METHODS OF USING ANTAGONISTS OF NAD BIOSYNTHESIS FROM NICOTINAMIDE

Figure 2c

Abstract: Provided herein are NAD biosynthesis from nicotinamide antagonists (e.g., Nampt antagonists and/or NMNAT antagonists) and methods of using the same.
METHODS OF USING ANTAGONISTS OF NAD BIOSYNTHESIS FROM NICOTINAMIDE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the priority benefit of provisional patent application U.S. Serial No. 61/646,090 filed May 11, 2012, which is hereby incorporated by reference in its entirety.

FIELD

[0002] Provided herein are therapies for the treatment of pathological conditions, such as cancer, and method of using NAD biosynthesis from nicotinamide antagonists (e.g., Nampt antagonists and/or NMNAT antagonists).

BACKGROUND

[0003] Nicotinamide phosphoribosyltransferase (Nampt) converts nicotinamide into to nicotinamide mononucleotide (NMN), a key intermediate in a salvage pathway that generates nicotinamide adenine dinucleotide (NAD), an essential enzyme cofactor in cellular redox reactions. Cancer cells rely heavily on this salvage pathway, as well as another pathway in which Nicotinic Acid Phosphoribosyltransferase 1 (NAPRT1) converts nicotinic acid (NA, niacin) to NA mononucleotide (NaMN), which is then converted to NA adenine dinucleotide (NaAD), and finally to NAD. Inhibitors of Nampt may be toxic to cancer cells because the cells rely more heavily on these salvage pathways as a result of their high metabolic requirements.

[0004] In pre-clinical studies, co-administration of NA mitigates the toxicity of Nampt inhibition and permits higher doses to be tolerated. Olesen et al., BMC Cancer 10:677 (2010). This is likely because the NAPRT1 pathway readily converts NA to NAD, compensating for inhibition of NAD synthesis via the Nampt pathway. Thus, in cancer cells that lack NAPRT1, the co-administration of NA and an Nampt inhibitor allows for high dosing of the Nampt inhibitor with no reduction in efficacy on the cancer because they lack the enzyme that converts NA to NAD. Watson et al., Mol. Cell Biol. 29(21):5872-88 (2009). To employ this strategy in a clinical setting, methods of identifying cancers that are deficient in NAPRT1 are required.

[0005] Although it has been reported that some cancer cells have low or undetectable levels of NAPRT1 (Olesen et al., APMIS 119(4-5):296-303 (2011)), this has not been explored extensively, and the mechanism of NAPRT1 suppression in cancer cells is not known. Therefore, there is a need to elucidate mechanisms of NAPRT1 regulation and develop additional strategies to identify cancers for which NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) are useful.
SUMMARY

[0006] Provided herein are methods of treating a disease or disorder in an individual comprising administering to the individual an effective amount of an NAD biosynthesis from nicotinamide antagonist, wherein treatment is based upon the individual having a disease or disorder comprising a positive NAPRTI methylation status.

[0007] Also provided herein are methods of treating a disease or disorder cell, wherein the disease or disorder cell comprises a positive NAPRTI methylation status, the method comprising providing an effective amount of an NAD biosynthesis from nicotinamide antagonist.

[0008] Additionally provided herein are methods of treating a disease or disorder in an individual provided that the individual has been found to have a disease or disorder comprising a positive NAPRTI methylation status, the method comprising administering to the individual an effective amount of an NAD biosynthesis from nicotinamide antagonist.

[0009] Also provided herein are methods for treating a disease or disorder in an individual, the method comprising: determining that a sample obtained from the individual comprises a positive NAPRTI methylation status, and administering an effective amount of a therapy comprising an NAD biosynthesis from nicotinamide antagonist to the individual, whereby the disease or disorder is treated.

[0010] Also provided herein are methods of treating a disease or disorder, comprising: (a) selecting an individual having the disease or disorder, wherein the disease or disorder comprises a positive NAPRTI methylation status; and (b) administering to the individual thus selected an effective amount of an NAD biosynthesis from nicotinamide antagonist, whereby the disease or disorder is treated.

[0011] Additionally provided herein are methods of identifying an individual with a disease or disorder who is more or less likely to exhibit benefit from treatment with a therapy comprising an NAD biosynthesis from nicotinamide antagonist, the method comprising: determining presence or absence of a positive NAPRTI methylation status in a sample obtained from the individual, wherein presence of the positive NAPRTI methylation status in the sample indicates that the individual is more likely to exhibit benefit from treatment with the therapy comprising the NAD biosynthesis from nicotinamide antagonist or absence of the positive NAPRTI methylation status indicates that the individual is less likely to exhibit benefit from treatment with the therapy comprising the NAD biosynthesis from nicotinamide antagonist.

[0012] Provided herein are methods for predicting whether an individual with a disease or disorder is more or less likely to respond effectively to treatment with a therapy comprising an NAD biosynthesis from nicotinamide antagonist, the method comprising determining a positive NAPRTI methylation status, whereby presence of the positive NAPRTI methylation status indicates that the individual is more likely to respond effectively to treatment with the NAD biosynthesis from nicotinamide antagonist and absence of the positive NAPRTI methylation status indicates that the
individual is less likely to respond effectively to treatment with the NAD biosynthesis from nicotinamide antagonist.

[0013] Additionally provided herein are methods of predicting the response or lack of response of an individual with a disease or disorder to an therapy comprising an NAD biosynthesis from nicotinamide antagonist comprising detecting in a sample obtained from the individual presence or absence of a positive NAPRTI methylation status, wherein presence of the positive NAPRTI methylation status is predictive of response of the individual to the therapy comprising the NAD biosynthesis from nicotinamide antagonist and absence of the positive NAPRTI methylation status is predictive of lack of response of the individual to the therapy comprising the NAD biosynthesis from nicotinamide antagonist.

[0014] Also provided herein are methods of treating an individual predicted to more likely exhibit benefit from treatment with a therapy comprising an NAD biosynthesis from nicotinamide antagonist according to the above methods, wherein the method comprises administering to the individual an effective amount of an NAD biosynthesis from nicotinamide antagonist.

[0015] In some embodiments of the invention, the NAD biosynthesis from nicotinamide antagonist is an Nampt antagonist. In other embodiments of the invention, the NAD biosynthesis from nicotinamide antagonist is an NMNAT antagonist. In further embodiments, the NAD biosynthesis from nicotinamide antagonist is an antibody, binding polypeptide, small molecule, or polynucleotide.

[0016] In some embodiments of the invention, the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of

![Chemical structures](images/chemistries.png)
In some embodiments, the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of:

wherein: \( R \) is bicyclic heteroaryl comprising 1, 2, 3 or 4 heteroatom(s) independently selected from N, S or O, wherein said heteroaryl may be substituted by one or more substituents selected from the group consisting of amino, oxo, and halo; and wherein said heteroaryl can comprise one or more N-oxide(s) formed with a N atom member of said heteroaryl;

\( R^1 \) is \(-\text{NHR}^4\) and \( R^4 \) is cycloalkyl, heterocycloalkyl, aryl or heteroaryl;

cycloalkyl;
aryl; or
heteroaryl;
wherein:

(i) each of said cycloalkyl, aryl, or heteroaryl is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents which can be the same or different and are independently selected from the group consisting of:

- deuterium, halo, hydroxy, hydroxyalkyl, cyano, -(CH₂)mNRA, oxo, alkyl, cyanoalkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl-, alkenyl, alkynyl, alkynylalkoxy, -CONH₂, -S-alkyl, -C(0)NH(alkyl), -C(0)N(alkyl)₂, -C(0)NH(cycloalkyl), -C(0)NH(aryl), -C(0)N(aryl)₂, arylalkyl-, arylalkoxy-, aryloxy-, cycloalkyl, heterocycloalkyl, aryl, (heterocycloalkyl)alkyl-, (heterocycloalkyl)alkoxy-, -C(0)heterocycloalkyl, heteroaryl, (heteroaryl)alkyl-, -S(0)₂-alkyl, -S(0)₂-aryl, -S(0)₂-CH₂F₃, -C(0)alkyl, -N(R₅)-C(0)-alkyl, -N(R₅)-C(0)-aryl, -S(0)₂N(alkyl), -S(0)₂N(aryl)₂, -N(H)(S0 ₂)(alkyl), and methylenedioxy, wherein each of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted by one or more halo, cyano, alkyl or alkoxy and;

(ii) each of said cycloalkyl, heterocycloalkyl, aryl, or heteroaryl may optionally additionally be fused with independently selected aryl, heteroaryl, heterocycloalkyl or cycloalkyl to from a bicyclic or tricyclic group that may be substituted by one or more halo, cyano, alkyl or alkoxy; R² and R³ can be independently selected from the group consisting of H and deuterium;

R⁵ is H, alkyl or arylalkyl-;
R² and R³ are independently selected from the group consisting of H, alkyl, alkoxy, alkoxyalkyl and haloalkyl;

m is 0, 1, 2, 3, 4, 5 or 6;
z is 0, 1 or 2.

[0018] In some embodiments, the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of:

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\[ \text{II} \]
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wherein

Ar¹ is aryl or heteroaryl, wherein said aryl or heteroaryl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of:

Ar¹ is aryl or heteroaryl, wherein said aryl or heteroaryl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of:
deuterium, halo, cyano, alkyl, cyanoalkyl, haloalkyl, alkenyl, alkynyl, alkoxy,
haloalkoxy, arylalkoxy, -NR²⁻R³⁻, -C(0)N(R⁴⁻R⁵⁻), -C(0)-alkyl, -C(0)-aryl, -S(0)-aryl, -NH-C(O)-alkyl, -NH-C(O)-aryl, (alkoxyalkyl)oxy-, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;
Ar² is unsubstituted aryl or heteroaryl;
R¹ is cycloalkyl, aryl, heterocycloalkyl, or heteroaryl,
(i) wherein each of said cycloalkyl, aryl, heterocycloalkyl and heteroaryl is either
unsubstituted or optionally independently substituted with 1, 2, 3, 4 or 5 substituents which
can be the same or different and are independently selected from the group consisting of:
deuterium, halo, cyano, alkyl, hydroxyalkyl, cyanoalkyl, haloalkyl, alkenyl, alkynyl, alkoxy,
alkylalkoxy, haloalkoxy, arylalkoxy, -NR²⁻R³⁻,-CONR²⁻R³⁻,-S(0)₂⁻alkyl, -S(0)₂⁻aryl, -S(0)₂⁻N(alkyl)₂⁻, -S(0)₂⁻CF₃⁻,-C(0)alkyl, -NH-C(0)alkyl, -NH-C(0)aryl, methylenedioxy, -(CH₂)ₗ-cycloalkyl, -(CH₂)ₗ-aryl, -(CH₂)ₗ-heteroaryl, and -(CH₂)ₗ-heterocycloalkyl,
(ii) wherein each of said cycloalkyl, aryl, heterocycloalkyl, and heteroaryl may
additionally be unsubstituted or substituted by one or more halo, cyano, alkyl or alkoxy or
may be be fused with independently selected aryl, heteroaryl, heterocycloalkyl or cyloalkyl;
R² and R³ are independently H, alkyl, alkoxy, aryl, alkoxycycloalkyl, -S(0)₂⁻alkyl and cycloalkyl or
R² and R³ can form a 5 or 6 membered heterocycloalkyl group together with the nitrogen atom to
which they are attached, wherein said heterocycloalkyl group may contain one or more additional
heteroatom(s) selected from N, S or O;
R² and R³ are H or deuterium;
m, n, p and q are independently 0, 1 or 2;
and pharmaceutically acceptable salts thereof.

[0019] In some embodiments, the NAD biosynthesis from nicotinamide antagonist is a small
molecule selected from the group consisting of:

wherein:
R¹ is 1, 2, 3 or 4 and can be selected from the group consisting of hydrogen, amino, oxo,
halo, alkoxy, alkyl, haloalkyl, -N(alkyl)₂⁻,-NH(CO)₀⁻alkyl 1H-pyrazol, 1H-imidazol, and-C(0)NH₂⁻;
and wherein said pyridine can comprise a N-oxide formed with its N atom member;
**[0020]** In some embodiments, the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of:

![Diagram](image)

1) 2) IB

wherein:

Ar is aryl or heteroaryl, each of said aryl and heteroaryl being either unsubstituted or optionally independently substituted with 1, 2, 3 or 4 substituents which can be the same or different and are independently selected from the group consisting of: deuterium, halo, cyano, amino, aminooalkyl-, (amino)alkoxy-, -CONH₂, -C(0)NH(alkyl), -C(0)N(alkyl)₂, -C(0)NH(aryl), -C(0)N(aryl)₂, -CH₂F₂, -OCH₂F₂, -alkyl, -alkenyl, -alkynyl, -alkoxy, (alkoxyalkyl) amino-, -N(R³)-C(0)-alkyl, -N(R³)-C(0)-aryl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

R¹ is -NR³R⁴, wherein R³ is H, alkyl or -S(0)₂alkyl and R⁴ is alkyl, hydroxyalkyl, -S(0)₂alkyl, -(CH₂)₄cycloalkyl, -(CH₂)₄heterocycloalkyl, aryl, arylalkyl-, -(CH₂)₄heteroaryl; haloalkyl; cycloalkyl; aryl; heterocycloalkyl; or heteroaryl;

wherein each of said cycloalkyl, aryl, heterocycloalkyl or heteroaryl is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents which can be the same or different and are independently selected from the group consisting of: halo, cyano, alkyl, hydroxyalkyl, hydroxyalkoxy, haloalkyl, alkoxy, alkylalkoxy, haloalkoxy, arylalkenyl-, arloxy, benzylxy, oxo, -(CH₂)₄-NR³R⁴, -(CH₂)₄-CONR³R⁴, -(CH₂)₄-S(0)₂alkyl, -(CH₂)₄-S(0)₂NH-alkyl, -(CH₂)₄-heterocycloalkyl, -(CH₂)₄-CF₃, -(C(0)alkyl, -(C(0)aryl, -C(0)alkenylnaryl, -(C(0)alkyl, -(CH₂)₄cycloalkyl, cycloalkylalkoxy-, aryl, arylalkyl-, -(CH₂)₄heteroaryl, and -(CH₂)₄heterocycloalkyl;

wherein each of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted by one or more halo, nitro, haloalkyl, haloalkoxy, oxo, cyano, alkyl, haloalkyl, or alkoxy;

R⁵ and R⁶ are independently selected from the group consisting of H, alkyl, hydroxyalkyl, alkoxy, aryl, alkoxyalkyl, -(C(0)₂alkyl and cycloalkyl or R⁵ and R⁶ can form a 5 or 6 membered heterocycloalkyl group together with the nitrogen atom to which they are attached, wherein said heterocycloalkyl group may contain one or more additional heteroatom(s) selected from N, S or O;

q is 0 or 1; and pharmaceutically acceptable salts thereof.
with 1, 2, 3, 4 or 5 substituents which can be the same or different and are independently selected from the group consisting of: deuterium, halo, cyano, alkyl, hydroxyl, hydroxyalkyl, hydroxyalkoxy, cyanoalkyl, haloalkyl, alkenyl, alkynyl, alkoxy, alkyalkoxy, haloalkoxy, arylalkenyl-, aryloxy, benzyloxy, oxo, -(CH₂)ᵣNRᵣ'Rᵈ, -(CH₂)ᵣ'-CONRᵣ'Rᵈ, -S(0)₂alkyl, -S(0)₂aryl, S(0)₂NH₂, -S(0)₂NH-alkyl, -S(0)₂N(alkyl)₂, -S(0)₂heterocycloalkyl, -S(0)₂CF₃, -C(0)alkyl, -C(0)aryl, -C(0)alkynylaryl, -C(0)₀-alkyl, -NH-C(0)aryl, -NH-C(0)aryl, methylenedioxy, -(CH₂)ᵣcycloalkyl, cycloalkylalkoxy-, aryl, aryalkyl-, -(CH₂)ᵣheteroaryl, and (CH₂)ᵣheterocycloalkyl,

wherein each of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted by one or more halo, nitro, haloalkyl, haloalkoxy, oxo, cyano, alkyl, haloalkyl, or alkoxy and;

Rᵣ and Rᵈ are independently selected from the group consisting of H, alkyl, hydroxyalkyl, alkoxy, aryl, alkoxycarbonyl, -S(0)₂alkyl and cycloalkyl or Rᵣ and Rᵈ can form a 5 or 6 membered heterocycloalkyl group together with the nitrogen atom to which they are attached, wherein said heterocycloalkyl group may contain one or more additional heteroatom(s) selected from N, S or O;

z is 0, 1 or 2;

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

and pharmaceutically acceptable salts thereof.

[0021] In some embodiments, the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of:

![Diagram](image_url)

wherein W is -C(O)-, -S(O)- or -S(0)₂; 

R is an aryl or bicyclic heteroaryl wherein the heteroatoms of each of said heteroaryl numbers 1, 2 or 3, and are independently selected from N, S or O, wherein each of said aryl, heteroaryl is optionally substituted with one or more substituents which can be the same or different and are independently selected from the group consisting of deuterium, halo, cyano, amino, aminoalkyl, (amino)alkoxy, -CONH₂, -C(0)NH(aryl), -C(0)N(alkyl)₂, -C(0)NH(aryl), -C(0)N(aryl)₂, -CF₃, -CHF₂, -CH₂F, -alkyl, alkoxy, hydroxyl, hydroxyalkyl, (alkoxyalkyl) amino, -N(R³)-C(0)-alkyl, -N(R³)-C(0)-aryl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, with the proviso that no two adjacent ring heteroatoms are both S or both O;

G is aryl, heteroaryl, cycloalkyl, heterocycloalkyl or -NR³'Rᵈ, with each of said aryl, heteroaryl, heterocycloalkyl and cycloalkyl being either unsubstituted or independently substituted with 1, 2, 3 or 4 substituents which can be the same or different and are independently selected from the group consisting of deuterium, halo, cyano, amino, aminoalkyl, (amino)alkoxy, -CONH₂, -
C(0)NH(alkyl), -C(0)N(alkyl) 2, -C(0)NH(aryl), -C(0)N(aryl) 2, -CF 3, -CHF 2, -CH 2 F, alkyl, alkenyl, alkynyl, alkoxy, hydroxy, hydroxyalkyl, aryloxy, (alkoxyalkyl)amino, -N(R 3)-C(0)-alkyl, -N(R 3)-C(0)-aryl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl.

\[ R^1 \text{ and } R^2 \text{ are the same or they are different, and are independently selected from } \text{H, } \text{C to C}_7 \text{ alkyl, } \text{C to C}_5 \text{ alkoxy, } \text{C to C}_4 \text{ hydroxyalkyl, aryl, heteroaryl, heterocycloalkyl and cycloalkyl, and wherein heteroatoms of said heteroaryl and heterocycloalkyl are independently selected from one or more } N, O \text{ and } S, \text{ with the proviso that no two adjacent ring heteroatoms are both } S \text{ or both } O, \text{ further wherein } R^1 \text{ and } R^2 \text{ can be either unsubstituted or optionally independently substituted with one or more substituents which can be the same or different and are independently selected from the group consisting of deuterium, halo, cyano, amino, aminolalkyl, (amino)alkoxy, -CONH, -CONH(alkyl), -C(0)N(alkyl) 2, -C(0)NH(aryl), -C(0)N(aryl) 2, -CF 3, -CHF 2, -CH 2 F, alkyl, hydroxyalkyl, alkoxy, hydroxyl, hydroxyalkyl, carboxyl, (alkoxyalkyl) amino, -alkylamine, aminocarbonyl, -CHO, -N(R 3)-C(0)-alkyl, -N(R 3)-C(0)-aryl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;}

\[ R^3 \text{ is } H, \text{ alkyl or arylalkyl; }
\]

\[ n \text{ is } 4, 5 \text{ or } 6; \]

\[ \text{or a pharmaceutically acceptable salt thereof.} \]

[0022] In some embodiments, the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of:

![Diagram](image)

wherein:

A is CH or N;

E is O or is absent;

R is (a) a bicyclic heteroaryl comprising one or more heteroatom ring members independently selected from N, S or O, wherein said bicyclic heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkyamino, dialkyamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy; and wherein one or more N ring members of said bicyclic heteroaryl is optionally an N-oxide; or

(b) a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or monocyclic heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is substituted with one or more substituent selected from the group consisting of deuterium, amino, alkyamino, dialkyamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy;

R 1 is (1) \( R^m \) or -alkenyln-R n, where \( R^m \) is cycloalkyl, heterocycloalkyl, phenyl, or monocyclic heteroaryl; wherein each of said cycloalkyl, heterocycloalkyl, phenyl, and heteroaryl is unsubstituted or is substituted with one or more substituents \( R^x \); wherein each \( R^x \) substituent is
independently selected from the group consisting of: deuterium, halo, hydroxy, hydroxyalkyl, cyano, -NR²R³, -alkenyln-NR²R³, oxo, alkyl, cyanoalkyl, haloalkyl, alkoxy, -S-alkyl, haloalkoxy, alkoxyalkyl-, alkenyl, alkynyl, -C(0)Calkyl, -C0₂alkyl, -C0₂H, -CONH₂, C(0)NH(alkyl), -C(0)NH(haloalkyl), -C(0)N(alkyl)₂, -C(0)NH(cycloalkyl), aryalkyl-, aryalkoxy-, aryloxy-, cycloalkyl, cycloalkyloxy, (cycloalkyl)alkyl, heterocycloalkyl, aryl, (heterocycloalkyl)alkyl-, (heterocycloalkyl)alkoxy-, -C(0)cycloalkyl, -C(0)heterocycloalkyl, heteroaryl, (heteroaryl)alkyl-, -S(0)alkyl, -S0₂alkyl, -S0₂aryl, -S0₂fluoroalkyl, -N(R²)-C(0)alkyl, -N(R²)-C(0)aryl, -N(R²)-C0₂alkyl, -S0₂NH₂, -S0₂NH(alkyl), -S0₂N(alkyl)₂, -S0₂NH(cycloalkyl), and -N(H)(S0₂alkyl), or two adjacent R² substituents on a phenyl or heteroaryl R₃ groups taken together form methylenedioxy, wherein each of said cycloalkyl, heterocycloalkyl, aryl, and heteroaryl within R² is unsubstituted or is substituted with one or more substituents independently selected from the group consisting of deuterium, alkyl, halo, hydroxy, cyano, alkoxy, amino, -C(0)alkyl, and -C0₂alkyl; wherein R² and R³ are each independently H, alkyl, alkoxy, alkoxyalkyl, cyanoalkyl, or haloalkyl; and R³ is H, alkyl or alkylnalkyl;

(2) alkyl unsubstituted or substituted with one or more substituents selected from the group consisting of deuterium, halo, hydroxy, cyano, alkoxy, haloalkoxy, -NR²R³, -C(0)alkyl, C0₂alkyl, -C0₂H, -CONR²R³, -SOalkyl, -S0₂alkyl, and -S0₂NR²R³; where R² and R³ are each independently H, alkyl, alkoxyalkyl, haloalkyl, -C(0)alkyl, or -C0₂alkyl; or

(3) -N(R²)R³, wherein R² is H, R₃m, -alkenyln-R₃m, hydroxyalkyl, cyanoalkyl, alkoxyalkyl, haloalkyl, -CONR²V, or -C(0)R³; where R₃m is as defined in (1) above; R² and R³ are each independently H or alkyl, or R² and R³ taken together with the nitrogen to which they are attached form a monocyclic heterocycloalkyl; and R³ is an alkyl unsubstituted or substituted with one or more substituents selected from the group consisting of: deuterium, halo, amino, hydroxy, alkoxy, cycloalkyl, heteroaryl, phenyl, and heterocycloalkyl; or a cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl, each unsubstituted or substituted with one or more substituents selected from the group consisting of: deuterium, alkyl, halo, amino, hydroxy, and alkoxy; and R² is H or R³;

R² and R³ are each independently selected from the group consisting of H and deuterium; and pharmaceutically acceptable salts of compounds of Formula I.

In one embodiment, R² is independently selected from the group consisting of: -C(0)alkyl or -C(0)alkyl-0-alkyl.

[0023] In some embodiments, the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of:
wherein:

E is O or is absent;

R is (a) an 8-, 9-, or 10-membered bicyclic heteroaryl comprising one heteroatom selected from N, S, and O, and one, two, or three additional N atoms, wherein said bicyclic heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy, and wherein one or more N atoms of said bicyclic heteroaryl is optionally an N-oxide; or

(b) a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or monocyclic six-membered heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy;

R¹ is (1) a saturated, monocyclic heterocycloalkyl, which is unsubstituted or substituted with one or more substituents R⁵; wherein each R⁵ substituent is independently selected from the group consisting of: deuterium, halo, hydroxy, cyano, -NR⁶R⁷, -alkylenyl-NR⁶R⁷, oxo, alkyl, hydroxyalkyl, cyanoalkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, -S-alkyl, alkenyl, alkynyl, aryl, arylalkyl, aryloxy, arylalkoxy, cycloalkoxy, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, (heterocycloalkyl)alkoxy, -C(0)alkyl, -C0₂alkyl, -C0₂H, -C(0)cycloalkyl, -C(0)heterocycloalkyl, -S(0)-alkyl, -SO₂alkyl, -SO₂aryl, -SO₂(haloalkyl), -CONH₂, C(0)NH(alkyl), -C(0)NH(haloalkyl), -C(0)N(alkyl)₂, -C(0)NH(cycloalkyl), heteroaryl, (heteroaryl)alkyl, -N(R⁶)-C(0)-alkyl, -N(R⁶)-C(0)-aryl, -N(R⁶)-C0₂alkyl, -SO₂NH₂, -SO₂NH(alkyl), -SO₂N(alkyl)₂, -SO₂NH(cycloalkyl), and -N(H)(SO₂alkyl), or two adjacent R⁵ substituents taken together form a phenyl ring, wherein each of said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and phenyl substituents within R⁵ is independently unsubstituted or substituted with one or more substituents selected from the group consisting of alkyl, halo, hydroxy, cyano, alkoxy, amino, -C(0)alkyl, and -C0₂alkyl; wherein R² and R³ are each independently H, alkyl, alkoxy, alkoxyalkyl, cyanoalkyl, or haloalkyl; and R⁴ is H or alkyl; or

(2) a saturated, bicyclic or tricyclic, nitrogen-linked heterocycloalkyl, wherein said heterocycloalkyl comprises a fused, bridged, or spiro bicyclic system, and said heterocycloalkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of: alkyl, halo, haloalkyl, hydroxy, hydroxyalkyl, alkoxy, cyano, cyanoalkyl, oxo, -NR⁶⁸, -alkylenyl-NR⁶⁸, -C(0)alkyl, -C0₂alkyl, and -SO₂alkyl; wherein R⁴ is H or alkyl and R⁶ is H, alkyl, haloalkyl, -C(0)alkyl, -C0₂alkyl, or -SO₂alkyl; and

R² and R³ are each independently H or deuterium; or a pharmaceutically acceptable salt thereof.

[0024] In one embodiment, R⁵ is selected from -C(0)aryl.

[0025] In one embodiment, each of said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and phenyl substituents within R⁵ is substituted with one or more -NHC0₂alkyl.
In some embodiments, the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of:

![NAD biosynthesis structure](image)

wherein:

R is (a) an 8-, 9-, or 10-membered bicyclic heteroaryl comprising one heteroatom selected from N, S, and O, and one, two, or three additional N atoms, wherein said bicyclic heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy, and wherein one or more N atoms of said bicyclic heteroaryl is optionally an N-oxide; or

(b) a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or monocyclic six-membered heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy; and

R\(^1\) is H, -(Ci\(_4\)alkylene)\(_0\)iC(O)R\(^a\), -(Ci\(_4\)alkylene)\(_0\)iCO\(_2\)R\(^a\), -(Ci\(_4\)alkylene)\(_0\)iS(O)R\(^a\), - (Ci\(_4\)alkylene)\(_0\)iSO\(_2\)R\(^a\), -C(0)NH(R\(^b\)), or -C(0)N(R\(^b\)\(_2\)) wherein each R\(^a\) is independently

(1) alkyl, unsubstituted or substituted with one or more R\(^m\) substituents, wherein each R\(^m\) is independently selected from the group consisting of hydroxy, -NR\(^b\)R\(^c\), alkoxy, cyano, halo, -C(0)alkyl, -CO\(_2\)alkyl, -CONR\(^b\)R\(^c\), -S(0)alkyl, -SO\(_2\)alkyl, -SO\(_2\)NR\(^b\)R\(^c\), aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, wherein R\(^b\) is H or alkyl; R\(^c\) is H, alkyl, alkoxyalkyl, haloalkyl, -C(0)alkyl, -CO\(_2\)alkyl, or -SO\(_2\)alkyl; and each aryl, heteroaryl, cycloalkyl, and heterocycloalkyl group within R\(^m\) is unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, hydroxy, amino, cyano, halo, -S(0)alkyl, -SO\(_2\)alkyl, haloalkyl, hydroxyalkyl, and alkoxy;

(2) phenyl, cycloalkyl, heteroaryl, or heterocycloalkyl, each unsubstituted or substituted with one or more hydroxy, -NR\(^b\)R\(^c\), alkoxy, cyano, halo, -C(0)alkyl, -CO\(_2\)alkyl, -CONR\(^b\)R\(^c\), -S(0)alkyl, -SO\(_2\)alkyl, or -SO\(_2\)NR\(^b\)R\(^c\) substituents; or

(3) -NR\(^3\)R\(^2\), where R\(^3\) is H or alkyl; and R\(^2\) is H, alkyl, alkoxyalkyl, haloalkyl, -C(0)alkyl, -CO\(_2\)alkyl, or -SO\(_2\)alkyl;

R\(^2\) and R\(^3\) are each independently H or deuterium; and

n is 1 or 2; or a stereoisomer thereof, or a pharmaceutically acceptable salt of such a compound or stereoisomer.

In some embodiments, the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of:
wherein:

R is (a) an 8-, 9-, or 10-membered bicyclic heteroaryl comprising one heteroatom selected from N, S, and O, and one, two, or three additional N atoms, wherein said bicyclic heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy, and wherein one or more N atoms of said bicyclic heteroaryl is optionally an N-oxide; or

(b) a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or monocyclic five- or six-membered heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy; and

R¹ is H, \((\text{Ci}_n\text{alkylene})_0\text{iC(O)R}^a, (\text{Ci}_n\text{alkylene})_0\text{iSO}_2\text{R}^a\), \((-\text{Ci}_n\text{alkylene})_0\text{iS}(\text{O})\text{R}^a\),
\(-\text{(Ci}_n\text{alkylene})_0\text{iSO}_2\text{R}^a, -\text{C}(0)\text{NH}(\text{R}^a), -\text{C}(0)\text{N}(\text{R}^a)_2, \text{or } -\text{C}(0)\text{C}(0)\text{NH}(\text{R}^a)\);

wherein each \(\text{R}^a\) is independently

(1) alkyl, unsubstituted or substituted with one or more \(\text{R}^m\) substituents,

wherein each \(\text{R}^m\) is independently selected from the group consisting of hydroxy, \(-\text{NR}^b\text{R}^c\), alkoxy, cyano, halo, \(-\text{C}(0)\text{alkyl}, -\text{C}(0)\text{alkyl}\), \(-\text{CONR}^b\text{R}^c, -\text{S}(0)\text{alkyl}\), \(-\text{SO}_2\text{alkyl}, -\text{SO}_2\text{NR}^b\text{R}^c\), aryl, heteroaryl, cycloalkyl, heterocycloalkyl, phenoxy, and \(-\text{O}-\text{alkyl-OH}\);

wherein \(\text{R}^b\) is H or alkyl;

\(\text{R}^c\) is H, alkyl, alkoxyalkyl, haloalkyl, \(-\text{C}(0)\text{alkyl}, -\text{C}(0)\text{alkyl}\), \(-\text{SO}_2\text{alkyl}, -\text{C}(0)\text{NH}_2\) or \(\text{C}(0)\text{H}\); and

each aryl, heteroaryl, cycloalkyl, and heterocycloalkyl group within \(\text{R}^m\) is unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, hydroxy, \(-\text{NR}^b\text{R}^c\), alkoxy, haloalkoxy, cyano, halo, oxo, \(-\text{C}(0)\text{alkyl}, -\text{C}(0)\text{alkyl}, -\text{C}(0)\text{-heterocycloalkyl}, -\text{CONR}^b\text{R}^c, -\text{S}(0)\text{alkyl}, -\text{SO}_2\text{alkyl}, -\text{SO}_2\text{-haloalkyl}, -\text{SO}_2\text{NR}^b\text{R}^c\), aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

wherein each alkyl or alkoxy is unsubstituted or substituted with \(-\text{NR}^b\text{R}^c\), heterocycloalkyl, heteroaryl, or \(-\text{C}(0)\text{alkyl}\); and

each aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is unsubstituted or substituted with alkyl, halo, or \(-\text{C}(0)\text{alkyl}\);

(2) phenyl, cycloalkyl, heteroaryl, or heterocycloalkyl, each unsubstituted or substituted with
one or more substituents selected from the group consisting of alkyl, haloalkyl, hydroxy, -NR^3R^c, alkoxy, haloalkoxy, cyano, halo, oxo, -C(O)alkyl, -C(O)_2alkyl, -C(O)-
\text{heterocycloalkyl}, -\text{CONR}^3R^c, -S(O)alkyl, -S(O)_2alkyl, -S(O)_2\text{haloalkyl}, -S(O)_2\text{NR}^3R^c, ary1, heteroaryl, cycloalkyl, and heterocycloalkyl;
\text{wherein each alkyl or alkoxy is unsubstituted or substituted with} -\text{NR}^3R^c,
\text{heterocycloalkyl, heteroaryl, or} -\text{C(O)alkyl}; \text{and}
\text{each aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is unsubstituted or substituted with}
\text{alkyl, halo, or} -\text{C(O)alkyl}; \text{or}
\text{(3)} -\text{NR}^3R^c,
\text{where} R^i \text{is H or alkyl}; \text{and}
R^j \text{is H, alkyl, alkoxyalkyl, haloalkyl, -C(O)alkyl, -C(O)_2alkyl, or}
-S(O)_2alkyl;
R^2 \text{and} R^3 \text{are each independently H or deuterium}; \text{and}
n \text{is 1 or 2};
\text{and stereoisomers thereof, and pharmaceutically acceptable salts of such compounds and}
stereoisomers.

[0028] In some embodiments, the NAD biosynthesis from nicotinamide antagonist is a small
molecule selected from the group consisting of:

\[ \text{\includegraphics[width=0.5\textwidth]{image.png}} \]

\text{wherein:}
\text{R is} \text{(a) a bicyclic heteroaryl comprising 1, 2, 3, or 4 heteroatom ring members}
\text{independently selected from} N, S \text{or} O, \text{wherein said bicyclic heteroaryl is unsubstituted or is}
\text{substituted with one or more substituents selected from the group consisting of deuterium, amino,}
al-\text{alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy; and}
\text{wherein one or more} N \text{ring members of said heteroaryl is optionally an} N\text{-oxide; or}
\text{(b) a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or}
\text{monocyclic heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is substituted with one}
or more substituent selected from the group consisting of deuterium, amino, al-\text{alkylamino,}
dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy;}
\text{R^1 is} \text{alkyl,} R^m, \text{or} -\text{alkylenyl}-R^m,\n\text{wherein said alkyl is unsubstituted or substituted with one or more substituents selected from the}
group consisting of deuterium, halo, hydroxy, cyano, alkoxy, -\text{NR}^3R^c, \text{hydroxyalkyl, cyanoalkyl,}
haloalkyl, haloalkoxy, alkoxyalkyl, -S-alkyl, -\text{C(O)alkyl}, -\text{C(O)}_2\text{alkyl, -C(O)}_2\text{H}, -\text{C(O)NH}_2,
-\text{C(O)NH}(\text{alkyl}), -\text{C(O)NH(haloalkyl)}; -\text{C(O)N(alkyl)}_2, -\text{S(O)}_2\text{NH}_2, -\text{S(O)}_2\text{NH(alkyl)}, \text{and} -\text{S(O)}_2\text{N(alkyl)}_2;
where R^2 and R^3 are each independently H, alkyl, alkoxyalkyl, haloalkyl, -C(0)alkyl, -CO_2alkyl, or -SO_2alkyl; and

R^m is cycloalkyl, phenyl, monocyclic heteroaryl, or heterocycloalkyl, each unsubstituted or substituted with one or more substituents R^s;

wherein each R^s substituent is independently selected from the group consisting of: deuterium, halo, hydroxy, hydroxyalkyl, cyano, -NR^R^s, -alkylene-NR^R^sR^b, oxo, alkyl, cyanoalkyl, haloalkyl, alkoxy, -S-alkyl, haloalkoxy, alkoxyalkyl-, alkenyl, alkynyl, -C(0)alkyl, -CONH_2, C(0)NH(alkyl), -C(0)NH(haloalkyl), -C(0)N(alkyl) _2, -C(0)NH(cycloalkyl), arylalkyl-, arylalkoxy-, aryloxy-, cycloalkyl, cycloalkoxy, (cycloalkyl)alkyl-, heterocycloalkyl, aryl, (heterocycloalkyl)alkyl-, (heterocycloalkyl)alkoxy-, -C(0)heterocycloalkyl, heteroaryl, (heteroaryl)alkyl-, -S(O)-alkyl, -SO_2-alkyl, -SO_2-aryl, -SO_2-fluoroalkyl, -N(R^s)-C(0)-alkyl, -N(R^s)-C(0)-aryl, -N(R^s)-C(0)-alkenyl, -CO_2H, -SO_2NH_2, -SO_2NH(alkyl), -SO_2N(alkyl) _2, -SO_2NH(cycloalkyl), and -N(H)(SO_2)(alkyl), or two adjacent phenyl or heteroaryl R^s substituents taken together form methylenedioxy;

wherein each of said cycloalkyl, heterocycloalkyl, aryl, and heteroaryl within R^s is unsubstituted or is substituted with 1, 2, or 3 substituents independently selected from the group consisting of alkyl, halo, hydroxy, cyano, alkoxy, amino, -C(0)alkyl, and -CO_2alkyl;

wherein R^a and R^b are each independently H, alkyl, alkoxy, alkoxyalkyl, cyanoalkyl, or haloalkyl; and

R^c is H, alkyl, or arylalkyl-; and

R^2 and R^3 are each independently selected from the group consisting of H and deuterium; or a pharmaceutically acceptable salt thereof.

[0029] In some embodiments, the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of:

![Diagram](image)

wherein:

E is O or is absent;

R is (a) an 8-, 9-, or 10-membered bicyclic heteroaryl comprising one heteroatom selected from N, S, and O, and one, two, or three additional N atoms, wherein said bicyclic heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy, and wherein one or more N atoms of said bicyclic heteroaryl is optionally an N-oxide; or

(b) a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or monocyclic six-membered heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is
substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy;

R^1 is (1) R^3, where R^3 is a phenyl, cycloalkyl, heterocycloalkyl, or monocyclic heteroaryl, unsubstituted or substituted with one or more R^6 substituents;

wherein each R^w substituent is independently selected from the group consisting of: halo, hydroxy, cyano, -NR^6R^7, -alkylamino, oxo, alkyl, hydroxyalkyl, cyanoalkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl-, -S-alkyl, alkenyl, alkynyl, aryl, arylalkyl-, arylalkoxy-, cycloalkyl, cycloalkyloxy, (cycloalkyl)alkyl-, heterocycloalkyl, (heterocycloalkyl)alkyl-, (heterocycloalkyl)alkoxy-, -C(0)alkyl, -C(0)alkoxy, -C(0)H, -C(0)cycloalkyl, -C(0)heterocycloalkyl, -S(0)-alkyl, -S(0)alkoxy, -S(0)aryalkyl, -aryloxyalkyl, -N(0)NH(alkyl), -C(0)NH(alkyl), -C(0)NH(haloalkyl), -C(0)N(alkyl)2, -C(0)N(alkyl)cycloalkyl), heteroaryl, (heteroaryl)alkyl-, -N(R^2)-C(0)-aryl, -N(R^2)-C(0)aryalkyl, -N(R^2)-C(0)alkyl, -S(0)NH2, -S(0)NH(alkyl), -S(0)NH(alkyl)2, -S(0)NH(cycloalkyl), and -N(H)(S0alkyl), or two adjacent R^w substituents taken together form a phenyl ring, wherein each of said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and phenyl substituents within R^w is independently unsubstituted or substituted with one or more substituents selected from the group consisting of alkyl, halo, hydroxy, cyano, alkoxy, amino, -C(0)alkyl, and -C(0)alkoxy;

R^4 and R^b are each independently H, alkyl, alkoxy, alkoxyalkyl, cyanoalkyl, or haloalkyl; and R^2 is H or alkyl;

(2) -alkoxyalkyl-R^6 or -C(0)-alkoxyalkyl-R^6, where R^6 is as defined in (1) above; or

(3) alkyl substituted with one or more R^6 substituents, wherein each R^6 is independently -CONR^6R^1, hydroxy, cyano, alkoxy, halo, or -C(0)R^1;

wherein R^b and R^1 are each independently H or alkyl, or R^b and R^1 taken together with the nitrogen to which they are attached form a monocyclic heterocycloalkyl; and

R^1 is alkyl, cycloalkyl, heterocycloalkyl, phenyl, or benzyl, each unsubstituted or substituted with one or more substituents selected from the group consisting of: alkyl, halo, amino, hydroxy, and alkoxy;

R^2 and R^3 are each independently H or deuterium; and

R^4 is H; an alkyl unsubstituted or substituted with one or more substituents selected from the group consisting of: deuterium, halo, amino, hydroxy, alkoxy, cycloalkyl, heteroaryl, phenyl, and heterocycloalkyl, wherein each cycloalkyl, heteroaryl, phenyl, and heterocycloalkyl is unsubstituted or substituted with one or more substituents selected from the group consisting of: deuterium, alkyl, halo, amino, hydroxy, and alkoxy; or a cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl, each unsubstituted or substituted with one or more substituents selected from the group consisting of: deuterium, alkyl, halo, amino, hydroxy, and alkoxy; with the proviso that R^4 is not H when R^1 is as defined in (1) above;

or a pharmaceutically acceptable salt thereof.
[0030] In some embodiments of the invention, the method further comprises administering niacin. In further embodiments, niacin is Niaspan®.

[0031] In some embodiments, the niacin reduces toxicity of the NAD biosynthesis from nicotinamide antagonist and/or increases the therapeutic index of the NAD biosynthesis from nicotinamide antagonist.

[0032] In some embodiments of any of the above embodiments, the positive NAPRT1 methylation status is methylation of at least one cytosine within a NAPRT1 DNA region. In some embodiments, the positive NAPRT1 methylation status is methylation of at least one cytosine within a CpG island of an NAPRT1 gene. In some embodiments, the positive NAPRT1 methylation status is methylation of at least one cytosine between about chromosome coordinates 144659500 and 144661000 of human chromosome. In some embodiments, wherein the positive NAPRT1 methylation status is methylation of at least one cytosine in the sequence represented between about position 1018 and about position 1545 of SEQ ID NO:1. In some embodiments, the positive NAPRT1 methylation status is methylation of at least one cytosine in the sequence represented between about position 1221 and about position 1288 of SEQ ID NO:1.

[0033] In some embodiments of the invention, the positive NAPRT1 methylation status is methylation of at least 25% of the cytosines within a portion of an NAPRT1 gene. In some embodiments, the positive NAPRT1 methylation status is methylation of at least 25% of the cytosines within a portion of an NAPRT1 gene, wherein the portion of the NAPRT1 gene corresponds to a portion of the human NAPRT1 sequence represented by SEQ ID NO:1. In some embodiments, the positive NAPRT1 methylation status is methylation of at least 25% of the cytosines within a promoter in an NAPRT1 gene. In some embodiments, the positive NAPRT1 methylation status is methylation of at least 25% of the cytosines within a CpG island of an NAPRT1 DNA region. In some embodiments, the positive NAPRT1 methylation status is methylation of at least 25% of the cytosines in a sequence corresponding to the sequence between about chromosome coordinates 144659500 and 144661000 of human chromosome 8. In some embodiments, the positive NAPRT1 methylation status is methylation of at least 25% of the cytosines in the sequence represented between about position 1018 and about position 1545 of SEQ ID NO:1. In some embodiments, the positive NAPRT1 methylation status is methylation of at least 25% of the cytosines in the sequence represented between about position 1221 and about position 1288 of SEQ ID NO:1.

[0034] In some embodiments of the invention, the disease or disorder or disease or disorder cell is cancer. In some embodiments, the cancer or cancer cell is breast cancer, colorectal cancer, endometrium cancer, kidney cancer, lung cancer, lymphoid cancer, ovarian cancer, pancreatic cancer, or stomach cancer.

[0035] Provided herein are methods of identifying a human cancer patient suitable for treatment with an NAD biosynthesis from nicotinamide antagonist comprising determining the level of
methylolation of cytosines of an NAPRT1 gene wherein greater than 25% methylation of the NAPRT1 gene indicates that the individual is more likely to benefit from treatment.

[0036] Provided herein are methods of identifying a human cancer patient suitable for treatment with an NAD biosynthesis from nicotinamide antagonist comprising determining the level of methylation of cytosines of an NAPRT1 promoter wherein greater than 25% methylation of the NAPRT1 promoter indicates that the individual is more likely to benefit from treatment.

[0037] Provided herein are methods of identifying a human cancer patient suitable for treatment with an NAD biosynthesis from nicotinamide antagonist comprising determining the level of methylation of cytosines of a CpG island in an NAPRT1 gene wherein greater than 25% methylation of the CpG island indicates that the individual is more likely to benefit from treatment.

[0038] Provided herein are methods of identifying a human cancer patient suitable for treatment with an NAD biosynthesis from nicotinamide antagonist comprising determining the level of methylation of cytosines of the sequence represented between about position 1018 and about position 1545 of SEQ ID NO:1 wherein greater than 25% methylation of the sequence that the individual is more likely to benefit from treatment.

[0039] Provided herein are methods of identifying a human cancer patient suitable for treatment with an NAD biosynthesis from nicotinamide antagonist comprising determining the level of methylation of cytosines of the sequence represented between about position 1221 and about position 1288 of SEQ ID NO:1 wherein greater than 25% methylation of the sequence that the individual is more likely to benefit from treatment.

[0040] Provided herein are methods of identifying an individual who is more likely to exhibit benefit from a therapy comprising an NAD biosynthesis from nicotinamide antagonist, said method comprising a) isolating DNA from a tumor sample the individual; b) incubating the DNA sample with sodium bisulfite sufficient to convert unmethylated cytosine in the DNA to uracil; c) sequencing the NAPRT1 promoter region of the DNA; d) determining the methylation level of the NAPRT1 promoter region by determining the number of cytosine residues that were not converted to uracil in step b); wherein greater than 25% methylation of the sequence that the individual is more likely to benefit from treatment.

[0041] Provided herein are methods of identifying an individual who is more likely to exhibit benefit from a therapy comprising an NAD biosynthesis from nicotinamide antagonist, said method comprising a) isolating DNA from a tumor sample the individual; b) incubating the DNA sample with sodium bisulfite sufficient to convert unmethylated cytosine in the DNA to uracil; c) sequencing a fragment of the DNA comprising a portion NAPRT1 CpG island; d) determining the methylation level of the NAPRT1 CpG island by determining the number cytosine residues that were not converted to uracil in step b); wherein greater than 25% methylation of the sequence that the individual is more likely to benefit from treatment. In some embodiments, the portion of the
NAPRTI CpG island comprises the sequence represented between about position 1018 and about position 1545 of SEQ ID NO:1.

[0042] Provided herein are methods of identifying an individual who is more likely to exhibit benefit from a therapy comprising an NAD biosynthesis from nicotinamide antagonist, said method comprising a) isolating DNA from a tumor sample the individual, b) incubating the DNA sample with sodium bisulfite sufficient to convert unmethylated cytosine in the DNA to uracil, c) amplifying a portion of the CpG island of the NAPRTI gene of the DNA sample using quantitative methylation specific PCR, d) determining the methylation level of the NAPRTI region by determining the -dCt value of the tumor sample with the -dCt value obtained from quantitative methylation specific PCR of non-methylated DNA, wherein greater than 25% methylation of the NAPRTI sequence that the individual is more likely to benefit from treatment. In some embodiments, the portion of the CpG island of the NAPRTI gene comprises the sequence represented between about position 1221 and about position 1288 of SEQ ID NO:1

[0043] In some embodiments of the above embodiments, the DNA from the tumor sample is isolated from a formalin-fixed paraffin embedded tumor sample. In some embodiments of the above embodiments, step c) further comprises a pre-amplification of the portion of the CpG island of the NAPRTI gene of the DNA sample prior to quantitative methylation specific PCR.

[0044] Provided herein are methods of treating a human cancer patient with an NAD biosynthesis from nicotinamide antagonist, said method comprising determining the level of methylation of cytosines of an NAPRTI gene in a tumor sample from the patient wherein greater than 25% methylation of the NAPRTI gene indicates that the patient is more likely to benefit from treatment; and administering an effective amount of an NAD biosynthesis from nicotinamide antagonist to the patient more likely to benefit from treatment.

[0045] Provided herein are methods of treating a human cancer patient suitable for treatment with an NAD biosynthesis from nicotinamide antagonist, said method comprising determining the level of methylation of cytosines of an NAPRTI promoter in a tumor sample from the patient wherein greater than 25% methylation of the NAPRTI promoter indicates that the patient is more likely to benefit from treatment, administering an effective amount of an NAD biosynthesis from nicotinamide antagonist to the patient more likely to benefit from treatment.

[0046] Provided herein are methods of treating a human cancer patient suitable for treatment with an NAD biosynthesis from nicotinamide antagonist, said method comprising determining the level of methylation of cytosines of a CpG island in an NAPRTI gene in a tumor sample from the patient wherein greater than 25% methylation of the CpG island indicates that the patient is more likely to benefit from treatment; and administering an effective amount of an NAD biosynthesis from nicotinamide antagonist to the patient more likely to benefit from treatment.

[0047] Provided herein are methods of treating a human cancer patient suitable for treatment with an NAD biosynthesis from nicotinamide antagonist, said method comprising determining the level of
methylation of cytosines of the sequence represented between about position 1018 and about position 1545 of SEQ ID NO:1 in a tumor sample from the patient wherein greater than 25% methylation of the sequence that the individual is more likely to benefit from treatment, and administering an effective amount of an NAD biosynthesis from nicotinamide antagonist to the patient more likely to benefit from treatment.

[0048] Provided herein are methods of treating a human cancer patient suitable for treatment with an NAD biosynthesis from nicotinamide antagonist, said method comprising determining the level of methylation of cytosines of the sequence represented between about position 1221 and about position 1288 of SEQ ID NO:1 in a tumor sample from the patient wherein greater than 25% methylation of the sequence that the patient is more likely to benefit from treatment, and administering an effective amount of an NAD biosynthesis from nicotinamide antagonist to the patient more likely to benefit from treatment.

[0049] Provided herein are methods of treating human cancer patient with an NAD biosynthesis from nicotinamide antagonist, said method comprising a) isolating DNA from a tumor sample the patient; b) incubating the DNA sample with sodium bisulfite sufficient to convert unmethylated cytosine in the DNA to uracil; c) sequencing the NAPRT1 promoter region of the DNA; d) determining the methylation level of the NAPRT1 promoter region by determining the number of cytosine residues that were not converted to uracil in step b) wherein greater than 25% methylation of the sequence that the patient is more likely to benefit from treatment; and e) administering an effective amount of an NAD biosynthesis from nicotinamide antagonist to the patient more likely to benefit from treatment.

[0050] Provided herein are methods of treating human cancer patient with an NAD biosynthesis from nicotinamide antagonist, said method comprising a) isolating DNA from a tumor sample the patient; b) incubating the DNA sample with sodium bisulfite sufficient to convert unmethylated cytosine in the DNA to uracil; c) sequencing a fragment of the DNA comprising a portion NAPRT1 CpG island; d) determining the methylation level of the NAPRT1 CpG island by determining the number cytosine residues that were not converted to uracil in step b), wherein greater than 25% methylation of the sequence that the patient is more likely to benefit from treatment; and e) administering an effective amount of an NAD biosynthesis from nicotinamide antagonist to the patient more likely to benefit from treatment. In some embodiments, the portion of the NAPRT1 CpG island comprises the sequence represented between about position 1018 and about position 1545 of SEQ ID NO:1.

[0051] Provided herein are methods of treating human cancer patient with an NAD biosynthesis from nicotinamide antagonist, said method comprising a) isolating DNA from a tumor sample the patient, b) incubating the DNA sample with sodium bisulfite sufficient to convert unmethylated cytosine in the DNA to uracil, c) amplifying a portion of the CpG island of the NAPRT1 gene of the DNA sample using quantitative methylation specific PCR, d) determining the methylation level of the
NAPRT1 region by determining the -dCt value of the tumor sample with the -dCt value obtained from quantitative methylation specific PCR of non-methylated DNA, wherein greater than 25% methylation of the NAPRT1 sequence that the patient is more likely to benefit from treatment; and e) administering an effective amount of an NAD biosynthesis from nicotinamide antagonist to the patient more likely to benefit from treatment. In some embodiments, the portion of the CpG island of the NAPRT1 gene comprises the sequence represented between about position 1221 and about position 1288 of SEQ ID NO:1.

[0052] In some embodiments of the above embodiments, the DNA from the tumor sample is isolated from a formalin-fixed paraffin embedded tumor sample.

[0053] In some embodiments of the above embodiments, step c) further comprises a pre-amplification of the portion of the CpG island of the NAPRT1 gene of the DNA sample prior to quantitative methylation specific PCR.

[0054] In some embodiments of the above methods of treating a human cancer patient, the method further comprises administering niacin. In some embodiments, the niacin reduces toxicity of the NAD biosynthesis from nicotinamide antagonist and/or increases the therapeutic index of the NAD biosynthesis from nicotinamide antagonist.

**BRIEF DESCRIPTION OF THE FIGURES**

[0055] Figure 1 is a representative series of graphs depicting nicotinic acid (NA) Rescue (A and B) or Non-Rescue (C and D) of CALU-6 or NCI-460 cells, respectively, after undergoing treatment with nicotinamide phosphoribosyltransferase (Nampt) inhibitors Compound B as measured by quantification of ATP (CellTiterGlo, Promega) or DNA (CyQuant, Promega).

[0056] Figure 2 is a series of graphs demonstrating that a low or intermediate Nicotinic Acid Phosphoribosyltransferase 1 (NAPRT1) methylation status correlates with high NAPRT1 gene expression and NA Rescue in a number of cancer cell lines. (A) Correlation between NAPRT1 mRNA and NAPRT1 protein levels. (B) Correlation between NAPRT1 mRNA levels and NAPRT1 methylation status. (C) Correlation between high NAPRT1 methylation status (solid bar) or low/intermediate NAPRT1 methylation status (striped bar) and no NA Rescue or NA Rescue in cancer cell lines, respectively.

[0057] Figure 3 is a graph depicting the relationship between average methylation across seven CpG island sites in the NAPRT1 promoter and NA Rescue in a number of cancer lines. Hatched bars indicate no rescue cells.

[0058] Figure 4 shows 5-aza-2-deoxycytidine (5-azadC) treatment induces NAPRT1 expression in cell lines with NAPRT1 CpG island methylation. These data show that most cell lines that cannot be rescued by nicotinic acid express very low levels of NAPRT1 transcript (DMSO) as determined by quantitative PCR. NAPRT1 is inducible by the DNA demethylating agent 5-azadC. Conversely, cells lines that could be rescued already express NAPRT1 transcript, which was not further induced by 5-azadC treatment.
Figure 5 is a diagram depicting nucleotide regions of the NAPRT1 CpG island aligned with regions amplified by BSP primers 1 through 8. From 5’ to 3’ of NAPRT1, alignment of DNA region amplified by BSP primers 6, 7, 8, 1, 5, 2, 4, and 3.

Figure 6 is a diagram depicting nucleotide regions of the NAPRT1 CpG island aligned with DNA regions amplified by BSP primers 1 through 8 along with DNA regions amplified by quantitative methylation-specific PCR primers and probes 1 through 7 used for mapping of methylation sites with a quantitative methylation specific PCR assay (QMSP) after initial sodium bisulfite modification. From 5’ to 3’ of NAPRT1, alignment of regions amplified by QMSP primers and probe sets 1, 2, 4, 5, and 3.

Figure 7A and 7B present the sequence of the NAPRT1 CpG island region following modification by sodium bisulfite treatment (SEQ ID NO: 2) aligned with regions amplified by BSP primers 1 through 8 along with regions amplified by methylation-specific PCR primers and probes 1 through 7 used for mapping of methylation sites with a quantitative methylation specific PCR assay (QMSP). QMSP forward and reverse primers as well as QMSP probes are depicted along with the amplicon produced by the quantitative methylation specific PCR assay.

Figure 8 is the NAPRT1 CpG island DNA sequence with 600 base pairs added upstream and downstream (SEQ ID NO: 1).

Figure 9 is the NAPRT1 CpG island DNA sequence with 600 base pairs added upstream and downstream, and after initial modification with sodium bisulfite assuming the sequence was fully methylated (SEQ ID NO: 2).

Figure 10A is the NAPRT1 genomic CpG island DNA sequence (SEQ ID NO: 3).

Figure 10B is the NAPRT1 CpG island DNA sequence following modification with sodium bisulfite assuming the sequence is fully methylated (SEQ ID NO: 4).

Figure 10C is the reverse complement strand of the NAPRT1 CpG island DNA sequence following modification with sodium bisulfite assuming the sequence was fully methylated (SEQ ID NO: 5).

Figure 11 is a depiction of NAPRT1 CpG island overlaid with representative sodium bisulfite sequencing data from a pool of peripheral blood monocyte DNA from 20 healthy donors. For the bisulfite sequencing data (black and white grids). Each row represents a single TA clone from the PCR product and each column represents an individual CpG site within the PCR amplified amplicon. Open boxes represent unmethylated CpG sites; filled boxes represent methylated sites; shaded boxes are undetermined. The black and white box on the left, labeled BSP7, shows the methylation pattern at the 3’ end of the CpG island. A commercially available methylation assay is targeted to this region as shown by the bar. An adjacent region, labeled BSP1/2 is also shown on the right side of the figure. The bar below the sequence data from BSP1/2 shows the approximate position of the QMSP3 assay.
Figure 12 is a diagram depicting the DNA methylation profile of CpG sites in NAPRT1 expressed by breast cancer cell lines. (A) A diagram of NAPRT1 genomic DNA and CpG island site recognized by BSP primers for sodium bisulfite sequencing. (B) Methylation profile of CpG sites in the HCC70 breast cancer cell line that demonstrated no rescue by NA when treated with Nampt inhibitors. (C) Methylation profile of CpG sites in MDA-MB-231 and CAL120 breast cancer cell lines that demonstrated rescue by NA when treated with Nampt inhibitors. Each row represents a cloned PCR product (alleles) of BSP1/2; each column represents a single CpG site within the cloned region. Open boxes represent unmethylated CpG sites; filled boxes represent methylated sites.

Figure 13 is a methylation profile of various non-small cell lung cancer (NSCLC) cell lines. (A) Methylation profile of CpG sites in H1155, H1650, H1703, and LXFL529 NSCLC cell lines that demonstrated no rescue by NA when treated with Nampt inhibitors. (B) Methylation profile of CpG sites in H1838, H2030, H2122, and H226 NSCLC cell lines that demonstrated rescue by NA when treated with Nampt inhibitors. Each row represents a cloned PCR product (alleles) of BSP1/2; each column represents a single CpG site within the cloned region. Open boxes represent unmethylated CpG sites; filled boxes represent methylated sites.

Figure 14 shows analysis of methylation (QMSP3) and gene expression of NAPRT1 in tumors (NSCLC) and matched normal (benign adjacent lung) tissue. Panel A shows methylation in matched tumor/normal; Panel B shows expression in the same tissues.

Figure 15. Analysis of methylation of NAPRT1 in DNA derived from IHC slides. Inserts show immunohistochemistry showing expression NAPRT1 in tumor samples. Tumor samples HP-7770, a small cell lung cancer tumor, has an IHC score of zero indicating no detectable expression of NAPRT1 (blue area). The brown area is non-malignant tissue. Tumor sample HP-7489, a non-small cell lung cancer tumor, has an IHC score of 3+ indicating expression of NAPRT1. The graph represents QMSP3 analysis of methylation of DNA isolated directly from the IHC slides.

Figure 16 is a diagram demonstrating the RNA level of NAPRT1 in tissues. Low levels of NAPRT1 RNA in malignant tumors originating from breast, colon, endometrium, head and neck, kidney, lung, lymphoid, neuroendocrine, ovary, pancreas, prostate, skin, soft tissue, thyroid, urinary tract, and stomach indicate potential benefits of Nampt inhibitor treatment in patients with these cancer types.

Figure 17A is a graph showing siRNA knockdown of NAPRT1 prevents NA rescue of A549 tumor cells following treatment with an Nampt inhibitor. Control siRNA indicates samples that received siRNAs not directed toward NAPRT1. NAPRT1 siRNA indicates cells treated with siRNAs specific for NAPRT1. +NA indicates cells further treated with nicotinic acid. Error bars represent the standard error of each data point (SEM).

Figure 17B is shows results of a western blot analysis showing NAPRT1 expression is specifically inhibited by siRNAs directed toward NAPRT1 in A549 cells. Bottom panel shows an actin loading control.
DETAILED DESCRIPTION

/ . Definitions

[0075] The terms "nicotinate phosphoribosyltransferase domain-containing protein 1" and "NAPRT1" refer herein to a native NAPRT1 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The terms encompass the genomic location (e.g., 8q24.3 cytogenetic band, chromosome 8: 142,656,955 - 146,364,022 bp, and/or GC08M144656), "full-length," unprocessed NAPRT1 as well as any form of NAPRT1 that result from processing in the cell. The term also encompasses naturally occurring variants of NAPRT1, e.g., splice variants or allelic variants. The sequence of an exemplary human NAPRT1 nucleic acid sequence is NM_145201 or an exemplary human NAPRT1 is amino acid sequence NP_660202.3.

[0076] The terms "nicotinamide phosphoribosyltransferase" and "Nampt" refer herein to a native Nampt from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The terms encompasses "full-length," unprocessed Nampt as well as any form of Nampt that result from processing in the cell. The term also encompasses naturally occurring variants of Nampt, e.g., splice variants or allelic variants (DNA Sequence: Chromosome 7, NC_000007.13 (10588873..105925638, complement; protein: NCBI Reference Sequence: NP_005737; NM_005746).

[0077] "Nampt variant," "nicotinamide phosphoribosyltransferase variant," or variations thereof, means an Nampt polypeptide or polynucleotide, generally being or encoding an active Nampt polypeptide, as defined herein having at least about 80% amino acid sequence identity with any of the Nampt as disclosed herein. Such Nampt variants include, for instance, Nampt wherein one or more nucleic acid or amino acid residues are added or deleted. Ordinarily, an Nampt variant will have at least about 80% sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity, to Nampt as disclosed herein. Ordinarily, Nampt variant are at least about 10 residues in length, alternatively at least about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600 in length, or more. Optionally, Nampt variant will have or encode a sequence having no more than one conservative amino acid substitution as compared to Nampt, alternatively no more than 2, 3, 4, 5, 6, 7, 8, 9, or 10 conservative amino acid substitution as compared to Nampt.

[0078] The terms "nicotinamide phosphoribosyltransferase" and "NMNAT" refer herein to a native NMNAT from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The terms encompasses "full-length," unprocessed NMNAT as well as any form of NMNAT that result from processing in the cell. The
term also encompasses naturally occurring variants of NMNAT, e.g., splice variants or allelic variants. Examples of sequences for NMNAT include NMNAT1: NM_022787; NMNAT2: NM_170706; and NMNAT3: NM_178177.

"NMNAT variant," "nicotinamide phosphoribosyltransferase variant," or variations thereof, means an NMNAT polypeptide or polynucleotide, generally being or encoding an active NMNAT polypeptide, as defined herein having at least about 80% amino acid sequence identity with any of the NMNAT as disclosed herein. Such NMNAT variants include, for instance, NMNAT wherein one or more nucleic acid or amino acid residues are added or deleted. Ordinarily, an NMNAT variant will have at least about 80% sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity, to NMNAT as disclosed herein. Ordinarily, NMNAT variant are at least about 10 residues in length, alternatively at least about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600 in length, or more. Optionally, NMNAT variant will have or encode a sequence having no more than one conservative amino acid substitution as compared to NMNAT, alternatively no more than 2, 3, 4, 5, 6, 7, 8, 9, or 10 conservative amino acid substitution as compared to NMNAT.

The term "NAD biosynthesis from nicotinamide antagonist" as defined herein is any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity mediated by, for example, Nampt and/or NMNAT. In some embodiments, the antagonist is an antagonist binding polypeptide. According to another embodiment, the antagonist is an antagonist antibody. According to another embodiment, the antagonist is a small molecule antagonist. According to another embodiment, the antagonist is a polynucleotide antagonist. Non-limiting examples of small molecule Nampt antagonists which can be used in methods according to the invention are given herein, for example Nampt antagonists as described in published PCT patent applications Nos. WO 2011006988, WO 2011109441, WO2012031196, WO2012031197, and WO2012031199.

DNA methylation as used herein refers to the presence of a methyl group at the C5 position of cytosine (i.e. 5-methylcytosine). 5-methylcytosine is typically found as part of a 5'-CpG sequence but may also be found at 5'-CpHpG sequence where H=A, T, or C. Methylation of cytosine bases in DNA provides a layer of epigenetic control of gene expression in eukaryotes. In some examples, the DNA contains 5-hydroxymethylcytosine.

The term "positive NAPRT1 methylation status" refers herein to methylation of CpG and/or CpHpG sites (where H=A, T or C) in the NAPRT1 gene that result in diminished or no expression of an NAPRT1 gene compared to a reference sample; for example, a cell not associated with a disease or disorder.

The term "negative NAPRT1 methylation status" refers herein to a lack of methylation of CpG and/or CpHpG sites (where H=A, T or C) in the NAPRT1 gene that results in no difference in
expression of an NAPRT1 gene compared to a reference sample; for example, a cell not associated
with a disease or disorder.

The term "CpG island" as used herein refers to a short stretch of DNA in which the
frequency of the CpG sequence is higher than other regions. CpG islands are typically located
around the promoters of housekeeping genes or other genes frequently expressed in a cell. In some
cases, CpG islands play a role in the epigenetic regulation of gene expression. For example, genes
are often expressed when the CpG sequences are hypomethylated, and are inactive when the CpG
island is methylated or hypermethylated. The CpG island of human NAPRT1 is located between
coordinates 144659746 and 144660635 of human chromosome 8.

"Polynucleotide," or "nucleic acid," as used interchangeably herein, refer to polymers of
nucleotides of any length, and include DNA and RNA. The nucleotides can be deoxyribonucleotides,
ribonucleotides, modified nucleotides or bases, and/or their analogs, or any substrate that can be
incorporated into a polymer by DNA or RNA polymerase, or by a synthetic reaction. A
polynucleotide may comprise modified nucleotides, such as methylated nucleotides and their analogs.
If present, modification to the nucleotide structure may be imparted before or after assembly of the
polymer. The sequence of nucleotides may be interrupted by non-nucleotide components. A
polynucleotide may be further modified after synthesis, such as by conjugation with a label. Other
types of modifications include, for example, "caps", substitution of one or more of the naturally
occurring nucleotides with an analog, internucleotide modifications such as, for example, those with
uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoamidates, carbamates, etc.)
and with charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), those containing
pendant moieties, such as, for example, proteins (e.g., nucleases, toxins, antibodies, signal peptides,
ply-L-lysine, etc.), those with intercalators (e.g., acridine, psoralen, etc.), those containing chelators
(e.g., metals, radioactive metals, boron, oxidative metals, etc.), those containing alkylators, those with
modified linkages (e.g., alpha anomic nucleic acids, etc.), as well as unmodified forms of the
polynucleotide(s). Further, any of the hydroxyl groups ordinarily present in the sugars may be
replaced, for example, by phosphonate groups, phosphate groups, protected by standard protecting
groups, or activated to prepare additional linkages to additional nucleotides, or may be conjugated to
solid or semi-solid supports. The 5’ and 3’ terminal OH can be phosphorylated or substituted with
amines or organic capping group moieties of from 1 to 20 carbon atoms. Other hydroxyls may also be
derivatized to standard protecting groups. Polynucleotides can also contain analogous forms of ribose
or deoxyribose sugars that are generally known in the art, including, for example, 2'-0-methyl-, 2'-0-
allyl, 2'-fluoro- or 2'-azido-ribose, carbocyclic sugar analogs, a-anomeric sugars, epimeric sugars such
as arabinose, xyloses or lyxoses, pyranose sugars, furanose sugars, sedoheptuloses, acyclic analogs
and abasic nucleoside analogs such as methyl riboside. One or more phosphodiester linkages may be
replaced by alternative linking groups. These alternative linking groups include, but are not limited
to, embodiments wherein phosphate is replaced by P(0)S("thioate"), P(S)S ("dithioate"), (0)NR 2

[0084]
"amidate"), \(P(0)R, P(0)OR', CO \text{ or } CH_2 ("formacetal"), \) in which each \(R \text{ or } R'\) is independently \(H \text{ or substituted or unsubstituted alkyl} (1-20 \text{ C})\) optionally containing an ether (-O-) linkage, aryl, alkenyl, cycloalkenyl, cycloalkenyl or araldyl. Not all linkages in a polynucleotide need be identical. The preceding description applies to all polynucleotides referred to herein, including RNA and DNA.

[0086] "Oligonucleotide," as used herein, generally refers to short, single stranded, polynucleotides that are, but not necessarily, less than about 250 nucleotides in length. Oligonucleotides may be synthetic. The terms "oligonucleotide" and "polynucleotide" are not mutually exclusive. The description above for polynucleotides is equally and fully applicable to oligonucleotides.

[0087] The term "primer" refers to a single stranded polynucleotide that is capable of hybridizing to a nucleic acid and following polymerization of a complementary nucleic acid, generally by providing a free 3'-OH group.

[0088] The term "small molecule" refers to any molecule with a molecular weight of about 2000 daltons or less, preferably of about 500 daltons or less.

[0089] The terms "host cell," "host cell line," and "host cell culture" are used interchangeably and refer to cells into which exogenous nucleic acid has been introduced, including the progeny of such cells. Host cells include "transformants" and "transformed cells," which include the primary transformed cell and progeny derived therefrom without regard to the number of passages. Progeny may not be completely identical in nucleic acid content to a parent cell, but may contain mutations. Mutant progeny that have the same function or biological activity as screened or selected for in the originally transformed cell are included herein.

[0090] The term "vector," as used herein, refers to a nucleic acid molecule capable of propagating another nucleic acid to which it is linked. The term includes the vector as a self-replicating nucleic acid structure as well as the vector incorporated into the genome of a host cell into which it has been introduced. Certain vectors are capable of directing the expression of nucleic acids to which they are operatively linked. Such vectors are referred to herein as "expression vectors."

[0091] An "isolated" antibody is one which has been separated from a component of its natural environment. In some embodiments, an antibody is purified to greater than 95% or 99% purity as determined by, for example, electrophoretic (e.g., SDS-PAGE, isoelectric focusing (IEF), capillary electrophoresis) or chromatographic (e.g., ion exchange or reverse phase HPLC). For review of methods for assessment of antibody purity, see, e.g., Flatman et al, J. Chromatogr. B 848:79-87 (2007).

[0092] An "isolated" nucleic acid refers to a nucleic acid molecule that has been separated from a component of its natural environment. An isolated nucleic acid includes a nucleic acid molecule contained in cells that ordinarily contain the nucleic acid molecule, but the nucleic acid molecule is present extrachromosomally or at a chromosomal location that is different from its natural chromosomal location.
The term "antibody" herein is used in the broadest sense and encompasses various antibody structures, including but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), and antibody fragments so long as they exhibit the desired antigen-binding activity.

The terms "anti-Nampt antibody" and "an antibody that binds to Nampt" refer to an antibody that is capable of binding Nampt with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting Nampt. In one embodiment, the extent of binding of an anti-Nampt antibody to an unrelated, non-Nampt protein is less than about 10% of the binding of the antibody to Nampt as measured, e.g., by a radioimmunoassay (RIA). In certain embodiments, an anti-Nampt antibody binds to an epitope of Nampt that is conserved among Nampt from different species.

The terms "anti-NMNAT antibody" and "an antibody that binds to NMNAT" refer to an antibody that is capable of binding NMNAT with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting NMNAT. In one embodiment, the extent of binding of an anti-NMNAT antibody to an unrelated, non-NMNAT protein is less than about 10% of the binding of the antibody to NMNAT as measured, e.g., by a radioimmunoassay (RIA). In certain embodiments, an anti-NMNAT antibody binds to an epitope of NMNAT that is conserved among NMNAT from different species.

A "blocking" antibody or an "antagonist" antibody is one which inhibits or reduces biological activity of the antigen it binds. Preferred blocking antibodies or antagonist antibodies substantially or completely inhibit the biological activity of the antigen.

"Affinity" refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen). Unless indicated otherwise, as used herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (e.g., antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (Kd). Affinity can be measured by common methods known in the art, including those described herein. Specific illustrative and exemplary embodiments for measuring binding affinity are described in the following.

An "affinity matured" antibody refers to an antibody with one or more alterations in one or more hypervariable regions (HVRs), compared to a parent antibody which does not possess such alterations, such alterations resulting in an improvement in the affinity of the antibody for antigen.

An "antibody fragment" refers to a molecule other than an intact antibody that comprises a portion of an intact antibody that binds the antigen to which the intact antibody binds. Examples of antibody fragments include but are not limited to Fv, Fab, Fab', Fab'-SH, F(ab')2; diabodies; linear antibodies; single-chain antibody molecules (e.g., scFv); and multispecific antibodies formed from antibody fragments.
[0100] An "antibody that binds to the same epitope" as a reference antibody refers to an antibody that blocks binding of the reference antibody to its antigen in a competition assay by 50% or more, and conversely, the reference antibody blocks binding of the antibody to its antigen in a competition assay by 50% or more. An exemplary competition assay is provided herein.

[0101] The term "chimeric" antibody refers to an antibody in which a portion of the heavy and/or light chain is derived from a particular source or species, while the remainder of the heavy and/or light chain is derived from a different source or species.

[0102] The "class" of an antibody refers to the type of constant domain or constant region possessed by its heavy chain. There are five major classes of antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgGi, IgG2, IgG3, IgG4, IgAi, and IgAx. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called α, δ, ε, γ, and μ, respectively.

[0103] The terms "full length antibody," "intact antibody," and "whole antibody" are used herein interchangeably to refer to an antibody having a structure substantially similar to a native antibody structure or having heavy chains that contain an Fc region as defined herein.

[0104] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical and/or bind the same epitope, except for possible variant antibodies, e.g., containing naturally occurring mutations or arising during production of a monoclonal antibody preparation, such variants generally being present in minor amounts. In contrast to polyclonal antibody preparations, which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody of a monoclonal antibody preparation is directed against a single determinant on an antigen. Thus, the modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by a variety of techniques, including but not limited to the hybridoma method, recombinant DNA methods, phage-display methods, and methods utilizing transgenic animals containing all or part of the human immunoglobulin loci, such methods and other exemplary methods for making monoclonal antibodies being described herein.

[0105] A "human antibody" is one which possesses an amino acid sequence which corresponds to that of an antibody produced by a human or a human cell or derived from a non-human source that utilizes human antibody repertoires or other human antibody-encoding sequences. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues.

[0106] A "humanized" antibody refers to a chimeric antibody comprising amino acid residues from non-human HVRs and amino acid residues from human FRs. In certain embodiments, a
humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the HVRs (e.g., CDRs) correspond to those of a non-human antibody, and all or substantially all of the FRs correspond to those of a human antibody. A humanized antibody optionally may comprise at least a portion of an antibody constant region derived from a human antibody. A "humanized form" of an antibody, e.g., a non-human antibody, refers to an antibody that has undergone humanization.

[0107] An “immunoconjugate” is an antibody conjugated to one or more heterologous molecule(s), including but not limited to a cytotoxic agent.

[0108] "Percent (%) amino acid sequence identity” with respect to a reference polypeptide sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU5 10087. The ALIGN-2 program is publicly available from Genentech, Inc., South San Francisco, California, or may be compiled from the source code. The ALIGN-2 program should be compiled for use on a UNIX operating system, including digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

[0109] In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

[0110] 100 times the fraction X/Y

[0111] where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program’s alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. Unless specifically stated
otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

[0112] The term "detection" includes any means of detecting, including direct and indirect detection.

[0113] The term "biomarker" as used herein refers to an indicator, e.g., predictive, diagnostic, and/or prognostic, which can be detected in a sample. The biomarker may serve as an indicator of a particular subtype of a disease or disorder (e.g., cancer) characterized by certain, molecular, pathological, histological, and/or clinical features. In some embodiments, a biomarker is a polypeptide and polynucleotide modifications (e.g., methylation). Biomarkers include, but are not limited to, polynucleotides (e.g., DNA, and/or RNA), polypeptides, polypeptide and polynucleotide modifications (e.g., posttranslational modifications), carbohydrates, and/or glycolipid-based molecular markers.

[0114] The "amount" or "level" of a biomarker associated with an increased clinical benefit to an individual is a detectable level in a biological sample. These can be measured by methods known to one skilled in the art and also disclosed herein. The expression level or amount of biomarker assessed can be used to determine the response to the treatment.

[0115] The terms "level of expression" or "expression level" in general are used interchangeably and generally refer to the amount of a biomarker in a biological sample. "Expression" generally refers to the process by which information (e.g., gene-encoded and/or epigenetic) is converted into the structures present and operating in the cell. Therefore, as used herein, "expression" may refer to transcription into a polynucleotide, translation into a polypeptide, or even polynucleotide and/or polypeptide modifications (e.g., posttranslational modification of a polypeptide). Fragments of the transcribed polynucleotide, the translated polypeptide, or polynucleotide and/or polypeptide modifications (e.g., posttranslational modification of a polypeptide) shall also be regarded as expressed whether they originate from a transcript generated by alternative splicing or a degraded transcript, or from a post-translational processing of the polypeptide, e.g., by proteolysis. "Expressed genes" include those that are transcribed into a polynucleotide as mRNA and then translated into a polypeptide, and also those that are transcribed into RNA but not translated into a polypeptide (for example, transfer and ribosomal RNAs).

[0116] "Elevated expression," "elevated expression levels," or "elevated levels" refers to an increased expression or increased levels of a biomarker in an individual relative to a control, such as an individual or individuals who are not suffering from the disease or disorder (e.g., cancer) or an internal control (e.g., housekeeping biomarker).

[0117] "Reduced expression," "reduced expression levels," or "reduced levels" refers to a decrease expression or decreased levels of a biomarker in an individual relative to a control, such as an individual or individuals who are not suffering from the disease or disorder (e.g., cancer) or an internal control (e.g., housekeeping biomarker).
The term "housekeeping biomarker" refers to a biomarker or group of biomarkers (e.g., polynucleotides and/or polypeptides) which are typically similarly present in all cell types. In some embodiments, the housekeeping biomarker is a "housekeeping gene." A "housekeeping gene" refers herein to a gene or group of genes which encode proteins whose activities are essential for the maintenance of cell function and which are typically similarly present in all cell types.

"Amplification," as used herein generally refers to the process of producing multiple copies of a desired sequence. "Multiple copies" mean at least two copies. A "copy" does not necessarily mean perfect sequence complementarity or identity to the template sequence. For example, copies can include nucleotide analogs such as deoxyinosine, intentional sequence alterations (such as sequence alterations introduced through a primer comprising a sequence that is hybridizable, but not complementary, to the template), and/or sequence errors that occur during amplification.

The term "multiplex-PCR" refers to a single PCR reaction carried out on nucleic acid obtained from a single source (e.g., an individual) using more than one primer set for the purpose of amplifying two or more DNA sequences in a single reaction.

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel et al., Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995).

"Stringent conditions" or "high stringency conditions", as defined herein, can be identified by those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50 mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) overnight hybridization in a solution that employs 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with a 10 minute wash at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) followed by a 10 minute high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

"Moderately stringent conditions" can be identified as described by Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989, and include
the use of washing solution and hybridization conditions (e.g., temperature, ionic strength and %SDS) less stringent that those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

[0124] The term "diagnosis" is used herein to refer to the identification or classification of a molecular or pathological state, disease or condition (e.g., cancer). For example, "diagnosis" may refer to identification of a particular type of cancer. "Diagnosis" may also refer to the classification of a particular subtype of cancer, e.g., by histopathological criteria, or by molecular features (e.g., a subtype characterized by expression of one or a combination of biomarkers (e.g., particular genes or proteins encoded by said genes)).

[0125] The term "aiding diagnosis" is used herein to refer to methods that assist in making a clinical determination regarding the presence, or nature, of a particular type of symptom or condition of a disease or disorder (e.g., cancer). For example, a method of aiding diagnosis of a disease or condition (e.g., cancer) can comprise measuring certain biomarkers in a biological sample from an individual.

[0126] The term "sample," as used herein, refers to a composition that is obtained or derived from a subject and/or individual of interest that contains a cellular and/or other molecular entity that is to be characterized and/or identified, for example based on physical, biochemical, chemical and/or physiological characteristics. For example, the phrase "disease sample" and variations thereof refers to any sample obtained from a subject of interest that would be expected or is known to contain the cellular and/or molecular entity that is to be characterized. Samples include, but are not limited to, primary or cultured cells or cell lines, cell supernatants, cell lysates, platelets, serum, plasma, vitreous fluid, lymph fluid, synovial fluid, follicular fluid, seminal fluid, amniotic fluid, milk, whole blood, blood-derived cells, urine, cerebro-spinal fluid, saliva, sputum, tears, perspiration, mucus, tumor lysates, and tissue culture medium, tissue extracts such as homogenized tissue, tumor tissue, cellular extracts, and combinations thereof. A tumor sample includes but is not limited to a sample from a solid tumor, a sample from a liquid tumor such as a leukemia, a sample from a primary tumor, a sample from a metastatic tumor, cultured tumor cells, and tumor lysates. In some cases the tumor sample can be cells derived from a tumor and found in a fluid such as plasma, serum, whole blood, vitreous fluid, lymph fluid, synovial fluid, follicular fluid, seminal fluid, amniotic fluid, milk, urine, cerebro-spinal fluid, saliva, sputum, tears, perspiration, and mucus.

[0127] By "tissue sample" or "cell sample" is meant a collection of similar cells obtained from a tissue of a subject or individual. The source of the tissue or cell sample may be solid tissue as from a fresh, frozen and/or preserved organ, tissue sample, biopsy, and/or aspirate; blood or any blood
constituents such as plasma; bodily fluids such as cerebral spinal fluid, amniotic fluid, peritoneal fluid, or interstitial fluid; cells from any time in gestation or development of the subject. The tissue sample may also be primary or cultured cells or cell lines. Optionally, the tissue or cell sample is obtained from a disease tissue/organ. The tissue sample may contain compounds which are not naturally intermixed with the tissue in nature such as preservatives, anticoagulants, buffers, fixatives, nutrients, antibiotics, or the like.

**[0128]** A "reference sample", "reference cell", "reference tissue", "control sample", "control cell", or "control tissue", as used herein, refers to a sample, cell, tissue, standard, or level that is used for comparison purposes. In one embodiment, a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is obtained from a healthy and/or non-diseased part of the body (e.g., tissue or cells) of the same subject or individual. For example, healthy and/or non-diseased cells or tissue adjacent to the diseased cells or tissue (e.g., cells or tissue adjacent to a tumor). In another embodiment, a reference sample is obtained from an untreated tissue and/or cell of the body of the same subject or individual. For example, the sample can be peripheral blood mononuclear cells. In yet another embodiment, a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is obtained from a healthy and/or non-diseased part of the body (e.g., tissues or cells) of an individual who is not the subject or individual. In even another embodiment, a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is obtained from an untreated tissue and/or cell of the body of an individual who is not the subject or individual.

**[0129]** For the purposes herein a "section" of a tissue sample is meant a single part or piece of a tissue sample, e.g. a thin slice of tissue or cells cut from a tissue sample. It is understood that multiple sections of tissue samples may be taken and subjected to analysis, provided that it is understood that the same section of tissue sample may be analyzed at both morphological and molecular levels, or analyzed with respect to both polypeptides and polynucleotides.

**[0130]** By "correlate" or "correlating" is meant comparing, in any way, the performance and/or results of a first analysis or protocol with the performance and/or results of a second analysis or protocol. For example, one may use the results of a first analysis or protocol in carrying out a second protocols and/or one may use the results of a first analysis or protocol to determine whether a second analysis or protocol should be performed. With respect to the embodiment of polynucleotide analysis or protocol, one may use the results of the polynucleotide expression analysis or protocol to determine whether a specific therapeutic regimen should be performed.

**[0131]** "Individual response" or "response" can be assessed using any endpoint indicating a benefit to the individual, including, without limitation, (1) inhibition, to some extent, of disease progression (e.g., cancer progression), including slowing down and complete arrest; (2) a reduction in tumor size; (3) inhibition (i.e., reduction, slowing down or complete stopping) of cancer cell infiltration into adjacent peripheral organs and/or tissues; (4) inhibition (i.e. reduction, slowing down or complete stopping) of metasisis; (5) relief, to some extent, of one or more symptoms associated with the
disease or disorder (e.g., cancer); (6) increase in the length of progression free survival; and/or (9)
decreased mortality at a given point of time following treatment.

[0132] The term "substantially the same," as used herein, denotes a sufficiently high degree of
similarity between two numeric values, such that one of skill in the art would consider the difference
between the two values to be of little or no biological and/or statistical significance within the context
of the biological characteristic measured by said values (e.g., Kd values or expression). The
difference between said two values is, for example, less than about 50%, less than about 40%, less
than about 30%, less than about 20%, and/or less than about 10% as a function of the
reference/comparator value.

[0133] The phrase "substantially different," as used herein, denotes a sufficiently high degree of
difference between two numeric values such that one of skill in the art would consider the difference
between the two values to be of statistical significance within the context of the biological
characteristic measured by said values (e.g., Kd values). The difference between said two values is,
for example, greater than about 10%, greater than about 20%, greater than about 30%, greater than
about 40%, and/or greater than about 50% as a function of the value for the reference/comparator
molecule.

[0134] The word "label" when used herein refers to a detectable compound or composition. The
label is typically conjugated or fused directly or indirectly to a reagent, such as a polynucleotide
probe or an antibody, and facilitates detection of the reagent to which it is conjugated or fused. The
label may itself be detectable (e.g., radioisotope labels or fluorescent labels) or, in the case of an
enzymatic label, may catalyze chemical alteration of a substrate compound or composition which
results in a detectable product.

[0135] An "effective amount" of an agent refers to an amount effective, at dosages and for periods
of time necessary, to achieve the desired therapeutic or prophylactic result.

[0136] A "therapeutically effective amount" of a substance/molecule of the invention, agonist or
antagonist may vary according to factors such as the disease state, age, sex, and weight of the
individual, and the ability of the substance/molecule, agonist or antagonist to elicit a desired response
in the individual. A therapeutically effective amount is also one in which any toxic or detrimental
effects of the substance/molecule, agonist or antagonist are outweighed by the therapeutically
beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and
for periods of time necessary, to achieve the desired prophylactic result. Typically but not
necessarily, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the
prophylactically effective amount will be less than the therapeutically effective amount.

[0137] The term "pharmaceutical formulation" refers to a preparation which is in such form as to
permit the biological activity of an active ingredient contained therein to be effective, and which
contains no additional components which are unacceptably toxic to a subject to which the
formulation would be administered.
A "pharmaceutically acceptable carrier" refers to an ingredient in a pharmaceutical formulation, other than an active ingredient, which is nontoxic to a subject. A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative.

As used herein, "treatment" (and grammatical variations thereof such as "treat" or "treating") refers to clinical intervention in an attempt to alter the natural course of the individual being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. In some embodiments, antibodies of the invention are used to delay development of a disease or to slow the progression of a disease.

The term "anti-cancer therapy" refers to a therapy useful in treating cancer. Examples of anti-cancer therapeutic agents include, but are limited to, e.g., chemotherapeutic agents, growth inhibitory agents, cytotoxic agents, agents used in radiation therapy, anti-angiogenesis agents, apoptotic agents, anti-tubulin agents, and other agents to treat cancer, anti-CD20 antibodies, platelet derived growth factor inhibitors (e.g., Gleevec™ (Imatinib Mesylate)), a COX-2 inhibitor (e.g., celecoxib), interferons, cytokines, antagonists (e.g., neutralizing antibodies) that bind to one or more of the following targets PDGFR-beta, BlyS, APRIL, BCMA receptor(s), TRAIL/Apo2, and other bioactive and organic chemical agents, etc. Combinations thereof are also included in the invention.

The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (e.g., At211, 113I, 1125, Y90, Rel86, Rel88, Sml53, Bi212, P32 and radioactive isotopes of Lu), chemotherapeutic agents e.g., methotrexate, adriamycin, vinca alkaloids (vincristine, vinblastine, etoposide), doxorubicin, melphalan, mitomycin C, chlorambucil, daunorubicin or other intercalating agents, enzymes and fragments thereof such as nucleolytic enzymes, antibiotics, and toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof, and the various antitumor or anticancer agents disclosed below. Other cytotoxic agents are described below. A tumoricidal agent causes destruction of tumor cells.

A "chemotherapeutic agent" refers to a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclophosphamide (CYTOXAN®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamlamelines including altretamine, triethyleneemelamine, triethylenephosphoramide, triethylenetriphosphoramide and trimethylomelamine; acetogenins (especially bullatacin and bullatacinone); delta-9-tetrahydrocannabinol (dronabinol, MARINOL®); beta-lapachone; lapachol;
colchicines; betulinic acid; a camptothecin (including the synthetic analogue toptotecan (HYCAMTIN®), CPT-11 (irinotecan, CAMPTOSAR®), acetylcamptothecin, scopolectin, and 9-aminocamptothecin); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); podophyllotoxin; podophyllinic acid; teniposide; cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherochin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chloromaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechloroethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carbustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin gammall and calicheamicin omegall (see, e.g., Nicolaou et al., Angew. Chem Intl. Ed. Engl., 33: 183-186 (1994)); CDP323, an oral alpha-4 integrin inhibitor; dynemicin, including dynemicin A; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabacin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including ADRIAMYCIN®, morpholino-doxorubicin, cyano morpholino-doxorubicin, 2-pyrrolino-doxorubicin, doxorubicin HC1 liposome injection (DOXIL®), liposomal doxorubicin TLC D-99 (MYOCET®), peglylated liposomal doxorubicin (CAELYX®), and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate, gemcitabine (GEMZAR®), tegafur (UFTORAL®), capecitabine (XELODA®), an epothilone, and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dimeoxyuridine, doxifluridine, enocitabine, flexuridine; androgens such as clustosterone, dromostanolone propionate, epitostanol, meptiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecol cine; diaziquone; elfornithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mophidamol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spi rogermanium; tenuazonic acid; triaziquone; 2,2', 2'-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine (ELDISINE®, FILDESIN®); dacarbazine; mannomustine;
mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); thiotepa; taxoid, e.g., paclitaxel (TAXOL®), albumin-engineered nanoparticle formulation of paclitaxel (ABRAXANETM), and docetaxel (TAXOTERE®); chloranbucil; 6-thioguanine; mercaptopurine; methotrexate; platinum agents such as cisplatin, oxaliplatin (e.g., ELOXATIN®), and carboplatin; vincas, which prevent tubulin polymerization from forming microtubules, including vinblastine (VELBAN®), vincristine (ONCOVIN®), vindesine (ELDISINE®, FILDESIN®), and vinorelbine (NAVELBINE®); etoposide (VP-16); ifosfamide; mitoxantrone; leucovorin; novantrone; edatrexate; daunomycin; aminopterin; ibandronate; topoisomerase inhibitor RFS 2000; difluoromethylnitidine (DMFO); retinoids such as retinoic acid, including bexarotene (TARGRETIN®); bisphosphonates such as clodronate (for example, BONEFOS® or OSTAC®), etidronate (DIDROCAL®), NE-58095, zoledronic acid/zoledronate (ZOMETA®), alendronate (FOSAMAX®), pamidronate (AREDIA®), tiludronate (SKELID®), or risedronate (ACTONEL®); troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); antisense oligonucleotides, particularly those that inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, such as, for example, PKC-alpha, Raf, H-Ras, and epidermal growth factor receptor (EGF-R); vaccines such as THERATOPE® vaccine and gene therapy vaccines, for example, ALLOVECTIN® vaccine, LEUVECTIN® vaccine, and VAXID® vaccine; topoisomerase 1 inhibitor (e.g., LURTOTECAN®); rmRH (e.g., ABARELIX®); BAY439006 (sorafenib; Bayer); SU-11248 (sunitinib, SUTENT®, Pfizer); perifosine, COX-2 inhibitor (e.g., celecoxib or etoricoxib), proteosome inhibitor (e.g., PS341); bortezomib (VELCADE®); CCI-779; tipifarnib (R11577); orafenib, ABT510; Bcl-2 inhibitor such as oblimersen sodium (GENASENSE®); pixantrone; EGFR inhibitors (see definition below); tyrosine kinase inhibitors (see definition below); serine-threonine kinase inhibitors such as rapamycin (sirolimus, RAPAMUNE®); farnesyltransferase inhibitors such as lonafarnib (SCH 6636, SARASARTM); and pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more of the above such as CHOP, an abbreviation for a combined therapy of cyclophosphamide, doxorubicin, vincristine, and prednisolone; and FOLFOX, an abbreviation for a treatment regimen with oxaliplatin (ELOXATINTM) combined with 5-FU and leucovorin.

Chemothterapeutic agents as defined herein include "anti-hormonal agents" or "endocrine therapeutics" which act to regulate, reduce, block, or inhibit the effects of hormones that can promote the growth of cancer. They may be hormones themselves, including, but not limited to: anti-estrogens with mixed agonist/antagonist profile, including, tamoxifen (NOLVADEX®), 4-hydroxytamoxifen, toremifene (FARESTON®), idoxifene, droloxifene, raloxifene (EVISTA®), trioxifene, keoxifene, and selective estrogen receptor modulators (SERMs) such as SERM3; pure anti-estrogens without agonist properties, such as fulvestrant (FASLODEX®), and EM800 (such agents may block estrogen receptor (ER) dimerization, inhibit DNA binding, increase ER turnover, and/or suppress ER levels); aromatase inhibitors, including steroidal aromatase inhibitors such as for mestane and exemestane (AROMASIN®), and nonsteroidal aromatase inhibitors such as anastrazole (ARIMIDEX®), letrozole
(FEMARA®) and aminoglutethimide, and other aromatase inhibitors include vorozole (RIVISOR®), megestrol acetate (MEGASE®), fadrozole, and 4(5)-imidazoles; lutenizing hormone-releaseing hormone agonists, including leuprolide (LUPRON® and ELIGARD®), goserelin, buserelin, and triptérelin; sex steroids, including progestines such as megestrol acetate and medroxyprogesterone acetate, estrogens such as diethylstilbestrol and premarin, and androgens/retinoids such as fluoxymesterone, all transretion acid and fenretinide; onapristone; anti-progesterones; estrogen receptor down-regulators (ERDs); anti-androgens such as flutamide, nilutamide and bicalutamide; and pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more of the above.

[0144] The term "prodrug" as used in this application refers to a precursor or derivative form of a pharmaceutically active substance that is less cytotoxic to tumor cells compared to the parent drug and is capable of being enzymatically activated or converted into the more active parent form. See, e.g., Wilman, "Prodrugs in Cancer Chemotherapy" Biochemical Society Transactions, 14, pp. 375-382, 615th Meeting Belfast (1986) and Stella et al., "Prodrugs: A Chemical Approach to Targeted Drug Delivery," Directed Drug Delivery, Borchardt et al., (ed.), pp. 247-267, Humana Press (1985). The prodrugs of this invention include, but are not limited to, phosphate-containing prodrugs, thiophosphate-containing prodrugs, sulfate-containing prodrugs, peptide-containing prodrugs, D-amino acid-modified prodrugs, glycosylated prodrugs, β-lactam-containing prodrugs, optionally substituted phenoxyacetamide-containing prodrugs or optionally substituted phenylacetamide-containing prodrugs, 5-fluorocytosine and other 5-fluorouridine prodrugs which can be converted into the more active cytotoxic free drug. Examples of cytotoxic drugs that can be derivatized into a prodrug form for use in this invention include, but are not limited to, those chemotherapeutic agents described above.

[0145] A "growth inhibitory agent" when used herein refers to a compound or composition which inhibits growth of a cell (e.g., a cell whose growth is dependent upon NAD biosynthesis from nicotinamide (e.g., Nampt and/or NMNAT) expression either in vitro or in vivo). Examples of growth inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such as agents that induce Gl arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), taxanes, and topoisomerase II inhibitors such as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest Gl also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechloroethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in The Molecular Basis of Cancer, Mendelsohn and Israel, eds., Chapter 1, entitled "Cell cycle regulation, oncogenes, and antineoplastic drugs" by Murakami et al. (WB Saunders: Philadelphia, 1995), especially p. 13. The taxanes (paclitaxel and docetaxel) are anticancer drugs both derived from the yew tree. Docetaxel (TAXOTERE®, Rhone-Poulenc Rorer), derived from the European yew, is a semisynthetic analogue of paclitaxel (TAXOL®, Bristol-Myers Squibb). Paclitaxel and docetaxel
promote the assembly of microtubules from tubulin dimers and stabilize microtubules by preventing depolymerization, which results in the inhibition of mitosis in cells.

[0146] By "radiation therapy" is meant the use of directed gamma rays or beta rays to induce sufficient damage to a cell so as to limit its ability to function normally or to destroy the cell altogether. It will be appreciated that there will be many ways known in the art to determine the dosage and duration of treatment. Typical treatments are given as a one time administration and typical dosages range from 10 to 200 units (Grays) per day.

[0147] An "individual" or "subject" is a mammal. Mammals include, but are not limited to, domesticated animals (e.g., cows, sheep, cats, dogs, and horses), primates (e.g., humans and non-human primates such as monkeys), rabbits, and rodents (e.g., mice and rats). In certain embodiments, the individual or subject is a human.

[0148] The term "concurrently" is used herein to refer to administration of two or more therapeutic agents, where at least part of the administration overlaps in time. Accordingly, concurrent administration includes a dosing regimen when the administration of one or more agent(s) continues after discontinuing the administration of one or more other agent(s).

[0149] By "reduce or inhibit" is meant the ability to cause an overall decrease of 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or greater. Reduce or inhibit can refer to the symptoms of the disorder being treated, the presence or size of metastases, or the size of the primary tumor.

[0150] The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, combination therapy, contraindications and/or warnings concerning the use of such therapeutic products.

[0151] An "article of manufacture" is any manufacture (e.g., a package or container) or kit comprising at least one reagent, e.g., a medicament for treatment of a disease or disorder (e.g., cancer), or a probe for specifically detecting a biomarker described herein. In certain embodiments, the manufacture or kit is promoted, distributed, or sold as a unit for performing the methods described herein.

[0152] A "target audience" is a group of people or an institution to whom or to which a particular medicament is being promoted or intended to be promoted, as by marketing or advertising, especially for particular uses, treatments, or indications, such as individuals, populations, readers of newspapers, medical literature, and magazines, television or internet viewers, radio or internet listeners, physicians, drug companies, etc.

[0153] As is understood by one skilled in the art, reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to "about X" includes description of "X".
[0154] It is understood that aspect and embodiments of the invention described herein include "consisting" and/or "consisting essentially of" aspects and embodiments. As used herein, the singular form "a", "an", and "the" includes plural references unless indicated otherwise.

[0155] II. Methods and Uses

[0156] Provided herein are methods utilizing one or more NAPRT1 biomarkers in therapies comprising a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist).

[0157] Provided herein are methods of treating a disease or disorder in an individual comprising administering to the individual an effective amount of a NAD biosynthesis from nicotinamide antagonist, wherein treatment is based upon the individual having a disease or disorder comprising one or more NAPRT1 biomarkers. For example, provided are methods of treating a disease or disorder in an individual comprising administering to the individual an effective amount of a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist), wherein treatment is based upon the individual having a disease or disorder comprising a positive NAPRT1 methylation status.

[0158] In addition, provided herein are methods of treating a disease or disorder cell, wherein the disease or disorder cell comprises one or more NAPRT1 biomarkers, the method comprising providing an effective amount of a NAD biosynthesis from nicotinamide antagonist. For example, methods of treating a disease or disorder cell, wherein the disease or disorder cell comprises a positive NAPRT1 methylation status, the method comprising providing an effective amount of a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist).

[0159] Provided herein are methods of treating a disease or disorder in an individual provided that the individual has been found to have a disease or disorder comprising one or more NAPRT1 biomarkers, the method comprising administering to the individual an effective amount of a NAD biosynthesis from nicotinamide antagonist. For example, provided are methods of treating a disease or disorder in an individual provided that the individual has been found to have a disease or disorder comprising a positive NAPRT1 methylation status, the method comprising administering to the individual an effective amount of a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist).

[0160] Further provided herein are method for treating a disease or disorder in an individual, the method comprising: determining that a sample obtained from the individual comprises one or more NAPRT1 biomarkers, and administering an effective amount of a therapy comprising a NAD biosynthesis from nicotinamide antagonist to the individual, whereby the disease or disorder is treated. For example, provided are method for treating a disease or disorder in an individual, the method comprising: determining that a sample obtained from the individual comprises a positive NAPRT1 methylation status, and administering an effective amount of a therapy comprising a NAD
biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) to the
individual, whereby the disease or disorder is treated.

[0161] Provided are methods of treating a disease or disorder, comprising: (a) selecting an
individual having the disease or disorder, wherein the disease or disorder comprises one or more
NAPRTI biomarkers; and (b) administering to the individual thus selected an effective amount of a
NAD biosynthesis from nicotinamide antagonist, whereby the disease or disorder is treated. For
example, provided are methods of treating a disease or disorder, comprising: (a) selecting an
individual having the disease or disorder, wherein the disease or disorder comprises a positive
NAPRTI methylation status; and (b) administering to the individual thus selected an effective
amount of a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT
antagonist), whereby the disease or disorder is treated.

[0162] Provided herein are also methods of identifying an individual with a disease or disorder
who is more or less likely to exhibit benefit from treatment with a therapy comprising a NAD
biosynthesis from nicotinamide antagonist, the method comprising: determining presence or absence
of one or more NAPRTI biomarkers in a sample obtained from the individual, wherein presence of
the one or more NAPRTI biomarkers in the sample indicates that the individual is more likely to
exhibit benefit from treatment with the therapy comprising the NAD biosynthesis from nicotinamide
antagonist or absence of the one or more NAPRTI biomarkers indicates that the individual is less
likely to exhibit benefit from treatment with the therapy comprising the NAD biosynthesis from
nicotinamide antagonist. For example, provided are methods of identifying an individual with a
disease or disorder who is more or less likely to exhibit benefit from treatment with a therapy
comprising a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or
NMNAT antagonist), the method comprising: determining presence or absence of a positive
NAPRTI methylation status in a sample obtained from the individual, wherein presence of the
positive NAPRTI methylation status in the sample indicates that the individual is more likely to
exhibit benefit from treatment with the therapy comprising the NAD biosynthesis from nicotinamide
antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) or absence of the positive NAPRTI
methylation status indicates that the individual is less likely to exhibit benefit from treatment with the
therapy comprising the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist
and/or NMNAT antagonist).

[0163] Provided herein are methods for predicting whether an individual with a disease or disorder
is more or less likely to respond effectively to treatment with a therapy comprising a NAD
biosynthesis from nicotinamide antagonist, the method comprising determining one or more NAPRTI
biomarkers, whereby presence of the one or more NAPRTI biomarkers indicates that the individual is
more likely to respond effectively to treatment with the NAD biosynthesis from nicotinamide
antagonist and absence of the one or more NAPRTI biomarkers indicates that the individual is less
likely to respond effectively to treatment with the NAD biosynthesis from nicotinamide antagonist.
For example, provided are methods for predicting whether an individual with a disease or disorder is more or less likely to respond effectively to treatment with a therapy comprising a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist), the method comprising determining a positive NAPRT1 methylation status, whereby presence of the positive NAPRT1 methylation status indicates that the individual is more likely to respond effectively to treatment with the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) and absence of the positive NAPRT1 methylation status indicates that the individual is less likely to respond effectively to treatment with the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist).

[0164] Provided herein are also methods of predicting the response or lack of response of an individual with a disease or disorder to an therapy comprising a NAD biosynthesis from nicotinamide antagonist comprising detecting in a sample obtained from the individual presence or absence of one or more NAPRT1 biomarkers, wherein presence of the one or more NAPRT1 biomarkers is predictive of response of the individual to the therapy comprising the NAD biosynthesis from nicotinamide antagonist and absence of the one or more NAPRT1 biomarkers is predictive of lack of response of the individual to the therapy comprising the NAD biosynthesis from nicotinamide antagonist. For example, provided herein are methods of predicting the response or lack of response of an individual with a disease or disorder to an therapy comprising a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) comprising detecting in a sample obtained from the individual presence or absence of a positive NAPRT1 methylation status, wherein presence of the positive NAPRT1 methylation status is predictive of response of the individual to the therapy comprising the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) and absence of the positive NAPRT1 methylation status is predictive of lack of response of the individual to the therapy comprising the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist).

[0165] In some embodiments of any of the methods, the one or more NAPRT1 biomarkers is expression levels of NAPRT. In some embodiments, the expression levels of NAPRT1 are expression levels of NAPRT1 mRNA. In some embodiments, the expression levels of NAPRT1 are expression levels of NAPRT1 polypeptide.

[0166] In some embodiments of any of the methods, the one or more NAPRT1 biomarkers is NAPRT1 methylation status. In some embodiments, the NAPRT1 methylation status is a positive NAPRT1 methylation status. In some embodiments, the positive NAPRT1 methylation status is methylation of at least one cytosine within a NAPRT1 DNA region; for example, the NAPRT1 region corresponding to SEQ ID NO:1. In some embodiments, the positive methylation status is methylation of at least one cytosine in the promoter region of the NAPRT1 gene. In some embodiments, the positive methylation status is methylation of at least one cytosine in
the CpG island of the NAPRT1 gene. In some embodiments, the positive methylation status is methylation of at least one cytosine between about chromosome coordinates 144659500 and 144661000 of human chromosome 8. In some embodiments, the positive methylation status is methylation of at least one cytosine between about chromosome coordinates 144659746 and 144660635 of human chromosome 8. In some embodiments, the positive methylation status is methylation of at least one cytosine between about chromosome coordinates 144659146 and 144661235 of human chromosome 8. In some embodiments, the positive methylation status is methylation of at least one cytosine between about chromosome coordinates 144660163 and 144660106 of human chromosome 8. In some embodiments, the positive methylation status is methylation of at least one cytosine between about chromosome coordinates 144660163 and 144660690 of human chromosome 8. In some embodiments, the positive methylation status is methylation of at least one cytosine in the sequence represented by SEQ ID NO:1 or SEQ ID NO:3. In some embodiments, the positive methylation status is methylation of at least one cytosine in the sequence represented between about position 1018 and about position 1545 of SEQ ID NO:1. In some embodiments, the positive methylation status is methylation of at least one cytosine in the sequence represented between about position 1221 and about position 1288 of SEQ ID NO:1. In some embodiments, the positive methylation status is methylation of at least one cytosine in any one of the genomic sequences corresponding to the sequences amplified by the primers set forth in Tables 2 and 3.

[0167] In some embodiments of any of the methods, the positive methylation status is a methylation of more than about any of 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the cytosines in the NAPRT1 region corresponding to SEQ ID NO:1. In some embodiments of any of the methods, the positive methylation status is a methylation of more than about any of 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the cytosines in the promoter region of NAPRT1 gene. In some embodiments of any of the methods, the positive methylation status is a methylation of more than about any of 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the cytosines in the 5’ region of the NAPRT1 gene. In some embodiments of any of the methods, the positive methylation status is a methylation of more than about any of 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the cytosines in the CpG island of the NAPRT1 gene. In some embodiments of any of the methods, the positive methylation status is a methylation of more than about any of 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the cytosines between about chromosome coordinates 144659500 and 144661000 of human chromosome 8. In some embodiments of any of the methods, the positive methylation status is a methylation of more than about any of 25%,
about any of 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the cytosines between about chromosome coordinates 144659746 and 14466035 of human chromosome 8. In some embodiments of any of the methods, the positive methylation status is a methylation of more than about any of 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the cytosines between about chromosome coordinates 144659146 and 144661235 of human chromosome 8. In some embodiments of any of the methods, the positive methylation status is a methylation of more than about any of 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the cytosines between about chromosome coordinates 144660163 and 144660106 of human chromosome 8. In some embodiments of any of the methods, the positive methylation status is a methylation of more than about any of 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the cytosines between about chromosome coordinates 144660411 and 144660433 of human chromosome 8. In some embodiments of any of the methods, the positive methylation status is a methylation of more than about any of 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the cytosines in the sequence represented by SEQ ID NO:1 or SEQ ID NO:3. In some embodiments of any of the methods, the positive methylation status is a methylation of more than about any of 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the cytosines in the sequence represented between about position 1018 and about position 1545 of SEQ ID NO:1. In some embodiments of any of the methods, the positive methylation status is a methylation of more than about any of 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the cytosines in the sequence represented between about position 1221 and about position 1288 of SEQ ID NO:1. In some embodiments, the positive methylation status is a methylation of more than about any of 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the cytosines in any one of the genomic sequences corresponding to the sequences amplified by the primers set forth in Tables 2 and 3.

[0168] Examples of cancers and cancer cells include, but are not limited to, carcinoma, lymphoma, blastoma (including medulloblastoma and retinoblastoma), sarcoma (including liposarcoma, synovial cell sarcoma and chondrosarcoma), neuroendocrine tumors (including carcinoid tumors, gastrinoma, and islet cell cancer), mesothelioma, schwannoma (including acoustic neuroma), meningioma, adenocarcinoma, melanoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include squamous cell cancer (e.g., epithelial squamous cell cancer), lung cancer including small-cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer,
gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer (including metastatic breast cancer), colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, testicular cancer, esophageal cancer, tumors of the biliary tract, as well as head and neck cancer. In some embodiments, the cancer is breast cancer, colorectal cancer, endometrium cancer, kidney cancer, lung cancer, lymphoid cancer, ovarian cancer, pancreatic cancer, or stomach cancer. In some embodiments, the cancer is lung cancer.

[0169] Presence and/or levels/amount of a biomarker can be determined qualitatively and/or quantitatively based on any suitable criterion known in the art. In certain embodiments, presence and/or levels/amount of a biomarker in a first sample is increased as compared to presence/absence and/or levels/amount in a second sample. In certain embodiments, presence/absence and/or levels/amount of a biomarker in a first sample is decreased as compared to presence and/or levels/amount in a second sample. In certain embodiments, the second sample is a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue. Additional disclosures for determining presence/absence and/or levels/amount of a biomarker are described herein.

[0170] In some embodiments of any of the methods, elevated levels/amount refers to an overall increase of about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or greater, in the level of biomarker (e.g., protein or nucleic acid modification), detected by standard art known methods such as those described herein, as compared to a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue. In certain embodiments, the elevated levels/amount refers to the increase in level/amount of a biomarker in the sample wherein the increase is at least about any of 1.5X, 1.75X, 2X, 3X, 4X, 5X, 6X, 7X, 8X, 9X, 10X, 25X, 50X, 75X, or 100X the level/amount of the respective biomarker in a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue. In some embodiments, elevated levels/amount refers to an overall increase of greater than about 1.5 fold, about 1.75 fold, about 2 fold, about 2.25 fold, about 2.5 fold, about 2.75 fold, about 3.0 fold, or about 3.25 fold as compared to a reference sample, reference cell, reference tissue, control sample, control cell, control tissue, or internal control (e.g., housekeeping gene).

[0171] In some embodiments of any of the methods, reduced levels/amount refers to an overall reduction of about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or greater, in the level of biomarker (e.g., protein or nucleic acid modification), detected by standard art known methods such as those described herein, as compared to a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue. In certain embodiments, reduced levels/amount refers to the decrease in level/amount of a biomarker in the sample wherein the decrease is at least about any of 0.9X, 0.8X, 0.7X, 0.6X, 0.5X, 0.4X, 0.3X, 0.2X, 0.1X, 0.05X, or
0.01X the level/amount of the respective biomarker in a reference sample, reference tissue, control sample, control cell, or control tissue.

[0172] Presence and/or level/amount of various biomarkers in a sample can be analyzed by a number of methodologies, many of which are known in the art and understood by the skilled artisan, including, but not limited to, immunohistochemical ("IHC"), Western blot analysis, immunoprecipitation, molecular binding assays, ELISA, ELIFA, fluorescence activated cell sorting ("FACS"), MassARRAY, proteomics, quantitative blood based assays (as for example Serum ELISA), biochemical enzymatic activity assays, in situ hybridization, Southern analysis, Northern analysis, whole genome sequencing, polymerase chain reaction ("PCR") including quantitative real time PCR ("qRT-PCR") and other amplification type detection methods, such as, for example, branched DNA, SISBA, TMA and the like), RNA-Seq, FISH, microarray analysis, gene expression profiling, and/or serial analysis of gene expression ("SAGE"), as well as any one of the wide variety of assays that can be performed by protein, gene, and/or tissue array analysis. Typical protocols for evaluating the status of genes and gene products are found, for example in Ausubel et al., eds., 1995, Current Protocols In Molecular Biology, Units 2 (Northern Blotting), 4 (Southern Blotting), 15 (Immunoblotting) and 18 (PCR Analysis). Multiplexed immunoassays such as those available from Rules Based Medicine or Meso Scale Discovery (“MSD”) may also be used.

[0173] In some embodiments, presence and/or level/amount of a biomarker is determined using a method comprising: (a) performing gene expression profiling, PCR (such as rtPCR), RNA-seq, microarray analysis, SAGE, MassARRAY technique, or FISH on a sample (such as a subject cancer sample); and b) determining presence and/or level/amount of a biomarker in the sample. In some embodiments, the microarray method comprises the use of a microarray chip having one or more nucleic acid molecules that can hybridize under stringent conditions to a nucleic acid molecule encoding a gene mentioned above or having one or more polypeptides (such as peptides or antibodies) that can bind to one or more of the proteins encoded by the genes mentioned above. In one embodiment, the PCR method is qRT-PCR. In one embodiment, the PCR method is multiplex-PCR. In some embodiments, gene expression is measured by microarray. In some embodiments, gene expression is measured by qRT-PCR. In some embodiments, expression is measured by multiplex-PCR.

[0174] Methods for evaluation of DNA methylation are well known. For example, Laird (2010) Nature Reviews Genetics 11:191-203 provides a review of DNA methylation analysis. In some embodiments, methods for evaluating methylation include randomly shearing or randomly fragmenting the genomic DNA, cutting the DNA with a methylation-dependent or methylation-sensitive restriction enzyme and subsequently selectively identifying and/or analyzing the cut or uncut DNA. Selective identification can include, for example, separating cut and uncut DNA (e.g., by size) and quantifying a sequence of interest that was cut or, alternatively, that was not cut. See, e.g., U.S. Pat. No. 7,186,512. In some embodiments, the method can encompass amplifying intact DNA
after restriction enzyme digestion, thereby only amplifying DNA that was not cleaved by the 
restriction enzyme in the area amplified. See, e.g., U.S. Patent Application Nos. 10/971,986; 
11/071,013; and 10/971,339. In some embodiments, amplification can be performed using primers 
that are gene specific. Alternatively, adaptors can be added to the ends of the randomly fragmented 
DNA, the DNA can be digested with a methylation-dependent or methylation-sensitive restriction 
enzyme, intact DNA can be amplified using primers that hybridize to the adaptor sequences. In some 
embodiments, a second step can be performed to determine the presence, absence or quantity of a 
particular gene in an amplified pool of DNA. In some embodiments, the DNA is amplified using real-
time, quantitative PCR.

[0175] In some embodiments, the methods comprise quantifying the average methylation density 
in a target sequence within a population of genomic DNA. In some embodiments, the method 
comprises contacting genomic DNA with a methylation-dependent restriction enzyme or methylation-
sensitive restriction enzyme under conditions that allow for at least some copies of potential 
restriction enzyme cleavage sites in the locus to remain uncleaved; quantifying intact copies of the 
locus; and comparing the quantity of amplified product to a control value representing the quantity of 
methylation of control DNA, thereby quantifying the average methylation density in the locus 
compared to the methylation density of the control DNA.

[0176] The quantity of methylation of a locus of DNA can be determined by providing a sample of 
genomic DNA comprising the locus, cleaving the DNA with a restriction enzyme that is either 
methylation-sensitive or methylation-dependent, and then quantifying the amount of intact DNA or 
quantifying the amount of cut DNA at the DNA locus of interest. The amount of intact or cut DNA 
will depend on the initial amount of genomic DNA containing the locus, the amount of methylation in 
the locus, and the number (i.e., the fraction) of nucleotides in the locus that are methylated in the 
genomic DNA. The amount of methylation in a DNA locus can be determined by comparing the 
quantity of intact DNA or cut DNA to a control value representing the quantity of intact DNA or cut 
DNA in a similarly-treated DNA sample. The control value can represent a known or predicted 
number of methylated nucleotides. Alternatively, the control value can represent the quantity of intact 
or cut DNA from the same locus in another (e.g., normal, non-diseased) cell or a second locus.

[0177] By using methylation-sensitive or methylation-dependent restriction enzyme under 
conditions that allow for at least some copies of potential restriction enzyme cleavage sites in the 
locus to remain uncleaved and subsequently quantifying the remaining intact copies and comparing 
the quantity to a control, average methylation density of a locus can be determined. If the 
methylation-sensitive restriction enzyme is contacted to copies of a DNA locus under conditions that 
allow for at least some copies of potential restriction enzyme cleavage sites in the locus to remain 
uncleaved, then the remaining intact DNA will be directly proportional to the methylation density, 
and thus may be compared to a control to determine the relative methylation density of the locus in 
the sample. Similarly, if a methylation-dependent restriction enzyme is contacted to copies of a DNA
locus under conditions that allow for at least some copies of potential restriction enzyme cleavage sites in the locus to remain uncleaved, then the remaining intact DNA will be inversely proportional to the methylation density, and thus may be compared to a control to determine the relative methylation density of the locus in the sample. Such assays are disclosed in, e.g., U.S. patent application Ser. No. 10/971,986.

[0178] In some embodiments, quantitative amplification methods (e.g., quantitative PCR or quantitative linear amplification) can be used to quantify the amount of intact DNA within a locus flanked by amplification primers following restriction digestion. Methods of quantitative amplification are disclosed in, e.g., U.S. Pat. Nos. 6,180,349; 6,033,854; and 5,972,602, as well as in, e.g., Gibson et al., Genome Research 6:995-1001 (1996); DeGraves et al., Biotechniques 34(1): 106-10, 112-5 (2003); Deiman B et al., Mol Biotechnol. 20(2): 163-79 (2002).

[0179] Additional methods for detecting DNA methylation can involve genomic sequencing before and after treatment of the DNA with bisulfite. See, e.g., Frommer et al., Proc. Natl. Acad. Sci. USA 89:1827-1831 (1992). When sodium bisulfite is contacted to DNA, unmethylated cytosine is converted to uracil, while methylated cytosine is not modified.


[0181] In some embodiments, a MethyLight assay is used alone or in combination with other methods to detect DNA methylation (see, Eads et al., Cancer Res. 59:2302-2306 (1999)). Briefly, in the MethyLight process genomic DNA is converted in a sodium bisulfite reaction (the bisulfite process converts unmethylated cytosine residues to uracil). Amplification of a DNA sequence of interest is then performed using PCR primers that hybridize to CpG dinucleotides. By using primers that hybridize only to sequences resulting from bisulfite conversion of unmethylated DNA, (or alternatively to methylated sequences that are not converted) amplification can indicate methylation status of sequences where the primers hybridize. Similarly, the amplification product can be detected with a probe that specifically binds to a sequence resulting from bisulfite treatment of an unmethylated (or methylated) DNA. If desired, both primers and probes can be used to detect methylation status. Thus, kits for use with MethyLight can include sodium bisulfite as well as primers or detectably-labeled probes (including but not limited to Taqman or molecular beacon probes) that distinguish between methylated and unmethylated DNA that have been treated with bisulfite. Other kit components can include, e.g., reagents necessary for amplification of DNA including but not limited to, PCR buffers, deoxynucleotides; and a thermostable polymerase.

[0182] In some embodiments, a Ms-SNuPE (Methylation-sensitive Single Nucleotid Primer Extension) reaction is used alone or in combination with other methods to detect DNA methylation (see Gonzalgo & Jones Nucleic Acids Res. 25:2529-2531 (1997)). The Ms-SNuPE technique is a quantitative method for assessing methylation differences at specific CpG sites based on bisulfite
treatment of DNA, followed by single-nucleotide primer extension. Briefly, genomic DNA is reacted with sodium bisulfite to convert unmethylated cytosine to uracil while leaving 5-methylcytosine unchanged. Amplification of the desired target sequence is then performed using PCR primers specific for bisulfite-converted DNA, and the resulting product is isolated and used as a template for methylation analysis at the CpG site(s) of interest.

In some embodiments, a methylation-specific PCR ("MSP") reaction is used alone or in combination with other methods to detect DNA methylation. An MSP assay entails initial modification of DNA by sodium bisulfite, converting all unmethylated, but not methylated, cytosines to uracil, and subsequent amplification with primers specific for methylated versus unmethylated DNA. See, Herman et al., Proc. Natl. Acad. Sci. USA 93:9821-9826, (1996); U.S. Pat. No. 5,786,146. In some embodiments, DNA methylation is detected by a QIAGEN PyroMark CpG Assay predesigned Pyrosequencing DNA Methylation assays.

In some embodiments, cell methylation status is determined using high-throughput DNA methylation analysis to determine sensitivity to NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist). Briefly, genomic DNA is isolated from a cell or tissue sample (e.g., a tumor sample or a blood sample) and is converted in a sodium bisulfite reaction (the bisulfite process converts unmethylated cytosine residues to uracil) using standard assays in the art. The bisulfite converted DNA product is amplified, fragmented and hybridized to an array containing CpG sites from across a genome using standard assays in the art. Following hybridization, the array is imaged and processed for analysis of the DNA methylation status using standard assays in the art. In some embodiments, the tissue sample is formalin-fixed paraffin embedded (FFPE) tissue. In some embodiments, the tissue sample is fresh frozen tissue. In some embodiments, the DNA isolated from the tissue sample is preamplified before bisulfite conversion. In some embodiments, the DNA isolated from the tissue sample is preamplified before bisulfite conversion by using the Invitrogen Superscript III One-Step RT-PCR System with Platinum Taq. In some embodiments, the DNA isolated from the tissue sample is preamplified before bisulfite conversion using a Taqman based assay. In some embodiments, the sodium bisulfite reaction is conducted using the Zymo EZ DNA Methylation Kit. In some embodiments, the bisulfite converted DNA is amplified and hybridized to an array using the Illumina Infinium HumanMethylation450 Beadchip Kit. In some embodiments, the array is imaged on an Illumina iScan Reader. In some embodiments, the images are processed with the GenomeStudio software methylation module. In some embodiments, the methylation data is analyzed using the Bioconductor lumi software package. See Du et al., Bioinformatics, 24(13): 1547-1548 (2008).

In some embodiments, NAPRT1 DNA methylation sites are identified using bisulfite sequencing PCR (BSP) to determine sensitivity to NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist). Briefly, genomic DNA is isolated from a cell or tissue sample (e.g., a tumor sample or a blood sample) and is converted in a sodium bisulfite reaction...
(the bisulfite process converts unmethylated cytosine residues to uracil) using standard assays in the
art. The bisulfite converted DNA product is amplified using primers designed to be specific to the
bisulfite converted DNA (e.g., bisulfite-specific primers) and ligated into vectors for transformation
into a host cell using standard assays in the art. After selection of the host cells containing the PCR
amplified bisulfite converted DNA product of interest, the DNA product is isolated and sequenced to
determine the sites of methylation using standard assays in the art. In some embodiments, the tissue
sample is formalin-fixed paraffin embedded (FFPE) tissue. In some embodiments, the tissue sample
is an FFPE tissue that has been processed for IHC analysis; for example, for NAPRT1 expression. In
some embodiments, the tissue sample is an FFPE tissue that showed little or no NAPRT1 expression
by IHC. In some embodiments, the tissue sample is fresh frozen tissue. In some embodiments, the
DNA isolated from the tissue sample is preamplified before bisulfite conversion. In some
embodiments, the DNA isolated from the tissue sample is preamplified before bisulfite conversion
using the Invitrogen Superscript III One-Step RT-PCR System with Platinum Taq. In some
embodiments, the DNA isolated from the tissue sample is preamplified before bisulfite conversion
using a Taqman based assay. In some embodiments, the sodium bisulfite reaction is conducted using
the Zymo EZ DNA Methylation-Gold Kit. In some embodiments, the primers designed to be specific
to the bisulfite converted DNA are designed using Applied Biosystems Methyl Primer Express
software. In some embodiments, the bisulfite converted DNA is amplified using the bisulfite-specific
primers in Table 2. In some embodiments, the bisulfite-specific primers are BSP1 primers and/or
BSP2 primers presented in Table 2. In some embodiments, the bisulfite converted DNA product is
PCR amplified using the Invitrogen Superscript III One-Step RT-PCR System with Platinum Taq. In
further embodiments, the PCR amplified bisulfite converted DNA product is ligated into a vector
using the Invitrogen TOPO TA Cloning kit. In some embodiments, the host cell is bacteria. In some
embodiments, the isolated PCR amplified bisulfite converted DNA product of interest is sequenced
using Applied Biosystems 3730x1 DNA Analyzer. In some embodiments, the primers designed to be
specific to the bisulfite converted DNA are designed using Qiagen PyroMark Assay Design software.
In some embodiments, the bisulfite converted DNA product is PCR amplified using the Invitrogen
Superscript III One-Step RT-PCR System with Platinum Taq. In further embodiments, the PCR
amplified bisulfite converted DNA product is sequenced using Qiagen Pyromark Q24 and analyzed
Qiagen with PyroMark software. In some embodiments, the coding DNA strand of all or a portion of
the NAPRT1 gene is sequenced. In some embodiments, the complementary DNA strand of all or a
portion of the NAPRT1 gene is sequenced. In some embodiments, the sense DNA strand and the
complementary DNA strands of all or a portion of the NAPRT1 gene are sequenced. In some
embodiments, a mixture of sense strands and complementary strands of all or a portion of the
NAPRT1 gene is sequenced. For example, in some embodiments, the coding strand of one PCR
amplicon from the NAPRT1 is sequenced and the complementary strand of another PCR amplicon
from NAPRT1 in sequenced.
In some embodiments, NAPRT1 DNA methylation sites are identified using quantitative methylation specific PCR (QMSP) to determine sensitivity to NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist). Briefly, genomic DNA is isolated from a cell or tissue sample and is converted in a sodium bisulfite reaction (the bisulfite process converts unmethylated cytosine residues to uracil) using standard assays in the art. In some embodiments, the tissue sample is formalin-fixed paraffin embedded (FFPE) tissue. In some embodiments, the tissue sample is an FFPE tissue that has been processed for IHC analysis; for example, for NAPRT1 expression. In some embodiments, the tissue sample is an FFPE tissue that showed little or no NAPRT1 expression by IHC. In some embodiments, the tissue sample is fresh frozen tissue. The bisulfite converted DNA product is amplified using primers designed to be specific to the bisulfite converted DNA (e.g., quantitative methylation specific PCR primers). The bisulfite converted DNA product is amplified with quantitative methylation specific PCR primers and analyzed for methylation using standard assays in the art. In some embodiments, the tissue sample is formalin-fixed paraffin embedded (FFPE) tissue. In some embodiments, the tissue sample is fresh frozen tissue. In some embodiments, the DNA isolated from the tissue sample is preamplified before bisulfite conversion using the Invitrogen Superscript III One-Step RT-PCR System with Platinum Taq. In some embodiments, the DNA isolated from the tissue sample is preamplified before bisulfite conversion. In some embodiments, the DNA isolated from the tissue sample is preamplified before bisulfite conversion using a Taqman based assay. In some embodiments, the sodium bisulfite reaction is conducted using a commercially available kit. In some embodiments, the sodium bisulfite reaction is conducted using the Zymo EZ DNA Methylation-Gold Kit. In some embodiments, the primers designed to be specific to the bisulfite converted DNA are designed using Applied Biosystems Methyl Primer Express software. In some embodiments, the bisulfite converted DNA is amplified using a Taqman based assay. In some embodiments, the bisulfite converted DNA is amplified using the quantitative methylation specific PCR primers and probes in Tables 3 and 4, respectively. In some embodiments, the bisulfite converted DNA is amplified using the QMSP3 primers and probes presented in Tables 3 and 4. In some embodiments, the bisulfite converted DNA is amplified on an Applied Biosystems 7900HT and analyzed using Applied Biosystems SDS software.

In some embodiments, the invention provides methods to determine NAPRT1 methylation by 1) IHC analysis of tumor samples, followed by 2) quantitative methylation specific PCR of DNA extracted from the tumor tissue used in the IHC analsyis of step 1. Briefly, coverslips from IHC slides are removed by one of two methods: the slide are placed in a freezer for at least 15 minutes, then the coverslip is pried off of the microscope slide using a razor blade. Slides are then incubated in xylene at room temp to dissolve the mounting media. Alternatively, slides are soaked in xylene until the coverslip fall off. This can take up to several days. All slides are taken through a deparaffinization procedure of 5 min xylene (x3), and 5 min 100% ethanol (x2). Tissues are scraped off slides with razor blades and placed in a tissue lysis buffer containing proteinase K and incubated
overnight at 56°C. In cases where tissue is still present after incubation, an extra 10 µl Proteinase K may be added and the tissue is incubated for another 30 min. DNA extraction was continued; for example, by using a QIAamp DNA FFPE Tissue kit. DNA extracted directly from IHC slides was subject to QMSP analysis using the QMSP3 primers and probes as described above.

[0188] In some embodiments, the bisulfite-converted DNA is sequenced by a deep sequencing. Deep sequencing is a process, such as direct pyrosequencing, where a sequence is read multiple times. Deep sequencing can be used to detect rare events such as rare mutations. Ultra-deep sequencing of a limited number of loci may be achieved by direct pyrosequencing of PCR products and by sequencing of more than 100 PCR products in a single run. A challenge in sequencing bisulphite-converted DNA arises from its low sequence complexity following bisulphite conversion of cytosine residues to thymine (uracil) residues. Reduced representation bisulphite sequencing (RRBS) may be introduced to reduce sequence redundancy by selecting only some regions of the genome for sequencing by size-fractionation of DNA fragments (Laird, PW Nature Reviews 11:195-203 (2010)). Targeting may be accomplished by array capture or padlock capture before sequencing. For example, targeted capture on fixed arrays or by solution hybrid selection can enrich for sequences targeted by a library of DNA or RNA oligonucleotides and can be performed before or after bisulphite conversion. Alternatively, padlock capture provides improved enrichment efficiency by combining the increased annealing specificity of two tethered probes, and subsequent amplification with universal primers allows for a more uniform representation than amplification with locus-specific primers.


[0190] In some embodiments, the expression of NAPRT1 in a cell is determined by evaluating NAPRT1 mRNA in a cell. Methods for the evaluation of mRNAs in cells are well known and include, for example, hybridization assays using complementary DNA probes (such as in situ hybridization using labeled riboprobes specific for the one or more genes, Northern blot and related techniques) and various nucleic acid amplification assays (such as RT-PCR using complementary primers specific for one or more of the genes, and other amplification type detection methods, such as, for example, branched DNA, SISBA, TMA and the like). In some embodiments, the expression of NAPRT1 in a test sample is compared to a reference sample. For example, the test sample may be a tumor tissue sample and the reference sample may be from normal tissue or cells such as PBMCs.

[0191] Samples from mammals can be conveniently assayed for mRNAs using Northern, dot blot or PCR analysis. In addition, such methods can include one or more steps that allow one to determine the levels of target mRNA in a biological sample (e.g., by simultaneously examining the levels a
comparative control mRNA sequence of a "housekeeping" gene such as an actin family member). Optionally, the sequence of the amplified target cDNA can be determined.

Optional methods of the invention include protocols which examine or detect mRNAs, such as target mRNAs, in a tissue or cell sample by microarray technologies. Using nucleic acid microarrays, test and control mRNA samples from test and control tissue samples are reverse transcribed and labeled to generate cDNA probes. The probes are then hybridized to an array of nucleic acids immobilized on a solid support. The array is configured such that the sequence and position of each member of the array is known. For example, a selection of genes whose expression correlates with increased or reduced clinical benefit of anti-angiogenic therapy may be arrayed on a solid support. Hybridization of a labeled probe with a particular array member indicates that the sample from which the probe was derived expresses that gene.

According to some embodiments, presence and/or level/amount is measured by observing protein expression levels of an aforementioned gene. In certain embodiments, the method comprises contacting the biological sample with antibodies to a biomarker described herein under conditions permissive for binding of the biomarker, and detecting whether a complex is formed between the antibodies and biomarker. Such method may be an in vitro or in vivo method. In one embodiment, an antibody is used to select subjects eligible for therapy with NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist), e.g., a NAPRTI biomarker for selection of individuals. For example, NAPRTI expression in a test sample is determined by IHC analysis using an NAPRTI detection agent such as an anti-NAPRTI antibody.

In certain embodiments, the presence and/or level/amount of biomarker proteins in a sample are examined using IHC and staining protocols. IHC staining of tissue sections has been shown to be a reliable method of determining or detecting presence of proteins in a sample. In one aspect, level of biomarker is determined using a method comprising: (a) performing IHC analysis of a sample (such as a subject cancer sample) with an antibody; and b) determining level of a biomarker in the sample. In some embodiments, IHC staining intensity is determined relative to a reference value.

Provided herein are methods of identifying an individual who is more likely to exhibit benefit from a therapy comprising an NAD biosynthesis from nicotinamide antagonist wherein DNA is isolated from a tumor sample, incubated with sodium bisulfite sufficient to convert unmethylated cytosine in the DNA to uracil, and sequencing all or part of the NAPRTI promoter region of the DNA. The methylation level of the NAPRTI gene is measured by determining the number of CpG and CpHpG sites where the cytosine residue was not converted to uracil. In some embodiments, greater than about any one of 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% methylation of the NAPRTI sequence indicates that the individual is more likely to benefit from treatment. In some embodiments, the part of the NAPRTI gene is the NAPRTI promoter. In some embodiments, the part of the NAPRTI gene is a CpG island. In some
embodiments, the part of the NAPRT1 gene is between about chromosome coordinates 144659500 and 144661000 of human chromosome 8. In some embodiments, the part of the NAPRT1 gene is between about chromosome coordinates 144659746 and 144660635 of human chromosome 8. In some embodiments, the part of the NAPRT1 gene is a between about chromosome coordinates 144659146 and 144661235 of human chromosome 8. In some embodiments, the part of the NAPRT1 gene is a between about chromosome coordinates 144660163 and 144660106 of human chromosome 8. In some embodiments, the part of the NAPRT1 gene is between about chromosome coordinates 144660163 and 144660690 of human chromosome 8. In some embodiments, the part of the NAPRT1 gene is a between about chromosome coordinates 144660411 and 144660433 of human chromosome 8. In some embodiments, the part of the NAPRT1 gene is the sequence represented by SEQ ID NO:1 or SEQ ID NO:3. In some embodiments, the part of the NAPRT1 gene comprises the sequence represented between about position 1221 and about position 1545 of SEQ ID NO:1.

[0196] Provided herein are methods of identifying an individual who is more likely to exhibit benefit from a therapy comprising an NAD biosynthesis from nicotinamide antagonist wherein DNA is isolated from a tumor sample, incubated with sodium bisulfite sufficient to convert unmethylated cytosine in the DNA to uracil. The methylation level of the NAPRT1 gene is measured by amplifying a portion of the NAPRT1 gene of the DNA sample using quantitative methylation specific PCR and determining the methylation level of the NAPRT1 region by determining the -dCt value of the tumor sample with the -dCt value obtained from quantitative methylation specific PCR of non-methylated DNA. In some embodiments the non-methylated DNA is recombinant DNA. In some embodiments, the non-methylated DNA is from normal tissue, for example, PBMCs or non-cancerous tissue. In some embodiments, greater than about any one of 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% methylation of the NAPRT1 sequence indicates that the individual is more likely to benefit from treatment. In some embodiments, the portion of the NAPRT1 gene amplified is from the NAPRT1 promoter. In some embodiments, the portion of the NAPRT1 gene amplified is from the a CpG island. In some embodiments, the portion of the NAPRT1 gene amplified is between about chromosome coordinates 144659500 and 144661000 of human chromosome 8. In some embodiments, the portion of the NAPRT1 gene amplified is between about chromosome coordinates 144659746 and 144660635 of human chromosome 8. In some embodiments, the portion of the NAPRT1 gene amplified is between about chromosome coordinates 144659146 and 144661235 of human chromosome 8. In some embodiments, the portion of the NAPRT1 gene amplified is between about chromosome coordinates 144660163 and 144660106 of human chromosome 8. In some embodiments, the portion of the NAPRT1 gene amplified is between about chromosome coordinates 144660163 and 144660690 of human chromosome 8. In some embodiments, portion of the NAPRT1 gene amplified is from the between about chromosome coordinates 144660411 and 144660433 of human chromosome 8. In some embodiments, the portion of the NAPRT1 gene amplified is from the sequence represented by
SEQ ID NO: 1 or SEQ ID NO:3. In some embodiments, the portion of the NAPRT1 gene amplified comprises the sequence represented between about position 1221 and about position 1288 of SEQ ID NO:1. In some embodiments, the portion of the NAPRT1 gene amplified comprises a genomic sequence corresponding to the sequence amplified by any of the primers set forth in Table 3. In some embodiments, the DNA from the tumor sample is isolated from a formalin-fixed paraffin embedded tumor sample. In some embodiments, the method portion of the NAPRT1 gene is pre-amplified prior to quantitative methylation specific PCR.

[0197] IHC may be performed in combination with additional techniques such as morphological staining and/or fluorescence in-situ hybridization. Two general methods of IHC are available; direct and indirect assays. According to the first assay, binding of antibody to the target antigen is determined directly. This direct assay uses a labeled reagent, such as a fluorescent tag or an enzyme-labeled primary antibody, which can be visualized without further antibody interaction. In a typical indirect assay, unconjugated primary antibody binds to the antigen and then a labeled secondary antibody binds to the primary antibody. Where the secondary antibody is conjugated to an enzymatic label, a chromogenic or fluorogenic substrate is added to provide visualization of the antigen. Signal amplification occurs because several secondary antibodies may react with different epitopes on the primary antibody.

[0198] The primary and/or secondary antibody used for IHC typically will be labeled with a detectable moiety. Numerous labels are available which can be generally grouped into the following categories: (a) Radioisotopes, such as 35S, 14C, 125I, 3H, and 131I; (b) colloidal gold particles; (c) fluorescent labels including, but are not limited to, rare earth chelates (europium chelates), Texas Red, rhodamine, fluorescein, dansyl, Lissamine, umbellif erone, phycocrytherin, phycocyanin, or commercially available fluorophores such SPECTRUM ORANGE7 and SPECTRUM GREEN7 and/or derivatives of any one or more of the above; (d) various enzyme-substrate labels are available and U.S. Patent No. 4,275,149 provides a review of some of these. Examples of enzymatic labels include luciferases (e.g., firefly luciferase and bacterial luciferase; U.S. Patent No. 4,737,456), luciferin, 2,3-dihydrophthalalizinediones, malate dehydrogenase, urease, peroxidase such as horseradish peroxidase (HRPO), alkaline phosphatase, β-galactosidase, glucoamylase, lysozyme, saccharide oxidases (e.g., glucose oxidase, galactose oxidase, and glucose-6-phosphate dehydrogenase), heterocyclic oxidases (such as uricase and xanthine oxidase), lactoperoxidase, microperoxidase, and the like.

[0199] Examples of enzyme-substrate combinations include, for example, horseradish peroxidase (HRPO) with hydrogen peroxidase as a substrate; alkaline phosphatase (AP) with para-Nitrophenyl phosphate as chromogenic substrate; and β-D-galactosidase (β-D-Gal) with a chromogenic substrate (e.g., p-nitrophenyl -β-D-galactosidase) or fluorogenic substrate (e.g., 4-methylumbelliferyl -β-D-galactosidase). For a general review of these, see U.S. Patent Nos. 4,275,149 and 4,318,980.
Specimens thus prepared may be mounted and coverslipped. Slide evaluation is then determined, e.g., using a microscope, and staining intensity criteria, routinely used in the art, may be employed. In some embodiments, a staining pattern score of about 1+ or higher is diagnostic and/or prognostic. In certain embodiments, a staining pattern score of about 2+ or higher in an IHC assay is diagnostic and/or prognostic. In other embodiments, a staining pattern score of about 3 or higher is diagnostic and/or prognostic. In one embodiment, it is understood that when cells and/or tissue from a tumor or colon adenoma are examined using IHC, staining is generally determined or assessed in tumor cell and/or tissue (as opposed to stromal or surrounding tissue that may be present in the sample).

In alternative methods, the sample may be contacted with an antibody specific for said biomarker under conditions sufficient for an antibody-biomarker complex to form, and then detecting said complex. The presence of the biomarker may be detected in a number of ways, such as by Western blotting and ELISA procedures for assaying a wide variety of tissues and samples, including plasma or serum. A wide range of immunoassay techniques using such an assay format are available, see, e.g., U.S. Pat. Nos. 4,016,043, 4,424,279 and 4,018,653. These include both single-site and two-site or "sandwich" assays of the non-competitive types, as well as in the traditional competitive binding assays. These assays also include direct binding of a labeled antibody to a target biomarker.

Presence and/or level/amount of a selected biomarker in a tissue or cell sample may also be examined by way of functional or activity-based assays. For instance, if the biomarker is an enzyme, one may conduct assays known in the art to determine or detect the presence of the given enzymatic activity in the tissue or cell sample.

In certain embodiments, the samples are normalized for both differences in the amount of the biomarker assayed and variability in the quality of the samples used, and variability between assay runs. Such normalization may be accomplished by detecting and incorporating the level of certain normalizing biomarkers, including well known housekeeping genes, such as ACTB. Alternatively, normalization can be based on the mean or median signal of all of the assayed genes or a large subset thereof (global normalization approach). On a gene-by-gene basis, measured normalized amount of a subject tumor mRNA or protein is compared to the amount found in a reference set. Normalized expression levels for each mRNA or protein per tested tumor per subject can be expressed as a percentage of the expression level measured in the reference set. The presence and/or expression level/amount measured in a particular subject sample to be analyzed will fall at some percentile within this range, which can be determined by methods well known in the art.

In certain embodiments, relative expression level of a gene is determined as follows:

Relative expression gene \( l = 2^{\text{exp} (\text{Ct housekeeping gene} - \text{Ct gene} l)} \) with Ct determined in a sample.

Relative expression gene reference RNA \( = 2^{\text{exp} (\text{Ct housekeeping gene} - \text{Ct gene} l)} \) with Ct determined in the reference sample.
Normalized relative expression \( \text{genel sample 1} = \frac{\text{relative expression genel sample 1}}{\text{relative expression genel reference RNA}} \times 100 \)

\[ \text{Ct} \] is the threshold cycle. The Ct is the cycle number at which the fluorescence generated within a reaction crosses the threshold line.

All experiments are normalized to a reference RNA, which is a comprehensive mix of RNA from various tissue sources (e.g., reference RNA #636538 from Clontech, Mountain View, CA). Identical reference RNA is included in each qRT-PCR run, allowing comparison of results between different experimental runs.

In one embodiment, the sample is a clinical sample. In another embodiment, the sample is used in a diagnostic assay. In some embodiments, the sample is obtained from a primary or metastatic tumor. Tissue biopsy is often used to obtain a representative piece of tumor tissue. Alternatively, tumor cells can be obtained indirectly in the form of tissues or fluids that are known or thought to contain the tumor cells of interest. For instance, samples of lung cancer lesions may be obtained by resection, bronchoscopy, fine needle aspiration, bronchial brushings, or from sputum, pleural fluid or blood. In some embodiments, the sample includes circulating tumor cells; for example, circulating cancer cells in blood, urine or sputum. Genes or gene products can be detected from cancer or tumor tissue or from other body samples such as urine, sputum, serum or plasma. The same techniques discussed above for detection of target genes or gene products in cancerous samples can be applied to other body samples. Cancer cells may be sloughed off from cancer lesions and appear in such body samples. By screening such body samples, a simple early diagnosis can be achieved for these cancers. In addition, the progress of therapy can be monitored more easily by testing such body samples for target genes or gene products.

In certain embodiments, a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is a single sample or combined multiple samples from the same subject or individual that are obtained at one or more different time points than when the test sample is obtained. For example, a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is obtained at an earlier time point from the same subject or individual than when the test sample is obtained. Such reference sample, reference cell, reference tissue, control sample, control cell, or control tissue may be useful if the reference sample is obtained during initial diagnosis of cancer and the test sample is later obtained when the cancer becomes metastatic.

In certain embodiments, a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is a combined multiple samples from one or more healthy individuals who are not the subject or individual. In certain embodiments, a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is a combined multiple samples from one or more individuals with a disease or disorder (e.g., cancer) who are not the subject or individual. In certain embodiments, a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is pooled RNA samples from normal tissues or pooled plasma
or serum samples from one or more individuals who are not the subject or individual. In certain embodiments, a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is pooled RNA samples from tumor tissues or pooled plasma or serum samples from one or more individuals with a disease or disorder (e.g., cancer) who are not the subject or individual.  

[0213] In some embodiments of any of the methods, the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) is an antibody, binding polypeptide, small molecule, or polynucleotide. In some embodiments, the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) is an antibody. In some embodiments, the antibody is a monoclonal antibody. In some embodiments, the antibody is a human, humanized, or chimeric antibody. In some embodiments, the antibody is an antibody fragment and the antibody fragment binds NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist). In some embodiment, the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) is a small molecule. In some embodiments, the NAD biosynthesis from nicotinamide antagonist is a Nampt antagonist. In some embodiments, the NAD biosynthesis from nicotinamide antagonist is a NMNAT antagonist. Further description of antagonists useful in these methods are provided below.  

[0214] In some embodiments of any of the methods, the individual according to any of the above embodiments may be a human.  

[0215] In some embodiments of any of the methods, the method comprises administering to an individual having such cancer an effective amount of a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist). In one such embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, as described below. In some embodiments, the individual may be a human.  

[0216] The NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) described herein can be used either alone or in combination with other agents in a therapy. For instance, a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) described herein may be co-administered with at least one additional therapeutic agent including another NAD biosynthesis from nicotinamide antagonist. In some embodiments of any of the methods described herein, the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) may be used combination with niacin, such as for example Niaspan®. In some embodiments, the niacin reduces toxicity of the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist). In some embodiments, the niacin increases the therapeutic index of the NAD biosynthesis from nicotinamide antagonist. In certain embodiments, an additional therapeutic agent is a chemotherapeutic agent.  

[0217] Such combination therapies noted above encompass combined administration (where two or more therapeutic agents are included in the same or separate formulations), and separate
administration, in which case, administration of the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) can occur prior to, simultaneously, and/or following, administration of the additional therapeutic agent and/or adjuvant. NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) can also be used in combination with radiation therapy.

[0218] A NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) (e.g., an antibody, binding polypeptide, and/or small molecule) described herein (and any additional therapeutic agent) can be administered by any suitable means, including parenteral, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. Dosing can be by any suitable route, e.g., by injections, such as intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic. Various dosing schedules including but not limited to single or multiple administrations over various time-points, bolus administration, and pulse infusion are contemplated herein.

[0219] NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) (e.g., an antibody, binding polypeptide, and/or small molecule) described herein may be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) need not be, but is optionally formulated with one or more agents currently used to prevent or treat the disorder in question. The effective amount of such other agents depends on the amount of the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) present in the formulation, the type of disorder or treatment, and other factors discussed above. These are generally used in the same dosages and with administration routes as described herein, or about from 1 to 99% of the dosages described herein, or in any dosage and by any route that is empirically/clinically determined to be appropriate.

[0220] For the prevention or treatment of disease, the appropriate dosage of a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) described herein (when used alone or in combination with one or more additional therapeutic agents) will depend on the type of disease to be treated, the severity and course of the disease, whether the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) is administered for preventive or therapeutic purposes, previous therapy, the subject's clinical history and response to the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist), and the discretion of the attending physician.
The NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) is suitably administered to the individual at one time or over a series of treatments. One typical daily dosage might range from about 1 µg/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment would generally be sustained until a desired suppression of disease symptoms occurs. Such doses may be administered intermittently, e.g., every week or every three weeks (e.g., such that the individual receives from about two to about twenty, or e.g., about six doses of the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist)). An initial higher loading dose, followed by one or more lower doses may be administered. An exemplary dosing regimen comprises administering. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

It is understood that any of the above formulations or therapeutic methods may be carried out using an immunoconjugate of the invention in place of or in addition to the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist).

III. Therapeutic Compositions

Described below are NAD biosynthesis from nicotinamide antagonists (e.g., Nampt antagonists and/or NMNAT antagonists) useful in the methods described herein. In some embodiments, the NAD biosynthesis from nicotinamide antagonists (e.g., Nampt antagonists and/or NMNAT antagonists) are an antibody, binding polypeptide, small molecule, and/or polynucleotide.

A. Antibodies

In one aspect, provided herein isolated antibodies that bind to Nampt and/or NMNAT. In any of the above embodiments, an antibody is humanized. In a further aspect of the invention, an anti-NAD biosynthesis from nicotinamide antibody (e.g., anti-Nampt antibody and/or anti-NMNAT antibody) according to any of the above embodiments is a monoclonal antibody, including a chimeric, humanized or human antibody. In one embodiment, an anti-NAD biosynthesis from nicotinamide antibody (e.g., anti-Nampt antibody and/or anti-NMNAT antibody) is an antibody fragment, e.g., a Fv, Fab, Fab’, scFv, diabody, or F(ab’)2 fragment. In another embodiment, the antibody is a full length antibody, e.g., an intact IgG1 antibody or other antibody class or isotype as defined herein.

In a further aspect, an anti-NAD biosynthesis from nicotinamide antibody (e.g., anti-Nampt antibody and/or anti-NMNAT antibody) according to any of the above embodiments may incorporate any of the features, singly or in combination, as described in Sections below:

Antibody Affinity

In certain embodiments, an antibody provided herein has a dissociation constant (Kd) of \( \leq 1 \) pM. In one embodiment, Kd is measured by a radiolabeled antigen binding assay (RIA) performed with the Fab version of an antibody of interest and its antigen as described by the following assay. Solution binding affinity of Fabs for antigen is measured by equilibrating Fab with a minimal
concentration of (125I)-labeled antigen in the presence of a titration series of unlabeled antigen, then capturing bound antigen with an anti-Fab antibody-coated plate (see, e.g., Chen et al., J. Mol. Biol. 293:865-881(1999)). To establish conditions for the assay, MICROTITER® multi-well plates (Thermo Scientific) are coated overnight with 5 µg/ml of a capturing anti-Fab antibody (Cappel Labs) in 50 mM sodium carbonate (pH 9.6), and subsequently blocked with 2% (w/v) bovine serum albumin in PBS for two to five hours at room temperature (approximately 23°C). In a non-adsorbent plate (Nunc #269620), 100 pM or 26 pM [125I]-antigen are mixed with serial dilutions of a Fab of interest (e.g., consistent with assessment of the anti-VEGF antibody, Fab-12, in Presta et al., Cancer Res. 57:4593-4599 (1997)). The Fab of interest is then incubated overnight; however, the incubation may continue for a longer period (e.g., about 65 hours) to ensure that equilibrium is reached. Thereafter, the mixtures are transferred to the capture plate for incubation at room temperature (e.g., for one hour). The solution is then removed and the plate washed eight times with 0.1% polysorbate 20 (TWEEN-20®) in PBS. When the plates have dried, 150 µl/well of scintillant (MICROSCINT-20 TM; Packard) is added, and the plates are counted on a TOPCOUNT TM gamma counter (Packard) for ten minutes. Concentrations of each Fab that give less than or equal to 20% of maximal binding are chosen for use in competitive binding assays.

According to another embodiment, Kd is measured using surface plasmon resonance assays using a BIACORE®-2000 or a BIACORE ®-3000 (BIAcore, Inc., Piscataway, NJ) at 25°C with immobilized antigen CM5 chips at -10 response units (RU). Briefly, carboxymethylated dextran biosensor chips (CM5, BIACORE, Inc.) are activated with N-ethyl-N’-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) and N-hydroxysuccinimide (NHS) according to the supplier’s instructions. Antigen is diluted with 10 mM sodium acetate, pH 4.8, to 5 µg/ml (-0.2 µM) before injection at a flow rate of 5 µl/minute to achieve approximately 10 response units (RU) of coupled protein. Following the injection of antigen, 1 M ethanolamine is injected to block unreacted groups. For kinetics measurements, two-fold serial dilutions of Fab (0.78 nM to 500 nM) are injected in PBS with 0.05% polysorbate 20 (TWEEN-20TM) surfactant (PBST) at 25°C at a flow rate of approximately 25 µl/min. Association rates (kon) and dissociation rates (koff) are calculated using a simple one-to-one Langmuir binding model (BIACORE ® Evaluation Software version 3.2) by simultaneously fitting the association and dissociation sensorgrams. The equilibrium dissociation constant (Kd) is calculated as the ratio koff/kon. See, e.g., Chen et al., J. Mol. Biol. 293:865-881 (1999). If the on-rate exceeds 106M-ls-l by the surface plasmon resonance assay above, then the on-rate can be determined by using a fluorescent quenching technique that measures the increase or decrease in fluorescence emission intensity (excitation = 295 nm; emission = 340 nm, 16 nm band-pass) at 25°C of a 20 nM anti-antigen antibody (Fab form) in PBS, pH 7.2, in the presence of increasing concentrations of antigen as measured in a spectrometer, such as a stop-flow equipped spectrophotometer (Aviv Instruments) or a 8000-series SLM-AMINCO TM spectrophotometer (ThermoSpectronic) with a stirred cuvette.
Antibody Fragments

In certain embodiments, an antibody provided herein is an antibody fragment. Antibody fragments include, but are not limited to, Fab, Fab', Fab'-SH, F(ab')2, Fv, and scFv fragments, and other fragments described below. For a review of certain antibody fragments, see Hudson et al., Nat. Med. 9:129-134 (2003). For a review of scFv fragments, see, e.g., Pluckthiin, in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenberg and Moore eds., (Springer-Verlag, New York), pp. 269-315 (1994); see also WO 93/16185; and U.S. Patent Nos. 5,571,894 and 5,587,458. For discussion of Fab and F(ab')2 fragments comprising salvage receptor binding epitope residues and having increased in vivo half-life, see U.S. Patent No. 5,869,046.

Diabodies are antibody fragments with two antigen-binding sites that may be bivalent or bispecific. See, for example, EP 404,097; WO 1993/01161; Hudson et al., Nat. Med. 9:129-134 (2003); and Hollinger et al., Proc. Natl. Acad. Sci. USA 90: 6444-6448 (1993). Triabodies and tetrabodies are also described in Hudson et al., Nat. Med. 9:129-134 (2003).

Single-domain antibodies are antibody fragments comprising all or a portion of the heavy chain variable domain or all or a portion of the light chain variable domain of an antibody. In certain embodiments, a single-domain antibody is a human single-domain antibody (Domantis, Inc., Waltham, MA; see, e.g., U.S. Patent No. 6,248,516 Bl).

Antibody fragments can be made by various techniques, including but not limited to proteolytic digestion of an intact antibody as well as production by recombinant host cells (e.g., E. coli or phage), as described herein.

Chimeric and Humanized Antibodies

In certain embodiments, an antibody provided herein is a chimeric antibody. Certain chimeric antibodies are described, e.g., in U.S. Patent No. 4,816,567; and Morrison et al., Proc. Natl. Acad. Sci. USA, 81:6851-6855 (1984)). In one example, a chimeric antibody comprises a non-human variable region (e.g., a variable region derived from a mouse, rat, hamster, rabbit, or non-human primate, such as a monkey) and a human constant region. In a further example, a chimeric antibody is a "class switched" antibody in which the class or subclass has been changed from that of the parent antibody. Chimeric antibodies include antigen-binding fragments thereof.

In certain embodiments, a chimeric antibody is a humanized antibody. Typically, a non-human antibody is humanized to reduce immunogenicity to humans, while retaining the specificity and affinity of the parental non-human antibody. Generally, a humanized antibody comprises one or more variable domains in which HVRs, e.g., CDRs, (or portions thereof) are derived from a non-human antibody, and FRs (or portions thereof) are derived from human antibody sequences. A humanized antibody optionally will also comprise at least a portion of a human constant region. In some embodiments, some FR residues in a humanized antibody are substituted with corresponding residues from a non-human antibody (e.g., the antibody from which the HVR residues are derived), e.g., to restore or improve antibody specificity or affinity.

Human framework regions that may be used for humanization include but are not limited to: framework regions selected using the "best-fit" method (see, e.g., Sims et al., J. Immunol. 151:2296 (1993)); framework regions derived from the consensus sequence of human antibodies of a particular subgroup of light or heavy chain variable regions (see, e.g., Carter et al., Proc. Natl. Acad. Sci. USA, 89:4285 (1992); and Presta et al., J. Immunol., 151:2623 (1993)); human mature (somatically mutated) framework regions or human germline framework regions (see, e.g., Almagro and Fransson, Front. Biosci. 13:1619-1633 (2008)); and framework regions derived from screening FR libraries (see, e.g., Baca et al., J. Biol. Chem. 272:10678-10684 (1997) and Rosok et al., J. Biol. Chem. 271:22611-22618 (1996)).

In certain embodiments, an antibody provided herein is a human antibody. Human antibodies can be produced using various techniques known in the art. Human antibodies are described generally in van Dijk and van de Winkel, Curr. Opin. Pharmacol. 5: 368-74 (2001) and Lonberg, Curr. Opin. Immunol. 20:450-459 (2008).

Human antibodies may be prepared by administering an immunogen to a transgenic animal that has been modified to produce intact human antibodies or intact antibodies with human variable regions in response to antigenic challenge. Such animals typically contain all or a portion of the human immunoglobulin loci, which replace the endogenous immunoglobulin loci, or which are present extrachromosomally or integrated randomly into the animal's chromosomes. In such transgenic mice, the endogenous immunoglobulin loci have generally been inactivated. For review of methods for obtaining human antibodies from transgenic animals, see Lonberg, Nat. Biotech. 23:1117-1125 (2005). See also, e.g., U.S. Patent Nos. 6,075,181 and 6,150,584 describing XENOMOUSE® technology; U.S. Patent No. 5,770,429 describing HuMab® technology; U.S. Patent No. 7,041,870 describing K-M MOUSE® technology, and U.S. Patent Application Publication No. US 2007/0061900, describing VelociMouse® technology). Human variable regions from intact antibodies generated by such animals may be further modified, e.g., by combining with a different human constant region.

Human antibodies can also be made by hybridoma-based methods. Human myeloma and mouse-human heteromyeloma cell lines for the production of human monoclonal antibodies have

[0245] Human antibodies may also be generated by isolating Fv clone variable domain sequences selected from human-derived phage display libraries. Such variable domain sequences may then be combined with a desired human constant domain. Techniques for selecting human antibodies from antibody libraries are described below.

[0246] Library-Derived Antibodies


[0248] In certain phage display methods, repertoires of VH and VL genes are separately cloned by polymerase chain reaction (PCR) and recombined randomly in phage libraries, which can then be screened for antigen-binding phage as described in Winter et al., Ann. Rev. Immunol., 12: 433-455 (1994). Phage typically display antibody fragments, either as single-chain Fv (scFv) fragments or as Fab fragments. Libraries from immunized sources provide high-affinity antibodies to the immunogen without the requirement of constructing hybridomas. Alternatively, the naive repertoire can be cloned (e.g., from human) to provide a single source of antibodies to a wide range of non-self and also self antigens without any immunization as described by Griffiths et al., EMBO J, 12: 725-734 (1993).

Finally, naive libraries can also be made synthetically by cloning unarranged V-gene segments from stem cells, and using PCR primers containing random sequence to encode the highly variable CDR3 regions and to accomplish rearrangement in vitro, as described by Hoogenboom and Winter, J. Mol. Biol., 227: 381-388 (1992). Patent publications describing human antibody phage libraries include, for example: US Patent No. 5,750,373, and US Patent Publication Nos. 2005/0079574,

[0249] Antibodies or antibody fragments isolated from human antibody libraries are considered human antibodies or human antibody fragments herein.

[0250] 6. Multispecific Antibodies

[0251] In certain embodiments, an antibody provided herein is a multispecific antibody, e.g., a bispecific antibody. Multispecific antibodies are monoclonal antibodies that have binding specificities for at least two different sites. In certain embodiments, one of the binding specificities is for Nampt and/or NMNAT and the other is for any other antigen. In certain embodiments, bispecific antibodies may bind to two different epitopes of Nampt and/or NMNAT. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express Nampt and/or NMNAT. Bispecific antibodies can be prepared as full length antibodies or antibody fragments.


[0253] Engineered antibodies with three or more functional antigen binding sites, including "Octopus antibodies," are also included herein (see, e.g., US 2006/0025576).

[0254] The antibody or fragment herein also includes a "Dual Acting FAb" or "DAF" comprising an antigen binding site that binds to Nampt and/or NMNAT as well as another, different antigen (see, US 2008/0069820, for example).

[0255] 7. Antibody Variants

[0256] Glycosylation variants

[0257] In certain embodiments, an antibody provided herein is altered to increase or decrease the extent to which the antibody is glycosylated. Addition or deletion of glycosylation sites to an antibody may be conveniently accomplished by altering the amino acid sequence such that one or more glycosylation sites is created or removed.

[0258] Where the antibody comprises an Fc region, the carbohydrate attached thereto may be altered. Native antibodies produced by mammalian cells typically comprise a branched, biantennary
oligosaccharide that is generally attached by an N-linkage to Asn297 of the CH2 domain of the Fc region. See, e.g., Wright et al., TIBTECH 15:26-32 (1997). The oligosaccharide may include various carbohydrates, e.g., mannose, N-acetyl glucosamine (GlcNAc), galactose, and sialic acid, as well as a fucose attached to a GlcNAc in the "stem" of the biantennary oligosaccharide structure. In some embodiments, modifications of the oligosaccharide in an antibody of the invention may be made in order to create antibody variants with certain improved properties.

[0259] In one embodiment, antibody variants are provided having a carbohydrate structure that lacks fucose attached (directly or indirectly) to an Fc region. For example, the amount of fucose in such antibody may be from 1% to 80%, from 1% to 65%, from 5% to 65% or from 20% to 40%. The amount of fucose is determined by calculating the average amount of fucose within the sugar chain at Asn297, relative to the sum of all glycostructures attached to Asn 297 (e.g., complex, hybrid and high mannose structures) as measured by MALDI-TOF mass spectrometry, as described in WO 2008/077546, for example. Asn297 refers to the asparagine residue located at about position 297 in the Fc region (Eu numbering of Fc region residues); however, Asn297 may also be located about ±3 amino acids upstream or downstream of position 297, i.e., between positions 294 and 300, due to minor sequence variations in antibodies. Such fucosylation variants may have improved ADCC function. See, e.g., US Patent Publication Nos. US 2003/0157108 (Presta, L.); US 2004/0093621 (Kyowa Hakko Kogyo Co., Ltd). Examples of publications related to "defucosylated" or "fucose-deficient" antibody variants include: US 2003/0157108; WO 2000/61739; WO 2001/29246; US 2003/0115614; US 2002/0164328; US 2004/0093621; US 2004/0132140; US 2004/0110704; US 2004/0110282; US 2004/0109865; WO 2003/085119; WO 2003/084570; WO 2005/035586; WO 2005/035778; WO2005/053742; WO2002/031140; Okazaki et al., J. Mol. Biol. 336:1239-1249 (2004); Yamane-Ohnuki et al., Biotech. Bioeng. 87: 614 (2004). Examples of cell lines capable of producing defucosylated antibodies include Led 3 CHO cells deficient in protein fucosylation (Ripka et al., Arch. Biochem. Biophys. 249:533-545 (1986); US 2003/0157108, Presta, L; and WO 2004/056312, Adams et al., especially at Example 11), and knockout cell lines, such as alpha1,6-fucosyltransferase gene, FUT8, knockout CHO cells (see, e.g., Yamane-Ohnuki et al., Biotech. Bioeng. 87: 614 (2004); Kanda, Y. et al., Biotechnol. Bioeng., 94(4):680-688 (2006); and WO2003/085107).

[0260] Antibodies variants are further provided with bisected oligosaccharides, e.g., in which a biantennary oligosaccharide attached to the Fc region of the antibody is bisected by GlcNAc. Such antibody variants may have reduced fucosylation and/or improved ADCC function. Examples of such antibody variants are described, e.g., in WO 2003/011878 (Jean-Mairet et al.); US Patent No. 6,602,684 (Umana et al.); and US 2005/0123546 (Umana et al.). Antibody variants with at least one galactose residue in the oligosaccharide attached to the Fc region are also provided. Such antibody variants may have improved CDC function. Such antibody variants are described, e.g., in WO 1997/30087 (Patel et al.); WO 1998/58964 (Raju, S.); and WO 1999/22764 (Raju, S.).
Fc region variants

In certain embodiments, one or more amino acid modifications may be introduced into the Fc region of an antibody provided herein, thereby generating an Fc region variant. The Fc region variant may comprise a human Fc region sequence (e.g., a human IgGl, IgG2, IgG3 or IgG4 Fc region) comprising an amino acid modification (e.g., a substitution) at one or more amino acid positions.

In certain embodiments, the invention contemplates an antibody variant that possesses some but not all effector functions, which make it a desirable candidate for applications in which the half life of the antibody in vivo is important yet certain effector functions (such as complement and ADCC) are unnecessary or deleterious. In vitro and/or in vivo cytotoxicity assays can be conducted to confirm the reduction/depletion of CDC and/or ADCC activities. For example, Fc receptor (FcR) binding assays can be conducted to ensure that the antibody lacks FcyR binding (hence likely lacking ADCC activity), but retains FcRn binding ability. The primary cells for mediating ADCC, NK cells, express FcRIII only, whereas monocytes express FcRI, FcRII and FcRIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, Annu. Rev. Immunol. 9:457-492 (1991). Non-limiting examples of in vitro assays to assess ADCC activity of a molecule of interest is described in U.S. Patent No. 5,500,362 (see, e.g., Hellstrom, I. et al., Proc. Nat'l Acad. Sci. USA 83:7059-7063 (1986)) and Hellstrom, I et al., Proc. Nat'l Acad. Sci. USA 82:1499-1502 (1985); 5,821,337 (see Bruggemann, M. et al., J. Exp. Med. 166:1351-1361 (1987)). Alternatively, non-radioactive assays methods may be employed (see, for example, ACTITM non-radioactive cytotoxicity assay for flow cytometry (CellTechnology, Inc. Mountain View, CA; and CytoTox 96® non-radioactive cytotoxicity assay (Promega, Madison, WI). Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed in vivo, e.g., in an animal model such as that disclosed in Clynes et al., Proc. Natl. Acad. Sci. USA 95:652-656 (1998). Clq binding assays may also be carried out to confirm that the antibody is unable to bind Clq and hence lacks CDC activity. See, e.g., Clq and C3c binding ELISA in WO 2006/029879 and WO 2005/100402. To assess complement activation, a CDC assay may be performed (see, for example, Gazzano-Santoro et al., J. Immunol. Methods 202:163 (1996); Cragg, M.S. et al., Blood 101:1045-1052 (2003); and Cragg, M.S. and M.J. Glennie, Blood 103:2738-2743 (2004)). FcRn binding and in vivo clearance/half life determinations can also be performed using methods known in the art (see, e.g., Petkova, S.B. et al., Int'l. Immunol. 18(12):1759-1769 (2006)).

Antibodies with reduced effector function include those with substitution of one or more Fc region residues 238, 265, 269, 270, 297, 327 and 329 (U.S. Patent No. 6,737,056). Such Fc mutants include Fc mutants with substitutions at two or more of amino acid positions 265, 269, 270, 297 and 327, including the so-called "DANA" Fc mutant with substitution of residues 265 and 297 to alanine (US Patent No. 7,332,581).
Certain antibody variants with improved or diminished binding to FcRs are described. (See, e.g., U.S. Patent No. 6,737,056; WO 2004/056312, and Shields et al., J. Biol. Chem. 9(2): 6591-6604 (2001).) In certain embodiments, an antibody variant comprises an Fc region with one or more amino acid substitutions which improve ADCC, e.g., substitutions at positions 298, 333, and/or 334 of the Fc region (EU numbering of residues). In some embodiments, alterations are made in the Fc region that result in altered (i.e., either improved or diminished) Clq binding and/or Complement Dependent Cytotoxicity (CDC), e.g., as described in US Patent No. 6,194,551, WO 99/51642, and Iduisogte et al., J. Immunol. 164: 4178-4184 (2000).

Antibodies with increased half lives and improved binding to the neonatal Fc receptor (FcRn), which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., J. Immunol. 117:587 (1976) and Kim et al., J. Immunol. 24:249 (1994), are described in US2005/0014934A1 (Hinton et al.). Those antibodies comprise an Fc region with one or more substitutions therein which improve binding of the Fc region to FcRn. Such Fc variants include those with substitutions at one or more of Fc region residues: 238, 256, 265, 272, 286, 303, 305, 307, 311, 312, 317, 340, 356, 360, 362, 376, 378, 380, 382, 413, 424 or 434, e.g., substitution of Fc region residue 434 (US Patent No. 7,371,826). See also Duncan & Winter, Nature 322:738-40 (1988); U.S. Patent No. 5,648,260; U.S. Patent No. 5,624,821; and WO 94/29351 concerning other examples of Fc region variants.

Cysteine engineered antibody variants

In certain embodiments, it may be desirable to create cysteine engineered antibodies, e.g., "thioMAbs," in which one or more residues of an antibody are substituted with cysteine residues. In particular embodiments, the substituted residues occur at accessible sites of the antibody. By substituting those residues with cysteine, reactive thiol groups are thereby positioned at accessible sites of the antibody and may be used to conjugate the antibody to other moieties, such as drug moieties or linker-drug moieties, to create an immunonoconjugate, as described further herein. In certain embodiments, any one or more of the following residues may be substituted with cysteine: V205 (Kabat numbering) of the light chain; A118 (EU numbering) of the heavy chain; and S400 (EU numbering) of the heavy chain Fc region. Cysteine engineered antibodies may be generated as described, e.g., in U.S. Patent No. 7,521,541.

Immunonoconjugates

Further provided herein are immunonoconjugates comprising an anti-NAD biosynthesis from nicotinamide antibody (e.g., anti-Nampt antibody and/or anti-NMNAT antibody) herein conjugated to one or more cytotoxic agents, such as chemotherapeutic agents or drugs, growth inhibitory agents, toxins (e.g., protein toxins, enzymatically active toxins of bacterial, fungal, plant, or animal origin, or fragments thereof), or radioactive isotopes.

In one embodiment, an immunonoconjugate is an antibody-drug conjugate (ADC) in which an antibody is conjugated to one or more drugs, including but not limited to a maytansinoid (see U.S. Patent Nos. 5,208,020, 5,416,064 and European Patent EP 0 425 235 BI); an auristatin such as

In another embodiment, an immunoconjugate comprises an antibody as described herein conjugated to an enzymatically active toxin or fragment thereof, including but not limited to diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from Pseudomonas aeruginosa), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes.

In another embodiment, an immunoconjugate comprises an antibody as described herein conjugated to a radioactive atom to form a radioconjugate. A variety of radioactive isotopes are available for the production of radioconjugates. Examples include At211, 1131, 1125, Y90, Rel86, Rel88, Sml53, Bi212, P32, Pb212 and radioactive isotopes of Lu. When the radioconjugate is used for detection, it may comprise a radioactive atom for scintigraphic studies, for example Te99 or 1123, or a spin label for nuclear magnetic resonance (NMR) imaging (also known as magnetic resonance imaging, MRI), such as iodine-123 again, iodine-131, indium-III, fluorine-19, carbon-13, nitrogen-15, oxygen-17, gadolinium, manganese or iron.

Conjugates of an antibody and cytotoxic agent may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyl-dithio) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-l-carboxylate (SMCC), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipiminate HC1), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzyol) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), disocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., Science 238:1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026. The linker may be a "cleavable linker" facilitating release of a cytotoxic drug in the cell. For example, an acid-labile linker,
paratase-sensitive linker, photolabile linker, dimethyl linker or disulfide-containing linker (Chari et al., Cancer Res. 52:127-131 (1992); U.S. Patent No. 5,208,020) may be used.

[0275] The immunoconjugates or ADCs herein expressively contemplate, but are not limited to such conjugates prepared with cross-linker reagents including, but not limited to, BMPS, EMCS, GMBS, HBVS, LC-SMCC, MBS, MPBH, SBAP, SIA, SIAB, SMCC, SMPB, SMPH, sulfo-EMCS, sulfo-GMBS, sulfo-KMUS, sulfo-MBS, sulfo-SIAB, sulfo-SMCC, and sulfo-SMPB, and SVSB (succinimidyl-(4-vinylsulfone)benzoate) which are commercially available (e.g., from Pierce Biotechnology, Inc., Rockford, IL, U.S.A).

[0276] C. Binding Polypeptides


[0278] In this regard, bacteriophage (phage) display is one well known technique which allows one to screen large polypeptide libraries to identify member(s) of those libraries which are capable of specifically binding to a target polypeptide, Nampt and/or NMNAT. Phage display is a technique by which variant polypeptides are displayed as fusion proteins to the coat protein on the surface of bacteriophage particles (Scott, J.K. and Smith, G. P. (1990) Science, 249: 386). The utility of phage display lies in the fact that large libraries of selectively randomized protein variants (or randomly

Although most phage display methods have used filamentous phage, lambdoid phage display systems (WO 95/34683; U.S. 5,627,024), T4 phage display systems (Ren et al., Gene, 215: 439 (1998); Zhu et al., Cancer Research, 58(15): 3209-3214 (1998); Jiang et al., Infection & Immunity, 65(11): 4770-4777 (1997); Ren et al., Gene, 195(2):303-311 (1997); Ren, Protein Sci., 5: 1833 (1996); Efimov et al., Virus Genes, 10: 173 (1995)) and T7 phage display systems (Smith and Scott, Methods in Enzymology, 217: 228-257 (1993); U.S. 5,766,905) are also known.

Additional improvements enhance the ability of display systems to screen peptide libraries for binding to selected target molecules and to display functional proteins with the potential of screening these proteins for desired properties. Combinatorial reaction devices for phage display reactions have been developed (WO 98/14277) and phage display libraries have been used to analyze and control bimolecular interactions (WO 98/20169; WO 98/20159) and properties of constrained helical peptides (WO 98/20036). WO 97/35196 describes a method of isolating an affinity ligand in which a phage display library is contacted with one solution in which the ligand will bind to a target molecule and a second solution in which the affinity ligand will not bind to the target molecule, to selectively isolate binding ligands. WO 97/46251 describes a method of biopanning a random phage display library with an affinity purified antibody and then isolating binding phage, followed by a micropanning process using microplate wells to isolate high affinity binding phage. The use of Staphylococcus aureus protein A as an affinity tag has also been reported (Li et al. (1998) Mol Biotech., 9:187). WO 97/47314 describes the use of substrate subtraction libraries to distinguish enzyme specificities using a combinatorial library which may be a phage display library. A method for selecting enzymes suitable for use in detergents using phage display is described in WO 97/09446. Additional methods of selecting specific binding proteins are described in U.S. Patent Nos. 5,498,538, 5,432,018, and WO 98/15833.

Methods of generating peptide libraries and screening these libraries are also disclosed in U.S. Patent Nos. 5,723,286, 5,432,018, 5,580,717, 5,427,908, 5,498,530, 5,770,434, 5,734,018, 5,698,426, 5,763,192, and 5,723,323.

D. Small molecules
Provided herein are small molecules for use as a NAD biosynthesis from nicotinamide small molecule antagonists (e.g., Nampt small molecule antagonist and/or NMNAT small molecule antagonist).

Small molecules are preferably organic molecules other than binding polypeptides or antibodies as defined herein that bind, preferably specifically, to Nampt and/or NMNAT as described herein. Binding organic small molecules may be identified and chemically synthesized using known methodology (see, e.g., PCT Publication Nos. WO 00/00823 and WO 00/39585). Binding organic small molecules are usually less than about 2000 daltons in size, alternatively less than about 1500, 750, 500, 250 or 200 daltons in size, wherein such organic small molecules that are capable of binding, preferably specifically, to a polypeptide as described herein may be identified without undue experimentation using well known techniques. In this regard, it is noted that techniques for screening organic small molecule libraries for molecules that are capable of binding to a polypeptide target are well known in the art (see, e.g., PCT Publication Nos. WO 00/00823 and WO 00/39585). Binding organic small molecules may be, for example, aldehydes, ketones, oximes, hydrazones, semicarbazones, carbazides, primary amines, secondary amines, tertiary amines, N-substituted hydrazines, hydrazides, alcohols, ethers, thiols, thioethers, disulfides, carboxylic acids, esters, amides, ureas, carbamates, carbonates, ketals, thioethers, acetals, thioacetals, aryl halides, aryl sulfonates, alkyl halides, alkyl sulfonates, aromatic compounds, heterocyclic compounds, anilines, alkenes, alkynes, diols, amino alcohols, oxazolidines, oxazolines, thiazolidines, thiazolines, enamines, sulfonamides, epoxides, aziridines, isocyanates, sulfonyl chlorides, diazo compounds, acid chlorides, or the like.

In some embodiments, the NAD biosynthesis from nicotinamide small molecule antagonist is a Nampt antagonist. In some embodiments, the NAD biosynthesis from nicotinamide antagonist is a NMNAT small molecule antagonist.

In some embodiments, the Nampt small molecule antagonist can be chosen from Nampt antagonists described in PCT Publication No. WO 2011006988, and in particular the following compounds:

<table>
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<th>APO866/FK866</th>
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![Image of APO866/FK866 structure]
In some embodiments, the Nampt small molecule antagonist can also be chosen from Nampt antagonists described in PCT Publication No. WO 2011109441, and in particular, compounds of Tables 1A, 1B, 2, 3A, 3B and 4.

In some embodiments, the Nampt small molecule antagonist can further be chosen from Nampt antagonists described in PCT patent application Nos. WO2012031196, WO2012031197,
WO2012031199 and in particular the following compounds or pharmaceutically acceptable salts thereof described in unpublished PCT patent application Nos. WO2012031197:

![Chemical Structure](image)

wherein:

R is bicyclic heteroaryl comprising 1, 2, 3 or 4 heteroatom(s) independently selected from N, S or O, wherein said heteroaryl may be substituted by one or more substituents selected from the group consisting of amino, oxo, and halo; and wherein said heteroaryl can comprise one or more N-oxide(s) formed with a N atom member of said heteroaryl;

R¹ is -NHR⁴ and R⁴ is cycloalkyl, heterocycloalkyl, aryl or heteroaryl;

cycloalkyl;

aryl; or

heteroaryl; wherein:

(iii) each of said cycloalkyl, aryl, or heteroaryl is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents which can be the same or different and are independently selected from the group consisting of:

deuterium, halo, hydroxy, hydroxyalkyl, cyano, -(CH₂)ₙNR₄⁻R₅⁻, oxo, alkyl, cyanoalkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl-alkenyl, alkynyl, alkynylalkoxy, -CONH₂, -S-alkyl, -C(0)NH(alkyl), -C(0)N(alkyl)₂, -C(0)NH(cycloalkyl), -C(0)NH(aryl), -C(0)N(aryl)₂, arylalkyl-, aryalkoxy-, aryloxy-, cycloalkyl, heterocycloalkyl, aryl, (heterocycloalkyl)alkyl-, (heterocycloalkyl)alkoxy-, -(heterocycloalkyl)alkoxy-, -(heterocycloalkyl)alkyl-, (arylalkyl)alkyl-, -(arylalkyl)alkoxy-, -(arylalkyl)alkoxy-, -(S(0)₂-alkyl, -(S(0)₂-aryl, -(S(0)₂-CH₂F₃)₂, -(C(0)alkyl, -(N(R³)-C(0)-alkyl, -(N(R³)-C(0)-aryl, -(S(0)₂-NH₂, -(S(0)₂-NH(alkyl), -(S(0)₂)N(alkyl)₂, -(N(H)(S0)₂)(alkyl), and methylenedioxy, wherein each of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted by one or more halo, cyano, alkyl or alkoxy and;

(iv) each of said cycloalkyl, heterocycloalkyl, aryl, or heteroaryl may optionally additionally be fused with independently selected aryl, heteroaryl, heterocycloalkyl or cycloalkyl to from a bicyclic or tricyclic group that may be substituted by one or more halo, cyano, alkyl or alkoxy;

R² and R³ can be independently selected from the group consisting of H and deuterium;

R⁵ is H, alkyl or arylalkyl-;

R⁶ and R⁷ are independently selected from the group consisting of H, alkyl, alkoxy, alkoxyalkyl and...
In some embodiments, the Nampt small molecule antagonist can further be chosen from Nampt antagonists selected from the group consisting of:

- N-[4-(piperidine-1-sulfonfonyl)phenyl]-3-(pyridin-3-yl)propanamide
- N-[4-(piperidine-1-sulfonfonyl)phenyl]-2-(pyridin-3-yloxy)acetamide
- N-[4-(piperidine-1-sulfonfonyl)phenyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
- N-[(4-(piperidine-1-sulfonfonyl)phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
- N-[(4-(piperidine-1-sulfonfonyl)phenyl)methyl]thieno[2,3-b]pyridine-2-carboxamide
- N-[(4-(piperidine-1-sulfonfonyl)phenyl)methyl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide
- N-[(4-(piperidine-1-sulfonfonyl)phenyl)methyl]pyridine-3-carboxamide
- N-[(4-(piperidine-1-sulfonfonyl)phenyl)methyl]-1H-1,3-benzodiazone-5-carboxamide
- N-[(4-(piperidine-1-sulfonfonyl)phenyl)methyl]-1,3-benothiazole-6-carboxamide
- N-[(4-(piperidine-1-sulfonfonyl)phenyl)methyl]furo[3,2-c]pyridine-2-carboxamide
- N-{[4-(5-chloro-2-methoxyphenyl)sulfamoyl]phenyl}methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
- N-{[4-(2-acetylphenyl)sulfamoyl]phenyl}methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
- N-{[4-(2-propoxyphenyl)sulfamoyl]phenyl}methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
- N-{[4-(5-fluoro-2-methoxyphenyl)sulfamoyl]phenyl}methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
- N-{[4-(8-oxa-3-azabicyclo[3.2.1]octane-3-sulfonyl)phenyl]methyl}thieno[2,3-c]pyridine-2-carboxamide
- N-{[4-(8-oxa-3-azabicyclo[3.2.1]octane-3-sulfonyl)phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
carboxamide
N-[(4-[(quinolin-8-yl)sulfamoyl]phenyl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(2-(piperidin-1-yl)phenyl)sulfamoyl]phenyl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(2-(morpholin-4-yl)phenyl)sulfamoyl]phenyl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(5-methoxy-2-methylphenyl)sulfamoyl]phenyl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(propan-2-yloxy)phenyl)sulfamoyl]phenyl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(2-hydroxyphenyl)sulfamoyl]phenyl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(3-methoxy-2-methylphenyl)sulfamoyl]phenyl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(4-fluoro-2-methoxyphenyl)sulfamoyl]phenyl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(trifluoromethoxy)phenyl)sulfamoyl]phenyl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(5,6,7,8-tetrahydronaphthalen-1-yl)sulfamoyl]phenyl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(2-methoxyphenyl)sulfamoyl]phenyl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(2-methoxy-6-methylphenyl)sulfamoyl]phenyl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(4-methoxy-2-methylphenyl)sulfamoyl]phenyl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(2-(2-dihydro-1,4-benzodioxin-6-yl)sulfamoyl]phenyl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(2-(hydroxyethoxy)phenyl)sulfamoyl]phenyl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(4-ethoxy-2-fluorophenyl)sulfamoyl]phenyl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(hydroxymethyl)phenyl)sulfamoyl]phenyl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(1-oxo-1H-isochromen-5-yl)sulfamoyl]phenyl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-benzenesulfonamidophenyl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(1-benzenesulfonylpiperidin-4-yl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-benzyldophenyl)methyl]-1H^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(2-(trifluoromethoxy)benzene)sulfo^carboxamide
N-[(4-[(2,5-dimethoxyphenyl)sulfamoyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(2-methoxy-5-(trifluoromethyl)phenyl)sulfamoyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[4-chloro-2-(trifluoromethoxy)phenyl)sulfamoyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(1H-indazol-6-yl)sulfamoyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-({4-[1-(3-chlorophenyl)-1H-pyrazole-4-sulfonyl]phenyl}methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
6-Amino-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide
IH-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(piperazine-1-sulfonyl)-benzylamide
IH-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(4-amino-cyclohexylsulfamoyl)-benzylamide
IH-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(3-amino-pyrrolidine-1-sulfonyl)-benzylamide
IH-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(3,8-diaza-bicyclo[3.2.1]octane-3-sulfonfyl)-benzylamide
Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(piperazine-1-sulfonyl)-benzylamide
Thieno[2,3-c]pyridine-2-carboxylic acid 4-(piperazine-1-sulfonyl)-benzylamide
IH-Pyrrozol[3,4-b]pyridine-5-carboxylic acid 4-(piperazine-1-sulfonyl)-benzylamide
Thieno[2,3-c]pyridine-2-carboxylic acid 4-(4-amino-cyclohexylsulfamoyl)-benzylamide
Furo[2,3-c]pyridine-2-carboxylic acid 4-(4-amino-cyclohexylsulfamoyl)-benzylamide
IH-Pyrrozol[3,4-b]pyridine-5-carboxylic acid 4-(4-amino-cyclohexylsulfamoyl)-benzylamide
Thieno[2,3-c]pyridine-2-carboxylic acid 4-(3-amino-pyrrolidine-1-sulfonyl)-benzylamide
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-amino-pyrrolidine-1-sulfonyl)-benzylamide
Furo[2,3-c]pyridine-2-carboxylic acid 4-(3-amino-pyrrolidine-1-sulfonyl)-benzylamide
IH-Pyrrozol[3,4-b]pyridine-5-carboxylic acid 4-(3-amino-pyrrolidine-1-sulfonyl)-benzylamide
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(piperazine-1-sulfonyl)-benzylamide
Furo[2,3-c]pyridine-2-carboxylic acid 4-(piperazine-1-sulfonyl)-benzylamide
Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(3-amino-pyrrolidine-1-sulfonyl)-benzylamide
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-amino-cyclohexylsulfamoyl)-benzylamide
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-amino-cyclohexylsulfamoyl)-benzylamide
IH-Pyrrozol[3,4-b]pyridine-5-carboxylic acid 4-(4-cyano-piperidine-1-sulfonyl)-benzylamide
IH-Pyrrozol[3,4-b]pyridine-5-carboxylic acid 4-(4-cyano-piperidine-1-sulfonyl)-benzylamide
IH-Pyrrozol[3,4-b]pyridine-5-carboxylic acid 4-(4-methoxy-piperidine-1-sulfonyl)-benzylamide
IH-Pyrrozol[3,4-b]pyridine-5-carboxylic acid 4-(4-amino-piperidine-1-sulfonyl)-benzylamide
IH-Pyrrozol[3,4-b]pyridine-5-carboxylic acid 4-[4-(2,2,2-trifluoro-ethylamino)-piperidine-1-sulfonyl]-benzylamide
N-((4-[1-(3-chlorophenyl)-IH-pyrazole-4-sulfonyl]phenyl)methyl)-IH-pyrrozol[3,4-b]pyridine-5-
N-(4-[(4-chloro-2-ethoxybenzene)sulfonyl]phenyl)methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-dimethyl-1,3-thiazole-5-sulfonyl)phenyl]methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-[(2-fluoro-4-(1H-pyrazol-1-yl)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(2-chloro-5-methylbenzene)sulfonyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-[(5-acetyl-2-methoxybenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(2-fluoro-4-methylbenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(2-fluoro-4-(lH-pyrazol-1-yl)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(3-iluoro-5-(2,2,2-trifluoroethoxy)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(4-[(2-fluoro-4-(1H-pyrazol-1-yl)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(2-fluoro-4-methylbenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(4-butoxy-3-chlorobenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(23-dimethylbenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(4-chloro-2-ethoxybenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(4-methoxy-3,5-dimethylbenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(3-propan-2-yloxy)benzene] sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-(4-[(4-acetylbenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-(4-[(2-chloro-6-fluorobenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[3-(morpholin-4-y)benzene] sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(4-butoxy-2-methylbenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(4-fluoro-2,5-dimethylbenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(2-methyl-4-(trifluoromethyl)benzene] sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(2-chloro-6-fluorobenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[(3-phenylbenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[(2-chloro-5-methylbenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[(2-chloro-3-fluorobenzene)sulfonyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-[(5-chloro-2-(2,2,2-trifluoroethoxy)benzene] sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[(4-butoxybenzene)sulfonyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-[(2,5-dimethylbenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(4-ethoxy-3-fluorobenzene)sulfonyl]phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N-[(4-[(4-chlorobenzene)sulfonyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide
N-[(4-[(4-ethylbenzene)sulfonyl]phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N-[(4-[(4-ethoxy-2-methylbenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[(3-chloro-5-fluorobenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-(1-cyanocyclopentyl)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[(3-fluoro-4-(trifluoromethoxy)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-(4-fluoro-2-methoxybenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(3-fluorobenzene)sulfonyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-[(5-chloro-3-methylpyridine-2-sulfonyl)phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-(isoquinoline-4-sulfonyl)phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N-[(4-[(3,4-difluorobenzene)sulfonyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide
N-[(4-[(3-fluoro-4-(2,2,2-trifluoroethoxy)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[(2-ethoxymethyl)benzene]sulfonyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-[(3,4-difluorobenzene)sulfonyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide
N-[(4-[(3-fluoro-4-(2,2,2-trifluoroethoxy)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[(3-fluoro-4-(2,2,2-trifluoroethoxy)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[(3-fluoro-2-methylbenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-quinoline-6-sulfonyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-1-methyl-1H-indazole-5-sulfonyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-[(1-propyl-1H-pyrazole-4-sulfonyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-[(3,4-dimethoxybenzene)sulfonyl]phenyl}methyl)thieno[2,3-c]pyridine-2-carboxamide
N-({4-[(3-fluoro-5-methoxybenzene)sulfonyl]phenyl}methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-[(4-ethylbenzene)sulfonyl]phenyl}methyl)furo[2,3-c]pyridine-2-carboxamide
N-({4-[(2,4,5-Methylbenzene)sulfonyl]phenyl}methyl)thieno[2,3-c]pyridine-2-carboxamide
N-({4-[( trifluoromethyl)imidazo[1,2-a]pyridine-6-sulfonyl]phenyl}methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-[(2-chlorobenzene)sulfonyl]phenyl}methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-({4-[(3-chloro-4-propoxybenzene)sulfonyl]phenyl}methyl)furo[2,3-c]pyridine-2-carboxamide
N-({4-[(2-fluoro-6-propoxybenzene)sulfonyl]phenyl}methyl)furo[2,3-c]pyridine-2-carboxamide
N-([4-{6-chloroimidazo[1,2-a]pyridine-3-sulfonyl}phenyl]methyl)furo[2,3-c]pyridine-2-carboxamide
N-([4-[(3-ethylbenzene)sulfonyl]phenyl}methyl)thieno[2,3-c]pyridine-2-carboxamide
N-([4-[(3-chlorobenzene)sulfonyl]phenyl}methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-{6-(dimethylamino)pyridine-3-sulfonyl}phenyl]methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-[(4-fluoro-3-methylbenzene)sulfonyl]phenyl}methyl)-1H-pyrrolo[3,4-b]pyridine-5-carboxamide
N-([4-[(3,4-dimethoxybenzene)sulfonyl]phenyl}methyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-[3-(methoxymethyl)benzene]sulfonyl]phenyl)methylimidazo[1,2-a]pyridine-6-carboxamide
N-(4-[2-butoxy-4-fluorobenzene]sulfonyl]phenyl)methylimidazo[1,2-a]pyridine-6-carboxamide
N-(4-[3-(hydroxybenzene)sulfonyl]phenyl)methylimidazo[1,2-a]pyridine-6-carboxamide
N-(4-[2-(ethoxymethyl)benzene]sulfonyl]phenyl)methylimidazo[1,2-a]pyrimidine-6-carboxamide
N-(4-[1-methyl-1H-indazole-4-sulfonyl]phenyl)methylimidazo[1,2-a]pyrimidine-6-carboxamide
N-(4-[4-ethoxy-3-fluorobenzene]sulfonyl]phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[3-lluoro-5-(morpholin-4-yl)benzene]sulfonyl]phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[2-fluoro-6-propoxybenzene]sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-(4-[4-phenylbenzene]sulfonyl]phenyl)methylthieno[2,3-c]pyridine-2-carboxamide
N-(4-[2-ethoxy-4-fluorobenzene]sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-(4-[2H-1,3-benzodioxole-5-sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-(4-[1R]-1-hydroxybutyl]benzene]sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-(4-[5-methylthiophene-2-sulfonyl]phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[3-(morpholin-4-yl)ethoxy]benzene]sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[benzenesulfonyl]phenyl)methyl)imidazo[1,2-a]pyrazine-2-carboxamide
N-(4-[4-ethoxybenzene]sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[quinoline-8-sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-(4-[3-(morpholin-4-yl)benzene]sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
carboxamide
N-[(4-(2-fluoro-3-methylbenzene)sulfonyl)phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[4-((4-fluoro-3-{(propan-2-yl)carbamoyl}benzene)sulfonyl)phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[4-{[2,4-bis(trifluoromethyl)benzene]sulfonyl}phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[4-[(2-methyl-4-propoxybenzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-(5-chloro-2-(prop-2-yn-1-yloxy)benzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-(3-formyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide)
N-[(4-(2H-1,3-benzodioxole-4-sulfamoyl)phenyl]methyl]thieno[2,3-c]pyridine-2-carboxamide
N-[(5-chloro-2-(prop-2-yloxy)benzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-{(3-phenylbenzene)sulfonyl]phenyl}methyl)furo[2,3-c]pyridine-2-carboxamide
N-[(4-{(6-diethylamino)pyridine-3-sulfonyl]phenyl}methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-[(5-chloro-2-propoxybenzene)sulfonyl]phenyl}methyl)thieno[2,3-c]pyridine-2-carboxamide
N-({4-[(4-methoxy-3,5-dimethylbenzene)sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-[(3-cyanobenzene)sulfonyl]phenyl}methyl)furo[2,3-c]pyridine-2-carboxamide
N-({4-[(3-fluoro-4-propoxybenzene)sulfonyl]phenyl}methyl)furo[2,3-c]pyridine-2-carboxamide
N-({4-[(2,6-dichloro-3-methylbenzene)sulfonyl]phenyl}methyl)furo[2,3-c]pyridine-2-carboxamide
N-({4-[2-(ethyl(methyl)amino)-13-thiazole-5-sulfonyl]phenyl}methyl)thieno[2,3-c]pyridine-2-carboxamide
N-({4-[(3-propoxybenzene)sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-[(4-fluoro-2-methylbenzene)sulfonyl]phenyl}methyl)furo[2,3-c]pyridine-2-carboxamide
N-({4-[1-propyl-1H-pyrazole-4-sulfonyl]phenyl}methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-({4-(2-methyl-2H-indazole-6-sulfonyl)phenyl}methyl)thieno[2,3-c]pyridine-2-carboxamide
N-({4-[3-methanesulfonylbenzene]sulfonyl]phenyl}methyl)furo[2,3-c]pyridine-2-carboxamide
N-({4-[4-chloro-3-(triluoromethyl)benzene]sulfonyl]phenyl}methyl)thieno[2,3-c]pyridine-2-carboxamide
N-({4-[(2,4-dimethoxybenzene)sulfonyl]phenyl}methyl)furo[2,3-c]pyridine-2-carboxamide
N-({4-[2-(dimethylamino)pyrimidine-5-sulfonyl]phenyl}methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-({4-[2-methyl-4-propoxybenzene]sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-[(2-methoxy-5-methylbenzene)sulfonyl]phenyl}methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-({4-[2,4-dimethoxybenzene]sulfonyl]phenyl}methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-({4-[2-(dimethylamino)pyrimidine-5-sulfonyl]phenyl}methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-[3-(morpholin-4-yl)benzene]sulfonyl]phenyl}methyl)thieno[2,3-c]pyridine-2-carboxamide
N-({4-l-(4-fluorophenyl)-1H-pyrazole-4-sulfonyl]phenyl}methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-({4-[4-methoxy-2-(triluoromethyl)benzene]sulfonyl]phenyl}methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-({4-[(4-ethoxy-3-triluorobenzene)sulfonyl]phenyl}methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
carboxamide
N-\{4-(4-methylpyridine-3-sulfonyl)phenyl\}methyl\-lH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-\{4-(3-[2-(morpholin-4-yl)ethoxy]benzene\}sulfonyl\}phenyl\}methyl\-imidazo[1,2-a]pyrimidine-6-carboxamide
N-\{4-(4-fluoro-3-methoxybenzene)sulfonyl\}phenyl\]methyl\-imidazo[1,2-a]pyrimidine-6-carboxamide
N-\{4-benzesulfonyl\}phenyl\}methyl\-3-(pyridin-2-yl)-lH-pyrazole-5-carboxamide
N-\{4-\{3-(5-methyl-1,2,4-oxadiazol-3-yl)benzene\}sulfonyl\}phenyl\}methyl\thieno[2,3-c]pyridine-2-carboxamide
N-\{4-(3-fluoro-4-methylbenzene)sulfonyl\}phenyl\}methyl\furo[2,3-c]pyridine-2-carboxamide
N-\{4-(2-methyl-1,3-thiazole-2-sulfonyl)phenyl\}methyl\thieno[2,3-c]pyridine-2-carboxamide
N-\{4-(2-(trifluoromethoxy)phenyl)sulfonyl\}benzyl\-imidazo[1,2-a]pyridine-6-carboxamide
N-\{4-\{6-methylpyrazine-2-sulfonyl\}phenyl\}methyl\thieno[2,3-c]pyridine-2-carboxamide
N-\{4-(3-fluoro-2-methoxybenzene)sulfonyl\}phenyl\}methyl\-imidazo[1,2-a]pyrimidine-6-carboxamide
N-\{4-(4,5-difluoro-2-methoxybenzene)sulfonyl\}phenyl\}methyl\-lH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-\{4-(2-(methylsulfamoyl)benzene)sulfonyl\}phenyl\}methyl\thieno[2,3-c]pyridine-2-carboxamide
N-\{4-(3-fluoro-4-methylbenzene)sulfonyl\}phenyl\}methyl\thieno[2,3-c]pyridine-2-carboxamide
N-\{4-(5-chloro-3-methylpyridine-2-sulfonyl)phenyl\}methyl\thieno[2,3-c]pyridine-2-carboxamide
N-\{4-(6-(trifluoromethyl)pyridine-2-sulfonyl)phenyl\}methyl\thieno[2,3-c]pyridine-2-carboxamide
N-\{4-(3-fluoro-2-methoxybenzene)sulfonyl\}phenyl\}methyl\thieno[2,3-c]pyridine-2-carboxamide
N-\{4-\{2-(ethoxymethyl)benzene\}sulfonyl\}phenyl\}methyl\thieno[3,2-c]pyridine-2-carboxamide
N-\{4-(3-chloro-1-(3-chlorophenyl)-lH-pyrazole-4-sulfonyl)phenyl\}methyl\thieno[2,3-c]pyridine-2-carboxamide
N-\{4-[2-(2-(3-chlorophenyl)-lH-pyrazole-4-sulfonyl)phenyl\}methyl\furo[2,3-c]pyridine-2-carboxamide
N-\{4-(4-[1-(3-chlorophenyl)-lH-pyrazole-4-sulfonyl]phenyl\}methyl\thieno[2,3-c]pyridine-2-carboxamide
N-\{4-(4-[3-methoxy-4-methylbenzene)sulfonyl]phenyl\}methyl\furo[2,3-c]pyridine-2-carboxamide
N-([4-(2-(3-fluorophenyl)-13-thiazole-4-sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-([3-(piperidin-1-ylmethyl)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-([3-fluoro-5-(2-methylpropoxy)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-([5-(trifluoromethyl)pyridine-3-sulfonyl]phenyl]methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-((4-([4-methoxybenzene]sulfonyl]phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-([4-(trifluoromethyl)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-([3-(ethanesulfonyl)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-([3-(2,2,2-trifluoroethoxy)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-([3-chloro-2-methylbenzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-([4-chloro-2-methylbenzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-([3-fluoro-4-methoxybenzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-([2-(3-fluorophenyl)-13-thiazole-4-sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-([2,4-dichloro-3-methoxybenzene]sulfonyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide
N-((4-([2-chloro-5-fluorobenzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-(phenylsulfonyl)benzyl]benzo[d]thiazole-5-carboxamide
N-([4-(quinoline-3-sulfonyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide
N-((4-([3,4-dimethylbenzene]sulfonyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide
N-((4-([3-chloro-2-methylbenzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-([4-ethoxy-3-fluorobenzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-(2H-13-benzodioxole-5-sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-(2H-13-benzodioxole-4-sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-(6-methylpyridine-3-sulfonyl]phenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-((4-([4-methoxy-3-methylbenzene]sulfonyl]phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N-((4-([5-(pyrrolidin-1-yl)pyridine-3-sulfonyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide
N-([4-([3-methoxy-5-methylbenzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-([5-(trifluoromethyl)pyridine-2-sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-
carboxamide
N-[(4-[3-(pyrimidin-2-yl)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[3-sulfamoylbenzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[5-fluoro-2-methoxybenzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[13-thiazole-2-sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[3-cyanobenzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[2,6-dichlorobenzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[2-fluoro-4-(trifluoromethyl)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[3-chloro-5-(trifluoromethyl)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[2-phenoxybenzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[4-ethylbenzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[4-(morpholin-4-yl)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[3-chloro-5-fluorobenzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[4-(ethoxy-2-methylbenzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[4-(3-(cyclopentylcarbamoyl)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
5-hydroxy-N-[(4-[4-(phenylbenzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[4-(ethoxyethyl)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[3-chloro-5-fluorobenzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[4-(morpholin-4-yl)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[4-(ethoxy-2-methylbenzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-({4-[(4-butoxy-3-chlorobenzene)sulfonyl]phenyl}methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-({4-[(4-methanesulfonylbenzene)sulfonyl]phenyl}methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-{8-oxatricyclo[7.4.0.0²,7]trideca-l(13),2,4,6,9,11-hexaene-6-sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-(1H-indole-7-sulfonyl)phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N-((4-{[2-(ethoxymethyl)benzene]sulfonyl}phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-[(4-(naphthalene-1-sulfonyle)-1-phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-(quinoline-3-sulfonyl)phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N-({4-[(4-chloro-3-methoxybenzene)sulfonyl]phenyl}methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-((4-[(5-chloropyridine-3-sulfonyl)phenyl]methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-({4-[(3-iluoro-5-methylbenzene)sulfonyl]phenyl}methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-{[3-(piperidin-l-yl)benzene]sulfonyl]phenyl}methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-((4-{[3-iluoro-4-(triiluoromethoxy)benzene]sulfonyl]phenyl}methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-((4-[(2-methoxy-5-(triiluoromethoxy)benzene)sulfonyl]phenyl)ethyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-((4-{[3-iluoro-4-(triiluoromethoxy)benzene]sulfonyl]phenyl}methyl)furo[2,3-c]pyridine-2-carboxamide
N-[(4-[(4-fluoro-3-methoxybenzene)sulfonyl]phenyl]methyl)furo[2,3-c]pyridine-2-carboxamide
N-((4-{[2-fluoro-3-oxadiazol-3-yl]benzene}sulfonyl)phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-((4-{[3-acetylbenzene]sulfonyl]phenyl}methyl)thieno[2,3-c]pyridine-2-carboxamide
N-((4-{[3-butoxy-4-fluorobenzene]sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-{[3-acetylbenzene]sulfonyl]phenyl}methyl)thieno[2,3-c]pyridine-2-carboxamide
N-((4-{[4-butoxy-2-methylbenzene]sulfonyl]phenyl}methyl)furo[2,3-c]pyridine-2-carboxamide
N-((4-{[2-butoxy-4-fluorobenzene]sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-\{4-([3-(propan-2-yl)carbamoyl]benzene}sulfonylphenyl\}methyl]imidazo[1,2-a]pyrimidine-6-carboxamide


N-\{4-([3,4-dichlorobenzene]sulfonylphenyl\}methyl]imidazo[1,2-a]pyrimidine-6-carboxamide

N-\{4-([3-chloro-4-(trifluoromethyl]benzene]sulfonylphenyl\}methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-\{4-([4-ethoxybenzene]sulfonylphenyl\}methyl]ruro[2,3-c]pyridine-2-carboxamide

N-\{4-([23-dimethylbenzene]sulfonylphenyl\}methyl]imidazo[1,2-a]pyrimidine-6-carboxamide

N-\{4-([3-chloro-4-methoxybenzene]sulfonylphenyl\}methyl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide


N-\{4-([4-propoxybenzene]sulfonylphenyl\}methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

N-\{4-([2-3-fluorophenyl]-1,3-thiazole-4-sulfonyl]phenyl\}methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

N-\{4-(benzenesulfonfylphenyl\}methyl]-1H-pyrrolo[2,3-b]pyridine-5-carboxamide


N-\{4-([3-chloro-4-methoxybenzene]sulfonylphenyl\}methyl]imidazo[1,2-a]pyrimidine-6-carboxamide

N-\{4-([2-methoxybenzene]sulfonylphenyl\}methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide


N-\{4-([4,5-difluoro-2-methoxybenzene]sulfonylphenyl\}methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

N-\{4-([4-fluoro-2,5-dimethylbenzene]sulfonylphenyl\}methyl]imidazo[1,2-a]pyrimidine-6-carboxamide

N-\{4-([4-(isooquinoline-4-sulfonyl]phenyl\}methyl]imidazo[1,2-a]pyrimidine-6-carboxamide


N-\{4-([4-ethylcarbamoyl]benzene]sulfonylphenyl\}methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-\{4-([isoquinoline-4-sulfonyl]phenyl\}methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-\{4-([3-fluorobenzene]sulfonylphenyl\}methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

N-\{4-([1-methyl-1H-1,3-benzodiazole-6-sulfonyl]phenyl\}methyl]imidazo[1,2-a]pyrimidine-6-carboxamide


N-\{4-([4-fluoro-2,5-dimethylbenzene]sulfonylphenyl\}methyl]imidazo[1,2-a]pyridine-6-carboxamide
carboxamide
N-({4-[5-(pyrrolidin-1-yl)pyridine-3-sulfonyl]phenyl}methyl)-lH^yrrolo[3,2-c]pyridine-2-carboxamide
N-[4-(benzenesulfonyl)phenyl[methyl]-[1,2,4]triazolo[43-a]pyridine-6-carboxamide
N-[4-((5-methyl-1,2,4-oxadiazol-3-yl)benzene sulfonylphenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-[6-(3,4-difluorophenyl)pyridine-2-sulfonyl]phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-((4-((3-ethoxybenzene)sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-((4-[(3-methylcarbamoyl]benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-((4-[(2,6-dimethoxy-4-methylbenzene)sulfonyl]phenyl)methyl)-lH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-((4-(benzenesulfonyl)phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-((4-[(5-fluoro-6-methylpyridine-2-sulfonyl]phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-((4-[(2,6-dichloro-3-methoxybenzene)sulfonyl]phenyl)methyl)-lH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-((4-[(2H-13-benzodioxole-4-sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-[(3-(pyrrolidin-1-yl)benzene sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-((4-[(4-fluoro-2-(trifluoromethyl)benzene)sulfonyl]phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-((4-[(isoquinoline-4-sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-[(2,4,5-trimethylbenzene)sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-((4-[(2,4-dichloro-3-methoxybenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-((5-fluoro-2-methoxyphenyl)sulfonyl]phenyl)methyl)-l-(pyridin-4-yl)guanidine
N-((4-(4-methoxy-3-methylbenzene)sulfonyl)phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-(6-(trifluoromethyl)pyridine-2-sulfonyl)phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-(4-methoxy-2-(trifluoromethyl)benzene)sulfonyl)phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N-((4-(1-methyl-1H-indazole-6-sulf oyl)phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-(4-(2-(trifluoromethyl)imidazo[1,2-a]pyridine-6-sulfonyl)phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-((4-[3-(piperidin-1-yl)benzene]sulfonyl)phenyl)methyl)-1,3-benzothiazole-6-carboxamide
N-((4-[(3-(piperidin-1-yl)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-[(4-ethoxybenzene)sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-((4-[(4-methoxy-2,5-dimethylbenzene)sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-((4-[(4-iluoro-2-methylbenzene)sulfonyl]phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-((4-([3-lluoro-5-(2,2,2-trifluoroethoxy)benzene]sulfonyl)phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-((4-(phenylmethane)sulfonyl)phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-((4-[6-(3,4-diiluorophenyl)pyridine-2-sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-((4-[[2-methoxy-4-(triiluoromethyl)benzene]sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-((4-[[4-methoxy-2,5-dimethylbenzene]sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-[[2-methyl-4-(triiluoromethyl)benzene]sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-[(4-{4-(trifluoromethoxy)benzene}sulfonyl]phenyl][methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-{3,4-difluorobenzene}sulfonyl]phenyl)[methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-{3,5-dimethoxybenzene}sulfonyl]phenyl)[methyl]thieno[2,3-c]pyridine-2-carboxamide
N-[(4-{4-chloro-2-(trifluoromethyl)benzene}sulfonyl]phenyl)[methyl]thieno[2,3-c]pyridine-2-carboxamide
N-(4-{5-{pyrrolidin-1-yl}pyridine-3-sulfonyl]phenyl}[methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-{2-methyl-4-(trifluoromethyl)benzene}sulfonyl]phenyl)[methyl]thieno[2,3-c]pyridine-2-carboxamide
N-[(4-{3-(3,5-dimethyl-1H-pyrazol-1-yl)benzene}sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-{3-chloro-4-(trifluoromethyl)benzene}sulfonyl]phenyl)[methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{2-chloro-4-methoxybenzene}sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-{3-chloro-5-methoxybenzene}sulfonyl]phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-{5-chloro-3-methylpyridine-2-sulfonyl]phenyl)[methyl]thieno[2,3-c]pyridine-2-carboxamide
N-[(4-{4-(pyrrolidin-1-yl)benzene}sulfonyl]phenyl)[methyl]-1H-pyrazolo[3,4-b]pyridine-6-carboxamide
N-(4-{2-(pyrrolidin-1-yl)-1,3-thiazole-5-sulfonyl]phenyl}[methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-{4-(morpholin-4-yl)benzene}sulfonyl]phenyl)methyl]thieno[23-c]pyridine-2-carboxamide
N-[(4-{2-methoxy-5-(trifluoromethoxy)benzene}sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-{4-methoxy-2,5-dimethylbenzene}sulfonyl]phenyl)methyl]furo[23-c]pyridine-2-carboxamide
N-[(4-{3-fluoro-4-(trifluoromethyl)benzene}sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-{3-(propan-2-yloxy)benzene}sulfonyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-(4-{2-chloro-5-methylbenzene}sulfonyl]phenyl}[methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(2-benzylsulfonyl)phenyl]methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[[2-(benzyloxy)-5-(trifluoromethyl)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(2-methoxy-4-((1H-pyrazol-1-yl)benzene)sulfonyl)phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(3-propan-2-yl)benzene]sulfonyl)phenyl]methyl]-1H-pyrrolo[3,4-b]pyridine-2-carboxamide
N-((4-(6-methoxypyridine-2-sulfonyl)phenyl)methyl)-1H-pyrrolo[3,4-b]pyridine-2-carboxamide
N-[(1,3-benzothiazol-6-ylmethyl)-4-[(3-chlorobenzene)sulfonyl]benzamide
N-((4-[[2,4-dichloro-3-methoxybenzene]sulfonyl]phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-((4-ethoxy-3-fluorobenzene)sulfonyl)phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-((4-(phenoxathiine-4-sulfonyl)phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-((4-[1-(4-fluorophenyl)-1H-pyrazole-4-sulfonyl]phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-[[2-((trifluoromethyl)sulfonyl)phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[[3-(cyclopentylcarbamoyl)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-[[3-(2-(morpholin-4-yl)ethoxy)benzene]sulfonyl]phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-((4-fluoro-3-(trifluoromethyl)benzene)sulfonyl)phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-((4-[[1-methyl-1H-indazole-7-sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-[[2-fluoro-3-methylbenzene]sulfonyl]phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-((4-[[3-(pyrimidin-2-yl)benzene]sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-[[2-fluoro-3-methylbenzene]sulfonyl]phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-((4-[[4-fluoro-2-(trifluoromethyl)benzene]sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-((4-[[2,3-dimethylbenzene]sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-((4-[[1-methyl-1H-indazole-7-sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-[(3-chloro-5-methoxybenzene)sulfonyl]phenyl}methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-({4-[(2-chloro-6-methoxybenzene)sulfonyl]phenyl}methyl)furo[2,3-c]pyridine-2-carboxamide
N-({4-[(3,4-dimethoxybenzene)sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-[(3,5-difluorobenzene)sulfonyl]phenyl}methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-[(3-fluoro-4-(trifluoromethyl)benzene)sulfonyl]phenyl}methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-({4-[(4-chloro-2-methoxybenzene)sulfonyl]phenyl}methyl)furo[2,3-c]pyridine-2-carboxamide
N-({4-[(5-fluoro-2-methylbenzene)sulfonyl]phenyl}methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-({4-[(2-chloro-4-methoxybenzene)sulfonyl]phenyl}methyl)thieno[2,3-c]pyridine-2-carboxamide
N-({4-[(4-butoxybenzene)sulfonyl]phenyl}methyl)thieno[2,3-c]pyridine-2-carboxamide
N-({4-[(2-acetylbenzene)sulfonyl]phenyl}methyl)thieno[2,3-c]pyridine-2-carboxamide
N-({4-[(4-butylbenzene)sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-[(3-chlorobenzene)sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-[(4-acetylbenzene)sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-[(5-acetyl-2-methoxybenzene)sulfonyl]phenyl}methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-[(2-chloro-5-methylbenzene)sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-[(2-acetylbenzene)sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-[(2-acetylbenzene)sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-[(3,5-dimethyl-1H-pyrazol-1-yl)benzene]sulfonyl}phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-({4-[(3-fluoro-4-(trifluoromethyl)benzene)sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-[(2-chloro-5-methoxybenzene)sulfonyl]phenyl}methyl)furo[2,3-c]pyridine-2-carboxamide
N-({4-[(4-chloro-2-(trifluoromethyl)benzene]sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-[(2-methoxy-5-methylbenzene)sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
carboxamide
N-(4-[(3-phenylbenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-(4-[(6-methoxynaphthalene-2-sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(4-(morpholin-4-yl)benzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-(4-[[3-(3-chlorophenyl)-1H-pyrazole-4-sulfonyl]phenyl]methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(4-fluoro-2-methylbenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-(4-[(4-ethoxy-2-methylbenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-(4-[[3-(piperidin-1-yl)benzene]sulfonyl]phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(3-chloro-4-methylbenzene)sulfonyl]phenyl)methyl)furo[23-c]pyridine-2-carboxamide
de
N-(4-[(benzenesulfonyl]phenyl)methyl)-5-(pyridin-3-yl)-1,2,4-oxadiazole-3-carboxamide
5-hydroxy-N-(4-[[3-(piperidin-1-yl)benzene]sulfonyl]phenyl)methyl]-1H-indole-2-carboxamide
N-(4-[(3-(dimethylsulfamoyl]benzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-(4-[(23-dihydro-1-benzofuran-7-sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
de
N-(4-[(6-methylpyridine-3-sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-(4-(6-(dimethylamino)pyridine-3-sulfonyl]phenyl)methyl)furo[23-c]pyridine-2-carboxamide
N-(4-[(2,4,5-trimethylbenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-(4-[(2,4-dimethylbenzene)sulfonyl]phenyl)methyl)furo[23-c]pyridine-2-carboxamide
N-(4-[[3-(3,5-dimethyl-1H-pyrazol-1-yl)benzene]sulfonyl]phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(2-chloro-4-methylbenzene)sulfonyl]phenyl)methyl)furo[23-c]pyridine-2-carboxamide
N-([4-(4-fluoro-3-methoxybenzene)sulfonyl]phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-1-(propan-2-yl)-1H-pyrazole-4-sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-([4-[(2-methoxy-6-(propan-2-yloxy)benzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-[(4-chloro-3-methoxybenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-((4-[(2,3-dimethylbenzene)sulfonyl]phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-([4-[(4-methoxy-2-methylbenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridinidine-6-carboxamide
N-((4-[(2,5-dimethylbenzene)sulfonyl]phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-((4-[(2-fluoro-5-methylbenzene)sulfonyl]phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-[(4-fluoro-2,5-dimethylbenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-([4-[(2-butoxy-5-chlorobenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-([4-[(2-chloro-3-(trifluoromethyl)benzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-[(2-chloro-3-fluorobenzene)sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-([4-[(2-fluoro-3-(trifluoromethyl)benzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-[(5-chloro-2-(2,2-difluoroethoxy)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-([4-[(5-chloro-2-(2,2-difluoroethoxy)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-([4-[(5-chloro-2-(2,2-difluoroethoxy)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-([4-[(2-chloro-3-(trifluoromethyl)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-([4-[(2-chloro-3-fluorobenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-[(3-fluoro-5-(2-methylpropoxy)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-([4-[(3-fluoro-4-propoxybenzene)sulfonyl]phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N-([4-[(2,4-bis(trifluoromethyl)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-(4-propoxybenzene)sulfonyl}phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-(2-ethoxybenzene)sulfonyl}phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-({4-(3-phenylbenzene)sulfonyl}phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-({4-[2-methoxy-4-(H¹razol-1-yl)benzene]sulfonyl}phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-[2-methoxy-3-(trifluoromethyl)benzene]sulfonyl}phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-({4-(4-fluoro-3-methylbenzene)sulfonyl}phenyl)methyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-({4-(2-ethoxy-4-fluorobenzene)sulfonyl}phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-(isoquinoline-4-sulfonyl)phenyl}methyl)furo[2,3-c]pyridine-2-carboxamide
N-({4-[2-chloro-5-(tri fluoromethyl)benzene]sulfonyl}phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-({4-(2-chloro-6-fluorobenzene)sulfonyl}phenyl)methyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-({4-(3-chloro-2-methylbenzene)sulfonyl}phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-[2-(pyrrolidin-1-yi)-1,3-thiazole-5-sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-[(4-fluoro-3-methylbenzene)sulfonyl]phenyl}methyl)furo[2,3-c]pyridine-2-carboxamide
N-({4-(5H,6H,7H,8H,9H-imidazo[1,2-a]azepine-3-sulfonyl]phenyl}methyl)furo[2,3-c]pyridine-2-carboxamide
N-({4-(4-butoxybenzene)sulfonyl}phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-({4-(3,5-dimethylbenzene)sulfonyl}phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-(5-chloro-2-methylbenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[(4-fluoro-2-(trifluoromethyl)benzene)sulfonyl]phenyl}methyl)furo[2,3-c]pyridine-2-carboxamide
N-([4-[(5-tert-butyl-2-methoxybenzene)sulfonyl]phenyl}methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-([4-[(4-fluoro-2-(trifluoromethyl)benzene]sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[(3-ethoxy-4-fluorobenzene)sulfonyl]phenyl}methyl)thieno[2,3-c]pyridine-2-carboxamide
N-([4-[(3-tert-butyl-2-methoxybenzene]sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[(3-ethoxy-4-fluorobenzene]sulfonyl]phenyl}methyl)thieno[2,3-c]pyridine-2-carboxamide
N-([4-[(3-tert-butyl-2-methoxybenzene]sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-(2-ethoxy-4-fluorobenzene]sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[(5-chloro-2-methylbenzene]sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-(4-fluoro-2-(trifluoromethyl)benzene]sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[(3-tert-butyl-2-methoxybenzene]sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[(3-ethoxy-4-fluorobenzene]sulfonyl]phenyl}methyl)thieno[2,3-c]pyridine-2-carboxamide
N-([4-[(3-tert-butyl-2-methoxybenzene]sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-butoxy-3-fluorobenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-methoxy-4-methylbenzene)sulfonyl]phenyl)methyl]pyridine-2-carboxamide
N-[4-(5-pyrrolidin-1-yl)pyridine-3-sulfonyl]phenyl)methyl]-1,3-benzothiazole-6-carboxamide
N-[4-(5-fluoro-6-methylpyridine-2-sulfonyl)phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-[4-(phenoxathiine-4-sulfonyl)phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide
N-[(4-(3,4-dimethylbenzene)sulfonyl)phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(3-methoxy-4-methylbenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-(5-fluoro-6-methylpyridine-2-sulfonyl)phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-(3-chloro-5-methoxybenzene)sulfonyl)phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-(2-(methylsulfamoyl)benzene)sulfonyl)phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-(4-ethoxybenzene)sulfonyl)phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-(trifluoromethyl)pyridine-2-sulfonyl)phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(5-fluoro-2-methylbenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(3,4-dimethylbenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(3-butoxy-3-fluorobenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(3-ethoxybenzene)sulfonyl]phenyl)methyl]-1H-pyrazolo[3,2-c]pyridine-2-carboxamide
N-[(4-(4-ethoxybenzene)sulfonyl)phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-(3-5-methoxybenzene)sulfonyl)phenyl)methyl]-1H-pyrazolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(3-ethoxybenzene)sulfonyl]phenyl)methyl]-1H-pyrazolo[3,2-c]pyridine-2-carboxamide
N-[(4-(3-5-methoxybenzene)sulfonyl)phenyl)methyl]-1H-pyrazolo[3,2-c]pyridine-2-carboxamide
N-[(4-(3-5-methoxybenzene)sulfonyl)phenyl)methyl]-1H-pyrazolo[3,2-c]pyridine-2-carboxamide
N-[(4-(3-5-methoxybenzene)sulfonyl)phenyl)methyl]-1H-pyrazolo[3,2-c]pyridine-2-carboxamide
N-[(4-(3-5-methoxybenzene)sulfonyl)phenyl)methyl]-1H-pyrazolo[3,2-c]pyridine-2-carboxamide
N-[(4-[3-(pyrrolidin-1-yl)benzene] sulfonyl]phenyl)methyl]-1,3-benzothiazole-6-carboxamide
N-((4-[3,5-dimethylbenzene]sulfonyl]phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-((4-[3-chloro-4-methylbenzene]sulfonyl]phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-([4-(4-IH-pyrazol-1-yl)benzene] sulfonyl]phenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-([4-[(3-propan-2-yl)carbamoyl]benzene] sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-
carboxamide
N-((4-[2,4-dimethoxybenzene]sulfonyl]phenyl)methyl)-IH-pyrrolo[3,4-b]pyridine-5-carboxamide
N-((4-[2,3-dimethoxy-5-methylbenzene]sulfonyl]phenyl)methyl)thieno[2,3-c]pyridine-2-
carboxamide
N-((4-[[2-fluoro-3-(propan-2-yloxy)benzene] sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-
carboxamide
N-([4-[(4-morpholin-4-yl)pyridine-3-sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-([4-[(3-(pyrrolidin-1-yl)benzene] sulfonyl]phenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[5-hydroxy-2-(trifluoromethoxy)benzene] sulfonyl]phenyl)methyl]furo[2,3-c]pyridine-2-
carboxamide
N-([4-[(4-chloro-3-(trifluoromethyl)benzene] sulfonyl]phenyl)methyl]-IH-pyrrolo[3,2-c]pyridine-2-
carboxamide
N-((4-[3-(morpholin-4-yl)benzene] sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[(2-butoxy-4-fluorobenzene] sulfonyl]phenyl)methyl]-IH-pyrrolo[3,2-c]pyridine-2-
carboxamide
N-(4-tosylphenyl)imidazo[1,2-a]pyridine-6-carboxyhydrazide
N-([4-[(3,4-dimethylbenzene] sulfonyl]phenyl)methyl]-IH-pyrrolo[3,4-b]pyridine-5-carboxamide
N-([4-[(isoquinoline-4-sulfonyl]phenyl)methyl]-IH-pyrrolo[3,4-b]pyridine-5-carboxamide
N-([4-[(4-methoxy-3,5-dimethylbenzene] sulfonyl]phenyl)methyl]-IH-pyrrolo[3,2-c]pyridine-2-
carboxamide
N-((4-[benzenesulfonyl]phenyl)methyl]-[1,2,3,4]tetrazolo[1,5-a]pyridine-6-carboxamide
N-\{(4-cyanobenzene)sulfonyl\}phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-\{\{3-\{\{propan-2-yl\}carbamoyl\}benzene\}sulfonyl\}phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-\{(2,4-dimethylbenzene)sulfonyl\}phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-\{(4-butoxy-3-fluorobenzene)sulfonyl\}phenyl)methyl)\-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-\{(4-methylpyridine-3-sulfonyl)phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-\{(2-trifluoromethoxy)benzene)sulfonyl\}phenyl)methyl)\-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-\{(4-ethoxybenzene)sulfonyl\}phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-\{(4-2-methoxybenzene)sulfonyl\}phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-\{(4-chloro-2-methylbenzene)sulfonyl\}phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-\{(4-1H4ndazole-4-sulfonyl)phenyl)methyl)thieno[23-c]pyridine-2-carboxamide
N-\{(4-chloro-3-methoxybenzene)sulfonyl\}phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-\{(4-cyanobenzene)sulfonyl\}phenyl)methyl)\-IH\-pyrrrolo[3,2-c]pyridine-2-carboxamide
N-\{(23-dihydro-1-benzofuran-7-sulfonyl)phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-\{(4-6-(dimethylamino)pyridine-3-sulfonyl)phenyl)methyl)\-IH\-pyrazolo[3,4-b]pyridine-5-carboxamide
N-\{(4-3-fluorobenzene)sulfonyl\}phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-\{(2-chloro-5-methoxybenzene)sulfonyl\}phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-\{(4-ethoxy-2-methylbenzene)sulfonyl\}phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-\{(2-benzyl\-oxo)benzene)sulfonyl\}phenyl)methyl)\-IH\-pyrrrolo[3,2-c]pyridine-2-carboxamide
N-\{(5-acetyl-2-methoxybenzene)sulfonyl\}phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-\{1-(3-chlorophenyl)-IH-pyrazole-4-sulfonyl\}phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-\{(4-chloro-3-(trifluoromethyl)benzene)sulfonyl\}phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-\{(2-butoxy-4-fluorobenzene)sulfonyl\}phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-\{(2-methoxy-5-(trifluoromethoxy)benzene)sulfonyl\}phenyl)methyl)\-IH\-pyrazolo[3,4-b]pyridine-5-carboxamide
N-\{2-\{ethyl\(\{\{methyl\)amino\}\}-13-thiazole-5-sulfonyl\}phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-\{(4-ethylbenzene)sulfonyl\}phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-\{(4-chloro-3-methoxybenzene)sulfonyl\}phenyl)methyl)\-IH\-pyrrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(2-chloro-5-methoxybenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide

N-({4-[(3-fluoro-4-methoxybenzene)sulfonyl]phenyl}methyl)-1H-pyrrolo[3,2-c]pyridine-5-carboxamide

N-({4-[(2-chloro-3-(trifluoromethyl)benzene)sulfonyl]phenyl}methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

N-({4-[(2-methyl-2H-indazole-6-sulfonyl)phenyl]methyl}-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

N-({4-[(2-chloro-5-methoxybenzene)sulfonyl]phenyl}methyl)imidazo[1,2-a]pyridine-6-carboxamide
carboxamide
N-[(4-{[4-fluoro-3-(trifluoromethyl)benzene]sulfonyl}phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine
N-[(4-{[2-cyanobenzene]sulfonyl}phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-{[2,4-dimethylbenzene]sulfonyl}phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-{[5-methylpyridine-3-sulfonyl}phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-{[2-chloro-5-(trifluoromethyl)benzene]sulfonyl}phenyl)methyl]imidazo[1,2-a]pyridim-6-carboxamide
N-[(4-{[2-chloro-4-(trifluoromethyl)benzene]sulfonyl}phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-{[4-(2-acetylbenzene]sulfonyl}phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-{[4-{[3-iluoro-2-methylbenzene]sulfonyl}phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-{8-thiatricyclo[7.4.0.0^2.7]trideca-l(13),2,4,6,9,ll-hexaene-6-sulfonyl}phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-{1-methyl-5-(trifluoromethyl)pyridine-5-sulfonyl}phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N-[(4-{8-thiatricyclo[7.4.0.0^2.7]trideca-l(13),2,4,6,9,ll-hexaene-6-sulfonyl}phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-{[4-fluoro-3-(trifluoromethyl)benzene]sulfonyl}phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-{[2-chloro-4-(trifluoromethyl)benzene]sulfonyl}phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-({4-[6-(3,4-difluorophenyl)pyridine-2-sulfo]ylphenyl}methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-({4-[6-(morpholin-4-yl)pyridine-3-sulfonyl]phenyl}methyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-(1,5-dimethyl-1H-imidazole-2-sulfonyl)phenyl]methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-[(4-chloro-3-fluorobenzene)sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-[(3-fluoro-5-methoxybenzene)sulfonyl]phenyl}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-({4-[2,6-dichlorobenzene]sulfonyl}phenyl)methyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-({4-[4-acetylbenzene]sulfonyl}phenyl)methyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-(3,5-dimethoxybenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-([4-(2-methyl-1H-indazole-7-sulfonyl)phenyl]methyl)thieno[2,3-c]pyridine-2-carboxamide
N-([4-((2,6-dichlorobenzene)4-phenyl]methyl)furo[2,3-c]pyridine-2-carboxamide
N-([4-(1-methyl-1H-indazole-7-sulfonyl)phenyl]methyl)thieno[2,3-c]pyridine-2-carboxamide
N-([4-([2-methyl-1H-indazole-6-sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-([2-ethylbenzene]sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-((3,4 dimethoxybenzene)sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-([4-(1,5-dimethyl-1H-imidazole-2-sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-([4-([3,5-dimethyl-1H-pyrazol-1-yl]benzene)sulfonyl]phenyl)methyl)-5-hydroxy-1H-indole-2-carboxamide
N-([4-([2,3-dimethoxy-5-methylbenzene]sulfonyl]phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-([4-((3-chloro-4-methoxybenzene)sulfonyl]phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-([4-([isoquinoline-4-sulfonyl]phenyl)methyl]-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-([2-(trifluoromethyl]benzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-(6-(dimethylamino)pyridine-3-sulfonyl)phenyl]methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-([4-([2-butoxy-6-fluorobenzene]sulfonyl)phenyl]methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-([4-([3-(ethanesulfonfyl)benzene]sulfonyl)phenyl]methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-([4-([benzenesulfonfyl]phenyl)methyl]-3-(pyridin-3-yl)-1,2-oxazole-5-carboxamide
N-([4-([3-(IH-pyrazol-1-yl)benzene]sulfonyl)phenyl]methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-([4-([3-chloro-4-propoxybenzene]sulfonyl)phenyl]methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-([3-(ethylcarbamoyl)benzene]sulfonyl)phenyl]methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-([5-tert-butyl-2-methoxybenzene]sulfonyl)phenyl]methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-([5-tert-butyl-2-methoxybenzene]sulfonyl)phenyl]methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-([2,3-dimethoxybenzene]sulfonyl)phenyl]methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-([4-acetylbenzene]sulfonyl)phenyl]methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-([4-methoxybenzene]sulfonyl)phenyl]methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-([3-fluoro-5-(trifluoromethyl)benzene]sulfonyl)phenyl]methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-([2,3-dimethoxybenzene]sulfonyl)phenyl]methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-([2,4-bis(trifluoromethyl)benzene]sulfonyl)phenyl]methyl)furo[2,3-c]pyridine-2-carboxamide
N-{4-(5-chloropyridine-3-sulfonyl)phenyl}imidazo[1,2-a]pyridine-6-carboxamide
N-{4-(2-fluoro-5-methylbenzene)sulfonyl]phenyl)methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-{4-(3-iluoro-5-methylbenzene)sulfonyl]phenyl)methylthieno[2,3-c]pyridine-2-carboxamide
N-{4-(4-fluorobenzene)sulfonyl]phenyl)methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-{4-[(4-methylpyridine-3-sulfonyl)phenyl]methyl}furo[2,3-c]pyridine-2-carboxamide
N-{4-[(4-propoxybenzene)sulfonyl]phenyl)methyl}imidazo[1,2-a]pyridine-6-carboxamide
N-{4-[(2-iluoro-4-methylbenzene)sulfonyl]phenyl)methyl}imidazo[1,2-a]pyrimidine-6-carboxamide
N-{4-[(2-chloro-5-methylbenzene) sulfonyl]phenyl)methyl} -1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-{4-[(23-dimethoxybenzene)sulfonyl]phenyl]methyl}imidazo[1,2-a]pyrimidine-6-carboxamide
N-{4-[(3-ethylbenzene)sulfonyl]phenyl)methyl}imidazo[1,2-a]pyrimidine-6-carboxamide
N-{4-[(2H-1,3-benzodioxole-5-sulfonyl)]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
N-{4-[(3-sulfamoylbenzene)sulfonyl]phenyl]methyl}imidazo[1,2-a]pyridine-6-carboxamide
N-{4-[(3,5-dimethoxybenzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-{4-[(3,5-dimethylbenzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-{4-[(3,5-dimethoxybenzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-{4-[(3,sulfamoylbenzene)sulfonyl]phenyl]methyl}imidazo[1,2-a]pyridine-6-carboxamide
N-{4-[(3,5-dimethylbenzene)sulfonyl]phenyl]methyl}imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{4-(4-methylpyridine-3-sulfonyl)phenyl]methyl}imidazo[1,2-a]pyridine-6-carboxamide
N-{4-(benzenesulfonyl]phenyl]methyl}imidazo[1,2-a]pyridine-6-carboxamide
N-{4-{[(3-fluoro-5-chlorobenzene)sulfonyl]phenyl]methyl}imidazo[1,2-a]pyridine-6-carboxamide
N-{4-{[(3-propoxybenzene)sulfonyl]phenyl]methyl}imidazo[1,2-a]pyridine-6-carboxamide
N-{4-{[(3,5-dimethylbenzene)sulfonyl]phenyl]methyl}imidazo[1,2-a]pyrimidine-6-carboxamide
N-{4-{[(3,5-dimethylbenzene)sulfonyl]phenyl]methyl}imidazo[1,2-a]pyrimidine-6-carboxamide
N-{4-{[(3,5-dimethylbenzene)sulfonyl]phenyl]methyl}imidazo[1,2-a]pyrimidine-6-carboxamide
N-{4-{[(3,5-dimethylbenzene)sulfonyl]phenyl]methyl}imidazo[1,2-a]pyrimidine-6-carboxamide
N-{4-{[(3,5-dimethylbenzene)sulfonyl]phenyl]methyl}imidazo[1,2-a]pyrimidine-6-carboxamide
N-{4-{[(3,5-dimethylbenzene)sulfonyl]phenyl]methyl}imidazo[1,2-a]pyrimidine-6-carboxamide
N-{4-{[(3,5-dimethylbenzene)sulfonyl]phenyl]methyl}imidazo[1,2-a]pyrimidine-6-carboxamide
N-{4-{[(3,5-dimethylbenzene)sulfonyl]phenyl]methyl}imidazo[1,2-a]pyrimidine-6-carboxamide
N-{4-{[(3,5-dimethylbenzene)sulfonyl]phenyl]methyl}imidazo[1,2-a]pyrimidine-6-carboxamide
N-{4-{[(3,5-dimethylbenzene)sulfonyl]phenyl]methyl}imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-(1-methyl-1H-indazole-4-sulfonyl)]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
N-[(4-benzencesulfonyl]phenyl]methyl}imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-2-chloro-4-methylbenzene)sulfonyl]phenyl)methyl}imidazo[1,2-a]pyridine-6-carboxamide
N-{4-{[(4-butoxy-3-chlorobenzene)sulfonyl]phenyl]methyl} -IH-pyrazolo[3,4-b]pyridine-5-
N-(6-(4-(morpholinomethyl)phenoxy)hexyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-((3-ethoxy-2-fluorobenzene)sulfonyl)phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[[4-(4-methylpiperazin-1-yl)benzene]sulfonyl]methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-(quinoline-8-sulfonyl)phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-[6-(dimethylamino)pyridine-3-sulfonyl]phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-((4-[5-chloro-2-methoxybenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-((4-[3-fluoro-4-(tri fluoromethyl)benzene]sulfonyl)phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-((4-[1,4-dimethyl-1H-imidazole-2-sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-((4-[benzenesulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-[3-propoxybenzene]sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-((4-[5-methylpyridine-3-sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-(4-[4-(trifluoromethyl)pyridine-2-sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-((4-[4-(trifluoromethyl)benzene]sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-[5H,6H,7H,8H,9H-imidazo[1,2-a]azepine-3-sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-((4-[3-fluoro-4-(1H-pyrazol-1-yl)benzene]sulfonyl]phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-((4-[6-methoxynaphthalene-2-sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-((4-[2-methyl-2H-indazole-6-sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-((4-[5-fluoropyridine-3-sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-[2,4-dichloro-3-methoxybenzene]sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-((4-[naphthalene-1-sulfonyl]phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-((4-[[2-(dimethylamino)ethyl]benzene]sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(2-methyl-4-(trifluoromethyl)benzene)sulfonfyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(2,3,6-Methoxybenzene)sulfonfyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide
N-[(4-[(3-butoxybenzene)sulfonfyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[(5-chloropyridine-3-sulfonfyl]phenyl)methyl]-IH^-yrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-[(4-(dimethylcarbamoyl)benzene)sulfonfyl]phenyl)methyl]-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(4-(hydroxymethyl)benzene)sulfonfyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[(3,4-dimethoxybenzene)sulfonfyl]phenyl)methyl]-IH^-yrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-[(1-methyl-1H-indazole-6-sulfonfyl)phenyl]methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(3,4-dihydro-1-benzofuran-7-sulfonfyl)phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N-[(4-[(4-H-indole-7-sulfonfyl)phenyl)methyl]-IH-pyrrolo[3,4-b]pyridine-5-carboxamide
N-[(4-[(3-tert-butylbenzene)sulfonfyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(4-propan-2-yloxy)benzene)sulfonfyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(benzenesulfonfyl]phenyl)methyl]-1,5-naphthyridine-2-carboxamide
5-hydroxy-N-[(4-[3-(pyrrolidin-1-yl)benzene]sulfonfyl]phenyl)methyl]-IH-indole-2-carboxamide
N-[(4-[(2-methyl-4-propoxybenzene)sulfonfyl]phenyl)methyl]-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(benzenesulfonfyl]phenyl)methyl]-1,5-naphthyridine-2-carboxamide
5-hydroxy-N-[(4-[3-(pyrrolidin-1-yl)benzene]sulfonfyl]phenyl)methyl]-IH-indole-2-carboxamide
N-[(4-[(2-methyl-4-propoxybenzene)sulfonfyl]phenyl)methyl]-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(3-chlorobenzene)sulfonfyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide
N-[(4-[(3-chlorobenzene)sulfonfyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide
N-((4-[2,5-dimethoxybenzene)sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-((4-[2,4,6-trimethylbenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[4-(4-methylpiperazin-1-yl)benzene)sulfonyl]phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N4-[2-methoxy-5-(trifluoromethyl)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-(4-chloro-2-ethoxybenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-(3-(dimethylamino)ethyl)benzene)sulfonyl]phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N-((4-[3,4-difluorobenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-(2,6-dichlorobenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-((4-[2-fluoro-5-methoxybenzene)sulfonyl]phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-([4-[3,5-difluorobenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[3,5-dimethyl-1H-pyrazol-1-yl]benzene)sulfonyl]phenyl)methyl]thieno[1,3-benzothiazole-6-carboxamide
N-([4-[4-(ethoxymethyl)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-([4-[5-(dimethylamino)pyrazine-2-sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-([4-[2-chloro-5-fluorobenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-([4-[2-ethylbenzene)sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-([4-[3,5-dimethyl-1H-pyrazol-1-yl]benzene)sulfonyl]phenyl)methyl]-1,3-benzothiazole-6-carboxamide
N-([4-[4-(ethoxymethyl)benzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-[5-(dimethylamino)pyrazine-2-sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-([4-[2-chloro-5-fluorobenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-([4-(benzenesulfonyl]phenyl)methyl]quinoline-6-carboxamide
N-([4-[3-butoxybenzene)sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-(4-[(4-methylbenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-(4-[(3-methanesulfonylbenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(2,6-dimethoxy-4-methylbenzene)sulfonyl]phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-[(4-fluoro-3-[(propan-2-yl)carbamoyl]benzene)sulfonyl]phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-[(5-chloro-2-ethoxybenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(3^-dichlorobenzene)sulfonyl]phenyl)methyl)-lH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-[(4-methylpiperazin-1-yl)benzene]sulfonyl]phenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-[(4-[(2-methylpropyl)carbamoyl]benzene}sulfonyl)phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide
N-[(4-[(3-chloro-5 -methylbenzene]sulfonyl]phenyl)methyl]-IH-pyr azolo [3,4-b]pyridine-5 -carboxamide
N-[(4- [(benzenesulf onyl]phenyl]methyl]-lH-pyrazolo[3,4-b]pyridine-5 -carboxamide
N-(4-[(2H-1,3-benzodioxole-5-sulfonyl]phenyl)methyl]-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(3,5-dimethoxybenzene)sulfonyl]phenyl)methyl]-IH-pyr azolo[3,4-b]pyridine-5-carboxamide
N-[(4- [2-(morpholin-4-ylmethyl)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(2,6-dichloro-3-methylbenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[(3-methoxy-4-methylbenzene)sulfonyl]phenyl]methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[(2-chloro-4-methylbenzene)sulfonyl]phenyl]methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[(6-methylpyridine-3-sulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-([4-(1,5-dimethyl-1H-imidazole-2-sulfonyl)phenyl]methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-([4-[(5-hydroxy-2-(trifluoromethoxy)benzene)sulfonyl]phenyl]methyl)-1H-pyrrolo[3,4-b]pyridine-5-carboxamide
N-([4-[(1H-imidazol-1-yl)benzene]sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-(benzenesulfonyl)phenyl]methyl)-1H-pyrrozolo[3,4-b]pyridine-3-carboxamide
N-([4-[(4-fluorobenzene)sulfonyl]phenyl]methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[(3,4-difluorobenzene)sulfonyl]phenyl]methyl)-1H-pyrrozolo[3,4-b]pyridine-5-carboxamide
N-([4-[(4-butoxy-3-chlorobenzene)sulfonyl]phenyl]methyl)thieno[2,3-c]pyridine-2-carboxamide
N-([4-[(1-methyl-1H-indazole-6-sulfonyl)phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-[(1H-imidazol-1-yl)benzene]sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[(3-chloro-4-methylbenzene)sulfonyl]phenyl]methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[(1,3-thiazole-2-sulfonyl)phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
N-([4-[(2-ethoxy-4-fluorobenzene)sulfonyl]phenyl]methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[(4-chloro-2-(trifluoromethyl)benzene)sulfonyl]phenyl]methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[(6-methoxynaphthalene-2-sulfonyl)phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-[(4-chloro-3-(trifluoromethyl)benzene)sulfonyl]phenyl]methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(2-methyl-4-(1H-pyrazol-1-yl)benzene)sulfonyl]phenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-((3-chloro-5-fluorobenzene)sulfonyl]phenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-((3-methylbenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-(2-cyanobenzene)sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-([4-benzencesulfonyl]phenyl)methyl]-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-((3-ethoxybenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-((3-iluoro-4-methylbenzene)sulfonyl]phenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-((4-but oxy-2-methylbenzene)sulfonyl]phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N-((4-(l-methyl-lH-indazole-5-sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-(4-iluoro-3-(triluoromethyl)benzene)sulfonyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide
N-([4-(4-fluoro-3-(trifluoromethyl)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-([4-(2-ethoxybenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-([3-(benzenesulfon yl]phenyl)methyl]-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-fluoro-3-(triluoromethyl)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-(2-ethoxybenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(2-methyl-4-(trifluoromethyl)phenyl)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(4-chlorobenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(3-fluoro-5-methylbenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(3-chloro-2-methylbenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(3-trifluoromethoxy)benzene]sulfonyl)phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-[(2-butoxy-5-chlorobenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(2-ethoxy-4-fluorobenzene)sulfonyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-[(2-chloro-5-fluorobenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(4-methylpyridine-3-sulfonyl)phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(3,4-dimethoxybenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(3-methoxy-5-methylbenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(3,4-dimethoxybenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(3-(2-methylpropoxy)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(3-acetylbenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(3-(trifluoromethyl)benzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(2-chloro-4-(trifluoromethyl)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(2,4-dimethylbenzene)sulfonyl]phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N-[(4-[(4-methoxybenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(2-(trifluoromethyl)benzene]sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(3-acetylbenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-{[4-{5-chloro-3-methylpyridine-2-sulfonyl}phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-{[4-{2-(3-fluorophenyl)-1,3-thiazole-4-sulfonyl]phenyl}methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-{[4-{3,5-dichlorobenzene}sulfonyl]phenyl}methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-{[4-{[3-(5-dimethyl-1H-pyrazol-1-yl)benzene]sulfonyl}phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
N-{[4-(5-methoxypyridine-3-sulfonyl)phenyl]methyl}-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-{[4-{[(2-fluoro-4-1H-pyrazol-1-yl)benzene]sulfonyl}phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-{[4-{[1-chloro-4-(trifluoromethyl)benzene]sulfonyl}phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-{[4-{[3-ethoxy-2-fluorobenzene]sulfonyl]phenyl}methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-{[4-{[3-fluoro-5-(2-methylpropoxy)benzene]sulfonyl]phenyl}methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-{[4-{[3-fluoro-2-(trifluoromethyl)benzene]sulfonyl]phenyl}methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-{[4-{[1-morpholin-4-yl]pyridine-3-sulfonyl}phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-{[4-{[4-chloro-2-(trifluoromethyl)benzene]sulfonyl]phenyl}methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-{[4-{[2-(4-methoxy-2,5-dimethylbenzene)sulfonyl]phenyl}methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-{[4-{[4-methoxy-2,5-dimethylbenzene]sulfonyl]phenyl}methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-((2,5-dimethoxybenzene)sulfonyl)phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-((4-((2-fluoro-4-methylbenzene)sulfonyl)phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-((4-((5-(pyrrolidin-1-yl)pyridine-3-sulfonyl)phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-(4-((3-phenylbenzene)sulfonyl)phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-((4-((dimethylamino)methyl)benzene)sulfonyl)phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-((3-diethylcarbamoyl)-5-fluorobenzene)sulfonyl)phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-((4-((2-methylbenzene)sulfonyl)phenyl)methyl)carboxamide
N-((4-((3-methoxy-5-methylbenzene)sulfonyl)phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-((3-chloro-5-fluorobenzene)sulfonyl)phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-((4-((4-(2-methyl-1,3-thiazole-4-sulfonyl)phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-((4-((4-fluoro-2,5-dimethylbenzene)sulfonyl)phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-((4-((2-methyl-1,3-thiazole-4-sulfonyl)phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-((4-((2,5-dimethoxy-5-methylbenzene)sulfonyl)phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-((4-((3-methoxy-5-methylbenzene)sulfonyl)phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-((3-chloro-5-fluorobenzene) sulfonyl)phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-((4-((4-(2-methyl-1,3-thiazole-4-sulfonyl)phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-((4-((2-methylbenzene)sulfonyl)phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-((2,5-dimethoxybenzene)sulfonyl)phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-((2-fluoro-4-methylbenzene)sulfonyl)phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-((4-((5-(pyrrolidin-1-yl)pyridine-3-sulfonyl)phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-((4-((3-(3-chlorophenyl)-1H-pyrazole-4-sulfonyl)phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-((4-((2-methyl-1,3-thiazole-4-sulfonyl)phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-(4-{5H,6H,7H,8H,9H4midazo[1,2-a]azepine-3-sulfonfyl)phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-((4-((3-methoxy-5-methylbenzene)sulfonyl)phenyl)methyl)thieno[23-c]pyridine-2-carboxamide
N-((4-((3-chloro-5-fluorobenzene) sulfonyl)phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-((4-((2-methyl-1,3-thiazole-4-sulfonyl)phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-((4-6-(4-methylpiperazin-1-yl)pyridine-3-sulfonfyl)phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-((4-fluoro-2,5-dimethylbenzene)sulfonyl)phenyl)methyl)furo[23-c]pyridine-2-carboxamide
N-((4-((2-methyl-1,3-thiazole-4-sulfonyl)phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-((4-(3-methoxy-5-methylbenzene)sulfonyl)phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide

N-[4-((2-methanesulfonylbenzene)sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-[4-[(4-propan-2-yl)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[4-(quinoline-8-sulfonyl]phenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-(1-methyl-IH-indazole-4-sulfonyl)phenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-{[4-(4-cyclohexylbenzene)sulfonyl]phenyl)methyl]-thieno[2,3-c]pyridine-2-carboxamide
N-[(4-(1-propyl-IH-pyrazole-4-sulfonyl)phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-(2-butoxy-6-fluorobenzene)sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-[(4-(5-fluoropyridine-3-sulfonyl)phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-{[3-[2-(dimethylamino)ethyl]benzene}sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-{[4-(2,6-dimethoxy-4-methylbenzene)sulfonyl]phenyl)methyl]-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[3-(morpholin-4-yl)benzene]sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-[(4-{[3-tert-butylbenzene}sulfonyl]phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N-[(4-[3-(trifluoromethyl)benzene]sulfonyl]phenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-[3-fluoro-4-methylsulfonyl]benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide
N-[(4-(4-butylbenzene)sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-[(4-[6-chloroimidazo[1,2-a]pyridine-3-sulfonyl]phenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-{[4-(4-phenylbenzene)sulfonyl]phenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-(4-(4-ethoxy-2-methylbenzene)sulfonyl]phenyl)methyl]-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-(5-chloro-3-methylpyridine-2-sulfonyl]phenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-[4-(ethylcarbamoyl)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-(4-(4-methylpyridine-3-sulfonyl)phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[2-methyl-4-propoxybenzene)sulfonyl]phenyl]methyl)furo[2,3-c]pyridine-2-carboxamide
N-(4-[1-methyl-3-(trifluoromethyl)-IH-pyrazole-4-sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[2-butoxy-5-chlorobenzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[4-fluoro-3-(trifluoromethyl)benzene] sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[6-(morpholin-4-yl)pyridine-3-sulfonyl]phenyl]methyl)furo[2,3-c]pyridine-2-carboxamide
N-(4-[4-butoxy-3-fluorobenzene] sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[3-ethoxy-4-fluorobenzene] sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-([4-(4-chlorobenzene)sulfonyl]phenyl)methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-(1-methyl-1H-indazole-4-sulfonyl]phenyl)methyl]-1,3-benzothiazole-6-carboxamide
N-([4-[[3-(difluoromethoxy)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[[4-propoxybenzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-([4-[[5-fluoro-2-(hydroxymethyl)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-([4-[[3-(pyrrolidin-1-yl)benzene]sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-[[3-fluoro-5-(pyrrolidin-1-yl)benzene]sulfonyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-([4-[[2-fluoro-3-methylbenzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-([4-[[2,6-dimethoxypyridine-3-sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-([4-[[2H-1,3-benzodioxole-4-sulfonyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide
N-([4-[[2,3-difluorobenzene]sulfonyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-([4-[[3-(2-methylpropoxy)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[[3-fluoro-4-(pyrrolidin-1-yl)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[[3-fluoro-5-(pyrrolidin-1-yl)benzene]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-([4-[benzenesulfonfyl]phenyl)methyl]-3-bromo-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-[[6-chloroimidazo[1,2-a]pyridine-3-sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(2-fluoro-5-methoxybenzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(2-methoxy-5-(trifluoromethoxy)benzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(2-methyl-13-thiazole-4-sulfonyl)phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide

N-[[4-(2-luoro-5-methoxybenzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(phenoxathiine-4-sulfonyl)phenyl]methyl]thieno[2,3-c]pyridine-2-carboxamide

N-[[4-(3-(2-methoxybenzene)sulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(5-fluoro-2-methoxybenzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide

N-[[4-(2-methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

N-[[4-(4-phenylbenzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(dimethyl-1,3-thiazole-4-sulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(2-methyl-4-propoxybenzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(2-butoxy-4-fluorobenzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(2H-1,3-benzodioxole-5-sulfonamide)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(2,5-dimethylbenzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(4-(trifluoromethyl)benzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(2-butoxy-4-fluorobenzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(2H-1,3-benzodioxole-5-sulfonamide)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(2,5-dimethylbenzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(4-(trifluoromethyl)benzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(2-chloro-5-(trifluoromethoxy)benzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(2-chloro-5-(trifluoromethoxy)benzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(2-butoxy-4-fluorobenzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(2H-1,3-benzodioxole-5-sulfonamide)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(2,5-dimethylbenzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(4-(trifluoromethyl)benzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

N-[[4-(2-chloro-5-(trifluoromethoxy)benzene)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-\{(4-(2-methyl-2H-indazole-5-sulfonyl)phenyl)methyl\}imidazo[1,2-a]pyridine-6-carboxamide
N-\{(4-[3-chloro-4-(trifluoromethyl)benzene]sulfonyl)phenyl\}methyl\}furo[2,3-c]pyridine-2-carboxamide
N-\{(4-[quinoxline-3-sulfonyl]phenyl)methyl\}imidazo[1,2-a]pyrimidine-6-carboxamide
N-\{(4-[2-(3-fluorophenyl)-4,3-thiazole-4-sulfonyl]phenyl\}methyl\}thieno[2,3-c]pyridine-2-carboxamide
5-hydroxy-N-\{(4-[3-(morpholin-4-yl)benzene]sulfonyl)phenyl\}methyl\}lH4ndole-2-carboxamide
N-\{(4-[2-(chlorobenzene]sulfonyl]phenyl\}methyl\}thieno[2,3-c]pyridine-2-carboxamide
N-\{(4-[1-benzothiophene-7-sulfonyl]phenyl)methyl\}thieno[2,3-c]pyridine-2-carboxamide
N-\{(4-[3-tert-butylbenzene]sulfonyl]phenyl\}methyl\}imidazo[1,2-a]pyridine-6-carboxamide
N-\{(4-[3-(propan-2-yl]benzene]sulfonyl]phenyl\}methyl\}imidazo[1,2-a]pyrimidine-6-carboxamide
N-\{(4-[4-chloro-2-ethoxybenzene]sulfonyl]phenyl\}methyl\}imidazo[1,2-a]pyridine-6-carboxamide
N-\{(4-[3-cyanobenzene]sulfonyl]phenyl\}methyl\}imidazo[1,2-a]pyrimidine-6-carboxamide
N-\{(4-[2-(benzenesulfonyl]ethyl\}phenyl\}methyl\}lH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-\{(4-[3-chloro-5-methylbenzene]sulfonyl]phenyl\}methyl\}imidazo[1,2-a]pyridine-6-carboxamide
N-\{(4-[1-methyl-1H-indazole-4-sulfonyl]phenyl\}methyl\}imidazo[1,2-a]pyridine-6-carboxamide
N-\{(4-[3-chloro-2-methylbenzene]sulfonyl]phenyl\}methyl\}imidazo[1,2-a]pyridine-6-carboxamide
N-\{(4-[4-methylthiophene-2-sulfonyl]phenyl\}methyl\}imidazo[1,2-a]pyridine-6-carboxamide
N-\{(4-[2-iluoro-4-methoxybenzene]sulfonyl]phenyl\}methyl\}lH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-\{(4-[benzenesulfonyl]phenyl\}methyl\}furo[2,3-c]pyridine-2-carboxamide
N-\{(4-[3-(morpholin-4-yl]benzene] sulfonyl]phenyl\}methyl\}imidazo[1,2-a]pyridine-6-carboxamide
N-\{(4-[2-(3-fluorophenyl)-1,3-thiazole-4-sulf onyl]phenyl\}methyl\}imidazo[1,2-a]pyridine-6-carboxamide
N-\{(4-[3-(methylcarbamoyl]benzene]sulfonyl]phenyl\}methyl\}imidazo[1,2-a]pyrimidine-6-carboxamide
N-\{(4-[2,6-dimethoxypyrindine-3-sulfonyl]phenyl\}methyl\}lH-pyrazolo[3,4-b]pyridine-5-carboxamide
carboxamide
N-[(4-[(4-methoxy-2-(trifluoromethyl)benzene)sulfonyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide
N-[(4-(pyridine-3-sulfonyl)phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(4-cyclohexylbenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(4-butoxybenzene)sulfonyl]phenyl)methyl]-IH^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(2-(pyrrolidin-1-yl)-1,3-miazole-5-sulfonyl]phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N-[(4-[(4-phenylbenzene)sulfonyl]phenyl)methyl]-IH^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(3-diethylcarbamoyl)-5-fluorobenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(5-methoxypyridine-2-sulfonyl)phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[(2,2,2-Mfluoroethoxy)-4-(trifluoromethyl)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[(3-chloro-5-(trifluoromethyl)benzene)sulfonyl]phenyl)methyl]-IH^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(4-ethoxyphenyl)benzene)sulfonyl]phenyl)methyl]-IH^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(3-chlorobenzene)sulfonyl]phenyl)methyl]-IH^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(3-fluoro-4-methoxybenzene)sulfonyl]phenyl)methyl]-IH^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(3-fluoro-4-propoxybenzene)sulfonyl]phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N-[(4-[(4-methoxy-2-methylbenzene)sulfonyl]phenyl)methyl]-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(4-methoxy-3-phenyl)sulfonyl]phenyl)methyl]-IH^pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-[(5-chloro-2-hydroxybenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[(4-[(3-fluoro-4-methoxybenzene)sulfonyl]phenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-[(3-fluoro-4-propoxybenzene)sulfonyl]phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N-[(4-[(4-methoxy-2-methylbenzene)sulfonyl]phenyl)methyl]-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(1-methyl-1H^-indazole-5-sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(6-methylpyridine-3-sulfonyl]phenyl)methyl]-IH^yrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(3-ethoxybenzene)sulfonyl]phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N-[(4-[(1H^-pyrazol-1-yl)benzene)sulfonyl]phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N-[(4-[(2-pyrrolidin-1-yl)-1,3-thiazole-5-sulfonyl]phenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
carboxamide
N-[(4-(4-methoxybenzene)sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-[(4-[(5-chloro-2-(propan-2-yloxy)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-{(2,4-dimethylbenzene)sulfonyl[phenyl]methyl})-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-{6-(morpholin-4-yl)pyridine-3-sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(3-(2-methylpropoxy)benzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-{(4-fluoro-2,5-dimethylbenzene)sulfonyl]phenyl)methyl)thieno[23-c]pyridine-2-carboxamide
N-[(4-[(2-chloro-5-(trifluoromethoxy)benzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-{(4-phenylbenzene)sulfonyl]phenyl)methyl)furo[23-c]pyridine-2-carboxamide
N-[(4-{(2-methoxybenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
de
N-[(4-{(3-ethoxy-4-fluorobenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
de
N-[(4-{[1-(3-chlorophenyl)-1H-pyrazole-4-sulfonyl]phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
N-[(4-[(2-fluoro-4-methylbenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(2-fluoro-3-methylbenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
de
N-[(4-((pyridine-2-sulfonyl)phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-[(4-{(3-butoxybenzene)sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-[(4-[(2,4-dichlorobenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-{(2,4-dimethoxybenzene)sulfonyl]phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-[(4-[(2-fluoro-4-(trifluoromethoxy)benzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-{(2-dimethylcarbamoyl)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-{(2-chloro-5-methoxybenzene)sulfonyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(4-{(4-methylpyridine-3-sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-[(4-{(4-butoxy-3-fluorobenzene)sulfonyl]phenyl)methyl)thieno[23-c]pyridine-2-carboxamide
N-[(4-{(3-ethylbenzene)sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-[(4-[(3-fluoro-5-(2-methylpropoxy)benzene)sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-\{(4-[\text{3-chloro-4-methoxybenzene}]+sulfonyl)phenyl\}methylthieno[2,3-c]pyridine-2-carboxamide
N-(\{4-\[(\text{3-chloro-4-methoxybenzene})+sulfonyl\]phenyl\}methyl)furo[2,3-c]pyridine-2-carboxamide
N-(\{4-\{(2-trifluoromethoxy)benzene\}+sulfonyl\}phenyl\}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-(\{4-[\text{2-ethoxy-6-fluorobenzene}]+sulfonyl\}phenyl\}methyl)furo[2,3-c]pyridine-2-carboxamide
N-(\{4-[\text{3,5-difluorobenzene}]+sulfonyl\}phenyl\}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-(\{4-fluoro-2-(propan-2-yloxy)benzene\}+sulfonyl\}phenyl\}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-(\{4-[\text{2-morpholin-4-yl}pyridine-3-sulfonyl\}phenyl\}methyl)furo[2,3-c]pyridine-2-carboxamide
N-(\{4-\{(\text{2-phenoxybenzene})+sulfonyl\}phenyl\}methyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(\{4-\{(\text{3-chloro-5-(diethylcarbamoyl)benzene})+sulfonyl\}phenyl\}methyl)furo[2,3-c]pyridine-2-carboxamide
N-(\{4-\{(4-fluoro-2-(propan-2-yloxy)benzene)\}+sulfonyl\}phenyl\}methyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(\{4-[\text{2-fluoro-3-methylbenzene}]+sulfonyl\}phenyl\}methyl)furo[2,3-c]pyridine-2-carboxamide
N-(\{4-\{(4-\{(\text{3-iluoro-2-methoxybenzene})+sulfonyl\}phenyl\}methyl\}imidazo[1,2-a]pyridine-6-carboxamide
N-(\{4-\{(\text{4-lluoro-2-methoxybenzene})+sulfonyl\}phenyl\}methyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(\{4-\{(4-chloro-2-methylbenzene)\}+sulfonyl\}phenyl\}methyl)furo[2,3-c]pyridine-2-carboxamide
N-(\{4-\{(2,6-dichloro-3-methylbenzene)\}+sulfonyl\}phenyl\}methyl)thieno[2,3-c]pyridine-2-carboxamide
N-(\{4-\{(2,5-dimethoxybenzene)\}+sulfonyl\}phenyl\}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-(\{4-\{(2-lluoro-5-(diethylcarbamoyl)benzene)\}+sulfonyl\}phenyl\}methyl)furo[2,3-c]pyridine-2-carboxamide
N-(\{4-\{(4-lluoro-2-methoxybenzene)\}+sulfonyl\}phenyl\}methyl)thieno[2,3-c]pyridine-2-carboxamide
N-(\{4-\{(3-lluoro-2-methoxybenzene)\}+sulfonyl\}phenyl\}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-(\{4-\{(3-lluoro-4-(triiluoromethyl)benzene)\}+sulfonyl\}phenyl\}methyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(\{4-\{(\text{4-fluoro-2-methoxybenzene})\}+sulfonyl\}phenyl\}methyl)thieno[2,3-c]pyridine-2-carboxamide
N-(\{4-\{(\text{2-pyrrolidin-1-yl})-1,3-miazole-5-sulfonyl\}phenyl\}methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-(\{4-(\text{3-(2,2,2-trifluorooethoxy)benzene})\}+sulfonyl\}phenyl\}methyl)furo[2,3-c]pyridine-2-carboxamide
N-(\{4-\{(\text{3-thiazo1-1,3-thiazo1-5-sulfonyl)phenyl\}methyl\}furo[2,3-c]pyridine-2-carboxamide
N-(\{4-\{(\text{6-methoxy)pyridine-2-sulfonyl)phenyl\}methyl\}imidazo[1,2-a]pyrimidine-6-carboxamide
N-(\{4-\{(\text{3-lluoro-4-(triluoromethyl)benzene})\}+sulfonyl\}phenyl\}methyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-\{4-(2,4,6-Mmethylbenzene)sulfonyl|phenyl|methyl\}-\text{-}1H\text{-}pyrrolo[3,2-c]pyridine-2-carboxamide
N-\{4-[(2-fluoro-3-(propan-2-yloxy)benzene) sulfonyl |phenyl|methyl\}imidazo[ 1,2-a]pyrimidine-6-carboxamide
N-\{4-(4-fluorobenzene)sulfonyl|phenyl\}methyl|imidazo[ 1,2-a]pyrimidine-6-carboxamide
N-\{4-(4-methoxy-2-methylbenzene)sulfonyl|phenyl\}methyl|imidazo[ 1,2-a]pyrimidine-6-carboxamide
N-\{4-(3-fluoro-5-methoxybenzene)sulfonyl|phenyl\}methyl|imidazo[ 1,2-a]pyrimidine-6-carboxamide
N-\{4-(4-methanesulfonylbenzene)sulfonyl|phenyl\}methyl|-lH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-\{4-(2-ethoxy-4-fluorobenzene) sulfonyl|phenyl\}methyl|-lH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-\{4-(4-ethoxy-2-methylbenzene)sulfonyl|phenyl\}methyl)-lH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-\{4-(6-methoxynaphthalene-2-sulfonyl)phenyl\}methyl|thieno[2,3-c]pyridine-2-carboxamide
N-\{4-(benzenesulf onyl)phenyl\}methyl |-lH-1H-pyr ole -5 -carboxamide
N-\{4-[(6-chloro-2-fluoro-3-methylbenzene)sulfonyl]phenyl\}methyl)furo[2,3-c]pyridine-2-carboxamide
N-(4-[(5-chloro-2-methylbenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(2,6-dimethoxy-4-methylbenzene)sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-(4-[(2-phenylethane)sulfonyl]phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(4-fluoro-3-methylbenzene)sulfonyl]phenyl)methyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-[(1-methyl-1H-indazole-4-sulfonyl)phenyl]methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(3-fluoro-5-methylbenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(2,6-dimethoxy-4-methylbenzene)sulfonyl]phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
N-(4-[(4-fluoro-3-methylbenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(3-fluoro-5-methylbenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(3,5-dimethoxybenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyrimidine-6-carboxamide
N-[(4-[(3-ethoxybenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(3-fluoro-5-methoxybenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(3,5-difluorobenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(4-cyanobenzene)sulfonyl]phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(3-ethoxbenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(3-methylbenzene)sulfonyl]phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(3-(methoxymethyl)benzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(3-(methoxymethyl)benzene)sulfonyl]phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(1-methyl-1H-indazole-7-sulfonyl)phenyl]methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(4-cyanobenzene)sulfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(2-phenylethane)sulfonyl]phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(2-cyanobenzene)sulfonyl]phenyl)methyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[(4-[(3,5-difluorobenzene)sulfonyl]phenyl)methyl]pyridine-2,5-diamido
N-((4-[(4-fluoro-3-methylbenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-({4-(benzenesulfonyl)phenyl}methyl)-1,6-naphthyridine-2-carboxamide
N-({4-(4-methoxy-3-methylbenzene)sulfonyl}phenyl)methylimidazo[1,2-a]pyridine-6-carboxamide
N-({4-(4-methanesulfonylbenzene)sulfonyl}phenyl)methylimidazo[1,2-a]pyridine-6-carboxamide
N-({4-(2-cyanobenzene)sulfonyl}phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-(3-methoxy-4-methylbenzene)sulfonyl}phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-([3-fluoro-4-(1H-1-yl)benzene]sulfonyl}phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-({4-(2H-13-benzodioxole-5-sulfonyl)phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-({4-(2-chlorobenzene)sulfonyl}phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-(4-fluoro-2,5-dimethylbenzene)sulfonyl}phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-(2,5-dimethylbenzene)sulfonyl}phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-(2-fluoro-6-methoxybenzene)sulfonyl}phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-({4-(4-chloro-2-(trifluoromethyl)benzene)sulfonyl}phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-(2,5-dimethoxybenzene)sulfonyl}phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-(2-fluoro-6-methoxybenzene)sulfonyl}phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-({4-(quinoline-8-sulfonyl)phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-({4-chloro-2-(trifluoromethyl)benzene)sulfonyl}phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-([4-(2,5-difluorobenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-([4-(4-methoxy-2-methylbenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
carboxamide
N-(4-[(3-ethylbenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(4-ethylbenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-[4-[(4-chloro-3-(trifluoromethyl)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[4-[(4-fluoro-2-(trifluoromethyl)benzene)sulfonyl]phenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[4-[(4-tert-butyl-2-methoxybenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(4-methylbenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(4,3-dimethoxybenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(2-fluoro-4-methylbenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(4-methylbenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-[4-[(2-methoxy-5-methylbenzene)sulfonyl]phenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[4-[(2,5-dimethoxybenzene)sulfonyl]phenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[4-[(2-chloro-3-(trifluoromethyl)benzene)sulfonyl]phenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[4-[(3-methyl-IH-pyrazole-4-sulfonyl)phenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[4-[(2-ethylbenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[4-[(2-fluoro-3-methoxybenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[2-(morpholin-4-yl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[4-[(2,4-difluoro-2-methoxybenzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-{[4-(5-methylthiophene-2-sulfonoyl)phenyl]methyl}-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-{[4-[5-fluoro-2-(hydroxymethyl)benzene)sulfonyl]phenyl]methyl}-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-{[4-(ethylcarbamoyl)benzene]sulfonyl]phenyl}methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-{[4-(methoxy-3,5-dimethylbenzene)sulfonyl]phenyl}methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-{[4-[3-fluoro-5-(2-methylpropoxy)benzene]sulfonyl]phenyl}methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-[3-propoxybenzene]sulfonyl]phenyl}methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-{[4-[2,4,5-trimethylbenzene]sulfonyl]phenyl}methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-[2-chloro-4-methoxybenzene]sulfonyl]phenyl}methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-{[4-[2,3,6-trimethoxybenzene]sulfonyl]phenyl}methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-{[4-[2-chloro-4-(trifluoromethyl)benzene]sulfonyl]phenyl}methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-[3-fluoro-2-methylbenzene]sulfonyl]phenyl}methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-[3-methylbenzene]sulfonyl]phenyl}methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-{[4-[2-methoxy-4-(1H-pyrazol-1-yl)benzene]sulfonyl]phenyl}methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-({4-[5-acetyl-2-methoxybenzene]sulfonyl]phenyl}methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-{[4-[4-chloro-2-methylbenzene]sulfonyl]phenyl}methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-{[4-[3-chloro-4-(trifluoromethyl)benzene]sulfonyl]phenyl}methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-[2-phenoxybenzene]sulfonyl]phenyl}methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-[4-chlorobenzene]sulfonyl]phenyl}methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-({4-[4-fluoro-3-(2,2,2-trifluoromethyl)benzene]sulfonyl]phenyl}methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-{[4-[4-fluoro-3-(2,2,2-trifluoroethoxy)benzene]sulfonyl]phenyl}methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-{[4-[2-chloro-3-(2,2,2-trifluoroethoxy)benzene]sulfonyl]phenyl}methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-{[4-[4-fluoro-3-(2,2,2-trifluoroethoxy)benzene]sulfonyl]phenyl}methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-{[4-[4-fluoro-3-(2,2,2-trifluoroethoxy)benzene]sulfonyl]phenyl}methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-{[4-(quinoline-6-sulfonyl)phenyl]methyl}imidazo[1,2-a]pyridine-6-carboxamide
N-{

N-[(4-[(3-(trifluoromethoxy)benzene)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-((4-[(2-methoxybenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-((4-[(4-fluoro-2-methylbenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(2-butoxy-4-fluorobenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(2,4-dichloro-3-methoxybenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(2-methoxy-5-methylbenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(2,5-dimethoxybenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(2-methoxybenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(3-chloro-5-(trifluoromethyl)benzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(2-methoxybenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(2,4-bis(trifluoromethyl)benzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(3-fluoro-4-methoxybenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(2,3-dimethylbenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(2,5-dimethylbenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(4-chloro-3-fluorobenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-([4-4-(2-methylpropoxy)benzene]sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(2-fluoro-4-methoxybenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(2,3-dimethylbenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(4-methoxybenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(2-butoxy-4-fluorobenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(3,5-dichlorobenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(3-methoxybenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(1-methyl-1H-indazole-5-sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(3-chloro-2-methylbenzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-((4-[(3-fluoro-5-(tri fluoromethyl)benzene)sulfonyl]phenyl)methyl)-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide
N-(4-[(3-fluorobenzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(ethoxymethyl)benzene}sulfonyl]phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-(4-[(2-chloro-4-methylbenzene)sulfonyl]phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-(4-[(cyanobenzene)sulfonyl]phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-(4-[(sulfamoylbenzene)sulfonyl]phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-(4-[(2-(benzyloxy)-5-(trifluoromethyl)benzene}sulfonyl]phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-((4-(naphthalene-1-sulfonyl)phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-(4-(benzenesulfonyl)phenyl)methyl)-IH-pyrrolo[3,2-c]pyridine-3-carboxamide
N-(4-(1-methyl-1H-indazole-7-sulfonyl)phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-(4-[(5-fluoro-2-methylbenzene)sulfonyl]phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-(4-(2H-1,3-benzodioxole-4-sulfonyl)phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-(4-[(5-chloro-2-propoxybenzene)sulfonyl]phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-(4-[3-fluoro-2-methoxybenzene)sulfonyl]phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-(4-[(2,3-dimethoxybenzene)sulfonyl]phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-(4-[4-butoxy-2-methylbenzene)sulfonyl]phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-(4-[(propan-2-yl)benzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(2,3-dimethoxybenzene)sulfonyl]phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-(4-[3-fluoro-4-propoxybenzene)sulfonyl]phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-(4-[(2-methylsulfamoyl)benzene)sulfonyl]phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-(4-[(2-methoxy-5-(propan-2-yl)benzene)sulfonyl]phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
N-(4-[(2-methyl-4-(1H-pyrazol-1-yl)benzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(2-fluoro-4-(1H-pyrazol-1-yl)benzene)sulfonyl]phenyl)methyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-(2-methylbenzene)sulfonyl]phenyl)methyl)-IH-pyrazolo[3,4-b]pyridine-5-carboxamide
In some other embodiments, the Nampt small molecule antagonist can further be chosen from the following compounds or pharmaceutically acceptable salts thereof described in PCT patent application No. WO2012031199, in particular the compounds of Formula II:

\[
\text{II, wherein }
\]

Ar\(^1\) is aryl or heteroaryl, wherein said aryl or heteroaryl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of:
- deuterium, halo, cyano, alkyl, cyanoalkyl, haloalkyl, alkenyl, alkynyl, alkoxy,
- haloalkoxy, arloxy, -NR\(^a\)R\(^b\), -C(0)N(R\(^a\)R\(^b\)), -C(0)-aryl, -S(0)-aryl, -NH-C(0)-aryl, -NH-C(0)-aryl, (alkoxyalkyloxy)-, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

Ar\(^2\) is unsubstituted aryl or heteroaryl;

R\(^1\) is cycloalkyl, aryl, heterocycloalkyl, or heteroaryl,

(i) wherein each of said cycloalkyl, aryl, heterocycloalkyl and heteroaryl is either unsubstituted or optionally independently substituted with 1, 2, 3, 4 or 5 substituents which can be the same or different and are independently selected from the group consisting of:
- deuterium, halo, cyano, alkyl, hydroxyalkyl, cyanoalkyl, haloalkyl, alkenyl, alkynyl, alkoxy, alkylalkoxy, haloalkoxy, arloxy, -NR\(^a\)R\(^b\), -CONR\(^a\)R\(^b\), -S(0)alkyl, -S(0)aryl, -S(0)alkyl, -S(0)aryl, -S(0)alkyl, -S(0)aryl, methylenedioxy, -(CH\(_2\))\(_{3}\)cycloalkyl, -(CH\(_2\))\(_{3}\)aryl, -(CH\(_2\))\(_{3}\)heteroaryl, and -(CH\(_2\))\(_{3}\)heterocycloalkyl,

(ii) wherein each of said cycloalkyl, aryl, heterocycloalkyl, and heteroaryl may additionally be unsubstituted or substituted by one or more halo, cyano, alkyl or alkoxy or may be be fused with independently selected aryl, heteroaryl, heterocycloalkyl or cycloalkyl;

R\(^a\) and R\(^b\) are independently H, alkyl, alkoxy, aryl, alkoxyalkyl, -S(0)alkyl and cycloalkyl or R\(^a\) and R\(^b\) can form a 5 or 6 membered heterocycloalkyl group together with the nitrogen atom to which they are attached, wherein said heterocycloalkyl group may contain one or more additional heteroatom(s) selected from N, S or O;

R\(^2\) and R\(^3\) are H or deuterium;

m, n, p and q are independently 0, 1 or 2;
and pharmaceutically acceptable salts thereof.

In some embodiments, the Nampt small molecule antagonist can further be chosen from Nampt antagonists selected from the group consisting of:

- 2-cyano-1-[[4-[[3-(dimethylsulamoyl)benzene]sulfonyl]phenyl]methyl]-3-(pyridin-4-yl)guanidine;
- (E)-3-[[4-[[3-chlorobenzene]sulfonyl]phenyl]methyl]-2-cyano-1-(pyridin-4-yl)guanidine;
- 1-[[4-[[4-chloro-3-(trifluoromethyl)benzene]sulfonyl]phenyl]methyl]-2-cyano-3-(pyridin-4-yl)guanidine;
- 2-cyano-1-[[4-[[3-(ethanesulfonyl)benzene]sulfonyl]phenyl]methyl]-3-(pyridin-4-yl)guanidine;
- 2-cyano-3-(pyridin-4-yl)-1-[[4-[[3-(trifluoromethoxy)benzene]sulfonyl]phenyl]methyl]-3-(pyridin-4-yl)guanidine;
- 2-cyano-3-(pyridin-4-yl)-1-[[4-[[quinoline-8-sulfonyl]phenyl]methyl]guanidine;
- 2-cyano-1-[[4-[[3,5-dimethylbenzene]sulfonyl]phenyl]methyl]-3-(pyridin-4-yl)guanidine;
- 2-cyano-3-(pyridin-4-yl)-1-[[4-[[quinoline-6-sulfonyl]phenyl]methyl ]guanidine ;
- 2-cyano-1-[[4-[[2-(morpholin-4-ylmethyl)benzene]sulfonyl]phenyl]methyl]-3-(pyridin-4-yl)guanidine;
- 2-cyano-1-[[4-[[2-methylpyridine-3-sulfonyl]phenyl]methyl]-3-(pyridin-4-yl)guanidine;
- 2-cyano-1-[[4-[[6-methylpyridine-3-sulfonyl]phenyl]methyl]-3-(pyridin-4-yl)guanidine;
- 2-cyano-1-[[4-[[4-(2-methylpyridine-3-sulfonyl)phenyl]methyl]-3-(pyridin-4-yl)guanidine;
- 2-cyano-1-[[4-[[4-(6-methylpyridine-3-sulfonyl)phenyl]methyl]-3-(pyridin-4-yl)guanidine;
- 2-cyano-1-[[4-[[4-(2-cyano-3-(pyridin-4-yl)carbamimidamido]methyl]benzene]sulfonyl]phenyl]methyl]-3-(pyridin-4-yl)guanidine;
- 2-cyano-1-[[4-[[4-(2-cyano-3-(pyridin-4-yl)carbamimidamido]methyl]benzene]sulfonyl]phenyl]methyl]-3-(pyridin-4-yl)guanidine;
- 2-cyano-1-[[4-[[4-(2-cyano-3-(pyridin-4-yl)carbamimidamido]methyl]benzene]sulfonyl]phenyl]methyl]-3-(pyridin-4-yl)guanidine;
- 2-cyano-1-[[4-[[4-(2-cyano-3-(pyridin-4-yl)carbamimidamido]methyl]benzene]sulfonyl]phenyl]methyl]-3-(pyridin-4-yl)guanidine;
- 2-cyano-1-[[4-[[4-(2-cyano-3-(pyridin-4-yl)carbamimidamido]methyl]benzene]sulfonyl]phenyl]methyl]-3-(pyridin-4-yl)guanidine;
- 2-cyano-1-[[4-[[4-(2-cyano-3-(pyridin-4-yl)carbamimidamido]methyl]benzene]sulfonyl]phenyl]methyl]-3-(pyridin-4-yl)guanidine;
- 2-cyano-1-[[4-[[4-(2-cyano-3-(pyridin-4-yl)carbamimidamido]methyl]benzene]sulfonyl]phenyl]methyl]-3-(pyridin-4-yl)guanidine;
cyclopentylbenzamide;

(E)-3-{[4-(benzenesulfonyl)phenyl]methyl}-2-cyano-1-(pyridin-3-ylmethyl)guanidine;
1-{{4-[(2H-1,3-benzodioxole-5-sulfonyl)phenyl]methyl}-2-cyano-3-(pyridin-4-yl)guanidine;
2-cyano-1-{{4-[(3,5-difluorobenzene)sulfonyl]phenyl}methyl}-3-(pyridin-4-yl)guanidine;
1-{{4-[3-chloro-2-(morpholin-4-yl)pyridine-4-sulfonyl]phenyl}methyl}-2-cyano-3-(pyridin-4-yl)guanidine;
3-{{4-[[2-cyano-3-(pyridin-4-yl)carbamimidamido]methyl}benzene}sulfonyl]-N,N-diethyl-4-fluorobenzamide;
2-cyano-1-{{4-[(3,5-dichlorobenzene)sulfonyl]phenyl}methyl}-3-(pyridin-4-yl)guanidine;
2-cyano-1-{{4-[[2-(dimethylamino)pyrimidine-5-sulfonyl]phenyl}methyl]-3-(pyridin-4-yl)guanidine;
2-cyano-1-{{4-[[3-(propan-2-yloxy)benzene]sulfonyl]phenyl}methyl]-3-(pyridin-4-yl)guanidine;
2-cyano-1-{{4-[[4-(2,6-dimethoxypyridine-3-sulfonyl)phenyl]methyl]3-(pyridin-4-yl)guanidine;
2-cyano-1-{{4-[[4-(3-fluoro-5-methoxybenzene)sulfonyl]phenyl}methyl]-3-(pyridin-4-yl)guanidine;
2-cyano-1-{{4-[[4-chloro-3-fluorobenzene)sulfonyl]phenyl}methyl]-3-(pyridin-4-yl)guanidine;
2-cyano-1-{{4-[[4-acetylbenzene)sulfonyl]phenyl}methyl]-3-(pyridin-4-yl)guanidine;
2-cyano-1-{{4-[[4-ethoxybenzene)sulfonyl]phenyl}methyl]-3-(pyridin-4-yl)guanidine;
2-cyano-1-{{4-[[phenylmethane)sulfonyl]phenyl}methyl]-3-(pyridin-4-yl)guanidine;
2-cyano-1-{{4-[3-[(morpholin-4-yl)carbonyl]benzene]sulfonyl]phenyl}methyl]-3-(pyridin-4-yl)guanidine;
2-cyano-1-{{4-[4-[[3-chloro-5-methylbenzene)sulfonyl]phenyl]methyl]-3-(pyridin-4-yl)guanidine;
2-cyano-1-([4-[(4-fluoro-3-methylbenzene)sulfonyl]phenyl]methyl)-3-(pyridin-4-yl)guanidine;  
1-([4-[(4-chloro-2-methoxybenzene)sulfonyl]phenyl]methyl)-2-cyano-3-(pyridin-4-yl)guanidine;  
2-cyano-1-([4-[(5-fluoro-2-methylbenzene)sulfonyl]phenyl]methyl)-3-(pyridin-4-yl)guanidine;  
1-([4-(2H-1,3-benzodioxole-4-sulfonyl)phenyl]methyl)-2-cyano-3-(pyridin-4-yl)guanidine;  
1-([4-[(5-chloro-2-methoxybenzene)sulfonyl]phenyl]methyl)-2-cyano-3-(pyridin-4-yl)guanidine;  
2-cyano-3-(pyridin-4-yl)-1-[(4-[[pyrrolidin-1-yl]carbonyl]benzene sulfonamido]methyl]-1-(pyridin-4-yl)carbamide benzene [sulfonyl]phenyl]methyl]guanidine;  
2-cyano-3-(pyridin-4-yl)-1-([4-[(trifluoromethyl]benzene]sulfonyl]phenyl) methyl]guanidine;  
2-cyano-1-([4-[(4-ethylbenzene)sulfonyl]phenyl]methyl)-3-(pyridin-4-yl)guanidine;  
2-cyano-1-([4-[(4-methoxy-3-methylbenzene)sulfonyl]phenyl]methyl)-3-(pyridin-4-yl)guanidine;  
1-([4-[(3-chloro-5-methoxybenzene)sulfonyl]phenyl]methyl)-2-cyano-3-(pyridin-4-yl)guanidine;  
2-cyano-1-([4-[(3-methylbenzene)sulfonyl]phenyl]methyl)-3-(pyridin-4-yl)guanidine;  
3-([4-[[2-cyano-3-(pyridin-4-yl)carbamimidamido]methyl]benzene sulfonamido]-N-methylpyridine-2-carboxamide;  
3-([4-[(4-cyclopropylphenylmethyl)benzene sulfonamido]methyl]benzene sulfonamido]-N-methylpyridine-2-carboxamide;  
2-cyano-1-([4-[(3-chloro-5-fluorobenzene)sulfonyl]phenyl]methyl)-3-(pyridin-4-yl)guanidine;  
5-([4-[[2-cyano-3-(pyridin-4-yl)carbamimidamido]methyl]benzene sulfonamido]-N-methylpyridine-2-carboxamide;  
2-cyano-1-([4-[(3-fluoro-4-methylbenzene)sulfonyl]phenyl]methyl)-3-(pyridin-4-yl)guanidine;  
3-([4-[(3,4-difluorobenzene)sulfonyl]phenyl]methyl)-2-cyano-1-(pyridin-3-yl)guanidine;  
1-([4-[(3-chloro-5-fluorobenzene)sulfonyl]phenyl]methyl)-2-cyano-3-(pyridin-4-yl)guanidine;  
2-cyano-3-(pyridin-4-yl)-1-[(4-[[3-(trifluoromethyl]benzene]sulfonyl]phenyl) methyl]guanidine;  
3-([4-benzenesulfonamido]phenyl]methyl)-2-cyano-1-(pyridin-3-yl)guanidine;  
1-([4-[(3,4-difluorobenzene)sulfonyl]phenyl]methyl)-3-(pyridin-4-yl)guanidine;  
2-cyano-1-([4-[(3-chloro-5-fluorobenzene)sulfonyl]phenyl]methyl)-3-(pyridin-4-yl)guanidine;  
2-cyano-1-([4-[(3,4-difluorobenzene)sulfonyl]phenyl]methyl)-3-(pyridin-4-yl)guanidine;  
2-cyano-1-([4-[(3-fluoro-4-(1H-pyrazol-1-yl)benzene]sulfonyl]phenyl)methyl]-3-(pyridin-4-yl)guanidine;  
1-([2-[[4-(benzenesulfonyl]phenyl]ethyl]-2-cyano-3-(pyridin-4-yl)guanidine;  
2-cyano-1-[(4-[[3-fluoro-4-methylbenzene]sulfonyl]phenyl]methyl]-3-(pyridin-4-yl)guanidine;  
2-cyano-3-([4-[[8-oxa-3-azabicyclo [3.2.1] octane-3-sulfamido]phenyl]methyl]-1-(pyridin-4-yl)guanidine;  
1-([4-[(3-chloro-5-fluorobenzene)sulfonyl]phenyl]methyl)-2-cyano-3-(pyridin-4-yl)guanidine;  
2-cyano-1-([4-[(3-fluoro-4-methylbenzene)sulfonyl]phenyl]methyl)-3-(pyridin-4-yl)guanidine;  
2-cyano-3-([4-[[8-oxa-3-azabicyclo [3.2.1] octane-3-sulfamido]phenyl]methyl]-1-(pyridin-4-yl)guanidine.
yl)guanidine;
2-cyano-1-((4-[(3-fluoro-4-methoxybenzene)sulfonyl]phenyl)methyl)-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(4-phenylbenzene)sulfonyl]phenyl)methyl)-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(3-fluoro-5-methylbenzene)sulfonyl]phenyl)methyl)-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(4-phenylbenzene)sulfonyl]phenyl)methyl)-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(4-methylbenzene)sulfonyl]phenyl)methyl)-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(5-fluoropyridine-3-sulfonyl)phenyl)methyl]-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(3-methoxy-4-methylbenzene)sulfonyl]phenyl)methyl)-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(1-methyl-1H-indazole-6-sulfonyl)phenyl)methyl]-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(4-methoxybenzene)sulfonyl]phenyl)methyl)-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(4-quinoline-3-sulfonyl)phenyl)methyl]-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(4-methoxybenzene)sulfonyl]phenyl)methyl)-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(4-methylbenzene)sulfonyl]phenyl)methyl)-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(2-acyl-2-methoxybenzene)sulfonyl]phenyl)methyl)-2-cyano-3-(pyridin-4-yl)guanidine;
2-cyano-3-(pyridin-4-yl)-1-((4-quinoline-3-sulfonyl)phenyl)methyl)-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(quinoline-3-sulfonyl)phenyl)methyl]-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(4-methoxybenzene)sulfonyl]phenyl)methyl)-3-(pyridin-4-yl)guanidine;
2-cyano-3-chloro-5-[(4-[(2-cyano-3-(pyridin-4-yl)carbamimidamido)phenyl)methyl]benzene)sulfonyl]-N,N-diethylbenzamide;
2-cyano-1-((4-[(2-methoxy-5-(propan-2-yl)benzene)sulfonyl]phenyl)methyl)-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(4-(morpholin-4-yl)benzene)sulfonyl]phenyl)methyl)-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(3-methoxy-4-methylbenzene)sulfonyl]phenyl)methyl)-3-(pyridin-4-yl)guanidine;
2-cyano-1-((pyridin-4-yl)-3-[(4-[(2-trifluoromethoxy)benzene)sulfonyl]phenyl)methyl]-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(3-fluoro-5-(2,2,2-trifluoroethoxy)benzene)sulfonyl]phenyl)methyl)-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(4-ethoxy-3-fluorobenzene)sulfonyl]phenyl)methyl)-3-(pyridin-4-yl)guanidine;
3-chloro-5-[(4-[(2-cyano-3-(pyridin-4-yl)carbamimidamido)phenyl)methyl]benzene)sulfonyl]-N,N-diethylbenzamide;
2-cyano-1-((4-[(2-methoxy-5-(propan-2-yl)benzene] sulfonyl ]phenyl)methyl]-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(2,4-dimethylbenzene)sulfonyl]phenyl)methyl)-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(3-chloro-5-(trifluoromethyl)benzene)sulfonyl]phenyl)methyl)-2-cyano-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(2,4-dimethylbenzene)sulfonyl]phenyl)methyl)-3-(pyridin-4-yl)guanidine;
3-chloro-5-[(4-[(2-cyano-3-(pyridin-4-yl)carbamimidamido)phenyl)methyl]benzene)sulfonyl]-N,N-diethylbenzamide;
2-cyano-1-((4-[(2,4-dimethylbenzene)sulfonyl]phenyl)methyl)-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(3-fluoro-5-(trifluoromethyl)benzene)sulfonyl]phenyl)methyl)-2-cyano-3-(pyridin-4-yl)guanidine;
2-cyano-1-((4-[(2-methylbenzene)sulfonyl]phenyl)methyl)-3-(pyridin-4-yl)guanidine;
or a pharmaceutically acceptable salt thereof.

[0292] In some other embodiments, the Nampt small molecule antagonist can further be chosen from the following compounds or pharmaceutically acceptable salts thereof described in PCT patent application No. WO2012/031196, in particular the compounds of Formula IIIA:
wherein:

\( R^a \) is 1, 2, 3 or 4 and can be selected from the group consisting of hydrogen, amino, oxo, halo, alkoxy, alkyl, haloalkyl, \(-N(alkyl)_{2}\), \(-NH(CO)0\)-alkyl \, \text{H}-pyrazol, \, \text{H}-imidazol, and \,-C(0)NH \,_{2}; \, \text{and wherein said pyridine can comprise a N-oxide formed with its N atom member; \\

\( R^l \) is \,-NR\,^{3}R^4 \, \text{wherein} \, R^3 \text{is H, alkyl or} \,-S(0)\,-_2\text{alkyl and} \, R^4 \text{is alkyl, hydroxyalkyl,} \,-S(0)\,-_2\text{alkyl,} \, -(CH_2)_q\,\text{cycloalkyl,} \, -(CH_2)_q\,\text{heterocycloalkyl, aryl, arylalkyl-,} \,-(CH_2)_q\,\text{heteroaryl;}
 halooalkyl;  
 cycloalkyl;  
 aryl;  
 heterocycloalkyl; or 
 heteroaryl;  
 wherein each of said cycloalkyl, aryl, heterocycloalkyl or heteroaryl is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents which can be the same or different and are independently selected from the group consisting of: 
 halo, cyano, alkyl, hydroxyl, hydroxyalkyl, hydroxyalkoxy, haloalkyl, 
 alkoxy, alkylalkoxy, haloalkoxy, arylalkenyl-, arlyloxy, benzyloxy, oxo, \,-(CH_2)_q\,-NR\,^2R^5, \,-(CH_2)_q\,-CONR\,^3R^6, \,-S(0)\,-_2\text{-alkyl,} \,-S(0)\,-_2\text{NH-alkyl,} \,-S(0)\,-_2\text{-heterocycloalkyl,} \,-S(0)\,-_2\text{CF}_3, \,-C(0)\text{-alkyl,} \,-C(0)\text{-aryl,} \,-C(0)\text{-alkylaryl,} \,-C(0)\,0\text{-alkyl,} \,-(CH_2)_q\,\text{cycloalkyl,} \, (CH_2)_q\,\text{heteroaryl,} \, \text{and} \,-(CH_2)_q\,\text{heterocycloalkyl;}
 wherein each of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted by one or more halo, nitro, haloalkyl, haloalkoxy, oxo, cyano, 
 alkyl, haloalkyl, or alkoxy;  
 \( R^b \) and \( R^c \) are independently selected from the group consisting of H, alkyl, hydroxyalkyl, alkoxy, 
 aryl, alkoxalkyl, \,-S(0)\,-_2\text{alkyl and cycloalkyl or} \, R^b \text{ and} \, R^c \text{can form a 5 or 6 membered}
 heterocycloalkyl group together with the nitrogen atom to which they are attached, wherein said heterocycloalkyl group may contain one or more additional heteroatom(s) selected from 
 N, S or O;
q is 0 or 1; and
pharmaceutically acceptable salts thereof.

[0293] In some embodiments, the Nampt small molecule antagonist can further be chosen from Nampt antagonists selected from the group consisting of:

1-(pyridin-3-ylmethyl)-3-(4-{[2-(trifluoromethoxy)benzene]sulfonyl}phenyl)urea;
3-{4-{[(4-bromobenzene)sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-{[(2-methyl-4-(1H-pyrazol-1-yl)benzene] sulfonyl}Jphenyl}-1-(pyridin-3-ylmethyl)urea;
N-[2-(pyridin-3-yl)ethyl]-4-{{[3-(trifluoromethoxy)benzene] sulfonyl}Jbenzamide;
3-{{4-[4-methoxy-2-methylbenzene]sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-{[(2,4-dimethoxybenzene]sulfonyl}phenyl}-1-(pyridin-3-ylmethyl)urea;
1-(6-aminopyridin-3-yl)methyl]-3-{4-[(4-fluorobenzene)sulfonyl]phenyl}urea;
3-{{4-[(3,5-dimethylbenzene]sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
1-(6-aminopyridin-3-yl)methyl]-3-{4-(benzenesulfonyl]phenyl}urea;
3-{4-{[4-{[(2-ethoxybenzene]sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-[4-{[4-(benzenesulfonyl)phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{{4-{[(6-aminopyridin-3-yl)methyl]-3-{4-(benzenesulfonyl]phenyl]urea;
3-{4-{[(4-benzencesulfonyl]phenyl]-1-[[6-(1H-pyrazol-1-yl)pyridin-3-yl]methyl]urea;
3-{4-{{[2-fluoro-4-(1H-pyrazol-1-yl)benzene] sulfonyl}Jphenyl}-1-(pyridin-3-ylmethyl)urea;
4-(benzenesulfonyl)-N-[(imidazo[1,2-a]pyridin-7-yl)Jbenzamide;
3-{4-{[(2-bromobenzene]sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
4-[4-(benzenesulfonyl)phenyl]-1-[(6-(1H-pyrazol-1-yl)methyl)urea;
3-{{4-{{[4-(3-bromobenzene]sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-{4-{[(4-chlorobenzene]sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
N-[imidazo[1,2-a]pyridin-6-ylmethyl]-4-{{3-(trifluoromethoxy)benzene] sulfonyl}Jbenzamide;
3-{4-{[(3-bromobenzene]sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{{4-{[(6-aminopyridin-3-yl)methyl]-3-{[6-(2-methylamino)pyridin-3-yl]methyl]urea;
3-{{4-{[4-chloro-2-methylbenzene]sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-[(2-fluoro-3-methoxybenzene)sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-[(2,3-difluorobenzene)sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-[(2-chloro-6-fluoro-3-methylbenzene)sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-(pyridin-3-ylmethyl)-1-[4-(pyridine-5-sulfonyl)phenyl]urea;
3-{4-[(3,5-diiodobenzene)sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
1-(6-(benzenesulfonyl)pyridin-3-yl)-3-(pyridin-3-ylmethyl)urea;
3-[(2,4-dichlorobenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(2,5-difluoro-4-methoxybenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
l-[(3-aminophenyl)methyl]-3-[4-(benzenesulfonyl)phenyl]urea;
3-[(4-ethylbenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(4-chlorobenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(2-chlorobenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(4-chloro-2-fluorobenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(4-chlorobenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(5-fluoro-2-methoxybenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(2-methoxybenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(4-fluorobenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-(2-methoxynaphthalene-1-sulfonyl)phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(4-chlorobenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(3-fluorobenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
1-(4-(2H-1,3-benzodioxole-5-sulfonyl)phenyl]-3-(pyridin-3-ylmethyl)urea;
4-[(2-chlorobenzene)sulfonyl]N-[(imidazo[1,2-a]pyridin-6-ylmethyl]benzamide;
4-[(3-chlorobenzene)sulfonyl]N-[(imidazo[1,2-a]pyridin-6-ylmethyl]benzamide;
3-[(2-chlorobenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(2-methoxybenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(2,3-dichlorobenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(2-fluoro-6-methoxybenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(3-fluoro-4-(1H-pyrazol-1-yl)benzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-(benzenesulfonyl)phenyl]-1-(quinolin-6-yl)urea;
3-{4-[2,5-dimethoxybenzene)sulfonyl]phenyl} - 1-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-[4-(trifluoromethane)sulfonfylphenyl]urea;
3-{4-[2-fluoro-4-methoxybenzene)sulfonyl]phenyl} - 1-(pyridin-3-ylmethyl)urea;
1-{4-[4-fluoro-2,6-dimethoxybenzene)sulfonyl]phenyl} - 1-(pyridin-3-ylmethyl)urea;
3-{4-[4-(3,5-dimethyl-1,2-oxazole-4-sulfonyl)phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-(4-chloro-3-fluorobenzene)sulfonyl]phenyl} - 1-(pyridin-3-ylmethyl)urea;
1-{imidazo[1,2-a]pyridin-6-ylmethyl} - 4-{[3-(trifluoromethane)benzene] sulfonyl}Jbenzamide;
3-{4-[2-chloro-5-(trifluoromethane)benzene] sulfonyl Jphenyl} - 1-(pyridin-3-ylmethyl)urea;
3-{4-[2-fluorobenzene)sulfonyl]phenyl} - 1-(pyridin-3-ylmethyl)urea;
1-{imidazo[1,2-a]pyridin-6-ylmethyl} - 4-{[3-(trifluoromethane)benzene] sulfonyl}Jbenzamide;
3-[4-(3,5-difluorobenzene)sulfonyl]phenyl} - 1-(pyridin-3-ylmethyl)urea;
3-[4-{imidazo[1,2-a]pyridin-6-ylmethyl}Jbenzamide;
1-(pyridin-3-ylmethyl)-3-[4-(2-(trifluoromethane)benzene)sulfonyl]phenyl]urea;
3-[4-[4-chloro-3-(trifluoromethane)benzene] sulfonyl Jphenyl} - 1-(pyridin-3-ylmethyl)urea;
3-[4-[4-fluoro-2-[propan-2-yl]pyridine-3-sulfonyl]phenyl} - 1-(pyridin-3-ylmethyl)urea;
3-[4-[2-fluoro-4-methylbenzene)sulfonyl]phenyl} - 1-(pyridin-3-ylmethyl)urea;
3-{4-[2-ethylbenzene)sulfonyl]phenyl} - 1-(pyridin-3-ylmethyl)urea;
3-{4-[2-chloro-6-(propan-2-yl)pyridine-3-sulfonyl]phenyl} - 1-(pyridin-3-ylmethyl)urea;
3-[4-[2-methoxy-5-methylbenzene)sulfonyl]phenyl} - 1-(pyridin-3-ylmethyl)urea;
3-{imidazo[1,2-a]pyridin-6-ylmethyl} - 4-{[3-chlorobenzene)sulfonyl]phenyl}Jbenzamide;
3-{4-[2-chloro-4-fluorobenzene)sulfonyl]phenyl} - 1-(pyridin-3-ylmethyl)urea;
3-[4-[2,4-difluorobenzene)sulfonyl]phenyl} - 1-(pyridin-3-ylmethyl)urea;
3-[4-[2,6-dimethoxybenzene)sulfonyl]phenyl} - 1-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-{4-[2-(trifluoromethane)phenyl]urea;
3-{4-[3-fluorobenzene}sulfonyl]phenyl} - 1-(pyridin-3-ylmethyl)urea;
3-{4-[5,7-dichlorobenzene] sulfonyl phenyl} - 1-(pyridin-3-ylmethyl)urea;
3-{4-[2-methoxy-3,5-dimethylbenzene)sulfonyl]phenyl} - 1-(pyridin-3-ylmethyl)urea;
3-{imidazo[1,2-a]pyridin-6-ylmethyl} - 4-{[3-(chlorobenzene)sulfonyl]phenyl}Jbenzamide;
3-{4-[2-methoxy-5-(propan-2-yl)benzene)sulfonyl]phenyl} - 1-(pyridin-3-ylmethyl)urea;
3-{4-[2-methoxy-4-(propan-2-yl)benzene)sulfonyl]phenyl} - 1-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-{4-[2,4,6-trimethylbenzene)sulfonyl]phenyl}urea;
3-{4-[3-fluorobenzene)sulfonyl]phenyl} - 1-(pyridin-3-ylmethyl)urea;
3-{4-[2-methylbenzene)sulfonyl]phenyl} - 1-(pyridin-3-ylmethyl)urea;
1-{4-(benzenesulfonyl)phenyl}-3-{thieno[2,3-c]pyridin-2-ylmethyl}urea;  
3-{4-[(2,4-dimethylbenzene)sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;  
3-{4-[(2,5-difluorobenzene)sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;  
3-{4-[(2-fluoro-5-methylbenzene)sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;  
1-(pyridin-3-ylmethyl)-3-{4[(benzenesulfonyl)phenyl]-1-(pyridin-3-ylmethyl)urea;  
3-{4-[(2,6-dimethylbenzene)sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;  
4-(benzenesulfonyl)-N-(pyridin-3-yl)benzamide;  
3-{4-[(4-chloro-3-methylphenyl)sulfonyl]phenyl}-3-(pyridin-3-ylmethyl)urea;  
3-(4-{[4-chloro-3-(trifluoromethyl)phenyl]sulfamoyl}phenyl)-l-(pyridin-3-ylmethyl)urea;  
3-{4-[(3,4-difluorobenzene)sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;  
N-methyl-5-{[(pyridin-3-ylmethyl)carbamoyl]amino}benzene)sulfonyl]pyridine-2-carboxamide;  
3-[(2R)-2-(methoxymethyl)pyrrolidine-1-sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;  
3-{4-[(3-fluoro-4-propoxybenzene)sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;  
3-[(3-fluoro-5-(2,2,2-trifluoroethoxy)benzene)sulfonyl]phenyl)-1-(pyridin-3-ylmethyl)urea;  
3-{4-[(4-methoxy-3-methylphenyl)sulfonyl]phenyl}-3-(pyridin-3-ylmethyl)urea;  
3-[4-[(3-fluoro-4,5-dimethylbenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;  
(2S)-N,N-dimethyl-l-[4-[(pyridin-3-ylmethyl)carbamoyl]amino]benzene)sulfonyl]pyrrolidine-2-carboxamide;
3-4-[(2-methoxyethyl) (methyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
1-4-[4-((2H)-1,3-benzenodioxol-5-yl)piperazine-1-sulfonyl]phenyl]-3-(pyridin-3-ylmethyl)urea;
3-4-[(2-methoxyphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-4-[(2-methoxyphenyl)methyl]sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-4-[(2-methoxyphenyl)methyl]sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
N-(2-fluoro-4-methylphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-4-[(2-fluoro-4-methylphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-(4-[[4-(2H)-1,3-benzenodioxol-5-yl)piperazine-1-sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-4-[[2-methoxyphenyl]methyl]sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
N-(2-methoxyphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-4-[(2-methoxyphenyl)methyl]sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
1-4-[[4-phenylphenyl)sulfamoyl]phenyl]-3-(pyridin-3-ylmethyl)urea;
3-4-[[2,4-difluorophenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-4-[[3-(dimethylsulfamoyl)benzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(4-[(2-methoxy-6-methylphenyl)sulfamoyl]phenyl)-1-(pyridin-3-ylmethyl)urea;
3-[(3-methanesulfonyl)phenyl]sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(4-chloro-2-fluorophenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
N-methyl-2-[(4-[[((pyridin-3-ylmethyl)carbamoyl]amino)benzene)sulfonfony]piperazine-1-
ylacetamide;
3-[(4-chloro-2-methoxy-5-methylphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(3-chloro-5-(trifluoromethyl)phenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(2,4-dimethylphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(2,5-dimethylphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(4-piperidine-1-sulfonyl)phenyl]-3-(pyridin-3-ylmethyl)urea;
1-[(4-[(3S)-3-cyanopiperidine-1-sulfonyl]phenyl]-3-(pyridin-3-ylmethyl)urea;
3-[(2S)-2-(methoxymethyl)pyrrolidine-1-sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
N-[[imidazo[1,2-a]pyridin-6-ylmethyl]-4-[(8-oxa-3-azabicyclo[3.2.1]octane-3-sulfonyl]benzamide;
1-[(4-[[5-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)sulfamoyl]phenyl]-3-(pyridin-3-ylmethyl)urea;
1-[(4-[[2-(morpholin-4-yl)-2-oxoethyl]piperazine-1-sulfonyl]phenyl]-3-(pyridin-3-ylmethyl)urea;
1-[(4-[(3-benzoylphenyl)sulfamoyl]phenyl]-3-(pyridin-3-ylmethyl)urea;
3-[(4-[(6-methoxy(pyridin-3-yl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(4-[(3-chloro-4-methoxyphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
N-ethyl-3-[(4-[[((pyridin-3-ylmethyl)carbamoyl]amino)benzene)sulfonfony]benzamide;
3-[(4-[[2-(methoxyethoxy)phenyl]sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(6-methoxynaphthalene-2-sulfonyl)phenyl]-1-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-[(4-[[4-(trifluoromethyl)phenyl]sulfamoyl]phenyl]urea;
3-[(4-cyclohexyl(methyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(4-[[3-methoxyphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(4-[(4-chlorophenoxy)phenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(2-ethylphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-(pyridin-3-ylmethyl)-1-[(4-[[piperidine-1-yl)carbamoyl]benzene)sulfonfony]phenyl]urea;
3-[(2-hydroxyethyl)phenyl]sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(3-chloro-2,6-dimethylphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-\{4-(2,5-dimethylphenyl)piperazine-1-sulfonylphenyl\}-1-(pyridin-3-ylmethyl)urea;
3-[4-[3-methylpiperidine-1-sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-\{4-[4-(bromophenyl)piperazine-1-sulfonyl]phenyl\}-1-(pyridin-3-ylmethyl)urea;
3-\{4-[3-methylpyridin-4-yl)sulfamoyl]phenyl\}-1-(pyridin-3-ylmethyl)urea;
3-\{4-[(5-fluoro-2-methylphenyl)sulfamoyl]phenyl\}-1-(pyridin-3-ylmethyl)urea;
1-[3-(4-difluorophenyl)methyl]-3-[4-(pyrrolidine-1-sulfonyl)phenyl]urea;
4-\{piperidine-1-sulfanyl\}phenyl N-(pyridin-3-ylmethyl)carbamate;
3-\{4-[(4-methoxyphenyl)sulfamoyl]phenyl\}-1-(pyridin-3-ylmethyl)urea;
3-\{4-[2-(3,4-dichlorophenyl)piperazine-1-sulfonyl]phenyl\}-1-(pyridin-3-ylmethyl)urea;
3-\{4-[(2S)-2-hydroxypropoxy]phenyl\}sulfamoyl]phenyl\}-1-(pyridin-3-ylmethyl)urea;
1-\{4-[3-(pyridin-3-ylmethyl)]-3-(pyridin-3-ylmethyl)urea;
3-\{4-[3-chloro-5-methylbenzene)sulfonyl]phenyl\}-1-(pyridin-3-ylmethyl)urea;
3-\{4-[4-(ethoxymethyl)benzene)sulfonyl]phenyl\}-1-(pyridin-3-ylmethyl)urea;
1-\{4-[(1-phenylcyclopentyl)sulfamoyl]phenyl\}-3-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-\{4-[(3-trifluoromethyl)piperidine-1-sulfonfyl]phenyl\}urea;
1-\{4-[3-phenylbenzene)sulfonfyl]phenyl\}-3-(pyridin-3-ylmethyl)urea;
3-\{4-[3,4-dichlorobenzene)sulfonfyl]phenyl\}-1-(pyridin-3-ylmethyl)urea;
1-\{4-[(pyridin-2-yl)sulfamoyl]phenyl\}-3-(pyridin-3-ylmethyl)urea;
(3S)-N,N-diethyl-l-\{4-[(pyridin-3-ylmethyl)carbamoyl]amino\}benzene)sulfonfyl]piperidine-3-carboxamide;
3-(pyridin-3-ylmethyl)-1-[4-(quinoline-6-sulfonfyl)phenyl]urea;
1-(4-\{[(5S,2S,4R)-bicyclo[2.2.1]heptan-2-yl)sulfamoyl]phenyl\}-3-(pyridin-3-ylmethyl)urea;
3-\{4-[(5-chloropyridin-3-yl)phenyl\}-1-[4-(piperidine-1-sulfonfyl]phenyl\}urea;
3-\{4-[4-(3-chlorophenyl)-4-cyanopiperidine-1-sulfonfyl]phenyl\}-1-(pyridin-3-ylmethyl)urea;
3-\{4-4-(methanesulfonfyl)piperazine-1-sulfonfyl]phenyl\}-1-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-\{4-[(lH-pyrrole-1-sulfonfyl]phenyl\}urea;
3-\{4-[4-(ethoxy-2-fluorophenyl)sulfamoyl]phenyl\}-1-(pyridin-3-ylmethyl)urea;
3-\{4-[4-(4-propylphenyl)sulfamoyl]phenyl\}-1-(pyridin-3-ylmethyl)urea;
3-\{4-4-(4-methoxyphenyl)piperidine-1-sulfonfyl]phenyl\}-1-(pyridin-3-ylmethyl)urea;
3-(4-\{[(4-chlorophenyl)methyl)sulfamoyl]phenyl\}-1-(pyridin-3-ylmethyl)urea;
1-\{3-(piperidine-1-sulfonfyl]phenyl\}-3-(pyridin-3-ylmethyl)urea;
3-\{4-4-(3-fluorophenoxypiperidine-1-sulfonfyl]phenyl\}-1-(pyridin-3-ylmethyl)urea;
1-\{4-[(pyridin-3-yl)sulfamoyl]phenyl\}-3-(pyridin-3-ylmethyl)urea;
3-(pyridin-3-ylmethyl)-1-[4-(thiomorpholine-4-sulfonfyl]phenyl]urea;
3-\{4-\{2-chloro-5-(trifluoromethoxy)benzene)sulfonfyl]phenyl\}-1-(pyridin-3-ylmethyl)urea;
3-(pyridin-3-ylmethyl)-1-[4-(pyrrolidine-1-sulfonfyl]phenyl\}urea;
2-methyl-N-\{3-[4-\{[(pyridin-3-}
ylmethyl)carbamoyl] amino ]benzene)sulfonyl]phenyl Jpropanamide;
1-[4-(cyclohexylsulfamoyl)phenyl]-3-(pyridin-3-ylmethyl)urea;
3-[4-(piperidine-1-sulfonfyl)phenyl]-1-[1-(pyridin-3-yl)ethyl]urea;
1-[4-[(pyridin-3-ylmethyl)carbamoyl] amino ]benzene)sulfonyl]piperidine-4-carboxamide;
3-[4-[(2-tert-butylphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-(4-[(4-methoxyphenyl)methyl]sulfamoyl]phenyl)-1-(pyridin-3-ylmethyl)urea;
3-[4-[(2-chloro-5-methylphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-(4-[(4-fluoro-3-(trifluoromethyl)phenyl)sulfamoyl]phenyl)-1-(pyridin-3-ylmethyl)urea;
1-(4-[(2-oxopyrrolidin-1-yl)methyl]piperidine-1-sulfonfyl)phenyl]-3-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-[4-[(2,4,6-trimethylphenyl)sulfamoyl]phenyl]urea;
3-[4-(piperidine-1-sulfonfyl)phenyl]-1-[2-(pyridin-3-yl)ethyl]urea;
1-[4-(4-cyclohexylpiperazine-1-sulfonfyl)phenyl]-3-(pyridin-3-ylmethyl)urea;
3-[4-[(2-chloro-4-fluorophenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-[(5-fluoro-2-methoxyphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-(methylsulfamoyl)phenyl]-1-(pyridin-3-ylmethyl)urea;
1-[4-[(2R,6S)-2,6-dimethylmorpholine-4-sulfonyl]phenyl]-3-imidazo[1,2-a]pyridin-6-ylmethyl]urea;
N-(propan-2-yl)-2-[(4-[(pyridin-3-ylmethyl)carbamoyl] amino ]benzene)sulfonfyl]piperazin-1-yljacetamide;
N,N-diethyl-2-[(4-[(pyridin-3-ylmethyl)carbamoyl] amino ]benzene)sulfonfyl]piperazin-1-yljacetamide;
3-(pyridin-3-ylmethyl)-1-[4-(quinoline-8-sulfonfyl)phenyl]urea;
1-(4-[(4-(piperidin-1-yl)phenyl)sulfamoyl]phenyl)-3-(pyridin-3-ylmethyl)urea;
3-[4-[(3,5-dichloropyridin-4-yl)piperazine-1-sulfonfyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
1-[4-(2R,6S)-2,6-dimethylmorpholine-4-sulfonyl]phenyl]-3-imidazo[1,2-a]pyridin-6-ylmethyl]urea;
N-[(3S)-1-[(4-[(pyridin-3-ylmethyl)carbamoyl] amino ]benzene)sulfonfyl]pyrrolidin-3-yl]acetamide;
3-(pyridin-3-ylmethyl)-1-[4-(quinoline-3-sulfonfyl)phenyl]urea;
3-(4-[(3-fluoro-5-(2-methylpropoxy)benzene)sulfonfyl]phenyl)-1-(pyridin-3-ylmethyl)urea;
3-(4-{4-{[4-fluorophenyl]carbonyl}piperidine-1-sulfonyl}phenyl)-1-(pyridin-3-ylmethyl)urea;
1-[4-(piperazine-1-sulfonyl)phenyl]-3-(pyridin-3-ylmethyl)urea;
3-{4-[(3S)-4-(4-methoxyphenyl)-3-methyl]piperazine-1-sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-[4-[(4-fluorophenyl)carbonyl]piperidine-1-sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-{4-[(3S)-4-(4-methoxyphenyl)-3-methyl]piperazine-1-sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-{4-[(3S)-3-(trifluoromethyl)piperidine-1-sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-{4-[methyl(oxolan-3-yl)sulfamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
1-[4-(2,3-dihydro-1-benzofuran-7-sulfonyl)phenyl]-3-(pyridin-3-ylmethyl)urea;
1-{4-[(2,3-dihydro-1,4-benzodioxin-6-sulfonyl)phenyl]-3-(pyridin-3-ylmethyl)urea;
1-{4-[4-(5-chloro-2-methylphenyl)piperazine-1-sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
1-{4-[(naphthalen-1-yl)sulfamoyl]phenyl}-3-(pyridin-3-ylmethyl)urea;
1-(4-4-[[5-((trifluoromethyl)pyridin-2-yl) methyl]sulfamoyl]phenyl]-3-(pyridin-3-ylmethyl)urea;
pyridin-3-ylmethyl N-[4-(piperidine-1-sulfonyl)phenyl]carbamate;
1-(4-[3-(piperidin-1-yl)phenyl]sulfamoyl)phenyl)-3-(pyridin-3-ylmethyl)urea;
3-(4-[2-(2-hydroxyethyl)phenyl]sulfamoyl phenyl) - 1-(pyridin-3-ylmethyl)urea;
3-benzy1-1-[4-(piperidine-1-sulfonyl)phenyl]urea;
3-[4-(2-hydroxyethyl)(methyl)sulfamoyl]phenyl) - 1-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-(4-[[4-(triﬂuoromethane)sulfonyl]phenyl]sulfamoyl phenyl)urea;
3-[4-[(4-chloro)benzene]sulfonyl]phenyl) - 1-(pyridin-3-ylmethyl)urea;
3-[4-[(3-ethanesulfonamido)benzene]sulfonyl]phenyl) - 1-(pyridin-3-ylmethyl)urea;
3-[4-(4-(4-chloro-3-methoxybenzene)sulfonyl]phenyl)-1-(pyridin-3-ylmethyl)urea;
3-[4-[(2,5-difluorophenyl)sulfamoyl]phenyl) - 1-(pyridin-3-ylmethyl)urea;
1-(4-[morpholine-4-sulfonyl]phenyl)-3-(pyridin-3-ylmethyl)urea;
3-(4-[(4-chlorophenyl)methyl]-(methyl)sulfonyl]phenyl) - 1-(pyridin-3-ylmethyl)urea;
3-[4-[methyl(2-methylpropyl)sulfonyl]phenyl) - 1-(pyridin-3-ylmethyl)urea;
3-[4-[(4-chlorophenyl)sulfamoyl]phenyl) - 1-(pyridin-3-ylmethyl)urea;
3-(4-[(1R)-1-phenylethyl]sulfonyl]phenyl) - 1-(pyridin-3-ylmethyl)urea;
3-[4-(2-chlorophenyl)piperazine-1-sulfonyl]phenyl) - 1-(pyridin-3-ylmethyl)urea;
3-[4-[(3-azatricyclo[7.3.1.0^5,10]trideca-1(13),5,7,9,11-pentaene-3-sulfonyl]phenyl) - 3-(pyridin-3-ylmethyl)urea;
3-[6-chloropyridin-3-yl)methyl]-1-[4-(piperidine-1-sulfonyl)phenyl]urea;
3-[4-[[5-methylfuran-2-yl)methyl]sulfamoyl phenyl) - 1-(pyridin-3-ylmethyl)urea;
1-(4-[2-oxo-2-(piperidine-1-yl)ethyl]piperazine-1-sulfonyl]phenyl) - 3-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-{4-(3,3,5-trimethylazepane-1-sulfonyl)phenyl}urea;
3-(4-{[3-(3,5-dimethyl-1H-pyrazol-1-yl)benzene]sulfonyl}phenyl)-1-(pyridin-3-ylmethyl)urea;
3-(4-{[3-(methoxymethyl)phenyl]sulfamoyl}phenyl)-1-(pyridin-3-ylmethyl)urea;
3-[1-propyl-1H-pyrazole-4-sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-(4-{[3-fluoro-5-(trifluoromethyl)benzene]sulfonyl}phenyl)-1-(pyridin-3-ylmethyl)urea;
1-(4-{[2-(morpholin-4-ylmethyl)benzene]sulfonyl}phenyl)-3-(pyridin-3-ylmethyl)urea;
N-[4-(pyridin-3-yl)-13-thiazol-2-yl]-4-(1,2,3,4-tetrahydroisoquinoline-2-sulfonyl)benzamide;
methyl 4-{[(pyridin-3-ylmethyl)carbamoyl]amino}benzoate;
3-(4-{[3-fluoro-5-(trifluoromethyl)benzene]sulfonyl}phenyl)-1-(pyridin-3-ylmethyl)urea;
1-(4-{[2-(propan-2-yl)phenyl]sulfamoyl}phenyl)-3-(pyridin-3-ylmethyl)urea;
3-(4-{[3-fluoro-4-(2,2,2-trifluoroethoxy)benzene]sulfonyl}phenyl)-1-(pyridin-3-ylmethyl)urea;
1-(4-{[(pyridin-3-ylmethyl)sulfamoyl]phenyl}-3-(pyridin-3-ylmethyl)urea;
N,N-diethyl-4-fluoro-3-{[4-[(pyridin-3-ylmethyl)carbamoyl]amino]benzene}sulfonyl]benzamide;
l-(4-{
{(4-(piperidine-1-sulfonyl)phenyl)sulfamoyl}phenyl}-3-(pyridin-3-ylmethyl)urea;
3-(4-{[3-fluoro-4-(2,2,2-trifluoroethoxy)benzene]sulfonyl}phenyl)-1-(pyridin-3-ylmethyl)urea;
l-[4-(dibenzylsulfamoyl)phenyl]-3-(pyridin-3-ylmethyl)urea;
(2S)-1-(4-{[(pyridin-3-ylmethyl)carbamoyl]amino}benzene)sulfonyl]pyrrolidine-2-carboxamide;
1-(4-{[3-oxa-8-azabicyclo[3.2.1]octane-8-sulfonyl]phenyl}-3-(pyridin-3-ylmethyl)urea;
1-4-{[(1H-indazol-5-yl)sulfonyl]phenyl}-3-(pyridin-3-ylmethyl)urea;
tert-butyl N-{5-[(4-piperidine-1-sulfonyl)phenyl]carbamoyl}amino)methyl]pyridin-2-yl)carbamate;
3-(4-{[2-(propan-2-yl)sulfamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{[4-(piperidine-1-sulfonyl)phenyl]sulfamoyl}phenyl]-3-(pyridin-3-ylmethyl)urea;
3-(4-{(2,2-dimethylpropyl)sulfamoyl}phenyl)-1-(pyridin-3-ylmethyl)urea;
l-{4-(2,4-dichlorophenyl)sulfamoyl}phenyl]-1-(pyridin-3-ylmethyl)urea;
N,N-diethyl-3-fluoro-5-{[4-{[(pyridin-3-ylmethyl)carbamoyl]amino}benzene}sulfonyl]benzamide;
3-{[4-(3-methanesulfonamidobenzene)sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
N,N-diethyl-3-fluoro-5-{[4-{[(pyridin-3-ylmethyl)carbamoyl]amino}benzene}sulfonyl]benzamide;
N,N-diethyl-3-fluoro-5-{[4-{[(pyridin-3-ylmethyl)carbamoyl]amino}benzene}sulfonyl]benzamide;
3-(4-{(2-[2-(propan-2-yl)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-(3-methanesulfonamidobenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
N,N-diethyl-3-fluoro-5-{[4-{[(pyridin-3-ylmethyl)carbamoyl]amino}benzene}sulfonyl]benzamide;
3-(4-{(2-[2-(propan-2-yl)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
1-(4-{[4-(3,3,5-trimethylazepane-1-sulfonoyl)phenyl]-1-(pyridin-3-ylmethyl)urea;
3-(4-[(4-fluorophenyl)methyl]sulfamoyl)phenyl)-1-(pyridin-3-ylmethyl)urea;
3-(4-[(4-ethoxyphenyl)sulfamoyl]phenyl)-1-(pyridin-3-ylmethyl)urea;
3-(4-[benzyl(propan-2-yl)sulfamoyl]phenyl)-1-(pyridin-3-ylmethyl)urea;
3-[(4-dimethylamino)phenyl)methyl]sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-[(benzyl(ethyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(4-acetylphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
1-[4-(4-[[2(R)-oxolan-2-yl]carbonyl]piperazine-1-sulfonyl]phenyl]-3-(pyridin-3-ylmethyl)urea;
2-methyl-N-[1-(4-[[4-(3-chloro-4-methylbenzene)sulfonyl]phenyl]-3-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-(4-[[4-(trifluoromethoxy)phenyl)sulfamoyl]phenyl)urea;
3-(pyridin-3-ylmethyl)-1-(4-[[4-(pyrrolidin-1-yl)phenyl)sulfamoyl]phenyl)urea;
3-(4-[(3-chlorophenyl)methyl]sulfamoyl]phenyl)-1-(pyridin-3-ylmethyl)urea;
3-(4-[(3-ethanesulfonyl)benzene]sulfonyl)phenyl)-1-(pyridin-3-ylmethyl)urea;
3-[4-[(4-hydroxypiperidine-1-sulfonyl)phenyl]-1-(pyridin-3-ylmethyl)urea;
3-(4-[(3-hydroxymethyl)phenyl]sulfamoyl]phenyl)-1-(pyridin-3-ylmethyl)urea;
3-[4-[(3-acetylphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-[(3- ethoxyphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
4-fluoro-N-(propan-2-yl)-3-[(4-[[pyridin-3-ylmethyl]carbamoyl]amino]benzene)sulfonyl]piperidin-4-ylpropanamide;
1-(pyridin-3-ylmethyl)-3-(4-[(4-(trifluoromethoxy)phenyl)sulfamoyl]phenyl)urea;
3-(pyridin-3-ylmethyl)-1-(4-[(4-(pyrrolidin-1-yl)phenyl)sulfamoyl]phenyl)urea;
3-(4-[(3-chlorophenyl)methyl]sulfamoyl]phenyl)-1-(pyridin-3-ylmethyl)urea;
3-(4-[(3-ethanesulfonyl)benzene]sulfonyl)phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-[(4-hydroxypiperidine-1-sulfonyl)phenyl]-1-(pyridin-3-ylmethyl)urea;
3-(4-[(3-hydroxymethyl)phenyl]sulfamoyl]phenyl)-1-(pyridin-3-ylmethyl)urea;
3-[4-[(3-acetylphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-[(3-ethoxyphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
4-fluoro-N-(propan-2-yl)-3-[(4-[[pyridin-3-ylmethyl]carbamoyl]amino]benzene)sulfonyl]benzamide;
3-[4-[(4-[(3-chlorophenyl)-4-hydroxypiperidine-1-sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-[(3S)-3-methyl-4-(3-methylphenyl)piperazine-1-sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(4-chloro-3-methoxybenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-[(2,3-dimethylphenyl)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-[(2,3-dichlorophenyl)piperazine-1-sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
1-[4-[(4-benzylpiperidine-1-sulfonyl)phenyl]-3-(pyridin-3-ylmethyl)urea;
1-(4-[(4-phenylphenyl)methyl]sulfamoyl]phenyl)-3-(pyridin-3-ylmethyl)urea;
3-(pyridin-3-ylmethyl)-1-[4-[[5,6,7,8-tetrahydronaphthalen-1-yl)sulfamoyl]phenyl]urea;
rel-3-[4-[(2R,6S)-2,6-dimethylmorpholine-4-sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
1-[4-[(decahydroquinoline-1-sulfonyl)phenyl]-3-(pyridin-3-ylmethyl)urea;
3-[4-[(4-fluoro-2-methoxyphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
1-[4-[(4-ethylphenyl)sulfamoyl]phenyl]-3-(pyridin-3-ylmethyl)urea;
3-[4-[(3-chloro-4-methylbenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-[(2-chloro-4,6-dimethylphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-[(3-fluoro-4-(trifluoromethoxy)benzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
1-[4-[(2R)-2-benzylpiperidine-1-sulfonyl]phenyl]-3-(pyridin-3-ylmethyl)urea;
3-[4-(piperidine-1-sulfonyl)phenyl]-1-(pyrazin-2-ylmethyl)urea;
3-{4-[(4-fluoro-3-methylbenzene)sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
1-[4-[(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)sulfamoyl]phenyl]-3-(pyridin-3-ylmethyl)urea;
3-{4-[4-(diethylamino)piperidine-1-sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-[4-(fluorophenyl)(methyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-(2-methylpyridine-3-sulfonyl)phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-[4-(4-propyl)phenyl)sulfinyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-(3-fluoro-5-methoxybenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[3-(5-fluoro-4-methanesulfonylpiperidine-1-sulfonyl)phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[imidazo[1,2-a]pyridin-6-ylmethyl]-1-(4-[(3-oxa-8-azabicyclo[3.2.1]octane-8-yl)methyl]urea;
3-[4-(2-methylpyridine-3-sulfonyl)phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[(5-chloro-2-methylphenyl)sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-(pyridin-3-ylmethyl)-1-[4-[(3-methanesulfonylbenzene)sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[(4-fluoro-3-methylbenzene)sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
rel-3-{4-[(4aR,8aS)-decahydroisoquinoline-2-sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-[4-(4-methanesulfonyl)piperidine-1-sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-(pyridin-3-ylmethyl)-1-[4-{[(2S)-2-(pyrrolidin-1-yl)methyl]pyrrolidin-1-sulfonyl]phenyl}Jurea;
3-[4-[(6-methylpyridin-2-yl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-{3-(2-chloro-4-fluorophenoxy)piperidine-1-sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-[4-chloro-3-(trifluoromethyl)phenyl]piperazine-1-sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-{4-(2-methylpropoxy)benzene)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-{4-(4-fluorophenyl)methyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[2-methyl(phenyl)benzene)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-(1-methyl-1H-indazole-5-sulfonyl)phenyl]-1-(pyridin-3-ylmethyl)urea;
1-[4-[(3-benzoxy)phenyl]sulfamoyl]phenyl]-3-(pyridin-3-ylmethyl)urea;
3-(pyridin-3-ylmethyl)-1-(4-{[(3-pyrrolidin-1-yl)sulfamoyl]phenyl}urea);
3-[4-[(4-ethoxy-3-fluorophenoxy)piperidine-1-sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[3,5-dichlorobenzene)sulfonfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[4-(3,4-dimethylphenyl)piperazine-1-sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-{4-[(3-trifluoromethyl)phenyl]sulfamoyl]phenyl}urea);
3-[4-[(4-fluorophenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-{4-methoxymethoxybenzene)sulfonfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[3-methoxy-4-methylbenzene)sulfonfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-(6-methyl)pyridine-3-sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-(pyridin-3-ylmethyl)-1-[4-{5,6,7,8-tetrahydro-1,6-naphthyridine-6-sulfonyl]phenyl}urea;
3-[4-{2,4-dimethoxypyrimidine-5-sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-[4-{5-methoxy-2-methylphenyl]sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-{4-(propan-2-yl)phenyl]sulfamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-[4-{5-chloro-2-methylphenyl]sulfamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-[(2-fluorophenyl)methyl]-1-{4-(piperidine-1-sulfonyl)phenyl}urea;
3-[(4-(2H-pyrazol-1-yl)benzene)sulfonyl]phenyl]urea;
1-{4-[(4-fluoro-3-methoxybenzene)sulfonyl]phenyl}urea;
3-(4-{(2-acetylphenyl)sulfamoyl}phenyl)-1-(pyridin-3-ylmethyl)urea;
1-{(3S)-3-methylpiperidine-1-sulfonyl}phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[4-(4-(5-methylpyrimidin-2-yl)piperazine-1-sulfamoyl]phenyl}urea;
3-{(2-acetylpiperazine-1-sulfamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-[4-(4-methylphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{2-(4-bromo-3-methoxybenzene)sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-[4-(2-oxo-2,3-dihydro-1H-indol-1-yl)piperidine-1-sulfamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-[4-(3,4-dichlorophenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
1-{[2-(trifluoromethoxy)phenyl]urea;
3-[4-(5-methyl-4-(3,5-dichloro-4-(trifluoromethyl)phenyl]sulfonyl]phenyl}urea;
3-{(2H-1,3-benzodioxole-4-sulfamoyl]phenyl}urea;
1-{6-isocyanopyridin-3-ylmethyl]-3-[4-(piperidine-1-sulfamoyl]phenyl}urea;
3-(4-{[[2-(3-chlorophenyl)ethyl[methyl)sulfamoyl]phenyl}urea;
1-{[4-(2H-1,3-benzodioxole-4-sulfamoyl]phenyl}urea;
3-[(4-methylphenyl)methylsulfamoyl]phenyl}urea;
1-{4-(3-fluoropyridin-3-ylmethyl)sulfamoyl]phenyl}urea;
3-[(2-fluorophenyl)methyl]-1-{4-(pyridin-3-ylmethyl)sulfamoyl]phenyl}urea;
3-[4-(2-fluorophenoxoxy)pyridin-3-yl]sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
1-{4-{[(4-methylphenyl)sulfamoyl]phenyl}]-3-(pyridin-3-ylmethyl)urea;
1-{[4-(1H-pyrazol-1-yl)benzene)sulfonyl]phenyl}urea;
1-{4-[((2-oxo-2,3-dihydro-1H-indol-1-yl)piperidine-1-sulfamoyl]phenyl}urea;
1-{[4-(5-fluoropyridine-3-sulfonyl)phenyl]-1-(pyridin-3-ylmethyl)urea;
3-(4-{[(2-fluorophenyl)methyl]-1-(pyridin-3-ylmethyl)sulfamoyl]phenyl}urea;
1-{4-[4-(azepane-1-yl)piperidine-1-sulfonyl]phenyl}]-3-(pyridin-3-ylmethyl)urea;
3-{4-[(4-fluoro-3-methoxybenzene)sulfonyl]phenyl}urea;
3-[(3-chloro-4-(trifluoromethyl)benzene]sulfonyl]phenyl}urea;
1-{4-{[(4-methylphenyl)sulfamoyl]phenyl}]-1-(pyridin-3-ylmethyl)urea;
1-(4-{2-oxa-8-azaspiro[4.5]decane-8-sulfonoyl}phenyl)-3-(pyridin-3-ylmethyl)urea;
1-{4-[4-(2-phenylacetyl)piperazine-1-sulfonoyl]phenyl}-3-(pyridin-3-ylmethyl)urea;
1-{4-[4-(3-phenylprop-2-en-1-yl)piperazine-1-sulfonoyl]phenyl}-3-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-{4-[3-sulfamoylbenezene)sulfonoyl]phenyl} urea;
N-methyl-2-{4-[(pyridin-3-ylmethyl)carbamoyl]amino}benzene)sulphonamido]benzamide;
3-{4-[(4-(propan-2-yloxy)phenyl]sulfamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-[2-hydroxyethyl](propan-2-yl) sulfamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
1-{4-[adamantan-1-y]sulfamoyl]phenyl}-3-(pyridin-3-ylmethyl)urea;
1-{4-[2(R)-2-(morpholin-4-yl)carbamoyl]amino}benzene)sulfonamido]benzamide;
3-(4-[(4-fluoro-3-methylphenyl)sulfamoyl]phenyl)-1-(pyridin-3-ylmethyl)urea;
3-[(4-[4-(3-methylpiperazine-1-sulfonoyl]phenyl)-1-(pyridin-3-ylmethyl)urea;
3-{4-[2-fluoro-5-methylphenyl]sulfamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
N-3-[(4-[(pyridin-3-ylmethyl)carbamoyl]amino]benzene)sulfonamido]benzamide;
N-methyl-3-[(4-[(pyridin-3-ylmethyl)carbamoyl]amino]benzene)sulfonamido]benzamide;
3-{4-[4-(4-chlorophenyl)-4-cyanopiperidine-1-sulfonoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-[4-methyl-3-(trifluoromethyl)phenyl]sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
1-[4-(4-piperidine-1-sulfonoyl]phenyl]-3-(pyridin-3-ylmethyl)urea;
3-[(3-acetylbenzene)sulfonoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[4-(methoxymethyl)piperidine-1-sulfonoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-fluoro-N,N-dimethyl-5-[(4-[(pyridin-3-ylmethyl)carbamoyl]amino]benzene)sulfonoyl]benzamide;
N-[2-(pyridin-3-yl)ethyl]-4-{[3-(trifluoromethoxy)phenyl]sulfamoyl]benzamide;
3-{4-[4-(3,4-dichlorophenyl)piperazine-1-sulfonoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-[(4-fluoro-3-methoxyphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[2-fluoro-5-(trifluoromethyl)phenyl]sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[(propan-2-yl)phenyl]methyl]piperazine-1-sulfonoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-{4-[4-(3-trifluoromethyl)phenyl]piperazine-1-sulfonoyl]phenyl]urea;
1-{4-[cyclopropylsulfamoyl]phenyl}-3-(pyridin-3-ylmethyl)urea;
4-{[5-chloro-2-methoxyphenyl]sulfamoyl]N-[2-(pyridin-3-yl)ethyl]benzamide;
3-{4-[(3-amino phenyl)(methanesulfonyl)sulfamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
1-{4-[(2,3-dihydro-1H-inden-5-yl)sulfamoyl]phenyl}-3-(pyridin-3-ylmethyl)urea;
3-[4-[3-chloro-4-(morpholin-4-yl)phenyl]sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[2-(dimethylamino)pyrimidine-5-sulfonoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[4-{1-(3-methoxyphenyl)-4-methylcyclohexyl]piperazine-1-sulfonoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[(5-ethylpyridin-2-yl)methyl]sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;

154
3-{4-[(3-chloro-4-propoxybenzene)sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-[(4-chloronaphthalen-1-yl)sulfamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-[(5-acetyl-2-methoxybenzene)sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-[(5-chloro-2-methoxyphenyl)sulfamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
1-{4-[(IR)-3-oxo-3H-spiro[2-benzofuran-1',3'-pyrrolidine]-1'-ylsulfonyle]phenyl}-3-(pyridin-3-
ymethyl)urea;
3-{4-[4-(2,4-dimethoxyphenyl)piperazine-1-sulfonyle]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-(piperidine-1-sulfonyle)phenyl]methyl}-1-(pyridin-3-yl)urea;
N-N-diethyl-2-((pyridin-3-ylmethyl)carbamoyl)amino)benzenesulfonamido]benzamide;
3-{4-[(3-ethylbenzene)sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-[4-(4-chloro-2-oxo-2-(pyrrol-1-yl)ethyl]piperazine-1-sulfonyle]phenyl)-3-(pyridin-3-
ymethyl)urea;
1-[(4-[(4-(2-oxopyrrolidin-1-yl)methyl)piperidine-1-sulfonyle]phenyl)-3-(pyridin-3-ylmethyl)urea;
3-(4-[(2-piperidine-1-yl)-5-(trifluoromethyl)phenyl]sulfamoyl]phenyl)-1-(pyridin-3-
ymethyl)urea;
3-(4-[(2-methoxy-5-(trifluoromethyl)pyridin-2-yl]piperazine-4-sulfamoyl]phenyl)
3-(2-methylpropyl)piperazine-1-sulfonyle]phenyl)-3-(pyridin-3-ylmethyl)urea;
1-[(4-[(2-oxo-2-(pyrrolidin-1-yl)ethyl]piperazine-1-sulfonyle]phenyl)-3-(pyridin-3-
ymethyl)urea;
1-(pyridin-3-ylmethyl)-3-{4-(4-sulfamoylphenyl)sulfamoyl]phenyl Jurea;
5-[(4-(piperidine-1-sulfonyle)phenyl]carbamoyl]amino)methyl]pyridine-2-carboxamide;
3-(4-[(4-(4-methylmorpholin-4-yl)pyridin-2-yl)piperazine-1-sulfonyle]phenyl)-1-(pyridin-3-
ymethyl)urea;
3-(4-[(azetidine-1-sulfonyle]phenyl)-1-(pyridin-3-ylmethyl)urea;
3-(pyridin-3-ylmethyl)-1-(4-[(2-[lH-pyrrol-1-yl)phenyl]sulfamoyl]phenyl)urea;
3-(4-[(4-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperazine-1-sulfonyle]phenyl)-1-(pyridin-3-
ymethyl)urea;
N,N-diethyl-2-((pyridin-3-ylmethyl)carbamoyl]amino)benzenesulfonamido]benzamide;
1-[(4-(piperidine-1-yl)carbonyl]phenyl]-3-(pyridin-3-ylmethyl)urea;
N-ethyl-N-[(3S)-1-[(4-[(pyridin-3-ylmethyl)carbamoyl]amino)benzene)sulfonyle]pyrrolidin-3-
yl acetamide;
3-(pyridin-3-ylmethyl)-1-(4-(pyrimidin-2-yl)piperazine-1-sulfonyle]phenyl Jurea;
3-{4-[(3-ethylbenzene)sulfonyle]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[(3-chloro-2-(morpholin-4-yl)pyridine-4-sulfonyle]phenyl)-1-(pyridin-3-ylmethyl)urea;
3-(pyridin-3-ylmethyl)-1-(4-{[(lS,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl]sulamoyl}phenyl)urea;
3-{4-[(fluoro-3-methylphenyl)sulamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-[(2-phenylpropan-2-yl)sulamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-[1-{(4R)-1-(4-chlorophenyl)ethyl]piperazine-1-sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-[(5-chloropyridine-3-sulfonyl)phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{3-fluorophenyl)methyl]-1-{4-(piperidine-1-sulfonyl)phenyl}urea;
3-{4-[(4-cyano-4-(4-methylphenyl)piperidine-1-sulfonyl)phenyl}-1-(pyridin-3-ylmethyl)urea;
1-{4-{(3-phenoxyphenyl)sulamoyl]phenyl}-3-(pyridin-3-ylmethyl)urea;
3-{4-[(2,5-dimethoxyphenyl)sulamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-[(3-fluoro-5-methylbenzene)sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-[(2-methoxy-5-methylphenyl)sulamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-(pyridin-3-ylmethyl)-1-{4-[(pyridin-3-ylmethyl)sulamoyl]phenyl}urea;
3-{4-[(3-methylphenyl)sulamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-(4-{4-(4-fluorophenyl)methyl][methyl)sulamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-(pyridin-3-ylmethyl)-1-{4-[(3S)-3-(pyrrolidin-1-yl)carbonyl]piperidine-1-sulfonyl]phenyl}urea;
3-{4-[(3-bromophenyl)sulamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
1-{4-[(4-fluorophenyl)methyl]-(4-chlorophenyl)ethyl]piperazine-1-sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
N,N-dimethyl-4-{4-[(pyridin-3-ylmethyl)carbamoyl]aniino]benzene}sulfonamido]benzamide;
1-{4-[(4-phenylbenzene)sulfonyl]phenyl}-3-(pyridin-3-ylmethyl)urea;
3-{4-{3,5-dimethylphenyl}sulamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-[(4-methylphenyl)piperazine-1-sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-[(4-acetyl-1,4-diazepe-1-sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
N-cyclopentyl-3-{4-[(pyridin-3-ylmethyl)carbamoyl]amiino]benzene}sulfonyl]benzamide;
3-{4-[(3,3-difluoroazetidine-1-sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
1-{4-{4-(methyl)benzene}sulfonyl]phenyl}-3-(pyridin-3-ylmethyl)urea;
3-{4-{[(lS)-1-hydroxyethyl]phenyl}sulamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[(3,5-difluorophenyl)sulamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-[(3,5-dimethoxyphenyl)sulamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-{ethyl(phenyl)sulamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-{4-[(2-trifluoromethyl)phenyl]sulamoyl]phenyl)urea;
3-{4-{3-(5-methyl-1,3,4-oxadiazol-2-yl)benzene}sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-{[(lS)-1-hydroxyethyl]phenyl}sulamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-{4-{3-methoxy-2-methylphenyl}sulamoyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
4-[(3-chlorophenyl)sulfamoyl]-N{-imidazo[l,2-a]pyridin-6-ylmethyl}benzamide;
3-[(4-tert-butyl-2-chlorophenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
1-(4-{8-azabicyclo[3.2.1]octane-8-sulfonyl}phenyl)-3-(pyridin-3-ylmethyl)urea;
1-[4-(cyclopentylsulfamoyl)phenyl]-3-(pyridin-3-ylmethyl)urea;
3-(4-{4-[4-(4-chlorophenyl)piperazine-1-sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
3-(4-{4-[2-(diethylamino)ethyl]methyl}sulfamoyl)phenyl]-1-(pyridin-3-ylmethyl)urea;
1-(4-{8-oxa-3-azabicyclo[3.2.1]octane-3-sulfonyl}phenyl)-3-(pyridin-3-ylmethyl)urea;
1-{4-[4-(4-acetylphenyl)piperazine-1-sulfonyl]phenyl}-1-(pyridin-3-ylmethyl)urea;
1-{4-[4-(3,4-dimethoxyphenyl)sulfamoyl]phenyl]-3-(pyridin-3-ylmethyl)urea;
1-(4-{4-[2-(difluoromethoxy)phenyl]sulfamoyl}phenyl)-3-(pyridin-3-ylmethyl)urea;
1-(4-{4-[3-(cyclopentylmethoxy)phenyl]sulfamoyl}phenyl)-3-(pyridin-3-ylmethyl)urea;
3-(4-[(3-methoxyphenyl)methyl]sulfamoyl)phenyl]-1-(pyridin-3-ylmethyl)urea;
3-[(4-(2,3-dihydro-1H-indole-1-sulfonyl)phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[4-acetylbenzene)sulfonamido]benzene)sulfonylamino]benzene)urea;
3-{4-[4-(2-chlorophenyl)methyl]sulfamoyl}phenyl]-1-(pyridin-3-ylmethyl)urea;
3-(4-{4-[2-fluorophenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[4-(difluoromethoxy)phenyl]sulfamoyl}phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[4-(3,5-dimethyl-1,2-oxazol-4-yl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
1-(pyridin-3-ylmethyl)-3-(4-{4-[5-(trifluoromethyl)pyridin-2-yl]piperazine-1 - sulfonamidol)urea;
3-{4-[4-(2,3-dihydro-1H-indole-1-sulfonyl)phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[4-acetylbenzene)sulfonamido]benzene)sulfonylamino]benzene)urea;
3-{4-[4-(2-fluoromethoxy)phenyl]sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[4-(cyanophenyl)sulfamoyl]phenyl]-3-(pyridin-3-ylmethyl)urea;
3-{4-[4-(3-fluoro-2-methylphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[4-(3-chloro-4-methylphenyl)sulfamoyl]phenyl]-1-(pyridin-3-ylmethyl)urea;
3-{4-[4-(3-fluorophenyl)ethyl](methyl)amino]piperidin-1-ylsulfonamido)urea;
1-(pyridin-3-ylmethyl)urea;
3-{4-[4-(2-methoxyethyl)(methyl)amino]piperidin-1-ylsulfonamido)urea;
1-(pyridin-3-ylmethyl)urea;
3-(pyridin-3-ylmethyl)-1-(4-[(2-(pyrrolidin-1-yl)phenyl)sulfamoyl]phenyl)urea；
3-([3-methoxy-4-methylphenyl]sulfamoyl]phenyl)-1-(pyridin-3-ylmethyl)urea；
3-([2-(4-nitrophenyl)piperazine-1-sulfonyl]phenyl)-1-(pyridin-3-ylmethyl)urea；
3-([2-chloro-4-fluorophenyl]piperidine-1-sulfonyl]phenyl)-1-(pyridin-3-ylmethyl)urea；
3-([4-(4-oxa-3-azabicyclo[3.2.1]octane-3-sulfonyl]phenyl]-1-(pyridin-3-ylmethyl)urea；
3-([2-(2-hydroxyethoxy)phenyl]sulfamoyl]phenyl)-1-(pyridin-3-ylmethyl)urea；
3-([2,6-dimethylmorpholine-4-sulfonyl]phenyl)-1-(pyridin-3-ylmethyl)urea；
3-([4-fluoro-2-methoxybenzene)sulfonyl]phenyl)-1-(pyridin-3-ylmethyl)urea；
3-([2-bromophenyl)sulfamoyl]phenyl)-1-(pyridin-3-ylmethyl)urea；
3-([3,4-dimethylphenyl)sulfamoyl]phenyl)-1-(pyridin-3-ylmethyl)urea；
3-([2-(iodophenyl)sulfamoyl]phenyl)-1-(pyridin-3-ylmethyl)urea；
3-([3,4-dimethylphenyl)sulfamoyl]phenyl)-1-(pyridin-3-ylmethyl)urea；
N-[(3-(trifluoromethoxy)phenyl)sulfamoyl]benzamide；
and
4-[(5-chloro-2-methoxyphenyl)sulfamoyl]N-[(imidazo[1,2-a]pyridin-6-ylmethyl]benzamide or a pharmaceutically acceptable salt thereof.

[0294] In some other embodiments, the Nampt small molecule antagonist can further be chosen from the following compounds of Formula IB:
wherein:

Ar is aryl or heteroaryl, each of said aryl and heteroaryl being either unsubstituted or optionally independently substituted with 1, 2, 3 or 4 substituents which can be the same or different and are independently selected from the group consisting of:

deuterium, halo, cyano, amino, aminoalkyl-, (amino)alkoxy-, -CONH2, -C(0)NH(alkyl), -C(0)N(alkyl)2, -C(0)NH(aryl), -C(0)N(aryl)2, -CH2F3, -OCH2F3, -alkyl, -alkenyl, -alkynyl, -alkoxy, (alkoxyalkyl)amino-, -N(R3)-C(0)-alkyl, -N(R3)-C(0)-aryl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

R1 is -NR2R3, wherein R² is H, alkyl or -S(0)2alkyl and R³ is alkyl, hydroxyalkyl, -S(0)2alkyl, -(CH2)q cycloalkyl, -(CH2)d heterocycloalkyl, aryl, arylalkyl-, -(CH2)d heteroaryl; cycloalkyl;

erterocycloalkyl;

aryl;

heteroaryl;

each of said cycloalkyl, heterocycloalkyl, aryl, or heteroaryl is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents which can be the same or different and are independently selected from the group consisting of:

deuterium, halo, cyano, alkyl, hydroxyl, hydroxyalkyl, hydroxyalkoxy, cyanoalkyl, haloalkyl, alkenyl, alkynyl, alkoxy, alkylalkoxy, haloalkoxy, arylalkenyl-, aryloxy, benzyloxy, oxo, -(CH2)q-NR2R3, -(CH2)d-CONR2R3, -S(0)2alkyl, -S(0)2aryl, S(0)2NH2, -S(0)2NH-alkyl, -S(0)2N(alkyl)2, -S(0)2 heterocycloalkyl, -S(0)2CF3, -C(0)alkyl, -C(0)aryl, -C(0)alkylenylaryl, -C(0)0-alkyl, -NH-C(0)alkyl, -NH-C(0)aryl, methylenedioxy, -(CH2)d cycloalkyl, cycloalkylalkoxy-, aryl, arylalkyl-, -(CH2)d heteroaryl, and -(CH2)d heterocycloalkyl,

wherein each of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted by one or more halo, nitro, haloalkyl, haloalkoxy, oxo, cyano, alkyl, haloalkyl, or alkoxy and;

R² and R³ are independently selected from the group consisting of H, alkyl, hydroxyalkyl, alkoxy, aryl, arkoxyalkyl, -S(0)2alkyl and cycloalkyl or R² and R³ can form a 5 or 6 membered heterocycloalkyl group together with the nitrogen atom to which they are attached, wherein said heterocycloalkyl group may contain one or more addional heteroatom(s) selected from N, S or O;

z is 0, 1 or 2;

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

and pharmaceutically acceptable salts thereof.
In some embodiments, the Nampt small molecule antagonist can further be chosen from Nampt antagonists selected from the group consisting of:

(2E)-N-(4-{[3-fluoro-5-(2-methylpropoxy)benzene]sulfonyl}phenyl)-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[3-fluoro-4-propoxybenzene]sulfonyl}phenyl]-3-(pyridin-3-yl)prop-2-enamide;
4-(phenoxathiine-4-sulfonyl)phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[2,5-dichlorobenzene]sulfonyl}phenyl]-3-(pyridin-3-yl)prop-2-enamide;
N-ethyl-3-{4-(2E)-3-(pyridin-3-yl)prop-2-enamido}benzene]sulfonyl]benzamide;
4-(2H-1,3-benzodioxole-5-sulfonyl)phenyl]-3-(pyridin-3-yl)prop-2-enamide;
4-(2,3-dihydro-1-benzofuran-7-sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-[4-(4-fluoro-3-methylbenzene)sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[4-chlorobenzene]sulfonyl}phenyl]-3-(pyridin-3-yl)prop-2-enamide;
N-ethyl-4-(4-(2E)-3-(pyridin-3-yl)prop-2-enamido]benzene]sulfonyl]benzamide;
(2E)-N-{4-[3-chloro-4-propoxybenzene]sulfonyl}phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[3-(IH-pyrazol-1-yl)benzene]sulfonyl}phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[5-chloro-2-ethoxybenzene]sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
4-(1-methyl-1H-indazole-6-sulfonyl)phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[3-chloro-4-methoxybenzene]sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-3-(pyridin-3-yl)-N-{4-[4-(trifluoromethyl)benzene]sulfonyl]phenyl]prop-2-enamide;
(2E)-3-(pyridin-3-yl)-N-{4-[3-(trifluoromethoxy)benzene]sulfonyl]phenyl]prop-2-enamide;
(2E)-N-{4-[2-methoxy-5-(propan-2-yl)benzene]sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[3-chloro-5-(trifluoromethyl)benzene]sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
4-{(1H-indole-7-sulfonyl)phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-3-(pyridin-3-yl)-N-{4-[5-(pyrrolidin-1-yl)pyridine-3-sulfonyl]phenyl]prop-2-enamide;
(2E)-N-{4-[3-chloro-5-(trifluoromethyl)benzene]sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
4-(1-methyl-1H-indole-2-sulfonyl)phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-3-(pyridin-3-yl)-N-{4-[5-(pyrrolidin-1-yl)pyridine-3-sulfonyl]phenyl]prop-2-enamide;
(2E)-N-{4-[3-chloro-5-(trifluoromethyl)benzene]sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
4-(6-methoxynaphthalene-2-sulfonyl)phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[4-ethoxy-3-fluorobenzene] sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[3-fluoro-5-methylbenzene]sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(3,4-dimethoxybenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(4-morpholin-4-yl)piperidine-1-sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-3-(pyridin-3-yl)-N-[4-(quinoline-3-sulfonyl)phenyl]prop-2-enamide;
(2E)-N-{4-[2-chloro-5-(trifluoromethoxy)benzene]sulfonyl}phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(4-phenylbenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(3-fluorobenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(3-methylbenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(3,5-dimethoxybenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
4-(5-methoxypyridine-3-sulfonyl)phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(3-chlorobenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(3-methanesulfonamidobenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(4-phenylbenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(3-chloro-5-(trifluoromethoxy)benzene) sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(3,4-dimethoxybenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(3-chloro-5-methoxybenzene) sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(3-methanesulfonamidobenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(4-phenylbenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(3-chlorobenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(3-chloro-5-methoxybenzene) sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(3-methanesulfonamidobenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
4-(5-methoxypyridine-3-sulfonyl)phenyl]-3-(pyridin-3-yl)prop-2-enamide;
4-(benzenesulfonamide)benzene]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(4-methoxy-3-methylbenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
4-(benzenesulfonamide)benzene]-3-(pyridin-3-yl)prop-2-enamide;
N-cyclopentyl-3-(pyridin-3-yl)-N-[4-[(2E)-3-(pyridin-3-yl)prop-2-enamido] benzene ]sulfonamide benzamide;
4-(benzenesulfonamide)benzene]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(4-methoxy-3-methylbenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
4-(benzenesulfonamide)benzene]-3-(pyridin-3-yl)prop-2-enamide;
N-cyclopentyl-3-(pyridin-3-yl)-N-[4-[(2E)-3-(pyridin-3-yl)prop-2-enamido] benzene ]sulfonamide benzamide;
(2E)-N-{4-[(3-methanesulfonamidobenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(2-morpholin-4-yl)pyridine-3-sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-3-(pyridin-3-yl)-N-[4-[(2-trifluoromethoxy)phenyl]sulfamoyl]phenyl]prop-2-enamide;
4-(5-methoxypyridine-3-sulfonyl)phenyl]-3-(pyridin-3-yl)prop-2-enamide;
4-(isoquinoline-4-sulfonyl)phenyl]-3-(pyridin-3-yl)prop-2-enamide;
N-(propan-2-yl)-3-(pyridin-3-yl)-N-[4-[(2E)-3-(pyridin-3-yl)prop-2-enamido] benzene ]sulfonamide benzamide;
4-(5-methoxypyridine-3-sulfonyl)phenyl]-3-(pyridin-3-yl)prop-2-enamide;
4-((1-benzothiophene-7-sulfonyl)phenyl ]-3-(pyridin-3-yl)prop-2-enamide;
3-chloro-N,N-diethyl-5-(pyridin-3-yl)prop-2-enamide benzene ]sulfonamide benzamide;
(2E)-N-{4-[(4-methoxy-3-methylbenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
4-(benzenesulfonamide)benzene]-3-(pyridin-3-yl)prop-2-enamide;
N-cyclopentyl-3-(pyridin-3-yl)-N-[4-[(2E)-3-(pyridin-3-yl)prop-2-enamido] benzene ]sulfonamide benzamide;
(2E)-N-{4-[(3-methanesulfonamidobenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(2-morpholin-4-yl)pyridine-3-sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-3-(pyridin-3-yl)-N-[4-[(2-trifluoromethoxy)phenyl]sulfamoyl]phenyl]prop-2-enamide;
N-(propan-2-yl)-3-(pyridin-3-yl)-N-[4-[(2E)-3-(pyridin-3-yl)prop-2-enamido] benzene ]sulfonamide benzamide;
(2E)-3-(pyridin-3-yl)-N-[4-[(3-trifluoromethyl)benzene] sulfonyl ]phenyl]prop-2-enamide;
4-(1-benzothiophene-7-sulfonyl)phenyl ]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(2-dimethylamino)pyrimidine-5-sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(4-ethoxybenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-{4-[(3-fluoro-4-methylbenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
4-(IH-indole-4-sulfonyl)phenyl ]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-[4-[benzenesulfonyl]phenyl]methyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-3-(pyridin-3-yl)-N-[4-(quinoline-8-sulfonyl)phenyl]prop-2-enamide ;
(2E)-N-(4-[(2-methoxy-5-(trifluoromethoxy)benzene)sulfonyl]phenyl)-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N- [4-(3-ethoxybenzene)sulfonyl]phenyl ]-3-(pyridin-3-yl)prop-2-enamide;
4-(5-methylthiophene-2-sulfonyl)phenyl ]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N- [4-[(4-chloro-3-methoxybenzene)sulfonyl]phenyl ]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-(4-[(2-methoxy-4-(trifluoromethyl)benzene)sulfonyl]phenyl)-3-(pyridin-3-yl)prop-2-enamide;
N-(2-methylpropyl)-3-(4-[(2E)-3-(pyridin-3-yl)prop-2-enamido]benzene)sulfonamide;  
N-cyclopropyl-3-(4-[(2E)-3-(pyridin-3-yl)prop-2-enamido]benzene)sulfonamide;
(2Z)-N-[4-(benzenesulfonyl)]phenyl]-2-fluoro-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-[4-[(3-fluoro-5-methoxybenzene)sulfonyl]phenyl ]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-(4-[(2-methyl-4-(trifluoromethyl)benzene]sulfonyl]phenyl)-3-(pyridin-3-yl)prop-2-enamide;
4-(1-propyl-1H-pyrazole-4-sulfonyl]phenyl ]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-(4-[(4-ethoxymethyl)benzene]sulfonyl]phenyl)-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-[4-[(4-methanesulfonylbenzene)sulfanyl]phenyl ]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-[4-[(4-methoxy-3,5-dimethylbenzene)sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-[4-[(5-chloro-2-methoxybenzene)sulfonyl]phenyl ]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-(4-[(morpholin-4-yl)benzene]sulfonyl]phenyl)-3-(pyridin-3-yl)prop-2-enamide;
(2E)-3-(pyridin-3-yl)-N-[4-(pyridine-3-sulfonyl]phenyl]prop-2-enamide;
(2E)-N-(4-[3-(propan-2-yloxy)benzene]sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-[4-[(4-chloro-2-methoxybenzene]sulfonyl]phenyl ]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-[4-[(3-[2-methyl]propoxy]benzene]sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-[4-[(3-ethylbenzene]sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-3-(pyridin-3-yl)-N-[4-(quinoline-6-sulfonyl]phenyl]prop-2-enamide;
(2E)-N- [4-[(3-chloro-5-methylbenzene] sulfonyl]phenyl ]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-[4-[(2-methoxy-5-methylbenzene]sulfonyl]phenyl ]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-[4-[(3,5-dichlorobenzene]sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-[4-[(5-fluoro-2-methoxybenzene)sulfonyl]phenyl ]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-[4-[(3,5-dimethyl-1H-pyrazol-1-yl)benzene]sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-[4-[(3-propoxybenzene]sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-(4-[(8-oxatricyclo[7.4.0.02,7]trideca-l(13),2,4,6,9,11-hexaene-6-sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-[4-[(5-fluoro-2-methoxybenzene]sulfonyl]phenyl ]-3-(pyridin-3-yl)prop-2-enamide;
4-(1-methyl-1H-indazole-5-sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-[4-[4-(propan-2-yloxy)benzene]sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N-(4-[[3-chloro-4-(trifluoromethyl)benzene]sulfonyl]phenyl)-3-(pyridin-3-yl)prop-2-enamide;
(2E)-3-(pyridin-3-yl)-N-{4-[(3-sulfamoylbenzene)sulfonyl]phenyl} prop-2-enamide;
(2E)-N- {4-[(3-methoxybenzene)sulfonyl]phenyl }-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N- {4-[(2-methylbenzene)sulfonyl]phenyl}-3-(pyridin-3-yl)prop-2-enamide;
4-(2H-1,3-benzodioxole-4-sulfonfonyl)phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N- [4-[(3-adamantanesulfonyl)benzene]sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
4-(4-methylpyridine-3-sulfonyl)phenyl]-3-(pyridin-3-yl)prop-2-enamide;
4-(1-methyl-1H-indazole-7-sulfonfonyl)phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N- [4-[(3,4-dichlorobenzene)sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
4-(1-methyl-1H-pyrazole-4-sulfonfonyl)phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N- [4-[(4-chloro-3-(trifluoromethyl)benzene)sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N- [4-[(2-methoxy-5-(trifluoromethyl)benzene)sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N- [4-[(4-chloro-2-ethoxybenzene)sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
(2E)-N- [4-[(3-phenylbenzene)sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
and
(2E)-N- [4-[(3,4-dichlorobenzene)sulfonyl]phenyl]-3-(pyridin-3-yl)prop-2-enamide;
on a pharmaceutically acceptable salt thereof.

[0296] In some other embodiments, the Nampt small molecule antagonist can further be chosen from the following compounds of Formula II, or pharmaceutically acceptable salts thereof:

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II
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Wherein W is -C(O)-, -S(O)- or -S(O) 2:
R is an aryl or bicyclic heteroaryl wherein the heteroatoms of each of said heteroaryl numbers 1, 2 or 3, and are independently selected from N, S or O, wherein each of said aryl, heteroaryl is optionally substituted with one or more substituents which can be the same or
different and are independently selected from the group consisting of deuterium, halo, cyano, amino, aminoalkyl, (amino)alkoxy, -CONH₂, -C(0)NH(alkyl), -C(0)N(alkyl)₂, -C(0)NH(aryl), -C(0)N(aryl)₂, -CF₃, -CHF₂, alkyl, alkoxy, hydroxyl, hydroxyalkyl, (alkoxyalkyl) amino, -N(R³)-C(0)-alkyl, -N(R³)-C(0)-aryl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, with the proviso that no two adjacent ring heteroatoms are both S or both O;

G is aryl, heteroaryl, cycloalkyl, heterocycloalkyl or - NR¹R², with each of said aryl, heteroaryl, heterocycloalkyl and cycloalkyl being either unsubstituted or independently substituted with 1, 2, 3 or 4 substituents which can be the same or different and are independently selected from the group consisting of deuterium, halo, cyano, amino, aminoalkyl, (amino)alkoxy-, -CONH₂, -C(0)NH(alkyl), -C(0)N(alkyl)₂, -C(0)NH(aryl), -C(0)N(aryl)₂, -CF₃, -CHF₂, alkyl, alkenyl, alkylnyl, alkoxy, hydroxyl, hydroxyalkyl, aryl, heteroaryl (alkoxyalkyl) amino, -N(R³)-C(0)-alkyl, -N(R³)-C(0)-aryl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

R¹ and R² are the same or they are different, and are independently selected from H, Ci to C₇ alkyl, Ci to C₄ hydroxyalkyl, aryl, heteroaryl, heterocycloalkyl and cycloalkyl, and wherein heteroatoms of said heteroaryl and heterocycloalkyl and cycloalkyl, and wherein heteroatoms of said heteroaryl and heterocycloalkyl are independently selected from one or more N, O and S, with the proviso that no two adjacent ring heteroatoms are both S or both O, further wherein R¹ and R² can be either substituted or optionally independently substituted with one or more substituents which can be the same or different and are independently selected from the group consisting of deuterium, halo, cyano, amino, aminoalkyl, (amino)alkoxy, -CONH₂, -C(0)NH(alkyl), -C(0)N(alkyl)₂, -C(0)NH(aryl), -C(0)N(aryl)₂, -CF₃, -CHF₂, alkyl, hydroxyalkyl, alkoxy, hydroxyl, hydroxyalkyl, carboxy, (alkoxyalkyl) amino, alkylamine, aminocarbonyl, -CHO, -N(R³)-C(0)-alkyl, -N(R³)-C(0)-aryl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

R³ is H, alkyl or arylalkyl;

n is 4, 5 or 6;

or a pharmaceutically acceptable salt thereof.

[0297] In some embodiments, the Nampt small molecule antagonist can further be chosen from Nampt antagonists selected from the group consisting of:

N-[4-{1-[3,5-dichlorophenyl]carbonyl}piperdin-4-yl]butyl]thieno[2,3-c]pyridine-2-carboxamide
N-[4-{1-[3-fluoro-4-methoxybenzene]sulfonyl}piperdin-4-yl]butyl]-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-[2-(trifluoromethyl)benzene] sulfonyl }piperdin-4-yl]butyl] imidazo[1,2-a]pyridine-6-carboxamide
N-[4-{1-[4-(trifluoromethyl)phenyl]carbonyl}piperdin-4-yl]butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[4-{1-[6-(morpholin-4-yl)pyridin-3-yl]carbonyl}piperdin-4-yl]butyl] -IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(dimethyl-1,3-thiazol-5-yl)carbonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-cyclohexanecarbonyl)piperidin-4-yl}butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-[(4-(propan-2-yl)oxy)phenyl]carbonyl)piperidin-4-yl}butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2-fluorophenyl)carbonyl)piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(4-chloro-2-methoxyphenyl)carbonyl)piperidin-4-yl}butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(propane-2-sulfonyl)carbonyl)piperidin-4-yl}butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(1-methyl-imidazol-4-yl)carbonyl)piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(5-fluoropyridin-2-yl)carbonyl)piperidin-4-yl}butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(4-fluorophenyl)carbonyl)piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(pyridin-4-yl)carbonyl)piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(3-fluorophenyl)carbonyl)piperidin-4-yl]butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2-fluorophenyl)carbonyl)piperidin-4-yl]butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2,6-dimethoxyphenyl)carbonyl)piperidin-4-yl]butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(pyridin-4-yl)carbonyl)piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(3-fluorophenyl)carbonyl)piperidin-4-yl]butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(3-(1-benzoylpiperidin-4-yl)propyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(2,6-difluorophenyl)carbonyl]piperidin-4-yl]butyl)irnidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(2,3-dimethoxyphenyl)carbonyl]piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(1-acetyl)piperidin-4-yl]carbonyl]piperidin-4-yl]butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(4-chloro benzene)sulfonyl]piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(2-fluoro-5-methylbenzene)sulfonyl]piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-(l-[2-(trifluoromethoxy)phenyl]carbonyl]piperidin-4-yl]butyl]imidazo[1,2-a]pyridin^ 6-carboxamide
N-(4-[(5-(methoxymethyl)pyridin-2-yl)carbonyl]piperidin-4-yl]butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(lH-indol-2-yl)carbonyl]piperidin-4-yl]butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(lH-indol-2-yl)carbonyl]piperidin-4-yl]butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(2,6-diiluorophenyl)carbonyl]piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(lH-indol-6-yl)carbonyl]piperidin-4-yl]butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(2,3-difluorophenyl)carbonyl]piperidin-4-yl]butyl]thieno[2,3-c]pyridine-2-carboxarnide
N-[4-(benzoylpiperazin-3-yl)butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(3-methoxyphenyl)carbonyl]piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(3-methoxypyrrozphin-3-yl)carbonyl]piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(2-ethoxyphenyl)carbonyl]piperidin-4-yl]butyl)thieno[2,3-c]pyridine-2-carboxarnide
N-(4-[(2,3-dichlorophenyl)carbonyl]piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(5-methylpyrazin-2-yl)carbonyl]piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(3-methoxyphenyl)carbonyl]piperidin-4-yl]butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(2-ethoxyphenyl)carbonyl]piperidin-4-yl]butyl)thieno[2,3-c]pyridine-2-carboxarnide
N-(4-[(2,3-dichlorophenyl)carbonyl]piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(furan-3-yl)carbonyl]piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(2,3-diiluorophenyl)carbonyl]piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(5-methylpyrazin-2-yl)carbonyl]piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(3-methoxypyrrozphin-3-yl)carbonyl]piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(2-ethoxyphenyl)carbonyl]piperidin-4-yl]butyl)thieno[2,3-c]pyridine-2-carboxarnide
N-(4-[(2,3-dichlorophenyl)carbonyl]piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(furan-3-yl)carbonyl]piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(2,3-diiluorophenyl)carbonyl]piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(5-methylpyrazin-2-yl)carbonyl]piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[(3-methoxypyrrozphin-3-yl)carbonyl]piperidin-4-yl]butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(2-ethoxyphenyl)carbonyl]piperidin-4-yl]butyl)thieno[2,3-c]pyridine-2-carboxarnide
N-(4-[(2,3-dichlorophenyl)carbonyl]piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
carboxamide
N-[4-(1-cyclohexanecarbonylpiperidin-4-yl)butyl]thieno[2,3-c]pyridine-2-carboxamide
N-(4-{1-[(5-chloro-2-methoxyphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2-ethoxypyridin-3-yl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-[4-{1-[benzenesulfonyl]piperidin-4-yl}butyl]-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(3,5-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-{1-[(3,4-difluorobenzene)sulfonyl]piperidin-4-yl}butyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(2,5-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-4-{1-[(4-(difluoromethoxy)phenyl)carbonyl]piperidin-4-yl}butyl]-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(3,4-difluorobenzene)sulfonyl]piperidin-4-yl}butyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(4-fluoro-3-methylbenzene)sulfonyl]piperidin-4-yl}butyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(4-methoxyphenyl)carbonyl]piperidin-4-yl}butyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(2,5-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(2-ethoxypyridin-3-yl)carbonyl]piperidin-4-yl}butyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(4-fluoro-3-methylbenzene)sulfonyl]piperidin-4-yl}butyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(5-chloro-2-methoxyphenyl)carbonyl]piperidin-4-yl}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-{1-[(2,6-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-[4-{1-cyclohexanecarbonylpiperidin-4-yl}butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2,6-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2,6-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2,6-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2,6-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2,6-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2,6-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2,6-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2,6-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2,6-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2,6-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2,6-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2,6-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2,6-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2,6-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2,6-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
carboxamide
N-{4-[(4-((pyrrolidin-1-yl)carbonyl)benzene sulfonyl)phenyl]methyl}-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[4-{1-[5-(methoxymethyl)pyridin-2-yl]carbonyl)piperidin-4-yl]butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-([4-1-{(2,5-diiodobenzene)sulfonyl}piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-([4-(trifluoromethoxy)phenyl]carbonyl)piperidin-4-yl]butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[4-[1-{(6-(propan-2-yl)pyridin-3-yl]carbonyl)piperidin-4-yl]butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-([4-1-{(3,4-dimethoxyphenyl]carbonyl)piperidin-4-yl]butyl]thieno[2,3-c]pyridine-2-carboxamide
N-([4-1-{(2-phenyl-1,3-thiazol-4-yl]carbonyl)piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-([4-1-{(2-phenyl-1,3-thiazol-4-yl]carbonyl)piperidin-4-yl]butyl]thieno[2,3-c]pyridine-2-carboxamide
N-([4-1-{(2-(trifluoromethyl)-1,3-thiazol-4-yl]carbonyl)piperidin-4-yl]butyl]thieno[2,3-c]pyridine-2-carboxamide
N-[4-1-{(5-fluoropyridin-2-yl]carbonyl)piperidin-4-yl]butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[4-1-{(5-fluoro-2-methylphenyl]carbonyl)piperidin-4-yl]butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-1-{(6-(morpholin-4-yl)pyridin-3-yl]carbonyl)piperidin-4-yl]butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[4-1-{(dimethyl-1,3-thiazol-5-yl]carbonyl)piperidin-4-yl]butyl]thieno[2,3-c]pyridine-2-carboxamide
N-[4-{1-[(2-(2-methyl-1,3-thiazol-4-yl)acetyl]piperidin-4-yl]butyl}-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-[2,5-dimethoxybenzene}sulfonyl]piperidin-4-yl]butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-{(2,6-dimethoxyphenyl]carbonyl)piperidin-4-yl]butyl}-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-[(2-ethoxyphenyl]carbonyl)piperidin-4-yl]butyl}-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

carboxamide
N-(4-{1-[(3-fluoro-2-methylphenyl)carbonyl]piperidin-4-yl}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-{1-[(5-fluoro-1H-indol-2-yl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2-(1-methyl-1H-indol-3-yl)acetyl)piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(4-fluoro-2-methylbenzene)sulfonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(2-fluorobenzene)sulfonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(3,4-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-\{4-\[4-(trifluoromethyl)pyridin-3-yl\]carbonyl\]piperidin-4-yl\}butyl\}-1H-pyrrolo[3,2-c]pyridine-6-carboxamide
N-(4-{1-[(3,5-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(5-fluoro-2-methoxybenzene)sulfonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(3-fluoro-4-methylphenyl)carbonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-\{4-\[(2,5-difluorophenyl)carbonyl\]piperidin-4-yl\}butyl\}-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(23-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2,5-difluorophenyl)carbonyl]piperidin-4-yl}butyl)imidazo[23-c]pyridine-2-carboxamide
N-(4-{1-[(3-cyanobenzene)sulfonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(3-methoxybenzene)sulfonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(6-(trifluoromethyl)pyridin-3-yl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2-chlorobenzene)sulfonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(3-methoxyphenyl)carbonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(pyridine-3-sulfonyl)piperidin-4-yl]butyl\}-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(4-(trifluoromethyl)benzene)sulfonyl]piperidin-4-yl}butyl\}-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

169
N-(4-{1-[(2-chlorophenyl)carbonyl]piperidin-4-yl}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-{1-[(3-fluoro-2-methylphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[4-(trifluoromethyl)phenyl]carbonyl}piperidin-4-yl)butyl]thieno[2,3-c]pyridine-2-carboxamide
N-(4-{1-{[2-chlorophenyl]carbonyl}piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-(1-[4-(trifluoromethoxy)benzene]sulfonyl]piperidin-4-yl]butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(5-fluoro-1H-indol-2-yl)carbonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(3,4-difluorophenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(5-fluoropyridin-2-yl)carbonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{4-[(2-(trifluoromethoxy)phenyl)carbonyl]piperidin-4-yl}butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[4-(difluoromethoxy)phenyl]carbonyl}piperidin-4-yl)butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[2-(methylsulfonyl)pyridin-3-yl]carbonyl]piperidin-4-yl}butyl] -1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-[2-(methoxybenzene)sulfonyl]piperidin-4-yl}butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(2H-1,3-benzodioxol-5-yl)carbonyl]piperidin-4-yl}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-{1-[(2,3-difluorophenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-[4-{1-[(2H-indol-5-yl)carbonyl]piperidin-4-yl}butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(5-fluoro-1H-indol-2-yl)carbonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-[(2,5-dichlorophenyl)carbonyl]piperidin-4-yl}butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2-ethoxyphenyl)carbonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(4-(trifluoromethyl)pyridin-3-yl)carbonyl]piperidin-4-yl}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-[4-{1-[4-(trifluoromethyl)phenyl]carbonyl]piperidin-4-yl}butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(4-(difluoromethoxy)phenyl)carbonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{[4-methyl-1,3-thiazol-5-yl]carbonyl)piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-[4-{1-[(2-(trifluoromethyl)-1,3-thiazol-4-yl)carbonyl]piperidin-4-yl}butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-[(2,4-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-[(2-trifluoromethoxy)phenyl]carbonyl}piperidin-4-yl}butyl]thieno[2,3-c]pyridine-2-carboxamide
N-[2-{1-benzoyl]piperidin-4-yl)ethyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-{[1H-pyrrolo[3,2-c]pyridin-2-yl]carbonyl}piperidin-4-yl}butyl]thieno[2,3-c]pyridine-2-carboxamide
N-[4-{1-[(3-fluoro-4-methylphenyl)carbonyl]piperidin-4-yl}butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[4-{1-[(3-fluoro-4-methoxyphenyl)carbonyl]piperidin-4-yl}butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[4-{1-[(3,4-dimethoxybenzene)sulfonyl]piperidin-4-yl}butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-[(4-methyl-1,3-thiazol-5-yl)carbonyl]piperidin-4-yl}butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-[(5-fluoro-1H-indol-2-yl)carbonyl]piperidin-4-yl}butyl]thieno[2,3-c]pyridine-2-carboxamide
N-[4-{1-[(2-(trifluoromethyl)pyrimidin-5-yl)carbonyl]piperidin-4-yl}butyl]thieno[2,3-c]pyridine-2-carboxamide
N-[4-{1-[(4-chloro-2-methoxyphenyl)carbonyl]piperidin-4-yl}butyl]thieno[2,3-c]pyridine-2-carboxamide
N-[4-{1-[(5-chloro-2-methoxyphenyl)carbonyl]piperidin-4-yl}butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-[(2,5-difluorophenyl)carbonyl]piperidin-4-yl}butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-[(4-methylpyridin-3-yl)carbonyl]piperidin-4-yl}butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-[(4-fluorobenzene)sulfonyl]piperidin-4-yl}butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-{[1-benzothiophen-2-yl)carbonyl]piperidin-4-yl}butyl]thieno[2,3-c]pyridine-2-carboxamide

N-(4-{{[(2-(methylsulfinyl)pyridin-3-yl)carbonyl]piperidin-4-yl}butyl}imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(pyridin-2-yl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(5-(trifluoromethyl)pyridin-2-yl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(1,3-benzothiazol-6-yl)carbonyl]piperidin-4-yl}butyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[1-methyl-IH-imidazol-4-yl]carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(4-methyl-1,3-thiazol-5-yl)carbonyl]piperidin-4-yl}butyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(1H-pyrrolo[3,2-c]pyridine-2-carboxamide)
N-(4-{1-[(3-fluorophenyl)carbonyl]piperidin-4-yl}butyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[4-(4-phenylphenyl)ethyl]IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(5-(trifluoromethyl)pyridin-2-yl)carbonyl]piperidin-4-yl]butyl}-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(2,4-dichlorophenyl)carbonyl]piperidin-4-yl]butyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(5-(propan-2-yl)pyridin-3-yl)carbonyl]piperidin-4-yl}butyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(2-methylpyridin-3-yl)carbonyl]piperidin-4-yl]butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2,4-dichlorophenyl)carbonyl]piperidin-4-yl]butyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(1H-indol-6-yl)carbonyl]piperidin-4-yl}butyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(2-methylpyridin-3-yl)carbonyl]piperidin-4-yl]butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(2,4-dichlorophenyl)carbonyl]piperidin-4-yl]butyl)-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(1H-benzoypiperidin-4-yl)butoyl]thieno[2,3-c]pyridine-2-carboxamide
N-(4-\{1-(4-methoxyphenyl)carbonyl]piperidin-4-yl\}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-\{1-(2,5-dimethoxyphenyl)carbonyl]piperidin-4-yl\}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-\{1-{(2-chlorophenyl)carbonyl]piperidin-4-yl\}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-\{1-(2-methylpyridin-3-yl)carbonyl]piperidin-4-yl\}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-\{1-{(3-fluorobenzene)sulfonyl]piperidin-4-yl\}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-\{1-{(2-fluorophenyl)carbonyl]piperidin-4-yl\}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-\{1-\{(2,5-dimethoxyphenyl)carbonyl]piperidin-4-yl\}butyl\}imidazo[1,2-a]pyridine-6-carboxamide
N-(4-\{1-{(2-methyl-1,3-thiazol-4-yl)carbonyl]piperidin-4-yl\}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-\{1-{(2-fluoro-3-methylphenyl)carbonyl]piperidin-4-yl\}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-\{1-{(3-methoxyphenyl)carbonyl]piperidin-4-yl\}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-\{1-{(3,5-dimethoxyphenyl)carbonyl]piperidin-4-yl\}butyl\}imidazo[1,2-a]pyridine-6-carboxamide
N-(4-\{1-{(6-(propan-2-yl)pyridin-3-yl)carbonyl]piperidin-4-yl\}butyl\}thieno[2,3-c]pyridine-2-carboxamide
N-(4-\{1-{(1-methyl-1H-indol-2-yl)carbonyl]piperidin-4-yl\}butyl\}1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-\{1-{(5-(propan-2-yl)pyridin-2-yl)carbonyl]piperidin-4-yl\}butyl\}1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-\{1-{(2,4-dilluorophenyl)carbonyl]piperidin-4-yl\}butyl\}1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-\{1-{(2,4-dimethoxyphenyl)carbonyl]piperidin-4-yl\}butyl\}thieno[2,3-c]pyridine-2-carboxamide
N-(4-\{1-{benzoyl]piperidin-4-yl\}butyl\}1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-\{1-{(3-chlorophenyl)carbonyl]piperidin-4-yl\}butyl\}1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-\{1-{(2-pyridin-3-yl)1,3-thiazol-4-yl)carbonyl]piperidin-4-yl\}butyl\}thieno[2,3-c]pyridine-2-carboxamide
N-(4-\{1-{(2-ethoxypyridin-3-yl)carbonyl]piperidin-4-yl\}butyl\}thieno[2,3-c]pyridine-2-carboxamide
N-(4-\{1-{(3-ethoxyphenyl)carbonyl]piperidin-4-yl\}butyl\}1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(2,4-dimethoxybenzene)sulfonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[2-(1-methyl-1H-indol-3-yl)acetyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-[(4-trifluoromethoxy)phenyl]carbonyl}piperidin-4-yl]butyl]thieno[2,3-c]pyridine-2-carboxamide
N-[4-{1-[(1H-pyrrolo[3,2-c]pyridin-2-yl)carbonyl]piperidin-4-yl]butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[6-(4-chlorophenoxo)hexyl]quinoline-6-carboxamide
N-(4-{1-[(2-methoxyphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-[4-(benzoylpiperazin-1-yl)butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-[(5-chloro-2-methoxyphenidin-3-yl)carbonyl]piperidin-4-yl}butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{4-[(3-methoxyphenyl)carbonyl]piperazin-1-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(3-fluoro-4-methoxyphenyl)carbonyl]piperidin-4-yl}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-{1-[(5-chloro-2-methoxyphenyl)carbonyl]piperidin-4-yl}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-[4-{1-[(2,6-difluorophenyl)carbonyl]piperidin-4-yl}butyl]thieno[2,3-c]pyridine-2-carboxamide
N-[4-{1-{imidazo[1,2-a]pyridin-6-yl]carbonyl}piperidin-4-yl}butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[4-{1-[(5-(methoxymethyl)pyridin-2-yl)carbonyl]piperidin-4-yl}butyl]thieno[2,3-c]pyridine-2-carboxamide
N-[4-(1-{[3-(trifluoromethyl)benzene)sulfonyl]piperidin-4-yl}butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-[(3-chlorophenyl)carbonyl]piperidin-4-yl}butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[4-{1-[(3,5-dichlorophenyl)carbonyl]piperidin-4-yl}butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(pyridin-2-yl)carbonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{1-[(2-(pyridin-3-yl)-1,3-thiazol-4-yl)carbonyl]piperidin-4-yl}butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[4-{1-[(1-methyl-1H-indol-2-yl)carbonyl]piperidin-4-yl}butyl]thieno[2,3-c]pyridine-2-carboxamide
N-(4-[(2-methylbenzene)sulfonyl]piperidin-4-yl)butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{(1-methyl-1H-indol-2-yl)carbonyl}piperidin-4-yl)butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-[4-(1-[(4-(trifluoromethoxy)phenyl)carbonyl]piperidin-4-yl)butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-{(2-(trifluoromethyl)-1,3-thiazol-4-yl)carbonyl}piperidin-4-yl)butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[(3-fluoro-4-methylphenyl)carbonyl]piperidin-4-yl)butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-[(2H-1,3-benzodioxol-5-yl)carbonyl]piperidin-4-yl]butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{(3,4-dimethoxyphenyl)carbonyl]piperidin-4-yl)butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{(3,4-dimethoxyphenyl)carbonyl]piperidin-4-yl)butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{(pyridin-3-yl)carbonyl]piperidin-4-yl)butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-[4-{(4-chloro-2-methoxyphenyl)carbonyl]piperidin-4-yl]butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{(3,4-dichlorophenyl)carbonyl]piperidin-4-yl)butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{(3,5-dichlorophenyl)carbonyl]piperidin-4-yl)butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-(benzyloxy)phenethyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{(6-methylpyridin-3-yl)carbonyl]piperidin-4-yl)butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-[4-{(5-(propan-2-yl)pyridin-2-yl)carbonyl]piperidin-4-yl]butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-{(3-ethoxyphenyl)carbonyl]piperidin-4-yl)butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-[4-{(2-(2-methyl-1,3-thiazol-4-yl)acetyl]piperidin-4-yl)butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-{(3,4-dichlorophenyl)carbonyl]piperidin-4-yl)butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-{1-[(1-acetylpiperidin-4-yl)carbonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(1-benzo[1]thiophen-2-yl)carbonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(4-(1H-pyrazol-1-yl)phenyl)carbonyl]piperidin-4-yl}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-{1-[(3-chlorobenzene)sulfonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(6-(trifluoromethyl)pyridin-3-yl)carbonyl]piperidin-4-yl}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-{1-[(2-methyl-1,3-thiazol-4-yl)carbonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(5-(propan-2-yl)pyridin-2-yl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(4-methoxyphenyl)carbonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(thieno[2,3-c]pyridin-2-yl)carbonyl]piperidin-4-yl}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-{1-[(3,5-diiluorobenzene)sulfonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(3-chloro-4-methoxybenzene)sulfonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(2,3-dimethoxyphenyl)carbonyl]piperidin-4-yl}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-{1-[(3,4-difluorophenyl)carbonyl]piperidin-4-yl}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-{1-[(2,4-difluorophenyl)carbonyl]piperidin-4-yl}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-{1-[(2-fluoro-3-methylphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(4-chlorophenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(4-chloro-phenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{1-[(1-methyl-1H-pyrazole-3-sulfonyl)piperidin-4-yl]butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(6-methylpyridin-3-yl)carbonyl]piperidin-4-yl}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-{1-[(2-ethoxypyrinidin-3-yl)carbonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[4-(1-benzoylpiperidin-4-yl)butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[[1H4ndol-6-yl]carbonyl]piperidin-4-yl)butyl]thieno[23-c]pyridine-2-carboxamide
N-(4-[[2-methyl-13-thiazol-4-yl]carbonyl]piperidin-4-yl)butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[2-[[1-(benzenesulfonyl)piperidin-4-yl]ethyl]H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-[[4-(propan-2-yl)-1,3-oxazol-5-yl]carbonyl]piperidin-4-yl)butyl]thieno[23-c]pyridine-2-carboxamide
N-(4-[[3,4-dichlorophenyl]carbonyl]piperidin-4-yl)butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(4-[[1,3-benzothiazol-6-yl]carbonyl]piperidin-4-yl)butyl]imidazo[1,2-a]pyridine-6-carboxamide
N-(4-{[3-chlorophenyl]carbonyl}piperazin-1-yl)butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[(IH4ndol-5-yl)carbonyl]piperidin-4-yl}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-{1-[(1-benzothiophen-2-yl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide
N-[4-{1-[(3-trifluoromethoxy)benzene]sulfonyl}piperidin-4-yl]butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-[2-(1-methyl-1H-indol-3-yl)acetyl]piperidin-4-yl}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-{1-{[6-(trifluoromethyl)phenyl]carbonyl}piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-{[(5-chloro-2-methoxypyridin-3-yl)carbonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(3-(1-benzoypiperidin-4-yl)butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-{[(4-fluorophenyl)carbonyl]piperidin-4-yl}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-{1-{[4-chlorophenyl]carbonyl]piperidin-4-yl}butyl)thieno[2,3-c]pyridine-2-carboxamide
N-(4-{1-{6-(trifluoromethyl)pyridine-3-sulfonyl}piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(3-(1-benzoypiperidin-4-yl)butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-{[4-fluorophenyl]carbonyl]piperidin-4-yl]butyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-{[(3-methoxyl)-1,3-oxazol-5-yl]carbonyl}piperidin-4-yl]butyl}-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-(4-{1-{(5-chloro-2-methoxypyridin-3-yl)carbonyl]piperidin-4-yl}butyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide, and
N-(4-{1-{[(5-fluoro-2-methylphenyl)carbonyl]piperidin-4-yl}butyl)imidazo[1,2-a]pyridine-6-carboxamide.

In some other embodiments, the Nampt small molecule antagonist can further be chosen from the group consisting of: 1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(2-trifluoromethoxy-
phenylsulfamoyl)-benzylamide;
Quinoline-6-carboxylic acid 4-(5-fluoro-2-methoxy-phenylsulfamoyl)-benzylamide;
IH-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(2-methoxy-5-methyl-phenylsulfamoyl)-benzylamide;
IH-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(2,4-dimethoxy-phenylsulfamoyl)-benzylamide;
IH-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(2-ethoxy-phenylsulfamoyl)-benzylamide;
IH-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(2-pyrrolidin-1-yl-phenylsulfamoyl)-benzylamide;
IH-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-[2-(2-hydroxy-ethyl)-phenylsulfamoyl]-benzylamide;
trans-Thieno[2,3-c]pyridine-2-carboxylic acid 4-(4-amino-cyclohexylsulfamoyl)-benzylamide;
Imidazo[1,2-b]pyridazine-6-carboxylic acid 4-benzenesulfonyl-benzylamide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(tetrahydro-pyran-4-ylsulfamoyl)-benzylamide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(tetrahydro-pyran-4-ylsulfamoyl)-benzylamide;
IH-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(tetrahydro-pyran-4-ylsulfamoyl)-benzylamide;
cis-Thieno[2,3-c]pyridine-2-carboxylic acid 4-(4-amino-cyclohexylsulfamoyl)-benzylamide;
[1,2,4]Triazolo[1,5-a]pyridine-6-carboxylic acid 4-benzenesulfonyl-benzylamide;
Furo[2,3-c]pyridine-2-carboxylic acid 4-(tetrahydro-pyran-4-ylsulfamoyl)-benzylamide;
IH-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(tetrahydro-pyran-3-ylsulfamoyl)-benzylamide;
trans-IH-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-[4-(2,2,2-trifluoro-ethylamino)-cyclohexylsulfamoyl]-benzylamide;
trans-Furo[2,3-c]pyridine-2-carboxylic acid 4-[4-(2,2,2-trifluoro-ethylamino)-cyclohexylsulfamoyl]-benzylamide;
Thieno[2,3-c]pyridine-2-carboxylic acid 4-(piperidin-4-ylsulfamoyl)-benzylamide;
Thieno[2,3-c]pyridine-2-carboxylic acid 4-(9-aza-bicyclo[3.3.1]non-3-ylsulfamoyl)-benzylamide;
Pyrazolo[1,5-a]pyrimidine-5-carboxylic acid 4-benzenesulfonyl-benzylamide;
3-Amino-imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3,5-difluoro-benzenesulfonyl)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(6-amino-pyridine-3-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(tetrahydro-pyran-3-ylsulfamoyl)-benzylamide;
Imidazo[1,2-b]pyridazine-6-carboxylic acid 4-(3,5-difluoro-benzenesulfonyl)-benzylamide;
Thieno[2,3-c]pyridine-2-carboxylic acid 4-(8-aza-bicyclo[3.2.1]oct-3-ylsulfamoyl)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(tetrahydro-pyran-3-ylsulfamoyl)-benzylamide;
[4-(4-[(Thieno[2,3-c]pyridine-2-carbonyl)-amino]-methyl)-benzenesulfonylamino]-bicyclo[2.2.2]oct-1-yl-carbamic acid methyl ester;
Imidazo[1,5-a]pyridine-7-carboxylic acid 4-benzenesulfonyl-benzylamide;  
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-acetyl-3-aza-bicyclo[3.1.0]hex-1-ylsulfamoyl)-benzylamide;  
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-hydroxy-3-methyl-cyclobutanesulfonyl)-benzylamide;  
Furo[2,3-c]pyridine-2-carboxylic acid 4-(3-hydroxy-3-methyl-cyclobutanesulfonyl)-benzylamide;  
1,3-Dihydro-pyrrolo[3,4-c]pyridine-2-carboxylic acid 4-(3,5-difluoro-benzenesulfonyl)-benzylamide;  
1,3-Dihydro-pyrrolo[3,4-c]pyridine-2-carboxylic acid 4-(6-methyl-pyridine-3-sulfonyl)-benzylamide;  
and  
Furo[2,3-c]pyridine-2-carboxylic acid 4-(6-methyl-pyridine-3-sulfonyl)-benzylamide and pharmaceutically acceptable salts thereof.

[0298] In some embodiments, the Nampt small molecule antagonist can further be chosen from compounds of Formula I as follows:

![Chemical structure](image)

wherein:

A is CH or N;  
E is O or is absent;  
R is (a) a bicyclic heteroaryl comprising one or more heteroatom ring members independently selected from N, S or O, wherein said bicyclic heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy; and wherein one or more N ring members of said bicyclic heteroaryl is optionally an N-oxide; or  
(b) a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or monocyclic heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is substituted with one or more substituent selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy;  
R¹ is (1) R'' or -alkylenyl-R'', where R'' is cycloalkyl, heterocycloalkyl, phenyl, or monocyclic heteroaryl;  
wherein each of said cycloalkyl, heterocycloalkyl, phenyl, and heteroaryl is unsubstituted or is substituted with one or more substituents R³;  
wherein each R³ substituent is independently selected from the group consisting of:  

deuterium, halo, hydroxy, hydroxyalkyl, cyano,
-NR^a R^b, -alkylidencyl-NR^a R^b, oxo, alkyl, cyanoalkyl, haloalkyl, alkoxy, -S-alkyl,
haloalkoxy, alkoxyalkyl-, alkenyl, alkynyl,
-C(0)alkyl, -C0 2alkyl, -C0 2H, -CONH 2, C(0)NH(alkyl),
-C(0)NH(haloalkyl), -C(0)N(alkyl) 2, -C(0)NH(cycloalkyl), arylalkyl-
arylaralkoxy-, aryloxy-, cycloalkyl, cycloalkylalkoxy, (cycloalkyl)alkyl,
heterocycloalkyl, aryl, (heterocycloalkyl)alkyl-, (heterocycloalkyl) alkoxy-, -
C(0)cycloalkyl,
-C(0)heterocycloalkyl, heteroaryl, (heteroaryl)alkyl-, -S(0)-alkyl, -S0 2alkyl, -
S0 2aryl, -S0 2fluoroalkyl, -N(R^a)-C(0)-alkyl,
-N(R^a)-C(0)-aryl, -N(R^a)-C0 2alkyl, -S0 2NH 2, -S0 2NH(alkyl),
-S0 2N(alkyl) 2, -S0 2NH(cycloalkyl), and -N(H)(S0 2alkyl), or two adjacent R^s
substituents on a phenyl or heteroaryl R^a groups taken together form
methylenedioxy,

wherein each of said cycloalkyl, heterocycloalkyl, aryl, and heteroaryl within R^s
is unsubstituted or is substituted with one or more substituents independently
selected from the group consisting of deuterium, alkyl, halo, hydroxy, cyano,
alkoxy, amino, -C(0)alkyl, and -C0 2alkyl;

wherein R^a and R^b are each independently H, alkyl, alkoxy, alkoxyalkyl,
cyanoalkyl, or haloalkyl; and

R^3 is H, alkyl or aryalkyl-;

(2) alkyl unsubstituted or substituted with one or more substituents selected from the group
consisting of deuterium, halo, hydroxy, cyano, alkoxy, haloalkoxy, -NR^aR^b, -C(0)alkyl,
-C0 2alkyl, -C0 2H, -CONR^aR^b, -SOalkyl,
-S0 2alkyl, and -S0 2NR^aR^b;

where R^a and R^b are each independently H, alkyl, alkoxyalkyl, haloalkyl,
-C(0)alkyl, or -C0 2alkyl; or

(3) -N(R^a)^bR^c,

wherein R^a is H, R^m, -alkylidencyl-R^m, hydroxyalkyl, cyanoalkyl, alkoxyalkyl, haloalkyl,
-CONR^a or -C(0)R^b;

where R^b is as defined in (1) above;

R^b and R^j are each independently H or alkyl, or R^b and R^j taken together with the
nitrogen to which they are attached form a monocyclic heterocycloalkyl; and

R^j is an alkyl unsubstituted or substituted with one or more substituents selected from
the group consisting of: deuterium, halo, amino, hydroxy, alkoxy, cycloalkyl,
heteroaryl, phenyl, and heterocycloalkyl; or a cycloalkyl, heterocycloalkyl,
phenyl, or heteroaryl, each unsubstituted or substituted with one or more

181
substituents selected from the group consisting of: deuterium, alkyl, halo, amino, 
hydroxy, and alkoxy; and

$R^1$ is H or $R^1$;

$R^2$ and $R^3$ are each independently selected from the group consisting of H and deuterium; 
and pharmaceutically acceptable salts of compounds of Formula I.

[0299] In one embodiment, $Rx$ is independently selected from the group consisting of: -C(0)alkyl 
or -C(0)alkyl-0-alkyl.

[0300] In some embodiments, the Nampt small molecule antagonist can further be chosen from 
Nampt antagonists selected from the group consisting of:

- IH-Pyrazolo[3,4-b]pyridine-5-carboxylic acid [5-(3,5-difluoro-benzenesulfonyl)-pyridin-2-
yl methyl]-amide;
- Imidazo[1,2-a]pyrimidine-6-carboxylic acid [5-(3,5-difluoro-benzenesulfonyl)-pyridin-2-
yl methyl]-amide;
- IH-Pyrrolo[3,2-c]pyridine-2-carboxylic acid [5-(3,5-difluoro-benzenesulfonyl)-pyridin-2-
yl methyl]-amide;
- Imidazo[1,2-a]pyridine-6-carboxylic acid [5-(3,5-difluoro-benzenesulfonyl)-pyridin-2-y lamethyl]-amide;
- Furo[2,3-c]pyridine-2-carboxylic acid [5-(3,5-difluoro-benzenesulfonyl)-pyridin-2-ylmethyl]- 
  amide;
- IH-Pyrazolo[3,4-b]pyridine-5-carboxylic acid (5-benzenesulfonyl-pyrimidin-2-ylmethyl) 
  -amide;
- IM-IDazo[1, 2-a]pyrimidine-6-carboxylic acid (5-benzenesulfonyl-pyrimidin-2-ylmethyl)-amide;
- IH-Pyrrolo[3,2-c]pyridine-2-carboxylic acid [5-(3,5-difluoro-benzenesulfinyl)-pyridin-2-
yl methyl]-amide (racemic);
- Imidazo[1,2-a]pyridine-6-carboxylic acid [5-(3-trifluoromethyl-benzenesulfonyl)-pyridin-2-
yl methyl]-amide;
- Furo[2,3-c]pyridine-2-carboxylic acid (5-benzenesulfonyl-pyrimidin-2-ylmethyl)-amide;
- Imidazo[1,2-a]pyrimidine-6-carboxylic acid (5-benzenesulfonyl-pyrimidin-2-ylmethyl)-amide;
- Imidazo[1,2-a]pyrimidine-6-carboxylic acid [5-(3-trifluoromethoxy-benzenesulfonyl)-pyridin-2-
yl methyl]-amide;
- Imidazo[1,2-a]pyridine-6-carboxylic acid [5-(3,5-difluoro-benzenesulfinyl)-pyridin-2-ylmethyl]- 
  amide (racemic);
- IH-Pyrazolo[3,4-b]pyridine-5-carboxylic acid [5-(3,5-difluoro-benzenesulfinyl)-pyridin-2-
yl methyl]-amide (racemic);
- IH-Pyrazolo[3,4-b]pyridine-5-carboxylic acid [5-(3-trifluoromethyl-benzenesulfonyl)-pyridin-2-
yl methyl]-amide;
- IH-Pyrrolo[3,2-c]pyridine-2-carboxylic acid [5-(3-trifluoromethyl-benzenesulfonyl)-pyridin-2-
yl methyl]-amide;
ylmethyl]-amide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid [5-(3-trifluoromethyl-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid [5-(3-trifluoromethoxy-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid [5-(3-trifluoromethoxy-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
1H-Pyrrole[3,2-c]pyridine-2-carboxylic acid [5-(3-trifluoromethoxy-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
Furo[2,3-c]pyridine-2-carboxylic acid [5-(3-trifluoromethyl-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
Furo[2,3-c]pyridine-2-carboxylic acid [5-(3-trifluoromethoxy-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid [5-(3,5-difluoro-benzenesulfinyl)-pyridin-2-ylmethyl]-amide (racemic);
Furo[2,3-c]pyridine-2-carboxylic acid [5-(3,5-difluoro-benzenesulfinyl)-pyridin-2-ylmethyl]-amide (racemic);
Furo[2,3-c]pyridine-2-carboxylic acid [5-(piperidine-4-sulfanyl)-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid [5-(piperidine-4-sulfanyl)-pyridin-2-ylmethyl]-amide;
Furo[2,3-c]pyridine-2-carboxylic acid [5-(3,5-difluoro-benzenesulfinyl)-pyridin-2-ylmethyl]-amide (stereoisomer 1);
Furo[2,3-c]pyridine-2-carboxylic acid [5-(3,5-difluoro-benzenesulfinyl)-pyridin-2-ylmethyl]-amide (stereoisomer 2);
Imidazo[1,2-a]pyrimidine-6-carboxylic acid [5-(4-morpholin-4-yl-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid [5-(4-morpholin-4-yl-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
Furo[2,3-c]pyridine-2-carboxylic acid [5-(3-methoxy-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid [5-(3-methoxy-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid [5-(3-methoxy-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid [5-(6-morpholin-4-yl-pyridine-3-sulfonyl)-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid [5-(1-methyl-1H-pyrazole-4-sulfonyl)-pyridin-2-ylmethyl]-amide;
Furo[2,3-c]pyridine-2-carboxylic acid [5-(4-morpholin-4-yl-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid [5-(4-morpholin-4-yl-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
Thieno[2,3-c]pyridine-2-carboxylic acid [5-(4-morpholin-4-yl-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
Thieno[2,3-c]pyridine-2-carboxylic acid [5-(1-methyl-1H-pyrazole-4-sulfonyl)-pyridin-2-ylmethyl]-amide;
1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid [5-(6-morpholin-4-yl-pyridine-3-sulfonyl)-pyridin-2-ylmethyl]-amide;
1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid [5-[1-(tetrahydro-pyran-4-yl)-piperidine-4-sulfonyl]-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid [5-(1-propyl-1H-pyrazole-4-sulfonyl)-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid [5-(1-isopropyl-1H-pyrazole-4-sulfonyl)-pyridin-2-ylmethyl]-amide;
Thieno[2,3-c]pyridine-2-carboxylic acid [5-(1-isopropyl-1H-pyrazole-4-sulfonyl)-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid [5-[6-(4-methyl-piperazin-1-yl)-pyridine-3-sulfonyl]-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid [5-[6-(4-methyl-piperazin-1-yl)-pyridine-3-sulfonyl]-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid [5-[4-(4-methyl-piperazin-1-yl)-benzenesulfonyl]-pyridin-2-ylmethyl]-amide;
1,3-Dihydro-pyrrolo[3,4-c]pyridine-2-carboxylic acid [5-(3-trifluoromethyl-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
1,3-Dihydro-pyrrolo[3,4-c]pyridine-2-carboxylic acid [5-(3-trifluoromethoxy-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
Furo[2,3-c]pyridine-2-carboxylic acid [5-(tetrahydro-pyran-4-sulfonyl)-pyridin-2-ylmethyl]-amide;
Furo[2,3-c]pyridine-2-carboxylic acid [5-(6-morpholin-4-yl-pyridine-3-sulfonyl)-pyridin-2-ylmethyl]-amide;
Thieno[2,3-c]pyridine-2-carboxylic acid [5-(tetrahydro-pyran-4-sulfonyl)-pyridin-2-ylmethyl]-amide;
Thieno[2,3-c]pyridine-2-carboxylic acid [5-(6-morpholin-4-yl-pyridine-3-sulfonyl)-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyridine-6-carboxylic acid [5-(3,5-diiluorobenzenesulfonyl)-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyridine-6-carboxylic acid [5-(3,5-diiluorobenzenesulfonyl)-pyridin-2-ylmethyl]-amide;
Thieno[2,3-c]pyridine-2-carboxylic acid [5-((1-oxetan-3-yl)piperidine-4-sulfonyl)-pyridin-2-ylmethyl]-amide;
2-Amino-5,7-dihydro-pyrrolo[3,4-d]pyrimidine-6-carboxylic acid (5-benzenesulfonyl-pyridin-2-ylmethyl)-amide;
Imidazo[1,2-a]pyridine-6-carboxylic acid [5-(3,5-difluoro-benzenesulfinyl)-pyridin-2-ylmethyl]-amide (racemic);
1,3-Dihydro-pyrrolo[3,4-c]pyridine-2-carboxylic acid (5-cyclohexanesulfonyl-pyridin-2-ylmethyl)-amide;
Imidazo[1,2-a]pyridine-6-carboxylic acid [5-(tetrahydro-pyran-4-sulfonyl)-pyridin-2-ylmethyl]-amide;
Furo[2,3-c]pyridine-2-carboxylic acid [5-(1-propyl-1H-pyrazole-4-sulfonyl)-pyridin-2-ylmethyl]-amide;
Furo[2,3-c]pyridine-2-carboxylic acid [5-(1-isopropyl-1H-pyrazole-4-sulfonyl)-pyridin-2-ylmethyl]-amide;
Furo[2,3-c]pyridine-2-carboxylic acid [5-(1-methyl-1H-pyrazole-4-sulfonyl)-pyridin-2-ylmethyl]-amide;
Thieno[2,3-c]pyridine-2-carboxylic acid [5-(3,4-dimethoxy-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyridine-6-carboxylic acid [5-(3,4-dimethoxy-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
Furo[2,3-c]pyridine-2-carboxylic acid [5-(3,4-dimethoxy-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
Furo[2,3-c]pyridine-2-carboxylic acid [5-(6-dimethylamino-pyridine-3-sulfonyl)-pyridin-2-ylmethyl]-amide;
1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid [5-(6-(4-methyl-piperazin-1-yl)-pyridine-3-sulfonyl)-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid [5-(6-dimethylamino-pyridine-3-sulfonyl)-pyridin-2-ylmethyl]-amide;
1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid [5-(3,4-dimethoxy-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyridine-6-carboxylic acid [5-(1-oxetan-3-yl-piperidine-4-sulfonyl)-pyridin-2-ylmethyl]-amide;
Furo[2,3-c]pyridine-2-carboxylic acid [5-(4-(4-methyl-piperazin-1-yl)-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
1,3-Dihydro-pyrrolo[3,4-c]pyridine-2-carboxylic acid [5-(3,5-difluoro-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyridine-6-carboxylic acid [5-(2-dimethylamino-thiazole-5-sulfonyl)-pyridin-2-ylmethyl]-amide;
Thieno[2,3-c]pyridine-2-carboxylic acid [5-(2-dimethylamino-thiazole-5-sulfonyl)-pyridin-2-ylmethyl]-amide;
Thieno[2,3-c]pyridine-2-carboxylic acid [5-(1-propyl-lH-pyrazole-4-sulfonfyl)-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyridine-6-carboxylic acid [5-(3-trifluoromethyl-benzensulfonfyl)-pyrimidin-2-ylmethyl]-amide;
Thieno[2,3-c]pyridine-2-carboxylic acid [5-(6-trifluoromethyl-pyridine-3-sulfonfyl)-pyridin-2-ylmethyl]-amide;
Furo[2,3-c]pyridine-2-carboxylic acid [5-(6-trifluoromethyl-pyridine-3-sulfonfyl)-pyridin-2-ylmethyl]-amide;
1,3-Dihydro-pyrrolo[3,4-c]pyridine-2-carboxylic acid [5-(1-isopropyl-lH-pyrazole-4-sulfonfyl)-pyridin-2-ylmethyl]-amide;
Furo[2,3-c]pyridine-2-carboxylic acid [5-(3-trifluoromethyl-benzensulfonfyl)-pyrimidin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyridine-6-carboxylic acid [5-(6-trifluoromethyl-pyridine-3-sulfonfyl)-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyridine-6-carboxylic acid [5-(6-dimethylamino-pyridine-3-sulfonfyl)-pyridin-2-ylmethyl]-amide;
1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid [5-(6-dimethylamino-pyridine-3-sulfonfyl)-pyridin-2-ylmethyl]-amide;
1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid [5-(3-fluoro-5-morpholin-4-yl-benzensulfonfyl)-pyridin-2-ylmethyl]-amide;
2-Amino-5,7-dihydro-pyrrolo[3,4-d]pyrimidine-6-carboxylic acid [5-(3,5-difluorobenzensulfonfyl)-pyridin-2-ylmethyl]-amide;
Furo[2,3-c]pyridine-2-carboxylic acid [5-(3-trifluoromethyl-benzensulfonfyl)-pyridin-2-ylmethyl]-amide (racemic);
Furo[2,3-c]pyridine-2-carboxylic acid [5-(3-fluoro-5-morpholin-4-yl-benzensulfonfyl)-pyridin-2-ylmethyl]-amide;
1,3-Dihydro-pyrrolo[3,4-c]pyridine-2-carboxylic acid [5-(3-trifluoromethoxy-benzensulfonfyl)-pyridin-2-ylmethyl]-amide (racemic);
Furo[2,3-c]pyridine-2-carboxylic acid [5-(3-trifluoromethoxy-benzensulfonfyl)-pyridin-2-ylmethyl]-amide (racemic);
Furo[2,3-c]pyridine-2-carboxylic acid [5-(4-pyrrolidin-1-yl-piperidine-1-sulfonfyl)-pyridin-2-ylmethyl]-amide;
Imidazo[1,2-a]pyridine-6-carboxylic acid [5-(6-methyl-pyridine-3-sulfonfyl)-pyridin-2-ylmethyl]-amide;
amide;  
Furo[2,3-c]pyridine-2-carboxylic acid [5-(6-methyl-pyridine-3-sulfonyl)-pyridin-2-ylmethyl]-amide;  
Thieno[2,3-c]pyridine-2-carboxylic acid [5-(6-methyl-pyridine-3-sulfonyl)-pyridin-2-ylmethyl]-amide;  
Imidazo[1,2-a]pyridine-6-carboxylic acid [5-(3-ethanesulfonyl-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;  
1,3-Dihydro-pyrrolo[3,4-c]pyridine-2-carboxylic acid [5-(4-morpholin-4-yl-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;  
1,3-Dihydro-pyrrolo[3,4-c]pyridine-2-carboxylic acid [5-(2-dimethylamino-thiazole-5-sulfonyl)-pyridin-2-ylmethyl]-amide;  
1,3-Dihydro-pyrrolo[3,4-c]pyridine-2-carboxylic acid [5-(1-methyl-1H-pyrazole-4-sulfonyl)-pyridin-2-ylmethyl]-amide;  
1,3-Dihydro-pyrrolo[3,4-c]pyridine-2-carboxylic acid [5-(3-fluoro-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;  
Imidazo[1,2-a]pyridine-6-carboxylic acid [5-(3-trifluoromethoxy-benzenesulfinyl)-pyridin-2-ylmethyl]-amide (racemic);  
Furo[2,3-c]pyridine-2-carboxylic acid [5-(1-isobutyl-piperidine-4-sulfonyl)-pyridin-2-ylmethyl]-amide (racemic);  
Furo[2,3-c]pyridine-2-carboxylic acid [5-(1-oxetan-3-yl-piperidine-4-sulfonyl)-pyridin-2-ylmethyl]-amide;  
1,3-Dihydro-pyrrolo[3,4-c]pyridine-2-carboxylic acid [5-(1-oxetan-3-yl-piperidine-4-sulfonyl)-pyridin-2-ylmethyl]-amide;  
Furo[2,3-c]pyridine-2-carboxylic acid {5-[1-(tetrahydro-pyran-4-yl)-piperidine-4-sulfonyl]-pyridin-2-ylmethyl}-amide;  
1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid [5-(3-ethanesulfonyl-benzenesulfonyl)-pyridin-2-ylmethyl]-amide;  
1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid [5-(6-trifluoromethyl-pyridine-3-sulfonyl)-pyridin-2-ylmethyl]-amide;  
1,3-Dihydro-pyrrolo[3,4-c]pyridine-2-carboxylic acid [5-(1-butyl-piperidine-4-sulfonyl)-pyridin-2-ylmethyl]-amide;  
N-[[1-(2,2,2-trifluoroethyl)-4-piperidyl]sulfonyl]-1-pyridyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide;
N-[[5-[(6-(4-methylpiperazin-1-yl)-3-pyridyl)sulfonyl]-2-pyridyl]methyl]furo[2,3-c]pyridine-2-carboxamide; and
N-[[5-(3-ethylsulfonylphenyl)sulfonyl-2-pyridyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide and pharmaceutically acceptable salts thereof.

[0301] In some embodiments, the Nampt small molecule antagonist can further be chosen from Nampt antagonists selected from the group consisting of:

N-[[5-[(3,5-difluorophenyl)sulfinyl-2-pyridyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[5-[(6-aniino-3-pyridyl)sulfonyl]-2-pyridyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[[5-[(1-(2,2,2-trifluoroethyl)-4-piperidyl)sulfinyl]-2-pyridyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[[5-[(1-tetrahydropyranyl-4-yl-4-piperidyl)sulfonyl]-2-pyridyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[5-[(3-(trifluoromethyl)phenyl)sulfonyl]-2-pyridyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[5-[(1-(2-methoxyacetyl)-4-piperidyl)sulfonyl]-2-pyridyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[5-[(1-(2-methoxyacetyl)-4-piperidyl)sulfonyl]-2-pyridyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[[5-[(1-tetrahydrofuran-3-yl-4-piperidyl)sulfonyl]-2-pyridyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[5-[(1-(2,2,2-trifluoroethyl)-4-piperidyl)sulfonyl]-2-pyridyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[[5-[(1-tetrahydrofuran-3-y1-4-piperidyl)sulfonyl]-2-pyridyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[[5-[(1-tetrahydrofuran-3-yl-4-piperidyl)sulfonyl]-2-pyridyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[5-[(1-1-tetrahydrofuran-3-yl-4-piperidyl)sulfonyl]-2-pyridyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[[5-[(1-1-tetrahydrofuran-3-yl-4-piperidyl)sulfonyl]-2-pyridyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
6-carboxamide; 
N-[[5-(3-methylsulfonylphenyl)sulfonyl-2-pyridyl]methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide; 
N-[[5-(3-ethylsulfonylphenyl)sulfonyl-2-pyridyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide 
N-[[5-(3-methylsulfonylphenyl)sulfonyl-2-pyridyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide 
N-[[5-(l-propylpyrazol-4-yl)sulfonyl-2-pyridyl]methyl]-I,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide 
N-[[5-[l-(2,2,2-trifluoroethyl)-4-piperidyl]sulfonyl-2-pyridyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide 
N-[[5-[2-[ethyl(methyl)amino]thiazol-5-yl]sulfonyl-2-pyridyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide 
N-[[5-[2-[ethyl(methyl)amino]thiazol-5-yl]sulfonyl-2-pyridyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide 
N-[[5-[(4-pyrrolidin-1-yl-1-piperidyl)sulfonyl]-2-pyridyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide 
N-[[5-[(4-pyrrolidin-1-yl-1-piperidyl)sulfonyl]-2-pyridyl]methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide 
N-[[5-[(6-amino-3-pyridyl)sulfonyl]-2-pyridyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide 
N-[[5-[[1-(2,2,2-trifluoroethyl)-4-piperidyl]sulfonyl]-2-pyridyl]methyl]imidazo[1,2-a]pyridine-6-
carboxamide
N-[5-[1-(2,2,2-trifluoroethyl)-4-piperidyl] sulfonyl]-2-pyridyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[5-(3-morpholinophenyl)sulfonyl-2-pyridyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[5-(3-cyanophenyl)sulfonyl-2-pyridyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[5-(3-morpholinophenyl) sulfonyl-2-pyridyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[5-(3-cyanophenyl) sulfonyl-2-pyridyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
N-[5-(3,5-difluorophenyl) sulfonyl-2-pyridyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide (enantiomer 1)
N-[5-(3,5-difluorophenyl) sulfonyl-2-pyridyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide (enantiomer 2)
N-[5-[(1-tetrahydropyran-4-yl)-4-piperidyl]) sulfonyl]-2-pyridyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[5-[(1-tetrahydropyran-4-yl)-4-piperidyl]) sulfonyl]-2-pyridyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[5-[(5-chloro-3-pyridyl)sulfonyl]-2-pyridyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[5-[(trifluoromethyl)-3-pyridyl] sulfonyl]-2-pyridyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[5-[(1-(2,2,2-trifluoroethyl)-4-piperidyl) sulfonyl]-2-pyridyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[5-(2-morpholinopyrimidin-5-yl)sulfonyl]-2-pyridyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[5-[(trifluoromethyl)-3-pyridyl] sulfonyl]-2-pyridyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[5-[(trifluoromethyl)-3-pyridyl] sulfonyl]-2-pyridyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[5-[(5-chloro-3-pyridyl)sulfonyl]-2-pyridyl]methyl]furo[2,3-c]pyridine-2-carboxamide
N-[5-[(trifluoromethyl)-3-pyridyl] sulfonyl]-2-pyridyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
N-[5-[(1-propylpyrazol-4-yl)sulfonyl]-2-pyridyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[5-[(1-isobutyl-4-piperidyl) sulfinyl]-2-pyridyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
N-[5-[(1-(2,2,2-trifluoroethyl)-4-piperidyl) sulfinyl]-2-pyridyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
carboxamide

N-[[5-[(5-cyano-3-pyridyl)sulfonyl]-2-pyridyl]methyl]furo[2,3-c]pyridine-2-carboxamide
N-[[5-[(1-isopropylpyrazol-4-yl)sulfonyl]-2-pyridyl]methyl]-IH-pyrrolo[3,2-c]pyridine-2-carboxamide
N-[[5-[(1-ethylpyrazol-4-yl)sulfonyl]-2-pyridyl]methyl]-3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
N-[[5-(benzenesulfonyl)-2-pyridyl]methyl]-4,6-dihydropyrrolo[3,4-c]pyrazole-5-carboxamide
N-[[5-(benzenesulfonyl)-2-pyridyl]methyl]-1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazole-5-carboxamide
N-[[5-(1-piperidylsulfonyl)-2-pyridyl]methyl]-4,6-dihydropyrrolo[3,4-c]pyrazole-5-carboxamide

and pharmaceutically acceptable salts thereof.

[0302] In some embodiments, the Nampt small molecule antagonist can further be chosen from compounds of Formula I as follows:

wherein:
E is O or is absent;
R is (a) an 8-, 9-, or 10-membered bicyclic heteroaryl comprising one heteroatom selected from N, S, and O, and one, two, or three additional N atoms, wherein said bicyclic heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy, and wherein one or more N atoms of said bicyclic heteroaryl is optionally an N-oxide; or
(b) a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or
monocyclic six-membered heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy;

R₁ is (1) a saturated, monocyclic heterocycloalkyl, which is unsubstituted or substituted with one or more substituents R³;

wherein each R³ substituent is independently selected from the group consisting of:
deuterium, halo, hydroxy, cyano, -NR²R³, -alkylaryl-NR²R³, oxo, alkyl, hydroxyalkyl, cyanoalkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl-, -S-alkyl, alkenyl, alkylnyl, aryl, arylalkyl-, aryloxy-, aryalkoxy-, cycloalkyl, cycloalkoxy, (cycloalkyl)alkyl-, heterocycloalkyl, (heterocycloalkyl)alkyl-, (heterocycloalkyl)alkoxy-, -C(0)alkyl, -C0₂alkyl, -C0₂H, -C(0)cycloalkyl, -C(0)heterocycloalkyl, -S(0)-alkyl, -S0₂-aryl, -S0₂-haloalkyl, -CONH₂, C(0)NH(alkyl), -C(0)NH(haloalkyl), -C(0)N(al(alkyl), -C(0)NH(cycloalkyl), heteroaryl, (heteroaryl)alkyl-, -N(R°)-C(0)-alkyl, -N(R°)-C(0)-aryl, -N(R°)-C₀₂alkyl, -S₀₂NH₂, -S₀₂NH(alkyl), -S₀₂N(al(alkyl), -S₀₂NH(cycloalkyl), and -N(H)S₀₂alkyl, or two adjacent R³ substituents taken together form a phenyl ring, wherein each of said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and phenyl substituents within R³ is independently unsubstituted or substituted with one or more substituents selected from the group consisting of alkyl, halo, hydroxy, cyano, alkoxy, amino,
-C(0)alkyl, and -C₀₂alkyl;

wherein R³ and R⁵ are each independently H, alkyl, alkoxy, alkoxyalkyl, cyanoalkyl, or haloalkyl; and

R² is H or alkyl; or

(2) a saturated, bicyclic or tricyclic, nitrogen-linked heterocycloalkyl, wherein said heterocycloalkyl comprises a fused, bridged, or spiro bicyclic system, and said heterocycloalkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of: alkyl, halo, haloalkyl, hydroxy, hydroxyalkyl, alkoxy, cyano, cyanoalkyl, oxo, -NR⁴R⁵, -alkylaryl-NR⁴R⁵, -C(0)alkyl, -C₀₂alkyl, and -S₀₂alkyl;

wherein R⁴ is H or alkyl and R⁵ is H, alkyl, haloalkyl, -C(0)alkyl, -C₀₂alkyl, or -S₀₂alkyl; and

R² and R³ are each independently H or deuterium;
or a pharmaceutically acceptable salt thereof.

[0303] In one embodiment, R² is selected from -C(0)aryl.
In one embodiment, each of said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and phenyl substituents within R is substituted with one or more -NHC0 alkyl.

In some embodiments, the Nampt small molecule antagonist can further be chosen from Nampt antagonists selected from the group consisting of:

5H-Imidazo[1,2-b]pyrazole-2-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide;

1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(8-oxa-3-aza-bicyclo[3.2.1]octane-3-sulfonyl)-benzylamide;

Thieno[2,3-c]pyridine-2-carboxylic acid 4-(8-oxa-3-aza-bicyclo[3.2.1]octane-3-sulfonyl)-benzylamide;

Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(8-oxa-3-aza-bicyclo[3.2.1]octane-3-sulfonyl)-benzylamide;

Furo[2,3-c]pyridine-2-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide;

Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide;

Furo[2,3-c]pyridine-2-carboxylic acid 4-(4-methoxy-piperidine-1-sulfonyl)-benzylamide;

Furo[2,3-c]pyridine-2-carboxylic acid 4-(morpholine-4-sulfonyl)-benzylamide;

1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(morpholine-4-sulfonyl)-benzylamide;

Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(morpholine-4-sulfonyl)-benzylamide;

Thieno[2,3-c]pyridine-2-carboxylic acid 4-(morpholine-4-sulfonyl)-benzylamide;

Furo[2,3-c]pyridine-2-carboxylic acid 4-(4-cyano-piperidine-1-sulfonyl)-benzylamide;

Furo[2,3-c]pyridine-2-carboxylic acid 4-(4-cyanomethyl-piperidine-1-sulfonyl)-benzylamide;

1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(morpholine-4-sulfonyl)-benzylamide;

Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(morpholine-4-sulfonyl)-benzylamide;

Imidazo[1,2-b]pyridazine-6-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide;

Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-methyl-piperazine-1-sulfonyl)-benzylamide;

Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-isopropyl-piperazine-1-sulfonyl)-benzylamide;

Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-hydroxy-piperidine-1-sulfonyl)-benzylamide (racemic);

1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(tetrahydro-pyran-4-sulfonyl)-benzylamide;

Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(tetrahydro-pyran-4-sulfonyl)-benzylamide;

Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(4-methyl-piperazine-1-sulfonyl)-benzylamide;

1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(tetrahydro-pyran-4-sulfonyl)-benzylamide;

Furo[2,3-c]pyridine-2-carboxylic acid 4-(tetrahydro-pyran-4-sulfonyl)-benzylamide;

Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(2,2,2-trifluoro-ethyl)-piperazine-1-sulfonyl]-benzylamide;

Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(8-oxa-3-aza-bicyclo[3.2.1]octane-3-sulfonyl)-benzylamide;

1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(8-oxa-3-aza-bicyclo[3.2.1]octane-3-sulfonyl)-
benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-hydroxy-piperidine-1-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(4-hydroxy-piperidine-1-sulfonyl)-benzylamide;
1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(4-hydroxy-piperidine-1-sulfonyl)-benzylamide;
1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(4-hydroxy-piperidine-1-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(3-hydroxy-piperidine-1-sulfonyl)-benzylamide (racemic);
1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(3-hydroxy-piperidine-1-sulfonyl)-benzylamide (racemic);
Furo[2,3-c]pyridine-2-carboxylic acid 4-(3-hydroxy-piperidine-1-sulfonyl)-benzylamide (racemic);
1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(3-hydroxy-piperidine-1-sulfonyl)-benzylamide (racemic);
Furo[2,3-c]pyridine-2-carboxylic acid 4-(4-hydroxy-piperidine-1-sulfonyl)-benzylamide;
1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-[4-(2,2-difluoro-ethylamino)-piperidine-1-sulfonyl]-benzylamide;
Furo[2,3-c]pyridine-2-carboxylic acid 4-[4-(2-methoxy-ethylamino)-piperidine-1-sulfonyl]-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-cyclohexyl-piperazine-1-sulfonyl)-benzylamide;
1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(piperidine-4-sulfonyl)-benzylamide;
Thieno[2,3-c]pyridine-2-carboxylic acid 4-((1R,3R,5S)-3-amino-8-aza-bicyclo[3.2.1]octane-8-sulfonyl)-benzylamide;
[1,2,4]Triazolo[1,5-a]pyridine-6-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide;
Thieno[2,3-c]pyridine-2-carboxylic acid 4-((3R,5S)-3,5-dimethyl-piperazine-1-sulfonyl)-benzylamide;
Furo[2,3-c]pyridine-2-carboxylic acid 4-[l-(tetrahydro-pyran-4-yl)-piperidine-4-sulfonyl]-benzylamide;
Pyrazolo[1,5-a]pyridine-5-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide;
1H-Pyrazolo[4,3-b]pyridine-6-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide;
1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(3-hydroxy-piperidine-1-sulfonyl)-benzylamide;
Furo[2,3-c]pyridine-2-carboxylic acid 4-((S)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide;
1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-((S)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((R)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((S)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide;
[1-(4-[[Imidazo[1,2-a]pyridine-6-carbonyl]-amino]-methyl]-benzenesulfonyl]-piperidin-4-yl]-
carbamic acid tert-butyl ester;
1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[l-(tetrahydro-pyran-4-yl)-piperidine-4-
sulfonyl]-benzylamide;
1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[4-(2-cyano-ethylamino)-piperidine-1-sulfonyle]-
benzylamide;
Pyrazolo[1,5-a]pyrimidine-5-carboxylic acid 4-(piperidine-1-sulfonyle)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(tetrahydro-pyran-4-yl)-piperazine-1-sulfonyle]-
benzylamide;
cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((3R,5S)-3,5-dimethyl-piperazine-1-sulfonyl)-
benzylamide;
cis-Furo[2,3-c]pyridine-2-carboxylic acid 4-((3R,5S)-3,5-dimethyl-piperazine-1-sulfonyle)-
benzylamide;
Furo[2,3-c]pyridine-2-carboxylic acid 4-(l-acetyl-piperidine-4-sulfonyl)-benzylamide;
1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[l-(2,2,2-trifluoro-ethyl)-piperidine-4-sulfonyle]-
benzylamide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-[1-(2,2,2-trifluoro-ethyl)-piperidine-4-sulfonyle]-
benzylamide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-[1-(2,2,2-trifluoro-ethyl)-piperidine-4-sulfonyle]-
benzylamide;
1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-[l-(2,2,2-trifluoro-ethyl)-piperidine-4-sulfonyle]-
benzylamide;
Furo[2,3-c]pyridine-2-carboxylic acid 4-[l-(2,2,2-trifluoro-ethyl)-piperidine-4-sulfonyle]-
benzylamide;
1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-[l-(tetrahydro-pyran-4-yl)-piperidine-4-sulfonyle]-
benzylamide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-[l-(tetrahydro-pyran-4-yl)-piperidine-4-sulfonyle]-
benzylamide;
cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((3aR,6aS)-5,5-difluoro-hexahydro-
cyclopenta[c]pyrrole-2-sulfonyl)-benzylamide;
cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((3aR,6aS)-(tetrahydro-furo[3,4-c]pyrrol-5-
yl)sulfonyl]-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(hexahydro-furo[2,3-c]pyrrole-5-sulfonyle)-
benzylamide (mixture of diastereomers);
cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4,4-difluoro-hexahydro-cyclopenta[c]pyrrole-2-
sulfonyl)-benzylamide (isomer A); 
cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4,4-difluoro-hexahydro-cyclopenta[c]pyrrole-2-sulfonyl)-benzylamide (isomer B);
IH-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-[(S)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-[(S)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[(S)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-[(S)-(tetrahydro-furan-3-yl)-piperidine-4-sulfonylethyl]-benzylamide;
IH-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-[(R)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-[(R)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[(R)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-[(R)-(tetrahydro-furan-3-yl)-piperidine-4-sulfonylethyl]-benzylamide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-[(S)-(3R,5S)-3,5-dimethyl-4-(2,2,2-trifluoro-ethyl)-piperazine-1-sulfonyl]-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[(3S,4S)-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)sulfonyl]-benzylamide;
IH-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[(1-acetyl-piperidine-4-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-[(1-acetyl-piperidine-4-sulfonyl)-benzylamide;
Furo[2,3-c]pyridine-2-carboxylic acid 4-[(R)-3-hydroxy-piperidine-1-sulfonyl]-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[(3R,5S)-3,5-dimethyl-4-(2,2,2-trifluoro-ethyl)-piperazine-1-sulfonyl]-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[(3S,4S)-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)sulfonyl]-benzylamide;
IH-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[(1-acetyl-piperidine-4-sulfonyl)-benzylamide;
Furo[2,3-c]pyridine-2-carboxylic acid 4-[(S)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide;
IH-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[(S)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide;
Furo[2,3-c]pyridine-2-carboxylic acid 4-[(R)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide;
IH-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[(R)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(piperidine-4-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-oxetan-3-yl-piperazine-1-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-acetyl-piperazine-1-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[(2-hydroxy-ethyl)-piperazine-1-sulfonyl]-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-cyano-piperidine-1-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-hydroxymethyl-piperidine-1-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-pyrrolidin-1-yl-piperidine-1-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-methoxy-ethyl-piperazine-1-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3,3-difluoro-pyrrolidine-1-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-acetyl-[1,4]diazepane-1-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[3-(acetyl-methyl-amino)-pyrrolidine-1-sulfonyle]-benzylamide (racemic);
7-(4-{[(imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl}-benzenesulfonyl)-2,7-diaza-spiro[4.5]decane-2-carboxylic acid tert-butyl ester (racemic);
8-(4-{[(imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl}-benzenesulfonyl)-2,8-diaza-spiro[4.5]decane-2-carboxylic acid tert-butyl ester;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(2-cyano-ethyl)-piperazine-1-sulfonyle]-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(2-dimethylamino-ethyl)-piperazine-1-sulfonyle]-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((R)-2-hydroxymethyl-pyrrolidine-1-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((S)-2-hydroxymethyl-pyrrolidine-1-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((S)-3-dimethylamino-pyrrolidine-1-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(4-methyl-piperazine-1-carbonyl)-piperidine-1-sulfonyl]-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(4-methyl-piperazine-1-yl)-piperidine-1-sulfonyle]-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-trifluoromethyl-pyrrolidine-1-sulfonyle)-benzylamide (racemic);
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4,4-difluoro-piperidine-1-sulfonyle)-benzylamide;
1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(1-acetyl-piperidine-4-sulfonyle)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(1-oxetan-3-yl-piperidine-4-sulfonyle)-benzylamide;
1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(1-oxetan-3-yl-piperidine-4-sulfonyle)-benzylamide;
Furo[2,3-c]pyridine-2-carboxylic acid 4-(1-oxetan-3-yl-piperidine-4-sulfonyle)-benzylamide;
1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(4-oxetan-3-yl-piperazine-1-sulfonyle)-benzylamide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(1-oxetan-3-yl-piperidine-4-sulfonyle)-benzylamide;
Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(4-oxetan-3-yl-piperazine-1-sulfonyle)-benzylamide;
Thieno[2,3-c]pyridine-2-carboxylic acid 4-(1-oxetan-3-yl-piperidine-4-sulfonyle)-benzylamide;
9-(4-{[(imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl}-benzenesulfonyl)-3,9-diaza-
spiro[5.5]undecane-3-carboxylic acid tert-butyl ester;
9-(4-{{imidazo[1,2-a]pyridine-6-carbonyl}-amino}-methyl)-benzenesulfonyl)-2,9-diazaspiro[5.5]undecane-2-carboxylic acid tert-butyl ester;
8-(4-{{imidazo[1,2-a]pyridine-6-carbonyl}-amino}-methyl}-benzenesulfonyl)-1,8-diazaspiro[5.5]undecane-1-carboxylic acid tert-butyl ester (racemic);
4-(4-{{imidazo[1,2-a]pyridine-6-carbonyl}-amino}-methyl}-benzenesulfonyl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylic acid tert-butyl ester;
8-(4-{{imidazo[1,2-a]pyridine-6-carbonyl}-amino}-methyl}-benzenesulfonyl)-1,8-diazaspiro[4.5]decane-1-carboxylic acid tert-butyl ester;
4-(4-{{imidazo[1,2-a]pyridine-6-carbonyl}-amino}-methyl}-benzenesulfonyl)-1,2-oxa-4,8-diazaspiro[5.5]undecane-8-carboxylic acid tert-butyl ester (racemic);
7-(4-{{imidazo[1,2-a]pyridine-6-carbonyl}-amino}-methyl}-benzenesulfonyl)-7-azaaspiro[3.5]non-2-yl-carbamic acid tert-butyl ester;
cis-3-(4-{{imidazo[1,2-a]pyridine-6-carbonyl}-amino}-methyl}-benzenesulfonyl)-3,6-diazbicyclo[3.2.0]heptane-6-carboxylic acid tert-butyl ester (racemic);
2-(4-{{imidazo[1,2-a]pyridine-6-carbonyl}-amino}-methyl}-benzenesulfonyl)-2-aza(bicyclo[2.1.1]hex-l-ylmethyl)-carbamic acid tert-butyl ester;
cis-4-(4-{{imidazo[1,2-a]pyridine-6-carbonyl}-amino}-methyl}-benzenesulfonyl)-hexahydro-pyrrolo[3,4-b][1,4]oxazine-6-carboxylic acid tert-butyl ester (racemic);
2-(4-{{imidazo[1,2-a]pyridine-6-carbonyl}-amino}-methyl}-benzenesulfonyl)-2,9-diazaspiro[5.5]undecane-9-carboxylic acid tert-butyl ester;
cis-[3-(4-{{imidazo[1,2-a]pyridine-6-carbonyl}-amino}-methyl}-benzenesulfonyl]-3-aza(bicyclo[3.1.0]hex-l-yl)-carbamic acid tert-butyl ester (racemic);
cis-7-(4-{{imidazo[1,2-a]pyridine-6-carbonyl}-amino}-methyl}-benzenesulfonyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester (racemic);
cis-4-(4-{{imidazo[1,2-a]pyridine-6-carbonyl}-amino}-methyl}-benzenesulfonyl)-hexahydro-pyrrolo[3,4-b][1,4]oxazine-6-carboxylic acid tert-butyl ester (racemic);
cis-1-(4-{{imidazo[1,2-a]pyridine-6-carbonyl}-amino}-methyl}-benzenesulfonyl)-hexahydro-pyrrolo[3,4-b]pyrrole-5-carboxylic acid tert-butyl ester (racemic);
cis-5-(4-{{imidazo[1,2-a]pyridine-6-carbonyl}-amino}-methyl}-benzenesulfonyl)-hexahydro-pyrrolo[3,4-b]pyrrole-1-carboxylic acid tert-butyl ester (racemic);
cis-5-(4-{{imidazo[1,2-a]pyridine-6-carbonyl}-amino}-methyl}-benzenesulfonyl)-hexahydro-pyrrolo[3,4-c]pyrrole-2-carboxylic acid tert-butyl ester (racemic);
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(9-hydroxy-3-oxa-7-aza(bicyclo[3.3.1]nonane-7-sulfonyl)]benzylamide (mixture of diastereomers);
trans-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-hydroxy-4-methyl-pyrrolidine-1-sulfonyl)]benzylamide (racemic);
cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(7-hydroxy-3-oxa-9-aza-bicyclo[3.3.1]nonane-9-sulfonyl)-benzylamide (racemic);
cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(5,5-difluoro-2-aza-bicyclo[2.2.1]heptane-2-sulfonyl)-benzylamide (racemic);
cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(7-methyl-9-oxa-3,7-diaza-bicyclo[3.3.1]nonane-3-sulfonyl)-benzylamide (racemic);
cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(5-methyl-hexahydro-pyrrolo[3,4-b]pyrrole-1-sulfonyl)-benzylamide (racemic);
cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(l-methyl-hexahydro-pyrrolo[3,4-b]pyrrole-5-sulfonyl)-benzylamide (racemic);
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-hydroxy-4-methyl-piperidine-1-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(hexahydro-furo[3,2-c]pyrrole-5-sulfonyl)-benzylamide (mixture of diastereomers);
cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(6,6-difluoro-3-aza-bicyclo[3.2.0]heptane-3-sulfonyl)-benzylamide (racemic);
Pyrazolo[1,5-a]pyrazine-2-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide;
Furo[2,3-c]pyridine-2-carboxylic acid 4-(4-oxetan-3-yl-piperazine-1-sulfonyl)-benzylamide;
Furo[2,3-c]pyridine-2-carboxylic acid 4-((S)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide;
Furo[2,3-c]pyridine-2-carboxylic acid 4-((R)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(2,8-diaza-spiro[4.5]decan-8-sulfonyl)-benzylamide;
Furo[2,3-c]pyridine-2-carboxylic acid 4-(tetrahydro-furo[3,4-c]pyrrole-5-sulfonyl)-benzylamide (mixture of diastereomers);
1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(tetrahydro-pyran-3-sulfonyl)-benzylamide (racemic);
1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(tetrahydro-pyran-3-sulfonyl)-benzylamide (racemic);
1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(4-pyrrolidin-1-yl-piperidine-1-sulfonyl)-benzylamide;
Furo[2,3-c]pyridine-2-carboxylic acid 4-(4-pyrrolidin-1-yl-piperidine-1-sulfonyl)-benzylamide;
1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(tetrahydro-furo[3,4-c]pyrrole-5-sulfonyl)-benzylamide (mixture of diastereomers);
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(2-aza-bicyclo[2.1.1]hexane-2-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-aza-bicyclo[3.1.0]hexane-3-sulfonyl)-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-hydroxy-3-methyl-pyrrolidine-1-sulfonyl)-benzylamide;
benzylamide (racemic);
cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(9-methyl-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane-7-sulfonyl)-benzylamide (racemic);
cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(5-acetyl-2,5-diaza-bicyclo[2.2.1]heptane-2-sulfonyl)-benzylamide (racemic);
cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(5-fluoro-2-aza-bicyclo[2.2.1]heptane-2-sulfonyl)-benzylamide (racemic);
cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-methyl-3,6-diaza-bicyclo[3.2.1]octane-6-sulfonyl)-benzylamide (racemic);
cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(2-aza-bicyclo[3.2.1]heptane-2-sulfonyl)-benzylamide (racemic);
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(2,6-dioxo-9-aza-spiro[4.5]decane-9-sulfonyl)-benzylamide (racemic);
Furo[2,3-c]pyridine-2-carboxylic acid 4-(tetrahydro-pyran-3-sulfonyl)-benzylamide (racemic);
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(tetrahydro-pyran-3-sulfonyl)-benzylamide (racemic);
Furo[2,3-c]pyridine-2-carboxylic acid 4-[4-(tetrahydro-pyran-4-yl)-piperazine-1-sulfonyl]-benzylamide;
Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(1-acetyl-piperidine-4-sulfonyl)-benzylamide;
cis-lH-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(2-oxa-5-aza-bicyclo[2.2.1]heptane-5-sulfonyl)-benzylamide (racemic);
IH-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[4-(2-methoxy-ethyl)-piperazine-1-sulfonyl]-benzylamide;
IH-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(4-hydroxymethyl-piperidine-1-sulfonyl)-benzylamide;
IH-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(3,3-difluoro-pyrrolidine-1-sulfonyl)-benzylamide;
cis-lH-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(4,4-difluoro-hexahydro-cyclopenta[c]pyrrole-2-sulfonyl)-benzylamide (racemic);
cis-lH-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(5,5-difluoro-hexahydro-cyclopenta[c]pyrrole-2-sulfonyl)-benzylamide (racemic);
cis-lH-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(hexahydro-furo[2,3-c]pyrrole-5-sulfonyl)-benzylamide (racemic);
Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(1-isobutyl-piperidine-4-sulfanyl)-benzylamide (racemic);
Furo[2,3-c]pyridine-2-carboxylic acid 4-(1-isobutyl-piperidine-4-sulfanyl)-benzylamide (racemic);
IH-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(1-isobutyl-piperidine-4-sulfanyl)-benzylamide
(racemic);
IH-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(1-isobutyl-piperidine-4-sulfinyl)-benzylamide (racemic);
8-(4-[[Imidazo[1,2-a]pyridine-6-carbonyl]-amino]-methyl)-benzenesulfonyl)-1,8-diazaspiro[4.6]undecane-1-carboxylic acid tert-butyl ester (racemic);
3-[4-[[Imidazo[1,2-a]pyridine-6-carbonyl]-amino]-methyl]-benzenesulfonylamino]-methyl]-1-oxa-8-aza-spiro[4.5]decane-8-carboxylic acid tert-butyl ester (racemic);
1-(4-[[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl]-benzenesulfonyl)-1,8-diazaspiro[4.5]decane-8-carboxylic acid tert-butyl ester;
3-[1-(4-[[Imidazo[1,2-a]pyridine-6-carbonyl]-amino]-methyl]-benzenesulfonyl]-2,3-dihydro-IH-indol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester (mixture of diastereomers);
N-(4-(1-isobutylpiperidin-4-ylsulfinyl)benzyl)H-imidazo[1,2-a]pyridine-6-carboxamide (racemic);
N-[4-[[1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide;
N-[4-[[1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[4-[[1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide (single isomer);
N-[4-[[1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide (single isomer);
N-[4-(2,8-diazaspiro[3.5]nonan-2-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
N-[4-(4-tetrahydropyran-4-ylpiperazin-1-yl)sulfonylphenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide; and

[0306] In some embodiments, the Nampt small molecule antagonist can further be chosen from Nampt antagonists selected from the group consisting of:
N-[(4-tetrahydropyran-4-ylsulfonylphenyl)methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[(4-tetrahydropyran-4-ylsulfonylphenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide;
N-[(4-tetrahydropyran-4-ylsulfonylphenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide;
N-[(4-tetrahydropyran-4-ylsulfonylphenyl)methyl]-IH-pyrrolo[3,2-c]pyridine-2-carboxamide;
N-[(4-tetrahydropyran-4-ylsulfonyl)phenyl]methyl]furo[23-c]pyridine-2-carboxamide;
N-[(4-(4-piperidylsulfonfonyl)phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[(4-(4-piperidylsulfonfonyl)phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide;
N-[(1-tetrahydropyr an-4-y1-4-piperidyl) sulfonfonylphenyl] methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[(1-tetrahydropyr an-4-y1-4-piperidyl) sulfonfonylphenyl] methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[(1-(2,2,24rifluoroethyl)-4-piperidyl)sulfonfonyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[(1-(2,2,24rifluoroethyl)-4-piperidyl)sulfonfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide;
N-[(1-(2,2,24rifluoroethyl)-4-piperidyl)sulfonfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide;
N-[(1-(2,2,24rifluoroethyl)-4-piperidyl)sulfonfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide;
N-[(1-(2,2,24rifluoroethyl)-4-piperidyl)sulfonfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide;
N-[(1-tetrahydropyr an-4-y1-4-piperidyl)sulfonfonyl]phenyl] methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
N-[(1-tetrahydropyr an-4-y1-4-piperidyl)sulfonfonyl]phenyl] methyl]imidazo[1,2-a]pyridine-6-carboxamide;
N-[(2,6-diazaspiro[3.4]octan-6-ylsulfonfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide;
N-[(1-oxa-7-azaspiro[4,4]nonan-7-yl)sulfonfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide;
N-[(3S)-tetrahydrofuran-3-yl)sulfonfonyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
N-[(3S)-tetrahydrofuran-3-yl)sulfonfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide;
N-[(3S)-tetrahydrofuran-3-yl)sulfonfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide;
N-[(1-tetrahydrofuran-4-yl)-4-piperidyl)sulfanyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide;
N-[(3R)-4-tetrahydrofuran-3-yl)sulfanyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
N-[(3R)-4-tetrahydrofuran-3-yl)sulfanyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide;
N-[(1-acetyl-4-piperidyl)sulfanyl]phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
N-[(1-acetyl-4-piperidyl)sulfanyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide;
N-[(1-acetyl-4-piperidyl)sulfanyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[(3R)-4-tetrahydrofuran-3-yl)sulfanyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[(3R)-4-tetrahydrofuran-3-yl)sulfanyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[(3S)-4-tetrahydrofuran-3-yl)sulfanyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[(3R)-4-tetrahydrofuran-3-yl)sulfanyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[(3R)-4-tetrahydrofuran-3-yl)sulfanyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;}
N-[4-(l-(oxetan-3-yl)-4-piperidyl)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide;
N-[4-(l-(oxetan-3-yl)-4-piperidyl)sulfonyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[4-[l-(oxetan-3-yl)-4-piperidyl]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide;
N-[4-[l-(oxetan-3-yl)-4-piperidyl]sulfonyl]phenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide;
N-[4-[(6-acetyl-2,6-diazaspiro[3.5]heptan-2-yl)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide;
2-amino-N-[(4-morpholinosulfonylphenyl)methyl]-5,7-dihydropyrrolo[3,4-d]pyrimidine-6-carboxamide;
N-[4-(2,7-diazaspiro[3.5]nonan-2-ylsulfonyl)phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide;
N-[4-(2,7-diazaspiro[3.4]octan-2-ylsulfonyl)phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide;
N-[(4-tetrahydropyran-3-ylsulfonyl)phenyl)methyl]-13-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[4-(l-acetyl-4-piperidyl)sulfonyl]phenyl)methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[(4-tetrahydropyran-3-ylsulfonyl)phenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
N-[(4-tetrahydropyran-3-ylsulfonyl)phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[(6-acetyl-2,6-diazaspiro[3.5]heptan-2-yl)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide;
N-[(4-tetrahydropyran-3-ylsulfonylphenyl)methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[(4-tetrahydropyran-3-ylsulfonylphenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide;
2-amino-N-[(4-tetrahydropyran-4-ylsulfonylphenyl)methyl]-5,7-dihydropyrrolo[3,4-d]pyrimidine-6-carboxamide;
N-[(4-(4-tetrahydropyran-4-ylpiperazin-1-yl)sulfonylphenyl)methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[(4-[(l-acetyl-4-piperidyl)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide;
N-[(4-[(oxetan-3-yl)piperazin-1-yl]sulfonylphenyl)methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[(4-(3,3-difluoroazetidin-1-yl)sulfonylphenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[(4-[(1-oxo-2,7-diazaspiro[4.4]nonan-7-yl)sulfonyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[(4-[(7-methyl-2,7-diazaspiro[3.4]octan-2-yl)sulfonyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[(4-[(3S,5R)-3,5-dimethyl-4-(oxetan-3-yl)piperazin-1-yl)sulfonyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[(4-[(1-oxetan-3-yl)-4-piperidyl]sulfonyl]phenyl)methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[(4-(4-methylpiperazin-1-yl)sulfonylphenyl)methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[(4-[(1-tetrahydropyran-4-yl-4-piperidyl)sulfonyl]phenyl)methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[(4-(7-oxa-2-azaspiro[3.5]nonan-2-yl)sulfonyl]phenyl)methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[(4-(4-pyrrolidin-1-yl-l-piperidyl)sulfonyl]phenyl)methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[(4-morpholinosulfonyl]phenyl)methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[(4-[(4,4-diiluoro-l,3,3a,5,6,6a-hexahydrocyclopenta[c]pyrrol-2-yl)sulfonyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[(4-[(5,5-diiluoro-l,3,3a,4,6,6a-hexahydrocyclopenta[c]pyrrol-2-yl)sulfonyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[[4-(3,3-difluoropyrrolidin-1-yl)sulfonyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[[4-(3,3-difluoroazetidin-1-yl)sulfonyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[[4-(2,3,3a,4,6,6a-hexahydropyrrol-5-yl)sulfonyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[[4-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)sulfonyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[[4-[(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide;
N-[[4-[(5-amino-3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide;
N-[[4-(1,8-diazaspiro[4.5]decan-8-yl)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide;
N-[4-(1-oxa-4,8-diazaspiro[5.5]undecan-4-ylsulfonyl)phenyl]methylimidazo[1,2-a]pyridine-6-
carboxamide;
N-[4-[2-amino-7-azaspiro[3.5]nonan-7-yl]sulfonyl]phenyl]methylimidazo[1,2-a]pyridine-6-
carboxamide;
N-[4-(3,9-diazaspiro[5.5]undecan-3-ylsulfonyl)phenyl]methylimidazo[1,2-a]pyridine-6-
carboxamide;
N-[4-(2,9-diazaspiro[5.5]undecan-9-ylsulfonyl)phenyl]methylimidazo[1,2-a]pyridine-6-
carboxamide;
N-[4-(1,8-diazaspiro[5.5]undecan-8-ylsulfonyl)phenyl]methylimidazo[1,2-a]pyridine-6-
carboxamide;
N-[4-(3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-4-ylsulfonyl)phenyl]methylimidazo[1,2-a]pyridine-6-carboxamide;
N-[4-[4-(aminomethyl)-3-azabicyclo[2.2.2]octan-3-yl]sulfonyl]phenyl]methylimidazo[1,2-a]pyridine-6-carboxamide;
N-[4-(233a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrol-5-ylsulfonyl)phenyl]methylimidazo[1,2-a]pyridine-6-carboxamide;
N-[4-(3,6-diazabicyclo[3.2.0]heptan-3-ylsulfonyl)phenyl]methylimidazo[1,2-a]pyridine-6-carboxamide;
N-[4-(2,9-diazaspiro[5.5]undecan-2-ylsulfonyl)phenyl]methylimidazo[1,2-a]pyridine-6-
carboxamide;
N-[4-(33a,4,5,6,6a-hexahydro-2H-pyrrole[23-c]pyrrol-1-ylsulfonyl)phenyl]methylimidazo[1,2-a]pyridine-6-carboxamide;
N-[[4-[(1-benzoyl-4-piperidyl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;  
N-[[4-[[1-(benzenesulfonyl)-3-piperidyl]sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;  
N-[[4-[[1-(benzenesulfonyl)pyrrolidin-3-yl]sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;  
N-[[4-([(1-acetyl-3-piperidyl)sulfonyl]phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;  
N-[[4-[[1-(benzenesulfonyl)-3-piperidyl]sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;  
N-[[4-[(1-methylsulfonyl-3-piperidyl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;  
N-[[4-[(1-benzoyl-3-piperidyl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;  
N-[[4-[(1-benzoylpyrrolidin-3-yl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;  
N-[[4-[(1-ethylsulfonyl-3-piperidyl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;  
N-[[4-[(1-ethylsulfonyl-3-piperidyl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;  
N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]-furo[2,3-c]pyridine-2-carboxamide;  
N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]-furo[2,3-c]pyridine-2-carboxamide;  
N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]-furo[2,3-c]pyridine-2-carboxamide;  
N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]-furo[2,3-c]pyridine-2-carboxamide;  
N-[[4-[(1-tetrahydropyran-4-yl-4-piperidyl)sulfinyl]phenyl]methyl]-furo[2,3-c]pyridine-2-carboxamide;  
N-[[4-[(1-tetrahydropyran-4-yl-4-piperidyl)sulfinyl]phenyl]methyl]-furo[2,3-c]pyridine-2-carboxamide;  
N-[[4-[(1-tetrahydropyran-4-yl-4-piperidyl)sulfinyl]phenyl]methyl]-furo[2,3-c]pyridine-2-carboxamide;  
N-[[4-[(1-tetrahydropyran-4-yl-4-piperidyl)sulfinyl]phenyl]methyl]-furo[2,3-c]pyridine-2-carboxamide;  
N-[[4-[(1-tetrahydropyran-4-yl-4-piperidyl)sulfinyl]phenyl]methyl]-furo[2,3-c]pyridine-2-carboxamide;  
N-[[4-[(1-tetrahydropyran-4-yl-4-piperidyl)sulfinyl]phenyl]methyl]-furo[2,3-c]pyridine-2-carboxamide;  
N-[[4-[(1-tetrahydropyran-4-yl-4-piperidyl)sulfinyl]phenyl]methyl]-furo[2,3-c]pyridine-2-carboxamide;  
N-[[4-[(1-tetrahydropyran-4-yl-4-piperidyl)sulfinyl]phenyl]methyl]-furo[2,3-c]pyridine-2-carboxamide;  
N-[[4-[(1-tetrahydropyran-4-yl-4-piperidyl)sulfinyl]phenyl]methyl]-furo[2,3-c]pyridine-2-carboxamide;  
N-[[4-[(1-tetrahydropyran-4-yl-4-piperidyl)sulfinyl]phenyl]methyl]-furo[2,3-c]pyridine-2-carboxamide;
N-[[4-(1-ethyl-4-piperidyl)sulfinyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide; 
N-[[4-(1-methyl-4-piperidyl)sulfinyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide; 
N-[[4-(1-ethyl-4-piperidyl)sulfinyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide; 
N-[[4-(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide; 
N-[[1 -((2,2,2-triuoroethyl)-4-piperidyl)sulfinyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide; 
N-[[4-(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide; 
N-[[4-(1-tetrahydropyr an-4-yl-4-piperidyl) sulfinyl]phenyl]methyl] -1H-pyrazolo [3,4-b]pyridine-5 -carboxamide; 
N-[[4-[(1-tetrahydropran-4-yl-4-piperidyl)sulfinyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide; 
N-[[4-(1-ethyl-4-piperidyl)sulfinyl]phenyl]methyl]l ,3-dihydropyrrolo[3,4-c]pyridine -2-carboxamide; 
N-[[4-[(1-ethyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ; 
N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl] -1H-pyr azolo [3,4-b]pyridine-5 -carboxamide ;
(b) a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or monocyclic six-membered heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy; and

\[ R^1 \text{ is } H, -(\text{alkylene})_n \text{C}(\text{O})R^2, -(\text{alkylene})_n \text{CO}_2R^3, -(\text{alkylene})_n \text{iSO}_2R^3, -\text{C}(0)\text{NH}(R^4), \text{ or } -\text{C}(0)\text{N}(R^4)^2; \]

wherein each \( R^a \) is independently

1. alkyl, unsubstituted or substituted with one or more \( R^m \) substituents, wherein each \( R^m \) is independently selected from the group consisting of hydroxy, -NR\(^{-}\)R\(^{\circ}\), alkoxy, cyano, halo, -C(0)alkyl, -C\(_2\)alkyl, -CONR\(^{\circ}\)R\(^{-}\), -S(0)alkyl, -SO\(_2\)alkyl, -SO\(_2\)NR\(^{-}\)R\(^{\circ}\), aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, wherein \( R^b \) is H or alkyl;

2. H, alkyl, alkoxyalkyl, haloalkyl, -C(0)alkyl, -C\(_2\)alkyl, or -SO\(_2\)alkyl; and each aryl, heteroaryl, cycloalkyl, and heterocycloalkyl group within \( R^m \) is unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, hydroxy, amino, cyano, halo, -S(0)alkyl, -SO\(_2\)alkyl, haloalkyl, hydroxyalkyl, and alkoxy;

2. phenyl, cycloalkyl, heteroaryl, or heterocycloalkyl, each unsubstituted or substituted with one or more hydroxy, -NR\(^{-}\)R\(^{\circ}\), alkoxy, cyano, halo, -C(0)alkyl, -C\(_2\)alkyl, -CONR\(^{\circ}\)R\(^{-}\), -S(0)alkyl, -SO\(_2\)alkyl, or -SO\(_2\)NR\(^{-}\)R\(^{\circ}\) substituents; or

3. -NR \(^{-}\)R\(^{\circ}\), where \( R^8 \) is H or alkyl; and

\( R^7 \) is H, alkyl, alkoxyalkyl, haloalkyl, -C(0)alkyl, -C\(_2\)alkyl, or -SO\(_2\)alkyl;

\( R^2 \) and \( R^3 \) are each independently H or deuterium; and

\( n \) is 1 or 2;

or a stereoisomer thereof, or a pharmacetically acceptable salt of such a compound or stereoisomer.

[0308] In some embodiments, the Nampt small molecule antagonist can further be chosen from Nampt antagonists selected from the group consisting of:

tert-butyl 2-[(1,3-dihydropyrrolo[3,4-c]pyridine-2-carbonylamino)methyl]-8-azaspiro[2.5]octane-8-carboxylate;

tert-butyl 2-[(thieno[2,3-c]pyridine-2-carbonylamino)methyl]-8-azaspiro[2.5]octane-8-carboxylate;
tert-butyl 2-[(imidazo[1,2-a]pyrimidine-6-carbonylamino)methyl]-8-azaspiro[2.5]octane-8-carboxylate;

tert-butyl 2-[(furo[2,3-c]pyridine-2-carbonylamino)methyl]-8-azaspiro[2.5]octane-8-carboxylate;

tert-butyl 2-[(imidazo[1,2-a]pyridine-6-carbonylamino)methyl]-8-azaspiro[2.5]octane-8-carboxylate;


and
tert-butyl 2-((imidazo[1,2-a]pyridine-6-carboxamido)methyl)-7-azaspiro[3,5]nonane-7-carboxylate and pharmaceutically acceptable salts thereof.

[0309] In some embodiments, the Nampt small molecule antagonist can further be chosen from Nampt antagonists selected from the group consisting of:

tert-butyl 2-[(imidazo[1,2-a]pyridine-6-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;

tert-butyl 2-[(furo[2,3-c]pyridine-2-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
tert-butyl 2-[(13-dihydropyrrolo[3,4-c]pyridine-2-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
tert-butyl 2-[(imidazo[1,2-a]pyridine-6-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
tert-butyl 2-[(imidazo[1,2-a]pyridine-6-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
N-[6-(3,3-dimethylbutanoyl)-6-azaspiro[2.5]octan-2-yl]methyl]-l,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
tert-butyl 2-[(13-dihydropyrrolo[3,4-c]pyridine-2-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
tert-butyl 2-[(13-dihydropyrrolo[3,4-c]pyridine-2-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
N-[[6-[3-(1,2,4-triazol-4-yl)benzoyl]-6-azaspiro[2.5]octan-2-yl]methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[[6-[4-(1,1-dioxo-1,4-thiazinan-4-yl)benzoyl]-6-azaspiro[2.5]octan-2-yl]methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[[6-(4-methyl-1,2,5-oxadiazole-3-carbonyl)-6-azaspiro[2.5]octan-2-yl]methyl]furo[2,3-c]pyridine-2-carboxamide;
isopropyl 2-[(13-dihydropyrrolo[3,4-c]pyridine-2-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
N-[[6-[(4-ripyridyl)acetyl]-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-(2-cyanoacetyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
ethyl 2-[[13-dihydropyrrolo[3,4-c]pyridine-2-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
tert-butyl 2-[[(H^yrrolo[3,2-c]pyridine-2-carbonylamino)methyl]-7-azaspiro[3.5]nonane-7-carboxylate;
tert-butyl 2-[(furo[2,3-c]pyridine-2-carbonylamino)methyl]-7-azaspiro[3.5]nonane-7-carboxylate;
N-[[6-[(2-cyclohexylacetyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-[(3-cyclohexylpropanoyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-[(2-morpholinoacetyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-[(3-phenylpropanoyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
tert-butyl 2-[(13-dihydropyrrolo[3,4-c]pyridine-2-carbonylamino)methyl]-7-azaspiro[3.5]nonane-7-carboxylate;
N-[[6-[[2(3,5-difluorophenyl)acetyl]-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-[(2-3-(trifluoromethyl)phenyl)acetyl]-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-[[2-(3-hydroxybenzyl)phenyl]acetyl]-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-[[2-(3-hydroxybenzyl)phenyl]acetyl]-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
[2,2,2-trideuterio-1,1-bis(trideuteriethyl)methyl] 2-[(1,3-dihydropyrrolo[3,4-c]pyridine-2-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
(2-methoxy-1,1-dimethyl-2-oxo-ethyl) 2-[(furo[2,3-c]pyridine-2-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
N-[[6-[[2-[(3-cyanophenyl)acetyl]-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-[[2-[(4-cyanophenyl)acetyl]-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-[[2-[(4-cyanophenyl)acetyl]-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[(6-benzylsulfonyl-6-azaspiro[2.5]octan-2-yl)methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-((1,3-dihydropyrrolo[3,4-c]pyridine-2-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
N-[[6-(2-tetrahydropyran-4-ylacetyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-(1,3,5-trimethylpyrazole-4-carbonyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-(1-methylpyrazole-4-carbonyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
(1-methylcyclobutyl)2-[(1,3-dihydropyrrolo[3,4-c]pyridine-2-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
N-[[6-(3-morpholinopropanoyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-(2,2-difluoro-2-phenyl-acetyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-(2,1,2,4-triazol-1-ylmethyl)benzoyl]-6-azaspiro[2.5]octan-2-yl]methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[[6-(4-(2,1,2,4-triazol-1-ylmethyl)benzoyl]-6-azaspiro[2.5]octan-2-yl]methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[[6-(4-(1H-1,2,4-triazol-5-yl)benzoyl)-6-azaspiro[2.5]octan-2-yl]methyl]furo[2,3-c]pyridine-2-carboxamide;
tert-butyl 2-[(4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-5-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
N-[[6-2-(1,4-dimethyl-4^iperidyl)acetyl]-6-azaspiro[2.5]octan-2-yl]methyl]furo[2,3-c]pyridine-2-carboxamide;
N-[[6-2-(3-hydroxy-3-methyl-cyclobutyl)acetyl]-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-(13-dimethylpyrazole-4-carbonyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-(2-pyrazin-2-ylacetyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-(3-thiazol-2-ylpropanoyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-(2-phenoxyacetyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-(3-tetrahydropyran-4-ylpropanoyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-(4-methylpyridine-3-carbonyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
N-[[6-(2-tert-butyl-4-methyl-pyrazole-3-carbonyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
N-[[6-(2,4-dimethylpyrazole-3-carbonyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
N-[[6-(1,3,5-trimethylpyrazole-4-carbonyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
N-[[6-(l-(l-isopropylpyrrolidin-3-yl)pyrazole-4-carbonyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;

tert-butyl 3-[2-[(furo[2,3-c]pyridine-2-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carbonyl]-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-5-carboxylate ;
N-[[6-[l-(l-methylpyrrolidin-3-yl)pyrazole-4-carbonyl]-6-azaspiro[2.5]octan-2-yl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
N-[6-[[4-[(4-methylpiperazin-1-yl)methyl]benzoyl]-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-(1,5-dimethylpyrazole-4-carbonyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
(3-methylloxetan-3-yl) 2-[(1,3-dihydropyrrolo[3,4-c]pyridine-2-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
(2-hydroxy-1,1-dimethyl-ethyl) 2-[(1,3-dihydropyrrolo[3,4-c]pyridine-2-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
N-[[6-(4-methylpyridine-3-carbonyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-(4-isoxazol-5-yl-1-methyl-pyrazole-3-carbonyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-(2,4-dimethyloxazole-5-carbonyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-[2-(1,4-dimethyl-4-piperidyl)acetyl]-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-[2-(2-cyanophenyl)acetyl]-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
(2-acetamido-1,1-dimethyl-ethyl) 2-[(1,3-dihydropyrrolo[3,4-c]pyridine-2-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
N-[[6-(2-thiazol-2-ylacetyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-(4-hydroxy-4-methyl-pentanoyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-[(3-methylloxetan-3-yl)carbamoyl]-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-[4-(4-methylpiperazin-1-yl)benzoyl]-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[(6-(1,3,5-trimethylpyrazole-4-carbonyl)-6-azaspiro[2.5]octan-2-yl)methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[(6-(1,3,5-trimethylpyrazole-4-carbonyl)-6-azaspiro[2.5]octan-2-yl)methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
tert-butyl 2-[(1 J33-tetradeteriopyrrolo[3,4-c]pyridine-2-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
N-[(6-(4-isoxazol-5-yl-l-methyl-pyrazole-3-carbonyl)-6-azaspiro[2.5]octan-2-yl)methyl]-lH-pyrrolo[3,2-c]pyridine-2-carboxamide;
N-[(6-(2,2-dimethylcyclopropanecarbonyl)-6-azaspiro[2.5]octan-2-yl)methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
(3-methyltetrahydrofuran-3-yl) 2-[(1,3-dihydropyrrolo[3,4-c]pyridine-2-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
(2-hydroxy-2-methyl-propyl) 2-[(1,3-dihydropyrrolo[3,4-c]pyridine-2-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
N-[(6-(2,2-dimethylpropylsulfonfyl)-6-azaspiro[2.5]octan-2-yl)methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[(6-(4,4,4-trifluorobutanoyl)-6-azaspiro[2.5]octan-2-yl)methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
tert-butyl 2-[(pyrazolo[1,5-b]pyridazine-5-carbonylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
N-[6-[2-methyl-4-(trifluoromethyl)thiazole-5-carbonyl]-6-azaspiro[2.5]octan-2-yl methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[6-(2,2-dimethylcyclopropane-carboxyl)-6-azaspiro[2.5]octan-2-yl methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
tert-butyl 2-[(imidazo[1,2-a]pyridin-6-ylmethylcarbamoylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
N-[6-[2-(2-hydroxy-2-methyl-propoxy)acetyl]-6-azaspiro[2.5]octan-2-yl methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[6-[6-amino-3-pyridyl]acetyl]-6-azaspiro[2.5]octan-2-yl methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[6-(morpholine-4-carbonyl)-6-azaspiro[2.5]octan-2-yl methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[6-[5-(trifluoromethyl)-1H-pyrazole-3-carbonyl]-6-azaspiro[2.5]octan-2-yl methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[6-(4-hydroxy-4-methylpentanoyl)-6-azaspiro[2.5]octan-2-yl methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
N-[6-[4-(trifluoromethyl)pyridine-3-carbonyl]-6-azaspiro[2.5]octan-2-yl methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[6-[2-(4-methyltetrahydropran-4-yl)acetyl]-6-azaspiro[2.5]octan-2-yl methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
(2-hydroxy-2-methyl-propyl) 2-[(1H-pyrrolo[3,2-c]pyridine-2-carbomylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
tert-butyl 2-[(imidazo[1,2-b]pyridazine-6-carbomylamino)methyl]-6-azaspiro[2.5]octane-6-carboxylate;
N-[6-[2-(4-methyl-1-(2,2,2-trifluoroethyl)-4-piperidyl)acetyl]-6-azaspiro[2.5]octan-2-yl methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[6-(2,4-dimethylthiazole-5-carbonyl)-6-azaspiro[2.5]octan-2-yl methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[6-[4-(1-methyl-4-piperidyl)benzoyl]-6-azaspiro[2.5]octan-2-yl methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
1,1,3,3-tetradeutero-N-[[6-(3-methylbutanoyl)-6-azaspiro[2.5]octan-2-yl]methyl]pyrrolo[3,4-c]pyridine-2-carboxamide;
(3-methyloxetan-3-yl) 2-[[1,1,3,3-tetradeuteriopyrrolo[3,4-c]pyridine-2-carbonyl]amino]methyl]-6-azaspiro[2.5]octane-6-carboxylate;
1,1,3,3-tetradeutero-N-[[6-(2,4-dimethyloxazole-5-carbonyl)-6-azaspiro[2.5]octan-2-yl]methyl]pyrrolo[3,4-c]pyridine-2-carboxamide;
N-[(6-benzoyl-6-azaspiro[2.5]octan-2-yl)methyl]-13-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
N-[[6-(4-methyloxazole-5-carbonyl)-6-azaspiro[2.5]octan-2-yl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
(3-methyloxetan-3-yl) 2-[[furo[2,3-c]pyridine-2-carbonylamino]methyl]-6-azaspiro[2.5]octane-6-carboxylate;
N-[(6-benzoyl-6-azaspiro[2.5]octan-2-yl)methyl]-13-dihydropyrrolo[3,4-c]pyridine-2-carboxamide; and
(3-methyloxetan-3 -yl) (2S)-2-[(1,3-dihydropyrrolo [3,4-c]pyridine-2-carbonylamino)methyl] -6-azaspiro[2.5]octane-6-carboxylate.

[0310] In some embodiments, the Nampt small molecule antagonist can further be chosen from compounds of Formula I as follows:

\[ \text{R is} \]

(a) a bicyclic heteroaryl comprising 1, 2, 3, or 4 heteroatom ring members independently selected from N, S or O, wherein said bicyclic heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alky, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy; and wherein one or more N ring members of said heteroaryl is optionally an N-oxide; or

(b) a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or
monocyclic heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is substituted with one or more substituent selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy;

$R^1$ is alkyl, $R^m$, or -alkenyl-R$^m$,

wherein said alkyl is unsubstituted or substituted with one or more substituents selected from the group consisting of deuterium, halo, hydroxy, cyano, alkoxy, -NR$^R$, hydroxyalkyl, cyanoalkyl, haloalkyl, haloalkoxy, alkoxyalkyl, -S-alkyl, -C(0)alkyl, -C0$_2$H, -C(0)NH$_2$, -C(0)NH(alkyl), -C(0)NH(haloalkyl), -C(0)N(alkyl)$_2$,

-SO$_2$NH$_2$, -SO$_2$NH(alkyl), and -SO$_2$N(alkyl)$_2$;

where $R^o$ and $R^s$ are each independently H, alkyl, alkoxyalkyl, haloalkyl, -C(0)alkyl, -C0$_2$alkyl, or -SO$_2$alkyl; and

$R^m$ is cycloalkyl, phenyl, monocyclic heteroaryl, or heterocycloalkyl, each unsubstituted or substituted with one or more substituents $R^x$;

wherein each $R^x$ substituent is independently selected from the group consisting of:

deuteronium, halo, hydroxy, hydroxyalkyl, cyano,

-NR$^R$, -alkenyl-NR$^R$, o xo, alkyl, cyanoalkyl, haloalkyl, alkoxy,

-S-alkyl, haloalkoxy, alkoxyalkyl-, alkenyl, alkynyl, -C(0)alkyl,

-CONH$_2$, C(0)NH(alkyl), -C(0)NH(haloalkyl), -C(0)N(alkyl)$_2$,

-C(0)NH(cycloalkyl), arylalkyl-, arylalkoxy-, aryloxy-, cycloalkyl, cycloalkyloxy, (cycloalkyl)alkyl-, heterocycloalkyl, aryl, (heterocycloalkyl)alkyl-, (heterocycloalkyl)alkoxy-,

-C(0)heterocycloalkyl, heteroaryl, (heteroarylm)alkyl-, -S(0)-alkyl,

-SO$_2$alkyl, -SO$_2$aryl, -SO$_2$fluoroalkyl, -N(R$^s$)-C(0)-alkyl, -N(R$^s$)-C(0)-aryl, -N(R$^s$)-

(C0)$_2$alkyl, -C0$_2$H, -SO$_2$H$_2$, -SO$_2$NH(alkyl),

-SO$_2$N(alkyl)$_2$, -SO$_2$NH(cycloalkyl), and -N(H)(SO$_2$)(alkyl), or two adjacent phenyl or heteroaryl $R^x$ substituents taken together form methylenedioxy,

wherein each of said cycloalkyl, heterocycloalkyl, aryl, and heteroaryl within $R^x$ is unsubstituted or is substituted with 1, 2, or 3 substituents independently selected from the group consisting of alkyl, halo, hydroxy, cyano, alkoxy, amino, -

-C(0)alkyl, and

-C0$_2$alkyl;

wherein $R^s$ and $R^b$ are each independently H, alkyl, alkoxy, alkoxyalkyl, cyanoalkyl, or haloalkyl; and

$R^c$ is H, alkyl, or aryalkyl-; and

$R^2$ and $R^3$ are each independently selected from the group consisting of H and deuterium;

or a pharmaceutically acceptable salt thereof.
In some embodiments, the Nampt small molecule antagonist can further be chosen from Nampt antagonists selected from the group consisting of:

\[
N-[[4-(3-(trifluoromethoxy)phenyl)sulfinylphenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
\]

\[
N-[[4-(3-(trifluoromethyl)phenyl)sulfinylphenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
\]

(R)-N-[[4-(3,5-difluorophenyl)sulfinylphenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide; and

(S)-N-[[4-(3,5-difluorophenyl)sulfinylphenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;

and stereoisomers thereof, and pharmaceutically acceptable salts of said compounds and stereoisomers.

In some embodiments, the Nampt small molecule antagonist can further be chosen from N-[[4-(3,5-difluorophenyl)sulfinylphenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide.

In some embodiments, the Nampt small molecule antagonist can further be chosen from compounds of Formula I:

\[
\text{Formula I:}
\]

\[
\]

wherein:

- \( E \) is \( O \) or is absent;
- \( R \) is (a) an 8-, 9-, or 10-membered bicyclic heteroaryl comprising one heteroatom selected from N, S, and O, and one, two, or three additional N atoms, wherein said bicyclic heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy, and wherein one or more N atoms of said bicyclic heteroaryl is optionally an N-oxide; or

(b) a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or monocyclic six-membered heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy;

- \( R^1 \) is (1) \( R^8 \), where \( R^8 \) is a phenyl, cycloalkyl, heterocycloalkyl, or monocyclic heteroaryl, unsubstituted or substituted with one or more \( R^m \) substituents; wherein each \( R^m \) substituent is independently selected from the group consisting of:

  halo, hydroxy, cyano, -NR\( ^b \), -alkylenyl-NR\( ^b \), oxo, alkyl, hydroxyalkyl, cyanoalkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, -S-alkyl, alkenyl, alkynyl, aryl, arylalkyl-, aryloxy-, aryalkoxy-, cycloalkyl, cycloalkyloxy, (cycloalkyl)alkyl-.
heterocycloalkyl, (heterocycloalkyl)alkyl-, (heterocycloalkyl)alkoxy-, -C(0)alkyl, -C0 2 alkyl, -C0 2 H, -C(0)cycloalkyl, -C(0)heterocycloalkyl, -S(0)-alkyl, -S(0) 2-alkyl, -S0 2-aryl, -S0 2-(haloalkyl), -CONH 2, C(0)NH(alkyl), -C(0)NH(haloalkyl), -C(0)N(alkyl) 2, -C(0)NH(cycloalkyl), heteroaryl, (heteroaryl)alkyl-, -N(R 2)-C(0)-alkyl, -N(R 2)-C(0)-aryl, -N(R 2)-C0 2-alkyl, -S0 2-NH 2, -S0 2-NH(alkyl), -S0 2-N(alkyl) 2, -S0 2-NH(cycloalkyl), and -N(H)(S0 2alkyl), or two adjacent R 2 substituents taken together form a phenyl ring, wherein each of said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and phenyl substituents within R 2 is independently unsubstituted or substituted with one or more substituents selected from the group consisting of alkyl, halo, hydroxy, cyano, alkoxy, amino, -C(0)alkyl, and -C0 2alkyl;
R 1 and R 2 are each independently H, alkyl, alkoxy, alkoxyalkyl, cyanoalkyl, or haloalkyl; and
R 3 is H or alkyl;
(2) -alkynyl-R 3 or -C(0)-alkynamyl-R 3, where R 3 is as defined in (1) above; or
(3) alkyl substituted with one or more R 2 substituents, wherein each R 2 is independently -CONR 2 3R 3, hydroxy, cyano, alkoxy, halo, or -C(0)R 3; wherein R 1 and R 2 are each independently H or alkyl, or R 1 and R 2 taken together with the nitrogen to which they are attached form a monocyclic heterocycloalkyl; and R 1 is alkyl, cycloalkyl, heterocycloalkyl, phenyl, or benzyl, each unsubstituted or substituted with one or more substituents selected from the group consisting of: alkyl, halo, amino, hydroxy, and alkoxy;
R 2 and R 3 are each independently H or deuterium; and
R 4 is H;
an alkyl unsubstituted or substituted with one or more substituents selected from the group consisting of: deuterium, halo, amino, hydroxy, alkoxy, cycloalkyl, heteroaryl, phenyl, and heterocycloalkyl, wherein each cycloalkyl, heteroaryl, phenyl, and heterocycloalkyl is unsubstituted or substituted with one or more substituents selected from the group consisting of: deuterium, alkyl, halo, amino, hydroxy, and alkoxy; or
a cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl, each unsubstituted or substituted with one or more substituents selected from the group consisting of: deuterium, alkyl, halo, amino, hydroxy, and alkoxy; with the proviso that R 4 is not H when R 1 is as defined in (1) above; or a pharmaceutically acceptable salt thereof.
In some embodiments, the Nampt small molecule antagonist can further be chosen from Nampt antagonists selected from the group consisting of:

- N-[4-(4-piperidylmethylsulfamoyl)phenyl]methyl]thieno[2,3-c]pyridine-2-carboxamide;
- N-[4-[bis((3-chlorophenyl)methyl)sulfamoyl]phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
- N-[4-[(dibenzylsulfamoyl)phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
- N-[4-[methyl-((1-methylpyrrolidin-3-yl)sulfamoyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
- N-[4-[methyl-((1-methylpyrrolidin-3-yl)sulfamoyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
- N-[4-[2-(dimethylamino)-2-oxo-ethyl]-methyl-sulfamoyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
- N-[4-[[cyanomethyl(methyl)sulfamoyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
- N-[4-[[methoxyethyl(methyl)sulfamoyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
- N-[4-[[2,3-dihydroxypropyl(methyl)sulfamoyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
- N-[4-[[1-ethylpyrrolidin-3-yl]methyl]-methyl-sulfamoyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
- N-[4-[[1-isopropylpyrrolidin-3-yl]methyl]-methyl-sulfamoyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide; and

N-[4-[(1-isopropyl-4-piperidyl)-methyl-sulfamoyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide and stereoisomers thereof, and pharmaceutically acceptable salts of said compounds and stereoisomers.

In some embodiments, the Nampt small molecule antagonist can further be chosen from Nampt antagonists selected from the group consisting of:
N-[4-[methyl(tetrahydropyran-4-yl)sulfamoyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide;


N-[4-[methyl(tetrahydropyran-4-yl)sulfamoyl]phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide;


N-[4-(2-oxa-9-azaspiro[5.5]undecan-3-ylmethylsulfamoyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide; and


[0316] All of the above Nampt small molecule antagonist described therein can be prepared by methods described in referenced published patent applications or methods that are within the skills of one skilled in the art.

E. Antagonist Polynucleotides

[0317] Provided herein are polynucleotide antagonists. The polynucleotide may be an antisense nucleic acid, an siRNA, and/or a ribozyme. The antisense nucleic acids comprise a sequence complementary to at least a portion of an RNA transcript of Nampt and/or NMNAT. However, absolute complementarity, although preferred, is not required.

[0318] A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded Nampt and/or NMNAT antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with an Nampt and/or NMNAT RNA it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

[0319] Polynucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., 1994, Nature 372:333-335. Thus, oligonucleotides complementary to either the 5'- or 3'-non-translated, non-coding regions of the Nampt and/or NMNAT gene, could be used in an antisense
approach to inhibit translation of endogenous Nampt and/or NMNAT mRNA. Polynucleotides complementary to the 5’ untranslated region of the mRNA should include the complement of the AUG start codon. Antisense polynucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of Nampt and/or NMNAT mRNA, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

In one embodiment, the Nampt and/or NMNAT antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the Nampt and/or NMNAT gene. Such a vector would contain a sequence encoding the Nampt and/or NMNAT antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others know in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding Nampt and/or NMNAT, or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, *Nature* 29:304-310 (1981), the promoter contained in the 3’ long terminal repeat of Rous sarcoma virus (Yamamoto *et al.*, *Cell* 22:787-797 (1980), the herpes thymidine promoter (Wagner *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 78:1441-1445 (1981), the regulatory sequences of the metallothionein gene (Brinster, *et al.*, *Nature* 296:39-42 (1982)), etc.

In some embodiments, the Nampt and/or NMNAT siRNA polynucleotide antagonists is an RNAi such as siRNA or miRNA, an RNAsymes, a DNAzymes, an oligonucleotides, a nucleotides, or any fragments of these, including DNA or RNA (e.g., mRNA, rRNA, tRNA) of genomic or synthetic origin, which may be single-stranded or double-stranded and may represent a sense or antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material, natural or synthetic in origin, including, e.g., iRNA, ribonucleoproteins (e.g., iRNPs). Examples of NAPRT siRNA molecules include ON-TARGET siRNAs available from Dharmacon (CAT# J-016912-09, J-016912-10, J-016912-11, J-016912-12).

In one embodiment, the Nampt and/or NMNAT siRNA nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the Nampt and/or NMNAT gene. Such a vector would contain a sequence encoding the Nampt and/or NMNAT siRNA nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by
recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others
known in the art, used for replication and expression in vertebrate cells. Expression of the sequence
encoding Nampt and/or NMNAT, or fragments thereof, can be by any promoter known in the art to
act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such
promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon,
Nature 29:304-310 (1981), the promoter contained in the 3' long terminal repeat of Rous sarcoma
virus (Yamamoto et al., Cell 22:787-797 (1980), the herpes thymidine promoter (Wagner et al., Proc.

F. Antibody and Binding Polypeptide Variants

[0323] In certain embodiments, amino acid sequence variants of the antibodies and/or the binding
polypeptides provided herein are contemplated. For example, it may be desirable to improve the
binding affinity and/or other biological properties of the antibody and/or binding polypeptide. Amino
acid sequence variants of an antibody and/or binding polypeptides may be prepared by introducing
appropriate modifications into the nucleotide sequence encoding the antibody and/or binding
polypeptide, or by peptide synthesis. Such modifications include, for example, deletions from, and/or
insertions into and/or substitutions of residues within the amino acid sequences of the antibody
and/or binding polypeptide. Any combination of deletion, insertion, and substitution can be made to
arrive at the final construct, provided that the final construct possesses the desired characteristics,
e.g., target-binding.

[0324] In certain embodiments, antibody variants and/or binding polypeptide variants having one
or more amino acid substitutions are provided. Sites of interest for substitutional mutagenesis include
the HVRs and FRs. Conservative substitutions are shown in Table 1 under the heading of
"conservative substitutions." More substantial changes are provided in Table 1 under the heading of
"exemplary substitutions," and as further described below in reference to amino acid side chain
classes. Amino acid substitutions may be introduced into an antibody and/or binding polypeptide of
interest and the products screened for a desired activity, e.g., retained/improved antigen binding,
decreased immunogenicity, or improved ADCC or CDC.

<table>
<thead>
<tr>
<th>Original Residue</th>
<th>Exemplary Substitutions</th>
<th>Preferred Substitutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ala (A)</td>
<td>Val; Leu; Ile</td>
<td>Val</td>
</tr>
<tr>
<td>Arg (R)</td>
<td>Lys; Gln; Asn</td>
<td>Lys</td>
</tr>
<tr>
<td>Asn (N)</td>
<td>Gln; His; Asp, Lys; Arg</td>
<td>Gln</td>
</tr>
<tr>
<td>Asp (D)</td>
<td>Glu; Asn</td>
<td>Glu</td>
</tr>
<tr>
<td>Cys (C)</td>
<td>Ser; Ala</td>
<td>Ser</td>
</tr>
<tr>
<td>Original Residue</td>
<td>Exemplary Substitutions</td>
<td>Preferred Substitutions</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Gin (Q)</td>
<td>Asn; Glu</td>
<td>Asn</td>
</tr>
<tr>
<td>Glu (E)</td>
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<td>Asp</td>
</tr>
<tr>
<td>Gly (G)</td>
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</tr>
<tr>
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<td>Arg</td>
</tr>
<tr>
<td>Ile (I)</td>
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</tr>
<tr>
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</tr>
<tr>
<td>Met (M)</td>
<td>Leu; Phe; Ile</td>
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</tr>
<tr>
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<tr>
<td>Val (V)</td>
<td>He; Leu; Met; Phe; Ala; Norleucine</td>
<td>Leu</td>
</tr>
</tbody>
</table>

[0325] Amino acids may be grouped according to common side-chain properties:

1. hydrophobic: Norleucine, Met, Ala, Val, Leu, He;
2. neutral hydrophilic: Cys, Ser, Thr, Asn, Gin;
3. acidic: Asp, Glu;
4. basic: His, Lys, Arg;
5. residues that influence chain orientation: Gly, Pro;
6. aromatic: Trp, Tyr, Phe.

[0326] Non-conservative substitutions will entail exchanging a member of one of these classes for another class.

[0327] One type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (e.g., a humanized or human antibody). Generally, the resulting variant(s) selected for further study will have modifications (e.g., improvements) in certain biological properties (e.g., increased affinity, reduced immunogenicity) relative to the parent antibody and/or will have substantially retained certain biological properties of the parent antibody. An exemplary substitutional variant is an affinity matured antibody, which may be conveniently generated, e.g., using phage display-based affinity maturation techniques such as those described herein. Briefly, one or more HVR residues are mutated and the variant antibodies displayed on phage and screened for a particular biological activity (e.g., binding affinity).
Alterations (e.g., substitutions) may be made in HVRs, e.g., to improve antibody affinity. Such alterations may be made in HVR "hotspots," i.e., residues encoded by codons that undergo mutation at high frequency during the somatic maturation process (see, e.g., Chowdhury, Methods Mol. Biol. 207:179-196 (2008)), and/or SDRs (a-CDRs), with the resulting variant VH or VL being tested for binding affinity. Affinity maturation by constructing and reselecting from secondary libraries has been described, e.g., in Hoogenboom et al. in Methods in Molecular Biology 178:1-37 (O'Brien et al., ed., Human Press, Totowa, NJ, (2001).) In some embodiments of affinity maturation, diversity is introduced into the variable genes chosen for maturation by any of a variety of methods (e.g., error-prone PCR, chain shuffling, or oligonucleotide-directed mutagenesis). A secondary library is then created. The library is then screened to identify any antibody variants with the desired affinity. Another method to introduce diversity involves HVR-directed approaches, in which several HVR residues (e.g., 4-6 residues at a time) are randomized. HVR residues involved in antigen binding may be specifically identified, e.g., using alanine scanning mutagenesis or modeling. CDR-H3 and CDR-L3 in particular are often targeted.

In certain embodiments, substitutions, insertions, or deletions may occur within one or more HVRs so long as such alterations do not substantially reduce the ability of the antibody to bind antigen. For example, conservative alterations (e.g., conservative substitutions as provided herein) that do not substantially reduce binding affinity may be made in HVRs. Such alterations may be outside of HVR "hotspots" or SDRs. In certain embodiments of the variant VH and VL sequences provided above, each HVR either is unaltered, or contains no more than one, two or three amino acid substitutions.

A useful method for identification of residues or regions of the antibody and/or the binding polypeptide that may be targeted for mutagenesis is called "alanine scanning mutagenesis" as described by Cunningham and Wells (1989) Science, 244:1081-1085. In this method, a residue or group of target residues (e.g., charged residues such as arg, asp, his, lys, and glu) are identified and replaced by a neutral or negatively charged amino acid (e.g., alanine or polyalanine) to determine whether the interaction of the antibody with antigen is affected. Further substitutions may be introduced at the amino acid locations demonstrating functional sensitivity to the initial substitutions. Alternatively, or additionally, a crystal structure of an antigen-antibody complex to identify contact points between the antibody and antigen. Such contact residues and neighboring residues may be targeted or eliminated as candidates for substitution. Variants may be screened to determine whether they contain the desired properties.

Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue. Other insertional variants of the antibody
molecule include the fusion to the N- or C-terminus of the antibody to an enzyme (e.g., for ADEPT) or a polypeptide which increases the serum half-life of the antibody.

**G. Antibody and Binding Polypeptide Derivatives**

[0332] In certain embodiments, an antibody and/or binding polypeptide provided herein may be further modified to contain additional nonproteinaceous moieties that are known in the art and readily available. The moieties suitable for derivatization of the antibody and/or binding polypeptide include but are not limited to water soluble polymers. Non-limiting examples of water soluble polymers include, but are not limited to, polyethylene glycol (PEG), copolymers of ethylene glycol/proplylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1, 3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids (either homopolymers or random copolymers), and dextran or poly(n-vinyl pyrrolidone)/poly ethylene glycol, propylene glycol homopolymers, propylene oxide/ethylene oxide co-polymers, polyoxleyethylated polyols (e.g., glycerol), polyvinyl alcohol, and mixtures thereof. Polyethylene glycol propionaldehyde may have advantages in manufacturing due to its stability in water. The polymer may be of any molecular weight, and may be branched or unbranched. The number of polymers attached to the antibody and/or binding polypeptide may vary, and if more than one polymer are attached, they can be the same or different molecules. In general, the number and/or type of polymers used for derivatization can be determined based on considerations including, but not limited to, the particular properties or functions of the antibody and/or binding polypeptide to be improved, whether the antibody derivative and/or binding polypeptide derivative will be used in a therapy under defined conditions, etc.

[0333] In another embodiment, conjugates of an antibody and/or binding polypeptide to nonproteinaceous moiety that may be selectively heated by exposure to radiation are provided. In one embodiment, the nonproteinaceous moiety is a carbon nanotube (Kam et al., Proc. Natl. Acad. Sci. USA 102: 11600-11605 (2005)). The radiation may be of any wavelength, and includes, but is not limited to, wavelengths that do not harm ordinary cells, but which heat the nonproteinaceous moiety to a temperature at which cells proximal to the antibody and/or binding polypeptide-nonproteinaceous moiety are killed.

**H. Recombinant Methods and Compositions**

[0334] Antibodies and/or binding polypeptides may be produced using recombinant methods and compositions, e.g., as described in U.S. Patent No. 4,816,567. In one embodiment, isolated nucleic acid encoding an anti-NAD biosynthesis from nicotinamide antibody (e.g., anti-Nampt antibody and/or anti-NMNAT antibody). Such nucleic acid may encode an amino acid sequence comprising the VL and/or an amino acid sequence comprising the VH of the antibody (e.g., the light and/or heavy chains of the antibody). In a further embodiment, one or more vectors (e.g., expression vectors) comprising such nucleic acid encoding the antibody and/or binding polypeptide are provided. In a further embodiment, a host cell comprising such nucleic acid is provided. In one such embodiment, a
host cell comprises (e.g., has been transformed with): (1) a vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antibody and an amino acid sequence comprising the VH of the antibody, or (2) a first vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antibody and a second vector comprising a nucleic acid that encodes an amino acid sequence comprising the VH of the antibody. In one embodiment, the host cell is eukaryotic, e.g., a Chinese Hamster Ovary (CHO) cell or lymphoid cell (e.g., Y0, NSO, Sp20 cell). In one embodiment, a method of making an antibody such as an anti-NAD biosynthesis from nicotinamide antibody (e.g., anti-Nampt antibody and/or anti-NMNAT antibody) and/or binding polypeptide is provided, wherein the method comprises culturing a host cell comprising a nucleic acid encoding the antibody and/or binding polypeptide, as provided above, under conditions suitable for expression of the antibody and/or binding polypeptide, and optionally recovering the antibody and/or polypeptide from the host cell (or host cell culture medium).

For recombinant production of an antibody such as an anti-NAD biosynthesis from nicotinamide antibody (e.g., anti-Nampt antibody and/or anti-NMNAT antibody) and/or a binding polypeptide, nucleic acid encoding the antibody and/or the binding polypeptide, e.g., as described above, is isolated and inserted into one or more vectors for further cloning and/or expression in a host cell. Such nucleic acid may be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody).

Suitable host cells for cloning or expression of vectors include prokaryotic or eukaryotic cells described herein. For example, antibodies may be produced in bacteria, in particular when glycosylation and Fc effector function are not needed. For expression of antibody fragments and polypeptides in bacteria, see, e.g., U.S. Patent Nos. 5,648,237, 5,789,199, and 5,840,523. (See also Charlton, *Methods in Molecular Biology*, Vol. 248 (B.K.C. Lo, ed., Humana Press, Totowa, NJ, 2003), pp. 245-254, describing expression of antibody fragments in E. coli.) After expression, the antibody may be isolated from the bacterial cell paste in a soluble fraction and can be further purified.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for vectors, including fungi and yeast strains whose glycosylation pathways have been "humanized," resulting in the production of an antibody with a partially or fully human glycosylation pattern. See Gerngross, *Nat. Biotechnol*. 22:1409-1414 (2004), and Li et al, *Nat. Biotechnol*. 24:210-215 (2006).

Suitable host cells for the expression of glycosylated antibody and/or glycosylated binding polypeptides are also derived from multicellular organisms (invertebrates and vertebrates). Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains have been identified which may be used in conjunction with insect cells, particularly for transfection of Spodoptera frugiperda cells.
Plant cell cultures can also be utilized as hosts. See, e.g., US Patent Nos. 5,959,177, 6,040,498, 6,420,548, 7,125,978, and 6,417,429 (describing PLANTIBODIES™ technology for producing antibodies in transgenic plants).

Vertebrate cells may also be used as hosts. For example, mammalian cell lines that are adapted to grow in suspension may be useful. Other examples of useful mammalian host cell lines are monkey kidney CVI line transformed by SV40 (COS-7); human embryonic kidney line (293 or 293 cells as described, e.g., in Graham et al., J. Gen Virol. 36:59 (1977)); baby hamster kidney cells (BHK); mouse Sertoli cells (TM4 cells as described, e.g., in Mather, Biol. Reprod. 23:243-251 (1980)); monkey kidney cells (CVI); African green monkey kidney cells (VERO-76); human cervical carcinoma cells (HELA); canine kidney cells (MDCK; buffalo rat liver cells (BRL 3A); human lung cells (W138); human liver cells (Hep G2); mouse mammary tumor (MMT 060562); TRI cells, as described, e.g., in Mather et al., Annals NY. Acad. Sci. 383:44-68 (1982); MRC 5 cells; and FS4 cells. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including DHFR CHO cells (Urlaub et al., Proc. Natl. Acad. Sci. USA 77:4216 (1980)); and myeloma cell lines such as Y0, NS0 and Sp2/0. For a review of certain mammalian host cell lines suitable for antibody production and/or binding polypeptide production, see, e.g., Yazaki and Wu, METHODS IN MOL. BIOL., Vol. 248 (B.K.C. Lo, ed., Humana Press, Totowa, NJ), pp. 255-268 (2003).

While the description relates primarily to production of antibodies and/or binding polypeptides by culturing cells transformed or transfected with a vector containing antibody- and binding polypeptide-encoding nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare antibodies and/or binding polypeptides. For instance, the appropriate amino acid sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques [see, e.g., Stewart et al., Solid-Phase Peptide Synthesis, W.H. Freeman Co., San Francisco, CA (1969); Merrifield, J, Am. Chem. Soc. 85:2149-2154 (1963)]. In vitro protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the antibody and/or binding polypeptide may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the desired antibody and/or binding polypeptide.

Methods of Screening and/or Identifying NAD biosynthesis from nicotinamide antagonists (e.g., Nampt antagonists and/or NMNAT antagonists) With Desired Function

Techniques for generating NAD biosynthesis from nicotinamide antagonists (e.g., Nampt antagonists and/or NMNAT antagonists) such as antibodies, binding polypeptides, and/or small molecules have been described above. Additional NAD biosynthesis from nicotinamide antagonists (e.g., Nampt antagonists and/or NMNAT antagonists) such as anti-NAD biosynthesis from nicotinamide antibodies (e.g., anti-Nampt antibody and/or anti-NMNAT antibody), binding polypeptides, and/or small molecules provided herein may be identified, screened for, or
characterized for their physical/chemical properties and/or biological activities by various assays known in the art.

[0343] Provided herein are methods of screening for and/or identifying a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) which inhibits NAD biosynthesis from nicotinamide, induces cancer cell cycle arrest, inhibits cancer cell proliferation, and/or promotes cancer cell death said method comprising: (a) contacting (i) a cancer cell, cancer tissue, and/or cancer sample, wherein the cancer cell, cancer tissue, and/or cancer comprises one or more NAPRT1 biomarkers, and (ii) a reference cancer cell, reference cancer tissue, and/or reference cancer sample with a nicotinamide candidate antagonist (e.g., Nampt candidate antagonist and/or NMNAT candidate antagonist), (b) determining the level of NAD biosynthesis from nicotinamide, distribution of cell cycle stage, level of cell proliferation, and/or level of cancer cell death, whereby decreased level of NAD biosynthesis from nicotinamide, a difference in distribution of cell cycle stage, decreased level of cell proliferation, and/or increased level of cancer cell death between the cancer cell, cancer tissue, and/or cancer sample, wherein the cancer cell, cancer tissue, and/or cancer comprises one or more NAPRT1 biomarkers, and reference cancer cell, reference cancer tissue, and/or reference cancer sample identifies the NAD biosynthesis from nicotinamide candidate antagonist (e.g., Nampt candidate antagonist and/or NMNAT candidate antagonist) as a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) which inhibits NAD biosynthesis form nicotinamide, induces cancer cell cycle arrest, inhibits cancer cell proliferation, and/or promotes cancer cell cancer death.

[0344] Further provided herein are methods of screening for and/or identifying a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) which inhibits NAD biosynthesis from nicotinamide, induces cancer cell cycle arrest, inhibits cancer cell proliferation, and/or promotes cancer cell death said method comprising: (a) contacting a cancer cell, cancer tissue, and/or cancer sample, wherein the cancer cell, cancer tissue, and/or cancer comprises one or more NAPRT1 biomarkers with a NAD biosynthesis from nicotinamide candidate antagonist (e.g., Nampt candidate antagonist and/or NMNAT candidate antagonist), (b) determining the level of NAD biosynthesis from nicotinamide, distribution of cell cycle stage, level of cell proliferation, and/or level of cancer cell death to the cancer cell, cancer tissue, and/or cancer sample in the absence of the NAD biosynthesis from nicotinamide candidate antagonist (e.g., Nampt candidate antagonist and/or NMNAT candidate antagonist), whereby decreased level of NAD biosynthesis from nicotinamide, a difference in distribution of cell cycle stage, decreased level of cell proliferation, and/or increased level of cancer cell death between the cancer cell, cancer tissue, and/or cancer sample in the presence of a nicotinamide candidate antagonist (e.g., Nampt candidate antagonist and/or NMNAT candidate antagonist) and the cancer cell, cancer tissue, and/or cancer sample in the absence of the NAD biosynthesis from nicotinamide candidate antagonist (e.g., Nampt candidate antagonist and/or NMNAT candidate antagonist) identifies the NAD biosynthesis from nicotinamide
candidate antagonist (e.g., Nampt candidate antagonist and/or NMNAT candidate antagonist) as a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) which inhibits NAD biosynthesis from nicotinamide, induces cancer cell cycle arrest, inhibits cancer cell proliferation, and/or promotes cancer cell cancer death.

**Methods of determining the level of NAD biosynthesis from nicotinamide** are known in the art; for example, by NAD mass spectrometry or by enzymatic assays. In some embodiments, the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) inhibits NAD biosynthesis from nicotinamide by reducing the level of NAD biosynthesis from nicotinamide by about any of 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100%.

**The growth inhibitory effects of a NAD biosynthesis from nicotinamide** antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) described herein may be assessed by methods known in the art, e.g., using cells which express Nampt and/or NMNAT either endogenously or following transfection with the respective gene(s). For example, appropriate tumor cell lines, and Nampt and/or NMNAT polypeptide-transfected cells may be treated with a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) described herein at various concentrations for a few days (e.g., 2-7) days and stained with crystal violet or MTT or analyzed by some other colorimetric assay. In some examples, cell proliferation is determined by measuring ATP (e.g., by CellTiterGlo). In some some examples, cell proliferation is determined by measuring nucleic acid (e.g., CyQuant). Another method of measuring proliferation would be by comparing ³H-thymidine uptake by the cells treated in the presence or absence an antibody, binding polypeptide or small molecule of the invention. After treatment, the cells are harvested and the amount of radioactivity incorporated into the DNA quantitated in a scintillation counter. Appropriate positive controls include treatment of a selected cell line with a growth inhibitory antibody known to inhibit growth of that cell line. Growth inhibition of tumor cells in vivo can be determined in various ways known in the art.

**Methods of determining the distribution of cell cycle stage, level of cell proliferation, and/or level of cell death** are known in the art and are described in the examples herein. In some embodiments, cancer cell cycle arrest is arrest in G1.

In some embodiments, the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) will inhibit cancer cell proliferation of the cancer cell, cancer tissue, or cancer sample in vitro or in vivo by about 25-100% compared to the untreated cancer cell, cancer tissue, or cancer sample, more preferably, by about 30-100%, and even more preferably by about 50-100% or about 70-100%. For example, growth inhibition can be measured at a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) concentration of about 0.5 to about 30 μg/ml or about 0.5 nM to about 200 nM in cell culture, where the growth inhibition is determined 1-10 days after exposure of the tumor cells to the NAD biosynthesis from nicotinamide candidate antagonist (e.g., Nampt candidate antagonist and/or
NMNAT candidate antagonist). The NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) is growth inhibitory in vivo if administration of the NAD biosynthesis from nicotinamide candidate antagonist (e.g., Nampt candidate antagonist and/or NMNAT candidate antagonist) at about 1 μg/kg to about 100 mg/kg body weight results in reduction in tumor size or reduction of tumor cell proliferation within about 5 days to 3 months from the first administration of the NAD biosynthesis from nicotinamide candidate antagonist (e.g., Nampt candidate antagonist and/or NMNAT candidate antagonist), preferably within about 5 to 30 days.

[0349] To select for a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) which induces cancer cell death, loss of membrane integrity as indicated by, e.g., propidium iodide (PI), trypan blue or 7AAD uptake may be assessed relative to a reference. A PI uptake assay can be performed in the absence of complement and immune effector cells. Nampt and/or NMNAT-expressing tumor cells are incubated with medium alone or medium containing the appropriate a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist). The cells are incubated for a 3-day time period. Following each treatment, cells are washed and aliquoted into 35 mm strainer-capped 12 x 75 tubes (1 ml per tube, 3 tubes per treatment group) for removal of cell clumps. Tubes then receive PI (10 μg/ml). Samples may be analyzed using a FACSCAN® flow cytometer and FACSCONVERT® CellQuest software (Becton Dickinson). Those NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonists) that induce statistically significant levels of cell death as determined by PI uptake may be selected as cell death-inducing antibodies, binding polypeptides or small molecules.

[0350] To screen for NAD biosynthesis from nicotinamide antagonists (e.g., Nampt antagonists and/or NMNAT antagonists) which bind to an epitope on or interact with a polypeptide bound by an antibody of interest, a routine cross-blocking assay such as that described in Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988), can be performed. This assay can be used to determine if a candidate NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) binds the same site or epitope as a known antibody. Alternatively, or additionally, epitope mapping can be performed by methods known in the art. For example, the antibody and/or binding polypeptide sequence can be mutagenized such as by alanine scanning, to identify contact residues. The mutant antibody is initially tested for binding with polyclonal antibody and/or binding polypeptide to ensure proper folding. In a different method, peptides corresponding to different regions of a polypeptide can be used in competition assays with the candidate antibodies and/or polypeptides or with a candidate antibody and/or binding polypeptide and an antibody with a characterized or known epitope.

[0351] In some embodiments of any of the methods of screening and/or identifying, the NAD biosynthesis from nicotinamide candidate antagonist (e.g., Nampt candidate antagonist and/or NMNAT candidate antagonist) is an antibody, binding polypeptide, small molecule, or polynucleotide. In some embodiments, the NAD biosynthesis from nicotinamide candidate antagonist
(e.g., Nampt candidate antagonist and/or NMNAT candidate antagonist) is an antibody. In some embodiments, the NAD biosynthesis from nicotinamide candidate antagonist (e.g., Nampt candidate antagonist and/or NMNAT candidate antagonist) is a small molecule.

[0352] In one aspect, a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) is tested for its antigen binding activity, e.g., by known methods such as ELISA, Western blot, etc.

K. Pharmaceutical Formulations

[0353] Pharmaceutical formulations of a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) as described herein are prepared by mixing such antibody having the desired degree of purity with one or more optional pharmaceutically acceptable carriers (REMINGTON'S PHARMA. SCI. 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. In some embodiments, the nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) is a small molecule, an antibody, binding polypeptide, and/or polynucleotide. Pharmaceutically acceptable carriers are generally nontoxic to recipients at the dosages and concentrations employed, and include, but are not limited to: buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride; benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, manniotil, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as polyethylene glycol (PEG). Exemplary pharmaceutically acceptable carriers herein further include interstitial drug dispersion agents such as soluble neutral-active hyaluronidase glycoproteins (sHASEGP), for example, human soluble PH-20 hyaluronidase glycoproteins, such as rHuPH20 (HYLENEX®, Baxter International, Inc.). Certain exemplary sHASEGPs and methods of use, including rHuPH20, are described in US Patent Publication Nos. 2005/0260186 and 2006/0104968. In one aspect, a sHASEGP is combined with one or more additional glycosaminoglycans such as chondroitinases.

[0354] Exemplary lyophilized formulations are described in US Patent No. 6,267,958. Aqueous antibody formulations include those described in US Patent No. 6,171,586 and WO 2006/044908, the latter formulations including a histidine-acetate buffer.

[0355] The formulation herein may also contain more than one active ingredients as necessary for the particular indication being treated, preferably those with complementary activities that do not
adversely affect each other. Such active ingredients are suitably present in combination in amounts
that are effective for the purpose intended.

[0356] Active ingredients may be entrapped in microcapsules prepared, for example, by
cocervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or
gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug
delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and
nanocapsules) or in macroemulsions. Such techniques are disclosed in REMINGTON’S PHARMA. SCI.

[0357] Sustained-release preparations may be prepared. Suitable examples of sustained-release
preparations include semipermeable matrices of solid hydrophobic polymers containing the NAD
biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist),
which matrices are in the form of shaped articles, e.g., films, or microcapsules.

[0358] The formulations to be used for in vivo administration are generally sterile. Sterility may be
readily accomplished, e.g., by filtration through sterile filtration membranes.

L. Articles of Manufacture

[0359] In another aspect of the invention, an article of manufacture containing materials useful for
the treatment, prevention and/or diagnosis of the disorders described above is provided. The article of
manufacture comprises a container and a label or package insert on or associated with the container.
Suitable containers include, for example, bottles, vials, syringes, IV solution bags, etc. The containers
may be formed from a variety of materials such as glass or plastic. The container holds a composition
which is by itself or combined with another composition effective for treating, preventing and/or
diagnosing the condition and may have a sterile access port (for example the container may be an
intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At
least one active agent in the composition is a NAD biosynthesis from nicotinamide antagonist (e.g.,
Nampt antagonist and/or NMNAT antagonist) described herein. The label or package insert indicates
that the composition is used for treating the condition of choice. Moreover, the article of manufacture
may comprise (a) a first container with a composition contained therein, wherein the composition
comprises an NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or
NMNAT antagonist); and (b) a second container with a composition contained therein, wherein the
composition comprises a further cytotoxic or otherwise therapeutic agent.

[0360] In some embodiments, the article of manufacture comprises a container, a label on said
container, and a composition contained within said container; wherein the composition includes one
or more reagents for detection of the one or more NAPRT1 biomarkers, the label on the container
indicating that the composition can be used to evaluate the presence of one or more biomarkers in a
sample, and instructions for using the reagents for evaluating the presence of one or more biomarkers
in a sample. The article of manufacture can further comprise a set of instructions and materials for
preparing the sample and utilizing the reagents. In some embodiments, the article of manufacture may
include, e.g., one or more of methylation-dependent restriction enzymes, methylation-sensitive restriction enzymes, amplification (e.g., PCR) reagents, probes and/or primers. In some embodiments, the articles of manufacturer include, but are not limited to: PCR primers for specific gene (or methylation-altered DNA sequence or CpG island); PCR probes for quantitative PCR and quantitative methylation specific PCR (QMSP), optimized PCR buffers and deoxynucleotides; gel extraction kit; positive control primers; Ms-SNuPE primers for a specific gene; reaction buffer (for the Ms-SNuPE reaction); buffers, reagents and probes for methylation specific sequencing (e.g. bisulfite sequencing, bisulfite pyrosequencing) and detectably-labeled nucleotides. Additionally, bisulfite conversion reagents may include: DNA denaturation buffer; sulfonation buffer; DNA recovery regent or kit (e.g., precipitation, ultrafiltration, affinity column); desulfonation buffer; and DNA recovery components.

In some embodiments of any of the article of manufacture, the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) is an antibody, binding polypeptide, small molecule, or polynucleotide. In some embodiments, the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) is a small molecule. In some embodiments, the NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist) is an antibody. In some embodiments, the antibody is a monoclonal antibody. In some embodiments, the antibody is a human, humanized, or chimeric antibody. In some embodiments, the antibody is an antibody fragment and the antibody fragment binds Nampt and/or NMNAT.

The article of manufacture in this embodiment of the invention may further comprise a package insert indicating that the compositions can be used to treat a particular condition. Alternatively, or additionally, the article of manufacture may further comprise a second (or third) container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

Other optional components in the article of manufacture include one or more buffers (e.g., block buffer, wash buffer, substrate buffer, etc), other reagents such as substrate (e.g., chromogen) which is chemically altered by an enzymatic label, epitope retrieval solution, control samples (positive and/or negative controls), control slide(s) etc.

It is understood that any of the above articles of manufacture may include an immunoconjugate described herein in place of or in addition to a NAD biosynthesis from nicotinamide antagonist (e.g., Nampt antagonist and/or NMNAT antagonist).

EXAMPLES

The following are examples of methods and compositions of the invention. It is understood that various other embodiments may be practiced, given the general description provided above.
Example 1 - Identification of Cancer Cell Lines Sensitive to Nampt Inhibitors

A functional NAPRT1 pathway that converts nicotinic acid (NA) to NAD may render cells insensitive to inhibition of the Nampt pathway by Nampt inhibitors. To identify cancer cell types that may benefit from Nampt inhibitor treatment, a panel of 52 cancer cell lines were tested for sensitivity to Nampt inhibitors in the presence or absence of nicotinic acid (NA).

Materials and Methods

Nicotinic acid and NAMPT inhibitor treatment: All of the cancer cell lines were purchased from the American Type Cell Culture Collection (ATCC). Cells were grown in RPMI 1640 supplemented with 10% fetal bovine serum and 2 mM L-Glutamine. Cells were treated with increasing concentrations of Nampt inhibitor Compound B (N-[[4-[3-(trifluoromethyl)phenyl]sulfonylphenyl]methyl]-IH-pyrazolo[3,4-b]pyridine-5-carboxamide) ranging from 1 x 10^{-5} \mu M to 1.0 \mu M in the presence or absence of 10 \mu M nicotinic acid. Cell viability was measured by quantification of ATP (CellTiterGlo, Promega) or DNA (CyQuant, Promega) after 96 hours exposure.

Results

Cell viability analysis of the treated cancer cell lines demonstrated that most cell lines were sensitive to Nampt inhibitor treatment (Figure 1). Addition of 10 \mu M NA to the cells rescued cell viability of several cell lines indicating they were no longer sensitive to Nampt inhibitor treatment (Figure 1A and B). In contrast, several other cell lines were not rescued with NA treatment and remained sensitive to Nampt inhibitor treatment (Figure 1C and D). These results demonstrate the NAPRT1 pathway may not be functional in certain cancer cell lines and therefore are susceptible to inhibition of cell viability by treatment with Nampt inhibitors.

Example 2: Sensitivity to Nampt inhibitor treatment is correlated to NAPRT1 gene expression regulation mediated by DNA methylation

To identify the mechanism underlying sensitivity, or lack thereof, to Nampt inhibitors in different cancer cell lines upon treatment with NA, expression of NAPRT1 was analyzed.

Materials and Methods

Gene expression: Using a panel of 42 cancer cell lines, NAPRT1 protein levels were measured by immunohistochemistry staining (IHC) using a rabbit polyclonal NAPRT1 antibody (HPA02401, Sigma). NAPRT1 mRNA expression levels were measured was evaluated with an Affymetrix HGU133Plus gene expression array.

Illumina Infinium Analysis: Using a bead array platform, NAPRT1 methylation was measured using the Illumina Infinium 450K Array. Microarray data was collected at Expression Analysis, Inc. (Durham, NC; www.expressionanalysis.com) using the IlluminaHumanMethylation450 BeadChip (Illumina). These arrays contain probes for approximately 450,000 CpG loci. Target was
prepared and hybridized according to the "Illumina Infinium HD Methylation Assay, Manual Protocol" (Illumina Part # 15019522 Rev. A). Cell lines in which CpG sites within the NAPRT1 CpG islands had greater than 90% methylation on most sites were considered heavily methylated.

[0372] Bisulfite Conversion: A bisulfite conversion reaction was employed using 500 ng of genomic DNA according to the manufacturer’s protocol for the Zymo EZ DNA Methylation kit (Zymo Research). DNA was added to Zymo M-Dilution buffer and incubated for 15 min at 37°C. CT-conversion reagent was then added and the mixture was denatured by heating to 95°C for 30 s followed by incubation for 1 h at 50°C. This denature/incubation cycle was repeated for a total of 16 h. After bisulfite conversion, the DNA was bound to a Zymo spin column and desulfonated on the column using desulfonation reagent per manufacturer’s protocol. The bisulfite-converted DNA was eluted from the column in 10 µl of elution buffer.

[0373] Infinium Methylation Assay: 4 µl of bisulfite converted product was transferred to a new plate with an equal amount of 0.1N NaOH and 20 µl of MA1 reagent (Illumina) then allowed to incubate at RT for 10 min. Immediately following incubation, 68 µl of MA2 reagent and 75 µl of MSM reagent (both Illumina) were added and the plate was incubated at 37°C overnight for amplification. After amplification, the DNA was fragmented enzymatically, precipitated and resuspended in RA1 hybridization buffer.

[0374] Hybridization and Scanning: Fragmented DNA was dispensed onto the multichannel HumanMethylation BeadChips and hybridization performed in an Illumina Hybridization oven for 20 h. BeadChips were washed, primer extended, and stained per manufacturer protocols. BeadChips were coated and then imaged on an Illumina iScan Reader and images were processed with GenomeStudio software methylation module (version 1.8 or later).

[0375] Infinium Analysis: Methylation data were processed using the Bioconductor lumi software package. Du et al., Bioinformatics, 24(13): 1547-1548 (2008). The Infinium 450K platform includes Infinium I and II assays on the same array. The Infinium I assay employs two bead types per CpG locus, with the methylated state reported by the red dye in some cases and the green dye in others (identical to the previous Infinium 27K platform). The Infinium II assay uses one bead type and always reports the methylated state with the same dye, making dye bias a concern. A two-stage normalization procedure was applied to the arrays: First, for each array, a color-bias correction curve was estimated from Infinium I data using a smooth quantile normalization method; this correction curve was then applied to all data from that array. Second, arrays were normalized to one another by applying standard quantile normalization to all color-corrected signals. After pre-processing, both methylation M-values (log2 ratios of methylated to unmethylated probes) and β-values (a rescaling of the M-values to the 0 and 1 range via logistic transform) were computed for each sample. Du et al., BMC Bioinformatics. 11:587 (2010). For visualization, agglomerative hierarchical clustering of β-values was performed using complete linkage and Euclidean distance.
Results

Comparison of NAPRT1 IHC scores to NAPRT1 mRNA expression from the panel of 42 cancer cell lines demonstrated a good correlation between the levels of NAPRT1 protein and NAPRT1 mRNA (Figure 2A; \( p<0.0001 \), Spearman \( r=0.7 \)). These results indicate that NAPRT1 is not regulated at the level of protein stability. In addition, upon analysis of public and private cancer genome databases, no obvious deletions in the NAPRT1 region were observed. Analysis of NAPRT1 methylation status the cell line panel showed a significant correlation with mRNA expression levels (Figure 2B, \( p<0.001 \)). Furthermore, comparison of cell line methylation status with the identified NA rescuable cell lines, defined as having at least a 10-fold decrease in Nampt inhibitor IC_{50} as determined by the CyQuant assay in the presence of 10 \( \mu \)M NA, demonstrated that all cell lines with intermediate or low levels of NAPRT1 methylation in the CpG island were rescuable with NA (Figure 2C and Figure 3). In contrast, 18 out of 19 cell lines with high levels of NAPRT1 promoter methylation were non-rescuable with NA (Figure 2C and Figure 3). This correlation was highly significant (\( p<0.0001 \), Fishers Exact Test), suggesting that promoter methylation is a sensitive assay for identification of cancers that would be sensitive to Nampt inhibitors irrespective of level of NA in a patient. Overall, these results demonstrate that methylation of NAPRT1 correlated with low mRNA level, low protein level and inability of NA to rescue the cytotoxicity of Nampt inhibitors. These results shows that differential methylation of the center (see arrow in Figure 3) of the CpG island correlates best with an inability to rescue with nicotinic acid. DNA methylation of NAPRT1 has not previously been reported, and assays to detect methylation of NAPRT1 could be used as a sensitive method to identify patients that are likely to benefit from Nampt inhibitors, either with or without co-administration of NA.

Example 3: 5-azadC Induces NAPRT1 in Cell Lines That Have CpG Island Methylation and Cannot be Rescued by Niacin

To further demonstrate that control of NAPRT1 expression depends on CpG island methylation, cells lines that either could or could not be rescued by niacin were treated with 5-azadC to inhibit DNA methyltransferase activity.

Materials and Methods

Cell lines used in these studies included cells capable of rescue by niacin including SW1573, EBC-1, H1651, H1781, HOP62, ABC-1, HOP92, H226, EKVX, SK-MES-1, Calu-6, H1793, KNS-62, H2030, H1568, CHA-GO-K-1, HOP18, H2122, H1435, H650, H838, H1299, H1975, H647, and H292 and cell lines not capable of rescue by niacin including A427, LXFL529, H460, H1650, H1703, H1155, H661, H322T, and H1355.

Cells were plated in 6-well culture plates such that the cells were at \( \sim 25 - 30\% \) confluency the next day. For adherent cells an appropriate amount of media was added to 15mL tubes. 1 mM and 100 \( \mu \)M 5'-azadC (stock solution 50 mM in DMSO) was added to the media as appropriate.
DMSO without drug was used as a control. Media in the wells of the 6-well plates was replaced by media containing 5-azadC at different concentrations. For cell suspension, cells needed to be separated upon each treatment because the drug is unstable. Plates were centrifuged and half the amount of media from each well was removed. 5-azadC was mixed with media at 2X the desired concentration and then added at a 1:1 ratio to the remaining half the amount of media in the plates.

For the 5-azadC treatment, cells were treated 3 X qod (every other day) and harvested 24 hrs after the last treatment. For tricostatin A (TSA) + 5-azadC, cells were treated with 5-azadC alone on the first day of treatment, and then treated with TSA + 5-azadC on the last two.

On day 7, RNA was extracted from the cells as follows. For adherent cells, cells were trypsinized and placed in a 15 ml tube. This step was omitted for suspension cells. Cells were then centrifuged immediately at 1000g for 5 mins. The supernatant was removed and cells were washed with ice cold PBS and spun again. The PBS was aspirate from the tube and cells were snap frozen. RNA from the cells was then used in a quantitative PCR assay to determine the level of NAPRT1 expression following treatment by 5-azadC.

Results

As shown in figure 4, 5-azadC induced expression of NAPRT1 in cells that had previously been refractory to rescue indicating that methylation plays a role in control of NAPRT1 expression.

Example 4: Mapping of NAPRT1 DNA methylation sites in cancer cell lines by bisulfite PCR sequencing and quantitative methylation specific PCR

Evaluation of epigenetic regulation of NAPRT1 by DNA methylation showed that NAPRT1 was methylated in a subset of cancer cell lines. To further characterize NAPRT1 methylation in NA rescuable and non-rescuable cell lines and develop assays for the identification of biomarkers for Nampt inhibitor sensitivity, NAPRT1 methylation sites were mapped using bisulfite PCR sequencing and quantitative methylation specific PCR.

Materials and Methods

Bisulfite sequencing and analysis: Genomic DNA was bisulfite-converted using the EZ DNA Methylation-Gold kit (Zymo Research) as described in Example 2. Primers specific to the converted DNA were designed using Methyl Primer Express software v1.0 (Applied Biosystems). PCR amplification was performed with 1 μl of bisulfite-converted DNA in a 25-μl reaction using Platinum PCR supermix (Invitrogen). The PCR thermocycling conditions were as follows: 1 initial denaturation cycle of 95°C for 10 minutes, followed by 10 cycles of 94°C for 30 seconds, 65°C for 1 minute and decreasing by 1°C every cycle, and 72°C for 1 minute, followed by 30 cycles of 94°C for 30 seconds, 55°C for 1.5 minutes, and 72°C for 1 minute, followed by a final extension at 72°C for 15 minutes. PCR products were resolved by electrophoresis using 2% agarose E-gels containing ethidium bromide (Invitrogen) and visualized using a FluorChem 8900 camera (Alpha Innotech). PCR products were ligated into the pCR4-TOPO vector using the TOPO TA Cloning kit (Invitrogen).
according to the manufacturer's instructions. 2 ?µl of ligated plasmid DNA were transformed into TOP10 competent bacteria (Invitrogen), and 100 µl transformed bacteria were plated on LB-agar plates containing 50 µg/ml carbenicillin (Teknova) and incubated overnight at 37°C. Twelve colonies per cell line for each candidate locus were inoculated into 1 ml of LB containing 50 µg/ml carbenicillin and grown overnight in a shaking incubator at 37°C. Plasmid DNA was isolated using a Qiaprep miniprep kit in 96- well format (Qiagen) and sequenced on a 3730x1 DNA Analyzer (Applied Biosystems).

Table 2. BSP primers

<table>
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<tr>
<th>Primer</th>
<th>Primer Sequence</th>
<th>Hg19-human chr8 start</th>
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[0385] Bisulfite sequencing analysis: Sequencing data were analyzed using Sequencher v 4.5 software and BiQ Analyzer software. Bock et al., Bioinformatics. 21(21):4067-4068 (2005).

[0386] Pyrosequencing: Bisulfite-specific PCR (BSP) primers were designed using Methyl Primer Express software v 1.0 (Applied Biosystems) or PyroMark Assay Design software v 2.0 (Qiagen). PCR primers were synthesized with a 5’ biotin label on either the forward or reverse primer to facilitate binding of the PCR product to Streptavidin Sepharose beads. Sequencing primers were designed in the reverse direction of the 5’-biotin-labeled PCR primer using PyroMark Assay Design software v 2.0 (Qiagen). 1 µl bisulfite modified DNA was amplified in a 25 µl reaction using Platinum PCR Supermix (Invitrogen) and 20 µl of PCR product was used for sequencing on the Pyromark Q24 (Qiagen). PCR products were incubated with Streptavidin Sepharose beads for 10 minutes followed by washes with 70% ethanol, PyroMark denaturation solution, and PyroMark wash buffer. Denatured PCR products were then sequenced using 0.3 µM sequencing primer. Pyrograms were visualized and evaluated for sequence quality, and percent methylation at individual CpG sites was determined using PyroMark software version 2.0.4 (Qiagen).
Quantitative Methylation Specific PCR: Quantitative methylation specific PCR (QMSP) assays targeting differentially methylated CpG sites (DMRs) identified by Infinium profiling were designed. Sodium bisulfite converted DNA was amplified with various 20x Custom Taqman Assays using TaqMan® Universal PCR Master Mix, No AmpErase® UNG (Applied Biosystems) with cycling conditions of 95°C 10 min, then 50 cycles of 95°C for 15 sec and 60°C for 1 min for production of QMSP amplicons (Table 5). Amplification was done on a 7900HT and analyzed using SDS software (Applied Biosystems). DNA content was normalized using meRNaseP Taqman assay. QMSP of FFPE material was performed using a pre-amplification procedure with the same QMSP primer (Table 3) and QMSP probe (Table 4) sets.

Table 3. NAPRT1 QMSP forward and reverse primers

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Table 4. NAPRT1 qMSP probes

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Table 5. NAPRT1 QMSP resulting amplicons

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**Pre-amplification of FFPE Tumor Material:** A pre-amplification method for methylation analysis of pico gram amounts of DNA extracted from formalin-fixed paraffin embedded (FFPE) tissue was designed. 2 µl (equivalent of 100 pg - 1 ng) bisulfite converted DNA was first amplified in a 20 µl reaction with 0.1x QMSP primer-probe concentrations using TaqMan® Universal PCR Master Mix, No AmpErase® UNG (Applied Biosystems, Cat No. 4324018) and cycling conditions of 95°C 10 min, then 14 cycles of 95°C for 15 sec and 60°C for 1 min. 1 µl of the pre-amplified material was then amplified in a second PCR reaction with cycling conditions of 95°C 10 min, then 50 cycles of 95°C for 15 sec and 60°C for 1 min. DNA content was confirmed using a pre-amplification with the reference mRNaseP Taqman assay and only samples that were positive for mRNaseP were included in further analysis of QMSP reactions. All reactions were performed in duplicate.

**Results**

Bisulfite PCR sequencing with bisulfite specific PCR (BSP) primers (Table 2 and Figures 5, 6 and 7) were designed to recognize a CpG island within the NAPRT1 promoter (Figure 10) as well as 600 bp upstream and downstream of this site (Figures 7 and 8). Identification of differential methylation status within the NAPRT1 promoter by sodium bisulfite sequencing was further confirmed by the identification of specific NAPRT1 DMRs using a Taqman-based quantitative MSP (QMSP) assay with NAPRT1-specific primers and probes in various cancer cell lines (Tables 3, and 4 and Figures 6 and 7).
[0390] Figure 11 demonstrates the development of a quantitative methylation assay for the NAPRT1 CpG island. Sodium bisulfite sequencing was conducted for samples of normal peripheral blood monocytes (PBMC) from 20 healthy donors. Sodium bisulfite sequencing using the BSP7 primers demonstrated high levels of methylation at the 3’ end of the CpG island (Figure 11, BSP7 grid). A commercially available methylation assay is targeted to this region as shown by the bar below the grid. As a result this region cannot be used to detect tumor specific methylation.

[0391] In contrast, much less methylation was seen in the NAPRT1 CpG island using the BSP 1 and 2 primer sets, indicating that tumor specific detection of methylation of the NAPRT1 gene is possible. Based on these results, a quantitative methylation PCR assay targeting this region of the CpG island can be used to detect tumor specific methylation of the NAPRT1 gene. The QMSP3 amplicon of the QMSP assay corresponds to a portion of the BSP1/2 primer sets (shown by the bar below the BSP1/2 grid.

[0392] Using pyrosequencing and quantitative methylation specific PCT, the DNA methylation profile of CpG sites in NAPRT1 showed that the level of methylated CpG sites correlated with the ability of NA to rescue cell cytotoxicity mediated by Nampt inhibitors. For example, sodium bisulfite using the BSP1 primer set for the HCC70 breast cancer cell line (Figure 12B) and the H1155, H1650, H1703, and LXFL529 NSCLC cell lines (Figure 13A) had a high DNA methylation profile and demonstrated no rescue by NA when treated with Nampt inhibitors. In contrast, using the same primer set, the MDA-MB-231 and CAL120 breast cancer cell lines (Figure 12C) and the H1838, H2030, H2122, and H226 NSCLC cell lines (Figure 13B) had a low DNA methylation profile and demonstrated rescue by NA when treated with Nampt inhibitors.

[0393] Figure 16 shows the level of NAPRT1 in a number of tissues. These results further underscore the utility of DNA methylation to identify cellular subtypes within cancer, such as NSCLC, as well as different cancer types, such as breast cancer, that may benefit from Nampt inhibitor treatment (Figure 16).

Example 5: QMSP assay directly from IHC slides

[0394] Methylation status of the NAPRT1 CpG island was determined directly from immunohistochemistry (IHC) slides thereby showing a direct correlation of NAPRT1 expression and methylation status.

Methods

[0395] Tumor samples were embedded in paraffin, sectioned and applied to slides according using standard procedures. Expression of NAPRT1 was detected using anti-NAPRT1 (Sigma; HPA024017).

[0396] Coverslips from IHC slides removed by one of 2 methods: the slide was placed in a freezer for at least 15 minutes, then the coverslip was pried off of the microscope slide using a razor blade. Slides were then incubated in xylene at room temp to dissolve the mounting media. Alternatively, slides were soaked in xylene until the coverslip fell off. This took up to several days. All slides
taken through a deparaffinization procedure of 5 min xylene (x3), and 5 min 100% ethanol (x2). Tissues were scraped off slides with razor blades and placed in Roche Tissue Lysis Buffer (Roche High Pure FFPE RNA Micro Kit, cat# 04823125001) containing Proteinase K and incubated overnight at 56°C. In cases where tissue was still present after incubation, an extra 10 µl Proteinase K was added and the tissue was incubated for another 30 min. DNA extraction was continued using a QIAamp DNA FFPE Tissue kit (Qiagen, cat# 56404, step 12, p. 15).

DNA extracted directly from IHC slides was subject to QMSP analysis using the QMSP3 primers and probes as described in Example 4.

Results

To evaluate if methylation of NAPRT1 occurred in tumors that did not express detectable NAPRT1 protein, DNA was extracted directly from slides used for immunohistochemical staining of NAPRT1 (Figure 15). HP-7770, a small cell lung cancer sample, has an IHC score of zero (blue area) indicating no detectable expression of NAPRT1. The brown area is non-malignant tissue. HP-7489, a non-small cell lung cancer tumor, has an IHC score of 3+, indicating expression of NAPRT1. Tumor DNA was subject to QMSP analysis using the QMSP3 primers and probes. QMSP analysis revealed that the NAPRT1 CpG island HP-7770, where no expression of NAPRT1 was detected by IHC, was heavily methylated. In contrast, the NAPRT1 CpG island of HP-7489, where active expression of NAPRT1 was detected by IHC, was hypomethylated. These data show that methylation is tumor specific and can be used to establish true negative expression in tumor tissue with adjacent non-malignant tissue.

Example 6: NAPRT1 knockdown followed by NMPT inhibitor treatment.

To demonstrate the relationship of NMPT inhibition and NAPRT1 expression, cells were treated with siRNA targeting NAPRT1 RNA to specifically knockdown expression of NAPRT.

H1299 and A549 cells were plated at 500,000 cells per 10 cm dish. After 24 hours, cells were treated with 50 nM Dharmacon ON-TARGET plus siRNA pools (ON-TARGET plus siNAPRT1: CAT# J-016912-09, J-016912-10, J-016912-11, J-016912-12) and Dharmafect 4 at 0.8 µl/ml. Control pools were siNADSYNI (ON-TARGET CAT# J-007723-9, J-007723-10, J-007723-11, J-007723-12) and si KYNU (ON-TARGET CAT# J-009867-06, J-009867-07, J-009867-08, J-009867-09). After 72 hours of continuous treatment, cells were dissociated from dishes with trypsin and placed in 96 well plates at ~3500 cells per well. After 24 hours, cells were retreated with siRNA and drugged with Compound B over a threefold dilution series starting at 3.33 µM. The final well of the dilution series was treated with DMSO only (.03%). %Viability was calculated by referencing cell proliferation in drug treated wells to the DMSO only control wells of each plate. After 48, 72, and 96 hours of drug treatment, cell proliferation was inferred from the relative abundance of ATP per well using Cell Titer-Glo reagent (Promega,100 µl to each well of a plate). Data was collected with an Envision fluorescence plate reader. %Viability was determined
from 2 biological replicates (Figure 17A). For each replicate, %Viability was calculated independently from two 96 well plates. Each of the 4 independent measurements was plotted with Graph Pad Prism 5. Error bars represent the standard error of each data point (SEM). Cells in which NAPRT1 expression was knocked down could not be rescued by NA whereas cells treated with a non-targeted pool of siRNA were rescued by NA treatment. Western blot analysis showed that expression of NAPRT1 was inhibited by NAPRT1-specific siRNAs but not by control siRNAs (Figure 17B).

[0401] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the invention. The disclosures of all patent and scientific literature cited herein are expressly incorporated in their entirety by reference.
WHAT IS CLAIMED IS:

1. A method of treating a disease or disorder in an individual comprising administering to the individual an effective amount of an NAD biosynthesis from nicotinamide antagonist, wherein treatment is based upon the individual having a disease or disorder comprising a positive NAPRT1 methylation status.

2. A method of treating a disease or disorder cell, wherein the disease or disorder cell comprises a positive NAPRT1 methylation status, the method comprising providing an effective amount of an NAD biosynthesis from nicotinamide antagonist.

3. A method of treating a disease or disorder in an individual provided that the individual has been found to have a disease or disorder comprising a positive NAPRT1 methylation status, the method comprising administering to the individual an effective amount of an NAD biosynthesis from nicotinamide antagonist.

4. A method for treating a disease or disorder in an individual, the method comprising: determining that a sample obtained from the individual comprises a positive NAPRT1 methylation status, and administering an effective amount of a therapy comprising an NAD biosynthesis from nicotinamide antagonist to the individual, whereby the disease or disorder is treated.

5. A method of treating a disease or disorder, comprising: (a) selecting an individual having the disease or disorder, wherein the disease or disorder comprises a positive NAPRT1 methylation status; and (b) administering to the individual thus selected an effective amount of an NAD biosynthesis from nicotinamide antagonist, whereby the disease or disorder is treated.

6. A method of identifying an individual with a disease or disorder who is more or less likely to exhibit benefit from treatment with a therapy comprising an NAD biosynthesis from nicotinamide antagonist, the method comprising: determining presence or absence of a positive NAPRT1 methylation status in a sample obtained from the individual, wherein presence of the positive NAPRT1 methylation status in the sample indicates that the individual is more likely to exhibit benefit from treatment with the therapy comprising the NAD biosynthesis from nicotinamide antagonist or absence of the positive NAPRT1 methylation status indicates that the individual is less likely to exhibit benefit from treatment with the therapy comprising the NAD biosynthesis from nicotinamide antagonist.
7. A method for predicting whether an individual with a disease or disorder is more or less likely to respond effectively to treatment with a therapy comprising an NAD biosynthesis from nicotinamide antagonist, the method comprising determining a positive NAPRT1 methylation status, whereby presence of the positive NAPRT1 methylation status indicates that the individual is more likely to respond effectively to treatment with the NAD biosynthesis from nicotinamide antagonist and absence of the positive NAPRT1 methylation status indicates that the individual is less likely to respond effectively to treatment with the NAD biosynthesis from nicotinamide antagonist.

8. A method of predicting the response or lack of response of an individual with a disease or disorder to an therapy comprising an NAD biosynthesis from nicotinamide antagonist comprising detecting in a sample obtained from the individual presence or absence of a positive NAPRT1 methylation status, wherein presence of the positive NAPRT1 methylation status is predictive of response of the individual to the therapy comprising the NAD biosynthesis from nicotinamide antagonist and absence of the positive NAPRT1 methylation status is predictive of lack of response of the individual to the therapy comprising the NAD biosynthesis from nicotinamide antagonist.

9. A method of treating an individual predicted to more likely exhibit benefit from treatment with a therapy comprising an NAD biosynthesis from nicotinamide antagonist according to the methods of claims 6-8, wherein the method comprises administering to the individual an effective amount of an NAD biosynthesis from nicotinamide antagonist.

10. The method of any one of claims 1-5 and 9, wherein the NAD biosynthesis from nicotinamide antagonist is an Nampt antagonist.

11. The method of any one of claims 1-5 and 9, wherein the NAD biosynthesis from nicotinamide antagonist is an NMNAT antagonist.

12. The method of any one of claims 1-5 and 9-11, wherein the NAD biosynthesis from nicotinamide antagonist is an antibody, binding polypeptide, small molecule, or polynucleotide.

13. The method of claim 12, wherein the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of
14. The method of claim 12, wherein the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of:

wherein:
R is bicyclic heteroaryl comprising 1, 2, 3 or 4 heteroatom(s) independently selected from N, S or O, wherein said heteroaryl may be substituted by one or more substituents selected from the group consisting of amino, oxo, and halo; and wherein said heteroaryl can comprise one or more N-oxide(s) formed with a N atom member of said heteroaryl;

R¹ is -NHR⁴ and R⁴ is cycloalkyl, heterocycloalkyl, aryl or heteroaryl;
cycloalkyl;
aryl or heteroaryl; wherein:
(v) each of said cycloalkyl, aryl, or heteroaryl is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents which can be the same or different and are independently selected from the group consisting of:
deuterium, halo, hydroxy, hydroxyalkyl, cyano, -(CH₂)ₙNₜRₕ, oxo, alkyl, cyanoalkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl-, alkenyl, alkynyl, alkynylalkoxy, -CONH₂, -S-alkyl, -C(0)NH(alkyl), -C(0)N(alkyl)₂, -C(0)NH(cycloalkyl), -C(0)NH(aryl), -C(0)N(aryl)₂, arylalkyl-, arylalkoxy-, aryloxy-, cycloalkyl, heterocycloalkyl, aryl, (heterocycloalkyl)alkyl-, (heterocycloalkyl)alkoxy-, -C(0)heterocycloalkyl, heteroaryl, (heteroaryl)alkyl-, -S(0)₂-alkyl, -S(0)₂-aryl, -S(0)₂-CHₓFᵧ, -C(0)alkyl, -N(R⁵)-C(0)-alkyl, -N(R⁵)-C(0)-aryl, -S(0)₂NH₂, -S(0)₂NH(alkyl), -S(0)₂N(alkyl)₂, -N(H)(S0 ₂)(alkyl), and methylenedioxy, wherein each of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted by one or more halo, cyano, alkyl or alkoxy and;
(vi) each of said cycloalkyl, heterocycloalkyl, aryl, or heteroaryl may optionally additionally be fused with independently selected aryl, heteroaryl, heterocycloalkyl or cycloalkyl to from a bicyclic or tricyclic group that may be substituted by one or more halo, cyano, alkyl or alkoxy;

R² and R³ can be independently selected from the group consisting of H and deuterium;
R^5 is H, alkyl or arylalkyl-;
R^a and R^b are independently selected from the group consisting of H, alkyl, alkoxy, alkoxyalkyl and haloalkyl;
N is 0, 1, 2, 3, 4, 5 or 6;
z is 0, 1 or 2.

15. The method of claim 12, wherein the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of:

```
Ar^1 - -(CH_2)_n - NH - (CR^2R^3)_m - Ar^2 - S - (CH_2)_p - R^1
```

wherein
Ar^1 is aryl or heteroaryl, wherein said aryl or heteroaryl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of:
- deuterium, halo, cyano, alky, cyanoalkyl, haloalkyl, alkenyl, alkynyl, alkoxy, haloalkoxy, aryl, -NR^aR^b, -C(0)N(R^aR^b), -(C(0)-alkyl, -(C(0)-aryl, -(S(0)-aryl, -(NH-C(0)-alkyl, -(NH-C(0)-aryl, (alkoxyalkyl)oxy-), cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;
Ar^2 is unsubstituted aryl or heteroaryl;
R^1 is cycloalkyl, aryl, heterocycloalkyl, or heteroaryl,
(i) wherein each of said cycloalkyl, aryl, heterocycloalkyl and heteroaryl is either unsubstituted or optionally independently substituted with 1, 2, 3, 4 or 5 substituents which can be the same or different and are independently selected from the group consisting of:
- deuterium, halo, cyano, alkyl, alkoxyalkyl, cyanoalkyl, haloalkyl, alkenyl, alkynyl, alkoxy,
- alkylalkoxy, haloalkoxy, aryl, alkoxy, -NR^aR^b, -CONR^aR^b, -(S(0)-alkyl, -(S(0)-aryl, -(S(0)-N(alkyl)_2, -(S(0)-CF_3, -(C(0)-alkyl, -(C(0)-aryl, -(C(0)-aryl, -(CH_2)_q-ary, -(CH_2)_q-heteroaryl, and -(CH_2)_q-heterocycloalkyl,
(ii) wherein each of said cycloalkyl, aryl, heterocycloalkyl, and heteroaryl may additionally be unsubstituted or substituted by one or more halo, cyano, alkyl or alkoxy or may be be fused with independently selected aryl, heterocycloalkyl or cycloalkyl;
R^a and R^b are independently H, alkyl, alkoxy, aryl, alkoxyalkyl, -(S(0)-alkyl and cycloalkyl or R^a and R^b can form a 5 or 6 membered heterocycloalkyl group together with the nitrogen atom to which they are attached, wherein said heterocycloalkyl group may contain one or more additional heteroatom(s) selected from N, S or O;
R^2 and R^3 are H or deuterium;
m, n, p and q are independently 0, 1 or 2; and pharmaceutically acceptable salts thereof.

16. The method of claim 12, wherein the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of:

![Chemical structure]

wherein:
- R^a is 1, 2, 3 or 4 and can be selected from the group consisting of hydrogen, amino, oxo, halo, alkoxy, alkyl, haloalkyl, -N(alkyl)_2, -NH(CO)0-alkyl 1H-pyrazol, 1H-imidazol, and -C(0)NH_2; and wherein said pyridine can comprise a N-oxide formed with its N atom member;
- R^1 = -NR^3R^4 wherein R^3 is H, alkyl or -S(0)alkyl and R^4 is alkyl, hydroxyalkyl, -S(0)alkyl, -(CH_2)_q-cycloalkyl, -(CH_2)_q-heterocycloalkyl, aryl, arylalkyl, -(CH_2)_q-heteroaryl; haloalkyl; cycloalkyl; aryl; heterocycloalkyl; or heteroaryl;

wherein each of said cycloalkyl, aryl, heterocycloalkyl or heteroaryl is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents which can be the same or different and are independently selected from the group consisting of:
- halo, cyano, alkyl, hydroxyl, hydroxyalkyl, hydroxyalkoxy, haloalkyl, alkoxy, alkylalkoxy, haloalkoxy, arylalkenyl-, arilloxy, benzyloxy, oxo, -(CH_2)_q-NR^5R^5, -(CH_2)_q-CNR^5R^5, -S(0)alkyl, -S(0)NH-alkyl, -S(0)alkenyl, -(CH_2)_q-heterocycloalkyl, -S(0)alkenyl, -C(0)alkyl, -C(0)alkylenylaryl, -C(0)alkylalkenyl, -(CH_2)_q-C(0)alkenyl, -C(0)alkenyl, -(CH_2)_q-cycloalkyl, cycloalkyloxy-, aryl, arylalkyl, -(CH_2)_q-heteroaryl, and -(CH_2)_q-heterocycloalkyl;

wherein each of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted by one or more halo, nitro, haloalkyl, haloalkoxy, oxo, cyano, alkyl, haloalkyl, or alkoxy;
- R^b and R^c are independently selected from the group consisting of H, alkyl, hydroxyalkyl, alkoxy, aryl, alkoxycarboxyl, -S(0)alkyl and cycloalkyl or R^b and R^c can form a 5 or 6 membered heterocycloalkyl group together with the nitrogen atom to which they are attached, wherein said
heterocycloalkyl group may contain one or more additional heteroatom(s) selected from N, S or O; 
q is 0 or 1; and 
pharmaceutically acceptable salts thereof.

17. The method of claim 12, wherein the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of:

\[
\begin{align*}
4) & \quad 5) \quad \text{IB}
\end{align*}
\]

wherein:
Ar is aryl or heteroaryl, each of said aryl and heteroaryl being either unsubstituted or optionally independently substituted with 1, 2, 3 or 4 substituents which can be the same or different and are independently selected from the group consisting of:
deuterium, halo, cyano, amino, aminoalkyl-, (amino)alkoxy-, -CONH₂, -C(0)NH(alkyl), -
C(0)N(alkyl)₂, -C(0)NH(aryl), -C(0)N(aryl)₂, -CHF₂, -OCHF₃, -alkyl, -alkenyl, -alkynyl, -
alkoxy, (alkoxyalkyl)amino-, -N(R³)₂-C(0)-alkyl, -N(R³)₂-C(0)-aryl, cycloalkyl, heterocycloalkyl, aryl
and heteroaryl;
R¹ is -NR³R⁶, wherein R³ is H, alkyl or -S(0)₂alkyl and R⁶ is alkyl, hydroxyalkyl, -S(0)₂alkyl, -
(CH₂)₄cycloalkyl, -(CH₂)₄heterocycloalkyl, aryl, arylalkyl-, -(CH₂)₄heteroaryl;
cycloalkyl;
heterocycloalkyl;
aryl;
heteroaryl;
each of said cycloalkyl, heterocycloalkyl, aryl, or heteroaryl is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents which can be the same or different and are independently selected from the group consisting of:
deuterium, halo, cyano, alkyl, hydroxyl, hydroxyalkyl, hydroxyalkoxy, cyanoalkyl, haloalkyl, alkenyl,
alkynyl, alkoxy, alkylalkoxy, haloalkoxy, arylalkenyl-, arl oxy, benzyloxy, oxo, -(CH₂)₉-NR³R⁶d, -
(CH₂)₉-CONR³R⁶d, -S(0)₂alkyl, -S(0)₂aryl, S(0)₂NH₂, -S(0)₂NH-alkyl, -S(0)₂N(alkyl)₂, -S(0)₂-
heterocycloalkyl, -S(0)₂CF₃, -C(0)alkyl, -C(0)aryl, -C(0)alkynylaryl, -C(0)alkoxyaryl, -NH-
C(0)alkyl, -NH-C(0)aryl, methylenedioxy, -(CH₂)₄cycloalkyl, cycloalkylalkoxy-, aryl, arylalkyl-, -
(CH₂)₉heteroaryl, and -(CH₂)₉heterocycloalkyl,
wherein each of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted by one or
more halo, nitro, haloalkyl, haloalkoxy, oxo, cyano, alkyl, haloalkyl, or alkoxy and;
R¹ and R⁴ are independently selected from the group consisting of H, alkyl, hydroxyalkyl, alkoxy, aryl, alkoxyalkyl, -S(0)₂alkyl and cycloalkyl or R² and R⁴ can form a 5 or 6 membered heterocycloalkyl group together with the nitrogen atom to which they are attached, wherein said heterocycloalkyl group may contain one or more additional heteroatom(s) selected from N, S or O; z is 0, 1 or 2; q is 0, 1, 2, 3 or 4; and pharmaceutically acceptable salts thereof.

18. The method of claim 12, wherein the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of:

Wherein W is -C(O)-, -S(O)- or -S(0)₂;
R is an aryl or bicyclic heteroaryl wherein the heteroatoms of each of said heteroaryl numbers 1, 2 or 3, and are independently selected from N, S or O, wherein each of said aryl, heteroaryl is optionally substituted with one or more substituents which can be the same or different and are independently selected from the group consisting of deuterium, halo, cyano, amino, aminoalkyl, (amino)alkoxy, -CONH₂, -C(0)NH(alkyl), -C(0)N(alkyl)₂, -C(0)NH(aryl), -C(0)N(aryl)₂, -CF₃, -CHF₂, -CH₂F, -alkyl, alkoxy, hydroxyl, hydroxyalkyl, (alkoxyalkyl) amino, -N(R³)-C(0)-alkyl, -N(R³)-C(0)-aryl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, with the proviso that no two adjacent ring heteroatoms are both S or both O;
G is aryl, heteroaryl, cycloalkyl, heterocycloalkyl or -NR¹R², with each of said aryl, heteroaryl, heterocycloalkyl and cycloalkyl being either unsubstituted or independently substituted with 1, 2, 3 or 4 substituents which can be the same or different and are independently selected from the group consisting of deuterium, halo, cyano, amino, aminoalkyl, (amino)alkoxy, -CONH₂, -C(0)NH(alkyl), -C(0)N(alkyl)₂, -C(0)NH(aryl), -C(0)N(aryl)₂, -CF₃, -CHF₂, -CH₂F, alkyl, alkenyl, alkynyl, alkoxy, hydroxyl, hydroxyalkyl, aryloxy, (alkoxyalkyl) amino, -N(R³)-C(0)-alkyl, -N(R³)-C(0)-aryl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;
R¹ and R² are the same or they are different, and are independently selected from H, Ci to C₂ alkyl, Ci to C₇ alkoxy, Ci to C₄ hydroxyalkyl, aryl, heteroaryl, heterocycloalkyl and cycloalkyl, and wherein heteroatoms of said heteroaryl and heterocycloalkyl are independently selected from one or more N,
O and S, with the proviso that no two adjacent ring heteroatoms are both S or both O, further wherein R₁ and R² can be either unsubstituted or optionally independently substituted with one or more substituents which can be the same or different and are independently selected from the group consisting of deuterium, halo, cyano, amino, aminoalkyl, (amino)alkoxy, -CONH₂, -C(0)NH(alkyl), -C(0)N(alkyl)₂, -C(0)NH(aryl), -C(0)N(aryl)₂, -CF₃, -CHF₂, alkyl, hydroxyalkyl, -alkoxy, hydroxyl, hydroxyalkyl, carboxy, (alkoxyalkyl) amino, -alkylamine, aminocarbonyl, -CHO, -N(R³)-C(0)-alkyl, -N(R³)-C(0)-aryl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; R³ is H, alkyl or arylalkyl; n is 4, 5 or 6; or a pharmaceutically acceptable salt thereof.

19. The method of claim 12, wherein the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of:

![Chemical Structure](image)

wherein:
A is CH or N;
E is O or is absent;
R is (a) a bicyclic heteroaryl comprising one or more heteroatom ring members independently selected from N, S or O, wherein said bicyclic heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy; and wherein one or more N ring members of said bicyclic heteroaryl is optionally an N-oxide; or
(b) a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or monocyclic heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is substituted with one or more substituent selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy;
R¹ is (1) Rᵐ or -alkylidenyl-Rᵐ, where Rᵐ is cycloalkyl, heterocycloalkyl, phenyl, or monocyclic heteroaryl;
wherein each of said cycloalkyl, heterocycloalkyl, phenyl, and heteroaryl is unsubstituted or is substituted with one or more substituents Rₘ;
wherein each Rₘ substituent is independently selected from the group consisting of: deuterium, halo, hydroxy, hydroxyalkyl, cyano,
-NR³R⁵, -alkylidenyl-NR³R⁵, oxo, alkyl, cyanoalkyl, haloalkyl, alkoxy, -S-alkyl, haloalkoxy, alkoxyalkyl-, alkenyl, alkynyl,
-C(0)Calkyl, -C(0)₂alkyl, -C(0)₂H, -CONH₂, C(0)NH(alkyl),

268
-C(0)NH(haloalkyl), -C(0)N(alkyl), -C(0)NH(cycloalkyl), arylalkyl-, arylalkoxy-, aryloxy-, cycloalkyl, cycloalkyloxy, (cycloalkyl)alkyl, heterocycloalkyl, aryl, (heterocycloalkyl)alkyl-, (heterocycloalkyl)alkoxy-, -C(0)cycloalkyl, -C(0)heterocycloalkyl, heteroaryl, (heteroaryl)alkyl-, -S(0)alkyl, -S0 2 -alkyl, -S0 2 -aryl, -S0 2 -fluoroalkyl, -N(R 1 )-C(0)-alkyl, -N(R 1 )-C(0)-aryl, -N(R 1 )-C0 2 -alkyl, -S0 2 NH 2 , -S0 2 NH(alkyl), -S0 2 N(alkyl) 2 , -S0 2 NH(cycloalkyl), and -N(H)(S0 2 alkyl), or two adjacent R 1 substituents on a phenyl or heteroaryl R m groups taken together form methylenedioxy, wherein each of said cycloalkyl, heterocycloalkyl, aryl, and heteroaryl within R 1 is unsubstituted or is substituted with one or more substituents independently selected from the group consisting of deuterium, alkyl, halo, hydroxy, cyano, alkoxy, amino, -C(0)alkyl, and -C0 2 alkyl; wherein R 1 and R 2 are each independently H, alkyl, alkoxy, alkoxyalkyl, cyanoalkyl, or haloalkyl; and R 3 is H, alkyl or arylalkyl;

(2) alkyl unsubstituted or substituted with one or more substituents selected from the group consisting of deuterium, halo, hydroxy, cyano, alkoxy, haloalkoxy, -NR 3 R 4 , -C(0)alkyl, -C0 2 alkyl, -C0 2 H, -CONR 3 R 4 , -SOalkyl, -S0 2 alkyl, and -S0 2 NR 3 R 4 ;

where R 1 and R 3 are each independently H, alkyl, alkoxyalkyl, haloalkyl, -C(0)alkyl, or -C0 2 alkyl; or

(3) -N(R 3 )R 0 ,

wherein R 0 is H, R m, -alkylenyl-R m, hydroxyalkyl, cyanoalkyl, alkoxyalkyl, haloalkyl, -CONR 3 , or -C(0)R 0 ;

where R m is as defined in (1) above;

R 1 and R 2 are each independently H or alkyl, or R 1 and R 2 taken together with the nitrogen to which they are attached form a monocyclic heterocycloalkyl; and

R 2 is an alkyl unsubstituted or substituted with one or more substituents selected from the group consisting of: deuterium, halo, amino, hydroxy, alkoxy, cycloalkyl, heteroaryl, phenyl, and heterocycloalkyl; or a cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl, each unsubstituted or substituted with one or more substituents selected from the group consisting of: deuterium, alkyl, halo, amino, hydroxy, and alkoxy; and

R 1 is H or R 2 ;

R 1 and R 2 are each independently selected from the group consisting of H and deuterium; and pharmaceutically acceptable salts of compounds of Formula I.

20. The method of claim 19, wherein Rx is independently selected from the group consisting of: -C(0)alkyl or -C(0)alkyl-0-alkyl.
21. The method of claim 12, wherein the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of:

\[
\begin{align*}
R^1 & \text{ is } (1) \text{ a saturated, monocyclic heterocycloalkyl, which is unsubstituted or substituted with one or more substituents } R^8; \\
\text{wherein each } R^8 \text{ substituent is independently selected from the group consisting of: } & \text{ deuterium, halo, hydroxy, cyano, } \text{-NR}^b\text{, -alkylamino, -alkyl, -NHR}, \text{ cyanoalkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, alkenyl, alkynyl, aryl, aryalkyl, aryloxy, arylalkoxy, cycloalkoxy, cycloalkenyl, cycloalkynyl, heterocycloalkyl, heteroarylalkyl, heterocycloalkylalkyl, heterocycloalkylalkoxy, -CN, -COalkyl, -C0=alkyl, -C0=H, -C0=cyloalkyl, -C(0)heterocycloalkyl, -S(0)-alkyl, -SO_{2}\text{-alkyl}, -SO_{2}\text{-aryl, -SO}_{2}\text{(haloalkyl), -CONH}_2, \\
& \text{-C(0)NH(alkyl), -C(0)NH(haloalkyl), -C(0)N(alkyl), -C(0)NH(cycloalkyl), heteroaryl, (heteroaryl)alkyl, -N(R^c)-C(0)-alkyl, -N(R^c)-C(0)-aryl, -N(R^c)-C0_{2}\text{-alkyl, -SO}_{2}\text{NH}_2,} \\
& \text{-SO}_{2}\text{NH(alkyl), -SO}_{2}\text{N(alkyl), -SO}_{2}\text{NH(cycloalkyl), and -N(H)(S0}_{2}\text{alkyl), or two adjacent } R^8 \text{ substituents taken together form a phenyl ring,}} \\
\text{wherein each of said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and phenyl substituents within } R^8 \text{ is independently unsubstituted or substituted with one or more substituents selected from the group consisting of alkyl, halo, hydroxy, cyano, alkoxy, amino,} \\
& \text{-C(0)alkyl, and -C0=alkyl; } \\
\text{wherein } R^a \text{ and } R^b \text{ are each independently } H, \text{ alkyl, alkoxy, alkoxyalkyl, cyanoalkyl, or haloalkyl; and } R^c \text{ is } H \text{ or alkyl; or } \\
\text{(2) a saturated, bicyclic or tricyclic, nitrogen-linked heterocycloalkyl, wherein said heterocycloalkyl comprises a fused, bridged, or spiro bicyclic system, and said heterocycloalkyl is unsubstituted or}
\end{align*}
\]
substituted with one or more substituents independently selected from the group consisting of: alkyl, halo, haloalkyl, hydroxy, hydroxyalkyl, alkoxy, cyano, cyanoalkyl, oxo, -NR<sup>i</sup>R<sup>j</sup>, -alkylenyl-NR<sup>i</sup>R<sup>j</sup>, -(C(0)alkyl, -C0<sub>2</sub>alkyl, and -S0<sub>2</sub>alkyl; wherein R<sup>i</sup> is H or alkyl and R<sup>j</sup> is H, alkyl, haloalkyl, -C(0)alkyl, -C0<sub>2</sub>alkyl, or -S0<sub>2</sub>alkyl; and
R<sup>2</sup> and R<sup>3</sup> are each independently H or deuterium; or a pharmaceutically acceptable salt thereof.

22. The method of claim 21, wherein R<sup>x</sup> is selected from -C(0)aryl.

23. The method of claim 21, wherein each of said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and phenyl substituents within R<sup>x</sup> is substituted with one or more -NHC0<sub>2</sub>alkyl.

24. The method of claim 12, wherein the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of:

![Chemical Structure](image)

wherein:

R is (a) an 8-, 9-, or 10-membered bicyclic heteroaryl comprising one heteroatom selected from N, S, and O, and one, two, or three additional N atoms, wherein said bicyclic heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy, and wherein one or more N atoms of said bicyclic heteroaryl is optionally an N-oxide; or (b) a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or monocyclic six-membered heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy; and

R<sup>1</sup> is H, -(Ci<sub>4</sub>alkylene)<sub>0</sub>-iC(O)R<sup>a</sup>, -(Ci<sub>4</sub>alkylene)<sub>0</sub>-iCO<sub>2</sub>R<sup>a</sub>, -(Ci<sub>4</sub>alkylene)<sub>0</sub>-iS(O)R<sup>a</sup>, -(Ci<sub>4</sub>alkylene)<sub>0</sub>-iSO<sub>2</sub>R<sup>a</sup>, -(C(0)NH(R<sup>2</sup>)), or -(C(0)N(R<sup>2</sup>))<sub>2</sub>; wherein each R<sup>a</sup> is independently

(1) alkyl, unsubstituted or substituted with one or more R<sup>0</sup> substituents,
wherein each R<sup>0</sup> is independently selected from the group consisting of hydroxy, -NR<sup>2</sup>R<sup>c</sup>, alkoxy, cyano, halo, -(C(0)alkyl, -C0<sub>2</sub>alkyl, -CONR<sup>0</sup>R<sup>c</sup>, -(S0<sub>2</sub>)alkyl, -S0<sub>2</sub>alkyl, -S0<sub>2</sub>NR<sup>0</sup>R<sup>c</sup>, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, wherein R<sup>0</sup> is H or alkyl;
R<sup>c</sup> is H, alkyl, alkoxyalkyl, haloalkyl, -(C(0)alkyl, -C0<sub>2</sub>alkyl, or
-SO₂alkyl; and

each aryl, heteroaryl, cycloalkyl, and heterocycloalkyl group within R² is unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, hydroxy, amino, cyano, halo, -S(0)alkyl, -SO₂alkyl, haloalkyl, hydroxyalkyl, and alkoxy;

(2) phenyl, cycloalkyl, heteroaryl, or heterocycloalkyl, each unsubstituted or substituted with one or more hydroxy, -NR₄R°, alkoxy, cyano, halo, -C(0)alkyl, -C(O)alkyl, -CONR°alkyl, -S(0)alkyl, -SO₂alkyl, or -SO₂NR°R° substituents; or

(3) -NR°R°,

where R° is H or alkyl; and

R⁰ is H, alkyl, alkoxyalkyl, haloalkyl, -C(0)alkyl, -C(O)alkyl, or -SO₂alkyl;

R² and R³ are each independently H or deuterium; and

n is 1 or 2;

or a stereoisomer thereof, or a pharmaceutically acceptable salt of such a compound or stereoisomer.

25. The method of claim 12, wherein the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of:

![Chemical Structure](image)

wherein:

R is (a) an 8-, 9-, or 10-membered bicyclic heteroaryl comprising one heteroatom selected from N, S, and O, and one, two, or three additional N atoms, wherein said bicyclic heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy, and wherein one or more N atoms of said bicyclic heteroaryl is optionally an N-oxide; or

(b) a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or monocyclic five- or six-membered heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy; and

R¹ is H, -(C₈₋₄alkylene)ₐ-C(O)R₄, -(C₈₋₄alkylene)ₐ-C(O)₂R₄, -(C₈₋₄alkylene)ₐ-iSO₂R₄, -(C₈₋₄alkylene)ₐ-C(O)NH(R °₄), -(C₈₋₄alkylene)ₐ-C(O)N(R °₄)₂, or -(C₈₋₄alkylene)ₐ-C(O)NH(R °₄);

wherein each R° is independently

(1) alkyl, unsubstituted or substituted with one or more R° substituents,
wherein each \( R^m \) is independently selected from the group consisting of hydroxy, -NR\(^b\)R\(^c\), alkoxy, cyano, halo, -C(0)alkyl, -C0\(^2\)alkyl, -CONR\(^b\)R\(^c\), -S(0)alkyl, -SO\(^2\)alkyl, -SO\(^2\)NR\(^b\)R\(^c\), aryl, heteroaryl, cycloalkyl, heterocycloalkyl, phenoxy, and -O-alkyl-OH;

wherein \( R^b \) is H or alkyl;

\( R^c \) is H, alkyl, alkoxyalkyl, haloalkyl, -C(0)alkyl, -C0\(^2\)alkyl,
-S0\(^2\)alkyl, -C(O)NH \(_2\), or C(0)H; and

each aryl, heteroaryl, cycloalkyl, and heterocycloalkyl group within \( R^m \) is unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, hydroxy, -NR\(^b\)R\(^c\), alkoxy, haloalkoxy, cyano, halo, oxo, -C(0)alkyl, -C0\(^2\)alkyl, -C(O)-heterocycloalkyl, -CONR\(^b\)R\(^c\), -S(0)alkyl, -SO\(^2\)alkyl, -SO\(^2\)-haloalkyl, -SO\(^2\)NR\(^b\)R\(^c\), aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

wherein each alkyl or alkoxy is unsubstituted or substituted with -NR\(^b\)R\(^c\), heterocycloalkyl, heteroaryl, or -C(0)alkyl; and
each aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is unsubstituted or substituted with alkyl, halo, or -C(0)alkyl;

(2) phenyl, cycloalkyl, heteroaryl, or heterocycloalkyl, each unsubstituted or substituted with one or more substituents selected from the group consisting of alkyl, haloalkyl, hydroxy, -NR\(^b\)R\(^c\), alkoxy, haloalkoxy, cyano, halo, oxo, -C(0)alkyl, -C0\(^2\)alkyl, -C(O)-heterocycloalkyl, -CONR\(^b\)R\(^c\), -S(0)alkyl, -SO\(^2\)alkyl, -SO\(^2\)-haloalkyl, -SO\(^2\)NR\(^b\)R\(^c\), aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

wherein each alkyl or alkoxy is unsubstituted or substituted with -NR\(^b\)R\(^c\), heterocycloalkyl, heteroaryl, or -C(0)alkyl; and
each aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is unsubstituted or substituted with alkyl, halo, or -C(0)alkyl; or

(3) -NR\(^b\)R\(^c\),

where \( R^x \) is H or alkyl; and

\( R^y \) is H, alkyl, alkoxyalkyl, haloalkyl, -C(0)alkyl, -C0\(^2\)alkyl, or
-S0\(^2\)alkyl;

\( R^2 \) and \( R^3 \) are each independently H or deuterium; and
\( n \) is 1 or 2;

and stereoisomers thereof, and pharmaceutically acceptable salts of such compounds and stereoisomers.

26. The method of claim 12, wherein the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of:
wherein:

R is (a) a bicyclic heteroaryl comprising 1, 2, 3, or 4 heteroatom ring members independently selected from N, S or O, wherein said bicyclic heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy; and wherein one or more N ring members of said heteroaryl is optionally an N-oxide; or

(b) a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or monocyclic heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is substituted with one or more substituent selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy;

R\textsuperscript{1} is alkyl, R\textsuperscript{m}, or -alkylenyl-R\textsuperscript{m}, wherein said alkyl is unsubstituted or substituted with one or more substituents selected from the group consisting of deuterium, halo, hydroxy, cyano, alkoxy, -NR\textsuperscript{2}R\textsuperscript{3}, hydroxyalkyl, cyanoalkyl, haloalkyl, haloalkoxy, alkoxyalkyl, -S-alkyl, -C(0)alkyl, -C(0)\textsubscript{2}alkyl, -C(0)\textsubscript{2}H,

-C(0)NH\textsubscript{2}, -C(0)NH(alkyl), -C(0)NH(haloalkyl), -C(0)N(alkyl)\textsubscript{2}, -S\textsubscript{0}\textsubscript{2}NH\textsubscript{2}, -S\textsubscript{0}\textsubscript{2}NH(alkyl), and -S\textsubscript{0}\textsubscript{2}N(alkyl)\textsubscript{2};

where R\textsuperscript{2} and R\textsuperscript{3} are each independently H, alkyl, alkoxyalkyl, haloalkyl, -C(0)alkyl, -C(0)\textsubscript{2}alkyl, or -S\textsubscript{0}\textsubscript{2}alkyl; and

R\textsuperscript{m} is cycloalkyl, phenyl, monocyclic heteroaryl, or heterocycloalkyl, each unsubstituted or substituted with one or more substituents R\textsuperscript{s};

wherein each R\textsuperscript{s} substituent is independently selected from the group consisting of: deuterium, halo, hydroxy, hydroxyalkyl, cyano,

-NR\textsuperscript{2}R\textsuperscript{3}, -alkylenyl-NR\textsuperscript{2}R\textsuperscript{3}, oxo, alkyl, cyanoalkyl, haloalkyl, alkoxy,

-S-alkyl, haloalkoxy, alkoxyalkyl-, alkenyl, alkynyl, -C(0)alkyl,

-CONH\textsubscript{2}, C(0)NH(alkyl), -C(0)NH(haloalkyl), -C(0)N(alkyl)\textsubscript{2}, -C(0)NH(cycloalkyl), aryalkyl-, aryloxyalkyl-, aryl-, cyanoalkyl, cycloalkyl, cycloalkyloxy, (cycloalkyl)alkyl-, heterocycloalkyl, aryl, (heterocycloalkyl)alkyl-, (heterocycloalkyl)alkoxy-, -C(0)heterocycloalkyl, heteroaryl, (heteroaryl)alkyl-, -S(0)-alkyl,

-S\textsubscript{0}\textsubscript{2}alkyl, -S\textsubscript{0}\textsubscript{2}aryl, -S\textsubscript{0}\textsubscript{2}fluoroalkyl, -N(R\textsuperscript{s})-C(0)-alkyl, -N(R\textsuperscript{s})-C(0)-aryl, -N(R\textsuperscript{s})-C(0)\textsubscript{2}alkyl, -C(0)\textsubscript{2}H, -S\textsubscript{0}\textsubscript{2}NH\textsubscript{2}, -S\textsubscript{0}\textsubscript{2}NH(alkyl), -S\textsubscript{0}\textsubscript{2}N(alkyl)\textsubscript{2}, -S\textsubscript{0}\textsubscript{2}NH(cycloalkyl), and -N(H)(S\textsubscript{0}\textsubscript{2})(alkyl), or two adjacent phenyl or heteroaryl R\textsuperscript{s} substituents taken together form methylenedioxy,

wherein each of said cycloalkyl, heterocycloalkyl, aryl, and heteroaryl within R\textsuperscript{s} is unsubstituted or is
substituted with 1, 2, or 3 substituents independently selected from the group consisting of alkyl, halo, hydroxy, cyano, alkoxy, amino, -C(O)alkyl, and -CO alkyl;

wherein R^a and R^b are each independently H, alkyl, alkoxy, alkoxyalkyl, cyanoalkyl, or haloalkyl; and R^c is H, alkyl, or arylalkyl; and R^d is an alkyl, haloalkyl, unsubstituted hydroxyalkyl, or a pharmaceutically acceptable salt thereof.

27. The method of claim 12, wherein the NAD biosynthesis from nicotinamide antagonist is a small molecule selected from the group consisting of:

![Chemical Structure](image)

wherein:

E is O or is absent;

R is (a) an 8-, 9-, or 10-membered bicyclic heteroaryl comprising one heteroatom selected from N, S, and O, and one, two, or three additional N atoms, wherein said bicyclic heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy, and wherein one or more N atoms of said bicyclic heteroaryl is optionally an N-oxide; or

(b) a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or monocyclic six-membered heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy; R^1 is (1) R^8, where R^8 is a phenyl, cycloalkyl, heterocycloalkyl, or monocyclic heteroaryl, unsubstituted or substituted with one or more R^m substituents;

wherein each R^m substituent is independently selected from the group consisting of: halo, hydroxy, cyano, -NR^b, -alkyl-NR^b, -alkenyl-NR^b, -alkynyl-NR^b, -alkoxyalkyl, alkenyl, alkenyloxy, alkynyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkyloxy, (cycloalkyl)alkyl-, heterocycloalkyl, (heterocycloalkyl)alkyl-, (heterocycloalkyl)alkoxy-, -C(O)alkyl, -CO alkyl, -C(O)H, -C(O)cycloalkyl, -C(O)heterocycloalkyl, -S(0)-alkyl, -S(0)-alkyl, -SO aryl, -SO aryl, -SO haloalkyl, -CONH aryl, C(O)NH(alkyl), -C(O)NH(haloalkyl), -C(O)N(alkyl), -C(O)NH(cycloalkyl), heteroaryl, (heteroaryl) alkyl-, -N(R^c)-C(O)-alkyl, -N(R^c)-C(O)-aryl, -N(R^c)-C(O)-alkyl, -SO NH.
-S\textsubscript{0} \textsuperscript{2} NH(alkyl), -S\textsubscript{0} \textsuperscript{2} N(alkyl)\textsubscript{2}, -S\textsubscript{0} \textsuperscript{2} NH(cycloalkyl), and
-N(H)(S\textsubscript{0} \textsuperscript{2} alkyl), or two adjacent R\textsuperscript{m} substituents taken together form a phenyl ring,
wherein each of said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and phenyl substituents within R\textsuperscript{m}
is independently unsubstituted or substituted with one or more substituents selected from the group
consisting of alkyl, halo, hydroxy, cyano, alkoxy, amino,
-C(0)alkyl, and -C\textsubscript{0} \textsuperscript{2} alkyl;
R\textsuperscript{2} and R\textsuperscript{3} are each independently H, alkyl, alkoxy, alkoxyalkyl, cyanoalkyl, or haloalkyl; and
R\textsuperscript{c} is H or alkyl;
(2) -alkylenyl-R \textsuperscript{x} or -C(0)-alkylenyl-R \textsuperscript{x}, where R\textsuperscript{x} is as defined in (1) above; or
(3) alkyl substituted with one or more R\textsuperscript{p} substituents,
wherein each R\textsuperscript{p} is independently -CONR\textsuperscript{b}R\textsuperscript{i}, hydroxy, cyano, alkoxy, halo, or -C(0)R\textsuperscript{l};
wherein R\textsuperscript{b} and R\textsuperscript{i} are each independently H or alkyl, or R\textsuperscript{b} and R\textsuperscript{i} taken together with the nitrogen to
which they are attached form a monocyclic heterocycloalkyl; and
R\textsuperscript{l} is alkyl, cycloalkyl, heterocycloalkyl, phenyl, or benzyl, each unsubstituted or substituted with one
or more substituents selected from the group consisting of: alkyl, halo, amino, hydroxy, and alkoxy;
R\textsuperscript{2} and R\textsuperscript{3} are each independently H or deuterium; and
R\textsuperscript{4} is H;
an alkyl unsubstituted or substituted with one or more substituents selected from the group consisting
of: deuterium, halo, amino, hydroxy, alkoxy, cycloalkyl, heteroaryl, phenyl, and heterocycloalkyl,
wherein each cycloalkyl, heteroaryl, phenyl, and heterocycloalkyl is unsubstituted or substituted with
one or more substituents selected from the group consisting of: deuterium, alkyl, halo, amino,
hydroxy, and alkoxy; or
a cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl, each unsubstituted or substituted with one or
more substituents selected from the group consisting of: deuterium, alkyl, halo, amino, hydroxy, and
alkoxy;
with the proviso that R\textsuperscript{4} is not H when R\textsuperscript{l} is as defined in (1) above;
or a pharmaceutically acceptable salt thereof.

28. The method of any one of claims 1-5 and 9-13, wherein the method further comprises
administering niacin.

29. The method of claim 28, wherein niacin is Niaspan\textsuperscript{®}.

30. The method of claim 28, wherein the niacin reduces toxicity of the NAD biosynthesis from
nicotinamide antagonist and/or increases the therapeutic index of the NAD biosynthesis from
nicotinamide antagonist.
31. The method of any one of claims 1-30, wherein the positive NAPRT1 methylation status is methylation of at least one cytosine within a NAPRT1 DNA region.

32. The method of claim 31, wherein the positive NAPRT1 methylation status is methylation of at least one cytosine within a CpG island of an NAPRT1 gene.

33. The method of claim 31, wherein the positive NAPRT1 methylation status is methylation of at least one cytosine between about chromosome coordinates 144659500 and 144661000 of human chromosome 8.

34. The method of claim 31, wherein the positive NAPRT1 methylation status is methylation of at least one cytosine in the sequence represented between about position 1018 and about position 1545 of SEQ ID NO:1.

35. The method of claim 31, wherein the positive NAPRT1 methylation status is methylation of at least one cytosine in the sequence represented between about position 1221 and about position 1288 of SEQ ID NO:1.

36. The method of any one of claims 1-30, wherein the positive NAPRT1 methylation status is methylation of at least 25% of the cytosines within a portion of an NAPRT1 gene.

37. The method of claim 36, wherein the positive NAPRT1 methylation status is methylation of at least 25% of the cytosines within a portion of an NAPRT1 gene, wherein the portion of the NAPRT1 gene corresponds to a portion of the human NAPRT1 sequence represented by SEQ ID NO:1

38. The method of claim 36, wherein the positive NAPRT1 methylation status is methylation of at least 25% of the cytosines within a promoter in an NAPRT1 gene.

39. The method of claim 36, wherein the positive NAPRT1 methylation status is methylation of at least 25% of the cytosines within a CpG island of an NAPRT1 DNA region.
40. The method of claim 36, wherein the positive NAPRT1 methylation status is methylation of at least 25% of the cytosines in a sequence corresponding to the sequence between about chromosome coordinates 144659500 and 144661000 of human chromosome 8.

41. The method of claim 36, wherein the positive NAPRT1 methylation status is methylation of at least 25% of the cytosines in the sequence represented between about position 1018 and about position 1545 of SEQ ID NO:1.

42. The method of claim 36, wherein the positive NAPRT1 methylation status is methylation of at least 25% of the cytosines in the sequence represented between about position 1221 and about position 1288 of SEQ ID NO:1.

43. The method of any of the preceding claims, wherein the disease or disorder or disease or disorder cell is cancer.

44. The method of claim 43, wherein the cancer or cancer cell is breast cancer, colorectal cancer, endometrium cancer, kidney cancer, lung cancer, lymphoid cancer, ovarian cancer, pancreatic cancer, or stomach cancer.

45. A method of identifying a human cancer patient suitable for treatment with an NAD biosynthesis from nicotinamide antagonist comprising determining the level of methylation of cytosines of an NAPRT1 gene wherein greater than 25% methylation of the NAPRT1 gene indicates that the individual is more likely to benefit from treatment.

46. A method of identifying a human cancer patient suitable for treatment with an NAD biosynthesis from nicotinamide antagonist comprising determining the level of methylation of cytosines of an NAPRT1 promoter wherein greater than 25% methylation of the NAPRT1 promoter indicates that the individual is more likely to benefit from treatment.

47. A method of identifying a human cancer patient suitable for treatment with an NAD biosynthesis from nicotinamide antagonist comprising determining the level of methylation of cytosines of a CpG island in an NAPRT1 gene wherein greater than 25% methylation of the CpG island indicates that the individual is more likely to benefit from treatment.
48. A method of identifying a human cancer patient suitable for treatment with an NAD biosynthesis from nicotinamide antagonist comprising determining the level of methylation of cytosines of the sequence represented between about position 1018 and about position 1545 of SEQ ID NO:1 wherein greater than 25% methylation of the sequence that the individual is more likely to benefit from treatment.

49. A method of identifying a human cancer patient suitable for treatment with an NAD biosynthesis from nicotinamide antagonist comprising determining the level of methylation of cytosines of the sequence represented between about position 1221 and about position 1288 of SEQ ID NO:1 wherein greater than 25% methylation of the sequence that the individual is more likely to benefit from treatment.

50. A method of identifying an individual who is more likely to exhibit benefit from a therapy comprising an NAD biosynthesis from nicotinamide antagonist, said method comprising

   a) isolating DNA from a tumor sample the individual;
   b) incubating the DNA sample with sodium bisulfite sufficient to convert unmethylated cytosine in the DNA to uracil;
   c) sequencing the NAPRT1 promoter region of the DNA;
   d) determining the methylation level of the NAPRT1 promoter region by determining the number of cytosine residues that were not converted to uracil in step b);

   wherein greater than 25% methylation of the sequence that the individual is more likely to benefit from treatment.

51. A method of identifying an individual who is more likely to exhibit benefit from a therapy comprising an NAD biosynthesis from nicotinamide antagonist, said method comprising

   a) isolating DNA from a tumor sample the individual;
   b) incubating the DNA sample with sodium bisulfite sufficient to convert unmethylated cytosine in the DNA to uracil;
   c) sequencing a fragment of the DNA comprising a portion NAPRT1 CpG island;
   d) determining the methylation level of the NAPRT1 CpG island by determining the number cytosine residues that were not converted to uracil in step b);
wherein greater than 25% methylation of the sequence that the individual is more likely to benefit from treatment.

52. The method of claim 51, wherein the portion of the NAPRT1 CpG island comprises the sequence represented between about position 1018 and about position 1545 of SEQ ID NO:1.

53. A method of identifying an individual who is more likely to exhibit benefit from a therapy comprising an NAD biosynthesis from nicotinamide antagonist, said method comprising

   a) isolating DNA from a tumor sample the individual,

   b) incubating the DNA sample with sodium bisulfite sufficient to convert unmethylated cytosine in the DNA to uracil,

   c) amplifying a portion of the CpG island of the NAPRT1 gene of the DNA sample using quantitative methylation specific PCR,

   d) determining the methylation level of the NAPRT1 region by determining the -dCt value of the tumor sample with the -dCt value obtained from quantitative methylation specific PCR of non-methylated DNA,

   wherein greater than 25% methylation of the NAPRT1 sequence that the individual is more likely to benefit from treatment.

54. The method of claim 53, wherein the portion of the CpG island of the NAPRT1 gene comprises the sequence represented between about position 1221 and about position 1288 of SEQ ID NO:1.

55. The method of any one of claims 50-54, wherein the DNA from the tumor sample is isolated from a formalin-fixed paraffin embedded tumor sample.

56. The method of any one of claims 53-55, wherein step c) further comprises a pre-amplification of the portion of the CpG island of the NAPRT1 gene of the DNA sample prior to quantitative methylation specific PCR.

57. A method of treating a human cancer patient with an NAD biosynthesis from nicotinamide antagonist, said method comprising
determining the level of methylation of cytosines of an NAPRT1 gene in a tumor sample from the patient wherein greater than 25% methylation of the NAPRT1 gene indicates that the patient is more likely to benefit from treatment; and

administering an effective amount of an NAD biosynthesis from nicotinamide antagonist to the patient more likely to benefit from treatment.

58. A method of treating a human cancer patient suitable for treatment with an NAD biosynthesis from nicotinamide antagonist, said method comprising

determining the level of methylation of cytosines of an NAPRT1 promoter in a tumor sample from the patient wherein greater than 25% methylation of the NAPRT1 promoter indicates that the patient is more likely to benefit from treatment,

administering an effective amount of an NAD biosynthesis from nicotinamide antagonist to the patient more likely to benefit from treatment.

59. A method of treating a human cancer patient suitable for treatment with an NAD biosynthesis from nicotinamide antagonist, said method comprising

determining the level of methylation of cytosines of a CpG island in an NAPRT1 gene in a tumor sample from the patient wherein greater than 25% methylation of the CpG island indicates that the patient is more likely to benefit from treatment; and

administering an effective amount of an NAD biosynthesis from nicotinamide antagonist to the patient more likely to benefit from treatment.

60. A method of treating a human cancer patient suitable for treatment with an NAD biosynthesis from nicotinamide antagonist, said method comprising

determining the level of methylation of cytosines of the sequence represented between about position 1018 and about position 1545 of SEQ ID NO:1 in a tumor sample from the patient wherein greater than 25% methylation of the sequence that the individual is more likely to benefit from treatment, and

administering an effective amount of an NAD biosynthesis from nicotinamide antagonist to the patient more likely to benefit from treatment.

61. A method of treating a human cancer patient suitable for treatment with an NAD biosynthesis from nicotinamide antagonist, said method comprising
determining the level of methylation of cytosines of the sequence represented between about position 1221 and about position 1288 of SEQ ID NO:1 in a tumor sample from the patient wherein greater than 25% methylation of the sequence that the patient is more likely to benefit from treatment, and

administering an effective amount of an NAD biosynthesis from nicotinamide antagonist to the patient more likely to benefit from treatment.

62. A method of treating human cancer patient with an NAD biosynthesis from nicotinamide antagonist, said method comprising

   a) isolating DNA from a tumor sample the patient;

   b) incubating the DNA sample with sodium bisulfite sufficient to convert unmethylated cytosine in the DNA to uracil;

   c) sequencing the NAPRT1 promoter region of the DNA;

   d) determining the methylation level of the NAPRT1 promoter region by determining the number of cytosine residues that were not converted to uracil in step b) wherein greater than 25% methylation of the sequence that the patient is more likely to benefit from treatment; and

   e) administering an effective amount of an NAD biosynthesis from nicotinamide antagonist to the patient more likely to benefit from treatment.

63. A method of treating human cancer patient with an NAD biosynthesis from nicotinamide antagonist, said method comprising

   a) isolating DNA from a tumor sample the patient;

   b) incubating the DNA sample with sodium bisulfite sufficient to convert unmethylated cytosine in the DNA to uracil;

   c) sequencing a fragment of the DNA comprising a portion NAPRT1 CpG island;

   d) determining the methylation level of the NAPRT1 CpG island by determining the number cytosine residues that were not converted to uracil in step b), wherein greater than 25% methylation of the sequence that the patient is more likely to benefit from treatment; and

   e) administering an effective amount of an NAD biosynthesis from nicotinamide antagonist to the patient more likely to benefit from treatment.
64. The method of claim 63, wherein the portion of the NAPRT1 CpG island comprises the sequence represented between about position 1018 and about position 1545 of SEQ ID NO:1.

65. A method of treating human cancer patient with an NAD biosynthesis from nicotinamide antagonist, said method comprising

   a) isolating DNA from a tumor sample the patient,

   b) incubating the DNA sample with sodium bisulfite sufficient to convert unmethylated cytosine in the DNA to uracil,

   c) amplifying a portion of the CpG island of the NAPRT1 gene of the DNA sample using quantitative methylation specific PCR,

   d) determining the methylation level of the NAPRT1 region by determining the -dCt value of the tumor sample with the -dCt value obtained from quantitative methylation specific PCR of non-methylated DNA, wherein greater than 25% methylation of the NAPRT1 sequence that the patient is more likely to benefit from treatment; and

   e) administering an effective amount of an NAD biosynthesis from nicotinamide antagonist to the patient more likely to benefit from treatment.

66. The method of claim 65, wherein the portion of the CpG island of the NAPRT1 gene comprises the sequence represented between about position 1221 and about position 1288 of SEQ ID NO:1.

67. The method of any one of claims 57-66, wherein the DNA from the tumor sample is isolated from a formalin-fixed paraffin embedded tumor sample.

68. The method of any one of claims 65-67, wherein step c) further comprises a pre-amplification of the portion of the CpG island of the NAPRT1 gene of the DNA sample prior to quantitative methylation specific PCR.

69. The method of any one of claims 57-68, wherein the method further comprises administering niacin.
70. The method of claim 69, wherein the niacin reduces toxicity of the NAD biosynthesis from
nicotinamide antagonist and/or increases the therapeutic index of the NAD biosynthesis from
nicotinamide antagonist.
Figure 1

A. Single compound dose response in CALU-6

B. Single compound dose response in CALU-6

C. Single compound dose response in NCI-460

D. Single compound dose response in NCI-460

- NA + NA

Compound B

NA Rescue

No NA Rescue
Figure 4
Figure 9

NAPRT1 BSF CpG island (600bp added upstream and downstream)
TGTTTTGGGTGTTATTATTTTTGTTTCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGAGTAGGTTTTTTGCTGTTTCTGTGTAAGGGGTGTTGGGTTGCTGTGTAAGGCTAAGGGTGGTTGGGTTGCTGTGTGGAGATAGTAGGGTGTGTTAGGAGAGGA
A. NAPRT1 Genomic CpG island
CGGCCGCACAGTCCGACGCGGCGCGCTGGGGCCAGCCATCCACTTCGATGCCAGCTTCTCTGTCAAGGCTGCCGAGCCACCTTG
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GTTTGGGAGGGCGACAGGGACTCGATGGAGGGTTTGGAGTGGGCTAATAGTATCGGGCAGCCCG (SEQ ID NO: 3)

B. NAPRT1 BSF CpG Island
CGTGCCGTTATAGTTTATAGTACCGGAGTTTCCGCGTTGGGTTTATTATGGATGGTTGCTGAGTTATTATTTGCGGT
AGTTGATTAGTTAGTAAGTTGCGGTTTTTTATAGTTATATTAGAGGCCTTCCGATATTTGATTAGGGGCAG
AGAAGTTTGCCTTGCCCTGGTTATATTGATTGTAGTGGCGATGTTGCTGGGATTTTTTTTTTTTTTTTTTTTTTTTTT
TGTGGTTGTGGTTGTGGTTGTGGTTGTGGTTGTGGTTGTGGTTGTGGTTGTGGTTGTGGTTGTGGTTGTGGTTGTGGTT
GTTTACCGGGAAGATAGATTATATATGTCAATAGTTGAGGGTTTTTTGTCGGCTGCGGCGGGTTTCTCCTGGCAGCTG
TGTTTGGGAGGGCGACAGGGACTCGATGGAGGGTTTGGAGTGGGCTAATAGTATCGGGCAGCCCG (SEQ ID NO: 4)
Figure 10C

CGACGC GCCG GATACTTTAACCCCAACCGGCTTCATCGAATCCCGTACC CGCTCCAAACGACAGTAAACCCCACAAAAA
ATACGCCATAAACGAAACGCGTCACGAAATCGAAACGAAATCCGAACGTCGAAACAAATAACGACGAAACAA
AACCCCGAAAACGCGCGACGACGACGCGACCGCTACTCAGCTACCTACCTACCATACAACCCATAAACGTAAACTTATTAAACGCGCG
AACCCGAACGCGAAACGCCCGCAAATTGAACTTTTCTTC (SEQ ID NO: 5)
Figure 13

RESCEU CpG Site

H1838  H2030  H2122  H226

NO RESCEU CpG Site

H1155  H1650  H1703  LXFL529
Figure 14

A) NAPRT1 Methylation

B) NAPRT1 QPCR
Figure 15

NAPRT1 IHC (0+)

NAPRT1 IHC (3+)

DNA from unstained slide

DNA from IHC slide

Increasing Methylation

2^{\Delta Ct}

10^{-8}

10^{-6}

10^{-4}

10^{-2}

10^0

10^2

10^4

HP-7770

HP-7489
Figure 16

NAPRT1 RNA Level

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/048613

A. CLASSIFICATION OF SUBJECT MATTER

A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>X</td>
<td>D. CERNA ET AL: &quot;Inhibition of Nicotinamide Phosphoribosyltransferase (NAMPT) Activity by Small Molecules GMX1778 Regulates Reactive Oxygen Species (ROS) Mediated Cytotoxicity in a p53- and Nicotinic Acid Phosphoribosyltransferase (NAPRT1)-Dependent Manner&quot;, JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 287, no. 26, 8 May 2012 (2012-05-08), pages 22408-22417, XP055076160, ISSN: 0021-9258, DOI: 10.1074/jbc.M112.357301 abstract page 22416, left-hand column, paragraph 1</td>
<td>1-70</td>
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X Further documents are listed in the continuation of Box C. X See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"Z" document member of the same patent family

Date of the actual completion of the international search: 23 August 2013
Date of mailing of the international search report: 02/09/2013

Name and mailing address of the ISA/Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV RIJSWIJK
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Langer, Oliver

Form PCT/ISA/210 (second sheet) (April 2005)
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<tr>
<td>X</td>
<td>WATSON M ET AL: &quot;The small molecule GMX1778 is a potent inhibitor of NAD&lt;-&gt; biosynthesis: Strategy for enhanced therapy in nicotinic acid phosphoribosyl transferase 1-deficient tumors&quot;, MOLECULAR AND CELLULAR BIOLOGY, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, US, vol. 29, no. 21, 1 November 2009 (2009-11-01), pages 5872-5888, XP002597402, ISSN: 0270-7306, DOI: 10.1128/MCB.00112-09 abstract page 5883, left-hand column, paragraph 2 - right-hand column, paragraph 2 --------</td>
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<td>A</td>
<td>U. H. OLESEN ET AL: &quot;A Preclinical Study on the Rescue of Normal Tissue by Nicotinic Acid in High-Dose Treatment with AP0866, a Specific Nicotinamide Phosphoribosyl transferase Inhibitor&quot;, MOLECULAR CANCER THERAPEUTICS, vol. 9, no. 6, 1 June 2010 (2010-06-01), pages 1609-1617, XP055076200, ISSN: 1535-7163, DOI: 10.1158/1535-7163.MCT-09-1130 the whole document --------</td>
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**INTERNATIONAL SEARCH REPORT**

**INTERNATIONAL application N o**

PCT/US2013/04Q613

**C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

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<tr>
<td>A</td>
<td>RYAN LISTER ET AL: &quot;Human DNA methylomes at base resolution show widespread epigenomic differences&quot;, NATURE, vol. 462, no. 7271, 19 November 2009 (2009-11-19), pages 315-322, XP055076298, ISSN: 0028-0836, DOI: 10.1038/nature08514 the whole document</td>
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<td>MIH0 M. SUZUKI ET AL: &quot;DNA methylomes and landscapes: provocative insights from epigenomic cs&quot;, NATURE REVIEWS GENETICS, vol. 9, no. 6, 1 June 2008 (2008-06-01), pages 465-476, XP055076295, ISSN: 1471-0056, DOI: 10.1038/nrg2341 abstract</td>
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