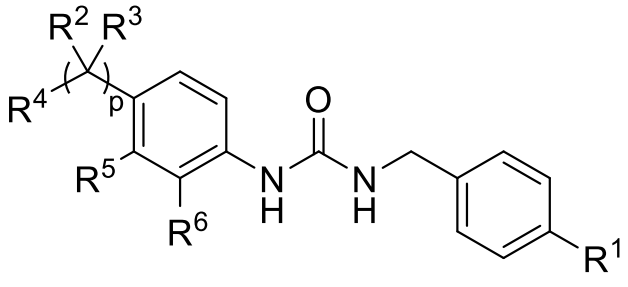
pathway or kynurenine pathway (ii) from NA in the Preiss-Handler pathway and (iii) from NAM, NR, and NMN in the salvage pathway (Verdin et al., *Science*. 2015, 350(6265):1208-13). Of these, the predominant NAD+ biosynthetic pathway involves the step of synthesis of nicotinamide mononucleotide (NMN) using nicotinamide and 5'-phosphoribosyl-pyrophosphate by the rate-limiting enzyme nicotinamide phosphoribosyl-transferase (NAMPT) that is critical to determination of longevity and responses to a variety of stresses (Fulco et al, *Dev Cell*. 2008, 14(5):661-73; Imai, *Curr Pharm Des*. 2009, 15(1):20-8; Revollo et al., *J Biol Chem*. 2004, 279(49):50754-63; Revollo et al., *Cell Metab*. 2007, Nov; 6(5):363-75; van der Veer et al., *J Biol Chem*. 2007, 282(15):10841-5; Yang et al., Cell. 2007, 130(6):1095-107). Thus, increasing the rate of NAMPT catalysis by a small molecule activator would be an effective strategy to boost NAD levels and thereby address a broad spectrum of disease states. These include cardiac diseases, chemotherapy induced tissue damage, renal diseases, metabolic diseases, muscular diseases, neurological diseases and injuries, diseases caused by impaired stem cell function, and DNA damage and primary mitochondrial disorders.

SUMMARY

[0007a] In an aspect of the present disclosure, there is provided a compound of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is halo or methoxy;

R^6 is hydrogen or halo; and

p is 0 or 1, wherein

when p is 1,

R^2 is hydrogen or C_1-C_6 alkyl or is taken together with Z^4 and the intervening atoms to form a 4-6 membered heterocycloalkyl or heterocycloalkenyl ring;

R^3 is hydrogen or C_1-C_6 alkyl;

R^4 is

a) $Z^1NR^aC(O)$–,

b) $Z^2C(O)NR^b$–,

c) $Z^3(CR^cR^d)_mNR^e$–,

d) $Z^4S(O)_2(CH_2)_n$–,

e) $Z^5OC(O)$–,

f) $NR^fR^gC(O)$–,

g) 5- to 10-membered heteroaryl optionally substituted with one or more independently selected C_1-C_6 alkyl or C_3-C_6 cycloalkyl substituents,

h) 3- to 10-membered heterocycloalkyl or heterocycloalkenyl optionally substituted with one or more substituents independently selected from the group consisting of halo, oxo, -OH, -CN, -C_1-C_6 alkyl optionally substituted with one or more independently selected R^y substituents, -C_1-C_6 alkoxy optionally substituted with one or more independently selected halo substituents, -$C(O)OC_1$-C_6 alkyl, -$C(O)C_1$-C_6 alkyl, -$S(O)_2$–C_1-C_6 alkyl, C_6-C_{12} aryl optionally substituted with one or more independently selected halo substituents, 3- to 6-membered heterocycloalkyl or heterocycloalkenyl optionally substituted with one or more independently selected oxo, 5- to 6-membered heteroaryl optionally substituted with one or more independently selected halo or -C_1-C_6 alkyl substituents, and C_3-C_6 cycloalkyl,

i) $Z^6S(O)_2N(R^s)$–,

j) $Z^7N(R^t)S(O)_2$–, or

k) Z^8-O-$(CH_2)_q$–; wherein

R^a and R^e are each independently hydrogen or C_1-C_6 alkyl;

R^b is hydrogen or C_1-C_6 alkyl or is taken together with R^5 and the intervening atoms to form a 5- to 6-membered heterocycloalkyl or heterocycloalkenyl ring;

R^c and R^d are each independently hydrogen or C_1-C_6 alkyl, or R^c and R^d together with the carbon to which they are attached form a C_3-C_6 cycloalkyl;

R^f and R^g together with the nitrogen to which they are attached form a 3- to 10-membered heterocycloalkyl or heterocycloalkenyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, -CN, oxo, -C_1-C_6 alkyl optionally substituted with one or more independently selected R^x substituents, -C_3-C_6 cycloalkyl, -C_1-C_6 alkoxy, -C(O)R^h, -NHC(O)OC_1-C_6 alkyl, -NR^jR^k, -C(O)NR^mR^n, 3- to 6-membered heterocycloalkyl or heterocycloalkenyl, and 5- to 6-membered heteroaryl;

each R^h is independently -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, or C_6-C_{12} aryl optionally substituted with one or more independently selected halo substituents;

each R^x is independently selected from the group consisting of halo, -OH, -C_3-C_6 cycloalkyl, -C_1-C_6 alkoxy, -NR^oR^p, 3- to 6-membered heterocycloalkyl or heterocycloalkenyl, and 5- to 6-membered heteroaryl;

each R^y is independently selected from the group consisting of halo, -OH, -CN, -C_1-C_6 alkoxy, -C(O)NR^qR^r, C_6-C_{12} aryl, and 5- to 6-membered heteroaryl;

each R^j, R^k, R^m, R^n, R^o, R^p, R^q, and R^r is independently hydrogen or C_1-C_6 alkyl;

R^s is hydrogen or -C_1-C_6 alkyl;

R^t is hydrogen or -C_1-C_6 alkyl;

m is 0 or 1;

n is 0, 1, or 2; and

q is 0 or 1;

Z^1 and Z^5 are each independently R^z;

Z^2 and Z^3 are each independently hydrogen or R^z;

Z^4 is hydrogen or R^z or is taken together with R^2 and the intervening atoms to form a 4-6 membered heterocycloalkyl or heterocycloalkenyl ring;

Z^6 is selected from the group consisting of 5- to 6-membered heterocycloalkyl or heterocycloalkenyl, 5- to 6-membered heteroaryl, and C_1-C_6 alkyl;

Z^7 is C_6-C_{12} aryl;

Z^8 is selected from the group consisting of 5- to 6-membered heteroaryl and C_3-C_6 cycloalkyl, and

R^z is selected from the group consisting of:

a) C_1-C_6 alkyl optionally substituted with one or more substituents independently selected from the group consisting of –OH, -CN, C_3-C_6 cycloalkyl, -NHC_1-C_6 alkyl, C_6-C_{12} aryl, 3- to 10-membered heterocycloalkyl or heterocycloalkenyl, and 5- to 10-membered heteroaryl, wherein the C_6-C_{12} aryl, 3- to 10-membered heterocycloalkyl or heterocycloalkenyl, and 5- to 10-membered heteroaryl are each independently optionally substituted with one or more substituents independently selected from the group consisting of halo, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

b) C_3-C_6 cycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of C_6-C_{12} aryl, C_1-C_6 alkyl, and C_1-C_6 alkoxy optionally substituted with 5- or 10-membered heteroaryl, wherein the 5- or 10-membered heteroaryl is optionally further substituted with one or more independently selected C_1-C_6 alkyl;

c) C_1-C_6 alkoxy;

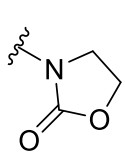
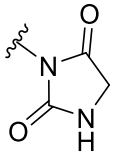
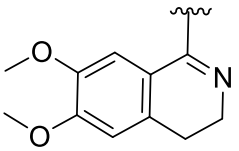
d) 3- to 10-membered heterocycloalkyl or heterocycloalkenyl optionally substituted with one or more substituents independently selected from the group consisting of halo, oxo, -OH, -CN, -C_1-C_6 alkyl optionally substituted with one or more independently selected R^w substituents, -C_1-C_6 alkoxy optionally substituted with one or more independently selected halo substituents, -C(O)OC_1-C_6 alkyl, -C(O)C_1-C_6 alkyl, -S(O)$_2$–C_1-C_6 alkyl, C_6-C_{12} aryl optionally substituted with one or more independently selected halo substituents, 3- to 6-membered heterocycloalkyl or heterocycloalkenyl, and 5- to 6-membered heteroaryl optionally substituted with one or more independently selected C_1-C_6 alkyl substituents; wherein each R^w is independently selected from the group consisting of halo, -OH, -CN, -C_1-C_6 alkoxy, -C(O)NR^uR^v, C_6-C_{12} aryl, and 5- to 6-membered heteroaryl; and wherein R^u and R^v are each independently hydrogen or C_1-C_6 alkyl;

e) C_6-C_{12} aryl; and

f) 5- to 10-membered heteroaryl optionally substituted with one or more independently selected C_1-C_6 alkyl substituents; and

R^5 is hydrogen, halo, or is taken together with R^b and the intervening atoms form a 5- to 6-membered heterocycloalkyl or heterocycloalkenyl ring, provided that

(1) when R^4 is $Z^1NR^aC(O)$–, Z^1 is other than methyl, unsubstituted cyclopropyl, –$C(CH_3)_2CH_2OH$, and –CH_2-thiofuran;

(2) R^4 is other than 4-methylpiperazinyl, 4-phenylpiperazinyl, 4-pyridylpiperazinyl, 4-(furanylmethyl)piperazinyl, , ,and ; and

(3) the compound of Formula (II) is not a compound of Table 1X; and

when p is 0, R^4 is

l) 3- to 6-membered heterocycloalkyl or heterocycloalkenyl comprising exactly two annular heteroatoms, both of which are nitrogen atoms, wherein the 3- to 6-membered heterocycloalkyl or heterocycloalkenyl is substituted with one or more independently selected –C_1-C_6 alkyl substituents and is optionally further substituted with one or more oxo substituents,

m) 3- to 6-membered heterocycloalkyl or heterocycloalkenyl comprising exactly one annular heteroatom, which is an oxygen atom, wherein the 3- to 6-membered heterocycloalkyl or heterocycloalkenyl is optionally substituted with one or more independently selected oxo or –C_1-C_6 alkyl substituents,

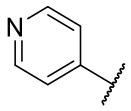
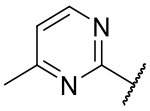
n) 3- to 6-membered heterocycloalkyl or heterocycloalkenyl substituted with one or more independently selected -$S(O)_2$-C_1-C_6alkyl substituents and optionally further substituted with one or more independently selected oxo or –C_1-C_6 alkyl substituents,

o) 5-membered heterocycloalkyl or heterocycloalkenyl comprising exactly two annular heteroatoms, one of which is a nitrogen atom and the other of which is an oxygen atom, wherein the 5-membered heterocycloalkyl or heterocycloalkenyl is optionally substituted with one or more independently selected oxo, C_1-C_6 alkyl, or -$S(O)_2$-(C_1-C_6 alkyl) substituents,

p) 6-membered heterocycloalkyl or heterocycloalkenyl comprising exactly two annular heteroatoms, one of which is a sulfur atom and the other of which is a nitrogen atom, wherein the 6-membered heterocycloalkyl or heterocycloalkenyl is optionally substituted with one or more independently selected oxo, C_1-C_6 alkyl, or -S(O)$_2$-(C_1-C_6 alkyl) substituents,

q) 5-membered heteroaryl comprising exactly two annular heteroatoms, one of which is a nitrogen atom and the other of which is an oxygen atom, wherein the 5-membered heteroaryl is substituted with exactly one methyl substituent,

r) 5-membered heteroaryl comprising exactly two annular heteroatoms, both of which are nitrogen atoms, wherein the 5-membered heteroaryl is substituted with one or more methyl substituents,

s) 6-membered heteroaryl comprising one or two annular heteroatoms and optionally substituted with one or more methyl substituents, wherein the 6-memebred heteroaryl is other than  or ,

t) Z^9-S(O)$_2$–,

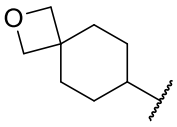
u) Z^{10}-S(O)$_2$–NH–,

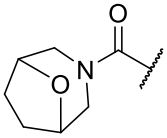
v) Z^{11}-C(O)-NH–,

w) Z^{12}-CH_2-O–,

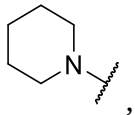
x) Z^{13}-O–,

y) Z^{14}-C(H)(C_1-C_6 alkyl)-NH-C(O)–,

z) , or

aa) , wherein

Z^9 is selected from the group consisting of cyclopropyl, C_6-C_{12} aryl, 3- to 10-membered heterocycloalkyl or hetercycloalkenyl optionally substituted with one or more independently selected R^A substituents, -NH(C_1-C_6 alkyl), -NH_2 substituted with one or more

independently selected R^B substituents, and C_1-C_6 alkyl optionally substituted with one or more independently selected R^C substituents, provided that Z^9 is other than , unsubstituted methyl, or unsubstituted ethyl, wherein:

R^A is -C_1-C_6 alkyl or -CN; and

R^B is (i) -C_1-C_6 alkyl-(5- to 10-membered heteroaryl), or (ii) 5- to 10-membered heteroaryl optionally substituted with one or more independently selected C_6-C_{12} aryl; and

R^C is 3- to 8-membered heterocycloalkyl or heterocycloalkenyl;

Z^{10} is C_1-C_6 alkyl substituted with one or more independently selected C_6-C_{12} aryl substituents;

Z^{11} is selected from the group consisting of C_3-C_{10} cycloalkyl and C_1-C_6 alkyl substituted with one or more independently selected 3- to 10-membered heterocycloalkyl or hetercycloalkenyl substituents, provided that, when Z^{11} is cyclopropyl, then R^1 is other than methoxy;

Z^{12} is selected from the group consisting of C_6-C_{12} aryl, 5- to 10-membered heteroaryl, 3- to 10-memebred heterocycloalkyl or heterocycloalkenyl, C_1-C_6 alkyl substituted with one or more independently selected 3- to 10-membered heterocycloalkyl or hetercycloalkenyl substituents or 5- to 10-membered heteroaryl substituents, and -C(O)-(3- to 10-membered heterocycloalkyl or heterocycloalkenyl);

Z^{13} is 5- to 10-membered heteroaryl substituted with one or more independently selected -C(O)-NH(C_1-C_6 alkyl) substituents; and

Z^{14} is 5- to 10-membered heteroaryl optionally substituted with one or more independently selected C_1-C_6 alkyl substituents; and

R^5 is hydrogen.

[0007b] In another aspect of the present disclosure, there is provided a compound selected from the group consisting of compounds of Table 1, or a pharmaceutically acceptable salt thereof.

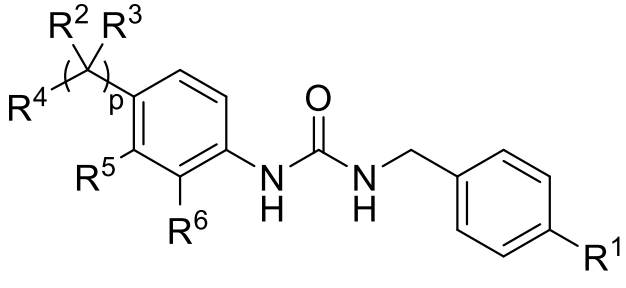
[0007c] In a further aspect of the present disclosure, there is provided a pharmaceutical

composition comprising a compound according to any one of claims 1-27, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0007d] In another aspect of the present disclosure, there is provided a use of a compound of any one of claims 1-27, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 28, in the manufacture of a medicament for treating a disease or condition mediated by NAMPT activity.

[0007e] In a further aspect of the present disclosure, there is provided a compound of any one of claims 1-27, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 28, for use in therapy.

[0008] In one example, provided herein is a compound of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

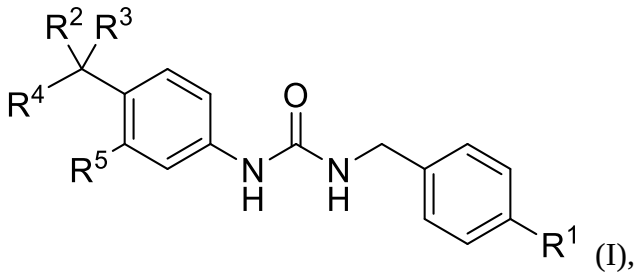
R^1 is halo or methoxy;

R^6 is hydrogen or halo; and

p is 0 or 1, wherein

when p is 1,

[0009] In another example, provided herein is a compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is halo or methoxy;

R^2 is hydrogen or C_1-C_6 alkyl or is taken together with Z^4 and the intervening atoms to form a 4-6 membered heterocycloalkyl or heterocycloalkenyl ring

R^3 is hydrogen or C_1-C_6 alkyl;

R^4 is

a) $Z^1NR^aC(O)$–,

b) $Z^2C(O)NR^b$–,

c) $Z^3(CR^cR^d)_mNR^e$–,

d) $Z^4S(O)_2(CH_2)_n$–,

e) $Z^5OC(O)$–,

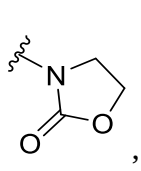
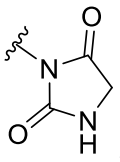
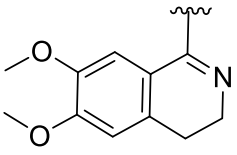
f) $NR^fR^gC(O)$–,

g) 5- to 10-membered heteroaryl optionally substituted with one or more independently selected C_1-C_6 alkyl substituents, or

h) 3- to 10-membered heterocycloalkyl or heterocycloalkenyl optionally substituted with one or more substituents independently selected from the group consisting of halo, oxo, -OH, -CN, -C_1-C_6 alkyl optionally substituted with one or more independently selected R^y substituents, -C_1-C_6 alkoxy optionally substituted with one or more independently selected halo substituents, -$C(O)OC_1$-C_6 alkyl, -$C(O)C_1$-C_6 alkyl, -$S(O)_2$–C_1-C_6 alkyl, C_6-C_{12} aryl optionally substituted with one or more independently selected halo substituents, 3- to 6-membered heterocycloalkyl or

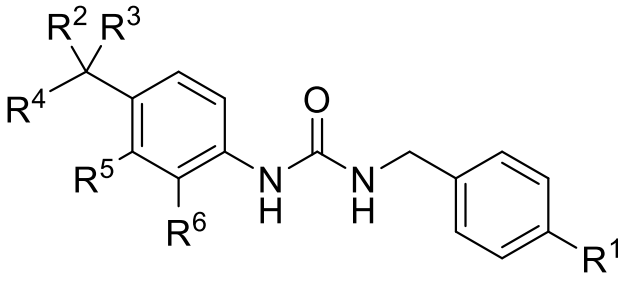
f) 5- to 10-membered heteroaryl optionally substituted with one or more independently selected C_1-C_6 alkyl substituents,

wherein (1) when R^4 is $Z^1NR^aC(O)$–, Z^1 is other than methyl, unsubstituted cyclopropyl, $–C(CH_3)_2CH_2OH$, and $–CH_2$-thiofuran;

(2) R^4 is other than 4-methylpiperazinyl, 4-phenylpiperazinyl, 4-pyridylpiperazinyl, 4-(furanylmethyl)piperazinyl,  ,  ,and  ; and

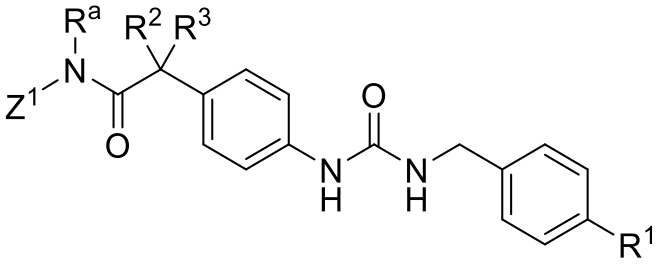
(3) the compound of Formula (I) is not a compound of Table 1X.

[0010] In another example, provided herein is a compound of Formula (I-G):

 (I-G),

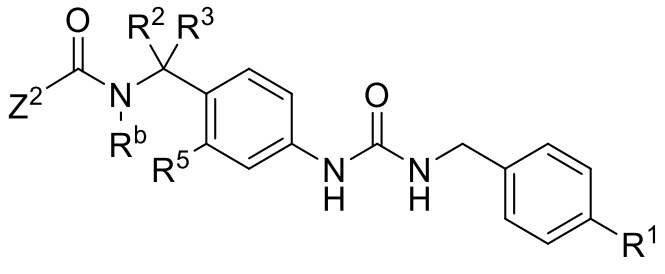
or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5, and R^6 are as defined for Formula (II) or any variation or example thereof.

[0011] In another example, provided herein is a compound of Formula (I-A):

 (I-A),

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^a, and Z^1 are as defined for Formula (II) or any variation or example thereof.

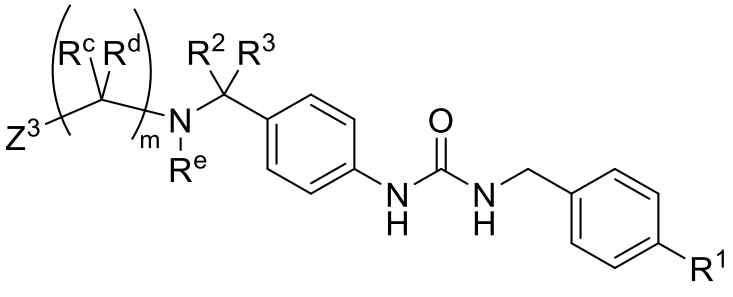
[0012] In another example, provided herein is a compound of Formula (I-B):



(I-B),

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^5, R^b, and Z^2 are as defined for Formula (II) or any variation or example thereof.

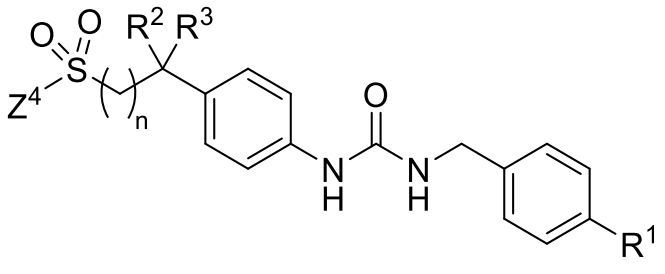
[0013] In another example, provided herein is a compound of Formula (I-C):



(I-C),

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^c, R^d, R^e, m, and Z^3 are as defined for Formula (II) or any variation or example thereof.

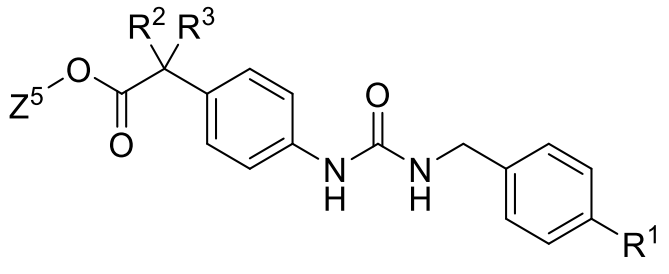
[0014] In another example, provided herein is a compound of Formula (I-D):



(I-D),

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, n, and Z^4 are as defined for Formula (II) or any variation or example thereof.

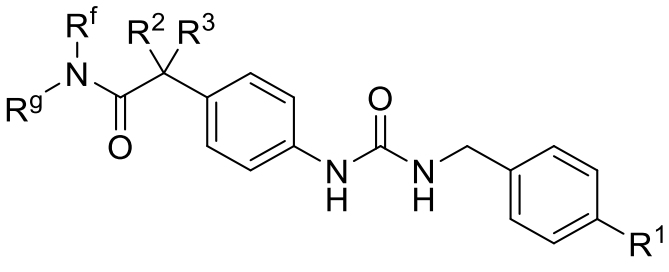
[0015] In another example, provided herein is a compound of Formula (I-E):



(I-E),

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, and Z^5 are as defined for Formula (II) or any variation or example thereof.

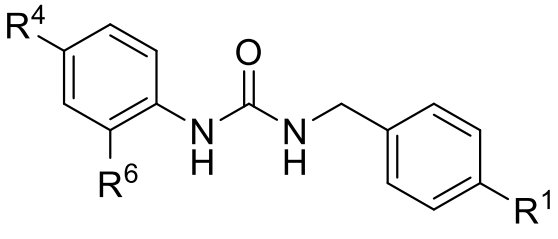
[0016] In another example, provided herein is a compound of Formula (I-F):



(I-F),

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^f, and R^g are as defined for Formula (II) or any variation or example thereof.

[0017] In another example, provided herein is a compound of Formula (II-A):



(II-A),

or a pharmaceutically acceptable salt thereof, wherein R^1, R^4, and R^6 are as defined for Formula (II) or any variation or example thereof.

[0018] In a further example, provided herein are pharmaceutical compositions comprising at least one compound of Formula (II), (I-G), (I), (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), or (II-A), such as a compound of Table 1, or a stereoisomer or tautomer thereof, or a

pharmaceutically acceptable salt of any of the foregoing, optionally further comprising a pharmaceutically acceptable excipient.

[0019] In another example, provided herein is a method of treating a disease or condition mediated by NAMPT activity in a subject in need thereof, comprising administering to the subject an effective amount of at least one compound Formula (II), (I-G), (I), (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), or (II-A), such as a compound of Table 1, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising at least one compound of Formula (II), (I-G), (I), (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), or (II-A). In some examples, the disease or condition is selected from the group consisting of cancer, a hyperproliferative disease or condition, an inflammatory disease or condition, a metabolic disorder, a cardiac disease or condition, chemotherapy induced tissue damage, a renal disease, a metabolic disease, a neurological disease or injury, a neurodegenerative disorder or disease, diseases caused by impaired stem cell function, diseases caused by DNA damage, primary mitochondrial disorders, or a muscule disease or muscle wasting disorder. In some examples, the disease or condition is selected from the group consisting of obesity, atherosclerosis, insulin resistance, type 2 diabetes, cardiovascular disease, Alzheimer’s disease, Huntington’s disease, Parkinson's disease, amyotrophic lateral sclerosis, depression, Down syndrome, neonatal nerve injury, aging, axonal degeneration, carpal tunnel syndrome, Guillain-Barre syndrome, nerve damage, polio (poliomyelitis), and spinal cord injury.

[0020] Additional examples, features, and advantages of the present disclosure will be apparent from the following detailed description and through practice of the present disclosure.

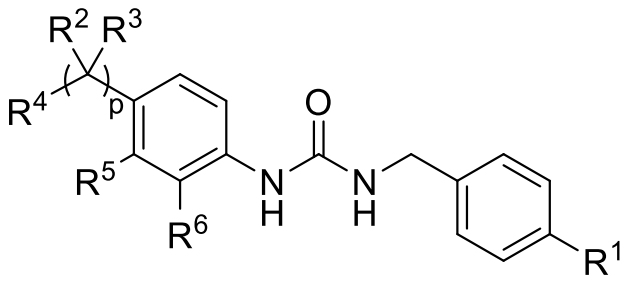
[0021] For the sake of brevity, the disclosures of publications cited in this specification, including patents, are herein incorporated by reference.

DETAILED DESCRIPTION

Definitions

CLAIMS

1. A compound of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is halo or methoxy;

R^6 is hydrogen or halo; and

p is 0 or 1, wherein

when p is 1,

R^2 is hydrogen or C_1-C_6 alkyl or is taken together with Z^4 and the intervening atoms to form a 4-6 membered heterocycloalkyl or heterocycloalkenyl ring;

R^3 is hydrogen or C_1-C_6 alkyl;

R^4 is

a) $Z^1NR^aC(O)$–,

b) $Z^2C(O)NR^b$–,

c) $Z^3(CR^cR^d)_mNR^e$–,

d) $Z^4S(O)_2(CH_2)_n$–,

e) $Z^5OC(O)$–,

f) $NR^fR^gC(O)$–,

g) 5- to 10-membered heteroaryl optionally substituted with one or more independently selected C_1-C_6 alkyl or C_3-C_6 cycloalkyl substituents,

h) 3- to 10-membered heterocycloalkyl or heterocycloalkenyl optionally substituted with one or more substituents independently selected from the group consisting of halo, oxo, -OH, -CN, -C_1-C_6 alkyl optionally substituted with one or more independently selected R^y substituents, -C_1-C_6 alkoxy optionally substituted with one or more independently selected halo substituents, -$C(O)OC_1$-C_6 alkyl, -$C(O)C_1$-C_6 alkyl, -$S(O)_2$–C_1-C_6 alkyl, C_6-C_{12} aryl optionally substituted with one or more independently selected halo substituents, 3- to 6-membered heterocycloalkyl or heterocycloalkenyl optionally substituted with one or more independently selected oxo, 5- to 6-membered

heteroaryl optionally substituted with one or more independently selected halo or -C_1-C_6 alkyl substituents, and C_3-C_6 cycloalkyl,

i) $Z^6S(O)_2N(R^s)$–,

j) $Z^7N(R^t)S(O)_2$–, or

k) Z^8-O-$(CH_2)_q$–; wherein

R^a and R^e are each independently hydrogen or C_1-C_6 alkyl;

R^b is hydrogen or C_1-C_6 alkyl or is taken together with R^5 and the intervening atoms to form a 5- to 6-membered heterocycloalkyl or heterocycloalkenyl ring;

R^c and R^d are each independently hydrogen or C_1-C_6 alkyl, or R^c and R^d together with the carbon to which they are attached form a C_3-C_6 cycloalkyl;

R^f and R^g together with the nitrogen to which they are attached form a 3- to 10-membered heterocycloalkyl or heterocycloalkenyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, -CN, oxo, -C_1-C_6 alkyl optionally substituted with one or more independently selected R^x substituents, -C_3-C_6 cycloalkyl, -C_1-C_6 alkoxy, -C(O)R^h, -NHC(O)OC_1-C_6 alkyl, -NR^jR^k, -C(O)NR^mR^n, 3- to 6-membered heterocycloalkyl or heterocycloalkenyl, and 5- to 6-membered heteroaryl;

each R^h is independently -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, or C_6-C_{12} aryl optionally substituted with one or more independently selected halo substituents;

each R^x is independently selected from the group consisting of halo, -OH, -C_3-C_6 cycloalkyl, -C_1-C_6 alkoxy, -NR^oR^p, 3- to 6-membered heterocycloalkyl or heterocycloalkenyl, and 5- to 6-membered heteroaryl;

each R^y is independently selected from the group consisting of halo, -OH, -CN, -C_1-C_6 alkoxy, -C(O)NR^qR^r, C_6-C_{12} aryl, and 5- to 6-membered heteroaryl;

each R^j, R^k, R^m, R^n, R^o, R^p, R^q, and R^r is independently hydrogen or C_1-C_6 alkyl;

R^s is hydrogen or -C_1-C_6 alkyl;

R^t is hydrogen or -C_1-C_6 alkyl;

m is 0 or 1;

n is 0, 1, or 2; and

q is 0 or 1;

Z^1 and Z^5 are each independently R^z;

Z^2 and Z^3 are each independently hydrogen or R^z;

Z^4 is hydrogen or R^z or is taken together with R^2 and the intervening atoms to form a 4-6 membered heterocycloalkyl or heterocycloalkenyl ring;

Z^6 is selected from the group consisting of 5- to 6-membered heterocycloalkyl or heterocycloalkenyl, 5- to 6-membered heteroaryl, and C_1-C_6 alkyl;

Z^7 is C_6-C_{12} aryl;

Z^8 is selected from the group consisting of 5- to 6-membered heteroaryl and C_3-C_6 cycloalkyl, and

R^z is selected from the group consisting of:

a) C_1-C_6 alkyl optionally substituted with one or more substituents independently selected from the group consisting of –OH, -CN, C_3-C_6 cycloalkyl, -NHC_1-C_6 alkyl, C_6-C_{12} aryl, 3- to 10-membered heterocycloalkyl or heterocycloalkenyl, and 5- to 10-membered heteroaryl, wherein the C_6-C_{12} aryl, 3- to 10-membered heterocycloalkyl or heterocycloalkenyl, and 5- to 10-membered heteroaryl are each independently optionally substituted with one or more substituents independently selected from the group consisting of halo, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

b) C_3-C_6 cycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of C_6-C_{12} aryl, C_1-C_6 alkyl, and C_1-C_6 alkoxy optionally substituted with 5- or 10-membered heteroaryl, wherein the 5- or 10-membered heteroaryl is optionally further substituted with one or more independently selected C_1-C_6 alkyl;

c) C_1-C_6 alkoxy;

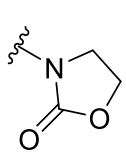
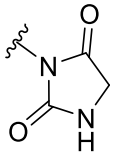
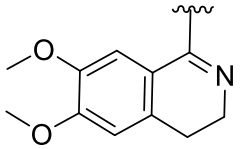
d) 3- to 10-membered heterocycloalkyl or heterocycloalkenyl optionally substituted with one or more substituents independently selected from the group consisting of halo, oxo, -OH, -CN, -C_1-C_6 alkyl optionally substituted with one or more independently selected R^w substituents, -C_1-C_6 alkoxy optionally substituted with one or more independently selected halo substituents, -C(O)OC_1-C_6 alkyl, -C(O)C_1-C_6 alkyl, -$S(O)_2$–C_1-C_6 alkyl, C_6-C_{12} aryl optionally substituted with one or more independently selected halo substituents, 3- to 6-membered heterocycloalkyl or heterocycloalkenyl, and 5- to 6-membered heteroaryl optionally substituted with one or more independently selected C_1-C_6 alkyl substituents; wherein each R^w is independently selected from the group consisting of halo, -OH, -CN, -C_1-C_6 alkoxy, -C(O)NR^uR^v, C_6-C_{12} aryl, and 5- to 6-membered heteroaryl; and wherein R^u and R^v are each independently hydrogen or C_1-C_6 alkyl;

e) C_6-C_{12} aryl; and

f) 5- to 10-membered heteroaryl optionally substituted with one or more independently selected C_1-C_6 alkyl substituents; and

R^5 is hydrogen, halo, or is taken together with R^b and the intervening atoms form a 5- to 6-membered heterocycloalkyl or heterocycloalkenyl ring, provided that

(1) when R^4 is $Z^1NR^aC(O)$–, Z^1 is other than methyl, unsubstituted cyclopropyl, –$C(CH_3)_2CH_2OH$, and –CH_2-thiofuran;

(2) R^4 is other than 4-methylpiperazinyl, 4-phenylpiperazinyl, 4-pyridylpiperazinyl, 4-(furanylmethyl)piperazinyl, , ,and ; and

(3) the compound of Formula (II) is not a compound of Table 1X; and

when p is 0, R^4 is

l) 3- to 6-membered heterocycloalkyl or heterocycloalkenyl comprising exactly two annular heteroatoms, both of which are nitrogen atoms, wherein the 3- to 6-membered heterocycloalkyl or heterocycloalkenyl is substituted with one or more independently selected –C_1-C_6 alkyl substituents and is optionally further substituted with one or more oxo substituents,

m) 3- to 6-membered heterocycloalkyl or heterocycloalkenyl comprising exactly one annular heteroatom, which is an oxygen atom, wherein the 3- to 6-membered heterocycloalkyl or heterocycloalkenyl is optionally substituted with one or more independently selected oxo or –C_1-C_6 alkyl substituents,

n) 3- to 6-membered heterocycloalkyl or heterocycloalkenyl substituted with one or more independently selected -$S(O)_2$-C_1-C_6alkyl substituents and optionally further substituted with one or more independently selected oxo or –C_1-C_6 alkyl substituents,

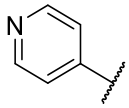
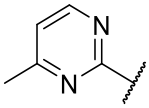
o) 5-membered heterocycloalkyl or heterocycloalkenyl comprising exactly two annular heteroatoms, one of which is a nitrogen atom and the other of which is an oxygen atom, wherein the 5-membered heterocycloalkyl or heterocycloalkenyl is optionally substituted with one or more independently selected oxo, C_1-C_6 alkyl, or -$S(O)_2$-(C_1-C_6 alkyl) substituents,

p) 6-membered heterocycloalkyl or heterocycloalkenyl comprising exactly two annular heteroatoms, one of which is a sulfur atom and the other of which is a nitrogen atom, wherein

the 6-membered heterocycloalkyl or heterocycloalkenyl is optionally substituted with one or more independently selected oxo, C_1-C_6 alkyl, or -$S(O)_2$-(C_1-C_6 alkyl) substituents,

q) 5-membered heteroaryl comprising exactly two annular heteroatoms, one of which is a nitrogen atom and the other of which is an oxygen atom, wherein the 5-membered heteroaryl is substituted with exactly one methyl substituent,

r) 5-membered heteroaryl comprising exactly two annular heteroatoms, both of which are nitrogen atoms, wherein the 5-membered heteroaryl is substituted with one or more methyl substituents,

s) 6-membered heteroaryl comprising one or two annular heteroatoms and optionally substituted with one or more methyl substituents, wherein the 6-memebred heteroaryl is other than  or ,

t) Z^9-$S(O)_2$–,

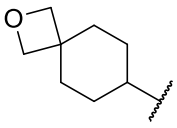
u) Z^{10}-$S(O)_2$–NH–,

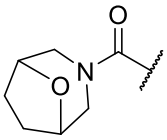
v) Z^{11}-C(O)-NH–,

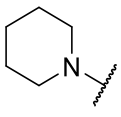
w) Z^{12}-CH_2-O–,

x) Z^{13}-O–,

y) Z^{14}-C(H)(C_1-C_6 alkyl)-NH-C(O)–,

z) , or

aa) , wherein

Z^9 is selected from the group consisting of cyclopropyl, C_6-C_{12} aryl, 3- to 10-membered heterocycloalkyl or hetercycloalkenyl optionally substituted with one or more independently selected R^A substituents, -NH(C_1-C_6 alkyl), -NH_2 substituted with one or more independently selected R^B substituents, and C_1-C_6 alkyl optionally substituted with one or more independently selected R^C substituents, provided that Z^9 is other than , unsubstituted methyl, or unsubstituted ethyl, wherein:

R^A is -C_1-C_6 alkyl or -CN; and

R^B is (i) -C_1-C_6 alkyl-(5- to 10-membered heteroaryl), or (ii) 5- to 10-membered heteroaryl optionally substituted with one or more independently selected C_6-C_{12} aryl; and

R^C is 3- to 8-membered heterocycloalkyl or heterocycloalkenyl;

Z^{10} is C_1-C_6 alkyl substituted with one or more independently selected C_6-C_{12} aryl substituents;

Z^{11} is selected from the group consisting of C_3-C_{10} cycloalkyl and C_1-C_6 alkyl substituted with one or more independently selected 3- to 10-membered heterocycloalkyl or hetercycloalkenyl substituents, provided that, when Z^{11} is cyclopropyl, then R^1 is other than methoxy;

Z^{12} is selected from the group consisting of C_6-C_{12} aryl, 5- to 10-membered heteroaryl, 3- to 10-memebred heterocycloalkyl or heterocycloalkenyl, C_1-C_6 alkyl substituted with one or more independently selected 3- to 10-membered heterocycloalkyl or hetercycloalkenyl substituents or 5- to 10-membered heteroaryl substituents, and -C(O)-(3- to 10-membered heterocycloalkyl or heterocycloalkenyl);

Z^{13} is 5- to 10-membered heteroaryl substituted with one or more independently selected -C(O)-NH(C_1-C_6 alkyl) substituents; and

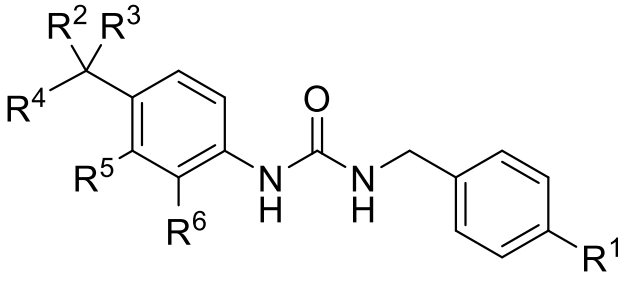
Z^{14} is 5- to 10-membered heteroaryl optionally substituted with one or more independently selected C_1-C_6 alkyl substituents; and

R^5 is hydrogen.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is Cl.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is methoxy.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (II) is a compound of Formula (I-G):



(I-G),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is halo or methoxy;

R^2 is hydrogen or C_1-C_6 alkyl or is taken together with Z^4 and the intervening atoms to form a 4-6 membered heterocycloalkyl or heterocycloalkenyl ring;

R^3 is hydrogen or C_1-C_6 alkyl;

R^4 is

a) $Z^1NR^aC(O)$–,

b) $Z^2C(O)NR^b$–,

c) $Z^3(CR^cR^d)_mNR^e$–,

d) $Z^4S(O)_2(CH_2)_n$–,

e) $Z^5OC(O)$–,

f) $NR^fR^gC(O)$–,

g) 5- to 10-membered heteroaryl optionally substituted with one or more independently selected C_1-C_6 alkyl or C_3-C_6 cycloalkyl substituents,

h) 3- to 10-membered heterocycloalkyl or heterocycloalkenyl optionally substituted with one or more substituents independently selected from the group consisting of halo, oxo, -OH, -CN, -C_1-C_6 alkyl optionally substituted with one or more independently selected R^y substituents, -C_1-C_6 alkoxy optionally substituted with one or more independently selected halo substituents, -$C(O)OC_1$-C_6 alkyl, -$C(O)C_1$-C_6 alkyl, -$S(O)_2$–C_1-C_6 alkyl, C_6-C_{12} aryl optionally substituted with one or more independently selected halo substituents, 3- to 6-membered heterocycloalkyl or heterocycloalkenyl optionally substituted with one or more independently selected oxo, 5- to 6-membered heteroaryl optionally substituted with one or more independently selected halo or -C_1-C_6 alkyl substituents, and C_3-C_6 cycloalkyl,

i) $Z^6S(O)_2N(R^s)$–,

j) $Z^7N(R^t)S(O)_2$–, or

k) Z^8-O-$(CH_2)_q$–; wherein

R^a and R^e are each independently hydrogen or C_1-C_6 alkyl;

R^b is hydrogen or C_1-C_6 alkyl or is taken together with R^5 and the intervening atoms to form a 5- to 6-membered heterocycloalkyl or heterocycloalkenyl ring;

R^c and R^d are each independently hydrogen or C_1-C_6 alkyl, or R^c and R^d together with the carbon to which they are attached form a C_3-C_6 cycloalkyl;

R^f and R^g together with the nitrogen to which they are attached form a 3- to 10-membered heterocycloalkyl or heterocycloalkenyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, -CN, oxo, -C_1-C_6 alkyl optionally substituted with one or more independently selected R^x substituents, -C_3-C_6 cycloalkyl, -C_1-C_6 alkoxy, -C(O)R^h, -NHC(O)OC_1-C_6 alkyl, -NR^jR^k, -C(O)NR^mR^n, 3- to 6-membered heterocycloalkyl or heterocycloalkenyl, and 5- to 6-membered heteroaryl;

each R^h is independently -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, or C_6-C_{12} aryl optionally substituted with one or more independently selected halo substituents;

each R^x is independently selected from the group consisting of halo, -OH, -C_3-C_6 cycloalkyl, -C_1-C_6 alkoxy, -NR^oR^p, 3- to 6-membered heterocycloalkyl or heterocycloalkenyl, and 5- to 6-membered heteroaryl;

each R^y is independently selected from the group consisting of halo, -OH, -CN, -C_1-C_6 alkoxy, -C(O)NR^qR^r, C_6-C_{12} aryl, and 5- to 6-membered heteroaryl;

each R^j, R^k, R^m, R^n, R^o, R^p, R^q, and R^r is independently hydrogen or C_1-C_6 alkyl;

R^s is hydrogen or -C_1-C_6 alkyl;

R^t is hydrogen or -C_1-C_6 alkyl;

m is 0 or 1;

n is 0, 1, or 2;

q is 0 or 1;

Z^2 and Z^3 are each independently hydrogen or R^z;

Z^4 is hydrogen or R^z or is taken together with R^2 and the intervening atoms to form a 4-6 membered heterocycloalkyl or heterocycloalkenyl ring;

Z^6 is selected from the group consisting of 5- to 6-membered heterocycloalkyl or heterocycloalkenyl, 5- to 6-membered heteroaryl, and C_1-C_6 alkyl;

Z^7 is C_6-C_{12} aryl;

Z^8 is selected from the group consisting of 5- to 6-membered heteroaryl and C_3-C_6 cycloalkyl, and

R^z is selected from the group consisting of:

a) C_1-C_6 alkyl optionally substituted with one or more substituents independently selected from the group consisting of –OH, -CN, C_3-C_6 cycloalkyl, -NHC_1-C_6 alkyl, C_6-C_{12} aryl, 3- to 10-membered heterocycloalkyl or heterocycloalkenyl, and 5- to 10-membered heteroaryl, wherein the C_6-C_{12} aryl, 3- to 10-membered heterocycloalkyl or heterocycloalkenyl, and 5- to 10-membered heteroaryl are each independently optionally substituted with one or more substituents independently selected from the group consisting of halo, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

b) C_3-C_6 cycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of C_6-C_{12} aryl, C_1-C_6 alkyl, and C_1-C_6 alkoxy optionally substituted with 5- or 10-membered heteroaryl, wherein the 5- or 10-membered heteroaryl is optionally further substituted with one or more independently selected C_1-C_6 alkyl;

c) C_1-C_6 alkoxy;

d) 3- to 10-membered heterocycloalkyl or heterocycloalkenyl optionally substituted with one or more substituents independently selected from the group consisting of halo, oxo, -OH, -CN, -C_1-C_6 alkyl optionally substituted with one or more independently selected R^w substituents, -C_1-C_6 alkoxy optionally substituted with one or more independently selected halo substituents, -C(O)OC_1-C_6 alkyl, -C(O)C_1-C_6 alkyl, -S(O)$_2$–C_1-C_6 alkyl, C_6-C_{12} aryl optionally substituted with one or more independently selected halo substituents, 3- to 6-membered heterocycloalkyl or heterocycloalkenyl, and 5- to 6-membered heteroaryl optionally substituted with one or more independently selected C_1-C_6 alkyl substituents; wherein each R^w is independently selected from the group consisting of halo, -OH, -CN, -C_1-C_6 alkoxy, -C(O)NR^uR^v, C_6-C_{12} aryl, and 5- to 6-membered heteroaryl; and wherein R^u and R^v are each independently hydrogen or C_1-C_6 alkyl;

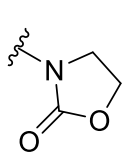
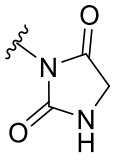
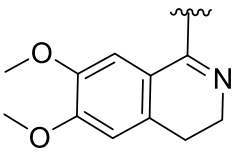
e) C_6-C_{12} aryl; and

f) 5- to 10-membered heteroaryl optionally substituted with one or more independently selected C_1-C_6 alkyl substituents;

R^5 is hydrogen, halo, or is taken together with R^b and the intervening atoms form a 5- to 6-membered heterocycloalkyl or heterocycloalkenyl ring; and

R^6 is hydrogen or halo, Z^1 and Z^5 are each independently R^z, provided that

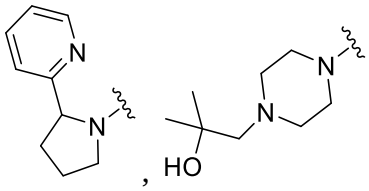
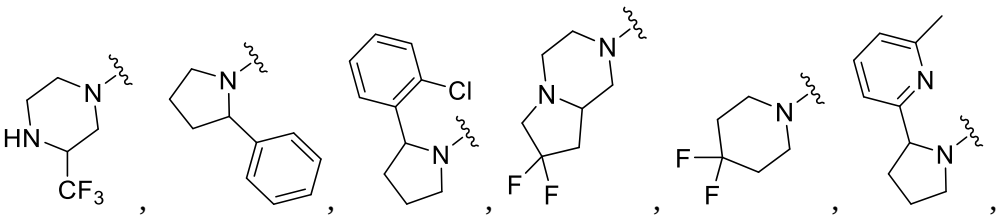
(1) when R^4 is $Z^1NR^aC(O)$–, Z^1 is other than methyl, unsubstituted cyclopropyl, –$C(CH_3)_2CH_2OH$, and –CH_2-thiofuran;

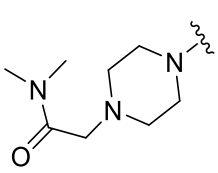
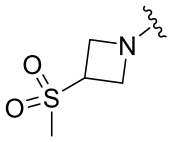
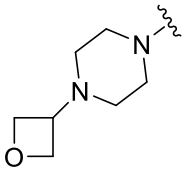
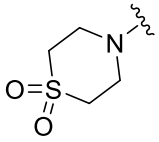
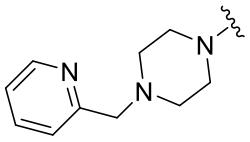
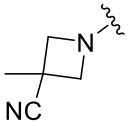
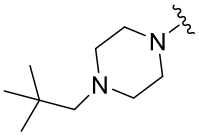
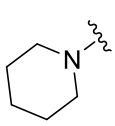
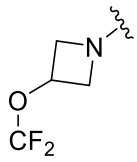
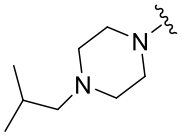
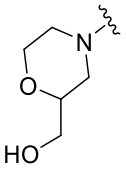
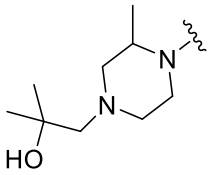
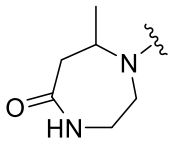
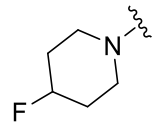
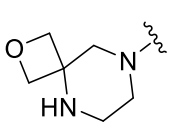
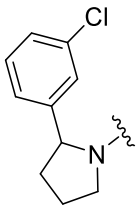
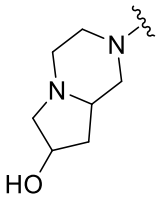
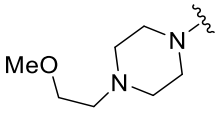
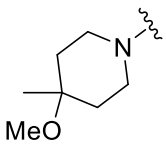
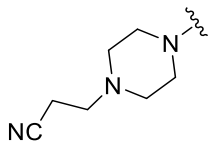
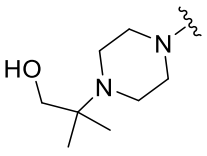
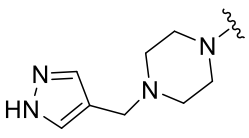
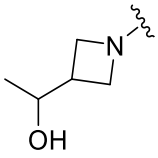
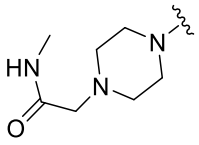
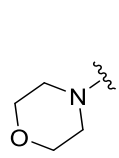
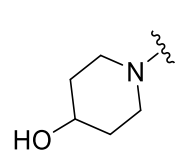
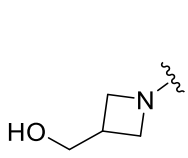
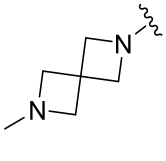
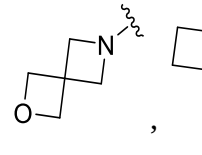
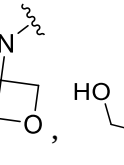
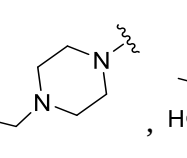
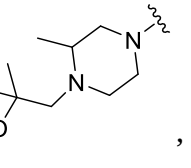
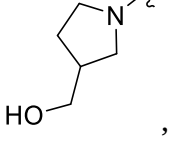
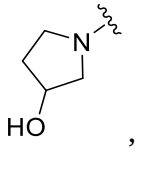
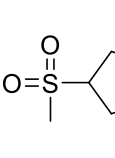
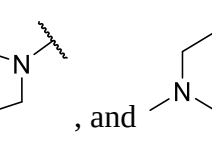
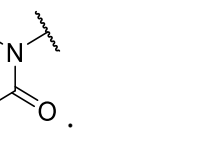
(2) R^4 is other than 4-methylpiperazinyl, 4-phenylpiperazinyl, 4-pyridylpiperazinyl, 4-(furanylmethyl)piperazinyl, , ,and ; and

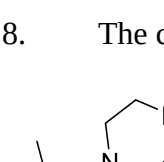
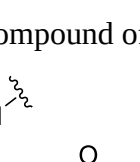
(3) the compound of Formula (I-G) is not a compound of Table 1X.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are each hydrogen.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R^4 is a 3- to 10-membered heterocycloalkyl or heterocycloalkenyl optionally substituted with one or more substituents independently selected from the group consisting of halo, oxo, -OH, -CN, -C_1-C_6 alkyl optionally substituted with one or more independently selected R^y substituents, -C_1-C_6 alkoxy optionally substituted with one or more independently selected halo substituents, -$C(O)OC_1$-C_6 alkyl, -$C(O)C_1$-C_6 alkyl, -$S(O)_2$–C_1-C_6 alkyl, C_6-C_{12} aryl optionally substituted with one or more independently selected halo substituents, 3- to 6-membered heterocycloalkyl or heterocycloalkenyl, and 5- to 6-membered heteroaryl optionally substituted with one or more independently selected C_1-C_6 alkyl substituents.

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from the group consisting of , .


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8. The compound of claim 7, or a pharmaceutically acceptable salt thereof, wherein R^4 is

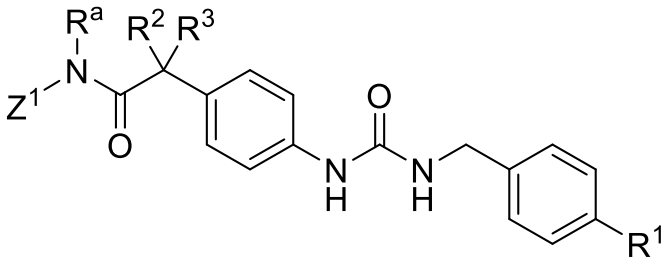
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, or

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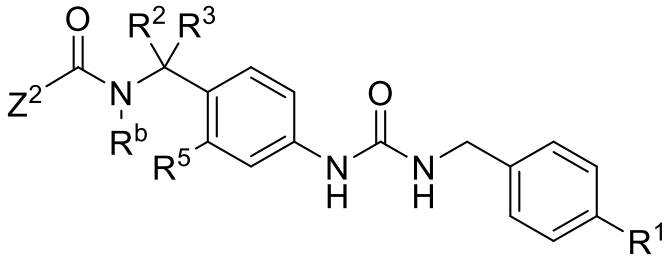
9. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula (I-A):



(I-A),

or a pharmaceutically acceptable salt thereof.

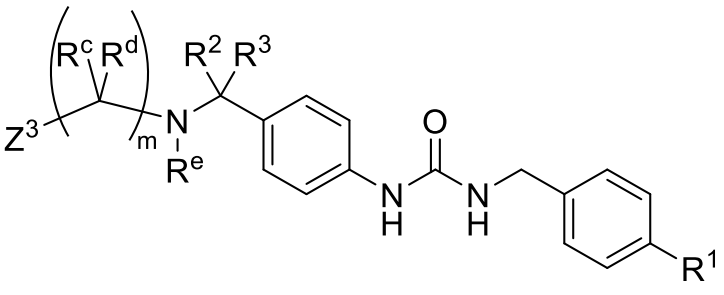
10. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula (I-B):



(I-B),

or a pharmaceutically acceptable salt thereof.

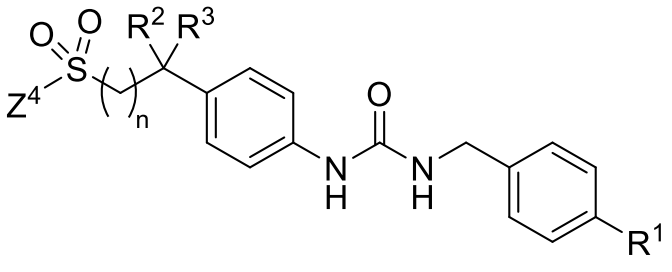
11. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula (I-C):



(I-C),

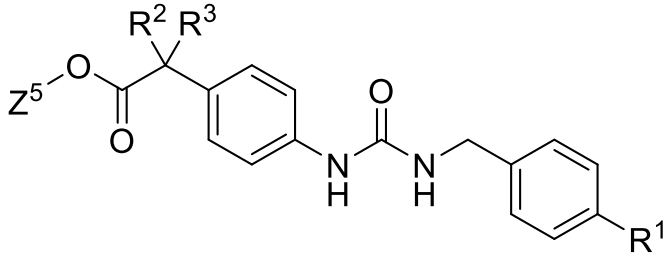
or a pharmaceutically acceptable salt thereof.

12. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula (I-D):


(I-D),

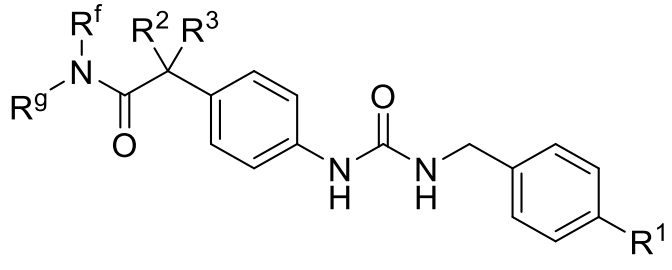
or a pharmaceutically acceptable salt thereof.

13. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula (I-E):


(I-E),

or a pharmaceutically acceptable salt thereof.

14. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula (I-F):

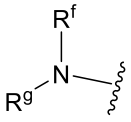
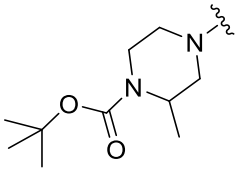
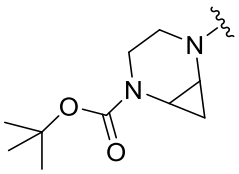
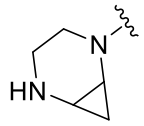
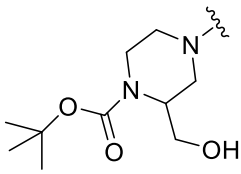
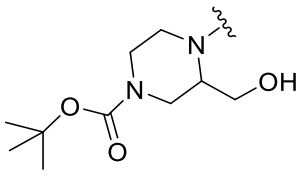
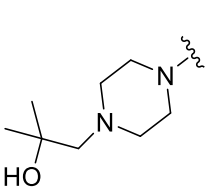
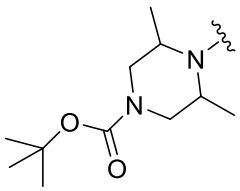
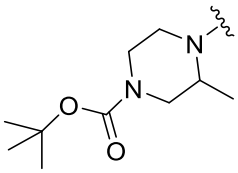
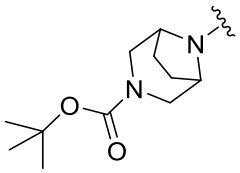
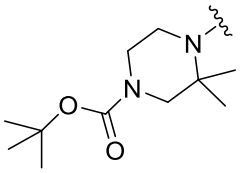
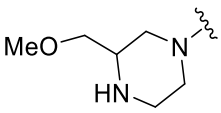
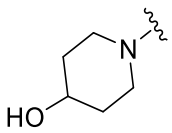
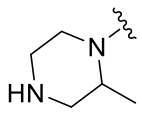
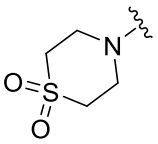
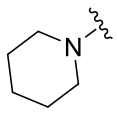
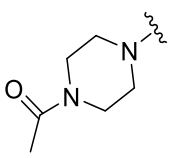
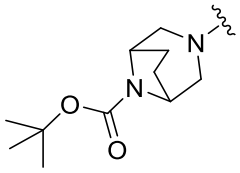
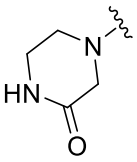
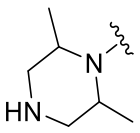
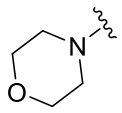
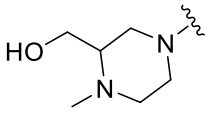
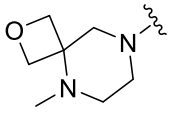
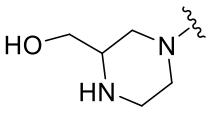
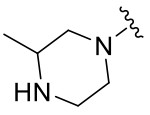
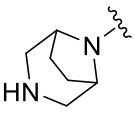
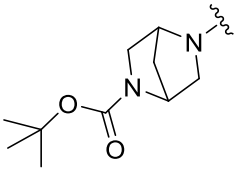
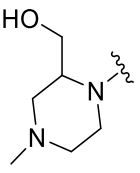
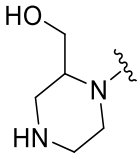
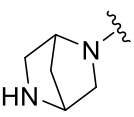
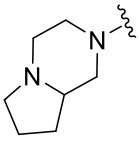
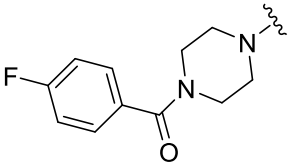
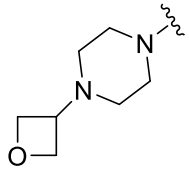
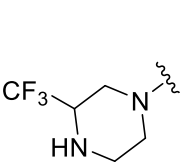

(I-F),

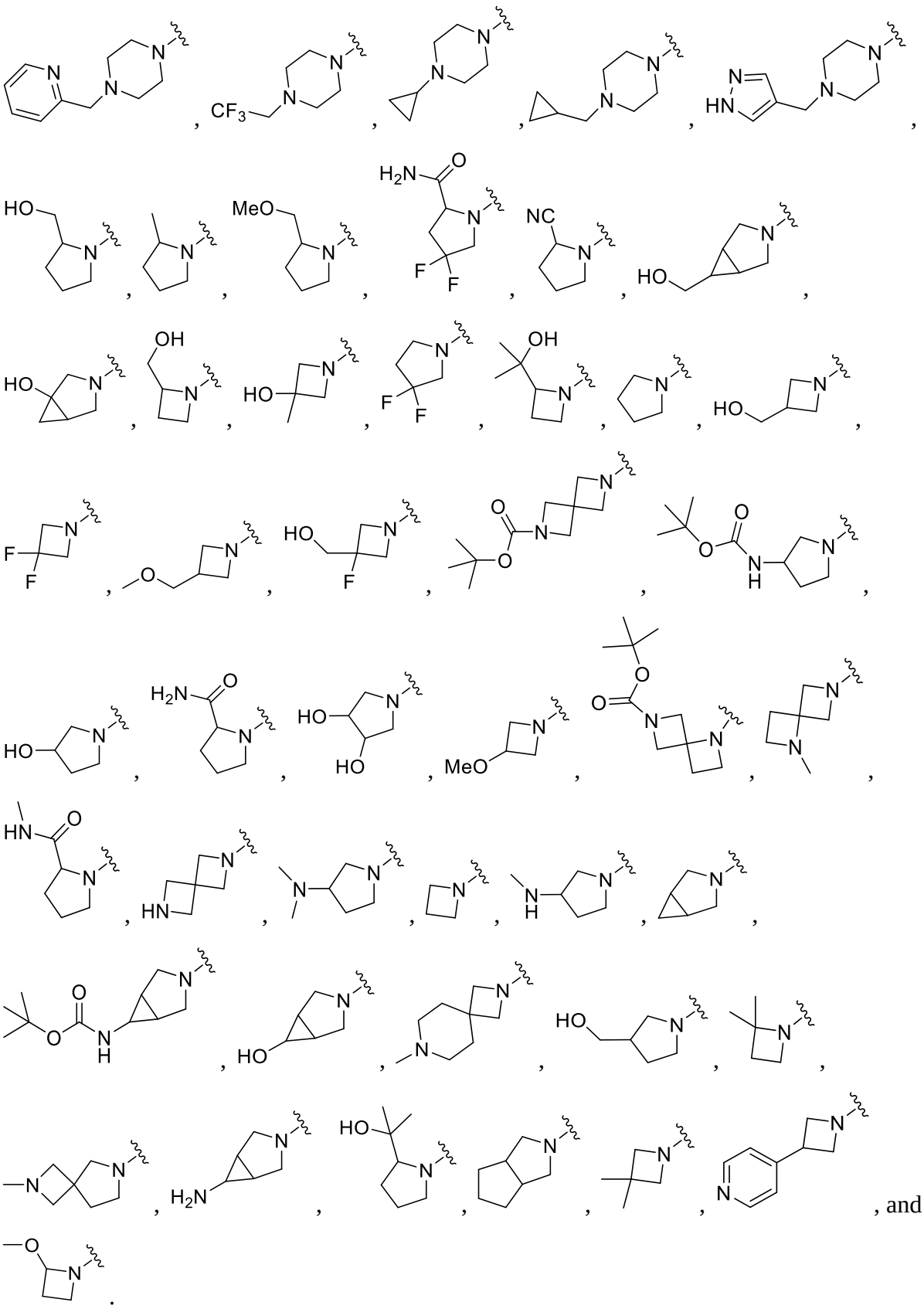
or a pharmaceutically acceptable salt thereof.

15. The compound of any one of claims 1-5 and 14, or a pharmaceutically acceptable salt thereof, wherein R^f and R^g together with the nitrogen to which they are attached form a 3- to 10-membered heterocycloalkyl or heterocycloalkenyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, -CN, oxo, -C_1-C_6 alkyl optionally substituted with one or more independently selected R^x substituents, -C_3-C_6 cycloalkyl, -C_1-C_6 alkoxy, -C(O)R^h, -NHC(O)OC_1-C_6 alkyl, -NR^jR^k, -C(O)NR^mR^n, 3- to 6-

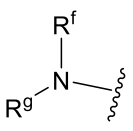
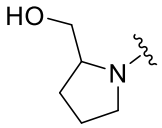
membered heterocycloalkyl or heterocycloalkenyl, and 5- to 6-membered heteroaryl.

16. The compound of any one of claims 1-5, 14, and 15, or a pharmaceutically acceptable salt thereof, wherein R^f and R^g together with the nitrogen to which they are attached form a 5- to 6-membered heterocycloalkyl or heterocycloalkenyl optionally substituted with -C_1-C_6 alkyl, wherein the -C_1-C_6 alkyl is optionally substituted with –OH.

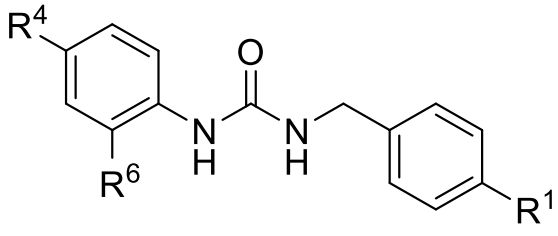
17. The compound of any one of claims 1-5 and 14-16, or a pharmaceutically acceptable salt thereof, wherein  is selected from the group consisting of , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , .



, and

18. The compound of any one of claims 1-5 and 14-17, or a pharmaceutically acceptable salt thereof, wherein  is .

19. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula (II-A):

 (II-A),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is halo or methoxy;

R^4 is

l) 3- to 6-membered heterocycloalkyl or heterocycloalkenyl comprising exactly two annular heteroatoms, both of which are nitrogen atoms, wherein the 3- to 6-membered heterocycloalkyl or heterocycloalkenyl is substituted with one or more independently selected –C_1-C_6 alkyl substituents and is optionally further substituted with one or more oxo substituents,

m) 3- to 6-membered heterocycloalkyl or heterocycloalkenyl comprising exactly one annular heteroatom, which is an oxygen atom, wherein the 3- to 6-membered heterocycloalkyl or heterocycloalkenyl is optionally substituted with one or more independently selected oxo or –C_1-C_6 alkyl substituents,

n) 3- to 6-membered heterocycloalkyl or heterocycloalkenyl substituted with one or more independently selected -$S(O)_2$-C_1-C_6alkyl substituents and optionally further substituted with one or more independently selected oxo or –C_1-C_6 alkyl substituents,

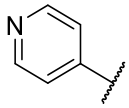
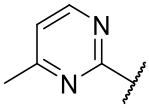
o) 5-membered heterocycloalkyl or heterocycloalkenyl comprising exactly two annular heteroatoms, one of which is a nitrogen atom and the other of which is an oxygen atom, wherein the 5-membered heterocycloalkyl or heterocycloalkenyl is optionally substituted with one or more independently selected oxo, –C_1-C_6 alkyl, or -$S(O)_2$-(C_1-C_6 alkyl) substituents,

p) 6-membered heterocycloalkyl or heterocycloalkenyl comprising exactly two annular heteroatoms, one of which is a sulfur atom and the other of which is a nitrogen atom, wherein

the 6-membered heterocycloalkyl or heterocycloalkenyl is optionally substituted with one or more independently selected oxo, –C_1-C_6 alkyl, or -S(O)$_2$-(C_1-C_6 alkyl) substituents,

q) 5-membered heteroaryl comprising exactly two annular heteroatoms, one of which is a nitrogen atom and the other of which is an oxygen atom, wherein the 5-membered heteroaryl is substituted with exactly one methyl substituent,

r) 5-membered heteroaryl comprising exactly two annular heteroatoms, both of which are nitrogen atoms, wherein the 5-membered heteroaryl is substituted with one or more methyl substituents,

s) 6-membered heteroaryl comprising one or two annular heteroatoms and optionally substituted with one or more methyl substituents, wherein the 6-memebred heteroaryl is other than  or ,

t) Z^9-S(O)$_2$–,

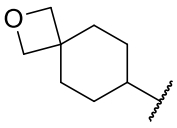
u) Z^{10}-S(O)$_2$–NH-,

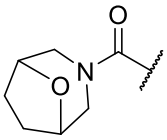
v) Z^{11}-C(O)-NH–,

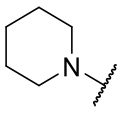
w) Z^{12}-CH_2-O–,

x) Z^{13}-O–,

y) Z^{14}-C(H)(C_1-C_6 alkyl)-NH-C(O)–,

z) , or

aa) , wherein

Z^9 is selected from the group consisting of cyclopropyl, C_6-C_{12} aryl, 3- to 10-membered heterocycloalkyl or hetercycloalkenyl optionally substituted with one or more independently selected R^A substituents, -NH(C_1-C_6 alkyl), -NH_2 substituted with one or more independently selected R^B substituents, and C_1-C_6 alkyl optionally substituted with one or more independently selected R^C substituents, provided that Z^9 is other than , unsubstituted methyl, or unsubstituted ethyl, wherein:

R^A is -C_1-C_6 alkyl or -CN; and

R^B is (i) -C_1-C_6 alkyl-(5- to 10-membered heteroaryl), or (ii) 5- to 10-membered heteroaryl optionally substituted with one or more independently selected C_6-C_{12} aryl; and

R^C is 3- to 8-membered heterocycloalkyl or heterocycloalkenyl;

Z^{10} is C_1-C_6 alkyl substituted with one or more independently selected C_6-C_{12} aryl substituents;

Z^{11} is selected from the group consisting of C_3-C_{10} cycloalkyl and C_1-C_6 alkyl substituted with one or more independently selected 3- to 10-membered heterocycloalkyl or hetercycloalkenyl substituents, provided that, when Z^{11} is cyclopropyl, then R^1 is other than methoxy;

Z^{12} is selected from the group consisting of C_6-C_{12} aryl, 5- to 10-membered heteroaryl, 3- to 10-memebred heterocycloalkyl or heterocycloalkenyl, C_1-C_6 alkyl substituted with one or more independently selected 3- to 10-membered heterocycloalkyl or hetercycloalkenyl substituents or 5- to 10-membered heteroaryl substituents, and -C(O)-(3- to 10-membered heterocycloalkyl or heterocycloalkenyl);

Z^{13} is 5- to 10-membered heteroaryl substituted with one or more independently selected -C(O)-NH(C_1-C_6 alkyl) substituents; and

Z^{14} is 5- to 10-membered heteroaryl optionally substituted with one or more independently selected C_1-C_6 alkyl substituents; and

R^6 is hydrogen or halo.

20. The compound of any one of claims 1-3 and 19, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from the group consisting of:

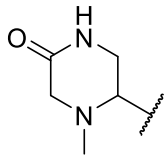
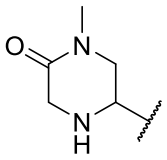
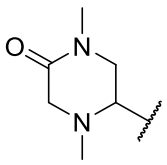
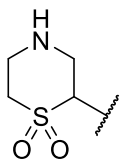
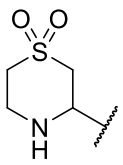
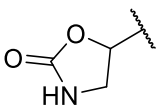
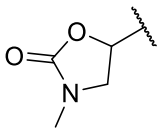
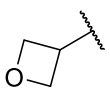
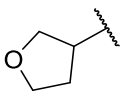
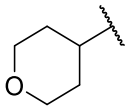
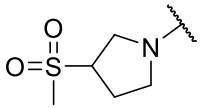
3- to 6-membered heterocycloalkyl or heterocycloalkenyl comprising exactly two annular heteroatoms, both of which are nitrogen atoms, wherein the 3- to 6-membered heterocycloalkyl or heterocycloalkenyl is substituted with one or more independently selected –C_1-C_6 alkyl substituents and is optionally further substituted with one or more oxo substituents,

3- to 6-membered heterocycloalkyl or heterocycloalkenyl comprising exactly one annular heteroatom, which is an oxygen atom, wherein the 3- to 6-membered heterocycloalkyl or heterocycloalkenyl is optionally substituted with one or more independently selected oxo or –C_1-C_6 alkyl substituents,

3- to 6-membered heterocycloalkyl or heterocycloalkenyl substituted with one or more independently selected -$S(O)_2$-C_1-C_6alkyl substituents and optionally further substituted with one or more independently selected oxo or –C_1-C_6 alkyl substituents,

5-membered heterocycloalkyl or heterocycloalkenyl comprising exactly two annular heteroatoms, one of which is a nitrogen atom and the other of which is an oxygen atom, wherein the 5-membered heterocycloalkyl or heterocycloalkenyl is optionally substituted with one or more independently selected oxo, –C_1-C_6 alkyl, or -$S(O)_2$-(C_1-C_6 alkyl) substituents, and

6-membered heterocycloalkyl or heterocycloalkenyl comprising exactly two annular heteroatoms, one of which is a sulfur atom and the other of which is a nitrogen atom, wherein the 6-membered heterocycloalkyl or heterocycloalkenyl is optionally substituted with one or more independently selected oxo, –C_1-C_6 alkyl, or -$S(O)_2$-(C_1-C_6 alkyl) substituents.

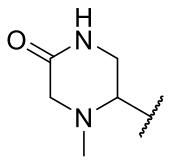
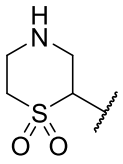
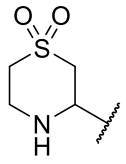
21. The compound of any one of claims 1-3, 19, and 20, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from the group consisting of , , , , , , , , , , and .

22. The compound of any one of claims 1-3, 19, and 20, or a pharmaceutically acceptable salt thereof, wherein R^4 is

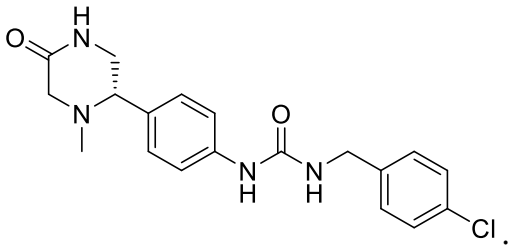
3- to 6-membered heterocycloalkyl or heterocycloalkenyl comprising exactly two annular heteroatoms, both of which are nitrogen atoms, wherein the 3- to 6-membered heterocycloalkyl or heterocycloalkenyl is substituted with one or more independently selected –C_1-C_6 alkyl substituents and is optionally further substituted with one or more oxo substituents, or

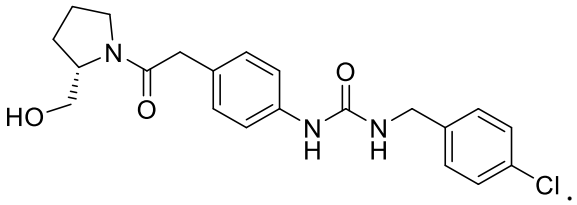
6-membered heterocycloalkyl or heterocycloalkenyl comprising exactly two annular heteroatoms, one of which is a sulfur atom and the other of which is a nitrogen atom, wherein

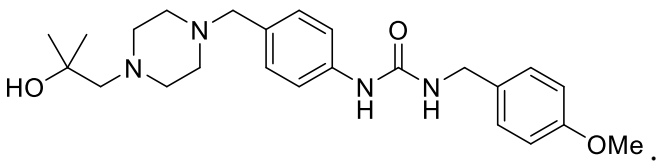
the 6-membered heterocycloalkyl or heterocycloalkenyl is optionally substituted with one or more independently selected oxo, $–C_1$-C_6 alkyl, or -$S(O)_2$-(C_1-C_6 alkyl) substituents.

23. The compound of any one of claims 1-3, 19, 20, and 22, or a pharmaceutically acceptable salt thereof, wherein R^4 is , , or .

24. A compound selected from the group consisting of compounds of Table 1, or a pharmaceutically acceptable salt thereof.

25. The compound of claim 24, or a pharmaceutically acceptable salt thereof, wherein the compound is .

26. The compound of claim 24, or a pharmaceutically acceptable salt thereof, wherein the compound is .

27. The compound of claim 24, or a pharmaceutically acceptable salt thereof, wherein the compound is .

28. A pharmaceutical composition comprising a compound according to any one of claims 1-27, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable

excipient.

29. Use of a compound of any one of claims 1-27, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 28, in the manufacture of a medicament for treating a disease or condition mediated by NAMPT activity.

30. The use of claim 29, wherein the disease or condition is selected from the group consisting of cancer, a hyperproliferative disease or condition, an inflammatory disease or condition, a metabolic disorder, a cardiac disease or condition, heart failure, heart failure with preserved ejection fraction, chemotherapy induced tissue damage, a renal disease, a metabolic disease, a neurological disease or injury, a neurodegenerative disorder or disease, diseases caused by impaired stem cell function, diseases caused by DNA damage, primary mitochondrial disorders, a muscle disease or muscle wasting disorder, obesity, atherosclerosis, insulin resistance, type 2 diabetes, cardiovascular disease, Alzheimer’s disease, Huntington’s disease, Parkinson's disease, amyotrophic lateral sclerosis, depression, Down syndrome, neonatal nerve injury, aging, axonal degeneration, carpal tunnel syndrome, Guillain-Barre syndrome, nerve damage, polio (poliomyelitis), and spinal cord injury.

31. A compound of any one of claims 1-27, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 28, for use in therapy.