

FURO-3-CARBOXAMIDE DERIVATIVES AND METHODS OF USE

BACKGROUND OF THE INVENTION

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Technical Field

The invention relates to furo-3-carboxamides that are inhibitors of TrkA (Tropomyosin receptor kinase isoform A), useful in treating diseases and conditions mediated and modulated by TrkA. Additionally, the invention relates to compositions containing
10 compounds of the invention and processes of their preparation.

Description of Related Technology

TrkA is member of the Trk (Tropomyosin receptor) receptor family. Currently this family is known to include three highly homologous isoforms, called TrkA, TrkB, and TrkC.
15 Trk receptors (Trks) are high affinity receptor tyrosine kinases. Trks bind adenosine triphosphate (ATP) and modulate intracellular signaling through their kinase enzymatic activity which is able to phosphorylate specific tyrosine residues of target proteins and peptides. Each Trk receptor isoform can be activated by endogenous peptidic factors known as neurotrophins (NT), which act as agonists of the Trk receptor. NGF (nerve growth factor)
20 is a high affinity activator of TrkA. BDNF (brain-derived neurotrophic factor) and NT-4/5 are high affinity activators of TrkB (Tropomyosin receptor kinase isoform B). NT3 is a high affinity activator of TrkC (Tropomyosin receptor kinase isoform C). Trks are expressed in neurons, and have been implicated in the development and function of the nervous system, as well as other physiological processes.

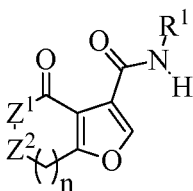
25 Neurotrophins and their Trk receptors have been implicated in pain sensation and in inflammation. Pezet S, et al. Ann Rev Neuroscience 2006;29:507-538; Mantyh PW, et al. Anesthesiology 2011;115:189-204; and Patapoutian A, et al. Current Opinion in Neurobiology 2001;11:272-280. Studies have shown that NGF, the agonist of TrkA, modulates pain in adult mammals. Dyck PJ, et al. Neurology 1997;48:501-505; and Deising
30 S, et al. Pain 2012;153:1673-1679. Studies have also shown that inhibitors of the NGF/TrkA pathway are effective in blocking pain. Lane NE, et al. New England J Med 2010;363:1521-1531; Schnitzer TJ, et al. Osteoarthritis Cartilage 2011;19:639-646; Katz N, et al. Pain 2011;152:2248-2258; Evans RJ, et al. J. Urology 2011;185:1716-1721; Shelton DL, et al. Pain 2005;116:8-16; Ro LS, et al. Pain 1999;79:265-274; and Ugolini G, et al. Proceedings of

the National Academy of Sciences of the USA 2007;104:2985-2990. TrkA inhibitors block NGF signaling through its receptor (TrkA) and have been found effective in reducing pain in animal models. Ghilardi JR, et al. Bone 2011;48:389-298; Ghilardi JR, et al. Molecular Pain 2010;6:87; Mantyh, WG, et al, Neuroscience 2010;17:588-598; and Hayashi K, et al. Journal of Pain 2011;12:1059-1068. The TrkA, TrkB, and TrkC isoforms have high structural homology. Of the potent Trk inhibitor structural classes described, testing of isoform selectivity has revealed a lack of selectivity for any particular Trk isoform, hence they have been termed 'pan-Trk' inhibitors (Albaugh P, et al. ACS Medicinal Chemistry Letters 2012;3:140-145), able to inhibit TrkA, TrkB, and TrkC. Wang T, et al. Expert Opinion on Therapeutic Patents 2009;19:305-319.

Although compounds and mechanisms exist that are used clinically to treat pain, there is need for new compounds that can effectively treat different types of pain. Pain of various types (e.g., inflammatory pain, post-surgical pain, osteoarthritis pain, neuropathic pain) afflicts virtually all humans and animals at one time or another, and a substantial number of medical disorders and conditions produce some sort of pain as a prominent concern requiring treatment. As such, it would be particularly beneficial to identify new compounds for treating the various types of pain.

SUMMARY

The invention is directed to furo-3-carboxamides having a structure of Formula (I):



(I)

or a pharmaceutically acceptable salt, ester, amide, or radiolabelled form thereof, wherein:

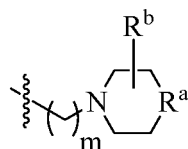
n is 1 or 2;

R¹ is phenyl or monocyclic heteroaryl, wherein the monocyclic heteroaryl contains one or two ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the phenyl or monocyclic heteroaryl is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C₁-C₆-alkyl; C₁-C₆-alkylcarbonylamino;

hydroxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxyC₁-C₆alkylcarbonylamino; C₁-C₆-alkoxy;

C₁-C₆-alkoxyC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl;
 C₁-C₆-alkoxycarbonylC₁-C₆-alkyl; aminocarbonyl; C₁-C₆-alkylaminocarbonyl;
 hydroxyC₁-C₆-alkylaminocarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylaminocarbonyl; cyano; carboxy;
 hydroxy; hydroxyC₁-C₆-alkoxy; hydroxyC₁-C₆-alkyl; di(hydroxy)C₁-C₆-alkyl;
 5 di(C₁-C₆-alkyl)amino; di(hydroxyC₁-C₆-alkyl)amino; di(C₁-C₆-alkoxyC₁-C₆-alkyl)amino;
 (C₁-C₆-alkoxyC₁-C₆-alkyl)(hydroxyC₁-C₆-alkyl)amino; haloC₁-C₆-alkyl; and halogen;
 wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to
 the amide nitrogen pendant on the furan ring; or

R¹ is fused-bicyclic heteroaryl, wherein the fused-bicyclic heteroaryl contains 1, 2, 3
 10 or 4 ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the fused-
 bicyclic heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents selected from the
 group consisting of C₁-C₆-alkyl; C₁-C₆-alkylcarbonylamino;
 hydroxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxy;
 C₁-C₆-alkoxyC₁-C₆-alkoxy; C₁-C₆-alkoxy-C₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl;
 15 C₁-C₆-alkoxycarbonylC₁-C₆-alkyl; C₃-C₇-cycloalkyloxy; M₄-M₇-heterocycleoxy, wherein the
 heterocycle of M₄-M₇-heterocycleoxy is optionally substituted with C₁-C₆-alkyl;
 aminocarbonyl; C₁-C₆-alkylaminocarbonyl; hydroxyC₁-C₆-alkylaminocarbonyl;
 C₁-C₆-alkoxyC₁-C₆-alkylaminocarbonyl; cyano; hydroxy; hydroxyC₁-C₆-alkoxy;
 hydroxyC₁-C₆-alkyl; di(C₁-C₆-alkyl)amino; di(hydroxyC₁-C₆-alkyl)amino;
 20 di(C₁-C₆-alkoxyC₁-C₆-alkyl)amino; (C₁-C₆-alkoxyC₁-C₆-alkyl)(hydroxyC₁-C₆-alkyl)amino;
 haloC₁-C₆-alkyl; halogen; C₁-C₆-alkylsulfonylaminoC₂-C₆-alkyl; and (i),



(i)

wherein R^a is selected from the group consisting of a bond, CH₂, CHR^b, O, S, and N-R^c;
 25 wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to
 the amide nitrogen pendant on the furan ring;

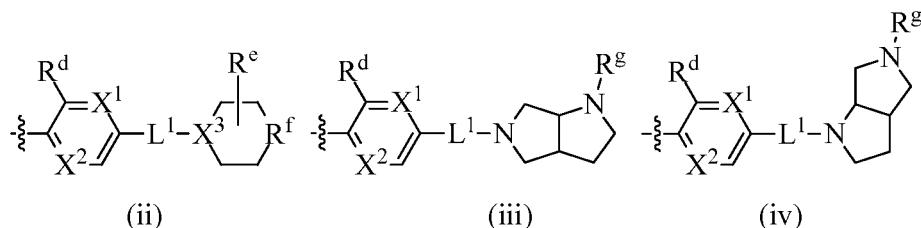
m is 2, 3 or 4 when (i) is attached to a ring nitrogen atom of the bicyclic heteroaryl; or

m is 0, 1, 2, 3 or 4 when (i) is attached to a ring carbon atom of the bicyclic
 heteroaryl;

30 R^b, at each occurrence, is independently selected from the group consisting of
 hydrogen, C₁-C₆-alkyl, haloC₁-C₆-alkyl, C₁-C₆-alkoxyC₁-C₆-alkyl, and hydroxyC₁-C₆-alkyl;

R^c is selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, C_1 - C_6 -alkoxycarbonyl, C_1 - C_6 -alkylcarbonyl, C_1 - C_6 -alkylsulfonyl, di(C_1 - C_6 -alkyl)aminosulfonyl, heterocyclecarbonyl, C_3 - C_7 -cycloalkylcarbonyl, $-C(O)NH_2$, $-C(O)NH(alkyl)$, $-C(O)N(alkyl)_2$ and $-C(=NCN)NHCH_3$; or

5 R^1 is (ii), (iii), or (iv);



wherein both X^1 and X^2 are CH, or one of X^1 and X^2 is N and the other is CH;

X^3 is CH or N;

10 L^1 is a bond, $C(O)$, or $-NHC(O)-$;

R^d is selected from the group consisting of hydrogen; C_1 - C_6 alkoxy; fluoro C_1 - C_6 -alkoxy; C_1 - C_6 -alkoxy C_1 - C_6 -alkoxy; C_3 - C_7 -cycloalkyloxy; C_3 - C_7 -cycloalkyl C_1 - C_6 -alkoxy; hydroxy C_1 - C_6 -alkoxy; phenyl C_1 - C_6 -alkoxy C_1 - C_6 -alkoxy; M_4 - M_7 -heterocycleoxy, wherein the heterocycle of heterocycleoxy is optionally substituted with C_1 - C_6 -alkyl or oxo; and phenoxy, wherein the phenyl of phenoxy is optionally substituted with hydroxy C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -alkoxy C_1 - C_6 -alkoxy, or C_1 - C_6 -alkoxycarbonyl;

R^e at each occurrence is independently selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, di(C_1 - C_6 -alkyl)amino, halo C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy C_1 - C_6 alkyl, and hydroxy C_1 - C_6 -alkyl;

R^f is selected from the group consisting of a bond, CH_2 , CHR^c , CH_2CH_2 , O, NR^g , and CH_2NR^g ;

R^g is selected from the group consisting of hydrogen; C_1 - C_6 -alkyl; C_1 - C_6 -alkoxycarbonyl; C_1 - C_6 -alkylcarbonyl; C_1 - C_6 -alkylsulfonyl; di(C_1 - C_6 -alkyl)aminosulfonyl; C_3 - C_7 -cycloalkylcarbonyl; C_1 - C_6 -alkoxy C_1 - C_6 -alkylcarbonyl; hydroxy C_2 - C_6 -alkyl; hydroxy C_1 - C_6 -alkylcarbonyl; formyl; $-C(O)NH_2$; $-C(O)NH(alkyl)$; $-C(O)N(alkyl)_2$; $-C(=NCN)NHCH_3$; and M_4 - M_7 -heterocyclecarbonyl, wherein the heterocycle of heterocyclecarbonyl is optionally substituted with C_1 - C_6 -alkyl;

30 Z^1 is NR^2 or CR^3R^4 ;

R^2 is selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, hydroxy C_2 - C_6 -alkyl, di(hydroxy) C_2 - C_6 -alkyl, C_1 - C_6 -alkoxy C_2 - C_6 -alkyl, hydroxy C_2 - C_6 -alkoxy C_2 - C_6 -alkyl, C_1 - C_6 -alkylcarbonyloxy C_2 - C_6 -alkyl, C_1 - C_6 -alkoxycarbonyl C_1 - C_6 -alkyl, C_1 - C_6 -alkylcarbonyl C_1 - C_6 -alkyl and
5 phenyl C_1 - C_6 -alkoxy C_2 - C_6 -alkyl;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, hydroxy C_1 - C_6 -alkyl, amino C_1 - C_6 -alkyl, and phenyl, wherein phenyl is optionally substituted with 1, 2, 3 or 4 substituents selected from halogen, C_1 - C_6 -alkyl, and cyano; or

10 R^3 and R^4 taken together with the carbon atom to which they are attached form a M_4 - M_7 -heterocycle optionally substituted with 1, 2 or 3 halogen, C_1 - C_6 -alkyl, cyano or oxo;

Z^2 is O, NR^5 , or CR^6R^7 ;

R^5 is selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, C_1 - C_6 -alkylsulfonyl, C_1 - C_6 -alkylcarbonyl, and C_1 - C_6 -alkoxycarbonyl; and
15

R^6 and R^7 are each independently selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy C_1 - C_6 -alkyl, hydroxy C_1 - C_6 -alkyl, amino C_1 - C_6 -alkyl, aminocarbonyl, and C_1 - C_6 -alkoxycarbonyl;

wherein one or more of R^3 , R^4 , R^6 and R^7 is other than hydrogen; or

20 R^6 and R^7 taken together with the carbon atom to which they are attached form a C_3 - C_6 -cycloalkyl or M_4 - M_7 -heterocycle, wherein the C_3 - C_6 -cycloalkyl or M_4 - M_7 -heterocycle are optionally substituted with 1, 2, or 3 substituents selected from C_1 - C_6 -alkyl, cyano, aminocarbonyl, halogen, oxo and C_1 - C_6 -alkylcarbonyl.

25 Another aspect of the invention relates to pharmaceutical compositions comprising compounds of the invention. Such compositions can be administered in accordance with a method of the invention, typically as part of a therapeutic regimen for treatment or prevention of conditions and disorders related to Trk receptor kinases (and particularly TrkA kinase) activity.

30 Yet another aspect of the invention relates to a method of selectively modulating TrkA receptor kinase activity. The method is useful for treating, or preventing conditions and disorders related to TrkA modulation in mammals. More particularly, the method is useful for treating or preventing conditions and disorders related to pain, neuropathy, inflammation, auto-immune disease, fibrosis, chronic kidney disease, and cancer. Accordingly, the

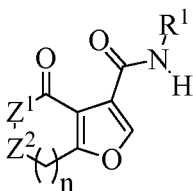
compounds and compositions of the invention are useful as a medicament for treating or preventing TrkA receptor kinases modulated disease.

The compounds, compositions comprising the compounds, methods for making the compounds, and methods for treating or preventing conditions and disorders by administering the compounds are further described herein.

These and other objects of the invention are described in the following paragraphs. These objects should not be deemed to narrow the scope of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Compounds of formula (I) are disclosed in this invention



(I)

wherein R¹, Z¹, Z², and n are as defined above in the Summary. Compositions comprising such compounds and methods for treating conditions and disorders using such compounds and compositions are also disclosed.

In various embodiments, the present invention provides at least one variable that occurs more than one time in any substituent or in the compound of the invention or any other formulae herein. Definition of a variable on each occurrence is independent of its definition at another occurrence. Further, combinations of substituents are permissible only if such combinations result in stable compounds. Stable compounds are compounds which can be isolated from a reaction mixture.

Definition of Terms

Certain terms as used in the specification are intended to refer to the following definitions, as detailed below.

The term "alkenyl" as used herein, means a straight or branched hydrocarbon chain containing from 2 to 10 carbons and containing at least one carbon-carbon double bond. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and 3-decenyl.

The term "alkoxy" as used herein means an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, *tert*-butoxy, pentyloxy, and hexyloxy.

5 The term "alkoxyalkoxy" as used herein, means an alkoxy group, as defined herein, appended to the parent molecular moiety through another alkoxy group, as defined herein. Representative examples of alkoxyalkoxy include, but are not limited to, *tert*-butoxymethoxy, 2-ethoxyethoxy, 2-methoxyethoxy, and methoxymethoxy.

10 The term "alkoxyalkyl" as used herein means an alkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxyalkyl include, but are not limited to, *tert*-butoxymethyl, 2-ethoxyethyl, 2-methoxyethyl, and methoxymethyl.

15 The term "alkoxyalkylamino" as used herein means an alkoxyalkyl group, as defined herein, appended to the parent molecular moiety through an amino group, as defined herein. Representative examples of alkoxyalkylamino include, but are not limited to, ethoxyethylamino, methoxyethylamino, and methoxypropylamino.

20 The term "alkoxyalkylaminocarbonyl" as used herein means an alkoxyalkylamino group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkoxyalkylaminocarbonyl include, but are not limited to, ethoxyethylaminocarbonyl, methoxyethylaminocarbonyl, and methoxypropylaminocarbonyl.

25 The term "alkoxyalkylcarbonyl" as used herein means an alkoxyalkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkoxyalkylcarbonyl include, but are not limited to, ethoxyethylcarbonyl, methoxyethylcarbonyl, and methoxypropylcarbonyl.

30 The term "alkoxyalkylcarbonylamino" as used herein means an alkoxycarbonyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkoxyalkylcarbonylamino include, but are not limited to, ethoxyethylcarbonylamino, methoxyethylcarbonylamino, and methoxypropylcarbonylamino.

The term "(alkoxyalkyl)(hydroxyalkyl)amino," as used herein, refers to one alkoxyalkyl group and one hydroxyalkyl group, as defined herein, appended to the parent molecular moiety through an amino group, as defined herein. Representative examples of (alkoxyalkyl)(hydroxyalkyl)amino include, but are not limited to,

(methoxyethyl)(hydroxyethyl)amino, (ethoxyethyl)(hydroxyethyl)amino, and (methoxyethyl)(hydroxypropyl)amino, and the like.

The term "alkoxycarbonyl" as used herein means an alkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein.

5 Representative examples of alkoxycarbonyl include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, and *tert*-butoxycarbonyl.

The term "alkoxycarbonylalkyl" as used herein, means an alkoxycarbonyl group, as defined herein, appended to the parent molecular moiety through an alkylene group, as defined herein. Representative examples of alkoxycarbonylalkyl include, but are not limited to, 3-methoxycarbonylpropyl, 4-ethoxycarbonylbutyl, and 2-*tert*-butoxycarbonylethyl.

The term "alkyl" as used herein, means a straight or branched, saturated hydrocarbon chain containing from 1 to 10 carbon atoms. The term "lower alkyl" or "C₁-C₆-alkyl" means a straight or branched chain hydrocarbon containing from 1 to 6 carbon atoms. The term "C₁-C₃-alkyl" means a straight or branched chain hydrocarbon containing from 1 to 3 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, *n*-heptyl, *n*-octyl, *n*-nonyl, and *n*-decyl.

The term "alkylamino" means an alkyl group appended to the parent molecular moiety through an amino group, as defined herein. Representative examples of alkylamino include, but are not limited to, methylamino, ethylamino, and *sec*-butylamino.

The term "alkylaminocarbonyl" means an alkylamino group appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkylaminocarbonyl include, but are not limited to, methylaminocarbonyl, ethylaminocarbonyl, and isopropylaminocarbonyl, and the like.

The term "alkylcarbonyl" as used herein means an alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkylcarbonyl include, but are not limited to, methylcarbonyl (acetyl), ethylcarbonyl, isopropylcarbonyl, *n*-propylcarbonyl, and the like.

30 The term "alkylcarbonylamino" means -N(H)-C(O)-alkyl.

The term "alkylcarbonylalkyl" refers to an alkylcarbonyl group appended to the parent molecular moiety through an alkylene moiety. Representative examples of alkylcarbonylalkyl include, but are not limited to, propan-2-onyl, and 3-methyl-butan-2-onyl.

The term "alkylcarbonyloxy" as used herein, means an alkylcarbonyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom.

Representative examples of alkylcarbonyloxy include, but are not limited to, acetyloxy, ethylcarbonyloxy, and tert-butylcarbonyloxy.

5 The term "alkylcarbonyloxyalkyl" refers to an alkylcarbonyloxy group appended to the parent molecular moiety through an alkylene moiety. Representative examples of alkylcarbonyloxyalkyl include, but are not limited to, 2-(acetyloxy)ethyl, 3-(acetyloxy)propyl, and 3-(propionyloxy)propyl.

10 The term "alkylene" denotes a divalent group derived from a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms. Representative examples of alkylene include, but are not limited to, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, and $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$.

The term "alkylsulfonyl," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein.

15 Representative examples of alkylsulfonyl include, but are not limited to, methylsulfonyl and ethylsulfonyl.

The term "alkylsulfonylamino," as used herein, refers to an alkylsulfonyl group, as defined herein, appended to the parent molecular moiety through an amino group, as defined herein. Representative examples of alkylsulfonylamino include, but are not limited to, methylsulfonylamino, ethylsulfonylamino, and n-butylsulfonylamino, and the like.

20 The term "alkylsulfonylaminoalkyl," as used herein, refers to an alkylsulfonylamino group, as defined herein, appended to the parent molecular moiety through an alkylene group, as defined herein. Representative examples of alkylsulfonylaminoalkyl include, but are not limited to, methylsulfonylaminoethyl, ethylsulfonylaminoethyl, and isopropylsulfonylaminoethyl, and the like.

The term "alkynyl" as used herein, means a straight or branched chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited to, acetylenyl, 1-propynyl, 2-propynyl, 3-butynyl, 2-pentynyl, and 1-butynyl.

30 The term "amino" as used herein means an $-\text{NH}_2$ group.

The term "aminocarbonyl" (alone or in combination with another term(s)) means $-\text{C}(\text{O})-\text{NH}_2$.

The term "aminoalkyl" as used herein, means at least one amino group, as defined herein, is appended to the parent molecular moiety through an alkylene group, as defined

herein. Representative examples of aminoalkyl include, but are not limited to, aminomethyl, 2-aminoethyl, 3-aminopropyl, and 4-amino-2-ethylheptyl.

The term "aryl" as used herein, means phenyl or a bicyclic aryl. The bicyclic aryl is naphthyl, or a phenyl fused to a monocyclic cycloalkyl, or a phenyl fused to a monocyclic cycloalkenyl. Representative examples of the aryl groups include, but are not limited to, dihydroindenyl, indenyl, naphthyl, dihydronaphthalenyl, and tetrahydronaphthalenyl. The bicyclic aryl is attached to the parent molecular moiety through any carbon atom contained within the bicyclic ring system. The aryl groups of the present invention can be unsubstituted or substituted.

The term "arylalkyl" as used herein, means an aryl group, as defined herein, appended to the parent molecular moiety through an alkylene group, as defined herein. Representative examples of arylalkyl include, but are not limited to, benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, and 2-naphth-2-ylethyl.

The term "aryloxy," as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of aryloxy include, but are not limited to, phenoxy, naphthyloxy, 3-bromophenoxy, 4-chlorophenoxy, 4-methylphenoxy, 3,5-dimethoxyphenoxy, and the like.

The term "carbonyl" as used herein means a -C(=O)- group.

The term "carboxy," as used herein, refers to a -CO₂H group.

The term "cyano" as used herein, means a -CN group.

The term "cycloalkenyl" or "cycloalkene" as used herein, means a monocyclic or a bicyclic hydrocarbon ring system. The monocyclic cycloalkenyl has four-, five-, six-, seven- or eight carbon atoms and zero heteroatoms. The four-membered ring systems have one double bond, the five- or six-membered ring systems have one or two double bonds, and the seven- or eight-membered ring systems have one, two or three double bonds. Representative examples of monocyclic cycloalkenyl groups include, but are not limited to, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl. The bicyclic cycloalkenyl is a monocyclic cycloalkenyl fused to a monocyclic cycloalkyl group, or a monocyclic cycloalkenyl fused to a monocyclic cycloalkenyl group, or a bridged monocyclic ring system in which two non-adjacent carbon atoms of the monocyclic ring are linked by an alkylene bridge containing one, two, three, or four carbon atoms. Representative examples of the bicyclic cycloalkenyl groups include, but are not limited to, 4,5,6,7-tetrahydro-3aH-indene, octahydronaphthalenyl and 1,6-dihydro-pentalene. The monocyclic and bicyclic

cycloalkenyl can be attached to the parent molecular moiety through any substitutable atom contained within the ring systems, and can be unsubstituted or substituted.

The term "cycloalkenylalkyl," as used herein, refers to a cycloalkenyl group attached to the parent molecular moiety through an alkyl group.

5 The term "cycloalkyl" or "cycloalkane" as used herein, means a monocyclic, a bicyclic, or a tricyclic cycloalkyl. The monocyclic cycloalkyl is a carbocyclic ring system containing three to eight carbon atoms, zero heteroatoms and zero double bonds. Examples of monocyclic ring systems include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The bicyclic cycloalkyl is a monocyclic cycloalkyl fused to a
10 monocyclic cycloalkyl ring, or a bridged monocyclic ring system in which two non-adjacent carbon atoms of the monocyclic ring are linked by an alkylene bridge containing one, two, three, or four carbon atoms. Representative examples of bicyclic ring systems include, but are not limited to, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, and bicyclo[4.2.1]nonane. Tricyclic cycloalkyls
15 are exemplified by a bicyclic cycloalkyl fused to a monocyclic cycloalkyl, or a bicyclic cycloalkyl in which two non-adjacent carbon atoms of the ring systems are linked by an alkylene bridge of 1, 2, 3, or 4 carbon atoms. Representative examples of tricyclic-ring systems include, but are not limited to, tricyclo[3.3.1.0^{3,7}]nonane (octahydro-2,5-methanopentalene or noradamantane), and tricyclo[3.3.1.1^{3,7}]decane (adamantane). The
20 monocyclic, bicyclic, and tricyclic cycloalkyls can be unsubstituted or substituted, and are attached to the parent molecular moiety through any substitutable atom contained within the ring system.

The term "cycloalkylalkyl" as used herein, means a cycloalkyl group appended to the parent molecular moiety through an alkyl group, as defined herein.

25 The term "cycloalkylalkoxy" as used herein, means cycloalkyl group, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of cycloalkylalkoxy include, but are not limited to, cyclopropylmethoxy, cyclobutylmethoxy, and cyclopentylethoxy, and the like.

30 The term "cycloalkylcarbonyl" as used herein, means cycloalkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of cycloalkylcarbonyl include, but are not limited to, cyclopropylcarbonyl, 2-cyclobutylcarbonyl, and cyclohexylcarbonyl.

The term "cycloalkyloxy" as used herein, means cycloalkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom, as defined herein.

Representative examples of cycloalkyloxy include, but are not limited to, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, and cyclooctyloxy.

The term "di(alkoxyalkyl)amino," as used herein, refers to two independent alkoxyalkyl groups, as defined herein, appended to the parent molecular moiety through an amino group, as defined herein. Representative examples of di(alkoxyalkyl)amino include, but are not limited to, di(methoxyethyl)amino, di(ethoxypropyl)amino, and (methoxyethyl)(ethoxyethyl)amino, and the like.

The term "di(alkyl)amino," as used herein, refers to two independent alkyl groups, as defined herein, appended to the parent molecular moiety through an amino group, as defined herein. Representative examples of di(alkyl)amino include, but are not limited to, dimethylamino, diethylamino, ethylmethylamino, butylmethylamino, ethylhexylamino, and the like.

The term "di(alkyl)aminosulfonyl," as used herein, refers to a di(alkyl)amino group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples of di(alkyl)aminosulfonyl include, but are not limited to, di(methyl)aminosulfonyl, di(ethyl)aminosulfonyl, and (methyl)(ethyl)aminosulfonyl, and the like.

The term "di(hydroxy)alkyl" as used herein, means two hydroxy groups, as defined herein, are appended to the parent molecular moiety through an alkylene group, as defined herein. Representative examples of di(hydroxy)alkyl include, but are not limited to, propane-1,2-diol and butane-1,3-diol.

The term "di(hydroxyalkyl)amino," as used herein, refers to two independent hydroxyalkyl groups, as defined herein, appended to the parent molecular moiety through an amino group, as defined herein. Representative examples of di(hydroxyalkyl)amino include, but are not limited to, di(2-hydroxyethyl)aminosulfonyl, di(3-hydroxyethyl)aminosulfonyl, and (2-hydroxyethyl)(2-hydroxypropyl)aminosulfonyl, and the like.

The term "fluoroalkoxy" as used herein, means an alkoxy group, as defined herein, in which one, two, three, four, five, six, seven or eight hydrogen atoms are replaced by fluorine. Representative examples of haloalkoxy include, but are not limited to, fluoromethoxy, 2-fluoroethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, trifluoromethoxy, difluoromethoxy, pentafluoroethoxy, 1,1,2-trifluoroisopropoxy, and trifluoropropyl such as 3,3,3-trifluoropropoxy.

The term "fluoroalkyl" as used herein, means an alkyl group, as defined herein, in which one, two, three, four, five, six, seven or eight hydrogen atoms are replaced by fluorine.

Representative examples of haloalkyl include, but are not limited to, fluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, trifluoromethyl, difluoromethyl, pentafluoroethyl, 1,1,2-trifluoroisopropyl, and trifluoropropyl such as 3,3,3-trifluoropropyl.

The term "formyl," as used herein, refers to a -C(O)H group.

5 The term "halo" or "halogen" as used herein, means Cl, Br, I, or F.

The term "haloalkyl" as used herein, means an alkyl group, as defined herein, in which one, two, three, four, five, six, seven or eight hydrogen atoms are replaced by halogen. Representative examples of haloalkyl include, but are not limited to, chloromethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, trifluoromethyl, difluoromethyl, pentafluoroethyl, 2-chloro-
10 3-fluoropentyl, and trifluoropropyl such as 3,3,3-trifluoropropyl.

The term "heteroaryl" as used herein, means a monocyclic heteroaryl or a bicyclic heteroaryl. The monocyclic heteroaryl is a five- or six-membered ring. The five-membered ring contains two double bonds. The five-membered ring may contain one heteroatom selected from O or S; or one, two, three, or four nitrogen atoms and optionally one oxygen or sulfur atom. The six-membered ring contains three double bonds and one, two, three or four
15 nitrogen atoms. Representative examples of monocyclic heteroaryl include, but are not limited to, furanyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, 1,3-oxazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, tetrazolyl, thiadiazolyl, 1,3-thiazolyl, thienyl, triazolyl, and triazinyl. The bicyclic heteroaryl consists of a monocyclic heteroaryl
20 fused to a phenyl, or a monocyclic heteroaryl fused to a monocyclic cycloalkyl, or a monocyclic heteroaryl fused to a monocyclic cycloalkenyl, or a monocyclic heteroaryl fused to a monocyclic heteroaryl, or a monocyclic heteroaryl fused to a monocyclic heterocycle. Representative examples of bicyclic heteroaryl groups include, but are not limited to, benzofuranyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzoxadiazolyl, 6,7-dihydro-1,3-
25 benzothiazolyl, imidazo[1,2-*a*]pyridinyl, indazolyl, indolyl, isoindolyl, isoquinolinyl, naphthyridinyl, pyridoimidazolyl, quinolinyl, thiazolo[5,4-*b*]pyridin-2-yl, thiazolo[5,4-*d*]pyrimidin-2-yl, and 5,6,7,8-tetrahydroquinolin-5-yl. The monocyclic and bicyclic heteroaryl groups of the present invention can be substituted or unsubstituted and are connected to the parent molecular moiety through any carbon atom or any nitrogen atom
30 contained within the ring systems.

The term "heteroarylalkyl" as used herein, means a heteroaryl, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

The term "heterocycle" or "heterocyclic" as used herein, means a monocyclic heterocycle, a bicyclic heterocycle, or a tricyclic heterocycle. The monocyclic heterocycle is

a three-, four-, five-, six-, seven-, or eight-membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S. The three- or four-membered ring contains zero or one double bond, and one heteroatom selected from the group consisting of O, N, and S. The five-membered ring contains zero or one double bond and one, two or three heteroatoms selected from the group consisting of O, N and S. The six-membered ring contains zero, one or two double bonds and one, two, or three heteroatoms selected from the group consisting of O, N, and S. The seven- and eight-membered rings contains zero, one, two, or three double bonds and one, two, or three heteroatoms selected from the group consisting of O, N, and S. Representative examples of monocyclic heterocycles include, but are not limited to, azetidiny, azepany, aziridiny, diazepany, 1,3-dioxany, 1,3-dioxolany, 1,3-dithiolany, 1,3-dithiany, imidazoliny, imidazolidiny, isothiazoliny, isothiazolidiny, isoxazoliny, isoxazolidiny, morpholiny, oxadiazoliny, oxadiazolidiny, oxazoliny, oxazolidiny, oxetany, piperaziny, piperidiny, pyranly, pyrazoliny, pyrazolidiny, pyrroliny, pyrrolidiny, tetrahydrofurany, tetrahydropyrany, tetrahydropyridiny, tetrahydrothieny, thiadiazoliny, thiadiazolidiny, 1,2-thiazinany, 1,3-thiazinany, thiazoliny, thiazolidiny, thiomorpholiny, 1,1-dioxidothiomorpholiny (thiomorpholine sulfone), thiopyranly, and trithiany. The bicyclic heterocycle is a monocyclic heterocycle fused to a phenyl group, or a monocyclic heterocycle fused to a monocyclic cycloalkyl, or a monocyclic heterocycle fused to a monocyclic cycloalkenyl, or a monocyclic heterocycle fused to a monocyclic heterocycle, or a bridged monocyclic heterocycle ring system in which two non-adjacent atoms of the ring are linked by an alkylene bridge of 1, 2, 3, or 4 carbon atoms, or an alkenylene bridge of two, three, or four carbon atoms. Representative examples of bicyclic heterocycles include, but are not limited to, benzopyranly, benzothiopyranly, chromany, 2,3-dihydrobenzofurany, 2,3-dihydrobenzothieny, 2,3-dihydroisoquinoline, azabicyclo[2.2.1]heptyl (including 2-azabicyclo[2.2.1]hept-2-yl), 2,3-dihydro-1*H*-indolyl, isoindoliny, octahydrocyclopenta[*c*]pyrroly, octahydropyrrolopyridiny, and tetrahydroisoquinoliny. Tricyclic heterocycles are exemplified by a bicyclic heterocycle fused to a phenyl group, or a bicyclic heterocycle fused to a monocyclic cycloalkyl, or a bicyclic heterocycle fused to a monocyclic cycloalkenyl, or a bicyclic heterocycle fused to a monocyclic heterocycle, or a bicyclic heterocycle in which two non-adjacent atoms of the bicyclic ring are linked by an alkylene bridge of 1, 2, 3, or 4 carbon atoms, or an alkenylene bridge of two, three, or four carbon atoms. Examples of tricyclic heterocycles include, but not limited to, octahydro-2,5-epoxypentalene, hexahydro-2*H*-2,5-methanocyclopenta[*b*]furan, hexahydro-1*H*-1,4-

methanocyclopenta[*c*]furan, aza-adamantane (1-azatricyclo[3.3.1.1^{3,7}]decane), and oxa-adamantane (2-oxatricyclo[3.3.1.1^{3,7}]decane). The monocyclic, bicyclic, and tricyclic heterocycles are connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the rings, and can be unsubstituted or substituted.

5 The term "heterocyclealkyl", as used herein, refers to a heterocycle group attached to the parent molecular moiety through an alkyl group.

 The term "heterocyclecarbonyl," as used herein, refers to a heterocycle, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein.

 The term "heterocycleoxy," as used herein, refers to a heterocycle, as defined herein,
10 appended to the parent molecular moiety through an oxy group, as defined herein.

 The term "heteroatom" as used herein, means a nitrogen, oxygen, or sulfur atom.

 The term "hydroxyl" or "hydroxy" as used herein, means an -OH group.

 The term "hydroxyalkoxy" as used herein, means at least one hydroxy group, as defined herein, is appended to the parent molecular moiety through an alkoxy group, as
15 defined herein. Representative examples of hydroxyalkoxy include, but are not limited to, 2-hydroxyethoxy, 2-hydroxypropoxy, and 3-hydroxypropoxy, and the like.

 The term "hydroxyalkyl" as used herein, means at least one hydroxy group, as defined herein, is appended to the parent molecular moiety through an alkylene group, as defined herein. Representative examples of hydroxyalkyl include, but are not limited to,
20 hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, and 2-ethyl-4-hydroxyheptyl.

 The term "hydroxyalkylamino" as used herein, means at least one hydroxyalkyl group, as defined herein, is appended to the parent molecular moiety through an amino group, as defined herein. Representative examples of hydroxyalkylamino include, but are not limited to, 2-hydroxyethylamino, 2-hydroxypropylamino, and 3-hydroxybutylamino, and the
25 like.

 The term "hydroxyalkylaminocarbonyl" as used herein, means a hydroxyalkylamino group, as defined herein, is appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of hydroxyalkylaminocarbonyl include, but are not limited to, 2-hydroxyethylaminocarbonyl, 2-hydroxypropylaminocarbonyl, and
30 3-hydroxybutylaminocarbonyl, and the like.

 The term "hydroxyalkoxyalkyl" as used herein, means a hydroxyalkoxy group, as defined herein, appended to the parent molecular moiety through an alkylene group, as defined herein. Representative examples of hydroxyalkoxyalkyl include, but are not limited to, (2-hydroxy-ethoxy)-ethyl, and (3-hydroxypropoxy)-ethyl.

The term "hydroxyalkylcarbonyl" as used herein, means a hydroxyalkyl group, as defined herein, as appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples include, but are not limited to, 2-hydroxyacetyl, and 4-hydroxybutanoyl.

5 The term "hydroxyalkylcarbonylamino" as used herein, means a hydroxyalkylcarbonyl group, as defined herein, as appended to the parent molecular moiety through an amino group, as defined herein. Representative examples include, but are not limited to, hydroxymethylcarbonylamino, 1-hydroxyethylcarbonylamino, and 2-hydroxyethylcarbonylamino.

10 The term "oxo" as used herein means (=O).

The term "oxy," as used herein, refers to a -O- group.

The term "phenyloxy" or "phenoxy," as used herein, refers to a phenyl group, optionally substituted, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of phenyloxy or phenoxy include, but are not limited to, phenoxy, 3-bromophenoxy, 4-chlorophenoxy, 4-methylphenoxy, 3,5-dimethoxyphenoxy, and the like.

15 The term "phenylalkoxyalkoxy," as used herein, refers to a phenyl group, optionally substituted, appended to the parent molecular moiety through an alkoxyalkoxy moiety, as defined herein. Representative examples of phenylalkoxyalkoxy include, but are not limited to, 2-(benzyloxy)ethoxy, 2-(1-phenylethoxy)ethoxy, and the like.

20 The term "phenylalkoxyalkyl," as used herein, refers to a phenyl group, optionally substituted, appended to the parent molecular moiety through an alkoxyalkyl moiety, as defined herein. Representative examples of phenylalkoxyalkyl include, but are not limited to, 2-(benzyloxy)ethyl, 2-(1-phenylethoxy)ethyl, and the like.

25 The term "sulfonyl," as used herein, refers to a -S(O)₂- group.

In some instances, the number of carbon atoms in a hydrocarbyl substituent (e.g., alkyl, alkenyl, alkynyl, or cycloalkyl) is indicated by the prefix "C_x-C_y-", wherein x is the minimum and y is the maximum number of carbon atoms in the substituent. Thus, for example, "C₁-C₆-alkyl" refers to an alkyl substituent containing from 1 to 6 carbon atoms. Illustrating further, C₃-C₆-cycloalkyl means a saturated hydrocarbyl ring containing from 3 to 6 carbon ring atoms.

As used herein, the number of ring atoms in a heterocyclic moiety can be identified by the prefix “M_x-M_y,” where x is the minimum and y is the maximum number of ring atoms in the heterocyclic moiety.

As used herein, the term “radiolabel” refers to a compound of the invention in which at least one of the atoms is a radioactive atom or radioactive isotope, wherein the radioactive atom or isotope spontaneously emits gamma rays or energetic particles, for example alpha particles or beta particles, or positrons. Examples of such radioactive atoms include, but are not limited to, ³H (tritium), ¹⁴C, ¹¹C, ¹⁵O, ¹⁸F, ³⁵S, ¹²³I, and ¹²⁵I.

10 Compounds of the Invention

Compounds of the invention can have the Formula (I) as described in the Summary.

Particular values of variable groups in compounds of Formula (I) are as follows.

Such values can be used where appropriate with any of the other values, definitions, claims or embodiments defined hereinbefore or hereinafter.

15 In one embodiment, n is 1 or 2.

In another embodiment, n is 1.

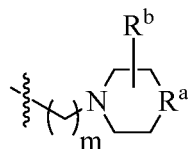
In another embodiment, n is 2.

In one embodiment, R¹ is phenyl or monocyclic heteroaryl, wherein the monocyclic heteroaryl contains one or two ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the phenyl or monocyclic heteroaryl is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C₁-C₆-alkyl; C₁-C₆-alkylcarbonylamino; hydroxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl; C₁-C₆-alkoxycarbonylC₁-C₆-alkyl; aminocarbonyl; C₁-C₆-alkylaminocarbonyl; hydroxyC₁-C₆-alkylaminocarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylaminocarbonyl; cyano; carboxy; hydroxy; hydroxyC₁-C₆-alkoxy; hydroxyC₁-C₆-alkyl; di(hydroxy)C₁-C₆-alkyl; di(C₁-C₆-alkyl)amino; di(hydroxyC₁-C₆-alkyl)amino; di(C₁-C₆-alkoxyC₁-C₆-alkyl)amino; (C₁-C₆-alkoxyC₁-C₆-alkyl)(hydroxyC₁-C₆-alkyl)amino; haloC₁-C₆-alkyl; and halogen; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring.

In another embodiment, R¹ is phenyl or monocyclic heteroaryl, wherein the monocyclic heteroaryl contains one or two ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the phenyl or monocyclic heteroaryl is optionally substituted with 1

or 2 substituents selected from the group consisting of C₁-C₆-alkyl; C₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₁-C₆-alkoxycarbonylC₁-C₆-alkyl; aminocarbonyl; cyano; carboxy; hydroxy; hydroxyC₁-C₆-alkyl; di(C₁-C₆alkyl)amino; di(hydroxyC₁-C₆-alkyl)amino; haloC₁-C₆-alkyl; and halogen; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring.

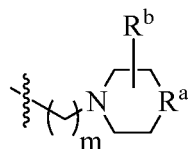
In one embodiment, R¹ is fused-bicyclic heteroaryl, wherein the fused-bicyclic heteroaryl contains 1, 2, 3 or 4 ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the fused-bicyclic heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of C₁-C₆-alkyl; C₁-C₆-alkylcarbonylamino; hydroxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₁-C₆alkoxy-C₁-C₆alkyl; C₁-C₆-alkoxycarbonyl; C₁-C₆-alkoxycarbonylC₁-C₆-alkyl; C₃-C₇-cycloalkyloxy; M₄-M₇-heterocycleoxy, wherein the heterocycle of M₄-M₇-heterocycleoxy is optionally substituted with C₁-C₆-alkyl; aminocarbonyl; C₁-C₆-alkylaminocarbonyl; hydroxyC₁-C₆-alkylaminocarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylaminocarbonyl; cyano; hydroxy; hydroxyC₁-C₆-alkoxy; hydroxyC₁-C₆-alkyl; di(C₁-C₆alkyl)amino; di(hydroxyC₁-C₆-alkyl)amino; di(C₁-C₆-alkoxyC₁-C₆-alkyl)amino; (C₁-C₆-alkoxyC₁-C₆-alkyl)(hydroxyC₁-C₆-alkyl)amino; haloC₁-C₆-alkyl; halogen; C₁-C₆-alkylsulfonylaminoC₂-C₆-alkyl; and (i),



(i)

wherein R^a is selected from the group consisting of a bond, CH₂, CHR^b, O, S, and N-R^c; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring; m is 2, 3 or 4 when (i) is attached to a ring nitrogen atom of the bicyclic heteroaryl; or m is 0, 1, 2, 3 or 4 when (i) is attached to a ring carbon atom of the bicyclic heteroaryl; R^b, at each occurrence, is independently selected from the group consisting of hydrogen, C₁-C₆-alkyl, haloC₁-C₆-alkyl, C₁-C₆-alkoxyC₁-C₆-alkyl, and hydroxyC₁-C₆-alkyl; and R^c is selected from the group consisting of hydrogen, C₁-C₆-alkyl, C₁-C₆-alkoxycarbonyl, C₁-C₆-alkylcarbonyl, C₁-C₆-alkylsulfonyl, di(C₁-C₆-alkyl)aminosulfonyl, heterocyclecarbonyl, C₃-C₇-cycloalkylcarbonyl, -C(O)NH₂, -C(O)NH(alkyl), -C(O)N(alkyl)₂ and -C(=NCN)NHCH₃.

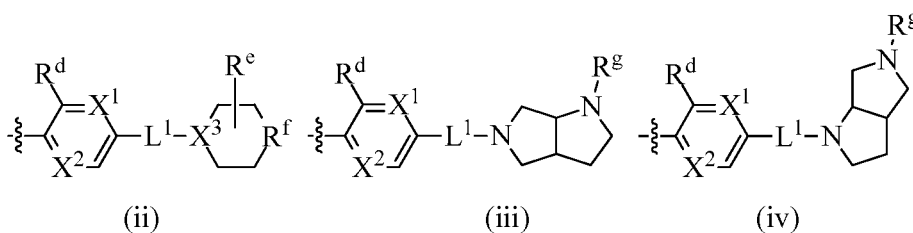
In another embodiment, R¹ is fused-bicyclic heteroaryl, wherein the fused-bicyclic heteroaryl contains 1 or 2 ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the fused-bicyclic heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of C₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl; hydroxyC₁-C₆-alkyl; halogen; C₁-C₆-alkylsulfonylaminoC₂-C₆-alkyl; and (i),



(i)

wherein R^a is selected from the group consisting of a bond, O, S, and N-R^c; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring; m is 2 when (i) is attached to a ring nitrogen atom of the bicyclic heteroaryl; R^b is hydrogen; and R^c is C₁-C₆-alkyl.

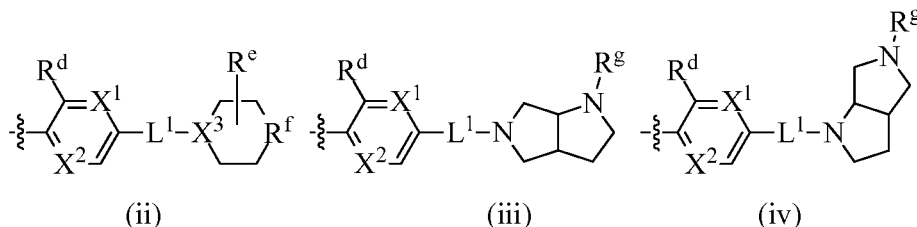
In one embodiment, R¹ is (ii), (iii), or (iv);



wherein both X¹ and X² are CH, or one of X¹ and X² is N and the other is CH; X³ is CH or N; L¹ is a bond, C(O), or -NHC(O)-; R^d is selected from the group consisting of hydrogen; C₁-C₆alkoxy; fluoroC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₃-C₇-cycloalkyloxy; C₃-C₇-cycloalkylC₁-C₆-alkoxy; hydroxyC₁-C₆-alkoxy; phenylC₁-C₆-alkoxyC₁-C₆-alkoxy; M₄-M₇-heterocycleoxy, wherein the heterocycle of heterocycleoxy is optionally substituted with C₁-C₆-alkyl or oxo; and phenoxy, wherein the phenyl of phenoxy is optionally substituted with hydroxyC₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkoxyC₁-C₆-alkoxy, or C₁-C₆-alkoxycarbonyl; R^e at each occurrence is independently selected from the group consisting of hydrogen, C₁-C₆-alkyl, di(C₁-C₆-alkyl)amino, haloC₁-C₆-alkyl, C₁-C₆-alkoxyC₁-C₆alkyl, and hydroxyC₁-C₆-alkyl; R^f is selected from the group consisting of a bond, CH₂, CHR^c, CH₂CH₂, O, NR^g, and CH₂NR^g; and R^g is selected from the group consisting of hydrogen; C₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl; C₁-C₆-alkylcarbonyl; C₁-C₆-alkylsulfonyl; di(C₁-C₆-alkyl)aminosulfonyl; C₃-C₇-cycloalkylcarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylcarbonyl; hydroxyC₂-C₆-alkyl; hydroxyC₁-C₆-alkylcarbonyl; formyl; -C(O)NH₂; -C(O)NH(alkyl);

-C(O)N(alkyl)₂; -C(=NCN)NHCH₃; and M₄-M₇-heterocyclecarbonyl, wherein the heterocycle of heterocyclecarbonyl is optionally substituted with C₁-C₆-alkyl.

In another embodiment, R¹ is (ii), (iii), or (iv);



wherein both X¹ and X² are CH, or one of X¹ and X² is N and the other is CH; X³ is CH or N; L¹ is a bond; R^d is selected from the group consisting of hydrogen; C₁-C₆alkoxy; fluoroC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; hydroxyC₁-C₆-alkoxy; phenylC₁-C₆-alkoxyC₁-C₆-alkoxy; M₄-M₇-heterocycleoxy, wherein the heterocycle of heterocycleoxy is optionally substituted with oxo; and phenoxy, wherein the phenyl of phenoxy is optionally substituted with hydroxyC₁-C₆-alkyl, or C₁-C₆-alkoxycarbonyl; R^e at each occurrence is independently selected from the group consisting of hydrogen, di(C₁-C₆-alkyl)amino, C₁-C₆-alkoxyC₁-C₆alkyl, and hydroxyC₁-C₆-alkyl; R^f is selected from the group consisting of a bond, CH₂, O, and NR^g; and R^g is selected from the group consisting of hydrogen; C₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl; C₁-C₆-alkylcarbonyl; C₁-C₆-alkylsulfonyl; di(C₁-C₆-alkyl)aminosulfonyl; hydroxyC₂-C₆-alkyl; formyl; -C(=NCN)NHCH₃; and M₄-M₇-heterocyclecarbonyl, wherein the heterocycle of heterocyclecarbonyl is optionally substituted with C₁-C₆-alkyl.

In one embodiment, Z¹ is NR² or CR³R⁴.

In another embodiment, Z¹ is NR².

In another embodiment, Z¹ is CR³R⁴.

In one embodiment, R² is selected from the group consisting of hydrogen, C₁-C₆-alkyl, hydroxyC₂-C₆-alkyl, di(hydroxy)C₂-C₆-alkyl, C₁-C₆-alkoxyC₂-C₆alkyl, hydroxyC₂-C₆-alkoxyC₂-C₆-alkyl, C₁-C₆-alkylcarbonyloxyC₂-C₆-alkyl, C₁-C₆-alkoxycarbonylC₁-C₆-alkyl, C₁-C₆-alkylcarbonylC₁-C₆-alkyl and phenylC₁-C₆-alkoxyC₂-C₆alkyl.

In another embodiment, R² is selected from the group consisting of hydrogen, C₁-C₆-alkyl, hydroxyC₂-C₆-alkyl, di(hydroxy)C₂-C₆-alkyl, C₁-C₆-alkoxyC₂-C₆alkyl, hydroxyC₂-C₆-alkoxyC₂-C₆-alkyl, C₁-C₆-alkylcarbonyloxyC₂-C₆-alkyl, and phenylC₁-C₆-alkoxyC₂-C₆alkyl.

In one embodiment, R^3 and R^4 are each independently selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, hydroxy C_1 - C_6 -alkyl, amino C_1 - C_6 -alkyl, and phenyl, wherein phenyl is optionally substituted with 1, 2, 3 or 4 substituents selected from halogen, C_1 - C_6 -alkyl, and cyano.

5 In another embodiment, R^3 and R^4 are each independently selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, hydroxy C_1 - C_6 -alkyl, amino C_1 - C_6 -alkyl, and phenyl, wherein phenyl is optionally substituted with 1 or 2 halogen.

In one embodiment, R^3 and R^4 taken together with the carbon atom to which they are attached form a M_4 - M_7 -heterocycle optionally substituted with 1, 2 or 3 halogen, C_1 - C_6 -alkyl,
10 cyano or oxo.

In another embodiment, R^3 and R^4 taken together with the carbon atom to which they are attached form a M_4 - M_7 -heterocycle.

In one embodiment, Z^2 is O, NR^5 , or CR^6R^7 .

In another embodiment, Z^2 is O.

15 In another embodiment, Z^2 is NR^5 .

In another embodiment, Z^2 is CR^6R^7 .

In one embodiment, R^5 is selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, C_1 - C_6 -alkylsulfonyl, C_1 - C_6 -alkylcarbonyl, and C_1 - C_6 -alkoxycarbonyl.

In another embodiment, R^5 is selected from the group consisting of hydrogen and
20 C_1 - C_6 -alkylsulfonyl.

In one embodiment, R^6 and R^7 are each independently selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy C_1 - C_6 -alkyl, hydroxy C_1 - C_6 -alkyl, amino C_1 - C_6 -alkyl, aminocarbonyl, and C_1 - C_6 -alkoxycarbonyl.

In another embodiment, R^6 and R^7 are each independently selected from the group
25 consisting of hydrogen, C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy C_1 - C_6 -alkyl, hydroxy C_1 - C_6 -alkyl, aminocarbonyl, and C_1 - C_6 -alkoxycarbonyl.

In one embodiment, R^6 and R^7 taken together with the carbon atom to which they are attached form a C_3 - C_6 -cycloalkyl or M_4 - M_7 -heterocycle, wherein the C_3 - C_6 -cycloalkyl or
30 M_4 - M_7 -heterocycle are optionally substituted with 1, 2, or 3 substituents selected from C_1 - C_6 -alkyl, cyano, aminocarbonyl, halogen, oxo and C_1 - C_6 -alkylcarbonyl.

In another embodiment, R^6 and R^7 taken together with the carbon atom to which they are attached form a C_3 - C_6 -cycloalkyl or M_4 - M_7 -heterocycle, wherein the C_3 - C_6 -cycloalkyl or
 M_4 - M_7 -heterocycle are optionally substituted with 1 C_1 - C_6 -alkylcarbonyl.

In one embodiment, n is 1 or 2; Z^1 is NR^2 ; Z^2 is CR^6R^7 ; and R^2 , R^6 and R^7 are as defined in the Summary. In another embodiment, n is 1 or 2; Z^1 is NR^2 ; Z^2 is CR^6R^7 ; R^1 is phenyl or monocyclic heteroaryl, wherein the monocyclic heteroaryl contains one or two ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the phenyl or

5 monocyclic heteroaryl is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C_1 - C_6 -alkyl; C_1 - C_6 -alkylcarbonylamino; hydroxy C_1 - C_6 -alkylcarbonylamino; C_1 - C_6 -alkoxy C_1 - C_6 -alkylcarbonylamino; C_1 - C_6 -alkoxy; C_1 - C_6 -alkoxy C_1 - C_6 -alkoxy; C_1 - C_6 -alkoxy C_1 - C_6 -alkyl; C_1 - C_6 -alkoxycarbonyl; C_1 - C_6 -alkoxycarbonyl C_1 - C_6 -alkyl; aminocarbonyl; C_1 - C_6 -alkylaminocarbonyl;

10 hydroxy C_1 - C_6 -alkylaminocarbonyl; C_1 - C_6 -alkoxy C_1 - C_6 -alkylaminocarbonyl; cyano; carboxy; hydroxy; hydroxy C_1 - C_6 -alkoxy; hydroxy C_1 - C_6 -alkyl; di(hydroxy) C_1 - C_6 -alkyl; di(C_1 - C_6 -alkyl)amino; di(hydroxy C_1 - C_6 -alkyl)amino; di(C_1 - C_6 -alkoxy C_1 - C_6 -alkyl)amino; (C_1 - C_6 -alkoxy C_1 - C_6 -alkyl)(hydroxy C_1 - C_6 -alkyl)amino; halo C_1 - C_6 -alkyl; and halogen; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to

15 the amide nitrogen pendant on the furan ring; and R^2 , R^6 and R^7 are as defined in the Summary.

In one embodiment, n is 1; Z^1 is NR^2 ; Z^2 is CR^6R^7 ; R^1 is phenyl optionally substituted with 1 or 2 substituents selected from the group consisting of C_1 - C_6 -alkyl; C_1 - C_6 -alkylcarbonylamino; aminocarbonyl; cyano; hydroxy; and di(C_1 - C_6 -alkyl)amino; wherein only

20 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring; or R^1 is monocyclic heteroaryl, wherein the monocyclic heteroaryl is pyridyl, pyrazinyl or isoxazolyl, wherein the monocyclic heteroaryl is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C_1 - C_6 -alkyl; C_1 - C_6 -alkoxy; C_1 - C_6 -alkoxycarbonyl C_1 - C_6 -alkyl; hydroxy C_1 - C_6 -alkyl; halo C_1 - C_6 -alkyl; and

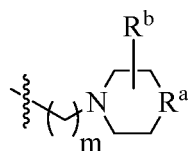
25 halogen; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring; R^2 is hydrogen or C_1 - C_6 -alkyl; and R^6 and R^7 are each hydrogen.

In one embodiment, n is 1; Z^1 is NR^2 ; Z^2 is CR^6R^7 ; R^1 is monocyclic heteroaryl, wherein the monocyclic heteroaryl is pyridyl, wherein the monocyclic heteroaryl is optionally

30 substituted with 1, 2, or 3 substituents selected from the group consisting of C_1 - C_6 -alkoxy; C_1 - C_6 -alkoxy C_1 - C_6 -alkoxy; carboxy; hydroxy C_1 - C_6 -alkyl; and di(hydroxy C_1 - C_6 -alkyl)amino; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring; R^2 is hydrogen or C_1 - C_6 -alkoxy C_2 - C_6 -alkyl; and R^6 and R^7 are each independently C_1 - C_6 -alkyl.

In one embodiment, n is 1 or 2; Z^1 is NR^2 ; Z^2 is CR^6R^7 ; R^1 is fused-bicyclic heteroaryl, wherein the fused-bicyclic heteroaryl contains 1, 2, 3 or 4 ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the fused-bicyclic heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of

5 C_1 - C_6 -alkyl; C_1 - C_6 -alkylcarbonylamino; hydroxy C_1 - C_6 -alkylcarbonylamino; C_1 - C_6 -alkoxy C_1 - C_6 -alkylcarbonylamino; C_1 - C_6 -alkoxy; C_1 - C_6 -alkoxy C_1 - C_6 -alkoxy; C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl; C_1 - C_6 -alkoxycarbonyl; C_1 - C_6 -alkoxycarbonyl C_1 - C_6 -alkyl; C_3 - C_7 -cycloalkyloxy; M_4 - M_7 -heterocycleoxy, wherein the heterocycle of M_4 - M_7 -heterocycleoxy is optionally substituted with C_1 - C_6 -alkyl; aminocarbonyl; C_1 - C_6 -alkylaminocarbonyl; hydroxy C_1 - C_6 -alkylaminocarbonyl; C_1 - C_6 -alkoxy C_1 - C_6 -alkylaminocarbonyl; cyano; hydroxy; hydroxy C_1 - C_6 -alkoxy; hydroxy C_1 - C_6 -alkyl; di(C_1 - C_6 -alkyl)amino; di(hydroxy C_1 - C_6 -alkyl)amino; di(C_1 - C_6 -alkoxy C_1 - C_6 -alkyl)amino; (C_1 - C_6 -alkoxy C_1 - C_6 -alkyl)(hydroxy C_1 - C_6 -alkyl)amino; halo C_1 - C_6 -alkyl; halogen; C_1 - C_6 -alkylsulfonylamino C_2 - C_6 -alkyl; and (i),



(i)

wherein R^a is selected from the group consisting of a bond, CH_2 , CHR^b , O, S, and $N-R^c$; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring; m is 2, 3 or 4 when (i) is attached to a ring nitrogen atom of the bicyclic heteroaryl; or m is 0, 1, 2, 3 or 4 when (i) is attached to a ring

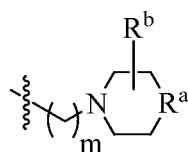
20 carbon atom of the bicyclic heteroaryl; R^b , at each occurrence, is independently selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, halo C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy C_1 - C_6 -alkyl, and hydroxy C_1 - C_6 -alkyl; and R^c is selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, C_1 - C_6 -alkoxycarbonyl, C_1 - C_6 -alkylcarbonyl, C_1 - C_6 -alkylsulfonyl, di(C_1 - C_6 -alkyl)aminosulfonyl, heterocyclecarbonyl, C_3 - C_7 -cycloalkylcarbonyl, $-C(O)NH_2$, $-C(O)NH(alkyl)$, $-C(O)N(alkyl)_2$ and $-C(=NCN)NHCH_3$; and R^2 , R^6 and R^7 are as defined in

25 the Summary.

In one embodiment, n is 1; Z^1 is NR^2 ; Z^2 is CR^6R^7 ; R^1 is fused-bicyclic heteroaryl, wherein the fused-bicyclic heteroaryl is 2*H*-indazol-5-yl, 1*H*-indazol-5-yl, 1*H*-benzimidazol-5-yl, 1,3-benzothiazol-6-yl, quinolin-6-yl, 1*H*-indazol-6-yl, 1,3-benzothiazol-2-yl, wherein

30 the fused-bicyclic heteroaryl is optionally substituted with 1, 2, or 3, substituents selected

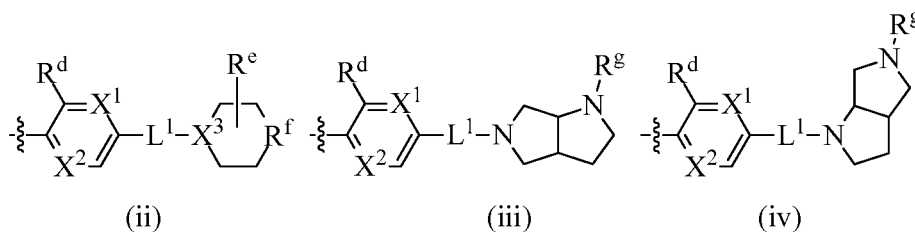
from the group consisting of C₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl; hydroxyC₁-C₆-alkyl; halogen; C₁-C₆-alkylsulfonylaminoC₂-C₆-alkyl; and (i),



(i)

- 5 wherein R^a is selected from the group consisting of a bond, O, and N-R^c; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring; m is 2; R^b is hydrogen; R^c is C₁-C₆-alkyl; R² is hydrogen or C₁-C₆-alkyl; and R⁶ and R⁷ are each hydrogen.

In one embodiment, n is 1 or 2; Z¹ is NR²; Z² is CR⁶R⁷; R¹ is (ii), (iii), or (iv);



(ii)

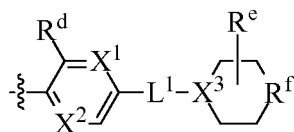
(iii)

(iv)

wherein both X¹ and X² are CH, or one of X¹ and X² is N and the other is CH; X³ is CH or N; L¹ is a bond, C(O), or -NHC(O)-; R^d is selected from the group consisting of hydrogen; C₁-C₆-alkoxy; fluoroC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₃-C₇-cycloalkoxy;

- 15 C₃-C₇-cycloalkylC₁-C₆-alkoxy; M₄-M₇-heterocycleoxy, wherein the heterocycle of heterocycleoxy is optionally substituted with C₁-C₆-alkyl or oxo; hydroxyC₁-C₆-alkoxy; phenylC₁-C₆-alkoxyC₁-C₆-alkoxy; and phenoxy, wherein the phenyl of phenoxy is optionally substituted with hydroxyC₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkoxyC₁-C₆-alkoxy, or C₁-C₆-alkoxycarbonyl; R^e at each occurrence is independently selected from the group consisting of
- 20 hydrogen, C₁-C₆-alkyl, di(C₁-C₆-alkyl)amino, haloC₁-C₆-alkyl, C₁-C₆-alkoxyC₁-C₆-alkyl, and hydroxyC₁-C₆-alkyl; R^f is selected from the group consisting of a bond, CH₂, CHR^e, CH₂CH₂, O, NR^g, and CH₂NR^g; and R^g is selected from the group consisting of hydrogen; C₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl; C₁-C₆-alkylcarbonyl; C₁-C₆-alkylsulfonyl; di(C₁-C₆-alkyl)aminosulfonyl; C₃-C₇-cycloalkylcarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylcarbonyl;
- 25 hydroxyC₂-C₆-alkyl; hydroxyC₁-C₆-alkylcarbonyl; formyl; -C(O)NH₂; -C(O)NH(alkyl); -C(O)N(alkyl)₂; -C(=NCN)NHCH₃; and M₄-M₇-heterocyclecarbonyl, wherein the heterocycle of heterocyclecarbonyl is optionally substituted with C₁-C₆-alkyl; and R², R⁶ and R⁷ are as defined in the Summary.

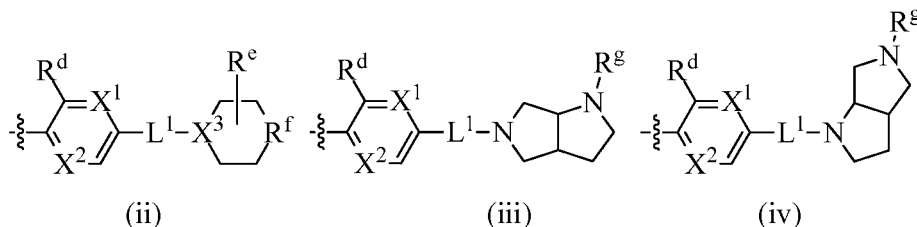
In one embodiment, n is 1 or 2; Z¹ is NR²; Z² is CR⁶R⁷; R¹ is (ii);



(ii)

wherein both X¹ and X² are CH, or one of X¹ and X² is N and the other is CH; X³ is N; L¹ is a
 5 bond; R^d is selected from the group consisting of hydrogen; C₁-C₆alkoxy; C₁-C₆-
 alkoxyC₁-C₆-alkoxy; hydroxyC₁-C₆-alkoxy; phenylC₁-C₆-alkoxyC₁-C₆-alkoxy; M₄-M₇-
 heterocycleoxy, wherein the heterocycle of heterocycleoxy is optionally substituted with C₁-
 C₆-alkyl or oxo; and phenoxy, wherein the phenyl of phenoxy is optionally substituted with
 hydroxyC₁-C₆-alkyl or C₁-C₆-alkoxycarbonyl; R^e at each occurrence is hydrogen; R^f is
 10 selected from the group consisting of a CH₂, O, and NR^g; R^g is selected from the group
 consisting of hydrogen; C₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl; C₁-C₆-alkylcarbonyl;
 di(C₁-C₆-alkyl)aminosulfonyl; -C(=NCN)NHCH₃; and M₄-M₇-heterocyclecarbonyl, wherein
 the heterocycle of heterocyclecarbonyl is optionally substituted with C₁-C₆-alkyl; R² is
 hydrogen, C₁-C₆-alkyl, hydroxyC₂-C₆-alkyl, C₁-C₆-alkoxyC₂-C₆-alkyl,
 15 hydroxyC₂-C₆-alkoxyC₂-C₆-alkyl, C₁-C₆-alkylcarbonyloxyC₂-C₆-alkyl, and
 phenylC₁-C₆-alkoxyC₂-C₆-alkyl; and R⁶ and R⁷ are each hydrogen.

In one embodiment, n is 1; Z¹ is NR²; Z² is CR⁶R⁷; R¹ is R¹ is (ii), (iii), or (iv);



(ii)

(iii)

(iv)

wherein both X¹ and X² are CH, or one of X¹ and X² is N and the other is CH; X³ is CH or N;
 L¹ is a bond; R^d is selected from the group consisting of C₁-C₆alkoxy; fluoroC₁-C₆-alkoxy;
 C₁-C₆-alkoxyC₁-C₆-alkoxy; and M₄-M₇-heterocycleoxy, wherein the heterocycle of
 heterocycleoxy is optionally substituted with oxo; R^e at each occurrence is independently
 selected from the group consisting of hydrogen, di(C₁-C₆-alkyl)amino, C₁-C₆-
 25 alkoxyC₁-C₆-alkyl, and hydroxyC₁-C₆-alkyl; R^f is selected from the group consisting of a
 bond, CH₂, and NR^g; R^g is selected from the group consisting of hydrogen; C₁-C₆-alkyl;
 C₁-C₆-alkylcarbonyl; C₁-C₆-alkylsulfonyl; hydroxyC₂-C₆-alkyl; formyl; -C(=NCN)NHCH₃;
 and M₄-M₇-heterocyclecarbonyl, wherein the heterocycle of heterocyclecarbonyl is
 optionally substituted with C₁-C₆-alkyl; R² is selected from the group consisting of hydrogen,

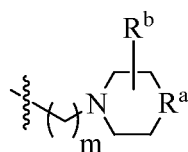
C₁-C₆-alkyl, hydroxyC₂-C₆-alkyl, di(hydroxy)C₂-C₆-alkyl, C₁-C₆-alkoxyC₂-C₆-alkyl, and hydroxyC₂-C₆-alkoxyC₂-C₆-alkyl; R⁶ is selected from the group consisting of hydrogen and C₁-C₆-alkyl; and R⁷ is selected from the group consisting of C₁-C₆-alkyl and hydroxyC₁-C₆-alkyl; or R⁶ and R⁷ taken together with the carbon atom to which they are attached form a C₃-C₆-cycloalkyl or M₄-M₇-heterocycle, wherein the M₄-M₇-heterocycle is optionally substituted with 1 or 2 substituents selected from C₁-C₆-alkyl, oxo and C₁-C₆-alkylcarbonyl.

In one embodiment, n is 1 or 2; Z¹ is CR³R⁴; Z² is NR⁵; and R³, R⁴ and R⁵ are as defined in the Summary.

In one embodiment, n is 1 or 2; Z¹ is CR³R⁴; Z² is NR⁵; R¹ is phenyl or monocyclic heteroaryl, wherein the monocyclic heteroaryl contains one or two ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the phenyl or monocyclic heteroaryl is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C₁-C₆-alkyl; C₁-C₆-alkylcarbonylamino; hydroxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl; C₁-C₆-alkoxycarbonylC₁-C₆-alkyl; aminocarbonyl; C₁-C₆-alkylaminocarbonyl; hydroxyC₁-C₆-alkylaminocarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylaminocarbonyl; cyano; carboxy; hydroxy; hydroxyC₁-C₆-alkoxy; hydroxyC₁-C₆-alkyl; di(hydroxy)C₁-C₆-alkyl; di(C₁-C₆-alkyl)amino; di(hydroxyC₁-C₆-alkyl)amino; di(C₁-C₆-alkoxyC₁-C₆-alkyl)amino; (C₁-C₆-alkoxyC₁-C₆-alkyl)(hydroxyC₁-C₆-alkyl)amino; haloC₁-C₆-alkyl; and halogen; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring; and R³, R⁴ and R⁵ are as defined in the Summary.

In one embodiment, n is 1 or 2; Z¹ is CR³R⁴; Z² is NR⁵; R¹ is fused-bicyclic heteroaryl, wherein the fused-bicyclic heteroaryl contains 1, 2, 3 or 4 ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the fused-bicyclic heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of C₁-C₆-alkyl; C₁-C₆-alkylcarbonylamino; hydroxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl; C₁-C₆-alkoxycarbonylC₁-C₆-alkyl; C₃-C₇-cycloalkyloxy; M₄-M₇-heterocycleoxy, wherein the heterocycle of M₄-M₇-heterocycleoxy is optionally substituted with C₁-C₆-alkyl; aminocarbonyl; C₁-C₆-alkylaminocarbonyl; hydroxyC₁-C₆-alkylaminocarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylaminocarbonyl; cyano; hydroxy; hydroxyC₁-C₆-alkoxy; hydroxyC₁-C₆-alkyl; di(C₁-C₆-alkyl)amino; di(hydroxyC₁-C₆-alkyl)amino;

di(C₁-C₆-alkoxyC₁-C₆-alkyl)amino; (C₁-C₆-alkoxyC₁-C₆-alkyl)(hydroxyC₁-C₆-alkyl)amino; haloC₁-C₆-alkyl; halogen; C₁-C₆-alkylsulfonylaminoC₂-C₆-alkyl; and (i),

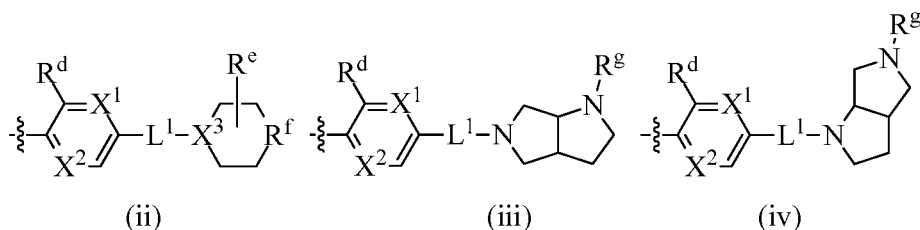


(i)

- 5 wherein R^a is selected from the group consisting of a bond, CH₂, CHR^b, O, S, and N-R^c; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring; m is 2, 3 or 4 when (i) is attached to a ring nitrogen atom of the bicyclic heteroaryl; or m is 0, 1, 2, 3 or 4 when (i) is attached to a ring carbon atom of the bicyclic heteroaryl; R^b, at each occurrence, is independently selected from the group consisting of hydrogen, C₁-C₆-alkyl, haloC₁-C₆-alkyl, C₁-C₆-alkoxyC₁-C₆-alkyl, and hydroxyC₁-C₆-alkyl; and R^c is selected from the group consisting of hydrogen, C₁-C₆-alkyl, C₁-C₆-alkoxycarbonyl, C₁-C₆-alkylcarbonyl, C₁-C₆-alkylsulfonyl, di(C₁-C₆-alkyl)aminosulfonyl, heterocyclecarbonyl, C₃-C₇-cycloalkylcarbonyl, -C(O)NH₂, -C(O)NH(alkyl), -C(O)N(alkyl)₂ and -C(=NCN)NHCH₃; and R³, R⁴ and R⁵ are as defined in the Summary.

In one embodiment, n is 1; Z¹ is CR³R⁴; Z² is NR⁵; R¹ is fused-bicyclic heteroaryl, wherein the fused-bicyclic heteroaryl is 2H-indazol-5-yl, wherein the fused-bicyclic heteroaryl is optionally substituted with 1 or 2 C₁-C₆-alkyl; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring; R³ and R⁴ are both hydrogen; and R⁵ is hydrogen or C₁-C₆-alkylsulfonyl.

In one embodiment, n is 1 or 2; Z¹ is CR³R⁴; Z² is NR⁵; R¹ is (ii), (iii), or (iv);



- wherein both X¹ and X² are CH, or one of X¹ and X² is N and the other is CH; X³ is CH or N; L¹ is a bond, C(O), or -NHC(O)-; R^d is selected from the group consisting of hydrogen; C₁-C₆alkoxy; fluoroC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₃-C₇-cycloalkyloxy; C₃-C₇-cycloalkylC₁-C₆-alkoxy; hydroxyC₁-C₆-alkoxy; phenylC₁-C₆-alkoxyC₁-C₆-alkoxy; M₄-M₇-heterocycleoxy, wherein the heterocycle of heterocycleoxy is optionally substituted

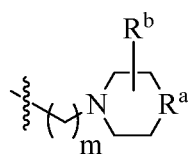
with C₁-C₆-alkyl or oxo; and phenoxy, wherein the phenyl of phenoxy is optionally substituted with hydroxyC₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkoxyC₁-C₆-alkoxy, or C₁-C₆-alkoxycarbonyl; R^e at each occurrence is independently selected from the group consisting of hydrogen, C₁-C₆-alkyl, di(C₁-C₆-alkyl)amino, haloC₁-C₆-alkyl, C₁-C₆-alkoxyC₁-C₆-alkyl, and hydroxyC₁-C₆-alkyl; R^f is selected from the group consisting of a bond, CH₂, CHR^e, CH₂CH₂, O, NR^g, and CH₂NR^g; R^g is selected from the group consisting of hydrogen; C₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl; C₁-C₆-alkylcarbonyl; C₁-C₆-alkysulfonyl; di(C₁-C₆-alkyl)aminosulfonyl; C₃-C₇-cycloalkylcarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylcarbonyl; hydroxyC₂-C₆-alkyl; hydroxyC₁-C₆-alkylcarbonyl; formyl; -C(O)NH₂; -C(O)NH(alkyl); -C(O)N(alkyl)₂; -C(=NCN)NHCH₃; and M₄-M₇-heterocyclecarbonyl, wherein the heterocycle of heterocyclecarbonyl is optionally substituted with C₁-C₆-alkyl; and R³, R⁴ and R⁵ are as defined in the Summary.

In one embodiment, n is 1 or 2; Z¹ is CR³R⁴; Z² is CR⁶R⁷; and R³, R⁴, R⁶ and R⁷ are as defined in the Summary.

In one embodiment, n is 1 or 2; Z¹ is CR³R⁴; Z² is CR⁶R⁷; R¹ is phenyl or monocyclic heteroaryl, wherein the monocyclic heteroaryl contains one or two ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the phenyl or monocyclic heteroaryl is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C₁-C₆-alkyl; C₁-C₆-alkylcarbonylamino; hydroxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl; C₁-C₆-alkoxycarbonylC₁-C₆-alkyl; aminocarbonyl; C₁-C₆-alkylaminocarbonyl; hydroxyC₁-C₆-alkylaminocarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylaminocarbonyl; cyano; carboxy; hydroxy; hydroxyC₁-C₆-alkoxy; hydroxyC₁-C₆-alkyl; di(hydroxy)C₁-C₆-alkyl; di(C₁-C₆-alkyl)amino; di(hydroxyC₁-C₆-alkyl)amino; di(C₁-C₆-alkoxyC₁-C₆-alkyl)amino; (C₁-C₆-alkoxyC₁-C₆-alkyl)(hydroxyC₁-C₆-alkyl)amino; haloC₁-C₆-alkyl; and halogen; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring; and R³, R⁴, R⁶ and R⁷ are as defined in the Summary.

In one embodiment, n is 1 or 2; Z¹ is CR³R⁴; Z² is CR⁶R⁷; R¹ is fused-bicyclic heteroaryl, wherein the fused-bicyclic heteroaryl contains 1, 2, 3 or 4 ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the fused-bicyclic heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of C₁-C₆-alkyl; C₁-C₆-alkylcarbonylamino; hydroxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₁-C₆-alkoxy-

C₁-C₆alkyl; C₁-C₆-alkoxycarbonyl; C₁-C₆-alkoxycarbonylC₁-C₆-alkyl; C₃-C₇-cycloalkyloxy; M₄-M₇-heterocycleoxy, wherein the heterocycle of M₄-M₇-heterocycleoxy is optionally substituted with C₁-C₆-alkyl; aminocarbonyl; C₁-C₆-alkylaminocarbonyl; hydroxyC₁-C₆-alkylaminocarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylaminocarbonyl; cyano; hydroxy; hydroxyC₁-C₆-alkoxy; hydroxyC₁-C₆-alkyl; di(C₁-C₆alkyl)amino; di(hydroxyC₁-C₆-alkyl)amino; di(C₁-C₆-alkoxyC₁-C₆-alkyl)amino; (C₁-C₆-alkoxyC₁-C₆-alkyl)(hydroxyC₁-C₆-alkyl)amino; haloC₁-C₆-alkyl; halogen; C₁-C₆-alkylsulfonylaminoC₂-C₆-alkyl; and (i),

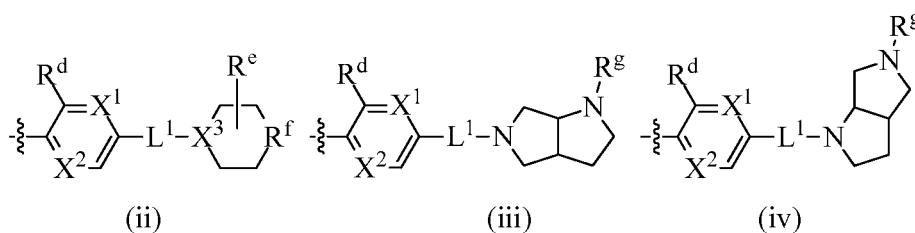


(i)

wherein R^a is selected from the group consisting of a bond, CH₂, CHR^b, O, S, and N-R^c; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring; m is 2, 3 or 4 when (i) is attached to a ring nitrogen atom of the bicyclic heteroaryl; or m is 0, 1, 2, 3 or 4 when (i) is attached to a ring carbon atom of the bicyclic heteroaryl; R^b, at each occurrence, is independently selected from the group consisting of hydrogen, C₁-C₆-alkyl, haloC₁-C₆-alkyl, C₁-C₆-alkoxyC₁-C₆-alkyl, and hydroxyC₁-C₆-alkyl; R^c is selected from the group consisting of hydrogen, C₁-C₆-alkyl, C₁-C₆-alkoxycarbonyl, C₁-C₆-alkylcarbonyl, C₁-C₆-alkylsulfonyl, di(C₁-C₆-alkyl)aminosulfonyl, heterocyclecarbonyl, C₃-C₇-cycloalkylcarbonyl, -C(O)NH₂, -C(O)NH(alkyl), -C(O)N(alkyl)₂ and -C(=NCN)NHCH₃; and R³, R⁴, R⁶ and R⁷ are as defined in the Summary.

In one embodiment, n is 1; Z¹ is CR³R⁴; Z² is CR⁶R⁷; R¹ is fused-bicyclic heteroaryl, wherein the fused-bicyclic heteroaryl is 1*H*-indazol-5-yl, 2*H*-indazol-5-yl, or 1*H*-benzimidazol-5-yl, wherein the fused-bicyclic heteroaryl is optionally substituted with 1 or 2 C₁-C₆-alkyl or hydroxyC₁-C₆-alkyl; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring; R³ is hydrogen or C₁-C₆-alkyl; R⁴ is hydrogen, C₁-C₆-alkyl, or hydroxyC₁-C₆-alkyl; R⁶ is selected from the group consisting of hydrogen and C₁-C₆-alkyl; and R⁷ is selected from the group consisting of hydrogen, C₁-C₆-alkyl, hydroxyC₁-C₆-alkyl, aminocarbonyl, and C₁-C₆-alkoxycarbonyl; or R⁶ and R⁷ taken together with the carbon atom to which they are attached form a C₃-C₆-cycloalkyl.

In one embodiment, n is 1 or 2; Z¹ is CR³R⁴; Z² is CR⁶R⁷; R¹ is (ii), (iii), or (iv);



wherein both X^1 and X^2 are CH, or one of X^1 and X^2 is N and the other is CH; X^3 is CH or N; L^1 is a bond, C(O), or -NHC(O)-; R^d is selected from the group consisting of hydrogen; C₁-

5 C₆alkoxy; fluoroC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₃-C₇-cycloalkyloxy;

C₃-C₇-cycloalkylC₁-C₆-alkoxy; hydroxyC₁-C₆-alkoxy; phenylC₁-C₆-alkoxyC₁-C₆-alkoxy;

M₄-M₇-heterocycleoxy, wherein the heterocycle of heterocycleoxy is optionally substituted with C₁-C₆-alkyl or oxo; and phenoxy, wherein the phenyl of phenoxy is optionally

substituted with hydroxyC₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkoxyC₁-C₆-alkoxy, or C₁-C₆-

10 alkoxycarbonyl; R^e at each occurrence is independently selected from the group consisting of hydrogen, C₁-C₆-alkyl, di(C₁-C₆-alkyl)amino, haloC₁-C₆-alkyl, C₁-C₆-alkoxyC₁-C₆-alkyl, and hydroxyC₁-C₆-alkyl; R^f is selected from the group consisting of a bond, CH₂, CHR^e,

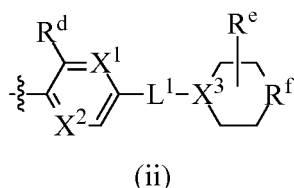
CH₂CH₂, O, NR^g, and CH₂NR^g; R^g is selected from the group consisting of hydrogen; C₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl; C₁-C₆-alkylcarbonyl; C₁-C₆-alkylsulfonyl;

15 di(C₁-C₆-alkyl)aminosulfonyl; C₃-C₇-cycloalkylcarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylcarbonyl; hydroxyC₂-C₆-alkyl; hydroxyC₁-C₆-alkylcarbonyl; formyl; -C(O)NH₂; -C(O)NH(alkyl);

-C(O)N(alkyl)₂; -C(=NCN)NHCH₃; and M₄-M₇-heterocyclecarbonyl, wherein the

heterocycle of heterocyclecarbonyl is optionally substituted with C₁-C₆-alkyl; and R^3 , R^4 , R^6 and R^7 are as defined in the Summary.

20 In one embodiment, n is 1; Z^1 is CR³R⁴; Z^2 is CR⁶R⁷; R^1 is (ii);



wherein both X^1 and X^2 are CH, or one of X^1 and X^2 is N and the other is CH; X^3 is N; L^1 is a bond; R^d is selected from the group consisting of hydrogen and C₁-C₆alkoxy; R^e at each

25 occurrence is hydrogen; R^f is NR^g; R^g is selected from the group consisting of hydrogen,

C₁-C₆-alkoxycarbonyl, C₁-C₆-alkylcarbonyl, and C₁-C₆-alkylsulfonyl; R^3 is selected from the group consisting of hydrogen or C₁-C₆-alkyl; R^4 is selected from the group consisting of

hydrogen, aminoC₁-C₆-alkyl, and phenyl, wherein phenyl is optionally substituted with 1, 2

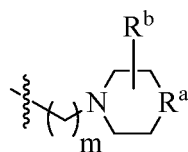
or 3 halogen; R^6 is selected from the group consisting of hydrogen and C₁-C₆-alkyl; and R^7

are is selected from the group consisting of hydrogen, C₁-C₆-alkyl, C₁-C₆-alkoxyC₁-C₆-alkyl, and hydroxyC₁-C₆-alkyl; or R⁶ and R⁷ taken together with the carbon atom to which they are attached form a M₄-M₇-heterocycle.

5 In one embodiment, n is 1 or 2; Z¹ is CR³R⁴; Z² is O; and R³ and R⁴ are as defined in the Summary.

In one embodiment, n is 1 or 2; Z¹ is CR³R⁴; Z² is O; R¹ is phenyl or monocyclic heteroaryl, wherein the monocyclic heteroaryl contains one or two ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the phenyl or monocyclic heteroaryl is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C₁-C₆-alkyl; C₁-C₆-alkylcarbonylamino; hydroxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl; C₁-C₆-alkoxycarbonylC₁-C₆-alkyl; aminocarbonyl; C₁-C₆-alkylaminocarbonyl; hydroxyC₁-C₆-alkylaminocarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylaminocarbonyl; cyano; carboxy; hydroxy; hydroxyC₁-C₆-alkoxy; hydroxyC₁-C₆-alkyl; di(hydroxy)C₁-C₆-alkyl; di(C₁-C₆-alkyl)amino; di(hydroxyC₁-C₆-alkyl)amino; di(C₁-C₆-alkoxyC₁-C₆-alkyl)amino; (C₁-C₆-alkoxyC₁-C₆-alkyl)(hydroxyC₁-C₆-alkyl)amino; haloC₁-C₆-alkyl; and halogen; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring; and R³ and R⁴ are as defined in the Summary.

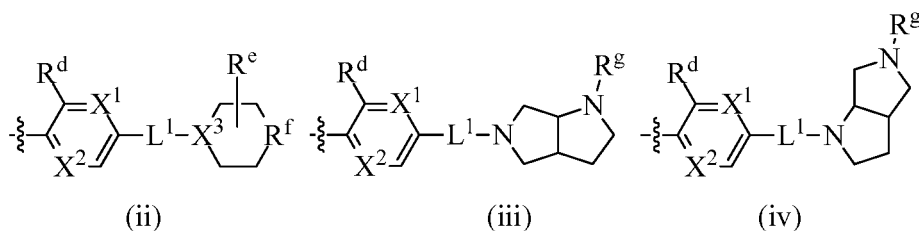
20 In one embodiment, n is 1 or 2; Z¹ is CR³R⁴; Z² is O; R¹ is fused-bicyclic heteroaryl, wherein the fused-bicyclic heteroaryl contains 1, 2, 3 or 4 ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the fused-bicyclic heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of C₁-C₆-alkyl; C₁-C₆-alkylcarbonylamino; hydroxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl; C₁-C₆-alkoxycarbonylC₁-C₆-alkyl; C₃-C₇-cycloalkyloxy; M₄-M₇-heterocycleoxy, wherein the heterocycle of M₄-M₇-heterocycleoxy is optionally substituted with C₁-C₆-alkyl; aminocarbonyl; C₁-C₆-alkylaminocarbonyl; hydroxyC₁-C₆-alkylaminocarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylaminocarbonyl; cyano; hydroxy; hydroxyC₁-C₆-alkoxy; hydroxyC₁-C₆-alkyl; di(C₁-C₆-alkyl)amino; di(hydroxyC₁-C₆-alkyl)amino; di(C₁-C₆-alkoxyC₁-C₆-alkyl)amino; (C₁-C₆-alkoxyC₁-C₆-alkyl)(hydroxyC₁-C₆-alkyl)amino; haloC₁-C₆-alkyl; halogen; C₁-C₆-alkylsulfonylaminoC₂-C₆-alkyl; and (i),



(i)

wherein R^a is selected from the group consisting of a bond, CH_2 , CHR^b , O, S, and $N-R^c$; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring; m is 2, 3 or 4 when (i) is attached to a ring nitrogen atom of the bicyclic heteroaryl; or m is 0, 1, 2, 3 or 4 when (i) is attached to a ring carbon atom of the bicyclic heteroaryl; R^b , at each occurrence, is independently selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, halo C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy C_1 - C_6 -alkyl, and hydroxy C_1 - C_6 -alkyl; R^c is selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, C_1 - C_6 -alkoxycarbonyl, C_1 - C_6 -alkylcarbonyl, C_1 - C_6 -alkylsulfonyl, di(C_1 - C_6 -alkyl)aminosulfonyl, heterocyclecarbonyl, C_3 - C_7 -cycloalkylcarbonyl, $-C(O)NH_2$, $-C(O)NH(alkyl)$, $-C(O)N(alkyl)_2$ and $-C(=NCN)NHCH_3$; and R^3 and R^4 are as defined in the Summary.

In one embodiment, n is 1 or 2; Z^1 is CR^3R^4 ; Z^2 is O; R^1 is (ii), (iii), or (iv);



(ii)

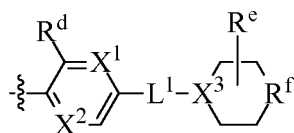
(iii)

(iv)

wherein both X^1 and X^2 are CH, or one of X^1 and X^2 is N and the other is CH; X^3 is CH or N; L^1 is a bond, $C(O)$, or $-NHC(O)-$; R^d is selected from the group consisting of hydrogen; C_1 - C_6 alkoxy; fluoro C_1 - C_6 -alkoxy; C_1 - C_6 -alkoxy C_1 - C_6 -alkoxy; C_3 - C_7 -cycloalkyloxy; C_3 - C_7 -cycloalkyl C_1 - C_6 -alkoxy; hydroxy C_1 - C_6 -alkoxy; phenyl C_1 - C_6 -alkoxy C_1 - C_6 -alkoxy; M_4 - M_7 -heterocycleoxy, wherein the heterocycle of heterocycleoxy is optionally substituted with C_1 - C_6 -alkyl or oxo; and phenoxy, wherein the phenyl of phenoxy is optionally substituted with hydroxy C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -alkoxy C_1 - C_6 -alkoxy, or C_1 - C_6 -alkoxycarbonyl; R^e at each occurrence is independently selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, di(C_1 - C_6 -alkyl)amino, halo C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy C_1 - C_6 alkyl, and hydroxy C_1 - C_6 -alkyl; R^f is selected from the group consisting of a bond, CH_2 , CHR^e , CH_2CH_2 , O, NR^g , and CH_2NR^g ; R^g is selected from the group consisting of hydrogen; C_1 - C_6 -alkyl; C_1 - C_6 -alkoxycarbonyl; C_1 - C_6 -alkylcarbonyl; C_1 - C_6 -alkylsulfonyl;

di(C₁-C₆-alkyl)aminosulfonyl; C₃-C₇-cycloalkylcarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylcarbonyl; hydroxyC₂-C₆-alkyl; hydroxyC₁-C₆-alkylcarbonyl; formyl; -C(O)NH₂; -C(O)NH(alkyl); -C(O)N(alkyl)₂; -C(=NCN)NHCH₃; and M₄-M₇-heterocyclecarbonyl, wherein the heterocycle of heterocyclecarbonyl is optionally substituted with C₁-C₆-alkyl; and R³ and R⁴ are as defined in the Summary.

In one embodiment, n is 1; Z¹ is CR³R⁴; Z² is O; R¹ is (ii);



(ii)

wherein both X¹ and X² are CH, or one of X¹ and X² is N and the other is CH; X³ is N; L¹ is a bond; R^d is C₁-C₆alkoxy; R^e at each occurrence is hydrogen; R^f is NR^g; R^g is C₁-C₆-alkylcarbonyl; and R³ and R⁴ are each independently C₁-C₆-alkyl; or R³ and R⁴ taken together with the carbon atom to which they are attached form a M₄-M₇-heterocycle.

Specific embodiments contemplated as part of the invention also include, but are not limited to, compounds of Formula (I), as defined, for example:

N-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5-methyl-*N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[4-(morpholin-4-yl)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5-methyl-*N*-(4-methylphenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

tert-butyl 4-(3-methoxy-4-{[(4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino}phenyl)piperazine-1-carboxylate;

N-[2-methoxy-4-(piperazin-1-yl)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[2-methoxy-6-(4-methylpiperazin-1-yl)pyridin-3-yl]-4-oxo-5,6,7,8-tetrahydro-4*H*-furo[3,2-*c*]azepine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[2-(benzyloxy)ethyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2-hydroxyethyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[4-(4-acetylpiperazin-1-yl)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5 *N*-(1-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(1*H*-benzimidazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(4-carbamoylphenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

10 *N*-(1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(2-methyl-1,3-benzothiazol-6-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[5-(4-methylpiperazin-1-yl)pyridin-2-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

15 *N*-[4-(4-methylpiperazin-1-yl)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

20 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-(2-methoxyethoxy)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-(oxetan-3-yloxy)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

25 5-methyl-*N*-[4-(4-methylpiperazin-1-yl)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(1*H*-indazol-5-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

30 5-methyl-*N*-(1-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5-methyl-*N*-[4-(morpholin-4-yl)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(4-carbamoylphenyl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(1*H*-benzimidazol-5-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[4-(4-acetylpiperazin-1-yl)phenyl]-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5 5-methyl-*N*-(2-methyl-1,3-benzothiazol-6-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(4-methylphenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(4-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(4-acetamidophenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

10 4-oxo-*N*-(quinolin-6-yl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(1*H*-indazol-6-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(2,6-dimethoxypyridin-3-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(1,2-oxazol-3-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

15 4-oxo-*N*-(pyrazin-2-yl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(5-methyl-1,2-oxazol-3-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(4-cyanophenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(5-fluoropyridin-2-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

20 *N*-(6-methoxypyridin-3-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(5-chloropyridin-2-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(3-cyanophenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(6-ethoxypyridin-3-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

25 *N*-(3-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(6-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

30 *N*-(1,3-benzothiazol-2-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

methyl 5- {[4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl]carbonyl}amino }-1*H*-indazole-3-carboxylate;

N-[4-(diethylamino)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[1-(2-hydroxypropyl)-1*H*-indazol-5-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(2-{2-[(methylsulfonyl)amino]ethyl}-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5 *N*-{2-[2-(4-methylpiperazin-1-yl)ethyl]-2*H*-indazol-5-yl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[1-(2-hydroxyethyl)-1*H*-indazol-5-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

10 4-oxo-*N*-{1-[2-(pyrrolidin-1-yl)ethyl]-1*H*-indazol-5-yl}-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[2-(2-hydroxypropyl)-2*H*-indazol-5-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{1-[2-(morpholin-4-yl)ethyl]-1*H*-indazol-5-yl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

15 *N*-{1-[2-(4-methylpiperazin-1-yl)ethyl]-1*H*-indazol-5-yl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(1-{2-[(methylsulfonyl)amino]ethyl}-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

20 *N*-(4-hydroxyphenyl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(4-acetamidophenyl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5-methyl-4-oxo-*N*-[4-(piperidin-1-yl)phenyl]-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

25 5-methyl-4-oxo-*N*-(quinolin-3-yl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5-methyl-4-oxo-*N*-(quinolin-6-yl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

30 *N*-(1*H*-indazol-6-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(2,6-dimethoxy-pyridin-3-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5-methyl-*N*-(5-methyl-1,2-oxazol-3-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(4-cyanophenyl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(5-fluoropyridin-2-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5 *N*-(6-methoxypyridin-3-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(5-chloropyridin-2-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

10 *N*-(3-cyanophenyl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(6-ethoxypyridin-3-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5-methyl-*N*-(3-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

15 5-methyl-*N*-(6-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(1,3-benzothiazol-2-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

20 5-methyl-4-oxo-*N*-[5-(trifluoromethyl)pyridin-2-yl]-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(6-chloro-1*H*-indazol-5-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5-methyl-*N*-(2-methyl-1*H*-benzimidazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

25 *N*-{4-[4-(3,3-dimethylbutanoyl)piperazin-1-yl]-2-methoxyphenyl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{2-methoxy-4-[4-(pyrrolidin-1-ylcarbonyl)piperazin-1-yl]phenyl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

30 *N*-{4-[4-(dimethylsulfamoyl)piperazin-1-yl]-2-methoxyphenyl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

methyl 4-{{[6-(4-methylpiperazin-1-yl)-3-{{[(4-oxo-5,6,7,8-tetrahydro-4*H*-furo[3,2-*c*]azepin-3-yl)carbonyl]amino}pyridin-2-yl]oxy}benzoate};

N-{2-[4-(hydroxymethyl)phenoxy]-6-(4-methylpiperazin-1-yl)pyridin-3-yl}-4-oxo-5,6,7,8-tetrahydro-4*H*-furo[3,2-*c*]azepine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2-methoxyethyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-(2-methoxyethoxy)pyridin-3-yl]-5-[2-(benzyloxy)ethyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5 *N*-{6-(4-acetylpiperazin-1-yl)-2-[2-(benzyloxy)ethoxy]pyridin-3-yl}-5-[2-(benzyloxy)ethyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-(2-methoxyethoxy)pyridin-3-yl]-5-(2-hydroxyethyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

10 *N*-[6-(4-acetylpiperazin-1-yl)-2-(2-hydroxyethoxy)pyridin-3-yl]-5-(2-hydroxyethyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(3-hydroxypropyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(4-hydroxybutyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

15 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[2-(2-hydroxyethoxy)ethyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

tert-butyl 4-(6-ethoxy-5-[(4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino)pyridin-2-yl)piperazine-1-carboxylate;

20 *N*-{6-[4-(*N*'-cyano-*N*-methylcarbamimidoyl)piperazin-1-yl]-2-ethoxypyridin-3-yl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

(2*R*)-1-[3-{[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]carbamoyl}-4-oxo-6,7-dihydrofuro[3,2-*c*]pyridin-5(4*H*)-yl]propan-2-yl acetate;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[(2*R*)-2-hydroxypropyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

25 (2*S*)-1-[3-{[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]carbamoyl}-4-oxo-6,7-dihydrofuro[3,2-*c*]pyridin-5(4*H*)-yl]propan-2-yl acetate;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[(2*S*)-2-hydroxypropyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

30 (2*R*)-2-[3-{[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]carbamoyl}-4-oxo-6,7-dihydrofuro[3,2-*c*]pyridin-5(4*H*)-yl]propyl acetate;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[(2*R*)-1-hydroxypropan-2-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

(2*S*)-2-[3-{[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]carbamoyl}-4-oxo-6,7-dihydrofuro[3,2-*c*]pyridin-5(4*H*)-yl]propyl acetate;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[(2*S*)-1-hydroxypropan-2-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(1-hydroxy-2-methylpropan-2-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5 1-[3-{[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]carbamoyl}-4-oxo-6,7-dihydrofuro[3,2-*c*]pyridin-5(4*H*)-yl]-2-methylpropan-2-yl acetate;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2-hydroxy-2-methylpropyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

10 *N*-{6-(4-acetylpiperazin-1-yl)-2-[(3*S*)-tetrahydrofuran-3-yloxy]pyridin-3-yl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[2-ethoxy-6-(morpholin-4-yl)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[2-(2-hydroxy-2-methylpropoxy)-6-(morpholin-4-yl)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

15 methyl (6-ethoxy-5-{[(4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino}pyridin-2-yl)acetate;

N-[2-ethoxy-6-(2-hydroxyethyl)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

20 *N*-[6-(4-acetylpiperazin-1-yl)-2-methoxypyridin-3-yl]-4-oxo-2',3',4,5',6',7'-hexahydro-5*H*-spiro[1-benzofuran-6,4'-pyran]-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4'-oxo-4',7'-dihydro-5'*H*-spiro[cyclobutane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4'-oxo-4',7'-dihydro-5'*H*-spiro[cyclohexane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide;

25 1-acetyl-*N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4'-oxo-4',7'-dihydro-5'*H*-spiro[azetidine-3,6'-furo[3,2-*c*]pyridine]-3'-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4-oxo-4,7-dihydro-5*H*-spiro[furo[3,2-*c*]pyridine-6,3'-oxetane]-3-carboxamide;

30 (6*R*)-*N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-6-[(1*R*)-1-hydroxyethyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5'-(2-hydroxyethyl)-4'-oxo-4',7'-dihydro-5'*H*-spiro[cyclobutane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4'-oxo-4',7'-dihydro-5'*H*-spiro[cyclopropane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide;

N-{6-[4-(*N*'-cyano-*N*-methylcarbamimidoyl)piperazin-1-yl]-2-ethoxypyridin-3-yl}-4'-oxo-4',7'-dihydro-5'*H*-spiro[cyclobutane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2,3-dihydroxypropyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5 *N*-[2-methoxy-4-(piperazin-1-yl)phenyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{2-methoxy-6-[4-(morpholin-4-ylcarbonyl)piperazin-1-yl]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

10 *N*-[6-(4-acetylpiperazin-1-yl)-2-methoxypyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{2-methoxy-6-[4-(pyrrolidin-1-ylcarbonyl)piperazin-1-yl]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[2-methoxy-4-(piperazin-1-yl)phenyl]-6-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

15 *N*-{2-methoxy-4-[4-(methylsulfonyl)piperazin-1-yl]phenyl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

20 *N*-[2-ethoxy-6-(piperazin-1-yl)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[(3*aR*,6*aR*)-hexahydropyrrolo[3,4-*b*]pyrrol-5(1*H*)-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

25 *N*-{2-methoxy-6-[(3*aR*,6*aR*)-5-methylhexahydropyrrolo[3,4-*b*]pyrrol-1(2*H*)-yl]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[(3*aS*,6*aS*)-1-(2-hydroxyethyl)hexahydropyrrolo[3,4-*b*]pyrrol-5(1*H*)-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

30 *N*-{2-isopropoxy-6-[(3*aR*,6*aR*)-1-[(4-methylpiperazin-1-yl)carbonyl]hexahydropyrrolo[3,4-*b*]pyrrol-5(1*H*)-yl]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[(3*S*)-4-acetyl-3-(hydroxymethyl)piperazin-1-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[(2*S*)-4-acetyl-2-(hydroxymethyl)piperazin-1-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[(2*S*)-2-(hydroxymethyl)-4-(morpholin-4-ylcarbonyl)piperazin-1-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[(3*S*)-3-(hydroxymethyl)piperidin-1-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[(3*R*)-4-acetyl-3-(hydroxymethyl)piperazin-1-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[(2*R*)-4-acetyl-2-(hydroxymethyl)piperazin-1-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[bis(2-hydroxyethyl)amino]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[2,6-bis(2-methoxyethoxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[(3*S*)-4-acetyl-3-(methoxymethyl)piperazin-1-yl]-2-(2-hydroxy-2-methylpropoxy)pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[2-ethoxy-6-(2-hydroxyethyl)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[2-ethoxy-6-(hydroxymethyl)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

6-ethoxy-5-({[5-(2-methoxyethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl]carbonyl} amino)pyridine-2-carboxylic acid;

6,6-dimethyl-*N*-(1-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

6,6-dimethyl-*N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

N-[4-(4-acetylpiperazin-1-yl)phenyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

6,6-dimethyl-4-oxo-*N*-[6-(piperazin-1-yl)pyridin-3-yl]-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

N-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,7-dihydro-5*H*-spiro[1-benzofuran-6,1'-cyclobutane]-3-carboxamide;

6,6-dimethyl-4-oxo-*N*-[5-(piperazin-1-yl)pyridin-2-yl]-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

5 6,6-dimethyl-*N*-{4-[4-(methylsulfonyl)piperazin-1-yl]phenyl}-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

N-[2-(2-hydroxyethyl)-2*H*-indazol-5-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

10 *N*-[2-(hydroxymethyl)-1*H*-benzimidazol-5-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

6,6-dimethyl-*N*-{5-[4-(methylsulfonyl)piperazin-1-yl]pyridin-2-yl}-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

N-[5-(4-acetylpiperazin-1-yl)pyridin-2-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

15 *N*-[2-methoxy-4-(piperazin-1-yl)phenyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

N-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

20 *N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,7-dihydro-5*H*-spiro[1-benzofuran-6,1'-cyclopropane]-3-carboxamide;

N-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine-3-carboxamide;

N-(2-methyl-2*H*-indazol-5-yl)-6-(methylsulfonyl)-4-oxo-4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine-3-carboxamide;

25 6-methyl-*N*³-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3,6-dicarboxamide;

methyl 6-methyl-3-[(2-methyl-2*H*-indazol-5-yl)carbamoyl]-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-6-carboxylate;

30 6-(hydroxymethyl)-6-methyl-*N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

tert-butyl 4-[4-({[6-(hydroxymethyl)-6-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-yl]carbonyl} amino)-3-methoxyphenyl]piperazine-1-carboxylate;

6-(methoxymethyl)-*N*-[2-methoxy-4-(piperazin-1-yl)phenyl]-6-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

5-(hydroxymethyl)-5-methyl-*N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

5,5-dimethyl-*N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

5 *N*-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-5-(aminomethyl)-5-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

N-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-4-oxo-4,7-dihydrospiro[furo[2,3-*c*]pyran-5,4'-piperidine]-3-carboxamide;

10 *N*-[6-(4-acetylpiperazin-1-yl)-2-methoxypyridin-3-yl]-5,5-dimethyl-4-oxo-4,7-dihydro-5*H*-furo[2,3-*c*]pyran-3-carboxamide;

N-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-4-oxo-4,7-dihydrospiro[furo[2,3-*c*]pyran-5,3'-oxetane]-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

15 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2-hydroxyethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2-methoxyethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

20 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[2-(2-hydroxyethoxy)ethyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-(2-methoxyethoxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-(2,2,2-trifluoroethoxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

25 *N*-[6-(4-acetylpiperazin-1-yl)-2-(oxetan-3-yloxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-(tetrahydro-2*H*-pyran-4-yloxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

30 *N*-{6-(4-acetylpiperazin-1-yl)-2-[(3*S*)-tetrahydrofuran-3-yloxy]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-formylpiperazin-1-yl)-2-(2-methoxyethoxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-(4-acetylpiperazin-1-yl)-2-[(1-oxidothietan-3-yl)oxy]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(1-acetylpiperidin-4-yl)-2-ethoxypyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide; and

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2,5-difluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide.

5

Compound names are assigned by using Name Release 12.00 v. 12.5 naming algorithm by Advanced Chemical Development or Struct=Name naming algorithm as part of CHEMDRAW® ULTRA v. 12.0.2.

10 Compounds of the invention may exist as stereoisomers wherein asymmetric or chiral centers are present. These stereoisomers are “*R*” or “*S*” depending on the configuration of substituents around the chiral carbon atom. The terms “*R*” and “*S*” used herein are configurations as defined in IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, in Pure Appl. Chem., 1976, 45: 13-30. The invention contemplates various stereoisomers and mixtures thereof and these are specifically included within the scope of
15 this invention. Stereoisomers include enantiomers and diastereomers, and mixtures of enantiomers or diastereomers. Individual stereoisomers of compounds of the invention may be prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by methods of resolution well-known to those of ordinary skill in the art. These methods of resolution are
20 exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and optional liberation of the optically pure product from the auxiliary as described in Furniss, Hannaford, Smith, and Tatchell, "Vogel's Textbook of Practical Organic Chemistry", 5th edition (1989), Longman Scientific & Technical, Essex CM20 2JE, England, or (2) direct separation of the
25 mixture of optical enantiomers on chiral chromatographic columns or (3) fractional recrystallization methods.

On occasion, the relative stereochemistry of an enantiomeric pair is known, however, the absolute configuration is not known. In that circumstance, the relative stereochemistry descriptor terms "*R**" and "*S**" are used. The terms "*R**" and "*S**" used herein are defined in
30 Eliel, E. L.; Wilen, S. H. Stereochemistry of Organic Compounds; John Wiley & Sons, Inc.: New York, 1994; pp 119-120 and 1206.

Compounds of the invention may exist as *cis* or *trans* isomers, wherein substituents on a ring may attached in such a manner that they are on the same side of the ring (*cis*) relative to each other, or on opposite sides of the ring relative to each other (*trans*). For

example, cyclobutane may be present in the *cis* or *trans* configuration, and may be present as a single isomer or a mixture of the *cis* and *trans* isomers. Individual *cis* or *trans* isomers of compounds of the invention may be prepared synthetically from commercially available starting materials using selective organic transformations, or prepared in single isomeric form by purification of mixtures of the *cis* and *trans* isomers. Such methods are well-known to those of ordinary skill in the art, and may include separation of isomers by recrystallization or chromatography.

It should be understood that the compounds of the invention may possess tautomeric forms, as well as geometric isomers, and that these also constitute an aspect of the invention.

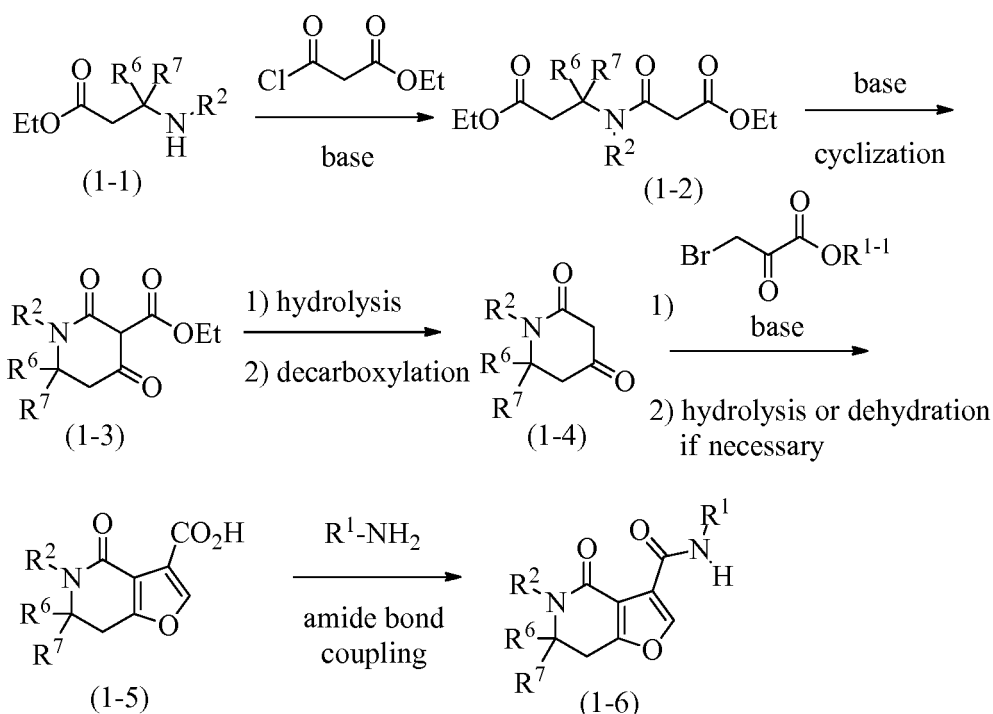
The present invention also includes isotopically-labeled compounds, which are identical to those recited in formula (I) or formula (II), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention are hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, and chlorine, such as, but not limited to ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Compounds incorporating positron-emitting isotopes are useful in medical imaging and positron-emitting tomography (PET) studies for determining the distribution of receptors. Suitable positron-emitting isotopes that can be incorporated in compounds of formula (I) or formula (II) are ^{11}C , ^{13}N , ^{15}O , and ^{18}F . Isotopically-labeled compounds of formula (I) or formula (II) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples using appropriate isotopically-labeled reagent in place of non-isotopically-labeled reagent.

Methods for Preparing Compounds of the Invention

The compounds of the invention can be better understood in connection with the following synthetic schemes and methods which illustrate a means by which the compounds can be prepared.

The compounds of this invention can be prepared by a variety of synthetic procedures. Representative procedures are shown in, but are not limited to, Schemes 1-10.

Scheme 1



As shown in Scheme 1, compounds of Formula (1-6) can be prepared from compounds of Formula (1-1), wherein R¹, R², R⁶ and R⁷ are as defined in the Summary.

- 5 Compounds of Formula (1-1) can be purchased commercially, or wherein R² is other than hydrogen prepared by reductive alkylation of the corresponding amino ester, or prepared by Michael reaction between an amine, R²NH₂, and ethyl acrylate. Compounds of Formula (1-1) can be reacted with a malonyl chloride (illustrated with ethyl malonyl chloride) in the presence of a base such as triethylamine or diisopropylethylamine in a solvent such as
- 10 dichloromethane initially at or near 0 °C with subsequent warming to ambient temperature over a total reaction time of 1-24 hours to give compounds of Formula (1-2). Treatment of compounds of Formula (1-2) with a base such as sodium ethoxide or potassium *tert*-butoxide in ethanol or sodium methoxide in methanol or potassium hydroxide in a mixture of methanol and water with optionally added tetrahydrofuran at room temperature to refluxing over 2-24
- 15 hours provides compounds of Formula (1-3). Compounds of Formula (1-3) can be transformed to compounds of Formula (1-4) in water or a mixture of water and acetonitrile at reflux over 30 minutes to 8 hours. Compounds of Formula (1-4) can be reacted with a bromopyruvate or bromopyruvic acid (BrCH₂C(O)CO₂R¹⁻¹, wherein R¹⁻¹ is hydrogen or C₁-C₆-alkyl) in the presence of a base such as potassium hydroxide, sodium bicarbonate, sodium
- 20 ethoxide, or potassium *tert*-butoxide in solvents such as methanol or ethanol optionally mixed

with water at ambient temperature over 1-24 hours to give compounds of Formula (1-5).

Dehydration can be required to complete aromatization of the furan ring. This can be achieved by treatment in heated (70-100 °C) aqueous hydrochloric acid, aqueous hydrochloric acid in tetrahydrofuran, or hydrochloric acid in dioxane for 1-24 hours, or with

5 treatment with acetic acid and acetic anhydride heated to 100-110 °C for 30 minutes to 24 hours, or with methanesulfonyl chloride and triethylamine in dichloromethane at room temperature from 30 minutes to 24 hours to give compounds of Formula (1-5). When R¹⁻¹ is

C₁-C₆-alkyl, hydrolysis of the intermediate furanyl ester may be required. This can be achieved under acidic conditions described above, or under basic conditions such as

10 treatment with lithium hydroxide or sodium hydroxide in methanol or a mixture of methanol and tetrahydrofuran at room temperature for 15 minutes to overnight to give compounds of Formula (1-5). Compounds of Formula (1-5) can be coupled with an amine, R¹-NH₂, to give compounds of Formula (1-6). Examples of conditions known to generate amides from a mixture of a carboxylic acid and an amine include but are not limited to adding a coupling

15 reagent such as but not limited to *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC, EDAC or EDCI), 1,3-dicyclohexylcarbodiimide (DCC), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl), 2-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate or O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU), O-
20 benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU), and 2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (HBTU).

The coupling reagents may be added as a solid, a solution, or as the reagent bound to a solid support resin. In addition to the coupling reagents, auxiliary-coupling reagents may facilitate the coupling reaction. Auxiliary coupling reagents that are often used in the coupling

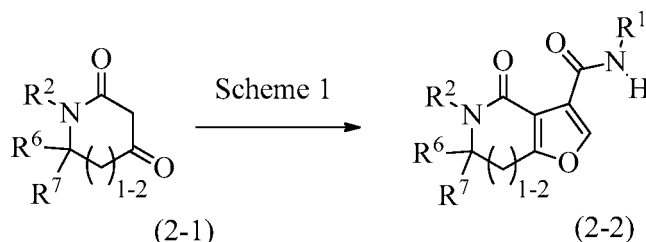
25 reactions include but are not limited to (dimethylamino)pyridine (DMAP), 1-hydroxy-7-azabenzotriazole (HOAT) and 1-hydroxybenzotriazole (HOBT). The reaction may be carried out optionally in the presence of a base such as triethylamine or diisopropylethylamine. The

coupling reaction may be carried out in solvents such as but not limited to tetrahydrofuran, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dichloromethane, and ethyl acetate. The

30 reaction may be conducted at ambient or elevated temperatures. Alternatively, compounds of Formula (1-5) can be reacted with a chloroformate such as ethyl chloroformate in the presence of a base such as triethylamine in solvents such as acetonitrile or tetrahydrofuran at ambient temperature and then treated with an amine, R¹-NH₂, and further reacted over 4-24

hours to give compounds of Formula (1-6). Compounds of Formula (1-6) are representative of compounds of Formula (I).

Scheme 2



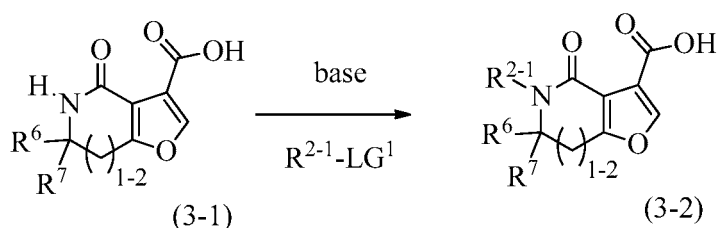
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As shown in Scheme 2, compounds of Formula (2-2) can be prepared from compounds of Formula (2-1), wherein R^1 , R^2 , R^6 and R^7 are as defined in the Summary. Specifically, R^6 and R^7 are each independently selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, and hydroxy C_1 - C_6 -alkyl or R^6 and R^7 taken together with the carbon atom to which they are attached form a C_3 - C_6 -cycloalkyl or M_4 - M_7 -heterocycle, wherein the C_3 - C_6 -cycloalkyl or M_4 - M_7 -heterocycle are optionally substituted with 1, 2, or 3 substituents selected from C_1 - C_6 -alkyl, cyano, aminocarbonyl, halogen, oxo and C_1 - C_6 -alkylcarbonyl. Compounds of Formula (2-1) can be either piperidine-2,4-diones or azepane-2,4-diones. The sequences described in Scheme 1 can be used to convert compounds of Formula (2-1) to compounds of Formula (2-2). Compounds of Formula (2-2) are representative of compounds of Formula (I).

10

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Scheme 3



(3-1)

(3-2)

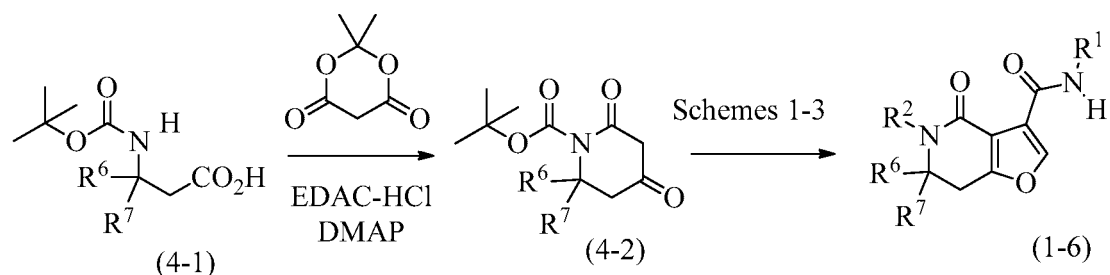
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As shown in Scheme 3, compounds of Formula (3-1), wherein R^6 and R^7 are as defined in the Summary, can be alkylated to give compounds of Formula (3-2). Compounds of Formula (3-1) can be reacted with an alkylating agent, R^{2-1} - LG^1 (wherein R^{2-1} is C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy C_2 - C_6 -alkyl, C_1 - C_6 -alkylcarbonyloxy C_2 - C_6 -alkyl, C_1 - C_6 -alkoxycarbonyl C_1 - C_6 -alkyl, C_1 - C_6 -alkylcarbonyl C_1 - C_6 -alkyl and phenyl C_1 - C_6 -alkoxy C_2 - C_6 -alkyl and LG^1 is chloro, bromo, iodo, or a sulfonate) in the presence of a base such as sodium hydride in a solvent such as *N,N*-dimethylformamide at 0

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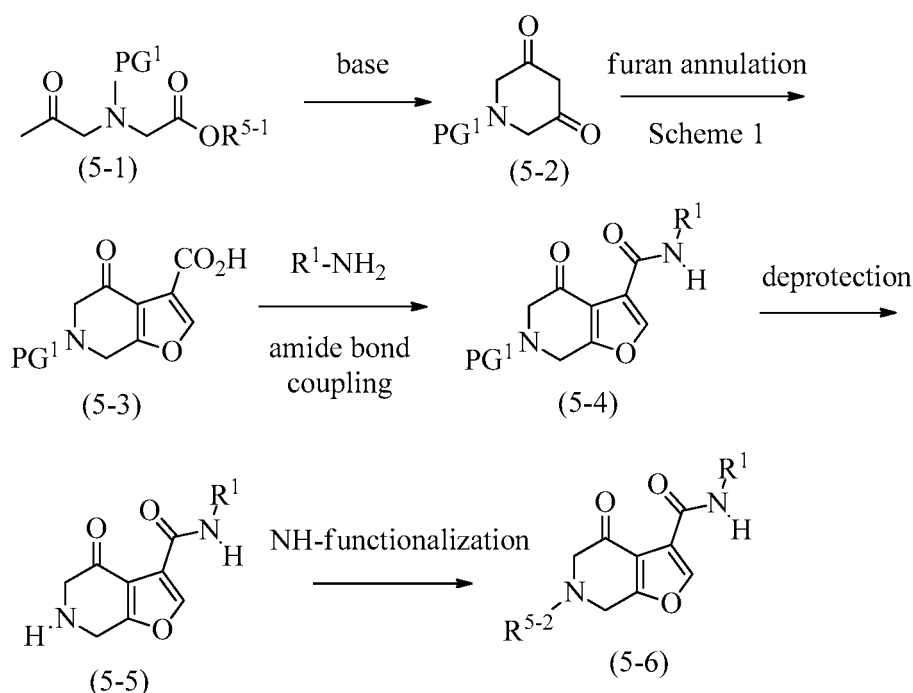
°C to room temperature over 4-24 hours to give compounds of Formula (3-2). In some instances the carboxylic acid will also react under these reaction conditions resulting in formation of an ester. The ester can be hydrolyzed using the conditions described in Scheme 1 to give compounds of Formula (3-2). Compounds of Formula (3-2) are representative of
 5 compounds of Formula (I).

Scheme 4



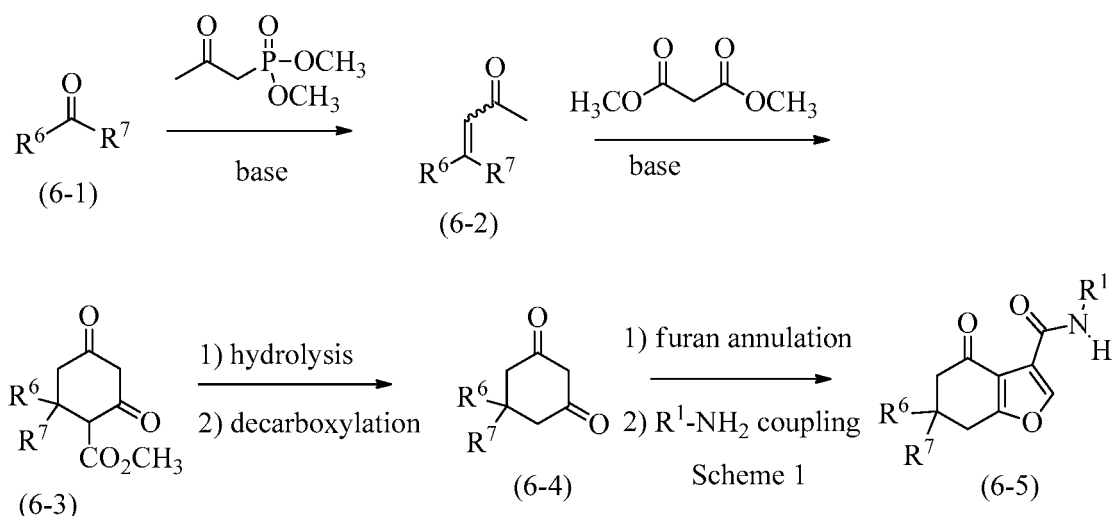
As shown in Scheme 4, compounds of Formula (4-1), wherein R^6 and R^7 are as
 10 defined in the Summary, can be converted to compounds of Formula (4-2). Compounds of
 Formula (4-1) can be reacted with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) in
 the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC-HCl)
 and dimethylaminopyridine (DMAP) in a solvent such as dichloromethane initially at 0 °C
 followed by warming to ambient temperature for 4-24 hours to give compounds of Formula
 15 (4-2). Compounds of Formula (4-2) can be converted to compounds of Formula (1-6) using
 the chemical sequences described in Schemes 1-3. The *tert*-butoxycarbonyl protecting group
 is removed in the course of these sequences.

Scheme 5



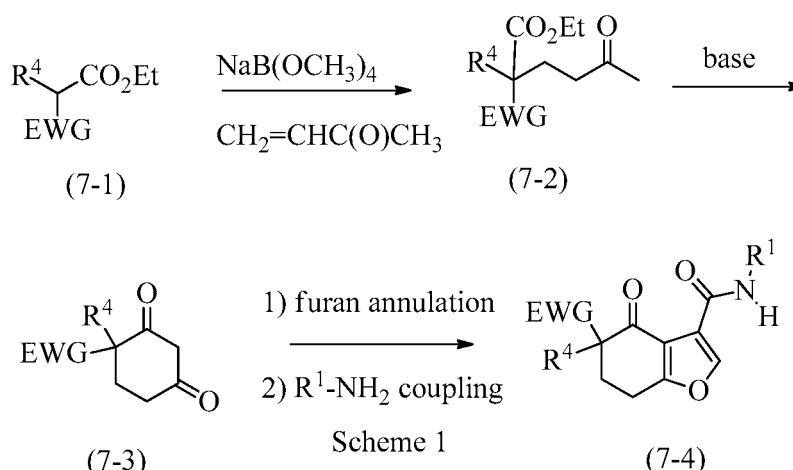
As shown in Scheme 5, compounds of Formulas (5-4), (5-5), and (5-6), wherein R^1 is as defined in the Summary, can be prepared from compounds of Formula (5-1). Compounds of Formula (5-1), wherein R^{5-1} is a C_1 - C_6 -alkyl and PG^1 is a nitrogen protecting group, can be reacted with a base such as potassium *tert*-butoxide in a solvent such as ether initially at 0 °C followed by warming to ambient temperature for 4-24 hours to give compounds of Formula (5-2). Compounds of Formula (5-2) can be converted to compounds of Formula (5-3) and Formula (5-4) using the chemical methodologies described in Scheme 1. Compounds of Formula (5-4), wherein PG^1 is C_1 - C_6 -alkoxycarbonyl, are representative of compounds of Formula (I). Compounds of Formula (5-4) can be deprotected using conditions dependent on the nitrogen protection group to give compounds of Formula (5-5) which are representative of compounds of Formula (I). Compounds of Formula (5-5) can be further functionalized by alkylation, sulfonamidation, amidation, and carbamoylation reactions to give compounds of Formula (5-6), wherein R^{5-2} is C_1 - C_6 -alkyl, C_1 - C_6 -alkylsulfonyl, C_1 - C_6 -alkylcarbonyl, and C_1 - C_6 -alkoxycarbonyl. Compounds of Formula (5-6) are representative of compounds of Formula (I).

Scheme 6



As shown in Scheme 6, compounds of Formula (6-5), wherein R^1 , R^6 and R^7 are as defined in the Summary, can be prepared from compounds of Formula (6-1). Compounds of Formula (6-1) can be reacted with dimethyl 2-oxopropylphosphonate in the presence of a base such as potassium hydroxide in a mixture of ethanol and water initially at 0 °C followed by warming to ambient temperature for 4-24 hours to give compounds of Formula (6-2). Compounds of Formula (6-2) can be reacted with dimethyl malonate in the presence of a base such as sodium methoxide in methanol at reflux for 1-12 hours to give compounds of Formula (6-3). Compounds of Formula (6-3) are converted to compounds of Formula (6-4) in a two-step process. The initial step is hydrolysis achieved with refluxing in aqueous sodium hydroxide over 1-6 hours. The subsequent step is decarboxylation accomplished in aqueous sulfuric acid heated to reflux for 1-6 hours and then at ambient temperature for 2-24 hours. Some compounds of Formula (6-4) are commercially available or are obtained from acid hydrolysis of the corresponding substituted 1,5-dimethoxycyclohexa-1,4-dienes. Compounds of Formula (6-4) are converted to compounds of Formula (6-5) following the furan annulation and amide bond formation sequences described in Scheme 1. Compounds of Formula (6-5) are representative of compounds of Formula (I).

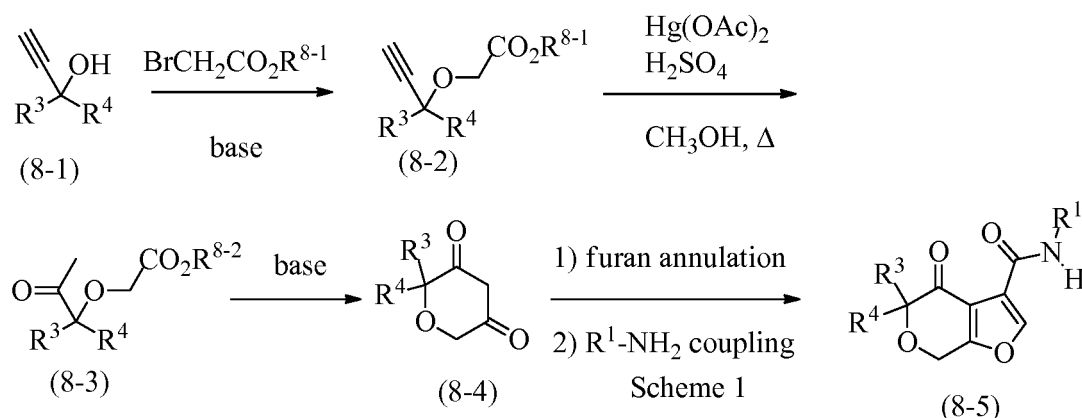
Scheme 7



As shown in Scheme 7, compounds of Formula (7-4), wherein R¹ and R⁴ are as described in the Summary and EWG represents an electron withdrawing group such as cyano, C₁-C₆-alkoxycarbonyl, or aminocarbonyl can be prepared from compounds of Formula (7-1).

- 5 Compounds of Formula (7-1) can be treated with methyl vinyl ketone in the presence of sodium tetramethoxyborate at room temperature in a solvent such as acetonitrile for 3-7 days to deliver compounds of Formula (7-2). Compounds of Formula (7-2) can be treated with a base such as potassium *tert*-butoxide in a solvent such as a mixture of ethanol and tetrahydrofuran at 0 °C. Compounds of Formula (7-3) are converted to compounds of
- 10 Formula (7-4) following the furan annulation and amide bond formation sequences described in Scheme 1. The electron withdrawing group of compounds of Formula (7-4) can be further transformed.

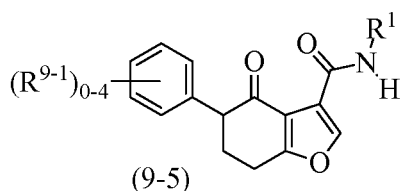
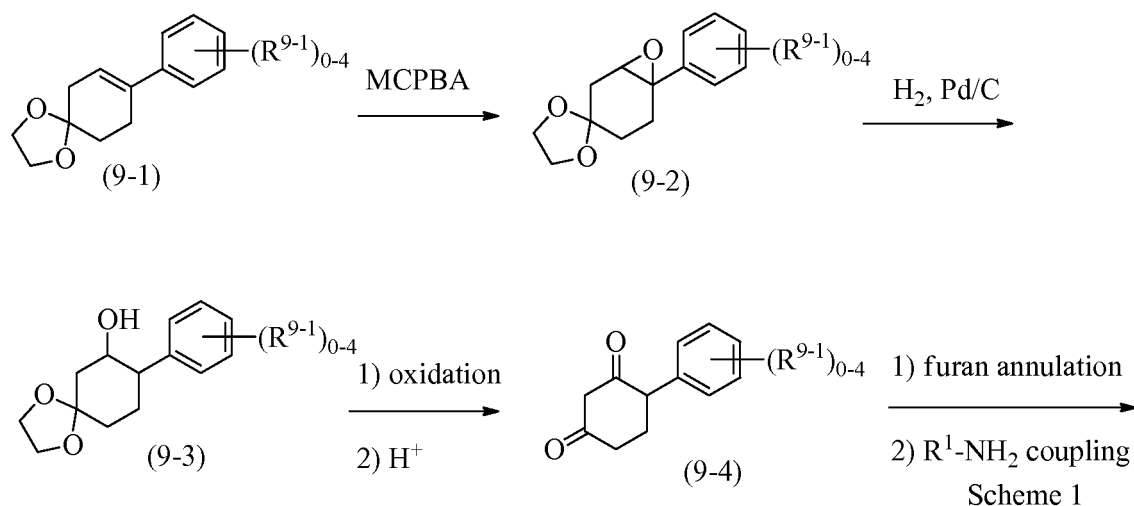
Scheme 8



As shown in Scheme 8, compounds of Formula (8-5), wherein R¹, R³ and R⁴ are as defined in the Summary can be prepared from compounds of Formula (8-1). Compounds of Formula (8-1) can be reacted with bromoacetic acid or a bromoacetate, such as ethyl

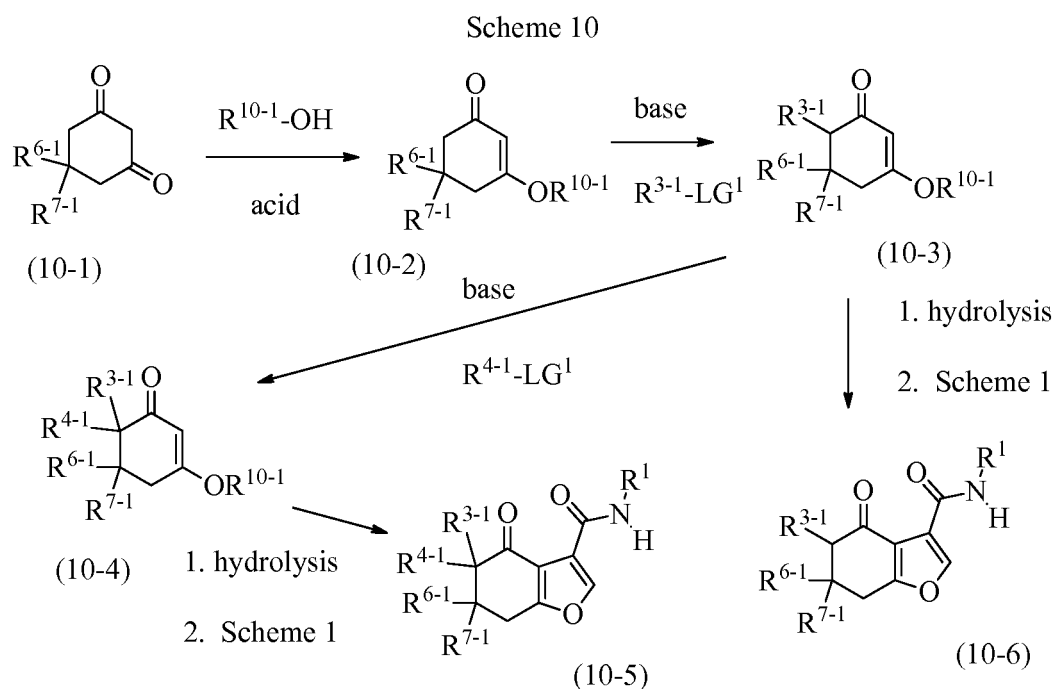
bromoacetate, wherein R^{8-1} is hydrogen or C_1 - C_6 -alkyl, in the presence of a base such as sodium hydride in tetrahydrofuran at ambient temperature over 6-24 hours to give compounds of Formula (8-2). Compounds of Formula (8-2) can be reacted with mercury(II) acetate and sulfuric acid in methanol heated to approximately 60 °C for 30 minutes to 4 hours to give compounds of Formula (8-3), wherein R^{8-2} is C_1 - C_6 -alkyl. When compounds of Formula (8-2) represent a carboxylic acid, compounds of Formula (8-2) are converted to the corresponding methyl esters of Formula (8-3). Compounds of Formula (8-3) can be treated with a base such as potassium *tert*-butoxide in ethanol or *t*-butanol and tetrahydrofuran at 0 °C for 30 minutes to 2 hours to give compounds of Formula (8-4). Compounds of Formula (8-4) are converted to compounds of Formula (8-5) following the furan annulation and amide bond formation sequences described in Scheme 1. Compounds of Formula (8-5) are representative of compounds of Formula (I).

Scheme 9



As shown in Scheme 9, compounds of Formula (9-1) can be transformed to compounds of Formula (9-5), wherein R^1 is as defined in the Summary and R^{9-1} are 0-4 independently selected substituents on the phenyl ring selected from halogen, C_1 - C_6 -alkyl and cyano. Compounds of Formula (9-1) can be epoxidized with 3-chloroperoxybenzoic acid

(MCPBA) in dichloromethane at ambient temperature over 4-24 hours to give compounds of Formula (9-2). Compounds of Formula (9-2) can be hydrogenated in the presence of palladium on carbon in methanol at ambient temperature over 4-24 hours to give compounds of Formula (9-3). The hydroxy group of compounds of Formula (9-3) can be first oxidized with a reagent such as Dess-Martin periodinane in dichloromethane at room temperature over 6-24 hours, and then the ketal can be hydrolyzed with hydrochloric acid in acetone heated in an 80 °C bath for 1-8 hours to give compounds of Formula (9-4). Compounds of Formula (9-4) are converted to compounds of Formula (9-5) following the furan annulation and amide bond formation sequences described in Scheme 1. Compounds of Formula (9-5) are representative of compounds of Formula (I).



As shown in Scheme 10, compounds of Formula (10-5) and Formula (10-6) can be prepared from compounds of Formula (10-1). Compounds of Formula (10-1) (wherein R^{6-1} and R^{7-1} are C_1 - C_6 -alkyl or C_1 - C_6 -alkoxy C_1 - C_6 -alkyl, or wherein R^{6-1} and R^{7-1} taken together with the carbon atom to which they are attached form a C_3 - C_6 -cycloalkyl or M_4 - M_7 -heterocycle, wherein the C_3 - C_6 -cycloalkyl or M_4 - M_7 -heterocycle are optionally substituted with 1, 2, or 3 substituents selected from C_1 - C_6 -alkyl, cyano, halogen, oxo and C_1 - C_6 -alkylcarbonyl, and wherein the M_4 - M_7 -heterocycle does not contain N-H) can be reacted with an alcohol, $R^{10-1}-OH$ (wherein R^{10-1} is C_1 - C_6 -alkyl) in the presence of an acid such as sulfuric acid or *p*-toluenesulfonic acid at ambient temperature to reflux to provide compounds of

Formula (10-2). Compounds of Formula (10-2) can be reacted with a base, such as lithium diisopropylamide, and an alkylating reagent, R^{3-1} -LG¹ (wherein R^{3-1} is C₁-C₆-alkyl and LG¹ is chloro, bromo, iodo, or a sulfonate), in a solvent such as tetrahydrofuran at -20 °C to -78 °C to give compounds of Formula (10-3). Compounds of Formula (10-3) can be reacted with a
5 base, such as lithium diisopropylamide, and an alkylating reagent, R^{4-1} -LG¹ (wherein R^{4-1} is C₁-C₆-alkyl and LG¹ is chloro, bromo, iodo, or a sulfonate) in a solvent such as tetrahydrofuran at -20 °C to -78 °C to give compounds of Formula (10-4). Compounds of Formula (10-4) can be hydrolyzed in the presence of an acid, such as hydrochloric acid, in water, methanol, or acetone, or mixtures thereof. Subsequently, using the chemical
10 sequences described in Scheme 1 to introduce the fused furan and amide groups give compounds of Formula (10-5), wherein R¹ is as described in the Summary. Similarly, compounds of Formula (10-3) can be converted to compounds of Formula (10-6). Compounds of Formula (10-5) and Formula (10-6) are representative of compounds of Formula (I).

15 The compounds and intermediates of the invention may be isolated and purified by methods well-known to those skilled in the art of organic synthesis. Examples of conventional methods for isolating and purifying compounds can include, but are not limited to, chromatography on solid supports such as silica gel, alumina, or silica derivatized with
20 alkylsilane groups, by recrystallization at high or low temperature with an optional pretreatment with activated carbon, thin-layer chromatography, distillation at various pressures, sublimation under vacuum, and trituration, as described for instance in "Vogel's Textbook of Practical Organic Chemistry", 5th edition (1989), by Furniss, Hannaford, Smith, and Tatchell, pub. Longman Scientific & Technical, Essex CM20 2JE, England.

25 Many of the compounds of the invention have at least one basic nitrogen whereby the compound can be treated with an acid to form a desired salt. For example, a compound may be reacted with an acid at or above room temperature to provide the desired salt, which is deposited, and collected by filtration after cooling. Examples of acids suitable for the reaction include, but are not limited to tartaric acid, lactic acid, succinic acid, as well as
30 mandelic, atrolactic, methanesulfonic, ethanesulfonic, toluenesulfonic, naphthalenesulfonic, benzenesulfonic, carbonic, fumaric, maleic, gluconic, acetic, propionic, salicylic, hydrochloric, hydrobromic, phosphoric, sulfuric, citric, hydroxybutyric, camphorsulfonic, malic, phenylacetic, aspartic, or glutamic acid, and the like.

Optimum reaction conditions and reaction times for each individual step can vary depending on the particular reactants employed and substituents present in the reactants used. Unless otherwise specified, solvents, temperatures and other reaction conditions can be readily selected by one of ordinary skill in the art. Specific procedures are provided in the

5 Examples section. Reactions can be worked up in the conventional manner, e.g. by eliminating the solvent from the residue and further purified according to methodologies generally known in the art such as, but not limited to, crystallization, distillation, extraction, trituration and chromatography. Unless otherwise described, the starting materials and reagents are either commercially available or can be prepared by one skilled in the art from

10 commercially available materials using methods described in the chemical literature.

Routine experimentations, including appropriate manipulation of the reaction conditions, reagents and sequence of the synthetic route, protection of any chemical functionality that cannot be compatible with the reaction conditions, and deprotection at a suitable point in the reaction sequence of the method are included in the scope of the

15 invention. Suitable protecting groups and the methods for protecting and deprotecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which can be found in PGM Wuts and TW Greene, in Greene's book titled Protective Groups in Organic Synthesis (4th ed.), John Wiley & Sons, NY (2006), which is incorporated herein by reference in its entirety. Synthesis of the compounds of the

20 invention can be accomplished by methods analogous to those described in the synthetic schemes described hereinabove and in specific examples.

Starting materials, if not commercially available, can be prepared by procedures selected from standard organic chemical techniques, techniques that are analogous to the synthesis of known, structurally similar compounds, or techniques that are analogous to the

25 above described schemes or the procedures described in the synthetic examples section.

When an optically active form of a compound of the invention is required, it can be obtained by carrying out one of the procedures described herein using an optically active starting material (prepared, for example, by asymmetric induction of a suitable reaction step), or by resolution of a mixture of the stereoisomers of the compound or intermediates using a

30 standard procedure (such as chromatographic separation, recrystallization or enzymatic resolution).

Similarly, when a pure geometric isomer of a compound of the invention is required, it can be obtained by carrying out one of the above procedures using a pure geometric isomer

as a starting material, or by resolution of a mixture of the geometric isomers of the compound or intermediates using a standard procedure such as chromatographic separation.

It can be appreciated that the synthetic schemes and specific examples as illustrated in the Examples section are illustrative and are not to be read as limiting the scope of the invention as it is defined in the appended claims. All alternatives, modifications, and equivalents of the synthetic methods and specific examples are included within the scope of the claims.

Compositions of the Invention

The invention also provides pharmaceutical compositions comprising a therapeutically effective amount of a compound of Formula (I) in combination with a pharmaceutically acceptable carrier. The compositions comprise compounds of the invention formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions can be formulated for oral administration in solid or liquid form, for parenteral injection or for rectal administration.

The term “pharmaceutically acceptable carrier”, as used herein, means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of one skilled in the art of formulations.

The pharmaceutical compositions of this invention can be administered to humans and other mammals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments or drops), buccally or as an oral or nasal spray. The term “parenterally”, as used herein, refers to modes of administration which

include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous, intraarticular injection and infusion.

Pharmaceutical compositions for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like, and suitable mixtures thereof), vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate, or suitable mixtures thereof. Suitable fluidity of the composition may be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservative agents, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Suspensions, in addition to the active compounds, may contain suspending agents, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, tragacanth, and mixtures thereof.

If desired, and for more effective distribution, the compounds of the invention can be incorporated into slow-release or targeted-delivery systems such as polymer matrices, liposomes, and microspheres. They may be sterilized, for example, by filtration through a bacteria-retaining filter or by incorporation of sterilizing agents in the form of sterile solid

compositions, which may be dissolved in sterile water or some other sterile injectable medium immediately before use.

Injectable depot forms are made by forming microencapsulated matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations also are prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic, parenterally acceptable diluent or solvent such as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, one or more compounds of the invention is mixed with at least one inert pharmaceutically acceptable carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and salicylic acid; b) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; e) solution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay; and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols,

sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using lactose or milk sugar as well as high molecular weight polyethylene glycols.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract in a delayed manner. Examples of materials which can be useful for delaying release of the active agent can include polymeric substances and waxes.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. A desired compound of the invention is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

5 Powders and sprays can contain, in addition to the compounds of this invention, lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Compounds of the invention may also be administered in the form of liposomes. As
10 is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes may be used. The present compositions in liposome form may contain, in addition to the compounds of the invention, stabilizers,
15 preservatives, and the like. The preferred lipids are the natural and synthetic phospholipids and phosphatidylcholines (lecithins) used separately or together.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N. Y., (1976), p 33 et seq.

20 Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers or propellants, which can be required. Ophthalmic formulations, eye ointments, powders and solutions are contemplated as being within the scope of this invention. Aqueous liquid
25 compositions comprising compounds of the invention also are contemplated.

The compounds of the invention can be used in the form of pharmaceutically acceptable salts or esters, or amides derived from inorganic or organic acids. The term "pharmaceutically acceptable salts and esters and amides", as used herein, refer to carboxylate salts, amino acid addition salts, zwitterions, and esters and amides of compounds
30 of Formula (I) which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

The term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well-known in the art. The salts can be prepared in situ during the final isolation and purification of the compounds of the invention or separately by reacting a free base function with a suitable organic acid. An example of a suitable salt is a hydrochloride salt.

Representative acid addition salts include, but are not limited to acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate.

Preferred salts of the compounds of the invention are the tartrate and hydrochloride salts.

Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates such as dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides such as benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which can be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, sulfuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid, and citric acid.

Basic addition salts can be prepared in situ during the final isolation and purification of compounds of this invention by reacting a carboxylic acid-containing moiety with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium, and aluminum salts, and the like, and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylammonium, dimethylammonium, trimethylammonium, triethylammonium, diethylammonium,

ethylammonium and the like. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

The term “pharmaceutically acceptable ester”, as used herein, refers to esters of compounds of the invention which hydrolyze in vivo and include those that break down readily in the human body to leave the parent compound or a salt thereof. Examples of pharmaceutically acceptable, non-toxic esters of the invention include C₁-to-C₆-alkyl esters and C₅-to-C₇-cycloalkyl esters, although C₁-to-C₄-alkyl esters are preferred. Esters of the compounds of Formula (I) may be prepared according to conventional methods. For example, such esters may be appended onto hydroxy groups by reaction of the compound that contains the hydroxy group with acid and an alkylcarboxylic acid such as acetic acid, or with acid and an arylcarboxylic acid such as benzoic acid. In the case of compounds containing carboxylic acid groups, the pharmaceutically acceptable esters are prepared from compounds containing the carboxylic acid groups by reaction of the compound with base such as triethylamine and an alkyl halide, alkyl triflate, for example with methyl iodide, benzyl iodide, cyclopentyl iodide. They also may be prepared by reaction of the compound with an acid such as hydrochloric acid and an alcohol such as methanol or ethanol.

The term “pharmaceutically acceptable amide”, as used herein, refers to non-toxic amides of the invention derived from ammonia, primary C₁-to-C₆-alkyl amines and secondary C₁-to-C₆-dialkyl amines. In the case of secondary amines, the amine may also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C₁-to-C₃-alkyl primary amides and C₁-to-C₂-dialkyl secondary amides are preferred. Amides of the compounds of Formula (I) may be prepared according to conventional methods. Pharmaceutically acceptable amides are prepared from compounds containing primary or secondary amine groups by reaction of the compound that contains the amino group with an alkyl anhydride, aryl anhydride, acyl halide, or aroyl halide. In the case of compounds containing carboxylic acid groups, the pharmaceutically acceptable esters are prepared from compounds containing the carboxylic acid groups by reaction of the compound with base such as triethylamine, a dehydrating agent such as dicyclohexyl carbodiimide or carbonyl diimidazole, and an alkyl amine, dialkylamine, for example with methylamine, diethylamine, piperidine. They also may be prepared by reaction of the compound with an acid such as sulfuric acid and an alkylcarboxylic acid such as acetic acid, or with acid and an arylcarboxylic acid such as benzoic acid under dehydrating conditions as with molecular

sieves added. The composition can contain a compound of the invention in the form of a pharmaceutically acceptable prodrug.

The invention contemplates pharmaceutically active compounds either chemically synthesized or formed by in vivo biotransformation to compounds of Formula (I)

5

Methods of the Invention

The compounds and compositions of the invention are useful for treating and preventing certain diseases and disorders in humans and animals. As an important consequence of the ability of the compounds of the invention to modulate the effects of Trk's in cells, the compounds described in the invention can affect physiological processes in humans and animals. In this way, the compounds and compositions described in the invention are useful for treating and preventing diseases and disorders modulated by Trk. Typically, treatment or prevention of such diseases and disorders can be effected by selectively modulating Trk's in a mammal, by administering a compound or composition of the invention, either alone or in combination with another active agent as part of a therapeutic regimen.

The compounds of the invention, including but not limited to those specified in the examples, possess an affinity for Trk and therefore, the compounds of the invention may be useful for the treatment and prevention of diseases or conditions such as pain, including osteoarthritis pain, joint pain, neuropathic pain, post-surgical pain, low back pain, and diabetic neuropathy, pain during surgery, cancer pain, chemotherapy induced pain, headaches, including cluster headache, tension headache, migraine pain, trigeminal neuralgia, shingles pain, post-herpetic neuralgia, carpal tunnel syndrome, inflammatory pain, pain from rheumatoid arthritis, colitis, pain of interstitial cystitis, visceral pain, pain from kidney stone, pain from gallstone, angina, fibromyalgia, chronic pain syndrome, thalamic pain syndrome, pain from stroke, phantom limb pain, sunburn, radiculopathy, complex regional pain syndrome, HIV sensory neuropathy, central neuropathic pain syndromes, multiple sclerosis pain, Parkinson disease pain, spinal cord injury pain, menstrual pain, toothache, pain from bone metastasis, pain from endometriosis, pain from uterine fibroids, nociceptive pain, hyperalgesias, and temporomandibular joint pain, inflammation, auto-immune disease, rheumatoid arthritis, psoriasis, psoriatic arthritis, asthma, Crohn's disease, inflammatory bladder cystitis, inflammatory bowel disease, joint swelling, diabetic nephropathy, kidney fibrosis, chronic kidney disease, cancer, neuroblastoma, melanoma, myeloma, cancers of the pancreas, prostate, ovary, colon, thyroid, lung, brain, esophagus, kidney, of bone, and blood.

Compounds of the invention are particularly useful for treating and preventing a condition or disorder affecting pain.

The ability of the compounds of the invention, including, but not limited to, those specified in the examples, to treat the pain of osteoarthritis may be demonstrated by Lane NE,
5 et al. New England J Med 2010;363:1521-1531; Schnitzer TJ, et al. Osteoarthritis Cartilage 2011;19:639-646.

The ability of the compounds of the invention, including, but not limited to, those specified in the examples, to treat lower back pain may be demonstrated by Katz N, et al. Pain 2011;152:2248-2258.

10 The ability of the compounds of the invention, including, but not limited to, those specified in the examples, to treat the pain of cystitis may be demonstrated by Evans RJ, et al. J. Urology 2011;185:1716-1721.

The ability of the compounds of the invention, including, but not limited to, those specified in the examples, to treat the pain of auto-immune arthritis may be demonstrated by
15 Shelton DL, et al. Pain 2005;116:8-16.

The ability of the compounds of the invention, including, but not limited to, those specified in the examples, to treat neuropathic pain or inflammatory pain may be demonstrated by Ro LS, et al. Pain 1999;79:265-274; Ugolini G, et al. Proceedings of the National Academy of Sciences of the USA 2007;104:2985-2990.

20 The ability of the compounds of the invention, including, but not limited to, those specified in the examples, to treat the pain of bone fracture may be demonstrated by Ghilardi JR, et al. Bone 2011;48:389-298.

The ability of the compounds of the invention, including, but not limited to, those specified in the examples, to treat myofascial pain syndrome may be demonstrated by
25 Hayashi K, et al. Journal of Pain 2011;12:1059-1068.

The ability of the compounds of the invention, including, but not limited to, those specified in the examples, to treat diabetic nephropathy and pathological kidney fibrosis may be demonstrated by Fragiadaki M, et al. Diabetes 2012;61:2280-2289.

The ability of the compounds of the invention, including, but not limited to, those specified in the examples, to treat cancer may be demonstrated by Albaugh P, et al. ACS Medicinal Chemistry Letters (2012;3:140-145.

The ability of the compounds of the invention, including, but not limited to, those specified in the examples, to treat neuroblastoma may be demonstrated by Wang T, et al.

ACS Medicinal Chemistry Letters 2012;3:705-709; Thress K, et al. Molecular Cancer Therapeutics 2009;8:1818-1827.

The ability of the compounds of the invention, including, but not limited to, those specified in the examples, to treat melanoma may be demonstrated by Truzzi F, et al. Journal of Investigative Dermatology 2008;128:2031-2040.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention can be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient, compositions and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

When used in the above or other treatments, a therapeutically effective amount of one of the compounds of the invention can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt or ester, or amide form. Alternatively, the compound can be administered as a pharmaceutical composition containing the compound of interest in combination with one or more pharmaceutically acceptable carriers. The phrase "therapeutically effective amount" of the compound of the invention means a sufficient amount of the compound to treat disorders, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

For treatment or prevention of disease, the total daily dose of the compounds of this invention administered to a human or lower animal may range from about 0.0003 to about 100 mg/kg/day. For purposes of oral administration, more preferable doses can be in the range of from about 0.0003 to about 30 mg/kg/day. If desired, the effective daily dose can be divided into multiple doses for purposes of administration; consequently, single dose compositions may contain such amounts or submultiples thereof to make up the daily dose.

The compounds and processes of the invention will be better understood by reference to the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention.

EXAMPLES

Abbreviations: APCI for atmospheric pressure chemical ionization; CAS for Chemical Abstracts Service; CI or chemical ionization; DCI for desorption chemical ionization; DMSO for dimethyl sulfoxide; ESI for electrospray ionization; HPLC for high performance liquid chromatography; and psi for pounds per square inch.

Example 1

N-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 1A

ethyl 3-(3-ethoxy-3-oxopropylamino)-3-oxopropanoate

To a solution of ethyl 3-aminopropanoate hydrochloride (20 g, 0.13 mol) dissolved in dichloromethane (400 mL) at 0 °C was added triethylamine (37.2 mL, 0.272 mol) dropwise. The mixture was stirred for 1 hour at 0 °C, and then ethyl malonyl chloride (16.8 mL, 0.13 mol) was added dropwise. The mixture was stirred for 1 hour, then poured into 75 mL of a saturated aqueous solution of ammonium chloride, and extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (2 × 50 mL), washed with water (50 mL), dried with Na₂SO₄, filtered, concentrated and purified by silica gel column chromatography eluted with petroleum ether/ethyl acetate (50:1) to give the titled compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.50 (s, 1H), 4.14-4.22 (m, 4H), 3.54-3.59 (m, 2H), 3.29 (s, 2H), 2.55 (t, *J* = 6.2 Hz, 2H), 1.25-1.30 (m, 6H).

Example 1B

ethyl 2,4-dioxopiperidine-3-carboxylate

Sodium metal (4.84 g, 0.21 mmol) was added to dry ethanol (200 mL) at room temperature with stirring under N₂. After complete disappearance of the sodium, the mixture was stirred for another 10 minutes, then a solution of the product from Example 1A (28.6 g, 0.123 mol) in dry ethanol (50 mL) was added dropwise. After the addition was complete, the reaction mixture was stirred at 90 °C for 6 hours, and then the mixture was cooled to room temperature. Concentrated HCl (17.5 mL) was added, and the mixture was concentrated under reduced pressure. The resulting residue was treated with water (50 mL), acidified with concentrated HCl (10 mL) and extracted thoroughly with a mixture of dichloromethane/methanol (5:1). The organic layers were combined, dried over Na₂SO₄, filtered and concentrated to give the titled compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 4.19-4.24 (m, 2H), 3.29 (t, *J* = 7.0 Hz, 2H), 2.51-2.55 (m, 3H), 1.23 (t, *J* = 7.2 Hz, 3H).

Example 1C

piperidine-2,4-dione

The product from Example 1B (20.5 g, 0.11 mol) was dissolved in acetonitrile (500 mL) and water (5 mL) was added. The resulting mixture was refluxed for 4 hours and then concentrated under reduced pressure to give a residue which was purified by silica gel column chromatography eluted with a gradient of 0% to 100% methanol in ethyl acetate to give the titled compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.07 (s, 1H), 3.28-3.45 (m, 2H), 3.24 (s, 2H), 2.43-2.49 (m, 2H).

Example 1D

ethyl 3-hydroxy-4-oxo-2,3,4,5,6,7-hexahydrofuro[3,2-*c*]pyridine-3-carboxylate

To a stirred solution of potassium hydroxide (2.97 g, 53 mmol) in methanol (60 mL) under nitrogen at 0 °C was added a solution of the product from Example 1C (6 g, 53 mmol) in methanol (10 mL) dropwise. After the addition was complete, the mixture was stirred at 0 °C for 1 hour, and then a solution of ethyl bromopyruvate (7.01 mL, 55.7 mmol) in methanol (10 mL) was added dropwise. After allowing the mixture to stir at ambient temperature for 2.5 hours, the solvent was removed, and the residue was purified by silica gel column chromatography eluted with methanol/dichloromethane (0-10%) to afford 3.4 g of crude product which was further purified via Teledyne Isco CombiFlash® Companion® XL eluted with methanol/10 mM ammonium acetate in water (0-50%) on a 120 g RediSep® C18 column to provide the titled compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.87 (s, 1H),

4.59 (d, $J = 10.0$ Hz, 1H), 4.34 (d, $J = 10.4$ Hz, 1H), 4.11 (m, 2H), 3.27-3.34 (m, 2H), 2.50-2.55 (m, 2H), 1.16 (t, $J = 7.2$ Hz, 3H).

Example 1E

5 4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxylic acid

A mixture of the product from Example 1D (3.4 g, 16.3 mmol), tetrahydrofuran (163 mL) and 2 *M* HCl (16.3 mL) was heated to 80 °C for 2 hours and then cooled to room temperature. The precipitate was filtered, washed with water and dried to afford the titled compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 15.01 (s, 1H), 8.68 (s, 1H), 8.43 (s, 1H),
10 3.59-3.63 (m, 2H), 3.04 (t, $J = 7.4$ Hz, 2H).

Example 1F

N-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

To a solution of the product from Example 1E (0.1 g, 0.552 mmol) in *N,N*-
15 dimethylformamide (4 mL) was added 2-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.210 g, 0.552 mmol) and triethylamine (0.077 mL, 0.552 mmol). After mixing, 2-methyl-2*H*-indazol-5-amine (0.081 g, 0.552 mmol) was added and the vial was shaken for 4 hours. The mixture was concentrated and triturated with methanol to provide the titled compound. ¹H NMR (DMSO-*d*₆) δ ppm 12.70 (s, 1H), 8.33 (s,
20 1H), 8.27 (m, 2H), 8.22 (bt, 1H), 7.59 (d, $J = 8$ Hz, 1H), 7.25 (d, $J = 8$ Hz, 1H), 4.14 (s, 3H), 3.56 (t, $J = 4$ Hz, 2H), 3.02 (t, $J = 4$ Hz, 2H); MS (APCI) m/z 311 (M+H)⁺.

Example 2

25 5-methyl-*N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 2A

methyl 5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxylate

A solution of the product from Example 1E (7.9 g, 43.6 mmol) in *N,N*-
30 dimethylformamide (450 mL) was cooled to 0 °C in an ice bath, and NaH (60%, 5.23 g, 131 mmol) was added. The mixture was stirred for 1 hour at room temperature and then cooled to 0 °C. Methyl iodide (14 mL, 218 mmol) was added, and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue was treated with 100 mL of water and extracted with ethyl acetate (10 × 30 mL). The combined

organic layers were dried with Na₂SO₄, filtered and concentrated to give a residue which was purified by silica gel column chromatography (100% ethyl acetate) to afford the titled compound. ¹H NMR (400 MHz, CD₃OD) δ ppm 7.96 (s, 1H), 3.72 (s, 3H), 3.59 (t, *J* = 7.2 Hz, 2H), 2.89-2.94 (m, 5H).

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Example 2B

5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxylic acid

A mixture of the product from Example 2A (5.3 g, 25.3 mmol), tetrahydrofuran (25.3 mL) and 2 *M* HCl (25.3 mL) was heated to 80 °C for 2 hours and then cooled to room temperature. The precipitate was filtered, washed with cold water and dried to afford the titled compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 15.01 (s, 1H), 8.42 (s, 1H), 3.79 (t, *J* = 7.6 Hz, 2H), 3.13 (t, *J* = 7.6 Hz, 2H), 3.02 (s, 3H).

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Example 2C

5-methyl-*N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

To a solution of the product from Example 2B (0.1 g, 0.512 mmol) in *N,N*-dimethylformamide (4 mL) was added 2-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.195 g, 0.512 mmol) and triethylamine (0.071 mL, 0.512 mmol). After mixing, 2-methyl-2*H*-indazol-5-amine (0.075 g, 0.512 mmol) was added, and the vial was shaken for 4 hours. The mixture was concentrated and triturated with methanol to provide the titled compound. ¹H NMR (DMSO-*d*₆) δ ppm 12.76 (s, 1H), 8.32 (s, 1H), 8.29 (s, 1H), 8.25 (d, *J* = 4 Hz, 1H), 7.60 (d, *J* = 12 Hz, 1H), 7.29 (d, *J* = 12 Hz, 1H), 4.41 (s, 3H), 3.75 (t, *J* = 8 Hz, 2H), 3.11 (t, *J* = 8 Hz, 2H), 3.06 (s, 3H); MS (ESI) *m/z* 325 (M+H)⁺.

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Example 3

N-[4-(morpholin-4-yl)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

In a 4 mL vial, a solution of the product from Example 1E (31 mg, 0.17 mmol) dissolved in *N,N*-dimethylacetamide (1.0 mL) was treated with a solution of 2-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (76 mg, 0.2 mmol) dissolved in *N,N*-dimethylacetamide (1.0 mL). Then a solution of 4-morpholinoaniline (36 mg, 0.2 mmol) dissolved in *N,N*-dimethylacetamide (0.7 mL) was added followed by neat

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triethylamine (73 μ L, 0.5 mmol). The reaction was shaken at 60 °C overnight and concentrated to dryness. The residue were dissolved in 1:1 dimethyl sulfoxide/methanol and purified by preparative HPLC on a Phenomenex® Luna® C8(2) 5 μ m 100Å AXIA™ column (30 mm $\times$ 75 mm). A gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) was used at a flow rate of 50 mL/minute (0-0.5 minutes 10% A, 0.5-6.0 minutes linear gradient 10-100% A, 6.0-7.0 minutes 100% A, 7.0-8.0 minutes linear gradient 100-10% A). Samples were injected in dimethyl sulfoxide/methanol (1:1, 1.5 mL). An Agilent 1100 Series Purification system was used, consisting of the following modules: Agilent 1100 Series LC/MSD SL mass spectrometer with API-electrospray source; two Agilent 1100 Series preparative pumps; Agilent 1100 Series isocratic pump; Agilent 1100 Series diode array detector with preparative (0.3 mm) flow cell; Agilent active-splitter, IFC-PAL fraction collector/autosampler. The make-up pump for the mass spectrometer used 3:1 methanol/water with 0.1% formic acid at a flow rate of 1 mL/minute. Fraction collection was automatically triggered when the extracted ion chromatogram (EIC) for the target mass exceeded the threshold. Concentration of selected fractions provided the titled compound as the trifluoroacetate. ^1H NMR (500 MHz, DMSO- d_6 /D $_2$ O) δ ppm 8.26 (s, 1H), 7.51 - 7.57 (m, 2H), 6.95 - 7.00 (m, 2H), 3.72 - 3.77 (m, 4H), 3.56 (t, J = 7.32 Hz, 2H), 3.06 - 3.10 (m, 4H), 3.01 (t, J = 7.32 Hz, 2H); MS (ESI) m/z 342 (M+H) $^+$.

Example 4

5-methyl-*N*-(4-methylphenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

In a 4 mL vial, a solution of the product from Example 2B (31 mg, 0.16 mmol) dissolved in *N,N*-dimethylacetamide (1.0 mL) was treated with a solution of 2-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (73 mg, 0.2 mmol) dissolved in *N,N*-dimethylacetamide (1.0 mL). Then a solution of *p*-toluidine (30 mg, 0.2 mmol) dissolved in *N,N*-dimethylacetamide (0.6 mL) was added followed by neat triethylamine (68 μ L, 0.5 mmol). The reaction was shaken at 60 °C overnight. The residue was dissolved in 1:1 dimethyl sulfoxide/methanol and purified by preparative HPLC on a Phenomenex® Luna® C8(2) 5 μ m 100Å AXIA™ column (30 mm $\times$ 75 mm). A gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) was used, at a flow rate of 50 mL/minute (0-0.5 minutes 10% A, 0.5-6.0 minutes linear gradient 10-100% A, 6.0-7.0 minutes 100% A, 7.0-8.0 minutes linear gradient 100-10% A). Samples were injected in dimethyl sulfoxide/methanol (1:1, 1.5 mL). An Agilent 1100 Series Purification system was

used consisting of the following modules: Agilent 1100 Series LC/MSD SL mass spectrometer with API-electrospray source; two Agilent 1100 Series preparative pumps; Agilent 1100 Series isocratic pump; Agilent 1100 Series diode array detector with preparative (0.3 mm) flow cell; Agilent active-splitter, IFC-PAL fraction collector / autosampler. The make-up pump for the mass spectrometer used 3:1 methanol/water with 0.1% formic acid at a flow rate of 1 mL/minute. Fraction collection was automatically triggered when the extracted ion chromatogram (EIC) for the target mass exceeded the threshold. Concentration of selected fractions provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 12.70 (s, 1H), 8.30 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 3.74 (t, *J* = 7.5 Hz, 2H), 3.10 (t, *J* = 7.5 Hz, 2H), 3.04 (s, 3H), 2.27 (s, 3H); MS (APCI) *m/z* 285 (M+H)⁺.

Example 5

tert-butyl 4-(3-methoxy-4-{[(4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino}phenyl)piperazine-1-carboxylate

A solution of the product from Example 1E (295 mg, 1.627 mmol), *tert*-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (CAS# 1246532-96-6) (500 mg, 1.627 mmol) and 2-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (680 mg, 1.789 mmol) in acetonitrile (15 mL) was treated with diisopropylethylamine (0.426 mL, 2.440 mmol) and stirred for 16 hours. The reaction mixture was partitioned between ethyl acetate (50 mL) and H₂O (20 mL). The organic layer was separated, washed with brine and dried with MgSO₄. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was chromatographed on a silica gel column eluted with 30-80% ethyl acetate in hexanes to provide the titled compound. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.91 (s, 1H), 8.25 (s, 1H), 8.04 (s, 1H), 7.94 (d, *J* = 8.8 Hz, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 6.49 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.79 (s, 3H), 3.52 (td, *J* = 7.2, 2.5 Hz, 2H), 3.48 – 3.42 (m, 4H), 3.11 – 3.06 (m, 4H), 2.99 (t, *J* = 7.3 Hz, 2H), 1.42 (s, 9H); MS (DCI) *m/z* 471 (M+H)⁺.

Example 6

N-[2-methoxy-4-(piperazin-1-yl)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The product from Example 5, *tert*-butyl 4-(3-methoxy-4-{[(4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino}phenyl)piperazine-1-carboxylate (753 mg, 1.6 mmol), was treated with trifluoroacetic acid (2 mL) at room temperature for 5 minutes. The mixture was concentrated under reduced pressure. The residue was dissolved in

dichloromethane (50 mL) and washed with saturated K₂CO₃ solution. The organic layer was separated, dried with MgSO₄ and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel eluted with concentrated

NH₄OH/methanol/dichloromethane (0.3/3/97) to provide the titled compound. ¹H NMR (300 MHz, CD₃OD) δ ppm 8.13 (s, 1H), 7.90 (s, 1H), 7.88 (d, *J* = 6.1 Hz, 1H), 6.65 (d, *J* = 2.5 Hz, 1H), 6.55 (dd, *J* = 8.8, 2.6 Hz, 1H), 3.87 (s, 3H), 3.65 (t, *J* = 7.3 Hz, 2H), 3.14 (dd, *J* = 6.2, 3.8 Hz, 4H), 3.02 (dd, *J* = 12.0, 4.6 Hz, 2H), 2.98 (dd, *J* = 6.2, 3.8 Hz, 4H); MS (DCI) *m/z* 371 (M+H)⁺.

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Example 7

N-[2-methoxy-6-(4-methylpiperazin-1-yl)pyridin-3-yl]-4-oxo-5,6,7,8-tetrahydro-4*H*-furo[3,2-*c*]azepine-3-carboxamide

Example 7A

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ethyl 3-hydroxy-4-oxo-3,4,5,6,7,8-hexahydro-2*H*-furo[3,2-*c*]azepine-3-carboxylate

A solution of azepane-2,4-dione (CAS # 29520-88-5, Coleman RS, et al. Organic Letters 2009; 11: 2133-2136) (2.18 g, 17.15 mmol) in methanol (40 mL) was added dropwise to a solution of KOH (1.14 g, 17.27 mmol) in water (10 mL). The resulting mixture was stirred at 0 °C for 1 hour, and then ethyl 3-bromo-2-oxopropanoate (3.35g, 17.18 mmol) was added dropwise. The resulting mixture was stirred at 25 °C for 1 hour. The solvent was removed under reduced pressure, and the crude material was used in the next step without purification. MS (CI) *m/z* 224 (M-H₂O+H)⁺.

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Example 7B

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4-oxo-5,6,7,8-tetrahydro-4*H*-furo[3,2-*c*]azepine-3-carboxylic acid

A solution of the product from Example 7A, ethyl 3-hydroxy-4-oxo-3,4,5,6,7,8-hexahydro-2*H*-furo[3,2-*c*]azepine-3-carboxylate (184 mg, 0.763 mmol) in H₂O (2 mL) and 10% HCl (1.159 mL, 3.81 mmol) was stirred at 100 °C for 3 hours. Solvent was removed under reduced pressure, and the crude material was purified via Teledyne Isco CombiFlash® Companion® XL eluted with acetonitrile/10 mM ammonium acetate in water (0-20%) on a 120 g RediSep® C18 column to provide the titled compound. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 16.23 (s, 1H), 9.10 (bt, 1H), 8.37 (s, 1H), 3.34 – 3.28 (m, 2H), 3.09 (t, *J* = 6.7 Hz, 2H), 2.03 – 1.91 (m, 2H); MS (ESI) *m/z* 196 (M+H)⁺.

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Example 7C

N-[2-methoxy-6-(4-methylpiperazin-1-yl)pyridin-3-yl]-4-oxo-5,6,7,8-tetrahydro-4*H*-furo[3,2-*c*]azepine-3-carboxamide

A solution of the product from Example 7B, 4-oxo-5,6,7,8-tetrahydro-4*H*-furo[3,2-*c*]azepine-3-carboxylic acid (30mg, 0.154 mmol), and triethylamine (0.032 mL, 0.231 mmol) in acetonitrile (5 mL) was treated with ethyl chloroformate (0.019 mL, 0.200 mmol) at 0 °C and stirred for 20 minutes. A solution of 2-methoxy-6-(4-methylpiperazin-1-yl)pyridin-3-amine (CAS # 1094787-95-7) in acetonitrile (5 mL) was added, and the mixture was stirred at ambient temperature for 16 hours. The reaction mixture was diluted with water (20 mL) and stirred for 10 minutes. The precipitate was filtered and washed with small amount of ether (5 mL). The solid was purified on a silica gel column eluted with concentrated NH₄OH/methanol/dichloromethane (0.2/2/98) to provide the titled compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.15 (s, 1H), 8.53 (t, *J* = 5.8 Hz, 1H), 8.29 – 8.09 (m, 2H), 6.29 (d, *J* = 8.6 Hz, 1H), 3.80 (s, 3H), 3.25 – 3.13 (m, 3H), 3.04 (t, *J* = 7.1 Hz, 2H), 2.42 – 2.34 (m, 4H), 2.20 (s, 3H), 2.02 – 1.90 (m, 2H); MS (DCI) *m/z* 400 (M+H)⁺.

Example 8

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[2-(benzyloxy)ethyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 8A

5-(2-(benzyloxy)ethyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxylic acid

A mixture of a 60% dispersion of sodium hydride in mineral oil (55.2 mg, 1.38 mmol) and benzyl 2-bromoethyl ether (356 mg, 1.66 mmol) in *N,N*-dimethylformamide (2 mL) was cooled to 0 °C and treated with the product from Example 1E (100 mg, 0.55 mmol). The reaction mixture was stirred at 0 °C for 15 minutes, and then it was stirred at room temperature overnight. The reaction mixture was treated with water (10 mL) and 1 *M* NaOH (1 mL) and then washed with Et₂O (2 × 30 mL, discarded). The aqueous layer was acidified with concentrated HCl and extracted with Et₂O (50 mL). This Et₂O layer was washed with brine, dried (MgSO₄), filtered, concentrated and chromatographed on silica gel eluted with a gradient of 0% to 50% ethyl acetate in [9:1 CH₂Cl₂:ethyl acetate] to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 14.59 (s, 1H), 8.04 (s, 1H), 7.38 – 7.26 (m, 5H), 4.53 (s, 2H), 3.89 (t, *J* = 7.4 Hz, 2H), 3.81 – 3.64 (m, 4H), 3.02 (t, *J* = 7.4 Hz, 2H).

Example 8B

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[2-(benzyloxy)ethyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

- 5 A solution of the product from Example 8A (30 mg, 0.095 mmol) in tetrahydrofuran (3 mL) was treated with triethylamine (33.2 μ L, 0.238 mmol) followed by treatment with ethyl chloroformate (9.14 μ L, 0.095 mmol). The mixture was stirred at room temperature for 45 minutes and then treated with 1-(4-(5-amino-6-ethoxypyridin-2-yl)piperazin-1-yl)ethanone (CAS# 1094927-44-2) (20.96 mg, 0.079 mmol). The reaction mixture was
- 10 stirred for approximately 60 hours and then partitioned between 1 *M* NaOH (5 mL) and CH₂Cl₂ (25 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (25 mL). The combined CH₂Cl₂ layers were washed with 1 *M* HCl (10 mL), dried (MgSO₄), filtered, concentrated and chromatographed on silica gel eluted with a gradient of 0% to 100% [20% ethanol in ethyl acetate] in ethyl acetate to provide the titled compound.
- 15 ¹H NMR (300 MHz, CDCl₃) δ ppm 12.00 (s, 1H), 8.53 (d, *J* = 8.5 Hz, 1H), 8.06 (s, 1H), 7.37 – 7.27 (m, 5H), 6.19 (d, *J* = 8.6 Hz, 1H), 4.53 (s, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.82 (t, *J* = 7.3 Hz, 2H), 3.77 – 3.70 (m, 6H), 3.61 – 3.41 (m, 6H), 2.98 (t, *J* = 7.2 Hz, 2H), 2.14 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H); MS (ESI) *m/z* 562 (M+H)⁺.

20 Example 9

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2-hydroxyethyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

- A mixture of the product from Example 8B and 10% Pd/C (~75 mg) in tetrahydrofuran (5 mL) was stirred under H₂ using a balloon for 2 hours, diluted with CH₂Cl₂
- 25 and filtered. The filtrate was concentrated and chromatographed on silica gel eluted with a gradient of 0% to 100% [20% ethanol in ethyl acetate] in ethyl acetate to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.84 (s, 1H), 8.54 (d, *J* = 8.5 Hz, 1H), 8.08 (s, 1H), 6.20 (d, *J* = 8.6 Hz, 1H), 4.41 (q, *J* = 7.0 Hz, 2H), 3.90 (t, *J* = 4.7 Hz, 2H), 3.82 (t, *J* = 7.3 Hz, 2H), 3.73 (dd, *J* = 9.6, 4.3 Hz, 4H), 3.63 – 3.40 (m, 6H), 3.06 (t, *J* = 7.3 Hz, 2H), 2.14
- 30 (s, 3H), 1.47 (t, *J* = 7.0 Hz, 3H); MS (ESI) *m/z* 472 (M+H)⁺.

Example 10

N-[4-(4-acetylpiperazin-1-yl)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 1F substituting 1-(4-(4-aminophenyl)piperazin-1-yl)ethanone for 2-methyl-2*H*-indazol-5-amine. ¹H NMR (DMSO-*d*₆) δ ppm 12.54 (s, 1H), 8.29 (s, 1H), 8.16 (s, 1H), 7.54 (d, *J* = 8 Hz, 2H), 6.97 (d, *J* = 8 Hz, 2H), 3.35-3.59 (m, 6H), 3.11 (t, *J* = 4 Hz, 2H), 2.99-3.06 (m, 4H), 2.04 (s, 3H); MS (APCI) *m/z* 383 (M+H)⁺.

Example 11

N-(1-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 1F substituting 1-methyl-1*H*-indazol-5-amine for 2-methyl-2*H*-indazol-5-amine. ¹H NMR (DMSO-*d*₆) δ ppm 12.79 (s, 1H), 8.34 (s, 1H), 8.27 (s, 1H), 8.22 (s, 1H), 7.64 (d, *J* = 8 Hz, 1H), 7.47 (d, *J* = 12 Hz, 1H), 4.03 (s, 3H), 3.57 (t, *J* = 8 Hz, 2H), 3.03 (t, *J* = 8 Hz, 2H); MS (APCI) *m/z* 311 (M+H)⁺.

Example 12

N-(1*H*-benzimidazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 1F substituting 1*H*-benzo[*d*]imidazol-5-amine for 2-methyl-2*H*-indazol-5-amine. ¹H NMR (DMSO-*d*₆) δ ppm 12.80 (d, br, 1H), 12.39 (s, 1H), 8.34 (s, 1H), 8.22 (s, 1H), 8.17 (s, 1H), 7.50-7.59 (m, 1H), 7.20-7.34 (d, br, 1H), 3.54-3.59 (m, 2H), 3.03 (t, *J* = 8 Hz, 2H); MS (APCI) *m/z* 297 (M+H)⁺.

Example 13

N-(4-carbamoylphenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 1F substituting 4-aminobenzamide for 2-methyl-2*H*-indazol-5-amine. ¹H NMR (DMSO-*d*₆) δ ppm 12.99 (s, 1H), 8.38 (s, 1H), 8.26 (s, 1H), 7.89 (d, *J* = 8 Hz, 2H), 7.71 (d, *J* = 8 Hz, 2H), 7.26 (s, 1H), 3.56 (t, *J* = 8 Hz, 2H), 3.03 (t, *J* = 8 Hz, 2H); MS (APCI) *m/z* 300 (M+H)⁺.

Example 14

N-(1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 1F substituting 1*H*-indazol-5-amine for 2-methyl-2*H*-indazol-5-amine. ¹H NMR (DMSO-*d*₆) δ ppm 13.02 (s, 1H), 12.76 (s, 1H), 8.34 (s, 1H), 8.27 (s, 1H), 8.21 (s, 1H), 8.05 (s, 1H), 7.54

(d, $J = 8$ Hz, 1H), 7.43 (d, $J = 8$ Hz, 1H), 3.57 (t, $J = 8$ Hz, 2H), 3.03 (t, $J = 8$ Hz, 2H); MS (ESI) m/z 297 (M+H)⁺.

Example 15

5 *N*-(2-methyl-1,3-benzothiazol-6-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 1F substituting 2-methylbenzo[*d*]thiazol-6-amine for 2-methyl-2*H*-indazol-5-amine. ¹H NMR (DMSO-*d*₆) δ ppm 12.98 (s, 1H), 8.51 (s, 1H), 8.37 (s, 1H), 8.26 (s, 1H), 7.88 (d, $J = 8$ Hz, 1H), 7.55 (d, $J = 8$ Hz, 1H), 3.58 (t, $J = 8$ Hz, 2H), 3.03 (t, $J = 8$ Hz, 2H), 2.77 (s, 3H); MS (APCI) m/z 327 (M+H)⁺.

Example 16

15 *N*-[5-(4-methylpiperazin-1-yl)pyridin-2-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 1F substituting 5-(4-methylpiperazin-1-yl)pyridin-2-amine for 2-methyl-2*H*-indazol-5-amine. ¹H NMR (DMSO-*d*₆) δ ppm 12.73 (s, 1H), 8.33 (s, 1H), 8.08 (s, 1H), 8.06 (s, 1H), 8.01 (s, 1H), 7.40 (dd, $J = 4, 8$ Hz, 1H), 3.52 (t, $J = 8$ Hz, 2H), 3.13 (t, $J = 8$ Hz, 4H), 2.99 (t, $J = 8$ Hz, 2H), 2.44 (t, $J = 8$ Hz, 4H), 2.21 (s, 3H); MS (APCI) m/z 356 (M+H)⁺.

Example 17

25 *N*-[4-(4-methylpiperazin-1-yl)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 1F substituting 4-(4-methylpiperazin-1-yl)aniline for 2-methyl-2*H*-indazol-5-amine. ¹H NMR (DMSO-*d*₆) δ ppm 12.5 (s, 1H), 8.26 (s, 1H), 8.16 (s, 1H), 7.50 (d, $J = 8$ Hz, 2H), 6.92 (d, $J = 8$ Hz, 2H), 3.53 (td, $H = 4, 8$, 2H), 3.07 (t, $J = 4$ Hz, 4H), 2.99 (t, $J = 8$ Hz, 2H), 2.43 (t, $J = 8$ Hz, 4H), 2.20 (s, 3H); MS (APCI) m/z 355 (M+H)⁺.

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Example 18

N-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

To a solution of the product from Example 6 (40 mg, 0.108 mmol) and triethylamine (0.023 mL, 0.15 mmol) in dichloromethane (10 mL) was added acetyl chloride (0.01 mL, 0.14 mmol). The mixture was stirred at room temperature for 10 minutes. The reaction mixture was concentrated under reduced pressure. The resulting residue was

5 chromatographed on a silica gel column eluted with concentrated NH₄OH/methanol/dichloromethane (0.2/2/98) to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.73 (d, *J* = 28.1 Hz, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 8.11 (s, 1H), 6.56 (d, *J* = 9.2 Hz, 2H), 5.68 (s, 1H), 3.92 (s, 3H), 3.78 – 3.55 (m, 6H), 3.17 (m, 4H), 3.04 (t, *J* = 7.2 Hz, 2H), 2.14 (s, 3H); MS (DCI) *m/z* 413 (M+H)⁺.

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Example 19

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

A solution of the product from Example 1E (50 mg, 0.276 mmol) in tetrahydrofuran (5 mL) was treated with triethylamine (96 μL, 0.69 mmol) followed by treatment with ethyl chloroformate (26.5 μL, 0.276 mmol). The mixture was stirred at room temperature for 45 minutes and then treated with 1-(4-(5-amino-6-ethoxypyridin-2-yl)piperazin-1-yl)ethanone (CAS# 1094927-44-2) (60.8 mg, 0.230 mmol). The reaction mixture was stirred for overnight and then partitioned between 1 *M* NaOH (5 mL) and CH₂Cl₂ (25 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (25 mL). The combined CH₂Cl₂ layers were washed with 1 *M* HCl (10 mL), dried (MgSO₄), filtered, concentrated and chromatographed on silica gel eluted with a gradient of 0% to 100% [20% ethanol in ethyl acetate] in ethyl acetate to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.67 (s, 1H), 8.49 (d, *J* = 8.5 Hz, 1H), 8.09 (s, 1H), 6.19 (d, *J* = 8.6 Hz, 1H), 5.62 (s, 1H), 4.43 (q, *J* = 7.0 Hz, 2H), 3.78 – 3.41 (m, 10H), 3.03 (t, *J* = 7.2 Hz, 2H), 2.14 (s, 3H), 1.45 (t, *J* = 7.0 Hz, 3H); MS (ESI) *m/z* 428 (M+H)⁺.

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Example 20

N-[6-(4-acetylpiperazin-1-yl)-2-(2-methoxyethoxy)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

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Example 20A

6-chloro-2-(2-methoxyethoxy)-3-nitropyridine

A solution of 2-methoxyethanol (1.348 mL, 17.10 mmol) in xylenes (100 mL) was treated with a 60% dispersion of sodium hydride in mineral oil (0.808 g, 20.21 mmol) followed by stirring at room temperature for 20 minutes. The mixture was cooled to 0 °C and treated with a solution of 2,6-dichloro-3-nitropyridine (3 g, 15.55 mmol) in xylenes (70 mL).
5 The reaction mixture was then stirred overnight at room temperature, treated with water (50 mL) and transferred to a separatory funnel with ether. The layers were separated, and the aqueous layer was extracted with ether (50 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated to provide the titled compound which was used without purification in the next step. ¹H NMR (300 MHz, CDCl₃) δ ppm 8.27 (d, *J*
10 = 8.2 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 4.68 – 4.64 (m, 2H), 3.83 – 3.79 (m, 2H), 3.46 (s, 3H).

Example 20B

1-(4-(6-(2-methoxyethoxy)-5-nitropyridin-2-yl)piperazin-1-yl)ethanone

15 A solution of the product from Example 20A (1.86 g, 8 mmol), 1-acetylpiperazine (1.538 g, 12.00 mmol) and triethylamine (3.35 mL, 24.00 mmol) in acetonitrile (20 mL) was heated to 80 °C for 1 hour, cooled and partitioned between ethyl acetate (100 mL) and 1 *M* HCl (60 mL). The ethyl acetate layer was washed with brine, dried (MgSO₄), filtered and concentrated to ~20 mL. The flask was scratched with a spatula, and a yellow solid
20 precipitated. After standing for 1 hour, the solid was collected by filtration, washed with ethyl acetate and dried under vacuum to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 8.30 (d, *J* = 9.1 Hz, 1H), 6.18 (d, *J* = 9.1 Hz, 1H), 4.55 (dd, *J* = 5.6, 4.5 Hz, 2H), 3.85 – 3.66 (m, 8H), 3.64 – 3.58 (m, 2H), 3.48 (s, 3H), 2.16 (s, 3H).

Example 20C

1-(4-(5-amino-6-(2-methoxyethoxy)pyridin-2-yl)piperazin-1-yl)ethanone

The product from Example 20B (5 g, 15 mmol) and tetrahydrofuran (30 mL) were added to Raney®-nickel 2800, water slurry, (2.5 g, 43 mmol) in a stainless steel pressure bottle and stirred at room temperature for 6 hours under a hydrogen atmosphere (30 psi). The
30 mixture was filtered through a nylon membrane and concentrated to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 6.92 (d, *J* = 8.1 Hz, 1H), 6.11 (d, *J* = 8.1 Hz, 1H), 4.50 – 4.45 (m, 2H), 3.79 – 3.71 (m, 4H), 3.58 (dd, *J* = 6.2, 4.2 Hz, 2H), 3.43 (s, 3H), 3.37 (dd, *J* = 6.3, 4.1 Hz, 2H), 3.32 – 3.26 (m, 2H), 2.13 (s, 3H).

Example 20D

N-[6-(4-acetylpiperazin-1-yl)-2-(2-methoxyethoxy)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

5 The titled compound was prepared using the procedure described for Example 19 substituting the product from Example 20C for 1-(4-(5-amino-6-ethoxypyridin-2-yl)piperazin-1-yl)ethanone. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.98 (s, 1H), 8.28 – 8.23 (m, 2H), 8.01 (t, *J* = 2.4 Hz, 1H), 6.36 (d, *J* = 8.6 Hz, 1H), 4.43 – 4.36 (m, 2H), 3.76 – 3.71 (m, 2H), 3.58 – 3.45 (m, 8H), 3.41 (d, *J* = 5.4 Hz, 2H), 3.29 (s, 3H), 2.99 (t, *J* = 7.3 Hz, 2H),
10 2.04 (s, 3H); MS (ESI) *m/z* 458 (M+H)⁺.

Example 21

N-[6-(4-acetylpiperazin-1-yl)-2-(oxetan-3-yloxy)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

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Example 21A

6-chloro-3-nitro-2-(oxetan-3-yloxy)pyridine

 The titled compound was prepared using the procedure described for Example 20A substituting oxetan-3-ol for 2-methoxyethanol and substituting a 3:1 mixture of
20 tetrahydrofuran/xylenes for xylenes. The residue was chromatographed on a silica gel column eluted with 20-100% [9:1 dichloromethane/ethyl acetate] in hexanes. ¹H NMR (300 MHz, CDCl₃) δ ppm 8.32 (d, *J* = 8.4 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 5.80 – 5.70 (m, 1H), 5.05 – 4.98 (m, 2H), 4.82 (ddd, *J* = 7.5, 5.4, 1.0 Hz, 2H).

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Example 21B

1-(4-(5-nitro-6-(oxetan-3-yloxy)pyridin-2-yl)piperazin-1-yl)ethanone

 The titled compound was prepared using the procedure described for Example 20B substituting the product from Example 21A for the product from Example 20A. ¹H NMR (300 MHz, CDCl₃) δ ppm 8.32 (d, *J* = 9.1 Hz, 1H), 6.23 (d, *J* = 9.1 Hz, 1H), 5.68 (p, *J* = 6.0
30 Hz, 1H), 4.96 (dd, *J* = 7.6, 6.7 Hz, 2H), 4.90 – 4.82 (m, 2H), 3.83 – 3.57 (m, 8H), 2.16 (s, 3H).

Example 21C

1-(4-(5-amino-6-(oxetan-3-yloxy)pyridin-2-yl)piperazin-1-yl)ethanone

The titled compound was prepared using the procedure described for Example 20C substituting the product from Example 21B for the product from Example 20B.

Example 21D

5 *N*-[6-(4-acetylpiperazin-1-yl)-2-(oxetan-3-yloxy)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 19 substituting the product from Example 21C for 1-(4-(5-amino-6-ethoxypyridin-2-yl)piperazin-1-yl)ethanone. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.86 (s, 1H), 8.57 (d, *J* = 8.6 Hz, 1H), 8.10 (s, 1H), 6.27 (d, *J* = 8.7 Hz, 1H), 5.70 – 5.59 (m, 1H), 5.55 (bs, 1H), 4.98 (t, *J* = 6.9 Hz, 2H), 4.95 – 4.89 (m, 2H), 3.77 – 3.67 (m, 4H), 3.61 – 3.53 (m, 2H), 3.52 – 3.35 (m, 4H), 3.05 (t, *J* = 7.2 Hz, 2H), 2.14 (s, 3H); MS (ESI) *m/z* 456 (M+H)⁺.

Example 22

15 5-methyl-*N*-[4-(4-methylpiperazin-1-yl)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 2C substituting 4-(4-methylpiperazin-1-yl)aniline for 2-methyl-2*H*-indazol-5-amine. ¹H NMR (DMSO-*d*₆) δ ppm 12.62 (s, 1H), 8.27 (s, 1H), 7.57 (d, *J* = 8 Hz, 2H), 7.01 (d, *J* = 8 Hz, 2H), 3.73 (t, *J* = 8 Hz, 2H), 3.32 (m, 4H), 3.09 (t, *J* = 8 Hz, 2H), 3.08 (s, 3H), 3.03 (s, 3H), 2.51 (m, 4H); MS (APCI) *m/z* 369 (M+H)⁺.

Example 23

N-(1*H*-indazol-5-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

25 The titled compound was prepared using the procedure described for Example 2C substituting 1*H*-indazol-5-amine for 2-methyl-2*H*-indazol-5-amine. ¹H NMR (DMSO-*d*₆) δ ppm 13.02 (s, 1H), 12.80 (s, 1H), 8.31 (s, 1H), 8.26 (s, 1H), 8.05 (s, 1H), 7.54 (d, *J* = 8 Hz, 1H), 7.47 (d, *J* = 8 Hz, 1H), 3.73 (t, *J* = 8 Hz, 2H), 3.11 (t, *J* = 8 Hz, 2H), 3.01 (s, 3H); MS (APCI) *m/z* 311 (M+H)⁺.

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Example 24

5-methyl-*N*-(1-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 2C substituting 1-methyl-1*H*-indazol-5-amine for 2-methyl-2*H*-indazol-5-amine. ¹H NMR (DMSO-*d*₆) δ ppm 12.82 (s, 1H), 8.32 (s, 1H), 8.25 (s, 1H), 8.02 (s, 1H), 7.63 (d, *J* = 8 Hz, 1H), 7.50 (d, *J* = 8 Hz, 1H), 4.02 (s, 3H), 3.74 (t, *J* = 8 Hz, 2H), 3.10 (t, *J* = 8 Hz, 2H), 3.05 (s, 3H); MS (APCI) *m/z* 325 (M+H)⁺.

Example 25

5-methyl-*N*-[4-(morpholin-4-yl)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 2C substituting 4-morpholinoaniline for 2-methyl-2*H*-indazol-5-amine. ¹H NMR (DMSO-*d*₆) δ ppm 12.57 (s, 1H), 8.26 (s, 1H), 7.54 (d, *J* = 8 Hz, 2H), 6.94 (d, *J* = 8 Hz, 2H), 3.71-3.73 (m, 6H), 3.03-3.10 (m, 9H); MS (APCI) *m/z* 356 (M+H)⁺.

Example 26

N-(4-carbamoylphenyl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 2C substituting 4-aminobenzamide for 2-methyl-2*H*-indazol-5-amine. ¹H NMR (DMSO-*d*₆) δ ppm 13.01 (s, 1H), 8.35 (s, 1H), 7.87-7.89 (m, 3H), 7.72 (d, *J* = 8 Hz, 2H), 7.25 (s, 1H), 3.74 (t, *J* = 8 Hz, 2H), 3.10 (t, *J* = 8 Hz, 2H), 3.04 (s, 3H); MS (APCI) *m/z* 314 (M+H)⁺.

Example 27

N-(1*H*-benzimidazol-5-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 2C substituting 1*H*-benzo[*d*]imidazol-5-amine for 2-methyl-2*H*-indazol-5-amine. ¹H NMR (DMSO-*d*₆) δ ppm 13.04 (s, 1H), 8.82 (s, 1H), 8.36-8.38 (m, 2H), 7.72 (d, *J* = 8 Hz, 1H), 7.42 (d, *J* = 9 Hz, 2H), 3.76 (t, *J* = 8 Hz, 2H), 3.12 (t, *J* = 8 Hz, 2H), 3.07 (s, 3H); MS (APCI) *m/z* 311 (M+H)⁺.

Example 28

N-[4-(4-acetylpiperazin-1-yl)phenyl]-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 2C substituting 1-(4-(4-aminophenyl)piperazin-1-yl)ethanone for 2-methyl-2*H*-indazol-5-amine. ¹H NMR (DMSO-*d*₆) δ ppm 12.60 (s, 1H), 8.28 (s, 1H), 7.54 (d, *J* = 12 Hz, 2H), 6.97 (d, *J* = 12 Hz, 2H), 3.74 (d, *J* = 4 Hz, 2H), 3.56-3.58(m, 4H), 3.05-2.12 (m, 6H), 3.04 (s, 3H), 2.04 (s, 3H); MS (APCI) *m/z* 397 (M+H)⁺.

Example 29

5-methyl-*N*-(2-methyl-1,3-benzothiazol-6-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 2C substituting 2-methylbenzo[*d*]thiazol-6-amine for 2-methyl-2*H*-indazol-5-amine. ¹H NMR (DMSO-*d*₆) δ ppm 13.03 (s, 1H), 8.50 (s, 1H), 8.36 (s, 1H), 7.89 (d, *J* = 8 Hz, 1H), 7.60 (d, *J* = 8 Hz, 1H), 3.76 (t, *J* = 8 Hz, 2H), 3.12 (t, *J* = 8 Hz, 2H), 3.06 (s, 3H), 2.77 (s, 3H); MS (APCI) *m/z* 342 (M+H)⁺.

Example 30

N-(4-methylphenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 3, substituting 4-methylaniline for 4-morpholinoaniline. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 12.65 (s, 1H), 8.31 (s, 1H), 8.19 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 3.55 (td, *J* = 7.4, 2.6 Hz, 2H), 3.01 (t, *J* = 7.4 Hz, 2H), 2.27 (s, 3H); MS (APCI) *m/z* 271 (M+H)⁺.

Example 31

N-(4-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 3, substituting 4-aminophenol for 4-morpholinoaniline, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.25 (s, 1H), 7.43 - 7.49 (m, 2H), 6.72 - 6.80 (m, 2H), 3.56 (t, *J* = 7.17 Hz, 2H), 3.01 (t, *J* = 7.48 Hz, 2H); MS (ESI) *m/z* 273 (M+H)⁺.

Example 32

N-(4-acetamidophenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 3, substituting *N*-(4-aminophenyl)acetamide for 4-morpholinoaniline, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ

ppm 8.29 (s, 1H), 7.51 - 7.62 (m, 4H), 3.57 (t, $J=7.48$ Hz, 2H), 3.02 (t, $J=7.32$ Hz, 2H), 2.04 (s, 3H); MS (ESI) m/z 314 (M+H)⁺.

Example 33

5 4-oxo-*N*-(quinolin-6-yl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 3, substituting quinolin-6-amine for 4-morpholinoaniline, provided the titled compound as the trifluoroacetate. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.99 (dd, $J = 4.88, 1.53$ Hz, 1H), 8.78 (d, $J = 8.24$ Hz, 1H), 8.64 (d, $J = 2.44$ Hz, 1H), 8.41 (s, 1H), 8.18 (d, $J = 9.16$ Hz, 1H), 8.05 (dd, $J = 9.16, 2.44$ Hz, 1H), 7.80 - 7.83 (m, 1H),
10 3.60 (t, $J = 7.32$ Hz, 2H), 3.06 (t, $J = 7.32$ Hz, 2H); MS (ESI) m/z 308 (M+H)⁺.

Example 34

N-(1*H*-indazol-6-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 3, substituting 1*H*-indazol-6-amine for 4-
15 morpholinoaniline, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.34 (s, 1H), 8.27 (s, 1H), 8.02 (s, 1H), 7.76 (d, $J=8.54$ Hz, 1H), 7.10 (dd, $J=8.70, 1.68$ Hz, 1H), 3.58 (t, $J=7.48$ Hz, 2H), 3.04 (t, $J=7.48$ Hz, 2H); MS (ESI) m/z 297 (M+H)⁺.

Example 35

20 *N*-(2,6-dimethoxypyridin-3-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 3, substituting 2,6-dimethoxypyridin-3-amine hydrochloride for 4-morpholinoaniline, provided the titled compound as the trifluoroacetate. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.25 - 8.31 (m, 2H), 6.40 (d, $J=8.54$ Hz, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 3.55 (t, $J=7.32$ Hz, 2H), 3.01 (t, $J=7.32$ Hz, 2H); MS (ESI) m/z 318
25 (M+H)⁺.

Example 36

N-(1,2-oxazol-3-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 3, substituting isoxazol-3-amine for 4-morpholinoaniline,
30 provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.80 (d, $J=1.83$ Hz, 1H), 8.41 (s, 1H), 7.04 (d, $J=1.83$ Hz, 1H), 3.57 (t, $J=7.48$ Hz, 2H), 3.03 (t, $J=7.48$ Hz, 2H); MS (ESI) m/z 248 (M+H)⁺.

Example 37

4-oxo-*N*-(pyrazin-2-yl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 3, substituting pyrazin-2-amine for 4-morpholinoaniline, provided the titled compound as the trifluoroacetate. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 9.47 (d, *J*=1.53 Hz, 1H), 8.39 - 8.46 (m, 3H), 3.57 (t, *J*=7.48 Hz, 2H), 3.04 (t, *J*=7.32 Hz, 2H); MS (ESI) *m/z* 259 (M+H)⁺.

Example 38

N-(5-methyl-1,2-oxazol-3-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 3, substituting 5-methylisoxazol-3-amine for 4-morpholinoaniline, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.39 (s, 1H), 6.73 (s, 1H), 3.56 (t, *J*=7.48 Hz, 2H), 3.02 (t, *J*=7.32 Hz, 2H), 2.40 (s, 3H); MS (ESI) *m/z* 262 (M+H)⁺.

Example 39

N-(4-cyanophenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 3, substituting 4-aminobenzonitrile for 4-morpholinoaniline, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.39 (s, 1H), 7.84 (s, 4H), 3.57 (t, *J*=7.32 Hz, 2H), 3.03 (t, *J*=7.32 Hz, 2H); MS (ESI) *m/z* 282 (M+H)⁺.

Example 40

N-(5-fluoropyridin-2-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 3, substituting 5-fluoropyridin-2-amine for 4-morpholinoaniline, provided the titled compound as the trifluoroacetate. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.38 (s, 1H), 8.34 (d, *J*=3.05 Hz, 1H), 8.27 (dd, *J*=9.00, 4.12 Hz, 1H), 7.73 - 7.80 (m, 1H), 3.56 (t, *J*=7.48 Hz, 2H), 3.02 (t, *J*=7.32 Hz, 2H); MS (ESI) *m/z* 276 (M+H)⁺.

Example 41

N-(6-methoxypyridin-3-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 3, substituting 6-methoxypyridin-3-amine for 4-morpholinoaniline, provided the titled compound as the trifluoroacetate. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.43 (t, *J*=2.14 Hz, 1H), 8.31 (s, 1H), 7.96 (dd, *J*=8.85, 2.75 Hz, 1H),

6.88 (d, $J=8.85$ Hz, 1H), 3.84 (s, 3H), 3.57 (t, $J=7.32$ Hz, 2H), 3.03 (t, $J=7.32$ Hz, 2H); MS (ESI) m/z 288 (M+H)⁺.

Example 42

5 *N*-(5-chloropyridin-2-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 3, substituting 5-chloropyridin-2-amine for 4-morpholinoaniline, provided the titled compound as the trifluoroacetate. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.38 - 8.40 (m, 2H), 8.26 (d, $J=9.77$ Hz, 1H), 7.94 (dd, $J=9.16$, 2.75 Hz, 1H), 3.56 (t, $J=7.32$ Hz, 2H), 3.02 (t, $J=7.32$ Hz, 2H); MS (ESI) m/z 292 (M+H)⁺.

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Example 43

N-(3-cyanophenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 3, substituting 3-aminobenzonitrile for 4-morpholinoaniline, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.38 (s, 1H), 8.18 - 8.21 (m, 1H), 7.78 - 7.82 (m, 1H), 7.54 - 7.62 (m, 2H), 3.58 (t, $J=7.48$ Hz, 2H), 3.03 (t, $J=7.48$ Hz, 2H); MS (ESI) m/z 282 (M+H)⁺.

15

Example 44

N-(6-ethoxypyridin-3-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

20 The procedure for Example 3, substituting 6-ethoxypyridin-3-amine for 4-morpholinoaniline, provided the titled compound as the trifluoroacetate. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.41 (t, $J=1.98$ Hz, 1H), 8.31 (s, 1H), 7.94 (dd, $J=8.39$, 3.20 Hz, 1H), 6.85 (d, $J=8.85$ Hz, 1H), 4.27 (q, $J=7.02$ Hz, 2H), 3.57 (t, $J=7.32$ Hz, 2H), 3.02 (t, $J=7.63$ Hz, 2H), 1.31 (t, $J=7.02$ Hz, 3H); MS (ESI) m/z 302 (M+H)⁺.

25

Example 45

N-(3-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 3, substituting 3-methyl-1*H*-indazol-5-amine for 4-morpholinoaniline, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.30 (s, 1H), 8.17 (s, 1H), 7.42 - 7.52 (m, 2H), 3.58 (t, $J=7.32$ Hz, 2H), 3.03 (t, $J=7.32$ Hz, 2H), 2.48 (s, 3H); MS (ESI) m/z 311 (M+H)⁺.

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Example 46

N-(6-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 3, substituting 6-methyl-1*H*-indazol-5-amine for 4-morpholinoaniline, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.30 (s, 1H), 8.00 - 8.07 (m, 2H), 7.43 (s, 1H), 3.57 (t, *J*=7.32 Hz, 2H), 3.03 (t, *J*=7.48 Hz, 2H), 2.41 (s, 3H); MS (ESI) *m/z* 311 (M+H)⁺.

5

Example 47

N-(1,3-benzothiazol-2-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 3, substituting benzo[*d*]thiazol-2-amine for 4-morpholinoaniline, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.55 (s, 1H), 8.01 (d, *J*=7.32 Hz, 1H), 7.80 (d, *J*=7.63 Hz, 1H), 7.44 - 7.54 (m, 1H), 7.32 - 7.39 (m, 1H), 3.60 (t, *J*=7.48 Hz, 2H), 3.07 (t, *J*=7.48 Hz, 2H); MS (ESI) *m/z* 314 (M+H)⁺.

10

Example 48

methyl 5-([(4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino)-1*H*-indazole-3-carboxylate

15

The procedure for Example 3, substituting methyl 5-amino-1*H*-indazole-3-carboxylate for 4-morpholinoaniline, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.60 (s, 1H), 8.34 (s, 1H), 7.68 - 7.73 (m, 1H), 7.57 - 7.63 (m, 1H), 3.93 (s, 3H), 3.58 (t, *J*=7.48 Hz, 2H), 3.04 (t, *J*=7.32 Hz, 2H); MS (ESI) *m/z* 355 (M+H)⁺.

20

Example 49

N-[4-(diethylamino)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 3, substituting *N*¹,*N*¹-diethylbenzene-1,4-diamine for 4-morpholinoaniline, provided the titled compound as the trifluoroacetate. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.35 (s, 1H), 7.83 (d, *J*=8.85 Hz, 2H), 7.51 (d, *J*=8.54 Hz, 2H), 3.52 - 3.63 (m, 6H), 3.04 (t, *J*=7.48 Hz, 2H), 1.03 (t, *J*=7.17 Hz, 6H); MS (ESI) *m/z* 328 (M+H)⁺.

25

Example 50

N-[1-(2-hydroxypropyl)-1*H*-indazol-5-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

30

Example 50A

1-(5-nitro-1*H*-indazol-1-yl)propan-2-ol

To a mixture of 5-nitro-1*H*-indazole (44.0 g, 270 mmol), cesium carbonate (176 g, 539 mmol) and potassium iodide (4.48 g, 27.0 mmol) in *N,N*-dimethylformamide (500 mL) was added 1-bromopropan-2-ol (48.7 g, 351 mmol) at room temperature, and the mixture was stirred at 80 °C for 2 hours. The mixture was treated with H₂O and extracted with ethyl acetate. The organic phase was washed with H₂O and brine. The organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluted with petroleum ether/ethyl acetate 2:1 to give the titled compound as the first isomer to elute from the column. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.71 (d, 1H), 8.22-8.27 (m, 2H), 7.53 (d, 1H), 4.27-4.45 (m, 3H), 2.84 (s, 1H), 1.29 (d, 3H).

Example 50B

1-(5-nitro-2*H*-indazol-2-yl)propan-2-ol

The procedure for Example 50A provided the titled compound as the second isomer to elute from the column. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.66 (dd, 1H), 8.21 (d, 1H), 8.05 (dd, 1H), 7.68 (dt, 1H), 4.46 (dd, 1H), 4.25-4.33 (m, 2H), 3.16 (d, 1H), 1.24 (d, 3H).

Example 50C

1-(5-amino-1*H*-indazol-1-yl)propan-2-ol

A mixture of the product from Example 50A (18 g, 81 mmol), 10% palladium on carbon (4.33 g) and methanol (75 mL) was hydrogenated (50 psi) at room temperature for 6 hours. The mixture was filtered through diatomaceous earth, and the filtrate was concentrated to dryness. The resulting residue was chromatographed on a silica gel column eluted with 1:2 petroleum ether/ethyl acetate to provide the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 7.71 (s, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.77 (d, *J* = 2.0 Hz, 1H), 4.22 (dd, *J* = 14.0, 6.5 Hz, 1H), 4.14 (dd, *J* = 14.0, 5.7 Hz, 1H), 4.03 (h, *J* = 6.2 Hz, 1H), 1.02 (d, *J* = 6.2 Hz, 3H); MS (ESI+) *m/z* 192 (M+H)⁺.

Example 50D

N-[1-(2-hydroxypropyl)-1*H*-indazol-5-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 3, substituting the product from Example 50C for 4-morpholinoaniline, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.33 (s, 1H), 8.25 (s, 1H), 8.03 - 8.05 (m, 1H), 7.67 (d, *J* = 8.85 Hz, 1H), 7.45 (dd,

$J=9.00$, 1.98 Hz, $1H$), $4.20 - 4.39$ (m, $2H$), $4.01 - 4.10$ (m, $1H$), 3.57 (t, $J=7.32$ Hz, $2H$), 3.03 (t, $J=7.32$ Hz, $2H$), 1.06 (d, $J=6.10$ Hz, $3H$); MS (ESI) m/z 355 ($M+H$)⁺.

Example 51

5 *N*-(2-{2-[(methylsulfonyl)amino]ethyl}-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 51A

tert-butyl 2-(5-nitro-2*H*-indazol-2-yl)ethylcarbamate

10 To a mixture of 5-nitro-1*H*-indazole (10 g, 61.3 mmol), cesium carbonate (39.9 g, 123 mmol) and KI (1.018 g, 6.13 mmol) in *N,N*-dimethylformamide (500 mL) was added *tert*-butyl 2-bromoethylcarbamate (17.86 g, 80 mmol) at room temperature, and the mixture was stirred at 80 °C for 3 hours. The mixture was diluted with H₂O and extracted with ethyl acetate. The combined organic layers were washed with H₂O and brine. The organic layer
15 was dried (Na₂SO₄), filtered and concentrated. The crude product was purified by chromatography on silica gel eluted with petroleum ether/ethyl acetate 2:1 to provide the titled compound as the second isomer to elute from the column.

Example 51B

20 *tert*-butyl 2-(5-nitro-1*H*-indazol-1-yl)ethylcarbamate

The procedure for Example 51A provided the titled compound as the first isomer to elute from the column. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.78 (d, $1H$), 8.37 (s, $1H$), 8.19 (dd, $1H$), 7.73 (d, $1H$), 6.67 (t, $1H$), 4.49 (t, $2H$), 3.35 (t, $2H$), 1.21 (s, $9H$).

Example 51C

2-(5-nitro-2*H*-indazol-2-yl)ethanamine hydrochloride

25 A mixture of the product from Example 51A (65 g, 212 mmol) in ethyl acetate (500 mL) at 0 °C was treated with a stream of HCl gas for 10 minutes. The mixture was allowed to warm to 15 °C with continued stirring at that temperature for 3 hours. The reaction
30 mixture was filtered through a Büchner funnel, and the filter cake was washed with ethyl acetate. The solid was dried under vacuum to yield the titled compound.

Example 51D

N-(2-(5-nitro-2*H*-indazol-2-yl)ethyl)methanesulfonamide

To a mixture of the product from Example 51C (50 g, 206 mmol) and triethylamine (41.7 g, 412 mmol) in dichloromethane (1000 mL) at 15 °C was added methanesulfonyl chloride (36.6 g, 320 mmol). The mixture was stirred at 15 °C for 3 hours. The reaction mixture was partitioned between water and dichloromethane. The aqueous layer was further
5 extracted with dichloromethane. The combined organic layers were washed with 2 *N* HCl, brine and water, dried over Na₂SO₄, and concentrated to dryness. The residue was purified via flash chromatography (petroleum ether/ethyl acetate=1:2) to yield the titled compound.

Example 51E

10 *N*-(2-(5-amino-2*H*-indazol-2-yl)ethyl)methanesulfonamide

The product from Example 51D (20 g, 70.4 mmol) and 10% Pd/C (2 g) were added to methanol (200 mL). The mixture was stirred at 25 °C under H₂ (50 psi) for 12 hours. The reaction mixture was filtered through diatomaceous earth. The filtrate was concentrated to dryness, and the residue was purified by column chromatography on silica gel (ethyl acetate)
15 to give the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 7.91 (d, *J* = 0.9 Hz, 1H), 7.36 (d, *J* = 9.0 Hz, 1H), 6.79 (dd, *J* = 9.1, 2.1 Hz, 1H), 6.62 (dd, *J* = 2.1, 0.8 Hz, 1H), 4.39 (t, *J* = 6.2 Hz, 2H), 3.47 (t, *J* = 6.2 Hz, 2H), 2.78 (s, 3H); MS (ESI+) *m/z* 255 (M+H)⁺.

Example 51F

20 *N*-(2-{2-[(methylsulfonyl)amino]ethyl}-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2- c]pyridine-3-carboxamide

The procedure for Example 3, substituting the product from Example 51E, (*N*-(2-(5-amino-2*H*-indazol-2-yl)ethyl)methanesulfonamide), for 4-morpholinoaniline, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.33 (d, *J* = 6.10 Hz, 2H), 8.29
25 (s, 1H), 7.62 (d, *J* = 9.16 Hz, 1H), 7.27 (dd, *J* = 9.16, 1.83 Hz, 1H), 4.49 (t, *J* = 6.26 Hz, 2H), 3.49 - 3.59 (m, 4H), 3.03 (t, *J* = 7.48 Hz, 2H), 2.81 (s, 3H); MS (ESI) *m/z* 418 (M+H)⁺.

Example 52

30 *N*-(2-[2-(4-methylpiperazin-1-yl)ethyl]-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2- c]pyridine-3-carboxamide

Example 52A

2-(5-nitro-2*H*-indazol-2-yl)ethanol

The procedure for Example 50A, substituting 2-bromoethanol for 1-bromopropan-2-ol, provided the titled compound as the as the second isomer to elute from the column. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.87 (dd, 1H), 8.76 (s, 1H), 7.99 (dd, 1H), 7.76 (dd, 1H), 5.01 (t, 1H), 4.52 (t, 2H), 3.88 (m, 2H).

5

Example 52B

2-(5-nitro-1H-indazol-1-yl)ethanol

The procedure for Example 50A, substituting 2-bromoethanol for 1-bromopropan-2-ol, provided the titled compound as the as the first isomer to elute from the column.

10

Example 52C

2-(5-nitro-2H-indazol-2-yl)ethyl methanesulfonate

To a mixture of the product from Example 52A (40 g, 193 mmol) and triethylamine (40 g, 396 mmol) in dichloromethane (400 mL) was added methanesulfonyl chloride (79.5 g, 697 mmol) at 15 °C. The mixture was stirred at 15 °C for 3 hours. The reaction mixture was partitioned between water (200 mL) and dichloromethane (200 mL). The aqueous layer was extracted with dichloromethane (200 mL). The combined organic layers were washed with brine and water, dried over Na₂SO₄ and concentrated to provide the titled compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.76 (dd, 1H), 8.37 (s, 1H), 8.14 (dd, 1H), 7.77 (dt, 1H), 4.81 (m, 4H), 2.91 (s, 3H).

20

Example 52D

2-(2-(4-methylpiperazin-1-yl)ethyl)-5-nitro-2H-indazole

The product from Example 52C (30 g, 105 mmol) was added to 1-methyl-piperazine (30 g). The mixture was stirred at 60 °C for 6 hours. The mixture was cooled to 20 °C and partitioned between ethyl acetate (150 mL) and H₂O (150 mL). The aqueous layer was extracted with ethyl acetate (2 × 150 mL). The combined organic phases were washed with water (200 mL) and brine (200 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated to give the titled compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.68 (dd, 1H), 8.27 (d, 1H), 8.03 (dd, 1H), 7.67 (d, 1H), 4.50 (t, 2H), 2.92 (t, 2H), 2.35-2.47 (m, 4H), 2.47-2.55 (m, 4H), 2.27 (s, 3H).

30

Example 52E

2-(2-(4-methylpiperazin-1-yl)ethyl)-2H-indazol-5-amine

The procedure for Example 51E, substituting the product from Example 52D for the product from Example 51D, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 7.91 (d, *J* = 0.9 Hz, 1H), 7.34 (d, *J* = 9.0 Hz, 1H), 6.77 (dd, *J* = 9.0, 2.1 Hz, 1H), 6.61 (dd, *J* = 2.1, 0.8 Hz, 1H), 4.39 (t, *J* = 6.6 Hz, 2H), 2.79 (t, *J* = 6.7 Hz, 2H), 2.47 –
5 2.16 (m, 8H), 2.12 (s, 3H); MS (ESI+) *m/z* 260 (M+H)⁺.

Example 52F

N-{2-[2-(4-methylpiperazin-1-yl)ethyl]-2*H*-indazol-5-yl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-
c]pyridine-3-carboxamide bis(2,2,2-trifluoroacetate)

10 The procedure for Example 3, substituting the product from Example 52E for 4-morpholinoaniline, provided the titled compound as the bistrifluoroacetate. MS (ESI) *m/z* 423 (M+H)⁺.

Example 53

N-[1-(2-hydroxyethyl)-1*H*-indazol-5-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-
15 carboxamide

The procedure for Example 3, substituting 2-(5-amino-1*H*-indazol-1-yl)ethanol (CAS# 885270-96-2) for 4-morpholinoaniline, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.36 (s, 1H), 8.29 (d, *J* = 1.22 Hz, 1H), 8.25 (s, 1H), 8.08 (s, 1H), 7.69 (d, *J* = 8.85 Hz, 1H), 7.48 (dd, *J* = 9.16, 1.83 Hz, 1H), 4.45 (t, *J* = 5.65 Hz, 2H), 3.82
20 (t, *J* = 5.80 Hz, 2H), 3.57 - 3.64 (m, 2H), 3.06 (t, *J* = 7.32 Hz, 2H); MS (ESI) *m/z* 341 (M+H)⁺.

Example 54

4-oxo-*N*-{1-[2-(pyrrolidin-1-yl)ethyl]-1*H*-indazol-5-yl}-4,5,6,7-tetrahydrofuro[3,2-
c]pyridine-3-carboxamide

25 The procedure for Example 3, substituting 1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-indazol-5-amine (CAS # 690265-60-2) for 4-morpholinoaniline, provided the titled compound as the trifluoroacetate. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.35 (s, 1H), 8.32 (s, 1H), 8.19 (s, 1H), 7.77 (d, *J* = 9.16 Hz, 1H), 7.55 (dd, *J* = 8.85, 1.83 Hz, 1H), 4.77 (t, *J* = 6.26 Hz, 2H), 3.73 (t, *J* = 6.26 Hz, 2H), 3.53 - 3.62 (m, 4H), 3.00 - 3.10 (m, 4H), 1.95 - 2.07 (m, 2H), 1.79 -
30 1.91 (m, 2H); MS (ESI) *m/z* 394 (M+H)⁺.

Example 55

N-[2-(2-hydroxypropyl)-2*H*-indazol-5-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-
carboxamide

Example 55A

1-(5-amino-2*H*-indazol-2-yl)propan-2-ol

The procedure for Example 51E, substituting the product from Example 50B for the product from Example 51D, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 7.87 (s, 1H), 7.34 (d, *J* = 9.0 Hz, 1H), 6.78 (dd, *J* = 9.0, 2.1 Hz, 1H), 6.62 (d, *J* = 2.0 Hz, 1H), 4.19 (dd, *J* = 6.0, 1.4 Hz, 2H), 4.08 (h, *J* = 6.1 Hz, 1H), 1.06 (d, *J* = 6.2 Hz, 3H); MS (ESI+) *m/z* 192 (M+H)⁺.

Example 55B

N-[2-(2-hydroxypropyl)-2*H*-indazol-5-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 3, substituting the product from Example 55A, (1-(5-amino-2*H*-indazol-2-yl)propan-2-ol), for 4-morpholinoaniline, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.32 (s, 1H), 8.28 (s, 2H), 7.60 (d, *J* = 8.85 Hz, 1H), 7.26 (dd, *J* = 9.16, 1.83 Hz, 1H), 4.23 - 4.34 (m, 2H), 4.09 - 4.16 (m, 1H), 3.56 (t, *J* = 7.32 Hz, 2H), 3.03 (t, *J* = 7.32 Hz, 2H), 1.08 (d, *J* = 6.41 Hz, 3H); MS (ESI) *m/z* 355 (M+H)⁺.

Example 56

N-{1-[2-(morpholin-4-yl)ethyl]-1*H*-indazol-5-yl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 3, substituting 1-(2-morpholinoethyl)-1*H*-indazol-5-amine (CAS # 854921-80-5) for 4-morpholinoaniline, provided the titled compound as the trifluoroacetate. MS (ESI) *m/z* 410 (M+H)⁺.

Example 57

N-{1-[2-(4-methylpiperazin-1-yl)ethyl]-1*H*-indazol-5-yl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 57A

2-(5-nitro-1*H*-indazol-1-yl)ethyl methanesulfonate

The procedure for Example 52C, substituting the product from Example 52B for the product from Example 52A, provided the titled compound. ¹H NMR (400 MHz, DMSO-*d*₆)

δ ppm 8.81 (d, $J=2.0$ Hz, 1H), 8.44 (s, 1H), 8.23 (dd, $J=9.2$, 2.0 Hz, 1H), 7.89 (d, $J=9.2$ Hz, 1H), 4.84 (t, $J=5.2$ Hz, 2H), 4.62 (t, $J=5.2$ Hz, 2H), 3.01 (s, 3H).

Example 57B

5 1-(2-(4-methylpiperazin-1-yl)ethyl)-5-nitro-1H-indazole

The procedure for Example 52D, substituting the product from Example 57A for the product from Example 52C, provided the titled compound.

Example 57C

10 1-(2-(4-methylpiperazin-1-yl)ethyl)-1H-indazol-5-amine

The procedure for Example 51E, substituting the product from Example 57B for the product from Example 51D, provided the titled compound. ^1H NMR (500 MHz, DMSO- $d_6/\text{D}_2\text{O}$) δ ppm 7.71 (d, $J=0.9$ Hz, 1H), 7.36 (d, $J=8.8$ Hz, 1H), 6.84 (dd, $J=8.8$, 2.1 Hz, 1H), 6.77 (d, $J=2.0$ Hz, 1H), 4.37 (t, $J=6.8$ Hz, 2H), 2.70 (t, $J=6.8$ Hz, 2H), 2.46 – 2.19 (m, 8H), 2.12 (s, 3H); MS (ESI+) m/z 260 ($\text{M}+\text{H}$) $^+$.

Example 57D

N-{1-[2-(4-methylpiperazin-1-yl)ethyl]-1H-indazol-5-yl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide bis(2,2,2-trifluoroacetate)

20 The procedure for Example 3, substituting the product from Example 57C for 4-morpholinoaniline, provided the titled compound as the bistrifluoroacetate. MS (ESI) m/z 423 ($\text{M}+\text{H}$) $^+$.

Example 58

25 *N*-(1-{2-[(methylsulfonyl)amino]ethyl}-1H-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 58A

N-(2-(5-amino-1H-indazol-1-yl)ethyl)methanesulfonamide

30 The procedures for Examples 51C, 51D and 51E, substituting the product of Example 51B for the product of Example 51A, provided the titled compound. ^1H NMR (500 MHz, DMSO- $d_6/\text{D}_2\text{O}$) δ ppm 7.76 (s, 1H), 7.36 (d, $J=8.8$ Hz, 1H), 6.86 (dd, $J=8.8$, 2.1 Hz, 1H), 6.79 (d, $J=2.0$ Hz, 1H), 4.37 (t, $J=6.3$ Hz, 2H), 3.38 (t, $J=6.3$ Hz, 2H), 2.72 (s, 3H); MS (ESI+) m/z 255 ($\text{M}+\text{H}$) $^+$.

Example 58B

N-(1-{2-[(methylsulfonyl)amino]ethyl}-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

5 The procedure for Example 3, substituting the product from Example 58A for 4-morpholinoaniline, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.34 (s, 1H), 8.27 (d, *J*=1.53 Hz, 1H), 8.09 (s, 1H), 7.66 (d, *J*=9.16 Hz, 1H), 7.49 (dd, *J*=8.85, 1.83 Hz, 1H), 4.47 (t, *J*=6.41 Hz, 2H), 3.54 - 3.61 (m, 2H), 3.42 (t, *J*=6.26 Hz, 2H), 3.03 (t, *J*=7.32 Hz, 2H), 2.73 - 2.79 (m, 3H); MS (ESI) *m/z* 418 (M+H)⁺.

10

Example 59

N-(4-hydroxyphenyl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

 The procedure for Example 4, substituting 4-aminophenol for *p*-toluidine, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.24 (s, 1H), 7.47 (dd, *J*=8.70, 1.37 Hz, 2H), 6.74 - 6.81 (m, 2H), 3.74 (t, 2H), 3.09 (t, *J*=7.48 Hz, 2H), 3.04 (s, 3H); MS (ESI) *m/z* 287 (M+H)⁺.

15

Example 60

N-(4-acetamidophenyl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

20 The procedure for Example 4, substituting *N*-(4-aminophenyl)acetamide for *p*-toluidine, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.27 (s, 1H), 7.53 - 7.62 (m, 4H), 3.74 (t, *J*=7.48 Hz, 2H), 3.10 (t, *J*=7.48 Hz, 2H), 3.05 (s, 3H), 2.04 (s, 3H); MS (ESI) *m/z* 328 (M+H)⁺.

20

Example 61

5-methyl-4-oxo-*N*-[4-(piperidin-1-yl)phenyl]-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

 The procedure for Example 4, substituting 4-(piperidin-1-yl)aniline for *p*-toluidine, provided the titled compound as the trifluoroacetate. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.34 (s, 1H), 7.76 - 7.88 (m, 2H), 7.59 - 7.72 (m, 2H), 3.77 (t, 2H), 3.49 - 3.57 (m, 4H), 3.11 (t, *J*=7.48 Hz, 2H), 3.05 (s, 3H), 1.85 - 1.97 (m, 4H), 1.67 (s, 2H); MS (ESI) *m/z* 354 (M+H)⁺.

25

30

Example 62

5-methyl-4-oxo-*N*-(quinolin-3-yl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 4, substituting quinolin-3-amine for *p*-toluidine, provided the titled compound as the trifluoroacetate. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 9.12 (s, 1H), 8.85 (d, *J*=2.14 Hz, 1H), 8.40 (s, 1H), 8.02 - 8.08 (m, 2H), 7.64 - 7.81 (m, 2H), 3.77 (t, *J*=7.63 Hz, 2H), 3.13 (t, *J*=7.48 Hz, 2H), 3.08 (s, 3H); MS (ESI) *m/z* 322 (M+H)⁺.

Example 63

5-methyl-4-oxo-*N*-(quinolin-6-yl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 4, substituting quinolin-6-amine for *p*-toluidine, provided the titled compound as the trifluoroacetate. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 9.01 (d, *J*=4.58 Hz, 1H), 8.84 (d, *J*=8.55 Hz, 1H), 8.65 (d, *J*=1.83 Hz, 1H), 8.39 (s, 1H), 8.15 - 8.22 (m, 1H), 8.08 (dd, *J*=9.16, 2.14 Hz, 1H), 7.85 (dd, *J*=8.54, 4.88 Hz, 1H), 3.78 (t, 2H), 3.13 (t, *J*=7.48 Hz, 2H), 3.08 (s, 3H); MS (ESI) *m/z* 322 (M+H)⁺.

Example 64

N-(1*H*-indazol-6-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 4, substituting 1*H*-indazol-6-amine for *p*-toluidine, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.33 (s, 1H), 8.26 (s, 1H), 8.03 (s, 1H), 7.77 (d, *J*=8.54 Hz, 1H), 7.14 (dd, *J*=8.70, 1.68 Hz, 1H), 3.76 (t, *J*=7.48 Hz, 2H), 3.11 (t, *J*=7.48 Hz, 2H), 3.07 (s, 3H); MS (ESI) *m/z* 311 (M+H)⁺.

Example 65

N-(2,6-dimethoxypyridin-3-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 4, substituting 2,6-dimethoxypyridin-3-amine hydrochloride for *p*-toluidine, provided the titled compound as the trifluoroacetate. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.20 - 8.28 (m, 2H), 6.40 (d, *J*=8.54 Hz, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.73 (t, 2H), 3.09 (t, *J*=7.48 Hz, 2H), 3.02 (s, 3H); MS (ESI) *m/z* 332 (M+H)⁺.

Example 66

5-methyl-*N*-(5-methyl-1,2-oxazol-3-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 4, substituting 5-methylisoxazol-3-amine for *p*-toluidine, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.38 (s, 1H), 6.73

(s, 1H), 3.74 (t, $J=7.48$ Hz, 2H), 3.10 (t, $J=7.48$ Hz, 2H), 3.03 (s, 3H), 2.40 (s, 3H); MS (ESI) m/z 276 (M+H)⁺.

Example 67

5 *N*-(4-cyanophenyl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 4, substituting 4-aminobenzonitrile for *p*-toluidine, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.37 (s, 1H), 7.85 (s, 4H), 3.76 (t, 2H), 3.11 (t, $J=7.48$ Hz, 2H), 3.06 (s, 3H); MS (ESI) m/z 296 (M+H)⁺.

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Example 68

N-(5-fluoropyridin-2-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 4, substituting 5-fluoropyridin-2-amine for *p*-toluidine, provided the titled compound as the trifluoroacetate. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.37 (s, 1H), 8.36 (d, $J=3.05$ Hz, 1H), 8.28 (dd, $J=9.31$, 4.12 Hz, 1H), 7.74 - 7.80 (m, 1H), 3.74 (t, 2H), 3.10 (t, $J=7.48$ Hz, 2H), 3.04 (s, 3H); MS (ESI) m/z 290 (M+H)⁺.

15

Example 69

N-(6-methoxypyridin-3-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

20

The procedure for Example 4, substituting 6-methoxypyridin-3-amine for *p*-toluidine, provided the titled compound as the trifluoroacetate. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.48 (d, $J=2.75$ Hz, 1H), 8.30 (s, 1H), 7.94 (dd, $J=8.85$, 2.75 Hz, 1H), 6.89 (d, $J=8.85$ Hz, 1H), 3.85 (s, 3H), 3.76 (t, 2H), 3.10 (t, $J=7.63$ Hz, 2H), 3.04 (s, 3H); MS (ESI) m/z 302 (M+H)⁺.

25

Example 70

N-(5-chloropyridin-2-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

30

The procedure for Example 4, substituting 5-chloropyridin-2-amine for *p*-toluidine, provided the titled compound as the trifluoroacetate. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.38 - 8.42 (m, 2H), 8.27 (d, $J=8.85$ Hz, 1H), 7.94 (dd, $J=9.00$, 2.59 Hz, 1H), 3.74 (t, 2H), 3.10 (t, $J=7.48$ Hz, 2H), 3.04 (s, 3H); MS (ESI) m/z 306 (M+H)⁺.

Example 71

N-(3-cyanophenyl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 4, substituting 3-aminobenzonitrile for *p*-toluidine, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.36 (s, 1H), 8.20 (s, 1H), 7.79 - 7.84 (m, 1H), 7.54 - 7.64 (m, 2H), 3.76 (t, *J*=7.48 Hz, 2H), 3.11 (t, *J*=7.48 Hz, 2H), 3.06 (s, 3H); MS (ESI) *m/z* 296 (M+H)⁺.

Example 72

N-(6-ethoxypyridin-3-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 4, substituting 6-ethoxypyridin-3-amine for *p*-toluidine, provided the titled compound as the trifluoroacetate. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.45 (d, *J*=2.75 Hz, 1H), 8.30 (s, 1H), 7.93 (dd, *J*=8.85, 2.75 Hz, 1H), 6.86 (d, *J*=8.85 Hz, 1H), 4.28 (q, *J*=7.02 Hz, 2H), 3.75 (t, 2H), 3.10 (t, *J*=7.48 Hz, 2H), 3.04 (s, 3H), 1.32 (t, 3H); MS (ESI) *m/z* 316 (M+H)⁺.

Example 73

5-methyl-*N*-(3-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 4, substituting 3-methyl-1*H*-indazol-5-amine for *p*-toluidine, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.29 (s, 1H), 8.19 (s, 1H), 7.41 - 7.53 (m, 2H), 3.75 (t, *J*=7.63 Hz, 2H), 3.11 (t, *J*=7.32 Hz, 2H), 3.07 (s, 3H), 2.48 (s, 3H); MS (ESI) *m/z* 325 (M+H)⁺.

Example 74

5-methyl-*N*-(6-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 4, substituting 6-methyl-1*H*-indazol-5-amine for *p*-toluidine, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.29 (s, 1H), 7.99 - 8.05 (m, 2H), 7.44 (s, 1H), 3.75 (t, *J*=7.63 Hz, 2H), 3.11 (t, *J*=7.48 Hz, 2H), 3.02 (s, 3H), 2.42 (s, 3H); MS (ESI) *m/z* 325 (M+H)⁺.

Example 75

N-(1,3-benzothiazol-2-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 4, substituting benzo[*d*]thiazol-2-amine for *p*-toluidine, provided the titled compound. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.54 (s, 1H), 8.01 (d, *J*=7.63 Hz, 1H), 7.82 (d, *J*=7.93 Hz, 1H), 7.43 - 7.53 (m, 1H), 7.36 (t, *J*=7.63 Hz, 1H), 3.78 (t, *J*=7.48 Hz, 2H), 3.15 (t, 2H), 3.09 (s, 3H); MS (ESI) *m/z* 328 (M+H)⁺.

Example 76

5-methyl-4-oxo-*N*-[5-(trifluoromethyl)pyridin-2-yl]-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 4, substituting 5-(trifluoromethyl)pyridin-2-amine for *p*-toluidine, provided the titled compound as the trifluoroacetate. ¹H NMR (500 MHz, DMSO-*d*₆/D₂O) δ ppm 8.74 - 8.76 (m, *J*=2.44 Hz, 1H), 8.41 - 8.45 (m, 2H), 8.23 (dd, *J*=9.00, 2.29 Hz, 1H), 3.75 (t, *J*=7.48 Hz, 2H), 3.11 (t, *J*=7.48 Hz, 2H), 3.05 (s, 3H); MS (ESI) *m/z* 340 (M+H)⁺.

Example 77

N-(6-chloro-1*H*-indazol-5-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 4, substituting 6-chloro-1*H*-indazol-5-amine for *p*-toluidine, provided the titled compound. MS (ESI) *m/z* 345 (M+H)⁺.

Example 78

5-methyl-*N*-(2-methyl-1*H*-benzimidazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 2C, substituting 2-methyl-1*H*-benzo[*d*]imidazol-5-amine for 2-methyl-2*H*-indazol-5-amine, provided the titled compound as the trifluoroacetate. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 14.37 (bs, 1H), 13.13 (s, 1H), 8.40 - 8.37 (m, 2H), 7.72 (d, *J*= 8.7 Hz, 1H), 7.44 (dd, *J*= 8.8, 1.8 Hz, 1H), 3.75 (t, *J*= 7.5 Hz, 2H), 3.12 (t, *J*= 7.5 Hz, 2H), 3.06 (s, 3H), 2.73 (s, 3H); MS (APCI) *m/z* 325 (M+H)⁺.

Example 79

N-{4-[4-(3,3-dimethylbutanoyl)piperazin-1-yl]-2-methoxyphenyl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described in Example 18 substituting 3,3-dimethylbutanoyl chloride for acetyl chloride. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.82 – 11.63 (m, 1H), 8.40 – 8.22 (m, 1H), 8.11 (s, 1H), 6.77 – 6.39 (m, 2H), 5.72 – 5.46 (m, 1H), 3.95 (s, 3H), 3.86 – 3.59 (m, 6H), 3.26 – 3.11 (m, 4H), 3.04 (t, *J* = 7.2 Hz, 2H),
5 2.31 (s, 2H), 1.08 (s, 9H); MS (DCI) *m/z* 469 (M+H)⁺.

Example 80

N-{2-methoxy-4-[4-(pyrrolidin-1-ylcarbonyl)piperazin-1-yl]phenyl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

10 The titled compound was prepared using the procedure described in Example 18 substituting pyrrolidine-1-carbonyl chloride for acetyl chloride. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.88 – 11.70 (m, 1H), 8.62 – 8.39 (m, 1H), 8.32 – 8.01 (m, 2H), 6.79 – 6.51 (m, 1H), 5.70 – 5.41 (m, 1H), 4.01 – 3.93 (m, 4H), 3.93 (s, 3H), 3.78 – 3.64 (m, 6H), 3.55 – 3.46 (m, 2H), 3.45 – 3.34 (m, 4H), 1.93 – 1.81 (m, 4H); MS (DCI) *m/z* 485 (M+NH₄)⁺.

Example 81

N-{4-[4-(dimethylsulfamoyl)piperazin-1-yl]-2-methoxyphenyl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

20 The titled compound was prepared using the procedure described in Example 18 substituting dimethylsulfamoyl chloride for acetyl chloride. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.79 (s, 1H), 8.36 (s, 1H), 8.12 (s, 1H), 6.60 (s, 1H), 5.54 (s, 1H), 5.54 (s, 1H), 3.94 (s, 3H), 3.70 (td, *J* = 7.2, 2.6 Hz, 2H), 3.65–3.44 (m, 3H), 3.31 (m, 3H), 3.15 – 2.98 (m, 3H), 2.87 (s, 6H); MS (DCI) *m/z* 478 (M+H)⁺.

Example 82

25 methyl 4-{[6-(4-methylpiperazin-1-yl)-3-{[(4-oxo-5,6,7,8-tetrahydro-4*H*-furo[3,2-*c*]azepin-3-yl)carbonyl]amino}pyridin-2-yl]oxy}benzoate

Example 82A

30 methyl 4-(6-chloro-3-nitropyridin-2-yloxy)benzoate

To a solution of methyl 4-hydroxybenzoate (1g, 6.57 mmol) in tetrahydrofuran (30 mL) was added NaH (0.342 g, 8.54 mmol) at 0 °C. After stirring for 25 minutes at 0 °C, a solution of 2,6-dichloro-3-nitropyridine (1.379 g, 6.57 mmol) in xylene (20 mL) was added over 5 minutes. After stirring for 16 hours, the reaction mixture was diluted with ether (100

mL) and quenched with H₂O (30 mL). The organic phase was separated, and the aqueous layer was extracted with additional ether (20 mL). The combined organic phases were washed with brine, dried with MgSO₄ and concentrated under reduced pressure. The resulting residue was purified on a silica gel column eluted with a gradient of 0-15% ethyl acetate/hexanes to provide the titled compound. MS (DCI) *m/z* 326 (M+NH₄)⁺.

Example 82B

methyl 4-(6-(4-methylpiperazin-1-yl)-3-nitropyridin-2-yloxy)benzoate

To a solution of the product from Example 82A, methyl 4-(6-chloro-3-nitropyridin-2-yloxy)benzoate (400mg, 1.296 mmol), and K₂CO₃ (358 mg, 2.59 mmol) in *N,N*-dimethylformamide (20 mL) was added 1-methylpiperazine (260 mg, 2.59 mmol), and the mixture was heated to 60 °C for 30 minutes. The reaction mixture was cooled to ambient temperature and then partitioned between ether (50 mL) and H₂O (30 mL). The organic phase was separated, and the aqueous layer was extracted with additional ether (50 mL). The combined organics were washed with brine, dried with MgSO₄ and concentrated under reduced pressure to provide the titled compound. MS (DCI) *m/z* 373 (M+H)⁺.

Example 82C

methyl 4-(3-amino-6-(4-methylpiperazin-1-yl)pyridin-2-yloxy)benzoate

To a solution of the product from Example 82B (450 mg, 1.2 mmol) in methanol (30 mL) was added Raney®-nickel, 2800 slurry in H₂O (500 mg), and the mixture was stirred under a hydrogen atmosphere using a balloon for 3 hours. The mixture was filtered and washed with additional methanol. The filtrate was concentrated under reduced pressure and azeotropically dried with toluene to provide the titled compound. MS (DCI) *m/z* 343 (M+H)⁺.

Example 82D

methyl 4- {[6-(4-methylpiperazin-1-yl)-3- {[(4-oxo-5,6,7,8-tetrahydro-4*H*-furo[3,2-*c*]azepin-3-yl)carbonyl]amino} pyridin-2-yl]oxy} benzoate

A solution of the product from Example 7B (220 mg, 1.13 mmol) , and triethylamine (0.220 mL, 1.577 mmol) in acetonitrile (10 mL) was treated with ethyl chloroformate (0.131 mL, 1.367 mmol) at 0 °C and stirred for 20 minutes. A solution of the product from Example 82C, methyl 4-(3-amino-6-(4-methylpiperazin-1-yl)pyridin-2-yloxy)benzoate (360mg, 1.051 mmol) in acetonitrile (5 mL) was added, and the mixture was stirred for 16 hours. The

mixture was diluted with ethyl acetate (50 mL) and H₂O (20mL). The organic phase was separated, and the aqueous phase was extracted with additional ethyl acetate (50 mL). The combined organic phases were washed with brine, dried with MgSO₄ and concentrated under reduced pressure. The residue was chromatographed on a silica gel column eluted with concentrated NH₄OH/methanol/dichloromethane (0.2/2/98) to provide the titled compound.

¹H NMR (300 MHz, CDCl₃) δ ppm 12.21 (s, 1H), 8.58 (d, *J* = 8.7 Hz, 1H), 8.15 (s, 1H), 8.11 – 7.95 (m, 2H), 7.37 – 7.28 (m, 2H), 6.39 (d, *J* = 8.8 Hz, 1H), 6.17 (t, *J* = 5.8 Hz, 1H), 3.91 (s, 3H), 3.45 – 3.29 (m, 6H), 3.08 (t, *J* = 7.2 Hz, 2H), 2.50 – 2.37 (m, 4H), 2.30 (s, 3H), 2.17 – 2.03 (m, 2H); MS (ESI) *m/z* 520 (M+H)⁺.

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Example 83

N-{2-[4-(hydroxymethyl)phenoxy]-6-(4-methylpiperazin-1-yl)pyridin-3-yl}-4-oxo-5,6,7,8-tetrahydro-4*H*-furo[3,2-*c*]azepine-3-carboxamide

A solution of the product from Example 82, (30 mg, 0.056 mmol) in anhydrous tetrahydrofuran (10 mL) was treated with lithium aluminum hydride (0.225 mL, 0.225 mmol, 1 *M* solution in tetrahydrofuran) and stirred at room temperature for 30 minutes. The reaction was quenched with 2 drops of H₂O, 2 drops of 1 *M* NaOH and 6 drops of H₂O, and stirred for 30 minutes. The mixture was filtered through diatomaceous earth that was then washed with ethyl acetate. The combined filtrates were concentrated under reduced pressure.

The resulting residue was chromatographed on a silica gel column eluted with concentrated NH₄OH/methanol/dichloromethane (0.3/3/97) to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 12.17 (s, 1H), 8.56 (d, *J* = 8.7 Hz, 1H), 8.15 (s, 1H), 7.36 – 7.31 (m, 2H), 7.26 (d, *J* = 2.8 Hz, 2H), 6.34 (d, *J* = 8.7 Hz, 1H), 6.16 (s, 1H), 5.30 (s, 1H), 4.68 (s, 2H), 3.43 – 3.29 (m, 6H), 3.08 (t, *J* = 7.2 Hz, 2H), 2.49 – 2.35 (m, 4H), 2.29 (s, 3H), 2.10 (dt, *J* = 6.8, 6.2 Hz, 2H); MS (ESI) *m/z* 492 (M+H)⁺.

25

Example 84

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2-methoxyethyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

30

Example 84A

5-(2-methoxyethyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxylic acid

The procedure for Example 8A, substituting 2-bromoethyl methylether for benzyl 2-bromoethyl ether, provided the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 14.61

(s, 1H), 8.04 (s, 1H), 3.88 (t, $J = 7.5$ Hz, 2H), 3.74 – 3.68 (m, 2H), 3.64 – 3.58 (m, 2H), 3.36 (s, 3H), 3.07 (t, $J = 7.5$ Hz, 2H).

Example 84B

5 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2-methoxyethyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 8B, substituting the product from Example 84A for the product from Example 8A, provided the titled compound. ^1H NMR (300 MHz, CDCl_3) δ ppm 12.00 (s, 1H), 8.53 (d, $J = 8.6$ Hz, 1H), 8.06 (s, 1H), 6.18 (d, $J = 8.6$ Hz, 1H), 4.40 (q, $J = 7.1$ Hz, 2H), 3.81 (t, $J = 7.3$ Hz, 2H), 3.72 (dd, $J = 11.3, 5.6$ Hz, 4H), 3.65 – 3.55 (m, 4H), 3.53 – 3.48 (m, 2H), 3.47 – 3.42 (m, 2H), 3.37 (s, 3H), 3.01 (t, $J = 7.2$ Hz, 2H), 2.14 (s, 3H), 1.48 (t, $J = 7.1$ Hz, 3H); MS (ESI) m/z 486 ($\text{M}+\text{H}$) $^+$.

Example 85

15 *N*-[6-(4-acetylpiperazin-1-yl)-2-(2-methoxyethoxy)pyridin-3-yl]-5-[2-(benzyloxy)ethyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide.

The procedure for Example 8B, substituting the product from Example 20C for 1-(4-(5-amino-6-ethoxypyridin-2-yl)piperazin-1-yl)ethanone, provided the titled compound. ^1H NMR (300 MHz, CDCl_3) δ ppm 11.98 (s, 1H), 8.53 (d, $J = 8.6$ Hz, 1H), 8.06 (s, 1H), 7.37 – 7.27 (m, 5H), 6.20 (d, $J = 8.6$ Hz, 1H), 4.54 (s, 2H), 4.50 (t, $J = 5.4$ Hz, 2H), 3.90 – 3.85 (m, 2H), 3.82 (t, $J = 7.3$ Hz, 2H), 3.78 – 3.70 (m, 6H), 3.60 – 3.55 (m, 2H), 3.54 – 3.48 (m, 2H), 3.48 – 3.42 (m, 2H), 3.41 (s, 3H), 2.98 (t, $J = 7.2$ Hz, 2H), 2.14 (s, 3H); MS (ESI) m/z 592 ($\text{M}+\text{H}$) $^+$.

Example 86

25 *N*-{6-(4-acetylpiperazin-1-yl)-2-[2-(benzyloxy)ethoxy]pyridin-3-yl}-5-[2-(benzyloxy)ethyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 86A

30 2-(2-(benzyloxy)ethoxy)-6-chloro-3-nitropyridine

The procedure for Example 20A, substituting 2-benzyloxyethanol for 2-methoxyethanol, provided the titled compound. ^1H NMR (300 MHz, CDCl_3) δ ppm 8.27 (d, $J = 8.2$ Hz, 1H), 7.37 – 7.26 (m, 5H), 7.03 (d, $J = 8.3$ Hz, 1H), 4.70 – 4.66 (m, 2H), 4.65 (s, 2H), 3.91 – 3.87 (m, 2H).

Example 86B

1-(4-(6-(2-(benzyloxy)ethoxy)-5-nitropyridin-2-yl)piperazin-1-yl)ethanone

The procedure for Example 20B, substituting the product from Example 86A for the product from Example 20A, provided the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 8.30 (d, *J* = 9.0 Hz, 1H), 7.40 – 7.27 (m, 5H), 6.17 (d, *J* = 9.1 Hz, 1H), 4.68 (s, 2H), 4.62 – 4.55 (m, 2H), 3.95 – 3.87 (m, 2H), 3.81 – 3.71 (m, 4H), 3.67 (dd, *J* = 6.5, 3.2 Hz, 2H), 3.57 (dd, *J* = 6.2, 4.2 Hz, 2H), 2.15 (s, 3H); MS (ESI) *m/z* 401 (M+H)⁺.

10

Example 86C

1-(4-(5-amino-6-(2-(benzyloxy)ethoxy)pyridin-2-yl)piperazin-1-yl)ethanone

A mixture of the product from Example 86B (1.95 g, 4.87 mmol), platinum(IV) oxide (195 mg), potassium carbonate (337 mg, 2.4 mmol) in ethyl acetate (30 mL) and ethanol (30 mL) was hydrogenated (50 psi) at room temperature for 3 hours. Filtration of the solids and evaporation of the filtrate provided the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.39 – 7.27 (m, 5H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.09 (d, *J* = 8.1 Hz, 1H), 4.61 (s, 2H), 4.53 – 4.48 (m, 2H), 3.87 – 3.82 (m, 2H), 3.75 – 3.69 (m, 2H), 3.58 – 3.53 (m, 2H), 3.40 (bs, 2H), 3.37 – 3.32 (m, 2H), 3.29 – 3.24 (m, 2H), 2.13 (s, 3H); MS (ESI) *m/z* 371 (M+H)⁺.

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Example 86D

N-{6-(4-acetylpiperazin-1-yl)-2-[2-(benzyloxy)ethoxy]pyridin-3-yl}-5-[2-(benzyloxy)ethyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 8B, substituting the product from Example 86C for 1-(4-(5-amino-6-ethoxypyridin-2-yl)piperazin-1-yl)ethanone, provided the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.98 (s, 1H), 8.49 (d, *J* = 8.5 Hz, 1H), 8.06 (s, 1H), 7.36 – 7.19 (m, 10H), 6.20 (d, *J* = 8.6 Hz, 1H), 4.61 (s, 2H), 4.54 (t, *J* = 5.6 Hz, 2H), 4.48 (s, 2H), 3.97 (t, *J* = 5.6 Hz, 2H), 3.78 (t, *J* = 7.3 Hz, 2H), 3.75 – 3.70 (m, 2H), 3.68 – 3.64 (m, 4H), 3.53 (dd, *J* = 14.1, 6.2 Hz, 4H), 3.46 – 3.40 (m, 2H), 2.96 (t, *J* = 7.2 Hz, 2H), 2.14 (s, 3H); MS (ESI) *m/z* 668 (M+H)⁺.

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Example 87

N-[6-(4-acetylpiperazin-1-yl)-2-(2-methoxyethoxy)pyridin-3-yl]-5-(2-hydroxyethyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 9, substituting the product from Example 85 for the product from Example 8B, provided the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.94 (s, 1H), 8.57 (d, *J* = 8.6 Hz, 1H), 8.07 (s, 1H), 6.20 (d, *J* = 8.6 Hz, 1H), 4.53 – 4.48 (m, 2H), 3.93 – 3.86 (m, 4H), 3.80 (t, *J* = 7.3 Hz, 2H), 3.76 – 3.70 (m, 4H), 3.61 – 3.54 (m, 2H), 3.53 – 3.48 (m, 2H), 3.47 – 3.42 (m, 2H), 3.44 (s, 3H), 3.05 (t, *J* = 7.3 Hz, 2H), 2.14 (s, 3H); MS (ESI) *m/z* 502 (M+H)⁺.

Example 88

N-[6-(4-acetylpiperazin-1-yl)-2-(2-hydroxyethoxy)pyridin-3-yl]-5-(2-hydroxyethyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 9, substituting the product from Example 86D for the product from Example 8B, provided the titled compound. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 12.07 (s, 1H), 8.46 (d, *J* = 8.6 Hz, 1H), 8.29 (s, 1H), 6.37 (d, *J* = 8.7 Hz, 1H), 4.81 (dt, *J* = 6.7, 6.0 Hz, 2H), 4.27 (t, *J* = 5.0 Hz, 2H), 3.84 – 3.76 (m, 4H), 3.63 – 3.58 (m, 2H), 3.57 – 3.51 (m, 6H), 3.49 – 3.44 (m, 2H), 3.42 – 3.37 (m, 2H), 3.07 (t, *J* = 7.3 Hz, 2H), 2.04 (s, 3H); MS (ESI) *m/z* 488 (M+H)⁺.

Example 89

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(3-hydroxypropyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 89A

5-(3-(benzyloxy)propyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxylic acid

The procedure for Example 8A, substituting benzyl 3-bromopropyl ether for benzyl 2-bromoethyl ether, provided the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 14.70 (s, 1H), 8.01 (s, 1H), 7.36 – 7.27 (m, 5H), 4.48 (s, 2H), 3.72 (t, *J* = 7.5 Hz, 2H), 3.64 (t, *J* = 6.9 Hz, 2H), 3.57 (t, *J* = 5.8 Hz, 2H), 2.95 (t, *J* = 7.4 Hz, 2H), 2.00 – 1.88 (m, 2H); MS (ESI) *m/z* 330 (M+H)⁺.

Example 89B

N-(6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl)-5-(3-(benzyloxy)propyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The procedure for Example 8B, substituting the product from Example 89A for the product from Example 8A, provided the titled compound.

Example 89C

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(3-hydroxypropyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

5 The procedure for Example 9, substituting the product from Example 89B for the product from Example 8B, provided the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.80 (s, 1H), 8.56 (d, *J* = 8.6 Hz, 1H), 8.09 (s, 1H), 6.18 (d, *J* = 8.6 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 3.72 (m, 6H), 3.65 – 3.49 (m, 8H), 3.44 (dd, *J* = 6.2, 4.4 Hz, 2H), 3.06 (t, *J* = 7.3 Hz, 2H), 2.14 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H); MS (ESI) *m/z* 486 (M+H)⁺.

Example 90

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(4-hydroxybutyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 90A

5-(4-(benzyloxy)butyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxylic acid

15 The procedure for Example 8A, substituting benzyl 4-bromobutyl ether for benzyl 2-bromoethyl ether, provided the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 14.70 (s, 1H), 8.03 (s, 1H), 7.38 – 7.27 (m, 5H), 4.50 (s, 2H), 3.73 (t, *J* = 7.5 Hz, 2H), 3.54 (dt, *J* = 11.9, 4.3 Hz, 4H), 3.05 (t, *J* = 7.4 Hz, 2H), 1.80 – 1.60 (m, 4H); MS (ESI) *m/z* 344 (M+H)⁺.

Example 90B

N-(6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl)-5-(4-(benzyloxy)butyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

25 The procedure for Example 8B, substituting the product from Example 90A for the product from Example 8A, provided the titled compound.

Example 90C

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(4-hydroxybutyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

30 The procedure for Example 9, substituting the product from Example 90B for the product from Example 8B, provided the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 12.04 (s, 1H), 8.55 (d, *J* = 8.5 Hz, 1H), 8.07 (s, 1H), 6.23 (d, *J* = 8.6 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.78 – 3.66 (m, 6H), 3.63 – 3.56 (m, 4H), 3.54 – 3.41 (m, 4H), 3.03 (t, *J* = 7.3

Hz, 2H), 2.14 (s, 3H), 1.82 – 1.60 (m, 4H), 1.49 (t, $J = 7.1$ Hz, 3H); MS (ESI) m/z 500 (M+H)⁺.

Example 91

5 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[2-(2-hydroxyethoxy)ethyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 91A

10 5-(2-(2-(benzyloxy)ethoxy)ethyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxylic acid

15 The procedure for Example 8A, substituting ((2-(2-bromoethoxy)ethoxy)methyl)benzene for benzyl 2-bromoethyl ether, provided the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 14.64 (s, 1H), 8.02 (s, 1H), 7.38 – 7.27 (m, 5H), 4.53 (s, 2H), 3.87 (t, $J = 7.5$ Hz, 2H), 3.71 (s, 4H), 3.69 – 3.57 (m, 4H), 2.94 (t, $J = 7.5$ Hz, 2H); MS (ESI) m/z 360 (M+H)⁺.

Example 91B

20 *N*-(6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl)-5-(2-(2-(benzyloxy)ethoxy)ethyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

25 The procedure for Example 8B, substituting the product from Example 91A for the product from Example 8A, provided the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 12.08 – 11.89 (m, 1H), 8.52 (d, $J = 8.5$ Hz, 1H), 8.05 (s, 1H), 7.36 – 7.26 (m, 5H), 6.18 (d, $J = 8.6$ Hz, 1H), 4.54 (s, 2H), 4.39 (q, $J = 7.0$ Hz, 2H), 3.80 (t, $J = 7.3$ Hz, 2H), 3.74 (d, $J = 8.2$ Hz, 6H), 3.69 – 3.54 (m, 6H), 3.54 – 3.41 (m, 4H), 2.92 (t, $J = 7.2$ Hz, 2H), 2.14 (s, 3H), 1.46 (t, $J = 7.1$ Hz, 3H); MS (ESI) m/z 606 (M+H)⁺.

Example 91C

30 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[2-(2-hydroxyethoxy)ethyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

30 The procedure for Example 9, substituting the product from Example 91B for the product from Example 8B, provided the titled compound. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 12.06 (s, 1H), 8.31 (d, $J = 8.6$ Hz, 1H), 8.26 (s, 1H), 6.34 (d, $J = 8.7$ Hz, 1H), 4.56 (t, $J = 5.3$ Hz, 1H), 4.31 (q, $J = 7.0$ Hz, 2H), 3.79 (t, $J = 7.3$ Hz, 2H), 3.63 (s, 4H), 3.58 – 3.35 (m,

12H), 3.05 (t, $J = 7.3$ Hz, 2H), 2.04 (s, 3H), 1.38 (t, $J = 7.1$ Hz, 3H); MS (ESI) m/z 516 (M+H)⁺.

Example 92

5 *tert*-butyl 4-(6-ethoxy-5-{[(4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino}pyridin-2-yl)piperazine-1-carboxylate

Example 92A

6-chloro-2-ethoxy-3-nitropyridine

10 The titled compound was prepared using the procedure described for Example 20A substituting ethanol for 2-methoxyethanol. ¹H NMR (300 MHz, CDCl₃) δ ppm 8.24 (d, $J = 8.4$ Hz, 1H), 7.00 (d, $J = 8.3$ Hz, 1H), 4.58 (q, $J = 7.1$ Hz, 2H), 1.47 (t, $J = 7.0$ Hz, 3H).

Example 92B

15 *tert*-butyl 4-(6-ethoxy-5-nitropyridin-2-yl)piperazine-1-carboxylate

The titled compound was prepared using the procedure described for Example 20B, substituting the product from Example 92A for the product from Example 20A, and substituting *tert*-butyl piperazine-1-carboxylate for 1-acetylpiperazine. ¹H NMR (500 MHz, CDCl₃) δ ppm 8.28 (d, $J = 9.1$ Hz, 1H), 6.15 (d, $J = 9.1$ Hz, 1H), 4.49 (q, $J = 7.1$ Hz, 2H),
20 3.75 – 3.67 (m, 4H), 3.58 – 3.52 (m, 4H), 1.49 (s, 9H), 1.46 (t, $J = 7.1$ Hz, 3H).

Example 92C

tert-butyl 4-(5-amino-6-ethoxypyridin-2-yl)piperazine-1-carboxylate

25 The titled compound was prepared using the procedure described for Example 20C, substituting the product from Example 92B for the product from Example 20B. ¹H NMR (300 MHz, CDCl₃) δ ppm 6.89 (d, $J = 8.0$ Hz, 1H), 6.10 (d, $J = 8.4$ Hz, 1H), 4.37 (q, $J = 7.0$ Hz, 2H), 3.60 – 3.51 (m, 4H), 3.33 – 3.26 (m, 4H), 1.48 (s, 9H), 1.39 (t, $J = 7.1$ Hz, 3H).

Example 92D

30 *tert*-butyl 4-(6-ethoxy-5-{[(4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino}pyridin-2-yl)piperazine-1-carboxylate

The titled compound was prepared using the procedure described for Example 19, substituting the product from Example 92C for 1-(4-(5-amino-6-ethoxypyridin-2-

yl)piperazin-1-yl)ethanone. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.96 (s, 1H), 8.23-8.26 (m, 2H), 8.02 (m, 1H), 6.34 (d, *J*=8.8 Hz, 1H), 4.32 (q, *J*=7.1 Hz, 2H), 3.52 (m, 2H), 3.42 (m, 8H), 2.99 (m, 2H), 1.42 (s, 9H), 1.34 (t, *J*=7.1 Hz, 3H); MS (ESI) *m/z* 486 (M+H)⁺.

5

Example 93

N-{6-[4-(*N*'-cyano-*N*-methylcarbamimidoyl)piperazin-1-yl]-2-ethoxypyridin-3-yl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 93A

10 *N*-[2-ethoxy-6-(piperazin-1-yl)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide 2,2,2-trifluoroacetate

A mixture of Example 92D (0.222 g, 0.457 mmol) and trifluoroacetic acid (2 mL, 26.0 mmol) was stirred at room temperature for 1 hour. The mixture was then concentrated in vacuo to afford the titled compound as the trifluoroacetate.

15

Example 93B

N-{6-[4-(*N*'-cyano-*N*-methylcarbamimidoyl)piperazin-1-yl]-2-ethoxypyridin-3-yl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide bis(2,2,2-trifluoroacetate)

A mixture of Example 93A (0.228 g, 0.457 mmol), methyl *N*'-cyano-*N*-methylcarbamimidothioate (0.065 g, 0.503 mmol), mercury(II) chloride (0.170 g, 0.626 mmol), and triethylamine (0.8 mL, 5.74 mmol) in *N,N*-dimethylformamide (4 mL) was stirred overnight at room temperature. The mixture was concentrated in vacuo. The residue was taken up in a 1:1 mixture of methanol and dimethylsulfoxide (2.5 mL) and filtered, and the filtrate was purified by preparative HPLC on a Phenomenex® Luna® C8(2) 5 μm 100Å AXIA™ column (30 mm × 75 mm). A gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) was used, at a flow rate of 50 mL/minute (0-0.5 minutes 10% A, 0.5-7.0 minutes linear gradient 10-95% A, 7.0-10.0 minutes 95% A, 10.0-12.0 minutes linear gradient 95-10% A). Samples were injected in dimethyl sulfoxide/methanol (1:1, 2.5 mL). A custom purification system was used, consisting of the following modules: Waters LC4000
25
30 preparative pump; Waters 996 diode-array detector; Waters 717+ autosampler; Waters SAT/IN module, Alltech Varex III evaporative light-scattering detector; Gilson 506C interface box; and two Gilson FC204 fraction collectors. The system was controlled using Waters Millennium32 software, automated using an AbbVie developed Visual Basic

application for fraction collector control and fraction tracking. Fractions were collected based upon UV signal threshold and selected fractions subsequently analyzed by flow injection analysis mass spectrometry using positive APCI ionization on a Finnigan LCQ using 70:30 methanol:10 mM NH₄OH(aqueous) at a flow rate of 0.8 mL/minute. Loop-injection mass spectra were acquired using a Finnigan LCQ running LCQ Navigator 1.2 software and a Gilson 215 liquid handler for fraction injection controlled by an AbbVie developed Visual Basic application. Concentration of selected fractions provided the titled compound as the bistrifluoroacetate. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.97 (s, 1H), 8.24-8.26 (m, 2H), 8.02 (m, 1H), 7.31 (m, 1H), 6.35 (d, *J*=8.5 Hz, 1H), 4.33 (q, *J*=7.1 Hz, 2H), 3.39-3.59 (m, 10H), 2.99 (m, 2H), 2.87 (d, *J*=4.4 Hz, 3H), 1.34 (t, *J*=7.1 Hz, 3H); MS (ESI) *m/z* 467 (M+H)⁺.

Example 94

(2*R*)-1-[3-{[6-(4-acetylpiperazin-1-yl)-2-ethoxy-pyridin-3-yl]carbonyl}-4-oxo-6,7-dihydrofuro[3,2-*c*]pyridin-5(4*H*)-yl]propan-2-yl acetate

Example 94A

(*R*)-ethyl 3-(2-hydroxypropylamino)propanoate

(*R*)-(-)-1-Amino-2-propanol (0.296 g, 3.94 mmol) was cooled to 0 °C, treated dropwise with ethyl acrylate (0.427 mL, 3.94 mmol) and stirred overnight at room temperature to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 4.15 (q, *J*=7.1 Hz, 2H), 3.75 (dq, *J*=9.3, 6.2, 3.1 Hz, 1H), 3.00 – 2.82 (m, 2H), 2.73 (dd, *J*=12.1, 3.1 Hz, 1H), 2.49 (t, *J*=6.4 Hz, 2H), 2.39 (dd, *J*=12.1, 9.4 Hz, 1H), 1.27 (t, *J*=7.2 Hz, 3H), 1.14 (d, *J*=6.2 Hz, 3H); MS (ESI) *m/z* 176 (M+H)⁺.

Example 94B

ethyl 1-((*R*)-2-hydroxypropyl)-2,4-dioxopiperidine-3-carboxylate

A solution of the product from Example 94A (0.690 g, 3.94 mmol) in tetrahydrofuran (12 mL) was cooled to 0 °C under N₂, treated with triethylamine (0.604 mL, 4.33 mmol), treated with trimethylsilyl chloride (0.554 mL, 4.33 mmol), stirred at room temperature for 30 minutes, concentrated to dryness, and partitioned between ether (100 mL) and brine (20 mL). The ether layer was isolated, dried (MgSO₄), filtered, and concentrated to provide (*R*)-ethyl 3-(2-(trimethylsilyloxy)propylamino)propanoate. ¹H NMR (300 MHz, CDCl₃) δ ppm

4.15 (q, $J = 7.1$ Hz, 2H), 3.99 – 3.88 (m, 1H), 2.89 (t, $J = 6.7$ Hz, 2H), 2.63 – 2.43 (m, 4H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.15 (d, $J = 6.2$ Hz, 3H), 0.13 (s, 9H); MS (ESI) m/z 248 (M+H)⁺.

The (*R*)-ethyl 3-(2-(trimethylsilyloxy)propylamino)propanoate was dissolved in CH₂Cl₂ (12 mL) under N₂, cooled to 0° C and treated with triethylamine (0.604 mL, 4.33 mmol). Ethyl malonyl chloride (0.549 mL, 4.33 mmol) was then added over 5 minutes, and the mixture was stirred at room temperature overnight. The mixture was concentrated to dryness and partitioned between ether (100 mL) and brine (20 mL). The ether layer was isolated, dried (MgSO₄), filtered, and concentrated to provide (*R*)-ethyl 3-((3-ethoxy-3-oxopropyl)(2-(trimethylsilyloxy)propyl)amino)-3-oxopropanoate.

A solution of ethanol (4.60 mL, 79 mmol) in tetrahydrofuran (30 mL) under N₂ was treated with potassium *tert*-butoxide (0.973 g, 8.67 mmol) and stirred until the mixture was homogeneous. This mixture was cooled to 0 °C and treated dropwise with a solution of (*R*)-ethyl 3-((3-ethoxy-3-oxopropyl)(2-(trimethylsilyloxy)propyl)amino)-3-oxopropanoate in tetrahydrofuran (10 mL). After stirring at room temperature overnight, the mixture was concentrated to dryness, dissolved in 1 M HCl (15 mL) and stirred for 10 minutes. The mixture was then treated with silica gel (2.5 g) and concentrated to dryness. This silica gel mixture was placed on top of a silica gel column and chromatographed eluting with a gradient of 0% to 100% [22:1:1 ethyl acetate/formic acid/water] in ethyl acetate to provide the titled compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 14.10 (s, 1H), 8.06 (s, 1H), 4.36 (q, $J = 7.1$ Hz, 2H), 4.11 – 4.03 (m, 1H), 3.54 (t, $J = 6.9$ Hz, 2H), 3.45 (d, $J = 5.8$ Hz, 2H), 2.70 (dd, $J = 11.5, 6.6$ Hz, 2H), 1.37 (t, $J = 7.1$ Hz, 3H), 1.21 (d, $J = 6.3$ Hz, 3H); MS (ESI) m/z 244 (M+H)⁺.

Example 94C

(*R*)-5-(2-acetoxypropyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxylic acid

A solution of the product from Example 94B (0.70 g, 2.88 mmol) in water (12 mL) was heated to reflux for 30 minutes and then cooled to 0°C. This mixture was treated with sodium bicarbonate (0.967 g, 11.5 mmol), then treated portion-wise over 45 minutes with a solution of 3-bromopyruvic acid (0.577 g, 3.45 mmol) in methanol (12 mL) and stirred at room temperature overnight. The mixture was concentrated to dryness, and the residue was treated with acetic acid (30 mL) and acetic anhydride (15 mL). This mixture was heated to 110 °C for 2 hours, cooled and concentrated to dryness. The residue was partitioned between ethyl acetate (200 mL) and 1 M HCl (50 mL). The layers were separated, and the aqueous

layer was extracted with ethyl acetate (25 mL). The combined ethyl acetate layers were washed with brine, dried (MgSO₄), filtered and concentrated. The residue was chromatographed on silica gel eluting with a gradient of 50–100% [200:1:1 ethyl acetate/formic acid/water] in heptanes to provide the titled compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 14.44 (s, 1H), 8.04 (s, 1H), 5.21 (dq, *J* = 12.9, 6.4, 3.6 Hz, 1H), 3.94 – 3.72 (m, 3H), 3.56 (dd, *J* = 14.3, 3.6 Hz, 1H), 3.16 – 3.01 (m, 2H), 2.04 (s, 3H), 1.30 (d, *J* = 6.4 Hz, 3H); MS (ESI) *m/z* 282 (M+H)⁺.

Example 94D

(2*R*)-1-[3-{[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]carbamoyl}-4-oxo-6,7-dihydrofuro[3,2-*c*]pyridin-5(4*H*)-yl]propan-2-yl acetate

A solution of the product from Example 94C (113 mg, 0.402 mmol) in tetrahydrofuran (8 mL) under nitrogen was treated with triethylamine (168 μL, 1.21 mmol) followed by treatment with ethyl chloroformate (38.6 μL, 0.402 mmol). The mixture was stirred at room temperature for 45 minutes and then 1-(4-(5-amino-6-ethoxypyridin-2-yl)piperazin-1-yl)ethanone (CAS# 1094927-44-2) (106 mg, 0.402 mmol) was added. The reaction mixture was stirred overnight and then diluted with ethyl acetate (100 mL). This organic layer was washed with 1 *M* HCl (25 mL), washed with saturated sodium bicarbonate solution (15 mL), washed with brine, dried (MgSO₄), filtered, concentrated and chromatographed on silica gel eluted with a gradient of 0% to 100% [10% ethanol in ethyl acetate] in ethyl acetate to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.92 (s, 1H), 8.53 (d, *J* = 8.6 Hz, 1H), 8.07 (s, 1H), 6.18 (d, *J* = 8.6 Hz, 1H), 5.27 – 5.14 (m, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.85 – 3.41 (m, 11H), 3.12 – 2.92 (m, 3H), 2.14 (s, 3H), 2.04 (s, 3H), 1.49 (t, *J* = 7.1 Hz, 3H), 1.30 (d, *J* = 6.4 Hz, 3H); MS (ESI) *m/z* 528 (M+H)⁺.

Example 95

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[(2*R*)-2-hydroxypropyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

A solution of the product from Example 94 (126 mg, 0.239 mmol) in tetrahydrofuran (2 mL) and methanol (2 mL) was treated with 1 *M* NaOH (1 mL). After stirring for 15 minutes, the mixture was partitioned between water (10 mL) and CH₂Cl₂ (50 mL). The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (25 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered and concentrated to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.87 (s, 1H), 8.54 (d, *J* = 8.6 Hz, 1H), 8.07

(s, 1H), 6.17 (d, $J = 8.6$ Hz, 1H), 4.40 (q, $J = 7.1$ Hz, 2H), 4.22 – 4.09 (m, 1H), 3.82 (t, $J = 7.3$ Hz, 2H), 3.77 – 3.70 (m, 2H), 3.61 – 3.41 (m, 8H), 3.04 (dd, $J = 7.5, 6.7$ Hz, 2H), 2.74 (d, $J = 4.6$ Hz, 1H), 2.14 (s, 3H), 1.48 (t, $J = 7.1$ Hz, 3H), 1.26 (d, $J = 6.3$ Hz, 3H); MS (ESI) m/z 486 (M+H)⁺.

5

Example 96

(2*S*)-1-[3-{[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]carbamoyl}-4-oxo-6,7-dihydrofuro[3,2-*c*]pyridin-5(4*H*)-yl]propan-2-yl acetate

The titled compound was prepared using the procedures described for Example 94 substituting (*S*)-1-aminopropan-2-ol for (*R*)-(-)-1-amino-2-propanol. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.92 (s, 1H), 8.53 (d, $J = 8.5$ Hz, 1H), 8.07 (s, 1H), 6.18 (d, $J = 8.6$ Hz, 1H), 5.27 – 5.15 (m, 1H), 4.41 (q, $J = 7.1$ Hz, 2H), 3.86 – 3.42 (m, 12H), 3.12 – 2.92 (m, 2H), 2.14 (s, 3H), 2.04 (s, 3H), 1.49 (t, $J = 7.1$ Hz, 3H), 1.30 (d, $J = 6.4$ Hz, 3H); MS (ESI) m/z 528 (M+H)⁺.

15

Example 97

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[(2*S*)-2-hydroxypropyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 95 substituting the product from Example 96 for the product from Example 94. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.86 (s, 1H), 8.54 (d, $J = 8.6$ Hz, 1H), 8.08 (s, 1H), 6.17 (d, $J = 8.6$ Hz, 1H), 4.40 (q, $J = 7.1$ Hz, 2H), 4.22 – 4.09 (m, 1H), 3.82 (t, $J = 7.3$ Hz, 2H), 3.77 – 3.71 (m, 2H), 3.61 – 3.40 (m, 8H), 3.05 (dd, $J = 7.5, 6.4$ Hz, 2H), 2.72 (d, $J = 4.6$ Hz, 1H), 2.14 (s, 3H), 1.48 (t, $J = 7.1$ Hz, 3H), 1.26 (d, $J = 6.3$ Hz, 3H); MS (ESI) m/z 486 (M+H)⁺.

25

Example 98

(2*R*)-2-[3-{[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]carbamoyl}-4-oxo-6,7-dihydrofuro[3,2-*c*]pyridin-5(4*H*)-yl]propyl acetate

The titled compound was prepared using the procedures described for Example 94 substituting (*R*)-2-aminopropan-1-ol for (*R*)-(-)-1-amino-2-propanol. ¹H NMR (500 MHz, CDCl₃) δ ppm 11.99 (s, 1H), 8.54 (d, $J = 8.5$ Hz, 1H), 8.07 (s, 1H), 6.18 (d, $J = 8.6$ Hz, 1H), 5.13 – 5.03 (m, 1H), 4.41 (q, $J = 7.0$ Hz, 2H), 4.25 (dd, $J = 11.6, 8.6$ Hz, 1H), 4.14 (dd, $J = 11.6, 4.6$ Hz, 1H), 3.76 – 3.71 (m, 2H), 3.62 (dd, $J = 10.1, 4.2$ Hz, 2H), 3.60 – 3.56 (m, 2H), 3.51 (dd, $J = 6.4, 3.2$ Hz, 2H), 3.47 – 3.42 (m, 2H), 2.99 (dd, $J = 12.8, 6.7$ Hz, 2H), 2.14 (s,

3H), 2.03 (s, 3H), 1.48 (t, $J = 7.0$ Hz, 3H), 1.26 (d, $J = 7.0$ Hz, 3H); MS (ESI) m/z 528 (M+H)⁺.

Example 99

5 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[(2*R*)-1-hydroxypropan-2-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 95 substituting the product from Example 98 for the product from Example 94. ¹H NMR (500 MHz, CDCl₃) δ ppm 12.00 (s, 1H), 8.51 (d, $J = 8.5$ Hz, 1H), 8.05 (s, 1H), 6.16 (d, $J = 8.6$ Hz, 1H), 4.75 – 4.68 (m, 1H), 4.40 (q, $J = 7.1$ Hz, 2H), 3.79 – 3.66 (m, 5H), 3.64 – 3.54 (m, 3H), 10 3.49 (dd, $J = 6.3, 3.7$ Hz, 2H), 3.43 (t, $J = 4.9$ Hz, 2H), 3.02 – 2.89 (m, 3H), 2.12 (s, 3H), 1.47 (t, $J = 7.1$ Hz, 3H), 1.25 (d, $J = 7.0$ Hz, 3H); MS (ESI) m/z 486 (M+H)⁺.

Example 100

15 (2*S*)-2-[3-{[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]carbamoyl}-4-oxo-6,7-dihydrofuro[3,2-*c*]pyridin-5(4*H*)-yl]propyl acetate

The titled compound was prepared using the procedures described for Example 94 substituting (*S*)-2-aminopropan-1-ol for (*R*)-(-)-1-amino-2-propanol. ¹H NMR (500 MHz, CDCl₃) δ ppm 11.99 (s, 1H), 8.54 (d, $J = 8.5$ Hz, 1H), 8.07 (s, 1H), 6.18 (d, $J = 8.6$ Hz, 1H), 20 5.16 – 5.03 (m, 1H), 4.41 (q, $J = 7.1$ Hz, 2H), 4.25 (dd, $J = 11.7, 8.6$ Hz, 1H), 4.14 (dd, $J = 11.6, 4.7$ Hz, 1H), 3.76 – 3.71 (m, 2H), 3.67 – 3.55 (m, 4H), 3.54 – 3.49 (m, 2H), 3.47 – 3.43 (m, 2H), 3.06 – 2.94 (m, 2H), 2.14 (s, 3H), 2.03 (s, 3H), 1.48 (t, $J = 7.1$ Hz, 3H), 1.26 (d, $J = 7.1$ Hz, 3H); MS (ESI) m/z 528 (M+H)⁺.

Example 101

25 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[(2*S*)-1-hydroxypropan-2-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 95 substituting the product from Example 100 for the product from Example 94. ¹H NMR (400 30 MHz, CDCl₃) δ ppm 11.96 (s, 1H), 8.52 (d, $J = 8.5$ Hz, 1H), 8.06 (s, 1H), 6.17 (d, $J = 8.6$ Hz, 1H), 4.76 – 4.66 (m, 1H), 4.41 (q, $J = 7.0$ Hz, 2H), 3.81 – 3.55 (m, 8H), 3.50 (dd, $J = 6.6, 3.7$ Hz, 2H), 3.46 – 3.42 (m, 2H), 3.05 – 2.90 (m, 2H), 2.62 (t, $J = 5.6$ Hz, 1H), 2.13 (s, 3H), 1.47 (t, $J = 7.1$ Hz, 3H), 1.26 (d, $J = 7.0$ Hz, 3H); MS (ESI) m/z 486 (M+H)⁺.

Example 102

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(1-hydroxy-2-methylpropan-2-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

5

Example 102A

2-(3-(6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-ylcarbamoyl)-4-oxo-6,7-dihydrofuro[3,2-*c*]pyridin-5(4*H*)-yl)-2-methylpropyl acetate

The titled compound was prepared using the procedures described for Example 94 substituting 2-amino-2-methylpropan-1-ol for (*R*)-(-)-1-amino-2-propanol.

10

Example 102B

N-(6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl)-5-(1-hydroxy-2-methylpropan-2-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 95 substituting the product from Example 102A for the product from Example 94. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.85 (s, 1H), 8.57 (d, *J* = 8.6 Hz, 1H), 8.07 (s, 1H), 6.18 (d, *J* = 8.6 Hz, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 4.25 (t, *J* = 7.1 Hz, 1H), 3.91 (d, *J* = 7.1 Hz, 2H), 3.79 – 3.70 (m, 4H), 3.61 – 3.41 (m, 6H), 2.93 (t, *J* = 6.9 Hz, 2H), 2.14 (s, 3H), 1.45 (t, *J* = 7.0 Hz, 3H), 1.44 (s, 6H); MS (ESI) *m/z* 500 (M+H)⁺.

20

Example 103

1-[3-{[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]carbamoyl}-4-oxo-6,7-dihydrofuro[3,2-*c*]pyridin-5(4*H*)-yl]-2-methylpropan-2-yl acetate

The titled compound was prepared using the procedures described for Example 94 substituting 1-amino-2-methylpropan-2-ol for (*R*)-(-)-1-amino-2-propanol. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.91 (s, 1H), 8.53 (d, *J* = 8.6 Hz, 1H), 8.08 (s, 1H), 6.18 (d, *J* = 8.6 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.81 (t, *J* = 7.1 Hz, 2H), 3.80 (s, 2H), 3.76 – 3.70 (m, 2H), 3.61 – 3.41 (m, 6H), 3.02 (t, *J* = 7.1 Hz, 2H), 2.14 (s, 3H), 2.02 (s, 3H), 1.54 (s, 6H), 1.47 (t, *J* = 7.1 Hz, 3H); MS (ESI) *m/z* 542 (M+H)⁺.

30

Example 104

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2-hydroxy-2-methylpropyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 95 substituting the product from Example 103 for the product from Example 94. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.82 (s, 1H), 8.54 (d, *J* = 8.6 Hz, 1H), 8.08 (s, 1H), 6.17 (d, *J* = 8.6 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.86 (t, *J* = 7.2 Hz, 2H), 3.77 – 3.70 (m, 2H), 3.56 (s, 2H), 3.62 – 3.41 (m, 6H), 3.05 (t, *J* = 7.2 Hz, 3H), 2.14 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H), 1.31 (s, 6H); MS (ESI) *m/z* 500 (M+H)⁺.

Example 105

N-{6-(4-acetylpiperazin-1-yl)-2-[(3*S*)-tetrahydrofuran-3-yloxy]pyridin-3-yl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared by sequentially using the procedures described for Example 20A, Example 20B, Example 20C and Example 19, substituting (*S*)-(+)-3-hydroxytetrahydrofuran for 2-methoxyethanol in Example 20A. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.74 (s, 1H), 8.55 (d, *J* = 8.6 Hz, 1H), 8.08 (s, 1H), 6.21 (d, *J* = 8.6 Hz, 1H), 5.65 (bs, 1H), 5.51 (ddd, *J* = 6.9, 5.2, 2.8 Hz, 1H), 4.16 – 4.00 (m, 3H), 3.89 (td, *J* = 8.1, 4.4 Hz, 1H), 3.76 – 3.71 (m, 2H), 3.68 (td, *J* = 7.3, 2.6 Hz, 2H), 3.62 – 3.41 (m, 6H), 3.03 (t, *J* = 7.2 Hz, 2H), 2.36 (dddd, *J* = 13.4, 6.7, 4.4, 2.4 Hz, 1H), 2.30 – 2.17 (m, 1H), 2.14 (s, 3H); MS (ESI) *m/z* 470 (M+H)⁺.

Example 106

N-[2-ethoxy-6-(morpholin-4-yl)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared by sequentially using the procedures described for Example 20B, Example 20C, and Example 19, substituting the product from Example 92A for the product from Example 20A in the procedure described in Example 20B, and substituting morpholine for 1-acetylpiperazine in the procedure described in Example 20B. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.63 (s, 1H), 8.48 (d, *J* = 8.6 Hz, 1H), 8.09 (s, 1H), 6.16 (d, *J* = 8.6 Hz, 1H), 5.55 (s, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 3.86 – 3.79 (m, 4H), 3.69 (td, *J* = 7.2, 2.6 Hz, 2H), 3.45 – 3.40 (m, 4H), 3.03 (t, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H); MS (ESI) *m/z* 386 (M+H)⁺.

Example 107

N-[2-(2-hydroxy-2-methylpropoxy)-6-(morpholin-4-yl)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 107A

2-(2-(benzyloxy)-2-methylpropoxy)-6-morpholinopyridin-3-amine

The titled compound was prepared using the procedures described for Example 20A,
5 Example 20B, and Example 86C, substituting 2-(benzyloxy)-2-methylpropan-1-ol for 2-methoxyethanol in Example 20A, and substituting morpholine for 1-acetylpiperazine in Example 20B.

Example 107B

10 *N*-(2-(2-(benzyloxy)-2-methylpropoxy)-6-morpholinopyridin-3-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

A solution of the product from Example 1E (50 mg, 0.276 mmol) and triethylamine (0.058 mL, 0.414 mmol) in acetonitrile (5 mL) under nitrogen was cooled to 0 °C, treated with ethyl chloroformate (0.034 mL, 0.359 mmol) and stirred for 20 minutes at 0 °C. A
15 solution of the product from Example 107A (99 mg, 0.276 mmol) in acetonitrile (2 mL) was then added, and the reaction was stirred for 2 hours. The mixture was diluted with ethyl acetate, washed with water, washed with brine, dried (MgSO₄), filtered, concentrated and chromatographed on silica gel eluted with a gradient of 20% to 40% ethyl acetate in hexanes to provide the titled compound.

Example 107C

20 *N*-[2-(2-hydroxy-2-methylpropoxy)-6-(morpholin-4-yl)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 9,
25 substituting the product from Example 107B for the product from Example 8B. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.86 (s, 1H), 8.71 (d, J = 8.6 Hz, 1H), 8.10 (s, 1H), 6.18 (d, J = 8.6 Hz, 1H), 5.80 (s, 1H), 5.20 (s, 1H), 4.19 (s, 2H), 3.87 – 3.79 (m, 4H), 3.70 (td, J = 7.3, 2.7 Hz, 2H), 3.45 – 3.39 (m, 4H), 3.05 (t, J = 7.3 Hz, 2H), 1.32 (s, 6H); MS (ESI) *m/z* 431 (M+H)⁺.

Example 108

30 methyl (6-ethoxy-5-{[(4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino}pyridin-2-yl)acetate

Example 108A

1-*tert*-butyl 3-methyl 2-(6-ethoxy-5-nitropyridin-2-yl)malonate

A mixture of a 60% dispersion of sodium hydride in mineral oil (1.185 g, 29.6 mmol) and the product from Example 92A (3.0 g, 14.8 mmol) in *N,N*-dimethylformamide (4 mL) was cooled to 0 °C and treated dropwise with *tert*-butyl methyl malonate (3.16 mL, 17.77 mmol). The mixture was stirred at room temperature overnight. The mixture was diluted with ether, washed with water, dried (MgSO₄), filtered and concentrated. The residue was purified by chromatography on silica gel eluting with a gradient of 10% to 40% ethyl acetate in heptanes. ¹H NMR (300 MHz, CDCl₃) δ ppm 8.26 (d, *J* = 8.1 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 4.78 (s, 1H), 4.60 – 4.49 (m, 2H), 3.79 (s, 3H), 1.47 (s, 9H), 1.43 (t, *J* = 7.1 Hz, 3H).

Example 108B

methyl 2-(6-ethoxy-5-nitropyridin-2-yl)acetate

A mixture of the product from Example 108A (4.1 g, 12 mmol) and 2,2,2-trifluoroacetic acid (13.7 g, 120 mmol) was stirred at room temperature for 10 minutes and then concentrated to dryness to provide the titled compound.

Example 108C

methyl 2-(5-amino-6-ethoxypyridin-2-yl)acetate

The titled compound was prepared using the procedure described for Example 20C, substituting the product from Example 108B for the product from Example 20B.

Example 108D

methyl (6-ethoxy-5-{[(4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino}pyridin-2-yl)acetate

The titled compound was prepared using the procedure described for Example 107B, substituting the product from Example 108C for the product from Example 107A. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.86 (s, 1H), 8.64 (d, *J* = 8.0 Hz, 1H), 8.11 (s, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 5.52 (s, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 3.74 – 3.66 (m, 7H), 3.04 (t, *J* = 7.2 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H); MS (ESI) *m/z* 374 (M+H)⁺.

Example 109

N-[2-ethoxy-6-(2-hydroxyethyl)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

A solution of the product from Example 108D (70 mg, 0.19 mmol) in tetrahydrofuran was treated with 1 *M* lithium aluminum hydride in tetrahydrofuran (0.56 mL, 0.56 mmol) and stirred for 30 minutes. The mixture was treated sequentially with 1 drop of water, 1 drop of 1 *M* NaOH, and 3 drops of water. After stirring for 1 hour, the mixture was filtered through a Whatman PuradiscTM 25 TF 0.45 μ m polytetrafluoroethylene (PTFE) membrane with polypropylene housing 25 mm diameter filter. The filtrate was concentrated and chromatographed on silica gel eluting with a gradient of 0% to 100% ethyl acetate in heptanes, followed by a gradient of 0% to 10% methanol in ethyl acetate to provide the titled compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 11.82 (s, 1H), 8.55 (d, *J* = 7.9 Hz, 1H), 8.05 (s, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 5.58 (s, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.16 (t, *J* = 5.3 Hz, 1H), 3.91 (dd, *J* = 10.5, 5.2 Hz, 2H), 3.63 (td, *J* = 7.2, 2.6 Hz, 2H), 2.97 (t, *J* = 7.2 Hz, 2H), 2.83 (t, *J* = 5.4 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H); MS (ESI) *m/z* 346 (M+H)⁺.

Example 110

N-[6-(4-acetylpiperazin-1-yl)-2-methoxypyridin-3-yl]-4-oxo-2',3',4,5',6',7-hexahydro-5*H*-spiro[1-benzofuran-6,4'-pyran]-3-carboxamide

Example 110A

1-(dihydro-2*H*-pyran-4(3*H*)-ylidene)propan-2-one

A mixture of potassium hydroxide (1.29 g, 22.99 mmol) in water (5 mL) and ethanol (20 mL) was cooled to 0 °C. Dihydro-2*H*-pyran-4(3*H*)-one (1.5 mL, 16.24 mmol) was added followed by dimethyl 2-oxopropylphosphonate (3.16 mL, 21.21 mmol). The reaction mixture was stirred overnight at room temperature. After this time, the mixture was concentrated in vacuo to remove most of the ethanol, and then the mixture was partitioned between ether (20 mL) and water (20 mL). The phases were separated, and the aqueous layer was extracted twice more with ether (20 mL each). The combined organic layers were dried over Na₂SO₄ and concentrated to yield the titled compound as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ ppm 6.06 (s, 1H), 3.70-3.81 (m, 4H), 2.98 (m, 2H), 2.30 (m, 2H), 2.19 (s, 3H); MS (DCI⁺) *m/z* 158 (M+NH₄)⁺.

Example 110B

methyl 8,10-dioxo-3-oxaspiro[5.5]undecane-7-carboxylate

A mixture of Example 110A (2.485 g, 17.73 mmol) and dimethyl malonate (2.342 g, 17.73 mmol) in methanol (13 mL) was treated with sodium methoxide (25% in methanol) (4.8 mL, 20.99 mmol), and the reaction mixture was refluxed for 4 hours. After cooling to room temperature, the mixture was concentrated in vacuo to afford the crude titled compound as an orange, waxy solid which was used in the next reaction without further purification.

Example 110C

3-oxaspiro[5.5]undecane-8,10-dione

A mixture of Example 110B (1 g, 4.16 mmol) and 2 N NaOH (6.9 mL, 13.8 mmol) was refluxed for 2 hours. The mixture was cooled briefly to room temperature, treated with 5 N H₂SO₄ (6.9 mL, 34.5 mmol), and refluxed for 1.5 hours before being cooled to room temperature and stirred overnight. After this time, the mixture was extracted with ethyl acetate (50 mL) and CH₂Cl₂ (50 mL). The combined organic washes were dried over Na₂SO₄ and concentrated to afford the titled compound as a gold oil, 0.445 g (59%). ¹H NMR (300 MHz, CDCl₃) δ ppm 3.67-3.71 (m, 4H), 3.39 (s, 2H), 2.69 (m, 4H), 1.47-1.50 (m, 4H).

Example 110D

ethyl 4-oxo-2',3',5,5',6',7-hexahydro-4*H*-spiro[benzofuran-6,4'-pyran]-3-carboxylate

A solution of Example 110C (0.445 g, 2.442 mmol) in ethanol (8.1 mL) was treated sequentially with sodium bicarbonate (2 g, 23.81 mmol) and ethyl bromopyruvate (0.37 mL, 2.94 mmol), and the mixture was stirred overnight at room temperature. After this time, the mixture was diluted with ethanol (15 mL) and filtered. The filtrate was concentrated. The residue was treated with acetic acid (23 mL) and acetic anhydride (11 mL), and the mixture was heated at 110 °C overnight. After cooling to room temperature, the mixture was concentrated. The residue was taken up in ethyl acetate (50 mL) and washed with saturated NaHCO₃ solution (15 mL) and brine (15 mL). The organic layer was dried over Na₂SO₄ and concentrated. Chromatography on silica gel (20 to 100% ethyl acetate-hexane, eluant) afforded the titled compound as a brown oil. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.92 (m, 1H), 4.34 (m, 2H), 3.68-3.73 (m, 4H), 2.92 (s, 2H), 2.61 (s, 2H), 1.60-1.66 (m, 4H), 1.36 (m, 3H); MS (DCI⁺) *m/z* 279 (M+H)⁺.

Example 110E

4-oxo-2',3',5,5',6',7-hexahydro-4*H*-spiro[benzofuran-6,4'-pyran]-3-carboxylic acid

The product from Example 110D (0.204 g, 0.733 mmol) and 1 M aqueous sodium hydroxide solution (2.2 mL, 2.20 mmol) were stirred in methanol (2.2 mL) and tetrahydrofuran (2.2 mL) overnight at room temperature. After this time, the mixture was concentrated in vacuo, and the aqueous residue was washed with CH₂Cl₂ (3 × 1 mL). The remaining (basic) aqueous layer was acidified to pH 1 with 6 N HCl, and the resulting tan precipitate was collected by filtration, washed with water, and air-dried to give the titled compound, 0.049 g (27%). ¹H NMR (300 MHz, CDCl₃) δ ppm 12.92 (s, 1H), 8.11 (sm, 1H), 3.66-3.79 (m, 4H), 3.02 (s, 2H), 2.73 (s, 2H), 1.67-1.71 (m, 4H); MS (DCI⁺) *m/z* 251 (M+H)⁺.

Example 110F

N-[6-(4-acetylpiperazin-1-yl)-2-methoxypyridin-3-yl]-4-oxo-2',3',4,5',6',7-hexahydro-5*H*-spiro[1-benzofuran-6,4'-pyran]-3-carboxamide

The titled compound was prepared according to the procedure of Example 8B, substituting 1-(4-(5-amino-6-methoxypyridin-2-yl)piperazin-1-yl)ethanone (CAS # 1094788-32-5) for 1-(4-(5-amino-6-ethoxypyridin-2-yl)piperazin-1-yl)ethanone and substituting the product from Example 110E for the product from Example 8A. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.19 (s, 1H), 8.38 (s, 1H), 8.31 (d, J=8.7 Hz, 1H), 6.38 (d, J=8.7 Hz, 1H), 3.91 (s, 3H), 3.42-3.62 (m, 12H), 3.09 (s, 2H), 2.72 (s, 2H), 2.04 (s, 3H), 1.54-1.58 (m, 4H); MS (ESI⁺) *m/z* 483 (M+H)⁺.

Example 111

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4'-oxo-4',7'-dihydro-5'*H*-spiro[cyclobutane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide

Example 111A

1-azaspiro[3.3]heptan-2-one

A solution of methylenecyclobutane (5 g, 73.4 mmol) in ether (30 mL) was cooled to -40 °C and treated dropwise with chlorosulfonyl isocyanate (3.3 mL, 38.0 mmol). The mixture was warmed to 10 °C, at which point an exothermic reaction and the formation of a precipitate was noted. The mixture was cooled to -20 °C and stirred at this temperature for 1 hour, then warmed to room temperature overnight. The mixture was then treated with saturated Na₂SO₃ solution (13 mL) and stirred vigorously at room temperature for 1 hour.

After this time, an additional portion of saturated Na₂SO₃ solution (13 mL) was added followed by solid NaHCO₃ to adjust the pH (~9). CH₂Cl₂ (70 mL) was added, and the phases were separated. The organic layer was dried over Na₂SO₄ and concentrated to afford the titled compound as a gold oil. ¹H NMR (300 MHz, CDCl₃) δ ppm 6.02 (br, 1H), 2.98 (m, 2H), 2.22-2.42 (m, 4H), 1.67-1.78 (m, 2H); MS (DCI⁺) *m/z* 112 (M+H)⁺.

Example 111B

tert-butyl 2-oxo-1-azaspiro[3.3]heptane-1-carboxylate

To a solution of di-*tert*-butyl dicarbonate (6.13 mL, 26.4 mmol), triethylamine (4.42 mL, 31.7 mmol), and 4-dimethylaminopyridine (0.323 g, 2.64 mmol) in CH₂Cl₂ (15 mL) was added a solution of Example 111A (2.936 g, 26.4 mmol) in CH₂Cl₂ (15 mL), and the reaction was stirred overnight at room temperature. After this time, the mixture was washed sequentially with 10% aqueous NH₄Cl solution, water, and saturated NaHCO₃ solution (10 mL each). The organic layer was dried over Na₂SO₄ and concentrated to afford the titled compound as a brown oil. ¹H NMR (300 MHz, CDCl₃) δ ppm 3.01 (s, 2H), 2.84-2.95 (m, 2H), 2.11-2.19 (m, 2H), 1.73-1.91 (m, 2H), 1.55 (s, 9H); MS (ESI⁺) *m/z* 228 (M+NH₄)⁺.

Example 111C

2-(1-(*tert*-butoxycarbonylamino)cyclobutyl)acetic acid

A solution of Example 111B (5.435 g, 25.7 mmol) in tetrahydrofuran (23 mL) was treated with 1 M aqueous lithium hydroxide solution (25.7 mL, 25.7 mmol), and the reaction mixture was stirred at room temperature for 2 hours. Ether (23 mL) and water (23 mL) were added with continued stirring at room temperature overnight. After this time, the phases were separated. The aqueous (lower) layer was washed twice with ether (50 mL each), then it was acidified to pH ~2 with 10% aqueous NaHSO₃ solution. The beige and orange precipitate which formed was collected by filtration, washed with additional water, and air-dried to afford the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 5.21 (br, 1H), 2.91 (m, 2H), 2.14-2.30 (m, 4H), 1.79-1.99 (m, 2H), 1.44 (s, 9H); MS (ESI⁺) *m/z* 252 (M+Na)⁺.

Example 111D

tert-butyl 6,8-dioxo-5-azaspiro[3.5]nonane-5-carboxylate

The product from Example 111C (2.0 g, 8.72 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.508g, 13.08 mmol), 4-dimethylaminopyridine (1.599 g,

13.08 mmol), and Meldrum's acid (1.257 g, 8.72 mmol) were mixed in CH₂Cl₂ (40 mL), and the mixture was stirred overnight at room temperature. After this time, the mixture was poured into a mixture of 1 N HCl (32 mL) and water (160 mL). The phases were separated, and the aqueous layer was extracted twice more with CH₂Cl₂ (40 mL each). The combined
5 organic phases were dried over Na₂SO₄ and concentrated in vacuo, then the residue was taken up in ethyl acetate (65 mL) and refluxed for 3 hours. After this time, the mixture was cooled to room temperature and concentrated to afford the titled compound as a yellow-orange waxy residue which was used directly in the next reaction without further purification.

10

Example 111E

ethyl 4'-oxo-5',7'-dihydro-4'*H*-spiro[cyclobutane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxylate

The titled compound was prepared according to the procedure of Example 110D substituting the product from Example 111D for the product from Example 110C. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.89 (s, 1H), 5.52 (br, 1H), 4.34 (q, J=7.1 Hz, 2H), 3.09 (s, 2H),
15 2.12-2.22 (m, 4H), 1.73-1.86 (m, 2H), 1.36 (t, J=7.1 Hz, 3H); MS (DCI⁺) *m/z* 250 (M+H)⁺.

Example 111F

4'-oxo-5',7'-dihydro-4'*H*-spiro[cyclobutane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxylic acid

The titled compound was prepared according to the procedure of Example 110E substituting the product from Example 111E for the product from Example 110D. ¹H NMR (300 MHz, CDCl₃) δ ppm 13.96 (s, 1H), 8.07 (s, 1H), 5.90 (br, 1H), 3.22 (s, 2H), 2.25-2.30
20 (m, 4H), 1.90-2.23 (m, 2H); MS (ESI⁺) *m/z* 222 (M+H)⁺.

Example 111G

25 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4'-oxo-4',7'-dihydro-5'*H*-spiro[cyclobutane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide

The titled compound was prepared according to the procedure for Example 8B substituting the product of Example 111F for the product of Example 8A. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.89 (s, 1H), 8.50 (s, 1H), 8.27 (m, 1H), 8.24 (m, 1H), 6.35 (m,
30 1H), 4.33 (q, J=7.1 Hz, 2H), 3.37-3.56 (m, 8H), 3.22 (s, 3H), 2.06-2.27 (m, 6H), 2.04 (s, 3H), 1.72-1.85 (m, 2H), 1.35 (t, J=7.1 Hz, 3H); MS (ESI⁺) *m/z* 468 (M+H)⁺.

Example 112

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4'-oxo-4',7'-dihydro-5'*H*-
spiro[cyclohexane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide

Example 112A

5 ethyl 3-(1-(2-methoxy-2-oxoethyl)cyclohexylamino)-3-oxopropanoate

A solution of methyl 2-(1-aminocyclohexyl)acetate hydrochloride (1 g, 4.81 mmol) and triethylamine (2.2 mL, 15.78 mmol) in CH₂Cl₂ (30 mL) at 0 °C was treated dropwise with ethyl malonyl chloride (0.59 mL, 4.61 mmol). After completion of the addition, the reaction mixture was brought to room temperature and stirred at this temperature for 1 hour.
10 The mixture was then poured into saturated NaHCO₃ solution (50 mL) and extracted with CH₂Cl₂ three times (30 mL each). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo to afford the titled compound as an orange oil which was used in the next reaction without further purification. ¹H NMR (300 MHz, CDCl₃) δ ppm 6.95 (br, 1H), 4.21 (m, 2H), 3.63 (s, 3H), 3.27 (s, 2H), 2.86 (s, 2H), 1.35-1.62 (m, 10H), 1.30 (m, 3H);
15 MS (DCI⁺) *m/z* 286 (M+H)⁺.

Example 112B

methyl 2,4-dioxo-1-azaspiro[5.5]undecane-3-carboxylate

Sodium metal (0.106 g, 4.61 mmol) was dissolved in dry methanol (5.6 mL). Then a
20 solution of Example 112A (1.315 g, 4.61 mmol) in dry toluene (17 mL) was added. The reaction mixture was refluxed for 1 hour, then cooled to room temperature and poured into water (50 mL). The mixture was washed three times with ether (20 mL each), and then the aqueous phase was acidified with 6 N HCl and concentrated in vacuo to dryness. The residue was further dried azeotropically with acetonitrile to afford the titled compound as a yellow
25 gel-like residue, which was carried on into the next reaction without further purification.

Example 112C

1-azaspiro[5.5]undecane-2,4-dione

The product from Example 112B (1.103 g, 4.61 mmol) was refluxed in acetonitrile
30 (18 mL) and water (2 mL) for 1 hour, then the mixture was cooled to room temperature and concentrated in vacuo. The residue was taken up in ethyl acetate-methanol (1:1, ~60 mL), and the white solid was removed by filtration. The yellow filtrate was concentrated in vacuo to afford the titled compound as a yellow residue, 1-azaspiro[5.5]undecane-2,4-dione (0.840

g, quantitative). ¹H NMR (300 MHz, CDCl₃) δ ppm 6.37 (br, 1H), 3.25 (s, 2H), 2.60 (s, 2H), 1.40-1.90 (m, 10H); MS (DCI⁺) *m/z* 182 (M+H)⁺.

Example 112D

5 ethyl 4'-oxo-5',7'-dihydro-4'*H*-spiro[cyclohexane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxylate

The titled compound was prepared according to the procedure for Example 110D substituting the product from Example 112C for the product from Example 110C. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.88 (s, 1H), 5.45 (br, 1H), 4.34 (q, J=7.1 Hz, 2H), 2.88 (s, 2H), 1.46-1.71 (m, 10H), 1.36 (t, J=7.1 Hz, 3H); MS (DCI⁺) *m/z* 278 (M+H)⁺.

10

Example 112E

4'-oxo-5',7'-dihydro-4'*H*-spiro[cyclohexane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxylic acid

The titled compound was prepared according to the procedure for Example 110E substituting the product from Example 112D for the product from Example 110D. ¹H NMR (300 MHz, CDCl₃) δ ppm 14.11 (br, 1H), 8.06 (s, 1H), 5.92 (br, 1H), 3.01 (s, 2H), 1.47-1.80 (m, 10H); MS (ESI⁺) *m/z* 250 (M+H)⁺.

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Example 112F

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4'-oxo-4',7'-dihydro-5'*H*-
20 spiro[cyclohexane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide

The titled compound was prepared according to the procedure of Example 8B substituting the product from Example 112E for the product from Example 8A. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.95 (s, 1H), 8.23-8.26 (m, 2H), 7.97 (s, 1H), 6.35 (m, 1H), 4.33 (q, J=7.1 Hz, 2H), 3.37-3.60 (m, 8H), 3.05 (s, 2H), 2.04 (s, 3H), 1.41-1.78 (m, 10H), 1.34 (t, J=7.1 Hz, 3H); MS (ESI⁺) *m/z* 496 (M+H)⁺.

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Example 113

1-acetyl-*N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4'-oxo-4',7'-dihydro-5'*H*-
30 spiro[azetidine-3,6'-furo[3,2-*c*]pyridine]-3'-carboxamide

30

Example 113A

tert-butyl 3-(2-methoxy-2-oxoethylidene)azetidine-1-carboxylate

tert-Butyl 3-oxoazetidine-1-carboxylate (5 g, 29.2 mmol) and methoxycarbonylmethylene-triphenylphosphorane (10.25 g, 30.7 mmol) were mixed in

toluene (15 mL), and the mixture was refluxed for 2.5 hour before being cooled to room temperature with continued stirring overnight. The precipitate was removed by filtration, and the filter pad was washed with ether. The combined filtrate and wash were concentrated, then the residue was chromatographed on silica gel (10 to 50% ethyl acetate-hexane, eluant) to afford the titled compound as a colorless oil, 5.532 g, (83%). ¹H NMR (300 MHz, CDCl₃) δ ppm 5.79 (m, 1H), 4.80-4.84 (m, 2H), 4.58-4.61 (m, 2H), 3.73 (s, 3H), 1.46 (s, 9H); MS (ESI⁺) *m/z* 228 (M+H)⁺.

Example 113B

tert-butyl 3-amino-3-(2-methoxy-2-oxoethyl)azetidine-1-carboxylate

The product from Example 113A (2 g, 8.80 mmol) was heated in ammonia (2 M in ethanol) (22 mL, 44 mmol) at 120 °C in a sealed tube overnight. After cooling to room temperature, the mixture was concentrated in vacuo, and then chromatographed on silica gel (50 to 100% ethyl acetate-hexane, eluant) to afford the titled compound as a colorless oil, 2.062 g (96%). ¹H NMR (300 MHz, CDCl₃) δ ppm 3.76-3.89 (m, 4H), 3.72 (s, 3H), 2.79 (s, 2H), 1.44 (s, 9H); MS (DCI⁺) *m/z* 245 (M+H)⁺.

Example 113C

tert-butyl 3-(3-ethoxy-3-oxopropanamido)-3-(2-methoxy-2-oxoethyl)azetidine-1-carboxylate

The titled compound was prepared according to the procedure for Example 112A substituting the product from Example 113B for methyl 2-(1-aminocyclohexyl)acetate hydrochloride. The material was used in the next reaction without further purification.

Example 113D

2-*tert*-butyl 7-methyl 6,8-dioxo-2,5-diazaspiro[3.5]nonane-2,7-dicarboxylate

The titled compound was prepared according to the procedure of Example 112B substituting the product from Example 113C for the product of Example 112A. ¹H NMR (300 MHz, CDCl₃) δ ppm 5.92 (br, 1H), 3.72 (s, 3H), 3.62-4.04 (m, 5H), 2.90 (m, 2H), 1.44 (s, 9H); MS (ESI⁺) *m/z* 313 (M+H)⁺.

Example 113E

tert-butyl 6,8-dioxo-2,5-diazaspiro[3.5]nonane-2-carboxylate

The titled compound was prepared according to the procedure of Example 112C substituting the product of Example 113D for the product of Example 112B. ¹H NMR (300

MHz, DMSO-*d*₆) δ ppm 3.57-3.95 (m, 6H), 3.06 (m, 2H), 1.37 (s, 9H); MS (ESI⁺) *m/z* 255 (M+H)⁺.

Example 113F

5 1-*tert*-butyl 3'-ethyl 4'-oxo-5',7'-dihydro-4'*H*-spiro[azetidine-3,6'-furo[3,2-*c*]pyridine]-1,3'-dicarboxylate

The product of Example 113E (1.897 g, 7.46 mmol) in ethanol (30 mL) was treated with sodium bicarbonate (6.14 g, 73.1 mmol) and then ethyl bromopyruvate (1.13 mL, 8.95 mmol). The reaction mixture was stirred overnight at room temperature. After this time, the mixture was diluted with ethanol (50 mL) and filtered. The filtrate was concentrated to a dark green oil, which was then taken up in CH₂Cl₂ (80 mL) and treated with triethylamine (12 mL, 86.4 mmol). The mixture was cooled to 0 °C, and then treated dropwise with methanesulfonyl chloride (4 mL, 51.6 mmol). After the addition was complete, the reaction mixture stirred at 0 °C for 1 hour, and then it was poured into water (100 mL). The mixture was extracted with CH₂Cl₂ (3 × 50 mL), then the extracts were dried over Na₂SO₄ and concentrated in vacuo. Chromatography on silica gel (40 to 100% ethyl acetate-hexane, eluant) afforded the titled compound as a tan solid, 0.296 g (11%). ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 8.29 (s, 1H), 8.19 (br, 1H), 4.21 (q, J=7.2 Hz, 2H), 3.88 (m, 4H), 3.26 (s, 2H), 1.38 (s, 9%), 1.25 (t, J=7.1 Hz, 3H); MS (ESI⁺) *m/z* 351 (M+H)⁺.

Example 113G

1-(*tert*-butoxycarbonyl)-4'-oxo-5',7'-dihydro-4'*H*-spiro[azetidine-3,6'-furo[3,2-*c*]pyridine]-3'-carboxylic acid

The titled compound was prepared according to the procedure of Example 110E substituting the product of Example 113F for the product of Example 110D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 14.48 (s, 1H), 9.36 (s, 1H), 8.47 (s, 1H), 3.96 (m, 4H), 3.46 (m, 2H), 1.39 (s, 9H); MS (ESI⁺) *m/z* 323 (M+H)⁺.

Example 113H

30 *tert*-butyl 3'-{[6-(4-acetyl)piperazin-1-yl]-2-ethoxypyridin-3-yl}carbamoyl}-4'-oxo-4',7'-dihydro-1*H*,5'*H*-spiro[azetidine-3,6'-furo[3,2-*c*]pyridine]-1-carboxylate

The titled compound was prepared according to the procedure of Example 8B substituting the product of Example of Example 113G for the product of Example 8A. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.76 (s, 1H), 8.79 (s, 1H), 8.26-8.32 (m, 2H), 6.35 (m,

1H), 4.33 (q, J=7.1 Hz, 2H), 3.93 (m, 4H), 3.40-3.55 (m, 10H), 2.04 (s, 3H), 1.39 (s, 9H), 1.36 (t, J=6.8 Hz, 3H); MS (ESI⁺) *m/z* 569 (M+H)⁺.

Example 113I

5 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4'-oxo-4',7'-dihydro-5'*H*-spiro[azetidine-3,6'-furo[3,2-*c*]pyridine]-3'-carboxamide trifluoroacetate

The product of Example 113H (0.040 g, 0.070 mmol) was stirred in trifluoroacetic acid (2 mL) at room temperature for 1 hour. After this time, the mixture was concentrated in vacuo, and the residue was dried under vacuum at 50 °C for 1 hour to provide the titled
10 compound as a brown solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.64 (s, 1H), 8.71-8.96 (m, 3H), 8.29-8.37 (m, 2H), 6.35 (m, 1H), 4.34 (m, 2H), 3.38-3.78 (m, 14H), 2.04 (s, 3H), 1.36 (m, 3H); MS (ESI⁺) *m/z* 469 (M+H)⁺.

Example 113J

15 1-acetyl-*N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4'-oxo-4',7'-dihydro-5'*H*-spiro[azetidine-3,6'-furo[3,2-*c*]pyridine]-3'-carboxamide

A mixture of Example 113I (29 mg, 0.049 mmol), acetic acid (0.014 mL, 0.245 mmol), *N,N*-diisopropylethylamine (0.17 mL, 0.980 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (12 mg, 0.064 mmol), and 1-hydroxybenzotriazole (7.5 mg,
20 0.049 mmol) in *N,N*-dimethylformamide (2 mL) was stirred overnight at room temperature. The mixture was then diluted with ethyl acetate (10 mL) and washed with water (4 × 2 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo, and the residue was triturated with ethyl acetate to afford the titled compound as a tan solid, 3.5 mg (14%). ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.76 (s, 1H), 8.84 (s, 1H), 8.27-8.33 (m, 2H), 6.35 (m,
25 1H), 4.33 (m, 2H), 3.33-3.57 (m, 14H), 2.04 (s, 3H), 1.77 (s, 3H), 1.36 (m, 3H); MS (ESI⁺) *m/z* 511 (M+H)⁺.

Example 114

30 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4-oxo-4,7-dihydro-5*H*-spiro[furo[3,2-*c*]pyridine-6,3'-oxetane]-3-carboxamide

Example 114A

methyl 2-(oxetan-3-ylidene)acetate

The titled compound was prepared according to the procedure of Example 113A substituting oxetan-3-one for *tert*-butyl 3-oxoazetidine-1-carboxylate. ¹H NMR (300 MHz, CDCl₃) δ ppm 5.65 (m, 1H), 5.51 (m, 2H), 5.31 (m, 2H), 3.72 (s, 3H); MS (DCI⁺) *m/z* 129 (M+H)⁺.

5

Example 114B

methyl 2-(3-aminooxetan-3-yl)acetate

The titled compound was prepared according to the procedure of Example 113B substituting the product of Example 114A for the product of Example 113A. ¹H NMR (300 MHz, CDCl₃) δ ppm 4.50-4.57 (m, 4H), 3.72 (s, 3H), 2.90 (s, 2H); MS (DCI⁺) *m/z* 146 (M+H)⁺.

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Example 114C

ethyl 3-(3-(2-methoxy-2-oxoethyl)oxetan-3-ylamino)-3-oxopropanoate

The titled compound was prepared according to the procedure for Example 112A substituting the product from Example 114B for methyl 2-(1-aminocyclohexyl)acetate hydrochloride. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.74 (br, 1H), 4.57-4.77 (m, 4H), 4.21 (m, 2H), 3.29 (s, 2H), 2.88 (s, 2H), 1.29 (m, 3H); MS (ESI⁺) *m/z* 260 (M+H)⁺.

15

20

Example 114D

methyl 6,8-dioxo-2-oxa-5-azaspiro[3.5]nonane-7-carboxylate

The titled compound was prepared according to the procedure of Example 112B substituting the product from Example 114C for the product of Example 112A. The compound was used in the next reaction without further purification.

25

Example 114E

2-oxa-5-azaspiro[3.5]nonane-6,8-dione

The titled compound was prepared according to the procedure of Example 112C substituting the product of Example 114D for the product of Example 112B. ¹H NMR (300 MHz, CDCl₃) δ ppm 4.61-4.71 (m, 4H), 3.25 (s, 2H), 3.07 (s, 2H); MS (DCI⁺) *m/z* 173 (M+NH₄).

30

Example 114F

ethyl 4-oxo-5,7-dihydro-4*H*-spiro[furo[3,2-*c*]pyridine-6,3'-oxetane]-3-carboxylate

The titled compound was prepared according to the procedure of Example 113F substituting the product from Example 114E for the product from Example 113E. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.92 (s, 1H), 5.83 (br, 1H), 4.57-4.68 (m, 4H), 4.35 (m, 2H), 3.41 (s, 2H), 1.36 (m, 3H); MS (ESI⁺) *m/z* 252 (M+H)⁺.

5

Example 114G

4-oxo-5,7-dihydro-4*H*-spiro[furo[3,2-*c*]pyridine-6,3'-oxetane]-3-carboxylic acid

The titled compound was prepared according to the procedure of Example 110E substituting the product of Example 114F for the product of Example 110D. ¹H NMR (300 MHz, CDCl₃) δ ppm 8.11 (s, 1H), 4.65-4.74 (m, 4H), 3.53 (s, 2H); MS (ESI⁺) *m/z* 224 (M+H)⁺.

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Example 114H

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4-oxo-4,7-dihydro-5*H*-spiro[furo[3,2-*c*]pyridine-6,3'-oxetane]-3-carboxamide

15

The titled compound was prepared according to the procedure of Example 8B substituting the product of Example of Example 114G for the product of Example 8A. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.77 (s, 1H), 9.00 (s, 1H), 8.26-8.32 (m, 2H), 6.35 (m, 1H), 4.50-4.66 (m, 4H), 4.35 (m, 2H), 3.38-3.57 (m, 10H), 2.04 (s, 3H), 1.36 (m, 3H); MS (ESI⁺) *m/z* 470 (M+H)⁺.

20

Example 115

(6*R*)-*N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-6-[(1*R*)-1-hydroxyethyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

25

Example 115A

(*R*)-*tert*-butyl 2-((*R*)-1-(benzyloxy)ethyl)-4,6-dioxopiperidine-1-carboxylate

(3*R*,4*R*)-4-(Benzyloxy)-3-(*tert*-butoxycarbonylamino)pentanoic acid (Aldrich; 1 g, 3.09 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (0.490 g, 3.40 mmol), and 4-dimethylaminopyridine (0.567 g, 4.64 mmol) were mixed in CH₂Cl₂ (26 mL) and cooled to 0 °C. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.711 g, 3.71 mmol) was added, and the reaction was stirred overnight at room temperature. The mixture was then washed with 5% aqueous sodium bisulfate (4 × 10 mL), and the organic layer was dried over Na₂SO₄ and concentrated. The crude material was taken up in ethyl acetate (25 mL) and

30

refluxed for 4 hours, then cooled to room temperature and concentrated in vacuo to afford the titled compound as a yellow oil, 1.2 g (quantitative). ¹H NMR (300 MHz, CDCl₃) δ ppm 7.21-7.37 (m, 5H), 4.74 (m, 1H), 4.26-4.52 (m, 2H), 3.58 (m, 1H), 3.10-3.40 (m, 2H), 2.56-2.75 (m, 2H), 1.54 (s, 9H), 1.22 (d, J=6.3 Hz, 3H); MS (ESI⁻) *m/z* 347 (M-H).

5

Example 115B

(R)-5-*tert*-butyl 3-ethyl 6-((R)-1-(benzyloxy)ethyl)-4-oxo-6,7-dihydrofuro[3,2-*c*]pyridine-3,5(4H)-dicarboxylate

The titled compound was prepared according to the procedure of Example 113F substituting the product from Example 115A for the product from Example 113E. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 8.26 (s, 1H), 7.08-7.33 (m, 5H), 4.77 (m, 1H), 4.27-4.50 (m, 2H), 4.23 (m, 2H), 3.65 (m, 1H), 3.41 (m, 1H), 2.97 (m, 1H), 1.44 (s, 9H), 1.26 (m, 3H), 1.07 (d, J=6.3 Hz, 3H); MS (ESI⁺) *m/z* 444 (M+H)⁺.

15

Example 115C

(R)-6-((R)-1-(benzyloxy)ethyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxylic acid

The titled compound was prepared according to the procedure of Example 110E substituting the product of Example 115B for the product of Example 110D. ¹H NMR (300 MHz, CDCl₃) δ ppm 8.05 (s, 1H), 7.25-7.47 (m, 5H), 4.41-4.76 (m, 2H), 3.87 (m, 1H), 3.62 (m, 1H), 3.35 (m, 1H), 2.92 (m, 1H), 1.31 (d, J=6.1 Hz, 3H); MS (ESI⁺) *m/z* 316 (M+H)⁺.

20

Example 115D

(6*R*)-*N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-6-[(1*R*)-1-(benzyloxy)ethyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

25

The titled compound was prepared according to the procedure of Example 8B substituting the product of Example of Example 115C for the product of Example 8A. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.91 (s, 1H), 8.24-8.27 (m, 2H), 7.83 (m, 1H), 7.23-7.34 (m, 5H), 6.35 (m, 1H), 4.44-4.59 (m, 2H), 4.33 (q, J=6.8 Hz, 2H), 3.90 (m, 1H), 3.67 (m, 1H), 3.41-3.56 (m, 8H), 2.91-3.16 (m, 2H), 2.04 (s, 3H), 1.34 (t, J=7.1 Hz, 3H), 1.16 (d, J=6.1 Hz, 3H); MS (ESI⁺) *m/z* 562 (M+H)⁺.

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Example 115E

(6*R*)-*N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-6-[(1*R*)-1-hydroxyethyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The product from Example 115D (0.010 g, 0.018 mmol) in tetrahydrofuran (1 mL) was hydrogenated (balloon) over 10% palladium on carbon at room temperature overnight. After this time, the catalyst was removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified by reverse-phase HPLC (Phenomenex® Luna® C8(2) 5 µm 100Å AXIA™ column (30 mm × 75 mm); acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) eluant; 20 to 50% (A), gradient; flow rate = 50 mL/minute) to afford the trifluoroacetate salt of the titled compound as an off-white solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.92 (s, 1H), 8.24-8.27 (m, 2H), 7.57 (s, 1H), 6.34 (s, 1H), 4.33 (q, J=7.1 Hz, 2H), 3.53-3.75 (m, 10H), 2.84-3.09 (m, 2H), 2.04 (s, 3H), 1.35 (t, J=7.1 Hz, 3H), 1.07 (d, J=5.7 Hz, 3H); MS (ESI⁺) *m/z* 472 (M+H)⁺.

Example 116

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5'-(2-hydroxyethyl)-4'-oxo-4',7'-dihydro-5'*H*-spiro[cyclobutane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide

Example 116A

5'-(2-(benzyloxy)ethyl)-4'-oxo-5',7'-dihydro-4'*H*-spiro[cyclobutane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxylic acid

A solution of the product of Example 111F (0.150 g, 0.678 mmol) in *N,N*-dimethylformamide (2 mL) was treated with 60% sodium hydride (0.060 g, 1.492 mmol) at room temperature. The mixture stirred at room temperature for 15 minutes and was then treated with a solution of ((2-bromoethoxy)methyl)benzene (0.438 g, 2.034 mmol) in *N,N*-dimethylformamide (0.5 mL). The reaction mixture was stirred overnight at room temperature. After this time, the mixture was partitioned between ether (20 mL) and 0.5 N HCl (10 mL). The phases were separated, and the ether layer was washed with additional 0.5 N HCl (2 × 5 mL) and then with brine (5 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo, and the residue was chromatographed on silica gel (0 to 10% ethyl acetate-CH₂Cl₂, eluant) to afford the titled compound as a colorless oil, 0.099 g (41%). ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 8.40 (m, 1H), 7.25-7.34 (m, 5H), 4.50 (s, 2H), 4.02 (m, 2H), 3.86 (m, 2H), 3.55 (m, 2H), 1.70-1.99 (m, 6H); MS (ESI⁺) *m/z* 356 (M+H)⁺.

Example 116B

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5'-[2-(benzyloxy)ethyl]-4'-oxo-4',7'-dihydro-5'*H*-spiro[cyclobutane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide

The titled compound was prepared according to the procedure of Example 8B substituting the product of Example of Example 116A for the product of Example 8A. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.98 (s, 1H), 8.28-8.35 (m, 2H), 7.27-7.34 (m, 5H), 6.33 (m, 1H), 4.53 (s, 2H), 4.30 (q, J=6.8 Hz, 2H), 3.87 (m, 2H), 3.23-3.60 (m, 12H), 2.04 (s, 3H), 1.74-2.05 (m, 6H), 1.38 (t, J=7.2 Hz, 3H); MS (ESI⁺) *m/z* 602 (M+H)⁺.

Example 116C

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5'-(2-hydroxyethyl)-4'-oxo-4',7'-dihydro-5'*H*-spiro[cyclobutane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide

The titled compound was prepared according to the procedure of Example 9 substituting the product of Example 116B for the product of Example 8B. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 12.00 (s, 1H), 8.28-8.31 (m, 2H), 6.33 (m, 1H), 4.78 (m, 1H), 4.31 (q, J=7.2 Hz, 2H), 3.71 (m, 2H), 3.37-3.55 (m, 12H), 2.04 (s, 3H), 1.72-2.06 (m, 6H), 1.39 (t, J=7.1 Hz, 3H); MS (ESI⁺) *m/z* 512 (M+H)⁺.

Example 117

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4'-oxo-4',7'-dihydro-5'*H*-spiro[cyclopropane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide

Example 117A

tert-butyl 1-(bromomethyl)cyclopropylcarbamate

A mixture of *tert*-butyl 1-(hydroxymethyl)cyclopropylcarbamate (CAS# 107017-73-2; 5g, 26.7 mmol), triphenylphosphine (9.5 g, 36.2 mmol), and carbon tetrabromide (11.9g, 35.9 mmol) in ether (120 mL) was stirred at room temperature for 24 hours. After this time, the mixture was filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (0 to 10% ethyl acetate-CH₂Cl₂, eluant) to afford the titled compound as a white solid, 3.594 g (54%). ¹H NMR (300 MHz, CDCl₃) δ ppm 5.11 (br, 1H), 3.58 (s, 2H), 1.45 (s, 9H), 1.07 (m, 2H), 0.91 (m, 2H); MS (DCI⁺) *m/z* 250/252 (M+H)⁺; ⁷⁹Br/⁸¹Br).

Example 117B

tert-butyl 1-(cyanomethyl)cyclopropylcarbamate

The product from Example 117A (3.594 g, 14.37 mmol), sodium cyanide (3.45 g, 70.4 mmol), and potassium iodide (0.286 g, 1.724 mmol) were stirred in dimethyl sulfoxide (33 mL) at room temperature for 72 hours. After this time, the mixture was poured into 10% aqueous Na₂CO₃ solution (60 mL) containing some NaCl. The mixture was extracted with ether (3 × 150 mL), then the combined ethereal extracts were washed with water (25 mL) and brine (25 mL), dried over Na₂SO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (20 to 100% ethyl acetate-hexane, eluant) to afford the titled compound as a white solid, 1.737 g (62%). ¹H NMR (300 MHz, CDCl₃) δ ppm 5.13 (br, 1H), 2.72 (s, 2H), 1.45 (s, 9H), 0.93 (m, 2H), 0.87 (m, 2H); MS (DCI⁺) *m/z* 197 (M+H)⁺.

10

Example 117C

methyl 2-(1-aminocyclopropyl)acetate

A solution of the product from Example 117B (4.049 g, 20.63 mmol) in methanol (75 mL) was cooled to 0 °C, then HCl gas was bubbled through the solution at a moderately strong rate for 15 minutes. The mixture was allowed to stir while slowly warming to ambient temperature overnight. After this time, volatiles were removed in vacuo. The residue was treated with a saturated solution of Na₂CO₃ (25 mL) and was extracted three times with CH₂Cl₂ (30 mL each). The combined extracts were dried over Na₂SO₄ and concentrated in vacuo, then the residue was chromatographed on silica gel (1 to 10% methanol-CH₂Cl₂, eluant) to yield the titled compound as a pale yellow oil (0.971 g, 36%). ¹H NMR (300 MHz, CDCl₃) δ ppm 3.72 (s, 3H), 2.43 (s, 2H), 0.68 (m, 2H), 0.51 (m, 2H); MS (DCI⁺) *m/z* 130 (M+H)⁺.

20

Example 117D

ethyl 3-(1-(2-methoxy-2-oxoethyl)cyclopropylamino)-3-oxopropanoate

The titled compound was prepared according to the procedure for Example 112A substituting the product from Example 117C for methyl 2-(1-aminocyclohexyl)acetate hydrochloride. ¹H NMR (300 MHz, CDCl₃) δ ppm 4.19 (q, J=7.2 Hz, 2H), 3.69 (s, 3H), 3.23 (s, 2H), 2.62 (s, 2H), 1.28 (t, J=7.1 Hz, 3H), 0.88 (m, 2H), 0.79 (m, 2H); MS (ESI⁺) *m/z* 244 (M+H)⁺.

30

Example 117E

methyl 5,7-dioxo-4-azaspiro[2.5]octane-6-carboxylate

The titled compound was prepared according to the procedure of Example 112B substituting the product from Example 117D for the product of Example 112A. ¹H NMR (300 MHz, CDCl₃) δ ppm 8.67 (br, 1H), 3.96 (m, 1H), 3.92 (s, 3H), 2.60-2.66 (m, 2H), 0.80 (m, 2H), 0.77 (m, 2H); MS (DCI⁺) *m/z* 198 (M+H)⁺.

5

Example 117F

4-azaspiro[2.5]octane-5,7-dione

The titled compound was prepared according to the procedure of Example 112C substituting the product of Example 117E for the product of Example 112B. ¹H NMR (300 MHz, CDCl₃) δ ppm 8.66 (br, 1H), 3.43 (s, 2H), 2.52 (s, 2H), 0.96 (m, 2H), 0.85 (m, 2H); MS (DCI⁺) *m/z* 140 (M+H)⁺.

10

Example 117G

ethyl 4'-oxo-5',7'-dihydro-4'*H*-spiro[cyclopropane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxylate

The titled compound was prepared according to the procedure of Example 113F substituting the product from Example 117F for the product from Example 113E. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.90 (s, 1H), 5.16 (br, 1H), 4.35 (q, J=7.1 Hz, 2H), 2.90 (s, 2H), 1.36 (t, J=7.1 Hz, 3H), 0.81-0.85 (m, 4H); MS (ESI⁺) *m/z* 236 (M+H)⁺.

15

Example 117H

4'-oxo-5',7'-dihydro-4'*H*-spiro[cyclopropane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxylic acid

The titled compound was prepared according to the procedure of Example 110E substituting the product of Example 117G for the product of Example 110D. ¹H NMR (300 MHz, CDCl₃) δ ppm 13.98 (s, 1H), 8.10 (s, 1H), 5.57 (br, 1H), 3.03 (s, 2H), 0.92-0.99 (m, 4H); MS (ESI⁺) *m/z* 208 (M+H)⁺.

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Example 117I

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4'-oxo-4',7'-dihydro-5'*H*-
spiro[cyclopropane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide

The titled compound was prepared according to the procedure of Example 8B substituting the product of Example of Example 117H for the product of Example 8A. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.92 (s, 1H), 8.20-8.29 (m, 3H), 6.35 (m, 1H), 4.33 (q, J=6.8 Hz, 2H), 3.37-3.58 (m, 8H), 3.03 (s, 2H), 2.04 (s, 3H), 1.34 (t, J=7.1 Hz, 3H), 0.87 (m, 2H), 0.79 (m, 2H); MS (ESI⁺) *m/z* 454 (M+H)⁺.

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Example 118

N-{6-[4-(*N*-cyano-*N*-methylcarbamimidoyl)piperazin-1-yl]-2-ethoxypyridin-3-yl}-4'-oxo-4',7'-dihydro-5'*H*-spiro[cyclobutane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide

5

Example 118A

tert-butyl 4-(6-ethoxy-5-{[(4'-oxo-4',7'-dihydro-5'*H*-spiro[cyclobutane-1,6'-furo[3,2-*c*]pyridin]-3'-yl)carbonyl]amino}pyridin-2-yl)piperazine-1-carboxylate

The titled compound was prepared according to the procedure for Example 8B

10 substituting the product of Example 92C for 1-(4-(5-amino-6-ethoxypyridin-2-yl)piperazin-1-yl)ethanone and the product of Example 111F for the product from Example 8A. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.88 (s, 1H), 8.50 (s, 1H), 8.23-8.28 (m, 2H), 6.33 (m, 1H), 4.33 (q, J=7.1 Hz, 2H), 3.42 (m, 8H), 3.22 (s, 2H), 2.05-2.27 (m, 4H), 1.70-1.85 (m, 2H), 1.42 (s, 9H), 1.34 (t, J=7.2 Hz, 3H); MS (ESI⁺) *m/z* 526 (M+H)⁺.

15

Example 118B

N-[2-ethoxy-6-(piperazin-1-yl)pyridin-3-yl]-4'-oxo-4',7'-dihydro-5'*H*-spiro[cyclobutane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide

The titled compound was prepared as the trifluoroacetate according to the procedure

20 of Example 93A substituting the product of Example 118A for the product of Example 92D. The resulting trifluoroacetate salt was used in the next reaction without further purification.

Example 118C

N-{6-[4-(*N*-cyano-*N*-methylcarbamimidoyl)piperazin-1-yl]-2-ethoxypyridin-3-yl}-4'-oxo-4',7'-dihydro-5'*H*-spiro[cyclobutane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide

25

The titled compound was prepared according to the procedure of Example 93B

substituting the product of Example 118B for the product of Example 93A. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.90 (s, 1H), 8.52 (s, 1H), 8.26 (m, 2H), 7.33 (m, 1H), 6.36 (m, 1H), 4.34 (q, J=7.1 Hz, 2H), 3.47-3.55 (m, 8H), 3.22 (s, 2H), 2.87 (d, J=4.3 HZ, 3H), 2.22 (m, 2H), 2.08 (m, 2H), 1.79 (m, 2H), 1.35 (t, J=6.7 Hz, 3H); MS (ESI⁺) *m/z* 507 (M+H)⁺.

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Example 119

N-[6-(4-acetyl)piperazin-1-yl]-2-ethoxypyridin-3-yl]-5-(2,3-dihydroxypropyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 119A

5-allyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxylic acid

A solution of the product from Example 120A (1 g, 4.78 mmol) in *N,N*-dimethylformamide (15 mL) was treated with 60% dispersion of sodium hydride in mineral oil (0.574 g, 14.34 mmol), and the mixture was stirred at room temperature for 15 minutes. It was then treated with allyl bromide (1.24 mL, 14.34 mmol), stirred at room temperature for 15 minutes, then heated to 50 °C overnight. The mixture was cooled to room temperature, treated with 1 M NaOH (15 mL), and stirred at room temperature for 30 minutes. It was diluted with water (60 mL) and washed with ether (2 × 50 mL). The aqueous (basic) layer was acidified with concentrated HCl and a white solid formed. The solid was collected by filtration, washed with ether, and dried under vacuum (ambient temperature) to afford the titled compound, 646 mg (54%). ¹H NMR (300 MHz, CDCl₃) δ ppm 14.68 (s, 1H), 8.05 (s, 1H), 5.89 (m, 1H), 5.19-5.27 (m, 2H), 4.19 (m, 2H), 3.01 (s, 2H), 1.48 (s, 6H); MS (ESI⁺) *m/z* 250 (M+H)⁺.

Example 119B

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-allyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared according to the procedure of Example 8B substituting the product of Example 119A for the product of Example 8A. ¹H NMR (300 MHz, CDCl₃) δ ppm 12.10 (s, 1H), 8.56 (m, 1H), 8.07 (s, 1H), 6.18 (m, 1H), 5.94 (m, 1H), 5.14-5.28 (m, 2H), 4.40 (q, J=7.2 Hz, 2H), 4.18 (m, 2H), 3.73 (m, 2H), 3.42-3.59 (m, 6H), 2.95 (s, 2H), 2.14 (s, 3H), 1.49 (t, J=7.1 Hz, 3H), 1.44 (s, 6H); MS (ESI⁺) 496 (M+H)⁺.

Example 119C

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2,3-dihydroxypropyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

A solution of the product of Example 119B (0.269 g, 0.543 mmol) in acetonitrile (20 mL) and *tert*-butyl alcohol (5 mL) was treated with 4-methylmorpholine *N*-oxide (50% weight solution in water) (0.16 mL, 0.772 mmol) and then osmium tetroxide (4% weight solution in water) (0.05 mL, 7.87 μmol). The reaction mixture was stirred overnight at room temperature. After this time, the mixture was treated with Na₂SO₃ (200 mg), stirred for 1 hour, and then filtered through a pad of Na₂SO₃. The filtrate was concentrated in vacuo to

yield a brown oil, which was purified by reverse-phase HPLC (Phenomenex® Luna® C8(2) 5 μ m 100Å AXIA™ column (30 mm $\times$ 75 mm); acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) eluant; 20 to 50% (A), gradient; flow rate = 50 mL/minute) to afford the titled compound (0.119 g, 41%). ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 12.09 (s, 1H), 8.37 (m, 1H), 8.28 (s, 1H), 6.33 (m, 1H), 4.32 (q, J=7.1 Hz, 2H), 3.22-3.56 (m, 13H), 3.09 (m, 2H), 2.04 (s, 3H), 1.45 (s, 3H), 1.38 (t, J=7.1 Hz, 3H), 1.35 (s, 3H); MS (ESI⁺) *m/z* 530 (M+H)⁺.

Example 120

10 *N*-[2-methoxy-4-(piperazin-1-yl)phenyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 120A

6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxylic acid

15 To a suspension of 6,6-dimethylpiperidine-2,4-dione (CAS#: 5239-39-4, 2g, 14.17 mmol) in water (10 mL) was added KOH (1.033 g, 18.42 mmol). The mixture became homogeneous and was cooled in an ice bath before a solution of 3-bromo-2-oxopropanoic acid (2.84 g, 17.00 mmol) in methanol (10 mL) was added dropwise. The mixture was stirred for about 2 hours and concentrated under reduced pressure. Water (20 mL) was added, and the mixture was acidified with 37% HCl and heated to reflux for 2 hours. The mixture was cooled (with stirring) and diluted with ether. The solid was collected by filtration, washed with H₂O and ether, and dried. The product 6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxylic acid (955mg, 4.57 mmol, 32.2% yield) was obtained as a brownish solid.

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Example 120B

tert-butyl 4-(4-{{[(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino}-3-methoxyphenyl)piperazine-1-carboxylate

The titled compound was prepared using the procedure described for Example 5 substituting Example 120A for Example 1E.

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Example 120C

N-[2-methoxy-4-(piperazin-1-yl)phenyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 6 substituting Example 120B for Example 5. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.65 (s, 1H), 8.33 – 8.18 (m, 1H), 8.10 (s, 1H), 6.67 – 6.36 (m, 2H), 5.32 (s, 1H), 3.91 (s, 3H), 3.13 (dd, *J* = 6.5, 3.1 Hz, 4H), 3.04 (dd, *J* = 6.5, 3.2 Hz, 4H), 2.94 (s, 2H), 1.43 (s, 6H); MS (DCI) *m/z* 499 (M+H)⁺.

Example 121

N-{2-methoxy-6-[4-(morpholin-4-ylcarbonyl)piperazin-1-yl]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 121A

6-chloro-2-methoxy-3-nitropyridine

To a solution of methanol (1.929 mL, 47.7 mmol) in xylene (200 mL) was added NaH (2.479 g, 60% dispersed in oil, 62.0 mmol) and the mixture was stirred at 0 °C for 30 minutes. Then, 2,6-dichloro-3-nitropyridine (10 g, 92% 47.7 mmol) in xylene (200 mL) was added over 30 minutes. The mixture was stirred at ambient temperature for 16 hours. The mixture was then diluted with ether (200 mL), quenched with H₂O, and partitioned. The aqueous layer was extracted with additional ether. The organic washes were combined, washed with brine, dried (MgSO₄) and concentrated under reduced pressure. The residue was passed through a short silica gel pad to provide the titled compound.

Example 121B

tert-butyl 4-(6-methoxy-5-nitropyridin-2-yl)piperazine-1-carboxylate

To a solution of the product from Example 121A, 6-chloro-2-methoxy-3-nitropyridine, (8.86 g, 47 mmol) and *tert*-butyl piperazine-1-carboxylate (11.38 g, 61.1 mmol) in *N,N*-dimethylformamide (60 mL) was added triethylamine (9.17 mL, 65.8 mmol). The mixture was heated to 50 °C for 1 hour and then cooled to room temperature. The reaction mixture was diluted with ether (150 mL) and water (100 mL), and the product precipitated as a yellow solid. The product was collected by filtration and washed with water and small amount of ether to provide the titled compound.

Example 121C

tert-butyl 4-(5-amino-6-methoxypyridin-2-yl)piperazine-1-carboxylate

To a solution of Example 121B, *tert*-butyl 4-(6-methoxy-5-nitropyridin-2-yl)piperazine-1-carboxylate (21.9 g, 64.7 mmol) in methanol (300 mL) under a nitrogen atmosphere was added Raney®-nickel (~3.8 g, Aldrich, W.R. Grace and Co. Raney® 2800, slurry in H₂O). The atmosphere in the reaction vessel was exchanged with hydrogen, and the reaction was stirred at ambient temperature for 5 hours. The atmosphere was exchanged with nitrogen and the mixture was filtered and washed with methanol. The filtrate was concentrated under reduced pressure to provide the titled compound.

Example 121D

tert-butyl 4-(5-{[(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino}-6-methoxypyridin-2-yl)piperazine-1-carboxylate

The titled compound was prepared using the procedure described for Example 5 substituting Example 120A for Example 1E, and substituting Example 121C for *tert*-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate.

Example 121E

N-[2-methoxy-6-(piperazin-1-yl)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 6 substituting Example 121D for Example 5.

Example 121F

N-{2-methoxy-6-[4-(morpholin-4-ylcarbonyl)piperazin-1-yl]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 18 substituting Example 121E for Example 6, and substituting 4-morpholinecarbonyl chloride for acetyl chloride. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.80 – 11.57 (m, 1H), 8.59 – 8.42 (m, 1H), 8.19 – 7.96 (m, 1H), 6.48 – 6.18 (m, 1H), 5.50 – 5.25 (m, 1H), 4.00 (s, 3H), 3.76 – 3.65 (m, 4H), 3.48 (dt, *J* = 14.7, 4.5 Hz, 8H), 3.35 – 3.28 (m, 4H), 2.94 (d, *J* = 8.7 Hz, 2H), 1.44 (s, 6H); MS (ESI) *m/z* 513 (M+H)⁺.

Example 122

N-[6-(4-acetylpiperazin-1-yl)-2-methoxypyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 18 substituting Example 121E for Example 6. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.84 – 11.63 (m, 1H), 8.62 – 8.44 (m, 1H), 8.22 – 8.01 (m, 1H), 6.55 – 6.35 (m, 1H), 5.48 – 5.32 (m, 1H), 4.01 (d, *J* = 1.5 Hz, 3H), 3.89 – 3.76 (m, 2H), 3.72 – 3.63 (m, 2H), 3.49 (ddd, *J* = 14.0, 9.3, 3.2 Hz, 3H), 2.95 (s, 2H), 2.15 (d, *J* = 3.8 Hz, 3H), 1.44 (s, 5H); MS (DCI) *m/z* 459 (M+NH₄)⁺.

Example 123

N-{2-methoxy-6-[4-(pyrrolidin-1-ylcarbonyl)piperazin-1-yl]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 18 substituting Example 121E for Example 6 and substituting 1-pyrrolidinecarbonyl chloride for acetyl chloride. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.77 – 11.56 (m, 1H), 8.59 – 8.37 (m, 1H), 8.17 – 7.99 (m, 1H), 6.34 – 6.09 (m, 1H), 5.42 – 5.33 (m, 1H), 4.00 (s, 3H), 3.57 – 3.35 (m, 8H), 2.95 (s, 2H), 1.89 – 1.76 (m, 4H), 1.43 (s, 6H); MS (DCI) *m/z* 514 (M+NH₄)⁺.

Example 124

N-[2-methoxy-4-(piperazin-1-yl)phenyl]-6-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 124A

6-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxylic acid

The titled compound was prepared using the procedure described for Example 120A substituting 6-methylpiperidine-2,4-dione (CAS#: 118263-99-3) for 6,6-dimethylpiperidine-2,4-dione.

Example 124B

tert-butyl 4-(3-methoxy-4-{[(6-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino}phenyl)piperazine-1-carboxylate

The titled compound was prepared using the procedure described for Example 5 substituting Example 124A for Example 1E.

Example 124C

N-[2-methoxy-4-(piperazin-1-yl)phenyl]-6-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 6 substituting Example 124B for Example 5. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.89 (s, 1H), 8.24 (s, 1H), 8.07 (s, 1H), 7.91 (dd, *J* = 14.0, 8.9 Hz, 1H), 6.59 (d, *J* = 2.5 Hz, 1H), 6.45 (dd, *J* = 8.9, 2.6 Hz, 1H), 4.01 – 3.85 (m, 1H), 3.79 (s, 3H), 3.14 – 3.04 (m, 1H), 3.03 (dd, *J* = 5.9, 4.0 Hz, 4H), 2.86 – 2.79 (m, 4H), 2.74 (dd, *J* = 16.8, 10.4 Hz, 1H), 1.27 (t, *J* = 6.4 Hz, 3H); MS (DCI) *m/z* 385 (M+H)⁺.

Example 125

N-{2-methoxy-4-[4-(methylsulfonyl)piperazin-1-yl]phenyl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 18 substituting Example 120 for Example 6, and substituting methanesulfonyl chloride for acetyl chloride. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.97 (s, 1H), 8.33 – 8.20 (m, 1H), 8.11 (s, 1H), 7.97 (t, *J* = 8.8 Hz, 1H), 6.67 (d, *J* = 2.5 Hz, 1H), 6.59 – 6.46 (m, 1H), 3.82 (d, *J* = 8.8 Hz, 3H), 3.25 (s, 8H), 2.96 (d, *J* = 12.8 Hz, 2H), 2.93 (s, 3H), 1.31 (s, 6H); MS (DCI) *m/z* 477 (M+H)⁺.

Example 126

N-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 18 substituting Example 120 for Example 6. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.68 (s, 1H), 8.29 (d, *J* = 8.8 Hz, 1H), 8.10 (d, *J* = 4.2 Hz, 1H), 6.53 (d, *J* = 7.4 Hz, 2H), 5.50 (s, 1H), 3.92 (s, 3H), 3.79 (s, 2H), 3.63 (s, 2H), 3.23 – 3.07 (m, 4H), 2.95 (s, 2H), 2.14 (s, 3H), 1.44 (s, 6H); MS (DCI) *m/z* 458 (M+NH₄)⁺.

Example 127

N-[2-ethoxy-6-(piperazin-1-yl)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 127A

tert-butyl 4-(4-[(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino)-3-ethoxyphenyl)piperazine-1-carboxylate

The titled compound was prepared using the procedure described for Example 5 substituting Example 120A for Example 1E and substituting Example 92C for *tert*-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate.

5 Example 127B

N-[2-ethoxy-6-(piperazin-1-yl)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 6 substituting Example 127D for Example 5. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.79 – 11.54 (s, 1H), 8.49 (d, *J* = 8.6 Hz, 1H), 8.09 (s, 1H), 6.17 (d, *J* = 8.6 Hz, 1H), 5.39 (s, 1H), 4.43 (q, *J* = 7.0 Hz, 2H), 3.56 – 3.38 (m, 4H), 3.12 – 3.01 (m, 4H), 2.94 (s, 3H), 1.55 – 1.30 (m, 9H); MS (DCI) *m/z* 414 (M+H)⁺.

Example 128

15 *N*-[6-(4-acetyl)piperazin-1-yl]-2-ethoxypyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 18 substituting Example 127 for Example 6. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.68 (s, 1H), 8.50 (d, *J* = 8.6 Hz, 1H), 8.09 (s, 1H), 6.18 (d, *J* = 8.6 Hz, 1H), 5.39 (s, 1H), 4.43 (d, *J* = 7.1 Hz, 2H), 3.74 (s, 2H), 3.63 – 3.54 (m, 2H), 3.53 – 3.39 (m, 4H), 2.94 (s, 2H), 2.14 (s, 3H), 1.43 (s, 9H); MS (ESI) *m/z* 456 (M+H)⁺.

Example 129

25 *N*-{6-[(3a*R*,6a*R*)-hexahydropyrrolo[3,4-*b*]pyrrol-5(1*H*)-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 129A

6-chloro-2-isopropoxy-3-nitropyridine

30 The titled compound was prepared using the procedure described for Example 121A substituting isopropyl alcohol for methanol.

Example 129B

tert-butyl (3a*R*,6a*R*)-5-(6-isopropoxy-5-nitropyridin-2-yl)hexahydropyrrolo[3,4-*b*]pyrrole-1(2*H*)-carboxylate

The titled compound was prepared using the procedure described for Example 121B substituting Example 129A for Example 121A and substituting (3a*R*,6a*R*)-*tert*-butyl hexahydropyrrolo[3,4-*b*]pyrrole-1(2*H*)-carboxylate (MFCD12198661, CAS#370880-09-4) for *tert*-butyl piperazine-1-carboxylate.

5

Example 129C

tert-butyl (3a*R*,6a*R*)-5-(5-amino-6-isopropoxy-pyridin-2-yl)hexahydropyrrolo[3,4-*b*]pyrrole-1(2*H*)-carboxylate

10 The titled compound was prepared using the procedure described for Example 121C substituting Example 129B for Example 121B.

Example 129D

tert-butyl (3a*R*,6a*R*)-5-(5-{{(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl}amino}-6-isopropoxy-pyridin-2-yl)hexahydropyrrolo[3,4-*b*]pyrrole-1(2*H*)-carboxylate

15

The titled compound was prepared using the procedure described for Example 5 substituting Example 120A for Example 1E, and substituting Example 129C for *tert*-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate.

20

Example 129E

N-{6-[(3a*R*,6a*R*)-hexahydropyrrolo[3,4-*b*]pyrrol-5(1*H*)-yl]-2-isopropoxy-pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 6 substituting Example 129D for Example 5. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.56 (s, 1H), 8.42 (d, *J* = 8.5 Hz, 1H), 8.09 (s, 1H), 5.90 (d, *J* = 8.5 Hz, 1H), 5.37 (s, 1H), 5.41 – 5.23 (m, 1H), 4.10 (t, *J* = 5.9 Hz, 1H), 3.57 (ddd, *J* = 15.2, 10.6, 8.5 Hz, 1H), 3.32 (dd, *J* = 10.6, 4.5 Hz, 1H), 3.14 (dtd, *J* = 16.5, 11.1, 5.5 Hz, 1H), 3.03 – 2.83 (m, 1H), 2.14 (dt, *J* = 20.5, 7.7 Hz, 1H), 1.81 (dt, *J* = 12.4, 5.9 Hz, 1H), 1.43 (s, 1H), 1.39 (dd, *J* = 6.2, 2.1 Hz, 1H); MS (DCI) *m/z* 454 (M+H)⁺.

30

Example 130

N-{2-methoxy-6-[(3a*R*,6a*R*)-5-methylhexahydropyrrolo[3,4-*b*]pyrrol-1(2*H*)-yl]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 130A

tert-butyl (3a*R*,6a*R*)-1-(6-methoxy-5-nitropyridin-2-yl)hexahydropyrrolo[3,4-*b*]pyrrole-5(1*H*)-carboxylate

The titled compound was prepared using the procedure described for Example 121B substituting *tert*-butyl (3a*R*,6a*R*)-hexahydropyrrolo[3,4-*b*]pyrrole-5(1*H*)-carboxylate (CAS#370882-39-6, which can be prepared according patent U.S. Patent Application Publication Number 2005101602A1) for *tert*-butyl piperazine-1-carboxylate.

Example 130B

tert-butyl (3a*R*,6a*R*)-1-(5-amino-6-methoxypyridin-2-yl)hexahydropyrrolo[3,4-*b*]pyrrole-5(1*H*)-carboxylate

The titled compound was prepared using the procedure described for Example 121C substituting Example 130A for Example 121B.

Example 130C

tert-butyl (3a*R*,6a*R*)-1-(5-{{[(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino}-6-methoxypyridin-2-yl)hexahydropyrrolo[3,4-*b*]pyrrole-5(1*H*)-carboxylate

The titled compound was prepared using the procedure described for Example 121D substituting Example 130B for Example 121C.

Example 130D

N-{6-[(3a*R*,6a*R*)-hexahydropyrrolo[3,4-*b*]pyrrol-1(2*H*)-yl]-2-methoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 6 substituting Example 130C for Example 5.

Example 130E

N-{2-methoxy-6-[(3a*R*,6a*R*)-5-methylhexahydropyrrolo[3,4-*b*]pyrrol-1(2*H*)-yl]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

To a solution of Example 130D, *N*-{6-[(3a*R*,6a*R*)-hexahydropyrrolo[3,4-*b*]pyrrol-1(2*H*)-yl]-2-methoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide (70 mg, 0.165 mmol) in methanol (5 mL) was added formaldehyde (24 μ L, 0.329 mmol) and a few drops of acetic acid. The resultant mixture was stirred for 5 minutes.

Then sodium triacetoxhydroborate (69.7 mg, 0.329 mmol) was added, and the mixture was stirred at room temperature for 2 hours. The mixture was diluted with ethyl acetate (10 mL) and washed with H₂O and brine. The organic layer was dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with NH₄OH (29%)/methanol/CH₂Cl₂ (0.3/3/97) to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.67 – 11.52 (m, 1H), 8.39 (d, *J* = 8.5 Hz, 1H), 8.08 (s, 1H), 5.94 (d, *J* = 8.5 Hz, 1H), 5.35 (s, 1H), 4.60 – 4.35 (m, 1H), 3.97 (s, 3H), 3.64 – 3.51 (m, 1H), 3.51 – 3.36 (m, 1H), 3.19 – 3.01 (m, 1H), 2.94 (s, 2H), 2.74 – 2.32 (m, 5H), 2.27 – 2.08 (m, 2H), 2.07 – 1.86 (m, 2H), 1.43 (s, 6H); MS (DCI) *m/z* 440 (M+H)⁺.

Example 131

N-{6-[(3a*S*,6a*S*)-1-(2-hydroxyethyl)hexahydropyrrolo[3,4-*b*]pyrrol-5(1*H*)-yl]-2-isopropoxy-pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 131A

tert-butyl (3a*S*,6a*S*)-5-(6-isopropoxy-5-nitropyridin-2-yl)hexahydropyrrolo[3,4-*b*]pyrrole-1(2*H*)-carboxylate

The titled compound was prepared using the procedure described for Example 121B substituting Example 129A for Example 121A, and substituting *tert*-butyl (3a*S*,6a*S*)-hexahydropyrrolo[3,4-*b*]pyrrole-1(2*H*)-carboxylate (CAS#: 185693-02-1) for *tert*-butyl piperazine-1-carboxylate.

Example 131B

tert-butyl (3a*S*,6a*S*)-5-(5-amino-6-isopropoxy-pyridin-2-yl)hexahydropyrrolo[3,4-*b*]pyrrole-1(2*H*)-carboxylate

The titled compound was prepared using the procedure described for Example 121C substituting Example 131A for Example 121B.

Example 131C

tert-butyl (3a*S*,6a*S*)-5-(5-{[(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino}-6-isopropoxy-pyridin-2-yl)hexahydropyrrolo[3,4-*b*]pyrrole-1(2*H*)-carboxylate

The titled compound was prepared using the procedure described for Example 5 substituting Example 120A for Example 1E and substituting Example 131B for *tert*-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate.

5 Example 131D

N-{6-[(3a*S*,6a*S*)-hexahydropyrrolo[3,4-*b*]pyrrol-5(1*H*)-yl]-2-isopropoxy-3-pyridin-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 6 substituting Example 131C for Example 5.

10

Example 131E

N-{6-[(3a*S*,6a*S*)-1-(2-hydroxyethyl)hexahydropyrrolo[3,4-*b*]pyrrol-5(1*H*)-yl]-2-isopropoxy-3-pyridin-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

15 To a solution of Example 131D, *N*-{6-[(3a*S*,6a*S*)-hexahydropyrrolo[3,4-*b*]pyrrol-5(1*H*)-yl]-2-isopropoxy-3-pyridin-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide (25mg, 0.055 mmol) in *N,N*-dimethylformamide (5 mL) was added 2-bromoethanol (13.8 mg, 0.11 mmol) and triethylamine (0.032 mL, 0.22 mmol) at room temperature, and the mixture was stirred for 16 hours. The mixture was diluted with ethyl acetate (10 mL) and washed with H₂O and brine. The organic layer was dried (MgSO₄),
20 filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with NH₄OH(29%)/methanol/CH₂Cl₂ (0.4/4/96) to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.61 (s, 1H), 8.48 (d, *J* = 11.9 Hz, 1H), 8.06 (s, 1H), 5.98 (d, *J* = 4.1 Hz, 1H), 5.28 (m, 2H), 3.94 (d, *J* = 40.7 Hz, 3H), 3.49 (d, *J* = 34.1 Hz, 4H),
25 3.20 (d, *J* = 48.3 Hz, 4H), 2.94 (s, 2H), 2.45 (m, 1H), 2.06 (m, 2H), 1.47 – 1.35 (m, 12H); MS (DCI) *m/z* 498 (M+H)⁺.

Example 132

30 *N*-{2-isopropoxy-6-[(3a*R*,6a*R*)-1-[(4-methylpiperazin-1-yl)carbonyl]hexahydropyrrolo[3,4-*b*]pyrrol-5(1*H*)-yl]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 18 substituting Example 129 for Example 6, and substituting 4-methylpiperazine-1-carbonyl chloride for acetyl chloride. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.53 (s, 1H), 8.40 (d, *J* =

17.2 Hz, 1H), 8.07 (s, 1H), 5.91 (d, $J = 8.5$ Hz, 1H), 5.30 (m, 2H), 3.98 (m, 1H), 3.51 (m, 3H), 3.24 (m, 1H), 3.09 (m, 1H), 2.97 (m, 2H), 2.93 (s, 2H), 2.02 (m, 1H), 1.73 (m, 6H), 1.41 (m, 12H); MS (ESI) m/z 580 (M+H)⁺.

5 Example 133

N-{6-[(3*S*)-4-acetyl-3-(hydroxymethyl)piperazin-1-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 133A

10 1-*tert*-butyl 2-methyl (2*S*)-4-(6-isopropoxy-5-nitropyridin-2-yl)piperazine-1,2-dicarboxylate

The titled compound was prepared using the procedure described for Example 121B substituting Example 129A for Example 121A, and substituting (*S*)-1-*tert*-butyl 2-methyl piperazine-1,2-dicarboxylate (CAS#: 796096-64-5) for *tert*-butyl piperazine-1-carboxylate.

15 Example 133B

1-*tert*-butyl 2-methyl (2*S*)-4-(5-amino-6-isopropoxypyridin-2-yl)piperazine-1,2-dicarboxylate

The titled compound was prepared using the procedure described for Example 121C substituting Example 133A for Example 121B.

20 Example 133C

1-*tert*-butyl 2-methyl (2*S*)-4-(5-([(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino)-6-isopropoxypyridin-2-yl)piperazine-1,2-dicarboxylate

The titled compound was prepared using the procedure described for Example 5 substituting Example 120A for Example 1E and substituting Example 133B for *tert*-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate.

Example 133D

tert-butyl (2*S*)-4-(5-([(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino)-6-isopropoxypyridin-2-yl)-2-(hydroxymethyl)piperazine-1-carboxylate

30 A solution of Example 133C (370 mg, 0.632 mmol) in anhydrous tetrahydrofuran (20 mL) was chilled with an ice bath. Lithium aluminum hydride (0.95 mL, 1 M in tetrahydrofuran) was added, and the mixture was stirred for 16 hours. The mixture was quenched with H₂O/1 N NaOH/H₂O (0.04 mL/0.04 mL/0.12 mL), sequentially. The mixture was stirred for 10 minutes, and then it was filtered and washed with additional ethyl acetate.

The filtrate was concentrated under reduced pressure. The resulting residue was chromatographed on silica gel eluting with (0-10%) methanol/ethyl acetate to provide the titled compound.

5 Example 133E

N-{6-[(3*S*)-3-(hydroxymethyl)piperazin-1-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 6 substituting Example 133D for Example 5.

10

Example 133F

N-{6-[(3*S*)-4-acetyl-3-(hydroxymethyl)piperazin-1-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 18 substituting Example 133E for Example 6. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.53 (s, 1H), 8.50 (d, *J* = 8.5 Hz, 1H), 8.08 (s, 1H), 6.13 (d, *J* = 8.5 Hz, 1H), 5.25 (d, *J* = 30.0 Hz, 2H), 4.77 (d, *J* = 26.1 Hz, 1H), 4.58 – 4.37 (m, 1H), 4.32 – 4.16 (m, 1H), 4.07 – 3.93 (m, 2H), 3.89 – 3.62 (m, 3H), 3.63 – 3.45 (m, 1H), 2.94 (s, 2H), 3.13 – 2.88 (m, 3H), 2.17 (s, 3H), 1.44 (s, 12H); MS (ESI) *m/z* 500 (M+H)⁺.

20

Example 134

N-{6-[(2*S*)-4-acetyl-2-(hydroxymethyl)piperazin-1-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 133 substituting (*S*)-1-*tert*-butyl 3-methyl piperazine-1,3-dicarboxylate (CAS#: 314741-39-4) for (*S*)-1-*tert*-butyl 2-methyl piperazine-1,2-dicarboxylate (CAS#: 796096-64-5) in Example 133A. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.64 (s, 1H), 8.49 (d, *J* = 13.4 Hz, 1H), 8.06 (s, 1H), 6.12 (d, *J* = 13.4 Hz, 1H), 5.37 – 5.12 (m, 2H), 4.73 – 4.33 (m, 1H), 3.94 – 3.55 (m, 3H), 3.55 – 3.38 (m, 2H), 3.22 – 2.97 (m, 2H), 2.94 (s, 2H), 2.19 (s, 3H), 1.45 – 1.36 (m, 12H); MS (ESI) *m/z* 500 (M+H)⁺.

30

Example 135

N-{6-[(2*S*)-2-(hydroxymethyl)-4-(morpholin-4-ylcarbonyl)piperazin-1-yl]-2-isopropoxy-pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 135A

N-{6-[(2*S*)-2-(hydroxymethyl)piperazin-1-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 133A through 133E substituting (*S*)-1-*tert*-butyl 3-methyl piperazine-1,3-dicarboxylate (CAS#: 314741-39-4) for (*S*)-1-*tert*-butyl 2-methyl piperazine-1,2-dicarboxylate (CAS#:) in Example 133A.

Example 135B

N-{6-[(2*S*)-2-(hydroxymethyl)-4-(morpholin-4-ylcarbonyl)piperazin-1-yl]-2-isopropoxy-pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 18 substituting Example 135A for Example 6 and substituting 1-morpholine-1-carbonyl chloride for acetyl chloride. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.62 (s, 1H), 8.48 (d, *J* = 8.6 Hz, 1H), 8.06 (s, 1H), 6.11 (d, *J* = 8.7 Hz, 1H), 5.26 (m, 2H), 4.51 – 4.38 (m, 1H), 4.21 – 4.08 (m, 1H), 3.85 – 3.57 (m, 8H), 3.44 – 3.05 (m, 8H), 2.93 (s, 2H), 1.43 (s, 6H), 1.40 (dd, *J* = 6.2, 2.0 Hz, 6H); MS (ESI) *m/z* 571 (M+H)⁺.

Example 136

N-{6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 136A

6-chloro-2-isopropoxypyridin-3-amine

The titled compound was prepared according the procedure described for Example 121C substituting Example 129A for Example 121B.

Example 136B

N-(6-chloro-2-isopropoxypyridin-3-yl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 5 substituting Example 120A for Example 1E, and substituting Example 136A for *tert*-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate.

Example 136C

N-{6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

10 A mixture of Example 136B (80 mg, 0.212 mmol), (*S*)-*N,N*-dimethylpyrrolidin-3-amine (48.4 mg, 0.423 mmol), 2'-(dicyclohexylphosphino)-*N,N*-dimethylbiphenyl-2-amine (8.3 mg, 0.021 mmol), tris(dibenzylideneacetone)dipalladium(0) (10 mg, 0.011 mmol) and potassium *tert*-butoxide (36 mg, 0.32 mmol) in anhydrous toluene (3 mL) was sparged with nitrogen, sealed in a microwave reactor vessel, and heated under microwave irradiation
15 (CEM Discover STM, maximum 300 W) to 150 °C for 20 minutes. The mixture was cooled to ambient temperature, filtered through a layer of filtering aid, and washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with NH₄OH (29%)/methanol/CH₂Cl₂ (0.3/3/97) to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.49 (s, 1H), 8.42 (d, *J* = 8.5 Hz, 1H), 8.07 (s, 1H), 5.85 (d, *J* = 8.5 Hz, 1H), 5.40 – 5.23 (m, 2H), 3.82 – 3.55 (m, 2H), 3.38 (td, *J* = 10.1, 6.9 Hz, 1H), 3.22 (d, *J* = 8.8 Hz, 1H), 2.93 (s, 2H), 2.89 – 2.75 (m, 1H), 2.32 (s, 6H), 2.25 – 2.09 (m, 1H), 1.97 – 1.80 (m, 1H), 1.43 (s, 6H), 1.40 (d, *J* = 6.3 Hz, 6H); MS (ESI) *m/z* 456 (M+H)⁺.
20

25 Example 137

N-{6-[(3*S*)-3-(hydroxymethyl)piperidin-1-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 137A

30 (*S*)-ethyl 1-(6-isopropoxy-5-nitropyridin-2-yl)piperidine-3-carboxylate

The titled compound was prepared using the procedure described for Example 121B substituting Example 129A for Example 121A, and substituting ethyl (3*S*)-piperidine-3-carboxylate (CAS#: 37675-18-6) for *tert*-butyl piperazine-1-carboxylate.

Example 137B

(*S*)-ethyl 1-(5-amino-6-isopropoxypyridin-2-yl)piperidine-3-carboxylate

The titled compound was prepared using the procedure described for Example 121C substituting Example 137A for Example 121B.

5

Example 137C

ethyl (3*S*)-1-(5-{[(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino}-6-isopropoxypyridin-2-yl)piperidine-3-carboxylate

The titled compound was prepared using the procedure described for Example 5 substituting Example 120A for Example 1E, and substituting Example 137B for *tert*-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate.

10

Example 137D

N-{6-[(3*S*)-3-(hydroxymethyl)piperidin-1-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

15

The titled compound was prepared using the procedure described for Example 133D substituting Example 137C for Example 133C. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.57 (s, 1H), 8.46 (d, *J* = 8.6 Hz, 1H), 8.07 (s, 1H), 6.18 (d, *J* = 8.7 Hz, 1H), 5.29 (p, *J* = 6.2 Hz, 1H), 5.29 (s, 1H), 3.98 (dd, *J* = 27.4, 12.1 Hz, 2H), 3.58 (d, *J* = 6.4 Hz, 2H), 3.07 – 2.85 (m, 3H), 2.95 (s, 2H), 1.80 (dd, *J* = 22.8, 18.5 Hz, 4H), 1.43 (s, 6H), 1.40 (dd, *J* = 6.2, 2.7 Hz, 6H); MS (ESI) *m/z* 457 (M+H)⁺.

20

Example 138

N-{6-[(3*R*)-4-acetyl-3-(hydroxymethyl)piperazin-1-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

25

The titled compound was prepared using the procedure described for Example 133 substituting (*R*)-1-*tert*-butyl 2-methyl piperazine-1,2-dicarboxylate (CAS#: 252990-05-9) for (*S*)-1-*tert*-butyl 2-methyl piperazine-1,2-dicarboxylate in Example 133A. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.65 (s, 1H), 8.51 (d, *J* = 8.6 Hz, 1H), 8.08 (s, 1H), 6.15 (d, *J* = 8.6 Hz, 1H), 5.37 – 5.16 (m, 2H), 4.58 – 4.37 (m, 1H), 4.27 – 3.95 (m, 2H), 3.84 – 3.67 (m, 3H), 3.63 – 3.47 (m, 1H), 3.16 – 2.95 (m, 2H), 2.94 (s, 2H), 2.18 (s, 2H), 1.44 (s, 6H), 1.41 (d, *J* = 6.2 Hz, 6H); MS (ESI) *m/z* 500 (M+H)⁺.

30

Example 139

N-{6-[(2*R*)-4-acetyl-2-(hydroxymethyl)piperazin-1-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 133 substituting (*R*)-1-*tert*-butyl 3-methyl piperazine-1,3-dicarboxylate (CAS#: 438631-77-7) for (*S*)-1-*tert*-butyl 2-methyl piperazine-1,2-dicarboxylate in Example 133A. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.65 (s, 1H), 8.50 (d, *J* = 12.8 Hz, 1H), 8.08 (s, 1H), 6.13 (d, *J* = 12.6 Hz, 1H), 5.37 – 5.12 (m, 2H), 4.76 – 4.30 (m, 2H), 3.95 – 3.56 (m, 3H), 3.55 – 3.36 (m, 2H), 3.21 – 2.97 (m, 2H), 2.94 (s, 2H), 2.19 (s, 3H), 1.43 (s, 26), 1.40 (dd, *J* = 6.1, 2.5 Hz, 6H); MS (ESI) *m/z* 500 (M+H)⁺.

Example 140

N-{6-[bis(2-hydroxyethyl)amino]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 140A

2,2'-((6-isopropoxy-5-nitropyridin-2-yl)azanediyl)diethanol

The titled compound was prepared using the procedure described for Example 121B substituting Example 129A for Example 121A, and substituting diethanolamine for *tert*-butyl piperazine-1-carboxylate.

Example 140B

2,2'-((5-amino-6-isopropoxypyridin-2-yl)azanediyl)diethanol

The titled compound was prepared using the procedure described for Example 121C substituting Example 140A for Example 121B.

Example 140C

N-{6-[bis(2-hydroxyethyl)amino]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 5 substituting Example 120A for Example 1E, and substituting Example 140B for *tert*-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.58 (s, 1H), 8.42 (d, *J* = 8.7 Hz, 1H), 8.08 (s, 1H), 6.06 (d, *J* = 8.7 Hz, 1H), 5.31 (s, 1H), 5.26 – 5.07 (m, 1H), 3.90 (t, *J* = 5.0 Hz, 4H), 3.68 (t, *J* = 5.0 Hz, 4H), 2.93 (s, 2H), 1.43 (s, 6H), 1.39 (d, *J* = 6.1 Hz, 6H); MS (ESI) *m/z* 447 (M+H)⁺.

Example 141

N-[2,6-bis(2-methoxyethoxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

5

Example 141A

6-(2-methoxyethoxy)-*N*-(2-methoxyethyl)-5-nitropyridin-2-amine

To a solution of 2-methoxyethanol (0.165 mL, 2.1 mmol) in tetrahydrofuran (20 mL) was added NaH (0.103 g, 60% dispersed in mineral oil, 2.57 mmol) at 0 °C, and the mixture was stirred at 0 °C for 25 minutes. Then a solution of 2,6-dichloro-3-nitropyridine (200 mg, 0.95 mmol) in tetrahydrofuran (10 mL) was added slowly, and the mixture was stirred overnight at room temperature. The mixture was then diluted with ether (50 mL) and quenched with H₂O, and the organic layer was separated. The aqueous layer was extracted with additional ether. The combined organic layers were washed with brine, dried with MgSO₄, filtered and concentrated under reduced pressure to provide the titled compound.

10
15

Example 141B

2,6-bis(2-methoxyethoxy)pyridin-3-amine

The titled compound was prepared using the procedure described for Example 121C substituting Example 141A for Example 121B.

20

Example 141C

N-[2,6-bis(2-methoxyethoxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 5 substituting Example 120A for Example 1E, and substituting Example 141B for *tert*-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.73 (s, 1H), 8.58 (d, *J* = 12.9 Hz, 1H), 8.07 (s, 1H), 6.37 (d, *J* = 8.5 Hz, 1H), 5.35 (s, 1H), 4.60 – 4.49 (m, 2H), 4.45 – 4.35 (m, 2H), 3.93 – 3.80 (m, 2H), 3.77 – 3.68 (m, 2H), 3.43 (s, 6H), 2.94 (s, 2H), 1.43 (s, 6H); MS (ESI) *m/z* 434 (M+H)⁺.

25
30

Example 142

N-{6-[(3*S*)-4-acetyl-3-(methoxymethyl)piperazin-1-yl]-2-(2-hydroxy-2-methylpropoxy)pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

5 Example 142A

2-(2-(benzyloxy)-2-methylpropoxy)-6-chloro-3-nitropyridine

The titled compound was prepared using the procedure described for Example 121A substituting 2-(benzyloxy)-2-methylpropan-1-ol (CAS#: 91968-71-7) for methanol.

10 Example 142B

(*S*)-1-*tert*-butyl 3-methyl 4-acetylpiperazine-1,3-dicarboxylate

To a solution of (*S*)-1-*tert*-butyl 3-methyl piperazine-1,3-dicarboxylate (500 mg, 2.05 mmol) in anhydrous dichloromethane (20 mL) at 0 °C was added triethylamine (311 mg 3.1 mmol) and acetyl chloride (0.16 mL, 2.25 mmol). The mixture was stirred for 30 minutes,
15 and then the mixture was diluted with dichloromethane. The organic layer was washed with H₂O, dried with MgSO₄, filtered and concentrated under reduced pressure to provide the titled compound.

Example 142C

20 (*S*)-*tert*-butyl 4-acetyl-3-(hydroxymethyl)piperazine-1-carboxylate

To a solution of Example 142B, (*S*)-1-*tert*-butyl 3-methyl 4-acetylpiperazine-1,3-dicarboxylate (625mg, 2.18 mmol), in methanol (30 mL) was added lithium tetrahydroborate (143 mg, 6.55 mmol). The mixture was heated to reflux for 16 hours. The mixture was concentrated under reduce pressure to a smaller volume and diluted with ethyl acetate. It was
25 washed with saturated NaHCO₃ and brine, dried with MgSO₄ and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel eluting with 30-80% ethyl acetate/heptanes to provide the titled compound.

Example 142D

30 (*S*)-*tert*-butyl 4-acetyl-3-(methoxymethyl)piperazine-1-carboxylate

To a solution of Example 142C (310 mg, 1.2 mmol) in anhydrous *N,N*-dimethylformamide (10 mL) was added sodium hydride (60% dispersed in oil, 68 mg, 1.7 mmol), and the mixture was stirred at the temperature for 30 minutes. Iodomethane (0.113 mL, 1.8 mmol) was added, and the resultant mixture was stirred at ambient temperature for 1

hour. The mixture was diluted with ether, quenched with water, and the organic layer was separated. The organic layer was further washed with brine, dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with 3-70% ethyl acetate/heptanes to provide the titled compound.

5

Example 142E

(*S*)-1-(2-(methoxymethyl)piperazin-1-yl)ethanone, trifluoroacetic acid salt

The product of Example 142D (310 mg, 1.14 mmol) was treated with trifluoroacetic acid (about 2 mL) and stirred for 10 minutes. The mixture was concentrated under reduced pressure. The residue was diluted with ether and concentrated again under reduced pressure. The operation was repeated a few times. Finally, the residue was dissolve in toluene and concentrated under reduced pressure and dried under vacuum to provide the crude titled compound.

15

Example 142F

(*S*)-1-(4-(6-(2-(benzyloxy)-2-methylpropoxy)-5-nitropyridin-2-yl)-2-(methoxymethyl)piperazin-1-yl)ethanone

The titled compound was prepared using the procedure described for Example 121B substituting Example 142A for Example 121A, and substituting Example 142E for *tert*-butyl piperazine-1-carboxylate.

20

Example 142G

(*S*)-1-(4-(5-amino-6-(2-hydroxy-2-methylpropoxy)pyridin-2-yl)-2-(methoxymethyl)piperazin-1-yl)ethanone

The titled compound was prepared using the procedure described for Example 121C substituting Example 142F for Example 121B.

25

Example 142H

N-{6-[(3*S*)-4-acetyl-3-(methoxymethyl)piperazin-1-yl]-2-(2-hydroxy-2-methylpropoxy)pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

30

The titled compound was prepared using the procedure described for Example 5 substituting Example 120A for Example 1E, and substituting Example 142G for *tert*-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate. ¹H NMR (300 MHz, CDCl₃) δ ppm

11.90 (s, 1H), 8.71 (d, $J = 8.6$ Hz, 1H), 8.10 (s, 1H), 6.21 (d, $J = 8.7$ Hz, 1H), 5.62 (s, 1H), 5.31 (s, 1H), 4.31- 4.01 (m, 3 H), 4.19 (s, 2H), 3.77 – 3.36 (m, 3H), 3.33 (s, 3H), 2.96 (s, 2H), 2.82 (dd, $J = 27.8, 12.5$ Hz, 2H), 2.18 (s, 3H), 1.42 (s, 6H), 1.33 (s, 6H); MS (ESI) m/z 544 (M+H)⁺.

5

Example 143

N-[2-ethoxy-6-(2-hydroxyethyl)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

10

Example 143A

6-chloro-2-ethoxy-3-nitropyridine

The titled compound was prepared using the procedure described for Example 121A substituting ethanol for methanol.

15

Example 143B

1-*tert*-butyl 3-methyl 2-(6-ethoxy-5-nitropyridin-2-yl)malonate

To a solution of Example 143A, 6-chloro-2-ethoxy-3-nitropyridine (3g, 14.81 mmol), in *N,N*-dimethylformamide (30 mL) at 0 °C was added sodium hydride (1.185 g, 29.6 mmol), and the mixture was stirred for 20 minutes. Then, *tert*-butyl methyl malonate (3.16 mL, 17.77 mmol) was added dropwise, and the mixture was stirred at ambient temperature for 2 hours. The mixture was diluted with ether and quenched with H₂O. The mixture was partitioned. The organic layer was washed with brine, dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel eluting with 0-20% ethyl acetate/heptanes to provide the titled compound.

25

Example 143C

methyl 2-(6-ethoxy-5-nitropyridin-2-yl)acetate

The titled compound was prepared using the procedure described for Example 142E substituting Example 143B for Example 142D.

30

Example 143D

methyl 2-(5-amino-6-ethoxypyridin-2-yl)acetate

The titled compound was prepared using the procedure described for Example 121C substituting Example 143C for Example 121B.

Example 143E

methyl (5-{[(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino}-
6-ethoxypyridin-2-yl)acetate

5 The titled compound was prepared using the procedure described for Example 5
substituting Example 120A for Example 1E, and substituting Example 143D for *tert*-butyl 4-
(4-amino-3-methoxyphenyl)piperazine-1-carboxylate.

Example 143F

10 *N*-[2-ethoxy-6-(2-hydroxyethyl)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-
c]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 133D
substituting Example 143E for Example 133C. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.90 (s,
1H), 8.64 (d, *J* = 7.9 Hz, 1H), 8.11 (s, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 5.34 (s, 1H), 4.43 (q, *J* =
15 7.1 Hz, 2H), 4.02 – 3.94 (m, 2H), 2.95 (s, 2H), 2.93 – 2.87 (m, 2H), 1.50 (t, *J* = 7.1 Hz, 3H),
1.44 (s, 6H); MS (DCI) *m/z* 374 (M+H)⁺.

Example 144

20 *N*-[2-ethoxy-6-(hydroxymethyl)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-
c]pyridine-3-carboxamide

Example 144A

6-hydroxy-5-nitropicolinic acid

25 A mixture of Example 143B, 1-*tert*-butyl 3-methyl 2-(6-ethoxy-5-nitropyridin-2-
yl)malonate (2.32 g, 6.82 mmol) and 70% nitric acid (60 mL) was heated to reflux for 10
hours. It was cooled to room temperature and concentrated under reduced pressure. The
resulting solid was washed with CHCl₃, filtered and dried under vacuum to provide the titled
compound.

30

Example 144B

ethyl 6-ethoxy-5-nitropicolinate

To a solution of Example 144A, 6-hydroxy-5-nitropicolinic acid (210mg, 1.141
mmol), in *N,N*-dimethylformamide (10 mL) was added triethylamine (0.477 mL, 3.42 mmol)
and iodoethane (0.277 mL, 3.42 mmol), and the mixture was heated to 50 °C for 16 hours.

The mixture was concentrated under reduced pressure and passed through a short silica gel pad to provide the crude titled compound.

Example 144C

5 ethyl 5-amino-6-ethoxypicolinate

The titled compound was prepared using the procedure described for Example 121C substituting Example 144B for Example 121B.

Example 144D

10 ethyl 5-{[(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino}-6-ethoxypyridine-2-carboxylate

The titled compound was prepared using the procedure described for Example 5 substituting Example 120A for Example 1E and substituting Example 144C for *tert*-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate.

15

Example 144E

N-[2-ethoxy-6-(hydroxymethyl)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

20 The titled compound was prepared using the procedure described for Example 133D substituting Example 144D for Example 133C. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.93 (s, 1H), 8.72 (d, *J* = 8.0 Hz, 1H), 8.10 (s, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 5.36 (s, 1H), 4.63 (s, 2H), 4.52 (q, *J* = 7.1 Hz, 2H), 2.96 (s, 2H), 1.50 (t, *J* = 7.1 Hz, 3H), 1.44 (s, 6H); MS (DCI) *m/z* 360 (M+H)⁺.

25

Example 145

6-ethoxy-5-({[5-(2-methoxyethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl]carbonyl} amino)pyridine-2-carboxylic acid

Example 145A

30 5-(2-methoxyethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxylic acid

To a solution of Example 120A, 6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxylic acid (2 g, 9.56 mmol), in *N,N*-dimethylformamide (30 mL) was added sodium hydride (0.803 g, 60% in mineral oil, 33.5 mmol) at 0°C, and the mixture was

stirred for 30 minutes. Then 1-bromo-2-methoxyethane (2.66 g, 19.12 mmol) was added and the mixture was stirred at ambient temperature for 5 hours. The mixture was acidified with HCl (1 N) to pH about 1 and diluted with ethyl acetate. The organic layer was separated. The aqueous layer was extracted with ethyl acetate thrice. The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography eluting with (0-10%) methanol/ethyl acetate to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 14.68 (s, 1H), 8.04 (s, 1H), 3.72 – 3.64 (m, 2H), 3.61 – 3.53 (m, 2H), 3.36 (s, 3H), 3.01 (s, 2H), 1.48 (s, 6H); MS (ESI) *m/z* 268 (M+H)⁺.

Example 145B

ethyl 6-ethoxy-5-({[5-(2-methoxyethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl]carbonyl} amino)pyridine-2-carboxylate

The titled compound was prepared using the procedure described for Example 5 substituting Example 145A for Example 1E, and substituting Example 144C for *tert*-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate.

Example 145C

6-ethoxy-5-({[5-(2-methoxyethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl]carbonyl} amino)pyridine-2-carboxylic acid

To a solution of Example 145B, ethyl 6-ethoxy-5-({[5-(2-methoxyethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl]carbonyl} amino)pyridine-2-carboxylate (80 mg, 0.174 mmol), in a mixture of methanol (10 mL), tetrahydrofuran (10 mL) and water (5 mL) was added lithium hydroxide hydrate (14.61 mg, 0.348 mmol). The mixture was stirred at ambient temperature for 5 hours. The mixture was then acidified with HCl (1 N) to pH = 2-3. It was diluted with ethyl acetate (30 mL) and partitioned. The aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography eluting with (0-10%) methanol/ethyl acetate to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 12.73 (s, 1H), 9.04 (d, *J* = 8.1 Hz, 1H), 8.13 (s, 1H), 7.86 (d, *J* = 8.1 Hz, 2H), 4.51 (q, *J* = 7.1 Hz, 2H), 3.69 (t, *J* = 5.6 Hz, 2H), 3.59 (t, *J* = 6.2 Hz, 2H), 3.38 (s, 3H), 2.99 (s, 2H), 1.61 (t, *J* = 7.1 Hz, 3H), 1.47 (s, 6H); MS (ESI) *m/z* 432 (M+H)⁺.

Example 146

6,6-dimethyl-*N*-(1-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

To a solution of 6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-3-carboxylic acid
5 (CAS#121625-78-3) (0.1 g, 0.48 mmol) in *N,N*-dimethylformamide (4 mL) was added 2-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.192 g, 0.504 mmol) and triethylamine (0.070 mL, 0.504 mmol). After mixing, 1-methyl-1*H*-indazol-5-amine (0.071 g, 0.480 mmol) was added, and the vial was shaken overnight. The mixture was concentrated, re-dissolved in CHCl₃ and methanol, passed through solid-phase extraction
10 cartridge containing silica-supported carbonate (SiliCycle®, Part # SPE-R66030B) eluted with CHCl₃ and concentrated. The residue was purified by flash chromatography 0-100% ethyl acetate/hexanes to provide the titled compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 11.75 (s, 1H), 8.36 (d, *J* = 1.6 Hz, 1H), 8.16 (s, 1H), 7.96 (s, 1H), 7.68 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.37 (d, *J* = 8.9 Hz, 1H), 4.08 (s, 1H), 2.87 (s, 1H), 2.57 (s, 1H), 1.22 (s, 1H); MS
15 (APCI) *m/z* 338 (M+H)⁺.

Example 147

6,6-dimethyl-*N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

20 The titled compound was prepared using the procedure described for Example 146 substituting 2-methyl-2*H*-indazol-5-amine for 1-methyl-1*H*-indazol-5-amine. ¹H NMR (400 MHz, CDCl₃) δ ppm 11.70 (bs, 1H), 8.45 (d, *J* = 1.9 Hz, 1H), 8.15 (s, 1H), 7.86 (s, 1H), 7.67 (d, *J* = 9.1 Hz, 1H), 7.43 (dd, *J* = 9.1, 2.0 Hz, 1H), 4.21 (s, 3H), 2.86 (s, 2H), 2.56 (s, 2H), 1.22 (s, 6H); MS (APCI) *m/z* 338 (M+H)⁺.

25

Example 148

N-[4-(4-acetylpiperazin-1-yl)phenyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

To a solution of 6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-3-carboxylic acid
30 (0.1 g, 0.480 mmol) in *N,N*-dimethylformamide (4 mL) was added 2-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.192 g, 0.504 mmol) and triethylamine (0.070 mL, 0.504 mmol). After mixing, 1-(4-(4-aminophenyl)piperazin-1-yl)ethanone (0.111 g, 0.504 mmol) was added, and the vial was shaken for 4 hours. The mixture was concentrated and triturated with methanol to provide the titled compound. ¹H

NMR (400 MHz, DMSO- d_6) δ ppm 11.54 (s, 1H), 8.37 (s, 1H), 7.56 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 9.1 Hz, 2H), 3.56 (dd, J = 8.3, 4.9 Hz, 4H), 3.13 – 3.09 (m, 2H), 3.07 – 3.03 (m, 2H), 2.90 (s, 2H), 2.57 (s, 2H), 2.03 (s, 3H), 1.10 (s, 6H); MS (APCI) m/z 410 (M+H)⁺.

5 Example 149

6,6-dimethyl-4-oxo-*N*-[6-(piperazin-1-yl)pyridin-3-yl]-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

Example 149A

10 *tert*-butyl 4-(5-{[(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-yl)carbonyl]amino}pyridin-2-yl)piperazine-1-carboxylate

The titled compound was prepared using the procedure described for Example 146 substituting *tert*-butyl 4-(5-aminopyridin-2-yl)piperazine-1-carboxylate (CAS# 119285-07-3) for 1-methyl-1*H*-indazol-5-amine. ¹H NMR (400 MHz, DMSO- d_6) δ ppm 11.52 (s, 1H), 8.43 (d, J = 2.0 Hz, 1H), 8.40 (s, 1H), 7.89 (dd, J = 9.0, 2.6 Hz, 1H), 6.90 (d, J = 9.1 Hz, 1H), 3.47 – 3.41 (m, 8H), 2.92 (bs, 2H), 2.58 (bs, 2H), 1.42 (s, 9H), 1.13 – 1.09 (m, 6H); MS (APCI) m/z 569.5 (M+H)⁺.

Example 149B

20 6,6-dimethyl-4-oxo-*N*-[6-(piperazin-1-yl)pyridin-3-yl]-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

To a solution of the product from Example 149A (24.56 g, 52.4 mmol) in dioxane (100 mL) was added a solution of 4 M hydrochloric acid (100 mL, 400 mmol) in dioxane. The mixture was stirred for 4 hours and a white precipitate formed. The product was concentrated, triturated from ether, and collected by filtration. This solid was mixed with water and potassium carbonate (21.73 g, 157 mmol) and extracted with ethyl acetate (2 × 250 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated to provide the titled compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 11.52 (bs, 1H), 8.53 (d, J = 2.7 Hz, 1H), 8.12 (s, 1H), 8.05 (dd, J = 9.1, 2.7 Hz, 1H), 6.67 (d, J = 9.1 Hz, 1H), 3.52 – 3.45 (m, 4H), 3.04 – 2.98 (m, 4H), 2.85 (s, 2H), 2.54 (s, 2H), 1.21 (s, 6H).

Example 150

N-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,7-dihydro-5*H*-spiro[1-benzofuran-6,1'-cyclobutane]-3-carboxamide

Example 150A

4-oxo-4,7-dihydro-5*H*-spiro[1-benzofuran-6,1'-cyclobutane]-3-carboxylic acid

To a solution of spiro[3.5]nonane-6,8-dione (CAS# 221342-48-9) (9.36 g, 61.5 mmol) in water (50 mL) was added potassium hydroxide (4.49 g, 80 mmol). The reaction was cooled in an ice bath, and then a solution of 3-bromo-2-oxopropanoic acid (10.27 g, 61.5 mmol) in methanol (50 mL) was added dropwise over 30 minutes. The mixture was concentrated under reduced pressure, and the residue was acidified with 37% HCl and heated to reflux overnight. The mixture was cooled and then extracted with CH₂Cl₂ (3 × 200mL). The combined CH₂Cl₂ layers were concentrated and purified by chromatography on silica gel eluting with CH₂Cl₂. Precipitation from methanol provided the titled compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 13.12 (s, 1H), 8.08 (s, 1H), 3.08 (s, 2H), 2.80 (s, 2H), 2.06 – 1.94 (m, 6H).

Example 150B

N-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,7-dihydro-5*H*-spiro[1-benzofuran-6,1'-cyclobutane]-3-carboxamide

The titled compound was prepared using the procedure described for Example 1F substituting the product from Example 150A for the product from Example 1E. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.70 (s, 1H), 8.42 (s, 1H), 8.30 (s, 1H), 8.27 (d, *J* = 1.9 Hz, 1H), 7.62 (d, *J* = 9.1 Hz, 1H), 7.31 (dd, *J* = 9.1, 2.0 Hz, 1H), 4.15 (s, 3H), 3.17 (s, 2H), 2.85 (s, 2H), 1.98 – 1.86 (m, 6H); MS (APCI) *m/z* 350 (M+H)⁺.

Example 151

6,6-dimethyl-4-oxo-*N*-[5-(piperazin-1-yl)pyridin-2-yl]-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

Example 151A

tert-butyl 4-(6-{[(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-yl)carbonyl]amino}pyridin-3-yl)piperazine-1-carboxylate

To a solution of 6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-3-carboxylic acid (0.987 g, 4.74 mmol) in tetrahydrofuran (40 mL) cooled to 0 °C was added triethylamine (1.322 mL, 9.48 mmol) and ethyl chloroformate (0.455 mL, 4.74 mmol). After stirring for 1 hour, *tert*-butyl 4-(6-aminopyridin-3-yl)piperazine-1-carboxylate (CAS# 571188-59-5) (1.2

g, 4.31 mmol) was added, and the mixture stirred at room temperature for 2 hours. The mixture was partitioned between brine and CHCl₃. The layers were separated and the aqueous layer was extracted with CHCl₃. The organic layers were combined, dried over Na₂SO₄, concentrated and purified by chromatography on silica gel eluting with a gradient of 0-100% ethyl acetate in hexane to provide the titled compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 12.74 and 12.15 (s and s, 1H), 8.41 – 7.38 (m, 4H), 3.75 – 3.68 (m, 2H), 3.62 – 3.55 (m, 2H), 3.30-3.24 (m, 2H), 3.02 – 2.95 (m, 2H), 2.78 and 2.77 (s and s, 2H), 2.52 and 2.48 (s and s, 2H), 1.43 and 1.42 (s and s, 9H), 1.13 and 1.12 (s and s, 6H); MS (APCI) *m/z* 469 (M+H)⁺.

Example 151B

6,6-dimethyl-4-oxo-*N*-[5-(piperazin-1-yl)pyridin-2-yl]-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

A mixture of Example 151A (0.57 g, 1.217 mmol) in 4 M HCl in dioxane (10 mL, 40 mmol) was stirred for 4 hours and blown dry under warm nitrogen. The product was dissolved in water (~15 mL), neutralized with potassium carbonate (0.673 g, 4.87 mmol), and extracted into CHCl₃. The organic phase was passed through a 20mL Biotage® ISOLUTE® phase separator cartridge and concentrated to provide the titled compound (0.388 g, 1.053 mmol, 87% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.97 (s, 1H), 8.99 (bs, 2H), 8.46 (s, 1H), 8.15 – 8.12 (m, 2H), 7.52 (dd, *J* = 9.1, 3.0 Hz, 1H), 3.42 – 3.35 (m, 4H), 3.28 – 3.21 (m, 4H), 2.92 (s, 2H), 2.57 (s, 2H), 1.11 (s, 6H); MS (APCI) *m/z* 369 (M+H)⁺.

Example 152

6,6-dimethyl-*N*-{4-[4-(methylsulfonyl)piperazin-1-yl]phenyl}-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

Example 152A

tert-butyl 4-(4-{[(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-yl)carbonyl]amino}phenyl)piperazine-1-carboxylate

The titled compound was prepared using the procedure described in Example 148 substituting *tert*-butyl 4-(4-aminophenyl)piperazine-1-carboxylate (CAS# 170911-92-9) for 1-(4-(4-aminophenyl)piperazin-1-yl)ethanone. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.55 (s, 1H), 8.38 (s, 1H), 7.57 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 3.49 – 3.43 (m, 4H), 3.09 – 3.03 (m, 4H), 2.91 (s, 2H), 2.58 (s, 2H), 1.42 (s, 9H), 1.11 (s, 6H).

Example 152B

6,6-dimethyl-4-oxo-*N*-[4-(piperazin-1-yl)phenyl]-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

5 The titled compound was prepared using the procedure described in Example 151B substituting the product from Example 152A for the product from Example 151A. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.57 (s, 1H), 9.17 (bs, 2H), 8.38 (s, 1H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 3.36 – 3.30 (m, 4H), 3.25 – 3.17 (m, 4H), 2.91 (s, 2H), 2.57 (s, 2H), 1.10 (s, 6H); MS (APCI) *m/z* 368 (M+H)⁺.

Example 152C

6,6-dimethyl-*N*-{4-[4-(methanesulfonyl)piperazin-1-yl]phenyl}-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

15 The titled compound was prepared using the procedure described in Example 18 substituting methanesulfonyl chloride for acetyl chloride, and substituting the product from Example 152B for the product from Example 6. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.56 (s, 1H), 8.38 (s, 1H), 7.58 (d, *J* = 9.0 Hz, 2H), 7.01 (d, *J* = 9.0 Hz, 2H), 3.27 – 3.19 (m, 8H), 2.93 (s, 3H), 2.92 (s, 2H), 2.58 (s, 2H), 1.11 (s, 6H); MS (APCI) *m/z* 446 (M+H)⁺.

Example 153

20 *N*-[2-(2-hydroxyethyl)-2*H*-indazol-5-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

Example 153A

25 2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-nitro-2*H*-indazole

A mixture of 5-nitro-1*H*-indazole (1.098 g, 6.731 mmol), Cs₂CO₃ (2.70 g, 8.29 mmol), (2-bromoethoxy)-*tert*-butyldimethylsilane (1.530 mL, 7.13 mmol) and *N,N*-dimethylformamide (15 mL) was heated at 120 °C for 30 minutes in a microwave (Biotage® Initiator, maximum 300 W). After cooling, the insoluble material was removed by filtration and rinsed with CHCl₃. The combined filtrates were concentrated and purified by chromatography on silica gel eluting with a gradient of 0 – 100% ethyl acetate in hexane providing 1-(2-(*tert*-butyldimethylsilyloxy)ethyl)-5-nitro-1*H*-indazole as the first isomer to elute and the titled compound as the second isomer to elute. ¹H NMR (400 MHz, CDCl₃) δ

ppm 8.77 (d, $J = 2.1$ Hz, 1H), 8.32 (s, 1H), 8.16 (dd, $J = 9.4, 2.1$ Hz, 1H), 7.78 (d, $J = 9.4$ Hz, 1H), 4.61 (t, $J = 5.0$ Hz, 2H), 4.12 (t, $J = 5.0$ Hz, 2H), 0.81 (s, 9H), -0.10 (s, 6H).

Example 153B

5 2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2*H*-indazol-5-amine

A solution of the product from Example 153A (.75 g, 2.333 mmol) in tetrahydrofuran (20 mL) was added to 5% Pd/C (0.150 g, 1.410 mmol) in a 50 mL pressure bottle and stirred at room temperature for 1 hour under H₂ (30 psi). The mixture was filtered, and the filtrate was concentrated and purified by chromatography on silica gel eluting with a gradient of 0 –
10 100% ethyl acetate in hexanes to provide the titled compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.83 (s, 1H), 7.31 (d, $J = 9.0$ Hz, 1H), 6.71 (dd, $J = 9.0, 2.1$ Hz, 1H), 6.54 (d, $J = 2.0$ Hz, 1H), 4.73 (bs, 2H), 4.34 (t, $J = 5.4$ Hz, 2H), 3.98 (t, $J = 5.4$ Hz, 2H), 0.76 (s, 9H), -0.14 (s, 6H).

15 Example 153C

N-[2-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-2*H*-indazol-5-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

The titled compound was prepared using the procedure described in Example 148 substituting the product from Example 153B for 1-(4-(4-aminophenyl)piperazin-1-
20 yl)ethanone. The crude product was purified by chromatography on silica gel eluting with a gradient of 0 – 100% ethyl acetate in hexane. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.69 (s, 1H), 8.41 (s, 1H), 8.29 (s, 1H), 8.26 (d, $J = 1.9$ Hz, 1H), 7.62 (d, $J = 9.1$ Hz, 1H), 7.31 (dd, $J = 9.1, 2.0$ Hz, 1H), 4.46 (t, $J = 5.2$ Hz, 2H), 4.03 (t, $J = 5.2$ Hz, 2H), 2.92 (s, 2H), 2.59 (s, 2H), 1.11 (s, 6H), 0.75 (s, 9H), -0.15 (s, 6H); MS (APCI) m/z 482 (M+H)⁺.

25

Example 153D

N-[2-(2-hydroxyethyl)-2*H*-indazol-5-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

To a solution of the product from Example 153C (.21 g, 0.436 mmol) in CHCl₃ (5
30 mL) was added a solution of 1 M tetrabutylammonium fluoride in tetrahydrofuran (1 mL, 1.0 mmol). After stirring for 4 hours, the mixture was partitioned with brine, and the organic layer was dried (MgSO₄), filtered, concentrated and purified chromatographically on silica gel eluted with a gradient of 0% to 10% methanol in ethyl acetate to provide the titled compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.69 (s, 1H), 8.41 (s, 1H), 8.31 (s, 1H),

8.27 (d, $J = 1.9$ Hz, 1H), 7.62 (d, $J = 9.1$ Hz, 1H), 7.31 (dd, $J = 9.1, 2.0$ Hz, 1H), 4.99 – 4.92 (m, 1H), 4.42 (t, $J = 5.5$ Hz, 2H), 3.88 – 3.82 (m, 2H), 2.92 (s, 2H), 2.59 (s, 2H), 1.11 (s, 6H); MS (APCI) m/z 368 (M+H)⁺.

5 Example 154

N-[2-(hydroxymethyl)-1*H*-benzimidazol-5-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

The titled compound was prepared using the procedure described for Example 148 substituting (5-amino-1*H*-benzimidazol-2-yl)methanol dihydrochloride for 1-(4-(4-aminophenyl)piperazin-1-yl)ethanone, and using four equivalents of triethylamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.31 (bs, 1H), 11.73 (s, 1H), 8.40 (s, 1H), 8.11 (d, $J = 1.9$ Hz, 1H), 7.48 (d, $J = 8.5$ Hz, 1H), 7.26 (dd, $J = 8.5, 1.2$ Hz, 1H), 5.67 (t, $J = 5.7$ Hz, 1H), 4.66 (d, $J = 5.5$ Hz, 2H), 2.91 (s, 2H), 2.59 (s, 2H), 1.21 – 1.02 (m, 6H); MS (APCI) m/z 354 (M+H)⁺.

15 Example 155

6,6-dimethyl-*N*-{5-[4-(methylsulfonyl)piperazin-1-yl]pyridin-2-yl}-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

The titled compound was prepared using the procedure described in Example 18 substituting methanesulfonyl chloride for acetyl chloride, and substituting the product from Example 151B for the product from Example 6. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.92 (s, 1H), 8.43 (s, 1H), 8.12 – 8.09 (m, 2H), 7.48 (dd, $J = 9.1, 3.0$ Hz, 1H), 3.26 (s, 8H), 2.92 (s, 3H), 2.91 (s, 2H), 2.56 (s, 2H), 1.10 (s, 6H); MS (APCI) m/z 447 (M+H)⁺.

Example 156

25 *N*-[5-(4-acetylpiperazin-1-yl)pyridin-2-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

The titled compound was prepared using the procedure described in Example 18 substituting the product from Example 151B for the product from Example 6. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.91 (s, 1H), 8.43 (s, 1H), 8.13 – 8.06 (m, 2H), 7.46 (dd, $J = 9.0, 3.1$ Hz, 1H), 3.61 – 3.54 (m, 4H), 3.19 – 3.15 (m, 2H), 3.12 – 3.08 (m, 2H), 2.90 (s, 2H), 2.56 (s, 2H), 2.03 (s, 3H), 1.10 (s, 6H); MS (APCI) m/z 411 (M+H)⁺.

Example 157

N-[2-methoxy-4-(piperazin-1-yl)phenyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

Example 157A

5 *tert*-butyl 4-(4-{{[(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-yl)carbonyl]amino}-3-methoxyphenyl})piperazine-1-carboxylate

The titled compound was prepared using the procedure described in Example 148 substituting *tert*-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (CAS# 1246532-96-6) for 1-(4-(4-aminophenyl)piperazin-1-yl)ethanone. The crude product was
10 purified by chromatography on silica gel eluting with a gradient of 0 – 100% ethyl acetate in hexane. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.24 (s, 1H), 8.36 (s, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 6.68 (d, *J* = 2.5 Hz, 1H), 6.50 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.87 (s, 3H), 3.52 – 3.39 (m, 4H), 3.16 – 3.07 (m, 4H), 2.90 (s, 2H), 2.55 (s, 2H), 1.42 (s, 9H), 1.11 (s, 6H); MS (ESI) *m/z* 498 (M+H)⁺.

15

Example 157B

N-[2-methoxy-4-(piperazin-1-yl)phenyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

To a solution of the product from Example 157A (2.38 g, 4.78 mmol) in CH₂Cl₂ (100
20 mL) and ethyl acetate (100 mL) at 0 °C was added a stream of HCl gas for 10 minutes. The mixture was placed in a warm (~50 °C) water bath and treated with a stream of N₂ until the total volume was ~ 50 mL. The mixture was diluted with ethyl acetate (50 mL), and the solid was collected by filtration and dried under vacuum to provide the titled compound as the di-HCl salt. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.26 (s, 1H), 9.14 (bs, 2H), 8.36 (s, 1H),
25 8.10 (d, *J* = 8.8 Hz, 1H), 6.72 (d, *J* = 2.5 Hz, 1H), 6.54 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.88 (s, 3H), 3.42 – 3.33 (m, 4H), 3.22 (s, 4H), 2.90 (s, 2H), 2.55 (s, 2H), 1.11 (s, 6H); MS (ESI) *m/z* 398 (M+H)⁺.

Example 158

30 *N*-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

The titled compound was prepared using the procedure described in Example 18 substituting the product from Example 157B for the product from Example 6. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.30 (s, 1H), 8.42 (s, 1H), 8.13 (d, *J* = 8.8 Hz, 1H), 6.75 (d, *J* = 2.5

Hz, 1H), 6.57 (dd, $J = 8.9, 2.5$ Hz, 1H), 3.94 (s, 3H), 3.68 – 3.61 (m, 4H), 3.26 – 3.13 (m, 4H), 2.96 (s, 2H), 2.61 (s, 2H), 2.11 (s, 3H), 1.17 (s, 6H); MS (ESI) m/z 440 (M+H)⁺.

Example 159

5 *N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,7-dihydro-5*H*-spiro[1-benzofuran-6,1'-cyclopropane]-3-carboxamide

Example 159A

4-oxo-5,7-dihydro-4*H*-spiro[benzofuran-6,1'-cyclopropane]-3-carboxylic acid

10 To a solution of spiro[2.5]octane-5,7-dione (CAS# 893411-52-4) (1.6g, 11.58 mmol) in water (8 mL) was added KOH (0.845 g, 15.05 mmol). The mixture was cooled to about 0 °C in an ice bath, and a solution of 3-bromo-2-oxopropanoic acid (2.320 g, 13.90 mmol) in methanol (15 mL) was added dropwise over 30 minutes. The methanol was removed under reduced pressure and water (8 mL) was added. The mixture was acidified with concentrated
15 HCl and heated to 100 °C for 2 hours. The mixture was cooled with stirring, and the product precipitated. The solid was collected by filtration, washed with water (3 × 15 mL) and dried under vacuum to provide the titled compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 13.19 (bs, 1H), 8.10 (s, 1H), 2.86 (s, 2H), 2.55 (s, 2H), 0.63 (s, 4H).

20 Example 159B

N-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,7-dihydro-5*H*-spiro[1-benzofuran-6,1'-cyclopropane]-3-carboxamide

A solution of the product from the Example from 159A (70.4 mg, 0.341 mmol) in tetrahydrofuran (7 mL) under N₂ was cooled to 0 °C, treated with triethylamine (119 μL, 0.854 mmol), treated with ethyl chloroformate (32.8 μL, 0.341 mmol), stirred at 0 °C for 1
25 hour, treated with 2-methyl-2*H*-indazol-5-amine (41.9 mg, 0.285 mmol), stirred at room temperature overnight and partitioned between 1 M NaOH (5 mL) and CH₂Cl₂ (25 mL). The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (25 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered, concentrated and purified by
30 chromatography on silica gel eluting with a gradient of 50-100% ethyl acetate in hexane to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.75 (s, 1H), 8.45 (d, $J = 1.3$ Hz, 1H), 8.14 (s, 1H), 7.86 (s, 1H), 7.67 (d, $J = 9.1$ Hz, 1H), 7.42 (dd, $J = 9.2, 2.0$ Hz, 1H), 4.21 (s, 3H), 2.85 (s, 2H), 2.54 (s, 2H), 0.62 (s, 4H); MS (ESI) m/z 336 (M+H)⁺.

Example 160

N-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine-3-carboxamide

Example 160A

5 potassium 1-(*tert*-butoxycarbonyl)-5-oxo-1,2,5,6-tetrahydropyridin-3-olate

A solution of ethyl 2-(*tert*-butoxycarbonyl(2-oxopropyl)amino)acetate (CAS# 873190-14-8) (13.26 g, 51.1 mmol) in anhydrous ether (250 mL) was added over 1 hour to a stirred 0 °C suspension of potassium *tert*-butoxide (6.31 g, 56.3 mmol) in anhydrous ether (250 mL). The mixture was stirred overnight at room temperature. The solid was collected
10 by filtration, washed with ether and dried under vacuum to provide the titled compound. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 4.48 (s, 0.5H), 3.55 (s, 4H), 1.39 (s, 9H).

Example 160B

6-(*tert*-butoxycarbonyl)-4-oxo-4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine-3-carboxylic acid

15 A mixture of the product from Example 160A (9.33 g, 37.1 mmol) and potassium *tert*-butoxide (0.833 g, 7.42 mmol) in water (37 mL) was treated over 30 minutes with a solution of 3-bromopyruvic acid (7.44 g, 44.5 mmol) in methanol (37 mL), stirred overnight and concentrated to dryness. To this residue was added acetic acid (190 mL, 3319 mmol) and acetic anhydride (95 mL, 1007 mmol), and this mixture was stirred at 100 °C for 30 minutes
20 and concentrated to an oil. This residue was dissolved in ethyl acetate (~ 50 mL), silica gel (~ 15 g) was added and the mixture was concentrated. The crude product as a silica gel suspension was purified by chromatography on silica gel eluting with a gradient of 33-100% [200:1:1 ethyl acetate/formic acid/water] in hexane. The residue was dried overnight under vacuum with heating to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm
25 8.17 (s, 1H), 4.84 (s, 2H), 4.40 (s, 2H), 1.50 (d, *J* = 4.8 Hz, 9H); MS (ESI) *m/z* 280 (M-H)⁻.

Example 160C

tert-butyl 3-[(2-methyl-2*H*-indazol-5-yl)carbamoyl]-4-oxo-4,7-dihydrofuro[2,3-*c*]pyridine-6(5*H*)-carboxylate

30 The titled compound was prepared using the procedure described in Example 159B substituting the product from Example 160C for the product from Example 159A. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.32 (s, 1H), 8.41 (s, 1H), 8.20 (s, 1H), 7.86 (s, 1H), 7.67 (d, *J* = 9.1 Hz, 1H), 7.39 (dd, *J* = 9.1, 1.6 Hz, 1H), 4.82 (s, 2H), 4.37 (s, 2H), 4.21 (s, 3H), 1.52 (s, 9H); MS (ESI) *m/z* 411 (M+H)⁺.

Example 160D

N-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine-3-carboxamide

A solution of the product from 160C (98.6 mg, 0.240 mmol) in ethyl acetate (5 mL)
5 and CH₂Cl₂ (5 mL) was cooled to 0 °C and treated with a stream of HCl for 5 minutes. After
stirring at 0 °C for 30 minutes, the mixture was allowed to warm to room temperature, and the
solvent was removed with a stream of nitrogen. The residue was dried under vacuum to
provide the titled compound as a dihydrochloride salt. ¹H NMR (300 MHz, DMSO-*d*₆) δ
ppm 11.04 (s, 1H), 10.67 (bs, 3H), 8.66 (s, 1H), 8.33 (s, 1H), 8.27 (s, 1H), 7.64 (d, *J* = 9.2
10 Hz, 1H), 7.32 (dd, *J* = 9.2, 1.7 Hz, 1H), 4.73 (s, 2H), 4.18 – 4.15 (m, 5H); MS (ESI) *m/z* 311
(*M*+H)⁺.

Example 161

N-(2-methyl-2*H*-indazol-5-yl)-6-(methylsulfonyl)-4-oxo-4,5,6,7-tetrahydrofuro[2,3-
15 *c*]pyridine-3-carboxamide

To a mixture of the product from Example 160D (56.8 mg, 0.148 mmol) and
triethylamine (0.10 mL, 0.74 mmol) in CH₂Cl₂ (0.5 mL) was added methanesulfonyl chloride
(17.32 μL, 0.222 mmol), and the reaction was stirred at room temperature overnight and then
partitioned between 1 M NaOH (5 mL) and CH₂Cl₂ (25 mL). The layers were separated and
20 the aqueous layer was extracted with CH₂Cl₂ (25 mL). The combined CH₂Cl₂ layers were
dried (MgSO₄), filtered, concentrated and purified by chromatography on silica gel eluting
with a gradient of 0-100% ethyl acetate in [9:1 CH₂Cl₂:ethyl acetate] to provide the titled
compound. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.13 (s, 1H), 8.57 (s, 1H), 8.31 (s, 1H),
8.28 – 8.26 (m, 1H), 7.65 – 7.61 (m, 1H), 7.31 (dd, *J* = 9.2, 2.0 Hz, 1H), 4.82 (s, 2H), 4.26 (s,
25 2H), 4.15 (s, 3H), 3.11 (s, 3H); MS (ESI) *m/z* 389 (*M*+H)⁺.

Example 162

6-methyl-*N*³-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3,6-
dicarboxamide

30

Example 162A

1-methyl-3,5-dioxocyclohexanecarboxamide

To a solution of 3,5-dimethoxy-1-methylcyclohexa-2,5-dienecarboxamide (CAS#
97294-69-4) (131 mg, 0.664 mmol) in tetrahydrofuran (10 mL) was added 1 M HCl (10 mL),

and the mixture was stirred overnight at room temperature and then concentrated to dryness. The residue was dissolved in CH₂Cl₂/methanol, silica gel (~ 1 gram) was added, and the mixture was concentrated to dryness. The crude product as a silica gel suspension was purified by chromatography on silica gel eluting with a gradient of 0-100% [22:1:1 ethyl acetate/formic acid/water] in [200:1:1 ethyl acetate/formic acid/water] to provide the titled compound. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.03 (s, 1H), 7.23 (s, 1H), 6.89 (s, 1H), 5.11 (s, 1H), 2.66 (d, *J* = 16.6 Hz, 2H), 2.21 (d, *J* = 16.7 Hz, 2H), 1.17 (s, 3H).

Example 162B

6-carbamoyl-6-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylic acid

To a solution of the product from Example 162A (64 mg, 0.378 mmol) in 1 M KOH (492 μL, 0.492 mmol) was added dropwise a solution of 3-bromopyruvic acid (76 mg, 0.454 mmol) in methanol (0.5 mL). After stirring at room temperature for overnight, the mixture was concentrated to dryness. A mixture of this residue in acetic acid (1 mL) and acetic anhydride (0.5 mL) was heated to 100 °C for 30 minutes, cooled and concentrated to dryness. This crude product was suspended on silica gel and purified by chromatography on silica gel eluting with a gradient of 0-100% [22:1:1 ethyl acetate/formic acid/water] in [200:1:1 ethyl acetate/formic acid/water] to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 8.09 (s, 1H), 6.00 (s, 2H), 3.59 (dd, *J* = 17.6, 1.1 Hz, 1H), 3.08 (dd, *J* = 17.0, 1.2 Hz, 1H), 2.94 (d, *J* = 17.6 Hz, 1H), 2.71 (d, *J* = 17.0 Hz, 1H), 1.52 (s, 3H); MS (ESI) *m/z* 238 (M+H)⁺.

Example 162C

6-methyl-*N*³-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3,6-dicarboxamide

The titled compound was prepared using the procedure described in Example 159B substituting the product from Example 162B for the product from Example 159A, except that the product was isolated directly as a solid after the reaction was partitioned between 1 M NaOH and CH₂Cl₂. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.75 (s, 1H), 8.39 (s, 1H), 8.30 (s, 1H), 8.27 (d, *J* = 1.3 Hz, 1H), 7.62 (d, *J* = 9.1 Hz, 1H), 7.54 (s, 1H), 7.32 (dd, *J* = 9.2, 2.0 Hz, 1H), 7.09 (s, 1H), 4.15 (s, 3H), 3.46 (d, *J* = 17.4 Hz, 1H), 3.05 (d, *J* = 17.2 Hz, 1H), 3.00 (d, *J* = 16.1 Hz, 1H), 2.73 (d, *J* = 16.4 Hz, 1H), 1.36 (s, 3H); MS (ESI) *m/z* 367 (M+H)⁺.

Example 163

methyl 6-methyl-3-[(2-methyl-2*H*-indazol-5-yl)carbamoyl]-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-6-carboxylate

Example 163A

5 6-(methoxycarbonyl)-6-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylic acid

To a mixture of methyl 3-hydroxy-1-methyl-5-oxocyclohex-3-enecarboxylate (CAS# 126395-85-5) (1.41 g, 7.66 mmol) and sodium bicarbonate (0.836 g, 9.95 mmol) in H₂O (10 mL) was added over 30 minutes in portions a solution of 3-bromopyruvic acid (1.534 g, 9.19 mmol) in methanol (10 mL). The mixture was stirred overnight and concentrated to dryness.

10 The residue was taken up in a mixture of acetic acid (24 mL) and acetic anhydride (12 mL), heated to 100 °C for 30 minutes, concentrated to an oil, re-dissolve in CH₂Cl₂, treated with 10 grams of silica gel and concentrated to dryness. The crude product as a silica gel suspension was purified by chromatography on silica gel eluting with a gradient of 33-100% [200:1:1 ethyl acetate/HCOOH/H₂O] in hexane to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 12.95 (s, 1H), 8.09 (s, 1H), 3.71 (s, 3H), 3.57 (dd, *J* = 17.6, 0.7 Hz, 1H), 3.16 (dd, *J* = 17.0, 0.9 Hz, 1H), 2.94 (d, *J* = 17.6 Hz, 1H), 2.65 (d, *J* = 17.0 Hz, 1H), 1.50 (s, 3H); MS (ESI) *m/z* 253 (M+H)⁺.

Example 163B

20 methyl 6-methyl-3-[(2-methyl-2*H*-indazol-5-yl)carbamoyl]-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-6-carboxylate

The titled compound was prepared using the procedure described in Example 159B substituting the product from Example 162A for the product from Example 159A, except that during the workup, sodium bicarbonate solution was used in place of 1 M NaOH and the

25 chromatography on silica gel was eluted with 0-100% (10 minutes) ethyl acetate in [9:1 CH₂Cl₂:ethyl acetate]. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.59 (s, 1H), 8.43 (d, *J* = 1.4 Hz, 1H), 8.13 (s, 1H), 7.85 (s, 1H), 7.67 (d, *J* = 9.2 Hz, 1H), 7.42 (dd, *J* = 9.2, 2.0 Hz, 1H), 4.21 (s, 3H), 3.71 (s, 3H), 3.56 (dd, *J* = 17.4, 1.1 Hz, 1H), 3.14 (dd, *J* = 16.6, 1.2 Hz, 1H), 2.93 (d, *J* = 17.4 Hz, 1H), 2.65 (d, *J* = 16.6 Hz, 1H), 1.49 (s, 3H); MS (ESI) *m/z* 382 (M+H)⁺.

30

Example 164

6-(hydroxymethyl)-6-methyl-*N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

Example 164A

6-(hydroxymethyl)-6-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylic acid

A mixture of (3,5-dimethoxy-1-methylcyclohexa-2,5-dienyl)methanol (CAS# 73696-80-7) (0.98 g, 5.32 mmol) in tetrahydrofuran (25 mL) and 1 M HCl (25 mL) was stirred at room temperature for 2 hours and concentrated to dryness. The residue was dissolved in a mixture of water (10 mL) and NaHCO₃ (1.8 g, 21 mmol), a solution of 3-bromopyruvic acid (1.066 g, 6.38 mmol) in methanol (5 mL) was then added in portions over 30 minutes, stirred overnight at room temperature, and concentrated to dryness. The residue was taken up in acetic acid (20 mL) and acetic anhydride (10 mL), heated to 100 °C for 30 minutes, cooled and concentrated to dryness. A solution of this residue in methanol (50 mL) and 1 M HCl (50 mL) was stirred at 80 °C for 3 hours, stirred at room temperature overnight, and concentrated to dryness. The residue was dissolved in a mixture of CH₂Cl₂ and methanol and silica gel (~ 6 g) was added. This mixture was concentrated to dryness. The crude product as a silica gel suspension was purified by chromatography on silica gel eluting with a gradient of 50-100% [200:1:1 ethyl acetate/formic acid/water] in hexane. This residue was treated with diethyl ether and the resulting yellow solid was collected by filtration and dried under vacuum to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 13.06 (bs, 1H), 8.10 (s, 1H), 3.56 (s, 2H), 3.23 (d, *J* = 17.9 Hz, 1H), 2.85 (d, *J* = 17.1 Hz, 1H), 2.71 (d, *J* = 17.9 Hz, 1H), 2.46 (dd, *J* = 17.1, 0.8 Hz, 1H), 1.18 (d, *J* = 17.5 Hz, 3H); MS (ESI) *m/z* 225 (M+H)⁺.

Example 164B

6-(hydroxymethyl)-6-methyl-*N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

The titled compound was prepared using the procedure described in Example 159B substituting the product from Example 164A for the product from Example 159A, except that the product was purified by precipitation from ethyl acetate and hexane. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.72 (s, 1H), 8.41 (s, 1H), 8.30 (s, 1H), 8.27 (d, *J* = 1.5 Hz, 1H), 7.62 (d, *J* = 9.1 Hz, 1H), 7.32 (dd, *J* = 9.2, 2.0 Hz, 1H), 5.01 (t, *J* = 5.4 Hz, 1H), 4.15 (s, 3H), 3.34 – 3.28 (m, 2H), 3.09 (d, *J* = 17.7 Hz, 1H), 2.79 – 2.71 (m, 2H), 2.50 – 2.41 (m, 1H), 1.03 (s, 3H); MS (ESI) *m/z* 354 (M+H)⁺.

Example 165

tert-butyl 4-[4-([6-(hydroxymethyl)-6-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-yl]carbonyl)amino]-3-methoxyphenyl]piperazine-1-carboxylate

The titled compound was prepared using the procedure described in Example 159B substituting the product from Example 164A for the product from Example 159A, and substituting *tert*-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (CAS# 1246532-96-6) for 2-methyl-2*H*-indazol-5-amine. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.28 (s, 1H), 8.29 (d, *J* = 8.7 Hz, 1H), 8.12 (s, 1H), 6.58 – 6.49 (m, 2H), 3.96 (s, 3H), 3.62 – 3.56 (m, 4H), 3.54 (dd, *J* = 5.1, 1.4 Hz, 2H), 3.20 – 3.08 (m, 5H), 2.76 (d, *J* = 16.5 Hz, 1H), 2.69 (d, *J* = 17.7 Hz, 1H), 2.43 (dd, *J* = 16.3, 0.5 Hz, 1H), 1.69 (t, *J* = 5.1 Hz, 1H), 1.49 (s, 9H), 1.15 (s, 3H); MS (ESI) *m/z* 514 (M+H)⁺.

Example 166

6-(methoxymethyl)-*N*-[2-methoxy-4-(piperazin-1-yl)phenyl]-6-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

Example 166A

6-(methoxymethyl)-6-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylic acid

A solution of 1,5-dimethoxy-3-(methoxymethyl)-3-methylcyclohexa-1,4-diene (CAS# 73696-81-8) (397 mg, 2 mmol) in tetrahydrofuran (10 mL) and 1 M HCl (10 mL) was stirred at room temperature for 4 hours and concentrated to dryness. This residue was dissolved in a mixture of water (5 mL) and sodium bicarbonate (670 mg, 8 mmol), treated portion-wise with a solution of 3-bromopyruvic acid (434 mg, 2.60 mmol) in methanol (5 mL) over 30 minutes, stirred at room temperature overnight, and concentrated to dryness. The residue was taken up in acetic acid (12 mL) and acetic anhydride (6 mL), heated to 100 °C for 30 minutes, concentrated to dryness, dissolved in CH₂Cl₂ (~ 30 mL), treated with silica gel (6 grams) and concentrated to dryness. The crude product as a silica gel suspension was purified by chromatography on silica gel eluting with 33-80% (10 minutes) [200:1:1 ethyl acetate/formic acid/water] in hexane to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 12.95 (s, 1H), 8.09 (s, 1H), 3.71 (s, 3H), 3.57 (dd, *J* = 17.6, 0.7 Hz, 1H), 3.16 (dd, *J* = 17.0, 0.9 Hz, 1H), 2.94 (d, *J* = 17.6 Hz, 1H), 2.65 (d, *J* = 17.0 Hz, 1H), 1.50 (s, 3H); MS (ESI) *m/z* 253 (M+H)⁺.

Example 166B

tert-butyl 4-[3-methoxy-4-({[6-(methoxymethyl)-6-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-yl]carbonyl} amino)phenyl]piperazine-1-carboxylate

The titled compound was prepared using the procedure described in Example 159B substituting the product from Example 166A for the product from Example 159A, and substituting *tert*-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (CAS# 1246532-96-6) for 2-methyl-2*H*-indazol-5-amine. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.30 (s, 1H), 8.29 (d, *J* = 8.7 Hz, 1H), 8.12 (s, 1H), 6.58 – 6.49 (m, 2H), 3.97 (s, 3H), 3.65 – 3.54 (m, 4H), 3.36 (s, 3H), 3.26 (d, *J* = 9.2 Hz, 1H), 3.22 (d, *J* = 9.2 Hz, 1H), 3.16 (d, *J* = 17.6 Hz, 1H), 3.15 – 3.08 (m, 4H), 2.78 (d, *J* = 16.6 Hz, 1H), 2.66 (d, *J* = 17.6 Hz, 1H), 2.40 (d, *J* = 16.6 Hz, 1H), 1.49 (s, 9H), 1.13 (s, 3H); MS (ESI) *m/z* 528 (M+H)⁺.

Example 166C

6-(methoxymethyl)-*N*-[2-methoxy-4-(piperazin-1-yl)phenyl]-6-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

The product from Example 166B (107.7 mg, 0.204 mmol) was dissolved in trifluoroacetic acid (5 mL), heated to 60 °C for 2 minutes and concentrated. This residue was diluted with CH₂Cl₂ (50 mL) and washed with 1 M NaOH (5 mL). The aqueous layer was extracted with CH₂Cl₂ (25 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered and concentrated to provide the titled compound. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.18 (s, 1H), 8.34 (s, 1H), 8.03 (d, *J* = 8.9 Hz, 1H), 6.62 (d, *J* = 2.5 Hz, 1H), 6.46 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.86 (s, 3H), 3.27 (s, 3H), 3.24 (s, 2H), 3.09 – 3.02 (m, 5H), 2.81 (dd, *J* = 13.7, 9.0 Hz, 5H), 2.69 (d, *J* = 16.4 Hz, 1H), 2.50 – 2.43 (m, 1H), 1.06 (s, 3H); MS (ESI) *m/z* 428 (M+H)⁺.

Example 167

5-(hydroxymethyl)-5-methyl-*N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

Example 167A

5-(acetoxymethyl)-5-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylic acid

The titled compound was prepared using the procedure described in Example 166A substituting 3-hydroxy-6-(hydroxymethyl)-6-methylcyclohex-2-enone (CAS# 1167996-92-0) for 1,5-dimethoxy-3-(methoxymethyl)-3-methylcyclohexa-1,4-diene, and was isolated as the second isomer to elute from the chromatography column. ¹H NMR (300 MHz, CDCl₃) δ

ppm 8.11 (s, 1H), 4.46 (d, $J = 11.1$ Hz, 1H), 4.09 (d, $J = 11.1$ Hz, 1H), 3.05 (dd, $J = 7.8, 5.0$ Hz, 2H), 2.43 (dt, $J = 13.9, 7.8$ Hz, 1H), 2.05 (s, 3H), 2.10 – 2.00 (m, 1H), 1.27 (s, 3H); MS (ESI) m/z 267 (M+H)⁺. The first isomer to elute from the chromatography column was 7-(acetoxymethyl)-7-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylic acid.

5

Example 167B

{5-methyl-3-[(2-methyl-2*H*-indazol-5-yl)carbamoyl]-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-5-yl} methyl acetate

The titled compound was prepared using the procedure described in Example 159B substituting the product from Example 167A for the product from Example 159A. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.74 (bs, 1H), 8.44 (d, $J = 1.9$ Hz, 1H), 8.16 (s, 1H), 7.87 (s, 1H), 7.69 (d, $J = 9.1$ Hz, 1H), 7.46 (dd, $J = 9.1, 2.0$ Hz, 1H), 4.50 (d, $J = 11.0$ Hz, 1H), 4.22 (s, 3H), 4.12 (d, $J = 11.0$ Hz, 1H), 3.05 (dd, $J = 7.9, 4.9$ Hz, 2H), 2.41 (dt, $J = 13.9, 7.9$ Hz, 1H), 2.06 (s, 3H), 2.07 – 2.02 (m, 1H), 1.28 (s, 3H); MS (ESI) m/z 396 (M+H)⁺.

15

Example 167C

5-(hydroxymethyl)-5-methyl-*N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

To a solution of the product from Example 167B (69 mg, 0.175 mmol) in tetrahydrofuran (4 mL) and methanol (4 mL) was added 1 M NaOH (2 mL), and the mixture was stirred for 1 hour at room temperature and partitioned between 1 M NaOH (5 mL) and CH₂Cl₂ (25 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (25 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered, and concentrated to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.70 (bs, 1H), 8.43 (d, $J = 1.9$ Hz, 1H), 8.14 (s, 1H), 7.86 (s, 1H), 7.68 (d, $J = 9.1$ Hz, 1H), 7.41 (dd, $J = 9.1, 2.0$ Hz, 1H), 4.21 (s, 3H), 3.97 (d, $J = 11.2$ Hz, 1H), 3.61 (d, $J = 11.2$ Hz, 1H), 3.10 – 3.01 (m, 2H), 2.48 (ddd, $J = 13.8, 9.1, 7.4$ Hz, 1H), 1.96 – 1.87 (m, 1H), 1.25 (s, 3H); MS (ESI) m/z 354 (M+H)⁺.

25
30

Example 168

5,5-dimethyl-*N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

Example 168A

ethyl 5,5-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylate

To a solution of 4,4-dimethylcyclohexane-1,3-dione (5 g, 35.7 mmol) and KOH (2.60 g, 46.4 mmol) in water (25.5 mL) was added a solution of 3-bromo-2-oxopropanoic acid (7.15 g, 42.8 mmol) in methanol (51.0 mL). After stirring for 2 hours, the methanol was removed by concentration under reduced pressure. Water (25.5 mL) was added, and the mixture was heated to reflux for 2 hours. Upon cooling, a mixture of 5,5-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylic acid and 7,7-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylic acid precipitated and was collected by filtration and dried in a vacuum oven. This solid was taken up in ethanol (100 mL), treated with concentrated sulfuric acid (0.1 mL), heated to 80 °C for 1 hour, cooled, treated with NaHCO₃ (5 g), stirred for 15 minutes and concentrated to approximately 20 mL total volume. The residue was partitioned between ethyl acetate and water. The ethyl acetate layer was dried (MgSO₄), filtered and concentrated. The residue was purified by chromatography on silica gel eluting with a gradient of 5-100% ethyl acetate in hexane to provide the titled compound as the first isomer to elute from the column. The second isomer to elute from the chromatography column was ethyl 7,7-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylate.

Example 168B

5,5-dimethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-3-carboxylic acid

To a solution of the product from Example 168A (108 mg, 0.457 mmol) in tetrahydrofuran (3 mL) and methanol (3 mL) was added 1 M NaOH (1 mL), and the mixture was stirred for 30 minutes. Ether (10 mL) and water (10 mL) were added. The resulting mixture was stirred vigorously as 1 M HCl was added until the aqueous layer was acidic. The mixture was extracted with ethyl acetate (50 mL). The organic layer was isolated, dried (MgSO₄), filtered and concentrated to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 13.43 (s, 1H), 8.09 (s, 1H), 2.99 (t, *J* = 6.3 Hz, 2H), 2.11 (t, *J* = 6.3 Hz, 2H), 1.28 (s, 6H); MS (ESI) *m/z* 209 (M+H)⁺.

Example 168C

5,5-dimethyl-*N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

The titled compound was prepared using the procedure described in Example 159B substituting the product from Example 168B for the product from Example 159A. ¹H NMR

(300 MHz, CDCl₃) δ ppm 11.91 (bs, 1H), 8.45 (dd, J = 2.0, 0.8 Hz, 1H), 8.14 (s, 1H), 7.85 (s, 1H), 7.68 (dt, J = 9.1, 0.9 Hz, 1H), 7.46 (dd, J = 9.1, 2.0 Hz, 1H), 4.21 (s, 3H), 2.99 (t, J = 6.3 Hz, 2H), 2.13 – 2.02 (m, 2H), 1.28 (s, 6H); MS (ESI) m/z 338 (M+H)⁺.

5 Example 169

N-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-5-(aminomethyl)-5-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

Example 169A

10 ethyl 2-cyano-2-methyl-5-oxohexanoate

To a solution of 2-cyanopropionic acid ethyl ester (10 g, 79 mmol) in acetonitrile (240 mL) was added sodium tetramethoxyborate (1.242 g, 7.87 mmol) followed by methyl vinyl ketone (6.49 mL, 79 mmol). After stirring at room temperature for 5 days, the mixture was concentrated. The residue was purified by chromatography on silica gel eluting with a
15 gradient of 10 – 50% ethyl acetate in hexane to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 4.27 (q, J = 7.1 Hz, 2H), 2.78 – 2.52 (m, 2H), 2.24 (ddd, J = 14.3, 10.0, 5.6 Hz, 1H), 2.19 (s, 3H), 2.05 (ddd, J = 14.3, 10.1, 5.6 Hz, 1H), 1.61 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); MS (ESI) m/z 215 (M+NH₄)⁺.

20 Example 169B

1-methyl-2,4-dioxocyclohexanecarbonitrile

To a solution of ethanol (80 mL, 1366 mmol) in tetrahydrofuran (450 mL) under nitrogen was added potassium *tert*-butoxide (16.86 g, 150 mmol). The mixture was cooled to 0 °C, and a solution of the product from Example 169A (13.47 g, 68.3 mmol) in
25 tetrahydrofuran (50 mL) was added over 15 minutes. The mixture was concentrated to remove most of the solvent, diluted with cold water (100 mL), acidified dropwise with concentrated HCl to pH ~5, and treated with ethyl acetate (100 mL). The aqueous layer of this mixture was neutral, so concentrated HCl was further added until the aqueous remained acidic. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2
30 $\times$ 100 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated to provide the titled compound. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.78 (s, 1H), 5.25 (s, 1H), 2.55 – 2.46 (m, 2H), 2.36 – 2.24 (m, 1H), 2.12 – 2.01 (m, 1H), 1.43 (s, 3H); MS (ESI) m/z 150 (M-H)⁻.

Example 169C

ethyl 5-cyano-5-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylate

To a mixture of the product from Example 169B (6 g, 39.7 mmol) and NaHCO₃ (13.34 g, 159 mmol) in ethanol (100 mL) was added ethyl bromopyruvate (6.47 mL, 51.6 mmol). The reaction was stirred overnight at room temperature, filtered to remove the solids, and the filtrate was concentrated to dryness. The residue was treated with acetic acid (200 mL) and acetic anhydride (100 mL), heated to 110 °C overnight, concentrated to an oil, diluted with ethyl acetate (300 mL) and washed with saturated NaHCO₃ solution. The aqueous solution was extracted with ethyl acetate, and the combined ethyl acetate layers were washed with brine, dried (MgSO₄), filtered and concentrated. The residue was purified by chromatography on silica gel eluting with a gradient of 15-50% ethyl acetate in hexane to provide the titled compound as the first isomer to elute from the column. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.95 (s, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.28 (ddd, *J* = 18.1, 10.0, 5.3 Hz, 1H), 3.03 (ddd, *J* = 18.1, 5.3, 4.1 Hz, 1H), 2.54 (ddd, *J* = 13.7, 5.3, 4.0 Hz, 1H), 2.28 – 2.16 (m, 1H), 1.64 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H); MS (ESI) *m/z* 248 (M+H)⁺. The second isomer to elute from the chromatography column was ethyl 7-cyano-7-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylate.

Example 169D

ethyl 5-{[(*tert*-butoxycarbonyl)amino]methyl}-5-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylate

The product from Example 169C (3.19 g, 12.90 mmol) in ethanol (155 mL) was added to a mixture of Raney®-nickel 2800 (water slurry) (15 g) and di-*tert*-butyl dicarbonate (7.49 mL, 32.3 mmol). The mixture was shaken under 30 psi of hydrogen at room temperature for 2 hours and filtered. The filtrate was concentrated to dryness, and the residue was purified by chromatography on silica gel eluting with a gradient of 10-50% ethyl acetate in hexane to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.89 (s, 1H), 5.19 (t, *J* = 5.9 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.44 (dd, *J* = 13.8, 6.3 Hz, 1H), 3.22 (dd, *J* = 13.8, 6.9 Hz, 1H), 3.01 – 2.94 (m, 2H), 2.29 – 2.14 (m, 1H), 1.90 (dt, *J* = 13.8, 4.6 Hz, 1H), 1.41 (s, 9H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.16 (s, 3H); MS (ESI) *m/z* 352 (M+H)⁺.

Example 169E

5-{[(*tert*-butoxycarbonyl)amino]methyl}-5-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylic acid

The titled compound was prepared using the procedure described in Example 168B substituting the product from Example 169D for the product from Example 168A. ¹H NMR (300 MHz, CDCl₃) δ ppm 13.14 (s, 1H), 8.10 (s, 1H), 4.90 (bt, 1H), 3.46 (dd, *J* = 14.1, 6.2 Hz, 1H), 3.34 (dd, *J* = 14.2, 7.4 Hz, 1H), 3.23 – 2.95 (m, 2H), 2.37 – 2.24 (m, 1H), 2.10 – 1.98 (m, 1H), 1.43 (s, 9H), 1.23 (s, 3H); MS (ESI) *m/z* 324 (M+H)⁺.

Example 169F

tert-butyl [(3-{[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]carbonyl}-5-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-5-yl)methyl]carbamate

The titled compound was prepared using the procedure described in Example 159B substituting the product from Example 169E for the product from Example 159A, and substituting 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone for 2-methyl-2*H*-indazol-5-amine. A gradient of 25-100% [20% ethanol in ethyl acetate] in ethyl acetate was used in place of 50 – 100% ethyl acetate in hexane as the eluent in the chromatography. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.32 (s, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 8.11 (d, *J* = 4.5 Hz, 1H), 6.58 – 6.49 (m, 2H), 5.05 – 4.97 (m, 1H), 3.96 (s, 3H), 3.82 – 3.76 (m, 2H), 3.68 – 3.59 (m, 2H), 3.50 (dd, *J* = 13.9, 6.2 Hz, 1H), 3.31 (dd, *J* = 13.9, 7.1 Hz, 1H), 3.22 – 3.09 (m, 4H), 3.03 (dd, *J* = 8.0, 4.7 Hz, 2H), 2.33 – 2.20 (m, 1H), 2.14 (s, 3H), 1.97 (dt, *J* = 13.4, 4.4 Hz, 1H), 1.43 (s, 9H), 1.22 (s, 3H); MS (ESI) *m/z* 555 (M+H)⁺.

Example 169G

N-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-5-(aminomethyl)-5-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

A solution of the product from Example 169F (1.42 g, 2.56 mmol) in 4 M HCl in dioxane (4 mL) and water (2 mL) was warmed to 60 °C for 2 minutes and concentrated with a stream of N₂. The residue was partitioned between 1 M NaOH (25 mL) and CH₂Cl₂ (50 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 × 25 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered, concentrated and chromatographed on silica gel eluting with a gradient of 2-10% (9:1 methanol:29% aqueous ammonium hydroxide solution) in CH₂Cl₂ to provide the free base of the titled compound. A solution of this free base in CH₂Cl₂ (20 mL) was cooled to 0 °C and HCl gas was bubbled into the solution for 1 minute. The solvent was removed with a stream of nitrogen, and ethyl acetate was added to the residue. The solid was collected by filtration, washed with ethyl acetate and dried under vacuum to provide the di-hydrochloric acid salt of the titled

compound. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 11.18 (s, 1H), 8.40 (s, 1H), 8.11 (s, 3H), 8.07 (d, *J* = 8.9 Hz, 1H), 6.82 (s, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 3.91 (s, 3H), 3.68 – 3.59 (m, 4H), 3.32 – 3.07 (m, 7H), 2.98 (dd, *J* = 13.1, 6.0 Hz, 1H), 2.27 (dt, *J* = 15.9, 8.0 Hz, 1H), 2.06 (s, 3H), 2.09 – 1.96 (m, 1H), 1.25 (s, 3H); MS (ESI) *m/z* 455 (M+H)⁺

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Example 170

N-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-4-oxo-4,7-dihydrospiro[furo[2,3-*c*]pyran-5,4'-piperidine]-3-carboxamide

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Example 170A

benzyl 4-(2-ethoxy-2-oxoethoxy)-4-ethynylpiperidine-1-carboxylate

To a solution of benzyl 4-ethynyl-4-hydroxypiperidine-1-carboxylate (CAS# 495415-65-1) (5.4 g, 20.8 mmol) in tetrahydrofuran (100 mL) was added a 60% dispersion of NaH in mineral oil (0.83 g, 20.8 mmol). After stirring at room temperature for 30 minutes, ethyl bromoacetate (2.55 mL, 22.91 mmol) was added, and the reaction was stirred at room temperature overnight and then treated with saturated NH₄Cl (50 mL). After stirring for 10 minutes, the mixture was concentrated under reduced pressure to remove a significant amount of the tetrahydrofuran. The residue was extracted with ethyl acetate (100 mL). The layers were separated and the aqueous layer was treated with water (10 mL) and extracted with ethyl acetate (50 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered, concentrated and purified by chromatography on silica gel eluting with a gradient of 16-50% ethyl acetate in hexane to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.41 – 7.27 (m, 5H), 5.13 (s, 2H), 3.92 – 3.78 (m, 2H), 3.44 – 3.31 (m, 2H), 2.54 (s, 1H), 2.05 (bs, 1H), 1.92 (d, *J* = 12.6 Hz, 2H), 1.80 – 1.67 (m, 2H); MS (ESI) *m/z* 346 (M+H)⁺.

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Example 170B

benzyl 3,5-dioxo-1-oxa-9-azaspiro[5.5]undecane-9-carboxylate

To a solution of the product Example 170A (3.66 g, 10.60 mmol) in methanol (300 mL) was added mercury(II) acetate (0.338 g, 1.060 mmol) followed by sulfuric acid (10 drops). The reaction was heated to 60 °C for 30 minutes and then concentrated under reduced pressure to approximately 100 mL total volume. 1 M HCl (200 mL) was added, and the resulting mixture was stirred for 5 minutes and partitioned between ethyl acetate (100 mL) and water (300 mL). The layers were separated, and the aqueous layer was extracted with

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ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated to provide a mixture of benzyl 4-acetyl-4-(2-methoxy-2-oxoethoxy)piperidine-1-carboxylate and benzyl 4-acetyl-4-(2-ethoxy-2-oxoethoxy)piperidine-1-carboxylate. In a separate flask, potassium *tert*-butoxide (2.62 g, 23.32 mmol) was added to a solution of ethanol (12.38 mL, 212 mmol) in tetrahydrofuran (80 mL) under N₂, and the resulting mixture was cooled to 0 °C. To this mixture was added a solution of benzyl 4-acetyl-4-(2-methoxy-2-oxoethoxy)piperidine-1-carboxylate and benzyl 4-acetyl-4-(2-ethoxy-2-oxoethoxy)piperidine-1-carboxylate in tetrahydrofuran (10 mL) dropwise over 15 minutes. The reaction was stirred at 0 °C for 30 minutes, concentrated to ~25 mL total volume, diluted with water (100 mL) and neutralized with concentrated HCl. The mixture was treated with ethyl acetate (100 mL) and further acidified to pH ~1. The mixture was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated to provide the titled compound. MS (ESI) *m/z* 335 (M+NH₄)⁺.

Example 170C

1'-[(benzyloxy)carbonyl]-4-oxo-4,7-dihydrospiro[furo[2,3-*c*]pyran-5,4'-piperidine]-3-carboxylic acid

To a solution of the product from Example 170B (3.36 g, 10.6 mmol) and NaHCO₃ (3.56 g, 42.4 mmol) in water (15 mL) was added a solution of 3-bromopyruvic acid (2.301 g, 13.78 mmol) in methanol (15 mL) in portions over 1 hour. The resultant mixture was stirred overnight at room temperature, concentrated to dryness, treated with acetic acid (150 mL) and acetic anhydride (75 mL), and heated to 100 °C for 30 minutes. The mixture was then concentrated to dryness. The residue was partitioned between 1 M HCl (100 mL) and CH₂Cl₂ (100 mL). The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (2 times, 50 mL and 25 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered, treated with silica gel (8 scupulas) and concentrated to dryness. The crude product as a silica gel suspension was purified by chromatography on silica gel eluting with a gradient of 40 – 100% [200:1:1 ethyl acetate/formic acid/water] in hexane to provide the titled compound as the second isomer to elute from the column. ¹H NMR (300 MHz, CDCl₃) δ ppm 8.17 (s, 1H), 7.41 – 7.29 (m, 5H), 5.15 (s, 2H), 4.95 (s, 2H), 4.25 – 4.04 (m, 2H), 3.32 – 3.06 (m, 2H), 2.11 – 1.95 (m, 2H), 1.94 – 1.79 (m, 2H); MS (ESI) *m/z* 403 (M+NH₄)⁺. The

first isomer to elute from the chromatography column was 1'-[(benzyloxy)carbonyl]-4-oxo-4,5-dihydrospiro[furo[2,3-*c*]pyran-7,4'-piperidine]-3-carboxylic acid.

Example 170D

5 benzyl 3-{[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]carbamoyl}-4-oxo-4,7-dihydro-1'*H*-spiro[furo[2,3-*c*]pyran-5,4'-piperidine]-1'-carboxylate

The titled compound was prepared using the procedure described in Example 159B substituting the product from Example 170C for the product from Example 159A, and substituting 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone for 2-methyl-2*H*-
10 indazol-5-amine. A gradient of 25-100% [20% ethanol in ethyl acetate] in ethyl acetate was used in place of 50 – 100% ethyl acetate in hexane as the eluent in the chromatography. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.00 (bs, 1H), 8.29 (d, *J* = 8.8 Hz, 1H), 8.18 (s, 1H), 7.40 – 7.28 (m, 5H), 6.62 – 6.51 (m, 2H), 5.16 (s, 2H), 4.92 (s, 2H), 4.25 – 4.05 (m, 2H), 3.96 (s, 3H), 3.80 (s, 2H), 3.70 – 3.60 (m, 2H), 3.28 – 3.07 (m, 7H), 2.15 (s, 3H), 2.13 – 2.02 (m, 2H),
15 1.94 – 1.81 (m, 1H); MS (ESI) *m/z* 617 (M+H)⁺.

Example 170E

N-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-4-oxo-4,7-dihydrospiro[furo[2,3-*c*]pyran-5,4'-piperidine]-3-carboxamide

20 A mixture of the product from Example 170D (0.34 g, 0.551 mmol), methanol (20 mL), and 20% Pd(OH)₂/C, wet, (0.068 g, 0.484 mmol) was stirred under a hydrogen atmosphere at 30 psi for 2 hours. The mixture was filtered to remove the solids, and the filtrate was concentrated. The residue was purified by chromatography on silica gel eluting with a gradient of 4-20% (9:1 methanol:29% ammonium hydroxide) in CH₂Cl₂ to provide the
25 free base of the titled compound. A solution of this free base in CH₂Cl₂ (20 mL) was cooled to 0 °C and HCl gas was bubbled into the solution for 1 minute. The solvent was removed with a stream of nitrogen, and ethyl acetate was added to the residue. The solid was collected by filtration, washed with ethyl acetate and dried under vacuum to provide the di-
hydrochloric acid salt of the titled compound. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 10.88
30 (s, 1H), 9.17 (d, *J* = 9.3 Hz, 1H), 9.04 – 8.84 (m, 1H), 8.55 (s, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 6.90 (bs, 1H), 6.72 (d, *J* = 7.4 Hz, 1H), 5.13 (s, 2H), 3.90 (s, 3H), 3.74 – 3.59 (m, 4H), 3.34 – 3.13 (m, 6H), 3.13 – 2.94 (m, 2H), 2.20 – 2.09 (m, 4H), 2.06 (s, 3H); MS (ESI) *m/z* 483 (M+H)⁺.

Example 171

N-[6-(4-acetylpiperazin-1-yl)-2-methoxypyridin-3-yl]-5,5-dimethyl-4-oxo-4,7-dihydro-5*H*-furo[2,3-*c*]pyran-3-carboxamide

5 Example 171A

ethyl 3-hydroxy-5,5-dimethyl-4-oxo-3,4,5,7-tetrahydro-2*H*-furo[2,3-*c*]pyran-3-carboxylate

To a mixture of 2,2-dimethyl-2*H*-pyran-3,5(4*H*,6*H*)-dione (CAS# 98272-63-0) (1.9 g, 13.37 mmol) and NaHCO₃ (4.49 g, 53.5 mmol) in ethanol (40 mL) was added ethyl bromopyruvate (3.39 g, 17.38 mmol), and the reaction was stirred overnight at room
10 temperature, diluted with ethanol, and filtered to remove the solids. The filtrate was concentrated to dryness, and the residue was purified by chromatography on silica gel eluting with 50% diethyl ether in hexane to provide the titled compound as the isomer first to elute from the column. ¹H NMR (300 MHz, CDCl₃) δ ppm 4.82 (d, *J* = 10.5 Hz, 1H), 4.61 (d, *J* = 10.5 Hz, 1H), 4.54 (s, 2H), 4.42 – 4.20 (m, 2H), 1.71 (bs, 1H), 1.38 (s, 3H), 1.34 (s, 3H), 1.28
15 (t, *J* = 7.1 Hz, 3H); MS (ESI) *m/z* 257 (M+H)⁺. The second isomer to elute from the chromatography column was ethyl 3-hydroxy-7,7-dimethyl-4-oxo-3,4,5,7-tetrahydro-2*H*-furo[2,3-*c*]pyran-3-carboxylate.

Example 171B

20 ethyl 5,5-dimethyl-4-oxo-4,7-dihydro-5*H*-furo[2,3-*c*]pyran-3-carboxylate

To a solution of the product from Example 171A (0.16 g, 0.624 mmol) and triethylamine (0.348 mL, 2.498 mmol) in CH₂Cl₂ (20 mL) was added methanesulfonyl chloride (0.097 mL, 1.249 mmol). After stirring at room temperature for 1 hour, the mixture was partitioned between saturated NaHCO₃ solution (10 mL) and CH₂Cl₂ (25 mL). The
25 layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (25 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered and concentrated. The residue was purified by chromatography on silica gel eluting with a gradient of 10-33% ethyl acetate in hexane to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.98 (s, 1H), 4.87 (s, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.44 (s, 6H), 1.38 (t, *J* = 7.1 Hz, 3H); MS (ESI) *m/z*
30 239 (M+H)⁺.

Example 171C

5,5-dimethyl-4-oxo-4,7-dihydro-5*H*-furo[2,3-*c*]pyran-3-carboxylic acid

The titled compound was prepared using the procedure described in Example 168B substituting the product from Example 171B for the product from Example 168A. ¹H NMR (300 MHz, CDCl₃) δ ppm 12.60 (s, 1H), 8.16 (s, 1H), 4.94 (s, 2H), 1.51 (s, 6H); MS (ESI) *m/z* 211 (M+H)⁺.

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Example 171D

N-[6-(4-acetylpiperazin-1-yl)-2-methoxypyridin-3-yl]-5,5-dimethyl-4-oxo-4,7-dihydro-5*H*-furo[2,3-*c*]pyran-3-carboxamide

The titled compound was prepared using the procedure described in Example 159B substituting the product from Example 171C for the product from Example 159A, and substituting 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone for 2-methyl-2*H*-indazol-5-amine. A gradient of 0-100% [10% ethanol in ethyl acetate] in ethyl acetate was used in place of 50 – 100% ethyl acetate in hexane as the eluent in the chromatography. ¹H NMR (300 MHz, CDCl₃) δ ppm 10.99 (s, 1H), 8.44 (d, *J* = 8.6 Hz, 1H), 8.15 (s, 1H), 6.20 (d, *J* = 8.6 Hz, 1H), 4.91 (s, 2H), 4.03 (s, 3H), 3.78 – 3.71 (m, 2H), 3.64 – 3.52 (m, 4H), 3.51 – 3.45 (m, 2H), 2.15 (s, 3H), 1.51 (s, 6H); MS (ESI) *m/z* 443 (M+H)⁺.

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Example 172

N-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-4-oxo-4,7-dihydrospiro[furo[2,3-*c*]pyran-5,3'-oxetane]-3-carboxamide

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Example 172A

2-((3-ethynyloxetan-3-yl)oxy)acetic acid

To a suspension of 60% dispersion of sodium hydride in mineral oil (0.912 g, 22.80 mmol) in tetrahydrofuran (20 mL) under nitrogen was added a solution of 3-ethynyloxetan-3-ol (CAS# 1352492-38-6) (0.559 g, 5.7 mmol) in tetrahydrofuran (5 mL). The mixture was stirred at room temperature for 30 minutes, and then a solution of bromoacetic acid (1.584 g, 11.40 mmol) in tetrahydrofuran (5 mL) was added dropwise. The mixture was diluted with tetrahydrofuran (7 mL), stirred overnight, cooled to 0 °C, treated with water (30 mL, dropwise at first), and concentrated to remove the tetrahydrofuran. This basic aqueous layer was washed with diethyl ether (2 × 50 mL, discarded), acidified with concentrated HCl and extracted with ethyl acetate (3 × 75 mL). The combined ethyl acetate layers were washed with brine, dried (MgSO₄), filtered and concentrated to provide the desired product which was carried onto the next step without further purification.

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Example 172B

methyl 2-((3-acetyloxetan-3-yl)oxy)acetate

To a solution of the product from Example 172A (890 mg, 5.7 mmol) in methanol (130 mL) was added mercury(II) acetate (182 mg, 0.570 mmol) followed by concentrated H₂SO₄ (~ 0.1 mL). The reaction was heated to 60 °C for 1 hour and cooled. NaHCO₃ (5 g) was added, and the mixture was stirred at room temperature for 10 minutes and concentrated to dryness. The residue was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with brine, dried (MgSO₄), filtered, concentrated and purified by chromatographed on silica gel eluting with a gradient of 15% to 50% ethyl acetate in hexane to provide the titled compound.

Example 172C

2,5-dioxaspiro[3.5]nonane-7,9-dione

To a solution of 1 M potassium *tert*-butoxide in *tert*-butanol (1.9 mL, 1.9 mmol) in tetrahydrofuran (10 mL) under N₂ cooled to 0 °C was added a solution of the product from Example 172B (181 mg, 0.962 mmol) in tetrahydrofuran (5 mL) dropwise over 5 minutes. The reaction was stirred at 0 °C for 30 minutes and concentrated to dryness. The residue was treated with 1 M HCl (5 mL) and extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with brine, dried (MgSO₄), filtered, and concentrated to provide the titled compound.

Example 172D

4-oxo-4,7-dihydrospiro[furo[2,3-*c*]pyran-5,3'-oxetane]-3-carboxylic acid

The titled compound was prepared using the procedure described in Example 163A substituting the product from Example 172C for methyl 3-hydroxy-1-methyl-5-oxocyclohex-3-enecarboxylate to provide the titled compound as the second isomer to elute from the column. ¹H NMR (300 MHz, CDCl₃) δ ppm 8.19 (s, 1H), 5.05 (s, 2H), 4.97 (dd, *J* = 7.1, 1.0 Hz, 2H), 4.80 (dd, *J* = 7.0, 0.9 Hz, 2H); MS (ESI) *m/z* 225 (M+H)⁺. The first isomer to elute from the chromatography column was 4-oxo-4,5-dihydrospiro[furo[2,3-*c*]pyran-7,3'-oxetane]-3-carboxylic acid.

Example 172E

N-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-4-oxo-4,7-dihydrospiro[furo[2,3-*c*]pyran-5,3'-oxetane]-3-carboxamide

The titled compound was prepared using the procedure described in Example 159B substituting the product from Example 172D for the product from Example 159A, and substituting 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone for 2-methyl-2*H*-indazol-5-amine. A gradient of 0-100% [10% ethanol in ethyl acetate] in ethyl acetate was used in place of 50 – 100% ethyl acetate in hexane as the eluent in the chromatography. ¹H NMR (300 MHz, CDCl₃) δ ppm 10.92 (s, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 8.19 (s, 1H), 6.58 – 6.48 (m, 2H), 5.05 – 4.98 (m, 4H), 4.78 (d, *J* = 6.8 Hz, 2H), 4.00 (s, 3H), 3.81 – 3.75 (m, 2H), 3.66 – 3.60 (m, 2H), 3.22 – 3.11 (m, 4H), 2.15 (s, 3H); MS (ESI) *m/z* 456 (M+H)⁺.

Example 173

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 173A

methyl 5,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxylate

To a solution of the product from Example 120A (100 mg, 0.478 mmol) in *N,N*-dimethylformamide (2.5 mL) under N₂ at 0 °C was added a 60% dispersion of sodium hydride in mineral oil (42.1 mg, 1.052 mmol). After stirring at 0 °C for 5 minutes, iodomethane (74.7 μL, 1.195 mmol) was added, and the reaction mixture was stirred at room temperature overnight. The mixture was diluted with diethyl ether (30 mL) and washed with water (twice, 20 mL and 20 mL), washed with brine, dried (MgSO₄), filtered and concentrated. The residue was purified by chromatography on silica gel eluting with a gradient of 50-100% (over 5 minutes) ethyl acetate in hexane to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.86 (s, 1H), 3.88 (s, 3H), 3.00 (s, 3H), 2.89 (s, 2H), 1.37 (s, 6H); MS (ESI) *m/z* 238 (M+H)⁺.

Example 173B

5,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxylic acid

The titled compound was prepared using the procedure described in Example 168B substituting the product from Example 173A for the product from Example 168A. ¹H NMR (300 MHz, CDCl₃) δ ppm 14.81 (s, 1H), 8.04 (s, 1H), 3.05 (s, 3H), 3.01 (s, 2H), 1.45 (s, 6H); MS (ESI) *m/z* 224 (M+H)⁺.

Example 173C

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

5 The titled compound was prepared using the procedure described in Example 159B substituting the product from Example 173B for the product from Example 159A, and substituting 1-(4-(5-amino-6-ethoxypyridin-2-yl)piperazin-1-yl)ethanone for 2-methyl-2*H*-indazol-5-amine. A gradient of 0-100% [10% ethanol in ethyl acetate] in ethyl acetate was used in place of 50 – 100% ethyl acetate in hexane as the eluent in the chromatography. ¹H
10 NMR (300 MHz, CDCl₃) δ ppm 12.18 (s, 1H), 8.59 (d, *J* = 8.5 Hz, 1H), 8.07 (s, 1H), 6.18 (d, *J* = 8.6 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 3.77 – 3.71 (m, 2H), 3.61 – 3.55 (m, 2H), 3.54 – 3.48 (m, 2H), 3.47 – 3.42 (m, 2H), 3.05 (s, 3H), 2.96 (s, 2H), 2.14 (s, 3H), 1.52 (t, *J* = 7.1 Hz, 3H), 1.41 (s, 6H); MS (ESI) *m/z* 470 (M+H)⁺.

15 Example 174

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2-hydroxyethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 174A

20 5-[2-(benzyloxy)ethyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxylic acid

To a solution of the product from Example 120A (5 g, 23.90 mmol) in *N,N*-dimethylformamide (80 mL) under N₂ was added a 60% dispersion of sodium hydride in mineral oil (2.87 g, 71.7 mmol). After stirring at room temperature for 10 minutes, ((2-bromoethoxy)methyl)benzene (15.42 g, 71.7 mmol) in *N,N*-dimethylformamide (20 mL) was added, and the reaction mixture was stirred at room temperature for 10 minutes, heated to 50 °C overnight, cooled, diluted with 50 mL of 1 M NaOH, diluted further with 50 mL of water, stirred for 15 minutes, diluted with water (400 mL) and washed with diethyl ether (2 × 100 mL). These diethyl ether washes were discarded. The aqueous layer was acidified with concentrated HCl and extracted with diethyl ether (3 × 100 mL). The combined diethyl ether extractions were washed with 0.1 M HCl (100 mL), washed with brine, dried (MgSO₄), filtered and concentrated. The residue was purified by chromatography on silica gel eluting with a gradient of 50-100% [9:1 CH₂Cl₂:ethyl acetate] in CH₂Cl₂ to provide the titled

compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 14.68 (s, 1H), 8.04 (s, 1H), 7.37 – 7.27 (m, 5H), 4.53 (s, 2H), 3.79 – 3.61 (m, 4H), 2.98 (s, 2H), 1.47 (s, 6H); MS (ESI) *m/z* 344 (M+H)⁺.

Example 174B

5 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[2-(benzyloxy)ethyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described in Example 159B substituting the product from Example 174A for the product from Example 159A, and substituting 1-(4-(5-amino-6-ethoxypyridin-2-yl)piperazin-1-yl)ethanone for 2-methyl-2*H*-
10 indazol-5-amine. A gradient of 0-100% [10% ethanol in ethyl acetate] in ethyl acetate was used in place of 50 – 100% ethyl acetate in hexane as the eluent in the chromatography. ¹H NMR (500 MHz, CDCl₃) δ ppm 12.10 (s, 1H), 8.59 (d, *J* = 8.5 Hz, 1H), 8.06 (s, 1H), 7.37 – 7.27 (m, 5H), 6.18 (d, *J* = 8.5 Hz, 1H), 4.54 (s, 2H), 4.40 (q, *J* = 7.0 Hz, 2H), 3.77 – 3.68 (m, 6H), 3.60 – 3.56 (m, 2H), 3.54 – 3.48 (m, 2H), 3.46 – 3.42 (m, 2H), 2.94 (s, 2H), 2.14 (s, 3H),
15 1.49 (t, *J* = 7.1 Hz, 3H), 1.44 (s, 6H); MS (ESI) *m/z* 590 (M+H)⁺.

Example 174C

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2-hydroxyethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

20 The titled compound was prepared using the procedure described in Example 9 substituting the product from Example 174B for the product from Example 8B. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.82 (s, 1H), 8.57 (d, *J* = 8.5 Hz, 1H), 8.09 (s, 1H), 6.18 (d, *J* = 8.6 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.90 – 3.82 (m, 2H), 3.77 – 3.70 (m, 4H), 3.61 – 3.41 (m, 6H), 3.30 (t, *J* = 4.6 Hz, 1H), 3.01 (s, 2H), 2.14 (s, 3H), 1.51 – 1.44 (m, 9H); MS (ESI)
25 *m/z* 500 (M+H)⁺.

Example 175

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2-methoxyethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

30 The titled compound was prepared using the procedure described in Example 159B substituting the product from Example 145A for the product from Example 159A, and substituting 1-(4-(5-amino-6-ethoxypyridin-2-yl)piperazin-1-yl)ethanone for 2-methyl-2*H*-indazol-5-amine. A gradient of 0-100% [10% ethanol in ethyl acetate] in ethyl acetate was used in place of 50 – 100% ethyl acetate in hexane as the eluent in the chromatography. ¹H

NMR (300 MHz, CDCl₃) δ ppm 12.09 (s, 1H), 8.59 (d, J = 8.5 Hz, 1H), 8.06 (s, 1H), 6.18 (d, J = 8.6 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 3.77 – 3.41 (m, 12H), 3.37 (s, 3H), 2.96 (s, 2H), 2.14 (s, 3H), 1.51 (t, J = 7.1 Hz, 3H), 1.45 (s, 6H); MS (ESI) m/z 514 (M+H)⁺.

5 Example 176

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[2-(2-hydroxyethoxy)ethyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 176A

10 5-{2-[2-(benzyloxy)ethoxy]ethyl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxylic acid

The titled compound was prepared using the procedure described in Example 8A substituting ((2-(2-bromoethoxy)ethoxy)methyl)benzene (CAS# 125562-32-5) for benzyl 2-bromoethyl ether, and substituting the product from Example 120A for the product from

15 Example 1E. MS (ESI) m/z 388 (M+H)⁺.

Example 176B

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-{2-[2-(benzyloxy)ethoxy]ethyl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

20 The procedure for Example 8B substituting the product from Example 176A for the product from Example 8A, provided the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 12.08 (s, 1H), 8.58 (d, J = 8.5 Hz, 1H), 8.06 (s, 1H), 7.35 – 7.27 (m, 5H), 6.18 (d, J = 8.6 Hz, 1H), 4.56 (s, 2H), 4.39 (q, J = 7.1 Hz, 2H), 3.82 – 3.36 (m, 16H), 2.92 (s, 2H), 2.14 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H), 1.44 (s, 6H); MS (ESI) m/z 634 (M+H)⁺.

25

Example 176C

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[2-(2-hydroxyethoxy)ethyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

30 The procedure for Example 9 substituting the product from Example 176B for the product from Example 8B, provided the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 12.03 (s, 1H), 8.58 (d, J = 8.5 Hz, 1H), 8.07 (s, 1H), 6.18 (d, J = 8.6 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 3.78 – 3.69 (m, 8H), 3.54 (dddd, J = 28.9, 19.3, 7.0, 3.3 Hz, 8H), 2.97 (s, 2H), 2.14 (s, 3H), 1.98 (t, J = 6.0 Hz, 1H), 1.50 (t, J = 7.1 Hz, 3H), 1.46 (s, 6H); MS (ESI) m/z 544 (M+H)⁺.

Example 177

N-[6-(4-acetylpiperazin-1-yl)-2-(2-methoxyethoxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

5 The titled compound was prepared using the procedure described for Example 19 substituting the product from Example 20C for 1-(4-(5-amino-6-ethoxypyridin-2-yl)piperazin-1-yl)ethanone, and substituting the product from Example 120A for the product from Example 1E. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.71 (s, 1H), 8.53 (d, *J* = 8.6 Hz, 1H), 8.08 (s, 1H), 6.20 (d, *J* = 8.6 Hz, 1H), 5.37 (bs, 1H), 4.51 (t, *J* = 5.3 Hz, 2H), 3.87 (t, *J* = 5.3 Hz, 2H), 3.77 – 3.70 (m, 2H), 3.60 – 3.42 (m, 6H), 3.44 (s, 3H), 2.94 (s, 2H), 2.14 (s, 3H), 1.43 (s, 6H); MS (ESI) *m/z* 486 (M+H)⁺.

Example 178

15 *N*-[6-(4-acetylpiperazin-1-yl)-2-(2,2,2-trifluoroethoxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 178A

1-(4-(5-amino-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)piperazin-1-yl)ethanone

20 The titled compound was prepared by sequentially using the procedures described for Example 20A, Example 20B, and Example 20C substituting 2,2,2-trifluoroethanol for 2-methoxyethanol in Example 20A. ¹H NMR (300 MHz, CDCl₃) δ ppm 6.97 (d, *J* = 8.2 Hz, 1H), 6.20 (d, *J* = 8.2 Hz, 1H), 4.74 (q, *J* = 8.6 Hz, 2H), 3.78 – 3.71 (m, 2H), 3.63 – 3.56 (m, 2H), 3.42 (bs, 2H), 3.40 – 3.34 (m, 2H), 3.31 – 3.26 (m, 2H), 2.14 (s, 3H); MS (ESI) *m/z* 319 (M+H)⁺.

25

Example 178B

N-[6-(4-acetylpiperazin-1-yl)-2-(2,2,2-trifluoroethoxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

30 The titled compound was prepared using the procedure described for Example 19 substituting the product from Example 178A for 1-(4-(5-amino-6-ethoxypyridin-2-yl)piperazin-1-yl)ethanone, and substituting the product from Example 120A for the product from Example 1E. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.82 (bs, 1H), 8.49 (d, *J* = 8.6 Hz, 1H), 8.09 (s, 1H), 6.31 (d, *J* = 8.6 Hz, 1H), 5.36 (bs, 1H), 4.80 (q, *J* = 8.6 Hz, 2H), 3.78 –

3.71 (m, 2H), 3.67 – 3.36 (m, 6H), 2.95 (s, 2H), 2.15 (s, 3H), 1.44 (s, 6H); MS (ESI) m/z 510 (M+H)⁺.

Example 179

5 *N*-[6-(4-acetylpiperazin-1-yl)-2-(oxetan-3-yloxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 19 substituting the product from Example 21C for 1-(4-(5-amino-6-ethoxypyridin-2-yl)piperazin-1-yl)ethanone, and substituting the product from Example 120A for the product
10 from Example 1E. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.88 (s, 1H), 8.59 (d, *J* = 8.6 Hz, 1H), 8.10 (s, 1H), 6.24 (d, *J* = 8.6 Hz, 1H), 5.64 (p, *J* = 5.8 Hz, 1H), 5.41 (bs, 1H), 5.04 – 4.87 (m, 4H), 3.76 – 3.69 (m, 2H), 3.61 – 3.54 (m, 2H), 3.51 – 3.31 (m, 4H), 2.96 (s, 2H), 2.14 (s, 3H), 1.45 (s, 6H); MS (ESI) m/z 484 (M+H)⁺.

Example 180

15 *N*-[6-(4-acetylpiperazin-1-yl)-2-(tetrahydro-2*H*-pyran-4-yloxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared by sequentially using the procedures described for Example 20A, Example 20B, Example 20C and Example 19 substituting tetrahydro-2*H*-
20 pyran-4-ol for 2-methoxyethanol in Example 20A and substituting the product from Example 120A for the product from Example 1E in Example 19. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.73 (s, 1H), 8.48 (d, *J* = 8.6 Hz, 1H), 8.09 (s, 1H), 6.21 (d, *J* = 8.6 Hz, 1H), 5.36 (bs, 1H), 5.33 – 5.24 (m, 1H), 4.17 – 3.99 (m, 2H), 3.77 – 3.70 (m, 2H), 3.67 – 3.55 (m, 4H), 3.52 – 3.39 (m, 4H), 2.95 (s, 2H), 2.14 (s, 3H), 2.11 – 1.88 (m, 4H), 1.44 (s, 6H); MS (ESI) m/z 512
25 (M+H)⁺.

Example 181

N-{6-(4-acetylpiperazin-1-yl)-2-[(3*S*)-tetrahydrofuran-3-yloxy]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

30 The titled compound was prepared by sequentially using the procedures described for Example 20A, Example 20B, Example 20C and Example 19 substituting (3*S*)-(+)-3-hydroxytetrahydrofuran for 2-methoxyethanol in Example 20A and substituting the product from Example 120A for the product from Example 1E in Example 19. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.76 (bs, 1H), 8.58 (d, *J* = 8.6 Hz, 1H), 8.08 (d, *J* = 3.2 Hz, 1H), 6.22 (d, *J* =

8.6 Hz, 1H), 5.56 – 5.46 (m, 1H), 5.37 (bs, 1H), 4.17 – 3.98 (m, 3H), 3.90 (td, $J = 8.1, 4.3$ Hz, 1H), 3.78 – 3.70 (m, 2H), 3.62 – 3.55 (m, 2H), 3.55 – 3.35 (m, 4H), 2.94 (s, 2H), 2.45 – 2.32 (m, 1H), 2.32 – 2.16 (m, 1H), 2.15 (s, 3H), 1.43 (s, 6H); MS (ESI) m/z 498 (M+H)⁺.

5 Example 182

N-[6-(4-formylpiperazin-1-yl)-2-(2-methoxyethoxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 182A

10 *tert*-butyl 4-[5-{{[(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino}-6-(2-methoxyethoxy)pyridin-2-yl]piperazine-1-carboxylate

The titled compound was prepared by sequentially using the procedures described for Example 20A, Example 20B, Example 20C and Example 19 substituting *tert*-butyl piperazine-1-carboxylate (CAS# 57260-71-6) for 1-acetylpiperazine in Example 20B, substituting the product from Example 120A for the product from Example 1E in Example 19, and washing the CH₂Cl₂ layers with 0 °C 0.1 M HCl in place of 1 M HCl in Example 19. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.68 (bs, 1H), 8.51 (d, $J = 8.5$ Hz, 1H), 8.08 (s, 1H), 6.19 (d, $J = 8.6$ Hz, 1H), 5.30 (bs, 1H), 4.51 (t, $J = 5.3$ Hz, 2H), 3.86 (t, $J = 5.3$ Hz, 2H), 3.56 – 3.51 (m, 4H), 3.44 – 3.44 (m, 4H), 3.44 (s, 3H), 2.94 (s, 2H), 1.48 (s, 9H), 1.43 (s, 6H); MS (ESI) m/z 544 (M+H)⁺.

Example 182B

N-[2-(2-methoxyethoxy)-6-(piperazin-1-yl)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide dihydrochloride

25 A solution of the product from Example 182A (0.5 g, 0.920 mmol) in CH₂Cl₂ (30 mL) at 0 °C was treated with a stream of HCl gas for 3 minutes until saturated. The mixture was warmed and allowed to stand at room temperature for 15 minutes. The mixture was concentrated with a stream of N₂. The residue was treated with ethyl acetate (50 mL), and the sides of the vessel were scraped with a spatula to free the solid. The solid was collected by filtration, washed with ethyl acetate and dried under vacuum with heating to provide the titled compound. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 12.05 (s, 1H), 9.13 (bs, 2H), 8.31 (d, $J = 8.6$ Hz, 1H), 8.28 (s, 1H), 8.04 (s, 1H), 6.44 (d, $J = 8.6$ Hz, 1H), 4.41 (t, $J = 5.0$ Hz, 2H), 3.76 – 3.71 (m, 2H), 3.70 – 3.63 (m, 4H), 3.29 (s, 3H), 3.18 (bs, 4H), 2.99 (s, 2H), 1.32 (s, 6H); MS (ESI) m/z 444 (M+H)⁺.

Example 182C

N-[6-(4-formylpiperazin-1-yl)-2-(2-methoxyethoxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

5 To a mixture of the product from Example 182B (53 mg, 0.103 mmol) in ethanol (1 mL) was added triethylamine (143 μ L, 1.026 mmol) and ethyl formate (167 μ L, 2.053 mmol). The reaction was heated to 80 °C for 24 hours, cooled, and partitioned between 1 M NaOH (20 mL) and CH₂Cl₂ (25 mL). The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (25 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered,
10 concentrated and purified by chromatography on silica gel eluting with a gradient of 0-100% [20% ethanol in ethyl acetate] in ethyl acetate to provide the titled compound. ¹H NMR (500 MHz, CDCl₃) δ ppm 11.77 (s, 1H), 8.53 (d, *J* = 8.5 Hz, 1H), 8.12 (s, 1H), 8.09 (s, 1H), 6.23 (d, *J* = 8.6 Hz, 1H), 5.61 (bs, 1H), 4.51 (t, *J* = 5.2 Hz, 2H), 3.87 (t, *J* = 5.2 Hz, 2H), 3.70 – 3.63 (m, 2H), 3.57 – 3.44 (m, 6H), 3.44 (s, 3H), 2.94 (s, 2H), 1.42 (s, 6H); MS (ESI) *m/z* 472
15 (M+H)⁺.

Example 183

N-{6-(4-acetylpiperazin-1-yl)-2-[(1-oxidothietan-3-yl)oxy]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

20

Example 183A

1-(4-(5-nitro-6-(thietan-3-yloxy)pyridin-2-yl)piperazin-1-yl)ethanone

The titled compound was prepared by sequentially using the procedures described for Example 20A and Example 20B substituting thietan-3-ol (CAS# 10304-16-2) for 2-methoxyethanol in Example 20A. The residue was purified by chromatography on silica gel eluting with a gradient of 25-100% [20% ethanol in ethyl acetate] in ethyl acetate to provide
25 the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 8.30 (d, *J* = 9.1 Hz, 1H), 6.21 (d, *J* = 9.1 Hz, 1H), 5.97 – 5.85 (m, 1H), 3.88 – 3.57 (m, 10H), 3.41 (dd, *J* = 9.7, 7.7 Hz, 2H), 2.16 (s, 3H).

30

Example 183B

1-(4-(5-nitro-6-((1-oxidothietan-3-yl)oxy)pyridin-2-yl)piperazin-1-yl)ethanone

A solution of 1-(4-(5-nitro-6-(thietan-3-yloxy)pyridin-2-yl)piperazin-1-yl)ethanone (72 mg, 0.213 mmol, Example 183A) in CH₂Cl₂ (2 mL) was treated with a solution of 3-

chloroperoxybenzoic acid (52.5 mg, 0.213 mmol) in CH₂Cl₂ stirred at room temperature overnight and partitioned between NaHCO₃ solution and CH₂Cl₂. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (25 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered and concentrated. The residue was purified by chromatography on silica gel eluting with a gradient of 10-100% [10% methanol in CH₂Cl₂] in CH₂Cl₂ to provide the titled compound.

Example 183C

1-(4-(5-amino-6-((1-oxidothietan-3-yl)oxy)pyridin-2-yl)piperazin-1-yl)ethanone

10 A solution of the product from Example 183B (50 mg, 0.141 mmol) and tetrahydrofuran (10 mL) was added to 5% Pd/C, wet, (10 mg) in a 50 mL pressure bottle and stirred for 16 hours under H₂ (30 psi). The mixture was filtered and concentrated to provide the titled compound. MS (APCI) *m/z* 325 (M+H)⁺.

Example 183D

15 *N*-{6-(4-acetylpiperazin-1-yl)-2-[(1-oxidothietan-3-yl)oxy]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

The titled compound was prepared using the procedure described for Example 19 substituting the product from Example 183C for 1-(4-(5-amino-6-ethoxypyridin-2-yl)piperazin-1-yl)ethanone, and substituting the product from Example 120A for the product from Example 1E. The residue was chromatographed on silica gel eluted with a gradient of 0% to 100% [50% ethanol in ethyl acetate] in ethyl acetate to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.85 (s, 1H), 8.66 (d, *J* = 8.7 Hz, 1H), 8.10 (s, 1H), 6.38 (d, *J* = 8.7 Hz, 1H), 6.19 – 6.06 (m, 1H), 3.99 – 3.90 (m, 2H), 3.77 (s, 2H), 3.66 – 3.55 (m, 20 4H), 3.45 (d, *J* = 25.8 Hz, 4H), 2.97 (s, 2H), 2.15 (s, 3H), 1.46 (s, 6H); MS (ESI) *m/z* 516 (M+H)⁺.

Example 184

30 *N*-[6-(1-acetylpiperidin-4-yl)-2-ethoxypyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

Example 184A

tert-butyl 6-ethoxy-5-nitro-5',6'-dihydro-[2,4'-bipyridine]-1'(2'H)-carboxylate

A mixture of 6-chloro-2-ethoxy-3-nitropyridine (CAS# 1094323-19-9) (370 mg, 1.826 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate (CAS# 286961-14-6) (490 mg, 1.585 mmol), tetrakis(triphenylphosphine)palladium(0) (92 mg, 0.079 mmol), 1.5 M sodium carbonate (2.64 mL, 3.96 mmol) and dioxane (6 mL) under nitrogen was heated to 80 °C for 24 hours and then allowed to cool to room temperature. The mixture was partitioned between ethyl acetate (75 mL) and water (25 mL). The layers were separated, and the organic layer was washed with brine, dried (MgSO₄), filtered, concentrated and purified by chromatography on silica gel eluting with a gradient of 15 to 50% ethyl acetate in heptane to provide the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 8.27 (d, *J* = 8.3 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.84 (bs, 1H), 4.59 (q, *J* = 7.0 Hz, 2H), 4.18 (q, *J* = 3.0 Hz, 2H), 3.65 (t, *J* = 5.7 Hz, 2H), 2.67 – 2.56 (m, 2H), 1.50 – 1.44 (m, 12H); MS (ESI) *m/z* 249 (M+H)⁺.

Example 184B

tert-butyl 4-(5-amino-6-ethoxypyridin-2-yl)piperidine-1-carboxylate

The titled compound was prepared using the procedure described for Example 20C substituting the product from Example 184A for the product from Example 20B. ¹H NMR (300 MHz, CDCl₃) δ ppm 6.98 (d, *J* = 7.6 Hz, 1H), 6.55 (d, *J* = 7.6 Hz, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 4.23 – 4.09 (m, 2H), 2.82 (t, *J* = 12.0 Hz, 2H), 2.67 (tt, *J* = 11.6, 3.5 Hz, 1H), 1.90 – 1.80 (m, 2H), 1.66 (qd, *J* = 12.7, 4.4 Hz, 2H), 1.48 (s, 9H), 1.40 (t, *J* = 7.0 Hz, 3H); MS (ESI) *m/z* 322 (M+H)⁺.

Example 184C

tert-butyl 4-(5-[(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino)-6-ethoxypyridin-2-yl)piperidine-1-carboxylate

To a solution of the product from Example 120A (100 mg, 0.479 mmol) in tetrahydrofuran (30 mL) under N₂ was added triethylamine (200 μL, 1.437 mmol) followed by ethyl chloroformate (46.0 μL, 0.479 mmol). After stirring at room temperature for 1 hour, The product of Example 184B, *tert*-butyl 4-(5-amino-6-ethoxypyridin-2-yl)piperidine-1-carboxylate (154 mg, 0.479 mmol), was added, and the reaction was stirred over the weekend, concentrated to dryness, suspended with ethyl acetate (75 mL), cooled to 0 °C, washed with 0 °C 0.1 M HCl (25 mL), washed with saturated NaHCO₃ solution, washed with brine, dried (MgSO₄), filtered, concentrated and purified by chromatography on silica gel eluting with a gradient of 0-100% ethyl acetate in [9:1 CH₂Cl₂:ethyl acetate] to provide the

titled compound. ^1H NMR (300 MHz, CDCl_3) δ ppm 11.86 (s, 1H), 8.60 (d, $J = 7.9$ Hz, 1H), 8.11 (s, 1H), 6.71 (d, $J = 8.0$ Hz, 1H), 5.36 (s, 1H), 4.52 (q, $J = 7.0$ Hz, 2H), 4.33 – 4.07 (m, 2H), 2.95 (s, 2H), 2.92 – 2.65 (m, 3H), 1.94 – 1.84 (m, 2H), 1.82 – 1.61 (m, 2H), 1.50 – 1.46 (m, 12H), 1.44 (s, 6H); MS (ESI) m/z 513 ($\text{M}+\text{H}$) $^+$.

5

Example 184D

N-[2-ethoxy-6-(piperidin-4-yl)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide dihydrochloride

The titled compound was prepared using the procedure described for Example 182B substituting the product from Example 184C for the product from Example 182A. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.30 (s, 1H), 9.15 (d, $J = 9.1$ Hz, 1H), 8.81 (d, $J = 9.5$ Hz, 1H), 8.49 (d, $J = 7.9$ Hz, 1H), 8.34 (s, 1H), 8.10 (s, 1H), 6.85 (d, $J = 8.0$ Hz, 1H), 4.41 (q, $J = 7.0$ Hz, 2H), 3.38 – 3.30 (m, 2H), 3.00 (s, 2H), 3.09 – 2.82 (m, 3H), 2.10 – 1.82 (m, 4H), 1.39 (t, $J = 7.0$ Hz, 3H), 1.33 (s, 6H); MS (ESI) m/z 413 ($\text{M}+\text{H}$) $^+$.

15

Example 184E

N-[6-(1-acetylpiperidin-4-yl)-2-ethoxypyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide

To a mixture of the product from Example 184D (68 mg, 0.140 mmol) and triethylamine (58.6 μL , 0.420 mmol) in CH_2Cl_2 (5 mL) was added acetic anhydride (26.4 μL , 0.280 mmol). The reaction was stirred at room temperature for 2 hours and concentrated to dryness. The residue was dissolved in tetrahydrofuran (2 mL) and methanol (2 mL). The solution was treated with 1 M NaOH (1 mL), stirred at room temperature for 15 minutes, and partitioned between 1 M HCl (15 mL) and ethyl acetate (50 mL). The layers were separated and the ethyl acetate layer was washed with saturated NaHCO_3 solution, washed with brine, dried (MgSO_4), filtered and concentrated to provide the titled compound. ^1H NMR (300 MHz, CDCl_3) δ ppm 11.90 (s, 1H), 8.63 (d, $J = 7.9$ Hz, 1H), 8.11 (s, 1H), 6.72 (d, $J = 7.9$ Hz, 1H), 5.35 (bs, 1H), 4.79 – 4.63 (m, 1H), 4.59 – 4.47 (m, 2H), 3.30 – 3.06 (m, 1H), 2.95 (s, 2H), 3.03 – 2.59 (m, 3H), 2.14 (s, 3H), 1.99 – 1.90 (m, 2H), 1.81 – 1.66 (m, 2H), 1.51 – 1.42 (m, 9H); MS (ESI) m/z 455 ($\text{M}+\text{H}$) $^+$.

30

Example 185

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2,5-difluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

Example 185A

6-(2,5-difluorophenyl)-7-oxaspiro[bicyclo[4.1.0]heptane-3,2'-[1,3]dioxolane]

To a solution of 8-(2,5-difluorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene (CAS#
5 1187537-71-8) (1.44 g, 5.71 mmol) (10436912-0842) in CH₂Cl₂ (30 mL) was added 3-chloroperoxybenzoic acid (1.92 g, 8.56 mmol), and the reaction was stirred at room temperature overnight. The mixture was diluted with CH₂Cl₂, washed with water, washed with saturated NaHCO₃ solution, washed with brine, dried (Na₂SO₄), filtered, and concentrated. The residue was purified by chromatography on silica gel eluting with 10%
10 ethyl acetate in heptane to provide the titled compound.

Example 185B

8-(2,5-difluorophenyl)-1,4-dioxaspiro[4.5]decan-7-ol

A mixture of 10% Pd/C (3.5 g, 3.29 mmol) and the product from Example 185A (10
15 g, 37.3 mmol) in methanol (150 mL) was stirred at room temperature under H₂ (50 psi) for 12 hours, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with 10% ethyl acetate in heptane to provide the titled compound.

Example 185C

20 8-(2,5-difluorophenyl)-1,4-dioxaspiro[4.5]decan-7-one

A mixture of Dess-Martin periodinane (CAS# 87413-09-0) (17.26 g, 40.7 mmol) and the product from Example 185B (10 g, 37.0 mmol) in CH₂Cl₂ (50 mL) was stirred at room temperature for 12 hours and concentrated. The residue was purified by chromatography on silica gel eluting with 10% ethyl acetate in heptane to provide the titled compound.

25

Example 185D

4-(2,5-difluorophenyl)cyclohexane-1,3-dione

To a solution of the product from Example 185C (4g, 14.91 mmol) in acetone (20 mL) was added 37% HCl (20 mL), and the mixture was stirred at 80 °C for 2 hours and
30 cooled to room temperature. The reaction mixture was diluted with saturated K₂CO₃ and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to provide the titled compound.

Example 185E

methyl 5-(2,5-difluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylate

To a solution of the product from Example 185D (4.05 g, 18.06 mmol) in ethanol (60 mL) at 0 °C was added sodium ethoxide (1.598 g, 23.48 mmol) portionwise, and the mixture
5 was stirred for 30 minutes at 0 °C. Ethyl bromopyruvate (2.95 mL, 23.48 mmol) was added dropwise, and the reaction mixture was stirred at 0 °C for 30 minutes, stirred at room temperature for 3 hours, and concentrated. The residue was taken up in 1,4-dioxane (80 mL) and 4 M HCl (80 mL) was added. The resulting mixture was stirred at 100 °C for 3 hours and concentrated to dryness and suspended in ethyl ether (100 mL). The solid was collected
10 and dried to afford a mixture of 5-(2,5-difluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylic acid and 7-(2,5-difluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylic acid. This solid was dissolved in methanol (50 mL) and concentrated H₂SO₄ (2 mL) was added. The mixture was heated to 80 °C for 16 hours, cooled and concentrated. The residue was purified by chromatography on silica gel eluting
15 with 30:1 petroleum ether/ethyl acetate to provide the titled compound as the first isomer to elute from the column. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.95 (s, 1H), 7.03 (td, *J* = 9.1, 4.6 Hz, 1H), 6.98 – 6.91 (m, 1H), 6.87 (ddd, *J* = 8.7, 5.6, 3.1 Hz, 1H), 3.97 (dd, *J* = 12.4, 4.5 Hz, 1H), 3.85 (s, 3H), 3.16 – 3.00 (m, 2H), 2.56 – 2.43 (m, 1H), 2.42 – 2.34 (m, 1H); MS (ESI) *m/z* 307 (M+H)⁺. The second isomer to elute from the chromatography column was methyl
20 7-(2,5-difluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylate.

Example 185F

5-(2,5-difluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylic acid

The titled compound was prepared using the procedure described for Example 168B
25 substituting the product from Example 185E for the product from Example 168A. ¹H NMR (400 MHz, DMSO-D₂O) δ ppm 9.92 – 9.84 (m, 1H), 8.44 (s, 1H), 7.37 (td, *J* = 9.4, 4.6 Hz, 1H), 7.26 (tdd, *J* = 9.0, 6.6, 3.3 Hz, 2H), 4.79 (dd, *J* = 9.7, 5.3 Hz, 1H), 2.85 (ddd, *J* = 16.7, 11.7, 4.8 Hz, 1H), 2.66 (dt, *J* = 17.0, 4.5 Hz, 1H), 2.47 (dq, *J* = 13.2, 5.0 Hz, 1H), 2.41 – 2.29 (m, 1H); MS (ESI) *m/z* 293 (M+H)⁺.

30

Example 185G

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2,5-difluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide

The procedure for Example 8B substituting the product from Example 185F for the product from Example 8A, provided the titled compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 11.37 (s, 1H), 8.55 (d, *J* = 8.5 Hz, 1H), 8.15 (s, 1H), 7.15 – 6.87 (m, 3H), 6.29 (d, *J* = 8.5 Hz, 1H), 4.34 – 4.20 (m, 2H), 4.04 (dd, *J* = 12.6, 4.7 Hz, 1H), 3.80 – 3.73 (m, 2H), 3.66 – 3.57 (m, 2H), 3.53 – 3.39 (m, 4H), 3.19 – 3.10 (m, 2H), 2.66 – 2.34 (m, 2H), 2.13 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); MS (ESI) *m/z* 539 (M+H)⁺.

Determination of Biological Activity

Abbreviations: ahx for 2-aminohexanoic acid; ATP for adenosine triphosphate; BSA for bovine serum albumin; EDTA for ethylenediaminetetraacetic acid; HEPES for HEPES for 2-(4-(2-hydroxyethyl)piperazin-1-yl)ethanesulfonic acid; LCK for leukocyte specific protein tyrosine kinase; Tween® 20 for polyethylene glycol sorbitan monolaurate.

Determination of inhibitory potency at TrkA kinase, TrkB kinase, and TrkC kinase

TrkA enzyme was obtained from Invitrogen (as catalog numbers PV3144, PV3616, and PV3617, respectively). Enzyme activity was measured in an HTRF® (homogeneous time resolved fluorescence) assay, which detects enzymatic phosphorylation of a biotinylated synthetic peptide substrate (an LCK peptide analog, biotin-ahx-GAEEEEIYAAFFA, from Genemed Synthesis). Phosphorylation is assessed by HTRF® in the presence of an anti-phosphotyrosine antibody conjugated to Eu³⁺ cryptate (Cisbio) as donor fluorophore, and streptavidin conjugated to allophycocyanin (ProZyme) as acceptor fluorophore. The HTRF® signal was detected at two different wavelengths (620 nm and 665 nm) which were used to calculate the fluorescence ratio.

TrkA enzyme was titrated to a concentration optimized to ensure accurate measurement of the initial reaction rate. To allow the TrkA enzyme to undergo activation and auto-phosphorylation, a 20 minute pre-incubation with ATP was carried out (at twice the final targeted enzyme and ATP concentration) prior to addition of test compound and the peptide substrate.

TrkA in vitro assays were performed by pre-incubating TrkA (2-10 nM) with ATP (200 μM) for 20 minutes at ambient temperature in 50 mM HEPES pH 7.4, 10 mM MgCl₂, 2 mM MnCl₂, 100 μM Na₃VO₄, 1 mM dithiothreitol, 0.01% BSA (bovine serum albumin). Then, to the activated Trk enzyme mixture was added the test compound in 2% dimethyl sulfoxide. After 10 minutes, the peptide substrate (125 nM) was added. After 1 hour,

enzyme reactions were terminated by addition of equal reaction volumes of detection/stop reagent (containing 0.2 µg/mL anti-phosphotyrosine monoclonal antibody labeled with europium from Cisbio (catalog# PT66-K), and 4 µg/mL PhycoLink® Streptavidin-Allophycocyanin conjugate from ProZyme (catalog# PJ25S) in 60 mM EDTA in 40 mM HEPES pH 7.4, 480 mM KF, 0.01% Tween® 20 and 0.1% BSA bovine serum albumin). Reaction plates were stored at 4 °C overnight before reading the fluorescence ratio signal on a PerkinElmer EnVision™ fluorescence detector. Individual reaction wells were stopped at time points to obtain reaction rates. The test inhibitor compounds were assayed in duplicate, at half-log serial dilutions over a range of concentrations (e.g. starting at 50 µM or 5 µM as the high compound concentration). The percent Trk enzyme inhibition was calculated from the initial rates of the inhibited reactions relative to the uninhibited control. IC₅₀ values were calculated by fitting the inhibition percent to the concentration of inhibitor [I] in the assay in equation 1 below, to solve for the IC₅₀.

$$\text{Inhibition \%} = 100[I]/([I] + [IC_{50}]) \quad \text{equation 1}$$

Example	IC ₅₀ TrkA [µM]	Example	IC ₅₀ TrkA [µM]
1	0.0442	94	0.0015
2	0.0602	95	0.0043
3	0.1730	96	0.0067
4	0.3750	97	0.0048
5	0.0544	98	0.0015
6	0.0467	99	0.0033
7	0.2120	100	0.0235
8	0.0695	101	0.0195
9	0.0051	102	0.0127
10	0.0559	103	0.0169
11	0.0640	104	0.0060
12	0.0996	105	0.0235
13	0.1660	106	0.0286
14	0.1108	107	0.0069
15	0.0693	108	0.2260

16	0.2790		109	0.2250
17	0.0814		110	0.0392
18	0.0598		111	0.0039
19	0.0163		112	0.0273
20	0.0259		113	0.0654
21	0.0216		114	0.0072
22	0.2000		115	0.0085
23	0.2568		116	0.0031
24	0.1890		117	0.0053
25	0.1120		118	0.0030
26	0.2020		119	0.0068
27	0.4280		120	0.0280
28	0.1100		121	0.0181
29	0.1690		122	0.0141
30	0.5210		123	0.0119
31	0.3900		124	0.0737
32	0.5540		125	0.0359
33	0.1110		126	0.0250
34	0.9100		127	0.0132
35	0.1170		128	0.0054
36	8.0100		129	0.0108
37	3.2100		130	0.0383
38	1.7200		131	0.0981
39	0.4300		132	0.0069
40	3.2400		133	0.0033
41	1.3900		134	0.0039
42	0.9180		135	0.0023
43	5.6400		136	0.0102
44	4.4700		137	0.0133
45	3.4800		138	0.0063
46	0.8550		139	0.0024
47	1.2200		140	0.0105

48	0.5060		141	0.0601
49	0.6310		142	0.0018
50	0.0907		143	0.0246
51	0.0189		144	0.0492
52	0.0184		145	0.0079
53	0.0675		146	0.0341
54	0.1080		147	0.0161
55	0.0208		148	0.0324
56	0.0485		149	0.1350
57	0.0346		150	0.0432
58	0.1050		151	0.0634
59	0.9840		152	0.0358
60	2.1100		153	0.0456
61	0.1950		154	0.0740
62	0.8270		155	0.0548
63	0.3190		156	0.0467
64	0.1340		157	0.0064
65	0.1460		158	0.0042
66	5.0800		159	0.0103
67	1.0800		160	0.2580
68	5.8200		161	0.8720
69	4.3400		162	0.0580
70	2.4900		163	0.1560
71	3.6700		164	0.0219
72	2.4800		165	0.0133
73	1.0800		166	0.1040
74	2.5900		167	0.0353
75	2.0500		168	0.0059
76	1.5300		169	0.0596
77	0.3670		170	0.0565
78	0.2360		171	0.0029
79	0.0447		172	0.0600

80	0.0677		173	0.0035
81	0.0658		174	0.0052
82	0.6820		175	0.0047
83	0.4960		176	0.0021
84	0.0053		177	0.0122
85	0.2660		178	0.0052
86	1.3200		179	0.0049
87	0.2240		180	0.0110
88	0.0950		181	0.0102
89	0.0047		182	0.0178
90	0.0047		183	0.0048
91	0.0070		184	0.0035
92	0.0182		185	0.0066
93	0.0163			

Determination of the efficacy of compounds to reduce osteoarthritis pain

Members of the TrkA inhibitors described above were tested and found effective in reducing osteoarthritis pain. The compounds tested were assessed in an in vivo model well known to those skilled in the art, the rat model of mono-iodoacetic acid induced osteoarthritis pain. A general review of various models of pain can be found in Joshi and Honore, Expert Opinion in Drug Discovery (2004) 1, pp. 323-334, and in the book 'Drug Discovery and Evaluation, 2nd edition (H. Gerhard Vogel, editor; Springer-Verlag, New York, 2002; pp. 702-706).

Activity in an Osteoarthritis Model

Pain behavior was assessed by measurement of hind limb grip force (GF) in adult osteoarthritic rats. Male Sprague Dawley rats, generally weighing 125-150 g, were injected in the unilateral knee joint with a single intra-articular injection of sodium monoiodoacetate (MIA). Rats were tested at 21-28 days following MIA injection. A behavioral measure of activity-induced pain was carried out. Measurements of the peak hind limb grip force were conducted by recording the maximum compressive force (CF_{max}), in grams of force, exerted on a hind limb strain gauge setup, in a commercially available grip force measurement system (Columbus Instruments, Columbus, OH).

During testing, each rat was gently restrained by grasping it around its rib cage and then allowed to grasp the wire mesh frame attached to the strain gauge. The experimenter then moved the animal in a rostral-to-caudal direction until the grip was broken. Each rat was sequentially tested twice at an approximately 2-3 minute interval to obtain a raw mean grip force (CF_{max}). This raw mean grip force data was in turn converted to a maximum hindlimb cumulative compressive force (CF_{max}), as the grams of force/kg of body weight, for each animal.

For evaluating the compound effects, the hind limb grip force testing in the MIA-treated rats was conducted generally 30-60 minutes after dosing with the test compound. A group of age-matched naïve (not injected with MIA) animals was added as a comparator to the drug-dosed groups. The vehicle control response for each group of MIA-treated animals was defined as the 0% response (0% effect), whereas the naïve control group was defined as the normal response and as 100% effect. The % effect = $(\text{Treatment } CF_{max} - \text{Vehicle } CF_{max}) / \text{Vehicle } CF_{max} \times 100$. Higher % effect numbers indicate increased relief from the pain in the model, with 100% indicating a return to the level of response seen in normal (non-osteoarthritic) animals. All experiments evaluating drug effects in this model were conducted in a randomized blinded fashion.

Animals, Compounds, and Dosing. Male Sprague Dawley rats (generally 250-300 g body weight at the time of testing) obtained from Charles River Laboratories (Wilmington, MA) were used for all experiments, unless indicated otherwise. The animals were housed in Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) approved facilities at AbbVie in a temperature-regulated environment under a controlled 12-hour light-dark cycle, with lights on at 6:00 a.m. Food and water were available *ad libitum* at all times except during testing. All testing was done following procedures outlined in protocols approved by AbbVie Institutional Animal Care and Use Committee.

The following table illustrates that compounds of the invention are effective in reducing osteoarthritis pain, with efficacy in the MIA model after oral dosing:

Compound Name (Example number)	dose (mg/kg, p.o.)	% Effect ¹
<i>N</i> -[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-	30	69 % **

(2-hydroxyethyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2- <i>c</i>]pyridine-3-carboxamide (Example 9)		
<i>N</i> -{2-methoxy-6-[4-(morpholin-4-ylcarbonyl)piperazin-1-yl]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2- <i>c</i>]pyridine-3-carboxamide (Example 121)	30	74 % ***
<i>N</i> -[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2- <i>c</i>]pyridine-3-carboxamide (Example 126)	100	47 % ** (tested 3 hours post dose)
<i>N</i> -[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2- <i>c</i>]pyridine-3-carboxamide (Example 128)	30	55 % *** (tested 3 hours post dose)
6,6-dimethyl- <i>N</i> -(2-methyl-2 <i>H</i> -indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide (Example 147)	300	69 % *** (tested 3 hours post dose)
<i>N</i> -[6-(4-acetylpiperazin-1-yl)-2-(2-methoxyethoxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2- <i>c</i>]pyridine-3-carboxamide (Example 177)	30	68 % ***

¹Data represent mean percent effect. Statistical significance * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ as compared to vehicle-treated animals. Abbreviations: SEM = standard error of the mean; p.o. = per os = oral dosed. Unless otherwise noted, testing was conducted 30-60 minutes postdosing of compound.

5

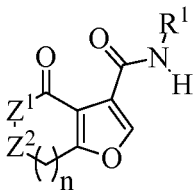
Representative compounds of the invention are active in this model, with preferred compounds of the invention active in the model at doses of ranging about 0.1 to 100 mg/kg of body weight.

It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, which is defined solely by the appended claims and their equivalents. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such
5 changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates, syntheses, formulations, or methods, or any combination of such changes and modifications of use of the invention, may be made without departing from the spirit and scope thereof.

10

WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

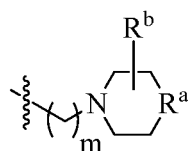
or a pharmaceutically acceptable salt, ester, amide, or radiolabelled form thereof,
wherein:

n is 1 or 2;

R¹ is phenyl or monocyclic heteroaryl, wherein the monocyclic heteroaryl contains
one or two ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the
phenyl or monocyclic heteroaryl is optionally substituted with 1, 2, or 3 substituents selected
from the group consisting of C₁-C₆-alkyl; C₁-C₆-alkylcarbonylamino;
hydroxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxy;
C₁-C₆-alkoxyC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl;
C₁-C₆-alkoxycarbonylC₁-C₆-alkyl; aminocarbonyl; C₁-C₆-alkylaminocarbonyl;
hydroxyC₁-C₆-alkylaminocarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylaminocarbonyl; cyano; carboxy;
hydroxy; hydroxyC₁-C₆-alkoxy; hydroxyC₁-C₆-alkyl; di(hydroxy)C₁-C₆-alkyl;
di(C₁-C₆-alkyl)amino; di(hydroxyC₁-C₆-alkyl)amino; di(C₁-C₆-alkoxyC₁-C₆-alkyl)amino;
(C₁-C₆-alkoxyC₁-C₆-alkyl)(hydroxyC₁-C₆-alkyl)amino; haloC₁-C₆-alkyl; and halogen;
wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to
the amide nitrogen pendant on the furan ring; or

R¹ is fused-bicyclic heteroaryl, wherein the fused-bicyclic heteroaryl contains 1, 2, 3
or 4 ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the fused-
bicyclic heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents selected from the
group consisting of C₁-C₆-alkyl; C₁-C₆-alkylcarbonylamino;
hydroxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxy;
C₁-C₆-alkoxyC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl;
C₁-C₆-alkoxycarbonylC₁-C₆-alkyl; C₃-C₇-cycloalkyloxy; M₄-M₇-heterocycleoxy, wherein the
heterocycle of M₄-M₇-heterocycleoxy is optionally substituted with C₁-C₆-alkyl;
aminocarbonyl; C₁-C₆-alkylaminocarbonyl; hydroxyC₁-C₆-alkylaminocarbonyl;

C₁-C₆-alkoxyC₁-C₆-alkylamincarbonyl; cyano; hydroxy; hydroxyC₁-C₆-alkoxy;
hydroxyC₁-C₆-alkyl; di(C₁-C₆alkyl)amino; di(hydroxyC₁-C₆-alkyl)amino;
di(C₁-C₆-alkoxyC₁-C₆-alkyl)amino; (C₁-C₆-alkoxyC₁-C₆-alkyl)(hydroxyC₁-C₆-alkyl)amino;
haloC₁-C₆-alkyl; halogen; C₁-C₆-alkylsulfonylaminoC₂-C₆-alkyl; and (i),



(i)

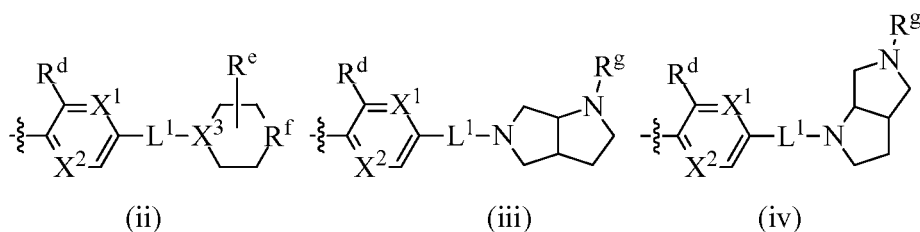
wherein R^a is selected from the group consisting of a bond, CH₂, CHR^b, O, S, and N-R^c;
wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to
the amide nitrogen pendant on the furan ring;

- 10 m is 2, 3 or 4 when (i) is attached to a ring nitrogen atom of the bicyclic heteroaryl; or
 m is 0, 1, 2, 3 or 4 when (i) is attached to a ring carbon atom of the bicyclic
heteroaryl;

R^b, at each occurrence, is independently selected from the group consisting of
hydrogen, C₁-C₆-alkyl, haloC₁-C₆-alkyl, C₁-C₆-alkoxyC₁-C₆-alkyl, and hydroxyC₁-C₆-alkyl;

- 15 R^c is selected from the group consisting of hydrogen, C₁-C₆-alkyl,
C₁-C₆-alkoxycarbonyl, C₁-C₆-alkylcarbonyl, C₁-C₆-alkylsulfonyl,
di(C₁-C₆-alkyl)aminosulfonyl, heterocyclecarbonyl, C₃-C₇-cycloalkylcarbonyl, -C(O)NH₂,
-C(O)NH(alkyl), -C(O)N(alkyl)₂ and -C(=NCN)NHCH₃; or

R¹ is (ii), (iii), or (iv);



20

wherein both X¹ and X² are CH, or one of X¹ and X² is N and the other is CH;

X³ is CH or N;

L¹ is a bond, C(O), or -NHC(O)-;

- 25 R^d is selected from the group consisting of hydrogen; C₁-C₆alkoxy;
fluoroC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₃-C₇-cycloalkyloxy;
C₃-C₇-cycloalkylC₁-C₆-alkoxy; hydroxyC₁-C₆-alkoxy; phenylC₁-C₆-alkoxyC₁-C₆-alkoxy;
M₄-M₇-heterocycleoxy, wherein the heterocycle of heterocycleoxy is optionally substituted

with C₁-C₆-alkyl or oxo; and phenoxy, wherein the phenyl of phenoxy is optionally substituted with hydroxyC₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkoxyC₁-C₆-alkoxy, or C₁-C₆-alkoxycarbonyl;

R^e at each occurrence is independently selected from the group consisting of
 5 hydrogen, C₁-C₆-alkyl, di(C₁-C₆-alkyl)amino, haloC₁-C₆-alkyl, C₁-C₆-alkoxyC₁-C₆-alkyl, and hydroxyC₁-C₆-alkyl;

R^f is selected from the group consisting of a bond, CH₂, CHR^e, CH₂CH₂, O, NR^g, and CH₂NR^g;

R^g is selected from the group consisting of hydrogen; C₁-C₆-alkyl;
 10 C₁-C₆-alkoxycarbonyl; C₁-C₆-alkylcarbonyl; C₁-C₆-alkylsulfonyl;
 di(C₁-C₆-alkyl)aminosulfonyl; C₃-C₇-cycloalkylcarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylcarbonyl;
 hydroxyC₂-C₆-alkyl; hydroxyC₁-C₆-alkylcarbonyl; formyl; -C(O)NH₂; -C(O)NH(alkyl);
 -C(O)N(alkyl)₂; -C(=NCN)NHCH₃; and M₄-M₇-heterocyclecarbonyl, wherein the
 heterocycle of heterocyclecarbonyl is optionally substituted with C₁-C₆-alkyl;

15 Z¹ is NR² or CR³R⁴;

R² is selected from the group consisting of hydrogen, C₁-C₆-alkyl,
 hydroxyC₂-C₆-alkyl, di(hydroxy)C₂-C₆-alkyl, C₁-C₆-alkoxyC₂-C₆-alkyl,
 hydroxyC₂-C₆-alkoxyC₂-C₆-alkyl, C₁-C₆-alkylcarbonyloxyC₂-C₆-alkyl,
 20 C₁-C₆-alkoxycarbonylC₁-C₆-alkyl, C₁-C₆-alkylcarbonylC₁-C₆-alkyl and
 phenylC₁-C₆-alkoxyC₂-C₆-alkyl;

R³ and R⁴ are each independently selected from the group consisting of hydrogen,
 C₁-C₆-alkyl, hydroxyC₁-C₆-alkyl, aminoC₁-C₆-alkyl, and phenyl, wherein phenyl is
 optionally substituted with 1, 2, 3 or 4 substituents selected from halogen, C₁-C₆-alkyl, and
 25 cyano; or

R³ and R⁴ taken together with the carbon atom to which they are attached form a
 M₄-M₇-heterocycle optionally substituted with 1, 2 or 3 halogen, C₁-C₆-alkyl, cyano or oxo;

Z² is O, NR⁵, or CR⁶R⁷;

30 R⁵ is selected from the group consisting of hydrogen, C₁-C₆-alkyl,
 C₁-C₆-alkylsulfonyl, C₁-C₆-alkylcarbonyl, and C₁-C₆-alkoxycarbonyl; and

R⁶ and R⁷ are each independently selected from the group consisting of hydrogen,
 C₁-C₆-alkyl, C₁-C₆-alkoxyC₁-C₆-alkyl, hydroxyC₁-C₆-alkyl, aminoC₁-C₆-alkyl,
 aminocarbonyl, and C₁-C₆-alkoxycarbonyl;

wherein one or more of R^3 , R^4 , R^6 and R^7 is other than hydrogen; or

R^6 and R^7 taken together with the carbon atom to which they are attached form a C_3 - C_6 -cycloalkyl or M_4 - M_7 -heterocycle, wherein the C_3 - C_6 -cycloalkyl or M_4 - M_7 -heterocycle are optionally substituted with 1, 2, or 3 substituents selected from C_1 - C_6 -alkyl, cyano, aminocarbonyl, halogen, oxo and C_1 - C_6 -alkylcarbonyl.

2. The compound of claim 1, wherein

Z^1 is NR^2 ; and

Z^2 is CR^6R^7 .

3. The compound of claim 2, wherein R^1 is phenyl or monocyclic heteroaryl, wherein the monocyclic heteroaryl contains one or two ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the phenyl or monocyclic heteroaryl is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C_1 - C_6 -alkyl; C_1 - C_6 -alkylcarbonylamino; hydroxy C_1 - C_6 -alkylcarbonylamino; C_1 - C_6 -alkoxy C_1 - C_6 -alkylcarbonylamino; C_1 - C_6 -alkoxy; C_1 - C_6 -alkoxy C_1 - C_6 -alkoxy; C_1 - C_6 -alkoxy C_1 - C_6 -alkyl; C_1 - C_6 -alkoxycarbonyl; C_1 - C_6 -alkoxycarbonyl C_1 - C_6 -alkyl; aminocarbonyl; C_1 - C_6 -alkylaminocarbonyl; hydroxy C_1 - C_6 -alkylaminocarbonyl; C_1 - C_6 -alkoxy C_1 - C_6 -alkylaminocarbonyl; cyano; carboxy; hydroxy; hydroxy C_1 - C_6 -alkoxy; hydroxy C_1 - C_6 -alkyl; di(hydroxy) C_1 - C_6 -alkyl; di(C_1 - C_6 -alkyl)amino; di(hydroxy C_1 - C_6 -alkyl)amino; di(C_1 - C_6 -alkoxy C_1 - C_6 -alkyl)amino; (C_1 - C_6 -alkoxy C_1 - C_6 -alkyl)(hydroxy C_1 - C_6 -alkyl)amino; halo C_1 - C_6 -alkyl; and halogen; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring.

4. The compound of claim 3, wherein

n is 1;

R^1 is phenyl optionally substituted with 1 or 2 substituents selected from the group consisting of C_1 - C_6 -alkyl; C_1 - C_6 -alkylcarbonylamino; aminocarbonyl; cyano; hydroxy; and di(C_1 - C_6 -alkyl)amino; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring; or

R^1 is monocyclic heteroaryl, wherein the monocyclic heteroaryl is pyridyl, pyrazinyl or isoxazolyl, wherein the monocyclic heteroaryl is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C_1 - C_6 -alkyl; C_1 - C_6 -alkoxy;

C₁-C₆-alkoxycarbonylC₁-C₆-alkyl; hydroxyC₁-C₆-alkyl; haloC₁-C₆-alkyl; and halogen;
wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to
the amide nitrogen pendant on the furan ring;

R² is hydrogen or C₁-C₆-alkyl; and

5 R⁶ and R⁷ are each hydrogen.

5. The compound of claim 3, wherein

n is 1;

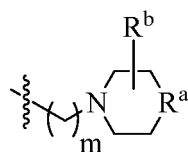
10 R¹ is monocyclic heteroaryl, wherein the monocyclic heteroaryl is pyridyl, wherein
the monocyclic heteroaryl is optionally substituted with 1, 2, or 3 substituents selected from
the group consisting of C₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; carboxy; hydroxyC₁-C₆-
alkyl; and di(hydroxyC₁-C₆-alkyl)amino; wherein only 1 substituent can be present on the
two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring;

R² is hydrogen or C₁-C₆-alkoxyC₂-C₆alkyl; and

15 R⁶ and R⁷ are each independently C₁-C₆-alkyl.

6. The compound of claim 2, wherein R¹ is fused-bicyclic heteroaryl, wherein the fused-
bicyclic heteroaryl contains 1, 2, 3 or 4 ring nitrogens and optionally one ring oxygen or one
ring sulfur, wherein the fused-bicyclic heteroaryl is optionally substituted with 1, 2, 3, or 4

20 substituents selected from the group consisting of C₁-C₆-alkyl; C₁-C₆-alkylcarbonylamino;
hydroxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxy;
C₁-C₆-alkoxyC₁-C₆-alkoxy; C₁-C₆alkoxy-C₁-C₆alkyl; C₁-C₆-alkoxycarbonyl;
C₁-C₆-alkoxycarbonylC₁-C₆-alkyl; C₃-C₇-cycloalkyloxy; M₄-M₇-heterocycleoxy, wherein the
heterocycle of M₄-M₇-heterocycleoxy is optionally substituted with C₁-C₆-alkyl;
25 aminocarbonyl; C₁-C₆-alkylaminocarbonyl; hydroxyC₁-C₆-alkylaminocarbonyl;
C₁-C₆-alkoxyC₁-C₆-alkylaminocarbonyl; cyano; hydroxy; hydroxyC₁-C₆-alkoxy;
hydroxyC₁-C₆-alkyl; di(C₁-C₆alkyl)amino; di(hydroxyC₁-C₆-alkyl)amino;
di(C₁-C₆-alkoxyC₁-C₆-alkyl)amino; (C₁-C₆-alkoxyC₁-C₆-alkyl)(hydroxyC₁-C₆-alkyl)amino;
haloC₁-C₆-alkyl; halogen; C₁-C₆-alkylsulfonylaminoC₂-C₆-alkyl; and (i),



(i)

wherein R^a is selected from the group consisting of a bond, CH_2 , CHR^b , O, S, and $N-R^c$;
 wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to
 the amide nitrogen pendant on the furan ring;

m is 2, 3 or 4 when (i) is attached to a ring nitrogen atom of the bicyclic heteroaryl; or

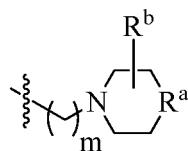
5 m is 0, 1, 2, 3 or 4 when (i) is attached to a ring carbon atom of the bicyclic
 heteroaryl;

R^b , at each occurrence, is independently selected from the group consisting of
 hydrogen, C_1 - C_6 -alkyl, halo C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy C_1 - C_6 -alkyl, and hydroxy C_1 - C_6 -alkyl;
 and

10 R^c is selected from the group consisting of hydrogen, C_1 - C_6 -alkyl,
 C_1 - C_6 -alkoxycarbonyl, C_1 - C_6 -alkylcarbonyl, C_1 - C_6 -alkylsulfonyl,
 di(C_1 - C_6 -alkyl)aminosulfonyl, heterocyclecarbonyl, C_3 - C_7 -cycloalkylcarbonyl, $-C(O)NH_2$,
 $-C(O)NH(alkyl)$, $-C(O)N(alkyl)_2$ and $-C(=NCN)NHCH_3$.

15 7. The compound of claim 6, wherein
 n is 1;

R^1 is fused-bicyclic heteroaryl, wherein the fused-bicyclic heteroaryl is 2*H*-indazol-5-
 yl, 1*H*-indazol-5-yl, 1*H*-benzimidazol-5-yl, 1,3-benzothiazol-6-yl, quinolin-6-yl, 1*H*-indazol-
 6-yl, 1,3-benzothiazol-2-yl, wherein the fused-bicyclic heteroaryl is optionally substituted
 20 with 1, 2, or 3, substituents selected from the group consisting of C_1 - C_6 -alkyl; C_1 - C_6 -
 alkoxycarbonyl; hydroxy C_1 - C_6 -alkyl; halogen; C_1 - C_6 -alkylsulfonylamino C_2 - C_6 -alkyl; and (i),



(i)

wherein R^a is selected from the group consisting of a bond, O, and $N-R^c$; wherein only 1
 25 substituent can be present on the two atoms adjacent to the atom connected to the amide
 nitrogen pendant on the furan ring;

m is 2;

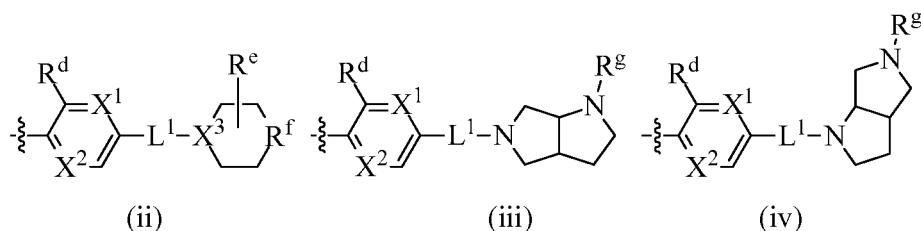
R^b is hydrogen;

R^c is C_1 - C_6 -alkyl;

30 R^2 is hydrogen or C_1 - C_6 -alkyl; and

R^6 and R^7 are each hydrogen.

8. The compound of claim 2, wherein R^1 is (ii), (iii), or (iv);



5 wherein both X¹ and X² are CH, or one of X¹ and X² is N and the other is CH;

X³ is CH or N;

L¹ is a bond, C(O), or -NHC(O)-;

R^d is selected from the group consisting of hydrogen; C₁-C₆alkoxy;

fluoroC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₃-C₇-cycloalkyloxy;

10 C₃-C₇-cycloalkylC₁-C₆-alkoxy; hydroxyC₁-C₆-alkoxy; phenylC₁-C₆-alkoxyC₁-C₆-alkoxy;
M₄-M₇-heterocycleoxy, wherein the heterocycle of heterocycleoxy is optionally substituted
with C₁-C₆-alkyl or oxo; and phenoxy, wherein the phenyl of phenoxy is optionally
substituted with hydroxyC₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkoxyC₁-C₆-alkoxy, or C₁-C₆-
alkoxycarbonyl;

15 R^e at each occurrence is independently selected from the group consisting of
hydrogen, C₁-C₆-alkyl, di(C₁-C₆-alkyl)amino, haloC₁-C₆-alkyl, C₁-C₆-alkoxyC₁-C₆-alkyl, and
hydroxyC₁-C₆-alkyl;

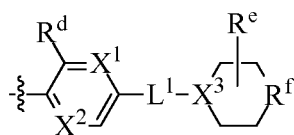
R^f is selected from the group consisting of a bond, CH₂, CHR^e, CH₂CH₂, O, NR^g, and
CH₂NR^g; and

20 R^g is selected from the group consisting of hydrogen; C₁-C₆-alkyl;
C₁-C₆-alkoxycarbonyl; C₁-C₆-alkylcarbonyl; C₁-C₆-alkylsulfonyl;
di(C₁-C₆-alkyl)aminosulfonyl; C₃-C₇-cycloalkylcarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylcarbonyl;
hydroxyC₂-C₆-alkyl; hydroxyC₁-C₆-alkylcarbonyl; formyl; -C(O)NH₂; -C(O)NH(alkyl);
-C(O)N(alkyl)₂; -C(=NCN)NHCH₃; and M₄-M₇-heterocyclecarbonyl, wherein the
25 heterocycle of heterocyclecarbonyl is optionally substituted with C₁-C₆-alkyl.

9. The compound of claim 8, wherein

n is 1 or 2;

R¹ is (ii);



(ii)

wherein both X^1 and X^2 are CH, or one of X^1 and X^2 is N and the other is CH;

X^3 is N;

5 L^1 is a bond;

R^d is selected from the group consisting of hydrogen; C_1 - C_6 alkoxy; C_1 - C_6 -alkoxy C_1 - C_6 -alkoxy; hydroxy C_1 - C_6 -alkoxy; phenyl C_1 - C_6 -alkoxy C_1 - C_6 -alkoxy; M_4 - M_7 -heterocycleoxy, wherein the heterocycle of heterocycleoxy is optionally substituted with C_1 - C_6 -alkyl or oxo; and phenoxy, wherein the phenyl of phenoxy is optionally substituted with
10 hydroxy C_1 - C_6 -alkyl or C_1 - C_6 -alkoxycarbonyl;

R^e at each occurrence is hydrogen;

R^f is selected from the group consisting of a CH_2 , O, and NR^g ;

R^g is selected from the group consisting of hydrogen; C_1 - C_6 -alkyl;
 C_1 - C_6 -alkoxycarbonyl; C_1 - C_6 -alkylcarbonyl; di(C_1 - C_6 -alkyl)aminosulfonyl;

15 $-C(=NCN)NHCH_3$; and M_4 - M_7 -heterocyclecarbonyl, wherein the heterocycle of heterocyclecarbonyl is optionally substituted with C_1 - C_6 -alkyl;

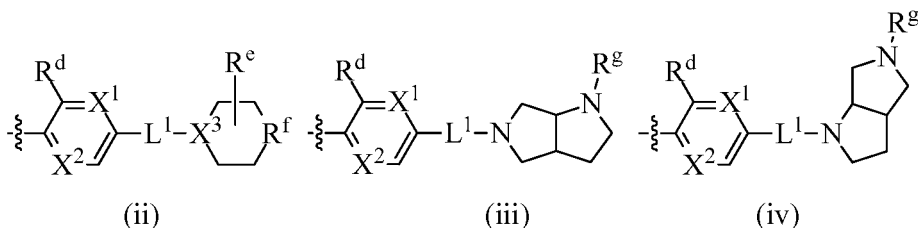
R^2 is hydrogen, C_1 - C_6 -alkyl, hydroxy C_2 - C_6 -alkyl, C_1 - C_6 -alkoxy C_2 - C_6 alkyl, hydroxy C_2 - C_6 -alkoxy C_2 - C_6 -alkyl, C_1 - C_6 -alkylcarbonyloxy C_2 - C_6 -alkyl, and phenyl C_1 - C_6 -alkoxy C_2 - C_6 alkyl; and

20 R^6 and R^7 are each hydrogen.

10. The compound of claim 8 wherein

n is 1;

R^1 is R^1 is (ii), (iii), or (iv);



25

wherein both X^1 and X^2 are CH, or one of X^1 and X^2 is N and the other is CH;

X^3 is CH or N;

L^1 is a bond;

R^d is selected from the group consisting of C_1 - C_6 alkoxy; fluoro C_1 - C_6 -alkoxy; C_1 - C_6 -alkoxy C_1 - C_6 -alkoxy; and M_4 - M_7 -heterocycleoxy, wherein the heterocycle of heterocycleoxy is optionally substituted with oxo;

R^e at each occurrence is independently selected from the group consisting of
 5 hydrogen, di(C_1 - C_6 -alkyl)amino, C_1 - C_6 -alkoxy C_1 - C_6 alkyl, and hydroxy C_1 - C_6 -alkyl;

R^f is selected from the group consisting of a bond, CH_2 , and NR^g ;

R^g is selected from the group consisting of hydrogen; C_1 - C_6 -alkyl; C_1 - C_6 -alkylcarbonyl; C_1 - C_6 -alkylsulfonyl; hydroxy C_2 - C_6 -alkyl; formyl; $-C(=NCN)NHCH_3$; and M_4 - M_7 -heterocyclecarbonyl, wherein the heterocycle of heterocyclecarbonyl is optionally
 10 substituted with C_1 - C_6 -alkyl;

R^2 is selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, hydroxy C_2 - C_6 -alkyl, di(hydroxy) C_2 - C_6 -alkyl, C_1 - C_6 -alkoxy C_2 - C_6 alkyl, and hydroxy C_2 - C_6 -alkoxy C_2 - C_6 -alkyl;

R^6 is selected from the group consisting of hydrogen and C_1 - C_6 -alkyl; and

15 R^7 is selected from the group consisting of C_1 - C_6 -alkyl and hydroxy C_1 - C_6 -alkyl; or

R^6 and R^7 taken together with the carbon atom to which they are attached form a C_3 - C_6 -cycloalkyl or M_4 - M_7 -heterocycle, wherein the M_4 - M_7 -heterocycle is optionally substituted with 1 or 2 substituents selected from C_1 - C_6 -alkyl, oxo and C_1 - C_6 -alkylcarbonyl.

20 11. The compound of claim 1, wherein

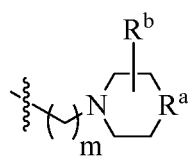
Z^1 is CR^3R^4 ; and

Z^2 is NR^5 .

12. The compound of claim 11, wherein R^1 is phenyl or monocyclic heteroaryl, wherein
 25 the monocyclic heteroaryl contains one or two ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the phenyl or monocyclic heteroaryl is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C_1 - C_6 -alkyl; C_1 - C_6 -alkylcarbonylamino; hydroxy C_1 - C_6 -alkylcarbonylamino; C_1 - C_6 -alkoxy C_1 - C_6 alkylcarbonylamino; C_1 - C_6 -alkoxy; C_1 - C_6 -alkoxy C_1 - C_6 -alkoxy; C_1 - C_6 -alkoxy C_1 - C_6 -alkyl; C_1 - C_6 -alkoxycarbonyl; C_1 - C_6 -alkoxycarbonyl C_1 - C_6 -alkyl;
 30 aminocarbonyl; C_1 - C_6 -alkylaminocarbonyl; hydroxy C_1 - C_6 -alkylaminocarbonyl; C_1 - C_6 -alkoxy C_1 - C_6 -alkylaminocarbonyl; cyano; carboxy; hydroxy; hydroxy C_1 - C_6 -alkoxy; hydroxy C_1 - C_6 -alkyl; di(hydroxy) C_1 - C_6 -alkyl; di(C_1 - C_6 alkyl)amino; di(hydroxy C_1 - C_6 -alkyl)amino; di(C_1 - C_6 -alkoxy C_1 - C_6 alkyl)amino; (C_1 - C_6 -alkoxy C_1 - C_6 -alkyl)(hydroxy C_1 - C_6 -

alkyl)amino; haloC₁-C₆-alkyl; and halogen; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring.

13. The compound of claim 11, wherein R¹ is fused-bicyclic heteroaryl, wherein the
 5 fused-bicyclic heteroaryl contains 1, 2, 3 or 4 ring nitrogens and optionally one ring oxygen
 or one ring sulfur, wherein the fused-bicyclic heteroaryl is optionally substituted with 1, 2, 3,
 or 4 substituents selected from the group consisting of C₁-C₆-alkyl; C₁-C₆-
 alkylcarbonylamino; hydroxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxyC₁-C₆-
 alkylcarbonylamino; C₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₁-C₆alkoxy-C₁-C₆alkyl; C₁-
 10 C₆-alkoxycarbonyl; C₁-C₆-alkoxycarbonylC₁-C₆-alkyl; C₃-C₇-cycloalkyloxy; M₄-M₇-
 heterocycleoxy, wherein the heterocycle of M₄-M₇-heterocycleoxy is optionally substituted
 with C₁-C₆-alkyl; aminocarbonyl; C₁-C₆-alkylaminocarbonyl; hydroxyC₁-C₆-
 alkylaminocarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylaminocarbonyl; cyano; hydroxy; hydroxyC₁-C₆-
 alkoxy; hydroxyC₁-C₆-alkyl; di(C₁-C₆alkyl)amino; di(hydroxyC₁-C₆-alkyl)amino;
 15 di(C₁-C₆-alkoxyC₁-C₆-alkyl)amino; (C₁-C₆-alkoxyC₁-C₆-alkyl)(hydroxyC₁-C₆-alkyl)amino;
 haloC₁-C₆-alkyl; halogen; C₁-C₆-alkylsulfonylaminoC₂-C₆-alkyl; and (i),



(i)

- wherein R^a is selected from the group consisting of a bond, CH₂, CHR^b, O, S, and N-R^c;
 20 wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the
 the amide nitrogen pendant on the furan ring;

m is 2, 3 or 4 when (i) is attached to a ring nitrogen atom of the bicyclic heteroaryl; or

m is 0, 1, 2, 3 or 4 when (i) is attached to a ring carbon atom of the bicyclic
 heteroaryl;

- 25 R^b, at each occurrence, is independently selected from the group consisting of
 hydrogen, C₁-C₆-alkyl, haloC₁-C₆-alkyl, C₁-C₆-alkoxyC₁-C₆-alkyl, and hydroxyC₁-C₆-alkyl;
 and

- R^c is selected from the group consisting of hydrogen, C₁-C₆-alkyl,
 C₁-C₆-alkoxycarbonyl, C₁-C₆-alkylcarbonyl, C₁-C₆-alkylsulfonyl,
 30 di(C₁-C₆-alkyl)aminosulfonyl, heterocyclecarbonyl, C₃-C₇-cycloalkylcarbonyl, -C(O)NH₂,
 -C(O)NH(alkyl), -C(O)N(alkyl)₂ and -C(=NCN)NHCH₃.

14. The compound of claim 13, wherein

n is 1;

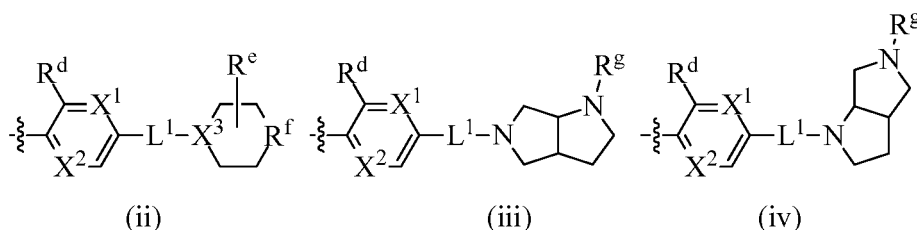
R^1 is fused-bicyclic heteroaryl, wherein the fused-bicyclic heteroaryl is 2*H*-indazol-5-yl, wherein the fused-bicyclic heteroaryl is optionally substituted with 1 or 2 C_1 - C_6 -alkyl; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring;

R^3 and R^4 are both hydrogen; and

R^5 is hydrogen or C_1 - C_6 -alkylsulfonyl.

10

15. The compounds of claim 11, wherein R^1 is (ii), (iii), or (iv);



wherein both X^1 and X^2 are CH, or one of X^1 and X^2 is N and the other is CH;

15 X^3 is CH or N;

L^1 is a bond, C(O), or -NHC(O)-;

R^d is selected from the group consisting of hydrogen; C_1 - C_6 alkoxy;

fluoro C_1 - C_6 -alkoxy; C_1 - C_6 -alkoxy C_1 - C_6 -alkoxy; C_3 - C_7 -cycloalkyloxy;

C_3 - C_7 -cycloalkyl C_1 - C_6 -alkoxy; hydroxy C_1 - C_6 -alkoxy; phenyl C_1 - C_6 -alkoxy C_1 - C_6 -alkoxy;

20 M_4 - M_7 -heterocycleoxy, wherein the heterocycle of heterocycleoxy is optionally substituted with C_1 - C_6 -alkyl or oxo; and phenoxy, wherein the phenyl of phenoxy is optionally substituted with hydroxy C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -alkoxy C_1 - C_6 -alkoxy, or C_1 - C_6 -alkoxycarbonyl;

R^e at each occurrence is independently selected from the group consisting of

25 hydrogen, C_1 - C_6 -alkyl, di(C_1 - C_6 -alkyl)amino, halo C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy C_1 - C_6 -alkyl, and hydroxy C_1 - C_6 -alkyl;

R^f is selected from the group consisting of a bond, CH_2 , CHR^e , CH_2CH_2 , O, NR^g , and CH_2NR^g ; and

R^g is selected from the group consisting of hydrogen; C_1 - C_6 -alkyl;

30 C_1 - C_6 -alkoxycarbonyl; C_1 - C_6 -alkylcarbonyl; C_1 - C_6 -alkylsulfonyl;

di(C_1 - C_6 -alkyl)aminosulfonyl; C_3 - C_7 -cycloalkylcarbonyl; C_1 - C_6 -alkoxy C_1 - C_6 -alkylcarbonyl;

hydroxyC₂-C₆-alkyl; hydroxyC₁-C₆-alkylcarbonyl; formyl; -C(O)NH₂; -C(O)NH(alkyl); -C(O)N(alkyl)₂; -C(=NCN)NHCH₃; and M₄-M₇-heterocyclecarbonyl, wherein the heterocycle of heterocyclecarbonyl is optionally substituted with C₁-C₆-alkyl.

16. The compound of claim 1, wherein

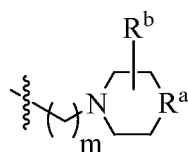
Z¹ is CR³R⁴; and

Z² is CR⁶R⁷.

17. The compound of claim 16, wherein R¹ is phenyl or monocyclic heteroaryl, wherein the monocyclic heteroaryl contains one or two ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the phenyl or monocyclic heteroaryl is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C₁-C₆-alkyl; C₁-C₆-alkylcarbonylamino; hydroxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl; C₁-C₆-alkoxycarbonylC₁-C₆-alkyl; aminocarbonyl; C₁-C₆-alkylaminocarbonyl; hydroxyC₁-C₆-alkylaminocarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylaminocarbonyl; cyano; carboxy; hydroxy; hydroxyC₁-C₆-alkoxy; hydroxyC₁-C₆-alkyl; di(hydroxy)C₁-C₆-alkyl; di(C₁-C₆-alkyl)amino; di(hydroxyC₁-C₆-alkyl)amino; di(C₁-C₆-alkoxyC₁-C₆-alkyl)amino; (C₁-C₆-alkoxyC₁-C₆-alkyl)(hydroxyC₁-C₆-alkyl)amino; haloC₁-C₆-alkyl; and halogen; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring.

18. The compound of claim 16, wherein R¹ is fused-bicyclic heteroaryl, wherein the fused-bicyclic heteroaryl contains 1, 2, 3 or 4 ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the fused-bicyclic heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of C₁-C₆-alkyl; C₁-C₆-alkylcarbonylamino; hydroxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl; C₁-C₆-alkoxycarbonylC₁-C₆-alkyl; C₃-C₇-cycloalkyloxy; M₄-M₇-heterocycleoxy, wherein the heterocycle of M₄-M₇-heterocycleoxy is optionally substituted with C₁-C₆-alkyl; aminocarbonyl; C₁-C₆-alkylaminocarbonyl; hydroxyC₁-C₆-alkylaminocarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylaminocarbonyl; cyano; hydroxy; hydroxyC₁-C₆-alkoxy; hydroxyC₁-C₆-alkyl; di(C₁-C₆-alkyl)amino; di(hydroxyC₁-C₆-alkyl)amino;

di(C₁-C₆-alkoxyC₁-C₆-alkyl)amino; (C₁-C₆-alkoxyC₁-C₆-alkyl)(hydroxyC₁-C₆-alkyl)amino; haloC₁-C₆-alkyl; halogen; C₁-C₆-alkylsulfonylaminoC₂-C₆-alkyl; and (i),



(i)

- 5 wherein R^a is selected from the group consisting of a bond, CH₂, CHR^b, O, S, and N-R^c;
wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to
the amide nitrogen pendant on the furan ring;

m is 2, 3 or 4 when (i) is attached to a ring nitrogen atom of the bicyclic heteroaryl; or

m is 0, 1, 2, 3 or 4 when (i) is attached to a ring carbon atom of the bicyclic

- 10 heteroaryl;

R^b, at each occurrence, is independently selected from the group consisting of
hydrogen, C₁-C₆-alkyl, haloC₁-C₆-alkyl, C₁-C₆-alkoxyC₁-C₆-alkyl, and hydroxyC₁-C₆-alkyl;
and

R^c is selected from the group consisting of hydrogen, C₁-C₆-alkyl,

- 15 C₁-C₆-alkoxycarbonyl, C₁-C₆-alkylcarbonyl, C₁-C₆-alkylsulfonyl,
di(C₁-C₆-alkyl)aminosulfonyl, heterocyclecarbonyl, C₃-C₇-cycloalkylcarbonyl, -C(O)NH₂,
-C(O)NH(alkyl), -C(O)N(alkyl)₂ and -C(=NCN)NHCH₃.

19. The compound of claim 18, wherein

- 20 n is 1;

R¹ is fused-bicyclic heteroaryl, wherein the fused-bicyclic heteroaryl is 1*H*-indazol-5-
yl, 2*H*-indazol-5-yl, or 1*H*-benzimidazol-5-yl, wherein the fused-bicyclic heteroaryl is
optionally substituted with 1 or 2 C₁-C₆-alkyl or hydroxyC₁-C₆-alkyl; wherein only 1
substituent can be present on the two atoms adjacent to the atom connected to the amide

- 25 nitrogen pendant on the furan ring;

R³ is hydrogen or C₁-C₆-alkyl;

R⁴ is hydrogen, C₁-C₆-alkyl, or hydroxyC₁-C₆-alkyl;

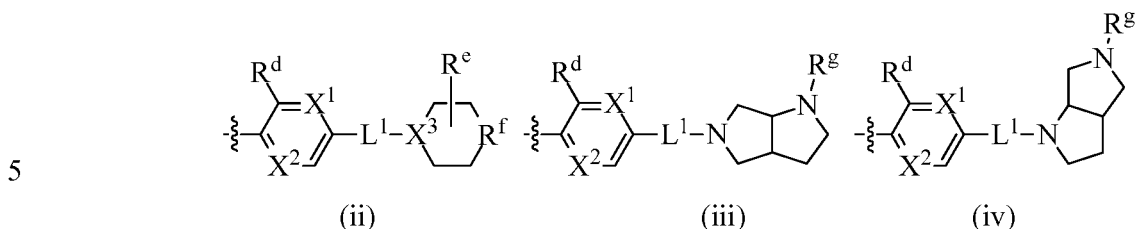
R⁶ is selected from the group consisting of hydrogen and C₁-C₆-alkyl; and

R⁷ is selected from the group consisting of hydrogen, C₁-C₆-alkyl, hydroxyC₁-C₆-

- 30 alkyl, aminocarbonyl, and C₁-C₆-alkoxycarbonyl; or

R^6 and R^7 taken together with the carbon atom to which they are attached form a C₃-C₆-cycloalkyl.

20. The compounds of claim 16, wherein R^1 is (ii), (iii), or (iv);



wherein both X^1 and X^2 are CH, or one of X^1 and X^2 is N and the other is CH;

X^3 is CH or N;

L^1 is a bond, C(O), or -NHC(O)-;

10 R^d is selected from the group consisting of hydrogen; C₁-C₆alkoxy; fluoroC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₃-C₇-cycloalkyloxy; C₃-C₇-cycloalkylC₁-C₆-alkoxy; hydroxyC₁-C₆-alkoxy; phenylC₁-C₆-alkoxyC₁-C₆-alkoxy; M₄-M₇-heterocycleoxy, wherein the heterocycle of heterocycleoxy is optionally substituted with C₁-C₆-alkyl or oxo; and phenoxy, wherein the phenyl of phenoxy is optionally substituted with hydroxyC₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkoxyC₁-C₆-alkoxy, or C₁-C₆-alkoxycarbonyl;

R^e at each occurrence is independently selected from the group consisting of hydrogen, C₁-C₆-alkyl, di(C₁-C₆-alkyl)amino, haloC₁-C₆-alkyl, C₁-C₆-alkoxyC₁-C₆-alkyl, and hydroxyC₁-C₆-alkyl;

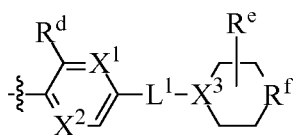
20 R^f is selected from the group consisting of a bond, CH₂, CHR^e, CH₂CH₂, O, NR^g, and CH₂NR^g; and

R^g is selected from the group consisting of hydrogen; C₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl; C₁-C₆-alkylcarbonyl; C₁-C₆-alkylsulfonyl; di(C₁-C₆-alkyl)aminosulfonyl; C₃-C₇-cycloalkylcarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylcarbonyl; 25 hydroxyC₂-C₆-alkyl; hydroxyC₁-C₆-alkylcarbonyl; formyl; -C(O)NH₂; -C(O)NH(alkyl); -C(O)N(alkyl)₂; -C(=NCN)NHCH₃; and M₄-M₇-heterocyclecarbonyl, wherein the heterocycle of heterocyclecarbonyl is optionally substituted with C₁-C₆-alkyl.

21. The compound of claim 20, wherein

30 n is 1;

R^1 is (ii);



(ii)

wherein both X^1 and X^2 are CH, or one of X^1 and X^2 is N and the other is CH;

X^3 is N;

5 L^1 is a bond;

R^d is selected from the group consisting of hydrogen and C₁-C₆alkoxy;

R^e at each occurrence is hydrogen;

R^f is NR^g;

10 R^g is selected from the group consisting of hydrogen, C₁-C₆-alkoxycarbonyl, C₁-C₆-alkylcarbonyl, and C₁-C₆-alkylsulfonyl;

R^3 is selected from the group consisting of hydrogen or C₁-C₆-alkyl;

R^4 is selected from the group consisting of hydrogen, aminoC₁-C₆-alkyl, and phenyl, wherein phenyl is optionally substituted with 1, 2 or 3 halogen;

R^6 is selected from the group consisting of hydrogen and C₁-C₆-alkyl; and

15 R^7 are is selected from the group consisting of hydrogen, C₁-C₆-alkyl, C₁-C₆-alkoxyC₁-C₆-alkyl, and hydroxyC₁-C₆-alkyl; or

R^6 and R^7 taken together with the carbon atom to which they are attached form a M₄-M₇-heterocycle.

20 22. The compound of claim 1, wherein

Z^1 is CR³R⁴; and

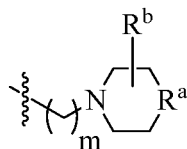
Z^2 is O.

23. The compound of claim 22, wherein R^1 is phenyl or monocyclic heteroaryl, wherein
 25 the monocyclic heteroaryl contains one or two ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the phenyl or monocyclic heteroaryl is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C₁-C₆-alkyl; C₁-C₆-alkylcarbonylamino; hydroxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl; C₁-C₆-alkoxycarbonylC₁-C₆-alkyl;
 30 aminocarbonyl; C₁-C₆-alkylaminocarbonyl; hydroxyC₁-C₆-alkylaminocarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylaminocarbonyl; cyano; carboxy; hydroxy; hydroxyC₁-C₆-alkoxy;

hydroxyC₁-C₆-alkyl; di(hydroxy)C₁-C₆-alkyl; di(C₁-C₆alkyl)amino; di(hydroxyC₁-C₆-alkyl)amino; di(C₁-C₆-alkoxyC₁-C₆alkyl)amino; (C₁-C₆-alkoxyC₁-C₆-alkyl)(hydroxyC₁-C₆-alkyl)amino; haloC₁-C₆-alkyl; and halogen; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring.

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24. The compound of claim 22, wherein R¹ is fused-bicyclic heteroaryl, wherein the fused-bicyclic heteroaryl contains 1, 2, 3 or 4 ring nitrogens and optionally one ring oxygen or one ring sulfur, wherein the fused-bicyclic heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of C₁-C₆-alkyl; C₁-C₆-alkylcarbonylamino; hydroxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxyC₁-C₆-alkylcarbonylamino; C₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₁-C₆alkoxy-C₁-C₆alkyl; C₁-C₆-alkoxycarbonyl; C₁-C₆-alkoxycarbonylC₁-C₆-alkyl; C₃-C₇-cycloalkyloxy; M₄-M₇-heterocycleoxy, wherein the heterocycle of M₄-M₇-heterocycleoxy is optionally substituted with C₁-C₆-alkyl; aminocarbonyl; C₁-C₆-alkylaminocarbonyl; hydroxyC₁-C₆-alkylaminocarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylaminocarbonyl; cyano; hydroxy; hydroxyC₁-C₆-alkoxy; hydroxyC₁-C₆-alkyl; di(C₁-C₆alkyl)amino; di(hydroxyC₁-C₆-alkyl)amino; di(C₁-C₆-alkoxyC₁-C₆-alkyl)amino; (C₁-C₆-alkoxyC₁-C₆-alkyl)(hydroxyC₁-C₆-alkyl)amino; haloC₁-C₆-alkyl; halogen; C₁-C₆-alkylsulfonylaminoC₂-C₆-alkyl; and (i),



(i)

wherein R^a is selected from the group consisting of a bond, CH₂, CHR^b, O, S, and N-R^c; wherein only 1 substituent can be present on the two atoms adjacent to the atom connected to the amide nitrogen pendant on the furan ring;

m is 2, 3 or 4 when (i) is attached to a ring nitrogen atom of the bicyclic heteroaryl; or

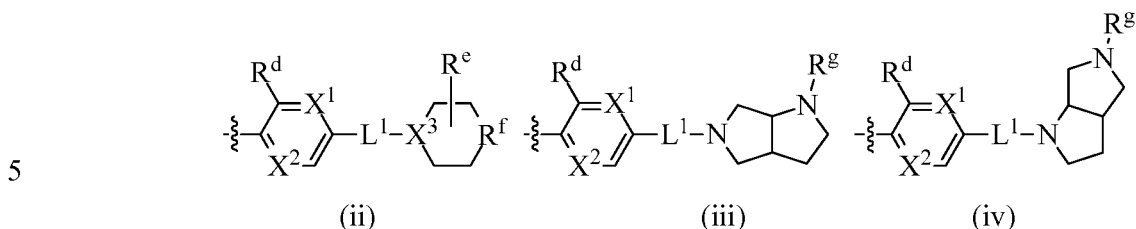
m is 0, 1, 2, 3 or 4 when (i) is attached to a ring carbon atom of the bicyclic heteroaryl;

R^b, at each occurrence, is independently selected from the group consisting of hydrogen, C₁-C₆-alkyl, haloC₁-C₆-alkyl, C₁-C₆-alkoxyC₁-C₆-alkyl, and hydroxyC₁-C₆-alkyl; and

R^c is selected from the group consisting of hydrogen, C₁-C₆-alkyl, C₁-C₆-alkoxycarbonyl, C₁-C₆-alkylcarbonyl, C₁-C₆-alkylsulfonyl,

di(C₁-C₆-alkyl)aminosulfonyl, heterocyclecarbonyl, C₃-C₇-cycloalkylcarbonyl, -C(O)NH₂, -C(O)NH(alkyl), -C(O)N(alkyl)₂ and -C(=NCN)NHCH₃.

25. The compounds of claim 22, wherein R¹ is (ii), (iii), or (iv);



wherein both X¹ and X² are CH, or one of X¹ and X² is N and the other is CH;

X³ is CH or N;

L¹ is a bond, C(O), or -NHC(O)-;

10 R^d is selected from the group consisting of hydrogen; C₁-C₆alkoxy; fluoroC₁-C₆-alkoxy; C₁-C₆-alkoxyC₁-C₆-alkoxy; C₃-C₇-cycloalkyloxy; C₃-C₇-cycloalkylC₁-C₆-alkoxy; hydroxyC₁-C₆-alkoxy; phenylC₁-C₆-alkoxyC₁-C₆-alkoxy; M₄-M₇-heterocycleoxy, wherein the heterocycle of heterocycleoxy is optionally substituted with C₁-C₆-alkyl or oxo; and phenoxy, wherein the phenyl of phenoxy is optionally substituted with hydroxyC₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkoxyC₁-C₆-alkoxy, or C₁-C₆-alkoxycarbonyl;

R^e at each occurrence is independently selected from the group consisting of hydrogen, C₁-C₆-alkyl, di(C₁-C₆-alkyl)amino, haloC₁-C₆-alkyl, C₁-C₆-alkoxyC₁-C₆-alkyl, and hydroxyC₁-C₆-alkyl;

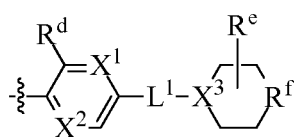
20 R^f is selected from the group consisting of a bond, CH₂, CHR^e, CH₂CH₂, O, NR^g, and CH₂NR^g; and

R^g is selected from the group consisting of hydrogen; C₁-C₆-alkyl; C₁-C₆-alkoxycarbonyl; C₁-C₆-alkylcarbonyl; C₁-C₆-alkylsulfonyl; di(C₁-C₆-alkyl)aminosulfonyl; C₃-C₇-cycloalkylcarbonyl; C₁-C₆-alkoxyC₁-C₆-alkylcarbonyl; 25 hydroxyC₂-C₆-alkyl; hydroxyC₁-C₆-alkylcarbonyl; formyl; -C(O)NH₂; -C(O)NH(alkyl); -C(O)N(alkyl)₂; -C(=NCN)NHCH₃; and M₄-M₇-heterocyclecarbonyl, wherein the heterocycle of heterocyclecarbonyl is optionally substituted with C₁-C₆-alkyl.

26. The compound of claim 25, wherein

30 n is 1;

R¹ is (ii);



(ii)

wherein both X¹ and X² are CH, or one of X¹ and X² is N and the other is CH;

X³ is N;

5 L¹ is a bond;

R^d is C₁-C₆alkoxy;

R^e at each occurrence is hydrogen;

R^f is NR^g;

R^g is C₁-C₆-alkylcarbonyl; and

10 R³ and R⁴ are each independently C₁-C₆-alkyl; or

R³ and R⁴ taken together with the carbon atom to which they are attached form a M₄-M₇-heterocycle.

27. The compound of claim 1, selected from:

15 *N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5-methyl-*N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

20 *N*-[4-(morpholin-4-yl)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5-methyl-*N*-(4-methylphenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

tert-butyl 4-(3-methoxy-4-[(4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino)phenyl)piperazine-1-carboxylate;

25 *N*-[2-methoxy-4-(piperazin-1-yl)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[2-methoxy-6-(4-methylpiperazin-1-yl)pyridin-3-yl]-4-oxo-5,6,7,8-tetrahydro-4*H*-furo[3,2-*c*]azepine-3-carboxamide;

30 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[2-(benzyloxy)ethyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2-hydroxyethyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[4-(4-acetylpiperazin-1-yl)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(1-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5 *N*-(1*H*-benzimidazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(4-carbamoylphenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

10 *N*-(2-methyl-1,3-benzothiazol-6-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[5-(4-methylpiperazin-1-yl)pyridin-2-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[4-(4-methylpiperazin-1-yl)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

15 *N*-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

20 *N*-[6-(4-acetylpiperazin-1-yl)-2-(2-methoxyethoxy)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-(oxetan-3-yloxy)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5-methyl-*N*-[4-(4-methylpiperazin-1-yl)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

25 *N*-(1*H*-indazol-5-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5-methyl-*N*-(1-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

30 5-methyl-*N*-[4-(morpholin-4-yl)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(4-carbamoylphenyl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(1*H*-benzimidazol-5-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[4-(4-acetylpiperazin-1-yl)phenyl]-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5-methyl-*N*-(2-methyl-1,3-benzothiazol-6-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5 *N*-(4-methylphenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;
N-(4-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;
N-(4-acetamidophenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

4-oxo-*N*-(quinolin-6-yl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(1*H*-indazol-6-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

10 *N*-(2,6-dimethoxypyridin-3-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(1,2-oxazol-3-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

4-oxo-*N*-(pyrazin-2-yl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(5-methyl-1,2-oxazol-3-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-

15 carboxamide;

N-(4-cyanophenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(5-fluoropyridin-2-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(6-methoxypyridin-3-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-

carboxamide;

20 *N*-(5-chloropyridin-2-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(3-cyanophenyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(6-ethoxypyridin-3-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(3-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-

carboxamide;

25 *N*-(6-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(1,3-benzothiazol-2-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

30 methyl 5-{[(4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino}-1*H*-indazole-3-carboxylate;

N-[4-(diethylamino)phenyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[1-(2-hydroxypropyl)-1*H*-indazol-5-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(2-{2-[(methylsulfonyl)amino]ethyl}-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{2-[2-(4-methylpiperazin-1-yl)ethyl]-2*H*-indazol-5-yl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5 *N*-[1-(2-hydroxyethyl)-1*H*-indazol-5-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

4-oxo-*N*-{1-[2-(pyrrolidin-1-yl)ethyl]-1*H*-indazol-5-yl}-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

10 *N*-[2-(2-hydroxypropyl)-2*H*-indazol-5-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{1-[2-(morpholin-4-yl)ethyl]-1*H*-indazol-5-yl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{1-[2-(4-methylpiperazin-1-yl)ethyl]-1*H*-indazol-5-yl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

15 *N*-(1-{2-[(methylsulfonyl)amino]ethyl}-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(4-hydroxyphenyl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

20 *N*-(4-acetamidophenyl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5-methyl-4-oxo-*N*-[4-(piperidin-1-yl)phenyl]-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5-methyl-4-oxo-*N*-(quinolin-3-yl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

25 5-methyl-4-oxo-*N*-(quinolin-6-yl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(1*H*-indazol-6-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

30 *N*-(2,6-dimethoxy-pyridin-3-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5-methyl-*N*-(5-methyl-1,2-oxazol-3-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(4-cyanophenyl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(5-fluoropyridin-2-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(6-methoxypyridin-3-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5 *N*-(5-chloropyridin-2-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-(3-cyanophenyl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

10 *N*-(6-ethoxypyridin-3-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5-methyl-*N*-(3-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5-methyl-*N*-(6-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

15 *N*-(1,3-benzothiazol-2-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5-methyl-4-oxo-*N*-[5-(trifluoromethyl)pyridin-2-yl]-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

20 *N*-(6-chloro-1*H*-indazol-5-yl)-5-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5-methyl-*N*-(2-methyl-1*H*-benzimidazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{4-[4-(3,3-dimethylbutanoyl)piperazin-1-yl]-2-methoxyphenyl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

25 *N*-{2-methoxy-4-[4-(pyrrolidin-1-ylcarbonyl)piperazin-1-yl]phenyl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{4-[4-(dimethylsulfamoyl)piperazin-1-yl]-2-methoxyphenyl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

30 methyl 4- {[6-(4-methylpiperazin-1-yl)-3- {[4-oxo-5,6,7,8-tetrahydro-4*H*-furo[3,2-*c*]azepin-3-yl)carbonyl]amino} pyridin-2-yl]oxy} benzoate;

N-{2-[4-(hydroxymethyl)phenoxy]-6-(4-methylpiperazin-1-yl)pyridin-3-yl}-4-oxo-5,6,7,8-tetrahydro-4*H*-furo[3,2-*c*]azepine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2-methoxyethyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-(2-methoxyethoxy)pyridin-3-yl]-5-[2-(benzyloxy)ethyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-(4-acetylpiperazin-1-yl)-2-[2-(benzyloxy)ethoxy]pyridin-3-yl}-5-[2-(benzyloxy)ethyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5 *N*-[6-(4-acetylpiperazin-1-yl)-2-(2-methoxyethoxy)pyridin-3-yl]-5-(2-hydroxyethyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-(2-hydroxyethoxy)pyridin-3-yl]-5-(2-hydroxyethyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

10 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(3-hydroxypropyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(4-hydroxybutyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[2-(2-hydroxyethoxy)ethyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

15 *tert*-butyl 4-(6-ethoxy-5-{[(4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino}pyridin-2-yl)piperazine-1-carboxylate;

N-{6-[4-(*N*'-cyano-*N*-methylcarbamimidoyl)piperazin-1-yl]-2-ethoxypyridin-3-yl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

20 (2*R*)-1-[3-{[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]carbamoyl}-4-oxo-6,7-dihydrofuro[3,2-*c*]pyridin-5(4*H*)-yl]propan-2-yl acetate;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[(2*R*)-2-hydroxypropyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

(2*S*)-1-[3-{[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]carbamoyl}-4-oxo-6,7-dihydrofuro[3,2-*c*]pyridin-5(4*H*)-yl]propan-2-yl acetate;

25 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[(2*S*)-2-hydroxypropyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

(2*R*)-2-[3-{[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]carbamoyl}-4-oxo-6,7-dihydrofuro[3,2-*c*]pyridin-5(4*H*)-yl]propyl acetate;

30 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[(2*R*)-1-hydroxypropan-2-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

(2*S*)-2-[3-{[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]carbamoyl}-4-oxo-6,7-dihydrofuro[3,2-*c*]pyridin-5(4*H*)-yl]propyl acetate;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[(2*S*)-1-hydroxypropan-2-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(1-hydroxy-2-methylpropan-2-yl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

1-[3-{[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]carbamoyl}-4-oxo-6,7-dihydrofuro[3,2-*c*]pyridin-5(4*H*)-yl]-2-methylpropan-2-yl acetate;

5 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2-hydroxy-2-methylpropyl)-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-(4-acetylpiperazin-1-yl)-2-[(3*S*)-tetrahydrofuran-3-yloxy]pyridin-3-yl}-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

10 *N*-[2-ethoxy-6-(morpholin-4-yl)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[2-(2-hydroxy-2-methylpropoxy)-6-(morpholin-4-yl)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

methyl (6-ethoxy-5-{[(4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl)carbonyl]amino}pyridin-2-yl)acetate;

15 *N*-[2-ethoxy-6-(2-hydroxyethyl)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-methoxypyridin-3-yl]-4-oxo-2',3',4,5',6',7'-hexahydro-5*H*-spiro[1-benzofuran-6,4'-pyran]-3-carboxamide;

20 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4'-oxo-4',7'-dihydro-5'*H*-spiro[cyclobutane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4'-oxo-4',7'-dihydro-5'*H*-spiro[cyclohexane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide;

1-acetyl-*N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4'-oxo-4',7'-dihydro-5'*H*-spiro[azetidine-3,6'-furo[3,2-*c*]pyridine]-3'-carboxamide;

25 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4-oxo-4,7-dihydro-5*H*-spiro[furo[3,2-*c*]pyridine-6,3'-oxetane]-3-carboxamide;

(6*R*)-*N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-6-[(1*R*)-1-hydroxyethyl]-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

30 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5'-(2-hydroxyethyl)-4'-oxo-4',7'-dihydro-5'*H*-spiro[cyclobutane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-4'-oxo-4',7'-dihydro-5'*H*-spiro[cyclopropane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide;

N-{6-[4-(*N*'-cyano-*N*-methylcarbamimidoyl)piperazin-1-yl]-2-ethoxypyridin-3-yl}-4'-oxo-4',7'-dihydro-5'*H*-spiro[cyclobutane-1,6'-furo[3,2-*c*]pyridine]-3'-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2,3-dihydroxypropyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[2-methoxy-4-(piperazin-1-yl)phenyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

5 *N*-{2-methoxy-6-[4-(morpholin-4-ylcarbonyl)piperazin-1-yl]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-methoxypyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

10 *N*-{2-methoxy-6-[4-(pyrrolidin-1-ylcarbonyl)piperazin-1-yl]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[2-methoxy-4-(piperazin-1-yl)phenyl]-6-methyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{2-methoxy-4-[4-(methylsulfonyl)piperazin-1-yl]phenyl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

15 *N*-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[2-ethoxy-6-(piperazin-1-yl)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

20 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[(3*aR*,6*aR*)-hexahydropyrrolo[3,4-*b*]pyrrol-5(1*H*)-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{2-methoxy-6-[(3*aR*,6*aR*)-5-methylhexahydropyrrolo[3,4-*b*]pyrrol-1(2*H*)-yl]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

25 *N*-{6-[(3*aS*,6*aS*)-1-(2-hydroxyethyl)hexahydropyrrolo[3,4-*b*]pyrrol-5(1*H*)-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

30 *N*-{2-isopropoxy-6-[(3*aR*,6*aR*)-1-[(4-methylpiperazin-1-yl)carbonyl]hexahydropyrrolo[3,4-*b*]pyrrol-5(1*H*)-yl]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[(3*S*)-4-acetyl-3-(hydroxymethyl)piperazin-1-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[(2*S*)-4-acetyl-2-(hydroxymethyl)piperazin-1-yl]-2-isopropoxypyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[(2*S*)-2-(hydroxymethyl)-4-(morpholin-4-ylcarbonyl)piperazin-1-yl]-2-isopropoxy-pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-2-isopropoxy-pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[(3*S*)-3-(hydroxymethyl)piperidin-1-yl]-2-isopropoxy-pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[(3*R*)-4-acetyl-3-(hydroxymethyl)piperazin-1-yl]-2-isopropoxy-pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[(2*R*)-4-acetyl-2-(hydroxymethyl)piperazin-1-yl]-2-isopropoxy-pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[bis(2-hydroxyethyl)amino]-2-isopropoxy-pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[2,6-bis(2-methoxyethoxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-[(3*S*)-4-acetyl-3-(methoxymethyl)piperazin-1-yl]-2-(2-hydroxy-2-methylpropoxy)pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[2-ethoxy-6-(2-hydroxyethyl)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[2-ethoxy-6-(hydroxymethyl)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

6-ethoxy-5-({[5-(2-methoxyethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-3-yl]carbonyl} amino)pyridine-2-carboxylic acid;

6,6-dimethyl-*N*-(1-methyl-1*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

6,6-dimethyl-*N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

N-[4-(4-acetylpiperazin-1-yl)phenyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

6,6-dimethyl-4-oxo-*N*-[6-(piperazin-1-yl)pyridin-3-yl]-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

N-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,7-dihydro-5*H*-spiro[1-benzofuran-6,1'-cyclobutane]-3-carboxamide;

6,6-dimethyl-4-oxo-*N*-[5-(piperazin-1-yl)pyridin-2-yl]-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

6,6-dimethyl-*N*-{4-[4-(methylsulfonyl)piperazin-1-yl]phenyl}-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

5 *N*-[2-(2-hydroxyethyl)-2*H*-indazol-5-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

N-[2-(hydroxymethyl)-1*H*-benzimidazol-5-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

10 6,6-dimethyl-*N*-{5-[4-(methylsulfonyl)piperazin-1-yl]pyridin-2-yl}-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

N-[5-(4-acetylpiperazin-1-yl)pyridin-2-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

N-[2-methoxy-4-(piperazin-1-yl)phenyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

15 *N*-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

N-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,7-dihydro-5*H*-spiro[1-benzofuran-6,1'-cyclopropane]-3-carboxamide;

20 *N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine-3-carboxamide;

N-(2-methyl-2*H*-indazol-5-yl)-6-(methylsulfonyl)-4-oxo-4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine-3-carboxamide;

6-methyl-*N*³-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3,6-dicarboxamide;

25 methyl 6-methyl-3-[(2-methyl-2*H*-indazol-5-yl)carbamoyl]-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-6-carboxylate;

6-(hydroxymethyl)-6-methyl-*N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

30 *tert*-butyl 4-[4-({[6-(hydroxymethyl)-6-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-yl]carbonyl} amino)-3-methoxyphenyl]piperazine-1-carboxylate;

6-(methoxymethyl)-*N*-[2-methoxy-4-(piperazin-1-yl)phenyl]-6-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

5-(hydroxymethyl)-5-methyl-*N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

5,5-dimethyl-*N*-(2-methyl-2*H*-indazol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

N-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-5-(aminomethyl)-5-methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

5 *N*-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-4-oxo-4,7-dihydrospiro[furo[2,3-*c*]pyran-5,4'-piperidine]-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-methoxypyridin-3-yl]-5,5-dimethyl-4-oxo-4,7-dihydro-5*H*-furo[2,3-*c*]pyran-3-carboxamide;

10 *N*-[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]-4-oxo-4,7-dihydrospiro[furo[2,3-*c*]pyran-5,3'-oxetane]-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2-hydroxyethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

15 *N*-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2-methoxyethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-[2-(2-hydroxyethoxy)ethyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

20 *N*-[6-(4-acetylpiperazin-1-yl)-2-(2-methoxyethoxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-(2,2,2-trifluoroethoxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(4-acetylpiperazin-1-yl)-2-(oxetan-3-yloxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

25 *N*-[6-(4-acetylpiperazin-1-yl)-2-(tetrahydro-2*H*-pyran-4-yloxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-(4-acetylpiperazin-1-yl)-2-[(3*S*)-tetrahydrofuran-3-yloxy]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

30 *N*-[6-(4-formylpiperazin-1-yl)-2-(2-methoxyethoxy)pyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-{6-(4-acetylpiperazin-1-yl)-2-[(1-oxidothietan-3-yl)oxy]pyridin-3-yl}-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide;

N-[6-(1-acetylpiperidin-4-yl)-2-ethoxypyridin-3-yl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-3-carboxamide; and

N-[6-(4-acetylpiperazin-1-yl)-2-ethoxypyridin-3-yl]-5-(2,5-difluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide.

28. A pharmaceutical composition comprising a therapeutically effective amount of a
5 compound of claim 1 in combination with a pharmaceutically acceptable carrier.

29. A method of selectively modulating the effects of TrkA receptor kinase activity in a mammal comprising administering an effective amount of a compound of claim 1.

10 30. A method of treating a condition or disorder modulated by TrkA (Tropomyosin receptor kinase isoform A) in a mammal comprising administering an effective amount of a compound of claim 1.

31. The method according to claim 30, wherein the condition or disorder is selected from
15 the group consisting of pain, including osteoarthritis pain, joint pain, neuropathic pain, post-surgical pain, low back pain, and diabetic neuropathy, pain during surgery, cancer pain, chemotherapy induced pain, headaches, including cluster headache, tension headache, migraine pain, trigeminal neuralgia, shingles pain, post-herpetic neuralgia, carpal tunnel syndrome, inflammatory pain, pain from rheumatoid arthritis, colitis, pain of interstitial
20 cystitis, visceral pain, pain from kidney stone, pain from gallstone, angina, fibromyalgia, chronic pain syndrome, thalamic pain syndrome, pain from stroke, phantom limb pain, sunburn, radiculopathy, complex regional pain syndrome, HIV sensory neuropathy, central neuropathic pain syndromes, multiple sclerosis pain, Parkinson disease pain, spinal cord injury pain, menstrual pain, toothache, pain from bone metastasis, pain from endometriosis,
25 pain from uterine fibroids, nociceptive pain, hyperalgesia, and temporomandibular joint pain, inflammation, auto-immune disease, rheumatoid arthritis, psoriasis, psoriatic arthritis, asthma, Crohn's disease, inflammatory bladder cystitis, inflammatory bowel disease, joint swelling, diabetic nephropathy, kidney fibrosis, chronic kidney disease, cancer, neuroblastoma, melanoma, myeloma, cancers of the pancreas, prostate, ovary, colon, thyroid,
30 lung, brain, esophagus, kidney, of bone, and blood.

32. The method according to claim 30, wherein the condition or disorder is selected from the group consisting of pain, including osteoarthritis pain, joint pain, neuropathic pain, post-surgical pain, low back pain, and diabetic neuropathy, pain during surgery, cancer pain,

chemotherapy induced pain, headaches, including cluster headache, tension headache, migraine pain, trigeminal neuralgia, shingles pain, post-herpetic neuralgia, carpal tunnel syndrome, inflammatory pain, pain from rheumatoid arthritis, colitis, pain of interstitial cystitis, visceral pain, pain from kidney stone, pain from gallstone, angina, fibromyalgia, chronic pain syndrome, thalamic pain syndrome, pain from stroke, phantom limb pain, sunburn, radiculopathy, complex regional pain syndrome, HIV sensory neuropathy, central neuropathic pain syndromes, multiple sclerosis pain, Parkinson disease pain, spinal cord injury pain, menstrual pain, toothache, pain from bone metastasis, pain from endometriosis, pain from uterine fibroids, nociceptive pain, hyperalgesia, and temporomandibular joint pain.

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