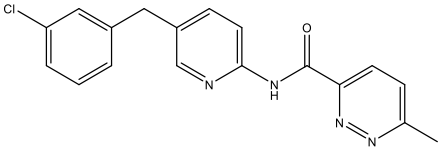
examples, the compound is any one of compounds 494, 497, 501, 503, 532, 559, 567, 572, 580, 603, 657, and 668 in Table 2.

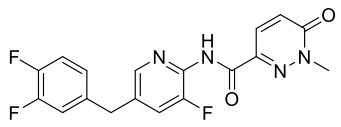
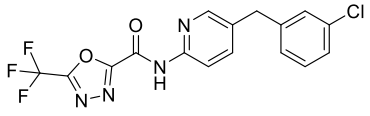
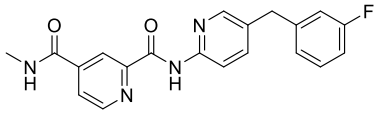
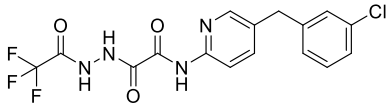
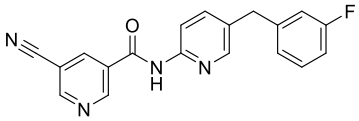
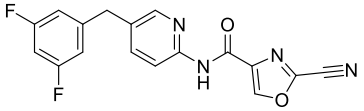
In some examples, the compound is any one of compounds 1-200, 238-305, 310-316, 318-321, 323-335, 337-339, 342, 344-346, 348, 349, 351, 352, 354-376, 379, 381-384, 387, 391-393, 396,

397, 401-403, 410-412, 415, 417, 418, 421, 423, 425-429, 433, 435-456, 458-460, 463, 467-472, 474, and 475 in Table 1 and 476-683 in Table 2. In some examples, the compound is any one of compounds 1-200, 238-305, 310-316, 318-321, 323-335, 337-339, 342, 344-346, 348, 349, 351, 352, 354-376, 379, 381-384, 387, 391-393, 396, 397, 401-403, 410-412, 415, 417, 418, 421, 423, 425-429, 433, 435-456, 458-460, 463, 467-472, 474, and 475 in Table 1. In some examples, the compound is any one of compounds 476-681 and 683 in Table 2. In some examples, the compound is any one of compounds 201-237, 317, 340, 341, 343, 345-347, 350, 353, 377, 378, 380, 385, 386, 388-390, 398-400, 404-409, 413, 414, 416, 419, 420, 422, 424, 430, 431, 461, 462, 464-466, and 473 in Table 1. In some examples, the compound is any one of compounds 305-309, 322, 336, 394, 432, 434, and 457 in Table 1. In some examples, the compound is any one of compounds 305-309 in Table 1.

As used herein, “CMPD” refers to “compound.”

Table 1. Compounds of the Invention

CMPD No.	Structure	CMPD No.	Structure
1		239	
2		240	
3		241	
4		242	
5		243	

CMPD No.	Structure	CMPD No.	Structure
577		681	
578		682	
579		683	

In an aspect, there is provided a compound, or pharmaceutically acceptable salt thereof, having the structure of any one of compounds 476-683 in Table 2.

In an aspect, this disclosure features 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 **Formula I** or **Formula II** and a pharmaceutically acceptable excipient.

In an example, this disclosure features 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 an aspect, there is provided the use of an effective amount of a compound, or pharmaceutically acceptable salt thereof, as defined above or a pharmaceutical composition as defined above in the manufacture of a medicament for the treatment of a neurological disorder in a subject in need thereof

In an example, this disclosure features 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 an aspect, there is provided the use of a compound, or pharmaceutically acceptable salt thereof, as defined above or a pharmaceutical composition as defined above in the manufacture of a medicament for inhibiting toxicity in a cell related to a protein.

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.

In an example, this disclosure features 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 an aspect, there is provided the use of an effective amount of a compound, or pharmaceutically acceptable salt as defined above or a pharmaceutical composition as defined above in the manufacture of a medicament for treating a stearoyl-CoA desaturase (SCD)-associated disorder in a subject in need thereof.

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 SCD1-associated disorder.

In some examples, the SCD-associated disorder is a SCD5-associated disorder.

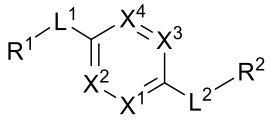
In an example, this disclosure features a method of inhibiting SCD5, the method comprising contacting a cell with an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof.

In another aspect, there is provided the use of an effective amount of a compound as defineda bove or a pharmaceutical composition as defined above in the manufacture of a medicament for inhibiting SCD5.

In an example, this disclosure features 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, there is provided the use of an effective amount of a compound as defined above or a pharmaceutical composition as defined above in the manufacture of a medicament for inhibiting SCD1.

In an example, this disclosure features a method of treating a primary brain cancer in a subject in need thereof, the method comprising administering an effective amount of a compound having the structure of **Formula I**:

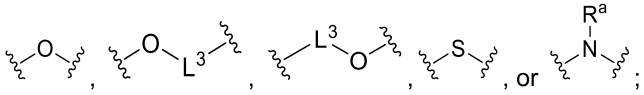


Formula I,

wherein

R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heteroaryl, or optionally substituted C_2-C_9 heterocyclyl;

L^1 is optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_2-C_6 alkenylene, optionally substituted C_2-C_6 alkynylene, optionally substituted C_3-C_6 carbocyclylene,



;

R^a is H or optionally substituted C_1-C_6 alkyl;

L^3 is optionally substituted C_2-C_9 heterocyclylene;

each of X^1, X^2, X^3, and X^4 is, independently, N or CH;

L^2 is optionally substituted C_1-C_6 alkylene or optionally substituted C_1-C_6 heteroalkylene; and

R^2 is optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl,

or a pharmaceutically acceptable salt thereof.

In some examples, the compound, or pharmaceutically acceptable salt thereof, has the structure of any one of compounds 1-475 in Table 1 or any one of compounds 476-683 in Table 2.

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 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.

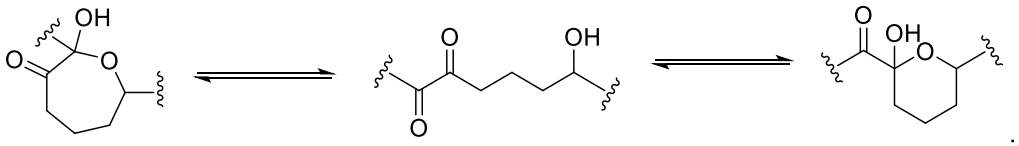
In some examples, the subject is further administered one or more additional therapeutic interventions. In some examples, one or more additional therapeutic interventions comprises surgery, radiation, and/or one or more additional chemotherapeutic agents. In some examples, one or more additional therapeutic 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.

Those skilled in the art will appreciate that certain compounds described herein can exist in one or more different isomeric (e.g., stereoisomers, geometric isomers, tautomers) and/or isotopic (e.g., in which one or more atoms has been substituted with a different isotope of the atom, such as hydrogen substituted for deuterium) forms. Unless otherwise indicated or clear from context, a depicted structure can be understood to represent any such isomeric or isotopic form, individually or in combination.

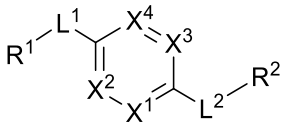
In some embodiments, one or more compounds depicted herein may exist in different tautomeric forms. As will be clear from context, unless explicitly excluded, references to such compounds encompass all such tautomeric forms. In some embodiments, tautomeric forms result from the swapping of a single bond with an adjacent double bond and the concomitant migration of a proton. In certain embodiments, a tautomeric formmay be a prototropic tautomer, which is an isomeric protonation states having the same empirical formula and total charge as a reference form. Examples of moieties with prototropic tautomeric forms are ketone – enol pairs, amide – imidic acid pairs, lactam – lactim pairs, amide – imidic acid pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, such as, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. In some embodiments, tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. In certain embodiments, tautomeric forms result from acetal interconversion, e.g., the interconversion illustrated in the scheme below:



Those skilled in the art will appreciate that, in some embodiments, isotopes of compounds described herein may be prepared and/or utilized in accordance with the present invention. “Isotopes”

Claims

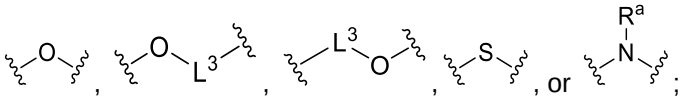
1. Use of a compoundhaving the structure of **Formula I**:



Formula I,

wherein

R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heteroaryl, or optionally substituted C_2-C_9 heterocyclyl;

L^1 is optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_2-C_6 alkenylene, optionally substituted C_2-C_6 alkynylene, optionally substituted C_3-C_6 carbocyclylene,  ;

R^a is H or optionally substituted C_1-C_6 alkyl;

L^3 is optionally substituted C_2-C_9 heterocyclylene;

each of X^1, X^2, X^3, and X^4 is, independently, N or CH;

L^2 is optionally substituted C_1-C_6 alkylene or optionally substituted C_1-C_6 heteroalkylene; and

R^2 is optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl,

or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for the treatment of a primary brain cancer in a subject in need thereof.

2. The use of claim 1, wherein the compound, or pharmaceutically acceptable salt thereof, has the structure of any one of compounds 1-475 in Table 1 or any one of compounds 476-683 in Table 2.

3. The use of claim 1 or 2, wherein the primary brain cancer is a glioma.

4. The use of claim 3, wherein the glioma is an astrocytoma.

5. The use of claim 4, wherein the astrocytoma is a glioblastoma.

6. The use of any one of claims 1-5, wherein the cancer is determined or predicted to be resistant to one or more chemotherapeutic agents.

7. The use of any one of claims 1-6, wherein the cancer has failed to respond to one or more chemotherapeutic agents.

8. The use of claim 6 or 7, wherein one or more chemotherapeutic agents is selected from the group of temozolomide, carmustine, bevacizumab, lomustine, everolimus, vincristine, or procarbazine.

9. The use of claim 8, wherein one or more chemotherapeutic agents is temozolomide.

10. The use of any one of claims 1-9, wherein one or more additional therapeutic interventions is to be administered to the subject.

11. The use of claim 10, wherein one or more additional therapeutic interventions comprises surgery, radiation, and/or one or more additional chemotherapeutic agents.

12. The use of claim 11, wherein one or more additional therapeutic interventions is one or more chemotherapeutic agents.

13. The use of claim 12, wherein one or more chemotherapeutic agents is selected from the group of temozolomide, carmustine, bevacizumab, lomustine, everolimus, vincristine, or procarbazine.

14. The use of claim 13, wherein one or more chemotherapeutic agents is temozolomide.

15. A compound, or pharmaceutically acceptable salt thereof, having the structure of any one of compounds 476-683 in Table 2.

16. A pharmaceutical composition comprising a compound, or pharmaceutically acceptable salt thereof, of claim 15, and a pharmaceutically acceptable excipient.

17. Use of an effective amount of a compound, or pharmaceutically acceptable salt thereof, of claim 15 or a pharmaceutical composition of claim 16 in the manufacture of a medicament for the treatment of a neurological disorder in a subject in need thereof.

18. Use of a compound, or pharmaceutically acceptable salt thereof, of claim 15 or a pharmaceutical composition of claim 16 in the manufacture of a medicament for inhibiting toxicity in a cell related to a protein.

19. The use of claim 18, wherein the toxicity is α-synuclein-related toxicity.

20. The use of claim 18, wherein the toxicity is ApoE4-related toxicity.

21. The use of any one of claims 18 to 20, wherein the cell is a mammalian neural cell.

22. Use of an effective amount of a compound, or pharmaceutically acceptable salt thereof, of claim 15 or a pharmaceutical composition of claim 16 in the manufacture of a medicament for treating a stearoyl-CoA desaturase (SCD)-associated disorder in a subject in need thereof.

23. The use of claim 22, wherein the SCD-associated disorder is a SCD5-associated disorder.

24. Use of an effective amount of a compound of claim 15 or a pharmaceutical composition of claim 16 in the manufacture of a medicament for inhibiting SCD5.

25. Use of an effective amount of a compound of claim 15 or a pharmaceutical composition of claim 16 in the manufacture of a medicament for inhibiting SCD1.