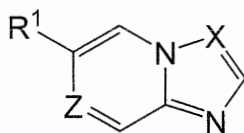


150-156, 2007). Small-molecule inhibitors of NAMPT have been shown to cause depletion of intracellular NAD<sup>+</sup> levels and ultimately induce tumor cell death (Hansen, CM et al. *Anticancer Res.* **20**, 42111-4220, 2000) as well as inhibit tumor growth in xenograft models (Olese, U.H. et al. *Mol 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<sup>+</sup> depletion in lymphocytes blocking the expansion that accompanies autoimmune disease progression whereas cell types expressing the other NAD<sup>+</sup> 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 aspect, therefore, pertains to compounds or pharmaceutically acceptable salts thereof, which are useful as inhibitors of NAMPT, the compounds having Formula (IB)



Formula (IB)

or a therapeutically acceptable salt thereof, wherein

X is N or CY<sup>1</sup>;

Y<sup>1</sup> is independently selected from the group consisting of hydrogen, alkyl, alkoxy, haloalkyl, hydroxyalkyl, OH, CN, F, Cl, Br, and I;

R<sup>1</sup> is independently selected from the group consisting of NHC(O)NHR<sup>3</sup>, NHC(O)NH(CH<sub>2</sub>)<sub>m</sub>R<sup>3x</sup>, CH<sub>2</sub>NHC(O)NHR<sup>3</sup>, NHC(O)R<sup>3</sup>, NHC(O)(CH<sub>2</sub>)<sub>n</sub>R<sup>3</sup>, C(O)NH(CH<sub>2</sub>)<sub>n</sub>R<sup>3</sup>, NHC(O)(CH<sub>2</sub>)<sub>m</sub>R<sup>3x</sup>, C(O)NH(CH<sub>2</sub>)<sub>m</sub>R<sup>3x</sup>, CH<sub>2</sub>C(O)NHR<sup>3</sup>, and CH<sub>2</sub>NHC(O)R<sup>3</sup>; and

Z is CH, C-F, C-Cl, C-Br, C-I or N; or

X is N or CY<sup>1</sup>;

5  $R^{11}$  at each occurrence, is independently selected from the group consisting of aryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkyl, alkenyl, and alkynyl; wherein each  $R^{11}$  alkyl is optionally substituted with  $NH(CH_3)$ , heterocyclyl,  $SCH_2CH(NH_2)C(O)OH$ ,  $OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2NH_2$ , or  $NHC(O)CH_2CH(NH_2)C(O)OH$ ;  $m$  is 4, 5, or 6; and  
 10  $n$  is 1 or 2;  
 with the provisos that  
 when  $X$  is  $CY^1$  and  $Y^1$  is hydrogen; and  $R^3$  is thiazolyl; the  $R^3$  thiazolyl is substituted with one substituent;  
 when  $X$  is  $CY^1$  and  $Y^1$  is hydrogen;  $R^1$  is  $NHC(O)R^3$ ;  $R^2$  is hydrogen; and  $R^3$  is  
 15 phenyl; the  $R^3$  phenyl is not substituted at the para position with phenyl;  
 when  $X$  is  $CY^1$  and  $Y^1$  is hydrogen;  $R^1$  is  $C(O)NH(CH_2)_nR^3$ ;  $n$  is 1;  $R^2$  is hydrogen; and  $R^3$  is phenyl; the  $R^3$  phenyl is not substituted at the para position with phenylmethoxy or 3-fluorophenoxy;  
 when  $X$  is  $CY^1$  and  $Y^1$  is hydrogen;  $R^1$  is  $C(O)NH(CH_2)_nR^3$ ;  $n$  is 1;  $R^2$  is hydrogen; and  $R^3$  is furanyl; the  $R^3$  furanyl is not substituted with benzyl, or 3-fluorophenyl methyl;  
 20 when  $X$  is  $CY^1$  and  $Y^1$  is hydrogen;  $R^1$  is  $C(O)NH(CH_2)_nR^3$ ;  $n$  is 1;  $R^2$  is hydrogen; and  $R^3$  is thienyl; the  $R^3$  thienyl is not substituted with phenoxy, 3-fluorophenoxy, or 3-chlorophenoxy; and  
 when  $X$  is  $CY^1$  and  $Y^1$  is hydrogen;  $R^1$  is  $C(O)NH(CH_2)_nR^3$ ;  $n$  is 1;  $R^2$  is hydrogen; and  $R^3$  is  $R^3$  phenyl; the phenyl is not substituted at the para position with  $SO_2R^4$  or  $SO_2NHR^4$ .  
 25 In ~~another one~~ embodiment of Formula (IB),  $R^1$  is  $NHC(O)NHR^3$ ; and  $R^2$  is hydrogen. In another embodiment of Formula (IB),  $R^1$  is  $CH_2NHC(O)R^3$ ; and  $R^2$  is hydrogen. In another embodiment of Formula (IB),  $R^1$  is hydrogen; and  $R^2$  is  $CH_2NHC(O)NHR^3$ . In  
 30 another embodiment of Formula (IB),  $R^1$  is hydrogen; and  $R^2$  is  $CH_2NHC(O)R^3$ . In one embodiment of Formula (IB),  $R^3$  is phenyl; wherein each  $R^3$  phenyl is substituted at the para position with one substituent independently selected from the group consisting of  $R^4$ ,  $OR^4$ ,  $C(O)R^4$ ,  $NHC(O)R^4$ ,  $NR^4C(O)R^4$ ,  $NHS(O)_2R^4$ ,  $NHC(O)OR^4$ , and  $C(O)NHR^4$ ; and wherein each  $R^3$  phenyl is optionally additionally substituted with one substituent independently  
 35 selected from the group consisting of F, Cl, Br and I. In one embodiment of Formula (IB),  $R^1$  is  $NHC(O)NHR^3$ ;  $R^2$  is hydrogen; and  $R^3$  is phenyl; wherein each  $R^3$  phenyl is substituted at the para position with one substituent independently selected from the group consisting of  $R^4$ ,  $OR^4$ ,  $C(O)R^4$ ,  $NHC(O)R^4$ ,  $NR^4C(O)R^4$ ,  $NHS(O)_2R^4$ ,  $NHC(O)OR^4$ , and  $C(O)NHR^4$ ; and wherein each  $R^3$  phenyl is optionally additionally substituted with one substituent  
 40 independently selected from the group consisting of F, Cl, Br and I. In one embodiment of Formula (IB),  $R^1$  is  $CH_2NHC(O)R^3$ ;  $R^2$  is hydrogen; and  $R^3$  is phenyl; wherein each  $R^3$  phenyl

5           4-[1-(3-cyano-5-fluorobenzoyl)piperidin-4-yl]-N-(imidazo[1,2-a]pyridin-7-  
ylmethyl)benzamide;  
          4-[1-(3-cyano-4-fluorobenzoyl)piperidin-4-yl]-N-(imidazo[1,2-a]pyridin-7-  
ylmethyl)benzamide;  
          N-(imidazo[1,2-a]pyridin-7-ylmethyl)-4-[1-(2-methoxy-6-methylbenzoyl)piperidin-4-  
10   yl]benzamide;  
          4-[1-(4-cyano-2,6-difluorobenzoyl)piperidin-4-yl]-N-(imidazo[1,2-a]pyridin-7-  
ylmethyl)benzamide; and pharmaceutically acceptable salts thereof.

          Another ~~embodiment~~ aspect pertains to a composition for treating inflammatory and  
tissue repair disorders; particularly rheumatoid arthritis, inflammatory bowel disease, asthma  
15   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 erythematosus, multiple sclerosis,  
psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease,  
stroke, athersclerosis, restenosis, diabetes, glomerulonephritis, cancer, particularly wherein  
20   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 telangiectasia, said composition  
comprising an excipient and a therapeutically effective amount of a compound of Formula  
25   (IB), or pharmaceutically acceptable salts thereof.

Another aspect pertains to a composition for use in 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  
30   damage; autoimmune diseases including systemic lupus erythematosus, 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  
35   infection and certain viral infections, including Acquired Immune Deficiency Syndrome  
(AIDS), adult respiratory distress syndrome, and ataxia telangiectasia, said composition  
comprising an excipient and a therapeutically effective amount of a compound of claim 1, or  
pharmaceutically acceptable salts thereof.

          Another ~~embodiment~~ aspect pertains to a method of treating inflammatory and tissue  
40   repair disorders; particularly rheumatoid arthritis, inflammatory bowel disease, asthma and  
COPD (chronic obstructive pulmonary disease), osteoarthritis, osteoporosis and fibrotic

5 diseases; dermatosis, including psoriasis, atopic dermatitis and ultra-violet induced skin  
damage; autoimmune diseases including systemic lupus erythematosus, multiple sclerosis,  
psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease,  
stroke, atherosclerosis, restenosis, diabetes, glomerulonephritis, cancer, particularly wherein  
10 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 telangiectasia in a patient, said  
method comprising administering to the patient a therapeutically effective amount of a  
compound of Formula (IB), or pharmaceutically acceptable salts thereof.

15 | Another ~~embodiment~~ aspect 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 erythematosus, 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 telangiectasia or spleen cancer in a patient, said method comprising administering to the patient therapeutically effective amount of the compound of Formula (IB), or pharmaceutically acceptable salts thereof; and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Another aspect pertains to the use of a therapeutically effective amount of a compound of claim 1, or pharmaceutically acceptable salts thereof in the manufacture of a medicament 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 erythematosus, 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 telangiectasia in a patient.

Another aspect pertains to the use of 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 in the manufacture of a medicament 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 erythematosus, 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

5        infection and certain viral infections, including Acquired Immune Deficiency  
Syndrome (AIDS), adult respiratory distress syndrome, and ataxia telangiectasia or spleen  
cancer in a patient

#### DETAILED DESCRIPTION OF THE INVENTION

10        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  
15        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  
20        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  
25        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  
30        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

5 | 10. A composition for use in 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  
erythematosus, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection,  
10 | 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 telangiectasia, said composition comprising an excipient and  
15 | a therapeutically effective amount of a compound of claim 1, or pharmaceutically acceptable salts  
thereof.

20 | 11. ~~A method~~ Use of a therapeutically effective amount of a compound of claim 1, or  
pharmaceutically acceptable salts thereof in the manufacture of a medicament 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 erythematosus, multiple sclerosis, psoriatic arthritis, ankylosing  
spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherosclerosis, restenosis, diabetes,  
25 | 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 telangiectasia in  
a patient, ~~said method comprising administering to the patient a therapeutically effective amount of a~~  
30 | ~~compound of claim 1, or pharmaceutically acceptable salts thereof.~~

35 | 12. ~~A method~~ Use of 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 in the manufacture of a medicament 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 erythematosus, multiple sclerosis, psoriatic  
arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherosclerosis,  
40 | 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

5 infections, including Acquired Immune Deficiency Syndrome (AIDS), adult respiratory  
distress syndrome, and ataxia telangiectasia or spleen cancer in a patient, ~~said method~~  
10 ~~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.~~

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