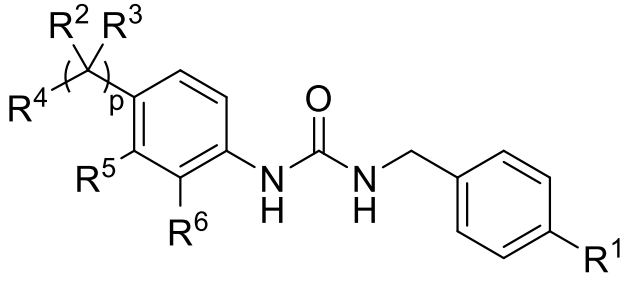
pathway or kynurenine pathway (ii) from NA in the Preiss-Handler pathway and (iii) from NAM, NR, and NMN in the salvage pathway (Verdin et al., *Science*. 2015, 350(6265):1208-13). Of these, the predominant NAD+ biosynthetic pathway involves the step of synthesis of nicotinamide mononucleotide (NMN)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

SUMMARY

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



(II),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is halo or methoxy;

R^6 is hydrogen or halo; and

p is 0;

R^4 is

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

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

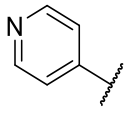
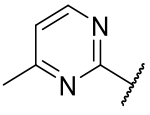
c) 3- to 6-membered heterocycloalkyl or heterocycloalkenyl substituted with one or more independently selected -$S(O)_2$-C_1-C_6alkyl substituents and optionally further substituted with one or more independently selected oxo or –C_1-C_6 alkyl substituents,

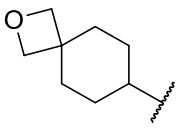
d) 5-membered heterocycloalkyl or heterocycloalkenyl comprising exactly two annular heteroatoms, one of which is a nitrogen atom and the other of which is an oxygen atom, wherein the 5-membered heterocycloalkyl or heterocycloalkenyl is optionally substituted with one or more independently selected oxo,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

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

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

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

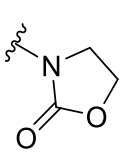
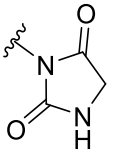
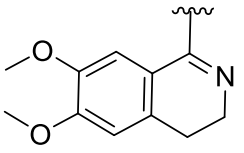
h) 6-membered heteroaryl comprising one or two annular heteroatoms and optionally substituted with one or more methyl substituents, wherein the 6-membered heteroaryl is other than  or , or

i) ;

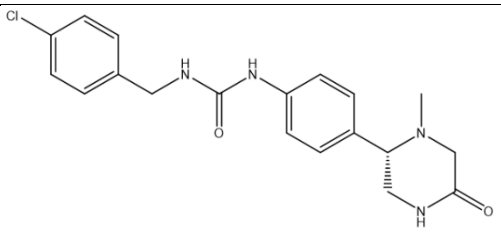
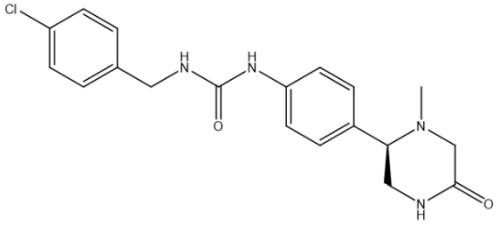
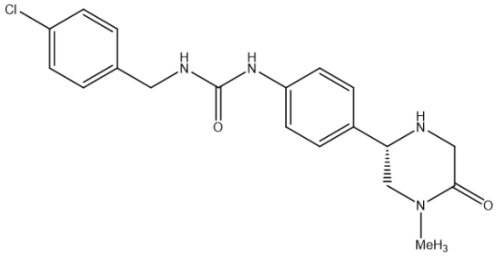
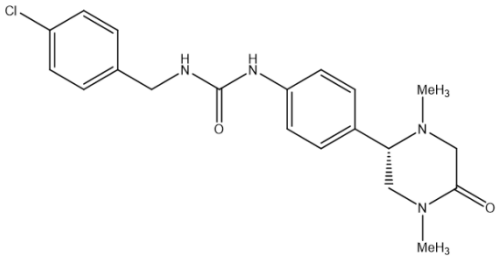
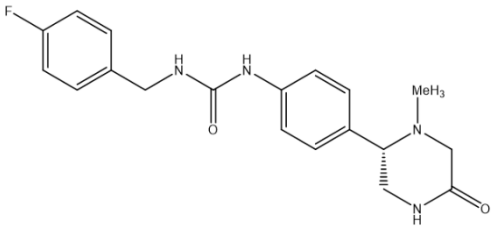
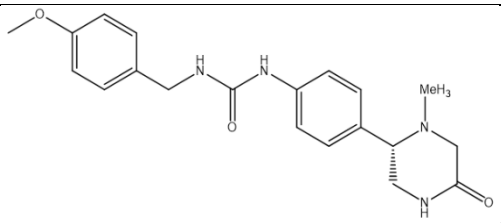
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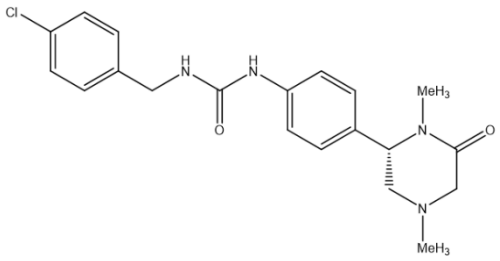
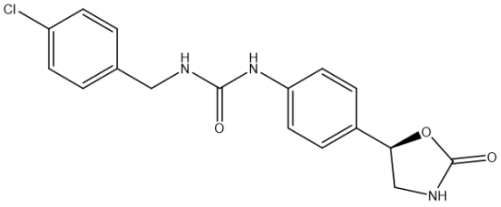
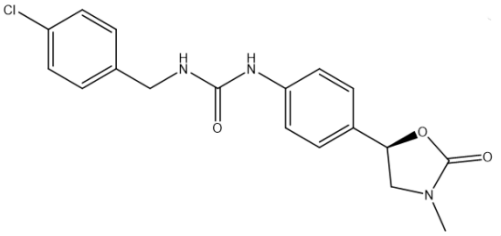
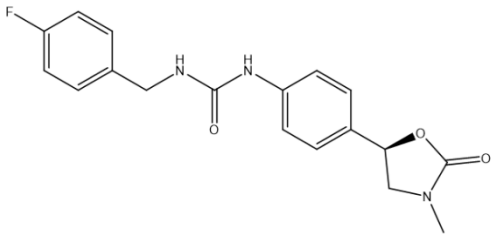
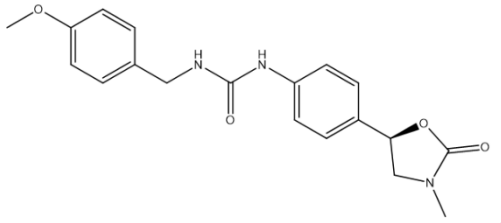
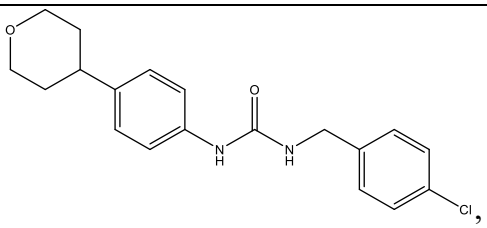
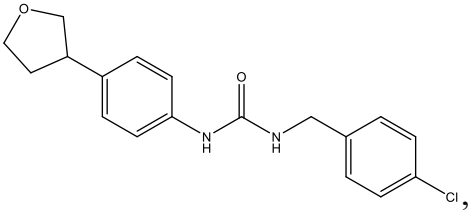
R^5 is hydrogen;

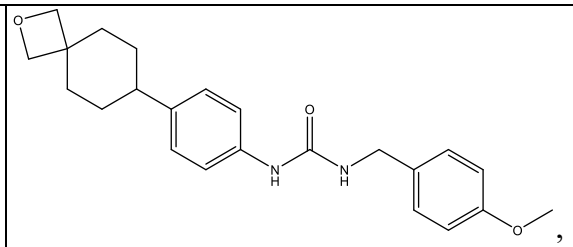
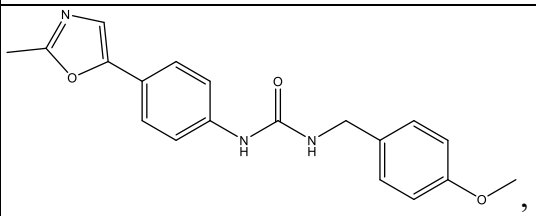
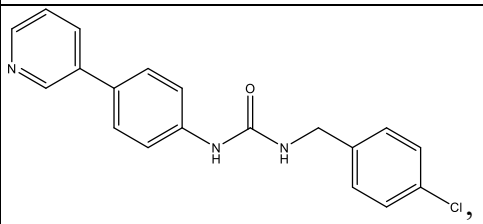
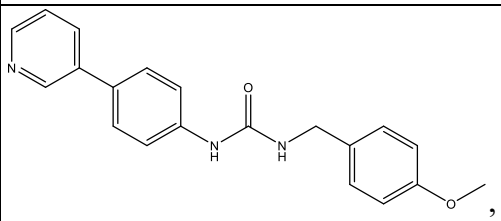
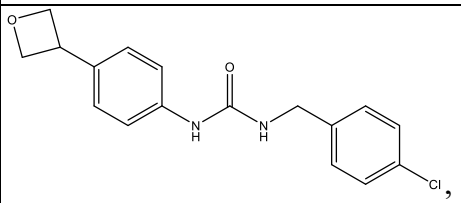
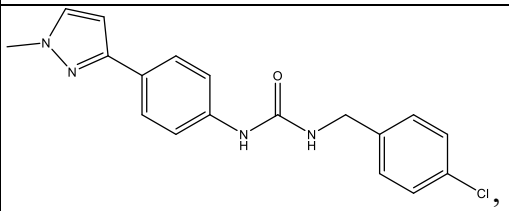
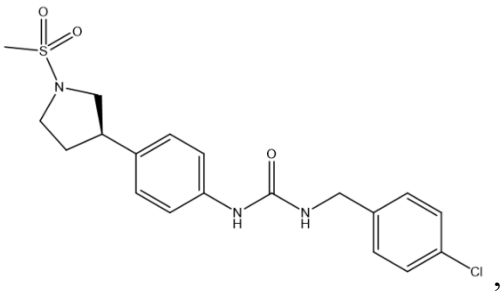
provided that for the compound of formula (II),

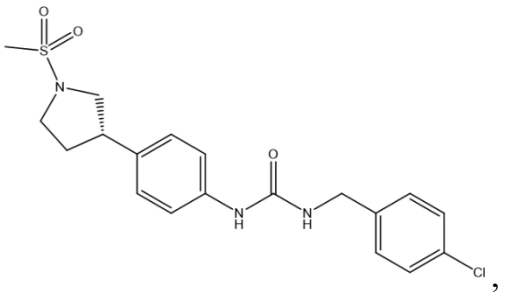
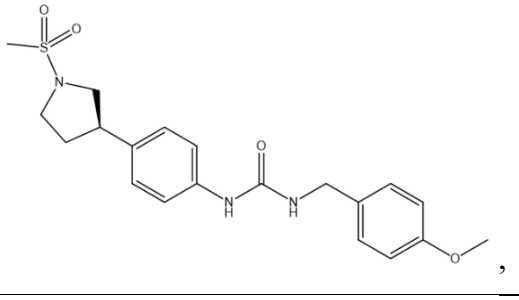
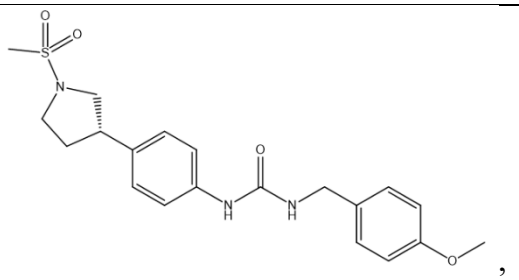
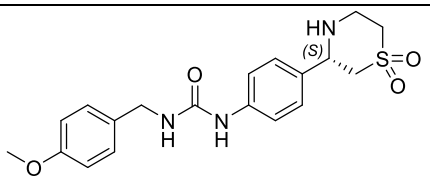
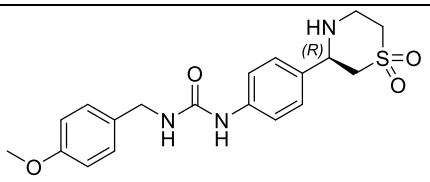
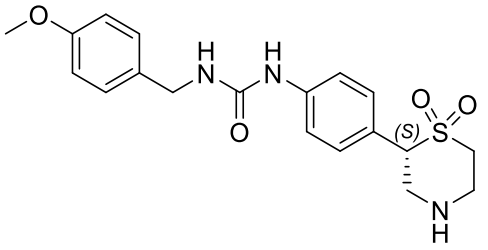
R^4 is other than 4-methylpiperazinyl, 4-phenylpiperazinyl, 4-pyridylpiperazinyl, 4-(furanylmethyl)piperazinyl, , , and .

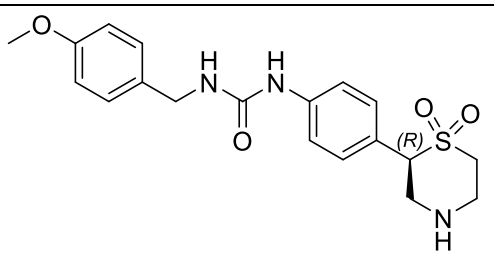
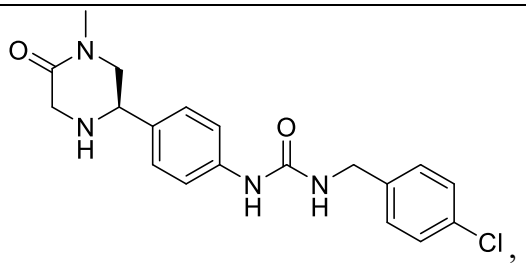
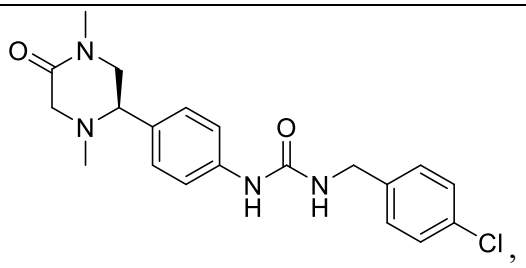
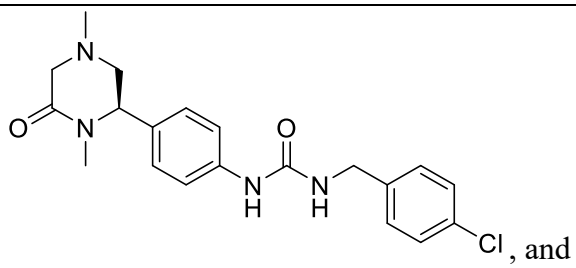
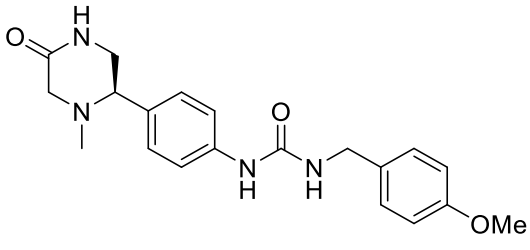
[0007b] In another aspect of the present disclosure, there is provided a compound selected from the group consisting of

Compound No.	Structure
392	 ,
393	 ,
396	 ,
397	 ,
398	 ,
399	 ,

400	 ,
403	 ,
407	 ,
412	 ,
413	 ,
435	 ,
440	 ,

460	
495	
503	
504	
507	
508	
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539	 ,
540	 ,
541	 ,
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or a pharmaceutically acceptable salt thereof.

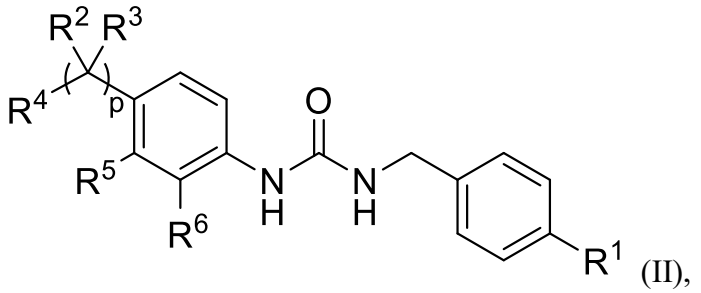
[0007c] In a further aspect of the present disclosure, there is provided a pharmaceutical

composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0007d] In another aspect of the present disclosure, there is provided use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a disease or condition mediated by NAMPT activity, wherein the disease or condition is selected from the group consisting of cancer, a hyperproliferative disease or condition, an inflammatory disease or condition, a metabolic disorder, a cardiac disease or condition, heart failure, heart failure with preserved ejection fraction, chemotherapy induced tissue damage, a renal disease, a metabolic disease, a neurological disease or injury, a neurodegenerative disorder or disease, diseases caused by impaired stem cell function, diseases caused by DNA damage, primary mitochondrial disorders, a muscle disease or muscle wasting disorder, obesity, atherosclerosis, insulin resistance, type 2 diabetes, cardiovascular disease, Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, depression, Down syndrome, neonatal nerve injury, aging, axonal degeneration, carpal tunnel syndrome, Guillain-Barre syndrome, nerve damage, polio (poliomyelitis), and spinal cord injury.

[0007e] In a further aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, for use in therapy.

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



(II),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is halo or methoxy;

R^6 is hydrogen or halo; and

p is 0 or 1, wherein

when p is 1,