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(54) Title: IL4I1 INHIBITORS AND METHODS OF USE

(I)

(57) Abstract: Described herein are compounds of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5, L, X and Y are as defined herein. The compounds of Formula (I) act as IL4I1 inhibitors and can be useful in preventing, treating or acting as a remedial agent for IL4I1-related diseases. Also provided herein are pharmaceutical compositions comprising the compounds of the invention, or their pharmaceutically acceptable salts, and a pharmaceutically acceptable carrier and methods of treatment with the compounds of the invention.

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TITLE OF THE INVENTION

IL4I1 INHIBITORS AND METHODS OF USE

FIELD OF THE INVENTION

The present invention is directed to IL4I1 inhibitors. Specifically, the IL4I1 inhibitors described herein can be useful in preventing, treating or acting as a remedial agent for IL4I1-related diseases.

BACKGROUND OF THE INVENTION

IL4I1 is a glycosylated protein that belongs to the L-amino-acid oxidase (LAAO) family of flavin adenine dinucleotide (FAD)-bound enzymes. IL4I1 is secreted from certain cells and performs oxidative deamination of phenylalanine into phenylpyruvate, liberating H_2O_2 and NH_3.

The highest production of IL4I1 is found in cells of myeloid origin (monocyte/macrophages and dendritic cells) of the human immune system, particularly after stimulation with inflammatory and T helper type 1 (Th1) stimuli. Accordingly, IL4I1 is strongly produced by dendritic cell and macrophage populations from chronic Th1 granulomas of sarcoidosis and tuberculosis, but not Th2 granulomas (schistosomiasis). Moreover, tumor-infiltrating macrophages from various histological types of tumors strongly produce IL4I1. Molinier-Frenkel V., Prévost-Blondel A. and Castellano F., The IL4I1 Enzyme: A New Player in the Immunosuppressive Tumor Microenvironment, *Cells*, 2019, *8*, 757-765.

The presence of IL4I1-producing cells in the tumor cell microenvironment restrains the anti-tumor immune response by directly limiting the proliferation and functionality of cytotoxic T cells and Th1 cells, or indirectly by facilitating the accumulation of Treg cells. Analyses of human tumor and normal tissue biopsies have identified increased expression of both IL4I1 mRNA and protein in tumor infiltrating myeloid cells. The Cancer Genome Atlas (TCGA) indicates that, among solid tumors, endometrial carcinoma contains the highest levels of IL4I1 mRNA expression, followed by serious ovarian and triple negative breast cancers. Phenylpyruvic acid, the product of phenylalanine oxidation by IL4I1, is elevated in endometrial and ovarian tumor samples relative to matched adjacent tissue from the same patients. Furthermore, accumulation of detectable phenylpyruvic acid in the tumor samples is dependent on the presence of IL4I1 itself.

Currently there are no specific inhibitors available against IL4I1. Some molecules have been shown to inhibit the related LAAOs found in snake venom, but they are generally non-selective and have little activity. Therefore, there is a need for specific inhibitors of IL4I1. More specifically there is a need for compounds that specifically inhibit IL4I1 and can be useful for the treatment of indications where IL4I1 is most expressed and/or active, including endometrial, ovarian and triple negative breast cancers.

BRIEF SUMMARY OF THE INVENTION

Compounds

Described herein are compounds of Formula I:

I

and pharmaceutically acceptable salts thereof, wherein are R^1, R^2, R^3, R^4, R^5 L, X and Y are described below.

The compounds described herein are IL4I1 inhibitors, which can be useful in the prevention, treatment or amelioration of IL4I1- related diseases.

Also described herein are methods of preventing, treating or ameliorating the symptoms of cancer comprising administering to a patient in need thereof a compound described herein, or a pharmaceutically acceptable salt thereof.

Also described are uses of a compound described herein, or a pharmaceutically acceptable salt thereof, to prevent, treat or ameliorate the conditions of cancer in a patient in need thereof.

Also described are pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Also described are pharmaceutical compositions comprising a compound described herein and a pharmaceutically acceptable carrier.

Also described herein are methods of preventing, treating or ameliorating the symptoms of cancer comprising administering to a patient in need thereof a compound described herein, or a pharmaceutically acceptable salt thereof, and another therapeutic agent.

Also described are uses of a compound described herein, or a pharmaceutically acceptable salt thereof, in combination with another therapeutic agent to prevent, treat or ameliorate the conditions of cancer in a patient in need thereof.

Also described are pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt thereof, another therapeutic agent and a pharmaceutically acceptable carrier.

Also described herein are pharmaceutical compositions comprising a compound described herein, another therapeutic agent, and a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE INVENTION

Described herein are compounds having a structural, Formula I:

I

or a pharmaceutically acceptable salt thereof, wherein,

R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl is unsubstituted or substituted with at least one substituent selected from the group consisting of oxo, -CN, -OH, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, phenyl, heteroaryl and C_3-C_6cycloalkyl and wherein the heteroaryl is unsubstituted or substituted with C_1-C_6alkoxy, or R^1, and the nitrogen to which R^1 is attached, is taken with R^4 and forms a nitrogen-containing ring;

R^2 is H, C_1-C_6alkyl or together with R^3 forms a bond;

R^3 is H, C_1-C_6alkyl or together with R^2 forms a bond;

R^4 is H, halogen, or C_1-C_6alkyl or R^4 is taken with R^1, and the nitrogen to which R^1 is attached, and forms a nitrogen-containing ring, or R^4 is taken with R^5 and forms a C_3-C_6cycloalkyl;

R^5 is H, halogen, or C_1-C_6alkyl, or R^5 is taken with R^4 and forms a C_3-C_6cycloalkyl;

L is a C_1-C_6alkylene or a C_3-C_6cycloalkylene linker;

X is phenyl, C_3-C_6cycloalkyl, or a nitrogen-containing ring, wherein the phenyl, C_3-C_6cycloalkyl or nitrogen-containing ring is unsubstituted or substituted with one or two substituents independently selected from the group consisting of halogen, -OH and oxo; and

Y is hydrogen, halogen, C_1-C_6alkoxy, phenyl, halogen-substituted phenyl, C^1-C^6alkyl-substituted phenyl, nitrogen-containing ring, CN-substituted phenyl, a halogen-substituted nitrogen-containing ring, or a haloC_1-C_6alkyl-substituted nitrogen containing ring.

In certain embodiments, described herein are compounds of Formula I:

I

wherein, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl is unsubstituted or substituted with one to three substituents independently selected independently from the group consisting of -CN, halogen, C_1-C_6alkyl, phenyl and C_3-C_6cycloalkyl;

R^2 is H, C_1-C_6alkyl or together with R^3 forms a bond;

R^3 is H, C_1-C_6alkyl or together with R^2 forms a bond;

R^4 is H, halogen, or C_1-C_6alkyl;

R^5 is H, halogen, or C_1-C_6alkyl;

L is a C_1-C_6alkylene or a C_3-C_6cycloalkylene linker;

X is phenyl, C_3-C_6cycloalkyl or a nitrogen-containing ring, wherein the phenyl, C_3-C_6cycloalkyl or nitrogen-containing ring is unsubstituted or substituted with at least one substituent selected from the group consisting of halogen and oxo; and

Y is hydrogen, halogen, C_1-C_6alkoxy, phenyl, halogen-substituted phenyl, nitrogen-containing ring, a halogen-substituted nitrogen-containing ring, or haloC_1-C_6alkyl-substituted nitrogen-containing ring.

With regards to the compounds described herein, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl is unsubstituted or substituted with at least one substituent selected from the group consisting of oxo, -CN, -OH, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, phenyl, heteroaryl and C_3-C_6cycloalkyl, wherein the heteroaryl is unsubstituted or substituted with C_1-C_6alkoxy, or R^1, and the nitrogen to which R^1 is attached, is taken with R^4 and forms a nitrogen-containing ring.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl is unsubstituted or substituted with at least one substituent selected from the group consisting of -CN, halogen, C_1-C_6alkyl, phenyl and C_3-C_6cycloalkyl.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl is unsubstituted. In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl is unsubstituted.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl is substituted with at least one substituent selected from the group consisting of oxo, -CN, -OH, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, phenyl, heteroaryl and C_3-C_6cycloalkyl, wherein the heteroaryl is unsubstituted or substituted with C_1-C_6alkoxy.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl is substituted with one to three substituents independently selected from the group consisting of oxo, -CN, -OH, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, phenyl, heteroaryl and C_3-C_6cycloalkyl, wherein the heteroaryl is unsubstituted or substituted with C_1-C_6alkoxy.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl is substituted with one substituent selected from the group consisting of oxo, -CN, -OH, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, phenyl, heteroaryl and C_3-C_6cycloalkyl, wherein the heteroaryl is unsubstituted or substituted with C_1-C_6alkoxy.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl is substituted with two substituents independently selected from the group consisting of oxo, -CN, -OH, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, phenyl, heteroaryl and C_3-C_6cycloalkyl, wherein the heteroaryl is unsubstituted or substituted with C_1-C_6alkoxy.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl is substituted with three substituents independently selected from the group consisting of oxo, -CN, -OH, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, phenyl, heteroaryl and C_3-C_6cycloalkyl, wherein the heteroaryl is unsubstituted or substituted with C_1-C_6alkoxy.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl is substituted.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl is substituted with one to three substituents.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl is substituted with one substituent.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl is substituted with two substituents.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl is substituted with three substituents.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl is substituted with at least one substituent selected from the group consisting of -CN, halogen, C_1-C_6alkyl, phenyl and C_3-C_6cycloalkyl.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl is substituted with a -CN. In certain embodiments, C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl is substituted with a halogen. Suitable halogens include, but are not limited to, fluorine, chlorine, bromine or iodine.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl is substituted with a C_1-C_6alkyl. Suitable alkyls include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, n-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl, and 1-ethyl-1-methylpropyl.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl is substituted with a phenyl.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl or heterocycloalkyl is substituted with a C_3-C_6cycloalkyl. Suitable cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In certain embodiments, R^1 is unsubstituted. In certain embodiments, R^1 is substituted with -CN, fluorine, methyl, phenyl or cyclopropyl.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl is substituted with an oxo group.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl is substituted with -CN.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl is substituted with a halogen. Suitable halogens include, but are not limited to, fluorine, chlorine, bromine or iodine.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl is substituted with C_1-C_6alkyl. Suitable alkyls include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, n-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl, and 1-ethyl-1-methylpropyl. In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl, wherein the C_1-C_6alkyl,

C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl is substituted with methyl.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl is substituted with C_1-C_6haloalkyl. Suitable haloalkyls include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl and trifluoromethyl.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl is substituted with phenyl.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl is substituted with a heteroaryl ring. In certain embodiments, the heteroaryl ring is a nitrogen-containing ring. In certain embodiments, the heteroaryl ring is pyridinyl. In certain embodiments, the heteroaryl is unsubstituted or substituted with C_1-C_6alkoxy.

In certain embodiments, R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl is substituted with C_3-C_6cycloalkyl. Suitable cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In certain embodiments, R^1 is C_1-C_6alkyl. Suitable alkyls include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, n-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl, and 1-ethyl-1-methylpropyl.

In certain embodiments, R^1 is isopropyl, tert-butyl or neopentyl. In certain embodiments, R^1 is isopropyl or tert-butyl. In certain embodiments, R^1 is isopropyl, tert-butyl or neopentyl, wherein

the isopropyl, tert-butyl or neopentyl is unsubstituted or substituted with fluorine. In certain embodiments, R^1 is isopropyl or tert-butyl, wherein the isopropyl or tert-butyl is unsubstituted or substituted with fluorine. In certain embodiments, R^1 is isopropyl. In certain embodiments, R^1 is tert-butyl. In certain embodiments, R^1 is neopentyl. In certain embodiments, R^1 is unsubstituted or substituted with fluorine.

In certain embodiments, R^1 is tert-butyl. In certain embodiments, R^1 is tert-butyl, substituted with heterocycle. In certain embodiments, R^1 is tert-butyl, substituted with pyridyl. In certain embodiments, R^1 is

or

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In certain embodiments, R^1 is C_3-C_6cycloalkyl. Suitable cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, bicyclo[1.1.1]pentan-1-yl, bicyclo[3.1.0] hexane and cyclohexyl. In certain embodiments, R^1 is selected from the group consisting of:

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and

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In certain embodiments, R^1 is

In certain embodiments, R^1 is C_1-C_6alkylC_3-C_6cycloalkyl. Suitable C_1-C_6alkylC_3-C_6cycloalkyl include, but are not limited to,

In certain embodiments, R^1 is aryl. Suitable aryls include, but are not limited to, phenyl and naphthyl. In certain embodiments, R^1 is phenyl.

In certain embodiments, R^1 is heteroaryl. Suitable heteroaryls include, but are not limited to, pyridyl (pyridinyl), oxazolyl, imidazolyl, triazolyl, furyl, triazinyl, thienyl, pyrimidyl, pyridazinyl, indolizinyl, cinnolinyl, phthalazinyl, quinazolinyl, naphthyridinyl, quinoxalinyl, purinyl, benzimidazolyl, quinolyl, and isoquinolyl.

In certain embodiments, R^1 is heterocycloalkyl. Suitable heterocycloalkyls include, but are not limited to, tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, dioxanyl, imidazolidinyl, 2,3-dihydrofuro(2,3-*b*)pyridyl, benzoxazinyl, benzoxazolinyl, 2-*H*-phthalazinyl, isoindolinyl, benzoxazepinyl, 5,6-dihydroimidazo[2,1-*b*]thiazolyl, tetrahydroquinolinyl, morpholinyl, tetrahydroisoquinolinyl, dihydroindolyl, and tetrahydropyran. The term also includes partially unsaturated monocyclic rings that are not aromatic, such as 2- or 4-pyridones attached

through the nitrogen or *N*-substituted-(1*H*, 3*H*)-pyrimidine-2,4-diones (*N*-substituted uracils). The term also includes bridged rings such as 5-azabicyclo[2.2.1]heptyl, 2,5-diazabicyclo[2.2.1]heptyl, 2-azabicyclo[2.2.1]heptyl, 7-azabicyclo[2.2.1]heptyl, 2,5-diazabicyclo[2.2.2]octyl, 2-azabicyclo[2.2.2]octyl, and 3-azabicyclo[3.2.2]nonyl, and azabicyclo[2.2.1]heptanyl. In particular embodiments, R^1 is tetrahydrofuranyl.

In certain embodiments, R^1 is .

In certain embodiments, R^1 is , , , , , , or , wherein R^1 is unsubstituted or substituted with -CN, fluorine, methyl, phenyl or cyclopropyl.

In certain embodiments, R^1 is C_1-C_6alkylOC_1-C_6alkyl. Suitable C_1-C_6alkylOC_1-C_6alkyls include, but are not limited to, .

In certain embodiments, R^1 is

In certain embodiments, R^1 is

, wherein R^1 is unsubstituted or substituted with one or two substituents independently selected from the group consisting of oxo, -CN, -OH, fluorine, methyl, phenyl, fluoromethyl, trifluoromethyl, pyridinyl, methoxypyridinyl and cyclopropyl.

In certain embodiments, R^1 and the nitrogen to which R^1 is attached is taken with R^4 and forms a nitrogen-containing ring. In certain embodiments, R^1 and the nitrogen to which R^1 is attached is taken with R^4 and forms a nitrogen-containing ring as shown below:

With regard to the compounds described herein, R^2 is H, C_1-C_6alkyl or together with R^3 forms a bond. In certain embodiments, R^2 is H.

In certain embodiments, R^2 is C_1-C_6alkyl. Suitable alkyls include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, n-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl, and 1-ethyl-1-methylpropyl. In particular embodiments, R^2 is methyl.

In certain embodiments, R^2 together with R^3 forms a bond.

With regard to the compounds described herein, R^3 is H, C_1-C_6alkyl or together with R^2 forms a bond. In certain embodiments, R^3 is H.

In certain embodiments, R^3 is C_1-C_6alkyl. Suitable alkyls include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, n-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl, and 1-ethyl-1-methylpropyl. In particular embodiments, R^3 is methyl.

In certain embodiments, R^3 together with R^2 forms a bond.

In certain embodiments, R^2 and R^3 are both hydrogen. In certain embodiments, R^2 is methyl. In certain embodiments, R^2 is methyl and R^3 is hydrogen. In certain embodiments, R^3 is methyl. In certain embodiments, R^3 is methyl and R^2 is hydrogen. In other embodiments, R^2 and R^3 form a bond as shown in Formula II:

II.

Concerning the compounds described herein, R^4 is H, halogen, or C_1-C_6alkyl. In certain embodiments, R^4 is H. In certain embodiments, R^4 is halogen. Suitable halogens include, but are not limited to, fluorine, bromine, iodine and chlorine. In certain embodiments, R^4 is C_1-C_6alkyl. Suitable alkyls include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, n-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl, and 1-ethyl-1-methylpropyl.

In certain embodiments, R^4 is taken with R^1 and the nitrogen to which R^1 is attached and forms a nitrogen-containing ring. In certain embodiments, R^4 is taken with R^1 and the nitrogen to which R^1 is attached and forms a nitrogen-containing ring as shown below:

In certain embodiments, R^4 is taken with R^5 and forms a C_3-C_6cycloalkyl. Suitable cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain embodiments, R^4 is taken with R^5 and forms a C_3-C_6cycloalkyl as shown below:

Concerning the compounds described herein, R^5 is H, halogen, or C_1-C_6alkyl. In certain embodiments, R^5 is H. In certain embodiments, R^5 is halogen. Suitable halogens include, but are not limited to, fluorine, bromine, iodine and chlorine. In certain embodiments, R^5 is C_1-C_6alkyl. Suitable alkyls include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, n-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl, and 1-ethyl-1-methylpropyl.

In certain embodiments, R^4 and R^5 are both hydrogen.

In certain embodiments, R^2, R^3, R^4 and R^5 are all hydrogen.

In certain embodiments, R^5 is taken with R^4 and forms a C_3-C_6cycloalkyl. Suitable cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain embodiments, R^4 is taken with R^5 and forms a C_3-C_6cycloalkyl as shown below:

With regard to the compounds described herein, L is a C_1-C_6alkylene or C_3-C_6cycloalkylene linker. In certain embodiments, L is a C_1-C_6alkylene linker. Suitable alkylene linkers include, but are not limited to, , , , , or .

In certain embodiments, L is . In certain embodiments, L is . In certain embodiments, L is . In certain embodiments, L is .

In certain embodiments, L is a C_3-C_6cycloalkylene linker. Suitable cycloalkylene linkers include, but are not limited to .

With regard to the compounds described herein, X is phenyl, C_3-C_6cycloalkyl or a nitrogen-containing ring, wherein the phenyl, C_3-C_6cycloalkyl or nitrogen-containing ring is unsubstituted or substituted with at least one substituent selected from the group consisting of halogen, -OH and oxo.

In certain embodiments, X is phenyl, C_3-C_6cycloalkyl or a nitrogen-containing ring, wherein the phenyl, C_3-C_6cycloalkyl or nitrogen-containing ring is unsubstituted.

In certain embodiments, X is phenyl, C_3-C_6cycloalkyl or a nitrogen-containing ring, wherein the phenyl, C_3-C_6cycloalkyl or nitrogen-containing ring is substituted with a substituent with -OH.

In certain embodiments, X is phenyl, C_3-C_6cycloalkyl or a nitrogen-containing ring, wherein the phenyl, C_3-C_6cycloalkyl or nitrogen-containing ring is unsubstituted or substituted with at least one substituent selected from the group consisting of halogen and oxo.

In certain embodiments, X is phenyl. In certain embodiments, X is unsubstituted phenyl. In certain embodiments, X is phenyl, wherein the phenyl is substituted with halogen. In certain embodiments, X is phenyl, wherein the phenyl is substituted with fluorine. In other embodiments, X is 2-fluorophenyl.

In certain embodiments, X is C_3-C_6cycloalkyl. Suitable cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, bicyclo[1.1.1]pentan-1-yl, bicyclo[3.1.0] hexane and cyclohexyl. In certain embodiments, X is

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In certain embodiments, X is C_3-C_6cycloalkyl, wherein the C_3-C_6cycloalkyl is unsubstituted. In certain embodiments, X is C_3-C_6cycloalkyl, wherein the C_3-C_6cycloalkyl is substituted. In certain embodiments, X is C_3-C_6cycloalkyl, wherein the C_3-C_6cycloalkyl is substituted with one or two substituents independently selected from the group consisting of halogen, -OH and oxo. In certain embodiments, X is C_3-C_6cycloalkyl, wherein the C_3-C_6cycloalkyl is substituted with two fluorines. In certain embodiments, X is

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In certain embodiments, X is a nitrogen-containing ring. In certain embodiments, X is a monocyclic nitrogen-containing ring. In certain embodiments, X is a bicyclic nitrogen-containing ring. In certain embodiments, X is a nitrogen-containing heteroaryl. Suitable heteroaryls include,

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In certain embodiments, X is a bicyclic nitrogen-containing heteroaryl. In certain embodiments, X is a monocyclic nitrogen-containing heteroaryl.

In certain embodiments, X is a nitrogen-containing heterocycloalkyl. Suitable heterocycloalkyls include

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and

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In certain embodiments, X is a bicyclic nitrogen-containing heterocycloalkyl. In certain embodiments, X is a monocyclic nitrogen-containing heterocycloalkyl. In certain embodiments, X is a partially unsaturated nitrogen-containing ring. In certain embodiments, X is a bicyclic partially unsaturated nitrogen-containing ring. In certain embodiments, X is a monocyclic partially unsaturated nitrogen-containing ring.

In certain embodiments, X is an unsubstituted nitrogen-containing ring. In certain embodiments, X is a substituted nitrogen-containing ring. In certain embodiments, X is a nitrogen-containing ring, wherein the nitrogen-containing ring is substituted with halogen. In certain embodiments, X is a nitrogen-containing ring, wherein the nitrogen-containing ring is substituted with fluorine. In certain embodiments, X is a nitrogen-containing ring, wherein the nitrogen-containing ring is substituted with an oxo group.

In certain embodiments, X is pyrazolyl, thiazolyl, isoxazolyl, thiadiazolyl, pyridine-3-yl, 3-fluoro-pyridin-2-yl, pyridine-1-oxide, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, 2-oxo-dihydroquinolinyl, 1-oxo-tetrahdyroisoquinolinyl, 1-oxo-dihydroisoquinolinyl, 2-cinnolinyl or 7-chlorocinnolinyl.

In certain embodiments, X is a nitrogen-containing ring, wherein the nitrogen containing ring is selected from the group consisting of

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In certain embodiments, the nitrogen-containing ring is selected from the group consisting of

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In certain embodiments, the nitrogen-containing ring is selected from the group consisting of

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wherein X is unsubstituted or substituted with one or two substituents independently selected from the group consisting of fluorine and an oxo group.

In certain embodiments X is a nitrogen-containing ring, wherein the nitrogen containing ring is , wherein X is substituted with fluorine.

In certain embodiments X is a nitrogen-containing ring, wherein the nitrogen containing ring is , , or , wherein X is substituted with an oxo group.

In certain embodiments X is or . Such compounds can exist as, or .

With regard to the compounds described herein, Y is hydrogen, halogen, C_1-C_6alkoxy, phenyl, a halogen-substituted phenyl, C_1-C_6alkyl-substituted phenyl, a nitrogen-containing ring, -

CN-substituted phenyl, a halogen-substituted nitrogen-containing ring, or a haloC_1-C_6alkyl-substituted nitrogen containing ring.

In certain embodiments, Y is hydrogen, halogen, C_1-C_6alkoxy, phenyl, a halogen-substituted phenyl, a nitrogen-containing ring, a halogen-substituted nitrogen-containing ring or a haloC_1-C_6alkyl-substituted nitrogen-containing ring.

In certain embodiments, Y is hydrogen. In certain embodiments, Y is halogen. Suitable halogens include, but are not limited to, chlorine, fluorine, bromine and iodine. In certain embodiments, Y is fluorine. In certain embodiments, Y is C_1-C_6alkoxy. Suitable alkoxys include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. In certain embodiments, Y is ethoxy or propoxy.

In certain embodiments, Y is phenyl. In certain embodiments, Y is a halogen-substituted phenyl. Suitable halogens include, but are not limited to, chlorine, fluorine, bromine and iodine. In certain embodiments, Y is phenyl substituted with fluorine. In certain embodiments, Y is phenyl substituted with one or two substituents independently selected from fluorine and bromine.

In certain embodiments, Y is a CN-substituted phenyl. In certain embodiments, Y is phenyl substituted with -CN.

In certain embodiments, Y is a C_1-C_6alkyl-substituted phenyl. In certain embodiments, Y is phenyl substituted with C_1-C_6alkyl. Suitable alkyls include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, n-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl, and 1-ethyl-1-methylpropyl. In certain embodiments, Y is phenyl substituted with methyl.

In certain embodiments, Y is a nitrogen-containing ring. In certain embodiments, Y is a halogen-substituted nitrogen-containing ring. In certain embodiments, Y is a haloC_1-C_6alkyl-substituted nitrogen-containing ring.

In certain embodiments, Y is phenyl, wherein the phenyl is substituted with one to two fluorines. In certain embodiments, Y is C_1-C_6alkoxy, wherein the C_1-C_6alkoxy is ethoxy, propoxy or butoxy. In certain embodiments, Y is C_1-C_6alkoxy, wherein the C_1-C_6alkoxy is propoxy.

In certain embodiments, Y is a monocyclic nitrogen-containing ring. Examples of a monocyclic nitrogen containing ring include , , , , , , , , , , , , , , and .

In certain embodiments, Y is a bicyclic nitrogen-containing ring. Examples of a bicyclic nitrogen-containing ring include . In certain embodiments, Y is a nitrogen-containing heteroaryl. Examples of a nitrogen-containing heteroaryl include, , ,

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and

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In certain embodiments, Y is nitrogen-containing heterocycloalkyl. Examples of suitable nitrogen-containing heterocycloalkyls include,
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and

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In certain embodiments, Y is a saturated nitrogen-containing ring. In certain embodiments, Y is a nitrogen-containing ring, wherein the nitrogen containing ring is selected from the group consisting of

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and

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In certain embodiments, Y is azetidinyl, azabicyclo[3.1.0]hexanyl, pyrrolindinyl, piperidinyl, morpholino, imidazolyl, pyrazolyl, triazolyl, thiazolyl, oxazolyl or pyridine-3-yl. In certain embodiments, Y is a halogen-substituted nitrogen-containing ring, wherein the halogen-substituted nitrogen containing ring is selected from the group consisting of

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and

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In certain embodiments, Y is a haloC_1-C_6alkyl-substituted nitrogen-containing ring, wherein the haloC_1-C_6alkyl-substituted nitrogen-containing ring is

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In certain embodiments, Y is hydrogen only when X is

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or

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Also, described herein are the following compounds:

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or a pharmaceutically acceptable salt thereof.

Definitions

The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding and except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names, common names, and chemical structures may be used interchangeably to describe the same structure. If a chemical compound is referred to using both a chemical structure and a chemical name and an ambiguity exists between the structure and the name, the structure predominates. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence, the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "hydroxyalkyl," "haloalkyl," "-O-alkyl," etc...

As used herein “H” and hydrogen are used interchangeably.

The term "alkylene," or “alkylenyl” by itself or as part of another substituent means a divalent straight or branched chain hydrocarbon radical having the stated number of carbon atoms. For example, -(C_1-C_5) alkylenyl, would include, *e.g.*, -CH_2-, -CH(CH3)-, -CH2-CH(CH3)-, -CH(CH3)-CH2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, -$CH_2CH(CH_3)CH_2$- or -$CH_2CH_2CH_2CH_2CH_2$-.

The term “halogen” includes fluorine, chlorine, bromine and iodine.

The term “C_1-C_6alkyl” encompasses straight alkyl having a carbon number of 1 to 6 and branched alkyl having a carbon number of 3 to 6. Specific examples thereof include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, n-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl, 1-ethyl-1-methylpropyl, and the like.

The term "C_3-C_6cycloalkyl" encompasses bridged, saturated or unsaturated cycloalkyl groups having 3 to 6 carbons. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl or bicyclo[1.1.1pentanyl, bicyclo[3.1.0]hexanyl.

The term "C_3-C_{10}cycloalkyl" encompasses bridged, saturated or unsaturated cycloalkyl groups having 3 to 10 carbons. "Cycloalkyl" also includes non-aromatic rings and monocyclic, non-aromatic rings fused to a saturated cycloalkyl group and aromatic rings fused to a saturated cycloalkyl group. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronaphthyl, decahydronaphthyl, indanyl and the like. Examples described by structure include: , and .

The term “halogen-substituted phenyl” or phenyl substituted with one or more halogens refers to a phenyl ring with the hydrogen atoms thereof being partially or completely substituted with halogen, examples thereof including fluorophenyl, difluorophenyl, or trifluorophenthyl.

The term “heteroaryl" means an aromatic ring that contains at least one ring heteroatom selected from O, S and N. Examples of heteroaryl groups include pyridyl (pyridinyl), oxazolyl, imidazolyl, triazolyl, furyl, triazinyl, thienyl, pyrimidyl, pyridazinyl, indolizinyl, cinnolinyl, phthalazinyl, quinazolinyl, naphthyridinyl, quinoxalinyl, purinyl, benzimidazolyl, quinolyl, isoquinolyl, and the like.

The term “heterocycloalkyl” means mono- or bicyclic or bridged partially unsaturated or saturated rings containing at least one heteroatom selected from N, S and O, each of said rings having from 3 to 10 atoms in which the point of attachment may be carbon or nitrogen. Examples include tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, dioxanyl, imidazolidinyl, 2,3-dihydrofuro(2,3-*b*)pyridyl, benzoxazinyl, benzoxazolinyl, 2-*H*-phthalazinyl, isoindolinyl, benzoxazepinyl, 5,6-dihydroimidazo[2,1-*b*]thiazolyl, tetrahydroquinolinyl, morpholinyl, tetrahydroisoquinolinyl, dihydroindolyl, and tetrahydropyran. The term also includes partially unsaturated monocyclic rings that are not aromatic, such as 2- or 4-pyridones attached through the nitrogen or *N*-substituted-(1*H*, 3*H*)-pyrimidine-2,4-diones (*N*-substituted uracils). The term also includes bridged rings such as 5-azabicyclo[2.2.1]heptyl, 2,5-diazabicyclo[2.2.1]heptyl, 2-azabicyclo[2.2.1]heptyl, 7-azabicyclo[2.2.1]heptyl, 2,5-diazabicyclo[2.2.2]octyl, 2-azabicyclo[2.2.2]octyl, and 3-azabicyclo[3.2.2]nonyl, and azabicyclo[2.2.1]heptanyl. Examples described by structure include:

The term “nitrogen-containing ring” means mono- or bicyclic or bridged saturated, unsaturated or aromatic ring containing at least one nitrogen, possible 1, 2, 3 or 4 nitrogens, each of said ring having from 5 to 11 atoms in which the point of attachment may be carbon or nitrogen. Additionally, the nitrogen-containing ring can contain other heteroatoms such as O or S.

The term “alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts of basic compounds encompassed within the term "pharmaceutically acceptable salt" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting

the free base with a suitable organic or inorganic acid. Representative salts of basic compounds of the present invention include, but are not limited to, the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide and valerate. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof include, but are not limited to, salts derived from inorganic bases including aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, mangamous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, cyclic amines, and basic ion-exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidinyl, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidinyl, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

The term “patient” refers to a mammalian patient, including a human, canine, feline, bovine, or porcine patient, preferably a human patient, receiving or about to receive medical treatment. A patient “in need of treatment” is an individual diagnosed with, suspected of having, or predisposed to a disease or disorder in which a compound or composition of the invention is intended to treat or ameliorate (e.g. an IL4I1-related diseases such as cancer), or a patient for whom prevention of such a disorder is desired.

"Treat" or "treatment" means to administer an agent, such as a composition containing any of the compounds described herein, internally or externally to a subject or patient having one or more

disease symptoms, or being suspected of having a disease, for which the agent has therapeutic activity. Typically, the agent is administered in an amount effective to alleviate one or more disease symptoms in the treated subject or population, whether by inducing the regression of or inhibiting, delaying or slowing the progression of such symptom(s) by any clinically measurable degree. The amount of an agent that is effective to alleviate any particular disease symptom may vary according to factors such as the disease state, age, and weight of the patient, and the ability of the drug to elicit a desired response in the subject. Whether a disease symptom has been alleviated can be assessed by any clinical measurement typically used by physicians or other skilled healthcare providers to assess the severity or progression status of that symptom. The term further includes a postponement of development of the symptoms associated with a disorder and/or a reduction in the severity of the symptoms of such disorder. The terms further include ameliorating existing uncontrolled or unwanted symptoms, preventing additional symptoms, and ameliorating or preventing the underlying causes of such symptoms. Thus, the terms denote that a beneficial result has been conferred on a vertebrate subject with a disorder, disease or symptom, or with the potential to develop such a disorder, disease or symptom.

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates, racemic mixtures, single enantiomers, diastereomeric mixtures, and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of these compounds.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein contain substituted cycloalkanes having cis-and trans-isomers, and unless specified otherwise, are meant to include both cis- and trans- geometric isomers.

The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the X-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration. If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be

carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

It will be understood that the present invention is meant to include the pharmaceutically acceptable salts, and also salts that are not pharmaceutically acceptable, of the compounds described herein, when they are used as precursors to the free compounds or their pharmaceutically acceptable salts or in other synthetic manipulations.

Solvates, and in particular, the hydrates of the compounds of the structural formulas described herein are included in the present invention as well.

Some of the compounds described herein may exist as tautomers, which have different points of attachment of hydrogen accompanied by one or more double bond shifts. For example, a ketone and its enol form are keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of the present invention.

In the compounds described herein, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of the formulas described herein. For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically enriched compounds can be

prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically enriched reagents or Intermediates.

It should be noted that chemically unstable compounds are excluded from the embodiments contained herein.

Methods of Treatment

Also encompassed by the present invention are methods of preventing, treating or ameliorating IL4I1-related diseases. The compounds described herein can be effective in preventing, treating or ameliorating various IL4I1-related diseases, such as cancer. Described herein are methods for treatment of cancer displaying IL4I1-expressing cells in a patient comprising administration of a compound of the invention, or a pharmaceutical salt thereof, to the patient. Described herein are methods for prevention of cancer displaying IL4I1-expressing cells in a patient comprising administration of a compound of the invention, or a pharmaceutical salt thereof, to the patient. Described herein are methods for ameliorating the symptoms or clinical effects of cancer displaying IL4I1-expressing cells in a patient comprising administration of a compound of the invention, or a pharmaceutical salt thereof, to the patient.

In one embodiment described herein, the cancer to be treated is selected from the group consisting of cancers displaying IL4I1-expressing cells and lymphomas displaying IL4I1-expressing cells. In certain embodiment, the cancers to be treated are solid tumors. In certain embodiments, the cancers to be treated are selected from carcinomas, sarcomas, mesotheliomas, blastomas and germ cell tumors. In another particular embodiment, the cancer to be treated is a cancer displaying IL4I1-expressing cells selected from the group consisting of mesotheliomas, non-small-cell lung carcinomas, colon carcinoma, breast carcinoma, thyroid carcinoma, testicular germ cell tumors and ovarian carcinoma.

In another specific embodiment, the cancer to be treated is a lymphoma displaying IL4I1-expressing cells such as a B- cell lymphoma displaying IL4I1-expressing cells.

In certain embodiments, the cancer to be treated is a cancer displaying IL4I1-expressing cells selected from the group consisting of PMBL (Primary Mediastinal large B-cell Lymphoma), classical Hodgkin lymphomas (cHL), NLPHL (Nodular lymphocyte predominant Hodgkin's lymphoma), non-mediastinal Diffuse Large B-Cell Lymphoma (DLBCL) and SLL/CLL (Small

Lymphocytic Lymphoma / Chronic Lymphocytic Leukemia). In another specific embodiment, the cancer to be treated is a lymphoma displaying IL4I1-expressing cells.

In one embodiment described herein, the cancer to be prevented is selected from the group consisting of cancers displaying IL4I1-expressing cells and lymphomas displaying IL4I1-expressing cells. In a certain embodiment, the cancer to be prevented is a solid tumor. In certain embodiments, the cancer to be prevented is selected from carcinomas, sarcomas, mesotheliomas, blastomas and germ cell tumors. In another particular embodiment, the cancer to be prevented is a cancer displaying IL4I1-expressing cells selected from the group consisting of mesotheliomas, non-small-cell lung carcinomas, colon carcinoma, breast carcinoma, thyroid carcinoma, testicular germ cell tumors and ovarian carcinoma.

In another specific embodiment, the cancer to be prevented is a lymphoma displaying IL4I1-expressing cells such as a B- cell lymphoma displaying IL4I1-expressing cells.

In certain embodiments, the cancer to be prevented is a cancer displaying IL4I1-expressing cells selected from the group consisting of PMBL, cHL, NLPHL, DLBCL and SLL/CLL. In another specific embodiment, the cancer to be treated is a lymphoma displaying IL4I1-expressing cells.

In one embodiment described herein, the cancer to be ameliorated is selected from the group consisting of cancers displaying IL4I1-expressing cells and lymphomas displaying IL4I1-expressing cells. In a certain embodiment, the cancer to be ameliorated is a solid tumor. In certain embodiments, the cancer to be ameliorated is selected from carcinomas, sarcomas, mesotheliomas, blastomas and germ cell tumors. In another particular embodiment, the cancer to be ameliorated is a cancer displaying IL4I1-expressing cells selected from the group consisting of mesotheliomas, non-small-cell lung carcinomas, colon carcinoma, breast carcinoma, thyroid carcinoma, testicular germ cell tumors and ovarian carcinoma.

In another specific embodiment, the cancer to be ameliorated is a lymphoma displaying IL4I1-expressing cells such as a B- cell lymphoma displaying IL4I1-expressing cells.

In certain embodiments, the cancer to be ameliorated is a cancer displaying IL4I1-expressing cells selected from the group consisting of PMBL, cHL, NLPHL, DLBCL and SLL/CLL. In another specific embodiment, the cancer to be treated is a lymphoma displaying IL4I1-expressing cells.

Pharmaceutical Compositions

Compounds described herein may be administered orally or parenterally. As formulated into a dosage form suitable for administration, the compounds described herein can be used as a pharmaceutical composition for the prevention, treatment, or remedy of the above diseases.

Accordingly, the invention relates to pharmaceutical compositions comprising a therapeutically effective amount of a compound of the invention (i.e. a compound of Formula I or II, or any IL4i1 inhibitor compound described herein), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. As used herein, a “therapeutically effective amount” is an amount sufficient to product the desired clinical outcome, e.g. treatment or prevention of cancer displaying Il4i1-expressing cells or amelioration of the clinical effects or presentation thereof. Such a therapeutically effective amount may be contained in a single dosage form (e.g. one tablet or injection) or split into more than one of the dosage form (e.g. more than one tablet or injection, which together contain a therapeutically effective amount).

In clinical use of the compounds described herein, usually, the compound is formulated into various preparations together with pharmaceutically acceptable additives according to the dosage form and may then be administered. By "pharmaceutically acceptable" it is meant the additive, carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. As such, various additives ordinarily used in the field of pharmaceutical preparations are usable. Specific examples thereof include gelatin, lactose, sucrose, titanium oxide, starch, crystalline cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, corn starch, microcrystalline wax, white petrolatum, magnesium metasilicate aluminate, anhydrous calcium phosphate, citric acid, trisodium citrate, hydroxypropyl cellulose, sorbitol, sorbitan fatty acid ester, polysorbate, sucrose fatty acid ester, polyoxymethylene, hardened castor oil, polyvinylpyrrolidone, magnesium stearate, light silicic acid anhydride, talc, vegetable oil, benzyl alcohol, gum arabic, propylene glycol, polyalkylene glycol, cyclodextrin, hydroxypropyl cyclodextrin, and the like.

Preparations to be formed with those additives include, for example, solid preparations such as tablets, capsules, granules, powders and suppositories; and liquid preparations such as syrups, elixirs and injections. These may be formulated according to conventional methods known in the field of pharmaceutical preparations. The liquid preparations may also be in such a form that may

be dissolved or suspended in water or in any other suitable medium in their use. Especially for injections, if desired, the preparations may be dissolved or suspended in physiological saline or glucose liquid, and a buffer or a preservative may be optionally added thereto.

The pharmaceutical compositions may contain the compound of the invention in an amount of from 1 to 99.9 % by weight, preferably from 1 to 60 % by weight of the composition. The compositions may further contain any other therapeutically-effective compounds.

In case where the compounds of the invention are used for prevention or treatment for the above-mentioned diseases, the dose and the dosing frequency may be varied, depending on the sex, the age, the body weight and the disease condition of the patient and on the type and the range of the intended remedial effect. In general, when orally administered, the dose may be from 0.001 to 50 mg/kg of body weight/day, and it may be administered at a time or in several times. In specific embodiments, the dose is from about 0.01 to about 25 mg/kg/day, in particular embodiments, from about 0.05 to about 10 mg/kg/day, or from about 0.001 to about 50 mg/kg/day. For oral administration, the compositions are preferably provided in the form of tablets or capsules containing from 0.01 mg to 1,000 mg. In specific embodiments, the dose is 0.01, 0.05, 0.1, 0.2, 0.5, 1.0, 2.5, 5, 10, 15, 20, 25, 30, 40, 50, 75, 100, 125, 150, 175, 200, 225, 250, 500, 750, 850 or 1,000 milligrams of a compound described herein. This dosage regimen may be adjusted to provide the optimal therapeutic response.

Combination Therapy

The compounds of the present invention are further useful in methods for the prevention or treatment of the aforementioned diseases, disorders and conditions in combination with other therapeutic agents.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment, prevention, suppression or amelioration of diseases or conditions for which compounds described herein or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered in an amount commonly used therefore, contemporaneously or sequentially with a compound described herein or a pharmaceutically acceptable salt thereof. When a compound described herein is used contemporaneously with one or more other drugs, the pharmaceutical composition may in specific embodiments contain such other drugs and the compound described herein or its

pharmaceutically acceptable salt in unit dosage form. However, the combination therapy may also include therapies in which the compound described herein or its pharmaceutically acceptable salt and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound described herein or a pharmaceutically acceptable salt thereof.

Examples of other active ingredients that may be administered in combination with a compound of any of the Formulas described herein (e.g. Formula I and II) or a pharmaceutically acceptable salt thereof and either administered separately or in the same pharmaceutical composition, include, but are not limited to pain relieving agents, anti-angiogenic agents, anti-neoplastic agents, anti-diabetic agents, anti-infective agents, or gastrointestinal agents, or combinations thereof.

Suitable compounds that may be used in combination with a compound according to the present invention include without limitation sildenafil, vardenafil, tadalafil and alprostadil, epoprostenol, iloprost, bosentan, amlodipine, diltiazem, nifedipine, ambrisentan and warfarin, fluticasone, budesonide, mometasone, flunisolide, beclomethasone, montelukast, zafirlukast, zileuton, salmeterol, formoterol, theophylline, albuterol, levalbuterol, pirbuterol, ipratropium, prednisone, methylprednisolone, omalizumab, corticosteroid and cromolyn, atorvastatin, lovastatin, simvastatin, pravastatin, fluvastatin, rosuvastatin, gemfibrozil, fenofibrate, nicotinic acid, and clopidogrel and pharmaceutically acceptable salts thereof.

Additionally, a compound of any of the Formulas disclosed herein (e.g. Formula I and II) may be used in combination with one or more other active agents, including but not limited to, other anti-cancer agents that are used in the prevention, treatment, control, amelioration, or reduction of risk of a particular disease or condition (e.g., cell proliferation disorders). In one embodiment, a compound disclosed herein is combined with one or more other anti-cancer agents for use in the prevention, treatment, control amelioration, or reduction of risk of a particular disease or condition for which the compounds disclosed herein are useful. Such other active agents may be administered,

by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention.

In one embodiment, the other active agent is selected from the group consisting of vascular endothelial growth factor (VEGF) receptor inhibitors, topoisomerase II inhibitors, smoothen inhibitors, alkylating agents, anti-tumor antibiotics, anti-metabolites, retinoids, and immunomodulatory agents including but not limited to anti-cancer vaccines, CTLA-4, LAG-3 and PD-1 antagonists.

PD-1 is recognized as having an important role in immune regulation and the maintenance of peripheral tolerance. PD-1 is moderately expressed on naive T-cells, B-cells and NKT-cells and up-regulated by T-cell and B-cell receptor signaling on lymphocytes, monocytes and myeloid cells (Sharpe et al., Nature Immunology (2007); 8:239-245).

Two known ligands for PD-1, PD-L1 (B7-H1) and PD-L2 (B7-DC) are expressed in human cancers arising in various tissues. In large sample sets of, for example, ovarian, renal, colorectal, pancreatic, and liver cancers, and in melanoma, it was shown that PD-L1 expression correlated with poor prognosis and reduced overall survival irrespective of subsequent treatment. (Dong et al., Nat Med. 8(8):793-800 (2002); Yang et al., Invest Ophthamol Vis Sci. 49: 2518-2525 (2008); Ghebeh et al., Neoplasia 8:190-198 (2006); Hamanishi et al., Proc. Natl. Acad. Sci. USA 104: 3360-3365 (2007); Thompson et al., Cancer 5: 206-211 (2006) ; Nomi et al., Clin. Cancer Research 13:2151-2157 (2007); Ohigashi et al., Clin. Cancer Research 11: 2947-2953; Inman et al., Cancer 109: 1499-1505 (2007); Shimauchi et al., Int. J. Cancer 121:2585-2590 (2007); Gao et al., Clin. Cancer Research 15: 971-979 (2009); Nakanishi J., Cancer Immunol Immunother. 56: 1173- 1182 (2007); and Hino et al., Cancer 00: 1-9 (2010)).

Similarly, PD-1 expression on tumor infiltrating lymphocytes was found to mark dysfunctional T-cells in breast cancer and melanoma (Ghebeh et al., BMC Cancer. 2008 8:5714-15 (2008); and Ahmadzadeh et al., Blood 114: 1537-1544 (2009)) and to correlate with poor prognosis in renal cancer (Thompson et al., Clinical Cancer Research 15: 1757-1761(2007)). Thus, it has been proposed that PD-L1 expressing tumor cells interact with PD-1 expressing T-cells to attenuate T-cell activation and to evade immune surveillance, thereby contributing to an impaired immune response against the tumor.

Immune checkpoint therapies targeting the PD-1 axis have resulted in groundbreaking improvements in clinical response in multiple human cancers (Brahmer, et al., N Engl J Med 2012, 366: 2455-65; Garon et al., N Engl J Med 2015, 372: 2018-28; Hamid et al., N Engl J Med 2013, 369: 134-44; Robert et al., Lancet 2014, 384: 1109-17; Robert et al., N Engl J Med 2015, 372: 2521-
5 32; Robert et al., N Engl J Med 2015, 372: 320-30; Topalian et al., N Engl J Med 2012, 366: 2443-54; Topalian et al., J Clin Oncol 2014, 32: 1020-30; and Wolchok et al., N Engl J Med 2013, 369: 122-33).

"PD-1 antagonist" means any chemical compound or biological molecule that blocks binding of PD-L1 expressed on a cancer cell to PD-1 expressed on an immune cell (T-cell, B-cell or NKT
10 cell) and preferably also blocks binding of PD-L2 expressed on a cancer cell to the immune-cell expressed PD-1. Alternative names or synonyms for PD-1 and its ligands include: PDCD1, PD1, CD279 and SLEB2 for PD-1; PDCD1L1, PDL1, B7H1, B7-4, CD274 and B7-H for PD-Ll; and PDCD1L2, PDL2, B7-DC, Btdc and CD273 for PD-L2. In any of the treatment methods, medicaments and uses of the present invention in which a human individual is being treated, the PD-
15 1 antagonist blocks binding of human PD-Ll to human PD-1, and preferably blocks binding of both human PD-Ll and PD-L2 to human PD-1. Human PD-1 amino acid sequences can be found in NCBI Locus No.: NP 005009. Human PD-Ll and PD-L2 amino acid sequences can be found in NCBI Locus No.: NP_054862 and NP_079515, respectively.

PD-1 antagonists useful in any of the treatment methods, medicaments and uses of the
20 present invention include a monoclonal antibody (mAb), or antigen binding fragment thereof, which specifically binds to PD-1 or PD-Ll, and preferably specifically binds to human PD-1 or human PD-Ll. The mAb may be a human antibody, a humanized antibody or a chimeric antibody, and may include a human constant region. In some embodiments the human constant region is selected from the group consisting of IgGl, IgG2, IgG3 and IgG4 constant regions, and in preferred embodiments,
25 the human constant region is an IgGl or IgG4 constant region. In some embodiments, the antigen binding fragment is selected from the group consisting of Fab, Fab'-SH, F(ab')2, scFv and Fv fragments. Examples of PD-1 antagonists include, but are not limited to, pembrolizumab (KEYTRUDA®, Merck and Co., Inc., Kenilworth, NJ, USA). “Pembrolizumab” (formerly known as MK-3475, SCH 900475 and lambrolizumab and sometimes referred to as “pembro”) is a
30 humanized IgG4 mAb with the structure described in WHO Drug Information, Vol. 27, No. 2, pages

161-162 (2013). Additional examples of PD-1 antagonists include nivolumab (OPDIVO®, Bristol-Myers Squibb Company, Princeton, NJ, USA), atezolizumab (MPDL3280A; TECENTRIQ®, Genentech, San Francisco, CA, USA), durvalumab (IMFINZI®, Astra Zeneca Pharmaceuticals, LP, Wilmington, DE, avelumab (BAVENCIO®, Merck KGaA, Darmstadt, Germany and Pfizer, Inc., New York, NY), cemiplimab (LIBTAYO®, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, and Sanofi-Aventis LLC, Bridgewater, NJ), dostarlimab (JEMPERLI®, GlaxoSmithKline LLC, Philadelphia, PA), Sasanlimab (PF-06801591), Retifanlimab (MGA012), Cetrelimab (JNJ-63723283), Tebotelimab (MGD013), Cadonilimab, (AK104), Ezabenlimab (BI754091), Budigalimab (ABBV-181), Spartalizumab (PDR001), Zimberelimab (AB122), Serplulimab (HLX10), Cosibelimab (CK-301), Sugemalimab (CS1001), Camrelizumab, Sintilimab, Tislelizumab, Toripalimab (TAB001), Penpulimab (AK105) and Adebrelimab (SHR-1316).

Examples of monoclonal antibodies (mAbs) that bind to human PD-1, which are useful in the treatment methods, medicaments and uses of the present invention, are described in US7488802, US7521051, US8008449, US8354509, US8168757, WO2004/004771, WO2004/072286, WO2004/056875, and US2011/0271358.

Examples of mAbs that bind to human PD-Ll, which are useful in the treatment methods, medicaments and uses of the present invention, are described in WO2013/019906, W02010/077634 Al and US8383796. Specific anti-human PD-Ll mAbs useful as the PD-1 antagonist in the treatment method, medicaments and uses of the present invention include MPDL3280A, BMS-936559, MEDI4736, MSB0010718C and an antibody which comprises the heavy chain and light chain variable regions of SEQ ID NO:24 and SEQ ID NO:21, respectively, of WO2013/019906.

Other PD-1 antagonists useful in any of the treatment methods, medicaments and uses of the present invention include an immunoadhesin that specifically binds to PD-1 or PD- L1, and preferably specifically binds to human PD-1 or human PD-Ll, e.g., a fusion protein containing the extracellular or PD-1 binding portion of PD-Ll or PD-L2 fused to a constant region such as an Fc region of an immunoglobulin molecule. Examples of immunoadhesin molecules that specifically bind to PD-1 are described in WO2010/027827 and WO2011/066342. Specific fusion proteins useful as the PD-1 antagonist in the treatment methods, medicaments and uses of the present invention include AMP-224 (also known as B7-DCIg), which is a PD-L2-FC fusion protein that binds to human PD-1.

Thus, one embodiment provides a method of treating cancer comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a PD-1 antagonist to a subject in need thereof. In such embodiments, a compound of the invention, or a pharmaceutically acceptable salt thereof, and a PD-1 antagonist are administered concurrently or sequentially.

Specific non-limiting examples of such cancers which can be treated in accordance with this embodiment include melanoma (including unresectable or metastatic melanoma), head & neck cancer (including recurrent or metastatic head and neck squamous cell cancer), classical Hodgkin lymphoma, urothelial carcinoma, gastric cancer, cervical cancer, primary mediastinal large-B-cell lymphoma, microsatellite instability-high cancer, non-small cell lung cancer, hepatocellular carcinoma, clear cell kidney cancer, colorectal cancer, breast cancer, squamous cell lung cancer, basal carcinoma, sarcoma, bladder cancer, endometrial cancer, pancreatic cancer, liver cancer, gastrointestinal cancer, multiple myeloma, renal cancer, mesothelioma, ovarian cancer, anal cancer, biliary tract cancer, esophageal cancer, and salivary cancer.

In one embodiment, there is provided a method of treating cancer comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, to a person in need thereof, in combination with a PD-1 antagonist, wherein said cancer is selected from unresectable or metastatic melanoma, recurrent or metastatic head and neck squamous cell cancer, classical Hodgkin lymphoma, urothelial carcinoma, gastric cancer, cervical cancer, primary mediastinal large-B-cell lymphoma, microsatellite instability-high or mismatch repair deficient cancer, esophageal cancer, renal cancer, endometrial carcinoma, tumor mutational burden-high cancer, triple negative breast cancer, non-small cell lung cancer, and hepatocellular carcinoma. In one such embodiment, the agent is a PD-1 antagonist. In one such embodiment, the agent is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, and dostarlimab, or any of the anti-PD-1 and anti-PD-L1 antobodies disclosed herein. In one such embodiment, the agent is pembrolizumab. In another such embodiment, the agent is nivolumab. In another such embodiment, the agent is atezolizumab.

Pembrolizumab is approved by the U.S. FDA for the treatment of patients with unresectable or metastatic melanoma, Stage IIB, IIC, or III melanoma following complete resection, non-small cell lung cancer (NSCLC), head and neck squamous cell cancer (HNSCC), classical Hodgkin

Lymphoma (cHL), microsatellite instability-high or mismatch repair deficient cancer, microsatellite instability-high or mismatch repair deficient colorectal cancer (CRC), primary mediastinal large B-cell lymphoma, gastric cancer, urothelial cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma (HCC), Merkel cell carcinoma (MCC), renal cell carcinoma (RCC), endometrial carcinoma, tumor mutational burden-high (TMB-H) cancer, triple-negative breast cancer (TNBC), as described in the Prescribing Information for KEYTRUDA™ (Merck & Co., Inc., Whitehouse Station, NJ USA; initial U.S. approval 2014, updated February 2022). In another embodiment, there is provided a method of treating cancer comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, to a person in need thereof, in combination with pembrolizumab, wherein said cancer is selected from unresectable or metastatic melanoma, Stage IIB, IIC, or III melanoma following complete resection, non-small cell lung cancer (NSCLC), head and neck squamous cell cancer (HNSCC), classical Hodgkin Lymphoma (cHL), microsatellite instability-high or mismatch repair deficient cancer, microsatellite instability-high or mismatch repair deficient colorectal cancer (CRC), gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma (HCC), Merkel cell carcinoma (MCC), renal cell carcinoma (RCC), endometrial carcinoma, tumor mutational burden-high (TMB-H) cancer, cutaneous squamous cell carcinoma (cSCC), triple-negative breast cancer (TNBC).

In another embodiment, there is provided a method of treating cancer comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof in combination with a PD-1 antagonist, to a person in need thereof, wherein said cancer is selected from unresectable or metastatic melanoma, Stage IIB, IIC, or III melanoma following complete resection, non-small cell lung cancer, head and neck squamous cell cancer, classical Hodgkin Lymphoma, microsatellite instability-high or mismatch repair deficient cancer, microsatellite instability-high or mismatch repair deficient colorectal cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, renal cell carcinoma, endometrial carcinoma, tumor mutational burden-high cancer, cutaneous squamous cell carcinoma, triple-negative breast cancer. In one such embodiment, the agent is a PD-1 antagonist. In one such embodiment, the agent is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, and dostarlimab, or any of the anti-PD-1 and anti-PD-L1 antobodies disclosed herein. In one such embodiment, the agent is

pembrolizumab. In another such embodiment, the agent is nivolumab. In another such embodiment, the agent is atezolizumab. In another such embodiment, the agent is durvalumab. In another such embodiment, the agent is avelumab. In another such embodiment, the agent is cemiplimab. In another such embodiment, the agent is dostarlimab.

In another embodiment, there is provided a method of treating cancer comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a PD-1 antagonist, to a person in need thereof, wherein said cancer is selected from melanoma, non-small cell lung cancer, small cell lung cancer, head and neck cancer, bladder cancer, breast cancer, gastrointestinal cancer, multiple myeloma, hepatocellular cancer, lymphoma, renal cancer, mesothelioma, ovarian cancer, esophageal cancer, anal cancer, biliary tract cancer, colorectal cancer, cervical cancer, thyroid cancer, and salivary cancer. In one such embodiment, the agent is a PD-1 antagonist. In one such embodiment, the agent is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, and dostarlimab. In one such embodiment, the agent is pembrolizumab. In another such embodiment, the agent is nivolumab. In another such embodiment, the agent is atezolizumab. In another such embodiment, the agent is durvalumab. In another such embodiment, the agent is avelumab. In another such embodiment, the agent is cemiplimab. In another such embodiment, the agent is dostarlimab.

In one embodiment, there is provided a method of treating unresectable or metastatic melanoma comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a PD-1 antagonist to a person in need thereof. In one such embodiment, the agent is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, and dostarlimab. In one such embodiment, the agent is pembrolizumab. In another such embodiment, the agent is nivolumab. In another such embodiment, the agent is atezolizumab. In another such embodiment, the agent is cemiplimab. In another such embodiment, the agent is dostarlimab.

In one embodiment, there is provided a method of treating recurrent or metastatic head and neck squamous cell cancer comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a PD-1 antagonist, to a person in need thereof. In one such embodiment, the agent is selected from the group consisting of

pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, and dostarlimab. In one such embodiment, the agent is pembrolizumab. In another such embodiment, the agent is nivolumab. In another such embodiment, the agent is atezolizumab. In another such embodiment, the agent is cemiplimab. In another such embodiment, the agent is dostarlimab.

In one embodiment, there is provided a method of treating classical Hodgkin lymphoma comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a PD-1 antagonist, to a person in need thereof. In one such embodiment, the agent is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, and dostarlimab. In one such embodiment, the agent is pembrolizumab. In another such embodiment, the agent is nivolumab. In another such embodiment, the agent is atezolizumab. In another such embodiment, the agent is cemiplimab. In another such embodiment, the agent is dostarlimab.

In one embodiment, there is provided a method of treating triple-negative breast cancer comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a PD-1 antagonist, to a person in need thereof. In one such embodiment, the agent is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, and dostarlimab. In one such embodiment, the agent is pembrolizumab. In another such embodiment, the agent is nivolumab. In another such embodiment, the agent is atezolizumab. In another such embodiment, the agent is cemiplimab. In another such embodiment, the agent is dostarlimab.

In one embodiment, there is provided a method of treating urothelial carcinoma comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a PD-1 antagonist, to a person in need thereof. In one such embodiment, the agent is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, and dostarlimab. In one such embodiment, the agent is pembrolizumab. In another such embodiment, the agent is nivolumab. In another such embodiment, the agent is atezolizumab. In another such embodiment, the agent is cemiplimab. In another such embodiment, the agent is dostarlimab.

In one embodiment, there is provided a method of treating gastric cancer comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable

salt thereof, in combination with a PD-1 antagonist, to a person in need thereof. In one such embodiment, the agent is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, and dostarlimab. In one such embodiment, the agent is pembrolizumab. In another such embodiment, the agent is nivolumab. In another such embodiment, the agent is atezolizumab. In another such embodiment, the agent is cemiplimab. In another such embodiment, the agent is dostarlimab.

In one embodiment, there is provided a method of treating cervical cancer comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a PD-1 antagonist, to a person in need thereof. In one such embodiment, the agent is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, and dostarlimab. In one such embodiment, the agent is pembrolizumab. In another such embodiment, the agent is nivolumab. In another such embodiment, the agent is atezolizumab. In another such embodiment, the agent is cemiplimab. In another such embodiment, the agent is dostarlimab.

In one embodiment, there is provided a method of treating primary mediastinal large-B-cell lymphoma comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a PD-1 antagonist, to a person in need thereof. In one such embodiment, the agent is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, and dostarlimab. In one such embodiment, the agent is pembrolizumab. In another such embodiment, the agent is nivolumab. In another such embodiment, the agent is atezolizumab. In another such embodiment, the agent is cemiplimab. In another such embodiment, the agent is dostarlimab.

In one embodiment, there is provided a method of treating microsatellite instability-high (MSI-H) cancer comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a PD-1 antagonist, to a person in need thereof. In one such embodiment, the agent is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, and dostarlimab. In one such embodiment, the agent is pembrolizumab. In another such embodiment, the agent is nivolumab. In another such embodiment, the agent is atezolizumab. In another such embodiment, the agent is cemiplimab. In another such embodiment, the agent is dostarlimab.

In one embodiment, there is provided a method of treating non-small cell lung cancer comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a PD-1 antagonist, to a person in need thereof. In one such embodiment, the agent is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, and dostarlimab. In one such embodiment, the agent is pembrolizumab. In another such embodiment, the agent is nivolumab. In another such embodiment, the agent is atezolizumab. In another such embodiment, the agent is cemiplimab. In another such embodiment, the agent is dostarlimab.

In one embodiment, there is provided a method of treating hepatocellular carcinoma comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a PD-1 antagonist, to a person in need thereof. In one such embodiment, the agent is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, and dostarlimab. In one such embodiment, the agent is pembrolizumab. In another such embodiment, the agent is nivolumab. In another such embodiment, the agent is atezolizumab. In another such embodiment, the agent is cemiplimab. In another such embodiment, the agent is dostarlimab.

In one embodiment, there is provided a method of treating Merkel cell carcinoma comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a PD-1 antagonist, to a person in need thereof. In one such embodiment, the agent is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, and dostarlimab. In one such embodiment, the agent is pembrolizumab. In another such embodiment, the agent is nivolumab. In another such embodiment, the agent is atezolizumab. In another such embodiment, the agent is cemiplimab. In another such embodiment, the agent is dostarlimab.

In one embodiment, there is provided a method of treating renal cell carcinoma comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a PD-1 antagonist, to a person in need thereof. In one such embodiment, the agent is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, and dostarlimab. In one such embodiment, the agent is pembrolizumab. In another such embodiment, the agent is nivolumab. In another such

embodiment, the agent is atezolizumab. In another such embodiment, the agent is cemiplimab. In another such embodiment, the agent is dostarlimab.

In one embodiment, there is provided a method of treating endometrial cell carcinoma comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a PD-1 antagonist, to a person in need thereof. In one such embodiment, the agent is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, and dostarlimab. In one such embodiment, the agent is pembrolizumab. In another such embodiment, the agent is nivolumab. In another such embodiment, the agent is atezolizumab. In another such embodiment, the agent is cemiplimab. In another such embodiment, the agent is dostarlimab.

In one embodiment, there is provided a method of treating cutaneous squamous cell carcinoma comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a PD-1 antagonist, to a person in need thereof. In one such embodiment, the agent is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, and dostarlimab. In one such embodiment, the agent is pembrolizumab. In another such embodiment, the agent is nivolumab. In another such embodiment, the agent is atezolizumab. In another such embodiment, the agent is cemiplimab. In another such embodiment, the agent is dostarlimab.

In one embodiment, there is provided a method of treating tumor mutational burden-high cancer comprising administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a PD-1 antagonist, to a person in need thereof. In one such embodiment, the agent is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, and dostarlimab. In one such embodiment, the agent is pembrolizumab. In another such embodiment, the agent is nivolumab. In another such embodiment, the agent is atezolizumab. In another such embodiment, the agent is cemiplimab. In another such embodiment, the agent is dostarlimab.

Examples of vascular endothelial growth factor (VEGF) receptor inhibitors include, but are not limited to, bevacizumab (sold under the trademark AVASTIN by Genentech/Roche), axitinib, (N-methyl-2-[[3-[([pound])-2-pyridin-2-ylethenyl]-l H-indazol-6-yl]sulfanyl]benzamide, also known as AG013736, and described in PCT Publication No. WO01/002369), Brivanib Alaninate ((S)-((R)-

l-(4-(4-Fluoro-2-methyl-lH-indol-5-yloxy)-5-methylpyrrolo[2,l-f][l,2,4]triazin-6-yloxy)propan-2-yl)2-aminopropanoate, also known as BMS-582664), motesanib (N-(2,3-dihydro-3,3-dimethyl-l H-indoi-6-yl)-2-[(4-pyridinyimethy)amino]-3-pyridinecarboxamide. and described in PCT Publication No. WO 02/068470), pasireotide (also known as SO 230, and described in PCT Publication No. WO02/010192), and sorafenib (sold under the tradename NEXAVAR).

Examples of topoisomerase II inhibitors include but are not limited to, etoposide (also known as VP-16 and Etoposide phosphate, sold under the tradenames TOPOSAR, VEPESID and ETOPOPHOS), and teniposide (also known as VM-26, sold under the tradename VUMON).

Examples of alkylating agents include but are not limited to, 5-azacytidine (sold under the trade name VIDAZA), decitabine (sold under the trade name of DECOGEN), temozolomide (sold under the trade names TEMODAR and TEMODAL by Merck & Co., Inc., Kenilworth, NJ, USA), dactinomycin (also known as actinomycin-D and sold under the tradename COSMEGEN), melphalan (also known as L-PAM, L-sarcolysin, and phenylalanine mustard, sold under the tradename ALKERAN), altretamine (also known as hexamethylmelamine (HMM), sold under the tradename HEXALEN), carmustine (sold under the tradename BCNU), bendamustine (sold under the tradename TREANDA), busulfan (sold under the tradenames BUSULFEX and MYLERAN), carboplatin (sold under the tradename PARAPLATIN), lomustine (also known as CCNU, sold under the tradename CeeNU), cisplatin (also known as CDDP, sold under the tradenames PLATINOL and PLATINOL-AQ), chlorambucil (sold under the tradename LEUKERAN), cyclophosphamide (sold under the tradenames CYTOXAN and NEOSAR), dacarbazine (also known as DTIC, DIC and imidazole carboxamide, sold under the tradename DTIC-DOME), altretamine (also known as hexamethylmelamine (HMM) sold under the tradename HEXALEN), ifosfamide (sold under the tradename IFEX), procarbazine (sold under the tradename MATULANE), mechlorethamine (also known as nitrogen mustard, mustine and mechloroethamine hydrochloride, sold under the tradename MUSTARGEN), streptozocin (sold under the tradename ZANOSAR), thiotepa (also known as thiophosphoamide, TESPA and TSPA, and sold under the tradename THIOPLEX).

Examples of anti-tumor antibiotics include, but are not limited to, doxorubicin (sold under the tradenames ADRIAMYCIN and RUB EX), bleomycin (sold under the tradename LENOXANE), daunorubicin (also known as dauorubicin hydrochloride, daunomycin, and rubidomycin

hydrochloride, sold under the tradename CERUBIDINE), daunorubicin liposomal (daunorubicin citrate liposome, sold under the tradename DAUNOXOME), mitoxantrone (also known as DHAD, sold under the tradename NOVANTRONE), epirubicin (sold under the tradename ELLENCE), idarubicin (sold under the tradenames IDAMYCIN, IDAMYCIN PFS), and mitomycin C (sold under the tradename MUTAMYCIN).

Examples of anti-metabolites include, but are not limited to, claribine (2-chlorodeoxyadenosine, sold under the tradename LEUSTATIN), 5-fluorouracil (sold under the tradename ADRUCIL), 6-thioguanine (sold under the tradename PURINETHOL), pemetrexed (sold under the tradename ALIMTA), cytarabine (also known as arabinosylcytosine (Ara-C), sold under the tradename CYTOSAR-U), cytarabine liposomal (also known as Liposomal Ara-C, sold under the tradename DEPOCYT), decitabine (sold under the tradename DACOGEN), hydroxyurea (sold under the tradenames HYDREA, DROXIA and MYLOCEL), fludarabine (sold under the tradename FLUDARA), floxuridine (sold under the tradename FUDR), cladribine (also known as 2-chlorodeoxyadenosine (2-CdA) sold under the tradename LEUSTATIN), methotrexate (also known as amethopterin, methotrexate sodium (MTX), sold under the tradenames RHEUMATREX and TREXALL), and pentostatin (sold under the tradename NIPENT).

Examples of retinoids include, but are not limited to, alitretinoin (sold under the tradename PANRETIN), tretinoin (all-trans retinoic acid, also known as ATRA, sold under the tradename VESANOID), Isotretinoin (13-c/s-retinoic acid, sold under the tradenames ACCUTANE, AMNESTEEM, CLARAVIS, CLARUS, DECUTAN, ISOTANE, IZOTECH, ORATANE, ISOTRET, and SOTRET), and bexarotene (sold under the tradename TARGRETIN).

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one agent may be prior to, concurrent to, or subsequent to the administration of other agent(s).

EXAMPLES

The meanings of the abbreviations in Examples are shown below.

ACN = CH_3CN = MeCN = acetonitrile

Ac = acetylv

AcOH = acetic acid

AIBN = azobisisobutyronitrile

APhos-Pd-G3 = Palladium G3-(4-(N,N-Dimethylamino)phenyl)di-tert-butylphosphine = [4-(Di-tert-butylphosphino)-N,N-dimethylaniline-2-(2′-aminobiphenyl)]palladium(II) methanesulfonate

APhos-Pd-G4 = 4-Ditert-butylphosphanyl-N,N-dimethylaniline;methanesulfonic acid;N-methyl-2-phenylaniline;palladium

Boc = tert-butyloxycarbonyl

Boc-Ser(Bzl)-OH = N-(tert-Butoxycarbonyl)-O-benzyl-L-serine

BPO = benzoyl peroxide

BrettPhos Pd G3 = [(2-Di-cyclohexylphosphino-3,6-dimethoxy-2′,4′,6′- triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′ -biphenyl)]palladium(II) methanesulfonate

cataCXium A ® = Di(1-adamantyl)-n-butylphosphine

CDI = 1,1'-carbonyldiimidazole

CELITE = diatomaceous earth

CF_3CH_2OH = 2,2,2-trifluoroethanol

Conc. = concentrated

CO_2= carbon dioxide

Cs_2CO_3 = cesium carbonate

DCE = dichloroethane

DCM = dichloromethane

DIEA= DIPEA= N,N-diisopropylethylamine = Hünig's base

DMA = Dimethylacetamide

DMAP = 4-Dimethylaminopyridine

DMF = N,N-dimethylformamide

DMSO = dimethyl sulfoxide

DPPE = 1,2-bis(diphenylphosphino)ethane

EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

EtOAc = ethyl acetate

EtOH = ethanol

h = hours

H_2 = hydrogen

H_2O = water

HATU = 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate

HBr = hydrogen bromide

HCl= hydrochloric acid

HFBA = heptafluorobutyric acid

HOBT = hydroxybenzotriazole

HPLC = high pressure liquid chromatography

K_2CO_3 = potassium carbonate

K_3PO_4= tripotassium phosphate

LCMS=liquid chromatography–mass spectrometry

LHMDS = LiHMDS= lithium bis(trimethylsilyl)amide

$LiAlH_4$ = LAH = lithium aluminum hydride

LG = leaving group

LiF = lithium fluoride

LiOH = lithium hydroxide

min = minutes

MeOH= methanol

$MgSO_4$ = magnesium sulfate

Ms = mesyl

MTBE = methyl *tert*-butyl ether

$NaBH_4$ = sodium borohydride

NaCl = sodium chloride

$NaHCO_3$ = sodium bicarbonate

NaOH = sodium hydroxide

Na_2SO_4= sodium sulfate

NaH = sodium hydride

NBS = N-Bromosuccinimide

NCS = N-Chlorosuccinimide

NH_4Cl = ammonium chloride

NH_4OH = ammonium hydroxide

NMP = N-methyl-2-pyrrolidone

OMs = mesylate

OTs = tosylate

OTf = triflates

Pd-C = palladium on carbon

$Pd(OH)_2/C$ = Pearlman's catalysts = palladium hydroxide on carbon

$Pd_2(dba)_3$ = Tris(dibenzylideneacetone)dipalladium(0)

$Pd(dppf)Cl_2$ = [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) dichloride

Pd (dtbpf) Cl_2 = [1,1′-Bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II)

RuPhos Pd G3 = (2-Dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate = RuPhos-G3-Palladacycle

SFC = supercritical fluid chromatography

sSPhos Pd G2 = chloro(sodium-2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl-3′-sulfonate)[2-(2′-amino-1,1′-biphenyl)]palladium(II)

TBAF = tetrabutyl ammonium fluoride

TEA = triethylamine

Tf = tryfly

TFA = trifluoroacetic acid

TFAA = trifluoroacetic anhydride

THF= tetrahydrofuran

Ts = tosyl

Xphos-Pd G2 = Chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) = X-Phos aminobiphenyl palladium chloride precatalyst

1 Standard atmosphere [atm] = 101325 pascal [Pa] = 14.6959488 psi

The meanings of the abbreviations in the nuclear magnetic resonance spectra are shown below:

s = singlet, d = doublet, dd = double doublet, dt = double triplet, ddd = double double doublet, Sept = septet, t = triplet, m = multiplet, br = broad, brs = broad singlet, q = quartet

J = coupling constant and Hz = hertz.

Compounds of this invention can be prepared using the intermediates and processes outlined below. The various starting materials used are commercially available or are readily made by a person skilled in the art.

SCHEMES

In general, intermediates and compounds of Formula I were synthesized according to one of Schemes 1-34.

Scheme 1

Certain intermediates of compounds of Formula I were synthesized by converting benzylic alcohol **1** to the mesylate **2** by reaction with methanesulfonyl chloride in the presence of base.

Scheme 2

Certain intermediates of compounds of Formula I were synthesized by the reductive amination of amine **3** with various ketones to afford the protected diamine **4**. Reaction of diamine **4** with methyl 2-chloro-2-oxoacetate followed by acidic deprotection affords the free amine **6** which was then cyclized in the presence of base to afford the diketopiperazine **7**.

Scheme 3

Certain intermediates of compounds of Formula I were synthesized by first reacting aryl bromide **8** with aryl boronic acid **9** under palladium catalyzed Suzuki conditions. The resulting biaryl **10** was converted to the bromide **11** by reaction with NBS and AIBN.

Scheme 4

Certain intermediates of compounds of Formula I were synthesized by first reacting aryl bromide **12** with aryl boronic acid **9** under palladium catalyzed Suzuki conditions. The resulting biaryl benzylic alcohol **13** was converted to the benzylic bromide **14** by reaction with carbon tetrabromide and triphenylphosphine.

Scheme 5

Certain intermediates of compounds of Formula I were synthesized by first reacting aryl bromide **8** with aryl boronic acid **9** under palladium catalyzed Suzuki conditions. The resulting biaryl **10** was converted to the bromide **11** by reaction with NBS and BPO.

Scheme 6

Certain intermediates of compounds of Formula I were synthesized by first reacting amine **15** with a 2-chloro-2-oxoacetate ester (where R = methyl or ethyl) to afford **16**. Subsequent alkylation of **16** with alkyl bromide **17,** followed by a separate step of oxidative cleavage afforded intermediate **19**.

Scheme 7

Certain intermediates of compounds of Formula I were synthesized by first reacting an aryl hydrazide **20** with either an α- or β-amino acid **21** to afford **22.** Subsequent cyclization with Lawesson's reagent followed by a separate acid mediated deprotection afforded the substituted thiadiazole **23.**

Scheme 8

Certain intermediates of compounds of Formula I were synthesized by the reaction of amine **15** with methyl 2-chloro-2-oxoacetate to afford **24**. Reaction of **24** with 2,2-dimethoxyethan-1-amine followed by a separate step of acidic deprotection/cyclization afforded the dihydro-diketopiperazine **26.**

Scheme 9

Certain intermediates of compounds of Formula I were synthesized by first reacting an aryl benzaldehyde oxime **27** with NCS to afford the hydroxybenzimidoyl chloride **28.** Subsequent reaction with propargyl alcohol gives the isoxazole **29.** The synthesis is completed by reaction with methanesulfonyl chloride to give the substituted isoxazole **30.**

Scheme 10

Certain intermediates of compounds of Formula I were synthesized by first reacting an ethynyl arene **31** with ethyl 2-chloro-2-(hydroxyimino)acetate to afford the substituted isoxazole **32**. Reduction followed by mesylation afforded the substituted isoxazole **34**.

Scheme 11

Certain intermediates of compounds of Formula I were synthesized by first reacting 3-chloro-6-methylpyridazine **35** with an aryl boronic acid **9** under palladium-catalyzed Suzuki conditions. The resulting biaryl **36** was converted to the benzyl chloride **37** by reaction with 1,3,5-trichloro-1,3,5-triazinane-2,4,6-trione.

Scheme 12

Certain intermediates of compounds of Formula I were synthesized by first reacting an aryl hydrazide **20** with chloroacetyl chloride to afford the hydrazide **38**. Subsequent cyclization with Lawesson's reagent afforded the substituted thiadiazole **39**.

Scheme 13

Certain intermediates of compounds of Formula I were synthesized by the alkylation of diketopiperazine **7** with various electrophiles **40** (where LG includes, but is not limited to, -Cl, -Br, -OMs, and -OTs) using either sodium hydride or a metal carbonate base to afford **41**.

Scheme 14

Certain intermediates of compounds of Formula I were synthesized by first reacting a bromoaryl nitrile **42** with aryl boronic acid **9** under palladium catalyzed Suzuki conditions. The resulting biaryl nitrile **43** was reduced by hydrogenation to the amine **44.** Subsequent reaction with ethyl 2-chloro-2-oxoacetate afforded **45.** Allylation followed by a separate step of ozonolysis afforded the aldehyde **47**.

Scheme 15

Certain intermediates of compounds of Formula I were synthesized by the reductive amination of aldehyde **48** with an amine **15** to give the substituted diketopiperazine **49**.

Scheme 16

Certain intermediates of compounds of Formula I were synthesized by the amination of aldehyde **48** with an amine **15** to give the substituted dihydro-diketopiperazine **50**.

Scheme 17

Certain intermediates of compounds of Formula I were synthesized by first reacting a biaryl benzylic chloride **51** with *tert*-butyl (2-aminoethyl)carbamate. The resulting diamine product **52**

was reacted with ethyl 2-chloro-2-oxoacetate to afford **53**. Subsequent BOC deprotection followed in a separate step by base-mediated cyclization afforded the diketopiperazine **55**.

Scheme 18

Certain intermediates of compounds of Formula I were synthesized by first reacting an aryl bromide **12** with a nitrogen-containing arene (Y) under copper-mediated conditions. The resulting biaryl **13** was converted to the chloride **56** by reaction with thionyl chloride.

Scheme 19

Certain intermediates of compounds of Formula I were synthesized by first reacting an aryl cloride **57** with a nitrogen-containing arene (Y) under S_NAr conditions. The resulting biaryl **58** was converted to the chloride **56** by reaction with thionyl chloride.

Scheme 20

Certain intermediates of compounds of Formula I were synthesized by first reacting an aryl aldehyde **59** with hydroxylamine hydrochloride to afford **27**. The aryl benzaldehyde oxime **27** was reacted with NCS to afford the hydroxybenzimidoyl chloride **28.** Subsequent reaction with

propargyl alcohol gives the isoxazole **29.** The synthesis was completed by reaction with methanesulfonyl chloride to give the substituted isoxazole **30.**

Scheme 21

Certain compounds of Formula I were synthesized by reacting either the aryl chloride or aryl bromide **41** with aryl boronic acid **9** under palladium catalyzed Suzuki conditions.

Scheme 22

Certain compounds of Formula I were synthesized by alkylating the diketopiperazine **7** with an electrophile **60** (where LG includes, but is not limited to, -Cl, -Br, -OMs, and -OTf).

Scheme 23

Certain compounds of Formula I were synthesized by coupling of a carboxylate **61** with an electrophile **62** (where LG includes, but is not limited to, halides and triflate) under photoredox conditions using catalytic irridium and nickel.

Scheme 24

Certain compounds of Formula I were synthesized by the reductive amination of aldehyde **47** with an amine **15**.

Scheme 25

Certain compounds of Formula I were synthesized by an S_NAr reaction where Y is a nucleophile and reacts with either the aryl chloride or aryl bromide **41** in the presence of either a tertiary alkylamine or metal carbonate base.

Scheme 26

Certain compounds of Formula I were synthesized by the amination of aldehyde **47** with an amine **15**.

Scheme 27

Certain compounds of Formula I were synthesized by reacting an alkyl boronate **63** with an aryl bromide **64** under palladium catalyzed Suzuki conditions.

Scheme 28

Certain compounds of Formula I were synthesized by the reductive amination of electrophile **19** with an amine **65**.

Scheme 29

Certain compounds of Formula I were synthesized by reacting either the aryl chloride or aryl bromide **41** with an aryl stannane (where R = alkyl) **66** under palladium catalyzed Stille conditions.

Scheme 30

Certain compounds of Formula I were synthesized by reacting either the aryl chloride or aryl bromide **41** under copper mediated C-N coupling conditions, where Y contains an -NH.

Scheme 31

Certain compounds of Formula I were synthesized by reacting either the aryl chloride or aryl bromide **41** under palladium mediated C-N coupling conditions, where Y contains an -NH.

Scheme 32

Certain compounds of Formula I were synthesized by reacting either the aryl chloride or aryl bromide **41** under palladium mediated C-H activation conditions, where Y is an heteroarene.

Scheme 33

Certain compounds of Formula I were synthesized by reacting an aryl iodide **68** with the arene **67** under palladium mediated C-H activation conditions.

Scheme 34

Certain compounds of Formula I were synthesized by reacting an aryl azide **69** with the arene **67** (wherein X = 1,2,3-triazole) under copper-mediated coupling conditions.

Intermediate 1

Preparation of 5-bromo-2-(bromomethyl)pyrimidine

N-Bromosuccinimide (309 mg, 1.73 mmol) was added to a mixture of 5-bromo-2-methylpyrimidine (250 mg, 1.45 mmol) and azobisisobutyronitrile (AIBN) (71 mg, 0.43 mmol) in carbon tetrachloride (5 mL) at room temperature. The reaction mixture was stirred and heated to 80 °C for 12 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 5-bromo-2-(bromomethyl)pyrimidine. LC/MS (m/z): 253 $(M+H)^+$

Intermediate 2

Preparation of bicyclo[3.1.0]hexan-3-amine

Step A: Benzyl cyclopent-3-en-1-ylcarbamate

102

Benzyl chloroformate (1.43 mL, 10.0 mmol) was added to a mixture of cyclopent-3-enamine hydrochloride (1.00 g, 8.36 mmol), triethylamine (3.50 mL, 25.1 mmol), and DMAP (0.102 g, 0.836 mmol) in DCM (20 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was warmed to 20 °C and stirred for 14 hours. The reaction mixture was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford benzyl cyclopent-3-en-1-ylcarbamate. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.39-7.26 (m, 5H), 5.67 (s, 2H), 5.07 (s, 2H), 4.93 (br s, 1H), 4.39-4.24 (m, 1H), 2.75-2.69 (m, 2H), 2.23-2.13 (m, 2H). LC/MS (m/z): 218 $(M+H)^+$

Step B: Benzyl bicyclo[3.1.0]hexan-3-ylcarbamate

103

A solution of diethylzinc in diethyl ether (1.0 M, 2.9 mL, 2.9 mmol) was added dropwise to a mixture of benzyl cyclopent-3-en-1-ylcarbamate (250 mg, 1.15 mmol) in DCM (10 mL) at 0 °C under a nitrogen atmosphere. Diiodomethane (770 mg, 2.88 mmol) was then added dropwise to the reaction mixture at 0 °C under a nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred for an additional four hours. The resulting mixture was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (2 x 20 mL). The organic layers were combined, washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford benzyl bicyclo[3.1.0]hexan-3-ylcarbamate. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.33-7.25 (m, 5H), 5.01 (s, 2H), 4.44 (br s, 1H),

4.17-4.07 (m, 1H), 2.32-2.15 (m, 2H), 1.55 (dd, J = 14.1 Hz, J = 1.8 Hz, 2H), 1.27-1.21 (m, 2H), 0.60-0.51 (m, 1H), 0.00 (br s, 1H). LC/MS (m/z): 232 $(M+H)^+$

Step C: Bicyclo[3.1.0]hexan-3-amine

104

A mixture of benzyl bicyclo[3.1.0]hexan-3-ylcarbamate (1.1 g, 4.8 mmol) and 5% Pd/C (0.506 g) was sparged with nitrogen. MeOH (15 mL) was added, and the mixture was degassed and backfilled with hydrogen gas (3X). The reaction mixture was stirred under a hydrogen atmosphere (15 psi) at room temperature for two hours. The reaction mixture was filtered, and the filtrate was diluted with HCl (4 M in 1,4-dioxane, 1 mL, 4 mmol) and stirred for 20 minutes. The reaction mixture was concentrated under reduced pressure to afford bicyclo[3.1.0]hexan-3-amine as a hydrochloride salt, which was used without purification in the next step. ^{1}H NMR (400 MHz, methanol-d_4) δ 3.68-3.55 (m, 1H), 2.30- 2.23 (m, 2H), 1.41-1.33 (m, 2H), 1.24-1.20 (m, 2H), 0.72-0.60 (m, 1H), 0.10-0.01 (m, 1H).

Intermediate 3

Preparation of (5-bromopyridin-2-yl)methyl methanesulfonate

84

Triethylamine (1.69 mL, 12.1 mmol) was added dropwise to a mixture of (5-bromopyridin-2-yl)methanol (1.90 g, 10.1 mmol) and methanesulfonic anhydride (1.94 g, 11.1 mmol) in dichloromethane (40 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 minutes after addition was complete. The reaction mixture was quenched with water (20 mL). The organic layer was separated, washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in hexanes) to afford (5-bromopyridin-2-yl)methyl methanesulfonate. LC/MS (m/z): 266, 268 $(M+H)^+$

Intermediate 4

Preparation of (5-bromo-3-fluoropyridin-2-yl)methyl methanesulfonate

Methanesulfonyl chloride (0.17 mL, 2.2 mmol) was added to a mixture of (5-bromo-3-fluoropyridin-2-yl)methanol (371 mg, 1.80 mmol) and Hunig's base (0.472 mL, 2.70 mmol) in DCM (6 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with DCM (30 mL) and water (30 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford (5-bromo-3-fluoropyridin-2-yl)methyl methanesulfonate, which was used without purification in the next step. LC/MS (m/z): 284, 286 $(M+H)^+$.

Intermediates shown in Intermediate Table 1 below were prepared according to procedures analogous to those outlined in Intermediate 4 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 1

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 5		(5-phenylisoxazol-3-yl)methyl methanesulfonate	254

Intermediate 6

Preparation of tert-butyl (2-(((cis)-bicyclo[3.1.0]hexan-3-yl)amino)ethyl)carbamate

A mixture of tert-butyl (2-bromoethyl)carbamate (384 g, 1.81 mol), bicyclo[3.1.0]hexan-3-amine hydroiodide (500 g, 1.71 mol), and potassium carbonate (474 g, 4.23 mol) in DMF (2.50 L) was stirred and heated at 60 °C for 12 hours. The reaction mixture was cooled to room temperature. The reaction mixture was quenched by the addition of water (5.0 L) at room temperature and then diluted with EtOAc (700 mL). The organic layer was separated. The aqueous layer was extracted with additional EtOAc (3 x 700 mL). The organic layers were combined, washed with brine (3 x 1.0 L), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford tert-butyl (2-(((cis)-bicyclo[3.1.0]hexan-3-yl)amino)ethyl)carbamate, which was used without purification. LC/MS (m/z): 241 $(M+H)^+$

Intermediate 7

Preparation of (5-bromoisoxazol-3-yl)methyl methanesulfonate

Step A: ethyl 5-(tributylstannyl)isoxazole-3-carboxylate

Potassium carbonate (2.41 g, 17.4 mmol) and tributyl(ethynyl)stannane (4.99 g, 15.8 mmol) were added to a mixture of ethyl (Z)-2-chloro-2-(hydroxyimino)acetate (2.40 g, 15.8 mmol) in DCM (40 mL) at room temperature. The reaction mixture was stirred at room temperature for two days. The reaction mixture was diluted with water (50 mL) and dichloromethane (250 mL). The organic layer was separated, washed with additional water (50 mL) and brine (50 mL). The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in hexanes) to afford ethyl 5-(tributylstannyl)isoxazole-3-carboxylate. LC/MS (m/z): 432 $(M+H)^+$

Step B: ethyl 5-bromoisoxazole-3-carboxylate

98

Bromine (0.952 mL, 18.5 mmol) was added to a mixture of ethyl 5-(tributylstannyl)isoxazole-3-carboxylate (5.30 g, 12.3 mmol) and sodium carbonate (1.50 g, 14.2 mmol) in DCM (75 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 day. The reaction mixture was quenched by the addition of saturated aqueous sodium thiosulfate (20 mL) and then diluted with water (50 mL) and dichloromethane (200 mL). The organic layer was separated and washed with brine (50 mL). The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in hexanes) to afford ethyl 5-bromoisoxazole-3-carboxylate. ^{1}H NMR (499 MHz, DMSO-d_6) δ 7.24 (s, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H).

Step C: (5-bromoisoxazol-3-yl)methanol

110

Diisobutylaluminium hydride (DIBAL-H) (1.0 M in hexanes, 20 mL, 20 mmol) was added slowly to a mixture of ethyl 5-bromoisoxazole-3-carboxylate (1.89 g, 8.59 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour. The reaction mixture was quenched by the slow addition of HCl (6.0 M in water, 6.6 mL, 40 mmol) at 0 °C. The mixture was stirred for 2 hours and then diluted with water (10 mL) and dichloromethane (100 mL), and then warmed to room temperature. The organic layer was separated, washed with brine (10 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford (5-bromoisoxazol-3-yl)methanol which was used without purification in the next step. LC/MS (m/z): 178, 180 $(M+H)^+$

Step D: (5-bromoisoxazol-3-yl)methyl methanesulfonate

Methanesulfonyl chloride (0.79 mL, 10 mmol) was added to a mixture of (5-bromoisoxazol-3-yl)methanol (1.50 g, 8.43 mmol) and triethylamine (1.65 mL, 11.8 mmol) in DCM (30 mL) at 0 °C. The reaction was stirred at 0 °C for 10 minutes. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluting [3:1 EtOAc:EtOH] in hexanes) to afford (5-bromoisoxazol-3-yl)methyl methanesulfonate. LC/MS (m/z): 256, 258 $(M+H)^+$ 111

Intermediate 8

Preparation of isoxazol-3-ylmethyl methanesulfonate

Step A: isoxazol-3-ylmethanol

112

Borane-THF (1.0 M in THF, 26.5 mL, 26.5 mmol) was added to a mixture of isoxazole-3-carboxylic acid (1.00 g, 8.84 mmol) in THF (10 ml) at 0 °C. The mixture was warmed to room 11 temperature and stirred for 12 hours. The reaction was quenched with MeOH (8 mL) and stirred at room temperature for 2 hours. The mixture was diluted with water and extracted with EtOAc (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford isoxazol-3-ylmethanol, which was used in the next step without purification.

Step B: isoxazol-3-ylmethyl methanesulfonate

113

Methanesulfonic anhydride (1.32 g, 7.57 mmol) was added to a mixture of isoxazol-3-ylmethanol (500 mg, 5.05 mmol) and TEA (1.41 ml, 10.1 mmol) in DCM (20 mL) at room

temperature. The mixture was stirred at room temperature for 1 hour. The mixture was concentrated under reduced pressure to afford isoxazol-3-ylmethyl, which was used in the next step without purification. LC/MS (m/z): 178 $(M+H)^+$

Intermediate 9

Preparation of cyclopentan-1-*d*-1-amine

Step A: N-cyclopentylidene-2-methylpropane-2-sulfinamide

114

2-methylpropane-2-sulfinamide (1.59 g, 13.1 mmol) was added to a mixture of cyclopentanone (1.00 g, 11.9 mmol) and titanium (IV) ethoxide (4.89 ml, 23.78 mmol) in THF (20 ml) at room temperature. The mixture was stirred for 12 hours at room temperature. The mixture was concentrated under reduced pressure, and the residue was partitioned between water (10 mL) and EtOAc (10 mL). The organic layer was separated, and the aqueous was re-extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford N-cyclopentylidene-2-methylpropane-2-sulfinamide, which was used in the next step without purification. LC/MS (m/z): 188 $(M+H)^+$

Step B: N-(cyclopentyl-1-*d*)-2-methylpropane-2-sulfinamide

115

A mixture of N-cyclopentylidene-2-methylpropane-2-sulfinamide (1.00 g, 5.34 mmol) and sodium borodeuteride (0.402 g, 9.61 mmol) in MeOD (15 mL) was degassed and backfilled with N_2 (three times) and then stirred at room temperature for 12 hours. The mixture was quenched with water and then partitioned between water (30 mL) and EtOAc (300 mL). The organic layer was

separated, and the aqueous was re-extracted with EtOAc (3 x 100 mL). The organic layers were combined, washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water with TFA modifier) to afford N-(cyclopentyl-1-*d*)-2-methylpropane-2-sulfinamide. LC/MS (m/z): 191 $(M+H)^+$

Step C: cyclopentan-1-*d*-1-amine

116

A mixture of N-(cyclopentyl-1-*d*)-2-methylpropane-2-sulfinamide (150 mg, 0.788 mmol) and hydrochloric acid (4.0 M in dioxane, 0.60 mL, 2.4 mmol) in 1,4-dioxane (5 mL) was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure to afford cyclopentan-1-*d*-1-amine, which was used in the next step without purification.

Intermediate 10

Preparation of 1-cyclobutylpiperazine-2,3-dione

Step A: *tert*-butyl (2-(cyclobutylamino)ethyl)carbamate

117

A mixture of cyclobutanone (273 g, 3.90 mol) and *tert*-butyl (2-aminoethyl)carbamate (625 g, 3.90 mol) in 1,2-dichloroethane (2.50 L) was cooled to 0 °C. Sodium triacetoxyborohydride (1.16 kg, 5.46 mol) was added portion-wise to the mixture at 0 °C over a period of 1 hour. The mixture was warmed to room temperature and stirred for an additional 11 hours. The mixture was added to water (1.5 L) and the pH was adjusted to ~8 by the addition of saturated aqueous sodium bicarbonate (1.5 L). The mixture was extracted with dichloromethane (2 x 1.5 L). The organic

layers were combined, washed with brine (1 L), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford *tert*-butyl (2-(cyclobutylamino)ethyl)carbamate, which was used in the subsequent step without purification.

Step B: methyl 2-((2-((*tert*-butoxycarbonyl)amino)ethyl)(cyclobutyl)amino)-2-oxoacetate

118

A mixture of *tert*-butyl (2-(cyclobutylamino)ethyl)carbamate (600 g, 1.12 mol) and sodium bicarbonate (470 g, 5.60 mol) in dichloromethane (2.4 L) was cooled to 0 °C. Methyl 2-chloro-2-oxoacetate (178 g, 1.46 mol) was added dropwise over a period of 1 hour at 0 °C. The mixture was warmed to room temperature and stirred for an additional 11 hours. The mixture was then added to water (1.5 L). The organic layer was separated and washed with HCl (1.0 N, 1 L) and brine (1 L), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford methyl 2-((2-((*tert*-butoxycarbonyl)amino)ethyl)(cyclobutyl)amino)-2-oxoacetate.

16

Step C: methyl 2-((2-aminoethyl)(cyclobutyl)amino)-2-oxoacetate hydrochloride

119

HCl (4.0 M in methanol, 3.6 mol, 900 mL) was added to a mixture of methyl 2-((2-((*tert*-butoxycarbonyl)amino)ethyl)(cyclobutyl)amino)-2-oxoacetate (300 g, 998 mmol) in methanol (600 mL) at room temperature. The mixture was stirred at room temperature for 12 hours and then concentrated under reduced pressure to afford methyl 2-((2-aminoethyl)(cyclobutyl)amino)-2-oxoacetate hydrochloride, which was used without purification in the next step. LC/MS (*m/z*): 201 $(M+H)^+$

Step D: 1-cyclobutylpiperazine-2,3-dione

67

A mixture of methyl 2-((2-aminoethyl)(cyclobutyl)amino)-2-oxoacetate hydrochloride (350 g, 1.48 mol) and $NaHCO_3$ (434 g, 5.18 mol) in methanol (2.1 L) was stirred at room temperature for three hours. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluting methanol in dichloromethane) to afford 1-cyclobutylpiperazine-2,3-dione. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 4.80 - 4.71 (m, 1H), 3.52 – 3.49 (m, 2H), 3.33 – 3.23 (m, 2H), 2.17 – 2.02 (m, 4H), 1.66 – 1.63 (m, 2H). LC/MS (*m/z*): 169 $(M+H)^+$

Intermediate 11

Preparation of 1-cyclopentylpiperazine-2,3-dione

Step A: *tert*-Butyl (2-(cyclopentylamino)ethyl)carbamate

121

A mixture of cyclopentanone (250 g, 2.97 mol) and *tert*-butyl (2-aminoethyl)carbamate (524 g, 3.27 mol) in methanol (1.75 L) was stirred at room temperature for 6 minutes. 15 Sodium triacetoxyborohydride (882 g, 4.16 mol) was added portion wise to the reaction mixture at room temperature over a period of 2 hours. The reaction mixture was then stirred at room temperature for 3 hours after the addition was complete. The reaction mixture was diluted with methyl tert-butyl ether (MTBE) (5.00 L) and the resulting mixture was then filtered (washing the collected solids with additional methyl tert-butyl ether (500 mL)). The combined filtrates were concentrated under reduced pressure to afford *tert*-butyl (2-(cyclopentylamino)ethyl)carbamate, which was used in the next step without purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.04 – 6.89 (m, 1H), 3.08 - 3.04

(m, 4H), 2.71 - 2.63 (m, 2H), 1.72 - 1.63 (m, 2H), 1.63 - 1.61 (m, 2H), 1.62 - 1.48 (m, 2H), 1.45 - 1.28 (m, 11H). LC/MS (m/z): 229 $(M+H)^+$

Step B: Methyl 2-((2-((*tert*-butoxycarbonyl)amino)ethyl)(cyclopentyl)amino)-2-oxoacetate

122

A mixture of *tert*-butyl (2-(cyclopentylamino)ethyl)carbamate (400 g, 1.75 mol) and triethylamine (532 g, 5.26 mol) in dichloromethane (3.2 L) was stirred for 6 minutes at room temperature. Methyl 2-chloro-2-oxoacetate (492 g, 4.03 mol) was added dropwise to the reaction mixture at room temperature over a period of two hours. The reaction mixture was stirred at room temperature for an additional two hours after the addition was complete. The reaction mixture was diluted with water (700 mL) and the organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford methyl 2-((2-((*tert*-butoxycarbonyl)amino)ethyl)(cyclopentyl)amino)-2-oxoacetate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.99 – 6.92 (m, 1H), 3.80 - 3.78 (m, 4H), 3.19 – 3.16 (m, 2H), 3.07 – 3.05 (m, 2H), 1.90 – 1.50 (m, 8H), 1.40 – 1.37 (m, 9H). LC/MS (m/z): 215 $(M+H-Boc)^+$

Step C: Methyl 2-((2-aminoethyl)(cyclopentyl)amino)-2-oxoacetate

123

HCl (4.0 M in methanol, 1.2 L, 4.8 mol) was added to a mixture of methyl 2-((2-((*tert*-butoxycarbonyl)amino)ethyl)(cyclopentyl)amino)-2-oxoacetate (300 g, 0.95 mol) in methanol (0.6 L) at room temperature. The reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure to afford methyl 2-((2-aminoethyl)(cyclopentyl)amino)-2-oxoacetate as an HCl salt and was used without purification in the next step. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 - 8.26 (m, 3H), 3.86 - 3.82 (m, 4H), 3.53 - 3.45 (m, 2H), 2.88 (br s, 2H), 1.79 - 1.50 (m, 8H).

Step D: 1-Cyclopentylpiperazine-2,3-dione

Triethylamine (124 g. 1.22 mol) was added dropwise to a mixture of methyl 2-((2-aminoethyl)(cyclopentyl)amino)-2-oxoacetate hydrochloride (150 g, 598 mmol) in methanol (3.0 L) at room temperature. The reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure. The residue was diluted with HCl (1.0 M in water, 2.0 L, 2.0 mol) and then extracted with a mixture of isopropyl alcohol /dichloromethane (1:10 mixture, 5 x 1.0 L). The organic layers were combined, washed with brine (1.0 L), dried over anhydrous sodium sulfate, filtered, and concentrated to afford 1-cyclopentylpiperazine-2,3-dione, which was used without purification. ^{1}H NMR (400 MHz, methanol-d_4) δ 4.84 - 4.78 (m, 1H), 3.54 - 3.52 (m, 2H), 3.47 - 3.31 (m, 2H), 1.90 - 1.88 (m, 2H), 1.78 - 1.77 (m, 2 H), 1.64 - 1.61 (m, 4H). LC/MS (m/z): 183 $(M+H)^+$

Intermediates shown in Intermediate Table 2 below, were prepared according to procedures analogous to those outlined in Intermediate 11 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 2

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 12		1-((cis)-bicyclo[3.1.0]hexan-3-yl)piperazine-2,3-dione 125	195
Intermediate 13		1-(1-(fluoromethyl)cyclopropyl)piperazine-2,3-dione 126	187

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 14		1-cyclobutylhexahydro-1H-cyclopenta[b]pyrazine-2,3-dione 127	209

Intermediate 15

Preparation of 5-(bromomethyl)-2-phenylpyridine

Step A: 5-Methyl-2-phenylpyridine

128

A mixture of 2-bromo-5-methylpyridine (2.00 g, 11.6 mmol), Pd(dppf)Cl_2 (0.43 g, 0.58 mmol), phenylboronic acid (1.56 g, 12.8 mmol), and K_3PO_4 (7.40 g, 34.9 mmol) in 1,4-dioxane (20 mL) and water (2 mL) was sparged with a stream of nitrogen at room temperature for 5 minutes. The reaction mixture was stirred and heated to 80 °C for 15 hours. The reaction mixture was cooled to room temperature, quenched with saturated aqueous ammonium chloride (30 mL), and extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 5-methyl-2-phenylpyridine. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.51 (d, J = 0.7 Hz, 1H), 7.99-7.91 (m, 2H), 7.65-7.59 (m, 1H), 7.57-7.51 (m, 1H), 7.49-7.42 (m, 2H), 7.40-7.33 (m, 1H), 2.36 (s, 3H). LC/MS (m/z): 170 $(M+H)^+$

Step B: 5-(bromomethyl)-2-phenylpyridine

129

A mixture of 5-methyl-2-phenylpyridine (400 mg, 2.36 mmol), *N*-bromosuccinimide (395 mg, 2.22 mmol), and azobisisobutyronitrile (78 mg, 0.47 mmol) in carbon tetrachloride (10 mL) was stirred and heated to 80 °C for 16 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 5-(bromomethyl)-2-phenylpyridine. LC/MS (m/z): 248, 250 $(M+H)^+$

Intermediates shown in Intermediate Table 3 below, were prepared according to procedures analogous to those outlined in Intermediate 15 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 3

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 16		2-(bromomethyl)-5-phenylpyridine 130	248, 250

Intermediate 17

Preparation of 5-(1-bromoethyl)-2-phenylpyridine

Step A: 1-(6-phenylpyridin-3-yl)ethan-1-ol

131

A mixture of 1-(6-bromopyridin-3-yl)ethanol (700 mg, 3.46 mmol), Pd(dppf)Cl_2 (76 mg, 0.10 mmol), phenylboronic acid (549 mg, 4.50 mmol), and K_3PO_4 (2206 mg, 10.39 mmol) in 1,4-dioxane (20 mL) and water (2 mL) at room temperature was sparged with a stream of nitrogen for 5 minutes. The reaction mixture was stirred and heated to 80 °C for 15 hours. The reaction mixture was cooled to room temperature, quenched with saturated aqueous ammonium chloride (30 mL), and extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 1-(6-phenylpyridin-3-yl)ethanol. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.62 (d, J = 2.2 Hz, 1H), 7.98-7.91 (m, 2H), 7.81-7.72 (m, 1H), 7.71-7.64 (m, 1H), 7.48-7.42 (m, 2H), 7.42-7.36 (m, 1H), 4.96 (q, J = 6.6 Hz, 1H), 1.53 (d, J = 6.6 Hz, 3H). LC/MS (m/z): 200 $(M+H)^+$

Step B: 5-(1-bromoethyl)-2-phenylpyridine

132

Carbon tetrabromide (374 mg, 1.13 mmol) was added to a mixture of 1-(6-phenylpyridin-3-yl)ethanol (150 mg, 0.753 mmol) and triphenylphosphine (355 mg, 1.36 mmol) in DCM (5 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 5-(1-bromoethyl)-2-phenylpyridine. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.70 (d, J = 2.2 Hz, 1H), 7.97 (dd, J = 1.2, 8.3 Hz, 2H), 7.85 (dd, J = 2.4, 8.3 Hz, 1H), 7.72 (d, J = 8.3 Hz, 1H), 7.53-7.40 (m, 3H), 5.25 (q, J = 6.8 Hz, 1H), 2.09 (d, J = 6.8 Hz, 3H). LC/MS (m/z): 262, 264 $(M+H)^+$

Intermediates shown in Intermediate Table 4 below, were prepared according to procedures analogous to those outlined in Intermediate 17 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 4

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 18		2-(1-bromoethyl)-5-phenylpyrazine 133	263, 265
Intermediate 19		2-(bromomethyl)-5-phenylpyrazine 134	249, 251

Intermediate 20

Preparation of 2-(4-cyclopentyl-2,3-dioxopiperazin-1-yl)acetic acid

Step A: *tert*-butyl 2-(4-cyclopentyl-2,3-dioxopiperazin-1-yl)acetate

135

NaH (0.285 g, 7.13 mmol) was added to a mixture of 1-cyclopentylpiperazine-2,3-dione (1.00 g, 5.49 mmol) in DMF (15 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 15

minutes. *tert*-Butyl 2-bromoacetate (0.975 mL, 6.04 mmol) was added to the reaction mixture at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 hours. The reaction mixture was quenched with water (60 mL) and extracted with EtOAc (3 x 60 mL). The organic layers were combined, washed with 10% aqueous LiCl (3 x 10 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting methanol in dichloromethane) to afford *tert*-butyl 2-(4-cyclopentyl-2,3-dioxopiperazin-1-yl)acetate. ^{1}H NMR (500 MHz, methanol-d_4) δ 4.84 - 4.75 (m, 1H), 4.15 (s, 2H), 3.66 - 3.56 (m, 4H), 1.96 - 1.86 (m, 2H), 1.83 - 1.74 (m, 2H), 1.70 - 1.58 (m, 4H), 1.48 (s, 9H). LC/MS (m/z): 297 $(M+H)^+$

Step B: 2-(4-cyclopentyl-2,3-dioxopiperazin-1-yl)acetic acid

HCl (4.0 M in dioxane, 3.0 ml, 12 mmol) was added to a mixture of *tert*-butyl 2-(4-cyclopentyl-2,3-dioxopiperazin-1-yl)acetate (1.20 g, 4.05 mmol) in DCM (4 mL). The reaction mixture was stirred at room temperature for 3.5 hours. The reaction mixture was concentrated under reduced pressure to afford 2-(4-cyclopentyl-2,3-dioxopiperazin-1-yl)acetic acid, which was used without purification in the next step. ^{1}H NMR (500 MHz, methanol-d_4) δ = 4.80 (quin, J = 8.3 Hz, 1H), 4.23 (s, 2H), 3.67 - 3.58 (m, 4H), 1.96 - 1.86 (m, 2H), 1.83 - 1.72 (m, 2H), 1.72 - 1.58 (m, 4H). LC/MS (m/z): 241 $(M+H)^+$

Intermediate 21

Preparation of 4-(bromomethyl)-3-fluoro-1,1'-biphenyl

Step A: 3-fluoro-4-methyl-1,1'-biphenyl

137

A mixture of (3-fluoro-4-methylphenyl)boronic acid (0.50 g, 3.3 mmol), bromobenzene (0.51 g, 3.3 mmol), potassium phosphate (0.90 g, 4.2 mmol) and $PdCl_2$(dppf) (0.19 g, 0.26 mmol) in 1,4-dioxane (10 mL) and water (2.0 mL) was sparged with nitrogen for 10 minutes at room temperature. The reaction mixture was stirred and heated to 60 °C for 2 hours. The reaction mixture was cooled to room temperature and diluted with EtOAc (50 mL) and water (40 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 3-fluoro-4-methyl-1,1'-biphenyl. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.61 - 7.52 (m, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.35 - 7.22 (m, 4H), 2.27 (d, J = 1.7 Hz, 3H).

Step B: 4-(bromomethyl)-3-fluoro-1,1'-biphenyl

138

A mixture of 3-fluoro-4-methyl-1,1'-biphenyl (500 mg, 2.68 mmol), *N*-bromosuccinimide (478 mg, 2.68 mmol), and benzoyl peroxide (65 mg, 0.27 mmol) in carbon tetrachloride (10 mL) was stirred and heated to 90 °C for 12 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 4-(bromomethyl)-3-fluoro-1,1'-biphenyl.

Intermediates shown in Intermediate Table 5 below, were prepared according to procedures analogous to those outlined in Intermediate 21 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 5

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 22		2-(bromomethyl)-5-phenylpyrimidine 139	249, 251
Intermediate 23		2-(bromomethyl)-3-fluoro-5-phenylpyridine 140	266, 268
Intermediate 24		5-(bromomethyl)-3-fluoro-2-phenylpyridine 141	266, 268
Intermediate 25		6-(bromomethyl)-3-phenyl-1,2,4-triazine 142	250, 252
Intermediate 26		5-(bromomethyl)-2-phenylpyrimidine 143	249, 251
Intermediate 27		3-(bromomethyl)-5-phenylisothiazole 144	254, 256

Intermediate 28

Preparation of (3-fluoro-5-(thiazol-2-yl)pyridin-2-yl)methyl methanesulfonate

145

A mixture of $PdCl_2$(dppf) (18 mg, 0.024 mmol), (5-bromo-3-fluoropyridin-2-yl)methanol (50 mg, 0.24 mmol), and 2-(tributylstannyl)thiazole (0.099 mL, 0.32 mmol) in 1,4-dioxane (2 mL) was sparged with nitrogen for 1 minute at room temperature. The reaction mixture was stirred and heated at 90 °C for 30 minutes. The reaction mixture was cooled to room temperature. Triethylamine (0.135 mL, 0.971 mmol) and methanesulfonyl chloride (0.038 mL, 0.49 mmol) were added to the reaction mixture. The reaction mixture was stirred for 2 hours. The reaction mixture was diluted with DCM and filtered through Celite. The reaction mixture was concentrated under reduced pressure, and the residue was purified by basic alumina chromatography (eluting EtOAc:EtOH (3:1) in hexanes) to afford (3-fluoro-5-(thiazol-2-yl)pyridin-2-yl)methyl methanesulfonate. LC/MS (*m/z*): 289 $(M+H)^+$

Intermediate 29

Preparation of methyl 2-(cyclopentyl(2-oxoethyl)amino)-2-oxoacetate

Step A: methyl 2-(cyclopentylamino)-2-oxoacetate

146

Hunig's base (4.35 mL, 25.0 mmol) was added to a mixture of cyclopentanamine (1.97 ml, 20.0 mmol) in DCM (100 mL) at 0 °C. Methyl 2-chloro-2-oxoacetate (1.84 mL, 20.0 mmol) was added dropwise to the reaction mixture at 0 °C. The reaction mixture was stirred for 5 hours and then was quenched with saturated aqueous sodium bicarbonate. The mixture was passed through a

phase separator. The organic layer was concentrated under reduced pressure to afford methyl 2-(cyclopentylamino)-2-oxoacetate, which was used without purification in the next step. LC/MS (*m/z*): 172 $(M+H)^+$

Step B: methyl 2-(allyl(cyclopentyl)amino)-2-oxoacetate

147

Sodium hydride (0.816 g, 20 mmol, 60% dispersion in mineral oil) was added to an oven-dried flask under a nitrogen atmosphere. DMF (60 mL) was added, and the mixture was placed in a water bath. A mixture of methyl 2-(cyclopentylamino)-2-oxoacetate (3.25 g, 19.0 mmol) in DMF (15.0 mL) was slowly added to the reaction mixture. The reaction mixture was cooled to 0 °C and allyl bromide (2.46 mL, 28.5 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 18 hours. The reaction mixture was cooled to 0 °C and quenched with isopropanol (1 mL) followed by water (10 mL). The mixture was stirred for 30 minutes, then diluted with water (100 mL) and extracted with diethyl ether (3 x 100 mL). The organic layers were combined, washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in hexanes) to afford methyl 2-(allyl(cyclopentyl)amino)-2-oxoacetate. LC/MS (*m/z*): 212 $(M+H)^+$

28

Step C: methyl 2-(cyclopentyl(2-oxoethyl)amino)-2-oxoacetate

148

A mixture of methyl 2-(allyl(cyclopentyl)amino)-2-oxoacetate (0.300 g, 1.42 mmol) in DCM (25 mL) was cooled to -78 °C in an acetone/dry ice bath and stirred for 5 minutes. Ozone was bubbled through the reaction mixture for 10 minutes using the Triogen ozonolysis machine (connected to compressed air). When the reaction was complete (monitored by LCMS), air was bubbled through the reaction mixture. Dimethyl sulfide (1.58 ml, 21.3 mmol) was added to the

reaction mixture, and the mixture was stirred at room temperature for 18 hours. The mixture was concentrated under reduced pressure to afford methyl 2-(cyclopentyl(2-oxoethyl)amino)-2-oxoacetate, which was used without purification in the next step. LC/MS (*m/z*): 214 $(M+H)^+$.

Intermediates, as shown in Intermediate Table 6 below, were or may be prepared according to procedures analogous to those outlined in Intermediate 29 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 6

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 30		methyl 2-(cyclobutyl(2-oxoethyl)amino)-2-oxoacetate 149	200
Intermediate 31		ethyl 2-(cyclobutyl(2-oxopropyl)amino)-2-oxoacetate 150	228
Intermediate 32		ethyl 2-(bicyclo[1.1.1]pentan-1-yl(2-oxoethyl)amino)-2-oxoacetate 151	226
Intermediate 33		ethyl 2-(((5-bromo-1,3,4-thiadiazol-2-yl)methyl)(2-oxoethyl)amino)-2-oxoacetate 75	336, 338

Intermediate 34

Preparation of (S)-1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethan-1-amine

Step A: *tert*-butyl (S)-(1-(2-benzoylhydrazineyl)-1-oxopropan-2-yl)carbamate

Hunig's base (3.58 mL, 20.5 mmol) and 1-propanephosphonic anhydride (50% in EtOAc, 6.25 mL, 10.5 mmoL) were added to a mixture of benzohydrazide (1.36 g, 10 mmol) and (*tert*-butoxycarbonyl)-*L*-alanine (1.9 g, 10 mmol) in DCM (100 mL) at room temperature. The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with water (50 mL), and the mixture was passed through a phase separator. The organic layer was dried with magnesium sulfate, filtered, and concentrated under reduced pressure to afford *tert*-butyl (S)-(1-(2-benzoylhydrazineyl)-1-oxopropan-2-yl)carbamate. LC/MS (*m/z*): 330 $(M+Na)^+$

Step B: (S)-1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethan-1-amine

THF (50 mL) was added to a mixture of *tert*-butyl (S)-(1-(2-benzoylhydrazineyl)-1-oxopropan-2-yl)carbamate (2.9 g, 9.5 mmol) and Lawessons reagent (7.68 g, 19.0 mmol) under a nitrogen atmosphere. The reaction mixture was stirred and heated to 65 °C under a reflux condenser for 15 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in hexanes) to afford the Boc-protected thiodiazole intermediate. The isolated intermediate was diluted with DCM (50 mL) and TFA (3.66 mL, 47.5 mmol). The mixture was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure to afford (S)-1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethan-1-amine, which was used without purification in the next step. LC/MS (*m/z*): 206 $(M+H)^+$

Intermediates shown in Intermediate Table 7 below, were or may be prepared according to procedures analogous to those outlined in Intermediate 34 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 7

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 35		(R)-1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethan-1-amine 156	206
Intermediate 36		2-(5-phenyl-1,3,4-thiadiazol-2-yl)ethan-1-amine 157	206
Intermediate 37		1-(5-phenyl-1,3,4-thiadiazol-2-yl)propan-2-amine 158	220
Intermediate 38		2-(5-phenyl-1,3,4-thiadiazol-2-yl)propan-1-amine 159	220

Intermediate 39

Preparation of 2-(chloromethyl)-5-phenylpyrimidine

Step A: (5-phenylpyrimidin-2-yl)methanol

160

A mixture of (5-bromopyrimidin-2-yl)methanol (940 mg, 4.97 mmol), phenylboronic acid (667 mg, 5.47 mmol), Pd(dppf)Cl_2-CH_2Cl_2 adduct (203 mg, 0.249 mmol), and potassium carbonate (1380 mg, 9.95 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was sparged with argon for 5 minutes at room temperature. The reaction mixture was heated to 60 °C and stirred under an argon atmosphere for 4 hours. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (25 mL). Magnesium sulfate (~ 5 g) was added, and the mixture was stirred at room temperature for 10 minutes. The mixture was filtered through CELITE, while washing with ethyl acetate. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluting ethyl acetate in hexanes) to afford (5-phenylpyrimidin-2-yl)methanol. LC/MS (*m/z*): 187 $(M+H)^+$

Step B: 2-(chloromethyl)-5-phenylpyrimidine

161

Methanesulfonyl chloride (0.500 mL, 6.42 mmol) was added to a mixture of (5-phenylpyrimidin-2-yl)methanol (920 mg, 4.94 mmol) and triethylamine (1.38 mL, 9.88 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 hours. The reaction mixture concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluting ethyl acetate in hexanes) to afford 2-(chloromethyl)-

5-phenylpyrimidine. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.19 (s, 2H), 7.87 – 7.82 (m, 2H), 7.56 (t, J = 7.4 Hz, 2H), 7.50 (t, J = 7.3 Hz, 1H), 4.88 (s, 2H). LC/MS (m/z): 205 $(M+H)^+$

Intermediate 40

Preparation of 1-cyclobutyl-1,4-dihydropyrazine-2,3-dione

Step A: ethyl 2-(cyclobutylamino)-2-oxoacetate

162

Ethyl 2-chloro-2-oxoacetate (0.79 mL, 7.0 mmol) was added to a mixture of cyclobutanamine (0.60 mL, 7.0 mmol) and triethylamine (0.98 mL, 7.0 mmol) in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 minutes. The reaction mixture was partially concentrated under reduced pressure (~1/2 volume) and then directly purified by silica gel chromatography (eluting ethyl acetate in hexanes) to afford ethyl 2-(cyclobutylamino)-2-oxoacetate. LC/MS (m/z): 172 $(M+H)^+$

Step B: N^1-cyclobutyl-N^2-(2,2-dimethoxyethyl)oxalamide

163

A mixture of ethyl 2-(cyclobutylamino)-2-oxoacetate (1.2 g, 7.0 mmol) and 2,2-dimethoxyethan-1-amine (1.53 mL, 14.0 mmol) in 2-propanol (10 mL) was stirred at 20 °C for 18 hours to afford a suspension of solids. The mixture was filtered, and the isolated solids were washed with additional 2-propanol (5 x 2 mL) and then dried under high vacuum to afford N^1-cyclobutyl-N^2-(2,2-dimethoxyethyl)oxalamide. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.00 (d, J = 8.3 Hz, 1H), 8.59 (t, J = 6.0 Hz, 1H), 4.49 (t, J = 5.5 Hz, 1H), 4.28 – 4.20 (m, 1H), 3.25 – 3.20 (m, 8H), 2.17 – 2.09 (m, 4H), 1.67 – 1.58 (m, 2H). LC/MS (m/z): 253 $(M+Na)^+$

Step C: 1-cyclobutyl-1,4-dihydropyrazine-2,3-dione

83

A mixture of N^1-cyclobutyl-N^2-(2,2-dimethoxyethyl)oxalamide (1.2 g, 5.2 mmol) and HCl (37% in water, 0.043 mL, 0.52 mmol) in acetic acid (3.0 mL) was heated to 100 °C and stirred for 1 hour. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting [1:3 ethanol/ethyl acetate] in dichloromethane) to afford 1-cyclobutyl-1,4-dihydropyrazine-2,3-dione. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.22 (s, 1H), 6.65 (d, J = 6.0 Hz, 1H), 6.35 (d, J = 6.0 Hz, 1H), 4.89 (p, J = 8.9 Hz, 1H), 2.28 – 2.21 (m, 4H), 1.78 – 1.68 (m, 2H). LC/MS (m/z): 167 $(M+H)^+$

Intermediates shown in Intermediate Table 8 below, were prepared according to procedures analogous to those outlined in Intermediate 40 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 8

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 41		1-(bicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione 53	179
Intermediate 42		1-(cis)-bicyclo[3.1.0]hexan-3-yl)-1,4-dihydropyrazine-2,3-dione 166	193
Intermediate 43		1-cyclopentyl-1,4-dihydropyrazine-2,3-dione 167	181

Intermediate 44		1-(1-methylcyclobutyl)-1,4-dihydropyrazine-2,3-dione 168	181
Intermediate 45		1-(1-methylcyclopropyl)-1,4-dihydropyrazine-2,3-dione 169	167
Intermediate 46		1-(2,3-dioxo-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 170	178
Intermediate 47		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione 171	197
Intermediate 48		1-(1-(fluoromethyl)cyclopropyl)-1,4-dihydropyrazine-2,3-dione 172	185

Intermediate 49

Preparation of 6-methyl-3-phenyl-1,2,4-triazine

Step A: N-(prop-2-yn-1-yl)benzamide

174

A solution of benzoyl chloride (2.46 mL, 21.3 mmol) in DCM (12 mL) was added dropwise to a mixture of propargylamine (1.57 mL, 24.5 mmol) and N,N-diethylethanamine (5.95 mL, 42.7 mmol) in DCM (48 mL) at 0 °C. The mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with HCl (1 N, 100 mL) and extracted with DCM (3 x 100 mL). The organic layers were combined, washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford *N*-(prop-2-yn-1-yl)benzamide. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.79 (d, J = 7.3 Hz, 2H), 7.54-7.49 (m, 1H), 7.47-7.41 (m, 2H), 6.33 (br s, 1H), 4.26 (dd, J = 2.4, 5.2 Hz, 2H), 2.29 (t, J = 2.4 Hz, 1H). LC/MS (m/z): 160 $(M+H)^+$

Step B: 6-methyl-3-phenyl-1,2,4-triazine

A mixture of N-(prop-2-yn-1-yl)benzamide (1.0 g, 6.3 mmol), BOC-hydrazine (644 µL, 6.28 mmol), and zinc trifluoromethanesulfonate ($Zn(OTf)_2$) (685 mg, 1.89 mmol) was stirred and heated at 120 °C for 4 hours under an inert atmosphere. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in toluene (80 mL) and then added to a mixture of potassium ferricyanide ($K_3[Fe(CN)_6]$) (3.10 g, 9.42 mmol) and NaOH (628 mg, 15.7 mmol) in water (50 mL) at room temperature. The biphasic mixture was vigorously stirred at room temperature for 12 hours. The organic phase was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 6-methyl-3-phenyl-1,2,4-triazine. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.54 (s, 1H), 8.53-8.48 (m, 2H), 7.56-7.52 (m, 3H), 2.76 (s, 3H). LC/MS (m/z): 172 $(M+H)^+$

Intermediate 50

Preparation of 3-(bromomethyl)-5-phenylisoxazole

Step A: (5-phenylisoxazol-3-yl)methanol

176

$BH_3 \cdot$dimethylsulfide (0.529 mL, 5.3 mmol, 10 M in THF) was added to a mixture of 5-phenylisoxazole-3-carboxylic acid (500 mg, 2.64 mmol) in THF (10 mL) at room temperature. The reaction mixture was stirred and heated to 60 °C for 4 hours. The reaction mixture was quenched with MeOH and concentrated under reduced pressure to afford (5-phenylisoxazol-3-yl)methanol which was used without purification. LC/MS (m/z): 176 $(M+H)^+$

36

Step B: 3-(bromomethyl)-5-phenylisoxazole

177

(5-Phenylisoxazol-3-yl)methanol (400 mg, 2.28 mmol) was added to a mixture of triphenylphosphine (898 mg, 3.42 mmol) and carbon tetrabromide (1140 mg, 3.42 mmol) in DCM (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 3-(bromomethyl)-5-phenylisoxazole. ^{1}H NMR (500 MHz, methanol-d_4) δ 7.86-7.82 (m, 2H), 7.58-7.38 (m, 3H), 6.90 (s, 1H), 4.56 (s, 2H). LC/MS (m/z): 238, 240 $(M+H)^+$

Intermediate 51

Preparation of 2-(1-bromoethyl)-5-phenylpyrimidine

Step A: 1-(5-phenylpyrimidin-2-yl)ethan-1-one

178

A mixture of 1-(5-bromopyrimidin-2-yl)ethanone (1.0 g, 5.0 mmol), phenylboronic acid (0.73 g, 6.0 mmol), K_3PO_4 (2.1 g, 10 mmol), and Pd(dppf)Cl_2 (0.36 g, 0.50 mmol) in 1,4-dioxane (10 mL) and water (2 mL) was sparged with N_2 at room temperature. The reaction mixture was then stirred and heated at 80 °C for 16 hours. The reaction mixture was cooled to room temperature, diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The organic layers were combined, washed with brine (15 mL), filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 1-(5-phenylpyrimidin-2-yl)ethan-1-one. ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.20-9.01 (m, 2H), 7.68-7.62 (m, 2H), 7.60-7.50 (m, 3H), 2.83 (s, 3H). LC/MS (m/z): 199 $(M+H)^+$

Step B: 1-(5-phenylpyrimidin-2-yl)ethan-1-ol

179

$NaBH_4$ (115 mg, 3.03 mmol) was added to a mixture of 1-(5-phenylpyrimidin-2-yl)ethan-1-one (500 mg, 2.52 mmol) in MeOH (25 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour. The mixture was concentrated under reduced pressure. The residue was partitioned between water (20 mL) and EtOAc (20 mL). The organic layer was separated, and the aqueous layer was washed with additional EtOAc (3 x 20 mL). The organic layers were combined, washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 1-(5-phenylpyrimidin-2-yl)ethan-1-ol. ^{1}H NMR (400 MHz, methanol-d_4) δ 9.03 (s, 2H), 7.72-7.70 (m, 2H), 7.57-7.45 (m, 3H), 5.00-4.96 (m, 1H), 1.57-1.55 (m, 3H). LC/MS (m/z): 201 $(M+H)^+$

Step C: 2-(1-bromoethyl)-5-phenylpyrimidine

180

1-(5-Phenylpyrimidin-2-yl)ethan-1-ol (300 mg, 1.50 mmol) was added to a mixture of triphenylphosphine (589 mg, 2.25 mmol) and carbon tetrabromide (745 mg, 2.25 mmol) in DCM (10 mL) at room temperature. The mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 2-(1-bromoethyl)-5-phenylpyrimidine. ^{1}H NMR (500 MHz, methanol-d_4) δ 9.04 (s, 2H), 7.76-7.70 (m, 2H), 7.59-7.45 (m, 3H), 5.38-5.34 (m, 1H), 2.11-2.10 (m, 3H). LC/MS (m/z): 263, 265 $(M+H)^+$

Intermediate 52

Preparation of 5-(bromomethyl)-2-(1H-1,2,3-triazol-1-yl)pyridine

Step A: 5-methyl-2-(1H-1,2,3-triazol-1-yl)pyridine

181

A mixture of 2H-1,2,3-triazole (1.24 g, 18.0 mmol), 2-fluoro-5-methylpyridine (1.00 g, 9.00 mmol), Cs_2CO_3 (8.80 g, 27.0 mmol) in DMF (30 mL) was stirred and heated at 70 °C for 2 hours. The mixture was cooled to room temperature and diluted with water (150 mL) and then extracted with EtOAc (200 mL). The organic layer was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford a mixture of 5-methyl-2-(1H-1,2,3-triazol-1-yl)pyridine as the first eluting peak and 5-methyl-2-(2H-1,2,3-triazol-2-yl)pyridine as the second eluting peak.

Peak 1: ^{1}H NMR (500 MHz, methanol-d_4) δ 8.75 (d, J = 1.2 Hz, 1H), 8.41 (br s, 1H), 8.09 - 8.04 (m, 1H), 7.92 - 7.88 (m, 2H), 2.45 (s, 3H). LC/MS (m/z): 161 $(M+H)^+$

Peak 2: ^{1}H NMR (500 MHz, methanol-d_4) δ 8.38 (s, 1H), 8.05 - 7.98 (m, 3H), 7.90 (br d, J = 8.4 Hz, 1H), 2.45 (s, 3H). LC/MS (m/z): 161 $(M+H)^+$

Step B: 5-(bromomethyl)-2-(1H-1,2,3-triazol-1-yl)pyridine

182

A mixture of 5-methyl-2-(1H-1,2,3-triazol-1-yl)pyridine (90 mg, 0.56 mmol), N-bromosuccinimide (0.100 g, 0.56 mmol) and benzoyl peroxide (BPO) (14 mg, 0.056 mmol) in carbon tetrachloride (5 mL) was stirred and heated at 90 °C for 12 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 5-(bromomethyl)-2-(1H-1,2,3-triazol-1-yl)pyridine. LC/MS (m/z): 239, 241 $(M+H)^+$

Intermediate 53

Preparation of 1-(bicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione

Step A: ethyl 2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoacetate

183

Ethyl 2-chloro-2-oxoacetate (1.87 mL, 16.7 mmol) was added to a mixture of bicyclo[1.1.1]pentan-1-amine hydrochloride (2.00 g, 16.7 mmol) and triethylamine (5.83 mL, 41.8 mmol) in dichloromethane (50 mL) at 0 °C. The mixture was stirred at 0 °C for 15 minutes. The mixture was partially concentrated under reduced pressure (~1/4 volume) and filtered to remove triethylammonium chloride. The filtrate was directly purified by silica gel chromatography (eluting ethyl acetate in hexanes) to afford ethyl 2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoacetate. LC/MS (m/z): 184 $(M+H)^+$

40

Step B: N^1-(bicyclo[1.1.1]pentan-1-yl)-N^2-(2,2-dimethoxyethyl)oxalamide

184

A mixture of ethyl 2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoacetate (3.08 g, 16.8 mmol) and 2,2-dimethoxyethan-1-amine (1.83 mL, 16.8 mmol) in 2-propanol (20 mL) was stirred at room temperature for 2 days. The mixture was concentrated under reduced pressure, and the isolated solids were dried under vacuum to afford N^1-(bicyclo[1.1.1]pentan-1-yl)-N^2-(2,2-dimethoxyethyl)oxalamide. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.27 (s, 1H), 8.56 (t, J = 5.9 Hz, 1H), 4.48 (t, J = 5.5 Hz, 1H), 3.25 (s, 6H), 3.25 – 3.22 (m, 2H), 2.43 (s, 1H), 2.03 (s, 6H). LC/MS (m/z): 265 $(M+Na)^+$

34

Step C: 1-(bicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione

53

A mixture of N^1-(bicyclo[1.1.1]pentan-1-yl)-N^2-(2,2-dimethoxyethyl)oxalamide (3.33 g, 13.7 mmol) and HCl (37% in water, 0.056 mL, 0.69 mmol) in acetic acid (10.0 mL) was heated to 100 °C and stirred for 1 hour. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting [1:3 ethanol/ethyl acetate] in dichloromethane) to afford 1-(bicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.21 (s, 1H), 6.33 (d, J = 5.9 Hz, 1H), 6.28 (d, J = 5.9 Hz, 1H), 2.61 (s, 1H), 2.23 (s, 7H). LC/MS (m/z): 179 $(M+H)^+$

Step D: 1-(bicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione

186

A mixture of 1-(bicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione (5.00 g, 28.1 mmol), $Pd(OH)_2$ (20% w/w, 0.394 g, 0.561 mmol), and palladium on carbon (Pd/C) (10% w/w, 1.792 g, 1.7 mmol) was degassed with nitrogen. MeOH (200 mL) was added, and the mixture was degassed and backfilled with H_2 (three times). The mixture was stirred under a H_2 atmosphere (Pressure: 50 psi) and heated at 60 °C for 24 hours. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by SFC (column Phenomenex-Cellulose-2 (250mm*50mm,10um); eluting 45% EtOH in CO_2 with 0.1% ammonia) to afford 1-(bicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (br s, 1H), 3.50 - 3.40 (m, 2H), 3.36 - 3.31 (m, 2H), 2.50 (s, 1H), 2.12 (s, 6H). LC/MS (*m/z*): 181 $(M+H)^+$

Intermediate 54

Preparation of 5-(bromomethyl)-2-(2H-1,2,3-triazol-2-yl)pyridine

A mixture of 5-methyl-2-(2H-1,2,3-triazol-2-yl)pyridine (100 mg, 0.624 mmol), N-bromosuccinimide (111 mg, 0.624 mmol), and benzoyl peroxide (15 mg, 0.062 mmol) in chloroform (12 mL) was stirred and heated at 80 °C for 12 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 5-(bromomethyl)-2-(2H-1,2,3-triazol-2-yl)pyridine. LC/MS (m/z): 239, 241 $(M+H)^+$

Intermediate 55

Preparation of 3-(2-bromoethyl)-5-phenylisoxazole

Step A: methyl 3,5-dioxo-5-phenylpentanoate

188

Lithium diisopropylamide (LDA) in (2.0 M in THF, 27.5 mL, 55 mmol) and tetramethylethylenediamine (3.33 mL, 22.0 mmol) were added to a mixture of methyl 3-oxobutanoate (3.2 g, 28 mmol) in THF (50 mL) at -78 °C. After stirring for 30 minutes at -78 °C, methyl benzoate (3.0 g, 22 mmol) was added to the mixture at -78 °C. The mixture was stirred at 0 °C for an additional 12 hours. The reaction mixture was quenched with 6 N HCl (100 mL) and extracted with EtOAc (3 x 100 mL). The organic layers were combined, washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford methyl 3,5-dioxo-5-phenylpentanoate. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.91-7.86 (m, 2H), 7.57-7.52 (m, 1H), 7.49-7.43 (m, 2H), 7.38-7.30 (m, 1H), 6.29 (s, 1H), 3.77 (s, 3H), 3.50 (s, 2H). LC/MS (m/z): 221 $(M+H)^+$

Step B: ethyl 2-(5-phenylisoxazol-3-yl)acetate

189

A mixture of methyl 3,5-dioxo-5-phenylpentanoate (0.100 g, 0.454 mmol) and hydroxylamine hydrochloride (95 mg, 1.4 mmol) in EtOH (3 mL) was stirred and heated at 80 °C for 2 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between water (10 mL) and EtOAc (10 mL). The organic layer was separated, and the aqueous layer was re-extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with ammonium bicarbonate modifier) to afford ethyl 2-(5-phenylisoxazol-3-yl)acetate. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.84-7.75 (m, 2H), 7.50-7.40 (m, 3H), 6.62 (s, 1H), 4.23 (q, J = 7.0 Hz, 2H), 3.79 (s, 2H), 1.30 (t, J = 7.0 Hz, 3H). LC/MS (m/z): 232 $(M+H)^+$

Step C: 2-(5-phenylisoxazol-3-yl)ethan-1-ol

190

Lithium borohydride (141 mg, 6.49 mmol) was added slowly to a mixture of ethyl 2-(5-phenylisoxazol-3-yl)acetate (0.500 g, 2.16 mmol) in THF (15 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 12 hours. The reaction mixture was quenched with saturated NH_4Cl aqueous solution (50 mL) and extracted with DCM (3 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 2-(5-phenylisoxazol-3-yl)ethan-1-ol. LC/MS (m/z): 190 $(M+H)^+$

Step D: 3-(2-bromoethyl)-5-phenylisoxazole

191

2-(5-phenylisoxazol-3-yl)ethan-1-ol (0.100 g, 0.529 mmol) was added to a mixture of triphenylphosphine (208 mg, 0.793 mmol) and carbon tetrabromide (263 mg, 0.793 mmol) in DCM (10 mL) at room temperature. The mixture was stirred at room temperature for 16 hours under a nitrogen atmosphere. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 3-(2-bromoethyl)-5-phenylisoxazole. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.82 (dd, J = 1.6, 7.9 Hz, 2H), 7.53-7.45 (m, 3H), 6.79 (s, 1H), 3.75 (t, J = 7.0 Hz, 2H), 3.30-3.27 (m, 2H). LC/MS (m/z): 252, 254 $(M+H)^+$

Intermediate 56

Preparation of (5-phenyl-1,3,4-thiadiazol-2-yl)methanamine

Step A: N'-(2-chloroacetyl)benzohydrazide

192

Chloroacetyl chloride (19.3 mL, 242 mmol) was added to a solution of benzohydrazide (30.0 g, 220 mmol) in ethyl acetate (460 mL) at 0 °C. The reaction mixture was stirred and heated to 65 °C for 13 hours. The mixture was cooled to room temperature and filtered. The isolated solids were

dried under reduced pressure to afford N'-(2-chloroacetyl)benzohydrazide, which was used in the next step without further purification. LC/MS (m/z): 213 $(M+H)^+$

Step B: 2-(chloromethyl)-5-phenyl-1,3,4-thiadiazole

193

Lawesson's reagent (18.3 g, 45.1 mmol) was added to a mixture of N'-(2-chloroacetyl)benzohydrazide (16 g, 75 mmol) in THF (340 mL). The mixture was stirred and heated at 70 °C for 4 hours. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (300 mL) and extracted with EtOAc (3 x 200 mL). The organic layers were combined, washed with brine (500 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 2-(chloromethyl)-5-phenyl-1,3,4-thiadiazole. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.99 - 7.94 (m, 2H), 7.54 - 7.47 (m, 3H), 4.98 (s, 2H). LC/MS (m/z): 211 $(M+H)^+$

Step C: (5-phenyl-1,3,4-thiadiazol-2-yl)methanamine

194

A mixture of 2-(chloromethyl)-5-phenyl-1,3,4-thiadiazole (0.200 g, 0.949 mmol) in ammonia (7.0 M in MeOH, 3.0 mL, 21 mmol) was stirred and heated at 50 °C for 12 hours. The reaction mixture was cooled to room temperature and concentrated under reduced to afford (5-phenyl-1,3,4-thiadiazol-2-yl)methanamine, which was used without purification. LC/MS (m/z): 192 $(M+H)^+$

Intermediate 57

Preparation of (5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanamine

Step A: 5-(2H-1,2,3-triazol-2-yl)picolinonitrile

195

A mixture of 2H-1,2,3-triazole (0.566 g, 8.19 mmol), Cs_2CO_3 (4.00 g, 12.3 mmol) and 5-fluoropicolinonitrile (0.50 g, 4.1 mmol) in DMF (30 mL) was stirred and heated at 80 °C for 12 hours. The mixture was cooled to room temperature and the residue was partitioned between water (50 mL) and EtOAc (30 mL). The organic layer was separated, and the aqueous was re-extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 5-(2H-1,2,3-triazol-2-yl)picolinonitrile. ^{1}H NMR (400 MHz, methanol-d_4) δ 9.46 (d, J = 2.0 Hz, 1H), 8.62 (dd, J = 2.5, 8.4 Hz, 1H), 8.09 (s, 2H), 8.06 (d, J = 8.5 Hz, 1H). LC/MS (m/z): 172 $(M+H)^+$

Step B: tert-butyl ((5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methyl)carbamate

196

Raney nickel (206 mg, 0.351 mmol) was added to a mixture of 5-(2*H*-1,2,3-triazol-2-yl)picolinonitrile (0.600 g, 3.51 mmol) and Boc-anhydride (1.6 mL, 7.0 mmol) in MeOH (20 mL) under an argon atmosphere at room temperature. The mixture was degassed and backfilled with H_2 (three times). The mixture was stirred under H_2 (50 psi) at room temperature for 16 hours. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford *tert*-butyl ((5-(2*H*-1,2,3-triazol-2-yl)pyridin-2-yl)methyl)carbamate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 (d, J = 2.0 Hz, 1H), 8.39-8.38 (m, 1H), 8.19 (s, 2H), 7.56-7.44 (m, 2H), 4.30-4.29 (m, 2H), 1.41 (s, 9H). LC/MS (m/z): 276 $(M+H)^+$

Step C: (5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanamine

197

A mixture of *tert*-butyl ((5-(2*H*-1,2,3-triazol-2-yl)pyridin-2-yl)methyl)carbamate (0.700 g, 2.54 mmol) in HCl (4.0 M in dioxane, 15 mL, 60 mmol) was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure to afford (5-(2*H*-1,2,3-triazol-2-yl)pyridin-2-yl)methanamine, which was used without purification in the next step. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26-9.25 (m, 1H), 8.55 (br s, 2H), 8.49-8.46 (m, 1H), 8.24 (s, 2H), 7.75-7.73 (m, 1H), 4.29-4.25 (m, 2H). LC/MS (m/z): 176 $(M+H)^+$

Intermediate 58

Preparation of (5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl methanesulfonate

Step A: ethyl 2-(2-(3-fluorobenzoyl)hydrazinyl)-2-oxoacetate

198

Ethyl 2-chloro-2-oxoacetate (5.49 mL, 49.1 mmol) was added dropwise to a mixture of 3-fluorobenzohydrazide (7.57 g, 49.1 mmol) and triethylamine (6.85 mL, 49.1 mmol) in dichloromethane (250 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes after addition was complete. The reaction mixture was quenched with water (100 mL) and diluted with ethyl acetate (500 mL), methanol (50 mL), and brine (100 mL). The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate (4 x 100 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford ethyl 2-(2-(3-fluorobenzoyl)hydrazineyl)-2-oxoacetate which was used without purification in the next step. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (s, 1H), 10.71 (s, 1H), 7.74 (d, J = 7.8 Hz,

1H), 7.66 (d, J = 9.2 Hz, 1H), 7.63 – 7.58 (m, 1H), 7.52 – 7.48 (m, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H). LC/MS (m/z): 255 $(M+H)^+$

Step B: ethyl 5-(3-fluorophenyl)-1,3,4-thiadiazole-2-carboxylate

199

Lawesson's reagent (3.98 g, 9.83 mmol) was added to a mixture of ethyl 2-(2-(3-fluorobenzoyl)hydrazineyl)-2-oxoacetate (2.50 g, 9.83 mmol) in tetrahydrofuran (70 mL) at room temperature. The reaction mixture was stirred and heated at 70 °C for 60 minutes after addition was complete. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in hexanes) to afford ethyl 5-(3-fluorophenyl)-1,3,4-thiadiazole-2-carboxylate. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 – 7.95 (m, 2H), 7.69 – 7.64 (m, 1H), 7.55 – 7.50 (td, J = 7.8, 7.2, 1.4 Hz, 1H), 4.47 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H). LC/MS (m/z): 253 $(M+H)^+$

Step C: (5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl)methanol

200

Sodium borohydride (1.04 g, 27.6 mmol) was added to a mixture of ethyl 5-(3-fluorophenyl)-1,3,4-thiadiazole-2-carboxylate (2.32 g, 9.20 mmol) in methanol (50 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred at 0 °C for 60 minutes after the addition was complete. The reaction mixture was quenched with acetic acid (1.58 mL, 27.6 mmol) at 0 °C. The mixture was concentrated under reduced pressure (to remove methanol prior to workup). The residue was partitioned between ethyl acetate (800 mL) and brine (150 mL). The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford (5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl)methanol, which was used without purification in the next step. ^{1}H NMR (499 MHz, DMSO-d_6) δ 7.87 – 7.81 (m, 2H), 7.65 – 7.58 (m,

1H), 7.46 – 7.41 (m, 1H), 6.34 (t, J = 5.9 Hz, 1H), 4.91 (d, J = 5.9 Hz, 2H). LC/MS (m/z): 211 $(M+H)^+$

Step D: (5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl methanesulfonate

201

Triethylamine (2.14 mL, 15.4 mmol) was added dropwise to a mixture of (5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl)methanol (2.69 g, 12.8 mmol) and methanesulfonic anhydride (2.45 g, 14.1 mmol) in dichloromethane (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour after the addition was complete. The reaction mixture was quenched with water (20 mL), and the organic layer was separated, washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in hexanes) to afford (5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl methanesulfonate. LC/MS (m/z): 289 $(M+H)^+$

Intermediate 59

Preparation of (3-phenylisoxazol-5-yl)methyl methanesulfonate

Step A: (Z)-N-hydroxybenzimidoyl chloride

202

N-Chlorosuccinimide (6.17 g, 46.2 mmol) was added to a mixture of (E)-benzaldehyde oxime (5.6 g, 46 mmol) and pyridine (0.374 mL, 4.62 mmol) in THF (70 mL) at room temperature. The mixture was stirred and heated at 50 °C for 1 hour. The mixture was concentrated under reduced pressure to afford (Z)-N-hydroxybenzimidoyl chloride, which was used without purification in the next step. LC/MS (m/z): 156 $(M+H)^+$

Step B: (3-phenylisoxazol-5-yl)methanol

95

Prop-2-yn-1-ol (3.24 mL, 56.2 mmol) and TEA (7.73 mL, 55.5 mmol) were added to a mixture of (Z)-N-hydroxybenzimidoyl chloride (7.19 g, 46.2 mmol) in THF (50 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred and heated at 50 °C for 2 hours. The mixture was cooled to room temperature and quenched by the addition of saturated aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford (3-phenylisoxazol-5-yl)methanol. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.70 - 7.42 (m, 2H), 7.27 - 7.26 (m, 3H), 6.36 (br d, *J* = 17.7 Hz, 1H), 4.75 - 4.37 (m, 2H). LC/MS (m/z): 176 $(M+H)^+$

Step C: (3-phenylisoxazol-5-yl)methyl methanesulfonate

204

Triethylamine (1.59 mL, 11.4 mmol) was added to a mixture of (3-phenylisoxazol-5-yl)methanol (1.00 g, 5.71 mmol) and methanesulfonic anhydride (1.49 g, 8.56 mmol) in DCM (20 mL) at room temperature. The mixture was stirred at room temperature for 1 hour. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford (3-phenylisoxazol-5-yl)methyl methanesulfonate. LC/MS (m/z): 254 $(M+H)^+$

Intermediates shown in Intermediate Table 9 below, were prepared according to procedures analogous to those outlined in Intermediate 59 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 9

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 60		(3-(2-fluorophenyl)isoxazol-5-yl)methyl methanesulfonate 205	272
Intermediate 61		(3-(4-fluorophenyl)isoxazol-5-yl)methyl methanesulfonate 206	272
Intermediate 62		(3-(3-fluorophenyl)isoxazol-5-yl)methyl methanesulfonate 207	272
Intermediate 63		(3-(pyridin-2-yl)isoxazol-5-yl)methyl methanesulfonate 208	255

Intermediate 64

Preparation of 4-(bromomethyl)-1-phenyl-1H-pyrazole

Step A: (1-phenyl-1H-pyrazol-4-yl)methanol

209

Borane-THF (1.0 M in THF, 2.7 mL, 2.7 mmol) was added to a mixture of 1-phenyl-1H-pyrazole-4-carboxylic acid (0.500 g, 2.66 mmol) in THF (20 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 16 hours. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford (1-phenyl-1H-pyrazol-4-yl)methanol. LC/MS (m/z): 175 $(M+H)^+$

51

Step B: 4-(bromomethyl)-1-phenyl-1H-pyrazole

210

A mixture of (1-phenyl-1H-pyrazol-4-yl)methanol (0.400 g, 2.30 mmol), tetrabromomethane (1.1 g, 3.4 mmol), and triphenylphosphine (903 mg, 3.44 mmol) in DCM (20 mL) was stirred at room temperature for 16 hours. The mixture concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 4-(bromomethyl)-1-phenyl-1H-pyrazole.

Intermediate 65

Preparation of 5-(bromomethyl)-3-phenylisothiazole

Step A: 5-methyl-3-phenylisothiazole

211

A mixture of potassium phosphate tribasic (884 mg, 4.16 mmol), Pd(dppf)Cl_2 (76 mg, 0.10 mmol), trimethylboroxine (1.52 mL, 5.21 mmol), and 5-bromo-3-phenylisothiazole (0.500 g, 2.08 mmol) in 1,4-dioxane (25 mL) was sparged with N_2. The mixture was stirred and heated to 90 °C for 24 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between water (10 mL) and EtOAc (10 mL). The organic layer was separated, and the aqueous was re-extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 5-methyl-3-phenylisothiazole. ^{1}H NMR (500 MHz, methanol-d_4) δ 7.95 - 7.89 (m, 2H), 7.52 (s, 1H), 7.47 - 7.38 (m, 3H), 2.71 - 2.59 (m, 3H). LC/MS (m/z): 176 $(M+H)^+$

Step B: 5-(bromomethyl)-3-phenylisothiazole

212

N-Bromosuccinimide (203 mg, 1.14 mmol) was added to a mixture of 5-methyl-3-phenylisothiazole (0.200 g, 1.14 mmol) and azobisisobutyronitrile (38 mg, 0.23 mmol) in chloroform (15 mL) at room temperature. The mixture was stirred at 80 °C for 2.5 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between water (10 mL) and DCM (10 mL). The organic layer was separated, and the aqueous was re-extracted with DCM (3 x 10 mL). The organic layers were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford the crude product. The residue was purified by reverse phase (eluting acetonitrile in water, with ammonium bicarbonate modifier) to afford 5-(bromomethyl)-3-phenylisothiazole. ^{1}H NMR

(400 MHz, chloroform-*d*) δ 7.94 - 7.89 (m, 2H), 7.59 (s, 1H), 7.49 - 7.39 (m, 3H), 4.74 (d, *J* = 0.8 Hz, 2H). LC/MS (m/z): 254, 256 $(M+H)^+$

Intermediate 66

Preparation of 1-(1-methylcyclobutyl)piperazine-2,3-dione

Pd(OH)$_2$ (0.394 g, 0.561 mmol) and palladium on carbon (1.79 g, 1.68 mmol) were added to a mixture of 1-(bicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione (5.0 g, 28 mmol) in MeOH (200 mL) under a stream of nitrogen. The mixture was degassed and backfilled with H_2 (three times). The mixture was stirred under a H_2 atmosphere (Pressure: 50 psi) and heated at 60 °C for 24 hours. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure to afford a mixture of 1-(1-methylcyclobutyl)piperazine-2,3-dione and 1-(bicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione. The mixture was resolved by Chiral-SFC (Column Phenomenex-Cellulose-2 [250mm x 50mm, 10um]; eluting 45% ethanol in CO_2 with 0.1% ammonia modifier) to afford 1-(bicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione as the first eluting peak and 1-(1-methylcyclobutyl)piperazine-2,3-dione as the second eluting peak.

Peak 1: 1-(bicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione: ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 8.59 (br s, 1H), 3.50 - 3.40 (m, 2H), 3.36 - 3.31 (m, 2H), 2.54 - 2.51 (m, 1H), 2.16 - 2.09 (m, 6H). LC/MS (m/z): 181 $(M+H)^+$

Peak 2: 1-(1-methylcyclobutyl)piperazine-2,3-dione: : ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 8.52 (br s, 1H), 3.33 - 3.28 (m, 4H), 2.28 - 2.16 (m, 2H), 1.98 - 1.89 (m, 2H), 1.80 - 1.59 (m, 2H), 1.35 (s, 3H). LC/MS (m/z): 183 $(M+H)^+$

Intermediate 67

Preparation of 3-(bromomethyl)-5-phenyl-1H-pyrazole

Step A: (5-phenyl-1H-pyrazol-3-yl)methanol

Borane-THF (1.0 M in THF, 2.1 mL, 2.1 mmol) was added to a mixture of 5-phenyl-1H-pyrazole-3-carboxylic acid (0.400 g, 2.13 mmol) in THF (6 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 hours. The reaction was quenched with MeOH (8 mL) and heated at 60 °C for 2 hours. The mixture was concentrated under reduced pressure. The residue was diluted with water and extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford (5-phenyl-1H-pyrazol-3-yl)methanol.

Step B: 3-(bromomethyl)-5-phenyl-1H-pyrazole

A mixture of (5-phenyl-1H-pyrazol-3-yl)methanol (0.050 g, 0.29 mmol) and phosphorus tribromide (0.014 mL, 0.14 mmol) in trichloromethane (5 mL) was stirred at room temperature for 1 hour. The mixture was concentrated under reduced pressure. The residue was partitioned between water (5 mL) and EtOAc (5 mL). The organic layer was separated, and the aqueous was re-extracted with EtOAc (3 x 5 mL). The organic layers were combined, washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 3-

(bromomethyl)-5-phenyl-1H-pyrazole which was used in the next step without purification. LC/MS (m/z): 237, 239 $(M+H)^+$

Intermediate 68

Preparation of (5-(pyridin-2-yl)isoxazol-3-yl)methyl methanesulfonate

Step A: ethyl 5-(pyridin-2-yl)isoxazole-3-carboxylate

217

2-ethynylpyridine (10 g, 97 mmol) was added to a mixture of ethyl (E)-2-chloro-2-(hydroxyimino)acetate (15 g, 97 mmol) and TEA (14 mL, 97 mmol) in THF (150 mL) at room temperature. The mixture was stirred at room temperature for 12 hours. The reaction mixture was quenched with saturated aqueous sodium bicarbonate (50 mL) and extracted with EtOAc (100 mL). The organic layer was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford ethyl 5-(pyridin-2-yl)isoxazole-3-carboxylate. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.73 (d, *J* = 4.6 Hz, 1H), 8.00 - 7.81 (m, 2H), 7.39 (dd, *J* = 4.9, 7.5 Hz, 1H), 7.31 (s, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H). LC/MS (m/z): 219 $(M+H)^+$

Step B: (5-(pyridin-2-yl)isoxazol-3-yl)methanol

218

$NaBH_4$ (0.721 g, 19.1 mmol) was added to a mixture of ethyl 5-(pyridin-2-yl)isoxazole-3-carboxylate (3.2 g, 15 mmol) in MeOH (50 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 2 hours. The mixture was quenched with saturated aqueous ammonium

chloride until the pH was ~7. The mixture was partially concentrated under reduced pressure and then diluted with DCM (100 mL). The mixture was washed with water (10 mL). The organic layer was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting methanol in dichloromethane) to afford (5-(pyridin-2-yl)isoxazol-3-yl)methanol. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.77 - 8.59 (m, 1H), 7.95 - 7.88 (m, 1H), 7.87 - 7.81 (m, 1H), 7.36 (ddd, *J* = 1.4, 4.9, 7.4 Hz, 1H), 7.00 (s, 1H), 4.85 (d, *J* = 6.3 Hz, 2H), 2.82 - 2.64 (m, 1H). LC/MS (m/z): 177 $(M+H)^+$

Step C: (5-(pyridin-2-yl)isoxazol-3-yl)methyl methanesulfonate

219

A mixture of (5-(pyridin-2-yl)isoxazol-3-yl)methanol (0.850 g, 4.82 mmol), methanesulfonic anhydride (1.26 g, 7.24 mmol), and TEA (1.35 mL, 9.65 mmol) in DCM (15 mL) was stirred at room temperature for 1 hour. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford (5-(pyridin-2-yl)isoxazol-3-yl)methyl methanesulfonate. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.83 - 8.57 (m, 1H), 7.94 - 7.88 (m, 1H), 7.87 - 7.81 (m, 1H), 7.40 - 7.33 (m, 1H), 7.09 - 7.00 (m, 1H), 5.44 - 5.34 (m, 2H), 3.13 - 3.04 (m, 3H). LC/MS (m/z): 255 $(M+H)^+$

Intermediates shown in Intermediate Table 10 below, were prepared according to procedures analogous to those outlined in Intermediate 68 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 10

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 69		(5-(pyridin-3-yl)isoxazol-3-yl)methyl methanesulfonate 220	255

Intermediate 70

Preparation of 3-(chloromethyl)-6-phenylpyridazine

Step A: 3-methyl-6-phenylpyridazine

221

A mixture of 3-chloro-6-methylpyridazine (7.00 g, 54.4 mmol), phenylboronic acid (6.97 g, 57.2 mmol), potassium phosphate tribasic (17 g, 82 mmol), and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(ii) dichloromethane complex (2.39 g, 3.27 mmol) in 1,4-dioxane (100 mL) was degassed with nitrogen at room temperature for 5 minutes. The mixture was stirred and heated at 80 °C for 2 hours. The reaction mixture was cooled to room temperature and diluted with water (50 mL). The mixture was extracted with EtOAc (100 mL). The organic layer was separated, washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was diluted with 1,2-dichloroethane (100 mL). $NaHSO_3$ (9.8 g, 94 mmol) was added, and the mixture was stirred and heated at 65 °C for 12 hours. The mixture was cooled to room temperature, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 3-methyl-6-phenylpyridazine. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.92 (dd, *J* = 7.9 Hz, 1.0 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.41 - 7.32 (m, 3H), 7.28 - 7.25 (m, 1H), 2.62 (s, 3H). LC/MS (*m/z*): 171 $(M+H)^+$

Step B: 3-(chloromethyl)-6-phenylpyridazine

91

1,3,5-trichloro-1,3,5-triazinane-2,4,6-trione (3.71 g, 16.0 mmol) was added to a mixture of 3-methyl-6-phenylpyridazine (6.8 g, 40 mmol) in trichloromethane (100 ml) at room temperature. The mixture was stirred and heated at 60 °C for 6 hours. The mixture was cooled to room temperature, filtered, and concentrated under reduced pressure. The residue was purified by silica gel

chromatography (eluting ethyl acetate in petroleum ether) to afford 3-chloro-6-(chloromethyl)pyridazine. LC/MS (*m/z*): 205 $(M+H)^+$

Intermediates shown in Intermediate Table 11 below, were prepared according to procedures analogous to those outlined in Intermediate 70 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 11

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 71		3-(chloromethyl)-6-(2-fluorophenyl)pyridazine 223	223
Intermediate 72		3-(chloromethyl)-6-(2,6-difluorophenyl)pyridazine 224	241
Intermediate 73		5-(6-(chloromethyl)pyridazin-3-yl)thiazole 225	212
Intermediate 74		3-(chloromethyl)-6-(pyridin-2-yl)pyridazine 226	206
Intermediate 75		3-(chloromethyl)-6-(pyridin-3-yl)pyridazine 227	206

Intermediate 76

Preparation of 2-(chloromethyl)-5-(2*H*-1,2,3-triazol-2-yl)pyridine

Step A: 2-methyl-5-(2*H*-1,2,3-triazol-2-yl)pyridine

228

A mixture of 5-bromo-2-methylpyridine (15.9 g, 92.0 mmol), $Pd_2(dba)_3$ (8.46 g, 9.24 mmol), 2-di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl (11.1 g, 23.1 mmol), and potassium phosphate (39.2 g, 185 mmol) was degassed with argon for 5 minutes. Toluene (200 mL) and 1*H*-1,2,3-triazole (8.0 mL, 140 mmol) were added to the reaction mixture, and the mixture was degassed with argon for an additional 5 minutes (sub-surface sparge). The reaction mixture was stirred under an argon atmosphere and heated to 110 °C for 2.5 days. The reaction mixture was cooled to room temperature and diluted with dichloromethane (400 mL). The mixture was filtered through a fritted funnel and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting methanol in dichloromethane) to afford the product as a mixture with minor impurities. The isolated material was re-purified by silica gel chromatography (eluting ethyl acetate in hexanes) to afford 2-methyl-5-(2*H*-1,2,3-triazol-2-yl)pyridine. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.10 (d, J = 2.5 Hz, 1H), 8.27 (dd, J = 8.4, 2.6 Hz, 1H), 8.18 (s, 2H), 7.48 (d, J = 8.4 Hz, 1H), 2.55 (s, 3H). LC/MS (*m/z*): 161 $(M+H)^+$

Step B: 2-(chloromethyl)-5-(2*H*-1,2,3-triazol-2-yl)pyridine

229

A mixture of 2-methyl-5-(2*H*-1,2,3-triazol-2-yl)pyridine (11.8 g, 73.4 mmol) and trichloroisocyanuric acid (17.1 g, 73.4 mmol) in carbon tetrachloride (200 mL) was stirred and heated at 80 °C for 18 hours. Additional trichloroisocyanuric acid (5.1 g, 22 mmol) was added to the reaction mixture, and the mixture was stirred for an additional 8 hours at 80 °C. The reaction mixture was cooled to room temperature. The mixture was filtered through a fritted funnel, and the solids were washed with DCM (200 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluting ethyl acetate in dichloromethane) to afford 2-(chloromethyl)-5-(2*H*-1,2,3-triazol-2-yl)pyridine. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.23 (d, J = 2.4 Hz, 1H), 8.44 (dd, J = 8.5, 2.6 Hz, 1H), 8.23 (s, 2H), 7.78 (d, J = 8.5 Hz, 1H), 4.88 (s, 2H). LC/MS (*m/z*): 195 $(M+H)^+$

Intermediate 77

Preparation of 2-(chloromethyl)-5-phenyl-1,3,4-thiadiazole

Step A: N'-(2-chloroacetyl)benzohydrazide

Cloroacetyl chloride (19.3 mL, 242 mmol) was added to a mixture of benzohydrazide (30.0 g, 220 mmol) in ethyl acetate (460 mL) at 0 °C. The mixture was stirred and heated at 65 °C for 13 hours. The mixture was cooled to room temperature and filtered. The isolated solids were dried under vacuum to afford N'-(2-chloroacetyl)benzohydrazide, which was used in the next step without further purification. LC/MS (*m/z*): 213 $(M+H)^+$

Step B: 2-(chloromethyl)-5-phenyl-1,3,4-thiadiazole

Lawesson's reagent (18.3 g, 45.1 mmol) was added to a mixture of N'-(2-chloroacetyl)benzohydrazide (16 g, 75 mmol) in THF (340 mL). The mixture was stirred and heated at 70 °C for 4 hours. The mixture was cooled to room temperature, diluted with saturated aqueous $NaHCO_3$ (300 mL), and extracted with EtOAc (3 x 200 mL). The organic layers were combined, washed with brine (500 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 2-(chloromethyl)-5-phenyl-1,3,4-thiadiazole. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.99 - 7.94 (m, 2H), 7.54 - 7.47 (m, 3H), 4.98 (s, 2H). LC/MS (*m/z*): 211 $(M+H)^+$

Intermediates shown in Intermediate Table 12 below, were prepared according to procedures analogous to those outlined in Intermediate 77 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 12

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 78		2-(chloromethyl)-5-(2-chlorophenyl)-1,3,4-thiadiazole 232	245
Intermediate 79		2-(chloromethyl)-5-(2-fluorophenyl)-1,3,4-thiadiazole 233	229

Intermediate 80

Preparation of 2-(chloromethyl)-5-(3-fluorophenyl)-1,3,4-thiadiazole

Step A: N'-(2-chloroacetyl)-3-fluorobenzohydrazide

234

2-Chloroacetyl chloride (2.58 mL, 32.4 mmol) was added dropwise to a mixture of 3-fluorobenzohydrazide (5.00 g, 32.4 mmol) in EtOAc (50 mL) at 0 °C. The mixture was stirred at room temperature for 7 hours. The mixture was cooled to room temperature and concentrated under reduced pressure to afford N'-(2-chloroacetyl)-3-fluorobenzohydrazide, which was used in the next step with purification. LC/MS (*m/z*): 231 $(M+H)^+$

Step B: 2-(chloromethyl)-5-(3-fluorophenyl)-1,3,4-thiadiazole

235

Lawesson's reagent (8.52 g, 21.07 mmol) was added portion wise to a mixture of N'-(2-chloroacetyl)-3-fluorobenzohydrazide (8.10 g, 35.1 mmol) in THF (90 mL) at 0 °C. The reaction mixture was stirred and heated at 80 °C for 12 hours. The reaction mixture was cooled to room temperature, diluted with saturated aqueous $NaHCO_3$ (50 mL), and extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 2-(chloromethyl)-5-(3-fluorophenyl)-1,3,4-thiadiazole. ^{1}H NMR (500 MHz, methanol-d_4) δ 7.83 - 7.75 (m, 2H), 7.61 - 7.54 (m, 1H), 7.33 (dt, J = 8.5 Hz, 2.4 Hz, 1H), 5.13 (s, 2H). LC/MS (m/z): 229 $(M+H)^+$

Intermediate 81

Preparation of (3-phenylbicyclo[1.1.1]pentan-1-yl)methyl 4-methylbenzenesulfonate

Step A: (3-phenylbicyclo[1.1.1]pentan-1-yl)methanol

236

Borane-THF (1.0 M in THF, 1.6 mL, 1.6 mmol) was added dropwise to a mixture of 3-phenylbicyclo[1.1.1]pentane-1-carboxylic acid (0.15 g, 0.80 mmol) in THF (4 mL) at 0 °C. The mixture was stirred for 1 hour 62 at 0 °C and then warmed to room temperature and stirred for 1 hour. The mixture was quenched by the dropwise addition of MeOH (5 mL), and the mixture was concentrated under reduced pressure. Saturated aqueous K_2CO_3 (20 mL) was added to the residue, and the mixture was extracted with DCM (2 × 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (3-

phenylbicyclo[1.1.1]pentan-1-yl)methanol, which was used in the next step without purification. LC/MS (*m/z*): 157 $(M+H-H_2O)^+$

Step B: (3-phenylbicyclo[1.1.1]pentan-1-yl)methyl 4-methylbenzenesulfonate

237

4-Toluenesulfonyl chloride (171 mg, 0.895 mmol) was added to a mixture of (3-phenylbicyclo[1.1.1]pentan-1-yl)methanol (0.120 g, 0.689 mmol) and TEA (0.192 ml, 1.377 mmol) in DCM (4 mL) at room temperature. The mixture was stirred for 12 hours at room temperature. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford (3-phenylbicyclo[1.1.1]pentan-1-yl)methyl 4-methylbenzenesulfonate. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.31 - 7.27 (m, 2H), 7.23 - 7.19 (m, 1H), 7.19 - 7.15 (m, 2H), 4.11 (s, 2H), 2.46 (s, 3H), 1.97 (s, 6H). LC/MS (*m/z*): 346 $(M+H_2O)^+$

Intermediate 82

Preparation of 1-((6-chloropyridazin-3-yl)methyl)-4-cyclopentylpiperazine-2,3-dione

238

Sodium hydride (27 mg, 0.68 mmol, 60% dispersion in mineral oil) was added to a mixture of 1-cyclopentylpiperazine-2,3-dione (0.100 g, 0.549 mmol) in DMF (5 mL) at 0 °C. The mixture was stirred for 5 minutes, and then 3-chloro-6-(chloromethyl)pyridazine (89 mg, 0.55 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (3 x 25 mL). The organic layers were combined, washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-((6-chloropyridazin-3-yl)methyl)-4-

cyclopentylpiperazine-2,3-dione. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.83-7.71 (m, 2H), 4.94 (s, 2H), 4.82-4.78 (m, 1H), 3.76-3.70 (m, 2H), 3.63-3.56 (m, 2H), 1.95-1.86 (m, 2H), 1.82-1.73 (m, 2H), 1.68-1.60 (m, 4H). LC/MS (m/z): 309 $(M+H)^+$

Examples shown in Intermediate Table 13 below, were prepared according to procedures analogous to those outlined in Intermediate 82 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 13

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 83		1-((5-bromopyrimidin-2-yl)methyl)-4-cyclopentylpiperazine-2,3-dione	353, 355
Intermediate 84		1-(4-bromo-2-fluorobenzyl)-4-cyclopentylpiperazine-2,3-dione 240	369, 371
Intermediate 85		1-(bicyclo[1.1.1]pentan-1-yl)-4-((6-chloropyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 241	305
Intermediate 86		1-((6-chloropyridazin-3-yl)methyl)-4-cyclobutyl-1,4-dihydropyrazine-2,3-dione 242	293
Intermediate 87		1-(4-bromobenzyl)-4-cyclobutylpiperazine-2,3-dione 243	337, 339

Intermediate 88		1-((5-bromo-3-fluoropyridin-2-yl)methyl)-4-cyclobutylpiperazine-2,3-dione 244	356, 358
Intermediate 89		1-((5-chloropyrazin-2-yl)methyl)-4-cyclobutylpiperazine-2,3-dione 245	295
Intermediate 90		1-(bicyclo[1.1.1]pentan-1-yl)-4-((6-chloropyridazin-3-yl)methyl)piperazine-2,3-dione 246	307
Intermediate 91		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-chloropyrazin-2-yl)methyl)piperazine-2,3-dione 247	307
Intermediate 92		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-bromo-3-fluoropyridin-2-yl)methyl)piperazine-2,3-dione 248	368, 370
Intermediate 93		1-((5-chloropyrazin-2-yl)methyl)-4-cyclopentylpiperazine-2,3-dione 249	309

Intermediate 94		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((6-chloropyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 250	319
Intermediate 95		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((6-chloropyridazin-3-yl)methyl)piperazine-2,3-dione 251	321
Intermediate 96		1-((6-chloropyridazin-3-yl)methyl)-4-cyclopentyl-1,4-dihydropyrazine-2,3-dione 252	307

Intermediate 97

Preparation of 1-((6-chloropyridazin-3-yl)methyl)-4-cyclobutylpiperazine-2,3-dione

253

3-Chloro-6-(chlorometh65yl)pyridazine (58.6 g, 359 mmol) was added portion wise to a mixture of 1-cyclobutylpiperazine-2,3-dione (55.0 g, 327 mmol) and Cs_2CO_3 (127 g, 392 mmol) in DMF (600 mL) at room tem67perature. The mixture was heated to 80 °C and stirred for 16 hours. The reaction mixture was cooled to room temperature and diluted with dichloromethane (400 mL) and then filtered through Celite. The filtrate was washed with water, and the aqueous layer was extracted with additional dichloromethane (2 x 100 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was

purified by silica gel chromatography (eluting methanol in dichloromethane), and the isolated product was then triturated with ethyl acetate (100 mL). The suspension was stirred at room temperature for 20 minutes and then filtered. The collected solids were dried under vacuum to afford 1-((6-chloropyridazin-3-yl)methyl)-4-cyclobutylpiperazine-2,3-dione. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.81 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 4.93 (s, 2H), 4.72 - 4.64 (m, 1H), 3.76 – 3.74 (m, 2H), 3.71 – 3.69 (m, 2H), 2.31 – 2.17 (m, 4H), 1.78 – 1.76 (m, 2H). LC/MS (*m/z*): 295 $(M+H)^+$

Intermediate 98

Preparation of 1-((6-chloropyridin-3-yl)methyl)-4-cyclopentylpiperazine-2,3-dione

254

A mixture of 1-cyclopentylpiperazine-2,3-dione (0.73 g, 4.0 mmol), 5-(bromomethyl)-2-chloropyridine (0.90 g, 4.4 mmol) and potassium carbonate (1.82 g, 13.1 mmol) in DMF (10 mL) was stirred and heated to 30 °C for 18 hours. The mixture was cooled, diluted with water, and extracted with isopropyl alcohol:chloroform (1:3). The organic layers were combined, washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting EtOAc:EtOH (3:1) in hexanes) to afford 1-((6-chloropyridin-3-yl)methyl)-4-cyclopentylpiperazine-2,3-dione. LC/MS (*m/z*): 308 $(M+H)^+$

Examples shown in Intermediate Table 14 below, were or may be prepared according to procedures analogous to those outlined in Intermediate 98 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 14

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 99		1-((5-chloro-1,3,4-thiadiazol-2-yl)methyl)-4-cyclopentylpiperazine-2,3-dione 255	315
Intermediate 100		1-((6-chloropyridazin-3-yl)methyl)-4-(3-phenylcyclobutyl)piperazine-2,3-dione 256	371
Intermediate 101		1-((5-bromo-3-fluoropyridin-2-yl)methyl)-4-cyclopentylpiperazine-2,3-dione 257	370, 372
Intermediate 102		1-((5-bromopyridin-2-yl)methyl)-4-cyclopentylpiperazine-2,3-dione 258	352, 354
Intermediate 103		1-((5-bromopyridin-2-yl)methyl)-4-cyclobutylpiperazine-2,3-dione 259	338, 340
Intermediate 104		1-(bicyclo[1.1.1]pentan-1-yl)-4-(4-bromobenzyl)piperazine-2,3-dione 260	349, 351

Intermediate 105		1-(bicyclo[1.1.1]pentan-1-yl)-4-(4-bromo-2-fluorobenzyl)piperazine-2,3-dione 261	367, 369
Intermediate 106		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 262	369, 371
Intermediate 107		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 263	371, 373
Intermediate 108		1-((5-bromoisoxazol-3-yl)methyl)-4-cyclobutyl-1,4-dihydropyrazine-2,3-dione 264	326, 328
Intermediate 109		1-((5-bromoisoxazol-3-yl)methyl)-4-cyclopentylpiperazine-2,3-dione 265	342, 344
Intermediate 110		1-((5-bromoisoxazol-3-yl)methyl)-4-cyclopentyl-1,4-dihydropyrazine-2,3-dione 266	340, 342

Intermediate 111		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-bromoisoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 267	352, 354
Intermediate 112		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-bromopyridin-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 268	362, 364
Intermediate 113		1-((5-bromothiazol-2-yl)methyl)-4-cyclobutylpiperazine-2,3-dione 269	344, 346
Intermediate 114		1-((2-bromothiazol-5-yl)methyl)-4-cyclobutylpiperazine-2,3-dione 270	344, 346
Intermediate 115		1-((6-bromopyridin-3-yl)methyl)-4-cyclobutyl-1,4-dihydropyrazine-2,3-dione 271	336, 338
Intermediate 116		1-((5-chloropyrazin-2-yl)methyl)-4-cyclobutyl-1,4-dihydropyrazine-2,3-dione 272	293

Intermediate 117		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-chloropyrazin-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 273	305
Intermediate 118		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-bromoisoxazol-3-yl)methyl)piperazine-2,3-dione 274	340, 342
Intermediate 119		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-bromoisoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 275	338, 340
Intermediate 120		1-(bicyclo[1.1.1]pentan-1-yl)-4-(isoxazol-3-ylmethyl)-1,4-dihydropyrazine-2,3-dione 276	260
Intermediate 121		1-cyclobutyl-4-(thiazol-2-ylmethyl)piperazine-2,3-dione 277	266
Intermediate 122		1-(isoxazol-3-ylmethyl)-4-(1-methylcyclobutyl)-1,4-dihydropyrazine-2,3-dione 278	262

Intermediate 123		1-(bicyclo[1.1.1]pentan-1-yl)-4-(isoxazol-3-ylmethyl)piperazine-2,3-dione 279	262
Intermediate 124		1-(bicyclo[1.1.1]pentan-1-yl)-4-(prop-2-yn-1-yl)-1,4-dihydropyrazine-2,3-dione 280	217
Intermediate 125		1-((5-bromopyridin-2-yl)methyl)-4-(1-methylcyclopropyl)-1,4-dihydropyrazine-2,3-dione 281	336, 338
Intermediate 126		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-bromopyridin-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 282	348, 350
Intermediate 127		1-(1-methylcyclopropyl)-4-(prop-2-yn-1-yl)-1,4-dihydropyrazine-2,3-dione 283	205

Intermediate 128		1-((6-chloropyridazin-3-yl)methyl)-4-(1-methylcyclopropyl)-1,4-dihydropyrazine-2,3-dione 284	293
Intermediate 129		1-(bicyclo[1.1.1]pentan-1-yl)-4-((6-bromopyridin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 285	348, 350
Intermediate 130		1-(4-((6-chloropyridazin-3-yl)methyl)-2,3-dioxo-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 286	304
Intermediate 131		1-((6-bromopyridin-3-yl)methyl)-4-(1-methylcyclopropyl)-1,4-dihydropyrazine-2,3-dione 287	336, 338
Intermediate 132		1-(4-((5-bromopyridin-2-yl)methyl)-2,3-dioxo-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 288	347, 349

Intermediate 133		1-(2,3-dioxo-4-(prop-2-yn-1-yl)-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 289	216
Intermediate 134		1-(bicyclo[1.1.1]pentan-1-yl)-4-((6-chloropyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 241	305
Intermediate 135		1-(4-((6-bromopyridin-3-yl)methyl)-2,3-dioxo-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 291	347, 349

Intermediate 136

Preparation of ethyl 2-oxo-2-((2-oxoethyl)((5-phenylpyrimidin-2-yl)methyl)amino)acetate

Step A: 5-phenylpyrimidine-2-carbonitrile

292

A mixture of 5-bromopyrimidine-2-carbonitrile (150 g, 0.81 mol), phenyl boronic acid (198 g, 1.63 mol), and potassium phosphate tribasic (346 g, 1.63 mol) in 1,4-dioxane (1.3 L) and water (0.2 L) was sparged with nitrogen for 5 minutes at room temperature. $PdCl_2$(dppf) (66 g, 0.080 mol) was added to the reaction mixture, and the mixture was stirred and heated at 80 °C for 30 minutes.

The reaction mixture was cooled to room temperature and quenched with water (1.0 L). The mixture was extracted with ethyl acetate (3 x 1.0 L). The organic layers were combined, washed with brine (500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was triturated with methanol, filtered, and the collected solids were dried under vacuum to afford 5-phenylpyrimidine-2-carbonitrile. ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.02 (s, 2H), 7.63-7.54 (m, 5H).

Step B: (5-phenylpyrimidin-2-yl)methanamine

293

A mixture of 5-phenylpyrimidine-2-carbonitrile (16 g. 0.086 mol) and palladium on carbon (10%, 1.50 g) was sparged with nitrogen. Methanol (300 mL) was added, and the mixture was purged with hydrogen gas. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 4 hours. The reaction mixture was filtered through Celite (washing with methanol). The filtrate was concentrated under reduced pressure to afford (5-phenylpyrimidin-2-yl)methanamine, which was used without purification in the next step. ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.90 (s, 2H), 7.58-7.45 (m, 5H), 4.17 (s, 2H).

Step C: ethyl 2-oxo-2-(((5-phenylpyrimidin-2-yl)methyl)amino)acetate

294

Ethyl 2-chloro-2-oxoacetate (66 g, 0.48 mol) was added dropwise to a mixture of (5-phenylpyrimidin-2-yl)methanamine (90 g, 0.48 mol) in DCM (900 mL) at 0 °C. Hunig's base (82 g, 0.63 mol) was then added to the reaction mixture at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 hour. The reaction mixture was quenched with saturated aqueous sodium bicarbonate and extracted with DCM (3 x 300 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue

was triturated with ethyl acetate, filtered, and the collected solids were dried under vacuum to afford ethyl 2-oxo-2-(((5-phenylpyrimidin-2-yl)methyl)amino)acetate. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.93 (s, 2H), 7.58-7.47 (m, 5H), 4.84-4.83 (m, 2H), 4.43-4.38 (q, J = 7.2 Hz, 2H), 1.43-1.40 (t, J = 7.2 Hz, 3H).

Step D: ethyl 2-(allyl((5-phenylpyrimidin-2-yl)methyl)amino)-2-oxoacetate

Allyl bromide (19.0 g, 0.157 mol) was added dropwise to a mixture of ethyl 2-oxo-2-(((5-phenylpyrimidin-2-yl)methyl)amino)acetate (18.0 g, 0.063 mol) and cesium carbonate (61 g, 0.19 mol) in DMF (100 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was poured into ice water (1.0 L) and extracted with ethyl acetate (3 x 1.0 L). The organic layers were separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford ethyl 2-(allyl((5-phenylpyrimidin-2-yl)methyl)amino)-2-oxoacetate. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.90 (s, 2H), 7.56-7.51 (m, 5H), 5.90-5.80 (m, 1H), 5.27-5.20 (m, 2H), 4.86-4.85 (m, 2H), 4.38-4.28 (m, 2H), 4.26-4.11 (m, 2H), 1.42-1.25 (m, 3H). LC/MS (*m/z*): 326 $(M+H)^+$

Step E: ethyl 2-oxo-2-((2-oxoethyl)((5-phenylpyrimidin-2-yl)methyl)amino)acetate

A mixture of ethyl 2-(allyl((5-phenylpyrimidin-2-yl)methyl)amino)-2-oxoacetate (1.1 g, 3.4 mmol) in DCM (35 ml) was sparged with a stream of ozone gas for 40 minutes at -78 °C. The mixture was then sparged with a stream of oxygen gas at -78 °C. The reaction mixture was warmed to room temperature and treated with dimethyl sulfide (4.94 mL, 67.6 mmol). The reaction mixture

was then stirred at room temperature for an additional 2 hours. The mixture was filtered, and the filtrate was concentrated under reduced pressure to afford ethyl 2-oxo-2-((2-oxoethyl)((5-phenylpyrimidin-2-yl)methyl)amino)acetate, which was used without purification in the next step. LC/MS (*m/z*): 328 $(M+H)^+$

Examples shown in Intermediate Table 15 below, were prepared according to procedures analogous to those outlined in Intermediate 136 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 15

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 137		ethyl 2-oxo-2-((2-oxoethyl)((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)amino)acetate	334

297

Intermediate 138

Preparation of 1-cyclopentyl-4-((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)methyl)piperazine-2,3-dione

298

A mixture of 1-((5-bromopyrimidin-2-yl)methyl)-4-cyclopentylpiperazine-2,3-dione (0.830 g, 2.35 mmol), bis(pinacolato)diboron (1190 mg, 4.70 mmol), tetrakis(triphenylphosphine)palladium(0) (272 mg, 0.235 mmol), and potassium acetate (692 mg, 7.05 mmol) in 1,4-dioxane (32 mL) was sparged with a stream of nitrogen for 5 minutes. The reaction mixture was then stirred and heated to 105 °C for 2 hours. The reaction mixture was cooled to room temperature, filtered through Celite, diluted with water (150 mL), and washed with petroleum ether (3 x 100 mL) and then EtOAc (2 x 100 mL). The aqueous layer was partially

concentrated under reduced pressure to remove residual organic solvents, and then lyophilized to afford 1-cyclopentyl-4-((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)methyl)piperazine-2,3-dione. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.85 (s, 2H), 4.90-4.89 (m, 1H), 4.85 (s, 2H), 3.78-3.70 (m, 2H), 3.68-3.63 (m, 2H), 1.96-1.87 (m, 2H), 1.84-1.74 (m, 2H), 1.70-1.62 (m, 4H), 1.27 (s, 12H).

Intermediate 139

Preparation of 1-(3-phenylcyclobutyl)piperazine-2,3-dione

Step A: *tert*-butyl (2-((3-phenylcyclobutyl)amino)ethyl)carbamate

Sodium triacetoxyborohydride (2.90 g, 13.7 mmol) was added to a mixture of 3-phenylcyclobutan-1-one (1.00 g, 6.84 mmol) and *tert*-butyl (2-aminoethyl)carbamate (1.21 g, 7.52 mmol) in dichloromethane (40 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 days. The reaction mixture was quenched with saturated aqueous sodium bicarbonate (50 mL) and then diluted with ethyl acetate (250 mL) and water (50 mL). The organic layer was separated, and the aqueous layer was washed with additional ethyl acetate (2x 50 mL). The organic layers were combined, washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in dichloromethane (20 mL), and the mixture was stirred at room temperature. Hexanes (80 mL) were added dropwise

via addition funnel to the mixture over a period of 15 minutes. The mixture was stirred for 4 days. The mixture was filtered, and the collected solids were washed with additional hexanes (20 mL) and then dried under vacuum to afford *tert*-butyl (2-((3-phenylcyclobutyl)amino)ethyl)carbamate as a mixture of cis/trans isomers. LC/MS (*m/z*): 291 $(M+H)^+$ 314

Step B: N^1-(3-phenylcyclobutyl)ethane-1,2-diamine

300

TFA (5.64 mL, 73.2 mmol) was added to a mixture of *tert*-butyl (2-((3-phenylcyclobutyl)amino)ethyl)carbamate (0.850 g, 2.93 mmol) in dichloromethane (20 mL) at room temperature. The reaction mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated under reduced pressure and dried under vacuum to afford N^1-(3-phenylcyclobutyl)ethane-1,2-diamine as a bis-TFA salt and a mixture of cis/trans isomers. LC/MS (*m/z*): 191 $(M+H)^+$ 305

Step C: 1-(3-phenylcyclobutyl)piperazine-2,3-dione

301

Diethyl oxalate (0.397 mL, 2.93 mmol) was added to a mixture of N^1-(3-phenylcyclobutyl)ethane-1,2-diamine bis(2,2,2-trifluoroacetate) (1220 mg, 2.93 mmol) and triethylamine (1.63 mL, 11.7 mmol) in ethanol (10 mL) at room temperature. The reaction mixture was heated to 80 °C and stirred for 6 days under a reflux condenser. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by

silica gel chromatography (eluting [1:3 ethanol:ethyl acetate] in dichloromethane) to afford 1-(3-phenylcyclobutyl)piperazine-2,3-dione as a mixture of cis/trans isomers. LC/MS (*m/z*): 245 $(M+H)^+$

Intermediate 140

Preparation of mixture of 1-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)-4-cyclobutylpiperazine-2,3-dione and 1-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)-4-cyclobutyl-1,4-dihydropyrazine-2,3-dione

Step A: 2-bromo-5-(bromomethyl)-1,3,4-thiadiazole

N-Bromosuccinimide (0.994 g, 5.59 mmol) and azobisisobutyronitrile (0.092 g, 0.56 mmol) were added to a mixture of 2-bromo-5-methyl-1,3,4-thiadiazole (1.0 g, 5.6 mmol) in carbon tetrachloride (20 mL) under an inert atmosphere at 20 °C. The mixture was then heated to 80 °C and stirred for 4 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was diluted with water (35 mL) and extracted with DCM (2 x 25 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting EtOAc/ hexanes) to afford 2-bromo-5-(bromomethyl)-1,3,4-thiadiazole. LC/MS (*m/z*): 259 $(M+H)^+$

Step B: N-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)prop-2-en-1-amine

Potassium carbonate (2.97 g, 21.5 mmol) was added to a mixture of prop-2-en-1-amine (1.41 mL, 18.7 mmol) and 2-bromo-5-(bromomethyl)-1,3,4-thiadiazole (1.85 g, 7.17 mmol) in THF (50 mL) at room temperature. The reaction mixture was stirred at room temperature for 13 hours. The mixture was filtered, and the filtrate was concentrated under reduced pressure to afford N-((5-

bromo-1,3,4-thiadiazol-2-yl)methyl)prop-2-en-1-amine, which was used without purification. LC/MS (*m/z*): 233, 235 $(M+H)^+$

Step C: ethyl 2-(allyl((5-bromo-1,3,4-thiadiazol-2-yl)methyl)amino)-2-oxoacetate

304

Ethyl 2-chloro-2-oxoacetate (1.15 mL, 10.8 mmol) was added to a mixture of N-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)prop-2-en-1-amine (1.68 g, 7.17 mmol) and TEA (3.00 mL, 21.5 mmol) in DCM (30 mL) at 0 °C. The reaction was stirred at room temperature for 1 hour. The mixture was diluted with DCM (30 mL) and water (50 mL). The organic layer was separated, washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford ethyl 2-(allyl((5-bromo-1,3,4-thiadiazol-2-yl)methyl)amino)-2-oxoacetate. ^{1}H NMR (400 MHz, chloroform-*d*) δ 5.87-5.68 (m, 1H), 5.39-5.24 (m, 2H), 4.86 (s, 2H), 4.40-4.29 (m, 2H), 4.06-3.96 (m, 2H), 1.44-1.32 (m, 3H). LC/MS (*m/z*): 334, 336 $(M+H)^+$

Step D: ethyl 2-(((5-bromo-1,3,4-thiadiazol-2-yl)methyl)(2-oxoethyl)amino)-2-oxoacetate

75

Osmium tetroxide (11 mg, 0.042 mmol) was added to a mixture of ethyl 2-(allyl((5-bromo-1,3,4-thiadiazol-2-yl)methyl)amino)-2-oxoacetate (0.140 g, 0.419 mmol) and sodium periodate (0.300 g, 1.40 mmol) in THF (3 mL) at 0 °C. The reaction was stirred at room temperature for 1.5 hours. The mixture was quenched with saturated aqueous sodium bisulfite and stirred for 15 minutes. The mixture was then diluted with EtOAc (30 mL) and water (50 mL). The organic layer was separated, washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford ethyl 2-(((5-bromo-1,3,4-thiadiazol-2-yl)methyl)(2-oxoethyl)amino)-2-oxoacetate which was used without purification in the next step. LC/MS (*m/z*): 336, 338 $(M+H)^+$

Step E: mixture of 1-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)-4-cyclobutylpiperazine-2,3-dione and 1-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)-4-cyclobutyl-1,4-dihydropyrazine-2,3-dione

306

Sodium triacetoxyborohydride (128 mg, 0.602 mmol) was added to a mixture of ethyl 2-(((5-bromo-1,3,4-thiadiazol-2-yl)methyl)(2-oxoethyl)amino)-2-oxoacetate (135 mg, 0.402 mmol) and cyclobutanamine (31 mg, 0.44 mmol) in DCE (5 mL) at room temperature. The mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting methanol in dichloromethane) to afford 1-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)-4-cyclobutylpiperazine-2,3-dione, which contained the alkene by-product 1-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)-4-cyclobutyl-1,4-dihydropyrazine-2,3-dione. The mixture was used without purification. 1160

Intermediate 141

Preparation of 1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione

307

Sodium triacetoxyborohydride (132 mg, 0.625 mmol) was added to a mixture of ethyl 2-(((5-bromo-1,3,4-thiadiazol-2-yl)methyl)(2-oxoethyl)amino)-2-oxoacetate (140 mg, 0.42 mmol) and bicyclo[1.1.1]pentan-1-amine hydrochloride (0.050 g, 0.42 mmol) in DCE (5 mL) at room temperature. The mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography

(eluting methanol in dichloromethane) to afford 1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione. LC/MS (*m/z*): 357, 359 $(M+H)^+$

Examples shown in Intermediate Table 16 below, were prepared according to procedures analogous to those outlined in Intermediate 141 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 16

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 142		(*cis*)-1-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)-4-(3-hydroxycyclopentyl)piperazine-2,3-dione 308	375, 377

Intermediate 143

Preparation of 1-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)-4-cyclopentyl-1,4-dihydropyrazine-2,3-dione

309

A mixture of ethyl 2-(((5-bromo-1,3,4-thiadiazol-2-yl)methyl)(2-oxoethyl)amino)-2-oxoacetate (0.150 g, 0.446 mmol) and cyclopentanamine (38 mg, 0.45 mmol) in DCE (10 mL) was stirred at room temperature for 12 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with ammonium bicarbonate modifier) to afford 1-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)-4-cyclopentyl-1,4-dihydropyrazine-2,3-dione. LC/MS (*m/z*): 357, 359 $(M+H)^+$

Examples shown in Intermediate Table 17 below, were prepared according to procedures analogous to those outlined in Intermediate 143 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 17

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 144		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 310	355, 357
Intermediate 145		1-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)-4-((trans)-3-phenylcyclobutyl)-1,4-dihydropyrazine-2,3-dione 311	419, 421
Intermediate 146		1-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)-4-((cis)-3-phenylcyclobutyl)-1,4-dihydropyrazine-2,3-dione 312	419, 421
Intermediate 147		1-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)-4-(1-methylcyclobutyl)-1,4-dihydropyrazine-2,3-dione 313	357, 359

Intermediate 148

Preparation of 6-((2-ethoxy-2-oxo-N-(2-oxoethyl)acetamido)methyl)-3-phenylpyridazine 1-oxide

Step A: 3-methyl-6-phenylpyridazine

221

A mixture of 3-chloro-6-methylpyridazine (5.0 g, 39 mmol), phenylboronic acid (4.74 g, 38.9 mmol), potassium phosphate tribasic (17 g, 78 mmol) and Pd(dppf)Cl_2 (2.28 g, 3.11 mmol) in 1,4-dioxane (40 mL) and water (8.0 mL) was sparged with nitrogen at room temperature. The mixture was stirred and heated 80 °C for 4 hours. The reaction mixture was cooled to room temperature and quenched with saturated aqueous NH_4Cl (50 mL). The mixture was extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 3-methyl-6-phenylpyridazine. LC/MS (*m/z*): 171 $(M+H)^+$

Step B: 3-(chloromethyl)-6-phenylpyridazine

91

1,3,5-trichloro-1,3,5-triazinane-2,4,6-trione (2.84 g, 12.2 mmol) was added to a mixture of 3-methyl-6-phenylpyridazine (5.2 g, 31 mmol) in trichloromethane (200 mL) at 20 °C. The mixture was stirred and heated at 60 °C for 12 hours. The mixture was cooled to room temperature, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 3-(chloromethyl)-6-phenylpyridazine. ^{1}H NMR

(400 MHz, methanol-d_4) δ 8.82 (br dd, J = 5.7, 8.4 Hz, 1H), 8.68 - 8.49 (m, 1H), 8.11 (dd, J = 1.4, 8.0 Hz, 2H), 7.80 - 7.65 (m, 3H), 5.08 (s, 2H). LC/MS (m/z): 205 $(M+H)^+$

Step C: N-((6-phenylpyridazin-3-yl)methyl)prop-2-en-1-amine

316

Prop-2-en-1-amine (2.0 mL, 27 mmol) was added to a mixture of 3-(chloromethyl)-6-phenylpyridazine hydrochloride (3.0 g, 12 mmol) and potassium carbonate (5.16 g, 37.3 mmol) in DMF (40 mL) at 20 °C. The mixture was stirred and heated at 40 °C for 12 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to afford ethyl 2-(allyl((6-phenylpyridazin-3-yl)methyl)amino)-2-oxoacetate which was used without purification in the next step. LC/MS (m/z): 226 $(M+H)^+$

74

Step D: ethyl 2-(allyl((6-phenylpyridazin-3-yl)methyl)amino)-2-oxoacetate

317

Ethyl oxalyl chloride (2.1 mL, 19 mmol) was added to a solution of N-((6-phenylpyridazin-3-yl)methyl)prop-2-en-1-amine (2.8 g, 12 mmol) and potassium carbonate (3.44 g, 24.9 mmol) in DMF (20 mL) at 0 °C. The mixture was stirred at room temperature for 3 hours. The reaction mixture was quenched with water (400 mL) and extracted with EtOAc (3 x 100 mL). The organic layers were combined, washed with brine (400 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford ethyl 2-(allyl((6-phenylpyridazin-3-yl)methyl)amino)-2-oxoacetate. ^{1}H NMR (500 MHz, methanol-d_4) δ 8.20 - 8.14 (m, 1H), 8.10 - 8.03 (m, 2H), 7.86 - 7.68 (m, 1H), 7.59 - 7.48 (m, 3H), 5.98 - 5.72 (m, 1H), 5.38 - 5.18 (m, 2H), 4.95 - 4.89 (m, 2H), 4.41 - 4.29 (m, 2H), 4.17 - 4.04 (m, 2H), 1.35 (t, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 1H). LC/MS (m/z): 326 $(M+H)^+$

Step E: 6-((N-allyl-2-ethoxy-2-oxoacetamido)methyl)-3-phenylpyridazine 1-oxide

318

meta-Chloroperoxybenzoic acid (66 mg, 0.31 mmol, 85%) was added to a mixture of ethyl 2-(allyl((6-phenylpyridazin-3-yl)methyl)amino)-2-oxoacetate (0.100 g, 0.307 mmol) in DCM (4 mL) at 0 °C. The mixture was stirred for 1 hour at room temperature. The mixture was concentrated under reduced pressure to afford 6-((N-allyl-2-ethoxy-2-oxoacetamido)methyl)-3-phenylpyridazine 1-oxide which was used without purification in the next step. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.10 (d, J = 1.6 Hz, 1H), 8.04-7.93 (m, 2H), 7.85-7.70 (m, 1H), 7.60-7.39 (m, 3H), 6.00-5.71 (m, 1H), 5.42-5.18 (m, 2H), 4.76 (s, 2H), 4.43-4.27 (m, 2H), 4.26-4.06 (m, 2H), 1.46-1.19 (m, 3H). LC/MS (*m/z*): 342 $(M+H)^+$

Step F: 6-((2-ethoxy-2-oxo-N-(2-oxoethyl)acetamido)methyl)-3-phenylpyridazine 1-oxide

319

Sodium periodate (188 mg, 0.879 mmol) and osmium(VIII) oxide (7 mg, 0.03 mmol) were added to a mixture of 3-((N-allyl-2-ethoxy-2-oxoacetamido)methyl)-6-phenylpyridazine 1-oxide (0.100 g, 0.293 mmol) in water (3 mL) and THF (3 mL) at 0 °C. The mixture was stirred for 1 hour at room temperature. The reaction mixture was quenched with saturated aqueous Na_2SO_3 (10 mL). The mixture was diluted with EtOAc (30 mL) and water (50 mL). The organic layer was separated, washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 3-((2-ethoxy-2-oxo-N-(2-oxoethyl)acetamido)methyl)-6-phenylpyridazine 1-oxide which was used in the next step without purification. LC/MS (*m/z*): 344 $(M+H)^+$

Intermediates 149 and 150

Preparation of 1-((6-chloropyridazin-3-yl)methyl)-4-((trans)-3-phenylcyclobutyl)piperazine-2,3-dione and 1-((6-chloropyridazin-3-yl)methyl)-4-((cis)-3-phenylcyclobutyl)piperazine-2,3-dione

1-((6-chloropyridazin-3-yl)methyl)-4-(3-phenylcyclobutyl)piperazine-2,3-dione (0.400, 1.08 mmol) was resolved by Chiral-SFC (Daicel Chiralcel OD-H (250mm x 30mm, 5um); eluting 40% EtOH in CO_2 with 0.1% aqueous ammonia) to give 1-((6-chloropyridazin-3-yl)methyl)-4-((trans)-3-phenylcyclobutyl)piperazine-2,3-dione (t_r = 1.112 min) as the first eluting peak and 1-((6-chloropyridazin-3-yl)methyl)-4-((cis)-3-phenylcyclobutyl)piperazine-2,3-dione (t_r = 2.364 min) as the second eluting peak.

Peak 1: ^{1}H NMR (400 MHz, methanol-d_4) δ 7.84 - 7.73 (m, 2H), 7.36 - 7.30 (m, 4H), 7.23 - 7.17 (m, 1H), 5.13 - 5.05 (m, 1H), 4.95 (s, 2H), 3.82 (s, 4H), 3.59 - 3.51 (m, 1H), 2.84 - 2.73 (m, 2H), 2.46 (ddd, *J*=3.9, 8.8, 13.1 Hz, 2H). LC/MS (*m/z*): 371 $(M+H)^+$

Peak 2: ^{1}H NMR (400 MHz, methanol-d_4) δ 7.82 - 7.73 (m, 2H), 7.33 - 7.24 (m, 4H), 7.21 - 7.14 (m, 1H), 4.94 (s, 2H), 4.84 - 4.73 (m, 1H), 3.81 - 3.69 (m, 4H), 3.29 - 3.18 (m, 1H), 2.70 - 2.60 (m, 2H), 2.40 - 2.27 (m, 2H). LC/MS (*m/z*): 371 $(M+H)^+$

Intermediate 151

Preparation of 1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-bromo-3-fluoropyridin-2-yl)methyl)piperazine-2,3-dione

Step A: 5-bromo-2-(bromomethyl)-3-fluoropyridine

322

A mixture of (5-bromo-3-fluoropyridin-2-yl)methanol (0.950 g, 4.61 mmol), carbon tetrabromide (2.30 g, 6.92 mmol), and triphenylphosphine (1.81 g, 6.92 mmol) in DCM (25 mL) was stirred at room temperature for 16 hours. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 5-bromo-2-(bromomethyl)-3-fluoropyridine. LC/MS (*m/z*): 270 $(M+H)^+$

Step B: ethyl 2-(allyl((5-bromo-3-fluoropyridin-2-yl)methyl)amino)-2-oxoacetate

323

NaH (67 mg, 1.7 mmol, 60% dispersion in mineral oil) was added to a mixture of ethyl 2-(allylamino)-2-oxoacetate (175 mg, 1.11 mmol) in DMF (5 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 30 minutes. 5-bromo-2-(bromomethyl)-3-fluoropyridine (299 mg, 1.11 mmol) was added to the mixture. The mixture was stirred at room temperature for 3 hours. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford ethyl 2-(allyl((5-bromo-3-fluoropyridin-2-yl)methyl)amino)-2-oxoacetate. LC/MS (*m/z*): 345, 347 $(M+H)^+$

Step C: ethyl 2-(((5-bromo-3-fluoropyridin-2-yl)methyl)(2-oxoethyl)amino)-2-oxoacetate

324

Osmium tetroxide (9 mg, 0.04 mmol) was added to a mixture of ethyl 2-(allyl((5-bromo-3-fluoropyridin-2-yl)methyl)amino)-2-oxoacetate (110 mg, 0.32 mmol) and sodium periodate (204 mg, 0.956 mmol) in THF (2 ml) at 0 °C. The reaction was stirred at room temperature for 2 hours. The mixture was quenched with saturated aqueous Na_2SO_3 (30 mL) and diluted with EtOAc (15 mL) and water (10 mL). The organic layer was separated, washed with brine (5 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford ethyl 2-(((5-bromo-3-fluoropyridin-2-yl)methyl)(2-oxoethyl)amino)-2-oxoacetate which was used without purification in the next step. LC/MS (*m/z*): 347, 349 $(M+H)^+$

Step D: 1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-bromo-3-fluoropyridin-2-yl)methyl)piperazine-2,3-dione

325

A mixture of ethyl 2-(((5-bromo-3-fluoropyridin-2-yl)methyl)(2-oxoethyl)amino)-2-oxoacetate (50 mg, 0.14 mmol), triethylamine (0.020 mL, 0.14 mmol) and bicyclo[3.1.0]hexan-3-ammonium iodide (33 mg, 0.15 mmol) in DCE (1.5 mL) was stirred at room temperature for 16 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluting methanol in dichloromethane) to afford 1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-bromo-3-fluoropyridin-2-yl)methyl)piperazine-2,3-dione. LC/MS (*m/z*): 382, 384 $(M+H)^+$

Intermediate 152

Preparation of 1-((5-bromopyridin-2-yl)methyl)-4-cyclobutyl-1,4-dihydropyrazine-2,3-dione

326

A mixture of 1-cyclobutyl-1,4-dihydropyrazine-2,3-dione (1.40 g, 8.42 mmol), (5-bromopyridin-2-yl)methyl methanesulfonate (3.14 g, 11.8 mmol), and potassium carbonate (1.75 g, 12.6 mmol) in acetonitrile (20 mL) was heated to 50 °C and stirred for 24 hours. The mixture was cooled to room temperature and diluted with dichloromethane (100 mL). The suspension was stirred at room temperature for 30 minutes and then filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluting with [3:1 ethyl acetate:ethanol] in dichloromethane) to afford 1-((5-bromopyridin-2-yl)methyl)-4-cyclobutyl-1,4-dihydropyrazine-2,3-dione. ^{1}H NMR (499 MHz, DMSO-d_6) δ 8.65 (d, J = 2.0 Hz, 1H), 8.04 (dd, J = 8.4, 2.4 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 6.2 Hz, 1H), 6.71 (d, J = 6.2 Hz, 1H), 5.00 (s, 2H), 4.91 (p, J = 8.6 Hz, 1H), 2.30 – 2.20 (m, 4H), 1.78 – 1.70 (m, 2H). LC/MS (m/z): 336, 338 $(M+H)^+$

Intermediate 153

Preparation of 4-(chloromethyl)-1-phenyl-1H-imidazole

327

Sulfurous dichloride (0.025 mL, 0.34 mmol) was added to a mixture of (1-phenyl-1H-imidazol-4-yl)methanol (30 mg, 0.17 mmol) in DCM (2 mL) at 0 °C. The mixture was stirred for 1.5 hours. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford 4-(chloromethyl)-1-phenyl-1H-imidazole, which was used without purification in the next step. LC/MS (m/z): 193 $(M+H)^+$

Intermediate 154

Preparation of 2-(bromomethyl)-5-(2H-tetrazol-2-yl)pyridine

Step A: 2-methyl-5-((tetrafluoro-Λ^5-boranyl)diazenyl)pyridine

328

A mixture of 6-methylpyridin-3-amine (0.500 g, 4.62 mmol) and trifluoroborane hydrofluoride (1.50 mL, 9.43 mmol) in ethanol (10 mL) was degassed and backfilled with nitrogen (3x) at 0 °C. After stirring for 10 minutes at 0 °C, *tert*-butyl nitrite (0.890 mL, 9.48 mmol) was added to the mixture at 0 °C. The mixture was stirred for an additional 6 hours at room temperature. The reaction was filtered and the collected solids were washed with EtOAc (2 × 10 mL) to afford 2-methyl-5-((tetrafluoro- Λ^5-boraneyl)diazenyl)pyridine, which was used without purificaction in the next step.

Step B: 2-methyl-5-(2H-tetrazol-2-yl)pyridine

329

Silver (I) trifluoromethanesulfonate (745 mg, 2.90 mmol) was added to a mixture of 2-methyl-5-((tetrafluoro- Λ^5-boraneyl)diazenyl)pyridine (0.500 g, 2.42 mmol) in THF (15 mL) at -78 °C and then stirred for 10 minutes. The mixture was warmed to room temperature, and triethylamine (0.51 mL, 3.6 mmol) was added. The mixture was stirred for an additional 10 hours. A mixture of CsF (1.10 g, 7.25 mmol) in MeOH (2 mL) was added and the mixture was stirred for 6 hours at room temperature. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford 2-methyl-5-(2H-tetrazol-2-yl)pyridine, which was used in the next step without purification. LC/MS (*m/z*): 162 $(M+H)^+$

Step C: 2-(bromomethyl)-5-(2H-tetrazol-2-yl)pyridine

330

A mixture of 2-methyl-5-(2H-tetrazol-2-yl)pyridine (0.050 g, 0.31 mmol), NBS (28 mg, 0.16 mmol), and AIBN (6 mg, 0.04 mmol) in DMF (1 ml) was stirred at 80 °C for 12 hours. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford 2-(bromomethyl)-5-(2H-tetrazol-2-yl)pyridine, which was used in the next step without purification. LC/MS (*m/z*): 240, 242 $(M+H)^+$

Intermediate 155

Preparation of (3-(pyridin-2-yl)bicyclo[1.1.1]pentan-1-yl)methyl methanesulfonate

Step A: methyl 3-((tert-butylperoxy)carbonyl)bicyclo[1.1.1]pentane-1-carboxylate

331

A mixture of 3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (0.500 g, 2.94 mmol) in DCM (10 mL) was cooled to 0 °C and stirred under a nitrogen atmosphere for 5 minutes. EDCI HCl (0.620 g, 3.23 mmol), DMAP (36 mg, 0.29 mmol), and 2-hydroperoxy-2-methylpropane (0.65 mL, 3.2 mmol) were added to the reaction mixture and stirred at 0 °C under a nitrogen atmosphere for 10 minutes. The reaction mixture was warmed to room temperature and stirred for an additional 6 hours. The reaction mixture was washed with water (20 mL) and extracted with DCM (3 x 20 mL). The organic layers were combined, washed with saturated aqueous sodium bisufite, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to

afford methyl 3-((tert-butylperoxy)carbonyl)bicyclo[1.1.1]pentane-1-carboxylate. ^{1}H NMR (400 MHz, chloroform-*d*) δ 3.68 (s, 3H), 2.36 (s, 6H), 1.30 (s, 9H).

Step B: methyl 3-(pyridin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate

332

A mixture of methyl 3-((tert-butylperoxy)carbonyl)bicyclo[1.1.1]pentane-1-carboxylate (0.100 g, 0.413 mmol) and O_2 in pyridine (2 mL) was stirred at 115 °C for 3 hours in a microwave reactor. The reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford methyl 3-(pyridin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate. LC/MS (*m/z*): 204 $(M+H)^+$

Step C: (3-(pyridin-2-yl)bicyclo[1.1.1]pentan-1-yl)methanol

333

$LiBH_4$ (16 mg, 0.75 mmol) was added to a mixture of methyl 3-(pyridin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (92 mg, 0.15 mmol) in THF (5 mL) at room temperature. The mixture was stirred for 2 hours at room temperature. The mixtuer was quenched with 1N HCl (1 mL). The mixture was filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford (3-(pyridin-2-yl)bicyclo[1.1.1]pentan-1-yl)methanol. LC/MS (*m/z*): 176 $(M+H)^+$

Step D: (3-(pyridin-2-yl)bicyclo[1.1.1]pentan-1-yl)methanol

333

Methanesulfonyl chloride (0.054 mL, 0.70 mmol) was added to a mixture of (3-(pyridin-2-yl)bicyclo[1.1.1]pentan-1-yl)methanol (35 mg, 0.067 mmol) and DIEA (0.035 mL, 0.20 mmol) in DCM (3 mL) at 0 °C. The mixture was stirred at 0 °C for 2 hours. The mixture was quenched with

water (10 mL) and extracted with DCM (15 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford (3-(pyridin-2-yl)bicyclo[1.1.1]pentan-1-yl)methyl methanesulfonate, which was used without purification in the next step. LC/MS (*m/z*): 254 $(M+H)^+$

Intermediate 156

Preparation of 1-cyclobutyl-6-methylpiperazine-2,3-dione

Step A: *tert*-butyl (2-(cyclobutylamino)propyl)carbamate

335

Sodium cyanoborohydride (4.63 g, 73.6 mmol) was added to a mixture of cyclobutanamine (3.56 g, 50.1 mmol) and *tert*-butyl (2-oxopropyl)carbamate (8.5 g, 49 mmol) in MeOH (70 mL). The mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (20 mL) and extracted with DCM (3 x 50 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting methanol in DCM) to afford *tert*-butyl (2-(cyclobutylamino)propyl)carbamate. LC/MS (*m/z*): 229 $(M+H)^+$

Step B: ethyl 2-((1-((*tert*-butoxycarbonyl)amino)propan-2-yl)(cyclobutyl)amino)-2-oxoacetate

336

Ethyl 2-chloro-2-oxoacetate (4.58 mL, 40.9 mmol) was added to a mixture of *tert*-butyl (2-(cyclobutylamino)propyl)carbamate (8.5 g, 37 mmol) and TEA (7.8 ml, 56 mmol) in DCM (70 ml)

at 0 °C. The mixture was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford ethyl 2-((1-((*tert*-butoxycarbonyl)amino)propan-2-yl)(cyclobutyl)amino)-2-oxoacetate. LC/MS (*m/z*): 229.1 $[M+H-Boc]^+$.

Step C: ethyl 2-((1-aminopropan-2-yl)(cyclobutyl)amino)-2-oxoacetate

337

A mixture of ethyl 2-((1-((*tert*-butoxycarbonyl)amino)propan-2-yl)(cyclobutyl)amino)-2-oxoacetate (7.7 g, 23 mmol) and HCl (4.0 M in dioxane, 15 mL, 60 mmol) in DCM (70 mL) was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure to afford ethyl 2-((1-aminopropan-2-yl)(cyclobutyl)amino)-2-oxoacetate hydrochloride, which was used in next step without purification. LC/MS (*m/z*): 229 $(M+H)^+$

Step D: (R or S)-1-cyclobutyl-6-methylpiperazine-2,3-dione and (S or R)- 1-cyclobutyl-6-methylpiperazine-2,3-dione

338 339

A mixture of ethyl 2-((1-aminopropan-2-yl)(cyclobutyl)amino)-2-oxoacetate hydrochloride (8.4 g, 32 mmol) and TEA (8.8 mL, 64 mmol) in EtOH (50 mL) was stirred and heated at 85 °C for 3 hours. The mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography (eluting MeOH in DCM) to afford 1-cyclobutyl-6-methylpiperazine-2,3-dione as a mixture of isomers. The mixture was resolved by Chiral-SFC (Column Daicel Chiralpak AS (250mm x 50mm, 10 μm): eluting 40% EtOH in CO_2 with 0.1% ammonia modifier) to afford (R or S)-1-cyclobutyl-6-methylpiperazine-2,3-dione (t_r = 3.87 min) as the first eluting peak and (S or R)-1-cyclobutyl-6-methylpiperazine-2,3-dione (t_r = 4.55 min) as the second eluting peak.

Peak 1: (R or S)-1-cyclobutyl-6-methylpiperazine-2,3-dione: ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.08 (br s, 1H), 4.82 - 4.63 (m, 1H), 3.80 (br d, *J* = 5.6 Hz, 1H), 3.73 (dd, *J* = 3.7,

13.0 Hz, 1H), 3.27 (br dd, *J* = 5.0, 12.8 Hz, 1H), 2.34 - 2.17 (m, 2H), 2.17 - 2.03 (m, 2H), 1.77 - 1.63 (m, 2H), 1.35 (d, *J* = 6.6 Hz, 3H). LC/MS (*m/z*): 183 $(M+H)^+$

Peak 2: (S or R)-1-cyclobutyl-6-methylpiperazine-2,3-dione: ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.04 - 6.77 (m, 1H), 4.81 - 4.64 (m, 1H), 3.89 - 3.70 (m, 2H), 3.23 (dd, *J* =5.1, 12.5 Hz, 1H), 2.37 - 2.19 (m, 2H), 2.16 - 1.99 (m, 2H), 1.80 - 1.65 (m, 2H), 1.37 (d, J = 6.4 Hz, 3H). LC/MS (*m/z*): 183 $(M+H)^+$

Intermediate 157

Preparation of 1-((6-phenylpyridazin-3-yl)methyl)piperazine-2,3-dione

Step A: *tert*-butyl (2-(((6-phenylpyridazin-3-yl)methyl)amino)ethyl)carbamate

3-(chloromethyl)-6-phenylpyridazine (0.550 g, 2.69 mmol) was added to a mixture of *tert*-butyl (2-aminoethyl)carbamate (1.29 g, 8.06 mmol) and potassium carbonate (743 mg, 5.37 mmol) in DMF (10 mL) at room temperature. The mixture was stirred and heated at 50 °C for 2 hours. The mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the residue was purfied by silica gel chromatography (eluting methanol in dichloromethane) to afford *tert*-butyl (2-(((6-phenylpyridazin-3-yl)methyl)amino)ethyl)carbamate. LC/MS (*m/z*): 329 $(M+H)^+$

Step B: ethyl 2-((2-((*tert*-butoxycarbonyl)amino)ethyl)((6-phenylpyridazin-3-yl)methyl)amino)-2-oxoacetate

341

Ethyl 2-chloro-2-oxoacetate (0.29 mL, 2.6 mmol) was added to a mixture of *tert*-butyl (2-(((6-phenylpyridazin-3-yl)methyl)amino)ethyl)carbamate (0.700 g, 2.13 mmol) and TEA (0.45 mL, 3.2 mmol) in DCM (10 mL) at 0 °C. The mixture was stirred room temperature for 2 hours. The mixture was directly purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford ethyl 2-((2-((*tert*-butoxycarbonyl)amino)ethyl)((6-phenylpyridazin-3-yl)methyl)amino)-2-oxoacetate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, J = 9.0 Hz, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.61 - 7.41 (m, 5H), 6.92 (br s, 1H), 4.86 (s, 2H), 4.31 (q, J = 7.0 Hz, 2H), 3.44 (br t, J = 5.5 Hz, 2H), 3.19 (q, J = 6.1 Hz, 2H), 1.37 (s, 9H), 1.30 (t, J = 7.0 Hz, 3H). LC/MS (*m/z*): 429 $(M+H)^+$

Step C: ethyl 2-((2-aminoethyl)((6-phenylpyridazin-3-yl)methyl)amino)-2-oxoacetate

342

A mixture of ethyl 2-((2-((*tert*-butoxycarbonyl)amino)ethyl)((6-phenylpyridazin-3-yl)methyl)amino)-2-oxoacetate (1.00 g, 2.33 mmol) and TFA (4.0 mL, 52 mmol) in DCM (10 mL) was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure to afford ethyl 2-((2-aminoethyl)((6-phenylpyridazin-3-yl)methyl)amino)-2-oxoacetate, which was used in the next step without purification. LC/MS (*m/z*): 329 $(M+H)^+$

Step D: 1-((6-phenylpyridazin-3-yl)methyl)piperazine-2,3-dione

343

TEA (0.891 mL, 6.40 mmol) was added to a mixture of ethyl 2-((2-aminoethyl)((6-phenylpyridazin-3-yl)methyl)amino)-2-oxoacetate (0.700 g, 2.13 mmol) in EtOH (15 mL) at room temperature. The mixture was stirred and heated at 80 °C for 12 hours. The mixture was concentrated under reduced pressure. The residue was diluted with MTBE and stirred at room temperature for 10 minutes. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford -((6-phenylpyridazin-3-yl)methyl)piperazine-2,3-dione, which was used without purification in the next step. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (br s, 1H), 8.22 (d, J = 8.9 Hz, 1H), 8.17 - 8.12 (m, 2H), 7.74 (d, J = 8.9 Hz, 1H), 7.60 - 7.52 (m, 3H), 4.92 (s, 2H), 3.70 - 3.63 (m, 2H), 3.44 - 3.38 (m, 2H). LC/MS (m/z): 283 $(M+H)^+$

Examples shown in Intermediate Table 18 below, were prepared according to procedures analogous to those outlined in Intermediate 157 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 18

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 158		1-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)piperazine-2,3-dione 344	301

Intermediate 159

Preparation of hexahydro-2H-pyrido[1,2-a]pyrazine-3,4-dione

345

A mixture of piperidin-2-ylmethanamine (2.00 g, 17.5 mmol), diethyl oxalate (5.12 g, 35.0 mmol), and TEA (3.66 mL, 26.3 mmol) in ethanol (25 mL) was stirred and heated at 90 °C for 2 hours. The mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography (eluting MeOH in DCM) to afford hexahydro-2H-pyrido[1,2-a]pyrazine-3,4-dione. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (br s, 1H), 4.29-4.21 (m, 1H), 3.61-3.51 (m, 1H), 3.38 (td, J = 4.34, 12.90 Hz, 1H), 3.19-3.12 (m, 1H), 2.65 (dt, J = 3.16, 12.90 Hz, 1H), 1.80-1.68 (m, 3H), 1.39-1.24 (m, 3H). LC/MS (m/z): 169 $(M+H)^+$

Intermediate 160

Preparation of 5-(chloromethyl)-3-phenylisoxazole

346

Thionyl chloride (0.167 mL, 2.28 mmol) was added to a mixture of (3-phenylisoxazol-5-yl)methanol (0.200 g, 1.14 mmol) in DCM (5 mL) at 0 °C. The mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to afford 5-(chloromethyl)-3-phenylisoxazole, which was used without purification in the next step. LC/MS (m/z): 194 $(M+H)^+$

Intermediate 161

Preparation of 1-(bicyclo[2.1.1]hexan-2-yl)piperazine-2,3-dione

Step A: *tert*-butyl (2-(bicyclo[2.1.1]hexan-2-ylamino)ethyl)carbamate

347

A mixture of bicyclo[2.1.1]hexan-2-amine HCl (191 mg, 1.43 mmol), *tert*-butyl (2-bromoethyl)carbamate (0.320 g, 1.43 mmol), and potassium phosphate tribasic (606 mg, 2.86 mmol) in DMF (7.1 mL) was stirred and heated to 60 °C for 24 hours. The mixture was filtered, and the filtrate was concentrated under reduced pressure to afford *tert*-butyl (2-(bicyclo[2.1.1]hexan-2-ylamino)ethyl)carbamate, which was used without purification in the next step. LC/MS (*m/z*): 241 $(M+H)^+$

Step B: N1-(bicyclo[2.1.1]hexan-2-yl)ethane-1,2-diamine hydrochloride

348

A mixture of *tert*-butyl (2-(bicyclo[2.1.1]hexan-2-ylamino)ethyl)carbamate (343 mg, 1.43 mmol), HCl (4.0 M in dioxane, 5.3 mL, 21 mmol) in dioxane (7 mL) was stirred and heated to 50 °C for 1 hour. The mixture was cooled to room temperature and concentrated under reduced pressure to afford N1-(bicyclo[2.1.1]hexan-2-yl)ethane-1,2-diamine hydrochloride, which was used without purification in the next step. LC/MS (*m/z*): 141 $(M+H)^+$

Step C: 1-(bicyclo[2.1.1]hexan-2-yl)piperazine-2,3-dione

349

A solution of diethyl oxalate (461 µL, 3.40 mmol) in EtOH (5.6 mL) was added to a mixture of N1-(bicyclo[2.1.1]hexan-2-yl)ethane-1,2-diamine hydrochloride (0.200 g, 1.13 mmol) and TEA (316 µl, 2.26 mmol) at room temperature. The mixture was stirred and heated at 80 °C for 18 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in hexanes) to afford 1-(bicyclo[2.1.1]hexan-2-yl)piperazine-2,3-dione. LC/MS (*m/z*): 195 $(M+H)^+$

Intermediate 162

Preparation of (5-(thiazol-2-yl)isoxazol-3-yl)methyl methanesulfonate

Step A: ethyl 5-(thiazol-2-yl)isoxazole-3-carboxylate

350

A mixture of ethyl 5-bromoisoxazole-3-carboxylate (360 mg, 1.64 mmol), $Pd(Ph_3P)_4$ (189 mg, 0.164 mmol), and 2-(tributylstannyl)thiazole (0.617 mL, 1.963 mmol) in toluene (6 mL) was degassed and backfilled with nitrogen (3x). The mixture was stirred and heated at 100 °C for 16 hours. The mixture was quenched with saturated aqueous KF (3 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (3 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford ethyl 5-(thiazol-2-yl)isoxazole-3-carboxylate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17-8.11 (m, 2H), 7.50 (s, 1H), 4.41 (q, J = 7.11 Hz, 2H), 1.37-1.33 (m, 3H). LC/MS (m/z): 225 $(M+H)^+$

Step B: (5-(thiazol-2-yl)isoxazol-3-yl)methanol

351

Sodium borohydride (68 mg, 1.8 mmol) was added to a mixture of ethyl 5-(thiazol-2-yl)isoxazole-3-carboxylate (0.200 g, 0.892 mmol) in MeOH (5 mL) at 0 °C. The mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with water (3 mL) and extracted with EtOAc (3 x 8 mL). The organic layers were combined, washed with brine (2 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure.

The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford (5-(thiazol-2-yl)isoxazol-3-yl)methanol. LC/MS (*m/z*): 183 $(M+H)^+$

Step C: (5-(thiazol-2-yl)isoxazol-3-yl)methyl methanesulfonate

352

Methanesulfonic anhydride (93 mg, 0.54 mmol) was added to a mixture of (5-(thiazol-2-yl)isoxazol-3-yl)methanol (65 mg, 0.36 mmol) and TEA (0.099 ml, 0.71 mmol) in DCM (4 mL). The mixture was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure to afford (5-(thiazol-2-yl)isoxazol-3-yl)methyl methanesulfonate, which was used in the next step without purification. LC/MS (*m/z*): 261 $(M+H)^+$

Intermediate 163

Preparation of (2,2-difluoro-3-phenylbicyclo[1.1.1]pentan-1-yl)methyl methanesulfonate

Step A: (2,2-difluoro-3-phenylbicyclo[1.1.1]pentan-1-yl)methanol

353

LAH (1.0 M in THF, 669 µl, 0.67 mmol) was added dropwise to a mixture of 2,2-difluoro-3-phenylbicyclo[1.1.1]pentane-1-carboxylic acid (50 mg, 0.22 mmol) in THF (2.2 mL) at room temperature. The mixture was stirred and heated to 60 °C for 2 hours. The mixture was cooled to 0 °C and quenched dropwise with saturated aqueous ammonium chloride. The mixture was washed with DCM (3 x 5 mL) and the organic layers were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford (2,2-difluoro-3-phenylbicyclo[1.1.1]pentan-1-yl)methanol, which was used without purification in the next step. ^{1}H NMR (499 MHz, chloroform-

d) δ 7.40 – 7.30 (m, 5H), 3.95 (s, 2H), 3.80 – 3.75 (m, 1H), 2.38 (s, 2H), 1.90 – 1.86 (m, 1H), 1.82 (t, *J* = 10.7 Hz, 2H).

Step B: (2,2-difluoro-3-phenylbicyclo[1.1.1]pentan-1-yl)methyl methanesulfonate

354

Methanesulfonyl chloride (40 µl, 0.52 mmol) was added to a mixture of (2,2-difluoro-3-phenylbicyclo[1.1.1]pentan-1-yl)methanol (0.050 g, 0.24 mmol) and triethylamine (80 µl, 0.57 mmol) in DCM (2.4 mL) at 0 °C. The mixture was stirred at 0 °C for 2 hours. The mixture was quenched with water (10 mL) and extracted with DCM (15 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford (2,2-difluoro-3-phenylbicyclo[1.1.1]pentan-1-yl)methyl methanesulfonate, which was used in the next step without purification. LC/MS (*m/z*): 311 $(M+Na)^+$

Intermediate 164

Preparation of 2-azidopyridine

355

NaN_3 (1.42 g, 21.8 mmol) and ammonium chloride (0.942 g, 17.6 mmol) were added to a mixture of 2-chloropyridine (1.00 g, 8.81 mmol) in DMF (15 mL) at room temperature over a period of 5 minutes. The mixture was stirred and heated to 110°C for 16 hours. The mixture was adjusted to pH > 9 by the addition of aqueous sodium bicarbonate and then extracted with EtOAc (5 x 40 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 2-azidopyridine, which was used in next step without purification. ^{1}H NMR (500 MHz, methanol-d_4) δ 9.14 (td, *J* = 1.03, 6.94 Hz, 1H), 8.12 (td, *J* = 0.99, 9.00 Hz, 1H), 8.00 (s, 1H), 7.90-7.86 (m, 1H).

701

Intermediate 165

Preparation of 3-azidopyridine

356

TBAF (1.0 M in THF, 19.5 mL, 20 mmol), TMS-N_3 (2.6 mL, 20 mmol), and CuCl (0.161 g, 1.63 mmol) were added to a mixture of pyridin-3-ylboronic acid (2.00 g, 16.3 mmol) in MeOH (40 mL) at room temperature. The mixture was stirred and heated at 80°C for 16 hours. The mixture was concentrated under reduced pressure and the residue was partitioned between water (20 mL) and EtOAc (20 mL). The organic layer was separated and the aqueous was re-extracted with EtOAc (3 x 15 mL). The organic layers were combined, washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 3-azidopyridine. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.23-8.14 (m, 2H), 7.51-7.44 (m, 1H), 7.33 (dd, J = 4.8, 8.4 Hz, 1H).

Intermediate 166

Preparation of 2-(6-(chloromethyl)pyridazin-3-yl)thiazole

Step A: 2-(6-methylpyridazin-3-yl)thiazole

357

A mixture of 3-bromo-6-methylpyridazine (0.500 g, 2.89 mmol), 2-(tributylstannyl)thiazole (1.82 mL, 5.78 mmol), and $Pd(Ph_3P)_4$ (334 mg, 0.289 mmol) in toluene (15 mL) was degassed and backfilled with N_2 (3x). The mixture was stirred and heated to 100 °C for 16 hours. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 2-(6-methylpyridazin-3-yl)thiazole. LC/MS (*m/z*): 178 $(M+H)^+$

Step B: 2-(6-(chloromethyl)pyridazin-3-yl)thiazole

358

A mixture of 2-(6-methylpyridazin-3-yl)thiazole (680 mg, 1.92 mmol) and trichloroisocyanuric acid (178 mg, 0.767 mmol) in $CHCl_3$ (18 mL) was stirred and heated at 60 °C for 3 hours. The mixture was filtered and the filtrate was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 2-(6-(chloromethyl)pyridazin-3-yl)thiazole. LC/MS (*m/z*): 212 $(M+H)^+$

Intermediate 167

Preparation of 2-(chloromethyl)-5-(1H-pyrazol-1-yl)pyridine

Step A: (5-(1H-pyrazol-1-yl)pyridin-2-yl)methanol

A mixture of (5-bromopyridin-2-yl)methanol (1.50 g, 7.98 mmol), 1H-pyrazole (0.815 g, 12.0 mmol), copper(I) iodide (0.152 g, 0.798 mmol), N1,N2-dimethylethane-1,2-diamine (0.105 g, 1.20 mmol), and potassium carbonate (1.65 g, 12.0 mmol) in DMF (20 mL) was stirred and heated at 100 °C for 16 hours. The mixture was quenched with water (20 mL) and extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford (5-(1H-pyrazol-1-yl)pyridin-2-yl)methanol. LC/MS (*m/z*): 176 $(M+H)^+$

Step B: 2-(chloromethyl)-5-(1H-pyrazol-1-yl)pyridine

Thionyl chloride (0.146 mL, 2.00 mmol) was added to a mixture of (5-(1H-pyrazol-1-yl)pyridin-2-yl)methanol (0.070 g, 0.40 mmol) in DCM (1 mL) at 0 °C. The mixture was stirred for

2.5 hours at 0 °C. The mixture was concentrated under reduced pressure to afford 2-(chloromethyl)-5-(1H-pyrazol-1-yl)pyridine, which was used in the next step without purification. LC/MS (*m/z*): 194 $(M+H)^+$

Examples shown in Intermediate Table 19 below, were prepared according to procedures analogous to those outlined in Intermediate 167 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 19

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 168		5-(chloromethyl)-2-(2H-1,2,3-triazol-2-yl)pyridine 361	195

Intermediate 169

Preparation of 5-(chloromethyl)-2-(1H-pyrazol-1-yl)pyridine

Step A: (6-(1H-pyrazol-1-yl)pyridin-3-yl)methanol

362

A mixture of (6-chloropyridin-3-yl)methanol (0.300 g, 2.09 mmol), 1H-pyrazole (427 mg, 6.27 mmol), and cesium carbonate 705 (2040 mg, 6.27 mmol) in NMP (5 mL) was stirred 704 and heated at 150 °C for 1 hour. The mixture was quenched with water (150 mL) and extracted with EtOAc (3 x 200 mL). The organic layers were combined, washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford (6-(1H-pyrazol-1-yl)pyridin-3-yl)methanol. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.57 (d, J = 2.4 Hz, 1H), 8.40 (d, J = 1.6 Hz,

1H), 7.99 (d, J = 8.4 Hz, 1H), 7.86 (dd, J = 2.2, 8.4 Hz, 1H), 7.75 (s, 1H), 6.52-6.44 (m, 1H), 4.77 (s, 2H). LC/MS (*m/z*): 176 $(M+H)^+$

Step B: 5-(chloromethyl)-2-(1H-pyrazol-1-yl)pyridine

363

Thionyl chloride (0.052 mL, 0.71 mmol) was added to a mixture of (6-(1H-pyrazol-1-yl)pyridin-3-yl)methanol (0.050 g, 0.29 mmol) in DCM (1 mL) 0 °C. The mixture was stirred at room temperature for 1 hour. The mixture was concentrated under reduced pressure to afford 5-(chloromethyl)-2-(1H-pyrazol-1-yl)pyridine, which was used in next step without purification. LC/MS (*m/z*): 194 $(M+H)^+$

Examples shown in Intermediate Table 20 below, were prepared according to procedures analogous to those outlined in Intermediate 169 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 20

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 170		5-(chloromethyl)-2-(1H-1,2,3-triazol-1-yl)pyridine 364	195

Intermediate 171

Preparation of (3-(pyridin-3-yl)isoxazol-5-yl)methyl methanesulfonate

Step A: nicotinaldehyde oxime

365

Hydroxylamine hydrochloride (7.78 g, 112 mmol) was added to a mixture of nicotinaldehyde (8.8 mL, 93 mmol) in EtOH (200 mL) at room temperature. After stirring for 5 minutes at room temperature, sodium acetate (15.3 g, 187 mmol) was added to the mixture. The mixture was stirred for another 2 hours at room temperature. The mixture was cooled, diluted with water (100 mL), and extracted with ethyl acetate (200 mL). The organic layer was washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford nicotinaldehyde oxime, which was used without purification in the next step. ^{1}H NMR (methanol-d_4, 500 MHz) δ 8.71 (d, J = 1.5 Hz, 1H), 8.50 – 8.49 (m, 1H), 8.20 - 8.10 (m, 1H), 8.14 - 8.06 (m, 1H), 7.45 – 7.42 (m, 1H).

Step B: N-hydroxynicotinimidoyl chloride

366

NCS (12.7 g, 95.0 mmol) was added to a mixture of nicotinaldehyde oxime (10.8 g, 88.0 mmol) and pyridine (0.715 mL, 8.84 mmol) in THF (150 mL) at room temperature. The mixture was stirred and heated at at 50 °C for 1 hour. The mixture was quenched with water (50 mL) and extracted with EtOAc (3 x 100 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford N-hydroxynicotinimidoyl chloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.70 (s, 1H), 8.96 (d, J = 1.9 Hz, 1H), 8.67 (dd, J = 1.3, 4.8 Hz, 1H), 8.14 (td, J = 1.9, 8.0 Hz, 1H), 7.53 (dd, J = 4.8, 8.0 Hz, 1H). LC/MS (*m/z*): 157 $(M+H)^+$

Step C: (3-(pyridin-3-yl)isoxazol-5-yl)methanol

367

Prop-2-yn-1-ol (4.9 mL, 82 mmol) and TEA (5.34 mL, 38.3 mmol) were added to a mixture of N-hydroxynicotinimidoyl chloride (5.00 g, 31.9 mmol) in THF (50 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred and heated at 50 °C for 16 hours. The

mixture was quenched with saturated aqueous $NaHCO_3$ (35 mL) and extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting neat ethyl acetate) to afford (3-(pyridin-3-yl)isoxazol-5-yl)methanol. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (d, J = 1.6 Hz, 1H), 8.69 (dd, J = 1.6, 4.9 Hz, 1H), 8.26 (td, J = 1.9, 8.0 Hz, 1H), 7.55 (dd, J = 4.8, 7.9 Hz, 1H), 7.05 (s, 1H), 5.76 (t, J = 6.0 Hz, 1H), 4.64 (d, J = 6.0 Hz, 2H). LC/MS (*m/z*): 177 $(M+H)^+$

Step D: (3-(pyridin-3-yl)isoxazol-5-yl)methyl methanesulfonate

368

TEA (0.593 mL, 4.26 mmol) and methanesulfonic anhydride (742 mg, 4.26 mmol) were added to a mixture of (3-(pyridin-3-yl)isoxazol-5-yl)methanol (0.500 g, 2.84 mmol) in DCM (10 mL) at 0 °C. The mixture was stirred at room temperature for 2 hours. The mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL) and extracted with DCM (3 x 20 mL). The organic layers were combined, washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford (3-(pyridin-3-yl)isoxazol-5-yl)methyl methanesulfonate, which was used without purification in the next step. LC/MS (*m/z*): 255 $(M+H)^+$

Examples shown in Intermediate Table 21 below, were prepared according to procedures analogous to those outlined in Intermediate 171 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Intermediate Table 21

Intermediate	Structure	Name	Mass $[M+H]^+$
Intermediate 172		(3-(pyridin-2-yl)isoxazol-5-yl)methyl methanesulfonate 208	255

Intermediate 173

Preparation of 1-(3-fluorobicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione

370

Pd-C (10% w/w, 1627 mg, 1.5 mmol) was added to a mixture of 1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione (0.300 g, 1.53 mmol) in MeOH (5 mL) under a N_2 atmosphere. The mixture was degassed and backfilled with H_2 (three times). The mixture was stirred under a H_2 atmosphere (15 psi) and heated at 60 °C for 1 hour. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford 1-(3-fluorobicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione, which was used without purification in the next step. LC/MS (*m/z*): 199 $(M+H)^+$

Intermediate 174

Preparation of 6'-(chloromethyl)-2,3'-bipyridine

Step A: [2,3'-bipyridin]-6'-ylmethanol

371

A mixture of (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)methanol (2.50 g, 10.6 mmol), 2-bromopyridine (1.34 g, 8.51 mmol), and $PdCl_2$(dppf) (0.389 g, 0.532 mmol) in a mixture of Na_2CO_3 (2.0 M in water, 16 mL, 32 mmol) and dioxane (50 mL) was stirred and heated at 100 °C for 2 hours. The mixture was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue

was purified by silica gel chromatography (eluting methanol in dichloromethane) to afford [2,3'-bipyridin]-6'-ylmethanol. LC/MS (*m/z*): 187 $(M+H)^+$

Step B: 6'-(chloromethyl)-2,3'-bipyridine

372

Thionyl chloride (353 µL, 4.84 mmol) was added to a mixture of [2,3'-bipyridin]-6'-ylmethanol (0.200 g, 1.07 mmol) in DCM (10 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 2 hours. The mixture was concentrated under reduced pressure to afford 6'-(chloromethyl)-2,3'-bipyridine, which was used in the next step without purification. LC/MS (*m/z*): 205 $(M+H)^+$

Intermediate 175

Preparation of 3-(chloromethyl)-6-(1H-1,2,3-triazol-1-yl)pyridazine

Step A: 3-methyl-6-(1H-1,2,3-triazol-1-yl)pyridazine

373

Cs_2CO_3 (3.80 g, 11.7 mmol) was added to a mixture of 3-chloro-6-methylpyridazine (1.00 g, 7.78 mmol) and 2H-1,2,3-triazole (1.40 mL, 23.3 mmol) in DMF (20 mL). The mixture was stirred and heated at 100 °C for 3 hours. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 3-methyl-6-(2H-1,2,3-triazol-2-yl)pyridazine. LC/MS (*m/z*): 162 $(M+H)^+$

Step B: 3-(chloromethyl)-6-(1H-1,2,3-triazol-1-yl)pyridazine

374

A mixture of 3-methyl-6-(1H-1,2,3-triazol-1-yl)pyridazine (0.400 g, 2.48 mmol) and trichloroisocyanuric acid (288 mg, 1.24 mmol) in $CHCl_3$ (15 mL) was stirred and heated at 60 °C for 3 hours. The mixture was filtered and the filtrate was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 3-(chloromethyl)-6-(1H-1,2,3-triazol-1-yl)pyridazine.

LC/MS (*m/z*): 196 $(M+H)^+$

Intermediate 176

Preparation of 3-(chloromethyl)-5-(pyridin-2-yl)isoxazole

375

Thionyl chloride (0.041 mL, 0.57 mmol) was added to a mixture of (5-(pyridin-2-yl)isoxazol-3-yl)methanol (0.050 g, 0.28 mmol) in DCM (2 mL) at 0 °C. The mixture was stirred at room temperature for 1 hour. The mixture was concentrated under reduced pressure to afford 3-(chloromethyl)-5-(pyridin-2-yl)isoxazole, which was used in the next step without purification.

218

LC/MS (*m/z*): 195 $(M+H)^+$

Intermediate 177

Preparation of 3-(chloromethyl)-5-(pyridin-3-yl)isoxazole

Step A: ethyl 5-(pyridin-3-yl)isoxazole-3-carboxylate

376

A mixture of 3-ethynylpyridine (2.00 g, 19.4 mmol), ethyl (E)-2-chloro-2-(hydroxyimino)acetate (8.82 g, 58.2 mmol), and $NaHCO_3$ (4.89 g, 58.2 mmol) in EtOAc (12 mL) was stirred and heated at 100 °C for 1 hour in a microwave. The mixture was filtered and the filtrate was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford ethyl 5-(pyridin-3-yl)isoxazole-3-carboxylate. LC/MS (*m/z*): 219 $(M+H)^+$

Step B: (5-(pyridin-3-yl)isoxazol-3-yl)methanol

377

$NaBH_4$ (1.98 g, 52.2 mmol) was added to a mixture of ethyl 5-(pyridin-3-yl)isoxazole-3-carboxylate (3.80 g, 17.4 mmol) in MeOH (50 mL) at 0 °C. The mixture was stirred and heated at 50 °C for 24 hours. The mixture was quenched with saturated aqueous NH_4Cl (100 mL) and extracted with EtOAc (3 x 100 mL). The organic layers were combined, washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford (5-(pyridin-3-yl)isoxazol-3-yl)methanol. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (d, J = 1.8 Hz, 1H), 8.68 (dd, J = 1.5, 4.8 Hz, 1H), 8.26 (td, J = 1.9, 8.0 Hz, 1H), 7.57 (dd, J = 4.8, 7.9 Hz, 1H), 7.17 (s, 1H), 5.59 (t, J = 5.9 Hz, 1H), 4.57 (d, J = 5.8 Hz, 2H). LC/MS (*m/z*): 177 $(M+H)^+$

Step C: 3-(chloromethyl)-5-(pyridin-3-yl)isoxazole

378

Thionyl chloride (0.041 mL, 0.57 mmol) was added to a mixture of (5-(pyridin-2-yl)isoxazol-3-yl)methanol (0.050 g, 0.28 mmol) in DCM (2 mL) at 0 °C. The mixture was stirred at

room temperature for 1 hour. The mixture was concentrated under reduced pressure to afford 3-(chloromethyl)-5-(pyridin-2-yl)isoxazole, which was used in the next step without purification. LC/MS (*m/z*): 195 $(M+H)^+$

Intermediate 178

Preparation of [2,3'-bipyridin]-6'-ylmethyl methanesulfonate

379

Methanesulfonic anhydride (103 mg, 0.591 mmol) was added to a mixture of [2,3'-bipyridin]-6'-ylmethanol (0.100 g, 0.537 mmol) and TEA (0.082 mL, 0.59 mmol) in DCM (4 mL) at 371 0 °C. The mixture was stirred at room temperature for 1 hour. The mixture was quenched with water (3 mL) and extracted with DCM (3 x 3 mL). The organic layers were combined, washed with brine (2 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford [2,3'-bipyridin]-6'-ylmethyl methanesulfonate, which was used in the next step without purification. LC/MS (*m/z*): 265 $(M+H)^+$

Intermediate 179

Preparation of 2-(4-(chloromethyl)-1H-1,2,3-triazol-1-yl)pyridine

Step A: methyl 1-(pyridin-2-yl)-1H-1,2,3-triazole-4-carboxylate

380

Methyl propiolate (6.67 mL, 74.9 mmol), $CuSO_4$ (0.399 g, 2.50 mmol), and (+)-sodium L-ascorbate (0.990 718 g, 5.00 mmol) were added sequentially to a mixture of 2-azidopyridine (3.00 g, 355

25.0 mmol) in t-BuOH (30 mL). The mixture was stirred and heated at 50 °C for 2 hours. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford methyl 1-(pyridin-2-yl)-1H-1,2,3-triazole-4-carboxylate. ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.10 (s, 1H), 8.54 (dd, J = 0.9, 4.8 Hz, 1H), 8.25 (d, J = 8.2 Hz, 1H), 7.97 (dt, J = 1.8, 7.8 Hz, 1H), 7.42 (ddd, J = 0.8, 4.9, 7.4 Hz, 1H), 4.01 (s, 3H). LC/MS (*m/z*): 205 $(M+H)^+$

Step B: (1-(pyridin-2-yl)-1H-1,2,3-triazol-4-yl)methanol

381

$LiBH_4$ (133 mg, 6.12 mmol) was added to a mixture of methyl 1-(pyridin-2-yl)-1H-1,2,3-triazole-4-carboxylate (0.500 g, 2.45 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at room temperature for 20 hours. The mixture was quenched with water (10 mL) and extracted with EtOAc (3 x 15 mL). The organic layers were combined, washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford (1-(pyridin-2-yl)-1H-1,2,3-triazol-4-yl)methanol. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.58 (s, 1H), 8.52 (dd, J = 1.0, 5.0 Hz, 1H), 8.21 (d, J = 8.2 Hz, 1H), 7.97 - 7.91 (m, 1H), 7.37 (ddd, J = 1.0, 4.9, 7.4 Hz, 1H), 4.92 (s, 2H). LC/MS (*m/z*): 177 $(M+H)^+$

Step C: 2-(4-(chloromethyl)-1H-1,2,3-triazol-1-yl)pyridine

382

Thionyl chloride (0.186 mL, 2.55 mmol) was added to a mixture of (1-(pyridin-2-yl)-1H-1,2,3-triazol-4-yl)methanol (0.150 g, 0.851 mmol) in DCM (3 mL) at 0 °C. The mixture was stirred at room temperature for 16 hours. The mixture was concentrated under reduced pressure to afford 2-(4-(chloromethyl)-1H-1,2,3-triazol-1-yl)pyridine, which was used without purification in the next step. LC/MS (*m/z*): 195 $(M+H)^+$

Intermediate 180

Preparation of 2-(chloromethyl)-5-(1H-1,2,3-triazol-1-yl)pyridine

Step A: 2-methyl-5-(1H-1,2,3-triazol-1-yl)pyridine

383

A mixture of 5-bromo-2-methylpyridine (5.00 g, 29.1 mmol), 1H-1,2,3-triazole (2.53 mL, 43.6 mmol), copper (I) iodide (0.554 g, 2.91 mmol), (S,S)-(+)-N,N′-dimethyl-1,2-cyclohexanediamine (0.620 g, 4.36 mmol) and potassium phosphate (12.3 g, 58.1 mmol) in DMF (120 mL) was stirred and heated at 100 °C for 16 hours. The mixture was quenched with water (150 mL) and extracted with EtOAc (3 x 150 mL). The organic layers were combined, washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 2-methyl-5-(1H-1,2,3-triazol-1-yl)pyridine. LC/MS (*m/z*): 161 $(M+H)^+$

Step B: 2-methyl-5-(1H-1,2,3-triazol-1-yl)pyridine 1-oxide

384

A mixture of 2-methyl-5-(1H-1,2,3-triazol-1-yl)pyridine (0.040 g, 0.25 mmol) and 3-chloroperoxybenzoic acid (47 mg, 0.28 mmol) in DCM (1 mL) was stirred at room temperature for 16 hours. The mixture was quenched with water (2 mL) and extracted with DCM (3 x 2 mL). The organic layers were combined, washed with brine (2 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 2-methyl-5-(1H-1,2,3-triazol-1-yl)pyridine 1-oxide, which was used in the next step without purification.

Step C: (5-(1H-1,2,3-triazol-1-yl)pyridin-2-yl)methanol

385

A mixture of 2-methyl-5-(1H-1,2,3-triazol-1-yl)pyridine 1-oxide (0.390 g, 2.21 mmol) and TFAA (0.688 mL, 4.87 mmol) in DCM (10 mL) was stirred at room temperature for 40 hours. The mixture was concentrated under reduced pressure and the residue was partitioned between water (10 mL) and EtOAc (10 mL). The organic layer was separated and the aqueous was re-extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford (5-(1H-1,2,3-triazol-1-yl)pyridin-2-yl)methanol. ^{1}H NMR (400 MHz, methanol-d_4) δ 9.02 (d, J = 2.5 Hz, 1H), 8.65 (d, J = 1.2 Hz, 1H), 8.34 (dd, J = 2.6, 8.5 Hz, 1H), 7.95 (d, J = 1.2 Hz, 1H), 7.78 (d, J = 8.58 Hz, 1H), 4.79 (s, 2H). LC/MS (*m/z*): 177 $(M+H)^+$

Step D: 2-(chloromethyl)-5-(1H-1,2,3-triazol-1-yl)pyridine

386

Thionyl chloride (0.435 mL, 5.96 mmol) was added to a mixture of (5-(1H-1,2,3-triazol-1-yl)pyridin-2-yl)methanol (0.350 g, 1.99 mmol) in DCM (5 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 16 hours. The mixture was concentrated under reduced pressure to afford 2-(chloromethyl)-5-(1H-1,2,3-triazol-1-yl)pyridine, which was used in the next step without purification. LC/MS (*m/z*): 195 $(M+H)^+$

Example 1

Preparation of 1-cyclobutyl-4-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)piperazine-2,3-dione

401

A mixture of 1-((6-chloropyridazin-3-yl)methyl)-4-cyclobutylpiperazine-2,3-dione (3.50 g, 11.9 mmol), (2-fluorophenyl)boronic acid (1.75 g, 12.5 mmol), Pd(dtbpf)Cl_2 (0.45 g, 0.69 mmol), and potassium phosphate tribasic (3.78 g, 17.8 mmol) in water (10 mL) and 1,4-dioxane (50 mL) was degassed with argon for 5 minutes. The mixture was stirred and heated at 80 °C for 3 hours. The mixture was cooled to room temperature, and the organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford the product. The product was dissolved in 1,2-dichloroethane (50 mL). Sodium bisulfite (4.58 g, 44.0 mmol) was added, and the mixture was stirred and heated at 65 °C for 12 hours. The mixture was cooled to room temperature, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 1-cyclobutyl-4-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)piperazine-2,3-dione. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.15 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.96 (d, *J* = 9.0 Hz, 1H), 7.72 (d, *J* = 8.9 Hz, 1H), 7.54 - 7.44 (m, 1H), 7.34 (td, *J* = 7.6, 1.0 Hz, 1H), 7.24 – 7.22 (m, 1H), 5.05 – 4.94 (m, 3H), 3.87 - 3.78 (m, 2H), 3.63 - 3.55 (m, 2H), 2.25 - 2.05 (m, 4H), 1.79 - 1.69 (m, 2H). LC/MS (*m/z*): 355 $(M+H)^+$

Example 2

Preparation of 1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione

A mixture of 1-(bicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione (0.800 g, 4.44 mmol), 2-(chloromethyl)-5-(3-fluorophenyl)-1,3,4-thiadiazole (1.02 g, 4.44 mmol), and Cs_2CO_3 (1.81 g, 13.3 mmol) in DMF (25 mL) was stirred and heated at 60 °C for 12 hours. The mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure, and the

residue was purified by silica gel chromatography (eluting methanol in dichloromethane) to afford 1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione. ^{1}H NMR (500 MHz, methanol-d_4) δ 7.80 - 7.72 (m, 2H), 7.55 (dt, J = 8.1 Hz, 5.7 Hz, 1H), 7.31 (dt, J = 8.5 Hz, 2.0 Hz, 1H), 5.07 (s, 2H), 3.80 - 3.73 (m, 2H), 3.64 – 3.60 (m, 2H), 2.50 (s, 1H), 2.20 (s, 6H). LC/MS (m/z): 373 $(M+H)^+$

Example 3

Preparation of 1-cyclopentyl-4-((6-phenylpyridazin-3-yl)methyl)piperazine-2,3-dione

A mixture of 1-((6-chloropyridazin-3-yl)methyl)-4-cyclopentylpiperazine-2,3-dione (10 mg, 0.032 mmol), Pd(dtbpf)Cl_2 (2 mg, 3 µmol), phenylboronic acid (5 mg, 0.04 mmol) and K_3PO_4 (21 mg, 0.097 mmol) in 1,4-dioxane (2 mL) was sparged with nitrogen for 5 minutes. The reaction mixture was stirred and heated to 80 °C under a nitrogen atmosphere for 16 hours. The reaction mixture was cooled to room temperature, quenched with water (10 mL), and extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-cyclopentyl-4-((6-phenylpyridazin-3-yl)methyl)piperazine-2,3-dione. ^{1}H NMR (500 MHz, chloroform-d) δ 8.07-8.03 (m, 2H), 7.92 (d, J = 8.7 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.57-7.51 (m, 3H), 5.00 (s, 2H), 4.89 (quin, J = 8.6 Hz, 1H), 3.84 – 3.77 (m, 2H), 3.51 – 3.44 (m, 2H), 1.95 – 1.87 (m, 2H), 1.74-1.59 (m, 4H), 1.50 – 1.42 (m, 2H). LC/MS (m/z): 351 $(M+H)^+$

Examples shown in Example Table 1 below, were or may be prepared according to procedures analogous to those outlined in Example 3 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Example Table 1

Example	Structure	Name	Mass $[M+H]^+$
Example 4		1-cyclopentyl-4-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione 404	351
Example 5		1-cyclopentyl-4-((5-(thiazol-5-yl)pyrimidin-2-yl)methyl)piperazine-2,3-dione 405	358
Example 6		1-cyclopentyl-4-((6-(oxazol-5-yl)pyridazin-3-yl)methyl)piperazine-2,3-dione 406	342
Example 7		1-(3-phenylcyclobutyl)-4-((6-phenylpyridazin-3-yl)methyl)piperazine-2,3-dione 407	413
Example 8		1-cyclopentyl-4-((5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 408	375

Example 9		1-cyclopentyl-4-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)piperazine-2,3-dione 409	369
Example 10		1-cyclopentyl-4-((3-fluoro-5-(thiazol-5-yl)pyridin-2-yl)methyl)piperazine-2,3-dione 410	375
Example 11		1-cyclopentyl-4-((6-(thiazol-5-yl)pyridazin-3-yl)methyl)piperazine-2,3-dione 411	358
Example 12		1-cyclobutyl-4-((6-phenylpyridazin-3-yl)methyl)piperazine-2,3-dione 412	337
Example 13		1-cyclopentyl-4-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 413	375

Example 14		1-cyclopentyl-4-((6-(3-fluorophenyl)pyridazin-3-yl)methyl)piperazine-2,3-dione 414	369
Example 15		1-((6-(1H-pyrazol-4-yl)pyridazin-3-yl)methyl)-4-cyclopentylpiperazine-2,3-dione 415	341
Example 16		1-cyclopentyl-4-((3-fluoro-5-(1H-pyrazol-4-yl)pyridin-2-yl)methyl)piperazine-2,3-dione 416	358
Example 17		1-cyclopentyl-4-((6-(thiazol-5-yl)pyridin-3-yl)methyl)piperazine-2,3-dione 417	357
Example 18		1-cyclopentyl-4-((6-(oxazol-5-yl)pyridin-3-yl)methyl)piperazine-2,3-dione 418	341

Example 19		1-cyclopentyl-4-(2-fluoro-4-(thiazol-5-yl)benzyl)piperazine-2,3-dione 419	374
Example 20		1-cyclobutyl-4-((6-(3-fluorophenyl)pyridazin-3-yl)methyl)piperazine-2,3-dione 420	355
Example 21		1-cyclobutyl-4-((6-(2,3-difluorophenyl)pyridazin-3-yl)methyl)piperazine-2,3-dione 421	373
Example 22		1-cyclobutyl-4-((6-(3,5-difluorophenyl)pyridazin-3-yl)methyl)piperazine-2,3-dione 422	373
Example 23		1-cyclopentyl-4-(2-fluoro-4-(1H-pyrazol-4-yl)benzyl)piperazine-2,3-dione 423	357

Example 24		1-((6-(1H-pyrazol-4-yl)pyridin-3-yl)methyl)-4-cyclopentylpiperazine-2,3-dione 424	340
Example 25		1-((6-(1H-pyrazol-4-yl)pyridazin-3-yl)methyl)-4-cyclobutylpiperazine-2,3-dione 425	327
Example 26		1-cyclobutyl-4-((5-phenylpyridin-2-yl)methyl)piperazine-2,3-dione 426	336
Example 27		1-cyclobutyl-4-((5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 427	361
Example 28		1-cyclobutyl-4-((5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 428	359

Example 29		1-cyclobutyl-4-((5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 429	361
Example 30		1-cyclobutyl-4-((5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 430	359
Example 31		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 431	373
Example 32		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 432	373
Example 33		1-cyclobutyl-4-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 433	361

Example 34		1-cyclobutyl-4-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 434	359
Example 35		1-cyclopentyl-4-((5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 435	373
Example 36		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 436	371
Example 37		1-cyclopentyl-4-((6-(pyridin-3-yl)pyridazin-3-yl)methyl)piperazine-2,3-dione 437	352
Example 38		1-(bicyclo[1.1.1]pentan-1-yl)-4-((6-phenylpyridazin-3-yl)methyl)piperazine-2,3-dione 438	349

Example 39		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 439	367
Example 40		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 440	387
Example 41		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 441	385
Example 42		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 442	387

Example 43		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 443	385
Example 44		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 444	387
Example 45		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 445	385
Example 46		1-cyclopentyl-4-((5-(2-fluorophenyl)pyrazin-2-yl)methyl)piperazine-2,3-dione 446	369

Example 47		1-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-4-((trans)-3-phenylcyclobutyl)-1,4-dihydropyrazine-2,3-dione 447	417
Example 48		1-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-4-((cis)-3-phenylcyclobutyl)-1,4-dihydropyrazine-2,3-dione 448	417
Example 49		1-cyclobutyl-4-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 449	353
Example 50		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 450	379

Example 51		1-((1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl)-4-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)piperazine-2,3-dione 451	381
Example 52		1-cyclopentyl-4-((6-phenylpyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 452	349
Example 53		1-cyclopentyl-4-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 453	367
Example 54		1-cyclobutyl-4-((5-(3-fluorophenyl)isoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 454	342
Example 55		1-cyclobutyl-4-((5-(4-fluorophenyl)isoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 455	342

Example 56		1-cyclobutyl-4-((5-phenylisoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 456	324
Example 57		1-cyclobutyl-4-((5-(2-fluorophenyl)isoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 457	342
Example 58		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((6-phenylpyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 458	361
Example 59		1-cyclopentyl-4-((6-(3-fluorophenyl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 459	367
Example 60		1-cyclopentyl-4-((5-(2-fluorophenyl)isoxazol-3-yl)methyl)piperazine-2,3-dione 460	358

Example 61		1-cyclopentyl-4-((5-(2-fluorophenyl)isoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 461	356
Example 62		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)piperazine-2,3-dione	381
Example 63		1-cyclobutyl-4-((6-(3-fluorophenyl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 463	353
Example 64		1-(bicyclo[1.1.1]pentan-1-yl)-4-((6-(3-fluorophenyl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 464	365
Example 65		1-(bicyclo[1.1.1]pentan-1-yl)-4-((6-(3-fluorophenyl)pyridazin-3-yl)methyl)piperazine-2,3-dione 465	367

Example 66		1-(bicyclo[1.1.1]pentan-1-yl)-4-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)piperazine-2,3-dione 466	367
Example 67		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-(3-fluorophenyl)isoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 467	368
Example 68		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 468	371
Example 69		1-cyclobutyl-4-((5-phenylthiazol-2-yl)methyl)piperazine-2,3-dione 469	342
Example 70		1-cyclobutyl-4-((2-phenylthiazol-5-yl)methyl)piperazine-2,3-dione 470	342

Example 71		1-cyclobutyl-4-((6-(2,3-difluorophenyl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 471	371
Example 72		1-cyclobutyl-4-((6-(2-fluorophenyl)pyridin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 472	352
Example 73		1-cyclobutyl-4-((5-(2-fluorophenyl)pyrazin-2-yl)methyl)piperazine-2,3-dione 473	355
Example 74		1-cyclobutyl-4-((5-(2-fluorophenyl)pyrazin-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 474	353
Example 75		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-(2-fluorophenyl)pyrazin-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 475	365

Example 76		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-(3-fluorophenyl)isoxazol-3-yl)methyl)piperazine-2,3-dione 476	356
Example 77		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-(2-fluorophenyl)isoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 477	354
Example 78		1-cyclobutyl-4-((2-(2-fluorophenyl)thiazol-5-yl)methyl)piperazine-2,3-dione 478	360
Example 79		1-cyclobutyl-4-((2-(3-fluorophenyl)thiazol-5-yl)methyl)piperazine-2,3-dione 479	360
Example 80		1-cyclobutyl-4-((6-(phenyl-d_5)pyridazin-3-yl)methyl)piperazine-2,3-dione 480	342

Example 81		1-((6-(5-bromo-2-fluorophenyl)pyridazin-3-yl)methyl)-4-cyclobutylpiperazine-2,3-dione 481	433, 435
Example 82		1-((5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)-4-(1-methylcyclobutyl)-1,4-dihydropyrazine-2,3-dione 482	373
Example 83		1-((5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)-4-(1-methylcyclobutyl)-1,4-dihydropyrazine-2,3-dione 483	373
Example 84		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-(o-tolyl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 484	369
Example 85		1-(bicyclo[1.1.1]pentan-1-yl)-4-((6-(pyridin-3-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 485	348

Example 86		1-([2,3'-bipyridin]-6'-ylmethyl)-4-(bicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione 486	347
Example 87		1-(1-methylcyclopropyl)-4-((6-(pyridin-2-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 487	336
Example 88		1-([2,3'-bipyridin]-6'-ylmethyl)-4-(1-methylcyclopropyl)-1,4-dihydropyrazine-2,3-dione 488	335
Example 89		1-(2,3-dioxo-4-((6-(pyridin-3-yl)pyridazin-3-yl)methyl)-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 489	347
Example 90		1-(1-methylcyclopropyl)-4-((6-(pyridin-3-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 490	336
Example 91		1-(2,3-dioxo-4-((6-(pyridin-2-yl)pyridazin-3-yl)methyl)-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 491	347

Example 92		1-(4-([2,3'-bipyridin]-6'-ylmethyl)-2,3-dioxo-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 492	346
Example 93		1-(bicyclo[1.1.1]pentan-1-yl)-4-((6-(pyridin-2-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 493	348
Example 94		1-(1-methylcyclopropyl)-4-((6-(thiazol-5-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 494	342
Example 95		1-(bicyclo[1.1.1]pentan-1-yl)-4-((6-(thiazol-5-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 495	354

Examples 96A and 96B

Preparation of *trans*-1-(3-phenylcyclobutyl)-4-((6-phenylpyridazin-3-yl)methyl)piperazine-2,3-dione and *cis*-1-(3-phenylcyclobutyl)-4-((6-phenylpyridazin-3-yl)methyl)piperazine-2,3-dione

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The isomeric mixture of 1-(3-phenylcyclobutyl)-4-((6-phenylpyridazin-3-yl)methyl)piperazine-2,3-dione was resolved by chiral SFC purification (SJ 21x250 mm column, 45% MeOH w/ 0.1% NH_4OH as cosolvent) to afford *trans*-1-(3-phenylcyclobutyl)-4-((6-phenylpyridazin-3-yl)methyl)piperazine-2,3-dione as the first eluting peak and *cis*-1-(3-phenylcyclobutyl)-4-((6-phenylpyridazin-3-yl)methyl)piperazine-2,3-dione as the second eluting peak.

Peak 1: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.23 (d, J = 8.8 Hz, 1H), 8.19 – 8.13 (m, 2H), 7.77 (d, J = 8.8 Hz, 1H), 7.61 – 7.52 (m, 3H), 7.38 – 7.36 (m, 4H), 7.25 – 7.21 (m, 1H), 5.01 (p, J = 8.3 Hz, 1H), 4.94 (s, 2H), 3.79 – 3.75 (m, 4H), 3.53 – 3.48 (m, 1H), 2.79 – 2.69 (m, 2H), 2.37 – 2.33 (m, 2H). LC/MS (*m/z*): 413 $(M+H)^+$

Peak 2: ^{1}H NMR (499 MHz, DMSO-d_6) δ 8.23 (d, J = 8.8 Hz, 1H), 8.16 – 8.14 (m, 2H), 7.76 (d, J = 8.9 Hz, 1H), 7.61 – 7.52 (m, 3H), 7.34 – 7.29 (m, 4H), 7.22 – 7.19 (m, 1H), 4.93 (s, 2H), 4.79 – 4.71 (m, 1H), 3.74 – 3.66 (m, 4H), 3.23 – 3.17 (m, 1H), 2.64 – 2.51 m, 2H), 2.33 – 2.24 (m, 2H). LC/MS (*m/z*): 413 $(M+H)^+$

Example 97

Preparation of 1-cyclopentyl-4-((6-phenylpyridin-3-yl)methyl)piperazine-2,3-dione

NaH (25 mg, 0.62 mmol, 60% dispersion in mineral oil) was added to a mixture of 1-cyclopentylpiperazine-2,3-dione (75 mg, 0.42 mmol) and 5-(bromomethyl)-2-phenylpyridine (102 mg, 0.42 mmol) in DMF (4 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 hours. The mixture was quenched with water (0.5 mL) and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluting methanol in dichloromethane) to afford 1-cyclopentyl-4-((6-phenylpyridin-3-yl)methyl)piperazine-2,3-dione. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.61 (s, 1H), 7.98-7.92 (m, 2H), 7.91-7.82 (m, 2H), 7.53-7.41 (m, 3H), 4.83-4.77 (m, 1H), 4.75 (s, 2H), 3.62-3.57 (m, 2H), 3.56-3.50 (m, 2H), 1.97-1.84 (m, 2H), 1.81-1.70 (m, 2H), 1.68-1.52 (m, 4H). LC/MS (*m/z*): 350 $(M+H)^+$

Examples shown in Example Table 2 below, were or may be prepared according to procedures analogous to those outlined in Example 97 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Example Table 2

Example	Structure	Name	Mass $[M+H]^+$
Example 98		1-cyclopentyl-4-((5-phenylpyridin-2-yl)methyl)piperazine-2,3-dione 499	350
Example 99 (Peak 1)		(R or S)-1-cyclopentyl-4-(1-(6-phenylpyridin-3-yl)ethyl)piperazine-2,3-dione 500	364
Example 100		1-cyclopentyl-4-((3-fluoro-[1,1'-biphenyl]-4-yl)methyl)piperazine-2,3-dione 501	367
Example 101		1-cyclopentyl-4-((3-fluoro-5-phenylpyridin-2-yl)methyl)piperazine-2,3-dione 502	368
Example 102		1-cyclopentyl-4-((5-fluoro-6-phenylpyridin-3-yl)methyl)piperazine-2,3-dione 503	368

Example 103		1-cyclopentyl-4-((3-phenyl-1,2,4-triazin-6-yl)methyl)piperazine-2,3-dione 504	352
Example 104		1-cyclopentyl-4-((5-phenylisoxazol-3-yl)methyl)piperazine-2,3-dione 505	340
Example 105		1-cyclobutyl-4-((5-phenylisoxazol-3-yl)methyl)piperazine-2,3-dione 506	326
Example 106		1-cyclobutyl-4-((3-fluoro-5-phenylpyridin-2-yl)methyl)piperazine-2,3-dione 507	354
Example 107		1-cyclobutyl-4-((2-phenylpyrimidin-5-yl)methyl)piperazine-2,3-dione 508	337

Example 108		1-cyclobutyl-4-(1-(5-phenylpyrazin-2-yl)ethyl)piperazine-2,3-dione 509	351
Example 109		1-((6-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)methyl)-4-cyclobutylpiperazine-2,3-dione 510	327
Example 110		1-(bicyclo[1.1.1]pentan-1-yl)-4-((2-phenylpyrimidin-5-yl)methyl)piperazine-2,3-dione 511	349
Example 111		1-(bicyclo[1.1.1]pentan-1-yl)-4-((2-phenylpyrimidin-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 512	347
Example 112		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-phenylpyrazin-2-yl)methyl)piperazine-2,3-dione 513	349
Example 113		1-((6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methyl)-4-cyclobutylpiperazine-2,3-dione 514	327

Example 114		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-phenylpyridin-2-yl)methyl)piperazine-2,3-dione 515	348
Example 115		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-phenylpyridin-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 516	346
Example 116		1-((6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methyl)-4-(bicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione 517	339
Example 117		1-((6-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)methyl)-4-(bicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione 518	339
Example 118		1-cyclobutyl-4-((5-phenylpyrazin-2-yl)methyl)piperazine-2,3-dione 519	337

Example 119		1-cyclopentyl-4-(2-(5-phenylisoxazol-3-yl)ethyl)piperazine-2,3-dione 520	354
Example 120		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 521	353
Example 121		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 522	355
Example 122		1-(bicyclo[1.1.1]pentan-1-yl)-4-((6-phenylpyridin-3-yl)methyl)piperazine-2,3-dione 523	348
Example 123		1-cyclobutyl-4-((5-fluoro-6-phenylpyridin-3-yl)methyl)piperazine-2,3-dione 524	354

Example 124		1-cyclopentyl-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 525	355
Example 125		1-(cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-phenylpyrazin-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 526	361
Example 126		1-cyclopentyl-4-((5-phenylpyrazin-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 527	349
Example 127		1-cyclobutyl-4-((5-phenylpyrazin-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 528	335
Example 128		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-fluoro-6-phenylpyridin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 529	378

Example 129		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-phenylpyrazin-2-yl)methyl)piperazine-2,3-dione 530	363
Example 130		1-cyclobutyl-4-((2-phenylpyrimidin-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 531	335
Example 131		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-fluoro-6-phenylpyridin-3-yl)methyl)piperazine-2,3-dione 532	380
Example 132		1-cyclopentyl-4-((3-phenylbicyclo[1.1.1]pentan-1-yl)methyl)piperazine-2,3-dione 533	339

Example 133

Preparation of (*R* or *S*)-1-cyclopentyl-4-(1-(5-phenylpyrimidin-2-yl)ethyl)piperazine-2,3-dione

534

Cs_2CO_3 (619 mg, 1.90 mmol) was added to a mixture of 1-cyclopentylpiperazine-2,3-dione (138 mg, 0.760 mmol) and 2-(1-bromoethyl)-5-phenylpyrimidine (0.200 g, 0.760 mmol) in DMF (2 mL) at room temperature. The reaction mixture was stirred and heated at 60 °C for 12 hours. The mixture was concentrated under reduced pressure. The residue was partitioned between water (10 mL) and DCM (10 mL). The organic layer was separated, and the aqueous layer was washed with additional DCM (3 x 10 mL). The organic layers were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford a mixture of (*R* and *S*)-1-cyclopentyl-4-(1-(5-phenylpyrimidin-2-yl)ethyl)piperazine-2,3-dione. The racemic mixture was resolved by chiral-SFC (Phenomenex Cellulose-2 (250 mm x 30 mm, 10 uM) 45% methanol with 0.1% ammonia as eluent) to afford (*R* or *S*)-1-cyclopentyl-4-(1-(5-phenylpyrimidin-2-yl)ethyl)piperazine-2,3-dione as the second eluting peak. ^{1}H NMR (500 MHz, methanol-d_4) δ = 9.03 (s, 2H), 7.71 (d, J=7.3 Hz, 2H), 7.56 - 7.51 (m, 2H), 7.50 - 7.45 (m, 1H), 5.82 (q, J=7.3 Hz, 1H), 4.84 - 4.77 (m, 1H), 3.71 - 3.66 (m, 3H), 3.61 - 3.55 (m, 1H), 1.97 - 1.87 (m, 2H), 1.79 (br s, 2H), 1.72 (d, *J*=7.3 Hz, 3H), 1.69 - 1.62 (m, 4H). LC/MS (*m/z*): 365 $(M+H)^+$

180

Example 134

Preparation of (*R* or *S*)-1-cyclobutyl-4-(1-(5-phenylpyrimidin-2-yl)ethyl)piperazine-2,3-dione

537

Cs_2CO_3 (226 mg, 0.694 mmol) was added to a mixture of 1-cyclobutylpiperazine-2,3-dione (47 mg, 0.28 mmol) and 2-(1-bromoethyl)-5-phenylpyrimidine (73 mg, 0.28 mmol) in DMF (3 mL) at room temperature. The mixture was stirred and heated at 60 °C for 1 hour. The reaction was cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between water (10 mL) and DCM (10 mL). The organic layer was separated, and the aqueous was washed with additional DCM (3 x 10 mL). The organic layers were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting methanol in dichloromethane) to afford a mixture of (*R* and *S*)-1-cyclobutyl-4-(1-(5-phenylpyrimidin-2-yl)ethyl)piperazine-2,3-dione. The racemic mixture was resolved by chiral-SFC (Phenomenex Cellulose-2 (250 mm x 30 mm, 10 uM) 45% methanol with 0.1% ammonia as eluent) to afford (*R* or *S*)-1-cyclobutyl-4-(1-(5-phenylpyrimidin-2-yl)ethyl)piperazine-2,3-dione as the second eluting peak. ^{1}H NMR (400 MHz, methanol-d_4) δ 9.03 (s, 2H), 7.72 - 7.69 (m, 2H), 7.56 - 7.51 (m, 1H), 7.50 - 7.45 (m, 1H), 5.89 - 5.75 (m, 1H), 4.77 (s, 1H), 3.78 - 3.64 (m, 4H), 2.32 - 2.16 (m, 4H), 1.84 - 1.74 (m, 2H), 1.74 - 1.70 (m, 3H). LC/MS (*m/z*): 351 $(M+H)^+$

539

Example 135

Preparation of 1-cyclobutyl-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione

540

A mixture of 1-cyclobutylpiperazine-2,3-dione (1.50 g, 8.92 mmol), 2-(chloromethyl)-5-phenyl-1,3,4-thiadiazole (1.88 g, 8.92 mmol), and Cs_2CO_3 (3.49 g, 10.7 mmol) in DMF (20 mL) was stirred and heated at 60 °C for 2 hours. The mixture was cooled to room temperature, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting methanol in dichloromethane) to afford 1-cyclobutyl-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.97 (dd, J = 7.6 Hz, 1.7 Hz, 2H), 7.65 - 7.50 (m, 3H), 5.03 (s, 2H), 4.80 – 4.70 (m, 1H), 3.73 - 3.68 (m, 2H), 3.66 - 3.57 (m, 2H), 2.25 - 2.11 (m, 2H), 2.10 – 2.00 (m, 2H), 1.73 - 1.60 (m, 2H). LC/MS (*m/z*): 343 $(M+H)^+$

Example 136

Preparation of 1-((5-(2*H*-1,2,3-triazol-2-yl)pyridin-2-yl)methyl)-4-cyclobutylpiperazine-2,3-dione

541

A mixture of 1-cyclobutylpiperazine-2,3-dione (8.56 g, 50.9 mmol), 2-(chloromethyl)-5-(2*H*-1,2,3-triazol-2-yl)pyridine (9.00 g, 46.2 mmol), and potassium carbonate (12.8 g, 92.0 mmol) in acetonitrile (100 mL) was heated to 65 °C and stirred for 3 days. The reaction mixture was cooled to room temperature and diluted with 10:1 DCM/methanol (500 mL). The mixture was stirred for

15 minutes and then filtered (to remove potassium salts). Silica gel (80 g) was added directly to the filtrate, and the filtrate was then concentrated under reduced pressure to afford the crude product adsorbed onto silica. The silica-adsorbed product was purified by silica gel chromatography (eluting methanol in dichloromethane) to afford the product as solids. The solids were suspended in 20% methanol in ethyl acetate (900 mL) at room temperature. The mixture was stirred and heated to 70 °C until all solids were dissolved (~1.5 hrs). The mixture was then concentrated under reduced pressure. The isolated residue was then dried under vacuum. The solids were suspended in ethyl acetate (250 mL) at room temperature. Hexanes (50 mL) were added dropwise to the stirred mixture over a period of 1 hour. The suspension was stirred at room temperature for 18 hours. The suspension was filtered, and the collected solids were washed with 1:1 ethyl acetate/hexanes (40 mL). The collected solids were dried under vacuum to afford 1-((5-(2*H*-1,2,3-triazol-2-yl)pyridin-2-yl)methyl)-4-cyclobutylpiperazine-2,3-dione. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.19 (d, J = 2.3 Hz, 1H), 8.37 (dd, J = 8.5, 2.6 Hz, 1H), 8.21 (s, 2H), 7.59 (d, J = 8.5 Hz, 1H), 4.82 – 4.73 (m, 1H), 4.76 (s, 2H), 3.63 (s, 4H), 2.24 – 2.14 (m, 2H), 2.10 – 2.03 (m, 2H), 1.70 – 1.62 (m, 2H). LC/MS (*m/z*): 327 $(M+H)^+$

Example 137

Preparation of 1-cyclobutyl-4-((6-phenylpyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione

542

A mixture of 1-cyclobutyl-1,4-dihydropyrazine-2,3-dione (2.44 g, 14.7 mmol), 3-(chloromethyl)-6-phenylpyridazine (3.00 g, 14.7 mmol), and Cs_2CO_3 (4.78 g, 14.7 mmol) in DMF (20 mL) was stirred and heated at 60 °C for 1 hour. The mixture was cooled to room temperature, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in dichloromethane) to afford 1-cyclobutyl-4-((6-phenylpyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione. ^{1}H NMR (500 MHz, chloroform-d) δ 8.10 - 8.03 (m, 2H), 7.92 - 7.84 (m, 1H), 7.82 - 7.76 (m, 1H), 7.58 - 7.47 (m, 3H), 6.61 (d, J = 6.3

91

Hz, 1H), 6.38 (d, J = 6.3 Hz, 1H), 5.28 (s, 2H), 5.10 - 4.92 (m, 1H), 2.41-2.38 (m, 2H), 2.17-2.14 (m, 2H), 1.89 - 1.74 (m, 2H). LC/MS (m/z): 335 $(M+H)^+$

Example 138

Preparation of 1-cyclobutyl-4-((5-(pyridin-2-yl)isoxazol-3-yl)methyl)piperazine-2,3-dione

543

A mixture of 1-cyclobutylpiperazine-2,3-dione (1.99 g, 11.8 mmol), (5-(pyridin-2-yl)isoxazol-3-yl)methyl methanesulfonate (3.00 g, 11.8 mmol), and Cs_2CO_3 (5.00 g, 15.3 mmol) in DMF (25 mL) was stirred 219 and heated at 60 °C for 2 hours. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluting methanol in dichloromethane) followed by purification by reverse phase HPLC (eluting acetonitrile in water, NH_4HCO_3 modifier) to afford 1-cyclobutyl-4-((5-(pyridin-2-yl)isoxazol-3-yl)methyl)piperazine-2,3-dione. ^{1}H NMR (400 MHz, chloroform-d) δ 8.79 - 8.48 (m, 1H), 7.97 - 7.73 (m, 2H), 7.40 - 7.31 (m, 1H), 6.93 (s, 1H), 4.99 (quin, J = 8.8 Hz, 1H), 4.81 (s, 2H), 3.65 - 3.58 (m, 2H), 3.58 - 3.52 (m, 2H), 2.25 - 2.15 (m, 2H), 2.12 - 2.00 (m, 2H), 1.80 - 1.71 (m, 2H). LC/MS (m/z): 327 $(M+H)^+$

Example 139

Preparation of 1-cyclopentyl-4-((3-fluoro-5-(thiazol-2-yl)pyridin-2-yl)methyl)piperazine-2,3-dione

544

A mixture of (3-fluoro-5-(thiazol-2-yl)pyridin-2-yl)methyl methanesulfonate (5 mg, 0.02 mmol), 1-cyclopentylpiperazine-2,3-dione (4 mg, 0.02 mmol), and Cs_2CO_3 (10 mg, 0.03 mmol) in DMF (0.5 mL) was stirred and heated at 80 °C for 1 hour. The reaction mixture was cooled to room temperature, diluted with DCM (3 mL), and filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by basic alumina chromatography (eluting [EtOAc:EtOH (3:1)] in hexanes) to afford 1-cyclopentyl-4-((3-fluoro-5-(thiazol-2-yl)pyridin-2-yl)methyl)piperazine-2,3-dione. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.25 (d, J = 10.5 Hz, 1H), 8.04 (d, J = 3.2 Hz, 1H), 7.95 (d, J = 3.2 Hz, 1H), 4.85 (s, 2H), 4.75 – 4.65 (m, 1H), 3.67 – 3.60 (m, 2H), 3.58 – 3.49 (m, 2H), 1.82 – 1.74 (m, 2H), 1.70 – 1.64 (m, 2H), 1.60 – 1.52 (m, 4H). LC/MS (m/z): 375 $(M+H)^+$

Examples shown in Example Table 3 below, were or may be prepared according to procedures analogous to those outlined in Example 139 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Example Table 3

Example	Structure	Name	Mass $[M+H]^+$
Example 140		1-(4-(2H-1,2,3-triazol-2-yl)benzyl)-4-cyclopentylpiperazine-2,3-dione 545	340
Example 141		1-(3-phenylcyclobutyl)-4-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione 546	413

Example 142		1-(3-phenylcyclobutyl)-4-((6-phenylpyridin-3-yl)methyl)piperazine-2,3-dione 547	412
Example 143		1-cyclobutyl-4-((5-phenylpyrimidin-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 548	335
Example 144		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 549	371
Example 145		1-cyclopentyl-4-((5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 550	373
Example 146		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-phenylisoxazol-3-yl)methyl)piperazine-2,3-dione 551	338

Example 147		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-phenylisoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 552	336
Example 148		1-cyclobutyl-4-((3-phenylisoxazol-5-yl)methyl)piperazine-2,3-dione 553	326
Example 149		1-cyclobutyl-4-((3-(2-fluorophenyl)isoxazol-5-yl)methyl)piperazine-2,3-dione 554	344
Example 150		1-cyclobutyl-4-((3-(4-fluorophenyl)isoxazol-5-yl)methyl)piperazine-2,3-dione 555	344
Example 151		1-cyclobutyl-4-((3-phenylisoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 556	324

Example 152		1-cyclobutyl-4-((3-(2-fluorophenyl)isoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 557	342
Example 153		1-cyclopentyl-4-((3-(3-fluorophenyl)isoxazol-5-yl)methyl)piperazine-2,3-dione 558	358
Example 154		1-cyclopentyl-4-((3-(2-fluorophenyl)isoxazol-5-yl)methyl)piperazine-2,3-dione 559	358
Example 155		1-cyclopentyl-4-((3-(3-fluorophenyl)isoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 560	356
Example 156		1-cyclopentyl-4-((3-(2-fluorophenyl)isoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 561	356

Example 157		1-cyclobutyl-4-((3-(3-fluorophenyl)isoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 562	342
Example 158		1-cyclobutyl-4-((3-(3-fluorophenyl)isoxazol-5-yl)methyl)piperazine-2,3-dione 563	344
Example 159		1-cyclobutyl-4-((3-(4-fluorophenyl)isoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 564	342
Example 160		1-cyclobutyl-4-((1-phenyl-1H-pyrazol-4-yl)methyl)-1,4-dihydropyrazine-2,3-dione 565	323
Example 161		1-cyclobutyl-4-((3-(pyridin-2-yl)isoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 566	325

Example 162		1-cyclopentyl-4-((3-(4-fluorophenyl)isoxazol-5-yl)methyl)piperazine-2,3-dione 567	358
Example 163		1-cyclopentyl-4-((3-(pyridin-2-yl)isoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 568	339
Example 164		1-cyclopentyl-4-((3-(4-fluorophenyl)isoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 569	356
Example 165		1-cyclobutyl-4-((3-phenylisothiazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 570	340
Example 166		1-(1-methylcyclobutyl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 571	357

Example 167		1-(1-methylcyclobutyl)-4-((5-phenylisoxazol-3-yl)methyl)piperazine-2,3-dione 572	340
Example 168		1-cyclobutyl-4-((3-phenyl-1H-pyrazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 573	323
Example 169		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-(pyridin-2-yl)isoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 574	337
Example 170		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((3-phenylisoxazol-5-yl)methyl)piperazine-2,3-dione 575	352
Example 171		1-(bicyclo[1.1.1]pentan-1-yl)-4-((3-phenylisoxazol-5-yl)methyl)piperazine-2,3-dione 576	338

Example 172		1-(bicyclo[1.1.1]pentan-1-yl)-4-((3-(pyridin-2-yl)isoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 577	337
Example 173		1-cyclobutyl-4-((5-phenylisothiazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 578	340
Example 174		1-cyclobutyl-4-((1-phenyl-1H-imidazol-4-yl)methyl)piperazine-2,3-dione 579	325
Example 175		1-cyclobutyl-4-((1-phenyl-1H-imidazol-4-yl)methyl)-1,4-dihydropyrazine-2,3-dione 580	323
Example 176		1-((5-(2H-tetrazol-2-yl)pyridin-2-yl)methyl)-4-cyclobutylpiperazine-2,3-dione 581	328

Example 177		1-cyclobutyl-4-((3-(pyridin-2-yl)bicyclo[1.1.1]pentan-1-yl)methyl)piperazine-2,3-dione 582	326
Example 178		1-((5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methyl)-4-cyclobutyl-5-methylpiperazine-2,3-dione 583	341
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Example 180		(R or S)-2-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)hexahydro-2H-pyrido[1,2-a]pyrazine-3,4-dione 585 588	343
Example 181		1-(1-methylcyclobutyl)-4-((3-phenylisoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 586	338

Example 182	588	(R or S)-2-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)hexahydro-2H-pyrido[1,2-a]pyrazine-3,4-dione	343
Example 183		1-(bicyclo[2.1.1]hexan-2-yl)-4-((6-phenylpyridazin-3-yl)methyl)piperazine-2,3-dione 590	363
Example 184		1-(bicyclo[2.1.1]hexan-2-yl)-4-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)piperazine-2,3-dione 591	381
Example 185		1-((3-(3-fluorophenyl)isoxazol-5-yl)methyl)-4-(1-methylcyclobutyl)piperazine-2,3-dione 592	358
Example 186		1-((3-(3-fluorophenyl)isoxazol-5-yl)methyl)-4-(1-methylcyclobutyl)-1,4-dihydropyrazine-2,3-dione 593	356

Example 187		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-(thiazol-2-yl)isoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 594	343
Example 188		1-((3-(4-fluorophenyl)isoxazol-5-yl)methyl)-4-(1-methylcyclobutyl)piperazine-2,3-dione 595	358
Example 189		1-((3-(4-fluorophenyl)isoxazol-5-yl)methyl)-4-(1-methylcyclobutyl)-1,4-dihydropyrazine-2,3-dione 596	356
Example 190		1-((2,2-difluoro-3-phenylbicyclo[1.1.1]pentan-1-yl)methyl)-4-(1-methylcyclobutyl)piperazine-2,3-dione 597	375
Example 191		1-(bicyclo[1.1.1]pentan-1-yl)-4-((2,2-difluoro-3-phenylbicyclo[1.1.1]pentan-1-yl)methyl)piperazine-2,3-dione 598	373

Example 192		1-cyclobutyl-4-((6-(2,6-difluorophenyl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 599	371
Example 193		1-(bicyclo[1.1.1]pentan-1-yl)-4-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 600	365
Example 194		1-(1-(fluoromethyl)cyclopropyl)-4-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 601	379
Example 195		1-(1-(fluoromethyl)cyclopropyl)-4-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)piperazine-2,3-dione 602	373
Example 196		1-(1-(fluoromethyl)cyclopropyl)-4-((3-phenylisoxazol-5-yl)methyl)piperazine-2,3-dione 603	344

Example 197		1-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)-4-(1-methylcyclopropyl)-1,4-dihydropyrazine-2,3-dione 604	353
Example 198		1-(4-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)-2,3-dioxo-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 605	364
Example 199		1-(1-methylcyclopropyl)-4-((3-(pyridin-2-yl)isoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 606	325
Example 200		1-(2,3-dioxo-4-((3-(pyridin-2-yl)isoxazol-5-yl)methyl)-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 607	336
Example 201		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 608	383

Example 202		1-((5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methyl)-4-(1-methylcyclopropyl)-1,4-dihydropyrazine-2,3-dione 609	325
Example 203		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((3-(pyridin-2-yl)isoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 610	355
Example 204		1-(2,3-dioxo-4-((6-(thiazol-2-yl)pyridazin-3-yl)methyl)-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 611	353
Example 205		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((6-(thiazol-2-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 612	372
Example 206		1-(1-methylcyclopropyl)-4-((5-(pyridin-2-yl)isoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 613	325

Example 207		1-(2,3-dioxo-4-((5-(pyridin-2-yl)isoxazol-3-yl)methyl)-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 614	336
Example 208		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((5-(pyridin-2-yl)isoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 615	355
Example 209		1-(1-methylcyclopropyl)-4-((5-(pyridin-3-yl)isoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 616	325
Example 210		1-(2,3-dioxo-4-((5-(pyridin-3-yl)isoxazol-3-yl)methyl)-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 617	336
Example 211		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((5-(pyridin-3-yl)isoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 618	355

Example 212		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-(pyridin-3-yl)isoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 619	337
Example 213		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((6-(thiazol-5-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 620	372
Example 214		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((6-(pyridin-2-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 621	366
Example 215		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((6-(pyridin-3-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 622	366
Example 216		1-((5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methyl)-4-(1-(fluoromethyl)cyclopropyl)-1,4-dihydropyrazine-2,3-dione 623	343

Example 217		1-((5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methyl)-4-(3-fluorobicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione 624	355
Example 218		1-((5-(1H-pyrazol-1-yl)pyridin-2-yl)methyl)-4-(1-(fluoromethyl)cyclopropyl)-1,4-dihydropyrazine-2,3-dione 625	342
Example 219		1-((5-(1H-pyrazol-1-yl)pyridin-2-yl)methyl)-4-(3-fluorobicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione 626	354
Example 220		1-((6-(1H-pyrazol-1-yl)pyridin-3-yl)methyl)-4-(3-fluorobicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione 627	354
Example 221		1-(1-methylcyclopropyl)-4-((3-(pyridin-3-yl)isoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 628	325

Example 222		1-(2,3-dioxo-4-((3-(pyridin-3-yl)isoxazol-5-yl)methyl)-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 629	336
Example 223		1-(bicyclo[1.1.1]pentan-1-yl)-4-((3-(pyridin-3-yl)isoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 630	337
Example 224		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((3-(pyridin-3-yl)isoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 631	355
Example 225		1-(1-(fluoromethyl)cyclopropyl)-4-((3-(pyridin-2-yl)isoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 632	343
Example 226		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((6-(pyridin-2-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 621	368

Example 227		1-(1-(fluoromethyl)cyclopropyl)-4-((6-(pyridin-3-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 634	354
Example 228		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)piperazine-2,3-dione 635	385
Example 229		1-([2,3'-bipyridin]-6'-ylmethyl)-4-(3-fluorobicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione 636	365
Example 230		1-((6-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)methyl)-4-(3-fluorobicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione 637	355
Example 231		1-((6-(1H-pyrazol-1-yl)pyridin-3-yl)methyl)-4-(1-(fluoromethyl)cyclopropyl)-1,4-dihydropyrazine-2,3-dione 638	342

Example 232		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((3-(pyridin-2-yl)isoxazol-5-yl)methyl)piperazine-2,3-dione 639	357
Example 233		1-(1-(fluoromethyl)cyclopropyl)-4-((6-(thiazol-2-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 640	360
Example 234		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((6-(thiazol-2-yl)pyridazin-3-yl)methyl)piperazine-2,3-dione 641	374
Example 235		1-((6-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)methyl)-4-(1-(fluoromethyl)cyclopropyl)-1,4-dihydropyrazine-2,3-dione 642	343
Example 236		1-((6-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)methyl)-4-(3-fluorobicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione 643	357

Example 237		1-((6-(1H-pyrazol-1-yl)pyridin-3-yl)methyl)-4-(3-fluorobicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione 644	356
Example 238		1-(1-(fluoromethyl)cyclopropyl)-4-((5-(pyridin-2-yl)isoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 645	343
Example 239		1-(1-(fluoromethyl)cyclopropyl)-4-((6-(pyridin-2-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 646	354
Example 240		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((3-(pyridin-3-yl)isoxazol-5-yl)methyl)piperazine-2,3-dione 647	357
Example 241		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((6-(pyridin-3-yl)pyridazin-3-yl)methyl)piperazine-2,3-dione 648	368

Example 242		1-(1-(fluoromethyl)cyclopropyl)-4-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 649	371
Example 243		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((6-(thiazol-5-yl)pyridazin-3-yl)methyl)piperazine-2,3-dione 650	374
Example 244		1-((5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methyl)-4-(3-fluorobicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione 651	357
Example 245		1-(1-(fluoromethyl)cyclopropyl)-4-((6-(thiazol-5-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 652	360
Example 246		1-(1-(fluoromethyl)cyclopropyl)-4-((3-(pyridin-3-yl)isoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione 653	343

Example 247		1-((6-(1H-1,2,3-triazol-1-yl)pyridazin-3-yl)methyl)-4-(1-(fluoromethyl)cyclopropyl)-1,4-dihydropyrazine-2,3-dione 654	344
Example 248		1-((6-(1H-1,2,3-triazol-1-yl)pyridazin-3-yl)methyl)-4-(3-fluorobicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione 655	356
Example 249		1-((6-(1H-1,2,3-triazol-1-yl)pyridazin-3-yl)methyl)-4-(3-fluorobicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione 656	358
Example 250		1-((5-(1H-pyrazol-1-yl)pyridin-2-yl)methyl)-4-(3-fluorobicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione 657	356
Example 251		1-([2,3'-bipyridin]-6'-ylmethyl)-4-(1-(fluoromethyl)cyclopropyl)-1,4-dihydropyrazine-2,3-dione 658	353

Example 252		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((5-(pyridin-2-yl)isoxazol-3-yl)methyl)piperazine-2,3-dione 659	357
Example 253		1-(1-(fluoromethyl)cyclopropyl)-4-((5-(pyridin-3-yl)isoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 660	343
Example 254		1-([2,3'-bipyridin]-6'-ylmethyl)-4-(3-fluorobicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione 661	367
Example 255		1-((6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methyl)-4-(3-fluorobicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione 662	355
Example 256		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((5-(pyridin-3-yl)isoxazol-3-yl)methyl)piperazine-2,3-dione 663	357

Example 257		1-(1-(fluoromethyl)cyclopropyl)-4-((1-(pyridin-2-yl)-1H-1,2,3-triazol-4-yl)methyl)-1,4-dihydropyrazine-2,3-dione 664	343
Example 258		1-(2,3-dioxo-4-((1-(pyridin-2-yl)-1H-1,2,3-triazol-4-yl)methyl)-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 665	336
Example 259		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((1-(pyridin-2-yl)-1H-1,2,3-triazol-4-yl)methyl)piperazine-2,3-dione 666	357
Example 260		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((1-(pyridin-2-yl)-1H-1,2,3-triazol-4-yl)methyl)-1,4-dihydropyrazine-2,3-dione 667	355
Example 261		1-((5-(1H-1,2,3-triazol-1-yl)pyridin-2-yl)methyl)-4-(1-(fluoromethyl)cyclopropyl)-1,4-dihydropyrazine-2,3-dione 668	343

Example 262		1-((5-(1H-1,2,3-triazol-1-yl)pyridin-2-yl)methyl)-4-(3-fluorobicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione 669	355
Example 263		1-((5-(1H-1,2,3-triazol-1-yl)pyridin-2-yl)methyl)-4-(3-fluorobicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione 670	357
Example 264		1-((6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methyl)-4-(1-(fluoromethyl)cyclopropyl)-1,4-dihydropyrazine-2,3-dione 671	343
Example 265		1-((6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methyl)-4-(3-fluorobicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione 672	357

Examples 266A and 266B

Preparation of *cis*-1-(3-phenylcyclobutyl)-4-((6-phenylpyridin-3-yl)methyl)piperazine-2,3-dione and *trans*-1-(3-phenylcyclobutyl)-4-((6-phenylpyridin-3-yl)methyl)piperazine-2,3-dione

673

674

The isomeric mixture of 1-(3-phenylcyclobutyl)-4-((6-phenylpyridin-3-yl)methyl)piperazine-2,3-dione was resolved by chiral SFC purification (CCA 21x250 mm column, 45% MeOH w/ 0.1% NH_4OH as cosolvent) to afford *cis*-1-(3-phenylcyclobutyl)-4-((6-phenylpyridin-3-yl)methyl)piperazine-2,3-dione as the first eluting peak and *trans*-1-(3-phenylcyclobutyl)-4-((6-phenylpyridin-3-yl)methyl)piperazine-2,3-dione as the second eluting peak.

Peak 1: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (d, J = 1.7 Hz, 1H), 8.08 (d, J = 7.3 Hz, 2H), 7.96 (d, J = 8.2 Hz, 1H), 7.82 (dd, J = 8.2, 2.1 Hz, 1H), 7.50 (t, J = 7.4 Hz, 2H), 7.44 (t, J = 7.2 Hz, 1H), 7.34 – 7.28 (m, 4H), 7.22 – 7.17 (m, 1H), 4.78 – 4.66 (m, 1H), 4.66 (s, 2H), 3.62 (dd, J = 7.2, 4.0 Hz, 2H), 3.57 (dd, J = 7.0, 3.8 Hz, 2H), 3.23 – 3.16 (m, 1H), 2.56 – 2.48 (m, 2H), 2.30 – 2.20 (m, 2H). LC/MS (*m/z*): 412 $(M+H)^+$

Peak 2: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (d, J = 1.8 Hz, 1H), 8.11 – 8.06 (m, 2H), 7.97 (d, J = 8.2 Hz, 1H), 7.83 (dd, J = 8.2, 2.2 Hz, 1H), 7.50 (t, J = 7.4 Hz, 2H), 7.44 (t, J = 7.3 Hz, 1H), 7.38 – 7.32 (m, 4H), 7.24 – 7.20 (m, 1H), 4.98 (p, J = 8.6 Hz, 1H), 4.67 (s, 2H), 3.72 (dd, J = 7.1, 4.3 Hz, 2H), 3.61 (dd, J = 7.0, 4.3 Hz, 2H), 3.51 – 3.46 (m, 1H), 2.76 – 2.66 (m, 2H), 2.37 – 2.30 (m, 2H). LC/MS (*m/z*): 412 $(M+H)^+$

Example 267

Preparation of 5-((4-cyclopentyl-2,3-dioxopiperazin-1-yl)methyl)-2-phenylpyridine 1-oxide

meta-Chloroperoxybenzoic acid (*m*-CPBA) (50 mg, 0.3 mmol, 85% wt) was added to a mixture of 1-cyclopentyl-4-((6-phenylpyridin-3-yl)methyl)piperazine-2,3-dione (32 mg, 0.091 mmol) in DCM (3 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 hours. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluting methanol in dichloromethane) to afford 5-((4-cyclopentyl-2,3-dioxopiperazin-1-yl)methyl)-2-phenylpyridine 1-oxide. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.44 (s, 1H), 7.96 (s, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.81-7.76 (m, 2H), 7.67-7.61 (m, 2H), 7.47-7.38 (m, 1H), 4.83-4.77 (m, 1H), 4.72 (s, 2H), 3.69-3.62 (m, 2H), 3.61-3.54 (m, 2H), 1.97-1.85 (m, 2H), 1.81-1.71 (m, 2H), 1.70-1.54 (m, 4H). LC/MS (*m/z*): 366 $(M+H)^+$

Example 268

Preparation of 1-(2-(7-chlorocinnolin-3-yl)ethyl)-4-cyclopentylpiperazine-2,3-dione

Step A: 7-chlorocinnolin-3-yl trifluoromethanesulfonate

387

Triflic anhydride (0.42 mL, 2.49 mmol) was added to a mixture of TEA (0.93 mL, 6.6 mmol) and 7-chlorocinnolin-3-ol (0.300 g, 1.66 mmol) in DCM (10 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 hours. The mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 7-chlorocinnolin-3-yl trifluoromethanesulfonate. LC/MS (*m/z*): 313 $(M+H)^+$

735

Step B: 7-chloro-3-vinylcinnoline

388

A mixture of 2,4,6-trivinylcyclotriboroxane pyridine complex (51 mg, 0.21 mmol), 7-chlorocinnolin-3-yl trifluoromethanesulfonate (220 mg, 0.71 mmol) and potassium carbonate (243 mg, 1.76 mmol) was flushed with nitrogen. 1,4-dioxane (10 mL) and water (1 mL) were added, and the mixture was sparged with nitrogen. Palladium-tetrakis(triphenylphosphine) (65 mg, 0.056 mmol) was added, and the reaction mixture was stirred and heated at 80 °C for 12 hours under a nitrogen atmosphere. The mixture was cooled to room temperature, diluted with ethyl acetate (20 mL), and washed with saturated aqueous sodium carbonate (20 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 7-chloro-3-vinylcinnoline. LC/MS (*m/z*): 191 $(M+H)^+$

736

Step C: 1-(2-(7-chlorocinnolin-3-yl)ethyl)-4-cyclopentylpiperazine-2,3-dione

676

Potassium carbonate (174 mg, 1.26 mmol) was added to a mixture of 1-cyclopentylpiperazine-2,3-dione (92 mg, 0.50 mmol) and 7-chloro-3-vinylcinnoline (80 mg, 0.42 mmol) in N-methyl-2-pyrrolidone (3 mL) at room temperature. The reaction mixture was stirred and heated at 80 °C for 12 hours under a nitrogen atmosphere. The mixture was cooled to room temperature, diluted with ethyl acetate (20 mL), and washed with water (50 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-(2-(7-chlorocinnolin-3-yl)ethyl)-4-cyclopentylpiperazine-2,3-dione. ^{1}H NMR (500 MHz, methanol-d_4) δ 8.46 (s, 1H), 8.23 (s, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.86 (dd, J = 8.9, 2.0 Hz 1H), 4.77-4.74 (m, 1H), 4.02 (t, J = 6.8 Hz, 2H), 3.65 (s, 2H), 3.58-3.51 (m, 4H), 1.91-1.84 (m, 2H), 1.77-1.76 (m, 2H), 1.68-1.58 (m, 4H). LC/MS (m/z): 373 $(M+H)^+$

Example 269

Preparation of 1-(2-(cinnolin-3-yl)ethyl)-4-cyclopentylpiperazine-2,3-dione

Step A: 1-cyclopentyl-4-(2-(1,2-dihydrocinnolin-3-yl)ethyl)piperazine-2,3-dione

389

Palladium on carbon (10% w/w, 4 mg, 4 µmol) was added to a mixture of 1-(2-(7-chlorocinnolin-3-yl)ethyl)-4-cyclopentylpiperazine-2,3-dione (15 mg, 0.040 mmol) in ammonia (30% aqueous, 0.05 mL) and MeOH (2.5 mL) under a nitrogen atmosphere at room temperature. The reaction mixture was degassed and backfilled with H_2 (three times). The reaction mixture was stirred under a hydrogen atmosphere at 30 °C for 3 hours. The mixture was filtered, and the filtrate was concentrated under reduced pressure to afford 1-cyclopentyl-4-(2-(1,2-dihydrocinnolin-3-yl)ethyl)piperazine-2,3-dione which was used in the next step without purification. LC/MS (*m/z*): 341 $(M+H)^+$

676

Step B: 1-(2-(cinnolin-3-yl)ethyl)-4-cyclopentylpiperazine-2,3-dione

677

Manganese dioxide (5 mg, 0.06 mmol) was added to a mixture of 1-cyclopentyl-4-(2-(1,2-dihydrocinnolin-3-yl)ethyl)piperazine-2,3-dione (13 mg, 0.038 mmol) in DCM (2 mL). The reaction mixture was stirred at room temperature for 4 hours under a nitrogen atmosphere. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was

purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-(2-(cinnolin-3-yl)ethyl)-4-cyclopentylpiperazine-2,3-dione. ^{1}H NMR (500 MHz, methanol-d_4) δ 8.45 (d, J = 8.5 Hz, 1H), 8.36 (s, 1H), 8.07 (d, J = 8.2 Hz, 1H), 8.03-7.98 (m, 1H), 7.96-7.92 (m, 1H), 4.78-4.72 (m, 1H), 4.03 (t, J = 6.9 Hz, 2H), 3.70-3.62 (m, 2H), 3.59-3.51 (m, 4H), 1.92-1.84 (m, 2H), 1.81-1.73 (m, 2H), 1.68-1.56 (m, 4H). LC/MS (m/z): 339 $(M+H)^+$

Example 270

Preparation of 1-cyclopentyl-4-((2-phenylpyrimidin-5-yl)methyl)piperazine-2,3-dione

A mixture of 5-bromo-2-phenylpyrimidine (117 mg, 0.499 mmol), 2-(4-cyclopentyl-2,3-dioxopiperazin-1-yl)acetic acid (100 mg, 0.4 mmol), Iridium(III) bis[2-(2,4-difluorophenyl)-5-methylpyridine-N,C20]-4,40-di-tert-butyl-2,20-bipyridine hexafluorophosphate (Ir[dF(Me)ppy]$_2$(dtbpy)PF$_6$) (4 mg, 4 µmol), picolinimidamide hydrochloride (1 mg, 8 µmol), nickel(II) bromide ethylene glycol dimethyl ether (3 mg, 8 µmol) and K_3PO_4 (265 mg, 1.25 mmol) in DMF (3 mL) was degassed and backfilled with nitrogen (three times). The reaction mixture was irradiated by 34 W blue LEDs (Kessil lamps) at room temperature for 18 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with ammonium bicarbonate modifier) to afford 1-cyclopentyl-4-((2-phenylpyrimidin-5-yl)methyl)piperazine-2,3-dione. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.86 (s, 2H), 8.43-8.38 (m, 2H), 7.50-7.49 (m, 3H), 4.84-4.77 (m, 1H), 4.72 (s, 2H), 3.69-3.63 (m, 2H), 3.58-3.53 (m, 2H), 1.95-1.84 (m, 2H), 1.77-1.74 (m, 2H), 1.69-1.56 (m, 4H). LC/MS (m/z): 351 $(M+H)^+$

Examples shown in Example Table 4 below, were or may be prepared according to procedures analogous to those outlined in Example 270 above using the appropriate starting

materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Example Table 4

Example	Structure	Name	Mass $[M+H]^+$
Example 271		1-cyclopentyl-4-((5-phenylpyrazin-2-yl)methyl)piperazine-2,3-dione 679	351
Example 272		1-cyclopentyl-4-((1-oxo-1,2-dihydroisoquinolin-7-yl)methyl)piperazine-2,3-dione 680	340
Example 273		1-cyclopentyl-4-((1-phenyl-1H-pyrazol-4-yl)methyl)piperazine-2,3-dione 681	339
Example 274		1-cyclopentyl-4-((3-phenyl-1H-pyrazol-5-yl)methyl)piperazine-2,3-dione 682	339

Example 275		1-cyclopentyl-4-((1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)piperazine-2,3-dione 683	342

Example 276

Preparation of 1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione

684

Bicyclo[1.1.1]pentan-1-amine (14 mg, 0.17 mmol) and sodium triacetoxyborohydride (97 mg, 0.46 mmol) were added to a mixture of ethyl 2-oxo-2-((2-oxoethyl)((5-phenylpyrimidin-2-yl)methyl)amino)acetate (0.050 g, 0.15 mmol) in 1,2-dichloroethane (2 mL) at room temperature. The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was poured into water (10 mL) and then extracted with DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with ammonium bicarbonate modifier) to afford 1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione. ^{1}H NMR (400 MHz, methanol-d_4) δ 9.02 (s, 2H), 7.71 (d, J = 7.1 Hz, 2H), 7.56 - 7.51 (m, 2H), 7.50 - 7.44 (m, 1H), 4.94 (s, 2H), 3.85 - 3.76 (m, 2H), 3.75 - 3.67 (m, 2H), 2.54 (s, 1H), 2.25 (s, 6H). LC/MS (m/z): 349 $(M+H)^+$

Examples shown in Example Table 5 below, were or may be prepared according to procedures analogous to those outlined in Example 276 above using the appropriate starting

materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Example Table 5

Example	Structure	Name	Mass $[M+H]^+$
Example 277		1-cyclobutyl-4-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione 685	337
Example 278		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione 686	363
Example 279		1-((5-phenylpyrimidin-2-yl)methyl)-4-(tetrahydrofuran-3-yl)piperazine-2,3-dione 687	353
Example 280		1-(cyclopropylmethyl)-4-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione 688	337
Example 281		1-(cyclobutylmethyl)-4-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione 689	351

Example 282		1-(2-methylcyclobutyl)-4-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione 690	351
Example 283		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 691	369
Example 284		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((6-phenylpyridazin-3-yl)methyl)piperazine-2,3-dione 692	363
Example 285		3-(2,3-dioxo-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazin-1-yl)cyclobutane-1-carbonitrile 693	368
Example 286		1-isopropyl-4-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione 694	325

Example 287		1-neopentyl-4-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione 695	353
Example 288		1-(1-fluoropropan-2-yl)-4-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione 696	343
Example 289		1-(3-methylcyclobutyl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 697	356
Example 290		1-(3-fluorocyclobutyl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 698	361
Example 291		1-(3-cyclopropylcyclobutyl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 699	383

Example 292		1-phenyl-4-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione 700	359
Example 293		1-(cyclopentyl-1-*d*)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 1001	356
Example 294		1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 1002	373
Example 295		3-(2,3-dioxo-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazin-1-yl)bicyclo[1.1.1]pentane-1-carbonitrile 1003	380
Example 296		1-(1-methyl-2-oxabicyclo[2.1.1]hexan-4-yl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 1004	385

Example 297		1-(1-(5-methoxypyridin-2-yl)cyclopropyl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 1005	436
Example 298		1-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-4-(1-(trifluoromethyl)cyclobutyl)piperazine-2,3-dione 1006	411
Example 299		1-(1-methoxy-2-methylpropan-2-yl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 1007	375
Example 300		1-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-4-(2-(pyridin-3-yl)propan-2-yl)piperazine-2,3-dione 1008	408
Example 301		1-(2-oxobicyclo[2.2.1]heptan-1-yl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 1009	397

Example 302		1-(3-methyloxetan-3-yl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 1010	359
Example 303		1-(1-methylcyclopropyl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 1011	343
Example 304		1-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-4-(1-(pyridin-4-yl)cyclopropyl)piperazine-2,3-dione 1012	406
Example 305		1-(1-(fluoromethyl)cyclopropyl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 1013	361
Example 306		1-(1-methylcyclohexyl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 1014	385

Example 307		1-(tert-butyl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 1015	345
Example 308		1-(2,3-dioxo-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazin-1-yl)cyclopropane-1-carbonitrile 1016	354

Example 309

Preparation of 1-cyclopentyl-4-((5-(piperidin-1-yl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione

1017

Piperidine (6 µL, 0.06 mmol) and Hunig's base (17 uL, 0.10 mmol) were added to a mixture of 1-((5-chloro-1,3,4-thiadiazol-2-yl)methyl)-4-cyclopentylpiperazine-2,3-dione (15 mg, 0.048 mmol) in DMF (95 µL) at room temperature. The reaction mixture was stirred at room temperature for 18 hours. The mixture was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-cyclopentyl-4-((5-(piperidin-1-yl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione as a TFA salt. ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.74 (s, 2H), 4.67

742 255

(p, J = 8.3 Hz, 1H), 3.55 (dd, J = 7.0, 4.3 Hz, 2H), 3.50 – 3.39 (m, 6H), 1.83 – 1.45 (m, 14H). LC/MS (m/z): 364 $(M+H)^+$

Examples shown in Example Table 6 below, were or may be prepared according to procedures analogous to those outlined in Example 309 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Example Table 6

Example	Structure	Name	Mass $[M+H]^+$
Example 310		1-cyclopentyl-4-((5-(pyrrolidin-1-yl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 1018	350
Example 311		(S)-1-cyclopentyl-4-((5-(3-fluoropyrrolidin-1-yl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 1019	368
Example 312		(S)-1-cyclopentyl-4-((5-(3-(fluoromethyl)pyrrolidin-1-yl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 1020	382

Example 313		1-((5-(3-azabicyclo[3.1.0]hexan-3-yl)-1,3,4-thiadiazol-2-yl)methyl)-4-cyclopentylpiperazine-2,3-dione 1021	362

Example 314

Preparation of 1-cyclopentyl-4-((6-(pyrrolidin-1-yl)pyridazin-3-yl)methyl)piperazine-2,3-dione

1022

Triethylamine (0.032 ml, 0.23 mmol) and pyrrolidine (16 mg, 0.23 mmol) were added to a mixture of 1-((6-chloropyridazin-3-yl)methyl)-4-cyclopentylpiperazine-2,3-dione (0.070 g, 0.23 mmol) in EtOH (2 mL) at room temperature. The reaction mixture was stirred and heated to 100 °C for 12 hours. The reaction mixture was cooled to room temperature and directly purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-cyclopentyl-4-((6-(pyrrolidin-1-yl)pyridazin-3-yl)methyl)piperazine-2,3-dione. ^{1}H NMR (500 MHz, methanol-d_4) δ = 7.80 (d, J = 9.8 Hz, 1H), 7.68 (d, J = 9.8 Hz, 1H), 4.85 – 4.75 (m, 1H), 4.78 (s, 2H), 3.75 - 3.52 (m, 8H), 2.20 – 2.08 (m, 4H), 2.00 - 1.85 (m, 2H), 1.83 - 1.72 (m, 2H), 1.70 - 1.56 (m, 4H). LC/MS (m/z): 344 $(M+H)^+$

744

Examples shown in Example Table 7 below, were or may be prepared according to procedures analogous to those outlined in Example 314 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Example Table 7

Example	Structure	Name	Mass $[M+H]^+$
Example 315		1-cyclopentyl-4-((6-(pyrrolidin-1-yl)pyridin-3-yl)methyl)piperazine-2,3-dione 1023	343
Example 316		1-cyclopentyl-4-((6-(piperidin-1-yl)pyridazin-3-yl)methyl)piperazine-2,3-dione 1024	358
Example 317		1-cyclopentyl-4-((6-morpholinopyridazin-3-yl)methyl)piperazine-2,3-dione 1025	360
Example 318		1-((6-(azetidin-1-yl)pyridazin-3-yl)methyl)-4-cyclopentylpiperazine-2,3-dione 1026	330
Example 319		1-cyclopentyl-4-((6-(3,3-difluoropyrrolidin-1-yl)pyridazin-3-yl)methyl)piperazine-2,3-dione 1027	380

Example 320		1-((6-(3-azabicyclo[3.1.0]hexan-3-yl)pyridazin-3-yl)methyl)-4-cyclopentylpiperazine-2,3-dione 1028	356

Example 321

Preparation of 1-((6-(1H-1,2,3-triazol-1-yl)pyridazin-3-yl)methyl)-4-cyclopentylpiperazine-2,3-dione

1029

A mixture of 1-((6-chloropyridazin-3-yl)methyl)-4-cyclopentylpiperazine-2,3-dione (0.030 g, 0.097 mmol), cesium carbonate (63 mg, 0.19 mmol), and 2H-1,2,3-triazole (7 µl, 0.1 mmol) in DMF (1 mL) was stirred and heated at 80 °C for 72 hours. The mixture 38 was cooled to room temperature and diluted with DCM (5 mL). The mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting [1:3 EtOH:ethyl acetate] in hexanes) followed by basic alumina chromatography (eluting [1:3 EtOH:ethyl acetate] in hexanes) to afford a 1:1 mixture of 1H- and 2-H triazole isomers. The isomeric mixture was resolved by chiral SFC purification (OJ-H 21x250 mm column, 35% MeOH w/ 0.1% NH_4OH as cosolvent) to afford 1-((6-(1H-1,2,3-triazol-1-yl)pyridazin-3-yl)methyl)-4-cyclopentylpiperazine-2,3-dione as the first eluting peak. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.10 (d, J = 1.1 Hz, 1H), 8.44 (d, J = 9.0 Hz, 1H), 8.10 (d, J = 1.1 Hz, 1H), 8.02 (d, J = 9.0 Hz, 1H), 4.96 (s, 2H), 4.78 – 4.64 (m, 1H), 3.70 – 3.66 (m, 2H), 3.54 – 3.51 (m, 2H), 1.82 – 1.74 (m, 2H), 1.70 – 1.64 (m, 2H), 1.60 – 1.52 (m, 4H). LC/MS (m/z): 342 $(M+H)^+$

Examples shown in Example Table 8 below, were or may be prepared according to procedures analogous to those outlined in Example 321 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Example Table 8

Example	Structure	Name	Mass $[M+H]^+$
Example 322		1-((6-(2H-1,2,3-triazol-2-yl)pyridazin-3-yl)methyl)-4-cyclopentylpiperazine-2,3-dione 1030	342
Example 323		1-((5-(2H-1,2,3-triazol-2-yl)-1,3,4-thiadiazol-2-yl)methyl)-4-cyclopentylpiperazine-2,3-dione 1031	348
Example 324		1-((5-(2H-1,2,3-triazol-2-yl)pyrazin-2-yl)methyl)-4-cyclobutylpiperazine-2,3-dione 1032	328
Example 325		1-((5-(2H-1,2,3-triazol-2-yl)pyrazin-2-yl)methyl)-4-(bicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione 1033	340

Example 326		1-((6-(2H-1,2,3-triazol-2-yl)pyridazin-3-yl)methyl)-4-((cis)-3-phenylcyclobutyl)piperazine-2,3-dione 1034	404
Example 327		1-((6-(1H-1,2,3-triazol-1-yl)pyridazin-3-yl)methyl)-4-((cis)-3-phenylcyclobutyl)piperazine-2,3-dione 1035	404
Example 328		1-((6-(1H-1,2,3-triazol-1-yl)pyridazin-3-yl)methyl)-4-cyclopentyl-1,4-dihydropyrazine-2,3-dione 1036	340
Example 329		1-((6-(1H-pyrazol-1-yl)pyridazin-3-yl)methyl)-4-cyclobutyl-1,4-dihydropyrazine-2,3-dione 1037	325
Example 330		1-((6-(1H-imidazol-1-yl)pyridazin-3-yl)methyl)-4-cyclobutyl-1,4-dihydropyrazine-2,3-dione 1038	325

Example 331		1-((6-(1H-1,2,3-triazol-1-yl)pyridazin-3-yl)methyl)-4-((cis)-bicyclo[3.1.0]hexan-3-yl)-1,4-dihydropyrazine-2,3-dione 1039	352
Example 332		1-((6-(2H-1,2,3-triazol-2-yl)pyridazin-3-yl)methyl)-4-(1-methylcyclopropyl)-1,4-dihydropyrazine-2,3-dione 1040	326
Example 333		1-(4-((6-(2H-1,2,3-triazol-2-yl)pyridazin-3-yl)methyl)-2,3-dioxo-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 1041	337
Example 334		1-((6-(1H-1,2,3-triazol-1-yl)pyridazin-3-yl)methyl)-4-(1-methylcyclopropyl)-1,4-dihydropyrazine-2,3-dione 1042	326
Example 335		1-(4-((6-(1H-1,2,3-triazol-1-yl)pyridazin-3-yl)methyl)-2,3-dioxo-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 1043	337

Example 336

Preparation of 1-((6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methyl)-4-cyclopentylpiperazine-2,3-dione

1044

A mixture of 1-((6-chloropyridin-3-yl)methyl)-4-cyclopentylpiperazine-2,3-dione (0.100 g, 0.325 mmol), cesium carbonate (212 mg, 0.650 mmol), and 2H-1,2,3-triazole (0.023 ml, 0.39 mmol) in DMF (1.0 mL) and N-methyl-2-pyrrolidone (1.0 mL) was stirred and heated at 200 °C in a microwave reaction for 1 hour. The mixture was cooled to room temperature and filtered. The filtrate was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-((6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methyl)-4-cyclopentylpiperazine-2,3-dione. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.18 (s, 2H), 8.01 – 8.00 (m, 2H), 4.71 – 4.65 (m, 1H), 4.68 (s, 2H), 3.56 – 3.52 (m, 2H), 3.48 – 3.44 (m, 2H), 1.80 – 1.71 (m, 2H), 1.68 – 1.62 (m, 2H), 1.58 – 1.50 (m, 4H). LC/MS (*m/z*): 341 $(M+H)^+$

Example 337

Preparation of 1-cyclopentyl-4-((5-phenylpyrimidin-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione

1045

Cyclopentanamine (57 mg, 0.67 mmol) was added to a mixture of ethyl 2-oxo-2-((2-oxoethyl)((5-phenylpyrimidin-2-yl)methyl)amino)acetate (200 mg, 0.6 mmol) in DCE (5 mL) at room temperature. The reaction mixture was stirred at room temperature for 16 hours. The mixture

was diluted with water (10 mL) and DCM (5 mL). The aqueous layer was separated and extracted with additional DCM (2 x 5 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-cyclopentyl-4-((5-phenylpyrimidin-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione. ^{1}H NMR (400 MHz, methanol-d_4) δ 9.00 (s, 2H), 7.73-7.67 (m, 2H), 7.56-7.45 (m, 3H), 6.73 (d, J = 6.1 Hz, 1H), 6.66 (d, J = 6.4 Hz, 1H), 5.29 (s, 2H), 5.07 (quin, J = 7.9 Hz, 1H), 2.21-2.08 (m, 2H), 1.95-1.71 (m, 6H). LC/MS (m/z): 349 $(M+H)^+$

Examples shown in Example Table 9 below, were or may be prepared according to procedures analogous to those outlined in Example 337 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Example Table 9

Example	Structure	Name	Mass $[M+H]^+$
Example 338		3-(2,3-dioxo-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-3,4-dihydropyrazin-1(2H)-yl)cyclopentane-1-carbonitrile 1046	380

Example 339

Preparation of 1-cyclopentyl-4-((6-propoxypyridazin-3-yl)methyl)piperazine-2,3-dione

1047

A mixture of 1-((6-chloropyridazin-3-yl)methyl)-4-cyclopentylpiperazine-2,3-dione (0.100 g, 0.3 mmol), propan-1-ol (58 mg, 0.97 mmol), RockPhos Pd G3 ([(2-Di-tert-butylphosphino-3-methoxy-6-methyl-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2-aminobiphenyl)]palladium(II) methanesulfonateprecatalyst) (3 mg, 3 µmol), and Cs_2CO_3 (211 mg, 0.648 mmol) in DMF (1 mL) was sparged with nitrogen at room temperature. The reaction mixture was stirred and heated to 90 °C for 12 hours. The reaction mixture was cooled to room temperature, filtered, and then directly purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-cyclopentyl-4-((6-propoxypyridazin-3-yl)methyl)piperazine-2,3-dione. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.68 (d, J = 9.4 Hz, 1H), 7.24 (d, J = 9.4 Hz, 1H), 4.85 (s, 2H), 4.80 (t, J = 8.2 Hz, 1H), 4.40 (t, J = 6.7 Hz, 2H), 3.73-3.65 (m, 2H), 3.61-3.54 (m, 2H), 1.95 – 1.83 (m, 4H), 1.81-1.72 (m, 2H), 1.70-1.54 (m, 4H), 1.05 (t, J = 7.4 Hz, 3H). LC/MS (m/z): 333 $(M+H)^+$

Example 340

Preparation of 1-cyclopentyl-4-((6-ethoxypyridazin-3-yl)methyl)piperazine-2,3-dione

Sodium ethoxide (110 mg, 1.6 mmol) was added to a mixture of 1-((6-chloropyridazin-3-yl)methyl)-4-cyclopentylpiperazine-2,3-dione (0.100 g, 0.32 mmol) in EtOH (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 4 hours. 2 M HCl was added dropwise to the reaction mixture until pH ~ 7. The mixture was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with formic acid modifier) to afford 1-cyclopentyl-4-((6-ethoxypyridazin-3-yl)methyl)piperazine-2,3-dione. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 (d, J = 9.05 Hz, 1H), 7.16 (d, J = 9.05 Hz, 1H), 4.72 (s, 2H), 4.62-4.68 (m, 1H), 4.38-4.42 (m, 2H), 3.51-3.58 (m, 2H), 3.37-3.47 (m, 2H), 1.78 – 1.67 (m, 2H), 1.67 – 1.57 (m, 2H), 1.57 – 1.43 (m, 4H), 1.33 (t, J = 6.97 Hz, 3H). LC/MS (m/z): 319 $(M+H)^+$

Example 341

Preparation of (*R* or *S*)-4-cyclopentyl-5-methyl-1-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione

Step A: ethyl 2-((2-methylallyl)amino)-2-oxoacetate

390

Ethyl 2-chloro-2-oxoacetate (1.6 mL, 14 mmol) was added to a mixture of 2-methylallylamine (1.0 g, 14 mmol) and triethylamine (5.9 mL, 42 mmol) in DCM (15 mL) at 0 °C. 750 The reaction mixture was warmed to room temperature and stirred for 15 hours. The reaction mixture was diluted with water (30 mL) and extracted with DCM (3 x 30 mL). The organic layers were combined, washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford ethyl 2-((2-methylallyl)amino)-2-oxoacetate. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.08 (s, 1H), 4.77 (s, 1H), 4.75 (s, 1H), 4.23 (q, J = 7.0 Hz, 2H), 3.66 (d, J = 6.0 Hz, 2H), 1.66 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H). LC/MS (*m/z*): 172 $(M+H)^+$

Step B: ethyl 2-((2-methylallyl)((5-phenylpyrimidin-2-yl)methyl)amino)-2-oxoacetate

391

NaH (83 mg, 2 mmol, 60% dispersion in mineral oil) was added to a mixture of ethyl 2-((2-methylallyl)amino)-2-oxoacetate (254 mg, 1.49 mmol) in DMF (5 mL) at 0 °C. The reaction

mixture was warmed to room temperature and stirred for 30 minutes. A mixture of 2-(bromomethyl)-5-phenylpyrimidine (370 mg, 1.49 mmol) in DMF (2 mL) was added to the reaction mixture at 0 °C. The reaction mixture was warmed to room temperature and stirred for an additional 1 hour. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford ethyl 2-((2-methylallyl)((5-phenylpyrimidin-2-yl)methyl)amino)-2-oxoacetate. LC/MS (*m/z*): 340 $(M+H)^+$

Step C: ethyl 2-oxo-2-((2-oxopropyl)((5-phenylpyrimidin-2-yl)methyl)amino)acetate

A mixture of ethyl 2-((2-methylallyl)((5-phenylpyrimidin-2-yl)methyl)amino)-2-oxoacetate (163 mg, 0.48 mmol), 2,6-dimethylpyridine (0.11 mL, 0.96 mmol), potassium osmate(VI) dihydrate (35 mg, 0.095 mmol), and sodium periodate (411 mg, 1.92 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was stirred at room temperature for 15 hours. The reaction mixture was quenched with saturated aqueous Na_2SO_3 (5 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford ethyl 2-oxo-2-((2-oxopropyl)((5-phenylpyrimidin-2-yl)methyl)amino)acetate. LC/MS (*m/z*): 342 $(M+H)^+$

Step D: (*R* or *S*)-4-cyclopentyl-5-methyl-1-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione

1049

Sodium triacetoxyborohydride (75 mg, 0.45 mmol) was added to a mixture of ethyl 2-oxo-2-((2-oxopropyl)((5-phenylpyrimidin-2-yl)methyl)amino)acetate (0.040 g, 0.12 mmol) and cyclopentanamine (10 mg, 0.1 mmol) in DCE (1.5 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was quenched with water (1 mL) and then concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 4-cyclopentyl-5-methyl-1-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione as a mixture of R and S enantiomers. The racemic mixture was resolved by chiral-SFC (eluting ammonia in methanol in CO_2) to afford (*R* or *S*)-4-cyclopentyl-5-methyl-1-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione as the second eluting peak. ^{1}H NMR (500 MHz, methanol-d_4) δ 9.02 (s, 2H), 7.72-7.68 (m, 2H), 7.56-7.50 (m, 2H), 7.49-7.43 (m, 1H), 5.07 – 5.00 (m, 1H), 4.87 – 4.83 (m, 1H), 4.44 – 4.34 (m, 1H), 4.18 – 4.12 (m, 1H), 3.90 – 3.84 (m, 1H), 3.49 – 3.44 (m, 1H), 2.03 – 1.90 (m, 2H), 1.90 – 1.78 (m, 3H), 1.76 – 1.58 (m, 3H), 1.48 (d, J = 6.5 Hz, 3H). LC/MS (*m/z*): 365 $(M+H)^+$

Example 342

Preparation of 1-cyclopentyl-4-((5-(pyridin-2-yl)pyrimidin-2-yl)methyl)piperazine-2,3-dione

1052

A mixture of 1-cyclopentyl-4-((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)methyl)piperazine-2,3-dione (20 mg, 50 µmol), 2-bromopyridine (10 mg, 60 µmol), potassium carbonate (21 mg, 150 µmol), and [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (2 mg, 3 µmol) in water (0.25 mL) and 1,4-dioxane (1.0 mL) was sparged with nitrogen at room temperature. The reaction mixture was stirred and heated at 80 °C for 16 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with water (1 mL) and washed with ethyl acetate (3 x 3 mL). The organic layers were combined, washed with additional water (2 x 1 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-cyclopentyl-4-((5-(pyridin-2-yl)pyrimidin-2-yl)methyl)piperazine-2,3-dione. LC/MS (*m/z*): 352 $(M+H)^+$

Examples shown in Example Table 10 below, were or may be prepared according to procedures analogous to those outlined in Example 342 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Example Table 10

Example	Structure	Name	Mass $[M+H]^+$
Example 343		1-cyclopentyl-4-((5-(4-fluoropyridin-2-yl)pyrimidin-2-yl)methyl)piperazine-2,3-dione 1053	370

Example 344

Preparation of (*R* or *S*, *R* or *S*)-1-(3-methylcyclopentyl)-4-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione

Sodium triacetoxyborohydride (285 mg, 1.34 mmol) was added to a mixture of ethyl 2-oxo-2-((2-oxoethyl)((5-phenylpyrimidin-2-yl)methyl)amino)acetate (220 mg, 0.67 mmol) and 3-methylcyclopentan-1-amine (133 mg, 1.34 mmol) in DCE (1 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 hours. The mixture was quenched with water and extracted with ethyl acetate (3x). The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with ammonium bicarbonate modifier) to afford 1-(3-methylcyclopentyl)-4-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione as a mixture of *R* and *S* isomers. The racemic mixture was resolved by chiral SFC (eluting ammonia in methanol in CO_2) to afford (*R* or *S, R* or *S*)-1-(3-methylcyclopentyl)-4-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione as the fourth eluting peak. ^{1}H NMR (500 MHz, methanol-d_4) δ = 8.91 (s, 2H), 7.64 - 7.55 (m, 2H), 7.47 - 7.40 (m, 2H), 7.38 – 7.34 (m, 1H), 4.85 (s, 2H), 4.82 – 4.75 (m, 1H), 3.74 - 3.68 (m, 2H), 3.64 - 3.56 (m, 2H), 1.97 - 1.87 (m, 2H), 1.79 - 1.74 (m, 1H), 1.70 - 1.61 (m, 1H), 1.29 - 1.10 (m, 3H), 0.99 (d, *J* = 6.1 Hz, 3H). LC/MS (*m/z*): 365 $(M+H)^+$

Example 345

Preparation of 1-(*tert*-butyl)-4-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione

1057

Sodium triacetoxyborohydride (194 mg, 0.916 mmol) was added to a mixture of 2-methylpropan-2-amine (25 mg, 0.34 mmol) and ethyl 2-oxo-2-((2-oxoethyl)((5-phenylpyrimidin-2-yl)methyl)amino)acetate (0.100 g, 0.31 mmol) in DCE (2 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 hours and then stirred and heated at 65 °C for an additional 12 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with water (5 mL) and extracted with DCM (4 x 5 mL). The organic layers were combined, washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with ammonium bicarbonate modifier) to afford 1-(tert-butyl)-4-((5-phenylpyrimidin-2-yl)methyl)piperazine-2,3-dione. ^{1}H NMR (400 MHz, methanol-d_4) δ 9.02 (s, 2H), 7.76 - 7.67 (m, 2H), 7.56-7.50 (m, 2H), 7.50-7.44 (m, 1H), 4.93 (s, 2H), 3.83-3.72 (m, 4H), 1.52 (s, 9H). LC/MS (*m/z*): 339 $(M+H)^+$

Example 346

Preparation of 1-cyclopentyl-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione

Acetic acid (26 µl, 0.45 mmol) and sodium triacetoxyborohydride (48 mg, 0.23 mmol) were added to a mixture of (5-phenyl-1,3,4-thiadiazol-2-yl)methanamine (29 mg, 0.15 mmol) and 4A powdered sieves (100 mg) in 1,2-dichloroethane (1 mL). A mixture of methyl 2-(cyclopentyl(2-oxoethyl)amino)-2-oxoacetate (42 mg, 0.20 mmol) in 1,2-dichloromethane (0.5 mL) was added, and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was quenched with water and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with NH_4OH as modifier) to afford 1-cyclopentyl-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.98 (d, J = 7.7 Hz, 2H), 7.61 – 7.51 (m, 3H), 5.03 (s, 2H), 4.73 – 4.62 (m, 1H), 3.72 – 3.62 (m, 2H), 3.53 – 3.45 (m, 2H), 1.80 – 1.72 (m, 2H), 1.72 – 1.62 (m, 2H), 1.60 – 1.46 (m, 4H). LC/MS (m/z): 357 $(M+H)^+$

Examples shown in Example Table 11 below, were or may be prepared according to procedures analogous to those outlined in Example 346 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Example Table 11

Example	Structure	Name	Mass $[M+H]^+$
Example 347		1-cyclopentyl-4-(1-(1-phenyl-1H-pyrazol-4-yl)ethyl)piperazine-2,3-dione 1059	353
Example 348		(*R*)-1-cyclopentyl-4-(1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethyl)piperazine-2,3-dione 1060	371
Example 349		(S)-1-cyclopentyl-4-(1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethyl)piperazine-2,3-dione 1061	371
Example 350		1-cyclopentyl-4-(2-(5-phenyl-1,3,4-thiadiazol-2-yl)ethyl)piperazine-2,3-dione 1062	371

Example 351		1-cyclopentyl-4-((5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 1063	375
Example 352		1-cyclopentyl-4-(1-(5-phenyl-1,3,4-thiadiazol-2-yl)propan-2-yl)piperazine-2,3-dione 1064	385
Example 353		1-cyclopentyl-4-(2-(5-phenyl-1,3,4-thiadiazol-2-yl)propyl)piperazine-2,3-dione 1065	385
Example 354		1-cyclopentyl-4-((2-oxo-1,2-dihydroquinolin-3-yl)methyl)piperazine-2,3-dione 1066	340
Example 355		(R)-1-cyclobutyl-4-(1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethyl)piperazine-2,3-dione 1067	357

Example 356		(S)-1-cyclobutyl-4-(1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethyl)piperazine-2,3-dione 1068	357
Example 357		1-cyclobutyl-5-methyl-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 1069	357

Examples 358A and 358B

Preparation of 1-cyclopentyl-4-((3-phenylisoxazol-5-yl)methyl)piperazine-2,3-dione and 1-cyclopentyl-4-((3-phenylisoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione

1070

1071

A mixture of (3-phenylisoxazol-5-yl)methanamine (43 mg, 0.25 mmol), ethyl 2-(cyclopentyl(2-oxoethyl)amino)-2-oxoacetate (56 mg, 0.25 mmol), and sodium triacetoxyborohydride (131 mg, 0.616 mmol) in DCE (3 mL) was stirred at room temperature for 16 hours. The mixture was concentrated under reduced pressure, and the residue was partitioned between water (5 mL) and DCM (5 mL). The organic layer was separated, and the aqueous was re-extracted with DCM (3 x 5 mL). The organic layers were combined, washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was

purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-cyclopentyl-4-((3-phenylisoxazol-5-yl)methyl)piperazine-2,3-dione and 1-cyclopentyl-4-((3-phenylisoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione as an inseparable mixture. The mixture was further resolved by chiral-SFC (Column Daicel Chiralcel OD-H [250 mm x 30 mm, 5um]; eluting 55% [0.1% ammonia in ethanol] in CO_2) to afford 1-cyclopentyl-4-((3-phenylisoxazol-5-yl)methyl)piperazine-2,3-dione) as the first eluting peak and 1-cyclopentyl-4-((3-phenylisoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione as the second eluting peak.

Peak 1: 1-cyclopentyl-4-((3-phenylisoxazol-5-yl)methyl)piperazine-2,3-dione): ^{1}H NMR (400 MHz, methanol-d_4) δ 7.86 - 7.81 (m, 2H), 7.51 - 7.45 (m, 3H), 6.89 (s, 1H), 4.89 - 4.88 (m, 2H), 4.81 (br t, J = 8.3 Hz, 1H), 3.77 - 3.67 (m, 2H), 3.64 - 3.58 (m, 2H), 1.98 - 1.85 (m, 2H), 1.78 (br s, 2H), 1.69 - 1.59 (m, 4H). LC/MS (m/z): 340 $(M+H)^+$

Peak 2: 1-cyclopentyl-4-((3-phenylisoxazol-5-yl)methyl)-1,4-dihydropyrazine-2,3-dione: ^{1}H NMR (400 MHz, methanol-d_4) δ 7.85 - 7.80 (m, 2H), 7.50 - 7.45 (m, 3H), 6.90 (s, 1H), 6.73 (d, J = 6.4 Hz, 1H), 6.62 (d, J = 6.4 Hz, 1H), 5.21 (s, 2H), 5.08 - 4.98 (m, 1H), 2.14 - 2.04 (m, 2H), 1.89 (br s, 2H), 1.80 - 1.70 (m, 4H). LC/MS (m/z): 338 $(M+H)^+$

Examples shown in Example Table 12 below, were or may be prepared according to procedures analogous to those outlined in Examples 358A and 358B above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Example Table 12

Example	Structure	Name	Mass $[M+H]^+$
Example 359		1-((5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methyl)-4-(bicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione 1072	339

Example	Structure	Name	Mass $[M+H]^+$
Example 360		1-((5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methyl)-4-(bicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione 1073	337

Example 361

Preparation of 1-cyclopentyl-4-((5-(thiazol-2-yl)pyrimidin-2-yl)methyl)piperazine-2,3-dione

1074

2-(Tributylstannyl)thiazole (0.052 ml, 0.11 mmol) was added to a mixture of 1-((5-bromopyrimidin-2-yl)methyl)-4-cyclopentylpiperazine-2,3-dione (0.030 g, 0.085 mmol) and Xphos-Pd G2 precatalyst (6.7 mg, 8.5 µmol) in 1,4-dioxane (0.5 mL) under a nitrogen atmosphere. The mixture was sparged with nitrogen for 1 minute. The reaction mixture was stirred and heated at 100 °C for 16 hours. The mixture was cooled to room temperature, diluted with DMSO, and filtered. The filtrate was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-cyclopentyl-4-((5-(thiazol-2-yl)pyrimidin-2-yl)methyl)piperazine-2,3-dione. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.32 (s, 2H), 8.07 (d, J = 3.2 Hz, 1H), 7.98 (d, J = 3.2 Hz, 1H), 4.89 (s, 2H), 4.76 – 4.69 (m, 1H), 3.72 – 3.68 (m, 2H), 3.58 – 3.55 (m, 2H), 1.83 – 1.76 (m, 2H), 1.71 – 1.66 (m, 2H), 1.61 – 1.53 (m, 4H). LC/MS (m/z): 358 $(M+H)^+$

Examples shown in Example Table 13 below, were or may be prepared according to procedures analogous to those outlined in Example 361 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Example Table 13

Example	Structure	Name	Mass $[M+H]^+$
Example 362		1-cyclopentyl-4-((6-(thiazol-2-yl)pyridazin-3-yl)methyl)piperazine-2,3-dione 1075	358
Example 363		1-cyclopentyl-4-((5-(thiazol-2-yl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 1076	364
Example 364		1-cyclopentyl-4-((6-(thiazol-2-yl)pyridin-3-yl)methyl)piperazine-2,3-dione 1077	357
Example 365		1-cyclobutyl-4-((6-(thiazol-2-yl)pyridazin-3-yl)methyl)piperazine-2,3-dione 1078	344
Example 366		1-(bicyclo[1.1.1]pentan-1-yl)-4-((6-(thiazol-2-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 1079	354

Example 367		1-cyclobutyl-4-((6-(thiazol-2-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 1080	342
Example 368		1-cyclopentyl-4-((6-(pyridin-2-yl)pyridazin-3-yl)methyl)piperazine-2,3-dione 1081	352
Example 369		1-cyclobutyl-4-((5-(pyridin-2-yl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione 1082	344
Example 370		1-cyclobutyl-4-((5-(pyridin-2-yl)-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 1083	342
Example 371		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((3-fluoro-5-(thiazol-2-yl)pyridin-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 1084	385

Example 372		1-((cis)-3-phenylcyclobutyl)-4-((5-(thiazol-2-yl)-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione 1085	424
Example 373		1-cyclobutyl-4-((5-(pyridin-2-yl)isoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 1086	325
Example 374		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((6-(thiazol-2-yl)pyridazin-3-yl)methyl)piperazine-2,3-dione 1087	370
Example 375		1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((5-(pyridin-2-yl)isoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 1088	351
Example 376		1-cyclobutyl-4-((5-(pyridin-2-yl)thiazol-2-yl)methyl)piperazine-2,3-dione 1089	343

Example 377		1-(1-methylcyclopropyl)-4-((6-(thiazol-2-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 1090	342

Example 378

Preparation of 1-((5-(2H-1,2,3-triazol-2-yl)pyrimidin-2-yl)methyl)-4-cyclopentylpiperazine-2,3-dione

1091

A mixture of 1-((5-bromopyrimidin-2-yl)methyl)-4-cyclopentylpiperazine-2,3-dione (0.050 g, 0.14 mmol), cesium carbonate (138 mg, 0.425 mmol), bis((Z)-2-methyl-1-(2-oxocyclohexylidene)propoxy)copper (28 mg, 0.071 mmol), and 2H-1,2,3-triazole (0.014 ml, 0.24 mmol) in 1,4-dioxane (1.5 mL) was sparged with nitrogen for 1 minute. 38 The reaction mixture was stirred and heated at 120 °C for 16 hours. The mixture was cooled to room temperature, diluted with DCM (3 mL), and filtered. The filtrate was purified by silica gel chromatography (eluting methanol in DCM) and by basic alumina chromatography (eluting [1:3 EtOH:EtOAc] in hexanes) to afford 1-((5-(2H-1,2,3-triazol-2-yl)pyrimidin-2-yl)methyl)-4-cyclopentylpiperazine-2,3-dione. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.41 (s, 2H), 8.29 (s, 2H), 4.91 (s, 2H), 4.76 – 4.69 (m, 1H), 3.72 – 3.68 (m, 2H), 3.57 – 3.54 (m, 2H), 1.84 – 1.76 (m, 2H), 1.72 – 1.66 (m, 2H), 1.61 – 1.52 (m, 4H). LC/MS (*m/z*): 342 $(M+H)^+$

Examples shown in Example Table 14 below, were or may be prepared according to procedures analogous to those outlined in Example 378 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Example Table 14

Example	Structure	Name	Mass $[M+H]^+$
Example 379		1-cyclopentyl-4-(2-fluoro-4-(2H-1,2,3-triazol-2-yl)benzyl)piperazine-2,3-dione 1092	358
Example 380		1-((5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methyl)-4-cyclopentylpiperazine-2,3-dione 1093	341
Example 381		1-((5-(1H-pyrazol-1-yl)pyridin-2-yl)methyl)-4-(1-methylcyclopropyl)-1,4-dihydropyrazine-2,3-dione 1094	324
Example 382		1-((5-(1H-pyrazol-1-yl)pyridin-2-yl)methyl)-4-(bicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione 1095	336
Example 383		1-((6-(1H-pyrazol-1-yl)pyridin-3-yl)methyl)-4-(1-methylcyclopropyl)-1,4-dihydropyrazine-2,3-dione 1096	324

Example 384		1-((6-(1H-pyrazol-1-yl)pyridin-3-yl)methyl)-4-(bicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione 1097	336
Example 385		1-((5-(1H-1,2,3-triazol-1-yl)pyridin-2-yl)methyl)-4-(1-methylcyclopropyl)-1,4-dihydropyrazine-2,3-dione 1098	325
Example 386		1-(4-((5-(1H-pyrazol-1-yl)pyridin-2-yl)methyl)-2,3-dioxo-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 1099	335
Example 387		1-(4-((5-(1H-1,2,3-triazol-1-yl)pyridin-2-yl)methyl)-2,3-dioxo-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 1100	336
Example 388		1-((5-(1H-1,2,3-triazol-1-yl)pyridin-2-yl)methyl)-4-(bicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione 1101	337
Example 389		1-(4-((6-(1H-pyrazol-1-yl)pyridin-3-yl)methyl)-2,3-dioxo-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 1102	335

Example 390		1-(4-((6-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)methyl)-2,3-dioxo-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 1103	336
Example 391		1-(4-((6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methyl)-2,3-dioxo-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 1104	336

Example 392

Preparation of 1-cyclopentyl-4-((6-(3,3-difluoropyrrolidin-1-yl)pyridin-3-yl)methyl)piperazine-2,3-dione

1105

A mixture of 1-((6-chloropyridin-3-yl)methyl)-4-cyclopentylpiperazine-2,3-dione (0.031g, 0.10 mmol), 3,3-difluoropyrrolidine hydrochloride (0.021 g, 0.15 mmol), RuPhos Pd G3 precatalyst (0.012 g, 0.015 mmol), 763 and sodium *tert*-butoxide (0.029 g, 0.30 mmol) in 1,4-dioxane (1 mL) was purged with argon for 5 minutes. The reaction mixture was stirred and heated to 80 °C for 1 hour. The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl, and extracted with DCM. The organic layer was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-cyclopentyl-4-((6-(3,3-difluoropyrrolidin-1-yl)pyridin-3-yl)methyl)piperazine-2,3-dione. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.07 – 7.99 (s, 1H), 7.58 (d, J = 8.7 Hz, 1H), 6.64 (d, J = 8.7 Hz, 1H), 4.65

(q, J = 8.2 Hz, 1H), 4.45 (s, 2H), 3.84 (t, J = 13.2 Hz, 2H), 3.54 – 3.47 (m, 4H), 3.44 – 3.34 (m, 4H), 1.80 – 1.69 (m, 2H), 1.63 (m, 2H), 1.50 (m, 4H). LC/MS (m/z): 379 $(M+H)^+$

Examples shown in Example Table 15 below, were or may be prepared according to procedures analogous to those outlined in Example 392 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Example Table 15

Example	Structure	Name	Mass $[M+H]^+$
Example 393		1-cyclopentyl-4-((6-(3-fluoropyrrolidin-1-yl)pyridin-3-yl)methyl)piperazine-2,3-dione 1106	361

Example 394

Preparation of 1-cyclobutyl-4-((6-(oxazol-5-yl)pyridazin-3-yl)methyl)piperazine-2,3-dione

1107

A mixture of 1-((6-chloropyridazin-3-yl)methyl)-4-cyclobutylpiperazine-2,3-dione (0.070 g, 0.24 mmol), K_2CO_3 (82 mg, 0.59 mmol), oxazole (0.031 mL, 0.48 mmol), pivalic acid (10 mg, 0.1 mmol), palladium(II) acetate (3 mg, 0.01 mmol) 764, and butyl di-1-adamantylphosphine (10 mg, 0.03 mmol) in DMA (3 mL) was sparged with N_2 at room temperature. The reaction mixture was stirred and heated to 110 °C for 12 hours. The mixture was cooled to room temperature and filtered. The filtrate was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-cyclobutyl-4-((6-(oxazol-5-yl)pyridazin-3-yl)methyl)piperazine-2,3-dione. ^{1}H NMR (500

MHz, methanol-d_4) δ 8.48 (s, 1H), 8.10 (d, J = 8.8 Hz, 1H), 7.99 (s, 1H), 7.85 (d, J = 8.9 Hz, 1H), 5.01 (s, 2H), 4.88-4.84 (m, 1H), 3.84-3.79 (m, 2H), 3.76-3.71 (m, 2H), 2.32-2.25 (m, 2H), 2.25-2.17 (m, 2H), 1.89-1.69 (m, 2H). LC/MS (m/z): 328 $(M+H)^+$

Examples shown in Example Table 16 below, were or may be prepared according to procedures analogous to those outlined in Example 394 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Example Table 16

Example	Structure	Name	Mass $[M+H]^+$
Example 395		1-cyclobutyl-4-((6-(thiazol-5-yl)pyridazin-3-yl)methyl)piperazine-2,3-dione 1108	344

Example 396

Preparation of 1-cyclobutyl-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione

Step A: N'-(2-chloroacetyl)benzohydrazide

192

Chloroacetyl chloride (6.7 mL, 84 mmol) was added dropwise to a mixture of benzohydrazide (9.5 g, 70 mmol) in ethyl acetate (140 mL) at 0 °C. The reaction mixture was stirred and heated at 80 °C for 3 hours. The mixture was concentrated under reduced pressure to give afford *N'*-(2-chloroacetyl)benzohydrazide which was used without purification. LC/MS (*m/z*): 213 $(M+H)^+$

Step B: 2-(chloromethyl)-5-phenyl-1,3,4-thiadiazole

193

Lawesson's reagent (17 g, 42 mmol) was added to a mixture of *N'*-(2-chloroacetyl)benzohydrazide (15 g, 70 mmol) in THF (300 mL). The mixture was stirred and heated at 70 °C for 4 hours. The reaction mixture was quenched with $NaHCO_3$ (1 N, 300 mL) and extracted with EtOAc (3 x 300 mL). The organic layers were combined, washed with brine (500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 2-(chloromethyl)-5-phenyl-1,3,4-thiadiazole. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.96 (dd, J = 1.5, 7.9 Hz, 2H), 7.56-7.47 (m, 3H), 4.98 (s, 2H). LC/MS (*m/z*): 211 $(M+H)^+$

Step C: N-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)prop-2-en-1-amine

395

Sodium iodide (1.28 g, 8.54 mmol) and 2-(chloromethyl)-5-phenyl-1,3,4-thiadiazole (1.8 g, 8.5 mmol) were added to a stirred mixture of K_2CO_3 (1.54 g, 11.1 mmol) and prop-2-en-1-amine (1.75 mL, 23.3 mmol) in THF (30 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture

was stirred at room temperature for 12 hours. The mixture was filtered, and the filtrate was concentrated under reduced pressure to afford *N*-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)prop-2-en-1-amine, which was used without purification. LC/MS (*m/z*): 232 $(M+H)^+$

Step D: ethyl 2-(allyl((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)amino)-2-oxoacetate

396

Triethylamine (3.6 mL, 26 mmol) was added to a mixture of *N*-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)prop-2-en-1-amine (2.0 g, 8.5 mmol) in DCM (40 mL). The mixture was stirred for 5 min at 0 °C, and then ethyl 2-chloro-2-oxoacetate (1.37 mL, 12.8 mmol) was added to the mixture at 0 °C. The reaction mixture was stirred at room temperature for an additional 2 hours. The mixture was concentrated under reduced pressure, and the residue was partitioned between water (80 mL) and EtOAc (60 mL). The organic layer was separated, and the aqueous layer was re-extracted with EtOAc (3 x 60 mL). The organic layers were combined, washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford ethyl 2-(allyl((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)amino)-2-oxoacetate. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.01-7.92 (m, 2H), 7.54-7.45 (m, 3H), 5.92-5.73 (m, 1H), 5.42-5.27 (m, 2H), 4.99-4.91 (m, 2H), 4.46-4.32 (m, 2H), 4.12-4.01 (m, 2H), 1.44-1.35 (m, 3H). LC/MS (*m/z*): 332 $(M+H)^+$

Step E: ethyl 2-oxo-2-((2-oxoethyl)((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)amino)acetate

297

OsO4 (Osmium tetroxide) (15 mg, 60 µmol) was added to a mixture of ethyl 2-(allyl((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)amino)-2-oxoacetate (100 mg, 300 µmol) and $NaIO_5$ (194 mg, 905 µmol) in THF (1.5 mL) and water (0.5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched with sodium bisulfite (saturated aqueous solution) and then stirred for 15 minutes. The mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (20 mL),

dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford ethyl 2-oxo-2-((2-oxoethyl)((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)amino)acetate, which was used without purification. LC/MS (*m/z*): 334 $(M+H)^+$

Step F: 1-cyclobutyl-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione

Sodium triacetoxyborohydride (127 mg, 600 µmol) was added to a mixture of ethyl 2-oxo-2-((2-oxoethyl)((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)amino)acetate (100 mg, 300 µmol) and cyclobutanamine (24 mg, 330 µmol) in 1,2-dichloroethane (3 mL) at room temperature. The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was quenched with MeOH (5 mL) and then concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with ammonia modifier) to give a mixture of 1-cyclobutyl-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione and 1-cyclobutyl-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione. The mixture was further resolved by Chiral-SFC (Chiral OD-H (250 mm * 30 mm) 50% EtOH with 0.1% ammonia modifier) to afford 1-cyclobutyl-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-1,4-dihydropyrazine-2,3-dione as the second eluting peak. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.96 (dd, J = 1.6, 7.8 Hz, 2H), 7.59-7.49 (m, 3H), 6.79 (s, 2H), 5.45 (s, 2H), 4.99-4.93 (m, 1H), 2.42-2.26 (m, 4H), 1.90-1.79 (m, 2H). LC/MS (*m/z*): 341 $(M+H)^+$

Example 397

Preparation of 1-((5-(2*H*-1,2,3-triazol-2-yl)pyridin-2-yl)methyl)-4-cyclobutyl-1,4-dihydropyrazine-2,3-dione

1111

A mixture of 1-((5-bromopyridin-2-yl)methyl)-4-cyclobutyl-1,4-dihydropyrazine-2,3-dione (2.50 g, 7.44 mmol), 2*H*-1,2,3-triazole (0.56 mL, 9.7 mmol), $Pd_2(dba)_3$ (0.68 g, 0.74 mmol), 2-di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl (0.89 g, 1.9 mmol) and potassium phosphate tribasic (3.16 g, 14.9 mmol) was degassed with argon for 5 minutes. Toluene (74 mL) was added, and the mixture was degassed with argon for an additional 5 minutes. The mixture was heated to 100 °C and stirred under an argon atmosphere for 18 hours. Additional $Pd_2(dba)_3$ (0.34 g, 0.37 mmol) and 2-di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl (0.43 g, 0.93 mmol) were added to the mixture, and the mixture was stirred and heated at 110 °C for an additional 24 hours. The reaction mixture was cooled to room temperature and diluted with dichloromethane (100 mL). The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with [3:1 ethyl acetate:ethanol] in dichloromethane) to afford the product as a mixture with impurities. The residue was suspended in ethyl acetate (200 mL) and stirred for 18 hours. The mixture was filtered, and the collected solids were re-purified by silica gel chromatography (eluting with [3:1 ethyl acetate:ethanol] in dichloromethane) followed by purification by SFC (eluting ammonia in methanol in CO_2) to afford 1-((5-(2*H*-1,2,3-triazol-2-yl)pyridin-2-yl)methyl)-4-cyclobutyl-1,4-dihydropyrazine-2,3-dione. ^{1}H NMR (499 MHz, DMSO-d_6) δ 9.18 (d, J = 2.4 Hz, 1H), 8.38 (dd, J = 8.5, 2.6 Hz, 1H), 8.21 (s, 2H), 7.55 (d, J = 8.5 Hz, 1H), 6.82 (d, J = 6.2 Hz, 1H), 6.75 (d, J = 6.2 Hz, 1H), 5.11 (s, 2H), 4.92 (p, J = 9.2, 8.7 Hz, 1H), 2.35 – 2.19 (m, 4H), 1.85 – 1.63 (m, 2H). LC/MS (*m/z*): 325 $(M+H)^+$

Example 398

Preparation of 1-((6-(2H-1,2,3-triazol-2-yl)pyridazin-3-yl)methyl)-4-cyclobutylpiperazine-2,3-dione

1112

A mixture of $Pd_2(dba)_3$ (8 mg, 8 µmol) and tri-*tert*-butylphosphonium tetrafluoroborate (5 mg, 0.02 mmol) were premixed in toluene (2 mL) and stirred at room temperature for 3 minutes under a nitrogen atmosphere. 1-((6-chloropyridazin-3-yl)methyl)-4-cyclobutylpiperazine-2,3-dione (0.050 g, 0.17 mmol), 2*H*-1,2,3-triazole (23 mg, 0.34 mmol) and K_3PO_4 (108 mg, 0.509 mmol) were added to the reaction mixture at room temperature under a nitrogen atmosphere. The reaction mixture was stirred and heated to 110 °C for 12 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford the product as mixture of triazole isomers, which was further resolved by Chiral-SFC (Chiralcel O*J*-H (250mm x 30mm, 5um); eluting 50% ethanol with 0.1% ammonia modifier) to afford 1-((6-(2*H*-1,2,3-triazol-2-yl)pyridazin-3-yl)methyl)-4-cyclobutylpiperazine-2,3-dione as the second eluting peak. ^{1}H NMR (500 MHz, methanol-d_4) δ 8.31 (d, J = 9.2 Hz, 1H), 8.04 (s, 2H), 7.86 (d, J = 9.0 Hz, 1H), 4.92 (s, 2H), 4.77-4.70 (m, 1H), 3.74-3.59 (m, 4H), 2.24-2.04 (m, 4H), 1.73-1.60 (m, 2H). LC/MS (*m/z*): 328 $(M+H)^+$

Examples shown in Example Table 17 below, were or may be prepared according to procedures analogous to those outlined in Example 398 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Example Table 17

Example	Structure	Name	Mass $[M+H]^+$
Example 399		1-(4-(2H-1,2,3-triazol-2-yl)benzyl)-4-cyclobutylpiperazine-2,3-dione 1113	326

Example 400		1-cyclobutyl-4-((3-fluoro-5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methyl)piperazine-2,3-dione 1114	345
Example 401		1-((6-(2H-1,2,3-triazol-2-yl)pyridazin-3-yl)methyl)-4-(bicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione 1115	340
Example 402		1-((6-(1H-1,2,3-triazol-1-yl)pyridazin-3-yl)methyl)-4-(bicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione 1116	340
Example 403		1-((6-(2H-1,2,3-triazol-2-yl)pyridazin-3-yl)methyl)-4-(bicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione 1117	338
Example 404		1-((6-(1H-1,2,3-triazol-1-yl)pyridazin-3-yl)methyl)-4-(bicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione 1118	338
Example 405		1-(bicyclo[1.1.1]pentan-1-yl)-4-((3-fluoro-5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methyl)piperazine-2,3-dione 1119	357

Example 406		1-(4-(2H-1,2,3-triazol-2-yl)benzyl)-4-(bicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione 1120	338
Example 407		1-(bicyclo[1.1.1]pentan-1-yl)-4-(2-fluoro-4-(2H-1,2,3-triazol-2-yl)benzyl)piperazine-2,3-dione 1121	356
Example 408		1-((5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methyl)-4-((cis)-bicyclo[3.1.0]hexan-3-yl)-1,4-dihydropyrazine-2,3-dione 1122	351
Example 409		1-((6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methyl)-4-cyclobutyl-1,4-dihydropyrazine-2,3-dione 1123	325
Example 410		1-((6-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)methyl)-4-cyclobutyl-1,4-dihydropyrazine-2,3-dione 1124	325
Example 411		1-((6-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)methyl)-4-(bicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione 1125	337

Example 412		1-((6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methyl)-4-(bicyclo[1.1.1]pentan-1-yl)-1,4-dihydropyrazine-2,3-dione 1126	337
Example 413		1-(4-((5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methyl)-2,3-dioxo-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 1127	336
Example 414		1-((6-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)methyl)-4-(1-methylcyclopropyl)-1,4-dihydropyrazine-2,3-dione 1128	325
Example 415		1-((6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methyl)-4-(1-methylcyclopropyl)-1,4-dihydropyrazine-2,3-dione 1129	325

Example 416

Preparation of 1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((6-(pyridin-3-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione

Step A: N-((6-chloropyridazin-3-yl)methyl)prop-2-en-1-amine

398

Prop-2-en-1-amine (5.20 mL, 69.2 mmol) was added to a mixture of 3-chloro-6-(chloromethyl)pyridazine hydrochloride (3.0 g, 15 mmol) and potassium carbonate (6.24 g, 45.1 mmol) in DMF (40 mL) at room temperature. The mixture was stirred and heated at 40 °C for 12 hours. The mixture was filtered and concentrated under reduced pressure to afford N-((6-chloropyridazin-3-yl)methyl)prop-2-en-1-amine, which was used without purification in the next step. LC/MS (*m/z*): 184 $(M+H)^+$

768

Step B: ethyl 2-(allyl((6-chloropyridazin-3-yl)methyl)amino)-2-oxoacetate

399

Ethyl oxalyl chloride (2.52 mL, 22.5 mmol) was added to a solution of N-((6-chloropyridazin-3-yl)methyl)prop-2-en-1-amine (2.76 g, 15.0 mmol) and potassium carbonate (4.15 g, 30.1 mmol) in DMF (20 mL) at 0 °C. The mixture was stirred at room temperature for 3 hours. The reaction mixture was quenched with water (400 mL) and extracted with EtOAc (3 x 100 mL). The organic layers were combined, washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford ethyl 2-(allyl((6-chloropyridazin-3-yl)methyl)amino)-2-oxoacetate. ^{1}H NMR (500 MHz, methanol-d_4) δ 7.87 - 7.68 (m, 2H), 5.96 - 5.69 (m, 1H), 5.38 - 5.15 (m, 2H), 4.87 (s, 2H), 4.44 - 4.28 (m, 2H), 4.14 - 4.07 (m, 2H), 1.39 - 1.26 (m, 3H). LC/MS (*m/z*): 284 $(M+H)^+$

Step C: 3-((N-allyl-2-ethoxy-2-oxoacetamido)methyl)-6-chloropyridazine 1-oxide

400

meta-Chloroperoxybenzoic acid (0.760 g, 3.52 mmol) was added to a solution of ethyl 2-(allyl((6-chloropyridazin-3-yl)methyl)amino)-2-oxoacetate (1.0 g, 3.5 mmol) in DCM (25 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 16 hours. The reaction mixture was quenched with Na_2SO_3 (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 3-((N-allyl-2-ethoxy-2-oxoacetamido)methyl)-6-chloropyridazine 1-oxide. LC/MS (*m/z*): 300 $(M+H)^+$

Step D: 6-chloro-3-((2-ethoxy-2-oxo-N-(2-oxoethyl)acetamido)methyl)pyridazine 1-oxide

901

Osmium(VIII) oxide (34 mg, 0.13 mmol) was added to a mixture of 3-((N-allyl-2-ethoxy-2-oxoacetamido)methyl)-6-chloropyridazine 1-oxide (0.400 g, 1.33 mmol) and sodium periodate (1.13 g, 5.30 mmol) in water (5 mL) and THF (5 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 1.5 hours. The mixture was concentrated under reduced pressure, and the residue was partitioned between water (5 mL) and EtOAc (5 mL). The organic layer was separated, and the aqueous was extracted with EtOAc (3 x 5 mL). The organic layers were combined, washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 6-chloro-3-((2-ethoxy-2-oxo-N-(2-

oxoethyl)acetamido)methyl)pyridazine 1-oxide which was used in the next step without purification. LC/MS (*m/z*): 302 $(M+H)^+$

Step E: 3-((4-((cis)-bicyclo[3.1.0]hexan-3-yl)-2,3-dioxo-3,4-dihydropyrazin-1(2H)-yl)methyl)-6-chloropyridazine-1-oxide

902

Triethylamine (0.069 ml, 0.50 mmol) was added to a mixture of cis-bicyclo[3.1.0]hexan-3-ammonium iodide (112 mg, 0.497 mmol) in DCE (2 mL) and acetic acid (0.5 mL) room 8 temperature. 6-chloro-3-((2-ethoxy-2-oxo-N-(2-oxoethyl)acetamido)methyl)pyridazine-1-oxide (0.150 g, 0.497 mmol) was added to the mixture at room temperature, and the mixture was stirred for 2 days. The mixture was concentrated under reduced pressure, and the residue was partitioned between water (5 mL) and DCM (5 mL). The organic layer was separated, and the aqueous was re-extracted with DCM (3 x 5 mL). The organic layers were combined, washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 3-((4-((cis)-bicyclo[3.1.0]hexan-3-yl)-2,3-dioxo-3,4-dihydropyrazin-1(2H)-yl)methyl)-6-(pyridin-3-yl)pyridazine 1-oxide. LC/MS (*m/z*): 335 $(M+H)^+$

Step F: 3-((4-((cis)-bicyclo[3.1.0]hexan-3-yl)-2,3-dioxo-3,4-dihydropyrazin-1(2H)-yl)methyl)-6-(pyridin-3-yl)pyridazine 1-oxide

905

A mixture of 3-((4-(bicyclo[3.1.0]hexan-3-yl)-2,3-dioxo-3,4-dihydropyrazin-1(2H)-yl)methyl)-6-chloropyridazine 1-oxide (10 mg, 0.03 mmol), pyridin-3-ylboronic acid (6 mg, 0.05 mmol), potassium phosphate tribasic (19 mg, 0.090 mmol), and Pd(dtbpf)Cl_2 (5 mg, 7 µmol) in 1,4-dioxane (1 mL) and water (0.2 mL) was degassed and backfilled with N_2 (three times). The mixture was heated to 80 °C and stirred for 16 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between water (10 mL) and DCM (10 mL). The organic layer was separated, and the aqueous was re-extracted with DCM (3 x 10 mL). The organic layers were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((6-(pyridin-3-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione. LC/MS (*m/z*): 378 $(M+H)^+$

Step G: 1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((6-(pyridin-3-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione

905

A mixture of 6-((4-((cis)-bicyclo[3.1.0]hexan-3-yl)-2,3-dioxo-3,4-dihydropyrazin-1(2H)-yl)methyl)-3-(pyridin-3-yl)pyridazine-1-oxide (5.5 mg, 0.015 mmol), palladium on carbon (10%

w/w, 3 mg, 3 μmol) and ammonium formate (3 mg, 0.04 mmol) in MeOH (1 mL) was stirred and heated at 50 °C for 1 hour. The mixture was cooled to room temperature, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-((cis)-bicyclo[3.1.0]hexan-3-yl)-4-((6-(pyridin-3-yl)pyridazin-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione. ^{1}H NMR (400 MHz, methanol-d_4) δ 9.41 (s, 1H), 8.89 - 8.63 (m, 2H), 8.35 - 8.07 (m, 1H), 7.99 - 7.75 (m, 2H), 6.87 - 6.72 (m, 1H), 6.62 - 6.54 (m, 1H), 5.36 (s, 2H), 5.30 - 5.21 (m, 1H), 2.43 (ddd, J = 4.5, 9.1, 14.0 Hz, 2H), 1.68 (br dd, J = 8.6, 13.9 Hz, 2H), 1.40 (br s, 2H), 0.96 - 0.88 (m, 1H), 0.45 (q, J = 4.2 Hz, 1H). LC/MS (m/z): 362 $(M+H)^+$

Example 417

Preparation of 1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-(3-fluorophenyl)isoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione

A mixture of silver(I) fluoride (69 mg, 0.54 mmol), bis(acetonitrile)dichloropalladium(II) ($PdCl_2(MeCN)_2$) (4 mg, 0.02 mmol), 1,2-bis(diphenylphosphaneyl)benzene (12 mg, 0.027 mmol), 1-fluoro-3-iodobenzene (0.120 g, 0.540 mmol), and 1-(bicyclo[1.1.1]pentan-1-yl)-4-(isoxazol-3-ylmethyl)-1,4-dihydropyrazine-2,3-dione (0.070 g, 0.27 mmol) in DMA (2 mL) was degassed with argon at room temperature. The mixture was stirred and heated at 100 °C for 12 hours. The mixture was cooled to room temperature, filtered, and directly purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-(3-fluorophenyl)isoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.67 - 7.62 (m, 1H), 7.60 - 7.54 (m, 1H), 7.54 - 7.46 (m, 1H), 7.23 (dt, J = 1.8, 8.5 Hz, 1H),

6.87 (s, 1H), 6.58 (d, J = 6.3 Hz, 1H), 6.49 (d, J = 6.3 Hz, 1H), 5.11 (s, 2H), 2.63 (s, 1H), 2.33 (s, 6H). LC/MS (m/z): 354 $(M+H)^+$

Examples shown in Example Table 18 below, were or may be prepared according to procedures analogous to those outlined in Example 417 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Example Table 18

Example	Structure	Name	Mass $[M+H]^+$
Example 418		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-(4-fluorophenyl)isoxazol-3-yl)methyl)piperazine-2,3-dione 1132	356
Example 419		1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-(4-fluorophenyl)isoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 1133	354
Example 420		1-(1-methylcyclobutyl)-4-((5-phenylisoxazol-3-yl)methyl)-1,4-dihydropyrazine-2,3-dione 1134	338

Example	Structure	Name	Mass $[M+H]^+$
Example 421		1-((5-(3-fluorophenyl)isoxazol-3-yl)methyl)-4-(1-methylcyclobutyl)-1,4-dihydropyrazine-2,3-dione 1135	356
Example 422		1-((5-(4-fluorophenyl)isoxazol-3-yl)methyl)-4-(1-methylcyclobutyl)-1,4-dihydropyrazine-2,3-dione 1136	356
Example 423		4-(3-((4-(bicyclo[1.1.1]pentan-1-yl)-2,3-dioxopiperazin-1-yl)methyl)isoxazol-5-yl)benzonitrile 1137	363
Example 424		2-(3-((4-(bicyclo[1.1.1]pentan-1-yl)-2,3-dioxopiperazin-1-yl)methyl)isoxazol-5-yl)benzonitrile 1138	363

Example 425

Preparation of 1-cyclobutyl-4-((5-(3-fluorophenyl)thiazol-2-yl)methyl)piperazine-2,3-dione

1139

A mixture of 1-cyclobutyl-4-(thiazol-2-ylmethyl)piperazine-2,3-dione (0.100 g, 0.377 mmol), potassium carbonate (104 mg, 0.754 mmol), pivalic acid (16 mg, 0.16 mmol), cataCXium A ® (14 mg, 0.039 mmol), palladium(II) acetate (9 mg, 0.04 mmol), and 1-fluoro-3-iodobenzene (126 mg, 0.565 mmol) in toluene (2 mL) was degassed with nitrogen for 5 minutes at room temperature. The mixture was stirred and heated at 100 ºC for 12 hours. The mixture was cooled to room temperature, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-cyclobutyl-4-((5-(3-fluorophenyl)thiazol-2-yl)methyl)piperazine-2,3-dione. ^{1}H NMR (500 MHz, methanol-d_4) δ 8.04 (s, 1H), 7.46 - 7.42 (m, 2H), 7.41 - 7.36 (m, 1H), 7.14 - 7.05 (m, 1H), 4.95 (s, 2H), 4.87 - 4.79 (m, 1H), 3.79 - 3.73 (m, 2H), 3.73 - 3.66 (m, 2H), 2.30 - 2.22 (m, 2H), 2.22 - 2.15 (m, 2H), 1.80 - 1.73 (m, 2H). LC/MS (*m/z*): 360 $(M+H)^+$

Examples shown in Example Table 19 below, were or may be prepared according to procedures analogous to those outlined in Example 425 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Example Table 19

Example	Structure	Name	Mass $[M+H]^+$
Example 426		1-cyclobutyl-4-((5-(2-fluorophenyl)thiazol-2-yl)methyl)piperazine-2,3-dione 1140	360

Example 427

Preparation of 1-(bicyclo[1.1.1]pentan-1-yl)-4-((1-(pyridin-2-yl)-1H-1,2,3-triazol-4-yl)methyl)-1,4-dihydropyrazine-2,3-dione

1141

A mixture of copper(II) sulfate (4 mg, 0.02 mmol) and (+)-sodium L-ascorbate (5 mg, 0.02 mmol) in water (0.1 mL) was added to a mixture of 1-(bicyclo[1.1.1]pentan-1-yl)-4-(prop-2-yn-1-yl)-1,4-dihydropyrazine-2,3-dione (0.050 g, 0.23 mmol) and 2-azidopyridine (56 mg, 0.46 mmol) in t-BuOH (0.9 mL) at room temperature. The mixture was stirred and heated at 50°C for 16 hours. The mixture was filtered and the filtrate was purified by reverse phase HPLC (eluting acetonitrile in water, with ammonium bicarbonate modifier) to afford 1-(bicyclo[1.1.1]pentan-1-yl)-4-((1-(pyridin-2-yl)-1H-1,2,3-triazol-4-yl)methyl)-1,4-dihydropyrazine-2,3-dione. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.75 (br s, 1H), 8.51 (br s, 1H), 8.16 (br s, 1H), 7.92 (t, J = 7.78 Hz, 1H), 7.38 (br s, 1H), 6.46 (d, J = 6.10 Hz, 1H), 6.16 (d, J = 5.95 Hz, 1H), 5.12 (s, 2H), 2.62 (s, 1H), 2.29 (s, 6H). LC/MS (*m/z*): 337 $(M+H)^+$

Examples shown in Example Table 20 below, were or may be prepared according to procedures analogous to those outlined in Example 427 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Example Table 20

Example	Structure	Name	Mass $[M+H]^+$
Example 428		1-(bicyclo[1.1.1]pentan-1-yl)-4-((1-(pyridin-3-yl)-1H-1,2,3-triazol-4-yl)methyl)-1,4-dihydropyrazine-2,3-dione 1142	337
Example 429		1-(1-methylcyclopropyl)-4-((1-(pyridin-3-yl)-1H-1,2,3-triazol-4-yl)methyl)-1,4-dihydropyrazine-2,3-dione 1143	325
Example 430		1-(1-methylcyclopropyl)-4-((1-(pyridin-2-yl)-1H-1,2,3-triazol-4-yl)methyl)-1,4-dihydropyrazine-2,3-dione 1144	325
Example 431		1-(2,3-dioxo-4-((1-(pyridin-3-yl)-1H-1,2,3-triazol-4-yl)methyl)-3,4-dihydropyrazin-1(2H)-yl)cyclopropane-1-carbonitrile 1145	336

Example 432

Preparation of 1-((4-bromo-5-(pyridin-2-yl)isoxazol-3-yl)methyl)-4-cyclobutylpiperazine-2,3-dione

NBS (327 mg, 1.84 mmol) was added to a mixture of 1-cyclobutyl-4-((5-(pyridin-2-yl)isoxazol-3-yl)methyl)piperazine-2,3-dione (0.200 g, 0.613 mmol) in DMF (2 ml) at room temperature. The mixture was stirred and heated to 100 °C for 12 hours. The mixture was concentrated under reduced pressure, and the residue was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-((4-bromo-5-(pyridin-2-yl)isoxazol-3-yl)methyl)-4-cyclobutylpiperazine-2,3-dione. ^{1}H NMR (500 MHz, methanol-d_4) δ 8.75 (d, J = 4.7 Hz, 1H), 8.13 (d, J =7.9 Hz, 1H), 8.06 – 8.00 (m, 1H), 7.58 – 7.56 (m, 1H), 4.91 - 4.89 (m, 2H), 4.86 - 4.83 (m, 1H), 3.72 (s, 4H), 2.31 - 2.24 (m, 2H), 2.24 - 2.16 (m, 2H), 1.81 - 1.73 (m, 2H). LC/MS (m/z): 405, 407 $(M+H)^+$

Example 433

Preparation of 1-((6-phenylpyridazin-3-yl)methyl)-4-(pyridin-2-yl)piperazine-2,3-dione

A mixture of 1-((6-phenylpyridazin-3-yl)methyl)piperazine-2,3-dione (0.050 g, 0.18 mmol), 2-iodopyridine (55 mg, 0.27 mmol), dimethylglycine (11 mg, 0.11 mmol), copper (I) iodide (10 mg, 0.055 mmol), and K_2CO_3 (73 mg, 0.53 mmol) in DMSO (1 mL) was stirred and heated at 100 °C for

4 hours. The mixture was filtered and the filtrate was directly purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-((6-phenylpyridazin-3-yl)methyl)-4-(pyridin-2-yl)piperazine-2,3-dione. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.45 (d, J = 3.9 Hz, 1H), 8.11 (d, *J* = 8.6 Hz, 1H), 8.07 - 8.00 (m, 3H), 7.99 - 7.92 (m, 1H), 7.83 - 7.76 (m, 1H), 7.59 - 7.54 (m, 3H), 7.19 (dd, J = 7.2, 4.9 Hz, 1H), 5.13 (s, 2H), 4.40 (br s, 2H), 4.00 (br s, 2H). LC/MS (*m/z*): 360 $(M+H)^+$

Example 434

Preparation of 1-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)-4-(3-hydroxycyclobutyl)piperazine-2,3-dione

Step A: 1-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)-4-(3-oxocyclobutyl)piperazine-2,3-dione

903

A mixture of 1-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)piperazine-2,3-dione (10 mg, 0.03 mmol), 3-bromocyclobutan-1-one (6 mg, 0.04 mmol), and Cs_2CO_3 (22 mg, 0.068 mmol) in DMF (1 mL) was stirred and heated at 60 °C for 12 hours. The mixture was concentrated under reduced pressure and the residue was partitioned between water (10 mL) and DCM (10 mL). The organic

layer was separated and the aqueous was re-extracted with DCM (3 x 10 mL). The organic layers were combined, washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure afford 1-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)-4-(3-oxocyclobutyl)piperazine-2,3-dione, which was used without purification in the next step. LC/MS (*m/z*): 369 $(M+H)^+$

Step B: 1-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)-4-(3-hydroxycyclobutyl)piperazine-2,3-dione

1148

A mixture of 1-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)-4-(3-oxocyclobutyl)piperazine-2,3-dione (0.100 g, 0.271 mmol) and $NaBH_4$ (10 mg, 0.3 mmol) in MeOH (4 ml) was stirred at room temperature for 12 hours. The mixture was quenched with water (1 mL). The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-((6-(2-fluorophenyl)pyridazin-3-yl)methyl)-4-(3-hydroxycyclobutyl)piperazine-2,3-dione. ^{1}H NMR (500 MHz, methanol-d_4) δ 8.07 (dd, *J* =1.8, 8.7 Hz, 1H), 7.95 (br t, J = 7.2 Hz, 1H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.62 - 7.54 (m, 1H), 7.38 (*t*, J = 7.6 Hz, 1H), 7.31 (dd, *J* = 8.4, 11.1 Hz, 1H), 5.04 (s, 2H), 4.45 - 4.35 (m, 1H), 4.02 (quin, *J* = 7.1 Hz, 1H), 3.91 - 3.69 (m, 4H), 2.69 - 2.54 (m, 2H), 2.16 - 2.04 (m, 2H). LC/MS (*m/z*): 371 $(M+H)^+$

Examples 435A and 435B

Preparation of 1-cyclobutyl-4-((6-phenylpyridazin-3-yl)methyl)hexahydro-1H-cyclopenta[b]pyrazine-2,3-dione (Trans stereoisomer; S,S or R,R) and 1-cyclobutyl-4-((6-

phenylpyridazin-3-yl)methyl)hexahydro-1H-cyclopenta[b]pyrazine-2,3-dione (Cis stereoisomer; S,R or R,S)

3-(Chloromethyl)-6-phenylpyridazine (44 mg, 0.22 mmol) was added to a mixture of 1-cyclobutylhexahydro-1H-cyclopenta[b]pyrazine-2,3-dione (45 mg, 0.22 mmol) and Cs_2CO_3 (141 mg, 0.432 mmol) in DMF (2 mL). The mixture was stirred and heated to 60 °C for 2 hours. The reaction mixture was filtered and the residue was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to give 1-cyclobutyl-4-((6-phenylpyridazin-3-yl)methyl)hexahydro-1H-cyclopenta[b]pyrazine-2,3-dione as a mixture of four isomers. The residue was resolved by chiral SFC (Column: Daicel Chiralpak AD, 250 x 30 mm, 10 µm; eluting 45% [0.1% ammonia in water] in isopropanol) to afford the product in two fractions, each a mixture of two stereoisomers. The second fraction was further resolved by chiral SFC (Column: Daicel Chiralpak AD, 250 x 30 mm, 10 µm; eluting 45% [0.1% ammonia in water] in isopropanol) to afford:

Peak 1: Example 435A: (S,S or R,R)-1-cyclobutyl-4-((6-phenylpyridazin-3-yl)methyl)hexahydro-1H-cyclopenta[b]pyrazine-2,3-dione. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.08 (dd, *J* = 1.5, 7.6 Hz, 2H), 7.89 - 7.84 (m, 1H), 7.82 - 7.79 (m, 1H), 7.56 - 7.47 (m, 3H), 5.15 (d, *J* = 14.5 Hz, 1H), 4.90 (d, *J* = 14.3 Hz, 1H), 4.19 (q, *J* = 5.4 Hz, 1H), 3.99 (q, *J* = 6.2 Hz, 1H), 3.59 (dd, *J* = 7.3, 14.2 Hz, 1H), 3.20 (dd, *J* = 7.0, 14.2 Hz, 1H), 2.20 - 2.08 (m, 1H), 1.96 - 1.88 (m, 1H), 1.74 - 1.65 (m, 2H), 1.03 - 0.97 (m, 1H), 0.61 - 0.46 (m, 2H), 0.40 - 0.23 (m, 2H). LC/MS (*m/z*): 377 $(M+H)^+$

Peak 2: Example 435B: (S,R or S,R)-1-cyclobutyl-4-((6-phenylpyridazin-3-yl)methyl)hexahydro-1H-cyclopenta[b]pyrazine-2,3-dione. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.14 - 8.01 (m, 2H), 7.88 - 7.82 (m, 1H), 7.81 - 7.74 (m, 1H), 7.56 - 7.46 (m, 3H), 5.17 (d, *J* = 14.6

Hz, 1H), 4.88 (d, J = 14.6 Hz, 1H), 4.73 - 4.62 (m, 1H), 4.16 (dt, J = 2.2, 5.1 Hz, 1H), 3.95 - 3.82 (m, 1H), 2.51 - 2.39 (m, 1H), 2.32 - 2.24 (m, 1H), 2.24 - 2.18 (m, 1H), 2.17 - 2.04 (m, 2H), 1.96 - 1.86 (m, 1H), 1.78 - 1.66 (m, 3H), 1.63 - 1.55 (m, 1H). LC/MS (m/z): 377 $(M+H)^+$

Example 436

Preparation of 2-(5-((4-(bicyclo[1.1.1]pentan-1-yl)-2,3-dioxopiperazin-1-yl)methyl)-1,3,4-thiadiazol-2-yl)benzonitrile

1151

A mixture of 1-(bicyclo[1.1.1]pentan-1-yl)-4-((5-(2-chlorophenyl)-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione (0.090 g, 0.23 mmol), potassium ferrocyanide trihydrate (49 mg, 0.12 mmol), and Brettphos Pd G3 (42 mg, 0.046 mmol)) in DMA (1 mL) and water (0.333 mL) was degassed and backfilled with nitrogen (3X). The mixture was stirred and heated at 100 °C for 4 hours. The mixture was filtered and the filtrate was directly purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 2-(5-((4-(bicyclo[1.1.1]pentan-1-yl)-2,3-dioxopiperazin-1-yl)methyl)-1,3,4-thiadiazol-2-yl)benzonitrile. ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (d, J = 7.6 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.85-7.79 (m, 1H), 7.75-7.68 (m, 1H), 5.11 (s, 2H), 3.81-3.76 (m, 2H), 3.64-3.59 (m, 2H), 2.49 (s, 1H), 2.19 (s, 6H). LC/MS (m/z): 380 $(M+H)^+$

Example 437

Preparation of (R or S)-1-cyclobutyl-5-methyl-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione

1069

(rac)-1-Cyclobutyl-5-methyl-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione (0.050 g, 0.106 mmol) was resolved by chiral SFC (Column: CCO F4 (21 x 250 mm, 5 µm); eluting 30% MeOH (with 0.1% ammonium hydroxide) in CO_2) to afford (R or S)-1-cyclobutyl-5-methyl-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione as the first eluting peak.

Peak 1: (R or S)-1-cyclobutyl-5-methyl-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione (t_r = 5.5 minutes): ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.00 – 7.96 (m, 2H), 7.60 – 7.54 (m, 3H), 5.16 (d, J = 15.7 Hz, 1H), 4.88 (d, J = 15.7 Hz, 1H), 4.82 (p, J = 8.9 Hz, 1H), 3.98 – 3.92 (m, 1H), 3.72 (dd, J = 13.3, 3.9 Hz, 1H), 3.53 (dd, J = 13.3, 2.6 Hz, 1H), 2.20 – 2.10 (m, 2H), 2.09 – 1.99 (m, 2H), 1.70 – 1.64 (m, 2H), 1.26 (d, J = 6.5 Hz, 3H). LC/MS (m/z): 357 $(M+H)^+$

Example 438

Preparation of (R,S or S,R)-1-(3-hydroxycyclopentyl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione

A mixture 1-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)-4-(3-hydroxycyclopentyl)piperazine-2,3-dione (0.100 g, 0.266 mmol), phenylboronic acid (49 mg, 0.40 mmol), potassium phosphate tribasic (0.170 g, 0.799 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) (20 mg, 0.027 mmol) in 1,4-dioxane (2 mL) was stirred and heated at 100 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford the product as a mixture of stereoisomers. The mixture was resolved by chiral SFC (Column: Phenomenex-Cellulose-2 (250mm x 30mm, 5 µm); eluting 5-40% ethanol (with 0.1% ammonium hydroxide modifier) in CO_2) to afford (R,S or S,R)-1-(3-hydroxycyclopentyl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione as the first eluting peak.

Peak 1: (R,S or S,R)-1-(3-hydroxycyclopentyl)-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)piperazine-2,3-dione (t_r = 3.67 minutes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.87 (m, 2H), 7.54-7.41 (m, 3H), 5.04 (s, 2H), 4.88-4.73 (m, 1H), 4.35-4.30 (m, 1H), 3.75-3.62 (m, 4H), 2.28-2.19 (m, 1H), 1.98-1.73 (m, 5H). LC/MS (*m/z*): 373 $(M+H)^+$

Example 439

Preparation of 1-(bicyclo[1.1.1]pentan-1-yl)-4-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperazine-2,3-dione

Step A: 1-(bicyclo[1.1.1]pentan-1-yl)-4-(prop-2-yn-1-yl)piperazine-2,3-dione

904

A mixture of 1-(bicyclo[1.1.1]pentan-1-yl)piperazine-2,3-dione (750 mg, 4.16 mmol), 3-bromoprop-1-yne (0.673 mL, 6.24 mmol) and Cs_2CO_3 (2030 mg, 6.24 mmol) in DMF (10 mL) was 785 stirred and heated at 60 °C for 16 hours. The mixture was diluted with EtOAc (30 mL) and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting ethyl acetate in petroleum ether) to afford 1-(bicyclo[1.1.1]pentan-1-yl)-4-(prop-2-yn-1-yl)piperazine-2,3-dione. ^{1}H NMR (400 MHz, chloroform-*d*) δ 4.34 (s, 2H), 3.68-3.61 (m, 2H), 3.56-3.49 (m, 2H), 2.55-2.52 (m, 1H), 2.31-2.27 (m, 1H), 2.20 (s, 6H). LC/MS (*m/z*): 219 $(M+H)^+$

Step B: 1-(bicyclo[1.1.1]pentan-1-yl)-4-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperazine-2,3-dione

1154

A mixture of copper (II) sulfate (3.7 mg, 0.023 mmol) and (+)-sodium L-ascorbate (4.5 mg, 0.023 mmol) in water (0.1 mL) was added to a mixture of 1-(bicyclo[1.1.1]pentan-1-yl)-4-(prop-2-yn-1-yl)piperazine-2,3-dione (0.050 g, 0.23 mmol) and azidobenzene (55 mg, 0.46 mmol) in t-BuOH (0.9 ml) at room temperature. The mixture was stirred 787 and heated at 50 °C for 16 hours. The mixture was filtered and the filtrate was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford 1-(bicyclo[1.1.1]pentan-1-yl)-4-((1-phenyl-1H-1,2,3-triazol-4-

yl)methyl)piperazine-2,3-dione. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.16 (s, 1H), 7.73 (d, J = 7.78 Hz, 2H), 7.56-7.51 (m, 2H), 7.48-7.43 (m, 1H), 4.79 (s, 2H), 3.78 (br s, 2H), 3.50 (br s, 2H), 2.52 (s, 1H), 2.18 (s, 6H). LC/MS (*m/z*): 338 $(M+H)^+$

Examples 440A, 440B, 440C and 440D

Preparation of (R or S, R or S)-1-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-4-(3-phenylcyclopentyl)piperazine-2,3-dione, (R or S, R or S)-1-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-4-(3-phenylcyclopentyl)piperazine-2,3-dione, (R or S, R or S)-1-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-4-(3-phenylcyclopentyl)piperazine-2,3-dione, and (R or S, R or S)-1-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-4-(3-phenylcyclopentyl)piperazine-2,3-dione

1156

1157

1158

1159

Sodium triacetoxyborohydride (636 mg, 3.00 mmol) was added to a mixture of ethyl 2-oxo-2-((2-oxoethyl)((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)amino)acetate (0.500 g, 1.50 mmol) and 3-phenylcyclopentan-1-amine oxalate (377 mg, 1.50 mmol) in DCM (10 ml) at 0 °C. The mixture was stirred at room temperature for 1 hour. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (eluting acetonitrile in water, with TFA modifier) to afford the product as a mixture of stereoisomers. The mixture was resolved by chiral SFC (Column: Daicel-Chiralcel-OJ (100 x 4.6 mm, 3 μm); eluting 60% methanol (with 0.1% ammonium hydroxide modifier) in CO_2) to afford:

Peak 1: Example 440A (R or S, R or S)-1-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-4-(3-phenylcyclopentyl)piperazine-2,3-dione (t_r = 3.50 minutes). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.07-7.89 (m, 2H), 7.68-7.49 (m, 3H), 7.38-7.32 (m, 2H), 7.28-7.21 (m, 3H), 5.29-5.17 (m, 1H),

5.12 (s, 2H), 3.82 (br t, J = 5.42 Hz, 2H), 3.68-3.52 (m, 2H), 3.37-3.16 (m, 1H), 2.30-2.18 (m, 2H), 2.16-1.99 (m, 2H), 1.74-1.68 (m, 2H). LC/MS (*m/z*): 433 $(M+H)^+$

Peak 2: Example 440B (R or S, R or S)-1-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-4-(3-phenylcyclopentyl)piperazine-2,3-dione (t_r = 3.87 minutes). ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.97 (br d, J = 6.56 Hz, 2H), 7.58-7.46 (m, 3H), 7.33 (q, J = 7.53 Hz, 2H), 7.28-7.22 (m, 3H), 5.20-5.11 (m, 1H), 5.10 (d, J = 1.68 Hz, 2H), 3.86-3.71 (m, 2H), 3.58 (br t, J = 5.72 Hz, 2H), 3.24-3.07 (m, 1H), 2.34 (td, J = 6.43, 12.32 Hz, 1H), 2.26-2.08 (m, 2H), 1.91-1.77 (m, 3H). LC/MS (*m/z*): 433 $(M+H)^+$

Peak 3: Example 440C (R or S, R or S)-1-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-4-(3-phenylcyclopentyl)piperazine-2,3-dione (t_r = 6.90 minutes). ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.98 (br d, J = 6.56 Hz, 2H), 7.56-7.50 (m, 3H), 7.37-7.31 (m, 2H), 7.25 (br d, J = 6.71 Hz, 3H), 5.28-5.20 (m, 1H), 5.12 (s, 2H), 3.83 (br t, J = 5.65 Hz, 2H), 3.67-3.58 (m, 2H), 3.31-3.19 (m, 1H), 2.28-2.17 (m, 2H), 2.16-2.06 (m, 2H), 1.78-1.69 (m, 2H). LC/MS (*m/z*): 433 $(M+H)^+$

Peak 4: Example 440D (R or S, R or S)-1-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)-4-(3-phenylcyclopentyl)piperazine-2,3-dione (t_r = 8.13 minutes). 7.97 (br d, J = 6.71 Hz, 2H), 7.56-7.49 (m, 3H), 7.36-7.31 (m, 2H), 7.25 (br d, J = 7.63 Hz, 3H), 5.18-5.12 (m, 1H), 5.11 (s, 2H), 3.79 (br d, J = 3.36 Hz, 2H), 3.57 (br t, J = 5.49 Hz, 2H), 3.25-3.09 (m, 1H), 2.39-2.10 (m, 4H), 1.91-1.73 (m, 2H). LC/MS (*m/z*): 433 $(M+H)^+$

Assay

IL4I1 Enzymatic Assay

Interleukin 4 inducible protein 1 (IL4I1) is an L-amino oxidase that catalyzes the oxidation of aromatic residues (Phe, Trp and Tyr): L-amino acid + H_2O + O_2 → 2-oxo acid + NH_3 + H_2O_2. Equal molar of H_2O_2 and the corresponding alpha-ketoacid are produced when IL4I1 and substrate are added. In this assay, the hydrogen peroxide generated by IL4I1 is then detected through a coupled reaction with Amplex® Red (10-acetyl-3,7-dihydroxyphenoxazine) and horseradish peroxidase (HRP) to produce resorufin product that could be detected in the form of fluorescence signals. The assessment of the inhibitory effect of small molecules (EC_{50}) on IL4I1 is measured by the effectiveness of the compounds to inhibit the production of H_2O_2.

Using this assay, the potency (EC_{50}) of each compound was determined from a ten-point (1:3 serial dilution) titration curve using the following outlined procedure. To each well of a black flat-

bottom Greiner (Cat# 781076) 384 well-plate, 25 nL of compound (0.1% DMSO in final assay volume of 25 µL) was dispensed, followed by the addition of 12.5 µL of 1x assay buffer (50 mM Hepes 7.0 and 0.005% Tween20 (Sigma, Cat#P8341; low peroxide grade)) containing 2 nM of recombinant IL4I1 (R&D Systems, Cat#5684-AO-020). Plates were placed in an ambient temperature humidified chamber for a four-hour pre-incubation with compound. Subsequently, each reaction was initiated by the addition of 12.5 µL 1x assay buffer containing 2 mM of each aromatic amino acids (Phe/Tyr/Trp), 0.1 mM Amplex Red and 2 U/mL of HRP. The final reaction in each well of 25 µL consisted of 1 nM of IL4I1, 1 mM of each residues (Phe, Tyr and Trp), 0.05 mM Amplex Red and 1 U/mL of HRP. It should be noted that the concentrations of Amplex Red and HRP used here were in excess such that the conversion of H_2O_2 to resorufin product occurred instantaneously and was non-rate limiting. Reactions were allowed to proceed for 120 minutes followed by fluorescence readout on a Spectramax with the following set parameters: 544 nm excitation / 590 nm emission, 570 nm cutoff (EnVision is an alternative reader). Dose-response curves were generated by plotting percent effect (% product conversion; Y-axis) vs. Log_{10} compound concentrations (X-axis). EC_{50} values were calculated using a non-linear regression, four-parameters sigmoidal dose-response model and are shown in Potency Table 1.

Potency Table 1

Example	**EC50 (nM) (240 min)**
Example 1	10
Example 2	9
Example 3	12
Example 4	19
Example 5	50
Example 6	43
Example 7	9
Example 8	7
Example 9	15
Example 10	21
Example 11	16
Example 12	8
Example 13	8
Example 14	6

Example 15	44
Example 16	16
Example 17	7
Example 18	41
Example 19	7
Example 20	5
Example 21	14
Example 22	22
Example 23	21
Example 24	30
Example 25	21
Example 26	6
Example 27	5
Example 28	8
Example 29	9
Example 30	8
Example 31	6
Example 32	5
Example 33	8
Example 34	34
Example 35	3
Example 36	6
Example 37	18
Example 38	23
Example 39	3
Example 40	4
Example 41	2
Example 42	5
Example 43	3
Example 44	7
Example 45	5
Example 46	13
Example 47	3
Example 48	2
Example 49	3
Example 50	4
Example 51	8
Example 52	4

Example 53	7
Example 54	2
Example 55	1
Example 56	1
Example 57	3
Example 58	4
Example 59	5
Example 60	10
Example 61	5
Example 62	4
Example 63	3
Example 64	4
Example 65	4
Example 66	7
Example 67	1
Example 68	5
Example 69	3
Example 70	4
Example 71	6
Example 72	2
Example 73	9
Example 74	5
Example 75	7
Example 76	4
Example 77	3
Example 78	6
Example 79	5
Example 80	15
Example 81	60
Example 82	10
Example 83	8
Example 84	13
Example 85	29
Example 86	27
Example 87	87
Example 88	69
Example 89	32
Example 90	63

Example 91	162
Example 92	155
Example 93	31
Example 94	35
Example 95	16
Example 96A	14
Example 96B	8
Example 97	5
Example 98	12
Example 99	12
Example 100	8
Example 101	8
Example 102	14
Example 103	11
Example 104	4
Example 105	2
Example 106	7
Example 107	13
Example 108	20
Example 109	24
Example 110	27
Example 111	8
Example 112	7
Example 113	15
Example 114	7
Example 115	4
Example 116	17
Example 117	14
Example 118	7
Example 119	4
Example 120	3
Example 121	7
Example 122	6
Example 123	5
Example 124	7
Example 125	3
Example 126	3
Example 127	3

Example 128	2
Example 129	6
Example 130	5
Example 131	9
Example 132	15
Example 133	22
Example 134	40
Example 135	6
Example 136	20
Example 137	6
Example 138	12
Example 139	26
Example 140	36
Example 141	23
Example 142	3
Example 143	15
Example 144	2
Example 145	1
Example 146	3
Example 147	2
Example 148	2
Example 149	3
Example 150	3
Example 151	1
Example 152	2
Example 153	3
Example 154	3
Example 155	2
Example 156	2
Example 157	1
Example 158	4
Example 159	1
Example 160	5
Example 161	5
Example 162	4
Example 163	6
Example 164	1
Example 165	12

Example 166	10
Example 167	9
Example 168	6
Example 169	7
Example 170	4
Example 171	6
Example 172	7
Example 173	14
Example 174	39
Example 175	14
Example 176	40
Example 177	84
Example 178	52
Example 179	13
Example 180	97
Example 181	10
Example 182	14
Example 183	24
Example 184	25
Example 185	8
Example 186	4
Example 187	8
Example 188	10
Example 189	4
Example 190	31
Example 191	35
Example 192	13
Example 193	8
Example 194	41
Example 195	48
Example 196	11
Example 197	33
Example 198	76
Example 199	24
Example 200	68
Example 201	30
Example 202	44
Example 203	19
Example 204	78

Example 205	24
Example 206	28
Example 207	43
Example 208	21
Example 209	26
Example 210	92
Example 211	61
Example 212	10
Example 213	29
Example 214	56
Example 215	57
Example 216	60
Example 217	42
Example 218	56
Example 219	59
Example 220	50
Example 221	14
Example 222	316
Example 223	10
Example 224	101
Example 225	41
Example 226	78
Example 227	69
Example 228	23
Example 229	54
Example 230	91
Example 231	22
Example 232	82
Example 233	54
Example 234	40
Example 235	18
Example 236	533
Example 237	346
Example 238	29
Example 239	82
Example 240	995
Example 241	40
Example 242	32
Example 243	30
Example 244	45

Example 245	43
Example 246	37
Example 247	44
Example 248	38
Example 249	148
Example 250	240
Example 251	100
Example 252	38
Example 253	45
Example 254	93
Example 255	47
Example 256	533
Example 257	68
Example 258	78
Example 259	78
Example 260	38
Example 261	178
Example 262	868
Example 263	995
Example 264	73
Example 265	114
Example 266A	4
Example 266B	4
Example 267	57
Example 268	15
Example 269	49
Example 270	24
Example 271	14
Example 272	35
Example 273	19
Example 274	34
Example 275	20
Example 276	26
Example 277	24
Example 278	16
Example 279	68
Example 280	38
Example 281	35
Example 282	30

Example 283	7
Example 284	8
Example 285	28
Example 286	34
Example 287	34
Example 288	37
Example 289	6
Example 290	8
Example 291	4
Example 292	64
Example 293	11
Example 294	16
Example 295	53
Example 296	63
Example 297	83
Example 298	32
Example 299	56
Example 300	86
Example 301	67
Example 302	69
Example 303	28
Example 304	98
Example 305	32
Example 306	27
Example 307	20
Example 308	35
Example 309	41
Example 310	41
Example 311	60
Example 312	69
Example 313	47
Example 314	43
Example 315	23
Example 316	32
Example 317	45
Example 318	36
Example 319	30
Example 320	20

Example 321	21
Example 322	28
Example 323	157
Example 324	53
Example 325	33
Example 326	20
Example 327	16
Example 328	7
Example 329	15
Example 330	16
Example 331	9
Example 332	76
Example 333	94
Example 334	29
Example 335	90
Example 336	20
Example 337	15
Example 338	12
Example 339	42
Example 340	70
Example 341	19
Example 342	69
Example 343	133
Example 344	49
Example 345	59
Example 346	7
Example 347	74
Example 348	18
Example 349	25
Example 350	5
Example 351	8
Example 352	13
Example 353	11
Example 354	20
Example 355	22
Example 356	28
Example 357	32
Example 358A	2

Example 358B	1
Example 359	22
Example 360	16
Example 361	96
Example 362	22
Example 363	25
Example 364	17
Example 365	17
Example 366	9
Example 367	9
Example 368	28
Example 369	32
Example 370	20
Example 371	42
Example 372	23
Example 373	8
Example 374	8
Example 375	6
Example 376	14
Example 377	71
Example 378	138
Example 379	24
Example 380	17
Example 381	40
Example 382	25
Example 383	26
Example 384	9
Example 385	42
Example 386	225
Example 387	677
Example 388	23
Example 389	369
Example 390	343
Example 391	170
Example 392	31
Example 393	33
Example 394	31
Example 395	8

Example 396	5
Example 397	11
Example 398	22
Example 399	19
Example 400	25
Example 401	48
Example 402	36
Example 403	17
Example 404	10
Example 405	23
Example 406	15
Example 407	27
Example 408	8
Example 409	9
Example 410	5
Example 411	7
Example 412	19
Example 413	66
Example 414	15
Example 415	138
Example 416	28
Example 417	2
Example 418	6
Example 419	2
Example 420	5
Example 421	5
Example 422	5
Example 423	19
Example 424	19
Example 425	8
Example 426	5
Example 427	19
Example 428	21
Example 429	29
Example 430	183
Example 431	130
Example 432	17
Example 433	37

Example 434	71
Example 435A	85
Example 435B	76
Example 436	20
Example 437	34
Example 438	40
Example 439	9
Example 440A	5
Example 440B	6
Example 440C	10
Example 440D	8

What is claimed is:

1. A compound having a structural Formula I:

I

or a pharmaceutically acceptable salt thereof, wherein,

R^1 is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, heteroaryl, C_1-C_6alkylOC_1-C_6alkyl or heterocycloalkyl is unsubstituted or substituted with one to three substituents independently selected from the group consisting of oxo, -CN, -OH, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, phenyl, heteroaryl and C_3-C_6cycloalkyl, wherein the heteroaryl is unsubstituted or substituted with C_1-C_6alkoxy, or R^1, and the nitrogen to which it is attached, is taken with R^4 and forms a nitrogen-containing ring;

R^2 is H, C_1-C_6alkyl or together with R^3 forms a bond;

R^3 is H, C_1-C_6alkyl or together with R^2 forms a bond;

R^4 is H, halogen, or C_1-C_6alkyl or R^4 is taken with R^1, and the nitrogen to which R^1 is attached, and forms a nitrogen-containing ring, or R^4 is taken with R^5 and forms a C_3-C_6cycloalkyl;

R^5 is H, halogen, or C_1-C_6alkyl, or R^5 is taken with R^4 and forms a C_3-C_6cycloalkyl;

L is a C_1-C_6alkylene or C_3-C_6cycloalkylene linker;

X is phenyl, C_3-C_6cycloalkyl, or a nitrogen-containing ring, wherein the phenyl, C_3-C_6cycloalkyl or nitrogen-containing ring is unsubstituted or substituted with one or two substituents independently selected from the group consisting of halogen, -OH and oxo; and

Y is hydrogen, halogen, C_1-C_6alkoxy, phenyl, halogen-substituted phenyl, C_1-C_6alkyl-substituted phenyl, nitrogen-containing ring, CN-substituted phenyl, a halogen-substituted nitrogen-containing ring, or a haloC_1-C_6alkyl-substituted nitrogen-containing ring.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_1-C_6alkyl.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is isopropyl, neopentyl or tert-butyl, wherein the isopropyl, neopentyl or tert-butyl is unsubstituted or substituted with fluorine or pyridinyl.

4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_3-C_6cycloalkyl.

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

or , wherein R^1 is unsubstituted or substituted with one or two substituents independently selected from the group consisting of oxo, -CN, -OH, fluorine, methyl, phenyl, fluoromethyl, trifluoromethyl, pyridinyl, methoxypyridinyl and cyclopropyl.

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

7. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R^2 is methyl.

8. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R^3 is methyl.

9. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 form a bond.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein R^4 and R^5 are both hydrogen.

11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein L is .

12. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein L is .

13. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein L is .

14. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein L is .

15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein X is phenyl, wherein the phenyl is unsubstituted or substituted one or two substitutents independently selected from the group consisting of fluorine or bromine.

16. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein X is a nitrogen-containing ring, wherein the nitrogen-containing ring is selected from the group consisting of

,
,
and
wherein X is unsubstituted or substituted one or two substitutents independently selected from the group conisiting of fluorine and an oxo group.

17. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein X is a nitrogen-containing ring, wherein the nitrogen containing ring is

, wherein X is substituted with a fluorine.

18. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein X is a C_3-C_6cycloalkyl, wherein the C_3-C_6cycloalkyl is , wherein X is unsubstituted or substituted with one or two fluorines.

19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein Y is phenyl.

20. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein the phenyl is substituted with one to two fluorines.

21. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein Y is C_1-C_6alkoxy, wherein the C_1-C_6alkoxy is ethoxy or propoxy.

22. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein Y is a nitrogen-containing ring, wherein the nitrogen containing ring is selected from the group consisting of

23. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein Y is a halogen-substituted nitrogen-containing ring or a haloC_1-C_6alkyl-substituted nitrogen-containing ring, wherein the halogen-substituted nitrogen containing ring or haloC_1-C_6alkyl-substituted nitrogen-containing ring is selected from the group consisting of

24. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein Y is hydrogen only when X is

25. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is taken with R^4 forms a nitrogen-containing ring.

26. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^4 is taken with R^5 forms a C_3-C_6cycloalkyl.

27. The compound of claim 1, selected from the group consisting of

403 ,	563 ,

404 ,	564 ,
405 ,	565 ,
406 ,	566 ,
407 ,	567 ,

408 ,	568 ,
409 ,	569 ,
410 ,	, 570
411 ,	571 ,

412 ,	572 ,
413 ,	573 ,
414 ,	574 ,
415 ,	575 ,

416 ,	576 ,
417 ,	577 ,
418 ,	673 ,
, 419	674 ,

401 ,	675 ,
420 ,	676 ,
421 ,	677 ,

579

580

422 ,	678 ,
423 ,	679 ,
424 ,	680 ,
425 ,	681 ,

426 ,	682 ,
427 ,	683 ,
428 ,	684 ,
429 ,	685 ,

430 ,	686 ,
431 ,	687 ,
402 ,	688 ,
432 ,	689 ,

433 ,	690 ,
434 ,	691 ,
435 ,	692 ,
436 ,	693 ,

437 ,	694 ,
438 ,	695 ,
439 ,	696 ,
440 ,	697 ,

441 ,	698 ,
442 ,	699 ,
443 ,	1017 ,
444 ,	1018 ,

445 ,	1019 ,
446	1020 ,
447 ,	1021 ,
448 ,	1022 ,

542 ,	1023 ,
449 ,	1024 ,
450 ,	1025 ,
451 ,	1026 ,
452 ,	1027 ,

453 ,	1028 ,
454 ,	1029 ,
455 ,	, 1030
456 ,	1031 ,

457 ,	, 1032
458 ,	1033 ,
459 ,	1034 ,
460 ,	1035 ,

461 ,	1036 ,
,	1037 ,
463 ,	1038 ,
464 ,	1039 ,

465 ,	1044 ,
466 ,	1045 ,
467 ,	1046 ,
468 ,	1047 ,

469 ,	1048 ,
470 ,	1049 ,
471 ,	1052 ,
472 ,	1053 ,

, 473	, 1055 1056
, 474	, 1057
, 475	, 1058
, 476	, 1059

477 ,	1060 ,
478 ,	1061 ,
479 ,	1062 ,
480 496 ,	1063 ,

497 ,	1064 ,
498 ,	1065 ,
499 ,	1066 ,
500 ,	1067 ,

501 ,	1068 ,
502 ,	1069 ,
503 ,	1070 ,
504 ,	1071 ,

505 ,	541
506 ,	1111 ,
507 ,	1072 ,
508 ,	1073 ,
509 ,	1074 ,

510 ,	1075 ,
511 ,	1076 ,
512 ,	1077 ,
513 ,	1078 ,
514 ,	1079 ,

515 ,	1080 ,
516 ,	1081 ,
517 ,	1082 ,
518 ,	1083 ,
519 ,	1084 ,

520 ,	1085 ,
521 ,	1086 ,
522 ,	1087 ,
523 ,	1088 ,

524 ,	1089 ,
525 ,	1091 ,
526 ,	1092 ,
527 ,	1093 ,

528 ,	1105 ,
529 ,	1106 ,
530 ,	1107 ,
531 ,	1108 ,

, 532	540 ,
534 ,	1109 ,
537 ,	1112 ,
539 544 ,	1113 ,

545 ,	1114 ,
546 ,	1115 ,
547 ,	1116 ,
548 ,	1117 ,

549 ,	1118 ,
550 ,	1119 ,
551 ,	, 1120
552 ,	, 1121

553 ,	1122 ,
554 ,	1123 ,
555 ,	1124 ,
556 ,	905 ,

, 557	1131 ,
558 ,	1132 ,
559 ,	1133 ,
560 ,	1139 ,

561 ,	543 ,
562 ,	1140 ,
700 ,	578 ,
540 1001 ,	533 ,

481 ,	649 ,
482 ,	650 ,
483 ,	651 ,
484 ,	652 ,

485 ,	653 ,
486 ,	654 ,
487 ,	655 ,
488 ,	656 ,
489 ,	657 ,

490 ,	658 ,
491 ,	659 ,
492 ,	660 ,
493 ,	661 ,

494 ,	662 ,
495 ,	663 ,
579 ,	664 ,
580 ,	665 ,

581 ,	666 ,
582 ,	667 ,
583 ,	668 ,
584 ,	669 ,

588

585 588 ,	670 ,
586 ,	671 ,
,	672 ,
590 ,	1002 ,

, 591	1003 ,
592 ,	1004 ,
593 ,	1005 ,
594 ,	1006 ,

595 ,	1007 ,
596 ,	1008 ,
597 ,	1009 ,
598 ,	1010 ,

599 ,	1011 ,
600 ,	1012 ,
601 ,	1013 ,
602 ,	1014 ,

603 ,	1015 ,
604 ,	1016 ,
605 ,	1040 ,
606 ,	1041 ,
607 ,	1042 ,

608 ,	1043 ,
609 ,	1090 ,
610 ,	1094 ,
611 ,	1095 ,
612 ,	1096 ,

613 ,	1097 ,
614 ,	1098 ,
615 ,	1099 ,
616 ,	1100 ,
617 ,	1101 ,

618 ,	1102 ,
619 ,	1103 ,
620 ,	, 1104
621 ,	,1125

622 ,	1126 ,
623 ,	1127 ,
624 ,	1128 ,
625 ,	1129 ,
626 ,	1134 ,

, 627	, 1135
, 628	, 1136
, 629	, 1137
, 630	, 1138

631 ,	1141 ,
632 ,	1142 ,
633 ,	1143 ,
634 ,	1144 ,

635 ,	1145 ,
636 ,	1146 ,
637 ,	1147 ,
638 ,	1148 ,

, 639	, 1149 1150
, 640	, 1151
, 641	,

, 642	1153 ,
643 ,	1154 ,
, 644	1156 1157 1158 1159 ,

, 645	, 647
, and 646	648

or a pharmaceutically acceptable salt thereof.

28. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is:

.

29. A compound, wherein the compound is:

30. A compound, or pharmaceutically acceptable salt thereof, wherein the compound is:

31. A compound, wherein the compound is:

32. A method of treating cancer in a patient comprising administering to a patient in need thereof a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-31.

33. The use of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-31 to treat cancer in a patient in need thereof.

34. A pharmaceutical composition comprising a compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

35. A pharmaceutical composition comprising a compound of any one of claims 1-31 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2022/026626

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61P35/00 C07D241/08 C07D401/06 C07D401/14 C07D403/06
C07D403/10 C07D403/14 C07D413/06 C07D413/14 C07D417/06
C07D417/10 C07D417/14 A61K31/501 A61K31/496 A61K31/506

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)

A61P C07D A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HORI T ET AL: "STUDIES ON ANTITUMOR-ACTIVE 2,3-DIOXOPIPERAZINE DERIVATIVES. 2. SYNTHESIS AND STRUCTRUE-ANTITUMOR ACTIVITY RELATIONSHIP OF 1-BENZYL-2,3-DIOXOPIPERAZINE DERIVATIVES", CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN, JP, vol. 29, no. 3, 1 January 1981 (1981-01-01), pages 684-698, XP000941482, ISSN: 0009-2363	1,2,6, 10,11, 32-35
A	table III; compounds 12a, 12b, 12j-12m	3-5,7-9, 12-31

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"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
2 August 2022	10/08/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sarakinos, Georgios

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HORI T ET AL: "STUDIES ON ANTITUMOR-ACTIVE 2,3-DIOXOPIPERAZINE DERIVATIVES. III. SYNTHESIS AND STRUCTURE-ANTITUMOR ACTIVITY RALATIONSHIP OF 1-(4-AMINOBENZYL)-2,3-DIOXOPIPERAZINE DERIVATIVES", CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN, JP, vol. 29, no. 5, 1 January 1981 (1981-01-01), pages 1253-1266, XP001063113, ISSN: 0009-2363	1,2,6, 10,11, 22,32-35
A	table II; compounds 11a, 11i	3-5,7-9, 12-21, 23-31

X	WO 2010/125103 A1 (GLAXO GROUP LTD [GB]; CHAMBERS LAURA JANE [GB] ET AL.) 4 November 2010 (2010-11-04)	1,6,7, 10,11, 15,34,35
A	examples 1-8, 12, 13, 16, 17, 19, 22, 24, 25, 27-29 examples 31, 32, 34-36, 38, 40-45, 47, 48, 55-57, 68 examples 70, 81-87, 89-92, 94, 96, 99-108, 112, 115-123, 12 claims 1, 13	2-5,8,9, 12-14, 16-33

X	WO 03/106405 A1 (SUNESIS PHARMACEUTICALS INC [US]; YANG WENJIN [US] ET AL.) 24 December 2003 (2003-12-24)	1,2,6, 10,11,15
A	Several compounds in the "Final Product" column; page 227 - page 230	3-5,7-9, 12-14, 16-35

X	BESHORE D C ET AL: "Efficient synthesis of unsymmetrical 1,4-disubstituted 2,3-diketopiperazines via tandem reductive amination-cyclization", TETRAHEDRON, ELSEVIER SIENCE PUBLISHERS, AMSTERDAM, NL, vol. 41, no. 45, 1 January 2000 (2000-01-01), pages 8735-8739, XP002585828, ISSN: 0040-4020	1-6,8, 10,12, 13,15
A	The products of entries 1-7, 10, 12 and 14; table 1 Scheme 2; compound 13	7,9,11, 14,16-35

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AUBERT CORINNE ET AL: "Cobalt-Mediated [2+2+2] Cycloaddition versus C?H and N?H Activation of Pyridones and Pyrazinones with Alkynes: An Experimental Study", CHEMISTRY - A EUROPEAN JOURNAL, vol. 13, no. 26, 7 September 2007 (2007-09-07), pages 7443-7465, XP055947414, DE ISSN: 0947-6539, DOI: 10.1002/chem.200601823	1,9-11, 15
A	Scheme 19; compound 65	2-8, 12-14, 16-35

X	DOLFEN JEROEN ET AL: "LiAlH 4 -Induced Selective Ring Rearrangement of 2-(2-Cyanoethyl)aziridines toward 2-(Aminomethyl)pyrrolidines and 3-Aminopiperidines as Eligible Heterocyclic Building Blocks", CHEMISTRY - A EUROPEAN JOURNAL, vol. 22, no. 14, 24 March 2016 (2016-03-24), pages 4945-4951, XP055947514, DE ISSN: 0947-6539, DOI: 10.1002/chem.201504853 Retrieved from the Internet: URL:https://api.wiley.com/onlinelibrary/tdm/v1/articles/10.1002%2Fchem.201504853>	1,6,11, 25
A	table 3; compounds 6a, 6b, 6c	2-5, 7-10, 12-24, 26-35

X	HUSSEIN MOSTAFA A.: "Design, Synthesis, and Antimicrobial Activity, of New 1,4-disubstituted Octahydroquinoxaline-2,3-dione Derivatives", BULLETIN OF THE KOREAN CHEMICAL SOCIETY, vol. 32, no. 5, 20 May 2011 (2011-05-20), pages 1511-1518, XP055947526, KR ISSN: 0253-2964, DOI: 10.5012/bkcs.2011.32.5.1511	1,6,11, 15,26, 34,35
A	table 2; compounds 2a-2d, 2i	2-5, 7-10, 12-14, 16-25, 27-33

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHAMORRO-ARENAS DELFINO ET AL: "Selective, Catalytic, and Dual C(sp 3)-H Oxidation of Piperazines and Morpholines under Transition-Metal-Free Conditions", THE JOURNAL OF ORGANIC CHEMISTRY, vol. 83, no. 24, 21 December 2018 (2018-12-21), pages 15333-15346, XP0055947090, ISSN: 0022-3263, DOI: 10.1021/acs.joc.8b02564	1,2,6, 10,11, 13,15
A	table 1; compound 12 table 2; compounds 14a, 14b, 14g, 14i, 14p	3-5,7-9, 12,14, 16-35

X	HUSSEIN MOSTAFA ET AL: "SYNTHESIS OF SOME NEW 1,4-DISUBSTITUTED PIPERAZINE-2,3-DIONE DERIVATIVES OF POTENTIAL ANTHELMINTIC ACTIVITY", BULLETIN OF PHARMACEUTICAL SCIENCES. ASSIUT, vol. 28, no. 1, 1 June 2005 (2005-06-01), pages 37-44, XP055947420, DOI: 10.21608/bfsa.2005.64993 Retrieved from the Internet: URL:https://bpsa.journals.ekb.eg/article_64993_bdf855ffe96e110e9bfb9e91c9c6199d.pdf>	1,6,10, 11,13, 15,34,35
A	table 2; compounds 2a-2g	2-5,7-9, 12,14, 16-33

X	FRANK P. HARRINGTON ET AL: "Structure-activity relationships in a series of piperazine2,3-dione containing penicillins and cephalosporins. II. Derivatives substituted at N(4) of the piperazine ring.", THE JOURNAL OF ANTIBIOTICS, vol. 42, no. 8, 1 January 1989 (1989-01-01), pages 1241-1247, XP055277908, London ISSN: 0021-8820, DOI: 10.7164/antibiotics.42.1241	1,6, 10-12,15
A	Four compounds (see WOISA)	2-5,7-9, 13,14, 16-35

X	GB 2 056 976 A (TOYAMA CHEMICAL CO LTD) 25 March 1981 (1981-03-25)	1-6,10, 11,13, 15,32-35
A	page 10; compound 31 Compound; page 59 page 30, line 33 - line 37 claim 1	7-9,12, 14,16-31

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2022/026626

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2010/066858 A1 (INST NAT SANTE RECH MED [FR]; MOLINIER-FRENKEL VALERIE [FR] ET AL.) 17 June 2010 (2010-06-17) the whole document	1-35

A	WO 2019/185907 A1 (UNIV PARIS VAL DE MARNE [FR]; INST NAT SANTE RECH MED [FR] ET AL.) 3 October 2019 (2019-10-03) the whole document	1-35

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Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2022/026626

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010125103 A1	04-11-2010	NONE	
WO 03106405 A1	24-12-2003	AU 2003276047 A1	31-12-2003
		CA 2489095 A1	24-12-2003
		EP 1515944 A1	23-03-2005
		JP 2005529953 A	06-10-2005
		US 2004132782 A1	08-07-2004
		WO 03106405 A1	24-12-2003
GB 2056976 A	25-03-1981	CA 1131640 A	14-09-1982
		DE 3027106 A1	19-02-1981
		FR 2461705 A1	06-02-1981
		GB 2056976 A	25-03-1981
		IT 1146962 B	19-11-1986
		JP H0557272 B2	23-08-1993
		JP S5618969 A	23-02-1981
		US 4436921 A	13-03-1984
		US 4448963 A	15-05-1984
		US 4460774 A	17-07-1984
		US 4477664 A	16-10-1984
		US 4477666 A	16-10-1984
WO 2010066858 A1	17-06-2010	NONE	
WO 2019185907 A1	03-10-2019	EP 3773909 A1	17-02-2021
		US 2021023034 A1	28-01-2021
		WO 2019185907 A1	03-10-2019

Key Substances in Patent

Mark	Page #	CAS RN	Name	Structure
1	p.122	7752-78-5	Pyrimidine, 5-bromo-2-methyl-	
101	p.122	1193116-74-3	Pyrimidine, 5-bromo-2-(bromomethyl)-	
2	p.123	501-53-1	Carbonochloridic acid, phenylmethyl ester	
3	p.123	91469-55-5	3-Cyclopenten-1-amine, hydrochloride (1:1)	
102	p.123	170708-34-6	Carbamic acid, *N*-3-cyclopenten-1-yl-, phenylmethyl ester	
103	p.123	1355328-26-5	Carbamic acid, *N*-bicyclo[3.1.0]hex-3-yl-, phenylmethyl ester	
104	p.124	79531-79-6	Bicyclo[3.1.0]hexan-3-amine	
4	p.124 p.222	88139-91-7	2-Pyridinemethanol, 5-bromo-	
5	p.124	7143-01-3	Methanesulfonic acid, 1,1'-anhydride	
84	p.124 p.207	380893-61-8	2-Pyridinemethanol, 5-bromo-, 2-methanesulfonate	
6	p.125 p.142 p.205	1206968-92-4	2-Pyridinemethanol, 5-bromo-3-fluoro-	
106	p.125	866641-27-2	3-Isoxazolemethanol, 5-phenyl-, 3-methanesulfonate	

107	p.125	2857175-87-0		
7	p.126 p.217	39684-80-5	Carbamic acid, *N*-(2-bromoethyl)-, 1,1-dimethylethyl ester	
8	p.126 p.352	2857808-32-1		
9	p.126	994-89-8	Stannane, tributylethynyl-	
10	p.126	95080-93-6	Acetic acid, 2-chloro-2-(hydroxyimino)-, ethyl ester, (2*Z*)-	
108	p.126	126085-91-4	3-Isoxazolecarboxylic acid, 5-(tributylstannyl)-, ethyl ester	
98	p.127 p.218	1914946-33-0	3-Isoxazolecarboxylic acid, 5-bromo-, ethyl ester	
110	p.127	1446408-51-0	3-Isoxazolemethanol, 5-bromo-	
111	p.128	2857175-88-1	3-Isoxazolemethanol, 5-bromo-, 3-methanesulfonate	
11	p.128	3209-71-0	3-Isoxazolecarboxylic acid	
112	p.128	89102-73-8	3-Isoxazolemethanol	
113	p.128	2144668-08-4	3-Isoxazolemethanol, 3-methanesulfonate	

12	p.129	146374-27-8	2-Propanesulfinamide, 2-methyl-	
13	p.129	120-92-3	Cyclopentanone	
114	p.129	899440-18-7	2-Propanesulfinamide, *N*-cyclopentylidene-2-methyl-	
115	p.129	2857175-89-2		
116	p.130	1628753-67-2	Cyclopentan-*1-d*-amine	
14	p.130	1191-95-3	Cyclobutanone	
15	p.130 p.132 p.194 p.213	57260-73-8	Carbamic acid, *N*-(2-aminoethyl)-, 1,1-dimethylethyl ester	
117	p.130	1326311-16-3	Carbamic acid, *N*-[2-(cyclobutylamino)ethyl]-, 1,1-dimethylethyl ester	
118	p.131	2857175-90-5	Acetic acid, 2-[cyclobutyl[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]amino]-2-oxo-, methyl ester	
16	p.131	5781-53-3	Acetic acid, 2-chloro-2-oxo-, methyl ester	
119	p.131	2857175-92-7	Acetic acid, 2-[(2-aminoethyl)cyclobutylamino]-2-oxo-, methyl ester, hydrochloride (1:1)	

67	p.132 p.182 p.266	2857175-93-8	2,3-Piperazinedione, 1-cyclobutyl-	
121	p.132	383888-62-8	Carbamic acid, *N*-[2-(cyclopentylamino)ethyl]-, 1,1-dimethylethyl ester	
122	p.133	2857175-94-9	Acetic acid, 2-[cyclopentyl[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]amino]-2-oxo-, methyl ester	
123	p.133	2857175-95-0	Acetic acid, 2-[(2-aminoethyl)cyclopentylamino]-2-oxo-, methyl ester	
125	p.134	2857175-97-2		
126	p.134	2858731-78-7	2,3-Piperazinedione, 1-[1-(fluoromethyl)cyclopropyl]-	
127	p.135 p.363	2858731-82-3	1*H*-Cyclopenta[*b*]pyrazine-2,3-dione, 1-cyclobutylhexahydro-	
18	p.135	3510-66-5	Pyridine, 2-bromo-5-methyl-	
19	p.135 p.236 p.366	98-80-6	Boronic acid, *B*-phenyl-	
128	p.135	27012-22-2	Pyridine, 5-methyl-2-phenyl-	
129	p.136 p.257	212573-56-3	Pyridine, 5-(bromomethyl)-2-phenyl-	
130	p.136	126268-58-4	Pyridine, 2-(bromomethyl)-5-phenyl-	
20	p.137	139042-62-9	3-Pyridinemethanol, 6-bromo-α-methyl-	

131	p.137	1373311-13-7	3-Pyridinemethanol, α-methyl-6-phenyl-	
132	p.137	2857175-98-3	Pyridine, 5-(1-bromoethyl)-2-phenyl-	
133	p.138	2857175-99-4	Pyrazine, 2-(1-bromoethyl)-5-phenyl-	
134	p.138	1373311-26-2	Pyrazine, 2-(bromomethyl)-5-phenyl-	
135	p.138	2857176-00-0	1-Piperazineacetic acid, 4-cyclopentyl-2,3-dioxo-, 1,1-dimethylethyl ester	
22	p.139	5292-43-3	Acetic acid, 2-bromo-, 1,1-dimethylethyl ester	
136	p.139 p.301	2857176-01-1	1-Piperazineacetic acid, 4-cyclopentyl-2,3-dioxo-	
23	p.140	168267-99-0	Boronic acid, *B*-(3-fluoro-4-methylphenyl)-	
24	p.140	108-86-1	Benzene, bromo-	
137	p.140	135227-04-2	1,1'-Biphenyl, 3-fluoro-4-methyl-	
138	p.140	193013-78-4	1,1'-Biphenyl, 4-(bromomethyl)-3-fluoro-	
139	p.141 p.322	146976-19-4	Pyrimidine, 2-(bromomethyl)-5-phenyl-	
140	p.141	1227587-29-2	Pyridine, 2-(bromomethyl)-3-fluoro-5-phenyl-	
141	p.141	1227598-53-9	Pyridine, 5-(bromomethyl)-3-fluoro-2-phenyl-	
142	p.141	2857176-02-2	1,2,4-Triazine, 6-(bromomethyl)-3-phenyl-	
143	p.141	184698-47-3	Pyrimidine, 5-(bromomethyl)-2-phenyl-	

144	p.141	56059-26-8	Isothiazole, 3-(bromomethyl)-5-phenyl-	
26	p.142 p.218 p.332	121359-48-6	Thiazole, 2-(tributylstannyl)-	
145	p.142	2857175-83-6	2-Pyridinemethanol, 3-fluoro-5-(2-thiazolyl)-, 2-methanesulfonate	
27	p.142 p.199 p.318	1003-03-8	Cyclopentanamine	
146	p.142	1564718-98-4	Acetic acid, 2-(cyclopentylamino)-2-oxo-, methyl ester	
28	p.143	106-95-6	1-Propene, 3-bromo-	
147	p.143	1861500-92-6	Acetic acid, 2-(cyclopentyl-2-propen-1-ylamino)-2-oxo-, methyl ester	
148	p.143 p.327	2857176-03-3	Acetic acid, 2-[cyclopentyl(2-oxoethyl)amino]-2-oxo-, methyl ester	
149	p.144	2857176-04-4	Acetic acid, 2-[cyclobutyl(2-oxoethyl)amino]-2-oxo-, methyl ester	
150	p.144	2857176-05-5	Acetic acid, 2-[cyclobutyl(2-oxopropyl)amino]-2-oxo-, ethyl ester	
151	p.144	2858731-98-1		
75	p.144 p.197 p.198 p.199	2857176-07-7	Acetic acid, 2-[[(5-bromo-1,3,4-thiadiazol-2-yl)methyl](2-oxoethyl)amino]-2-oxo-, ethyl ester	

29	p.145 p.159 p.342	613-94-5	Benzoic acid, hydrazide	
30	p.145	15761-38-3	L-Alanine, *N*-[(1,1-dimethylethoxy)carbonyl]-	
153	p.145	1429181-99-6	Benzoic acid, 2-[2-[[(1,1-dimethylethoxy)carbonyl]amino]-1-oxopropyl]hydrazide	
154	p.145	1429182-00-2	Carbamic acid, *N*-[(1*S*)-1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethyl]-, 1,1-dimethylethyl ester	
155	p.145	1429182-01-3	1,3,4-Thiadiazole-2-methanamine, α-methyl-5-phenyl-, (α*S*)-	
156	p.146	2857176-08-8	1,3,4-Thiadiazole-2-methanamine, α-methyl-5-phenyl-, (α*R*)-	
157	p.146	933698-42-1	1,3,4-Thiadiazole-2-ethanamine, 5-phenyl-	
158	p.146	2857176-09-9	1,3,4-Thiadiazole-2-ethanamine, α-methyl-5-phenyl-	
159	p.146	2857176-10-2	1,3,4-Thiadiazole-2-ethanamine, β-methyl-5-phenyl-	
31	p.147	22433-12-1	2-Pyrimidinemethanol, 5-bromo-	
160	p.147	126230-85-1	2-Pyrimidinemethanol, 5-phenyl-	
161	p.147	147937-38-0	Pyrimidine, 2-(chloromethyl)-5-phenyl-	
32	p.148	4755-77-5	Acetic acid, 2-chloro-2-oxo-, ethyl ester	
33	p.148 p.211	2516-34-9	Cyclobutanamine	
162	p.148	722486-87-5	Acetic acid, 2-(cyclobutylamino)-2-oxo-, ethyl ester	
163	p.148	2857176-11-3	Ethanediamide, *N*[1]-cyclobutyl-*N*[2]-(2,2-dimethoxyethyl)-	

34	p.148 p.156	22483-09-6	Ethanamine, 2,2-dimethoxy-	
83	p.149 p.207	2857175-79-0	2,3-Pyrazinedione, 1-cyclobutyl-1,4-dihydro-	
53	p.149 p.156 p.169	2857175-77-8	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-	
166	p.149	2857176-12-4		
167	p.149	2097993-16-1	2,3-Pyrazinedione, 1-cyclopentyl-1,4-dihydro-	
168	p.150	2858732-14-4	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclobutyl)-	
169	p.150	2858732-18-8	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclopropyl)-	
170	p.150	2858732-19-9		
171	p.150 p.227	2858732-20-2		
172	p.150	2858732-21-3	2,3-Pyrazinedione, 1-[1-(fluoromethyl)cyclopropyl]-1,4-dihydro-	

174	p.150	1464-98-8	Benzamide, *N*-2-propyn-1-yl-	
35	p.151	98-88-4	Benzoyl chloride	
173	p.151	2450-71-7	2-Propyn-1-amine	
175	p.151	37967-82-1	1,2,4-Triazine, 6-methyl-3-phenyl-	
36	p.152	14441-90-8	3-Isoxazolecarboxylic acid, 5-phenyl-	
176	p.152	1619-37-0	3-Isoxazolemethanol, 5-phenyl-	
177	p.152	154016-50-9	Isoxazole, 3-(bromomethyl)-5-phenyl-	
37	p.153	1189169-37-6	Ethanone, 1-(5-bromo-2-pyrimidinyl)-	
178	p.153	1552931-53-9	Ethanone, 1-(5-phenyl-2-pyrimidinyl)-	
179	p.153	2857176-13-5	2-Pyrimidinemethanol, α-methyl-5-phenyl-	
180	p.154 p.265 p.266	2857175-80-3	Pyrimidine, 2-(1-bromoethyl)-5-phenyl-	
38	p.154 p.161 p.228 p.314 p.336	288-36-8	1*H*-1,2,3-Triazole	
39	p.154	2369-19-9	Pyridine, 2-fluoro-5-methyl-	
181	p.154	2857176-14-6	Pyridine, 5-methyl-2-(1*H*-1,2,3-triazol-1-yl)-	
182	p.155	2853616-56-3	Pyridine, 5-(bromomethyl)-2-(1*H*-1,2,3-triazol-1-yl)-	

40	p.155 p.198	22287-35-0	Bicyclo[1.1.1]pentan-1-amine, hydrochloride (1:1)	
183	p.155	2857176-15-7	Acetic acid, 2-(bicyclo[1.1.1]pent-1-ylamino)-2-oxo-, ethyl ester	
184	p.156	2857176-16-8	Ethanediamide, *N*[1]-bicyclo[1.1.1]pent-1-yl-*N*[2]-(2,2-dimethoxyethyl)-	
186	p.156	2857175-78-9	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-	
42	p.157	2857175-76-7	Pyridine, 5-methyl-2-(2*H*-1,2,3-triazol-2-yl)-	
187	p.157	2857176-17-9	Pyridine, 5-(bromomethyl)-2-(2*H*-1,2,3-triazol-2-yl)-	
43	p.158	105-45-3	Butanoic acid, 3-oxo-, methyl ester	
44	p.158	93-58-3	Benzoic acid, methyl ester	
188	p.158	36568-12-4	Benzenepentanoic acid, β,δ-dioxo-, methyl ester	
189	p.158	3929-70-2	3-Isoxazoleacetic acid, 5-phenyl-, ethyl ester	
190	p.158	1619-38-1	3-Isoxazoleethanol, 5-phenyl-	
191	p.159	2857176-18-0	Isoxazole, 3-(2-bromoethyl)-5-phenyl-	
45	p.159 p.176 p.342	79-04-9	Acetyl chloride, 2-chloro-	
192	p.159 p.176 p.342	50677-24-2	Benzoic acid, 2-(2-chloroacetyl)hydrazide	

193	p.160 p.176 p.342	70390-94-2	1,3,4-Thiadiazole, 2-(chloromethyl)-5-phenyl-	
194	p.160 p.327	85730-57-0	1,3,4-Thiadiazole-2-methanamine, 5-phenyl-	
48	p.161	327056-62-2	2-Pyridinecarbonitrile, 5-fluoro-	
195	p.161	2113795-24-5	2-Pyridinecarbonitrile, 5-(2*H*-1,2,3-triazol-2-yl)-	
196	p.161	2858732-23-5		
197	p.162	2858732-24-6	2-Pyridinemethanamine, 5-(2*H*-1,2,3-triazol-2-yl)-	
49	p.162 p.177	499-55-8	Benzoic acid, 3-fluoro-, hydrazide	
198	p.162	2101417-09-6	Ethanedioic acid, 1-ethyl ester, 2-[2-(3-fluorobenzoyl)hydrazide]	
199	p.163	1984038-28-9	1,3,4-Thiadiazole-2-carboxylic acid, 5-(3-fluorophenyl)-, ethyl ester	
200	p.163	2162667-40-3	1,3,4-Thiadiazole-2-methanol, 5-(3-fluorophenyl)-	
201	p.164	2857176-20-4	1,3,4-Thiadiazole-2-methanol, 5-(3-fluorophenyl)-, 2-methanesulfonate	
50	p.164	622-31-1	Benzaldehyde, oxime, [*C*(*E*)]-	
202	p.164	934-16-7	Benzenecarboximidoyl chloride, *N*-hydroxy-, [*C*(*Z*)]-	
95	p.165 p.216	90924-12-2	5-Isoxazolemethanol, 3-phenyl-	
204	p.165	188877-91-0	5-Isoxazolemethanol, 3-phenyl-, 5-methanesulfonate	
205	p.166	1643437-13-1	5-Isoxazolemethanol, 3-(2-fluorophenyl)-, 5-methanesulfonate	
206	p.166	937189-03-2	5-Isoxazolemethanol, 3-(4-fluorophenyl)-, 5-methanesulfonate	

207	p.166	2857176-21-5	5-Isoxazolemethanol, 3-(3-fluorophenyl)-, 5-methanesulfonate	
208	p.166 p.226	1380649-05-7	5-Isoxazolemethanol, 3-(2-pyridinyl)-, 5-methanesulfonate	
51	p.167	1134-50-5	1*H*-Pyrazole-4-carboxylic acid, 1-phenyl-	
209	p.167	70817-26-4	1*H*-Pyrazole-4-methanol, 1-phenyl-	
210	p.167	153863-63-9	1*H*-Pyrazole, 4-(bromomethyl)-1-phenyl-	
52	p.168	13363-44-5	Isothiazole, 5-bromo-3-phenyl-	
211	p.168	13369-71-6	Isothiazole, 5-methyl-3-phenyl-	
212	p.168	2102086-01-9	Isothiazole, 5-(bromomethyl)-3-phenyl-	
213	p.169	2857176-22-6	2,3-Piperazinedione, 1-(1-methylcyclobutyl)-	
54	p.170	5071-61-4	1*H*-Pyrazole-3-carboxylic acid, 5-phenyl-	
215	p.170	179057-19-3	1*H*-Pyrazole-3-methanol, 5-phenyl-	
216	p.170	2459929-68-9	1*H*-Pyrazole, 3-(bromomethyl)-5-phenyl-	
55	p.171	1945-84-2	Pyridine, 2-ethynyl-	
56	p.171 p.230	861135-87-7	Acetic acid, 2-chloro-2-(hydroxyimino)-, ethyl ester, (2*E*)-	
217	p.171	893638-49-8	3-Isoxazolecarboxylic acid, 5-(2-pyridinyl)-, ethyl ester	
218	p.171 p.229	369382-27-4	3-Isoxazolemethanol, 5-(2-pyridinyl)-	

219	p.172 p.269	2387133-77-7	3-Isoxazolemethanol, 5-(2-pyridinyl)-, 3-methanesulfonate	
220	p.172	2386369-63-5	3-Isoxazolemethanol, 5-(3-pyridinyl)-, 3-methanesulfonate	
57	p.173 p.201 p.228	1121-79-5	Pyridazine, 3-chloro-6-methyl-	
221	p.173 p.201	41398-19-0	Pyridazine, 3-methyl-6-phenyl-	
91	p.173 p.201 p.213 p.268 p.363	2857175-82-5	Pyridazine, 3-(chloromethyl)-6-phenyl-	
223	p.174	2858732-25-7	Pyridazine, 3-(chloromethyl)-6-(2-fluorophenyl)-	
224	p.174	1405127-63-0	Pyridazine, 3-(chloromethyl)-6-(2,6-difluorophenyl)-	
225	p.174	2858732-26-8	Pyridazine, 3-(chloromethyl)-6-(5-thiazolyl)-	
226	p.174	1405128-14-4	Pyridazine, 3-(chloromethyl)-6-(2-pyridinyl)-	
227	p.174	2858732-27-9	Pyridazine, 3-(chloromethyl)-6-(3-pyridinyl)-	
58	p.175 p.233	3430-13-5	Pyridine, 5-bromo-2-methyl-	
59	p.175 p.233	288-35-7	2*H*-1,2,3-Triazole	
228	p.175	1884570-65-3	Pyridine, 2-methyl-5-(2*H*-1,2,3-triazol-2-yl)-	
229	p.175	2857175-81-4		
232	p.177	1221289-99-1	1,3,4-Thiadiazole, 2-(chloromethyl)-5-(2-chlorophenyl)-	
233	p.177	851983-39-6	1,3,4-Thiadiazole, 2-(chloromethyl)-5-(2-fluorophenyl)-	

234	p.177	905118-28-7	Benzoic acid, 3-fluoro-, 2-(2-chloroacetyl)hydrazide	
235	p.178 p.235	1495521-21-5	1,3,4-Thiadiazole, 2-(chloromethyl)-5-(3-fluorophenyl)-	
62	p.178	83249-04-1	Bicyclo[1.1.1]pentane-1-carboxylic acid, 3-phenyl-	
236	p.178	2165347-55-5	Bicyclo[1.1.1]pentane-1-methanol, 3-phenyl-	
63	p.179	98-59-9	Benzenesulfonyl chloride, 4-methyl-	
237	p.179	2489274-18-0	Bicyclo[1.1.1]pentane-1-methanol, 3-phenyl-, 1-(4-methylbenzenesulfonate)	
65	p.179 p.182	120276-59-7	Pyridazine, 3-chloro-6-(chloromethyl)-	
238	p.179	2857176-23-7	2,3-Piperazinedione, 1-[(6-chloro-3-pyridazinyl)methyl]-4-cyclopentyl-	
240	p.180	2857176-25-9	2,3-Piperazinedione, 1-[(4-bromo-2-fluorophenyl)methyl]-4-cyclopentyl-	
241	p.180 p.190	2857176-26-0	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[(6-chloro-3-pyridazinyl)methyl]-1,4-dihydro-	
242	p.180	2857176-27-1	2,3-Pyrazinedione, 1-[(6-chloro-3-pyridazinyl)methyl]-4-cyclobutyl-1,4-dihydro-	
243	p.180	2857176-28-2	2,3-Piperazinedione, 1-[(4-bromophenyl)methyl]-4-cyclobutyl-	
244	p.181	2857176-29-3	2,3-Piperazinedione, 1-[(5-bromo-3-fluoro-2-pyridinyl)methyl]-4-cyclobutyl-	
245	p.181	2857176-30-6	2,3-Piperazinedione, 1-[(5-chloro-2-pyrazinyl)methyl]-4-cyclobutyl-	
246	p.181	2857176-31-7	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[(6-chloro-3-pyridazinyl)methyl]-	

247	p.181	2857176-32-8		
248	p.181	2857176-33-9		
249	p.181	2857176-34-0	2,3-Piperazinedione, 1-[(5-chloro-2-pyrazinyl)methyl]-4-cyclopentyl-	
250	p.182	2857176-35-1		
251	p.182	2857176-36-2		
252	p.182	2857176-37-3	2,3-Pyrazinedione, 1-[(6-chloro-3-pyridazinyl)methyl]-4-cyclopentyl-1,4-dihydro-	
253	p.182	2857176-38-4	2,3-Piperazinedione, 1-[(6-chloro-3-pyridazinyl)methyl]-4-cyclobutyl-	
254	p.183 p.318	2857176-39-5	2,3-Piperazinedione, 1-[(6-chloro-3-pyridinyl)methyl]-4-cyclopentyl-	
255	p.184 p.310	2857176-40-8	2,3-Piperazinedione, 1-[(5-chloro-1,3,4-thiadiazol-2-yl)methyl]-4-cyclopentyl-	
256	p.184	2857176-41-9	2,3-Piperazinedione, 1-[(6-chloro-3-pyridazinyl)methyl]-4-(3-phenylcyclobutyl)-	
257	p.184	2857176-42-0	2,3-Piperazinedione, 1-[(5-bromo-3-fluoro-2-pyridinyl)methyl]-4-cyclopentyl-	
258	p.184	2857176-43-1	2,3-Piperazinedione, 1-[(5-bromo-2-pyridinyl)methyl]-4-cyclopentyl-	
259	p.184	2857176-44-2	2,3-Piperazinedione, 1-[(5-bromo-2-pyridinyl)methyl]-4-cyclobutyl-	

260	p.184	2857176-45-3	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[(4-bromophenyl)methyl]-	
261	p.185	2857176-46-4	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[(4-bromo-2-fluorophenyl)methyl]-	
262	p.185	2857176-47-5		
263	p.185	2857176-48-6		
264	p.185	2857176-49-7	2,3-Pyrazinedione, 1-[(5-bromo-3-isoxazolyl)methyl]-4-cyclobutyl-1,4-dihydro-	
265	p.185	2857176-50-0	2,3-Piperazinedione, 1-[(5-bromo-3-isoxazolyl)methyl]-4-cyclopentyl-	
266	p.185	2857176-51-1	2,3-Pyrazinedione, 1-[(5-bromo-3-isoxazolyl)methyl]-4-cyclopentyl-1,4-dihydro-	
267	p.186	2857176-52-2		
268	p.186	2857176-53-3		
269	p.186	2857176-54-4	2,3-Piperazinedione, 1-[(5-bromo-2-thiazolyl)methyl]-4-cyclobutyl-	
270	p.186	2857176-55-5	2,3-Piperazinedione, 1-[(2-bromo-5-thiazolyl)methyl]-4-cyclobutyl-	
271	p.186	2857176-56-6	2,3-Pyrazinedione, 1-[(6-bromo-3-pyridinyl)methyl]-4-cyclobutyl-1,4-dihydro-	
272	p.186	2857176-57-7	2,3-Pyrazinedione, 1-[(5-chloro-2-pyrazinyl)methyl]-4-cyclobutyl-1,4-dihydro-	

273	p.187	2857176-58-8		
274	p.187	2857176-59-9		
275	p.187	2857176-60-2		
276	p.187 p.354	2857176-61-3	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-(3-isoxazolylmethyl)-	
277	p.187	2858732-28-0	2,3-Piperazinedione, 1-cyclobutyl-4-(2-thiazolylmethyl)-	
278	p.187	2858732-29-1	2,3-Pyrazinedione, 1,4-dihydro-1-(3-isoxazolylmethyl)-4-(1-methylcyclobutyl)-	
279	p.188	2858732-30-4	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-(3-isoxazolylmethyl)-	
280	p.188 p.358	2858732-31-5	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-(2-propyn-1-yl)-	
281	p.188	2858732-32-6	2,3-Pyrazinedione, 1-[(5-bromo-2-pyridinyl)methyl]-1,4-dihydro-4-(1-methylcyclopropyl)-	
282	p.188	2858732-33-7		
283	p.188	2858732-34-8	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclopropyl)-4-(2-propyn-1-yl)-	
284	p.189	2858732-35-9	2,3-Pyrazinedione, 1-[(6-chloro-3-pyridazinyl)methyl]-1,4-dihydro-4-(1-methylcyclopropyl)-	

285	p.189	2858732-36-0		
286	p.189	2858732-37-1		
287	p.189	2858732-38-2	2,3-Pyrazinedione, 1-[(6-bromo-3-pyridinyl)methyl]-1,4-dihydro-4-(1-methylcyclopropyl)-	
288	p.189	2858732-39-3		
289	p.190	2858732-40-6		
291	p.190	2858732-41-7		
68	p.190	38275-57-9	2-Pyrimidinecarbonitrile, 5-bromo-	
292	p.190	85386-18-1	2-Pyrimidinecarbonitrile, 5-phenyl-	
293	p.191	944903-70-2	2-Pyrimidinemethanamine, 5-phenyl-	
294	p.191	2857176-63-5	Acetic acid, 2-oxo-2-[[(5-phenyl-2-pyrimidinyl)methyl]amino]-, ethyl ester	
295	p.192	2857176-64-6	Acetic acid, 2-oxo-2-[[(5-phenyl-2-pyrimidinyl)methyl]-2-propen-1-ylamino]-, ethyl ester	
296	p.192 p.303 p.318 p.325 p.326	2857175-85-8	Acetic acid, 2-oxo-2-[(2-oxoethyl)[(5-phenyl-2-pyrimidinyl)methyl]amino]-, ethyl ester	
297	p.193 p.343 p.368	2857176-65-7	Acetic acid, 2-oxo-2-[(2-oxoethyl)[(5-phenyl-1,3,4-thiadiazol-2-yl)methyl]amino]-, ethyl ester	

69	p.193	73183-34-3	2,2'-Bi-1,3,2-dioxaborolane, 4,4,4',4',5,5,5',5'-octamethyl-	
298	p.193	2857176-66-8	2,3-Piperazinedione, 1-cyclopentyl-4-[[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyrimidinyl]methyl]-	
70	p.193	2857176-24-8	2,3-Piperazinedione, 1-[(5-bromo-2-pyrimidinyl)methyl]-4-cyclopentyl-	
71	p.194	52784-31-3	Cyclobutanone, 3-phenyl-	
299	p.194	2857176-67-9		
300	p.195	2857176-69-1		
301	p.195	2857176-73-7		
305	p.195	2857176-71-5		
314	p.195	2857176-72-6		
73	p.196	54044-79-0	1,3,4-Thiadiazole, 2-bromo-5-methyl-	
302	p.196	1454906-50-3	1,3,4-Thiadiazole, 2-bromo-5-(bromomethyl)-	
74	p.196 p.202 p.342	107-11-9	2-Propen-1-amine	
303	p.196	2857176-75-9	1,3,4-Thiadiazole-2-methanamine, 5-bromo-*N*-2-propen-1-yl-	
315	p.196	2857176-74-8	2,3-Piperazinedione, 1-(*trans*-3-phenylcyclobutyl)-	
304	p.197	2857176-76-0	Acetic acid, 2-[[(5-bromo-1,3,4-thiadiazol-2-yl)methyl]-2-propen-1-ylamino]-2-oxo-, ethyl ester	
306	p.198	2857176-77-1	2,3-Piperazinedione, 1-[(5-bromo-1,3,4-thiadiazol-2-yl)methyl]-4-cyclobutyl-	

307	p.198	2857176-79-3		
1160	p.198	2857176-78-2	2,3-Pyrazinedione, 1-[(5-bromo-1,3,4-thiadiazol-2-yl)methyl]-4-cyclobutyl-1,4-dihydro-	
308	p.199	2858732-42-8		
309	p.199	2858732-43-9	2,3-Pyrazinedione, 1-[(5-bromo-1,3,4-thiadiazol-2-yl)methyl]-4-cyclopentyl-1,4-dihydro-	
310	p.200	2857176-81-7		
311	p.200	2857176-82-8	2,3-Pyrazinedione, 1-[(5-bromo-1,3,4-thiadiazol-2-yl)methyl]-1,4-dihydro-4-(*trans*-3-phenylcyclobutyl)-	
312	p.200	2857176-83-9		
313	p.200	2858732-44-0	2,3-Pyrazinedione, 1-[(5-bromo-1,3,4-thiadiazol-2-yl)methyl]-1,4-dihydro-4-(1-methylcyclobutyl)-	
316	p.202	2857176-84-0	3-Pyridazinemethanamine, 6-phenyl-*N*-2-propen-1-yl-	
317	p.202	2857176-85-1	Acetic acid, 2-oxo-2-[[(6-phenyl-3-pyridazinyl)methyl]-2-propen-1-ylamino]-, ethyl ester	
318	p.203	2857176-86-2		
319	p.203	2857176-87-3		
320	p.204	2857176-88-4	2,3-Piperazinedione, 1-[(6-chloro-3-pyridazinyl)methyl]-4-(*trans*-3-phenylcyclobutyl)-	
321	p.204	2857176-89-5		

322	p.205	1227586-42-6	Pyridine, 5-bromo-2-(bromomethyl)-3-fluoro-	
323	p.205	2857176-90-8	Acetic acid, 2-[[(5-bromo-3-fluoro-2-pyridinyl)methyl]-2-propen-1-ylamino]-2-oxo-, ethyl ester	
82	p.205	52781-10-9	Acetic acid, 2-oxo-2-(2-propen-1-ylamino)-, ethyl ester	
324	p.206	2857176-91-9	Acetic acid, 2-[[(5-bromo-3-fluoro-2-pyridinyl)methyl](2-oxoethyl)amino]-2-oxo-, ethyl ester	
325	p.206	2857176-92-0		
326	p.207	2857175-86-9	2,3-Pyrazinedione, 1-[(5-bromo-2-pyridinyl)methyl]-4-cyclobutyl-1,4-dihydro-	
85	p.207	94128-94-6	1*H*-Imidazole-4-methanol, 1-phenyl-	
327	p.207	1314935-79-9	1*H*-Imidazole, 4-(chloromethyl)-1-phenyl-	
86	p.208	3430-14-6	3-Pyridinamine, 6-methyl-	
328	p.208	186199-18-8	3-Pyridinediazonium, 6-methyl-, tetrafluoroborate(1-) (1:1)	
329	p.208	2858732-45-1	Pyridine, 2-methyl-5-(2*H*-tetrazol-2-yl)-	
330	p.209	2858732-46-2		
87	p.209	83249-10-9	Bicyclo[1.1.1]pentane-1,3-dicarboxylic acid, 1-methyl ester	
88	p.209	75-91-2	Hydroperoxide, 1,1-dimethylethyl	

331	p.209	131515-58-7	Bicyclo[1.1.1]pentane-1-carboxylic acid, 3-[[(1,1-dimethylethyl)dioxy]carbonyl]-, methyl ester	
332	p.210	2756616-23-4	Bicyclo[1.1.1]pentane-1-carboxylic acid, 3-(2-pyridinyl)-, methyl ester	
333	p.210 p.210	2858732-47-3	Bicyclo[1.1.1]pentane-1-methanol, 3-(2-pyridinyl)-	
90	p.211	170384-29-9	Carbamic acid, *N*-(2-oxopropyl)-, 1,1-dimethylethyl ester	
335	p.211	1692292-30-0	Carbamic acid, *N*-[2-(cyclobutylamino)propyl]-, 1,1-dimethylethyl ester	
336	p.211	2858732-48-4		
337	p.212	2858732-49-5	Acetic acid, 2-[(2-amino-1-methylethyl)cyclobutylamino]-2-oxo-, ethyl ester	
338	p.212	2858732-50-8	2,3-Piperazinedione, 1-cyclobutyl-6-methyl-, (6*R*)-	
339	p.212	2858732-51-9	2,3-Piperazinedione, 1-cyclobutyl-6-methyl-, (6*S*)-	
340	p.213	2858732-52-0		
341	p.214	2858732-53-1	Acetic acid, 2-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl][(6-phenyl-3-pyridazinyl)methyl]amino]-2-oxo-, ethyl ester	
342	p.214	2858732-54-2	Acetic acid, 2-[(2-aminoethyl)[(6-phenyl-3-pyridazinyl)methyl]amino]-2-oxo-, ethyl ester	
343	p.215 p.360	2858732-55-3	2,3-Piperazinedione, 1-[(6-phenyl-3-pyridazinyl)methyl]-	
344	p.215 p.361	2858732-56-4	2,3-Piperazinedione, 1-[[6-(2-fluorophenyl)-3-pyridazinyl]methyl]-	

93	p.216	22990-77-8	2-Piperidinemethanamine	
94	p.216	95-92-1	Ethanedioic acid, 1,2-diethyl ester	
345	p.216	2758-82-9	2*H*-Pyrido[1,2-*a*]pyrazine-3,4-dione, hexahydro-	
346	p.216	1011-37-6	Isoxazole, 5-(chloromethyl)-3-phenyl-	
347	p.217	2858732-57-5		
96	p.217	102781-57-7	Bicyclo[2.1.1]hexan-2-amine, hydrochloride (1:1)	
348	p.217	2858732-59-7	1,2-Ethanediamine, *N*1-bicyclo[2.1.1]hex-2-yl-, hydrochloride (1:1)	
349	p.217	2858732-60-0		
350	p.218	2740652-63-3	3-Isoxazolecarboxylic acid, 5-(2-thiazolyl)-, ethyl ester	
351	p.218	1508666-02-1	3-Isoxazolemethanol, 5-(2-thiazolyl)-	
352	p.219	2858732-61-1	3-Isoxazolemethanol, 5-(2-thiazolyl)-, 3-methanesulfonate	
353	p.219	2381247-98-7	Bicyclo[1.1.1]pentane-1-methanol, 2,2-difluoro-3-phenyl-	
100	p.219	2309454-98-4	Bicyclo[1.1.1]pentane-1-carboxylic acid, 2,2-difluoro-3-phenyl-	
354	p.220	2825007-11-0		

701	p.220	109-09-1	Pyridine, 2-chloro-	
355	p.220 p.231 p.358	39910-65-1	Pyridine, 2-azido-	
356	p.220	10296-29-4	Pyridine, 3-azido-	
702	p.221	65202-58-6	Pyridazine, 3-bromo-6-methyl-	
357	p.221	1405127-65-2	Pyridazine, 3-methyl-6-(2-thiazolyl)-	
358	p.221	1405127-66-3	Pyridazine, 3-(chloromethyl)-6-(2-thiazolyl)-	
704	p.222 p.223	288-13-1	1*H*-Pyrazole	
359	p.222	2144244-16-4	2-Pyridinemethanol, 5-(1*H*-pyrazol-1-yl)-	
360	p.222	1256812-78-8	Pyridine, 2-(chloromethyl)-5-(1*H*-pyrazol-1-yl)-	
361	p.223	1854085-39-4	Pyridine, 5-(chloromethyl)-2-(2*H*-1,2,3-triazol-2-yl)-	
705	p.223	21543-49-7	3-Pyridinemethanol, 6-chloro-	
362	p.223	748796-38-5	3-Pyridinemethanol, 6-(1*H*-pyrazol-1-yl)-	
363	p.224	748796-39-6	Pyridine, 5-(chloromethyl)-2-(1*H*-pyrazol-1-yl)-	
364	p.224	1854085-41-8	Pyridine, 5-(chloromethyl)-2-(1*H*-1,2,3-triazol-1-yl)-	
365	p.224	1193-92-6	3-Pyridinecarboxaldehyde, oxime	
707	p.225	500-22-1	3-Pyridinecarboxaldehyde	

366	p.225	35447-76-8	3-Pyridinecarboximidoyl chloride, *N*-hydroxy-	
367	p.225	158840-79-0	5-Isoxazolemethanol, 3-(3-pyridinyl)-	
708	p.225	107-19-7	2-Propyn-1-ol	
368	p.226	2858732-62-2	5-Isoxazolemethanol, 3-(3-pyridinyl)-, 5-methanesulfonate	
370	p.227	2858732-63-3	2,3-Piperazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-	
710	p.227	1078575-71-9	2-Pyridinemethanol, 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-	
711	p.227	109-04-6	Pyridine, 2-bromo-	
371	p.227 p.231	1934924-22-7	[2,3'-Bipyridine]-6'-methanol	
372	p.228	1935509-06-0	2,3'-Bipyridine, 6'-(chloromethyl)-	
373	p.228	30597-95-6	Pyridazine, 3-methyl-6-(1*H*-1,2,3-triazol-1-yl)-	
374	p.229	2858732-64-4	Pyridazine, 3-(chloromethyl)-6-(1*H*-1,2,3-triazol-1-yl)-	
375	p.229	1013634-98-4	Pyridine, 2-[3-(chloromethyl)-5-isoxazolyl]-	
715	p.230	2510-23-8	Pyridine, 3-ethynyl-	
376	p.230	215870-77-2	3-Isoxazolecarboxylic acid, 5-(3-pyridinyl)-, ethyl ester	
377	p.230	372152-48-2	3-Isoxazolemethanol, 5-(3-pyridinyl)-	
378	p.230	1009562-98-4	Pyridine, 3-[3-(chloromethyl)-5-isoxazolyl]-	
379	p.231	2858732-65-5	[2,3'-Bipyridine]-6'-methanol, 6'-methanesulfonate	

718	p.231	922-67-8	2-Propynoic acid, methyl ester	
380	p.231	23947-14-0	1*H*-1,2,3-Triazole-4-carboxylic acid, 1-(2-pyridinyl)-, methyl ester	
381	p.232	1043389-28-1	1*H*-1,2,3-Triazole-4-methanol, 1-(2-pyridinyl)-	
382	p.232	2518596-62-6	Pyridine, 2-[4-(chloromethyl)-1*H*-1,2,3-triazol-1-yl]-	
383	p.233	2858732-66-6	Pyridine, 2-methyl-5-(1*H*-1,2,3-triazol-1-yl)-	
384	p.233	2858732-67-7	Pyridine, 2-methyl-5-(1*H*-1,2,3-triazol-1-yl)-, 1-oxide	
385	p.234	2858732-68-8	2-Pyridinemethanol, 5-(1*H*-1,2,3-triazol-1-yl)-	
386	p.234	2858732-69-9	Pyridine, 2-(chloromethyl)-5-(1*H*-1,2,3-triazol-1-yl)-	
401	p.234 p.394	2857177-06-9	2,3-Piperazinedione, 1-cyclobutyl-4-[[6-(2-fluorophenyl)-3-pyridazinyl]methyl]-	
722	p.235	1993-03-9	Boronic acid, *B*-(2-fluorophenyl)-	
402	p.235 p.397	2857177-07-0	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-	
403	p.236 p.389	2857177-08-1		
404	p.237 p.390	2857177-09-2		
405	p.237 p.390	2857177-10-5	2,3-Piperazinedione, 1-cyclopentyl-4-[[5-(5-thiazolyl)-2-pyrimidinyl]methyl]-	
406	p.237 p.390	2857177-11-6	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(5-oxazolyl)-3-pyridazinyl]methyl]-	

407	p.237 p.390	2857177-12-7		
408	p.237 p.391	2857177-13-8	2,3-Piperazinedione, 1-cyclopentyl-4-[[5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-	
409	p.238 p.391	2857177-14-9	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(2-fluorophenyl)-3-pyridazinyl]methyl]-	
410	p.238 p.391	2857177-15-0	2,3-Piperazinedione, 1-cyclopentyl-4-[[3-fluoro-5-(5-thiazolyl)-2-pyridinyl]methyl]-	
411	p.238 p.391	2857177-16-1	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(5-thiazolyl)-3-pyridazinyl]methyl]-	
412	p.238 p.392	2857177-17-2		
413	p.238 p.392	2857177-18-3	2,3-Piperazinedione, 1-cyclopentyl-4-[[5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-	
414	p.239 p.392	2857177-19-4	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(3-fluorophenyl)-3-pyridazinyl]methyl]-	
415	p.239 p.392	2857177-20-7	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(1*H*-pyrazol-4-yl)-3-pyridazinyl]methyl]-	
416	p.239 p.393	2857177-21-8	2,3-Piperazinedione, 1-cyclopentyl-4-[[3-fluoro-5-(1*H*-pyrazol-4-yl)-2-pyridinyl]methyl]-	
417	p.239 p.393	2857177-22-9	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(5-thiazolyl)-3-pyridinyl]methyl]-	
418	p.239 p.393	2857177-23-0	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(5-oxazolyl)-3-pyridinyl]methyl]-	
419	p.240 p.393	2857177-24-1		
420	p.240 p.394	2857177-25-2	2,3-Piperazinedione, 1-cyclobutyl-4-[[6-(3-fluorophenyl)-3-pyridazinyl]methyl]-	
421	p.240 p.394	2857177-26-3	2,3-Piperazinedione, 1-cyclobutyl-4-[[6-(2,3-difluorophenyl)-3-pyridazinyl]methyl]-	

422	p.240 p.395	2857177-27-4	2,3-Piperazinedione, 1-cyclobutyl-4-[[6-(3,5-difluorophenyl)-3-pyridazinyl]methyl]-	
423	p.240 p.395	2857177-28-5	2,3-Piperazinedione, 1-cyclopentyl-4-[[2-fluoro-4-(1*H*-pyrazol-4-yl)phenyl]methyl]-	
424	p.241 p.395	2857177-29-6	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(1*H*-pyrazol-4-yl)-3-pyridinyl]methyl]-	
425	p.241 p.395	2857177-30-9	2,3-Piperazinedione, 1-cyclobutyl-4-[[6-(1*H*-pyrazol-4-yl)-3-pyridazinyl]methyl]-	
426	p.241 p.396	2857177-31-0		
427	p.241 p.396	2857177-32-1	2,3-Piperazinedione, 1-cyclobutyl-4-[[5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-	
428	p.241 p.396	2857177-33-2	2,3-Pyrazinedione, 1-cyclobutyl-4-[[5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-1,4-dihydro-	
429	p.242 p.396	2857177-34-3	2,3-Piperazinedione, 1-cyclobutyl-4-[[5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-	
430	p.242 p.397	2857177-35-4	2,3-Pyrazinedione, 1-cyclobutyl-4-[[5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-1,4-dihydro-	
431	p.242 p.397	2857177-36-5	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-	
432	p.242 p.397	2857177-37-6	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-	
433	p.242 p.398	2857177-38-7	2,3-Piperazinedione, 1-cyclobutyl-4-[[5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-	
434	p.243 p.398	2857177-39-8	2,3-Pyrazinedione, 1-cyclobutyl-4-[[5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-1,4-dihydro-	
435	p.243 p.398	2857177-40-1	2,3-Pyrazinedione, 1-cyclopentyl-4-[[5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-1,4-dihydro-	
436	p.243 p.398	2857177-41-2	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-1,4-dihydro-	
437	p.243 p.399	2857177-42-3	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(3-pyridinyl)-3-pyridazinyl]methyl]-	

438	p.243 p.399	2857177-43-4		
439	p.244 p.399	2857177-44-5		
440	p.244 p.399	2857177-45-6		
441	p.244 p.400	2857177-46-7		
442	p.244 p.400	2857177-47-8		
443	p.245 p.400	2857177-48-9		
444	p.245 p.400	2857177-49-0		
445	p.245 p.401	2857177-50-3		
446	p.245 p.401	2857177-51-4	2,3-Piperazinedione, 1-cyclopentyl-4-[[5-(2-fluorophenyl)-2-pyrazinyl]methyl]-	
447	p.246 p.401	2857177-52-5		
448	p.246 p.401	2857177-53-6		
449	p.246 p.402	2857177-54-7	2,3-Pyrazinedione, 1-cyclobutyl-4-[[6-(2-fluorophenyl)-3-pyridazinyl]methyl]-1,4-dihydro-	
450	p.246 p.402	2857177-55-8		
451	p.247 p.402	2857177-56-9		

452	p.247 p.402	2857177-57-0		
453	p.247 p.403	2857177-58-1	2,3-Pyrazinedione, 1-cyclopentyl-4-[[6-(2-fluorophenyl)-3-pyridazinyl]methyl]-1,4-dihydro-	
454	p.247 p.403	2857177-59-2	2,3-Pyrazinedione, 1-cyclobutyl-4-[[5-(3-fluorophenyl)-3-isoxazolyl]methyl]-1,4-dihydro-	
455	p.247 p.403	2857177-60-5	2,3-Pyrazinedione, 1-cyclobutyl-4-[[5-(4-fluorophenyl)-3-isoxazolyl]methyl]-1,4-dihydro-	
456	p.248 p.403	2857177-61-6	2,3-Pyrazinedione, 1-cyclobutyl-1,4-dihydro-4-[(5-phenyl-3-isoxazolyl)methyl]-	
457	p.248 p.404	2857177-62-7	2,3-Pyrazinedione, 1-cyclobutyl-4-[[5-(2-fluorophenyl)-3-isoxazolyl]methyl]-1,4-dihydro-	
458	p.248 p.404	2857177-63-8		
459	p.248 p.404	2857177-64-9	2,3-Pyrazinedione, 1-cyclopentyl-4-[[6-(3-fluorophenyl)-3-pyridazinyl]methyl]-1,4-dihydro-	
460	p.248 p.404	2857177-65-0		
461	p.249 p.405	2857177-66-1	2,3-Pyrazinedione, 1-cyclopentyl-4-[[5-(2-fluorophenyl)-3-isoxazolyl]methyl]-1,4-dihydro-	
463	p.249 p.405	2857177-67-2	2,3-Pyrazinedione, 1-cyclobutyl-4-[[6-(3-fluorophenyl)-3-pyridazinyl]methyl]-1,4-dihydro-	
464	p.249 p.405	2857177-68-3	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[6-(3-fluorophenyl)-3-pyridazinyl]methyl]-1,4-dihydro-	
465	p.249 p.406	2857177-69-4	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[6-(3-fluorophenyl)-3-pyridazinyl]methyl]-	
466	p.250 p.406	2857177-70-7	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[6-(2-fluorophenyl)-3-pyridazinyl]methyl]-	
467	p.250 p.406	2857177-71-8		
468	p.250 p.406	2857177-72-9	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-1,4-dihydro-	

469	p.250 p.407	2857179-85-0		
470	p.250 p.407	2857177-74-1	2,3-Piperazinedione, 1-cyclobutyl-4-[(2-phenyl-5-thiazolyl)methyl]-	
471	p.251 p.407	2857177-75-2	2,3-Pyrazinedione, 1-cyclobutyl-4-[[6-(2,3-difluorophenyl)-3-pyridazinyl]methyl]-1,4-dihydro-	
472	p.251 p.407	2857177-76-3	2,3-Pyrazinedione, 1-cyclobutyl-4-[[6-(2-fluorophenyl)-3-pyridinyl]methyl]-1,4-dihydro-	
473	p.251 p.408	2857177-77-4	2,3-Piperazinedione, 1-cyclobutyl-4-[[5-(2-fluorophenyl)-2-pyrazinyl]methyl]-	
474	p.251 p.408	2857177-78-5	2,3-Pyrazinedione, 1-cyclobutyl-4-[[5-(2-fluorophenyl)-2-pyrazinyl]methyl]-1,4-dihydro-	
475	p.251 p.408	2857177-79-6	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[5-(2-fluorophenyl)-2-pyrazinyl]methyl]-1,4-dihydro-	
476	p.252 p.408	2857177-80-9		
477	p.252 p.409	2857177-81-0	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[5-(2-fluorophenyl)-3-isoxazolyl]methyl]-1,4-dihydro-	
478	p.252 p.409	2857177-82-1	2,3-Piperazinedione, 1-cyclobutyl-4-[[2-(2-fluorophenyl)-5-thiazolyl]methyl]-	
479	p.252 p.409	2857177-83-2	2,3-Piperazinedione, 1-cyclobutyl-4-[[2-(3-fluorophenyl)-5-thiazolyl]methyl]-	
480	p.252 p.409	2857177-84-3		
481	p.253 p.424	2858732-70-2	2,3-Piperazinedione, 1-[[6-(5-bromo-2-fluorophenyl)-3-pyridazinyl]methyl]-4-cyclobutyl-	
482	p.253 p.424	2858732-71-3	2,3-Pyrazinedione, 1-[[5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-1,4-dihydro-4-(1-methylcyclobutyl)-	
483	p.253 p.424	2858732-72-4	2,3-Pyrazinedione, 1-[[5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-1,4-dihydro-4-(1-methylcyclobutyl)-	

484	p.253 p.424	2858732-73-5	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[5-(2-methylphenyl)-1,3,4-thiadiazol-2-yl]methyl]-	
485	p.253 p.425	2858732-74-6	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-[[6-(3-pyridinyl)-3-pyridazinyl]methyl]-	
486	p.254 p.425	2858732-75-7		
487	p.254 p.425	2858732-76-8	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclopropyl)-4-[[6-(2-pyridinyl)-3-pyridazinyl]methyl]-	
488	p.254 p.425	2858732-77-9	2,3-Pyrazinedione, 1-([2,3'-bipyridin]-6'-ylmethyl)-1,4-dihydro-4-(1-methylcyclopropyl)-	
489	p.254 p.425	2858732-78-0		
490	p.254 p.426	2858732-79-1	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclopropyl)-4-[[6-(3-pyridinyl)-3-pyridazinyl]methyl]-	
491	p.254 p.426	2858732-80-4		
492	p.255 p.426	2858732-81-5		
493	p.255 p.426	2858732-82-6	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-[[6-(2-pyridinyl)-3-pyridazinyl]methyl]-	
494	p.255 p.427	2858732-83-7	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclopropyl)-4-[[6-(5-thiazolyl)-3-pyridazinyl]methyl]-	
495	p.255 p.427	2858732-84-8	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-[[6-(5-thiazolyl)-3-pyridazinyl]methyl]-	
496	p.256 p.409	2857177-85-4		
497	p.256 p.410	2857177-86-5		

498	p.257 p.297 p.410	2857176-93-1		
499	p.258 p.410	2857177-87-6		
500	p.258 p.410	2857177-88-7	2,3-Piperazinedione, 1-cyclopentyl-4-[1-(6-phenyl-3-pyridinyl)ethyl]-	
501	p.258 p.411	2857177-89-8	2,3-Piperazinedione, 1-cyclopentyl-4-[(3-fluoro[1,1'-biphenyl]-4-yl)methyl]-	
502	p.258 p.411	2857177-90-1	2,3-Piperazinedione, 1-cyclopentyl-4-[(3-fluoro-5-phenyl-2-pyridinyl)methyl]-	
503	p.258 p.411	2857177-91-2	2,3-Piperazinedione, 1-cyclopentyl-4-[(5-fluoro-6-phenyl-3-pyridinyl)methyl]-	
504	p.259 p.411	2857177-92-3	2,3-Piperazinedione, 1-cyclopentyl-4-[(3-phenyl-1,2,4-triazin-6-yl)methyl]-	
505	p.259 p.412	2857177-93-4	2,3-Piperazinedione, 1-cyclopentyl-4-[(5-phenyl-3-isoxazolyl)methyl]-	
506	p.259 p.412	2857177-94-5	2,3-Piperazinedione, 1-cyclobutyl-4-[(5-phenyl-3-isoxazolyl)methyl]-	
507	p.259 p.412	2857177-95-6	2,3-Piperazinedione, 1-cyclobutyl-4-[(3-fluoro-5-phenyl-2-pyridinyl)methyl]-	
508	p.259 p.412	2857177-96-7	2,3-Piperazinedione, 1-cyclobutyl-4-[(2-phenyl-5-pyrimidinyl)methyl]-	
509	p.260 p.412	2857177-97-8	2,3-Piperazinedione, 1-cyclobutyl-4-[1-(5-phenyl-2-pyrazinyl)ethyl]-	
510	p.260 p.413	2857177-98-9	2,3-Piperazinedione, 1-cyclobutyl-4-[[6-(1*H*-1,2,3-triazol-1-yl)-3-pyridinyl]methyl]-	
511	p.260 p.413	2857177-99-0	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[(2-phenyl-5-pyrimidinyl)methyl]-	
512	p.260 p.413	2857178-00-6		

513	p.260 p.413	2857178-01-7		
514	p.260 p.413	2857178-02-8	2,3-Piperazinedione, 1-cyclobutyl-4-[[6-(2*H*-1,2,3-triazol-2-yl)-3-pyridinyl]methyl]-	
515	p.261 p.414	2857178-03-9		
516	p.261 p.414	2857178-04-0		
517	p.261 p.414	2857178-05-1	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[6-(2*H*-1,2,3-triazol-2-yl)-3-pyridinyl]methyl]-	
518	p.261 p.414	2857178-06-2	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[6-(1*H*-1,2,3-triazol-1-yl)-3-pyridinyl]methyl]-	
519	p.261 p.414	2857178-07-3		
520	p.262 p.415	2857178-08-4	2,3-Piperazinedione, 1-cyclopentyl-4-[2-(5-phenyl-3-isoxazolyl)ethyl]-	
521	p.262 p.415	2857178-09-5		
522	p.262 p.415	2857178-10-8		
523	p.262 p.415	2857178-11-9		
524	p.262 p.416	2857178-12-0	2,3-Piperazinedione, 1-cyclobutyl-4-[(5-fluoro-6-phenyl-3-pyridinyl)methyl]-	
525	p.263 p.416	2857178-13-1		
526	p.263 p.416	2857178-14-2		
527	p.263 p.416	2857178-15-3		

528	p.263 p.417	2857178-16-4		
529	p.263 p.417	2857178-17-5		
530	p.264 p.417	2857178-18-6		
531	p.264 p.417	2857178-19-7		
532	p.264 p.418	2857178-20-0		
533	p.264 p.423	2857178-21-1	2,3-Piperazinedione, 1-cyclopentyl-4-[(3-phenylbicyclo[1.1.1]pent-1-yl)methyl]-	
534	p.265 p.418	2857178-22-2	2,3-Piperazinedione, 1-cyclopentyl-4-[1-(5-phenyl-2-pyrimidinyl)ethyl]-	
537	p.266 p.418	2857178-23-3	2,3-Piperazinedione, 1-cyclobutyl-4-[1-(5-phenyl-2-pyrimidinyl)ethyl]-	
539	p.266 p.418	823-96-1	Boroxin, 2,4,6-trimethyl-	
540	p.267 p.344 p.418 p.423	2857177-73-0		
541	p.267 p.412	2857178-24-4	2,3-Piperazinedione, 1-cyclobutyl-4-[[5-(2*H*-1,2,3-triazol-2-yl)-2-pyridinyl]methyl]-	
542	p.268 p.402	2857178-25-5		
543	p.269 p.360 p.423	2857178-26-6	2,3-Piperazinedione, 1-cyclobutyl-4-[[5-(2-pyridinyl)-3-isoxazolyl]methyl]-	
544	p.269 p.418	2857178-27-7	2,3-Piperazinedione, 1-cyclopentyl-4-[[3-fluoro-5-(2-thiazolyl)-2-pyridinyl]methyl]-	

545	p.270 p.419	2857178-28-8	2,3-Piperazinedione, 1-cyclopentyl-4-[[4-(2*H*-1,2,3-triazol-2-yl)phenyl]methyl]-	
546	p.270 p.419	2857178-29-9		
547	p.271 p.419	2857178-30-2		
548	p.271 p.419	2857178-31-3		
549	p.271 p.420	2857178-32-4	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-1,4-dihydro-	
550	p.271 p.420	2857178-33-5	2,3-Pyrazinedione, 1-cyclopentyl-4-[[5-(3-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-1,4-dihydro-	
551	p.271 p.420	2857178-34-6		
552	p.272 p.420	2857178-35-7	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-[(5-phenyl-3-isoxazolyl)methyl]-	
553	p.272 p.421	2857178-36-8	2,3-Piperazinedione, 1-cyclobutyl-4-[(3-phenyl-5-isoxazolyl)methyl]-	
554	p.272 p.421	2857178-37-9	2,3-Piperazinedione, 1-cyclobutyl-4-[[3-(2-fluorophenyl)-5-isoxazolyl]methyl]-	
555	p.272 p.421	2857178-38-0	2,3-Piperazinedione, 1-cyclobutyl-4-[[3-(4-fluorophenyl)-5-isoxazolyl]methyl]-	
556	p.272 p.421	2857178-39-1	2,3-Pyrazinedione, 1-cyclobutyl-1,4-dihydro-4-[(3-phenyl-5-isoxazolyl)methyl]-	
557	p.273 p.422	2857178-40-4	2,3-Pyrazinedione, 1-cyclobutyl-4-[[3-(2-fluorophenyl)-5-isoxazolyl]methyl]-1,4-dihydro-	
558	p.273 p.422	2857178-41-5	2,3-Piperazinedione, 1-cyclopentyl-4-[[3-(3-fluorophenyl)-5-isoxazolyl]methyl]-	
559	p.273 p.422	2857178-42-6	2,3-Piperazinedione, 1-cyclopentyl-4-[[3-(2-fluorophenyl)-5-isoxazolyl]methyl]-	
560	p.273 p.422	2857178-43-7	2,3-Pyrazinedione, 1-cyclopentyl-4-[[3-(3-fluorophenyl)-5-isoxazolyl]methyl]-1,4-dihydro-	

561	p.273 p.423	2857178-44-8	2,3-Pyrazinedione, 1-cyclopentyl-4-[[3-(2-fluorophenyl)-5-isoxazolyl]methyl]-1,4-dihydro-	
562	p.274 p.423	2857178-45-9	2,3-Pyrazinedione, 1-cyclobutyl-4-[[3-(3-fluorophenyl)-5-isoxazolyl]methyl]-1,4-dihydro-	
563	p.274 p.389	2857178-46-0	2,3-Piperazinedione, 1-cyclobutyl-4-[[3-(3-fluorophenyl)-5-isoxazolyl]methyl]-	
564	p.274 p.390	2857178-47-1	2,3-Pyrazinedione, 1-cyclobutyl-4-[[3-(4-fluorophenyl)-5-isoxazolyl]methyl]-1,4-dihydro-	
565	p.274 p.390	2857178-48-2	2,3-Pyrazinedione, 1-cyclobutyl-1,4-dihydro-4-[(1-phenyl-1*H*-pyrazol-4-yl)methyl]-	
566	p.274 p.390	2857178-49-3	2,3-Pyrazinedione, 1-cyclobutyl-1,4-dihydro-4-[[3-(2-pyridinyl)-5-isoxazolyl]methyl]-	
567	p.275 p.390	2857179-86-1	2,3-Piperazinedione, 1-cyclopentyl-4-[[3-(4-fluorophenyl)-5-isoxazolyl]methyl]-	
568	p.275 p.391	2857178-50-6	2,3-Pyrazinedione, 1-cyclopentyl-1,4-dihydro-4-[[3-(2-pyridinyl)-5-isoxazolyl]methyl]-	
569	p.275 p.391	2857178-51-7	2,3-Pyrazinedione, 1-cyclopentyl-4-[[3-(4-fluorophenyl)-5-isoxazolyl]methyl]-1,4-dihydro-	
570	p.275 p.391	2857178-52-8	2,3-Pyrazinedione, 1-cyclobutyl-1,4-dihydro-4-[(3-phenyl-5-isothiazolyl)methyl]-	
571	p.275 p.391	2857178-53-9		
572	p.276 p.392	2857178-54-0	2,3-Piperazinedione, 1-(1-methylcyclobutyl)-4-[(5-phenyl-3-isoxazolyl)methyl]-	
573	p.276 p.392	2857178-55-1	2,3-Pyrazinedione, 1-cyclobutyl-1,4-dihydro-4-[(5-phenyl-1*H*-pyrazol-3-yl)methyl]-	
574	p.276 p.392	2857178-56-2	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-[[5-(2-pyridinyl)-3-isoxazolyl]methyl]-	
575	p.276 p.392	2857178-57-3		
576	p.276 p.393	2857178-58-4	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[(3-phenyl-5-isoxazolyl)methyl]-	

577	p.277 p.393	2857178-59-5	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-[[3-(2-pyridinyl)-5-isoxazolyl]methyl]-	
578	p.277 p.423	2857178-60-8	2,3-Pyrazinedione, 1-cyclobutyl-1,4-dihydro-4-[(5-phenyl-3-isothiazolyl)methyl]-	
579	p.277 p.395 p.427	2858732-99-5	2,3-Piperazinedione, 1-cyclobutyl-4-[(1-phenyl-1*H*-imidazol-4-yl)methyl]-	
580	p.277 p.395 p.427	2858733-00-1	2,3-Pyrazinedione, 1-cyclobutyl-1,4-dihydro-4-[(1-phenyl-1*H*-imidazol-4-yl)methyl]-	
581	p.277 p.428	2858733-01-2	2,3-Piperazinedione, 1-cyclobutyl-4-[[5-(2*H*-tetrazol-2-yl)-2-pyridinyl]methyl]-	
582	p.278 p.428	2858733-02-3	2,3-Piperazinedione, 1-cyclobutyl-4-[[3-(2-pyridinyl)bicyclo[1.1.1]pent-1-yl]methyl]-	
583	p.278 p.428	2858733-03-4	2,3-Piperazinedione, 4-cyclobutyl-5-methyl-1-[[5-(2*H*-1,2,3-triazol-2-yl)-2-pyridinyl]methyl]-	
584	p.278 p.364 p.428	2858733-04-5	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[5-(2-chlorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-	
585	p.278 p.429	2858733-05-6	2*H*-Pyrido[1,2-*a*]pyrazine-3,4-dione, hexahydro-2-[(5-phenyl-1,3,4-thiadiazol-2-yl)methyl]-, (9a*R*)-	
586	p.278 p.429	2858733-06-7	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclobutyl)-4-[(3-phenyl-5-isoxazolyl)methyl]-	
588	p.278 p.279 p.429 p.429	2858733-07-8	2*H*-Pyrido[1,2-*a*]pyrazine-3,4-dione, hexahydro-2-[(5-phenyl-1,3,4-thiadiazol-2-yl)methyl]-, (9a*S*)-	
590	p.279 p.429	2858733-08-9		
591	p.279 p.430	2858733-09-0	2,3-Piperazinedione, 1-bicyclo[2.1.1]hex-2-yl-4-[[6-(2-fluorophenyl)-3-pyridazinyl]methyl]-	
592	p.279 p.430	2858733-10-3	2,3-Piperazinedione, 1-[[3-(3-fluorophenyl)-5-isoxazolyl]methyl]-4-(1-methylcyclobutyl)-	
593	p.279 p.430	2858733-11-4	2,3-Pyrazinedione, 1-[[3-(3-fluorophenyl)-5-isoxazolyl]methyl]-1,4-dihydro-4-(1-methylcyclobutyl)-	

594	p.280 p.430	2858733-12-5	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-[[5-(2-thiazolyl)-3-isoxazolyl]methyl]-	
595	p.280 p.431	2858733-13-6	2,3-Piperazinedione, 1-[[3-(4-fluorophenyl)-5-isoxazolyl]methyl]-4-(1-methylcyclobutyl)-	
596	p.280 p.431	2858733-14-7	2,3-Pyrazinedione, 1-[[3-(4-fluorophenyl)-5-isoxazolyl]methyl]-1,4-dihydro-4-(1-methylcyclobutyl)-	
597	p.280 p.431	2858733-15-8		
598	p.280 p.431	2858733-16-9	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[(2,2-difluoro-3-phenylbicyclo[1.1.1]pent-1-yl)methyl]-	
599	p.281 p.432	2858733-17-0		
600	p.281 p.432	2858733-18-1	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[6-(2-fluorophenyl)-3-pyridazinyl]methyl]-1,4-dihydro-	
601	p.281 p.432	2858733-19-2	2,3-Piperazinedione, 1-[1-(fluoromethyl)cyclopropyl]-4-[[5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-	
602	p.281 p.432	2858733-20-5	2,3-Piperazinedione, 1-[1-(fluoromethyl)cyclopropyl]-4-[[6-(2-fluorophenyl)-3-pyridazinyl]methyl]-	
603	p.281 p.433	2858733-21-6	2,3-Piperazinedione, 1-[1-(fluoromethyl)cyclopropyl]-4-[(3-phenyl-5-isoxazolyl)methyl]-	
604	p.282 p.433	2858733-22-7	2,3-Pyrazinedione, 1-[[6-(2-fluorophenyl)-3-pyridazinyl]methyl]-1,4-dihydro-4-(1-methylcyclopropyl)-	
605	p.282 p.433	2858733-23-8		
606	p.282 p.433	2858733-24-9	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclopropyl)-4-[[3-(2-pyridinyl)-5-isoxazolyl]methyl]-	
607	p.282 p.433	2858733-25-0		

608	p.282 p.434	2858733-26-1	2,3-Pyrazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-4-[[6-(2-fluorophenyl)-3-pyridazinyl]methyl]-1,4-dihydro-	
609	p.283 p.434	2858733-27-2	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclopropyl)-4-[[5-(2*H*-1,2,3-triazol-2-yl)-2-pyridinyl]methyl]-	
610	p.283 p.434	2858733-28-3	2,3-Pyrazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-1,4-dihydro-4-[[3-(2-pyridinyl)-5-isoxazolyl]methyl]-	
611	p.283 p.434	2858733-29-4		
612	p.283 p.434	2858733-30-7	2,3-Pyrazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-1,4-dihydro-4-[[6-(2-thiazolyl)-3-pyridazinyl]methyl]-	
613	p.283 p.435	2858733-31-8	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclopropyl)-4-[[5-(2-pyridinyl)-3-isoxazolyl]methyl]-	
614	p.284 p.435	2858733-32-9		
615	p.284 p.435	2858733-33-0	2,3-Pyrazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-1,4-dihydro-4-[[5-(2-pyridinyl)-3-isoxazolyl]methyl]-	
616	p.284 p.435	2858733-34-1	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclopropyl)-4-[[5-(3-pyridinyl)-3-isoxazolyl]methyl]-	
617	p.284 p.435	2858733-35-2		
618	p.284 p.436	2858733-36-3	2,3-Pyrazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-1,4-dihydro-4-[[5-(3-pyridinyl)-3-isoxazolyl]methyl]-	
619	p.285 p.436	2858733-37-4	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-[[5-(3-pyridinyl)-3-isoxazolyl]methyl]-	
620	p.285 p.436	2858733-38-5	2,3-Pyrazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-1,4-dihydro-4-[[6-(5-thiazolyl)-3-pyridazinyl]methyl]-	
621	p.285 p.287 p.436	2858733-39-6	2,3-Pyrazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-1,4-dihydro-4-[[6-(2-pyridinyl)-3-pyridazinyl]methyl]-	
622	p.285 p.437	2858733-40-9	2,3-Pyrazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-1,4-dihydro-4-[[6-(3-pyridinyl)-3-pyridazinyl]methyl]-	

623	p.285 p.437	2858733-41-0	2,3-Pyrazinedione, 1-[1-(fluoromethyl)cyclopropyl]-1,4-dihydro-4-[[5-(2*H*-1,2,3-triazol-2-yl)-2-pyridinyl]methyl]-	
624	p.286 p.437	2858733-42-1	2,3-Pyrazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-1,4-dihydro-4-[[5-(2*H*-1,2,3-triazol-2-yl)-2-pyridinyl]methyl]-	
625	p.286 p.437	2858733-43-2		
626	p.286 p.437	2858733-44-3		
627	p.286 p.438	2858733-45-4	2,3-Pyrazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-1,4-dihydro-4-[[6-(1*H*-pyrazol-1-yl)-3-pyridinyl]methyl]-	
628	p.286 p.438	2858733-46-5	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclopropyl)-4-[[3-(3-pyridinyl)-5-isoxazolyl]methyl]-	
629	p.287 p.438	2858733-47-6		
630	p.287 p.438	2858733-48-7	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-[[3-(3-pyridinyl)-5-isoxazolyl]methyl]-	
631	p.287 p.439	2858733-49-8	2,3-Pyrazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-1,4-dihydro-4-[[3-(3-pyridinyl)-5-isoxazolyl]methyl]-	
632	p.287 p.439	2858733-50-1	2,3-Pyrazinedione, 1-[1-(fluoromethyl)cyclopropyl]-1,4-dihydro-4-[[3-(2-pyridinyl)-5-isoxazolyl]methyl]-	
634	p.288 p.439	2858733-51-2	2,3-Pyrazinedione, 1-[1-(fluoromethyl)cyclopropyl]-1,4-dihydro-4-[[6-(3-pyridinyl)-3-pyridazinyl]methyl]-	
635	p.288 p.440	2858733-52-3	2,3-Piperazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-4-[[6-(2-fluorophenyl)-3-pyridazinyl]methyl]-	
636	p.288 p.440	2858733-53-4		
637	p.288 p.440	2858733-54-5	2,3-Pyrazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-1,4-dihydro-4-[[6-(1*H*-1,2,3-triazol-1-yl)-3-pyridinyl]methyl]-	
638	p.288 p.440	2858733-55-6	2,3-Pyrazinedione, 1-[1-(fluoromethyl)cyclopropyl]-1,4-dihydro-4-[[6-(1*H*-pyrazol-1-yl)-3-pyridinyl]methyl]-	

639	p.289 p.441	2858733-56-7	2,3-Piperazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-4-[[3-(2-pyridinyl)-5-isoxazolyl]methyl]-	
640	p.289 p.441	2858733-57-8	2,3-Pyrazinedione, 1-[1-(fluoromethyl)cyclopropyl]-1,4-dihydro-4-[[6-(2-thiazolyl)-3-pyridazinyl]methyl]-	
641	p.289 p.441	2858733-58-9	2,3-Piperazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-4-[[6-(2-thiazolyl)-3-pyridazinyl]methyl]-	
642	p.289 p.442	2858733-59-0	2,3-Pyrazinedione, 1-[1-(fluoromethyl)cyclopropyl]-1,4-dihydro-4-[[6-(1*H*-1,2,3-triazol-1-yl)-3-pyridinyl]methyl]-	
643	p.289 p.442	2858733-60-3	2,3-Piperazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-4-[[6-(1*H*-1,2,3-triazol-1-yl)-3-pyridinyl]methyl]-	
644	p.290 p.442	2858733-61-4	2,3-Piperazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-4-[[6-(1*H*-pyrazol-1-yl)-3-pyridinyl]methyl]-	
645	p.290 p.443	2858733-62-5	2,3-Pyrazinedione, 1-[1-(fluoromethyl)cyclopropyl]-1,4-dihydro-4-[[5-(2-pyridinyl)-3-isoxazolyl]methyl]-	
646	p.290 p.443	2858733-63-6	2,3-Pyrazinedione, 1-[1-(fluoromethyl)cyclopropyl]-1,4-dihydro-4-[[6-(2-pyridinyl)-3-pyridazinyl]methyl]-	
647	p.290 p.443	2858733-64-7	2,3-Piperazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-4-[[3-(3-pyridinyl)-5-isoxazolyl]methyl]-	
648	p.290 p.443	2858733-65-8	2,3-Piperazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-4-[[6-(3-pyridinyl)-3-pyridazinyl]methyl]-	
649	p.291 p.424	2858733-66-9	2,3-Pyrazinedione, 1-[1-(fluoromethyl)cyclopropyl]-4-[[6-(2-fluorophenyl)-3-pyridazinyl]methyl]-1,4-dihydro-	
650	p.291 p.424	2858733-67-0	2,3-Piperazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-4-[[6-(5-thiazolyl)-3-pyridazinyl]methyl]-	
651	p.291 p.424	2858733-68-1	2,3-Piperazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-4-[[5-(2*H*-1,2,3-triazol-2-yl)-2-pyridinyl]methyl]-	
652	p.291 p.424	2858733-69-2	2,3-Pyrazinedione, 1-[1-(fluoromethyl)cyclopropyl]-1,4-dihydro-4-[[6-(5-thiazolyl)-3-pyridazinyl]methyl]-	
653	p.291 p.425	2858733-70-5	2,3-Pyrazinedione, 1-[1-(fluoromethyl)cyclopropyl]-1,4-dihydro-4-[[3-(3-pyridinyl)-5-isoxazolyl]methyl]-	

654	p.292 p.425	2858733-71-6	2,3-Pyrazinedione, 1-[1-(fluoromethyl)cyclopropyl]-1,4-dihydro-4-[[6-(1*H*-1,2,3-triazol-1-yl)-3-pyridazinyl]methyl]-	
655	p.292 p.425	2858733-72-7	2,3-Pyrazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-1,4-dihydro-4-[[6-(1*H*-1,2,3-triazol-1-yl)-3-pyridazinyl]methyl]-	
656	p.292 p.425	2858733-73-8	2,3-Piperazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-4-[[6-(1*H*-1,2,3-triazol-1-yl)-3-pyridazinyl]methyl]-	
657	p.292 p.425	2858733-74-9		
658	p.292 p.426	2858733-75-0	2,3-Pyrazinedione, 1-([2,3'-bipyridin]-6'-ylmethyl)-4-[1-(fluoromethyl)cyclopropyl]-1,4-dihydro-	
659	p.293 p.426	2858733-76-1	2,3-Piperazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-4-[[5-(2-pyridinyl)-3-isoxazolyl]methyl]-	
660	p.293 p.426	2858733-77-2	2,3-Pyrazinedione, 1-[1-(fluoromethyl)cyclopropyl]-1,4-dihydro-4-[[5-(3-pyridinyl)-3-isoxazolyl]methyl]-	
661	p.293 p.426	2858733-78-3	2,3-Piperazinedione, 1-([2,3'-bipyridin]-6'-ylmethyl)-4-(3-fluorobicyclo[1.1.1]pent-1-yl)-	
662	p.293 p.427	2858733-79-4	2,3-Pyrazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-1,4-dihydro-4-[[6-(2*H*-1,2,3-triazol-2-yl)-3-pyridinyl]methyl]-	
663	p.293 p.427	2858733-80-7	2,3-Piperazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-4-[[5-(3-pyridinyl)-3-isoxazolyl]methyl]-	
664	p.294 p.427	2858733-81-8	2,3-Pyrazinedione, 1-[1-(fluoromethyl)cyclopropyl]-1,4-dihydro-4-[[1-(2-pyridinyl)-1*H*-1,2,3-triazol-4-yl]methyl]-	
665	p.294 p.427	2858733-82-9		
666	p.294 p.428	2858733-83-0	2,3-Piperazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-4-[[1-(2-pyridinyl)-1*H*-1,2,3-triazol-4-yl]methyl]-	
667	p.294 p.428	2858733-84-1	2,3-Pyrazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-1,4-dihydro-4-[[1-(2-pyridinyl)-1*H*-1,2,3-triazol-4-yl]methyl]-	
668	p.294 p.428	2858733-85-2	2,3-Pyrazinedione, 1-[1-(fluoromethyl)cyclopropyl]-1,4-dihydro-4-[[5-(1*H*-1,2,3-triazol-1-yl)-2-pyridinyl]methyl]-	

669	p.295 p.428	2858733-86-3	2,3-Pyrazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-1,4-dihydro-4-[[5-(1*H*-1,2,3-triazol-1-yl)-2-pyridinyl]methyl]-	
670	p.295 p.429	2858733-87-4	2,3-Piperazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-4-[[5-(1*H*-1,2,3-triazol-1-yl)-2-pyridinyl]methyl]-	
671	p.295 p.429	2858733-88-5	2,3-Pyrazinedione, 1-[1-(fluoromethyl)cyclopropyl]-1,4-dihydro-4-[[6-(2*H*-1,2,3-triazol-2-yl)-3-pyridinyl]methyl]-	
672	p.295 p.429	2858733-89-6	2,3-Piperazinedione, 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-4-[[6-(2*H*-1,2,3-triazol-2-yl)-3-pyridinyl]methyl]-	
673	p.296 p.393	2857178-61-9		
674	p.296 p.393	2857178-62-0		
675	p.297 p.394	2857178-63-1	2,3-Piperazinedione, 1-cyclopentyl-4-[(1-oxido-6-phenyl-3-pyridinyl)methyl]-	
735	p.298	101494-93-3	3(2*H*)-Cinnolinone, 7-chloro-	
387	p.298	1351334-87-6	Methanesulfonic acid, 1,1,1-trifluoro-, 7-chloro-3-cinnolinyl ester	
388	p.298	2857176-94-2	Cinnoline, 7-chloro-3-ethenyl-	
736	p.298	95010-17-6	Boron, ethenyl[(*B*-ethenylboronic acid-κ*O*) bimol. monoanhydridato(2-)](pyridine)-, (*T*-4)-	
676	p.299 p.300 p.394	2857175-84-7	2,3-Piperazinedione, 1-[2-(7-chloro-3-cinnolinyl)ethyl]-4-cyclopentyl-	
389	p.300	2857176-95-3	2,3-Piperazinedione, 1-cyclopentyl-4-[2-(1,2-dihydro-3-cinnolinyl)ethyl]-	
677	p.300 p.394	2857178-64-2	2,3-Piperazinedione, 1-[2-(3-cinnolinyl)ethyl]-4-cyclopentyl-	
738	p.301	38696-20-7	Pyrimidine, 5-bromo-2-phenyl-	

678	p.301 p.395	2857178-65-3	2,3-Piperazinedione, 1-cyclopentyl-4-[(2-phenyl-5-pyrimidinyl)methyl]-	
679	p.302 p.395	2857178-66-4		
680	p.302 p.395	2857178-67-5	2,3-Piperazinedione, 1-cyclopentyl-4-[(1,2-dihydro-1-oxo-7-isoquinolinyl)methyl]-	
681	p.302 p.395	2857178-68-6	2,3-Piperazinedione, 1-cyclopentyl-4-[(1-phenyl-1*H*-pyrazol-4-yl)methyl]-	
682	p.302 p.396	2857178-69-7	2,3-Piperazinedione, 1-cyclopentyl-4-[(5-phenyl-1*H*-pyrazol-3-yl)methyl]-	
683	p.303 p.396	2857178-70-0	2,3-Piperazinedione, 1-cyclopentyl-4-[(1,2,3,4-tetrahydro-1-oxo-7-isoquinolinyl)methyl]-	
740	p.303	177287-49-9	Bicyclo[1.1.1]pentan-1-amine	
684	p.303 p.396	2857178-71-1		
685	p.304 p.396	2857178-72-2		
686	p.304 p.397	2858733-90-9		
687	p.304 p.397	2857178-74-4	2,3-Piperazinedione, 1-[(5-phenyl-2-pyrimidinyl)methyl]-4-(tetrahydro-3-furanyl)-	
688	p.304 p.397	2857178-75-5		
689	p.304 p.397	2857178-76-6		
690	p.305 p.398	2857178-77-7		

691	p.305 p.398	2857178-78-8		
692	p.305 p.398	2858733-91-0		
693	p.305 p.398	2857178-80-2		
694	p.305 p.399	2857178-81-3		
695	p.306 p.399	2857178-82-4		
696	p.306 p.399	2857178-83-5		
697	p.306 p.399	2857178-84-6		
698	p.306 p.400	2857178-85-7		
699	p.306 p.400	2857178-86-8		
700	p.307 p.423	2857178-87-9		
1001	p.307 p.423	2857178-88-0		
1002	p.307 p.429	2858733-95-4		
1003	p.307 p.430	2858733-96-5		
1004	p.307 p.430	2858733-97-6		

1005	p.308 p.430	2858733-98-7		
1006	p.308 p.430	2858733-99-8	2,3-Piperazinedione, 1-[(5-phenyl-1,3,4-thiadiazol-2-yl)methyl]-4-[1-(trifluoromethyl)cyclobutyl]-	
1007	p.308 p.431	2858734-00-4		
1008	p.308 p.431	2858734-01-5		
1009	p.308 p.431	2858734-02-6		
1010	p.309 p.431	2858734-03-7		
1011	p.309 p.432	2858734-04-8		
1012	p.309 p.432	2858734-05-9	2,3-Piperazinedione, 1-[(5-phenyl-1,3,4-thiadiazol-2-yl)methyl]-4-[1-(4-pyridinyl)cyclopropyl]-	
1013	p.309 p.432	2858734-06-0		
1014	p.309 p.432	2858734-07-1		
1015	p.310 p.433	2858734-08-2		
1016	p.310 p.433	2858734-09-3		
1017	p.310 p.400	2857178-89-1	2,3-Piperazinedione, 1-cyclopentyl-4-[[5-(1-piperidinyl)-1,3,4-thiadiazol-2-yl]methyl]-	

742	p.310	110-89-4	Piperidine	
1018	p.311 p.400	2857178-91-5	2,3-Piperazinedione, 1-cyclopentyl-4-[[5-(1-pyrrolidinyl)-1,3,4-thiadiazol-2-yl]methyl]-	
1019	p.311 p.401	2857178-92-6	2,3-Piperazinedione, 1-cyclopentyl-4-[[5-[(3*S*)-3-fluoro-1-pyrrolidinyl]-1,3,4-thiadiazol-2-yl]methyl]-	
1020	p.311 p.401	2857178-93-7	2,3-Piperazinedione, 1-cyclopentyl-4-[[5-[(3*S*)-3-(fluoromethyl)-1-pyrrolidinyl]-1,3,4-thiadiazol-2-yl]methyl]-	
1021	p.312 p.401	2857178-94-8	2,3-Piperazinedione, 1-[[5-(3-azabicyclo[3.1.0]hex-3-yl)-1,3,4-thiadiazol-2-yl]methyl]-4-cyclopentyl-	
744	p.312	123-75-1	Pyrrolidine	
1022	p.312 p.401	2857178-95-9	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(1-pyrrolidinyl)-3-pyridazinyl]methyl]-	
1023	p.313 p.402	2857178-96-0	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(1-pyrrolidinyl)-3-pyridinyl]methyl]-	
1024	p.313 p.402	2857178-97-1	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(1-piperidinyl)-3-pyridazinyl]methyl]-	
1025	p.313 p.402	2857178-98-2	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(4-morpholinyl)-3-pyridazinyl]methyl]-	
1026	p.313 p.402	2857178-99-3	2,3-Piperazinedione, 1-[[6-(1-azetidinyl)-3-pyridazinyl]methyl]-4-cyclopentyl-	
1027	p.313 p.402	2857179-00-9	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(3,3-difluoro-1-pyrrolidinyl)-3-pyridazinyl]methyl]-	
1028	p.314 p.403	2857179-01-0	2,3-Piperazinedione, 1-[[6-(3-azabicyclo[3.1.0]hex-3-yl)-3-pyridazinyl]methyl]-4-cyclopentyl-	
1029	p.314 p.403	2857179-02-1	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(1*H*-1,2,3-triazol-1-yl)-3-pyridazinyl]methyl]-	
1030	p.315 p.403	2857179-03-2	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(2*H*-1,2,3-triazol-2-yl)-3-pyridazinyl]methyl]-	

1031	p.315 p.403	2857179-04-3	2,3-Piperazinedione, 1-cyclopentyl-4-[[5-(2*H*-1,2,3-triazol-2-yl)-1,3,4-thiadiazol-2-yl]methyl]-	
1032	p.315 p.404	2858734-10-6	2,3-Piperazinedione, 1-cyclobutyl-4-[[5-(2*H*-1,2,3-triazol-2-yl)-2-pyrazinyl]methyl]-	
1033	p.315 p.404	2857179-06-5	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[5-(2*H*-1,2,3-triazol-2-yl)-2-pyrazinyl]methyl]-	
1034	p.316 p.404	2857179-07-6		
1035	p.316 p.404	2857179-08-7		
1036	p.316 p.405	2857179-09-8	2,3-Pyrazinedione, 1-cyclopentyl-1,4-dihydro-4-[[6-(1*H*-1,2,3-triazol-1-yl)-3-pyridazinyl]methyl]-	
1037	p.316 p.405	2857179-10-1	2,3-Pyrazinedione, 1-cyclobutyl-1,4-dihydro-4-[[6-(1*H*-pyrazol-1-yl)-3-pyridazinyl]methyl]-	
1038	p.316 p.405	2857179-11-2		
1039	p.317 p.405	2857179-12-3		
1040	p.317 p.433	2858734-11-7	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclopropyl)-4-[[6-(2*H*-1,2,3-triazol-2-yl)-3-pyridazinyl]methyl]-	
1041	p.317 p.433	2858734-12-8		
1042	p.317 p.433	2858734-13-9	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclopropyl)-4-[[6-(1*H*-1,2,3-triazol-1-yl)-3-pyridazinyl]methyl]-	
1043	p.317 p.434	2858734-14-0		
1044	p.318 p.406	2857179-13-4	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(2*H*-1,2,3-triazol-2-yl)-3-pyridinyl]methyl]-	

1045	p.318 p.406	2857179-14-5		
1046	p.319 p.406	2857179-15-6		
1047	p.319 p.406	2857179-16-7	2,3-Piperazinedione, 1-cyclopentyl-4-[(6-propoxy-3-pyridazinyl)methyl]-	
749	p.320	71-23-8	1-Propanol	
1048	p.320 p.407	2857179-17-8	2,3-Piperazinedione, 1-cyclopentyl-4-[(6-ethoxy-3-pyridazinyl)methyl]-	
750	p.321	2878-14-0	2-Propen-1-amine, 2-methyl-	
390	p.321	1597841-82-1	Acetic acid, 2-[(2-methyl-2-propen-1-yl)amino]-2-oxo-, ethyl ester	
391	p.321	2857176-96-4	Acetic acid, 2-[(2-methyl-2-propen-1-yl)[(5-phenyl-2-pyrimidinyl)methyl]amino]-2-oxo-, ethyl ester	
392	p.322	2857176-97-5	Acetic acid, 2-oxo-2-[(2-oxopropyl)[(5-phenyl-2-pyrimidinyl)methyl]amino]-, ethyl ester	
1049	p.323 p.407	2857179-18-9	2,3-Piperazinedione, 4-cyclopentyl-5-methyl-1-[(5-phenyl-2-pyrimidinyl)methyl]-	
1052	p.323 p.407	2857179-19-0	2,3-Piperazinedione, 1-cyclopentyl-4-[[5-(2-pyridinyl)-2-pyrimidinyl]methyl]-	
1053	p.324 p.407	2857179-20-3		
754	p.325	52430-83-8	Cyclopentanamine, 3-methyl-	
1055	p.325 p.408	2857179-22-5		
1056	p.325 p.408	2857179-21-4		

755	p.326	75-64-9	2-Propanamine, 2-methyl-	
1057	p.326 p.408	2857179-24-7		
1058	p.327 p.408	2857179-25-8		
1059	p.328 p.408	2857179-26-9	2,3-Piperazinedione, 1-cyclopentyl-4-[1-(1-phenyl-1*H*-pyrazol-4-yl)ethyl]-	
1060	p.328 p.409	2857179-27-0	2,3-Piperazinedione, 1-cyclopentyl-4-[(1*R*)-1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethyl]-	
1061	p.328 p.409	2857179-28-1	2,3-Piperazinedione, 1-cyclopentyl-4-[(1*S*)-1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethyl]-	
1062	p.328 p.409	2857179-29-2	2,3-Piperazinedione, 1-cyclopentyl-4-[2-(5-phenyl-1,3,4-thiadiazol-2-yl)ethyl]-	
1063	p.329 p.409	2857179-30-5	2,3-Piperazinedione, 1-cyclopentyl-4-[[5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl]-	
1064	p.329 p.410	2857179-31-6	2,3-Piperazinedione, 1-cyclopentyl-4-[1-methyl-2-(5-phenyl-1,3,4-thiadiazol-2-yl)ethyl]-	
1065	p.329 p.410	2857179-32-7	2,3-Piperazinedione, 1-cyclopentyl-4-[2-(5-phenyl-1,3,4-thiadiazol-2-yl)propyl]-	
1066	p.329 p.410	2857179-33-8	2,3-Piperazinedione, 1-cyclopentyl-4-[(1,2-dihydro-2-oxo-3-quinolinyl)methyl]-	
1067	p.329 p.410	2857179-34-9	2,3-Piperazinedione, 1-cyclobutyl-4-[(1*R*)-1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethyl]-	
1068	p.330 p.411	2857179-35-0	2,3-Piperazinedione, 1-cyclobutyl-4-[(1*S*)-1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethyl]-	
1069	p.330 p.365 p.411	2857179-36-1		
759	p.330	54408-35-4	5-Isoxazolemethanamine, 3-phenyl-	

1070	p.330 p.411	2857179-37-2	2,3-Piperazinedione, 1-cyclopentyl-4-[(3-phenyl-5-isoxazolyl)methyl]-	
1071	p.330 p.411	2857179-38-3	2,3-Pyrazinedione, 1-cyclopentyl-1,4-dihydro-4-[(3-phenyl-5-isoxazolyl)methyl]-	
1072	p.331 p.412	2857179-39-4	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[5-(2*H*-1,2,3-triazol-2-yl)-2-pyridinyl]methyl]-	
1073	p.332 p.412	2857179-40-7	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-[[5-(2*H*-1,2,3-triazol-2-yl)-2-pyridinyl]methyl]-	
1074	p.332 p.412	2857179-41-8	2,3-Piperazinedione, 1-cyclopentyl-4-[[5-(2-thiazolyl)-2-pyrimidinyl]methyl]-	
1075	p.333 p.413	2857179-42-9	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(2-thiazolyl)-3-pyridazinyl]methyl]-	
1076	p.333 p.413	2857179-43-0	2,3-Piperazinedione, 1-cyclopentyl-4-[[5-(2-thiazolyl)-1,3,4-thiadiazol-2-yl]methyl]-	
1077	p.333 p.413	2857179-44-1	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(2-thiazolyl)-3-pyridinyl]methyl]-	
1078	p.333 p.413	2857179-45-2	2,3-Piperazinedione, 1-cyclobutyl-4-[[6-(2-thiazolyl)-3-pyridazinyl]methyl]-	
1079	p.333 p.413	2857179-46-3	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-[[6-(2-thiazolyl)-3-pyridazinyl]methyl]-	
1080	p.334 p.414	2857179-47-4	2,3-Pyrazinedione, 1-cyclobutyl-1,4-dihydro-4-[[6-(2-thiazolyl)-3-pyridazinyl]methyl]-	
1081	p.334 p.414	2857179-48-5	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(2-pyridinyl)-3-pyridazinyl]methyl]-	
1082	p.334 p.414	2857179-49-6	2,3-Piperazinedione, 1-cyclobutyl-4-[[5-(2-pyridinyl)-1,3,4-thiadiazol-2-yl]methyl]-	
1083	p.334 p.414	2857179-50-9	2,3-Pyrazinedione, 1-cyclobutyl-1,4-dihydro-4-[[5-(2-pyridinyl)-1,3,4-thiadiazol-2-yl]methyl]-	
1084	p.334 p.414	2857179-51-0		

1085	p.335 p.415	2857179-52-1		
1086	p.335 p.415	2857179-53-2	2,3-Pyrazinedione, 1-cyclobutyl-1,4-dihydro-4-[[5-(2-pyridinyl)-3-isoxazolyl]methyl]-	
1087	p.335 p.415	2857179-54-3		
1088	p.335 p.415	2858734-16-2	2,3-Pyrazinedione, 1-bicyclo[3.1.0]hex-3-yl-1,4-dihydro-4-[[5-(2-pyridinyl)-3-isoxazolyl]methyl]-	
1089	p.335 p.416	2857179-56-5	2,3-Piperazinedione, 1-cyclobutyl-4-[[5-(2-pyridinyl)-2-thiazolyl]methyl]-	
1090	p.336 p.434	2858734-17-3	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclopropyl)-4-[[6-(2-thiazolyl)-3-pyridazinyl]methyl]-	
1091	p.336 p.416	2857179-57-6	2,3-Piperazinedione, 1-cyclopentyl-4-[[5-(2*H*-1,2,3-triazol-2-yl)-2-pyrimidinyl]methyl]-	
1092	p.337 p.416	2857179-58-7	2,3-Piperazinedione, 1-cyclopentyl-4-[[2-fluoro-4-(2*H*-1,2,3-triazol-2-yl)phenyl]methyl]-	
1093	p.337 p.416	2857179-59-8	2,3-Piperazinedione, 1-cyclopentyl-4-[[5-(2*H*-1,2,3-triazol-2-yl)-2-pyridinyl]methyl]-	
1094	p.337 p.434	2858734-18-4		
1095	p.337 p.434	2858734-19-5		
1096	p.337 p.434	2858734-20-8	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclopropyl)-4-[[6-(1*H*-pyrazol-1-yl)-3-pyridinyl]methyl]-	
1097	p.338 p.435	2858734-21-9	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-[[6-(1*H*-pyrazol-1-yl)-3-pyridinyl]methyl]-	
1098	p.338 p.435	2858734-22-0	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclopropyl)-4-[[5-(1*H*-1,2,3-triazol-1-yl)-2-pyridinyl]methyl]-	
1099	p.338 p.435	2858734-23-1		

1100	p.338 p.435	2858734-24-2		
1101	p.338 p.435	2858734-25-3	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-[[5-(1*H*-1,2,3-triazol-1-yl)-2-pyridinyl]methyl]-	
1102	p.338 p.436	2858734-26-4		
1103	p.339 p.436	2858734-27-5		
1104	p.339 p.436	2858734-28-6		
1105	p.339 p.417	2857179-60-1	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(3,3-difluoro-1-pyrrolidinyl)-3-pyridinyl]methyl]-	
763	p.339	163457-23-6	Pyrrolidine, 3,3-difluoro-, hydrochloride (1:1)	
1106	p.340 p.417	2857179-61-2	2,3-Piperazinedione, 1-cyclopentyl-4-[[6-(3-fluoro-1-pyrrolidinyl)-3-pyridinyl]methyl]-	
1107	p.340 p.417	2857179-62-3	2,3-Piperazinedione, 1-cyclobutyl-4-[[6-(5-oxazolyl)-3-pyridazinyl]methyl]-	
764	p.340	288-42-6	Oxazole	
1108	p.341 p.417	2857179-63-4	2,3-Piperazinedione, 1-cyclobutyl-4-[[6-(5-thiazolyl)-3-pyridazinyl]methyl]-	
395	p.342	2857176-98-6	1,3,4-Thiadiazole-2-methanamine, 5-phenyl-*N*-2-propen-1-yl-	
396	p.343	2857176-99-7	Acetic acid, 2-oxo-2-[[(5-phenyl-1,3,4-thiadiazol-2-yl)methyl]-2-propen-1-ylamino]-, ethyl ester	

1109	p.344 p.418	2857179-64-5		
1111	p.345 p.412	2857179-65-6	2,3-Pyrazinedione, 1-cyclobutyl-1,4-dihydro-4-[[5-(2*H*-1,2,3-triazol-2-yl)-2-pyridinyl]methyl]-	
1112	p.346 p.418	2857179-66-7	2,3-Piperazinedione, 1-cyclobutyl-4-[[6-(2*H*-1,2,3-triazol-2-yl)-3-pyridazinyl]methyl]-	
1113	p.346 p.418	2857179-67-8	2,3-Piperazinedione, 1-cyclobutyl-4-[[4-(2*H*-1,2,3-triazol-2-yl)phenyl]methyl]-	
1114	p.347 p.419	2857179-68-9	2,3-Piperazinedione, 1-cyclobutyl-4-[[3-fluoro-5-(2*H*-1,2,3-triazol-2-yl)-2-pyridinyl]methyl]-	
1115	p.347 p.419	2857179-69-0	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[6-(2*H*-1,2,3-triazol-2-yl)-3-pyridazinyl]methyl]-	
1116	p.347 p.419	2857179-70-3	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[6-(1*H*-1,2,3-triazol-1-yl)-3-pyridazinyl]methyl]-	
1117	p.347 p.419	2857179-71-4	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-[[6-(2*H*-1,2,3-triazol-2-yl)-3-pyridazinyl]methyl]-	
1118	p.347 p.420	2857179-72-5	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-[[6-(1*H*-1,2,3-triazol-1-yl)-3-pyridazinyl]methyl]-	
1119	p.347 p.420	2857179-73-6	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[3-fluoro-5-(2*H*-1,2,3-triazol-2-yl)-2-pyridinyl]methyl]-	
1120	p.348 p.420	2857179-74-7	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[4-(2*H*-1,2,3-triazol-2-yl)phenyl]methyl]-	
1121	p.348 p.420	2857179-75-8	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[2-fluoro-4-(2*H*-1,2,3-triazol-2-yl)phenyl]methyl]-	
1122	p.348 p.421	2857179-76-9		
1123	p.348 p.421	2857179-77-0	2,3-Pyrazinedione, 1-cyclobutyl-1,4-dihydro-4-[[6-(2*H*-1,2,3-triazol-2-yl)-3-pyridinyl]methyl]-	
1124	p.348 p.421	2857179-78-1	2,3-Pyrazinedione, 1-cyclobutyl-1,4-dihydro-4-[[6-(1*H*-1,2,3-triazol-1-yl)-3-pyridinyl]methyl]-	

1125	p.348 p.436	2858734-29-7	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-[[6-(1*H*-1,2,3-triazol-1-yl)-3-pyridinyl]methyl]-	
1126	p.349 p.437	2858734-30-0	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-[[6-(2*H*-1,2,3-triazol-2-yl)-3-pyridinyl]methyl]-	
1127	p.349 p.437	2858734-31-1		
1128	p.349 p.437	2858734-32-2	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclopropyl)-4-[[6-(1*H*-1,2,3-triazol-1-yl)-3-pyridinyl]methyl]-	
1129	p.349 p.437	2858734-33-3	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclopropyl)-4-[[6-(2*H*-1,2,3-triazol-2-yl)-3-pyridinyl]methyl]-	
768	p.350	1420865-79-7	Pyridazine, 3-chloro-6-(chloromethyl)-, hydrochloride (1:1)	
398	p.350	2857177-00-3	3-Pyridazinemethanamine, 6-chloro-*N*-2-propen-1-yl-	
399	p.350	2857177-01-4	Acetic acid, 2-[[(6-chloro-3-pyridazinyl)methyl]-2-propen-1-ylamino]-2-oxo-, ethyl ester	
400	p.351	2857177-02-5	Acetic acid, 2-[[(6-chloro-1-oxido-3-pyridazinyl)methyl]-2-propen-1-ylamino]-2-oxo-, ethyl ester	
901	p.351	2857177-03-6	Acetic acid, 2-[[(6-chloro-1-oxido-3-pyridazinyl)methyl](2-oxoethyl)amino]-2-oxo-, ethyl ester	
902	p.352	2857177-04-7		
905	p.353 p.353 p.421	2857179-79-2		
770	p.354 p.357	1121-86-4	Benzene, 1-fluoro-3-iodo-	

1131	p.354 p.422	2857179-80-5	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[5-(3-fluorophenyl)-3-isoxazolyl]methyl]-1,4-dihydro-	
1132	p.355 p.422	2857179-83-8		
1133	p.355 p.422	2857179-84-9	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[[5-(4-fluorophenyl)-3-isoxazolyl]methyl]-1,4-dihydro-	
1134	p.355 p.437	2858734-34-4	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclobutyl)-4-[(5-phenyl-3-isoxazolyl)methyl]-	
1135	p.356 p.438	2858734-35-5	2,3-Pyrazinedione, 1-[[5-(3-fluorophenyl)-3-isoxazolyl]methyl]-1,4-dihydro-4-(1-methylcyclobutyl)-	
1136	p.356 p.438	2858734-36-6	2,3-Pyrazinedione, 1-[[5-(4-fluorophenyl)-3-isoxazolyl]methyl]-1,4-dihydro-4-(1-methylcyclobutyl)-	
1137	p.356 p.438	2858734-37-7	Benzonitrile, 4-[3-[(4-bicyclo[1.1.1]pent-1-yl-2,3-dioxo-1-piperazinyl)methyl]-5-isoxazolyl]-	
1138	p.356 p.438	2858734-38-8	Benzonitrile, 2-[3-[(4-bicyclo[1.1.1]pent-1-yl-2,3-dioxo-1-piperazinyl)methyl]-5-isoxazolyl]-	
1139	p.357 p.422	2857179-81-6	2,3-Piperazinedione, 1-cyclobutyl-4-[[5-(3-fluorophenyl)-2-thiazolyl]methyl]-	
1140	p.358 p.423	2857179-82-7	2,3-Piperazinedione, 1-cyclobutyl-4-[[5-(2-fluorophenyl)-2-thiazolyl]methyl]-	
1141	p.358 p.439	2858734-39-9	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-[[1-(2-pyridinyl)-1*H*-1,2,3-triazol-4-yl]methyl]-	
1142	p.359 p.439	2858734-40-2	2,3-Pyrazinedione, 1-bicyclo[1.1.1]pent-1-yl-1,4-dihydro-4-[[1-(3-pyridinyl)-1*H*-1,2,3-triazol-4-yl]methyl]-	
1143	p.359 p.439	2858734-41-3	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclopropyl)-4-[[1-(3-pyridinyl)-1*H*-1,2,3-triazol-4-yl]methyl]-	
1144	p.359 p.439	2858734-42-4	2,3-Pyrazinedione, 1,4-dihydro-1-(1-methylcyclopropyl)-4-[[1-(2-pyridinyl)-1*H*-1,2,3-triazol-4-yl]methyl]-	
1145	p.359 p.440	2858734-43-5		
1146	p.360 p.440	2858734-44-6	2,3-Piperazinedione, 1-[[4-bromo-5-(2-pyridinyl)-3-isoxazolyl]methyl]-4-cyclobutyl-	

777	p.360	5029-67-4	Pyridine, 2-iodo-	
1147	p.360 p.440	2858734-45-7	2,3-Piperazinedione, 1-[(6-phenyl-3-pyridazinyl)methyl]-4-(2-pyridinyl)-	
903	p.361	2858733-93-2	2,3-Piperazinedione, 1-[[6-(2-fluorophenyl)-3-pyridazinyl]methyl]-4-(3-oxocyclobutyl)-	
779	p.361	23761-24-2	Cyclobutanone, 3-bromo-	
1148	p.362 p.440	2858734-46-8	2,3-Piperazinedione, 1-[[6-(2-fluorophenyl)-3-pyridazinyl]methyl]-4-(3-hydroxycyclobutyl)-	
1149	p.363 p.441	2858734-47-9		
1150	p.363 p.441	2858734-48-0		
1151	p.364 p.441	2858734-49-1	Benzonitrile, 2-[5-[(4-bicyclo[1.1.1]pent-1-yl-2,3-dioxo-1-piperazinyl)methyl]-1,3,4-thiadiazol-2-yl]-	
1153	p.366 p.442	2858734-50-4		
1154	p.366 p.367 p.442	2858734-51-5	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl]-	
904	p.367	2858733-94-3	2,3-Piperazinedione, 1-bicyclo[1.1.1]pent-1-yl-4-(2-propyn-1-yl)-	
785	p.367	106-96-7	1-Propyne, 3-bromo-	
787	p.367	622-37-7	Benzene, azido-	
789	p.368	2858733-92-1	Cyclopentanamine, 3-phenyl-, ethanedioate (1:1)	
1156	p.368 p.442	2858734-52-6		

1157	p.368 p.442	2858734-53-7		
1158	p.368 p.442	2858734-54-8		
1159	p.368 p.442	2858734-55-9		
633	p.439	75-31-0	2-Propanamine	

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