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(54) Title: NAMPT INHIBITORS

(57) Abstract: Disclosed are compounds which inhibit the activity of NAMPT, compositions containing the compounds and methods of treating diseases during which NAMPT is expressed.

NAMPT INHIBITORS

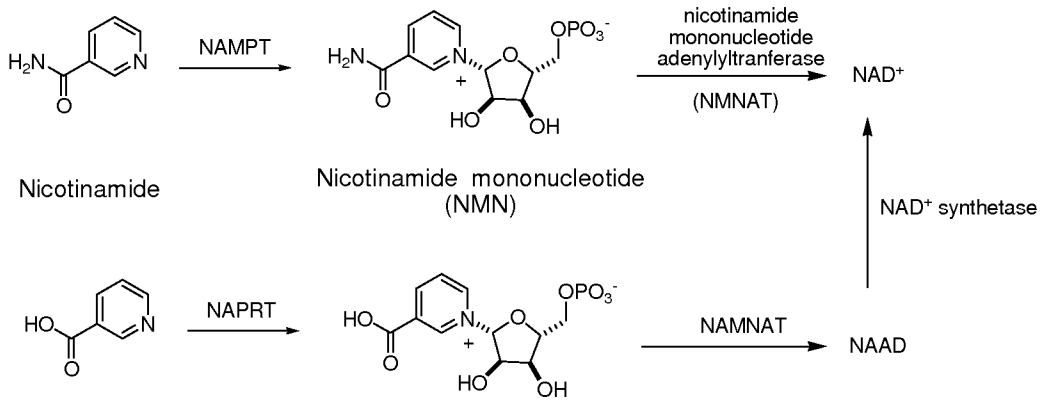
FIELD OF THE INVENTION

This invention pertains to compounds which inhibit the activity of NAMPT, compositions containing the compounds, and methods of treating diseases during which NAMPT is expressed.

BACKGROUND OF THE INVENTION

NAD+ (nicotinamide adenine dinucleotide) is a coenzyme that plays a critical role in many physiologically essential processes (Ziegkel, M. *Eur. J. Biochem.* **267**,1550-1564, 2000). NAD is necessary for several signaling pathways including among others poly ADP-ribosylation in DNA repair, mono-ADP-ribosylation in both the immune system and G-protein-coupled signaling, and NAD is also required by sirtuins for their deacetylase activity (Garten, A. et al *Trends in Endocrinology and Metabolism*, **20**, 130-138, 2008).

NAMPT (also known as pre-B-cell-colony-enhancing factor (PBEF) and visfatin) is an enzyme that catalyzes the phosphoribosylation of nicotinamide and is the rate-limiting enzyme in one of two pathways that salvage NAD.



Increasing evidence suggests that NAMPT inhibitors have potential as anticancer agents. Cancer cells have a higher basal turnover of NAD and also display higher energy requirements compared with normal cells. Additionally, increased NAMPT expression has been reported in colorectal cancer (Van Beijnum, J.R. et al *Int. J. Cancer* **101**, 118-127, 2002) and NAMPT is involved in angiogenesis (Kim, S.R. et al. *Biochem. Biophys. Res. Commun.* **357**, 150-156, 2007). Small-molecule inhibitors of NAMPT have been shown to cause depletion of intracellular NAD+ levels and ultimately induce tumor cell death (Hansen, CM et al. *Anticancer Res.* **20**, 42111-4220, 2000) as well as inhibit tumor growth in xenograft models (Olese, U.H. et al. *Mol Cancer Ther.* **9**, 1609-1617, 2010).

NAMPT inhibitors also have potential as therapeutic agents in inflammatory and metabolic disorders (Galli, M. et al *Cancer Res.* **70**, 8-11, 2010). For example, NAMPT is the predominant enzyme in T and B lymphocytes. Selective inhibition of NAMPT leads to NAD+ depletion in lymphocytes blocking the expansion that accompanies autoimmune disease progression whereas cell types expressing the other NAD+ generating pathways might be spared. A small molecule NAMPT inhibitor (FK866) has been shown to selectively block proliferation and induce apoptosis of activated T cells and was efficacious in animal models of arthritis (collagen –induced arthritis) (Busso, N.et al. *Plos One* **3**, e2267, 2008). FK866 ameliorated the manifestations of experimental autoimmune encephalomyelitis (EAE), a model of T-cell mediated autoimmune disorders. (Bruzzone, Set al. *Plos One* **4**, e7897, 2009). NaMPT activity increases NF-kB transcriptional activity in human vascular endothelial cell, resulting in MMP-2 and MMP-9 activation, suggesting a role for NAMPT inhibitors in the prevention of inflammatory mediated complications of obesity and type 2 diabetes (Adya, R. et. Al. *Diabetes Care*, **31**, 758-760, 2008).

SUMMARY OF THE INVENTION

One embodiment of this invention pertains to compounds and pharmaceutically acceptable salts thereof, which are useful as inhibitors of NAMPT, the compounds chosen from

N-(4-{[2-(azepan-1-yl)ethyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{4-[(2-hydroxypropyl)carbamoyl]phenyl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(4-{[2-(2-oxoimidazolidin-1-yl)ethyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(4-{[2-(tetrahydro-2H-pyran-2-yl)ethyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(4-{[(2-methyltetrahydrofuran-2-yl)methyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(4-{[2-methyl-2-(morpholin-4-yl)propyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{4-[(1-oxa-8-azaspiro[4.5]dec-3-ylmethyl)carbamoyl]phenyl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2-oxa-7-azaspiro[3.5]non-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(hexahydrofuro[3,2-c]pyridin-5(4H)-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(hexahydro-5H-furo[2,3-c]pyrrol-5-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,6-dioxa-9-azaspiro[4.5]dec-9-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2-oxa-6-azaspiro[3.3]hept-6-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2-oxa-6-azaspiro[3.5]non-6-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2-oxa-7-azaspiro[4.4]non-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(10,10-difluoro-2,7-diazaspiro[4.5]dec-2-yl)carbonyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(3-cyano-1-oxa-8-azaspiro[4.5]dec-8-yl)carbonyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(7-oxa-2-azaspiro[3.5]non-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(1-oxa-7-azaspiro[4.4]non-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(10-fluoro-2,7-diazaspiro[4.5]dec-2-yl)carbonyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(3,9-diazaspiro[5.5]undec-3-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,7-diazaspiro[4.5]dec-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,8-diazaspiro[4.5]dec-8-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(7-azaspiro[3.5]non-1-ylcarbamoyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2-azaspiro[3.3]hept-5-ylcarbamoyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(1R,5S)-3-azabicyclo[3.1.0]hex-6-ylcarbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(6-{[(7R)-octahydropyrrolo[1,2-a]pyrazin-7-ylmethyl]carbamoyl}pyridazin-3-yl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,6-diazaspiro[3.5]non-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,7-diazaspiro[3.5]non-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,6-diazaspiro[3.4]oct-6-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(2-oxa-9-azaspiro[5.5]undec-3-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(1-oxa-8-azaspiro[4.5]dec-2-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(1-oxa-8-azaspiro[4.5]dec-3-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,7-diazaspiro[3.5]non-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,8-diazaspiro[4.5]dec-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(6-{[3-(azetidin-3-yl)pyrrolidin-1-yl]carbonyl}pyridazin-3-yl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(1-oxa-8-azaspiro[4.5]dec-3-ylcarbamoyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a][1,4]diazepin-3-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(6-azaspiro[2.5]oct-1-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(5-oxa-2-azaspiro[3.4]oct-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-3-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(6-{[(4-fluoropiperidin-4-yl)methyl]carbamoyl}pyridazin-3-yl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,6-diazaspiro[3.3]hept-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(6-oxa-2-azaspiro[3.4]oct-7-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(5-oxa-2-azaspiro[3.5]non-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(6-{[1-(trifluoromethyl)-2,8-diazaspiro[4.5]dec-2-yl]carbonyl}pyridazin-3-yl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(7-azaspiro[3.5]non-2-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(5,6,7,8-tetrahydro-4H-[1,2,3]triazolo[1,5-a][1,4]diazepin-3-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide; and pharmaceutically acceptables salt thereof.

Another embodiment pertains to a composition for treating inflammatory and tissue repair disorders; particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease), osteoarthritis, osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultra-violet induced skin damage; autoimmune diseases including systemic upus erythematosis, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherscleros is, restenosis, diabetes, glomerulonephritis, cancer, particularly wherein the cancer is selected from breast, prostate, lung, colon, cervix, ovary, skin, CNS, bladder, pancreas, leukemia, lymphoma or Hodgkin's disease, cachexia, inflammation associated with infection and certain viral infections, including Acquired Immune Deficiency Syndrome (AIDS), adult respiratory distress syndrome, and ataxia telengiectasia, said composition comprising an excipient and a therapeutically effective amount of a compound chosen from Example 1-49 herein, or pharmaceutically acceptable salts thereof.

Another embodiment pertains to a method of treating inflammatory and tissue repair disorders; particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease), osteoarthritis, osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultra-violet induced skin damage; autoimmune diseases including systemic lupus erythematosis, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherscleros is, restenosis, diabetes, glomerulonephritis, cancer, particularly wherein the cancer is selected from breast, prostate, lung, colon, cervix, ovary, skin, CNS, bladder, pancreas, leukemia, lymphoma or Hodgkin's disease, cachexia, inflammation associated with infection and certain viral infections, including Acquired Immune Deficiency Syndrome (AIDS), adult respiratory distress syndrome, and ataxia telengiectasia in a patient, said method comprising administering to the patient a therapeutically effective amount of a compound chosen from Example 1-49 herein or pharmaceutically acceptable salts thereof.

Another embodiment pertains to a method of treating inflammatory and tissue repair disorders; particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD

(chronic obstructive pulmonary disease), osteoarthritis, osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultra-violet induced skin damage; autoimmune diseases including systemic lupus erythematosis, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherscleros is, restenosis, diabetes, glomerulonephritis, cancer, particularly wherein the cancer is selected from breast, prostate, lung, colon, cervix, ovary, skin, CNS, bladder, pancreas, leukemia, lymphoma or Hodgkin's disease, cachexia, inflammation associated with infection and certain viral infections, including Acquired Immune Deficiency Syndrome (AIDS), adult respiratory distress syndrome, and ataxia telengiectasia or spleen cancer in a patient, said method comprising administering to the patient therapeutically effective amount of a compound chosen from Example 1-49 herein or pharmaceutically acceptable salts thereof; and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

DETAILED DESCRIPTION OF THE INVENTION

This detailed description is intended only to acquaint others skilled in the art with Applicants' invention, its principles, and its practical application so that others skilled in the art may adapt and apply the invention in its numerous forms, as they may be best suited to the requirements of a particular use. This description and its specific examples are intended for purposes of illustration only. This invention, therefore, is not limited to the embodiments described in this patent application, and may be variously modified.

Abbreviations and Definitions

Unless otherwise defined herein, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. The meaning and scope of the terms should be clear, however, in the event of any latent ambiguity, definitions provided herein take precedent over any dictionary or extrinsic definition. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, the use of the term "including", as well as other forms, such as "includes" and "included", is not limiting. With reference to the use of the words "comprise" or "comprises" or "comprising" in this patent application (including the claims), Applicants note that unless the context requires otherwise, those words are used on the basis and clear understanding that they are to be interpreted inclusively, rather than exclusively, and that Applicants intend each of those words to be so interpreted in construing this patent application, including the claims below. For a variable that occurs more than one time in any substituent or in the compound of the invention or any other formulae herein, its definition on each occurrence is independent of its definition at every other occurrence. Combinations of substituents are permissible only if such combinations result in stable compounds. Stable

compounds are compounds which can be isolated in a useful degree of purity from a reaction mixture.

It is meant to be understood that proper valences are maintained for all combinations herein, that monovalent moieties having more than one atom are attached through their left ends, and that divalent moieties are drawn from left to right.

As used in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated:

The term "alkyl" (alone or in combination with another term(s)) means a straight-or branched-chain saturated hydrocarbyl substituent typically containing from 1 to about 10 carbon atoms; or in another embodiment, from 1 to about 8 carbon atoms; in another embodiment, from 1 to about 6 carbon atoms; and in another embodiment, from 1 to about 4 carbon atoms. Examples of such substituents include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, and hexyl and the like.

The term "alkenyl" (alone or in combination with another term(s)) means a straight-or branched-chain hydrocarbyl substituent containing one or more double bonds and typically from 2 to about 10 carbon atoms; or in another embodiment, from 2 to about 8 carbon atoms; in another embodiment, from 2 to about 6 carbon atoms; and in another embodiment, from 2 to about 4 carbon atoms. Examples of such substituents include ethenyl (vinyl), 2-propenyl, 3-propenyl, 1,4-pentadienyl, 1,4-butadienyl, 1-butenyl, 2-butenyl, and 3-butenyl and the like.

The term "alkynyl" (alone or in combination with another term(s)) means a straight-or branched-chain hydrocarbyl substituent containing one or more triple bonds and typically from 2 to about 10 carbon atoms; or in another embodiment, from 2 to about 8 carbon atoms; in another embodiment, from 2 to about 6 carbon atoms; and in another embodiment, from 2 to about 4 carbon atoms. Examples of such substituents include ethynyl, 2-propynyl, 3-propynyl, 2-butynyl, and 3-butynyl and the like.

The term "carbocyclyl" (alone or in combination with another term(s)) means a saturated cyclic (*i.e.*, "cycloalkyl"), partially saturated cyclic (*i.e.*, "cycloalkenyl"), or completely unsaturated (*i.e.*, "aryl") hydrocarbyl substituent containing from 3 to 14 carbon ring atoms ("ring atoms" are the atoms bound together to form the ring or rings of a cyclic substituent). A carbocyclyl may be a single-ring (monocyclic) or polycyclic ring structure.

A carbocyclyl may be a single ring structure, which typically contains from 3 to 8 ring atoms, more typically from 3 to 6 ring atoms, and even more typically 5 to 6 ring atoms. Examples of such single-ring carbocyclyls include cyclopropyl (cyclopropanyl), cyclobutyl (cyclobutanyl), cyclopentyl (cyclopentanyl), cyclopentenyl, cyclopentadienyl, cyclohexyl (cyclohexanyl), cyclohexenyl, cyclohexadienyl, and phenyl. A carbocyclyl may alternatively be polycyclic (i.e., may contain more than one ring). Examples of polycyclic carbocyclyls include bridged, fused, and spirocyclic carbocyclyls. In a spirocyclic carbocyclyl, one atom is

common to two different rings. An example of a spirocyclic carbocyclyl is spiropentanyl. In a bridged carbocyclyl, the rings share at least two common non-adjacent atoms. Examples of bridged carbocyclyls include bicyclo[2.2.1]heptanyl, bicyclo[2.2.1]hept-2-enyl, and adamantanyl. In a fused-ring carbocyclyl system, two or more rings may be fused together, such that two rings share one common bond. Examples of two- or three-fused ring carbocyclyls include naphthalenyl, tetrahydronaphthalenyl (tetralinyl), indenyl, indanyl (dihydroindenyl), anthracenyl, phenanthrenyl, and decalinyl.

The term "cycloalkyl" (alone or in combination with another term(s)) means a saturated cyclic hydrocarbyl substituent containing from 3 to 14 carbon ring atoms. A cycloalkyl may be a single carbon ring, which typically contains from 3 to 8 carbon ring atoms and more typically from 3 to 6 ring atoms. Examples of single-ring cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. A cycloalkyl may alternatively be polycyclic or contain more than one ring. Examples of polycyclic cycloalkyls include bridged, fused, and spirocyclic carbocyclyls.

The term "aryl" (alone or in combination with another term(s)) means an aromatic carbocyclyl containing from 6 to 14 carbon ring atoms. An aryl may be monocyclic or polycyclic (i.e., may contain more than one ring). In the case of polycyclic aromatic rings, only one ring the polycyclic system is required to be unsaturated while the remaining ring(s) may be saturated, partially saturated or unsaturated. Examples of aryls include phenyl, naphthalenyl, indenyl, indanyl, and tetrahydronapthyl.

In some instances, the number of carbon atoms in a hydrocarbyl substituent (e.g., alkyl, alkenyl, alkynyl, or cycloalkyl) is indicated by the prefix "C_x-C_y-", wherein x is the minimum and y is the maximum number of carbon atoms in the substituent. Thus, for example, "C_1-C_6-alkyl" refers to an alkyl substituent containing from 1 to 6 carbon atoms. Illustrating further, C_3-C_8-cycloalkyl means a saturated hydrocarbyl ring containing from 3 to 8 carbon ring atoms.

The term "hydrogen" (alone or in combination with another term(s)) means a hydrogen radical, and may be depicted as -H.

The term "hydroxy" (alone or in combination with another term(s)) means -OH.

The term "carboxy" (alone or in combination with another term(s)) means -C(O)-OH.

The term "amino" (alone or in combination with another term(s)) means $-NH_2$.

The term "halogen" or "halo" (alone or in combination with another term(s)) means a fluorine radical (which may be depicted as -F), chlorine radical (which may be depicted as -Cl), bromine radical (which may be depicted as -Br), or iodine radical (which may be depicted as -I).

If a substituent is described as being "substituted", a non-hydrogen radical is in the place of hydrogen radical on a carbon or nitrogen of the substituent. Thus, for example, a

substituted alkyl substituent is an alkyl substituent in which at least one non-hydrogen radical is in the place of a hydrogen radical on the alkyl substituent. To illustrate, monofluoroalkyl is alkyl substituted with a fluoro radical, and difluoroalkyl is alkyl substituted with two fluoro radicals. It should be recognized that if there are more than one substitution on a substituent, each non-hydrogen radical may be identical or different (unless otherwise stated).

If a substituent is described as being "optionally substituted", the substituent may be either (1) not substituted or (2) substituted. If a substituent is described as being optionally substituted with up to a particular number of non-hydrogen radicals, that substituent may be either (1) not substituted; or (2) substituted by up to that particular number of non-hydrogen radicals or by up to the maximum number of substitutable positions on the substituent, whichever is less. Thus, for example, if a substituent is described as a heteroaryl optionally substituted with up to 3 non-hydrogen radicals, then any heteroaryl with less than 3 substitutable positions would be optionally substituted by up to only as many non-hydrogen radicals as the heteroaryl has substitutable positions. To illustrate, tetrazolyl (which has only one substitutable position) would be optionally substituted with up to one non-hydrogen radical. To illustrate further, if an amino nitrogen is described as being optionally substituted with up to 2 non-hydrogen radicals, then a primary amino nitrogen will be optionally substituted with up to 2 non-hydrogen radicals, whereas a secondary amino nitrogen will be optionally substituted with up to only 1 non-hydrogen radical.

This patent application uses the terms "substituent" and "radical" interchangeably.

The prefix "halo" indicates that the substituent to which the prefix is attached is substituted with one or more independently selected halogen radicals. For example, haloalkyl means an alkyl substituent in which at least one hydrogen radical is replaced with a halogen radical. Examples of haloalkyls include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, and 1,1,1-trifluoroethyl. It should be recognized that if a substituent is substituted by more than one halogen radical, those halogen radicals may be identical or different (unless otherwise stated).

The prefix "perhalo" indicates that every hydrogen radical on the substituent to which the prefix is attached is replaced with independently selected halogen radicals, *i.e.*, each hydrogen radical on the substituent is replaced with a halogen radical. If all the halogen radicals are identical, the prefix typically will identify the halogen radical. Thus, for example, the term "perfluoro" means that every hydrogen radical on the substituent to which the prefix is attached is substituted with a fluorine radical. To illustrate, the term "perfluoroalkyl" means an alkyl substituent wherein a fluorine radical is in the place of each hydrogen radical.

The term "carbonyl" (alone or in combination with another term(s)) means -C(O)-.

The term "aminocarbonyl" (alone or in combination with another term(s)) means -C(O)-NH_2.

The term "oxo" (alone or in combination with another term(s)) means (=O).

The term "oxy" (alone or in combination with another term(s)) means an ether substituent, and may be depicted as -O-.

The term "alkylhydroxy" (alone or in combination with another term(s)) means –alkyl-OH.

The term "alkylamino" (alone or in combination with another term(s)) means –alkyl-NH_2.

The term "alkyloxy" (alone or in combination with another term(s)) means an alkylether substituent, i.e., -O-alkyl. Examples of such a substituent include methoxy (-O-CH_3), ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, and tert-butoxy.

The term "alkylcarbonyl" (alone or in combination with another term(s)) means -C(O)-alkyl.

The term "aminoalkylcarbonyl" (alone or in combination with another term(s)) means -C(O)-alkyl-NH_2.

The term "alkyloxycarbonyl" (alone or in combination with another term(s)) means -C(O)-O-alkyl.

The term "carbocyclylcarbonyl" (alone or in combination with another term(s)) means -C(O)-carbocyclyl.

Similarly, the term "heterocyclylcarbonyl" (alone or in combination with another term(s)) means -C(O)-heterocyclyl.

The term "carbocyclylalkylcarbonyl" (alone or in combination with another term(s)) means -C(O)-alkyl-carbocyclyl.

Similarly, the term "heterocyclylalkylcarbonyl" (alone or in combination with another term(s)) means -C(O)-alkyl-heterocyclyl.

The term "carbocyclyloxycarbonyl" (alone or in combination with another term(s)) means -C(O)-O-carbocyclyl.

The term "carbocyclylalkyloxycarbonyl" (alone or in combination with another term(s)) means -C(O)-O-alkyl-carbocyclyl.

The term "thio" or "thia" (alone or in combination with another term(s)) means a thiaether substituent, *i.e.*, an ether substituent wherein a divalent sulfur atom is in the place of the ether oxygen atom. Such a substituent may be depicted as -S-. This, for example, "alkyl-thio-alkyl" means alkyl-S-alkyl (alkyl-sulfanyl-alkyl).

The term "thiol" or "sulfhydryl" (alone or in combination with another term(s)) means a sulfhydryl substituent, and may be depicted as -SH.

The term "(thiocarbonyl)" (alone or in combination with another term(s)) means a carbonyl wherein the oxygen atom has been replaced with a sulfur. Such a substituent may be depicted as -C(S)-.

The term "sulfonyl" (alone or in combination with another term(s)) means $-S(O)_2-$.

The term "aminosulfonyl" (alone or in combination with another term(s)) means $-S(O)_2-NH_2$.

The term "sulfinyl" or "sulfoxido" (alone or in combination with another term(s)) means -S(O)-.

The term "heterocyclyl" (alone or in combination with another term(s)) means a saturated (*i.e.*, "heterocycloalkyl"), partially saturated (*i.e.*, "heterocycloalkenyl"), or completely unsaturated (*i.e.*, "heteroaryl") ring structure containing a total of 3 to 14 ring atoms. At least one of the ring atoms is a heteroatom (*i.e.*, oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heterocyclyl may be a single-ring (monocyclic) or polycyclic ring structure.

A heterocyclyl may be a single ring, which typically contains from 3 to 7 ring atoms, more typically from 3 to 6 ring atoms, and even more typically 5 to 6 ring atoms. Examples of single-ring heterocyclyls include 1,2,3,6-tetrahydropyridine, thiomorpholinyl, tetrahydropyranyl, furanyl, dihydrofuranyl, tetrahydrofuranyl, thiophenyl (thiofuranyl), dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, oxazolyl, oxazolidinyl, isoxazolidinyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxadiazolyl (including 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl (furazanyl), or 1,3,4-oxadiazolyl), oxatriazolyl (including 1,2,3,4-oxatriazolyl or 1,2,3,5-oxatriazolyl), dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, or 1,3,4-dioxazolyl), oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl, dihydropyranyl, thiopyranyl, tetrahydrothiopyranyl, pyridinyl (azinyl), piperidinyl, diazinyl (including pyridazinyl (1,2-diazinyl), pyrimidinyl (1,3-diazinyl), or pyrazinyl (1,4-diazinyl)), piperazinyl, pyrrolidin-2-only, triazinyl (including 1,3,5-triazinyl, 1,2,4-triazinyl, and 1,2,3-triazinyl)), oxazinyl (including 1,2-oxazinyl, 1,3-oxazinyl, or 1,4-oxazinyl)), oxathiazinyl (including 1,2,3-oxathiazinyl, 1,2,4-oxathiazinyl, 1,2,5-oxathiazinyl, or 1,2,6-oxathiazinyl)), oxadiazinyl (including 1,2,3-oxadiazinyl, 1,2,4-oxadiazinyl, 1,4,2-oxadiazinyl, or 1,3,5-oxadiazinyl)), morpholinyl, azepinyl, oxepinyl, thiepinyl, and diazepinyl.

A heterocyclyl may alternatively be polycyclic (i.e., may contain more than one ring). Examples of polycyclic heterocyclyls include bridged, fused, and spirocyclic heterocyclyls. In a spirocyclic heterocyclyl, one atom is common to two different rings. In a bridged heterocyclyl, the rings share at least two common non-adjacent atoms. In a fused-ring heterocyclyl, two or more rings may be fused together, such that two rings share one common bond. Examples include hexahydro-furo[3,4-c]pyrrole, hexahydro-furo[3,4-b]pyrrole,

octahydro-pyrrolo[3,4-b]pyridine, octahydro-pyrrolo[3,4-c]pyridine, (3aR,6aR)-5-methyl-octahydro-pyrrolo[3,4-b]pyrrole, (3aR,6aR)-octahydro-pyrrolo[3,4-b]pyrrole, 6-methyl-2,6-diaza-bicyclo[3.2.0]heptane, (3aS,6aR)-2-methyl-octahydro-pyrrolo[3,4-c]pyrrole, decahydro-[1,5]naphthyridine, 2,3-dihydrobenzofuranyl, 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indolyl, thieno[3,2-c]pyridinyl, furo[3,2-c]pyridinyl, phthalazin-1(2H)-onyl, isoquinolinyl, isoquinolin-1(2H)-onyl, 5,6,7,8-tetrahydrophthalazin-1(2H)-onyl, fluorophthalazin-1(2H)-onyl, (Z)-3H-benzo[d][1,2]diazepin-4(5H)-onyl, (trifluoromethyl)phthalazin-1(2H)-onyl, pyrrolo[1,2-d][1,2,4]triazin-1(2H)-onyl, 1,2,3,4-tetrahydroisoquinolinyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, 5,6,7,8-tetrahydrophthalazin-1(2H)-onyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,5-a]pyrazinyl, thieno[3,2-c]pyridinyl, furo[3,2-c]pyridinyl, indolizinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl (including pyrido[3,4-b]-pyridinyl, pyrido[3,2-b]-pyridinyl, or pyrido[4,3-b]-pyridinyl), and pteridinyl. Other examples of fused-ring heterocyclyls include benzo-fused heterocyclyls, such as benzimidazolyl, benzo[d][1,3]dioxolyl, indolyl, isoindolyl (isobenzazolyl, pseudoisoindolyl), indoleninyl (pseudoindolyl), isoindazolyl (benzpyrazolyl), benzazinyl (including quinolinyl (1-benzazinyl) or isoquinolinyl (2-benzazinyl)), phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl (including cinnolinyl (1,2-benzodiazinyl) or quinazolinyl (1,3-benzodiazinyl)), benzopyranyl (including chromanyl or isochromanyl), benzoxazinyl (including 1,3,2-benzoxazinyl, 1,4,2-benzoxazinyl, 2,3,1-benzoxazinyl, or 3,1,4-benzoxazinyl), and benzisoxazinyl (including 1,2-benzisoxazinyl or 1,4-benzisoxazinyl). Examples of spirocyclic heterocyclyls include 1,4-dioxa-8-azaspiro[4.5]decanyl.

The term "heterocycloalkyl" (alone or in combination with another term(s)) means a saturated heterocyclyl.

The term "heteroaryl" (alone or in combination with another term(s)) means an aromatic heterocyclyl containing from 5 to 14 ring atoms. A heteroaryl may be a single ring or 2 or 3 fused rings. Examples of heteroaryl substituents include 6-membered ring substituents such as pyridyl, pyrazyl, pyrimidinyl, pyridazinyl, and 1,3,5-, 1,2,4- or 1,2,3-triazinyl; 5-membered ring substituents such as imidazyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl; 6/5-membered fused ring substituents such as benzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl, and anthranilyl; and 6/6-membered fused rings such as benzopyranyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and benzoxazinyl.

A prefix attached to a multi-component substituent only applies to the first component. To illustrate, the term "alkylcycloalkyl" contains two components: alkyl and cycloalkyl. Thus, the C_1-C_6- prefix on C_1-C_6-alkylcycloalkyl means that the alkyl component of the alkylcycloalkyl contains from 1 to 6 carbon atoms; the C_1-C_6-prefix does not describe

the cycloalkyl component. To illustrate further, the prefix "halo" on haloalkyloxyalkyl indicates that only the alkyloxy component of the alkyloxyalkyl substituent is substituted with one or more halogen radicals. If halogen substitution may alternatively or additionally occur on the alkyl component, the substituent would instead be described as "halogen-substituted alkyloxyalkyl" rather than "haloalkyloxyalkyl." And finally, if the halogen substitution may only occur on the alkyl component, the substituent would instead be described as "alkyloxyhaloalkyl."

The terms "treat", "treating" and "treatment" refer to a method of alleviating or abrogating a disease and/or its attendant symptoms.

The terms "prevent", "preventing" and "prevention" refer to a method of preventing the onset of a disease and/or its attendant symptoms or barring a subject from acquiring a disease. As used herein, "prevent", "preventing" and "prevention" also include delaying the onset of a disease and/or its attendant symptoms and reducing a subject's risk of acquiring a disease.

The term "therapeutically effective amount" refers to that amount of the compound being administered sufficient to prevent development of or alleviate to some extent one or more of the symptoms of the condition or disorder being treated.

The term "modulate" refers to the ability of a compound to increase or decrease the function, or activity, of a kinase. "Modulation", as used herein in its various forms, is intended to encompass antagonism, agonism, partial antagonism and/or partial agonism of the activity associated with kinase. Kinase inhibitors are compounds that, e.g., bind to, partially or totally block stimulation, decrease, prevent, delay activation, inactivate, desensitize, or down regulate signal transduction. Kinase activators are compounds that, e.g., bind to, stimulate, increase, open, activate, facilitate, enhance activation, sensitize or up regulate signal transduction.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The "subject" is defined herein to include animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In preferred embodiments, the subject is a human.

Isotope Enriched or Labeled Compounds

Compounds of the invention can exist in isotope-labeled or -enriched form containing one or more atoms having an atomic mass or mass number different from the atomic mass or

mass number most abundantly found in nature. Isotopes can be radioactive or non-radioactive isotopes. Isotopes of atoms such as hydrogen, carbon, phosphorous, sulfur, fluorine, chlorine, and iodine include, but are not limited to, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, and ^{125}I. Compounds that contain other isotopes of these and/or other atoms are within the scope of this invention.

In another embodiment, the isotope-labeled compounds contain deuterium (^{2}H), tritium (^{3}H) or ^{14}C isotopes. Isotope-labeled compounds of this invention can be prepared by the general methods well known to persons having ordinary skill in the art. Such isotope-labeled compounds can be conveniently prepared by carrying out the procedures disclosed in the Examples disclosed herein and Schemes by substituting a readily available isotope-labeled reagent for a non-labeled reagent. In some instances, compounds may be treated with isotope-labeled reagents to exchange a normal atom with its isotope, for example, hydrogen for deuterium can be exchanged by the action of a deuteric acid such as D_2SO_4/D_2O. In addition to the above, relevant procedures and intermediates are disclosed, for instance, in Lizondo, J et al., *Drugs Fut*, 21(11), 1116 (1996); Brickner, S J *et al., J Med Chem*, 39(3), 673 (1996); Mallesham, B et al., *Org Lett*, 5(7), 963 (2003); PCT publications WO1997010223, WO2005099353, WO1995007271, WO2006008754; US Patent Nos. 7538189; 7534814; 7531685; 7528131; 7521421; 7514068; 7511013; and US Patent Application Publication Nos. 20090137457; 20090131485; 20090131363; 20090118238; 20090111840; 20090105338; 20090105307; 20090105147; 20090093422; 20090088416; and 20090082471, the methods are hereby incorporated by reference.

The isotope-labeled compounds of the invention may be used as standards to determine the effectiveness of Bcl-2 inhibitors in binding assays. Isotope containing compounds have been used in pharmaceutical research to investigate the in vivo metabolic fate of the compounds by evaluation of the mechanism of action and metabolic pathway of the nonisotope-labeled parent compound (Blake et al. *J. Pharm. Sci.* 64, 3, 367-391 (1975)). Such metabolic studies are important in the design of safe, effective therapeutic drugs, either because the *in vivo* active compound administered to the patient or because the metabolites produced from the parent compound prove to be toxic or carcinogenic (Foster et al., Advances in Drug Research Vol. 14, pp. 2-36, Academic press, London, 1985; Kato et al., J. *Labelled Comp. Radiopharmaceut.*, 36(10):927-932 (1995); Kushner et al., *Can. J. Physiol. Pharmacol.*, 77, 79-88 (1999).

In addition, non-radio active isotope containing drugs, such as deuterated drugs called "heavy drugs," can be used for the treatment of diseases and conditions related to Bcl-2 activity. Increasing the amount of an isotope present in a compound above its natural abundance is called enrichment. Examples of the amount of enrichment include from about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 21, 25, 29, 33, 37, 42, 46, 50, 54, 58, 63, 67, 71, 75, 79,

84, 88, 92, 96, to about 100 mol %. Replacement of up to about 15% of normal atom with a heavy isotope has been effected and maintained for a period of days to weeks in mammals, including rodents and dogs, with minimal observed adverse effects (Czajka D M and Finkel A J, Ann. N.Y. Acad. Sci. 1960 84: 770; Thomson J F, Ann. New York Acad. Sci 1960 84: 736; Czakja D M et al., Am. J. Physiol. 1961 201: 357). Acute replacement of as high as 15%-23% in human fluids with deuterium was found not to cause toxicity (Blagojevic N et al. in "Dosimetry & Treatment Planning for Neutron Capture Therapy", Zamenhof R, Solares G and Harling O Eds. 1994. Advanced Medical Publishing, Madison Wis. pp.125-134; Diabetes Metab. 23: 251 (1997)).

Stable isotope labeling of a drug can alter its physico-chemical properties such as pKa and lipid solubility. These effects and alterations can affect the pharmacodynamic response of the drug molecule if the isotopic substitution affects a region involved in a ligand-receptor interaction. While some of the physical properties of a stable isotope-labeled molecule are different from those of the unlabeled one, the chemical and biological properties are the same, with one important exception: because of the increased mass of the heavy isotope, any bond involving the heavy isotope and another atom will be stronger than the same bond between the light isotope and that atom. Accordingly, the incorporation of an isotope at a site of metabolism or enzymatic transformation will slow said reactions potentially altering the pharmacokinetic profile or efficacy relative to the non-isotopic compound.

Compounds

Still another embodiment pertains to compounds which are

N-(4-{[2-(azepan-1-yl)ethyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{4-[(2-hydroxypropyl)carbamoyl]phenyl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(4-{[2-(2-oxoimidazolidin-1-yl)ethyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(4-{[2-(tetrahydro-2H-pyran-2-yl)ethyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(4-{[(2-methyltetrahydrofuran-2-yl)methyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(4-{[2-methyl-2-(morpholin-4-yl)propyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{4-[(1-oxa-8-azaspiro[4.5]dec-3-ylmethyl)carbamoyl]phenyl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2-oxa-7-azaspiro[3.5]non-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(hexahydrofuro[3,2-c]pyridin-5(4H)-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(hexahydro-5H-furo[2,3-c]pyrrol-5-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,6-dioxa-9-azaspiro[4.5]dec-9-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2-oxa-6-azaspiro[3.3]hept-6-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2-oxa-6-azaspiro[3.5]non-6-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2-oxa-7-azaspiro[4.4]non-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(10,10-difluoro-2,7-diazaspiro[4.5]dec-2-yl)carbonyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(3-cyano-1-oxa-8-azaspiro[4.5]dec-8-yl)carbonyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(7-oxa-2-azaspiro[3.5]non-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(1-oxa-7-azaspiro[4.4]non-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(10-fluoro-2,7-diazaspiro[4.5]dec-2-yl)carbonyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(3,9-diazaspiro[5.5]undec-3-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,7-diazaspiro[4.5]dec-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,8-diazaspiro[4.5]dec-8-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(7-azaspiro[3.5]non-1-ylcarbamoyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2-azaspiro[3.3]hept-5-ylcarbamoyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(1R,5S)-3-azabicyclo[3.1.0]hex-6-ylcarbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(6-{[(7R)-octahydropyrrolo[1,2-a]pyrazin-7-ylmethyl]carbamoyl}pyridazin-3-yl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,6-diazaspiro[3.5]non-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,7-diazaspiro[3.5]non-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,6-diazaspiro[3.4]oct-6-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(2-oxa-9-azaspiro[5.5]undec-3-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(1-oxa-8-azaspiro[4.5]dec-2-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(1-oxa-8-azaspiro[4.5]dec-3-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,7-diazaspiro[3.5]non-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,8-diazaspiro[4.5]dec-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(6-{[3-(azetidin-3-yl)pyrrolidin-1-yl]carbonyl}pyridazin-3-yl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(1-oxa-8-azaspiro[4.5]dec-3-ylcarbamoyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a][1,4]diazepin-3-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(6-azaspiro[2.5]oct-1-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(5-oxa-2-azaspiro[3.4]oct-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-3-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(6-{[(4-fluoropiperidin-4-yl)methyl]carbamoyl}pyridazin-3-yl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,6-diazaspiro[3.3]hept-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(6-oxa-2-azaspiro[3.4]oct-7-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(5-oxa-2-azaspiro[3.5]non-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(6-{[1-(trifluoromethyl)-2,8-diazaspiro[4.5]dec-2-yl]carbonyl}pyridazin-3-yl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(7-azaspiro[3.5]non-2-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(5,6,7,8-tetrahydro-4H-[1,2,3]triazolo[1,5-a][1,4]diazepin-3-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide; and pharmaceutically acceptable salts thereof.

Pharmaceutical Compositions, Combination Therapies, Methods of Treatment, and Administration

Another embodiment comprises pharmaceutical compositions comprising a compound chosen from Example 1-49 herein or pharmaceutically acceptable salts thereof, and an excipient.

Still another embodiment comprises methods of treating cancer in a mammal comprising administering thereto a therapeutically acceptable amount of a compound chosen from Example 1-49 herein or pharmaceutically acceptable salts thereof.

Still another embodiment pertains to compositions for treating diseases during which NAMPT is expressed, said compositions comprising an excipient and a therapeutically effective amount of the compound chosen from Example 1-49 herein and pharmaceutically acceptable salts thereof.

Still another embodiment pertains to methods of treating disease in a patient during which NAMPT is expressed, said methods comprising administering to the patient a therapeutically effective amount of a compound chosen from Example 1-49 herein or pharmaceutically acceptable salts thereof.

Still another embodiment pertains to compositions for treating inflammatory and tissue repair disorders; particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease), osteoarthritis, osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultra-violet induced skin damage; autoimmune diseases including systemic lupus erythematosis, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherosclerosis, restenosis, diabetes, glomerulonephritis, cancer, particularly wherein the cancer is selected from breast, prostate, lung, colon, cervix, ovary, skin, CNS, bladder, pancreas, leukemia, lymphoma or Hodgkin's disease, cachexia, inflammation associated with infection and certain viral infections, including Acquired Immune Deficiency Syndrome

(AIDS), adult respiratory distress syndrome, and ataxia telengiectasia, said compositions comprising an excipient and a therapeutically effective amount of the compound chosen from Example 1-49 herein or pharmaceutically acceptable salts thereof.

Still another embodiment pertains to methods of treating inflammatory and tissue repair disorders; particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease), osteoarthritis, osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultra-violet induced skin damage; autoimmune diseases including systemic lupus erythematosis, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherosclerosis, restenosis, diabetes, glomerulonephritis, cancer, particularly wherein the cancer is selected from breast, prostate, lung, colon, cervix, ovary, skin, CNS, bladder, pancreas, leukemia, lymphoma or Hodgkin's disease, cachexia, inflammation associated with infection and certain viral infections, including Acquired Immune Deficiency Syndrome (AIDS), adult respiratory distress syndrome, and ataxia telengiectasia in a patient, said methods comprising administering to the patient a therapeutically effective amount of a compound chosen from Example 1-49 herein or pharmaceutically acceptable salts thereof.

Still another embodiment pertains to compositions for treating diseases during which NAMPT is expressed, said compositions comprising an excipient and a therapeutically effective amount of the compound chosen from Example 1-49 herein or pharmaceutically acceptable salts thereof, and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Still another embodiment pertains to methods of treating disease in a patient during which NAMPT is expressed, said methods comprising administering to the patient a therapeutically effective amount of a compound chosen from Example 1-49 herein orpharmaceutically acceptable salts thereof, and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Still another embodiment pertains to compositions for treating inflammatory and tissue repair disorders; particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease), osteoarthritis, osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultra-violet induced skin damage; autoimmune diseases including systemic lupus erythematosis, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherosclerosis, restenosis, diabetes, glomerulonephritis, cancer, particularly wherein the cancer is selected from breast, prostate, lung, colon, cervix, ovary, skin, CNS, bladder, pancreas, leukemia, lymphoma or Hodgkin's disease, cachexia, inflammation associated with infection and certain viral infections, including Acquired Immune Deficiency Syndrome (AIDS), adult respiratory distress syndrome, and ataxia telengiectasia, said compositions

comprising an excipient and a therapeutically effective amount of the compound chosen from Example 1-49 herein and pharmaceutically acceptable salts thereof, or a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Still another embodiment pertains to methods of treating inflammatory and tissue repair disorders; particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease), osteoarthritis, osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultra-violet induced skin damage; autoimmune diseases including systemic lupus erythematosis, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherscleros is, restenosis, diabetes, glomerulonephritis, cancer, particularly wherein the cancer is selected from breast, prostate, lung, colon, cervix, ovary, skin, CNS, bladder, pancreas, leukemia, lymphoma or Hodgkin's disease, cachexia, inflammation associated with infection and certain viral infections, including Acquired Immune Deficiency Syndrome (AIDS), adult respiratory distress syndrome, and ataxia telengiectasia in a patient, said methods comprising administering to the patient a therapeutically effective amount of the compound chosen from Example 1-49 herein or pharmaceutically acceptable salts thereof, and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Metabolites of compounds chosen from Example 1-49 herein or pharmaceutically acceptable salts thereof, produced by in vitro or in vivo metabolic processes, may also have utility for treating diseases associated with NAMPT.

Certain precursor compounds which may be metabolized in vitro or in vivo to form compounds chosen from Example 1-49 herein or pharmaceutically acceptable salts thereof, may also have utility for treating diseases associated with NAMPT.

Compounds chosen from Example 1-49 herein and pharmaceutically acceptable salts thereof, may exist as acid addition salts, basic addition salts or zwitterions. Salts of the compounds are prepared during isolation or following purification of the compounds. Acid addition salts of the compounds are those derived from the reaction of the compounds with an acid. For example, the acetate, adipate, alginate, bicarbonate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsufonate, digluconate, formate, fumarate, glycerophosphate, glutamate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, lactobionate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, phosphate, picrate, propionate, succinate, tartrate, thiocyanate, trichloroacetic, trifluoroacetic, para-toluenesulfonate, and undecanoate salts of the compounds are contemplated as being embraced by this invention. Basic addition salts of the compounds

are those derived from the reaction of the compounds with the hydroxide, carbonate or bicarbonate of cations such as lithium, sodium, potassium, calcium, and magnesium.

The compounds chosen from Example 1-49 herein and pharmaceutically acceptable salts thereof, may be administered, for example, bucally, ophthalmically, orally, osmotically, parenterally (intramuscularly, intraperitoneally intrasternally, intravenously, subcutaneously), rectally, topically, transdermally or vaginally.

Therapeutically effective amounts of compounds chosen from Example 1-49 herein and pharmaceutically acceptable salts thereof, depend on the recipient of the treatment, the disorder being treated and the severity thereof, the composition containing the compound, the time of administration, the route of administration, the duration of treatment, the compound potency, its rate of clearance and whether or not another drug is co-administered. The amount of a compound of this invention having Formula (I) used to make a composition to be administered daily to a patient in a single dose or in divided doses is from about 0.03 to about 200 mg/kg body weight. Single dose compositions contain these amounts or a combination of submultiples thereof.

Compounds chosen from Example 1-49 herein and pharmaceutically acceptable salts thereof, may be administered with or without an excipient. Excipients include, for example, encapsulating materials or additives such as absorption accelerators, antioxidants, binders, buffers, coating agents, coloring agents, diluents, disintegrating agents, emulsifiers, extenders, fillers, flavoring agents, humectants, lubricants, perfumes, preservatives, propellants, releasing agents, sterilizing agents, sweeteners, solubilizers, wetting agents and mixtures thereof.

Excipients for preparation of compositions comprising a compound chosen from Example 1-49 herein and pharmaceutically acceptable salts thereof, to be administered orally in solid dosage form include, for example, agar, alginic acid, aluminum hydroxide, benzyl alcohol, benzyl benzoate, 1,3-butylene glycol, carbomers, castor oil, cellulose, cellulose acetate, cocoa butter, corn starch, corn oil, cottonseed oil, cross-povidone, diglycerides, ethanol, ethyl cellulose, ethyl laureate, ethyl oleate, fatty acid esters, gelatin, germ oil, glucose, glycerol, groundnut oil, hydroxypropylmethyl cellulose, isopropanol, isotonic saline, lactose, magnesium hydroxide, magnesium stearate, malt, mannitol, monoglycerides, olive oil, peanut oil, potassium phosphate salts, potato starch, povidone, propylene glycol, Ringer's solution, safflower oil, sesame oil, sodium carboxymethyl cellulose, sodium phosphate salts, sodium lauryl sulfate, sodium sorbitol, soybean oil, stearic acids, stearyl fumarate, sucrose, surfactants, talc, tragacanth, tetrahydrofurfuryl alcohol, triglycerides, water, and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having Formula (I) to be administered ophthalmically or orally in liquid dosage forms include, for example, 1,3-butylene glycol, castor oil, corn oil, cottonseed oil, ethanol, fatty

acid esters of sorbitan, germ oil, groundnut oil, glycerol, isopropanol, olive oil, polyethylene glycols, propylene glycol, sesame oil, water and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having Formula (I) to be administered osmotically include, for example, chlorofluorohydrocarbons, ethanol, water and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having Formula (I) to be administered parenterally include, for example, 1,3-butanediol, castor oil, corn oil, cottonseed oil, dextrose, germ oil, groundnut oil, liposomes, oleic acid, olive oil, peanut oil, Ringer's solution, safflower oil, sesame oil, soybean oil, U.S.P. or isotonic sodium chloride solution, water and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having Formula (I) to be administered rectally or vaginally include, for example, cocoa butter, polyethylene glycol, wax and mixtures thereof.

Compounds chosen from Example 1-49 herein and pharmaceutically acceptable salts thereof, are expected to be useful when used with alkylating agents, angiogenesis inhibitors, antibodies, antimetabolites, antimitotics, antiproliferatives, antivirals, aurora kinase inhibitors, apoptosis promoters (for example, Bcl-xL, Bcl-w and Bfl-1) inhibitors, activators of death receptor pathway, Bcr-Abl kinase inhibitors, BiTE (Bi-Specific T cell Engager) antibodies, antibody drug conjugates, biologic response modifiers, cyclin-dependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors, DVDs, leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors, hormonal therapies, immunologicals, inhibitors of inhibitors of apoptosis proteins (IAPs), intercalating antibiotics, kinase inhibitors, kinesin inhibitors, Jak2 inhibitors, mammalian target of rapamycin inhibitors, microRNA's, mitogen-activated extracellular signal-regulated kinase inhibitors, multivalent binding proteins, non-steroidal anti-inflammatory drugs (NSAIDs), poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, platinum chemotherapeutics, polo-like kinase (Plk) inhibitors, phosphoinositide-3 kinase (PI3K) inhibitors, proteosome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, retinoids/deltoids plant alkaloids, small inhibitory ribonucleic acids (siRNAs), topoisomerase inhibitors, ubiquitin ligase inhibitors, and the like, and in combination with one or more of these agents .

BiTE antibodies are bi-specific antibodies that direct T-cells to attack cancer cells by simultaneously binding the two cells. The T-cell then attacks the target cancer cell. Examples of BiTE antibodies include adecatumumab (Micromet MT201), blinatumomab (Micromet MT103) and the like. Without being limited by theory, one of the mechanisms by which T-cells elicit apoptosis of the target cancer cell is by exocytosis of cytolytic granule components, which include perforin and granzyme B. In this regard, Bcl-2 has been shown to attenuate the induction of apoptosis by both perforin and granzyme B. These data suggest

that inhibition of Bcl-2 could enhance the cytotoxic effects elicited by T-cells when targeted to cancer cells (V.R. Sutton, D.L. Vaux and J.A. Trapani, *J. of Immunology* **1997**, 158 (12), 5783).

SiRNAs are molecules having endogenous RNA bases or chemically modified nucleotides. The modifications do not abolish cellular activity, but rather impart increased stability and/or increased cellular potency. Examples of chemical modifications include phosphorothioate groups, 2'-deoxynucleotide, 2'-OCH_3-containing ribonucleotides, 2'-F-ribonucleotides, 2'-methoxyethyl ribonucleotides, combinations thereof and the like. The siRNA can have varying lengths (e.g., 10-200 bps) and structures (e.g., hairpins, single/double strands, bulges, nicks/gaps, mismatches) and are processed in cells to provide active gene silencing. A double-stranded siRNA (dsRNA) can have the same number of nucleotides on each strand (blunt ends) or asymmetric ends (overhangs). The overhang of 1-2 nucleotides can be present on the sense and/or the antisense strand, as well as present on the 5'- and/ or the 3'-ends of a given strand.

Multivalent binding proteins are binding proteins comprising two or more antigen binding sites. Multivalent binding proteins are engineered to have the three or more antigen binding sites and are generally not naturally occurring antibodies. The term "multispecific binding protein" means a binding protein capable of binding two or more related or unrelated targets. Dual variable domain (DVD) binding proteins are tetravalent or multivalent binding proteins binding proteins comprising two or more antigen binding sites. Such DVDs may be monospecific (i.e., capable of binding one antigen) or multispecific (i.e., capable of binding two or more antigens). DVD binding proteins comprising two heavy chain DVD polypeptides and two light chain DVD polypeptides are referred to as DVD Ig's. Each half of a DVD Ig comprises a heavy chain DVD polypeptide, a light chain DVD polypeptide, and two antigen binding sites. Each binding site comprises a heavy chain variable domain and a light chain variable domain with a total of 6 CDRs involved in antigen binding per antigen binding site.

Alkylating agents include altretamine, AMD-473, AP-5280, apaziquone, bendamustine, brostallicin, busulfan, carboquone, carmustine (BCNU), chlorambucil, CLORETAZINE® (laromustine, VNP 40101M), cyclophosphamide, decarbazine, estramustine, fotemustine, glufosfamide, ifosfamide, KW-2170, lomustine (CCNU), mafosfamide, melphalan, mitobronitol, mitolactol, nimustine, nitrogen mustard N-oxide, ranimustine, temozolomide, thiotepa, TREANDA® (bendamustine), treosulfan, trofosfamide and the like.

Angiogenesis inhibitors include endothelial-specific receptor tyrosine kinase (Tie-2) inhibitors, epidermal growth factor receptor (EGFR) inhibitors, insulin growth factor-2 receptor (IGFR-2) inhibitors, matrix metalloproteinase-2 (MMP-2) inhibitors, matrix

metalloproteinase-9 (MMP-9) inhibitors, platelet-derived growth factor receptor (PDGFR) inhibitors, thrombospondin analogs, vascular endothelial growth factor receptor tyrosine kinase (VEGFR) inhibitors and the like.

Antimetabolites include ALIMTA® (pemetrexed disodium, LY231514, MTA), 5-azacitidine, XELODA® (capecitabine), carmofur, LEUSTAT® (cladribine), clofarabine, cytarabine, cytarabine ocfosfate, cytosine arabinoside, decitabine, deferoxamine, doxifluridine, eflornithine, EICAR (5-ethynyl-1-β -D-ribofuranosylimidazole-4-carboxamide), enocitabine, ethnylcytidine, fludarabine, 5-fluorouracil alone or in combination with leucovorin, GEMZAR® (gemcitabine), hydroxyurea, ALKERAN®(melphalan), mercaptopurine, 6-mercaptopurine riboside, methotrexate, mycophenolic acid, nelarabine, nolatrexed, ocfosfate, pelitrexol, pentostatin, raltitrexed, Ribavirin, triapine, trimetrexate, S-1, tiazofurin, tegafur, TS-1, vidarabine, UFT and the like.

Antivirals include ritonavir, hydroxychloroquine and the like.

Aurora kinase inhibitors include ABT-348, AZD-1152, MLN-8054, VX-680, Aurora A-specific kinase inhibitors, Aurora B-specific kinase inhibitors and pan-Aurora kinase inhibitors and the like.

Bcl-2 protein inhibitors include AT-101 ((-)gossypol), GENASENSE® (G3139 or oblimersen (Bcl-2-targeting antisense oligonucleotide)), IPI-194, IPI-565, N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide) (ABT-737), N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide (ABT-263), GX-070 (obatoclax) and the like.

Bcr-Abl kinase inhibitors include DASATINIB® (BMS-354825), GLEEVEC® (imatinib) and the like.

CDK inhibitors include AZD-5438, BMI-1040, BMS-032, BMS-387, CVT-2584, flavopyridol, GPC-286199, MCS-5A, PD0332991, PHA-690509, seliciclib (CYC-202, R-roscovitine), ZK-304709 and the like.

COX-2 inhibitors include ABT-963, ARCOXIA® (etoricoxib), BEXTRA® (valdecoxib), BMS347070, CELEBREX® (celecoxib), COX-189 (lumiracoxib), CT-3, DERAMAXX® (deracoxib), JTE-522, 4-methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoylphenyl-1H-pyrrole), MK-663 (etoricoxib), NS-398, parecoxib, RS-57067, SC-58125, SD-8381, SVT-2016, S-2474, T-614, VIOXX® (rofecoxib) and the like.

EGFR inhibitors include ABX-EGF, anti-EGFR immunoliposomes, EGF-vaccine, EMD-7200, ERBITUX® (cetuximab), HR3, IgA antibodies, IRESSA® (gefitinib), TARCEVA® (erlotinib or OSI-774), TP-38, EGFR fusion protein, TYKERB® (lapatinib) and the like.

ErbB2 receptor inhibitors include CP-724-714, CI-1033 (canertinib), HERCEPTIN® (trastuzumab), TYKERB® (lapatinib), OMNITARG® (2C4, petuzumab), TAK-165, GW-572016 (ionafarnib), GW-282974, EKB-569, PI-166, dHER2 (HER2 vaccine), APC-8024 (HER-2 vaccine), anti-HER/2neu bispecific antibody, B7.her2IgG3, AS HER2 trifunctional bispecfic antibodies, mAB AR-209, mAB 2B-1 and the like.

Histone deacetylase inhibitors include depsipeptide, LAQ-824, MS-275, trapoxin, suberoylanilide hydroxamic acid (SAHA), TSA, valproic acid and the like.

HSP-90 inhibitors include 17-AAG-nab, 17-AAG, CNF-101, CNF-1010, CNF-2024, 17-DMAG, geldanamycin, IPI-504, KOS-953, MYCOGRAB® (human recombinant antibody to HSP-90), NCS-683664, PU24FCl, PU-3, radicicol, SNX-2112, STA-9090 VER49009 and the like.

Inhibitors of inhibitors of apoptosis proteins include HGS1029, GDC-0145, GDC-0152, LCL-161, LBW-242 and the like.

Antibody drug conjugates include anti-CD22-MC-MMAF, anti-CD22-MC-MMAE, anti-CD22-MCC-DM1, CR-011-vcMMAE, PSMA-ADC, MEDI-547, SGN-19Am SGN-35, SGN-75 and the like

Activators of death receptor pathway include TRAIL, antibodies or other agents that target TRAIL or death receptors (e.g., DR4 and DR5) such as Apomab, conatumumab, ETR2-ST01, GDC0145 (lexatumumab), HGS-1029, LBY-135, PRO-1762 and trastuzumab.

Kinesin inhibitors include Eg5 inhibitors such as AZD4877, ARRY-520; CENPE inhibitors such as GSK923295A and the like.

JAK-2 inhibitors include CEP-701 (lesaurtinib), XL019 and INCB018424 and the like.

MEK inhibitors include ARRY-142886, ARRY-438162 PD-325901, PD-98059 and the like.

mTOR inhibitors include AP-23573, CCI-779, everolimus, RAD-001, rapamycin, temsirolimus, ATP-competitive TORC1/TORC2 inhibitors, including PI-103, PP242, PP30, Torin 1 and the like.

Non-steroidal anti-inflammatory drugs include AMIGESIC® (salsalate), DOLOBID® (diflunisal), MOTRIN® (ibuprofen), ORUDIS® (ketoprofen), RELAFEN® (nabumetone), FELDENE® (piroxicam), ibuprofen cream, ALEVE® (naproxen) and NAPROSYN® (naproxen), VOLTAREN® (diclofenac), INDOCIN® (indomethacin), CLINORIL® (sulindac), TOLECTIN® (tolmetin), LODINE® (etodolac), TORADOL® (ketorolac), DAYPRO® (oxaprozin) and the like.

PDGFR inhibitors include C-451, CP-673, CP-868596 and the like.

Platinum chemotherapeutics include cisplatin, ELOXATIN® (oxaliplatin) eptaplatin, lobaplatin, nedaplatin, PARAPLATIN® (carboplatin), satraplatin, picoplatin and the like.

Polo-like kinase inhibitors include BI-2536 and the like.

Phosphoinositide-3 kinase (PI3K) inhibitors include wortmannin, LY294002, XL-147, CAL-120, ONC-21, AEZS-127, ETP-45658, PX-866, GDC-0941, BGT226, BEZ235, XL765 and the like.

Thrombospondin analogs include ABT-510, ABT-567, ABT-898, TSP-1 and the like.

VEGFR inhibitors include AVASTIN® (bevacizumab), ABT-869, AEE-788, ANGIOZYME™ (a ribozyme that inhibits angiogenesis (Ribozyme Pharmaceuticals (Boulder, CO.) and Chiron, (Emeryville, CA)) , axitinib (AG-13736), AZD-2171, CP-547,632, IM-862, MACUGEN (pegaptamib), NEXAVAR® (sorafenib, BAY43-9006), pazopanib (GW-786034), vatalanib (PTK-787, ZK-222584), SUTENT® (sunitinib, SU-11248), VEGF trap, ZACTIMA™ (vandetanib, ZD-6474) and the like.

Antibiotics include intercalating antibiotics aclarubicin, actinomycin D, amrubicin, annamycin, adriamycin, BLENOXANE® (bleomycin), daunorubicin, CAELYX® or MYOCET® (liposomal doxorubicin), elsamitrucin, epirbucin, glarbuicin, ZAVEDOS® (idarubicin), mitomycin C, nemorubicin, neocarzinostatin, peplomycin, pirarubicin, rebeccamycin, stimalamer, streptozocin, VALSTAR® (valrubicin), zinostatin and the like.

Topoisomerase inhibitors include aclarubicin, 9-aminocamptothecin, amonafide, amsacrine, becatecarin, belotecan, BN-80915, CAMPTOSAR® (irinotecan hydrochloride), camptothecin, CARDIOXANE® (dexrazoxine), diflomotecan, edotecarin, ELLENCE® or PHARMORUBICIN® (epirubicin), etoposide, exatecan, 10-hydroxycamptothecin, gimatecan, lurtotecan, mitoxantrone, orathecin, pirarbucin, pixantrone, rubitecan, sobuzoxane, SN-38, tafluposide, topotecan and the like.

Antibodies include AVASTIN® (bevacizumab), CD40-specific antibodies, chTNT-1/B, denosumab, ERBITUX® (cetuximab), HUMAX-CD4® (zanolimumab), IGF1R-specific antibodies, lintuzumab, PANOREX® (edrecolomab), RENCAREX® (WX G250), RITUXAN® (rituximab), ticilimumab, trastuzimab, CD20 antibodies types I and II and the like.

Hormonal therapies include ARIMIDEX® (anastrozole), AROMASIN® (exemestane), arzoxifene, CASODEX® (bicalutamide), CETROTIDE® (cetrorelix), degarelix, deslorelin, DESOPAN® (trilostane), dexamethasone, DROGENIL® (flutamide), EVISTA® (raloxifene), AFEMA™ (fadrozole), FARESTON® (toremifene), FASLODEX® (fulvestrant), FEMARA® (letrozole), formestane, glucocorticoids, HECTOROL® (doxercalciferol), RENAGEL® (sevelamer carbonate), lasofoxifene, leuprolide acetate, MEGACE® (megesterol), MIFEPREX® (mifepristone), NILANDRON™ (nilutamide), NOLVADEX® (tamoxifen citrate), PLENAXIS™ (abarelix), prednisone, PROPECIA® (finasteride), rilostane, SUPREFACT® (buserelin), TRELSTAR® (luteinizing hormone releasing hormone (LHRH)),

VANTAS® (Histrelin implant), VETORYL® (trilostane or modrastane), ZOLADEX® (fosrelin, goserelin) and the like.

Deltoids and retinoids include seocalcitol (EB1089, CB1093), lexacalcitrol (KH1060), fenretinide, PANRETIN® (aliretinoin), ATRAGEN® (liposomal tretinoin), TARGRETIN® (bexarotene), LGD-1550 and the like.

PARP inhibitors include ABT-888 (veliparib), olaparib, KU-59436, AZD-2281, AG-014699, BSI-201, BGP-15, INO-1001, ONO-2231 and the like.

Plant alkaloids include, but are not limited to, vincristine, vinblastine, vindesine, vinorelbine and the like.

Proteasome inhibitors include VELCADE® (bortezomib), MG132, NPI-0052, PR-171 and the like.

Examples of immunologicals include interferons and other immune-enhancing agents. Interferons include interferon alpha, interferon alpha-2a, interferon alpha-2b, interferon beta, interferon gamma-1a, ACTIMMUNE® (interferon gamma-1b) or interferon gamma-n1, combinations thereof and the like. Other agents include ALFAFERONE® ,(IFN-α), BAM-002 (oxidized glutathione), BEROMUN® (tasonermin), BEXXAR® (tositumomab), CAMPATH® (alemtuzumab), CTLA4 (cytotoxic lymphocyte antigen 4), decarbazine, denileukin, epratuzumab, GRANOCYTE® (lenograstim), lentinan, leukocyte alpha interferon, imiquimod, MDX-010 (anti-CTLA-4), melanoma vaccine, mitumomab, molgramostim, MYLOTARG™ (gemtuzumab ozogamicin), NEUPOGEN® (filgrastim), OncoVAC-CL, OVAREX® (oregovomab), pemtumomab (Y-muHMFG1), PROVENGE® (sipuleucel-T), sargaramostim, sizofilan, teceleukin, THERACYS® (Bacillus Calmette-Guerin), ubenimex, VIRULIZIN® (immunotherapeutic, Lorus Pharmaceuticals), Z-100 (Specific Substance of Maruyama (SSM)), WF-10 (Tetrachlorodecaoxide (TCDO)), PROLEUKIN® (aldesleukin), ZADAXIN® (thymalfasin), ZENAPAX® (daclizumab), ZEVALIN® (90Y-Ibritumomab tiuxetan) and the like.

Biological response modifiers are agents that modify defense mechanisms of living organisms or biological responses, such as survival, growth or differentiation of tissue cells to direct them to have anti-tumor activity and include krestin, lentinan, sizofiran, picibanil PF-3512676 (CpG-8954), ubenimex and the like.

Pyrimidine analogs include cytarabine (ara C or Arabinoside C), cytosine arabinoside, doxifluridine, FLUDARA® (fludarabine), 5-FU (5-fluorouracil), floxuridine, GEMZAR® (gemcitabine), TOMUDEX® (ratitrexed), TROXATYL™ (triacetyluridine troxacitabine) and the like.

Purine analogs include LANVIS® (thioguanine) and PURI-NETHOL® (mercaptopurine).

Antimitotic agents include batabulin, epothilone D (KOS-862), N-(2-((4-hydroxyphenyl)amino)pyridin-3-yl)-4-methoxybenzenesulfonamide, ixabepilone (BMS 247550), paclitaxel, TAXOTERE® (docetaxel), PNU100940 (109881), patupilone, XRP-9881 (larotaxel), vinflunine, ZK-EPO (synthetic epothilone) and the like.

Ubiquitin ligase inhibitors include MDM2 inhibitors, such as nutlins, NEDD8 inhibitors such as MLN4924 and the like.

Compounds of this invention can also be used as radiosensitizers that enhance the efficacy of radiotherapy. Examples of radiotherapy include external beam radiotherapy, teletherapy, brachytherapy and sealed, unsealed source radiotherapy and the like.

Additionally, compounds having Formula (I) may be combined with other chemotherapeutic agents such as ABRAXANE™ (ABI-007), ABT-100 (farnesyl transferase inhibitor), ADVEXIN® (Ad5CMV-p53 vaccine), ALTOCOR® or MEVACOR® (lovastatin), AMPLIGEN® (poly I:poly C12U, a synthetic RNA), APTOSYN® (exisulind), AREDIA® (pamidronic acid), arglabin, L-asparaginase, atamestane (1-methyl-3,17-dione-androsta-1,4-diene), AVAGE® (tazarotene), AVE-8062 (combreastatin derivative) BEC2 (mitumomab), cachectin or cachexin (tumor necrosis factor), canvaxin (vaccine), CEAVAC® (cancer vaccine), CELEUK® (celmoleukin), CEPLENE® (histamine dihydrochloride), CERVARIX® (human papillomavirus vaccine), CHOP® (C: CYTOXAN® (cyclophosphamide); H: ADRIAMYCIN® (hydroxydoxorubicin); O: Vincristine (ONCOVIN®); P: prednisone), CYPAT™ (cyproterone acetate), combrestatin A4P, DAB(389)EGF (catalytic and translocation domains of diphtheria toxin fused via a His-Ala linker to human epidermal growth factor) or TransMID-107R™ (diphtheria toxins), dacarbazine, dactinomycin, 5,6-dimethylxanthenone-4-acetic acid (DMXAA), eniluracil, EVIZON™ (squalamine lactate), DIMERICINE® (T4N5 liposome lotion), discodermolide, DX-8951f (exatecan mesylate), enzastaurin, EPO906 (epithilone B), GARDASIL® (quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine), GASTRIMMUNE®, GENASENSE®, GMK (ganglioside conjugate vaccine), GVAX® (prostate cancer vaccine), halofuginone, histerelin, hydroxycarbamide, ibandronic acid, IGN-101, IL-13-PE38, IL-13-PE38QQR (cintredekin besudotox), IL-13-pseudomonas exotoxin, interferon-α, interferon-γ, JUNOVAN™ or MEPACT™ (mifamurtide), lonafarnib, 5,10-methylenetetrahydrofolate, miltefosine (hexadecylphosphocholine), NEOVASTAT®(AE-941), NEUTREXIN® (trimetrexate glucuronate), NIPENT® (pentostatin), ONCONASE® (a ribonuclease enzyme), ONCOPHAGE® (melanoma vaccine treatment), ONCOVAX® (IL-2 Vaccine), ORATHECIN™ (rubitecan), OSIDEM® (antibody-based cell drug), OVAREX® MAb (murine monoclonal antibody), paclitaxel, PANDIMEX™ (aglycone saponins from ginseng comprising 20(S)protopanaxadiol (aPPD) and 20(S)protopanaxatriol (aPPT)), panitumumab, PANVAC®-VF (investigational cancer vaccine), pegaspargase, PEG Interferon A,

phenoxodiol, procarbazine, rebimastat, REMOVAB® (catumaxomab), REVLIMID® (lenalidomide), RSR13 (efaproxiral), SOMATULINE® LA (lanreotide), SORIATANE® (acitretin), staurosporine (Streptomyces staurospores), talabostat (PT100), TARGRETIN® (bexarotene), TAXOPREXIN® (DHA-paclitaxel), TELCYTA® (canfosfamide, TLK286), temilifene, TEMODAR® (temozolomide), tesmilifene, thalidomide, THERATOPE® (STn-KLH), thymitaq (2-amino-3,4-dihydro-6-methyl-4-oxo-5-(4-pyridylthio)quinazoline dihydrochloride), TNFERADE™ (adenovector: DNA carrier containing the gene for tumor necrosis factor-α), TRACLEER® or ZAVESCA® (bosentan), tretinoin (Retin-A), tetrandrine, TRISENOX® (arsenic trioxide), VIRULIZIN®, ukrain (derivative of alkaloids from the greater celandine plant), vitaxin (anti-alphavbeta3 antibody), XCYTRIN® (motexafin gadolinium), XINLAY™ (atrasentan), XYOTAX™ (paclitaxel poliglumex), YONDELIS® (trabectedin), ZD-6126, ZINECARD® (dexrazoxane), ZOMETA® (zolendronic acid), zorubicin and the like.

Data

Determination of the utility of compounds chosen from Example 1-49 herein and pharmaceutically acceptable salts thereof, as binders to and inhibitors of NAMPT was performed using a Time-Resolved Fluorescence Resonance Energy Transfer (TR-FRET) binding assay.

Time-Resolved Fluorescence Resonance Energy Transfer (TR-FRET) Binding Assay of NAMPT

The assay was carried out in 18 uL low volume plates (Owens Corning) in reaction buffer (50 mM HEPES (NaOH), pH 7.5, 100 mM NaCl, 10 mM $MgCl_2$, 1 mM DTT, 1% Glycerol) using 6.8 nM recombinant, human, C-terminally-His tagged NAMPT, 1 nM Tb-anti-His antibody (Invitrogen, Cat # PV5895), and 200 nM probe (Oregon Green 488-conjugated APO866; A-1251667.0). Plates were covered, and reactions were carried out for 2-3 hours. Plates were read with Envision (Laser Lantha low volume protocol) after 2 to 3 hours. Excitation was carried out at 337 nm, and the ratio of emission of Oregon Green (520 nm) to terbium (492 nm) was determined and used to calculate IC_{50} values of test compounds.

TABLE 1 shows the utility of compounds chosen from Examples 1-49 herein or pharmaceutically acceptable salts thereof; to functionally inhibit NAMPT.

Table 1

Example	TR-FRET Binding - IC50(μM)	Example	TR-FRET Binding - IC50(μM)
1	0.0556	26	2.89

2	0.0264	27	0.602
3	0.0326	28	3.15
4	0.00408	29	0.454
5	0.00692	30	7.19
6	0.0639	31	0.253
7	0.00739	32	0.782
8	0.0922	33	0.284
9	0.442	34	0.218
10	0.952	35	0.404
11	0.27	36	0.791
12	2.05	37	0.934
13	0.626	38	0.869
14	0.885	39	3.26
15	0.578	40	0.648
16	0.116	41	0.344
17	0.158	42	1.97
18	0.388	43	2.88
19	0.394	44	10.0
20	0.406	45	2.14
21	0.101	46	.261
22	1.27	47	5.85
23	0.14	48	0.0689
25	2.88	49	4.7

Compounds which inhibit NAMPT are useful for treating diseases in which activation of NF-KB is implicated. Such methods are useful in the treatment of a variety of diseases including inflammatory and tissue repair disorders; particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease), osteoarthritis, osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultra-violet induced skin damage; autoimmune diseases including systemic lupus erythematosis, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, athersclerosis, restenosis, diabetes, glomerulonephritis, cancer, particularly wherein the cancer is selected from breast, prostate, lung, colon, cervix, ovary, skin, CNS, bladder, pancreas, leukaemia, lymphoma or Hodgkin's disease, cachexia, inflammation associated with infection and certain viral infections, including Acquired Immune Deficiency Syndrome (AIDS), adult respiratory distress syndrome, and ataxia telengiectasia.

Involvement of NAMPT in the treatment of cancer is described in WO 97/48696. Involvement of NAMPT in immuno-supression is described in WO 97/48397. Involvement of NAMPT for the treatment of diseases involving angiogenesis is described in WO 2003/80054. Involvement of NAMPT for the treatment of rheumatoid arthritis and septic shock is described in WO 2008/025857. Involvement of NAMPT for the prophlaxis and treatment of ischaemia is described in WO 2009/109610.

Cancers include, but are not limited to, hematologic and solid tumor types such as acoustic neuroma, acute leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute t-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer (including estrogen-receptor positive breast cancer), bronchogenic carcinoma, Burkitt's lymphoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, gastric carcinoma, germ cell testicular cancer, gestational trophobalstic disease, glioblastoma, head and neck cancer, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, liposarcoma, lung cancer (including small cell lung cancer and non-small cell lung cancer), lymphangioendothelio-sarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (lymphoma, including diffuse large B-cell lymphoma, follicular lymphoma, Hodgkin's lymphoma and non-Hodgkin's

lymphoma), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, peripheral T-cell lymphoma, pinealoma, polycythemia vera, prostate cancer (including hormone-insensitive (refractory) prostate cancer), rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, testicular cancer (including germ cell testicular cancer), thyroid cancer, Waldenström's macroglobulinemia, testicular tumors, uterine cancer, Wilms' tumor and the like.

Schemes and Experimentals

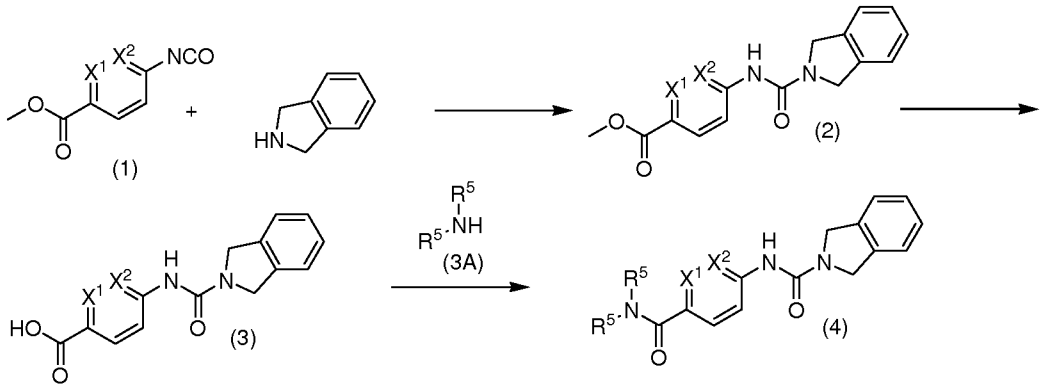
The following abbreviations have the meanings indicated. ADDP means 1,1'-(azodicarbonyl)dipiperidine; AD-mix-β means a mixture of $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, and K_2SO_4; 9-BBN means 9-borabicyclo(3.3.1)nonane; Boc means tert-butoxycarbonyl; $(DHQD)_2PHAL$ means hydroquinidine 1,4-phthalazinediyl diethyl ether; DBU means 1,8-diazabicyclo[5.4.0]undec-7-ene; DIBAL means diisobutylaluminum hydride; DIEA means diisopropylethylamine; DMAP means N,N-dimethylaminopyridine; DMF means N,N-dimethylformamide; dmpe means 1,2-bis(dimethylphosphino)ethane; DMSO means dimethylsulfoxide; dppb means 1,4-bis(diphenylphosphino)-butane; dppe means 1,2-bis(diphenylphosphino)ethane; dppf means 1,1'-bis(diphenylphosphino)ferrocene; dppm means 1,1-bis(diphenylphosphino)methane; EDAC·HCl means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; Fmoc means fluorenylmethoxycarbonyl; HATU means O-(7-azabenzotriazol-1-yl)-N,N'N'N'-tetramethyluronium hexafluorophosphate; HMPA means hexamethylphosphoramide; IPA means isopropyl alcohol; MP-BH_3 means macroporous triethylammonium methylpolystyrene cyanoborohydride; TEA means triethylamine; TFA means trifluoroacetic acid; THF means tetrahydrofuran; NCS means N-chlorosuccinimide; NMM means N-methylmorpholine; NMP means N-methylpyrrolidine; PPh_3 means triphenylphosphine.

The following schemes are presented to provide what is believed to be the most useful and readily understood description of procedures and conceptual aspects of this invention. Compounds of this invention may be made by synthetic chemical processes, examples of which are shown herein. It is meant to be understood that the order of the steps in the processes may be varied, that reagents, solvents and reaction conditions may be

substituted for those specifically mentioned, and that vulnerable moieties may be protected and deprotected, as necessary.

Schemes

Scheme 1



As shown in Scheme 1, isoindole can be reacted with compounds of formula (1) wherein X^1 and X^2 are CH or N, to provide compounds of formula (2). The reaction is typically performed in a solvent such as but not limited to tetrahydrofuran. The compounds of formula (2) are typically added at low temperature followed by stirring at room temperature. Compounds of formula (3) can be prepared by reacting compounds of formula (2) with aqueous lithium hydroxide. The reaction is typically performed in a solvent such as but not limited to tetrahydrofuran, methanol, or mixtures thereof. Compounds of formula (3) can be reacted with amine of formula (3A), wherein each R^5 is as described in Examples 1-49 herein, using coupling conditions known to those skilled in the art and readily available in the literature to provide compounds of formula (4), which are representative of the compounds of the invention.

Experimentals

The following examples are presented to provide what is believed to be the most useful and readily understood description of procedures and conceptual aspects of this invention. The exemplified compounds were named using ACD/ChemSketch Version 12.01 (13 May 2009), Advanced Chemistry Development Inc., Toronto, Ontario), or ChemDraw® Ver. 9.0.5 (CambridgeSoft, Cambridge, MA). Intermediates were named using ChemDraw® Ver. 9.0.5 (CambridgeSoft, Cambridge, MA).

Example 1

N-(4-{[2-(azepan-1-yl)ethyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide

Example 1A

ethyl 4-isocyanatobenzoate

To a solution of compound ethyl 4-aminobenzoate (20 g, 121 mmol) and triethylamine (14.6 g, 145 mmol) in anhydrous toluene (1.5 L) was added a solution of

triphosgene (36 g, 121 mmol) in anhydrous toluene (0.2 L) slowly at 0°C. The reaction mixture was stirred for 2 hours at room temperature and stirred at 90°C for 4 hrs. After the reaction was completed, additional toluene (500 mL) and water (500 mL) were added to the mixture. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound.

Example 1B

ethyl 4-(isoindoline-2-carboxamido)benzoate

A solution of compound ethyl 4-isocyanatobenzoate (24 g, 126 mmol) in tetrahydrofuran (600 mL) was stirred at 0°C. Then isoindole (16.5 g, 138 mmol) in tetrahydrofuran (100 mL) was added. The reaction was stirred at room temperature overnight. After removing the solvent, the solid was washed with ethyl acetate to give the title compound as a white solid.

Example 1C

4-(isoindoline-2-carboxamido)benzoic acid

Compound ethyl 4-(isoindoline-2-carboxamido)benzoate (29 g, 94 mmol) was dissolved in ethanol/tetrahydrofuran (1:1, 460 mL) and aqueous LiOH (2 mol/L, 230 mL) was added. The mixture was heated at 80°C for 2 hours. After removing the solvent, the solution was adjusted by addition of 1 N HCl to pH=3 and filtered. The solid was washed with water and dried to give the title compound.

Example 1D

N-(4-{[2-(azepan-1-yl)ethyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide

A solution of 4-(isoindoline-2-carboxamido)benzoic acid (100 mg, 0.35 mmol), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (82 mg, 0.43 mmol), 1-hydroxybenzotriazole hydrate (48 mg, 0.35 mmol) and triethylamine (107 mg, 1.06 mmol) in dichloromethane (2 mL) was stirred at room temperature for 30 minutes. Then 2-(azepan-1-yl)ethanamine (61 mg, 0.43 mmol) was added. The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure to give a residue, which was purified by prep-HPLC to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.40 (s, 1H), 8.64 (s, 1H), 8.58-8.56 (m, 1H), 7.79-7.76 (d, J =8.8 Hz, 2H), 7.70-7.68 (d, J =9.2 Hz, 2H), 7.36-7.29 (m, 4H), 4.77 (s, 4H), 3.61-3.57 (m, 2H), 3.47-3.42 (m, 2H), 3.29-3.25 (m, 2H), 3.21-3.14 (m, 2H), 1.82-1.71 (m, 4H), 1.61-1.57 (m, 4H); MS (ESI(+)) m/e 407 $(M+H)^+$.

Table 1.

The following examples were prepared essentially as described in example 1, substituting the appropriate amine in Example 1D. Products were purified by reverse-phase HPLC and, accordingly, were isolated as trifluoroacetic acid salts.

Ex		Name	^{1}H NMR	MS
2		N-{4-[(2-hydroxypropyl)carbamoyl]phenyl}-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.57 (s, 1H), 8.22-8.19 (m, 1H), 7.78-7.64 (m, 4H), 7.36-7.29 (m, 4H), 4.77 (s, 4H), 4.39 (s, 1H), 3.76-3.73 (m, 1H), 3.18-3.15 (m, 2H), 1.05-1.03 (d, J =6.4 Hz, 3H)	(ESI(+)) m/e 340 $(M+H)^+$
3		N-(4-{[2-(2-oxoimidazolidin-1-yl)ethyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.56 (s, 1H), 8.34-8.31 (d, J =5.6 Hz, 1H), 7.74-7.72 (d, J =8.4 Hz, 2H), 7.65-7.63 (d, J =8.8 Hz, 2H), 7.36-7.29 (m, 4H), 6.27 (s, 1H), 4.77 (s, 4H), 3.41-3.31 (m, 4H), 3.21-3.18 (m, 4H)	(ESI(+)) m/e 394 $(M+H)^+$
4		N-(4-{[2-(tetrahydro-2H-pyran-2-yl)ethyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.55 (s, 1H), 8.23-8.20 (t, J =4.2 Hz, 1H), 7.75-7.72 (d, J =8.4 Hz, 2H), 7.65-7.63 (d, J =8.4 Hz, 2H), 7.36-7.28 (m, 4H), 4.77 (s, 4H), 3.86-3.83 (d, J =10 Hz, 1H), 3.27-3.22 (m, 4H), 1.73 (s, 1H), 1.63-1.55 (m, 3H), 1.43 (s, 3H), 1.20-1.12 (m, 1H)	(ESI(+)) m/e 394 $(M+H)^+$
5		N-(4-{[(2-methyltetrahydrofuran-2-yl)methyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.57 (s, 1H), 8.18-8.14 (t, J =6.4 Hz, 1H), 7.79-7.77 (d, J =8.4 Hz, 2H), 7.66-7.64 (m, 2H), 7.36-7.29 (m, 4H), 4.77 (s, 4H), 3.76-3.71 (m, 2H), 3.32-3.28 (m, 2H), 1.90-1.83 (m, 3H), 1.55-1.49 (m, 1H), 1.13 (s, 3H)	(ESI(+)) m/e 380 $(M+H)^+$
6		N-(4-{[2-methyl-2-(morpholin-4-yl)propyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.39 (s, 1H), 8.67 (s, 1H), 8.56-8.53 (m, 1H), 7.84-7.82 (d, J =8.8 Hz, 2H), 7.72-7.70 (d, J =8.8 Hz, 2H), 7.36-7.29 (m, 4H), 4.77 (s, 4H), 4.03-3.99 (d, J =12.4 Hz, 2H), 3.75-3.69 (t, J =12 Hz, 2H), 3.59-3.56 (m, 4H), 3.18-3.16 (m, 2H), 1.33 (s, 6H)	(ESI(+)) m/e 423 $(M+H)^+$
7		N-{4-[(1-oxa-8-azaspiro[4.5]dec-3-ylmethyl)carbamoyl]phenyl}-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.73 (s, 2H), 8.62 (s, 1H), 8.42-8.40 (t, J =5.6 Hz, 1H), 7.77-7.75 (d, J =7.6 Hz, 2H), 7.67-7.65 (d, J =7.6 Hz, 2H), 7.36-7.29 (m, 4H), 4.78 (s, 4H), 3.85-3.81 (t, J	(ESI(+)) m/e 435 $(M+H)^+$

			=7.6 Hz, 1H), 3.57-3.53 (t, J =7.6 Hz, 1H), 3.30-3.21 (m, 2H), 3.05-3.00 (m, 4H), 2.58-2.53 (m, 1H), 1.95-1.90 (m, 1H), 1.82-1.68 (m, 4H), 1.51-1.46 (m, 1H)	

Example 8

N-[6-(2-oxa-7-azaspiro[3.5]non-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide

Example 8A

methyl 6-aminopyridazine-3-carboxylate

To a solution of 6-chloropyridazin-3-amine (32 g, 248 mmol), and triethylamine (75 mL, 744 mmol) in methanol (500 mL), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane (12 g, 16.4 mmol) was added and the mixture was heated at 60 °C overnight under CO atmosphere at 50 psi. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was washed with methanol and the precipitate was dried by high vacuum to give the title compound as a solid.

Example 8B

methyl 6-isocyanatopyridazine-3-carboxylate

To the solution of methyl 6-aminopyridazine-3-carboxylate (14 g, 91.5 mmol) in anhydrous toluene (700 mL) was added triethylamine (11.1, 109.8 mmol). A solution of triphosgene (27.2 g, 91.5 mmol) in anhydrous toluene was added slowly at 0 °C. The reaction mixture was stirred for 2 hours at room temperature and then heated at 90 °C for 5 hours. After cooling to room temperature, toluene and water were added to the mixture, the mixture was separated and the organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound.

Example 8C

methyl 6-(isoindoline-2-carboxamido)pyridazine-3-carboxylate

To a solution of methyl 6-isocyanatopyridazine-3-carboxylate (5.26 g, 29.4 mmol) in tetrahydrofuran (100 mL), a solution of isoindoline (5.24 g, 4.41 mmol) in tetrahydrofuran (50 mL) was added at 0 °C. The reaction mixture was stirred overnight at room temperature. The reaction mixture was filtered and the precipitate was washed with cold ethyl acetate and dried under high vacuum to give the title compound.

Example 8D

6-(isoindoline-2-carboxamido)pyridazine-3-carboxylic acid

To a solution of methyl 6-(isoindoline-2-carboxamido)pyridazine-3-carboxylate (3.7 g, 12.4 mmol) in methanol (40 mL) and tetrahydrofuran (40 mL), a solution of LiOH (0.7 g, 29.2 mmol) in water (10 mL) was added at room temperature. The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into water (100 mL), extracted with ethyl acetate (2 × 50 mL) and the aqueous layer was acidified by addition of 2 N aqueous HCl to pH 3 to give a precipitate. The precipitate was washed with water and dried under high vacuum to give the title compound.

Example 8E

N-[6-(2-oxa-7-azaspiro[3.5]non-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide

To a solution of 6-(isoindoline-2-carboxamido)pyridazine-3-carboxylic acid (50 mg, 0.176 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (100 mg, 0.264 mmol) in N,N-dimethylformamide (2 mL) were added diisopropylethylamine (0.046 mL, 0.264 mmol) and 2-oxa-7-azaspiro[3.5]nonane (25 mg, 0.193 mmol). The mixture was stirred at room temperature overnight. Then the mixture was diluted with water (10 mL). The aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phase was washed with brine (3×10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give, after chromatography, the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.89 (s, 1H), 8.25-8.23 (d, J = 9.6, 1H), 7.76-7.74 (d, J = 9.2, 1H), 7.35-7.29 (m, 4H), 4.84 (s, 4H), 4.36-4.31 (q, J =6.0, 4H), 3.6-3.58(t, J =5.2,2H), 3.38-3.35(t, J = 5.6,2H), 1.87-1.79 (m, 4H); MS (ESI(+)) m/e 394 $(M+H)^+$.

Table 2.

The following examples were essentially prepared as described in example 1, substituting the appropriate amine in Example 2E. Some products were purified by flash chromatography while others were purified by reverse-phase HPLC; some compounds also required Boc-deprotection after amide coupling as in Example 2D. Accordingly, some examples were isolated as trifluoroacetic acid salts.

Ex		Name	^{1}H NMR	MS
9		N-[6-(tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.93 (s, 1H), 8.26-8.24 (d, J = 9.2, 1H), 7.89-7.86 (d, J = 9.2, 1H), 7.37-7.29 (m, 4H), 4.85 (s, 4H), 3.95-3.49 (m, 8H), 2.95(s, 2H), 4.17-4.14 (m, 4H), 1.57-1.56 (m, 4H)	(ESI(+)) m/e 380 $(M+H)^+$
10		N-[6-(hexahydrofuro[3,2-c]pyridin-5(4H)-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.90 (s, 1H), 8.26-8.23 (d, J = 9.2, 1H), 7.79-7.76(dd, J =2.8, J =9.6, 1H),	(ESI(+)) m/e 394 $(M+H)^+$

			7.36-7.29(m, 4H), 4.85-4.7(m, 5H), 3.89-3.83(m, 3H), 3.2-2.6(m, 3H),2.11-1.35(m, 5H)	
11		N-[6-(hexahydro-5H-furo[2,3-c]pyrrol-5-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.95-9.92 (d, J = 13.2, 1H), 8.27-8.24(dd, J = 3.2, J = 9.2, 1H), 7.9-7.87 (dd, J = 3.6, J = 9.2, 1H), 7.37-7.29 (m, 4H), 4.86 (s, 4H),4.46-4.62(m, 1H), 3.96-3.44(m, 9H), 2.94-2.93(m,1H), 2.1-2.01(m,1H), 1.9-1.6 (m,1H)	(ESI(+)) m/e 380 $(M+H)^+$
12		N-[6-(2,6-dioxa-9-azaspiro[4.5]dec-9-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.98-9.92 (d, J = 24,1H), 8.48 (s, 1H), 8.29-8.25 (dd, J = 6.4, J = 8.4, 1H), 7.85-7.81 (dd, J = 6.8, J =8.8, 1H), 7.35-7.29 (m, 4H), 4.85 (s, 4H), 3.8-3.5 (m, 10H), 1.99-1.94 (m, 2H)	(ESI(+)) m/e 410 $(M+H)^+$
13		N-[6-(2-oxa-6-azaspiro[3.3]hept-6-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.99 (s, 1H), 8.28-8.26 (d, J = 9.2, 1H), 8.01-7.99 (d, J = 9.2, 1H), 7.34-7.30 (m, 4H), 4.84-4.69 (m, 10H), 4.26(s, 2H)	(ESI(+)) m/e 366 $(M+H)^+$
14		N-[6-(2-oxa-6-azaspiro[3.5]non-6-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.97-9.88 (m, 1H), 8.30-8.23 (dd, J = 9.2, J = 20, 1H), 7.81-7.75 (dd, J = 9.6, J =17.2,2 1H), 7.35-7.29 (m, 4H), 4.85 (s, 4H), 4.26-4.2(dd, J = 6.0, J = 20.4, 4H), 3.9(s, 1H), 3.65(s, 1H), 3.57-3.55(t, J = 6.8,1H), 3.35-3.33 (t, J = 4.8, 1H), 1.86-1.85 (d,J = 5.6, 4H), 1.50-1.46(m, 2H)	(ESI(+)) m/e 394 $(M+H)^+$
15		N-[6-(2-oxa-7-azaspiro[4.4]non-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.94 (s, 1H), 8.27-8.24 (dd, J = 2.0, J = 9.2, 1H), 7.92-7.89 (dd, J = 4.4, J = 9.2, 1H), 7.37-7.29 (m, 4H), 4.86 (s, 4H), 3.90-3.49 (m, 8H), 1.95-1.81 (m, 4H)	(ESI(+)) m/e 394 $(M+H)^+$
16		N-{6-[(10,10-difluoro-2,7-diazaspiro[4.5]dec-2-yl)carbonyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.96 (s, 1H), 9.21 (s, 1H), 8.29-8.26 (d, J = 9.2, 1H), 7.94-7.91 (dd, J = 1.6, J = 9.2, 1H), 7.36-7.29 (m, 4H), 4.86 (s, 4H), 4.07-3.73(m, 4H), 3.4-3.24 (m, 4H), 2.32-2.06 (m, 4H)	(ESI(+)) m/e 443 $(M+H)^+$

17		N-{6-[(3-cyano-1-oxa-8-azaspiro[4.5]dec-8-yl)carbonyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.90 (s, 1H), 8.25-8.23 (d, J = 9.6, 1H), 7.78-7.76 (d, J = 9.2, 1H), 7.34-7.28 (m, 4H), 4.84 (s, 4H), 3.96-3.90(m, 2H), 3.53-3.35 (m, 4H), 2.24-2.15(m, 1H), 2.05-1.96(m,1H), 1.78-1.59 (m, 4H), 1.2-1.05(m,1H)	(ESI(+)) m/e 433 $(M+H)^+$
18		N-[6-(7-oxa-2-azaspiro[3.5]non-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.95 (s, 1H), 8.29-8.26 (d, J =9.6,1H), 8.04-8.02 (d, J = 9.6, 1H), 7.36-7.29 (m, 4H), 4.86 (s, 4H), 4.33(s, 2H), 3.85(s, 2H), 3.52 (s, 4H), 1.74-1.72 (t, J = 4.8, 4H)	(ESI(+)) m/e 394 $(M+H)^+$
19		N-[6-(1-oxa-7-azaspiro[4.4]non-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.90(s, 1H), 8.27-8.24 (dd, J = 1.6, J = 9.6, 1H), 7.91-7.89 (t, J = 7.6, 1H), 7.35-7.31 (m, 4H), 4.85 (m, 4H), 3.80-3.60(m, 6H), 1.96-1.86 (m, 6H)	(ESI(+)) m/e 394 $(M+H)^+$
20		N-{6-[(10-fluoro-2,7-diazaspiro[4.5]dec-2-yl)carbonyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.95-9.91 (d, J = 18, 1H), 9.08-8.98 (d, 37.2,H), 8.62-8.47 (d, J = 17.2, 1H), 8.28-8.25 (dd, J = 4.4, J = 9.2, 1H), 7.93-7.90 (dd, J = 4.8, J = 9.2, 4H), 7.36-7.29 (m, 4H), 4.90-4.75(m, 5H), 3.92-3.50(m, 4H), 3.31-3.03 (m, 4H), 2.11-1.9 (m, 4H)	(ESI(+)) m/e 425 $(M+H)^+$
21		N-[6-(3,9-diazaspiro[5.5]undec-3-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.81 (s, 1H), 8.38 (s, 2H), 8.19-8.17 (d, J = 9.2, 1H), 7.71-7.68 (d, J = 9.2, 1H), 7.3-7.22 (m, 4H), 4.78 (m, 4H), 3.59-3.58(d, J = 5.6, 2H), 2.98 (s, 4H), 1.59-1.57 (d, J = 5.6, 4H),1.497(s, 2H),1.413(s, 2H)	(ESI(+)) m/e 422 $(M+H)^+$
22		N-[6-(2,7-diazaspiro[4.5]dec-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.89 (m, 1H), 8.90 (m, 2H),8.60 (m, 1H), 8.22-8.18 (dd, J = 3.6, J = 9.2, 1H), 7.74-7.70 (dd, J = 4.0, J = 9.2, 1H), 7.30-7.23 (m, 4H), 4.79 (s, 4H), 3.98-3.74(m, 1H), 3.50-3.37 (m, 2H), 3.29-2.82 (m, 7H),2.02-1.85(m,1H),1.68-1.62(m,5H)	(ESI(+)) m/e 407 $(M+H)^+$

23		N-[6-(2,8-diazaspiro[4.5]dec-8-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.89 (s, 1H), 8.86 (s, 2H), 8.26-8.24 (d, J = 9.2, 1H), 7.78-7.75 (d, J = 9.2, 1H), 7.36-7.29 (m, 4H), 4.85 (s, 4H), 3.77-3.70(m, 1H), 3.66-3.60 (m, 1H), 3.47 (m, 2H),3.27-3.25(m,2H),3.08-3.04(m,2H),1.88-1.83(m,2H),1.66-1.55(m, 4H)	(ESI(+)) m/e 407 $(M+H)^+$
24		-[6-(7-azaspiro[3.5]non-1-ylcarbamoyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.91 (s, 1H),9.14-9.12(d,J=8.0,1H), 8.38(s,1H),8.31-8.24 (t, J = 4.6, 1H), 8.09-8.06 (d, J = 4.6, 1H), 7.37-7.29 (m, 4H), 4.87 (s, 4H), 4.29-4.23(q, J=8.4,1H), 3.09 (m, 1H), 2.85 (s, 2H),2.82(m, 1H),2.48-2.3(m, 1H),2.17-2.13(m, 1H),1.96-1.89(m, 1H), 1.78-1.70 (m, 4H),1.59-1.52 (m, 1H)	(ESI(+)) m/e 407 $(M+H)^+$
25		N-[6-(2-azaspiro[3.3]hept-5-ylcarbamoyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.95 (s, 1H), 9.38-9.36(d, J = 7.6, 1H), 8.74(s, 1H), 8.34-8.31 (dd, J =0.8, J = 9.2, 1H), 8.15-8.13 (dd, J = 0.8, J = 9.6, 1H), 7.36-7.29 (m, 4H), 4.87 (s, 4H), 4.51-4.45(q, J = 8, 1H), 4.13-4.00 (m, 2H), 3.85-3.81(m,2H), 2.21-2.17(m,1H), 2.04-1.99 (m, 3H)	(ESI(+)) m/e 379 $(M+H)^+$
26		N-{6-[(1R,5S)-3-azabicyclo[3.1.0]hex-6-ylcarbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.93 (s, 1H), 9.19-9.17 (d, J = 5.2,1H), 9.09-9.06 (t, J = 5.2, 1H), 8.52-8.50 (t, J = 2, 1H), 8.30-8.28 (t, J = 9.6, 1H), 8.09-8.07(d, J = 9.2,1H), 4.86 (m, 4H), 3.4-3.37(t, J = 6.4,2H), 3.07 (s, 1H), 2.14 (s, 2H)	(ESI(+)) m/e 365 $(M+H)^+$
27		N-(6-{[(7R)-octahydropyrrolo[1,2-a]pyrazin-7-ylmethyl]carbamoyl}pyridazin-3-yl)-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.95 (s, 1H), 8.54 (bs, 1H), 9.27-9.24(t, J = 6.0, 1H), 8.31-8.29 (d, J = 10.4, 1H), 8.11-8.09 (d, J = 9.2, 1H), 7.36-7.28 (m, 4H), 4.84(s,4H), 3.69(s, 2H), 3.48-3.17 (m, 9H), 2.84-2.76(m, 1H), 2.33-2.28(m,1H), 1.54-1.52 (d, J = 7.6, 1H)	(ESI(+)) m/e 423 $(M+H)^+$
28		N-[6-(2,6-diazaspiro[3.5]non-2-	^{1}H NMR (400 MHz, DMSO-	(ESI(+))

		ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	d_6) δ ppm 9.94 (s, 1H), 8.55 (s, 1H), 8.29-8.27 (d, J = 9.6, 1H), 8.05-8.03 (d, J = 9.6, 1H), 7.37-7.3 (m, 4H), 4.85 (s, 4H), 4.5-4.47(d, J =10.4, 2H),4.32-4.29(d, J =10.4, 2H), 4.0-3.98(d, J =10, 2H), 3.82-3.79(d, J =10.4, 2H), 3.32-3.29(m, 2H), 2.96 (s, 2H), 1.85-1.84 (d, J =6.0, 4H), 1.68 (s, 2H)	m/e 393 $(M+H)^+$
29		N-[6-(2,7-diazaspiro[3.5]non-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.92 (s, 1H), 8.52 (s, 2H), 8.28-8.26 (d, J = 9.6, 1H), 8.04-8.02 (d, J = 9.2, 1H), 7.37-7.29 (m, 4H), 4.7-4.6 (m, 4H), 4.37(s, 2H), 3.9-3.8 (m, 2H), 3.06 (s, 4H), 1.94-1.91 (t, J = 5.2, 4H)	(ESI(+)) m/e 393 $(M+H)^+$
30		N-[6-(2,6-diazaspiro[3.4]oct-6-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.91 (s, 1H), 8.98-8.90 (m, 1H), 8.77-8.66 (m, 1H), 8.27-8.24 (t, J =8.8, 1H), 7.92-7.89(dd, J = 3.2, J = 9.2,1H), 7.35-7.29 (m, 4H), 4.87-4.85 (m, 6H), 3.99-3.95 (m, 5H), 3.80-3.77(t, J = 6.4, 2H), 3.59-3.55(t, J = 7.2,2H) , 2.2-2.15 (m, 2H)	(ESI(+)) m/e 379 $(M+H)^+$
31		N-{6-[(2-oxa-9-azaspiro[5.5]undec-3-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.96 (s, 1H), 8.79 (s, 1H), 8.41(s, 2H), 8.31-8.29 (dd, J = 1.6, J = 9.6, 1H), 8.10-8.08 (dd, J =1.6, J = 9.2, 1H), 7.36-7.29 (m, 4H), 4.87 (m, 4H),3.78-3.75(d, J = 11.2, 1H), 3.45-3.3 (m, 3H), 3.12-3.0(m, 5H) , 1.78-1.65 (m, 3H), 1.5-1.29(m,5H)	(ESI(+)) m/e 452 $(M+H)^+$
32		N-{6-[(1-oxa-8-azaspiro[4.5]dec-2-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.95 (s, 1H), 8.92-8.88(t, J = 6, 1H), 8.41 (s,1H), 8.32-8.29 (d, J = 9.2, 1H),8.11-8.10 (d, J = 9.2, 1H), 7.35-7.30 (m, 4H), 4.87 (s, 4H), 4.27(s, 2H), 4.18-4.15 (t, J = 6.0, 4H), 3.09(m, 5H), 2.03-1.95(m,1H), 1.78-1.67 (m, 8H)	(ESI(+)) m/e 438 $(M+H)^+$
33		N-{6-[(1-oxa-8-azaspiro[4.5]dec-3-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.93 (s, 1H), 9.14-9.11 (t, J = 6.0, 1H), 8.37(s, 1H), 8.30-8.27 (d, J = 9.6,	(ESI(+)) m/e 438 $(M+H)^+$

			1H), 8.10-8.07 (d, J = 9.2, 1H), 7.34-7.29 (m, 4H), 4.87 (s, 4H), 3.85-3.81(t, J = 8, 1H), 3.59-3.54(m, 1H), 3.06(m, 1H), 3.02(s, 1H), 2.68-2.61 (m, 4H), 1.95-1.90 (m, 1H),1.76-1.51 (m, 5H)	
34		N-[6-(2,7-diazaspiro[3.5]non-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.89 (s, 1H), 8.75 (s, 2H), 8.25-8.23 (dd, J = 0.8, J = 9.2, 1H), 7.76-7.73 (dd, J = 1.2, J = 9.2, 1H), 7.35-7.29 (m, 4H), 4.84-4.75 (m, 6H), 4.27(s, 2H), 4.17-4.14 (m, 4H), 1.57-1.56 (m, 4H)	(ESI(+)) m/e 393 $(M+H)^+$
35		N-[6-(2,8-diazaspiro[4.5]dec-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.93 (s, 1H), 8.48 (s, 2H), 8.29-8.24 (dd, J = 1.2, J = 9.2, 1H), 7.91-7.86 (dd, J = 8.4, J = 9.2, 1H), 7.35-7.29 (m, 4H), 4.85 (s, 4H), 3.64-3.61(m,2H),3.51(s, 1H), 3.15-3.01 (m, 4H), 1.88-1.84(t, J = 7.2, 2H), 1.75-1.63(m, 4H)	(ESI(+)) m/e 407 $(M+H)^+$
36		N-(6-{[3-(azetidin-3-yl)pyrrolidin-1-yl]carbonyl}pyridazin-3-yl)-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.92 (s, 1H), 8.68-8.63 (d, J = 18.8, 2H), 8.27-8.23 (dd, J = 4.4, J = 9.2, 1H), 7.90-7.86 (dd, J =3.6, J =9.6, 1H), 7.36-7.29 (m, 4H), 4.86 (s, 4H), 3.85-3.7(m, 7H), 3.52-3.47 (m, 1H), 3.32-3.27 (dd, J = 7.6, J = 11.2, 1H), 3.19-3.14(dd, J =7.2, J = 12.4, 1H) , 2.88-2.75(m, 1H), 2.04-1.98 (m, 1H), 1.57-1.53(m, 1H)	(ESI(+)) m/e 393 $(M+H)^+$
37		N-{6-[(4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.07 (s, 1H), 9.73-9.70 (t, J = 5.6, 1H), 9.45 (s, 1H), 8.35-8.33 (d, J = 9.2, 1H), 8.14-8.11 (d, J = 9.2, 1H), 7.35-7.30 (m, 4H), 4.88-4.76 (m, 6H), 4.27(s, 2H), 3.43(s, 2H), 2.89-2.88 (d, J = 5.2, 2H), 1.57-1.56 (m, 4H)	(ESI(+)) m/e 419 $(M+H)^+$
38		N-[6-(1-oxa-8-azaspiro[4.5]dec-3-ylcarbamoyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.92 (s, 1H), 9.03-9.01(d, J = 7.2, 1H), 8.52-8.40(m, 2H), 8.30-8.28 (d, J = 9.2, 1H), 8.09-8.07 (d, J =	(ESI(+)) m/e 423 $(M+H)^+$

			9.2, 1H), 7.37-7.29 (m, 4H), 4.95 (m, 4H), 4.64-4.58(m, 1H), 4.03-4.0(m, 1H), 3.78-3.74(m, 1H), 3.1-3.07 (m, 4H), 2.21-2.15(dd, J = 4.4, J = 4.4,1H), 2.05-2.0(dd, J = 6.8, J = 7.2,1H), 1.87-1.72 (m, 4H)	
39		N-{6-[(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a][1,4]diazepin-3-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.02 (s, 1H), 9.58-9.55 (t, J =5.6, 1H), 9.29(s, 2H), 8.32-8.30 (d, J = 5.2, 1H), 8.11-8.08 (d, J = 9.6, 1H), 7.35-7.28 (m, 4H), 4.86 (s, 4H), 4.71-4.69(d, J = 6.0,2H), 4.56(s, 2H), 4.38-4.36 (t, J = 4.4, 4H),3.4(s, 2H), 2.02 (s, 2H)	(ESI(+)) m/e 434 $(M+H)^+$
40		N-{6-[(6-azaspiro[2.5]oct-1-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.60 (s, 1H), 8.78-8.75 (t, J = 5.2, 1H), 8.21(s, 1H), 8.09(s,1H), 7.97-7.94 (dd, J = 0.8, J = 9.2, 1H), 7.77-7.75 (d, J = 9.2, 1H), 7.01-6.95 (m, 4H), 4.61 (s, 4H),3.17-2.96(m, 2H), 2.68(s, 4H), 1.48-1.43(m,1H),1.32-1.2 (m, 2H),1.07-1.04(t, J = 4.8, 1H), 0.835-0.8(t, J = 6.8, 1H), 1.57-1.56 (m, 4H), 0.3-0.25(m,1H), 0.1-0.0(m,1H)	(ESI(+)) m/e 407 $(M+H)^+$
41		N-[6-(5-oxa-2-azaspiro[3.4]oct-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.98 (s, 1H), 8.29-8.27 (d, J = 9.6, 1H), 8.04-8.02 (d, J = 9.2, 1H), 7.35-7.29 (m, 4H), 4.85 (s, 4H), 4.62-4.51 (m, 2H), 4.16-4.02(m, 2H), 3.79-3.75 (m, 2H),2.11-2.07(t, J = 3.2, 2H) ,1.88-1.84 (m, 2H)	(ESI(+)) m/e 380 $(M+H)^+$
42		N-{6-[(5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-3-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.03 (s, 1H), 9.61-9.58 (m, 2H), 8.33-8.31 (t, J = 7.6, 1H), 8.12-8.09 (dd, J = 2.0, J = 9.2, 1H), 7.36-7.29 (m, 4H), 4.89 (m, 4H), 4.69-4.68(d, J = 6.0, 2H), 4.53(s, 2H), 4.32-4.29 (t, J = 4.8, 2H), 3.63-3.60 (t, J = 5.2,2H)	(ESI(+)) m/e 420 $(M+H)^+$
43		N-(6-{[(4-fluoropiperidin-4-yl)methyl]carbamoyl}pyridazin-3-yl)-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.0 (s, 1H), 9.18 (s, 1H), 8.75 (s, 1H),8.42 (s,	(ESI(+)) m/e 399 $(M+H)^+$

			1H),8.33-8.31 (d, J = 9.6, 1H), 8.13-8.11 (d, J = 9.2, 1H), 7.36-7.29 (m, 4H), 4.87 (s, 4H), 3.65-3.59(dd, J = 6.4, J = 19.2, 2H), 3.25(s, 2H), 3.0-2.99 (d, J = 6.8,2H), 1.97-1.93 (m, 4H)	
44		N-[6-(2,6-diazaspiro[3.3]hept-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.99 (s, 1H), 8.48 (s, 1H), 8.29-8.27 (d, J = 13.6, 1H), 8.03-8.01 (d, J = 9.2, 1H), 7.36-7.29 (m, 4H), 4.84-4.75 (m, 6H), 4.27(s, 2H), 4.17-4.14 (m, 4H), 1.57-1.56 (m, 4H)	(ESI(+)) m/e 365 $(M+H)^+$
45		N-{6-[(6-oxa-2-azaspiro[3.4]oct-7-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.96 (s, 1H), 8.97-8.94 (t, J = 6.0, 1H), 8.87-8.80 (m, 2H), 8.32-8.30 (d, J = 9.2, 1H), 8.11-8.09 (d, J = 9.2, 1H), 7.36-7.28 (m, 4H), 4.89(s, 4H), 4.24-4.18 (m, 1H), 4.06-3.97(m, 4H), 3.44-3.32(m, 2H), 2.25-2.19(m, 1H), 2.15-2.07(m, 1H), 2.01-1.93(m, 1H), 1.73-1.63 (m, 1H)	(ESI(+)) m/e 409 $(M+H)^+$
46		N-[6-(5-oxa-2-azaspiro[3.5]non-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.96 (s, 1H), 8.29-8.27 (d, J = 9.2, 1H), 8.04-8.02 (d, J = 9.6, 1H), 7.37-7.28 (m, 4H), 4.85 (s, 4H), 4.44-4.37(q, J = 10.8,2H), 3.98-3.90(q, J = 10.4, 2H), 3.6-3.58(t, J =5.2,2H), 1.74-1.72(m,2H), 4.27(s, 2H), 1.58 (s, 2H), 1.44 (s, 2H)	(ESI(+)) m/e 394 $(M+H)^+$
47		N-(6-{[1-(trifluoromethyl)-2,8-diazaspiro[4.5]dec-2-yl]carbonyl}pyridazin-3-yl)-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.0 (s, 1H), 8.69-8.61 (d, J = 31.6, 1H), 8.33-8.28 (dd, J = 9.2, J= 11.2, 1H), 7.97-7.93 (dd, J = 4.4, J = 9.2, 1H), 7.37-7.29 (m, 4H), 4.85 (m, 4H), 4.14-4.09(t, J = 10.8,1H), 3.22-3.02 (m, 5H), 2.2-1.6 (m, 6H)	(ESI(+)) m/e 475 $(M+H)^+$
48		N-{6-[(7-azaspiro[3.5]non-2-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.93 (s, 1H), 8.98-8.95 (t, J = 6.0, 1H), 8.30-8.27 (d, J = 9.6, 3H), 8.09-8.07 (d, J = 9.2, 1H), 7.34-7.29 (m, 4H), 4.86 (s, 4H), 3.38-3.35(t, J =6.4,2H), 2.97(s, 2H), 2.90(s,2H), 1.92-	(ESI(+)) m/e 422 $(M+H)^+$

			1.86 (t, J = 10.8, 2H),1.68-1.67(d, J =5.6,2H), 1.62-1.55 (m, 4H)	
49		N-{6-[(5,6,7,8-tetrahydro-4H-[1,2,3]triazolo[1,5-a][1,4]diazepin-3-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.99 (s, 1H), 9.50-9.47 (t, J = 10.0, 1H), 9.01(s, 2H), 8.33-8.31 (d, J = 9.2, 1H), 8.10-8.08 (d, J = 9.2, 1H), 7.35-7.29 (m, 4H), 4.88 (s, 4H), 4.67(s, 4H), 4.59-4.57 (d, J = 5.6, 2H), 3.45-3.44 (d, J = 3.6,2H), 2.05 (s, 2H)	(ESI(+)). m/e 434 $(M+H)^+$

We Claim:

1. A compound chosen from:

N-(4-{[2-(azepan-1-yl)ethyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{4-[(2-hydroxypropyl)carbamoyl]phenyl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(4-{[2-(2-oxoimidazolidin-1-yl)ethyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(4-{[2-(tetrahydro-2H-pyran-2-yl)ethyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(4-{[(2-methyltetrahydrofuran-2-yl)methyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(4-{[2-methyl-2-(morpholin-4-yl)propyl]carbamoyl}phenyl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{4-[(1-oxa-8-azaspiro[4.5]dec-3-ylmethyl)carbamoyl]phenyl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2-oxa-7-azaspiro[3.5]non-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(hexahydrofuro[3,2-c]pyridin-5(4H)-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(hexahydro-5H-furo[2,3-c]pyrrol-5-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,6-dioxa-9-azaspiro[4.5]dec-9-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2-oxa-6-azaspiro[3.3]hept-6-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2-oxa-6-azaspiro[3.5]non-6-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2-oxa-7-azaspiro[4.4]non-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(10,10-difluoro-2,7-diazaspiro[4.5]dec-2-yl)carbonyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(3-cyano-1-oxa-8-azaspiro[4.5]dec-8-yl)carbonyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(7-oxa-2-azaspiro[3.5]non-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(1-oxa-7-azaspiro[4.4]non-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(10-fluoro-2,7-diazaspiro[4.5]dec-2-yl)carbonyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(3,9-diazaspiro[5.5]undec-3-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,7-diazaspiro[4.5]dec-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,8-diazaspiro[4.5]dec-8-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(7-azaspiro[3.5]non-1-ylcarbamoyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2-azaspiro[3.3]hept-5-ylcarbamoyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(1R,5S)-3-azabicyclo[3.1.0]hex-6-ylcarbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(6-{[(7R)-octahydropyrrolo[1,2-a]pyrazin-7-ylmethyl]carbamoyl}pyridazin-3-yl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,6-diazaspiro[3.5]non-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,7-diazaspiro[3.5]non-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,6-diazaspiro[3.4]oct-6-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(2-oxa-9-azaspiro[5.5]undec-3-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(1-oxa-8-azaspiro[4.5]dec-2-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(1-oxa-8-azaspiro[4.5]dec-3-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,7-diazaspiro[3.5]non-7-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,8-diazaspiro[4.5]dec-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(6-{[3-(azetidin-3-yl)pyrrolidin-1-yl]carbonyl}pyridazin-3-yl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(1-oxa-8-azaspiro[4.5]dec-3-ylcarbamoyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a][1,4]diazepin-3-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(6-azaspiro[2.5]oct-1-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(5-oxa-2-azaspiro[3.4]oct-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-3-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(6-{[(4-fluoropiperidin-4-yl)methyl]carbamoyl}pyridazin-3-yl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(2,6-diazaspiro[3.3]hept-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(6-oxa-2-azaspiro[3.4]oct-7-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-[6-(5-oxa-2-azaspiro[3.5]non-2-ylcarbonyl)pyridazin-3-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

N-(6-{[1-(trifluoromethyl)-2,8-diazaspiro[4.5]dec-2-yl]carbonyl}pyridazin-3-yl)-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(7-azaspiro[3.5]non-2-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

N-{6-[(5,6,7,8-tetrahydro-4H-[1,2,3]triazolo[1,5-a][1,4]diazepin-3-ylmethyl)carbamoyl]pyridazin-3-yl}-1,3-dihydro-2H-isoindole-2-carboxamide;

and pharmaceutically acceptable salts thereof.

2. A composition for treating inflammatory and tissue repair disorders; particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease), osteoarthritis, osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultra-violet induced skin damage; autoimmune diseases including systemic lupus erythematosis, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, athersclerosis, restenosis, diabetes, glomerulonephritis, cancer, particularly wherein the cancer is selected from breast, prostate, lung, colon, cervix, ovary, skin, CNS, bladder, pancreas, leukemia, lymphoma or Hodgkin's disease, cachexia, inflammation associated with infection and certain viral infections, including Acquired Immune Deficiency Syndrome (AIDS), adult respiratory distress syndrome, and ataxia telengiectasia, said composition comprising an excipient and a therapeutically effective amount of a compound of claim 1, or pharmaceutically acceptable salts thereof.

3. A method of treating inflammatory and tissue repair disorders; particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease), osteoarthritis, osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultra-violet induced skin damage; autoimmune diseases including systemic lupus erythematosis, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, athersclerosis, restenosis, diabetes, glomerulonephritis, cancer, particularly wherein the cancer is selected from breast, prostate, lung, colon, cervix, ovary, skin, CNS, bladder, pancreas, leukemia, lymphoma or Hodgkin's disease, cachexia, inflammation associated with infection and certain viral infections, including Acquired Immune Deficiency Syndrome (AIDS), adult respiratory distress syndrome, and ataxia telengiectasia in a patient, said method comprising administering to the patient a therapeutically effective amount of a compound of claim 1, or pharmaceutically acceptable salts thereof.

4. A method of treating inflammatory and tissue repair disorders; particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease), osteoarthritis, osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultra-violet induced skin damage; autoimmune diseases including systemic lupus erythematosis, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, athersclerosis, restenosis, diabetes, glomerulonephritis, cancer, particularly wherein the cancer is selected from breast,

prostate, lung, colon, cervix, ovary, skin, CNS, bladder, pancreas, leukemia, lymphoma or Hodgkin's disease, cachexia, inflammation associated with infection and certain viral infections, including Acquired Immune Deficiency Syndrome (AIDS), adult respiratory distress syndrome, and ataxia telengiectasia or spleen cancer in a patient, said method comprising administering to the patient therapeutically effective amount of the compound of claim 1 or pharmaceutically acceptable salts thereof; and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2011/082108

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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)

IPC: C07D,A61K,A61P

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)

WPI, EPODOC, CPRS(CN), CNKI, CTMPD(CN), CHEMICAL PHARMACEUTICAL ABSTRACT(CPA), CAPLUS, REGISTRY: isoindole, dihydro, carboxamide, pyridazin, phenyl, carbamoyl, carbonyl, NAMPT, inhibit+, ABBOTT LABORATORIES TRADING, STN structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO2010033349A1 (MERCK & CO., INC), 25 Mar. 2010 (25.03.2010), see whole document	1-4
A	WO2008116814A1 (GLAXO GROUP LIMITED), 02 Oct. 2008 (02.10.2008), see whole document	1-4
A	WO2011006803A1 (NERVIANO MEDICAL SCIENCES S.R.L.), 20 Jan. 2011 (20.01.2011), see whole document	1-4

☐ Further documents are listed in the continuation of Box C. ☒ 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

"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 Jul. 2012 (13.07.2012)	**23 Aug. 2012 (23.08.2012)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer FAN,Chanjuan Telephone No. (86-10)62411209

Form PCT/ISA /210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2011/082108

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 3,4
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 3-4 are directed to a method of treatment of the human/animal body (Rule 39. 1(iv) PCT), however, the search has been carried out and based on the reasonably anticipant subjects i.e. the use of said compound for the manufacture of a medicament for treating inflammatory and tissue repair disorders.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2011/082108

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
WO2010033349A1	25.03.2010	CA2737699A1	25.03.2010
		EP2334181A1	22.06.2011
		US2011318266A1	29.12.2011
WO2008116814A1	02.10.2008	EP2142502A1	13.01.2010
		JP2010522709A	08.07.2010
		US2010210705A1	19.08.2010
		US7935832B2	03.05.2011
WO2011006803A1	20.01.2011	WO2011006803A8	17.03.2011
		WO2011006803A9	05.05.2011
		TW201105653A	16.02.2011
		EP2454237A1	23.05.2012

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2011/082108

CLASSIFICATION OF SUBJECT MATTER (According to International Patent Classification (IPC) or to both national lassification and IPC)

C07D 209/44 (2006.01) i
C07D 471/04 (2006.01) i
A61K 31/4035 (2006.01) i
A61P 3/10 (2006.01) i
A61P 11/06 (2006.01) i
A61P 13/12 (2006.01) i
A61P 17/00 (2006.01) i
A61P 17/06 (2006.01) i
A61P 19/04 (2006.01) i
A61P 19/10 (2006.01) i
A61P 25/28 (2006.01) i
A61P 29/00 (2006.01) i
A61P 31/12 (2006.01) i
A61P 31/18 (2006.01) i
A61P 35/00 (2006.01) i
A61P 37/00 (2006.01) i
A61P 43/00 (2006.01) i