

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 June 2008 (12.06.2008)

PCT

(10) International Publication Number
WO 2008/070014 A2

(51) International Patent Classification:
A01N 43/40 (2006.01)

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(21) International Application Number:
PCT/US2007/024717

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(22) International Filing Date:
28 November 2007 (28.11.2007)

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/868,366 4 December 2006 (04.12.2006) US
60/887,171 30 January 2007 (30.01.2007) US

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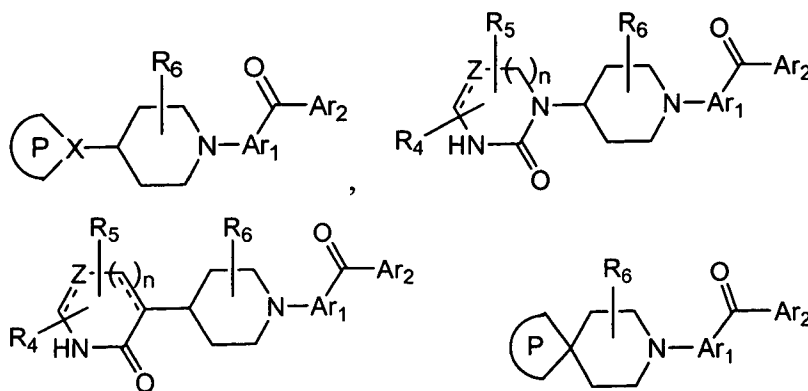
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(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

(54) Title: BIARYL KETONE-SUBSTITUTED PIPERIDINES



(57) Abstract: Biaryl ketone-substituted piperidines of the following Formulas are provided; and in which the variables are as described herein. Such compounds may be used to modulate calcitonin gene-related peptide (CGRP) receptor activity in vivo or in vitro, and are particularly useful in the treatment of conditions responsive to CGRP modulation in humans, domesticated companion animals and livestock animals, including headache such as migraine. Pharmaceutical compositions and methods for using them to treat such disorders are provided, as are methods for using such compounds for receptor localization studies and various in vitro assays.

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BIARYL KETONE-SUBSTITUTED PIPERIDINES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Nos. 60/868,366, filed
20 December 4, 2006 and 60/887,171, filed January 30, 2007, the entireties of which are
incorporated herein by reference.

FIELD OF THE INVENTION

This invention relates generally to biaryl ketone-substituted piperidines and related
compounds, and to the use of such compounds to treat conditions responsive to calcitonin gene-
25 related peptide (CGRP) receptor modulation. The invention further relates to the use of such
compounds as reagents for the identification of other agents that bind to CGRP receptor, and as
probes for the detection and localization of CGRP receptor.

BACKGROUND OF THE INVENTION

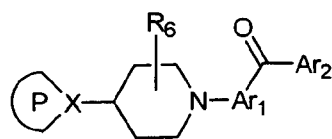
Calcitonin gene-related peptide (CGRP) is a naturally occurring peptide that is widely
30 distributed in both the peripheral and central nervous systems. This peptide is primarily
localized in sensory afferent and central neurons, where it exerts a number of biological effects,
including vasodilation. CGRP is released from trigeminal ganglia nerves after nerve activation
and is a strong cerebral and dural vessel dilator. Accordingly, CGRP regulates blood flow to the
brain and meninges (which are pain-sensitive), and is involved in the pathophysiology of
35 conditions such as migraine and cluster headaches.

CGRP exerts its biological actions by binding to specific cell surface receptors (CGRP receptors), which are G-protein coupled and in turn activate intracellular adenylate cyclase. CGRP receptors generally have three discrete components: (1) a transmembrane calcitonin receptor-like receptor (CRLR or CLR); (2) a transmembrane receptor activity modifying protein type one (RAMP1) and (3) an intracellular receptor component protein (RCP), all of which are required in order to form a functional CGRP receptor complex. Evans et al. (1996) *J. Biol. Chem* 40:31438-43. CGRP receptor antagonists inhibit the action of CGRP at such receptors, and are useful in the treatment of a variety of conditions associated with CGRP receptor modulation, including pain, headache and migraine.

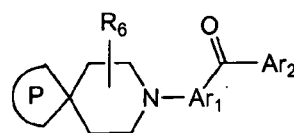
There is thus a need in the art for CGRP antagonists. The present invention fulfills this need and provides further related advantages.

SUMMARY OF THE INVENTION

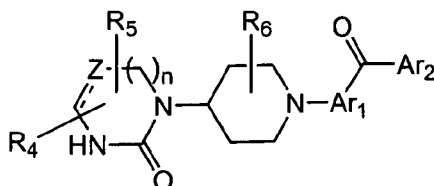
The present invention provides biaryl ketone-substituted piperidines that satisfy Formula A or Formula I or Formula II or Formula XI:



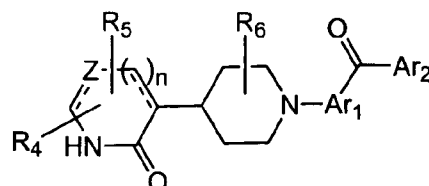
Formula A



Formula II



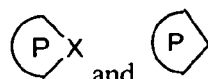
Formula I



Formula XI

Within Formulas A, I, II, and XI,

== represents a single or double bond;



and are each a 5- or 6-membered heterocycle that:

(a) comprises at least one ring nitrogen atom;

(b) is substituted with oxo;

(c) is optionally substituted with C₁-C₄alkyl; and

(d) is:

(i) substituted with a phenyl or 5- or 6-membered heteroaryl substituent; or

(ii) fused to a phenyl or 5- or 6-membered heterocyclic ring;

each of which (i) and (ii) is optionally substituted and is preferably substituted with from 0 to 4 substituents independently chosen from halogen, hydroxy, cyano, amino, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₆alkoxy, and mono- or di-(C₁-C₆alkyl)aminoC₀-C₄alkyl;

5 X is C, CH, or N;

Z is C, CH, CH₂, N or NH;

n is 0, 1 or 2;

Ar₁ is phenyl or a 5- or 6-membered heteroaryl, each of which is optionally substituted and each of which is preferably substituted with from 0 to 3 substituents independently chosen from R_A;

Ar₂ is phenyl or a 5- or 6-membered heteroaryl, each of which is substituted with from 0 to 5 substituents independently chosen from:

(i) halogen, hydroxy, cyano, amino, aminocarbonyl and aminosulfonyl;

(ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈haloalkyl, C₁-C₈hydroxyalkyl, C₂-C₈alkyl ether, C₁-C₈alkoxy, C₁-C₈alkoxycarbonyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, mono- or di-(C₁-C₈alkyl)aminoC₀-C₄alkyl, phenylC₀-C₄alkyl and (4- to 12-membered heterocycle)C₀-C₄alkyl; each of which is substituted with from 0 to 6 substituents independently chosen from hydroxy, oxo, halogen, amino, aminocarbonyl, aminosulfonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkylthio, C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl, C₁-C₆alkylsulfinyl, C₁-C₆alkoxycarbonyl, mono- or di-(C₁-C₆alkyl)aminocarbonyl, and mono- or di-(C₁-C₆alkyl)aminosulfonyl; and

(iii) substituents that are taken together to form a fused 5- to 7-membered carbocycle or heterocycle that is optionally substituted and is preferably substituted with from 0 to 4 substituents independently chosen from C₁-C₆alkyl;

Each R_A is independently chosen from:

(i) halogen, hydroxy, cyano and amino;

(ii) C₁-C₆alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, and (4- to 7-membered heterocycle)C₀-C₄alkyl; each of which is optionally substituted and each of which is preferably substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, amino, C₁-C₄alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl and (4- to 10-membered heterocycle)C₀-C₄alkyl; and

(iii) substituents that are taken together to form a fused 5- to 7-membered carbocycle or heterocycle that is optionally substituted and is preferably substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, C₁-C₆alkyl, (C₃-

C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, and (4- to 7-membered heterocycle)C₀-C₄alkyl;

R₄ represents zero substituents or:

(i) oxo;

(ii) a phenyl or 5- or 6-membered heteroaryl substituent; or

(iii) a fused phenyl or 5- or 6-membered heterocyclic ring;

each of which (ii) and (iii) is optionally substituted and is preferably substituted with from 0 to 4 substituents independently chosen from:

(a) halogen, hydroxy, cyano, amino and oxo; and

(b) C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, mono- or di-(C₁-C₆alkyl)aminoC₀-C₄alkyl, and (4- to 10-membered heterocycle)C₀-C₄alkyl; each of which is optionally substituted and each of which is preferably substituted with from 0 to 4 substituents independently chosen from hydroxy, oxo, halogen, amino, aminocarbonyl, aminosulfonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkylthio, C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl, C₁-C₆alkylsulfinyl, C₁-C₆alkoxycarbonyl, mono- or di-(C₁-C₆alkyl)aminocarbonyl, and mono- or di-(C₁-C₆alkyl)aminosulfonyl;

R₅ represents from 0 to 4 substituents independently chosen from C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, and (C₃-C₈cycloalkyl)C₀-C₄alkyl; and

R₆ represents from 0 to 4 substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy and C₁-C₆alkyl ether.

Within certain aspects, biaryl ketone-substituted piperidines provided herein are CGRP receptor modulators and exhibit an EC₅₀ or IC₅₀ of no greater than 10 micromolar, 5 micromolar, 2 micromolar, 1 micromolar, 500 nanomolar, 100 nanomolar, 50 nanomolar or 10 nanomolar in an assay for determination of CGRP receptor agonist or antagonist activity.

In preferred embodiments, CGRP receptor modulators provided herein are CGRP receptor antagonists; in certain embodiments, such antagonists exhibit no detectable CGRP receptor agonist activity above background at their EC₅₀ for CGRP receptor.

Within certain aspects, biaryl ketone-substituted piperidines provided herein are labeled with a detectable marker (*e.g.*, radiolabeled or fluorescein conjugated).

The present invention further provides pharmaceutical compositions comprising at least one biaryl ketone-substituted piperidine provided herein in combination with a physiologically acceptable carrier or excipient.

Methods are further provided for inhibiting agonist-induced CGRP receptor activity. Within certain embodiments, the inhibition takes place *in vitro*. Such methods comprise contacting a CGRP receptor with at least one CGRP receptor antagonist as described herein, under conditions and in an amount or concentration sufficient to detectably inhibit agonist-induced CGRP receptor activity. Within other such aspects, the CGRP receptor is in a patient. Such methods comprise contacting cells expressing a CGRP receptor in a patient with a CGRP receptor antagonist as described herein in an amount or concentration that would be sufficient to detectably inhibit agonist-induced CGRP receptor activity in cells expressing CGRP receptor *in vitro*.

The present invention further provides methods for treating a condition responsive to CGRP receptor modulation in a patient, comprising administering to the patient a therapeutically effective amount of at least one biaryl ketone-substituted piperidine provided herein.

Within other aspects, methods are provided for treating migraine or other headache in a patient, comprising administering to a patient suffering from (or at risk for) headache a therapeutically effective amount of at least one biaryl ketone-substituted piperidine provided herein.

Within further aspects, the present invention provides methods for determining the presence or absence of CGRP receptor in a sample, comprising: (a) contacting a sample with a biaryl ketone-substituted piperidine provided herein under conditions that permit binding of the compound to CGRP receptor; and (b) detecting a signal indicative of a level of the compound bound to CGRP receptor.

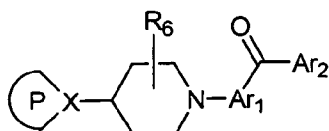
In yet another aspect, the present invention provides methods of preparing the compounds disclosed herein, including the intermediates.

These and other aspects of the present invention will become apparent upon reference to the following detailed description.

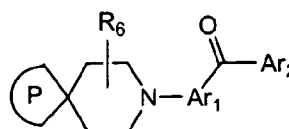
DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

As noted above, the present invention provides biaryl ketone-substituted piperidines, which may be used *in vitro* or *in vivo* in a variety of contexts, as described herein.

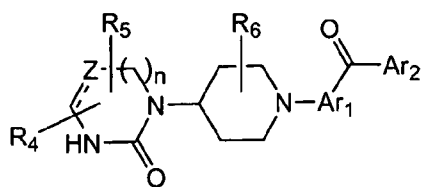
The present invention provides biaryl ketone-substituted piperidines that satisfy Formula A or Formula I or Formula II or Formula XI:



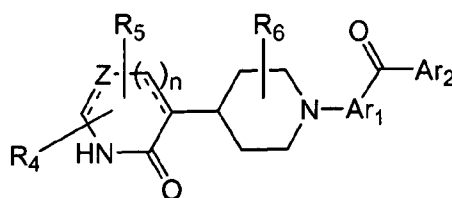
Formula A



Formula II



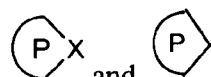
Formula I



Formula XI

Within Formulas A, I, II, and XI,

==== represents a single or double bond;



and are each a 5- or 6-membered heterocycle that:

(a) comprises at least one ring nitrogen atom;

(b) is substituted with oxo;

(c) is optionally substituted with C₁-C₄alkyl; and

(d) is:

(i) substituted with a phenyl or 5- or 6-membered heteroaryl substituent; or

(ii) fused to a phenyl or 5- or 6-membered heterocyclic ring;

each of which (i) and (ii) is optionally substituted and is preferably substituted with from 0 to 4 substituents independently chosen from halogen, hydroxy, cyano, amino, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₆alkoxy, and mono- or di-(C₁-C₆alkyl)aminoC₀-C₄alkyl;

X is C, CH, or N;

Z is C, CH, CH₂, N or NH;

n is 0, 1 or 2;

Ar₁ is phenyl or a 5- or 6-membered heteroaryl, each of which is optionally substituted and each of which is preferably substituted with from 0 to 3 substituents independently chosen from R_A;

Ar₂ is phenyl or a 5- or 6-membered heteroaryl, each of which is substituted with from 0 to 5 substituents independently chosen from:

(i) halogen, hydroxy, cyano, amino, aminocarbonyl and aminosulfonyl;

(ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈haloalkyl, C₁-C₈hydroxyalkyl, C₂-C₈alkyl ether, C₁-C₈alkoxy, C₁-C₈alkoxycarbonyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, mono- or di-(C₁-C₈alkyl)aminoC₀-C₄alkyl, phenylC₀-C₄alkyl and (4- to 12-membered heterocycle)C₀-C₄alkyl; each of which is substituted with from 0 to 6 substituents independently chosen from hydroxy, oxo, halogen, amino, aminocarbonyl, aminosulfonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-

C₆alkylthio, C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl, C₁-C₆alkylsulfinyl, C₁-C₆alkoxycarbonyl, mono- or di-(C₁-C₆alkyl)aminocarbonyl, and mono- or di-(C₁-C₆alkyl)aminosulfonyl; and

(iii) substituents that are taken together to form a fused 5- to 7-membered carbocycle or heterocycle that is optionally substituted and is preferably substituted with from 0 to 4

5 substituents independently chosen from C₁-C₆alkyl;

Each R_A is independently chosen from:

(i) halogen, hydroxy, cyano and amino;

(ii) C₁-C₆alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, and (4- to 7-membered heterocycle)C₀-C₄alkyl;

10 each of which is optionally substituted and each of which is preferably substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, amino, C₁-C₄alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl and (4- to 10-membered heterocycle)C₀-C₄alkyl; and

(iii) substituents that are taken together to form a fused 5- to 7-membered carbocycle or heterocycle that is optionally substituted and is preferably substituted with from 0 to 3

15 substituents independently chosen from halogen, hydroxy, amino, C₁-C₆alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, and (4- to 7-membered heterocycle)C₀-C₄alkyl;

R₄ represents zero substituents or:

(i) oxo;

20 (ii) a phenyl or 5- or 6-membered heteroaryl substituent; or

(iii) a fused phenyl or 5- or 6-membered heterocyclic ring;

each of which (ii) and (iii) is optionally substituted and is preferably substituted with from 0 to 4 substituents independently chosen from:

(a) halogen, hydroxy, cyano, amino and oxo; and

25 (b) C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, mono- or di-(C₁-C₆alkyl)aminoC₀-C₄alkyl, and (4- to 10-membered heterocycle)C₀-C₄alkyl; each of which is optionally substituted and each of which is preferably substituted with from 0 to 4 substituents independently chosen from hydroxy, oxo, halogen, amino, aminocarbonyl, aminosulfonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkylthio, C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl, C₁-C₆alkylsulfinyl, C₁-C₆alkoxycarbonyl, mono- or di-(C₁-C₆alkyl)aminocarbonyl, and mono- or di-(C₁-C₆alkyl)aminosulfonyl;

R₅ represents from 0 to 4 substituents independently chosen from C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, and (C₃-C₈cycloalkyl)C₀-C₄alkyl; and

R₆ represents from 0 to 4 substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy and C₁-C₆alkyl ether.

TERMINOLOGY

5 Compounds are generally described herein using standard nomenclature. For compounds having asymmetric centers, it should be understood that (unless otherwise specified) all of the optical isomers and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in Z- and E- forms, with all isomeric forms of the compounds being included in the present invention unless otherwise specified. If a compound exists in
10 various tautomeric forms, a recited compound is not limited to any one specific tautomer, but rather is intended to encompass all tautomeric forms. Certain compounds are described herein using a general formula that includes variables (*e.g.*, Z, Ar₁, R₁). Unless otherwise specified, each variable within such a formula is defined independently of any other variable, and any variable that occurs more than one time in a formula is defined independently at each occurrence.

15 The term "biaryl ketone-substituted piperidine" encompasses any compound that satisfies Formula A or Formula I or Formula II or Formula XI, and optionally further satisfies one or more additional formulas provided herein. This term further includes pharmaceutically acceptable salts, solvates (*e.g.*, hydrates) and esters of such compounds.

 A "pharmaceutically acceptable salt" of a compound recited herein is an acid or base salt
20 that is suitable for use in contact with the tissues of human beings or animals without excessive toxicity or carcinogenicity, and preferably without irritation, allergic response, or other problem or complication. Such salts include mineral and organic acid salts of basic residues such as amines, as well as alkali or organic salts of acidic residues such as carboxylic acids. Specific pharmaceutically acceptable anions for use in salt formation include, but are not limited to,
25 acetate, 2-acetoxybenzoate, ascorbate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, carbonate, chloride, citrate, dihydrochloride, diphosphate, edetate, estolate (ethylsuccinate), formate, fumarate, gluceptate, gluconate, glutamate, glycolate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroiodide, hydroxymaleate, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate,
30 mandelate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phenylacetate, phosphate, polygalacturonate, propionate, salicylate, stearate, subacetate, succinate, sulfamate, sulfanilate, sulfate, sulfonates including besylate (benzenesulfonate), camsylate (camphorsulfonate), edisylate (ethane-1,2-disulfonate), esylate (ethanesulfonate) 2-hydroxyethylsulfonate, mesylate (methanesulfonate), triflate

(trifluoromethanesulfonate) and tosylate (*p*-toluenesulfonate), tannate, tartrate, teoclate and triethiodide. Similarly, pharmaceutically acceptable cations for use in salt formation include, but are not limited to ammonium, benzathine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, and metals such as aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Those of ordinary skill in the art will recognize further pharmaceutically acceptable salts for the compounds provided herein. In general, a pharmaceutically acceptable acid or base salt can be synthesized from a parent compound that contains a basic or acidic moiety by any conventional chemical method. Briefly, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, the use of nonaqueous media, such as ether, ethyl acetate, ethanol, methanol, isopropanol or acetonitrile, is preferred.

It will be apparent that each compound provided herein may, but need not, be formulated as a solvate (*e.g.*, a hydrate) or non-covalent complex. In addition, the various crystal forms and polymorphs are within the scope of the present invention. Also provided herein are prodrugs of the compounds provided herein. A "prodrug" is a compound that may not fully satisfy the structural requirements of a formula provided herein, but is modified *in vivo*, following administration to a patient, to produce a compound within the scope of such formula. For example, a prodrug may be an acylated derivative of a compound as provided herein. Prodrugs include compounds wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxy, amino or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, phosphate and benzoate derivatives of alcohol and amine functional groups within the compounds provided herein. Prodrugs of the compounds provided herein may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved *in vivo* to yield the parent compounds.

As used herein, the term "alkyl" refers to a straight or branched chain saturated aliphatic hydrocarbon. Alkyl groups include groups having from 1 to 8 carbon atoms (C₁-C₈alkyl), from 1 to 6 carbon atoms (C₁-C₆alkyl) and from 1 to 4 carbon atoms (C₁-C₄alkyl), such as methyl, ethyl, propyl, isopropyl, n-butyl, *sec*-butyl, *tert*-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl or 3-methylpentyl. In some instances, a substituent of an alkyl group is specifically indicated. For example, "C₁-C₆aminoalkyl" refers to a C₁-C₆alkyl that has at least one -NH₂ substituent, and "C₁-C₄hydroxyalkyl" refers to a C₁-C₄alkyl substituted with at least one -OH. "C₀-C₄alkyl" refers to a single covalent bond (C₀) or an alkylene group having 1, 2, 3

MISSING UPON FILING

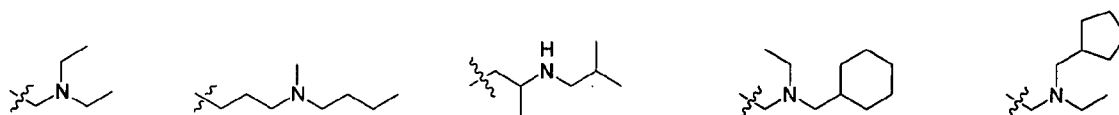
C₁-C₄alkoxycarbonyl groups, which have from 1 to 8, 6 or 4 carbon atoms, respectively, in the alkyl portion of the group. "C₁alkoxycarbonyl" refers to -C(=O)-O-CH₃.

The term "alkanoyl" refers to an acyl group (*e.g.*, -(C=O)-alkyl), in which carbon atoms are in a linear or branched alkyl arrangement and where attachment is through the carbon of the keto group. Alkanoyl groups have the indicated number of carbon atoms, with the carbon of the keto group being included in the numbered carbon atoms. For example a C₂alkanoyl group is an acetyl group having the formula -(C=O)CH₃; "C₁alkanoyl" refers to -(C=O)H. Alkanoyl groups include, for example, C₁-C₈alkanoyl, C₁-C₆alkanoyl and C₁-C₄alkanoyl groups, which have from 1 to 8, from 1 to 6 or from 1 to 4 carbon atoms, respectively.

"Alkanoylamino," as used herein, refers to an alkanoyl group linked via a nitrogen bridge (*i.e.*, a group having the general structure -N(R)-C(=O)-alkyl), in which R is hydrogen or C₁-C₆alkyl). Alkanoylamino groups include, for example, (C₁-C₆alkanoyl)amino groups, which have from 1 to 6 carbon atoms within the alkanoyl group.

"Alkylamino" refers to a secondary or tertiary amine that has the general structure -NH-alkyl or -N(alkyl)(alkyl), wherein each alkyl is selected independently from alkyl, cycloalkyl and (cycloalkyl)alkyl groups. Such groups include, for example, mono- and di-(C₁-C₈alkyl)amino groups, in which each C₁-C₈alkyl may be the same or different, as well as mono- and di-(C₁-C₆alkyl)amino groups and mono- and di-(C₁-C₄alkyl)amino groups.

"Alkylaminoalkyl" refers to an alkylamino group linked via an alkylene moiety (*i.e.*, a group having the general structure -alkylene-NH-alkyl or -alkylene-N(alkyl)(alkyl)) in which each alkyl is selected independently from alkyl, cycloalkyl and (cycloalkyl)alkyl groups. Alkylaminoalkyl groups include, for example, mono- and di-(C₁-C₈alkyl)aminoC₁-C₆alkyl, and mono- and di-(C₁-C₆alkyl)aminoC₁-C₄alkyl. "Mono- or di-(C₁-C₆alkyl)aminoC₀-C₄alkyl" refers to a mono- or di-(C₁-C₆alkyl)amino group linked via a single covalent bond or a C₁-C₄alkylene group. The following are representative alkylaminoalkyl groups:



It will be apparent that the definition of "alkyl" as used in the terms "alkylamino" and "alkylaminoalkyl" differs from the definition of "alkyl" used for all other alkyl-containing groups, in the inclusion of cycloalkyl and (cycloalkyl)alkyl groups (*e.g.*, (C₃-C₇cycloalkyl)C₀-C₂alkyl).

The term "aminocarbonyl" refers to an amide group (*i.e.*, -C(=O)NH₂). The term "mono- or di-(C₁-C₆alkyl)aminocarbonyl" refers to groups of the formula -(C=O)-N(R)₂, in which the

carbonyl is the point of attachment, one R is C₁-C₆alkyl and the other R is hydrogen or an independently chosen C₁-C₆alkyl.

Similarly, "aminosulfonyl" refers to a sulfonamide group (*i.e.*, -SO₂NH₂). The term "mono- or di-(C₁-C₆alkyl)aminosulfonyl" refers to groups of the formula -(SO₂)-N(R)₂, in which the sulfonyl is the point of attachment, one R is C₁-C₆alkyl and the other R is hydrogen or an independently chosen C₁-C₆alkyl.

The term "halogen" refers to fluorine, chlorine, bromine or iodine.

The term "oxo" is used herein to refer to an oxygen substituent of a carbon atom that results in the formation of a carbonyl group (C=O). An oxo group that is a substituent of a nonaromatic carbon atom results in a conversion of -CH₂- to -C(=O)-. An oxo group that is a substituent of an aromatic carbon atom results in a conversion of -CH- to -C(=O)- and may result in a loss of aromaticity.

A "haloalkyl" is an alkyl group that is substituted with 1 or more independently chosen halogens (*e.g.*, "C₁-C₈haloalkyl" groups have from 1 to 8 carbon atoms; "C₁-C₆haloalkyl" groups have from 1 to 6 carbon atoms). Examples of haloalkyl groups include, but are not limited to, mono-, di- or tri-fluoromethyl; mono-, di- or tri-chloromethyl; mono-, di-, tri-, tetra- or penta-fluoroethyl; mono-, di-, tri-, tetra- or penta-chloroethyl; and 1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl. Typical haloalkyl groups are trifluoromethyl and difluoromethyl.

A dash ("-") that is not between two letters or numbers is used to indicate a point of attachment for a substituent. For example, -C(=O)NH₂ is attached through the carbon atom.

A "carbocycle" or "carbocyclic group" comprises at least one ring formed entirely by carbon-carbon bonds (referred to herein as a carbocyclic ring), and does not contain a heterocycle. Unless otherwise specified, each ring within a carbocycle may be independently saturated, partially saturated or aromatic, and is optionally substituted as indicated. A carbocycle generally has from 1 to 3 fused, pendant or spiro rings; carbocycles within certain embodiments have one ring or two fused rings. Typically, each ring contains from 3 to 8 ring members (*i.e.*, C₃-C₈); rings having from 5 to 7 ring members are recited in certain embodiments. Carbocycles comprising fused, pendant or spiro rings typically contain from 9 to 14 ring members. Certain representative carbocycles are cycloalkyl as described above. Other carbocycles are aryl (*i.e.*, contain at least one aromatic carbocyclic ring, with or without one or more additional aromatic and/or cycloalkyl rings). Such aryl carbocycles include, for example, phenyl, naphthyl (*e.g.*, 1-naphthyl and 2-naphthyl), fluorenyl, indanyl and 1,2,3,4-tetrahydronaphthyl.

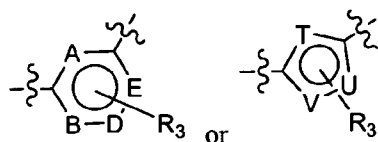
Certain 3- to 8-membered carbocycles are linked via a single covalent bond or C₁-C₄alkylene; and are accordingly designated "(C₃-C₈carbocycle)C₀-C₄alkyl." Such groups

include, for example, aryl and arylalkyl moieties (such as phenyl, indanyl, and groups in which either of the foregoing is linked via C₁-C₄alkylene; for example, a phenylC₀-C₄alkyl refers to a phenyl group linked via a single covalent bond or C₁-C₄alkylene) and (cycloalkyl)alkyl moieties as described above.

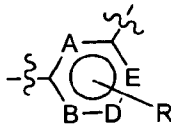
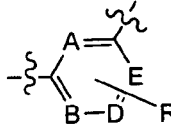
5 A "heterocycle" (also referred to herein as a "heterocyclic group") has from 1 to 3 fused, pendant or spiro rings, at least one of which is a heterocyclic ring (*i.e.*, one or more ring atoms is a heteroatom independently chosen from oxygen, sulfur and nitrogen, with the remaining ring atoms being carbon). Typically, a heterocyclic ring comprises 1, 2, 3 or 4 heteroatoms; within
 10 ring generally contains from 4 to 8 ring members (rings having from 4 or 5 to 7 ring members are recited in certain embodiments) and heterocycles comprising fused, pendant or spiro rings typically contain from 9 to 14 ring members. Certain heterocycles comprise a sulfur atom as a ring member; in certain embodiments, the sulfur atom is oxidized to SO or SO₂. Heterocycles may be optionally substituted with a variety of substituents, as indicated. Certain heterocycles
 15 are 4- to 12-membered or 4- to 10-membered and comprise one or two rings; in certain embodiments, such heterocycles are monocyclic (*e.g.*, 4- to 8-membered, 5- to 8-membered, 4- to 7-membered, or 5- or 6-membered).

Certain heterocycles are heteroaryl groups (*i.e.*, at least one heterocyclic ring within the group is aromatic), such as a 5- or 6-membered heteroaryl (*e.g.*, thienyl, imidazolyl, pyridyl or
 20 pyrimidyl). Other heterocycles are heterocycloalkyl groups (*i.e.*, do not comprise an aromatic heterocyclic ring). If so designated, a heterocycle may be linked by a single covalent bond or an alkylene group; for example, "(4- to 12-membered heterocycle)C₀-C₄alkyl" refers to a 4- to 12-membered heterocycle having 1 or 2 rings, which is linked via a single covalent bond or via an alkylene group having from 1 to 6 carbons. "(4- to 7-membered heterocycle)C₀-C₄alkyl" refers
 25 to a 4- to 7-membered heterocyclic ring that is linked via a single covalent bond or an alkylene group having from 1 to 4 carbons. methylene or ethylene linker. When substituted, it will be apparent that substituent(s) may be attached on the ring and/or the alkylene linker.

Certain heteroaryls are indicated in various Formulas with the following notation:



in which the variables are as described herein, such that the ring retains aromaticity. It will be

apparent, for example, that  and  are interchangeable notations.

A "substituent," as used herein, refers to a molecular moiety that is covalently bonded to an atom within a molecule of interest. For example, a "ring substituent" may be a moiety such as a halogen, alkyl group, haloalkyl group or other group discussed herein that is covalently bonded to an atom (such as a carbon or nitrogen atom) that is a ring member. The term "substitution" refers to replacing a hydrogen atom in a molecular structure with a substituent as described above, such that the valence on the designated atom is not exceeded, and such that a chemically stable compound (*i.e.*, a compound that can be isolated, characterized, and tested for biological activity) results from the substitution.

Groups that are "optionally substituted" are unsubstituted or are substituted by other than hydrogen at one or more available positions, typically 1, 2, 3, 4 or 5 positions, by one or more suitable groups (which may be the same or different). Optional substitution is also indicated by the phrase "substituted with from 0 to X substituents," where X is the maximum number of possible substituents. Certain optionally substituted groups are substituted with from 0 to 2, 3 or 4 independently selected substituents (*i.e.*, are unsubstituted or substituted with up to the recited maximum number of substituents).

"CGRP receptor," as used herein, refers to any functional CGRP receptor complex, comprising a ligand binding protein CRLR and a chaperone protein RAMP1. In general, such a receptor complex further comprises a coupling protein RCP. In certain embodiments, each complex component is human: human CRLR includes, for example, the polypeptide having the sequence provided at Genbank accession number NM_005795, and human RAMP1 includes, for example, the polypeptide having the sequence provided at Genbank accession number NM_005855. One or more components of the receptor complex may be expressed endogenously; in certain embodiments it is convenient to use cells that express CRLR and RAMP1 recombinantly, with RCP expressed endogenously. Alternatively, any of a variety of cells such as the human neuroblastoma cell line SK-N-MS (DSMZ, Braunschweig, Germany), which naturally express functional CGRP receptor, may be a convenient source for CGRP receptor and receptor-containing membrane preparations.

The term "CGRP receptor agonist" refers to a compound that binds CGRP receptor and induces signal transduction mediated by CGRP receptor. CGRP receptor agonists include, for

example, CGRP (*e.g.*, human CGRP), as well as peptide portions or variants thereof that bind CGRP receptor and retain CGRP-receptor activating activity.

A "CGRP receptor antagonist" is a compound that detectably inhibits signal transduction mediated by CGRP receptor. Such inhibition may be determined using the representative calcium mobilization assay provided in Example 5. Preferred CGRP receptor antagonists have an IC_{50} of 10 μ M or less in this assay, more preferably 5 μ M or less, and still more preferably 1 μ M or less, 500 nM or less, or 100 nM or less. Certain CGRP receptor antagonists exhibit minimal agonist activity (*i.e.*, they induce an increase in the basal activity of CGRP receptor that is less than 5% of the increase that would be induced by one EC_{50} of the peptide agonist CGRP) and more preferably exhibit no detectable agonist activity within the assay described in Example 5. CGRP receptor antagonists for use as described herein are generally non-toxic. CGRP receptor antagonists include neutral antagonists and inverse agonists.

A "neutral antagonist" of CGRP receptor is a compound that inhibits the activity of CGRP receptor agonist at CGRP receptor, but when present at its IC_{50} (determined using the calcium mobilization assay as described in Example 5) does not significantly change the basal activity of the receptor. The effect on the basal activity may be determined using the calcium mobilization assay described in Example 5 performed in the absence of agonist. Preferably, within such an assay, CGRP receptor activity is reduced by no more than 10%, more preferably by no more than 5%, and even more preferably by no more than 2%; most preferably, there is no detectable reduction in activity. Neutral antagonists may, but need not, also inhibit the binding of agonist to CGRP receptor.

An "inverse agonist" of CGRP receptor is a compound that reduces the activity of CGRP receptor below its basal activity level in the absence of activating concentrations of agonist. Inverse agonists may also inhibit the activity of agonist at CGRP receptor, and/or may inhibit binding of CGRP receptor agonist to CGRP receptor. The reduction in basal activity of CGRP receptor produced by an inverse agonist may be determined from a calcium mobilization assay, such as the assay of Example 5.

A "therapeutically effective amount" (or dose) is an amount that, upon administration to a patient, results in a discernible patient benefit (*e.g.*, provides detectable relief from a condition being treated). Such relief may be detected using any appropriate criteria. A therapeutically effective amount or dose generally results in a concentration of compound(s) in a body fluid (such as blood, plasma, serum, CSF, synovial fluid, lymph, cellular interstitial fluid, tears or urine) that is sufficient to result in detectable alteration in CGRP receptor-mediated signal transduction (using an assay provided herein). The discernible patient benefit may be apparent

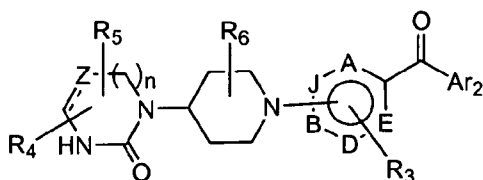
after administration of a single dose, or may become apparent following repeated administration of the therapeutically effective dose according to a predetermined regimen, depending upon the indication for which the compound is administered.

A "patient" is any individual treated with a biaryl ketone-substituted piperidine as provided herein. Patients include humans, as well as other animals such as companion animals (e.g., dogs and cats) and livestock; in certain embodiments, human patients are preferred. Patients may be experiencing one or more symptoms of a condition responsive to CGRP receptor modulation or may be free of such symptom(s) (*i.e.*, treatment may be prophylactic in a patient considered to be at risk for the development of such symptoms).

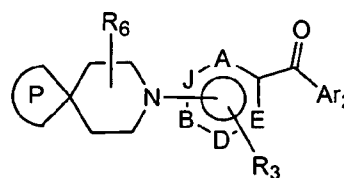
BIARYL KETONE-SUBSTITUTED PIPERIDINES

As noted above, the present invention provides biaryl ketone-substituted piperidines of Formula A, Formula I, Formula II, and Formula XI, above. Such biaryl ketone-substituted piperidines may be used in a variety of contexts, including in the treatment of conditions responsive to CGRP receptor modulation. Such compounds may also be used within *in vitro* assays (e.g., assays for CGRP receptor activity), as probes for the detection and localization of CGRP receptor and within assays to identify other CGRP receptor antagonists.

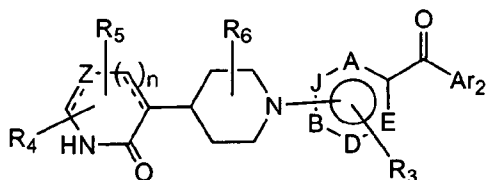
Within certain biaryl ketone-substituted piperidines of Formulas A, I, II, and XI, Ar₁ is a 6-membered heteroaryl, such as pyridyl or pyrimidyl, each of which is optionally substituted as described above. Certain such compounds further satisfy III, IV or XII, respectively:



Formula III



Formula IV



Formula XII

wherein A, B, D, E and J are each independently C, CH or N; and

R₃ represents from 0 to 3 substituents independently chosen from:

(i) halogen, hydroxy, cyano and amino; and

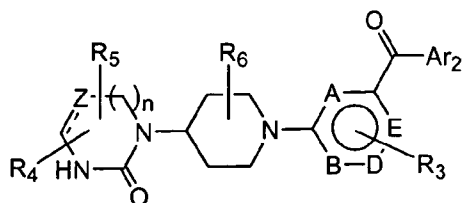
(ii) C₁-C₆alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, and (4- to 7-membered heterocycle)C₀-C₄alkyl; each of which is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, amino, C₁-C₄alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl and (4- to 10-membered

5 heterocycle)C₀-C₄alkyl;

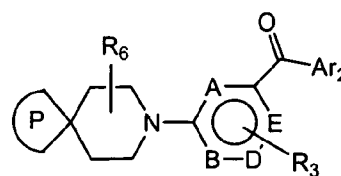
or two substituents represented by R₃ are taken together to form a fused 5- to 7-membered carbocycle or heterocycle that is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, C₁-C₆alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, and
 10 (4- to 7-membered heterocycle)C₀-C₄alkyl; and the remaining variables are as described above.

It will be apparent that, within Formulas III, IV, and XII any of A, B, D, E and J that is CH may be substituted with a substituent represented by R₃ or with the piperidine moiety.

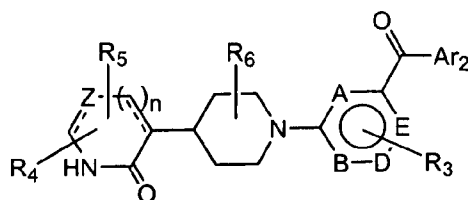
Certain such compounds further satisfy Formula IIIa, IVa or XIIa, respectively:



Formula IIIa

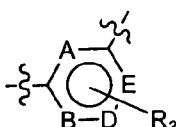
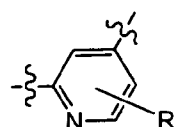
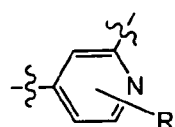


Formula IVa

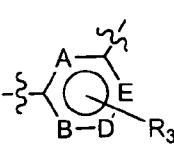
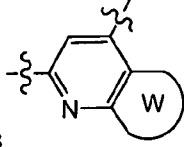


Formula XIIa

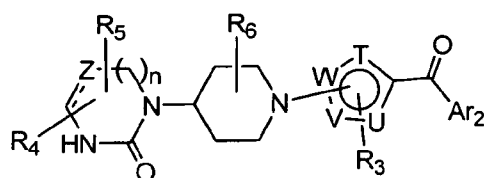
wherein A, B, D and E are each CH or N, such that exactly one or two of A, B, D and E
 15 are N; and R₃ is as described above.

The group designated  is  or  within certain
 such compounds.

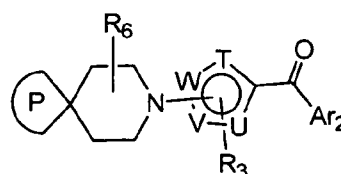
R₃, in certain embodiments, represents from 0 to 2 substituents independently chosen from halogen, C₁-C₄alkyl, C₁-C₄alkoxy, C₂-C₄alkyl ether and mono- or di-(C₁-C₄alkyl)amino. In
 20 certain embodiments, R₃ represents 0 substituents or one C₁-C₄alkyl substituent (e.g., methyl,

ethyl or propyl). Within other compounds,  is , wherein  represents a 5- or 6-membered carbocycle or heterocycle, each of which is substituted with from 0 to 4 substituents independently chosen from halogen, hydroxy, amino, C₁-C₆alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, and (4- to 7-membered heterocycle)C₀-C₄alkyl; and all other variables are as described above.

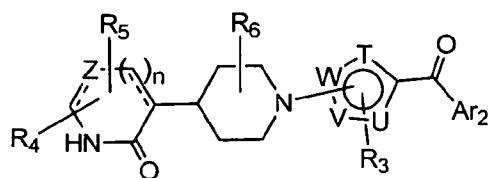
Within other biaryl ketone-substituted piperidines of Formula A, I, II and XI, Ar₁ is a 5-membered heteroaryl, such as thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl or triazolyl, each of which is substituted with from 0 to 2 substituents independently chosen from R_A. Certain such compounds further satisfy Formula V, Formula VI or Formula XIII, respectively:



Formula V

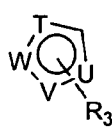


Formula VI



Formula XIII

wherein:

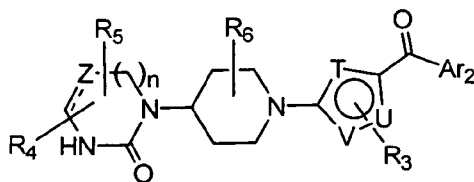
T, U, V and W are independently CH, N, NH, S and O; and  is aromatic; and R₃ represents from 0 to 2 substituents independently chosen from:

- (i) halogen, hydroxy, cyano and amino; and
- (ii) C₁-C₆alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, and (4- to 7-membered heterocycle)C₀-C₄alkyl; each of which is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, amino, C₁-C₄alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl and (4- to 10-membered heterocycle)C₀-C₄alkyl;

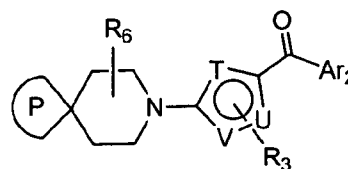
or two substituents represented by R_3 are taken together to form a fused 5- to 7-membered carbocycle or heterocycle that is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, C_1 - C_6 alkyl, (C_3 - C_8 carbocycle) C_0 - C_4 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkyl ether, mono- or di-(C_1 - C_6 alkyl)amino C_0 - C_2 alkyl, and (4- to 7-membered heterocycle) C_0 - C_4 alkyl; and all other variables are as described above.

In certain embodiments, at least one of T, U, V and W is N. It will be apparent that, within Formulas V and VI, any of T, U, V and W that is CH may be substituted with a substituent represented by R_3 or with the piperidine moiety.

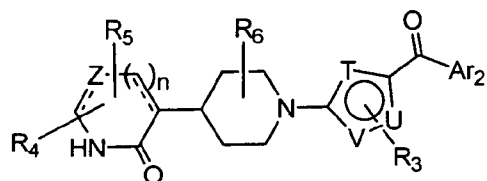
Certain such compounds further satisfy Formula Va, VIa or XIIIa, respectively:



Formula Va



Formula VIa



Formula XIIIa

wherein:

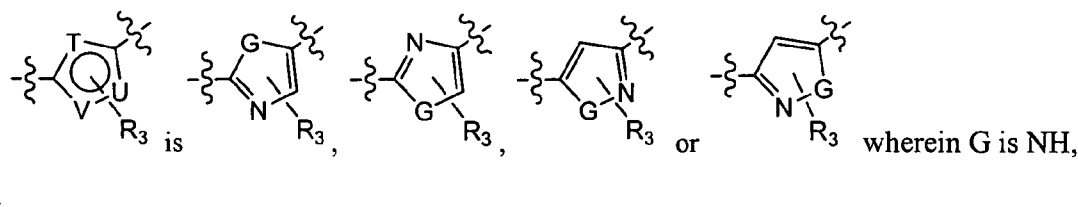
T, U and V are independently c, CH, N, NH, S and O, such that at least one of T, U and

V is N; and  is aromatic; and

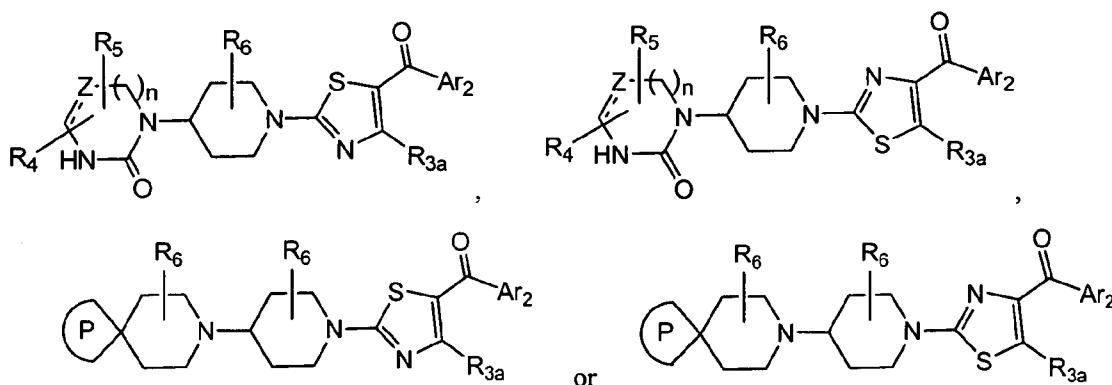
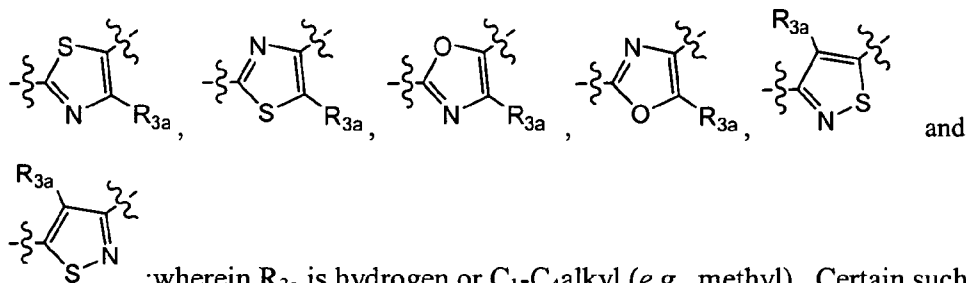
R_3 is as described for Formulas V, VI and XIII; and all other variables are as described above.

Within certain such compounds, exactly one of T, U and V is CH. Within further such compounds, R_3 represents from 0 to 2 substituents independently chosen from halogen, C_1 - C_4 alkyl, C_2 - C_4 alkyl ether and mono- or di-(C_1 - C_4 alkyl)amino. In certain embodiments, R_3 represents 0 substituents or one C_1 - C_4 alkyl substituent (e.g., methyl, ethyl or propyl).

Within certain compounds in which Ar_1 is a 5-membered heteroaryl, the group:



Representative such Ar₁ moieties include, for example:

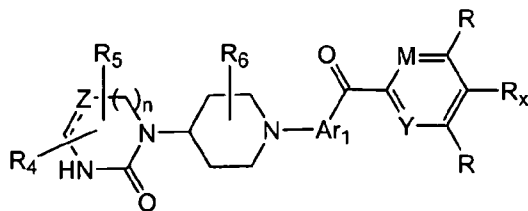


Within certain biaryl ketone-substituted piperidines of the various Formulas provided

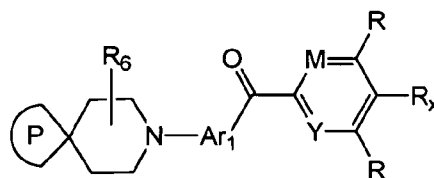
- 10 herein, Ar₂ is phenyl, pyridyl or pyrimidinyl, each of which is substituted with from 0 to 5 substituents independently chosen from: (i) halogen, hydroxy, cyano, amino, aminocarbonyl and aminosulfonyl; (ii) C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, mono- or di-(C₁-C₆alkyl)aminoC₀-C₄alkyl, phenyl, and 4- to 7-membered heterocycle; each of which is
- 15 substituted with from 0 to 4 substituents independently chosen from hydroxy, oxo, halogen, amino, aminocarbonyl, aminosulfonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkylthio, C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl, C₁-C₆alkylsulfinyl, C₁-C₆alkoxycarbonyl, mono- or di-(C₁-C₆alkyl)aminocarbonyl, and mono- or di-(C₁-C₆alkyl)aminosulfonyl; and (iii) substituents that are taken together to form a fused 5- or 6-membered carbocycle or heterocycle.

- 20 Certain representative such Ar₂ moieties include, for example, phenyl, pyridyl, pyrimidinyl, naphthyl, indanyl, indenyl, indolyl, indazolyl, benzimidazolyl, quinolinyl, quinazolinyl and naphthyridinyl. For example, in certain compounds, Ar₂ is phenyl, pyridyl or

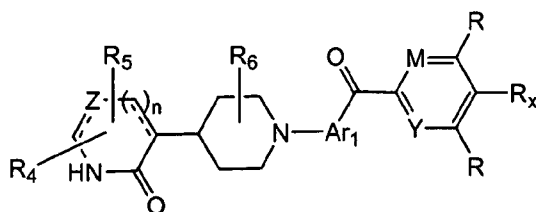
pyrimidinyl, each of which is mono-, di- or tri-substituted. Representative such biaryl ketone-substituted piperidines further satisfy Formula VII, VIII or XIV:



Formula VII



Formula VIII



Formula XIV

in which:

M and Y are independently CH or N;

- 5 R_x is (i) halogen, hydroxy, cyano, amino, aminocarbonyl and aminosulfonyl; or (ii) C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_1 - C_8 haloalkyl, C_1 - C_8 hydroxyalkyl, C_2 - C_8 alkyl ether, C_1 - C_8 alkoxy, C_1 - C_8 alkoxycarbonyl, (C_3 - C_8 cycloalkyl) C_0 - C_4 alkyl, mono- or di-(C_1 - C_8 alkyl)amino C_0 - C_4 alkyl, phenyl C_0 - C_4 alkyl and (4- to 12-membered heterocycle) C_0 - C_4 alkyl; each of which is substituted with from 0 to 6 substituents independently chosen from hydroxy, oxo, halogen, amino, aminocarbonyl, aminosulfonyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_1 - C_6 alkanoyl, C_1 - C_6 alkylsulfonyl, C_1 - C_6 alkylsulfinyl, C_1 - C_6 alkoxycarbonyl, mono- or di-(C_1 - C_6 alkyl)aminocarbonyl, and mono- or di-(C_1 - C_6 alkyl)aminosulfonyl;

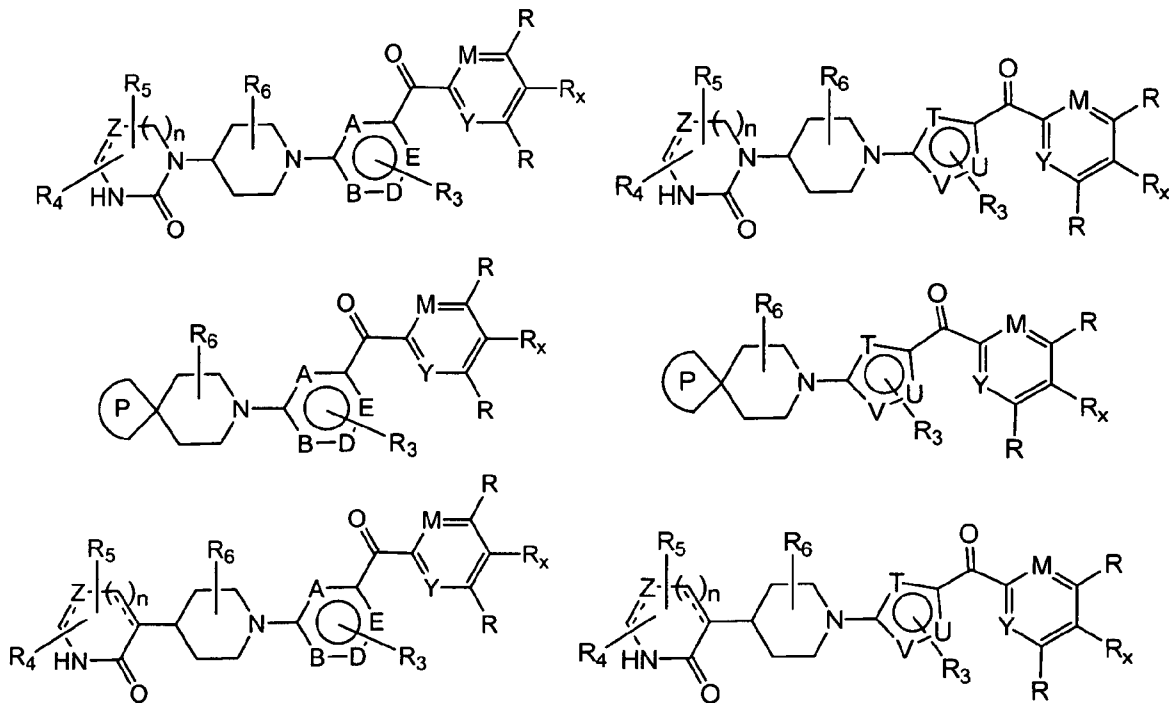
- each R is independently (i) hydrogen, halogen, hydroxy, cyano, amino, aminocarbonyl and aminosulfonyl; or (ii) C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_1 - C_8 haloalkyl, C_1 - C_8 hydroxyalkyl, C_2 - C_8 alkyl ether, C_1 - C_8 alkoxy, C_1 - C_8 alkoxycarbonyl, (C_3 - C_8 cycloalkyl) C_0 - C_4 alkyl, mono- or di-(C_1 - C_8 alkyl)amino C_0 - C_4 alkyl, phenyl C_0 - C_4 alkyl and (4- to 12-membered heterocycle) C_0 - C_4 alkyl; each of which is substituted with from 0 to 6 substituents independently chosen from hydroxy, oxo, halogen, amino, aminocarbonyl, aminosulfonyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_1 - C_6 alkanoyl, C_1 - C_6 alkylsulfonyl, C_1 - C_6 alkylsulfinyl, C_1 - C_6 alkoxycarbonyl, mono- or di-(C_1 - C_6 alkyl)aminocarbonyl, and mono- or di-(C_1 - C_6 alkyl)aminosulfonyl;

and the remaining variables are as described above. Within certain such compounds, R_x is halogen, hydroxy, cyano, amino, aminocarbonyl and aminosulfonyl C_1 - C_8 alkyl, C_2 - C_8 alkenyl,

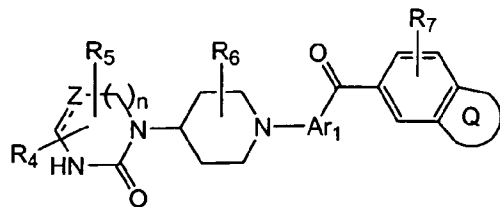
C₂-C₈alkynyl, C₁-C₈haloalkyl, C₁-C₈hydroxyalkyl, C₂-C₈alkyl ether, C₁-C₈alkoxy, C₁-C₈alkoxycarbonyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, or mono- or di-(C₁-C₈alkyl)aminoC₀-C₄alkyl.

Within further such compounds, R_x is hydroxy or C₁-C₈alkoxy and each R is other than hydrogen (e.g., C₁-C₆alkyl). Representative compounds of Formula VII, Formula VIII or Formula XIV

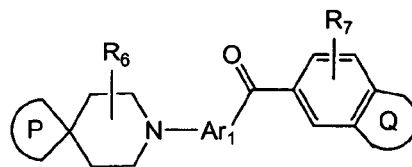
5 further satisfy one of the following formulas, in which all variables are as described above:



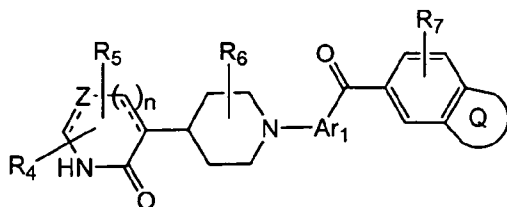
Other biaryl ketone-substituted piperidines further satisfy Formula IX, X or XV:



Formula IX



Formula X



Formula XV

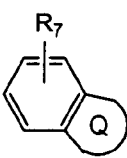
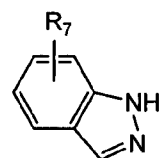
wherein:

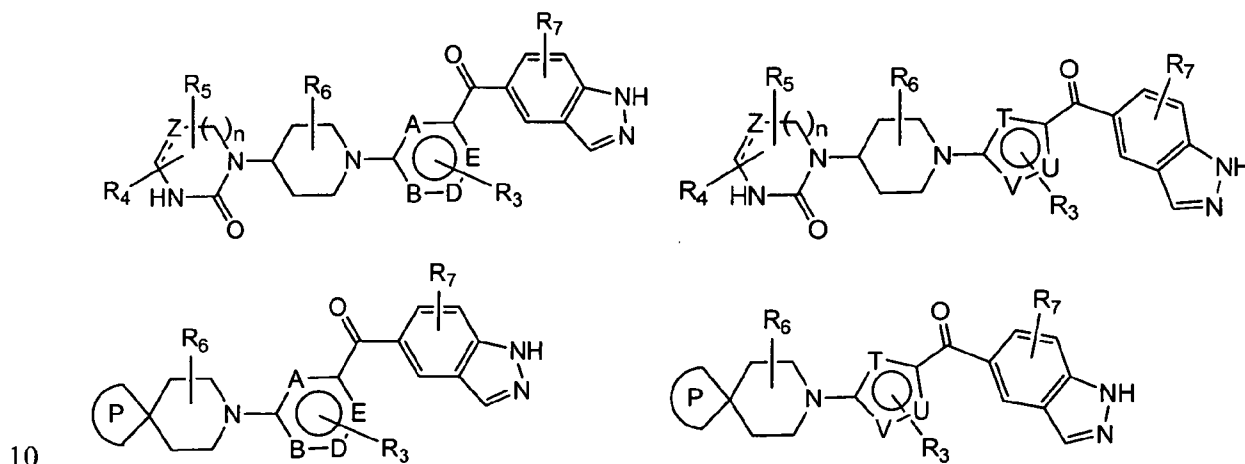
R₇ represents from 0 to 3 substituents independently chosen from:

(i) halogen, hydroxy and amino; and

(ii) C₁-C₆alkyl, C₁-C₆alkoxy, mono- or di-(C₁-C₆alkyl)amino, C₁-C₆alkoxycarbonyl, C₂-C₆alkyl ether, phenyl and 4- to 7-membered heterocycle, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, amino, oxo, C₁-C₄alkyl, C₁-C₄alkoxy and mono- or di-(C₁-C₄alkyl)amino;

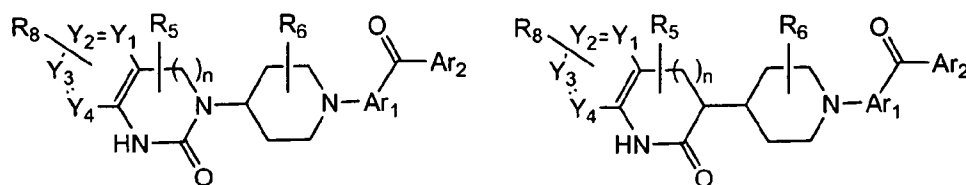
5  is a 5- or 6-membered heterocycle that is optionally substituted with C₁-C₄alkyl; and the remaining variables are as described above.

Within certain such compounds,  is , as illustrated in the following representative formulas, in which all variables are as described above.



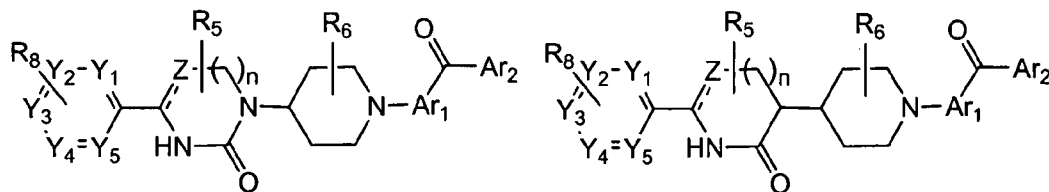
R₇, within certain such compounds, represents one or two methyl substituents.

Within certain compounds, R₄ represents a substituent, selected from oxo, pendant rings and fused rings as described above. Certain R₄ moieties are indicated as "fused phenyl or 5- or 6-membered heterocyclic rings." In such groups, the ring represented by R₄ is fused to the Z-
15 containing ring, as in the following representative subformulas:



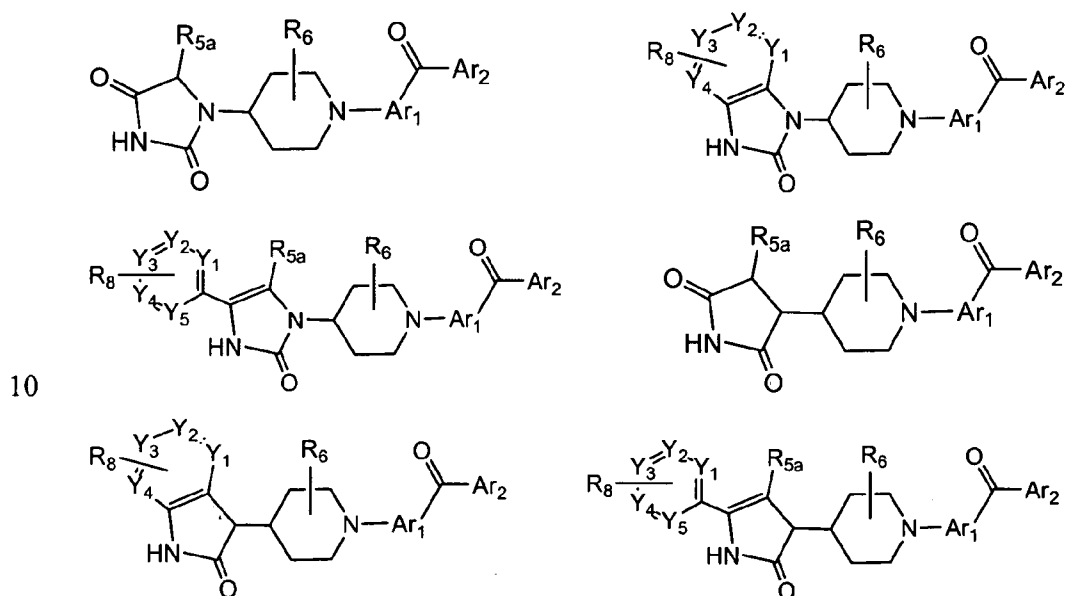
in which Y₁, Y₂, Y₃ and Y₄ are independently C, N or CH and R₈ represents from 0 to 4 substituents independently chosen from halogen, hydroxy, cyano, amino, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₆alkoxy, and mono- or di-(C₁-
20 C₆alkyl)aminoC₀-C₄alkyl. In certain embodiments, Y₁ is N and Y₂, Y₃ and Y₄ are each CH; in other embodiments, Y₄ is N and Y₁, Y₂ and Y₃ are each CH.

Other R_4 moieties are "a phenyl or 5- or 6-membered heteroaryl substituent." In such groups, the ring represented by R_4 is pendant, as in the following representative subformulas:



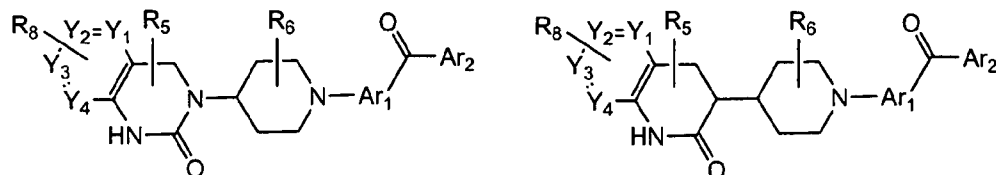
in which Y_1 , Y_2 , Y_3 , Y_4 and Y_5 are independently C, N or CH; and R_8 is as described above. In certain embodiments, Y_1 is N and Y_2 , Y_3 , Y_4 and Y_5 are each CH.

Within certain biaryl ketone-substituted piperidines of Formulas I and XI, and the various subformulas thereof, n is 0. Certain such compounds further satisfy one of the following Formulas:



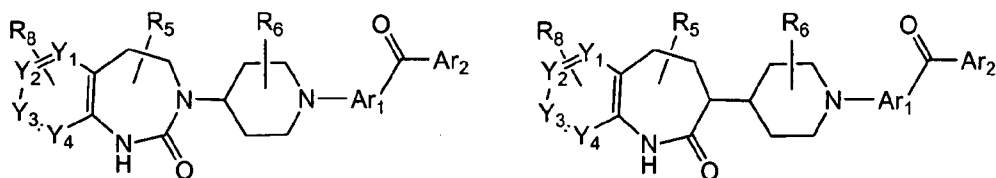
wherein Y_1 , Y_2 , Y_3 , Y_4 and Y_5 are independently C, N or CH; R_8 is as described above; and R_{5a} is hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl or $(C_3$ - C_8 cycloalkyl) C_0 - C_4 alkyl.

Within other biaryl ketone-substituted piperidines of Formulas I and XI, and the various subformulas thereof, n is 1. Certain such compounds further satisfy the following Formulas:



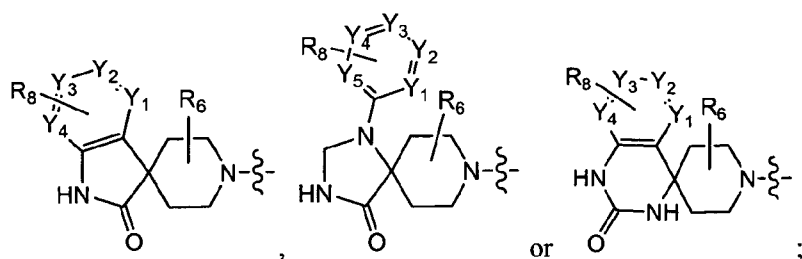
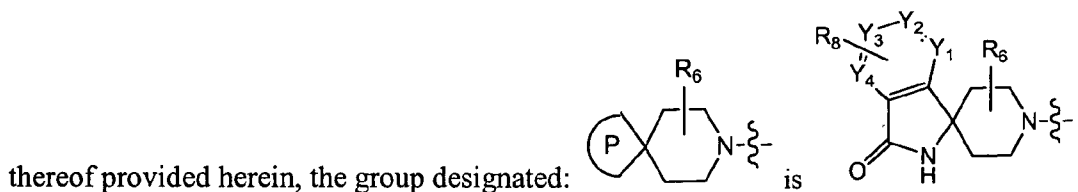
wherein Y_1 , Y_2 , Y_3 and Y_4 are independently C, N or CH; and R_8 is as described above.

Within further biaryl ketone-substituted piperidines of Formulas I and XI, and the various subformulas thereof, n is 2. Certain such compounds further satisfy the following Formulas:



wherein Y_1 , Y_2 , Y_3 and Y_4 are independently C, N or CH; and R_8 is as described above.

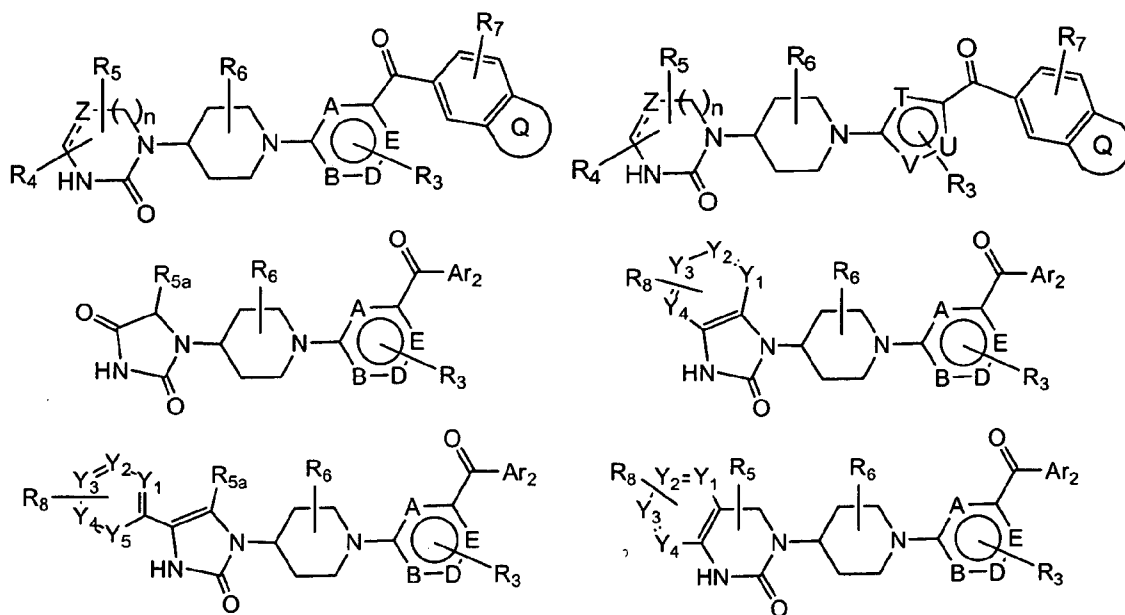
Within certain biaryl ketone-substituted piperidines of Formula II, and other subformulas

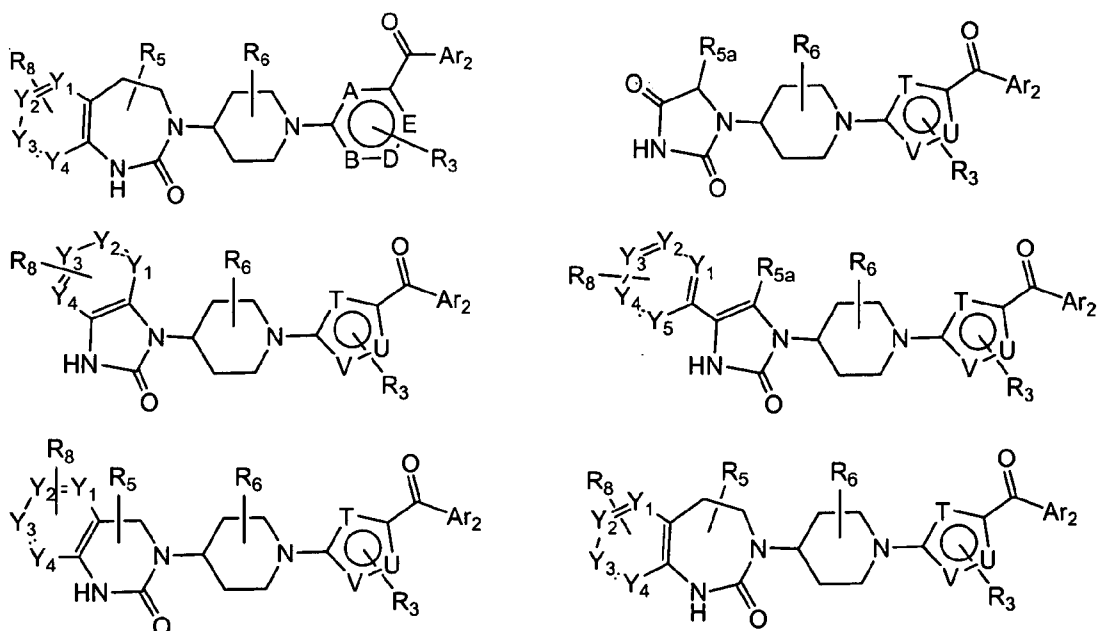


wherein Y_1 , Y_2 , Y_3 , Y_4 and Y_5 are independently C, N or CH; and R_8 is as described above.

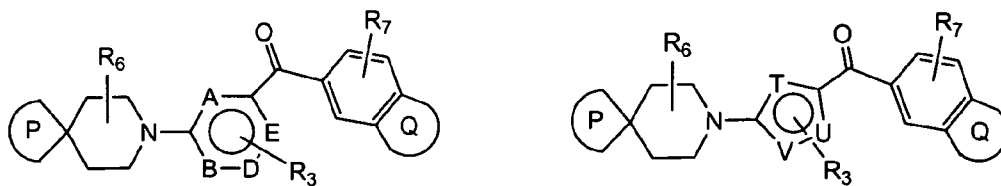
The variables R_5 , R_6 and/or R_8 each represent 0 substituents within certain compounds provided herein.

Certain biaryl ketone-substituted piperidines of Formula I further satisfy one of the following Formulas, in which all variables are as described above:

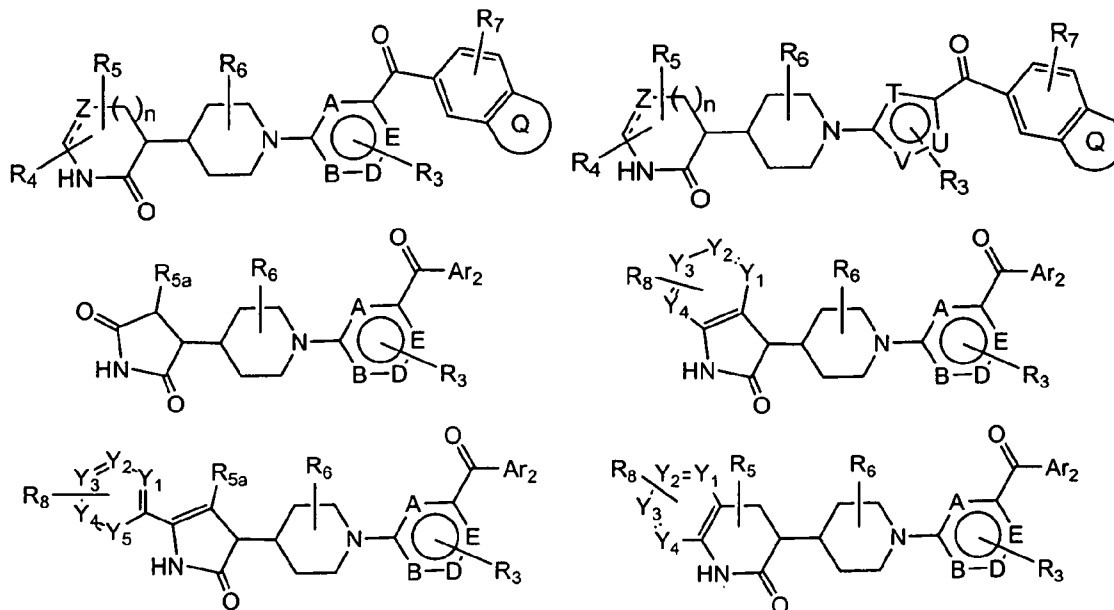


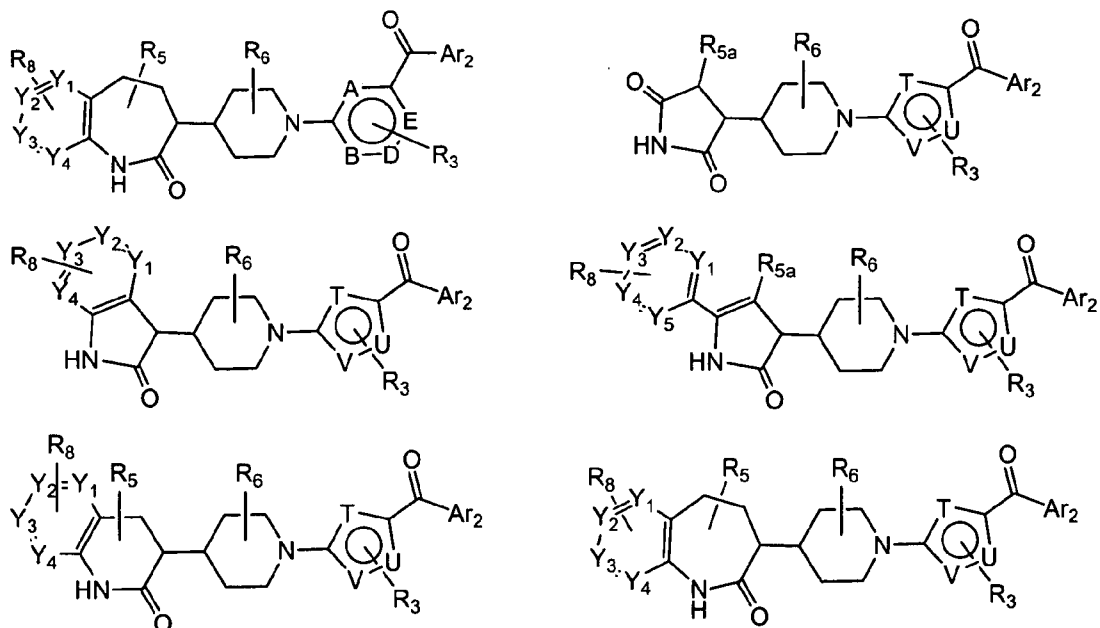


Certain biaryl ketone-substituted piperidines of Formula II further satisfy one of the following Formulas, in which all variables are as described above:



Certain biaryl ketone-substituted piperidines of Formula XI further satisfy one of the following Formulas, in which all variables are as described above:





Representative biaryl ketone-substituted piperidines provided herein include, but are not limited to, those specifically described in the Examples below. It will be apparent that the specific compounds recited herein are representative only, and are not intended to limit the scope of the present invention. Further, as noted above, all compounds of the present invention may be present as a free acid or base or as a pharmaceutically acceptable salt, hydrate or ester.

As noted above, within certain aspects, biaryl ketone-substituted piperidines provided herein are CGRP receptor modulators. CGRP receptor modulator activity may be confirmed using a calcium mobilization assay, such as the assay described in Example 5, herein.

If desired, compounds provided herein may be evaluated for certain pharmacological properties including, but not limited to, oral bioavailability (preferred compounds are orally bioavailable to an extent allowing for therapeutically effective doses of less than 140 mg/kg, preferably less than 50 mg/kg, more preferably less than 30 mg/kg, even more preferably less than 10 mg/kg, still more preferably less than 1 mg/kg and most preferably less than 0.1 mg/kg), toxicity (a preferred compound is nontoxic when a therapeutically effective amount is administered to a subject), side effects (a preferred compound produces side effects comparable to placebo when a therapeutically effective amount of the compound is administered to a subject), serum protein binding and *in vitro* and *in vivo* half-life (a preferred compound exhibits an *in vivo* half-life allowing for Q.I.D. dosing, preferably T.I.D. dosing, more preferably B.I.D. dosing, and most preferably once-a-day dosing). In addition, differential penetration of the blood brain barrier may be desirable. Routine assays that are well known in the art may be used to assess these properties, and identify superior compounds for a particular use. For example, assays used to predict bioavailability include transport across human intestinal cell monolayers,

including Caco-2 cell monolayers. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound (*e.g.*, intravenously). Serum protein binding may be predicted from albumin binding assays. Compound half-life is inversely proportional to the frequency of dosage of a compound.

- 5 *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described herein.

As noted above, preferred compounds provided herein are nontoxic. In general, the term "nontoxic" as used herein shall be understood in a relative sense and is intended to refer to any substance that has been approved by the United States Food and Drug Administration ("FDA")
10 for administration to mammals (preferably humans) or, in keeping with established criteria, is susceptible to approval by the FDA for administration to mammals (preferably humans). In addition, a highly preferred nontoxic compound generally satisfies one or more of the following criteria: (1) does not substantially inhibit cellular ATP production; (2) does not significantly prolong heart QT intervals; (3) does not cause substantial liver enlargement, or (4) does not
15 cause substantial release of liver enzymes.

As used herein, a compound that does not substantially inhibit cellular ATP production is a compound that satisfies the criteria set forth in Example 6, herein. In other words, cells treated as described in Example 6 with a 100 μ M concentration of such a compound exhibit ATP levels that are at least 50% of the ATP levels detected in untreated cells. In more highly preferred
20 embodiments, such cells exhibit ATP levels that are at least 80% of the ATP levels detected in untreated cells.

A compound that does not significantly prolong heart QT intervals is a compound that does not result in a statistically significant prolongation of heart QT intervals (as determined by electrocardiography) in guinea pigs, minipigs or dogs upon administration of a dose that yields a
25 serum concentration equal to the EC_{50} or IC_{50} for the compound. In certain preferred embodiments, a dose of 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally does not result in a statistically significant prolongation of heart QT intervals. By "statistically significant" is meant results varying from control at the $p < 0.1$ level or more preferably at the $p < 0.05$ level of significance as measured using a standard parametric assay of
30 statistical significance such as a student's T test.

A compound does not cause substantial liver enlargement if daily treatment of laboratory rodents (*e.g.*, mice or rats) for 5-10 days with a dose that yields a serum concentration equal to the EC_{50} or IC_{50} for the compound results in an increase in liver to body weight ratio that is no more than 100% over matched controls. In more highly preferred embodiments, such doses do

not cause liver enlargement of more than 75% or 50% over matched controls. If non-rodent mammals (*e.g.*, dogs) are used, such doses should not result in an increase of liver to body weight ratio of more than 50%, preferably not more than 25%, and more preferably not more than 10% over matched untreated controls. Preferred doses within such assays include 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally.

Similarly, a compound does not promote substantial release of liver enzymes if administration of twice the minimum dose that yields a serum concentration equal to the EC_{50} or IC_{50} for the compound does not elevate serum levels of ALT, LDH or AST in laboratory rodents by more than 100% over matched mock-treated controls. In more highly preferred embodiments, such doses do not elevate such serum levels by more than 75% or 50% over matched controls. Alternatively, a compound does not promote substantial release of liver enzymes if, in an *in vitro* hepatocyte assay, concentrations (in culture media or other such solutions that are contacted and incubated with hepatocytes *in vitro*) that are equal to the EC_{50} or IC_{50} for the compound do not cause detectable release of any of such liver enzymes into culture medium above baseline levels seen in media from matched mock-treated control cells. In more highly preferred embodiments, there is no detectable release of any of such liver enzymes into culture medium above baseline levels when such compound concentrations are five-fold, and preferably ten-fold the EC_{50} or IC_{50} for the compound.

In other embodiments, certain preferred compounds do not inhibit or induce microsomal cytochrome P450 enzyme activities, such as CYP1A2 activity, CYP2A6 activity, CYP2C9 activity, CYP2C19 activity, CYP2D6 activity, CYP2E1 activity or CYP3A4 activity at a concentration equal to the EC_{50} or IC_{50} for the compound.

Certain preferred compounds are not clastogenic (*e.g.*, as determined using a mouse erythrocyte precursor cell micronucleus assay, an Ames micronucleus assay, a spiral micronucleus assay or the like) at a concentration equal the EC_{50} or IC_{50} for the compound. In other embodiments, certain preferred compounds do not induce sister chromatid exchange (*e.g.*, in Chinese hamster ovary cells) at such concentrations.

For detection purposes, as discussed in more detail below, compounds provided herein may be isotopically-labeled or radiolabeled. For example, such compounds may have one or more atoms replaced by an atom of the same element having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be present in the compounds provided herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl . In addition, substitution with heavy 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.

5 PREPARATION OF BIARYL KETONE-SUBSTITUTED PIPERIDINES

Compounds provided herein may generally be prepared using standard synthetic methods. In general, starting materials are commercially available from suppliers such as Sigma-Aldrich Corp. (St. Louis, MO), or may be synthesized from commercially available precursors using established protocols. By way of example, a synthetic route similar to that
 10 shown in any of the following Schemes may be used, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon appreciated by those skilled in the art. It will be apparent that the reagents and synthetic transformations in the following Schemes and in the art can be readily modified to produce additional biaryl ketone-substituted piperidines. Each variable in the following Schemes refers to any group consistent with the description of the
 15 compounds provided herein.

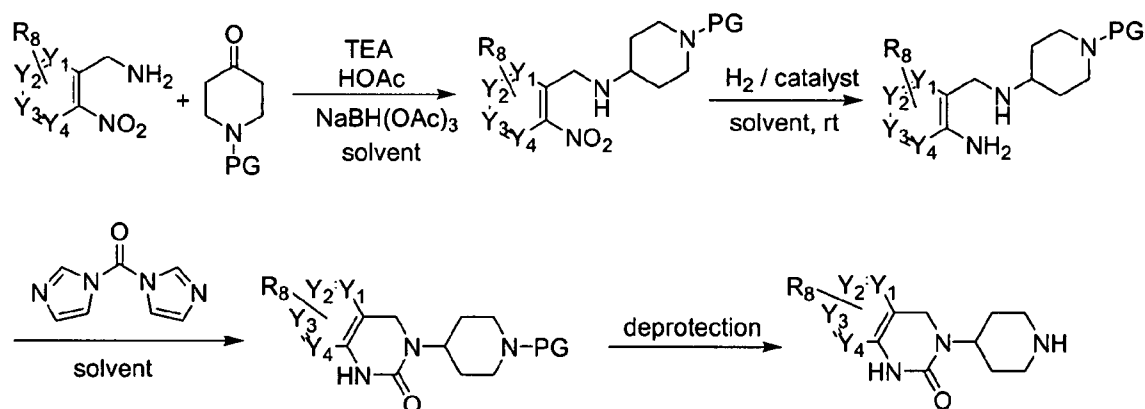
When a protecting group is required, an optional deprotection step may be employed. Suitable protecting groups and methodology for protection and deprotection, such as those described in *Protecting Groups in Organic Synthesis* by T. Greene, are well known. Compounds and intermediates requiring protection/deprotection will be readily apparent.

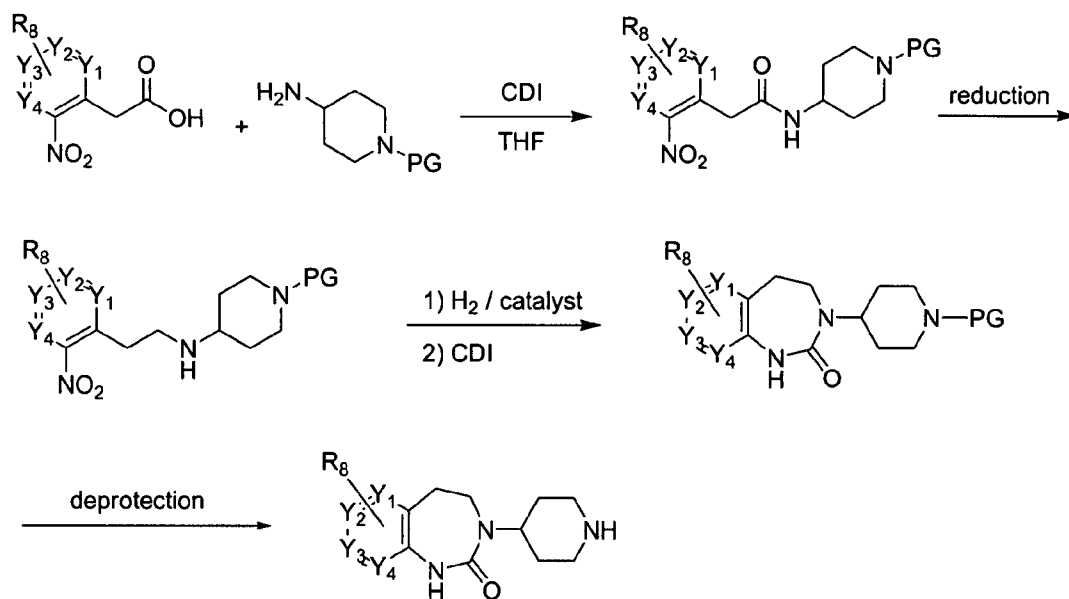
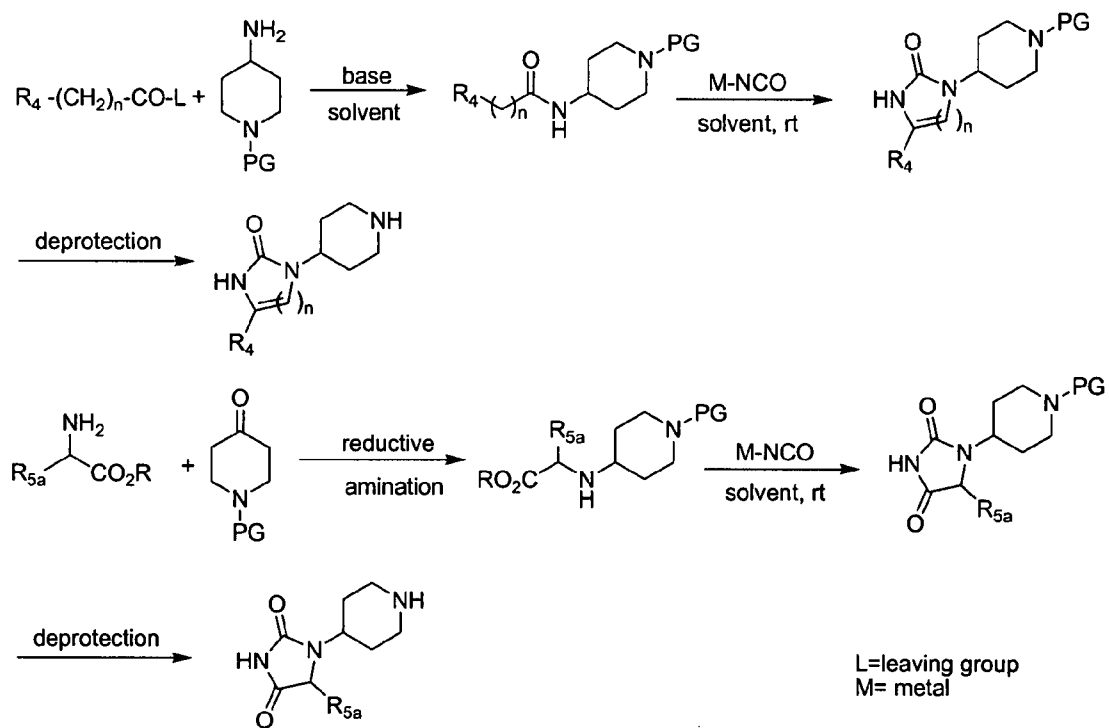
20 Certain abbreviations used in the following Schemes and elsewhere herein include:

	BINAP	(<i>rac</i>)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
	BOC	<i>tert</i> -butoxycarbonyl
	BOP	benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate
25	CDI	<i>N,N</i> -carbonyldiimidazole
	DCE	1,1-dichloroethane
	DIEA	<i>N,N</i> -diisopropylethylamine
	DMA	<i>N,N</i> -dimethylacetamide
	DMF	dimethylformamide
30	DMSO	dimethylsulfoxide
	Eq.	equivalent(s)
	EtOAc	ethyl acetate
	Fmoc	fluorenyl methoxycarbonyl
	h	hour(s)

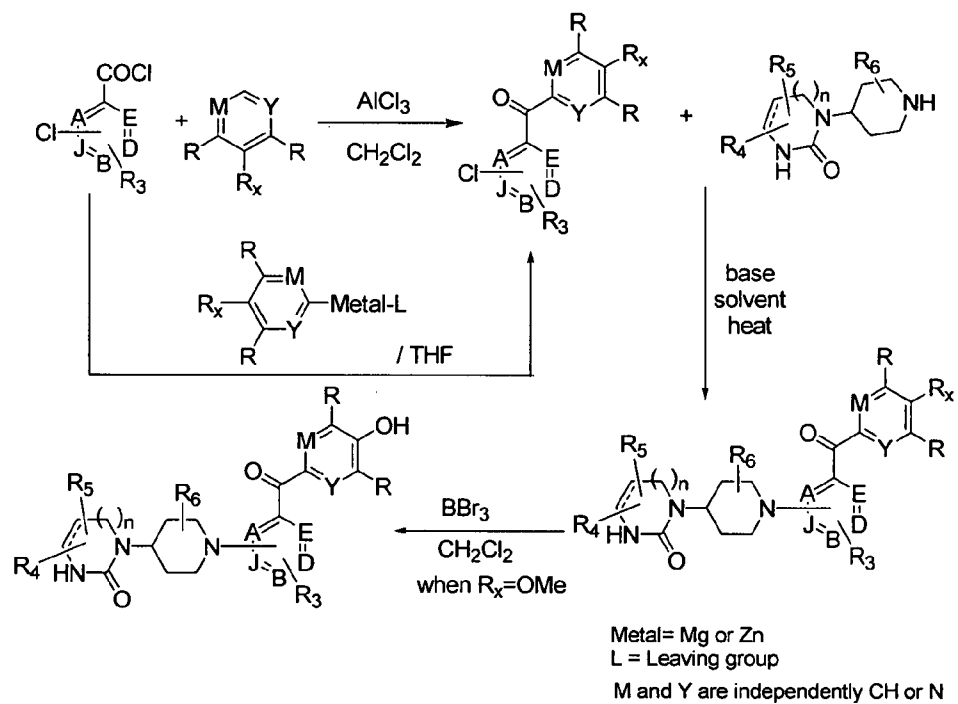
	¹ H NMR	proton nuclear magnetic resonance
	HOAc	acetic acid
	LC-MS	liquid chromatography/mass spectrometry
	MCPBA	<i>m</i> -chloroperoxybenzoic acid
5	MeOH	methanol
	MHz	megahertz
	M+H or M+1	mass + 1
	min	minute(s)
	MS	mass spectrometry
10	NMP	1-methyl-2-pyrrolidone
	δ	chemical shift
	rt	room temperature
	PG	protecting group
	Ph	phenyl
15	PTLC	preparative thin layer chromatography
	<i>t</i> -Bu	<i>tert</i> -butyl
	TEA	triethylamine
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran

20

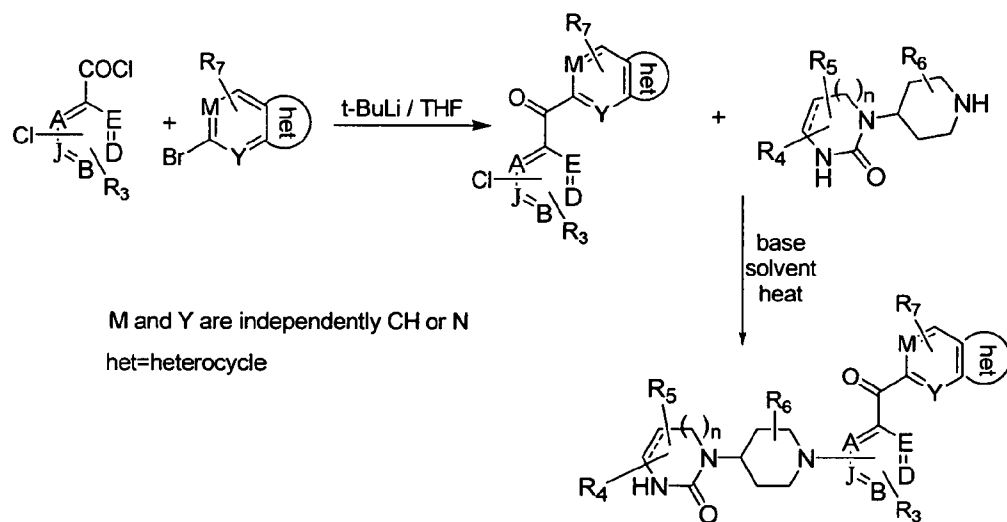
Scheme 1

Scheme 2Scheme 3

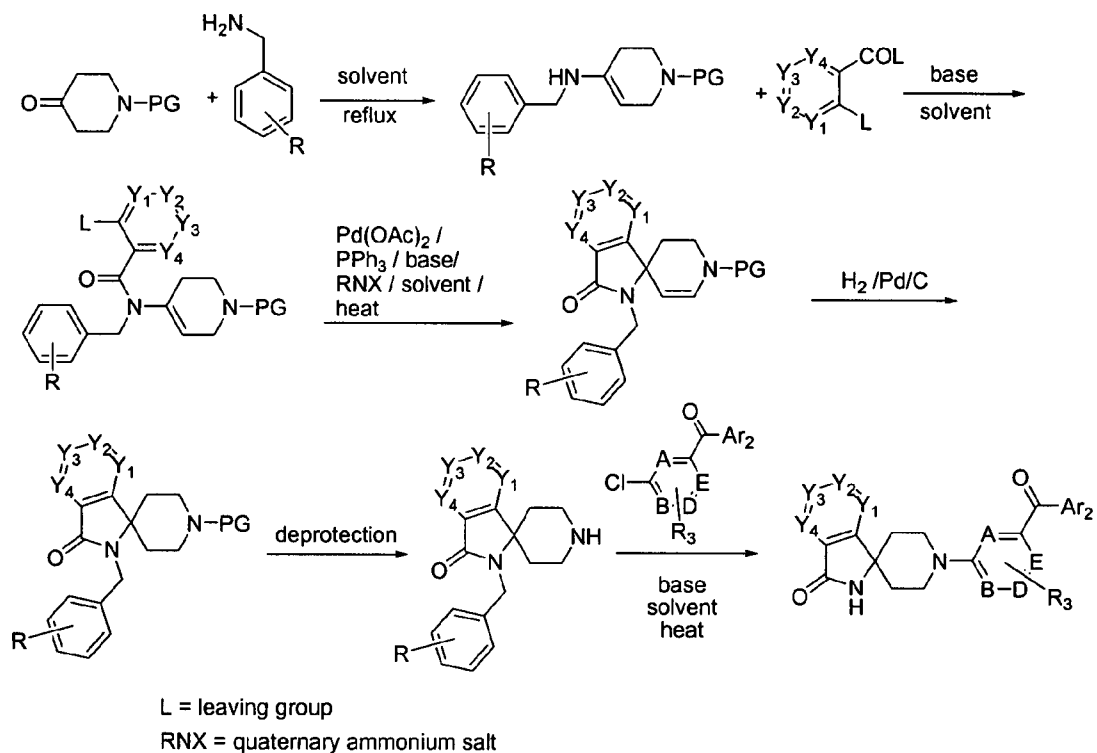
Scheme 4



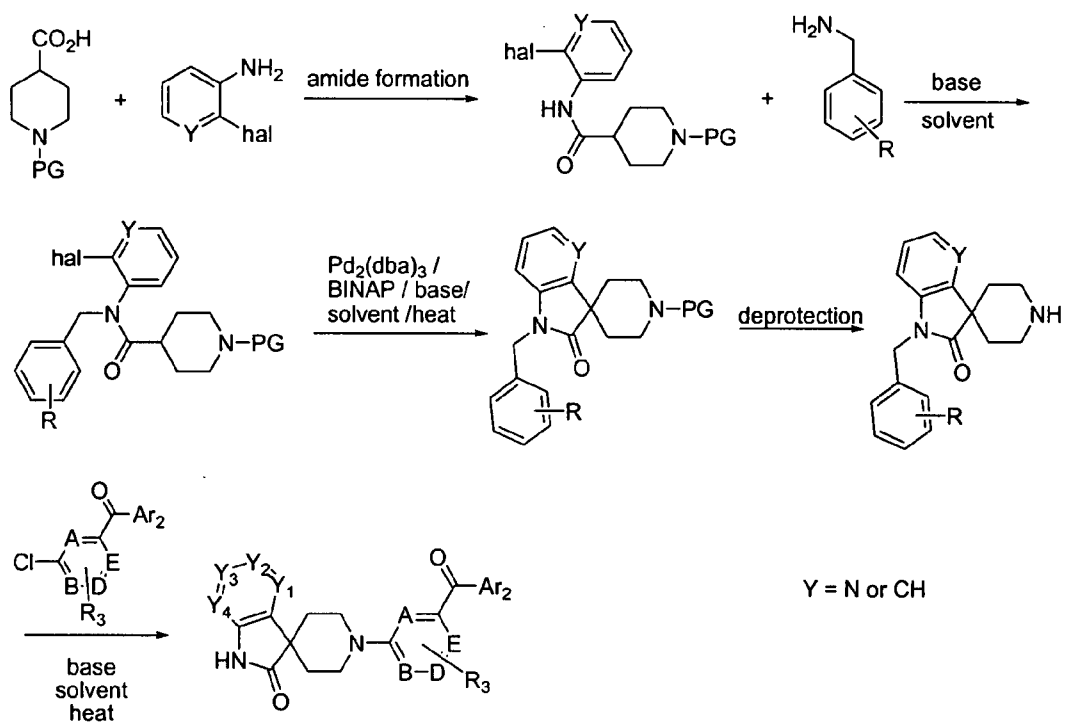
Scheme 5

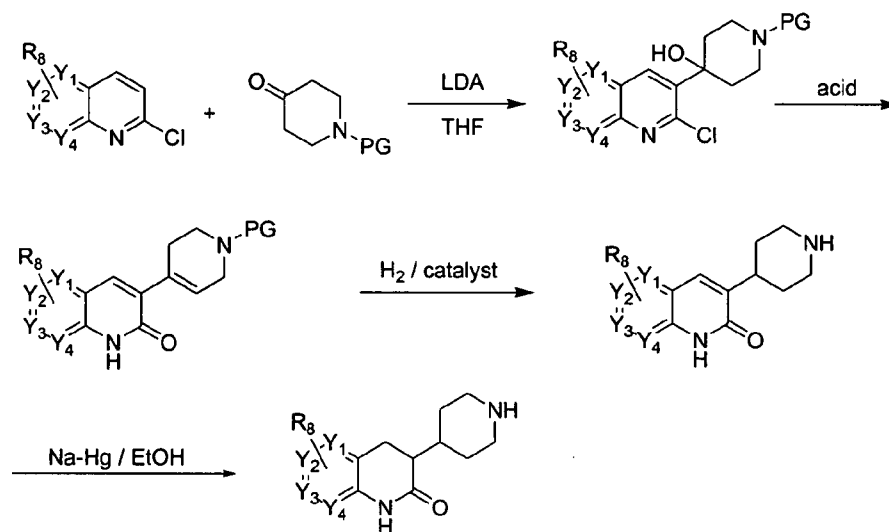
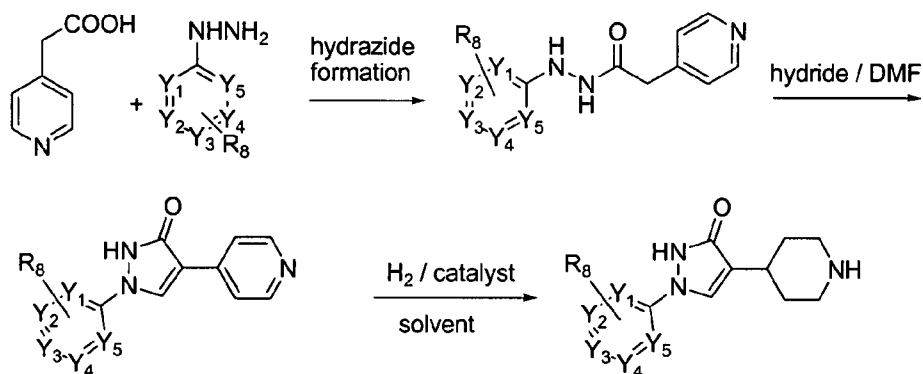


Scheme 6

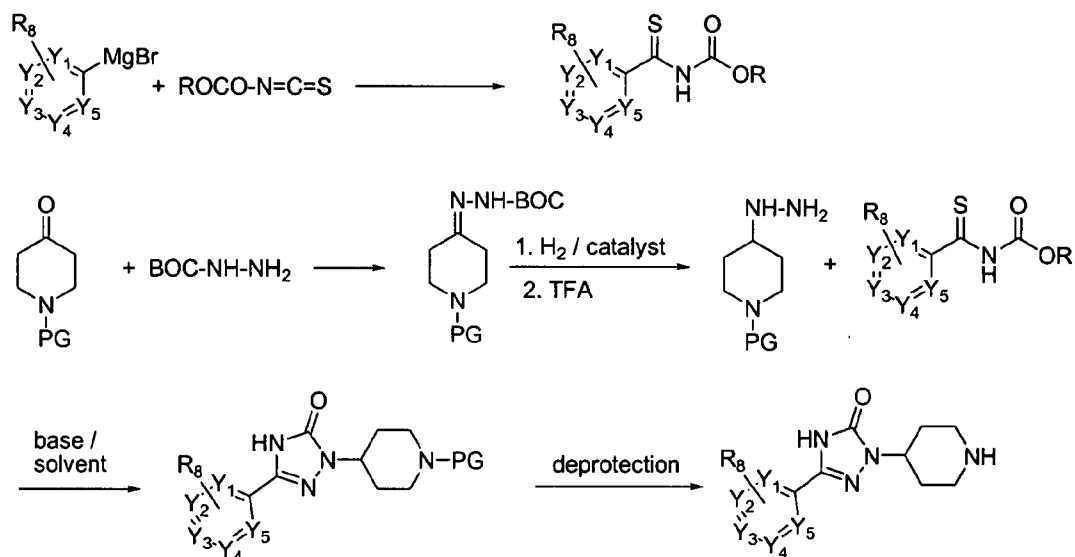


Scheme 7

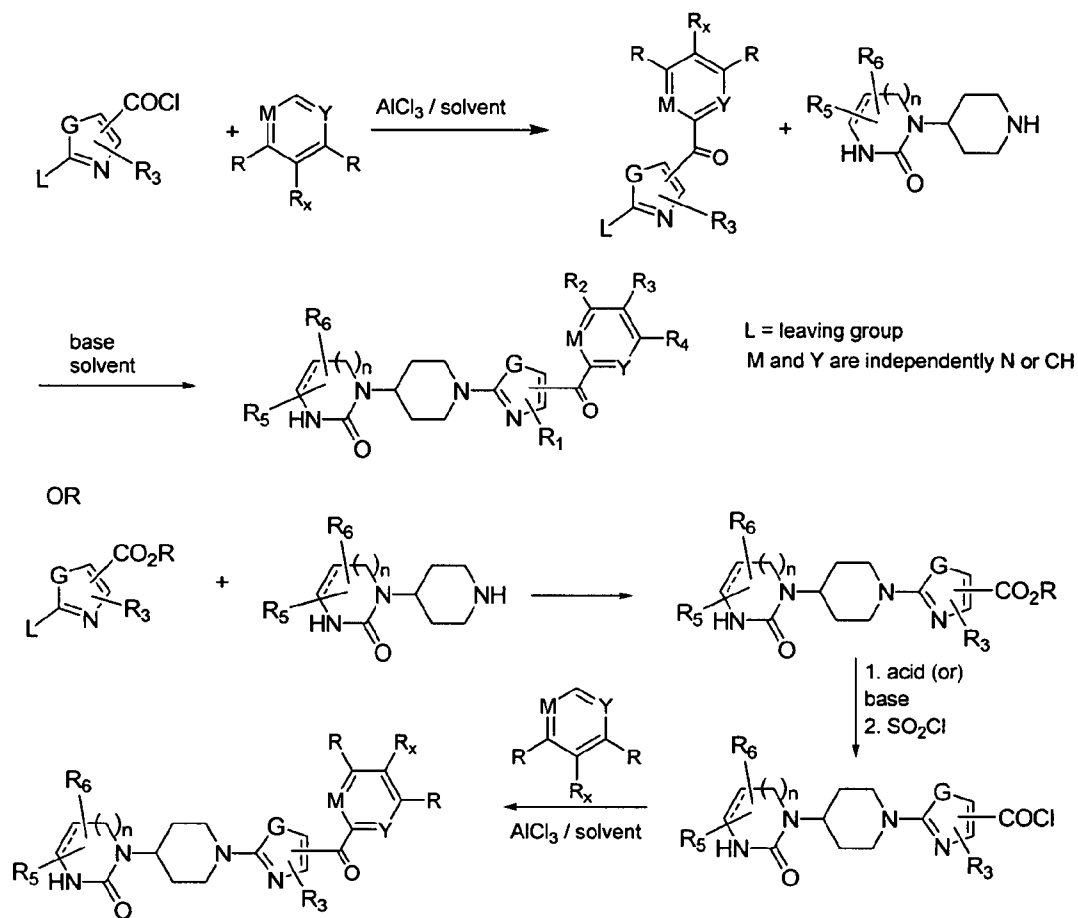


Scheme 8Scheme 9

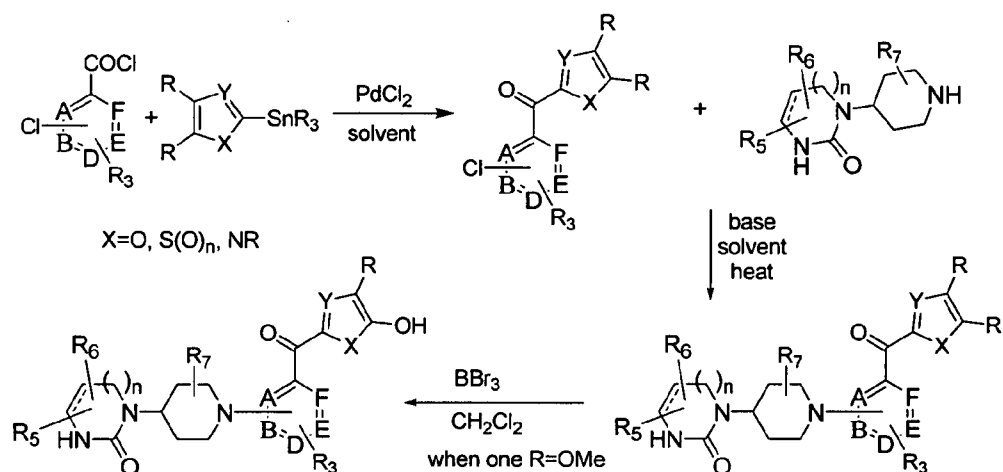
5

Scheme 10

Scheme 11



Scheme 12



In certain embodiments, a compound provided herein may contain one or more asymmetric carbon atoms, so that the compound can exist in different stereoisomeric forms. Such forms can be, for example, racemates or optically active forms. As noted above, all stereoisomers are encompassed by the present invention. Nonetheless, it may be desirable to obtain single enantiomers (*i.e.*, optically active forms). Standard methods for preparing single

enantiomers include asymmetric synthesis and resolution of racemates. Resolution of racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography using, for example a chiral HPLC column.

Compounds may be radiolabeled by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. Each radioisotope is preferably carbon (*e.g.*, ^{14}C), hydrogen (*e.g.*, ^3H), sulfur (*e.g.*, ^{35}S) or iodine (*e.g.*, ^{125}I). Tritium labeled compounds may also be prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas using the compound as substrate. In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate. Preparation of radiolabeled compounds may be conveniently performed by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds.

PHARMACEUTICAL COMPOSITIONS

The present invention also provides pharmaceutical compositions comprising one or more biaryl ketone-substituted piperidines provided herein, together with at least one physiologically acceptable carrier or excipient. Pharmaceutical compositions may comprise, for example, one or more of water, buffers (*e.g.*, sodium bicarbonate, neutral buffered saline or phosphate buffered saline), ethanol, mineral oil, vegetable oil, dimethylsulfoxide, carbohydrates (*e.g.*, glucose, mannose, sucrose, starch, mannitol or dextrans), proteins, adjuvants, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione and/or preservatives. In addition, other active ingredients may (but need not) be included in the pharmaceutical compositions provided herein.

Pharmaceutical compositions may be formulated for any appropriate manner of administration, including, for example, topical, oral (including, but not limited to, sublingual), nasal, rectal or parenteral administration. The term parenteral as used herein includes subcutaneous, intradermal, intravascular (*e.g.*, intravenous), intramuscular, spinal, intracranial, intrathecal and intraperitoneal injection, as well as any similar injection or infusion technique. In certain embodiments, compositions suitable for oral use are preferred. Such compositions include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Within yet other embodiments, compositions of the present invention may be formulated as a lyophilizate.

Compositions intended for oral use may further comprise one or more components such as sweetening agents, flavoring agents, coloring agents and/or preserving agents in order to

provide appealing and palatable preparations. Tablets contain the active ingredient in admixture with physiologically acceptable excipients that are suitable for the manufacture of tablets. Such excipients include, for example, inert diluents (*e.g.*, calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate), granulating and disintegrating agents (*e.g.*, corn starch or alginic acid), binding agents (*e.g.*, starch, gelatin or acacia) and lubricating agents (*e.g.*, magnesium stearate, stearic acid or talc). The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (*e.g.*, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium (*e.g.*, peanut oil, liquid paraffin or olive oil).

Aqueous suspensions contain the active material(s) in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include suspending agents (*e.g.*, sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia); and dispersing or wetting agents (*e.g.*, naturally-occurring phosphatides such as lecithin, condensation products of an alkylene oxide with fatty acids such as polyoxyethylene stearate, condensation products of ethylene oxide with long chain aliphatic alcohols such as heptadecaethyleneoxycetanol, condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides such as polyethylene sorbitan monooleate). Aqueous suspensions may also comprise one or more preservatives, such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient(s) in a vegetable oil (*e.g.*, arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and/or flavoring agents may be added to provide palatable oral preparations. Such suspensions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting

agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, such as sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions may also be formulated as oil-in-water emulsions. The oily phase may be a vegetable oil (*e.g.*, olive oil or arachis oil), a mineral oil (*e.g.*, liquid paraffin) or a mixture thereof. Suitable emulsifying agents include naturally-occurring gums (*e.g.*, gum acacia or gum tragacanth), naturally-occurring phosphatides (*e.g.*, soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol), anhydrides (*e.g.*, sorbitan monoleate) and condensation products of partial esters derived from fatty acids and hexitol with ethylene oxide (*e.g.*, polyoxyethylene sorbitan monoleate). An emulsion may also comprise one or more sweetening and/or flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, such as glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also comprise one or more demulcents, preservatives, flavoring agents and/or coloring agents.

Formulations for topical administration typically comprise a topical vehicle combined with active agent(s), with or without additional optional components. Suitable topical vehicles and additional components are well known in the art, and it will be apparent that the choice of a vehicle will depend on the particular physical form and mode of delivery. Topical vehicles include water; organic solvents such as alcohols (*e.g.*, ethanol or isopropyl alcohol) or glycerin; glycols (*e.g.*, butylene, isoprene or propylene glycol); aliphatic alcohols (*e.g.*, lanolin); mixtures of water and organic solvents and mixtures of organic solvents such as alcohol and glycerin; lipid-based materials such as fatty acids, acylglycerols (including oils, such as mineral oil, and fats of natural or synthetic origin), phosphoglycerides, sphingolipids and waxes; protein-based materials such as collagen and gelatin; silicone-based materials (both non-volatile and volatile); and hydrocarbon-based materials such as microsponges and polymer matrices. A composition may further include one or more components adapted to improve the stability or effectiveness of the applied formulation, such as stabilizing agents, suspending agents, emulsifying agents, viscosity adjusters, gelling agents, preservatives, antioxidants, skin penetration enhancers, moisturizers and sustained release materials. Examples of such components are described in Martindale--The Extra Pharmacopoeia (Pharmaceutical Press, London 1993) and Martin (ed.), Remington's Pharmaceutical Sciences. Formulations may comprise microcapsules, such as hydroxymethylcellulose or gelatin-microcapsules, liposomes, albumin microspheres, microemulsions, nanoparticles or nanocapsules.

A topical formulation may be prepared in a variety of physical forms including, for example, solids, pastes, creams, foams, lotions, gels, powders, aqueous liquids and emulsions. Typical modes of delivery for topical compositions include application using the fingers; application using a physical applicator such as a cloth, tissue, swab, stick or brush; spraying (including mist, aerosol or foam spraying); dropper application; sprinkling; soaking; and rinsing. Controlled release vehicles can also be used.

A pharmaceutical composition may be prepared as a sterile injectible aqueous or oleaginous suspension. The compound(s) provided herein, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Such a composition may be formulated according to the known art using suitable dispersing, wetting and/or suspending agents such as those mentioned above. Among the acceptable vehicles and solvents that may be employed are water, 1,3-butanediol, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectible compositions, and adjuvants such as local anesthetics, preservatives and/or buffering agents can be dissolved in the vehicle.

Compounds may also be formulated as suppositories (*e.g.*, for rectal administration). Such compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Pharmaceutical compositions may be formulated for release at a pre-determined rate. Instantaneous release may be achieved, for example, via sublingual administration (*i.e.*, administration by mouth in such a way that the active ingredient(s) are rapidly absorbed via the blood vessels under the tongue rather than via the digestive tract). Controlled release formulations (*i.e.*, formulations such as a capsule, tablet or coated tablet that slows and/or delays release of active ingredient(s) following administration) may be administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at a target site. In general, a controlled release formulation comprises a matrix and/or coating that delays disintegration and absorption in the gastrointestinal tract (or implantation site) and thereby provides a delayed action or a sustained action over a longer period. One type of controlled-release formulation is a sustained-release formulation, in which at least one active ingredient is continuously released over a period of time at a constant rate. Preferably, the therapeutic agent is released at such a

rate that blood (*e.g.*, plasma) concentrations are maintained within the therapeutic range, but below toxic levels, over a period of time that is at least 4 hours, preferably at least 8 hours, and more preferably at least 12 hours. Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of modulator release. The amount of modulator contained within a sustained release formulation depends upon, for example, the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Controlled release may be achieved by combining the active ingredient(s) with a matrix material that itself alters release rate and/or through the use of a controlled-release coating. The release rate can be varied using methods well known in the art, including (a) varying the thickness or composition of coating, (b) altering the amount or manner of addition of plasticizer in a coating, (c) including additional ingredients, such as release-modifying agents, (d) altering the composition, particle size or particle shape of the matrix, and (e) providing one or more passageways through the coating. The amount of modulator contained within a sustained release formulation depends upon, for example, the method of administration (*e.g.*, the site of implantation), the rate and expected duration of release and the nature of the condition to be treated or prevented.

The matrix material, which itself may or may not serve a controlled-release function, is generally any material that supports the active ingredient(s). For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. Active ingredient(s) may be combined with matrix material prior to formation of the dosage form (*e.g.*, a tablet). Alternatively, or in addition, active ingredient(s) may be coated on the surface of a particle, granule, sphere, microsphere, bead or pellet that comprises the matrix material. Such coating may be achieved by conventional means, such as by dissolving the active ingredient(s) in water or other suitable solvent and spraying. Optionally, additional ingredients are added prior to coating (*e.g.*, to assist binding of the active ingredient(s) to the matrix material or to color the solution). The matrix may then be coated with a barrier agent prior to application of controlled-release coating. Multiple coated matrix units may, if desired, be encapsulated to generate the final dosage form.

In certain embodiments, a controlled release is achieved through the use of a controlled release coating (*i.e.*, a coating that permits release of active ingredient(s) at a controlled rate in aqueous medium). The controlled release coating should be a strong, continuous film that is

smooth, capable of supporting pigments and other additives, non-toxic, inert and tack-free.

Coatings that regulate release of the modulator include pH-independent coatings, pH-dependent coatings (which may be used to release modulator in the stomach) and enteric coatings (which allow the formulation to pass intact through the stomach and into the small intestine, where the coating dissolves and the contents are absorbed by the body). It will be apparent that multiple coatings may be employed (*e.g.*, to allow release of a portion of the dose in the stomach and a portion further along the gastrointestinal tract). For example, a portion of active ingredient(s) may be coated over an enteric coating, and thereby released in the stomach, while the remainder of active ingredient(s) in the matrix core is protected by the enteric coating and released further down the GI tract. pH dependent coatings include, for example, shellac, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate, methacrylic acid ester copolymers and zein.

In certain embodiments, the coating is a hydrophobic material, preferably used in an amount effective to slow the hydration of the gelling agent following administration. Suitable hydrophobic materials include alkyl celluloses (*e.g.*, ethylcellulose or carboxymethylcellulose), cellulose ethers, cellulose esters, acrylic polymers (*e.g.*, poly(acrylic acid), poly(methacrylic acid), acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxy ethyl methacrylates, cyanoethyl methacrylate, methacrylic acid alkamide copolymer, poly(methyl methacrylate), polyacrylamide, ammonio methacrylate copolymers, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride) and glycidyl methacrylate copolymers) and mixtures of the foregoing. Representative aqueous dispersions of ethylcellulose include, for example, AQUACOAT® (FMC Corp., Philadelphia, PA) and SURELEASE® (Colorcon, Inc., West Point, PA), both of which can be applied to the substrate according to the manufacturer's instructions. Representative acrylic polymers include, for example, the various EUDRAGIT® (Rohm America, Piscataway, NJ) polymers, which may be used singly or in combination depending on the desired release profile, according to the manufacturer's instructions.

The physical properties of coatings that comprise an aqueous dispersion of a hydrophobic material may be improved by the addition of one or more plasticizers. Suitable plasticizers for alkyl celluloses include, for example, dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate and triacetin. Suitable plasticizers for acrylic polymers include, for example, citric acid esters such as triethyl citrate and tributyl citrate, dibutyl phthalate, polyethylene glycols, propylene glycol, diethyl phthalate, castor oil and triacetin.

Controlled-release coatings are generally applied using conventional techniques, such as by spraying in the form of an aqueous dispersion. If desired, the coating may comprise pores or channels to facilitate release of active ingredient. Pores and channels may be generated by well known methods, including the addition of organic or inorganic material that is dissolved, extracted or leached from the coating in the environment of use. Certain such pore-forming materials include hydrophilic polymers, such as hydroxyalkylcelluloses (*e.g.*, hydroxypropylmethylcellulose), cellulose ethers, synthetic water-soluble polymers (*e.g.*, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone and polyethylene oxide), water-soluble polydextrose, saccharides and polysaccharides and alkali metal salts. Alternatively, or in addition, a controlled release coating may include one or more orifices, which may be formed by methods such as those described in US Patent Nos. 3,845,770; 4,034,758; 4,077,407; 4,088,864; 4,783,337 and 5,071,607. Controlled-release may also be achieved through the use of transdermal patches, using conventional technology (*see, e.g.*, US Patent No. 4,668,232).

Further examples of controlled release formulations, and components thereof, may be found, for example, in US Patent Nos. 4,572,833; 4,587,117; 4,606,909; 4,610,870; 4,684,516; 4,777,049; 4,994,276; 4,996,058; 5,128,143; 5,202,128; 5,376,384; 5,384,133; 5,445,829; 5,510,119; 5,618,560; 5,643,604; 5,891,474; 5,958,456; 6,039,980; 6,143,353; 6,126,969; 6,156,342; 6,197,347; 6,387,394; 6,399,096; 6,437,000; 6,447,796; 6,475,493; 6,491,950; 6,524,615; 6,838,094; 6,905,709; 6,923,984; 6,923,988; and 6,911,217; each of which is hereby incorporated by reference for its teaching of the preparation of controlled release dosage forms.

In addition to or together with the above modes of administration, a compound provided herein may be conveniently added to food or drinking water (*e.g.*, for administration to non-human animals including companion animals (such as dogs and cats) and livestock). Animal feed and drinking water compositions may be formulated so that the animal takes in an appropriate quantity of the composition along with its diet. It may also be convenient to present the composition as a premix for addition to feed or drinking water.

Biaryl ketone-substituted piperidines provided herein are generally administered in a therapeutically effective amount. Preferred systemic doses are no higher than 50 mg per kilogram of body weight per day (*e.g.*, ranging from about 0.001 mg to about 50 mg per kilogram of body weight per day), with oral doses generally being about 5-20 fold higher than intravenous doses (*e.g.*, ranging from 0.01 to 40 mg per kilogram of body weight per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage unit will vary depending, for example, upon the patient being treated and the particular mode of administration. Dosage units will generally contain from about 10 µg to about 500 mg

of an active ingredient. Optimal dosages may be established using routine testing, and procedures that are well known in the art.

Pharmaceutical compositions provided herein may, but need not, further comprise one or more additional pharmaceutical agents, such as an anti-inflammatory agent, analgesic, anti-migraine agent, serotonin agonist, anti-hypertensive and/or anticonvulsant.

Anti-inflammatory agents include, for example, non-steroidal anti-inflammatory drugs (NSAIDs), non-specific and cyclooxygenase-2 (COX-2) specific cyclooxygenase enzyme inhibitors, gold compounds, corticosteroids, methotrexate, leflunomide, cyclosporine A, IM gold, minocycline, azathioprine, tumor necrosis factor (TNF) receptor antagonists, soluble TNF alpha receptor (etanercept), anti-TNF alpha antibodies (*e.g.*, infliximab and adalimumab), anti-C5 antibodies, interleukin-1 (IL-1) receptor antagonists (*e.g.*, anakinra or IL-1 trap), IL-18 binding protein, CTLA4-Ig (*e.g.*, abatacept), anti-human IL-6 receptor monoclonal antibody (*e.g.*, tocilizumab), LFA-3-Ig fusion proteins (*e.g.*, alefacept), LFA-1 antagonists, anti-VLA4 monoantibody (*e.g.*, natalizumab), anti-CD11a monoclonal antibody, anti-CD20 monoclonal antibody (*e.g.*, rituximab), anti-IL-12 monoclonal antibody, anti-IL-15 monoclonal antibody, CDP 484, CDP 870, chemokine receptor antagonists, selective NOS inhibitors, p38 kinase inhibitors, integrin antagonists, angiogenesis inhibitors, and TMI-1 dual inhibitors. Further anti-inflammatory agents include meloxicam, rofecoxib, celecoxib, etoricoxib, parecoxib, valdecoxib and tilicoxib.

NSAIDs include, but are not limited to, ibuprofen, flurbiprofen, naproxen or naproxen sodium, diclofenac, combinations of diclofenac sodium and misoprostol, sulindac, oxaprozin, diflunisal, piroxicam, indomethacin, etodolac, fenoprofen calcium, ketoprofen, sodium nabumetone, sulfasalazine, tolmetin sodium, and hydroxychloroquine. One class of NSAIDs consists of compounds that inhibit cyclooxygenase (COX) enzymes; such compounds include celecoxib and rofecoxib. NSAIDs further include salicylates such as acetylsalicylic acid or aspirin, sodium salicylate, choline and magnesium salicylates, and salsalate, as well as corticosteroids such as cortisone, dexamethasone, methylprednisolone, prednisolone, prednisolone sodium phosphate, and prednisone.

Certain analgesics for use in combination with CGRP receptor modulators provided herein are also anti-inflammatory agents, and are listed above. Other such medications include narcotic agents which typically act at one or more opioid receptor subtypes (*e.g.*, μ , κ and/or δ), preferably as agonists or partial agonists. Such agents include opiates, opiate derivatives and opioids, as well as pharmaceutically acceptable salts and hydrates thereof. Specific examples of narcotic analgesics include, within preferred embodiments, alfentanil, alphaprodine, anileridine,

bezitramide, buprenorphine, butorphanol, codeine, diacetyldihydromorphine, diacetylmorphine, dihydrocodeine, diphenoxylate, ethylmorphine, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, levomethorphan, levorphanol, meperidine, metazocine, methadone, methorphan, metopon, morphine, nalbuphine, opium extracts, opium fluid extracts, powdered
 5 opium, granulated opium, raw opium, tincture of opium, oxycodone, oxymorphone, paregoric, pentazocine, pethidine, phenazocine, piminodine, propoxyphene, racemethorphan, racemorphan, sulfentanil, thebaine and pharmaceutically acceptable salts and hydrates of the foregoing agents.

Other examples of narcotic analgesic agents include acetorphone, acetyldihydrocodeine, acetylmethadol, allylprodine, alpracetilmethadol, alphameprodine, alphamethadol,
 10 benzethidine, benzylmorphine, betacetylmethadol, betameprodine, betamethadol, betaprodine, clonitazene, codeine methylbromide, codeine-N-oxide, cyprenorphine, desomorphine, dextromoramide, diampromide, diethylthiambutene, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiamubutene, dioxaphetyl butyrate, dipipanone, drotebanol, ethanol, ethylmethylthiambutene, etonitazene, etorphine, etoxeridine, furethidine, hydromorphenol,
 15 hydroxypethidine, ketobemidone, levomoramide, levophenacetylmorphan, methyl-desorphine, methyldihydromorphine, morpheridine, morphine methylpromide, morphine methylsulfonate, morphine-N-oxide, myrophin, naloxone, naltrexone, nicocodeine, nicomorphine, noracetylmethadol, norlevorphanol, normethadone, normorphine, norpipanone, pentazocaine, phenadoxone, phenampromide, phenomorphan, phenoperidine, piritramide, pholcodine,
 20 proheptazoline, properidine, propiran, racemoramide, thebacon, trimeperidine and the pharmaceutically acceptable salts and hydrates thereof.

Further specific representative analgesic agents include, for example acetaminophen (paracetamol); aspirin and other NSAIDs described above; NR2B antagonists; bradykinin antagonists; anti-migraine agents; anticonvulsants such as oxcarbazepine and carbamazepine;
 25 antidepressants (such as TCAs, SSRIs, SNRIs, substance P antagonists, etc.); spinal blocks; pentazocine/naloxone; meperidine; levorphanol; buprenorphine; hydromorphone; fentanyl; sufentanyl; oxycodone; oxycodone/acetaminophen, nalbuphine and oxymorphone. Still further analgesic agents include CB2-receptor agonists, such as AM1241, capsaicin receptor antagonists and compounds that bind to the $\alpha 2\delta$ subunit of voltage-gated calcium channels, such as
 30 gabapentin and pregabalin.

Representative anti-migraine agents for use in combination with a CGRP receptor modulator provided herein include caffeine; beta-adrenergic receptor antagonists such as timolol, propranolol, atenolol or nadolol; bradykinin-1 receptor antagonists; adenosine A1 receptor agonists; NMDA antagonists; NK-1 receptor antagonists; opiate agonists; ergotamines;

methysergide; calcium channel blockers such as flunarizine; selective serotonin uptake inhibitors such as fluoxetine, paroxetine, sertraline, duloxetine, escitalopram, or citalopram; 5-HT₁ agonists, such as sumatriptan, naratriptan, zolmatriptan, eletriptan, almotriptan, frovatriptan, donitriptan and rizatriptan; inhibitors of nitric oxide synthesis; and cyclooxygenase inhibitors, as described above.

Additionally, or alternatively, additional pharmaceutical agents include decongestants such as phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, epinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxy-ephedrine; sedating or non-sedating antihistamines; and/or asthma treatments such as beta-adrenergic receptor agonists; leukotriene D₄ antagonists (*e.g.*, montelukast or zafirlukast).

Pharmaceutical compositions may be packaged for treating conditions responsive to CGRP receptor modulation (*e.g.*, treatment of pain, such as migraine or headache, or other disorder(s) recited herein). Packaged pharmaceutical preparations generally comprise a container holding a therapeutically effective amount of a pharmaceutical composition as described above and instructions (*e.g.*, labeling) indicating that the composition is to be used for treating a condition responsive to CGRP receptor modulation in a patient (*e.g.*, pain, such as migraine or headache, or other disorder as indicated herein). In certain embodiments, a packaged pharmaceutical preparation comprises one or more biaryl ketone-substituted piperidines provided herein and one or more additional agents in the same package, either in separate containers within the package or in the same container (*i.e.*, as a mixture). Preferred mixtures are formulated for oral administration (*e.g.*, as pills, capsules, tablets or the like). In certain embodiments, the package comprises a label bearing indicia indicating that the components are to be taken together for the treatment of pain.

METHODS OF USE

Within certain aspects, the present invention provides methods for treating a condition responsive to CGRP receptor modulation in a patient. The patient may be afflicted with such a condition, or may be free of symptoms but considered at risk for developing such a condition. A condition is "responsive to CGRP receptor modulation" if the condition or symptom(s) thereof are alleviated, attenuated, delayed or otherwise improved by modulation of CRP receptor activity. In general, such methods comprise administering to the patient a therapeutically effective amount of at least one biaryl ketone-substituted piperidine as provided herein.

Conditions responsive to CGRP receptor modulation include, for example pain (*e.g.*, headache such as migraine), vasodilation (*e.g.*, neurogenic vasodilation or in the treatment of shock, sepsis and hot flashes associated with menopause or hormone treatment), inflammation

(*e.g.*, neurogenic inflammation, inflammatory diseases of the joints such as arthritis, and airway inflammatory diseases such as asthma and chronic obstructive pulmonary disease), bronchial hyperreactivity, high blood pressure, hypotonia, tachycardia, diabetes (*e.g.*, non-insulin-dependent diabetes mellitus), nausea, vomiting, diarrhea, loss of appetite, diabetic gastroparesis, polydipsia, thermal injury, cardiovascular diseases, morphine tolerance, skin diseases (*e.g.*, dermatitis, psoriasis, thermal and radiation-induced skin damage such as sunburn), encephalitis, brain trauma, ischemia, epilepsy, neurodegenerative diseases, tinnitus, inflammatory bowel disease, irritable bowel syndrome, cystitis and allergic rhinitis.

Headache that may be treated as described herein includes, for example, sinus, cluster (*i.e.*, migrainous neuralgia) and tension headaches, temporomandibular pain and maxillary sinus pain. Migraine headache and other migraine symptoms may also be treated; for example, migraine headaches may be prevented by administration of a compound provided herein as soon as a pre-migrainous aura is experienced by the patient.

Other pain that may be treated using the CGRP receptor modulators provided herein may be chronic or acute and includes, but is not limited to, peripheral nerve-mediated pain (especially neuropathic pain, such as pain due to diabetes, postherpetic neuralgia, nerve injury, vulvodynia, root avulsions, painful traumatic neuropathy and painful polyneuropathy). Compounds provided herein may also be used in the treatment of, for example, visceral pain (*e.g.*, pancreatitis, interstitial cystitis and renal colic), persistent hyperalgesia, inflammatory pain, repetitive motion pain, carpal tunnel syndrome, perioperative pain, allodynia, oral neuropathic pain, toothache (dental pain), denture pain, ocular pain, postherpetic neuralgia, diabetic neuropathy, chemotherapy-induced neuropathy, reflex sympathetic dystrophy, trigeminal neuralgia, bone and joint pain (*e.g.*, pain associated with osteoarthritis), rheumatoid arthritis, myofascial pain (*e.g.*, muscular injury and fibromyalgia), Guillain-Barre syndrome, meralgia paresthetica, burning-mouth syndrome and/or pain associated with nerve and root damage, including as pain associated with peripheral nerve disorders (*e.g.*, nerve entrapment and brachial plexus avulsions, amputation, peripheral neuropathies including bilateral peripheral neuropathy, tic douloureux, atypical facial pain, nerve root damage, and arachnoiditis). Additional neuropathic pain conditions include causalgia (reflex sympathetic dystrophy - RSD, secondary to injury of a peripheral nerve), neuritis (including, for example, sciatic neuritis, peripheral neuritis, polyneuritis, optic neuritis, postfebrile neuritis, migrating neuritis, segmental neuritis and Gombault's neuritis), neuronitis, neuralgias (*e.g.*, those mentioned above, cervicobrachial neuralgia, cranial neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, migrainous neuralgia, idiopathic neuralgia, intercostals neuralgia, mammary neuralgia, mandibular joint

neuralgia, Morton's neuralgia, nasociliary neuralgia, occipital neuralgia, red neuralgia, Sluder's neuralgia, splenopalatine neuralgia, supraorbital neuralgia and vidian neuralgia), musculoskeletal pain, AIDS-related neuropathy, MS-related neuropathy, central nervous system pain (*e.g.*, pain due to brain stem damage, sciatica, and ankylosing spondylitis), spinal pain, including spinal cord injury-related pain. Further pain conditions that may be treated include Charcot's pains, intestinal gas pains, ear pain, heart pain, muscle pain, eye pain, orofacial pain (*e.g.*, odontalgia), abdominal pain, gynaecological pain (*e.g.*, menstrual pain, dysmenorrhoea, pain associated with cystitis, labor pain, chronic pelvic pain, chronic prostatitis and endometriosis), acute and chronic back pain (*e.g.*, lower back pain), gout, scar pain, hemorrhoidal pain, dyspeptic pains, pain associated with angina, nerve root pain, "non-painful" neuropathies, complex regional pain syndrome, homotopic pain and heterotopic pain – including pain associated with carcinoma, often referred to as cancer pain (*e.g.*, in patients with bone cancer), pain (and inflammation) associated with venom exposure (*e.g.*, due to snake bite, spider bite, or insect sting) and trauma associated pain (*e.g.*, post-surgical pain such as postmastectomy, postthoracotomy and stump pain; phantom limb pain, episiotomy pain, pain from cuts, musculoskeletal pain, bruises and broken bones, and burn pain, especially primary hyperalgesia associated therewith). Additional pain conditions that may be treated as described herein include pain associated with respiratory disorders as described above, autoimmune diseases, immunodeficiency disorders, hot flashes, inflammatory bowel disease, gastroesophageal reflux disease (GERD), irritable bowel syndrome and/or inflammatory bowel disease.

It will be apparent that biaryl ketone-substituted piperidines provided herein may be administered alone or in combination with one or more additional agents that are suitable for treating the disorder of interest. Within such combination therapy, the compound(s) and additional agent(s) may be present in the same pharmaceutical composition, or may be administered separately in either order. Representative additional pharmaceutical agents for use in combination therapy include those indicated above.

Within certain aspects, CGRP receptor modulators provided herein may be used within combination therapy for the treatment of headache and/or migraine. Within such combination therapy, a CGRP receptor modulator is administered to a patient along with an additional agent suitable for the treatment of such condition(s). The CGRP receptor modulator and additional agent may be present in the same pharmaceutical composition, or may be administered separately, simultaneously or in either order.

Administration to the patient can be by way of any means discussed above, including oral, topical, nasal or transdermal administration, or intravenous, intramuscular, subcutaneous,

intrathecal, epidural, intracerebroventricular or like injection. Oral administration is preferred in certain embodiments (*e.g.*, formulated as pills, capsules, tablets or the like).

Treatment regimens may vary depending on the compound used and the particular condition to be treated. In general, a dosage regimen of 4 times daily or less is preferred, with 1 or 2 times daily particularly preferred. Dosage may be on an as-needed basis (*e.g.*, the patient may self-administer upon the onset of symptoms). It will be understood, however, that the specific dose and treatment regimen for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex and diet of the patient, the time of administration, the route of administration, the rate of excretion, any drug combination and the severity of the particular disease undergoing therapy. Dosages are generally as described above; in general, the use of the minimum dose sufficient to provide effective therapy is preferred. Patients may generally be monitored for therapeutic effectiveness using medical or veterinary criteria suitable for the condition being treated or prevented.

Suitable dosages for CGRP receptor modulators (either alone or within such combination therapy) are generally as described above. Dosages and methods of administration of any additional agent(s) can be found, for example, in the manufacturer's instructions or in the *Physician's Desk Reference*. In certain embodiments, combination administration results in a reduction of the dosage of the additional agent required to produce a therapeutic effect (*i.e.*, a decrease in the minimum therapeutically effective amount). Thus, preferably, the dosage of additional agent in a combination or combination treatment method of the invention is less than the maximum dose advised by the manufacturer for administration of the agent without combination with a CGRP receptor modulator provided herein. More preferably this dose is less than $\frac{3}{4}$, even more preferably less than $\frac{1}{2}$, and highly preferably less than $\frac{1}{4}$ of the maximum dose, while most preferably the dose is less than 10% of the maximum dose advised by the manufacturer for administration of the agent(s) when administered without combination administration as described herein. It will be apparent that the dose of compound as provided herein needed to achieve the desired effect may similarly be affected by the dose and potency of the additional agent.

Within separate aspects, the present invention provides a variety of non-pharmaceutical *in vitro* and *in vivo* uses for the compounds provided herein. For example, such compounds may be labeled and used as probes for the detection and localization of CGRP receptor (in samples such as cell preparations or tissue sections, preparations or fractions thereof). In addition, compounds provided herein that comprise a suitable reactive group (such as an aryl carbonyl,

nitro or azide group) may be used in photoaffinity labeling studies of receptor binding sites. In addition, compounds provided herein may be used as positive controls in assays for receptor activity, as standards for determining the ability of a candidate agent to bind to CGRP receptor, or as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT). Such methods can be used to characterize CGRP receptors in living subjects. For example, a compound may be labeled using any of a variety of well known techniques (*e.g.*, radiolabeled with a radionuclide such as tritium, as described herein), and incubated with a sample for a suitable incubation time (*e.g.*, determined by first assaying a time course of binding). Following incubation, unbound compound is removed (*e.g.*, by washing), and bound compound detected using any method suitable for the label employed (*e.g.*, autoradiography or scintillation counting for radiolabeled compounds; spectroscopic methods may be used to detect luminescent groups and fluorescent groups). As a control, a matched sample containing labeled compound and a greater (*e.g.*, 10-fold greater) amount of unlabeled compound may be processed in the same manner. A greater amount of detectable label remaining in the test sample than in the control indicates the presence of CGRP receptor in the sample. Detection assays, including receptor autoradiography (receptor mapping) of CGRP receptor in cultured cells or tissue samples may be performed as described by Kuhar in sections 8.1.1 to 8.1.9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York.

The following Examples are offered by way of illustration and not by way of limitation.

Unless otherwise specified all reagents and solvent are of standard commercial grade and are used without further purification. Using routine modifications, the starting materials may be varied and additional steps employed to produce other compounds provided herein.

EXAMPLES

Mass spectroscopy in the following Examples is Electrospray MS, obtained in positive ion mode using a Waters ZMD II Mass Spectrometer (Waters Corp.; Milford, MA), equipped with a Waters 600 pump (Waters Corp.), Waters 996 photodiode array detector (Waters Corp.), and a Gilson 215 autosampler (Gilson, Inc.; Middleton, WI). MassLynx™ (Waters Corp.; Milford, MA) version 4.0 software with OpenLynx processing is used for data collection and analysis. MS conditions are: capillary voltage = 3.5 kV; cone voltage = 30 V, desolvation and source temperature = 250 °C and 100 °C, respectively; mass range = 100-750 with a scan time of 0.75 seconds and an interscan delay of 0.15 minutes. LCMS conditions are as follows:

Column	4.6x50mm, Chromolith SpeedRod (Merck KGaA);
UV	5 spectra/sec

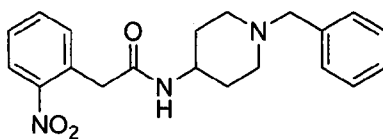
Extracted wavelengths	220 and 254nm
Flow rate	6.0 mL/min
Injection Volume	1-10 μ l;
Mobile phase A	95% Water, 5% Methanol with 0.05% Formic acid
Mobile phase B	95% Methanol, 5% Water with 0.025% Formic acid
Gradient:	

	<u>Time(min)</u>	<u>%B</u>
	0	5
	0.01	5
10	1.0	100
	2	100
	2.1	5

EXAMPLE 1. SYNTHESIS OF REPRESENTATIVE INTERMEDIATES

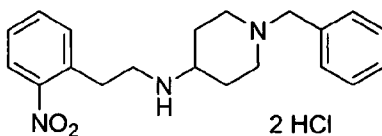
This Example illustrates the preparation of representative intermediates useful in the synthesis of certain biaryl ketone-substituted piperidines.

1. N-(1-Benzylpiperidin-4-yl)-2-(2-nitrophenyl)acetamide



A solution of 2-nitrophenylacetic acid (60 g, 331 mmol) in 150 mL of THF is added to a suspension of CDI (59 g, 364 mmol) in 150 mL of THF, during which time CO₂ (g) evolution occurs. After the addition, the brown reaction mixture is stirred for 30 min. at rt. A solution of 4-amino-1-benzylpiperidine (67.5 mL, 331 mmol) in 30 mL of THF is then added dropwise (the amine addition is mildly exothermic). The resulting reaction mixture is stirred for 2 h at rt. A little THF (about 150 mL) is removed *in vacuo*, and water (600 mL) is added. The resulting suspension is stirred for 1 h at 0 °C. The solid is filtered, washed with Et₂O, and dried *in vacuo* to give the title compound as a white solid. MS: 354.16 (M+H).

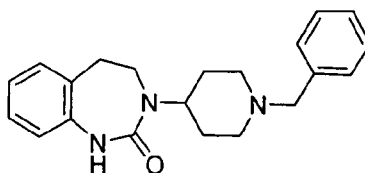
2. 1-Benzyl-N-[2-(2-nitrophenyl)ethyl]piperidin-4-amine bis-hydrochloride



A solution of N-(1-benzylpiperidin-4-yl)-2-(2-nitrophenyl)acetamide (42 g, 119 mmol) in 350 mL of THF is heated to 60 °C, and chlorotrimethylsilane (54 mL, 428.4 mmol) is added. A white solid precipitates from solution. Lithium borohydride (2.0M in THF, 143 mL, 285.6 mmol) is then added dropwise over 15-20 min., during which time gas evolution is observed and

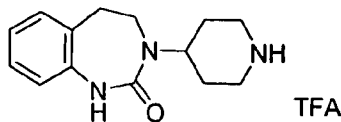
the solids in the mixture slowly dissolve. After the addition, the reaction mixture is stirred for 4 h at 60 °C. After cooling to rt, 35 mL of MeOH is added, followed by 65 mL of 30% aq. HCl. The resulting mixture is refluxed for 2.5 h, and then once again cooled to rt. The pH is adjusted to 9-10 with a 50% aq. NaOH solution, the mixture is transferred to a separating funnel and the milky white aqueous layer is separated. To the organic phase is added 30 mL of 30% aq. HCl, and the resulting mixture is heated to reflux for 1 h. The mixture is then cooled to 0 °C and kept at that temperature overnight. The solid is then filtered, washed with Et₂O, and dried *in vacuo* to give the title compound as a white solid. MS: 340.20 (M+H).

3. 3-(1-Benzylpiperidin-4-yl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one



To a suspension of 1-benzyl-N-[2-(2-nitrophenyl)ethyl]piperidin-4-amine bis-hydrochloride (30 g, 73 mmol) in 150 mL of toluene and 150 mL of water is added 18 g of a 50% aq. NaOH solution. The resulting mixture is stirred for 1 h at 50 °C. The layers are separated, and the organic phase is washed with water and concentrated *in vacuo*. The brown oily residue is dissolved in 150 mL of MeOH and treated with Raney Ni (2.7 g, slurry in water), and the resulting reaction mixture is hydrogenated under 30-40 psi of H₂(g) for 2.5 h. The mixture is filtered through Celite, and the Celite is washed well with MeOH. The filtrate is then concentrated to give a dark brown oil, which is dissolved in 60 mL of THF and added dropwise to a suspension of CDI (22 g, 128 mmol) in 60 mL of THF. After the addition, the reaction is stirred for 1 h at rt. Half of the THF is removed *in vacuo*, and the remaining solution is cooled to 0 °C in an ice bath. Water (100 mL) is added, and the resulting precipitate is filtered, washed with Et₂O, and dried *in vacuo* to give the title compound as an off-white solid. MS: 336.19 (M+H).

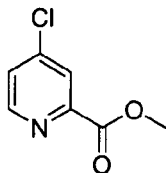
4. 3-Piperidin-4-yl-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one trifluoroacetate



A mixture of 3-(1-benzylpiperidin-4-yl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one (22.5 g, 67.1 mmol) and 10% Pd/C (2.2 g) in 500 mL of MeOH is hydrogenated at rt under 40 psi of H₂ (g) for 3 days. The catalyst is removed by filtration through Celite, and the Celite is washed well with MeOH. The filtrate is concentrated *in vacuo* to give a brown solid, which is

taken up in CH_2Cl_2 , cooled to $0\text{ }^\circ\text{C}$, and treated with TFA (12-13 mL). The resulting mixture is concentrated, and the residue is triturated with Et_2O and filtered to give the title compound as an off-white solid. MS: 245.15 (M+H).

5. Methyl 4-chloropicolinate

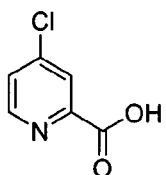


5

A mixture of picolinic acid (15 g, 122 mmol) sodium bromide (1.88 g, 18.3 mmol), and thionyl chloride (45 mL) is heated to reflux and stirred for 20 h. After cooling to rt, the excess thionyl chloride is removed *in vacuo*. The resulting residue is taken up in toluene (100 mL) and cooled to $0\text{ }^\circ\text{C}$. MeOH (7 mL) is added dropwise, after which time the reaction is warmed to rt and stirred an additional 1.5 h. The precipitated solid is collected by filtration, washed with toluene, and partitioned between EtOAc (200 mL) and water (100 mL). The mixture is neutralized to pH=7-8 with solid NaHCO_3 . The EtOAc layer is dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give the title compound as a light brown solid. MS: 171.94 (M+H).

10

6. 4-Chloropicolinic acid

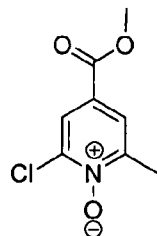


15

A 50% aq. NaOH solution (8 mL) is added to a solution of methyl 4-chloropicolinate (3.6 g, 21 mmol) in 20 mL of MeOH at $0\text{ }^\circ\text{C}$. After the addition, the ice bath is removed, and the suspension is stirred at rt for 15 minutes. The MeOH is removed *in vacuo*, and the residue is diluted with water (20 mL) and acidified to pH=2 with 6N HCl. The mixture is then filtered, and the solid is dried *in vacuo* to give the title compound as an off-white solid. MS: 158.10 (M+H).

20

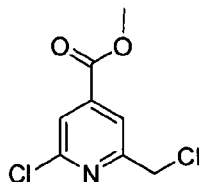
7. Methyl 2-chloro-6-methylpyridine-4-carboxylate-N-oxide



A solution of MCPBA (6.6 g, 29.6 mmol) in 50 mL of CH_2Cl_2 is added dropwise to a solution of methyl 2-chloro-6-methylpyridine-4-carboxylate (5.0 g, 26.9 mmol) in 30 mL of

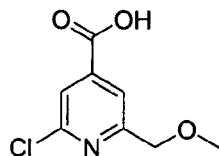
CH₂Cl₂ at RT. The reaction mixture is stirred for 2 days, and then it is evaporated to dryness. Sat. NaHCO₃ (20 mL) and EtOAc (30 mL) are added. The layers are separated, and the aqueous layer is extracted twice more with EtOAc (30 mL each). The combined organic extracts are dried (Na₂SO₄), filtered, and evaporated *in vacuo* to give an off-white solid. Purification by silica gel column chromatography (gradient from Hex to EtOAc) affords the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.0 (1H, s), 7.80 (1H, s), 3.94 (3H, s), 2.57 (3H, s).

8. Methyl 2-chloro-6-(chloromethyl)isonicotinate



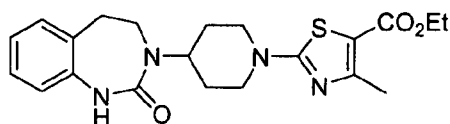
A mixture of methyl 2-chloro-6-methylpyridine-4-carboxylate-N-oxide (3.4 g, 16.9 mmol) and phosphorous oxychloride (5.0 mL) is heated to 100 °C and stirred for 48 h. The excess POCl₃ is removed *in vacuo*, and the residue is dissolved in CH₂Cl₂ and washed with sat. NaHCO₃. The CH₂Cl₂ layer is dried (Na₂SO₄), filtered, and evaporated *in vacuo* to give a dark brown oil. Purification by silica gel column chromatography (gradient from Hex to 20% EtOAc/Hex) affords the title compound as yellow/brown oil. MS: 220.01 (M+H).

9. 2-Chloro-6-(methoxymethyl)isonicotinic acid



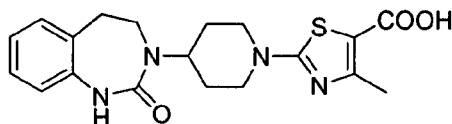
A sodium methoxide solution (25 wt. % in MeOH, 5.2 mL, 22.8 mmol) is added dropwise to a solution of methyl 2-chloro-6-(chloromethyl)isonicotinate (2.5 g, 11.4 mmol) in 20 mL of THF and 2 mL of water at rt. After 3.5 h, the reaction is diluted with water and extracted with Et₂O. The aqueous layer is cooled to 0 °C and acidified to pH=2 with conc. HCl. The cloudy mixture is extracted with CH₂Cl₂ (2 × 30 mL), and the combined organic extracts are dried (Na₂SO₄), filtered, and evaporated *in vacuo* to give the title compound as a brown solid. MS: 202.07 (M+H).

10. Ethyl 4-methyl-2-(4-(2-oxo-1,2,4,5-tetrahydrobenzo[d][1,3]diazepin-3-yl)piperidin-1-yl)thiazole-5-carboxylate



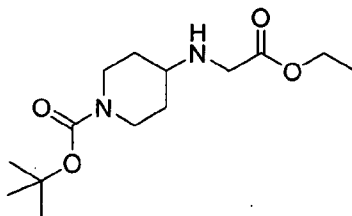
3-Piperidin-4-yl-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one trifluoroacetate (3 g, 8.35 mmol), ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (2.1 g, 8.35 mmol) and potassium carbonate (3.46 g, 25.1 mmol) in NMP (20 mL) is heated at 150 °C for 2 hours. The mixture is then cooled to rt, diluted with EtOAc, washed with water and brine, dried over Na₂SO₄, and concentrated under reduced pressure. Purification by silica gel chromatography (hexane / EtOAc = 1/1) affords the title compound as a white solid. ¹H-NMR (400 MHz, CDCl₃) δ: 7.11 (m, 1H), 7.05 (d, 1H), 6.91 (m, 1H), 6.70 (d, 1H), 6.42 (s, 1H), 4.51 (m, 1H), 4.26 (q, 2H), 4.13-4.20 (m, 2H), 3.45-3.47 (m, 2H), 3.13-3.20 (m, 2H), 2.96-3.00 (m, 2H), 2.55 (s, 3H), 1.74-1.89 (m, 4H), 1.33 (t, 3H). MS: 415.25 (M+H).

11. 4-Methyl-2-(4-(2-oxo-1,2,4,5-tetrahydrobenzo[d][1,3]diazepin-3-yl)piperidin-1-yl)thiazole-5-carboxylic acid



Ethyl 4-methyl-2-(4-(2-oxo-1,2,4,5-tetrahydrobenzo[d][1,3]diazepin-3-yl)piperidin-1-yl)thiazole-5-carboxylate (1.56 g, 3.77 mmol) is treated with 1N aq. NaOH (18.8 mL) and EtOH (18.8 mL) at 70 °C for 4 hours. The reaction is cooled to rt, and EtOH is removed under reduced pressure to give a white suspension. The pH of this suspension is adjusted to 5. The white precipitates are collected via filtration, and dried under vacuum overnight to afford the title compound. ¹H-NMR (400 MHz, CDCl₃) δ: 7.45 (s, 1H), 7.11 (m, 1H), 7.05 (d, 1H), 6.91 (m, 1H), 6.82 (d, 1H), 4.55 (m, 1H), 4.21 (d, 2H), 3.47 (bs, 2H), 3.16-3.22 (m, 2H), 3.00 (bs, 2H), 2.58 (s, 3H), 1.78-1.90 (m, 5H). MS: 387.18 (M+1).

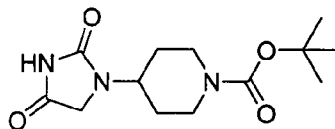
12. tert-Butyl 4-[(2-ethoxy-2-oxoethyl)amino]piperidine-1-carboxylate



To a solution of 1-Boc-4-piperidone (25 g, 125 mmol) and glycine ethyl ester hydrochloride (17.5 g, 125 mmol) in 625 mL of methanol is added sodium cyanoborohydride (9.45 g, 150 mmol) in small portions. Evolution of gas is observed. After 16 h, the mixture is quenched with sat. NH₄Cl, concentrated, and partitioned between CH₂Cl₂ and sat. NaHCO₃. The organic layer is washed with brine, dried (Na₂SO₄), filtered, and concentrated. Purification by

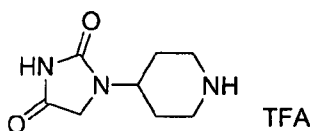
silica column chromatography [gradient from CH₂Cl₂ to 95% CH₂Cl₂/5% (10% NH₄OH/MeOH)] affords the title compound as clear, viscous oil.

13. *tert*-Butyl 4-(2,4-dioxoimidazolidin-1-yl)piperidine-1-carboxylate



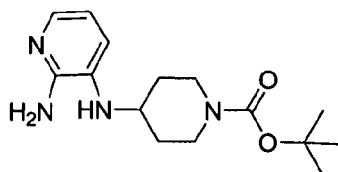
5 Potassium cyanate (8.7 g, 107 mmol) is added to a solution of *tert*-butyl 4-[(2-ethoxy-2-oxoethyl)amino]piperidine-1-carboxylate (30.5 g, 107 mmol) in water (600 mL). The pH of the reaction mixture is adjusted to 4-5 with acetic acid, and the resulting reaction mixture is heated to 40 °C for 16 h. After cooling to rt, the mixture is filtered and the solid dried *in vacuo* to give the title compound (with some inorganic salts) as a white solid which is used without further
10 purification.

14. 1-Piperidin-4-ylimidazolidine-2,4-dione trifluoroacetate



TFA (25 mL) is added to a solution of *tert*-butyl 4-(2,4-dioxoimidazolidin-1-yl)piperidine-1-carboxylate (5 g) in 100 mL of CH₂Cl₂. After stirring for 5 h at rt, the excess
15 TFA is removed *in vacuo* to give the title compound (with some inorganic salts) as a white solid which is used without further purification. ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.80 (1H, s), 8.64 (1H, bs), 8.27 (1H, bs), 3.98 (1H, m), 3.90 (2H, s), 3.30 (2H, m), 2.98 (2H, m), 1.78 (4H, m).

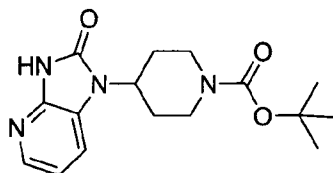
15. *tert*-Butyl 4-[(2-aminopyridin-3-yl)amino]piperidine-1-carboxylate



20 Sodium triacetoxyborohydride (29.1 g, 137.4 mmol) is added to a solution of 1,2-diaminopyridine (10 g, 91.6 mmol) and 1-Boc-4-piperidone (19.2 g, 96.2 mmol) in 150 mL of DCE at rt. After 5h, another 3.6 g of sodium triacetoxyborohydride is added, followed by an additional 12 h of stirring. The reaction is quenched with 5% aq. NaOH, and the mixture is extracted four times with CH₂Cl₂. The combined organic extracts are washed with 5% aq.
25 NaOH, water, and brine, dried (Na₂SO₄), filtered, and evaporated *in vacuo* to give dark brown oil. Purification by silica gel column chromatography (gradient from CH₂Cl₂ to 5%

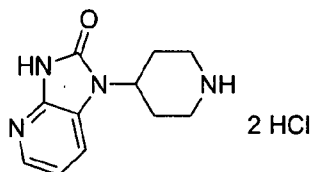
MeOH/CH₂Cl₂/2% Et₃N) affords a reddish-brown oil, which is triturated with Et₂O to give the title compound as a light brown solid. MS: 293.22 (M+H).

16. *tert*-Butyl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate



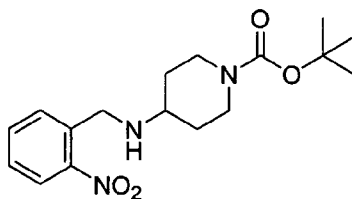
- 5 To a stirred solution of *tert*-butyl 4-[(2-aminopyridin-3-yl)amino]piperidine-1-carboxylate (10.6 g, 36.3 mmol) in 300 mL of CH₃CN at RT is added CDI (6.5 g, 39.9 mmol). After 4 h, an additional 7.5 g of CDI is added, followed by a further 19 h of stirring. The solvent is removed *in vacuo*, and the brown oily residue is taken up in CH₂Cl₂ (200 mL), washed with water (100 mL) and brine (100 mL), dried (Na₂SO₄), filtered, and evaporated *in vacuo* to give a
- 10 gooey brown oil/solid mix. This is dissolved in Et₂O, and the product is crystallized by the addition of hexane. Filtration of the solid affords the title compound as a light brown solid. MS: 219.16 (M+H (-Boc)).

17. 1-Piperidin-4-yl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one bis-hydrochloride



- 15 A 1M solution of HCl in Et₂O (150 mL, 150 mmol) is added at rt to a solution of *tert*-butyl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate (9.6 g, 30.2 mmol) in 230 mL of MeOH. After stirring for 17 h, the reaction mixture is concentrated *in vacuo* to give the title compound as a light brown solid. MS: 219.16 (M+H).

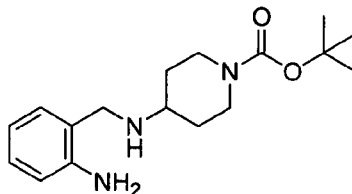
18. *tert*-Butyl 4-[(2-nitrobenzyl)amino]piperidine-1-carboxylate



- 20 To a mixture of 2-nitrobenzylamine hydrochloride (20.0 g, 106.0 mmol) in DCE (250 mL) is added TEA (10.73 g, 106.0 mmol). The mixture is allowed to stir at rt for 5 min. To this mixture N-Boc-4-piperidone (21.13 g, 106.0 mmol), and HOAC (7.96 g, 132.5 mmol), is added and stirred at rt for another 5 min. NaBH(OAc)₃ (25.28 g, 119.3 mmol) is added in portions and
- 25 the mixture is stirred at rt for 1 hr before it is washed with 10 % Na₂CO₃ solution (100 mL × 3)

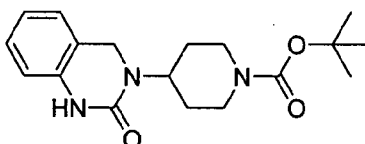
and brine (50 mL $\times$ 2). The organic phase is dried over Na₂SO₄. The solvent is removed *in vacuo* to afford the title compound as a red oil, which is used without further purification in subsequent steps.

19. *tert*-Butyl 4-[(2-aminobenzyl)amino]piperidine-1-carboxylate



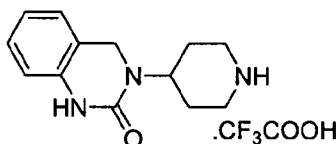
tert-Butyl 4-[(2-nitrobenzyl)amino]piperidine-1-carboxylate (40 g) is dissolved in EtOH (200 mL) and then added 10 % Pd/C (3 g, 2.82 mmol). The mixture is hydrogenated at rt for 2 h. The mixture is passed through celite, the celite is washed with EtOH, and the combined solution is concentrated *in vacuo* to afford the title compound as a yellow oil, which is used without further purification in subsequent steps.

20. *tert*-Butyl 4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carboxylate



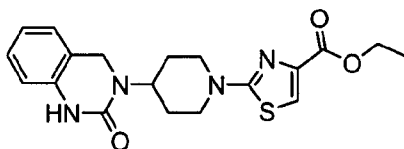
To a solution of *tert*-butyl 4-[(2-aminobenzyl)amino]piperidine-1-carboxylate (30 g) in DCE (250 mL), is added CDI (20.0 g, 122.8 mmol) in portions. The mixture is stirred at rt overnight. The mixture is washed with 1 M citric acid (50 mL $\times$ 2), 10 % K₂CO₃ aqueous solution (50 mL $\times$ 3) and dried over MgSO₄. The dried extract is filtered and concentrated under vacuum to afford the title compound as a white solid, which is used without further purification in subsequent steps.

21. 3-Piperidin-4-yl-3,4-dihydroquinazolin-2(1H)-one trifluoroacetate



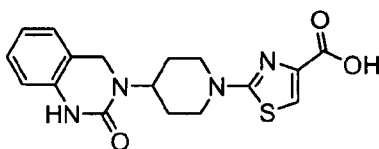
tert-Butyl 4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carboxylate (26.5 g, 80 mmol) is dissolved in CH₂Cl₂. TFA (61.4 g, 538.5 mmol) is added and the resulting mixture is stirred at rt overnight. The volatiles are removed *in vacuo* and the resulting solid is rinsed with ether (150 mL $\times$ 2) to afford the title compound as an orange solid. MS: 232.15 (M⁺).

22. Ethyl 2-[4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidin-1-yl]-1,3-thiazole-4-carboxylate



A mixture of 3-piperidin-4-yl-3,4-dihydroquinazolin-2(1H)-one trifluoroacetate (1.00 g, 2.90 mmol), ethyl 2-chloro-4-thiazolocarboxylate (0.771 g, 4.34 mmol), K_2CO_3 (1.20 g, 8.70 mmol) and DMA (2 mL) is heated at 150 °C overnight. The mixture is filtered, concentrated *in vacuo* and purified by silica gel column chromatography to afford the title compound as a white solid. MS: 373.12 (M+H).

23. 2-[4-(2-Oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidin-1-yl]-1,3-thiazole-4-carboxylic acid

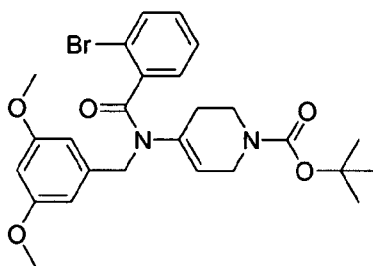


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A mixture of ethyl 2-[4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidin-1-yl]-1,3-thiazole-4-carboxylate (0.380 g, 1.02 mmol), NaOH (0.20 g, 5.10 mmol), H_2O (1 mL), and EtOH (6 mL) is refluxed overnight. The mixture is concentrated *in vacuo*, HCl (1 N) solution is added to adjust pH to 3. The resulting white solid is collected and washed with water (1 mL $\times$ 5) and dried by vacuum to afford the title compound. MS: 359.08 (M+H).

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24. *tert*-butyl 4-(N-(3,5-dimethoxybenzyl)-2-bromobenzamido)-5,6-dihydropyridine-1(2H)-carboxylate

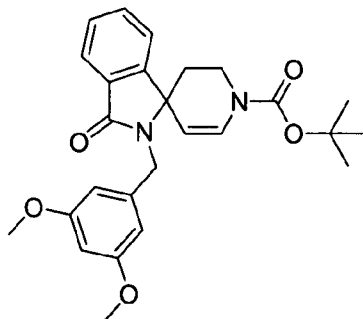


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A mixture of N-Boc-piperidone (7.36 g, 36.96 mmol) and 3,5-dimethoxybenzylamine (36.96 mmol) in toluene (60 mL) is refluxed for 4 h with a Dean-Stark trap to remove water formed. Solvent is removed *in vacuo*, the resulting thick oil is dissolved in toluene (70 mL) and TEA (10.3 mL, 73.92 mmol) is added followed by 2-bromobenzoyl chloride (36.96 mmol). The mixture is heated at 80 °C for 2 h and is then cooled to rt. Water (80 mL) is added, the layers are separated and the aqueous layer is extracted with EtOAc (60 mL). The combined extracts are

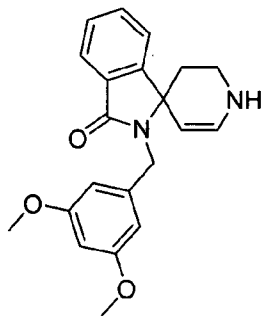
washed with brine (60 mL), dried over Na_2SO_4 and evaporated. The residue is purified by silica gel column chromatography to afford the title compound as a light yellow oil.

25. N-Boc-Spiropiperidine intermediate



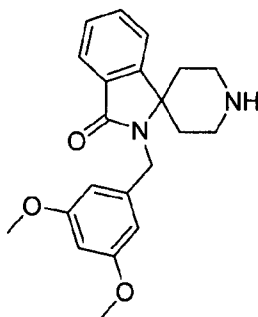
5 A mixture of *tert*-butyl 4-(3,5-dimethoxybenzylamino)-5,6-dihydropyridine-1(2H)-carboxylate (4.63 mmol), $\text{Pd}(\text{OAc})_2$ (73 mg, 0.32 mmol, 7 mol%), PPh_3 (170 mg, 0.65 mmol, 14 mol%), K_2CO_3 (959 mg, 6.95 mmol) and Et_4NCl (537 mg, 3.24 mmol) in CH_3CN (30 mL) is degassed by Ar for 15 min then heated at 110 °C in a sealed tube overnight. Water (40 mL) is added, the layers are separated and the aqueous layer is extracted with EtOAc (40 mL). The combined extracts are washed with brine (40 mL), dried over Na_2SO_4 and evaporated. The residue is purified by silica gel column chromatography to afford title compound as light yellow oil.

26. Dihydropiropiperidine intermediate



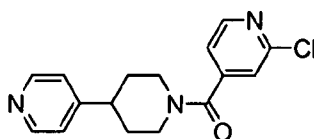
15 To solution of the above N-Boc-spiropiperidine_intermediate (4 mmol) in dioxane (10 mL) is added HCl solution in dioxane (4N, 15 mL, 60 mmol) and the mixture is stirred at rt overnight. The solvent is removed and to the residue is added aqueous NaHCO_3 solution (30 mL) and EtOAc (30 mL). The layers are separated and the aqueous layer is extracted with EtOAc (30 mL). The combined extracts are washed with brine (30 mL), dried over Na_2SO_4 and evaporated. The residue is purified by silica gel column chromatography to afford the title compound as an off-white solid.

27. 2-(3,5-Dimethoxybenzyl)spiro[isoindole-1,4'-piperidin]-3(2H)-one



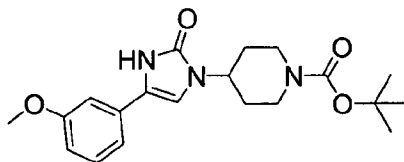
To a solution of the above dihydrospiro piperidine intermediate (3.6 mmol) in HOAc (20 mL) is added 10% Pd on C (100 mg) and the mixture is hydrogenated at 50 psi overnight. The catalyst is filtered and washed with MeOH (2 × 10 mL) and the combined filtrate is evaporated to dryness. The residue is partitioned between aqueous NaHCO₃ solution (30 mL) and EtOAc (30 mL). The layers are separated and the aqueous layer is extracted with EtOAc (30 mL). The combined extracts are washed with brine (30 mL), dried over Na₂SO₄ and evaporated. The resulting light yellow solid is used in subsequent reactions without further purification.

28. 2-Chloro-4-[(4-pyridin-4-yl)piperidin-1-yl]carbonyl]pyridine



4-Piperidin-4-ylpyridine (324 mg, 2.0 mmol) is added to DCE (1 mL), and the resulting mixture is cooled to 0 °C. To this suspension is added a mixture of 2-chloroisonicotinoyl chloride (352 mg, 2.0 mmol) and CH₂Cl₂ (10 mL). The resulting mixture is stirred at 0 °C to rt overnight. H₂O (10 mL) is added and the resulting mixture is extracted with CH₂Cl₂ (30 mL × 3). The extracts are dried over MgSO₄ and solvent is removed *in vacuo*. Silica gel column chromatography affords the title compound as yellow solid. MS: 302.09 (M⁺).

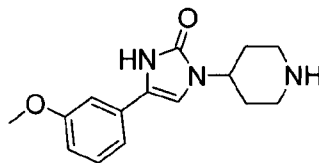
29. *tert*-Butyl 4-[4-(3-methoxyphenyl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl]piperidine-1-carboxylate



To a CH₂Cl₂ solution (60 mL) of *tert*-butyl 4-aminopiperidine-1-carboxylate (5.0 g, 25.0 mmol) and DIEA (5.7 mL, 32.5 mmol) at rt is added in portions 2-bromo-3'-methoxyacetophenone (6.9 g, 30.0 mmol). After 4 h, potassium cyanate (4.1 g, 50.0 mmol) is added, and the resulting mixture is cooled to 0 °C and acidified with glacial acetic acid. The resulting mixture is

stirred overnight while slowly warming to rt. The orange solution is then washed thoroughly with water, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give a yellow/orange solid. Trituration with Et_2O affords the title compound as a white solid. MS: 396.16 (M+Na).

30. 4-(3-Methoxyphenyl)-1-piperidin-4-yl-1,3-dihydro-2H-imidazol-2-one

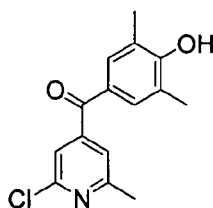


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TFA (15 mL) is added to a mixture of *tert*-butyl 4-[4-(3-methoxyphenyl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl]piperidine-1-carboxylate (6.5 g, 17.4 mmol) in 50 mL of CH_2Cl_2 . The resulting brown solution is stirred at rt for 2 h. The volatiles are removed *in vacuo* to give a brown oil. This oil is diluted with water and neutralized to pH=8-9 with solid NaHCO_3 while cooling in an ice bath. The mixture is then concentrated, and the residual solids are suspended in water and stirred for 5 min. The remaining solid is collected by vacuum filtration and dried *in vacuo* to give the title compound as an off-white solid. MS: 274.15 (M+H).

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31. (2-Chloro-6-methylpyridin-4-yl)(4-hydroxy-3,5-dimethylphenyl)methanone

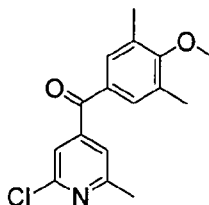


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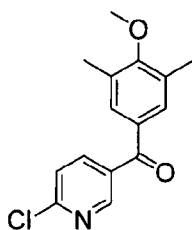
A mixture of 2-chloro-6-methylpyridine-4-carboxylic acid (5.0 g, 29.1 mmol) and thionyl chloride (20 mL) is heated to reflux and stirred for 5 h. The volatiles are removed *in vacuo* to give the acid chloride as light purple oil, which solidifies while standing in the freezer. Aluminum chloride (7.6 g, 56.8 mmol) is added to a stirred solution of this acid chloride (5.4 g, 28.4 mmol) in 100 mL of CH_2Cl_2 at rt. A solution of 2,6-dimethylphenol (10.4 g, 85.2 mmol) in 60 mL of CH_2Cl_2 is then added dropwise, and the resulting mixture is stirred at rt for 24 h. The reaction is quenched with 1N HCl (50 mL), and the layers are separated. The aqueous layer is washed two additional times with CH_2Cl_2 (20 mL each), and the combined organic extracts are dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give a brown oil/solid mix. The crude material is diluted with Et_2O , and the desired product is crystallized by the addition of hexane. The solid is collected by vacuum filtration and dried *in vacuo* to give the title compound as a brown solid. MS: 276.15 (M+H).

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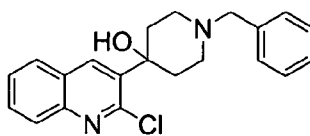
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32. (2-Chloro-6-methylpyridin-4-yl)(4-methoxy-3,5-dimethylphenyl)methanone

A mixture of (2-chloro-6-methylpyridin-4-yl)(4-hydroxy-3,5-dimethylphenyl)methanone (3.0 g, 10.9 mmol), iodomethane (0.75 mL, 11.99 mmol), and cesium carbonate (3.9 g, 11.99 mmol) in 20 mL of DMF is stirred at rt for 2 h. The DMF is removed *in vacuo* and the residue is partitioned between CH₂Cl₂ (50 mL) and water (30 mL). The layers are separated, and the aqueous layer is extracted once more with CH₂Cl₂ (50 mL). The combined CH₂Cl₂ extracts are dried (Na₂SO₄), filtered, and evaporated to give a brown solid. The crude solid is triturated with hexane and filtered to give the title compound as a pale brown solid. MS: 290.18 (M+H).

33. (6-Chloropyridin-3-yl)(4-methoxy-3,5-dimethylphenyl)methanone

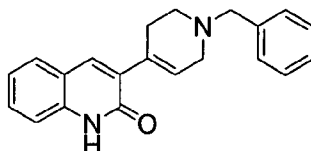
6-Chloronicotiny chloride (1.76 g, 0.01 moles) is dissolved in THF (25 mL) and cooled to -78 °C under nitrogen atmosphere. To this stirred mixture is added drop wise 0.5 M THF solution of 3,5-dimethyl-4-methoxyphenyl magnesium bromide (20 mL, 0.01 moles) over a period of 15 min. The mixture is and gradually allowed to warm to rt and stirred overnight. The reaction mixture is concentrated under vacuum and purified by silica gel column chromatography using 5% EtOAc / hexane to afford the title compound as white solid.

34. 1-Benzyl-4-(2-chloroquinolin-3-yl)piperidin-4-ol

A solution of n-BuLi in hexane (1.6 M, 76.4 mL, 122 mmol) is added drop wise to a solution of diisopropylamine (17.2 mL, 122 mmol) in 250 mL of THF at -78 °C under N₂. After stirring for 1 h, a solution of 2-chloroquinoline (20 g, 122 mmol) in 50 mL of THF is added via a dropping funnel over 30 min. After a further 1 h, a solution of 1-benzyl-4-piperidone (22.6 mL, 122 mmol) in 10 mL of THF is added to the brown reaction mixture, and stirring is continued for an additional 40 min. The reaction is then allowed to slowly warm to rt. After cooling the

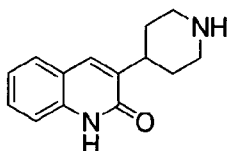
mixture back to -20 °C, the reaction is carefully quenched with water (100 mL). The resulting mixture is extracted with EtOAc, and the organic phase is washed with brine, dried (Na₂SO₄), filtered and evaporated. Silica gel chromatographic purification (gradient from CH₂Cl₂ to 10% [5% NH₄OH/MeOH]/CH₂Cl₂) affords the title compound. MS: 353.15 (M+H).

5 35. 3-(1-Benzyl-1,2,3,6-tetrahydropyridin-4-yl)quinolin-2(1H)-one



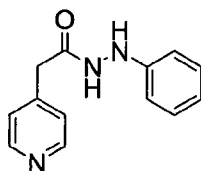
A mixture of 1-benzyl-4-(2-chloroquinolin-3-yl)piperidin-4-ol (22 g, 62.3 mmol) in 300 mL of 6N HCl is stirred under reflux for 10 h. The reaction mixture is cooled to rt and diluted with water (200 mL). The precipitated solid is collected and dried *in vacuo* to give the title compound. MS: 317.18 (M+H).

10 36. 3-Piperidin-4-ylquinolin-2(1H)-one



A mixture of 3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)quinolin-2(1H)-one (4.0 g, 12.6 mmol) in 200 mL of MeOH is degassed with N₂ (g) for 5 min, and 10% Pd/C (1.2 g) is added. The resulting reaction mixture is hydrogenated under 30 psi of H₂ (g) at 50 °C for 18 h on a Parr shaker. The mixture is filtered through celite, and the celite is washed well with MeOH. The filtrate is concentrated *in vacuo* to give the title compound as a white solid. MS: 229.16 (M+H).

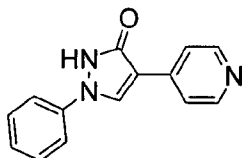
15 37. N'-Phenyl-2-pyridin-4-ylacetohydrazide



20 To a solution of pyridin-4-ylacetic acid hydrochloride (20 g, 115 mmol) in 130 mL of DMF at rt is added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (26.5 g, 138 mmol), 1-hydroxybenzotriazole (18.6 g, 138 mmol), DIEA (60 mL, 345 mmol), and phenylhydrazine (11.3 mL, 115 mmol). After stirring for 22 h, the reaction mixture is diluted with CH₂Cl₂ (300 mL) and washed with sat. NaHCO₃ (300 mL). The aqueous phase is extracted
25 twice more with CH₂Cl₂ (100 mL each), and the combined organic extracts are dried (Na₂SO₄),

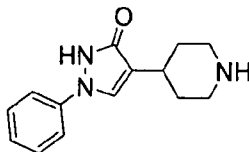
filtered and evaporated *in vacuo* to give a red solid. This solid is suspended in EtOAc and heated to 50 °C for 15 min with vigorous stirring. After cooling, the solid is collected by vacuum filtration and dried *in vacuo* to give the title compound as an off-white solid. MS: 228.18 (M+H).

5 38. 1-Phenyl-4-pyridin-4-yl-1,2-dihydro-3H-pyrazol-3-one



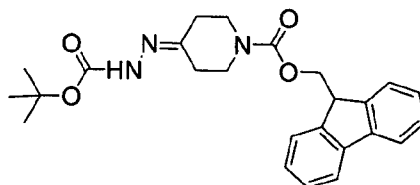
Calcium hydride (2.8 g, 67.5 mmol) is added to a DMF solution (100 mL) of N'-phenyl-2-pyridin-4-ylacetohydrazide (9.3 g, 40.9 mmol), and the reaction mixture is heated to 170 °C and stirred for 14 h. After cooling to rt, the mixture is filtered, and the filtrate is concentrated *in vacuo* to give a reddish-brown residue. This residue is dissolved in CH₂Cl₂, and hexane is added with stirring until a solid precipitates from solution. The solid is collected by filtration and dried *in vacuo* to give the title compound as a brown solid. MS: 238.17 (M+H).

10 39. 1-Phenyl-4-piperidin-4-yl-1,2-dihydro-3H-pyrazol-3-one



15 Platinum oxide (3.4 g) is added to a mixture of 1-phenyl-4-pyridin-4-yl-1,2-dihydro-3H-pyrazol-3-one (9.7 g, 40.9 mmol) in 120 mL of glacial AcOH, 1.0 mL of conc. HCl, and 50 mL of water. The resulting mixture is purged with N₂ (g) for 5-10 min., and then it is hydrogenated under 40-50 psi of H₂ (g) on a Parr shaker for 36 h at rt. The mixture is filtered through celite, and the filtrate is concentrated *in vacuo* to give a gooey, yellow solid. Trituration with Et₂O affords the title compound as a yellow solid. MS: 244.12 (M+H).

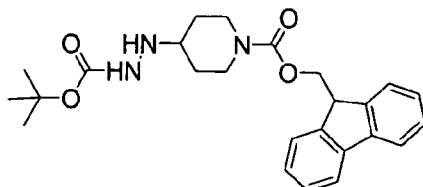
20 40. 9H-Fluoren-9-ylmethyl 4-[(*tert*-butoxycarbonyl)hydrazono]piperidine-1-carboxylate



To a solution of 1-Fmoc-4-piperidone (25 g, 78 mmol) in 390 mL of EtOH is added *tert*-butyl carbazate (11.3 g, 86.6 mmol), and the reaction mixture is heated to reflux and stirred for 1 h. The solution is cooled to rt and concentrated *in vacuo* to give white foam. Et₂O (150 mL) is

added, and the solution is stirred at rt for 30 min, at which time a solid precipitates from solution. The solid is collected by vacuum filtration and dried *in vacuo* to give the title compound as a white solid

41. 9H-Fluoren-9-ylmethyl 4-[2-(*tert*-butoxycarbonyl)hydrazino]piperidine-1-carboxylate

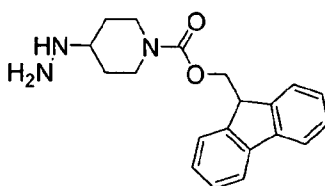


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Platinum oxide (3.3 g) is added to a solution of 9H-fluoren-9-ylmethyl 4-[(*tert*-butoxycarbonyl)-hydrazono]piperidine-1-carboxylate (32.7 g, 75 mmol) in acetic acid (200 mL). The resulting mixture is hydrogenated on a Parr shaker under 45 psi of H₂(g) for 2 h. The solution is filtered through celite, and the filtrate is concentrated *in vacuo* to give the title compound.

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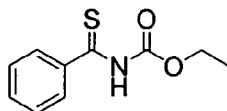
42. 9H-Fluoren-9-ylmethyl 4-hydrazinopiperidine-1-carboxylate trifluoroacetate



A solution of 9H-fluoren-9-ylmethyl 4-[2-(*tert*-butoxycarbonyl)hydrazino]piperidine-1-carboxylate (32 g, 73 mmol) in 160 mL of TFA is stirred at rt for 3 h. The mixture is concentrated *in vacuo* to give the title compound as reddish-brown viscous oil, which is suitable for further use without any additional purification.

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43. Ethyl (phenylcarbonothioyl)carbamate



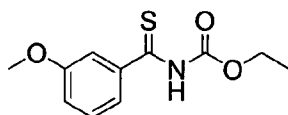
Aluminum chloride (13.3 g, 100 mmol) is added portionwise to an ice-cold solution of ethoxycarbonyl isothiocyanate (5.9 mL, 50 mmol) and benzene (4.4 mL, 50 mmol) in 30 mL of CH₂Cl₂. The reaction mixture is stirred at 0 °C for 4 h, and then it is quenched by careful addition of cold 1N HCl. Enough CH₂Cl₂ is added to dissolve any solid organic material, and the resulting mixture is extracted with 10% NaOH (4 × 50 mL). The combined aqueous phases are further basified to pH=11-12 to dissolve all the solids in the mixture. This basic aqueous solution is extracted with Et₂O and acidified to pH=3-4 with conc. HCl while cooling in an ice

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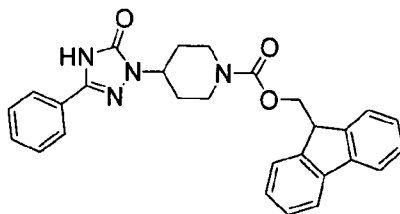
bath. The cloudy mixture is extracted with CH_2Cl_2 (4x), and the combined organic extracts are dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a red oil. Purification by silica gel column chromatography (gradient from Hex to 30% EtOAc/Hex) affords a red oil, which is dissolved in Et_2O and cooled in a dry-ice/acetone bath. Hexane is slowly added while scratching the flask with a spatula, and eventually a solid precipitates from solution. This solid is collected by vacuum filtration and dried *in vacuo* to give the title compound as a yellow solid. MS: 210.08 (M+H).

44. Ethyl [(3-methoxyphenyl)carbonothioyl]carbamate



A solution of ethoxycarbonyl isothiocyanate (5.0 g, 38.1 mmol) in 20 mL of THF is cooled to 0 °C and treated with 3-methoxyphenylmagnesium bromide (1M in THF, 38.1 mL, 38.1 mmol) by dropwise addition. The resulting mixture is stirred for 2 h at 0 °C, quenched with 15-20 mL of 1N HCl, and diluted with CH_2Cl_2 and 20% NaOH (100 mL each). The resulting mixture is filtered through celite, and the filtrate is transferred to a separatory funnel. The layers are separated, and the organic layer is extracted twice more with 20% NaOH (50 mL each). The combined aqueous extracts are washed with Et_2O (2 × 75 mL) and acidified to pH=3-4 with conc. HCl while cooling in an ice bath. The cloudy mixture is extracted two times with CH_2Cl_2 , and the combined organic extracts are dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a red oil. Purification by silica gel column chromatography (gradient from Hex to 30% EtOAc/Hex) affords the title compound as a red oil. MS: 240.10 (M+H).

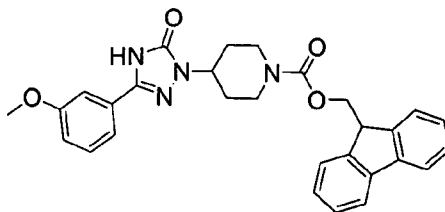
45. 9H-Fluoren-9-ylmethyl 4-(5-oxo-3-phenyl-4,5-dihydro-1H-1,2,4-triazol-1-yl)piperidine-1-carboxylate



A solution of 9H-fluoren-9-ylmethyl 4-hydrazinopiperidine-1-carboxylate trifluoroacetate (3.0 g, 6.65 mmol), ethyl (phenylcarbonothioyl)carbamate (1.5 g, 7.32 mmol), and DIEA (1.3 mL, 7.32 mmol) in 30 mL of THF is stirred under reflux for 48 h (at the end of the first day, an additional 3.0 g of 9H-fluoren-9-ylmethyl 4-hydrazinopiperidine-1-carboxylate trifluoroacetate is added). After cooling to rt, the reaction is concentrated to give reddish-brown

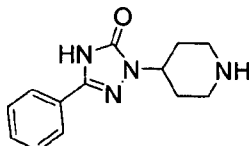
oil. This oil is dissolved in acetonitrile with heating, and then cooled back to rt. The resulting precipitate is filtered and dried *in vacuo* to give the title compound as an off-white solid. MS: 467.14 (M+H).

46. 9H-Fluoren-9-ylmethyl 4-[3-(3-methoxyphenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl]piperidine-1-carboxylate



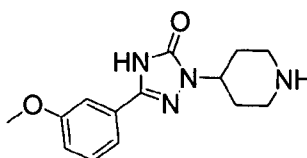
A solution of 9H-fluoren-9-ylmethyl 4-hydrazinopiperidine-1-carboxylate trifluoroacetate (3.0 g, 6.65 mmol), ethyl [(3-methoxyphenyl)carbonothioyl]carbamate (1.75 g, 7.32 mmol), and DIEA (1.3 mL, 7.32 mmol) in 30 mL of THF is stirred under reflux for 72 h (at the end of the first day, an additional 3.0 g of 9H-fluoren-9-ylmethyl 4-hydrazinopiperidine-1-carboxylate trifluoroacetate is added). After cooling to RT, the reaction is concentrated to give a brown oil/solid mix. This crude material is dissolved in acetonitrile with heating and filtered. The collected solid is dried *in vacuo* to give the title compound as a white solid. MS: 497.16 (M+H).

47. 5-Phenyl-2-piperidin-4-yl-2,4-dihydro-3H-1,2,4-triazol-3-one



A solution of 9H-fluoren-9-ylmethyl 4-(5-oxo-3-phenyl-4,5-dihydro-1H-1,2,4-triazol-1-yl)piperidine-1-carboxylate (1.25 g, 2.68 mmol) and diethylamine (10 mL) in THF (10 mL) is stirred for 21 h at rt. The mixture is concentrated, and the residue is purified by silica gel column chromatography (gradient from CH₂Cl₂ to 10%[5% NH₄OH/MeOH]/ CH₂Cl₂) to give the title compound as a white solid. MS: 245.21 (M+H).

48. 5-(3-Methoxyphenyl)-2-piperidin-4-yl-2,4-dihydro-3H-1,2,4-triazol-3-one

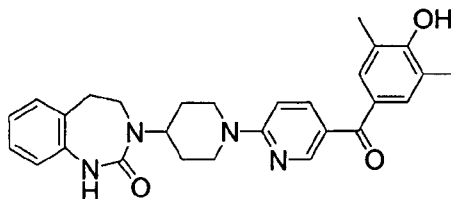


A solution of 9H-fluoren-9-ylmethyl 4-[3-(3-methoxyphenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl]piperidine-1-carboxylate (1.39 g, 2.80 mmol) and diethylamine (15 mL) in THF (15 mL) is stirred for 1 week at rt. The mixture is concentrated, and the residue is purified by silica gel column chromatography (gradient from CH₂Cl₂ to 15%[5% NH₄OH/MeOH]/CH₂Cl₂) to give the title compound as a white solid. MS: 275.16 (M+H).

EXAMPLE 2. SYNTHESIS OF REPRESENTATIVE BIARYL KETONE-SUBSTITUTED PIPERIDINES

This Example illustrates the synthesis of certain representative biaryl ketone-substituted piperidines of Formula I, Formula II or Formula XI. All biaryl ketone-substituted piperidines in this Example are CGRP receptor antagonists, and have an IC₅₀ (determined as described in Example 5) that is 2 micromolar or less (*i.e.*, the concentration of such compounds that is required to provide a 50% decrease in the fluorescence response of cells exposed to one IC₅₀ of CGRP is 2 micromolar or less).

A. 3-(1-(5-(4-Hydroxy-3,5-dimethylbenzoyl)pyridin-2-yl)piperidin-4-yl)-4,5-dihydro-1H-benzo[d][1,3]diazepin-2(3H)-one

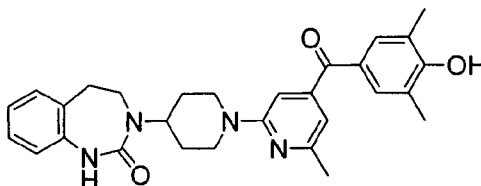


Step 1: A mixture of (6-chloropyridin-3-yl)(4-methoxy-3,5-dimethylphenyl)-methanone (163 mg, 0.593 mmol), 3-piperidin-4-yl-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one trifluoroacetate (213 mg, 0.593 mmol), and potassium carbonate (245 mg, 1.78 mmol) in 3.0 mL of DMA is heated to 140 °C in a sealed tube. After 4 h, the reaction is cooled to rt and the DMA is removed *in vacuo*. The residue is purified by silica gel column chromatography (gradient from CH₂Cl₂ to 2% MeOH / CH₂Cl₂) to afford 3-(1-(5-(4-methoxy-3,5-dimethylbenzoyl)pyridin-2-yl)piperidin-4-yl)-4,5-dihydro-1H-benzo[d][1,3]diazepin-2(3H)-one as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.61 (1H, s), 8.02 (1H, d), 7.44 (2H, s), 7.11 (1H, t), 7.03 (1H, d), 6.90 (1H, d), 6.70 (2H, m), 6.49 (1H, s), 4.62 (3H, m), 3.78 (3H, s), 3.44 (2H, m), 2.97 (4H, m), 2.33 (6H, s), 1.89 (2H, m), 1.62 (2H, m). MS: 485.26 (M+H).

Step 2: A mixture of 3-(1-(5-(4-methoxy-3,5-dimethylbenzoyl)pyridin-2-yl)piperidin-4-yl)-4,5-dihydro-1H-benzo[d][1,3]diazepin-2(3H)-one (97 mg, 0.2 mmol) is dissolved in CH₂Cl₂ (10 mL) and cooled to -78 °C under nitrogen atmosphere. To this mixture is added drop wise 1.0 M CH₂Cl₂ solution of BBr₃ (0.5 mL) and the mixture is gradually allowed to warm to rt and stirred for 2 days. The reaction mixture is quenched with ice (10 g), the pH is adjusted to 7.0

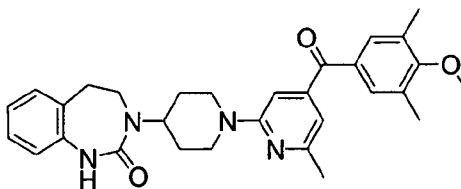
using saturated NaHCO_3 , and the solution is extracted with CH_2Cl_2 (3×10 mL) and dried with MgSO_4 . The dried extract is filtered and concentrated under vacuum to afford crude product, which is purified by silica gel column chromatography (1:1 EtOAc / CH_2Cl_2) to afford the title compound as a light pink solid. ^1H NMR (400 MHz, CDCl_3) δ 8.60 (1H, s), 7.99 (1H, dd), 7.48 (2H, s), 7.03 (2H, m), 6.90 (1H, t), 6.69 (2H, m), 6.48 (1H, s), 5.31 (1H, s), 4.60 (3H, m), 3.43 (2H, m), 2.96 (4H, m), 2.30 (6H, s), 1.88 (2H, m), 1.62 (2H, m). MS: 471.32 (M+H).

B. 3-{1-[4-(4-Hydroxy-3,5-dimethylbenzoyl)-6-methylpyridin-2-yl]piperidin-4-yl}-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one



A mixture of (2-chloro-6-methylpyridin-4-yl)(4-hydroxy-3,5-dimethylphenyl)methanone (100 mg, 0.36 mmol), 3-piperidin-4-yl-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one trifluoroacetate (129 mg, 0.36 mmol), and potassium carbonate (149 mg, 1.08 mmol) in 1.0 mL of NMP is heated to 150 °C in a sealed tube. After 39 h, the reaction is cooled to rt and the NMP is removed *in vacuo*. The residue is purified by silica gel column chromatography (gradient from CH_2Cl_2 to 50% EtOAc/ CH_2Cl_2) to give the title compound as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.34 (1H, s), 8.49 (1H, s), 7.41 (2H, s), 7.01 (3H, m), 6.78 (1H, m), 6.67 (1H, s), 6.54 (1H, s), 4.44 (2H, d, J 12.3), 4.31 (1H, m), 2.85 (4H, m), 2.68 (1H, s), 2.36 (3H, s), 2.19 (6H, s), 1.88 (1H, m), 1.66 (4H, m). MS: 485.35 (M+H).

C. 3-{1-[4-(4-Methoxy-3,5-dimethylbenzoyl)-6-methylpyridin-2-yl]piperidin-4-yl}-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

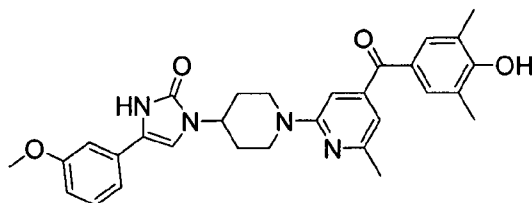


A mixture of (2-chloro-6-methylpyridin-4-yl)(4-methoxy-3,5-dimethylphenyl)methanone (1.0 g, 3.45 mmol), 3-piperidin-4-yl-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one trifluoroacetate (1.2 g, 3.45 mmol), and potassium carbonate (1.4 g, 10.35 mmol) in 5.0 mL of NMP is heated to 150 °C in a sealed tube. After 16 h, the reaction is cooled to rt and the NMP is removed *in vacuo*. The residue is purified by column chromatography (gradient from CH_2Cl_2 to

60% CH₂Cl₂/EtOAc) to give the title compound as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.52 (1H, s), 7.26 (1H, s), 7.08 (2H, m), 6.90 (1H, t, *J* 7.6), 6.69 (2H, m), 6.64 (1H, s), 6.45 (1H, s), 4.51 (3H, m), 3.79 (3H, s), 3.45 (2H, m), 2.97 (4H, m), 2.46 (3H, s), 2.32 (6H, s), 1.84 (2H, m), 1.72 (2H, m). MS: 499.27 (M+H).

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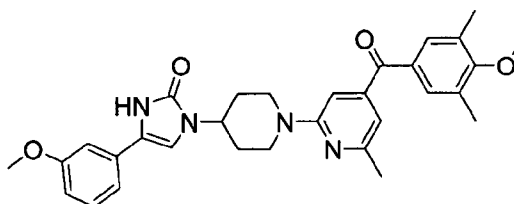
D. 1-{1-[4-(4-Hydroxy-3,5-dimethylbenzoyl)-6-methylpyridin-2-yl]piperidin-4-yl}-4-(3-methoxyphenyl)-1,3-dihydro-2H-imidazol-2-one



A mixture of (2-chloro-6-methylpyridin-4-yl)(4-hydroxy-3,5-dimethylphenyl)methanone (100 mg, 0.36 mmol), 4-(3-methoxyphenyl)-1-piperidin-4-yl-1,3-dihydro-2H-imidazol-2-one (148 mg, 0.54 mmol), and DIEA (0.13 mL, 0.72 mmol) in 1.0 mL of NMP is heated to 150 °C in a sealed tube. After 21 h, the reaction is cooled to rt and the NMP is removed *in vacuo*. The residue is purified by silica gel column chromatography (gradient from 20% EtOAc/CH₂Cl₂ to 1% MeOH/EtOAc) to give the title compound as a pale brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ 10.68 (1H, s), 9.34 (1H, s), 7.42 (2H, s), 7.21 (2H, m), 7.08 (2H, m), 6.69 (2H, m), 6.56 (1H, s), 4.49 (2H, d, *J* 12.8), 4.13 (1H, m), 3.73 (3H, s), 2.93 (2H, t, *J* 12), 2.37 (3H, s), 2.19 (6H, s), 1.74 (4H, m). MS: 513.19 (M+H).

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E. 1-{1-[4-(4-Methoxy-3,5-dimethylbenzoyl)-6-methylpyridin-2-yl]piperidin-4-yl}-4-(3-methoxyphenyl)-1,3-dihydro-2H-imidazol-2-one



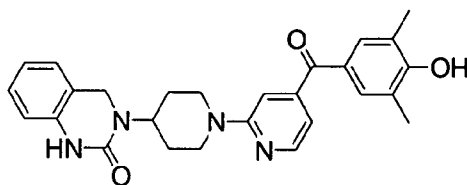
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A mixture of (2-chloro-6-methylpyridin-4-yl)(4-methoxy-3,5-dimethylphenyl)methanone (100 mg, 0.35 mmol), 4-(3-methoxyphenyl)-1-piperidin-4-yl-1,3-dihydro-2H-imidazol-2-one (145 mg, 0.53 mmol), and DIEA (0.12 mL, 0.70 mmol) in 1.0 mL of NMP is heated to 150 °C in a sealed tube. After 21 h, the reaction is cooled to rt and the NMP is removed *in vacuo*. The residue is purified by silica gel column chromatography (gradient from 20% EtOAc/CH₂Cl₂ to EtOAc) to give the title compound as a yellow, fluffy solid. ¹H NMR (400 MHz, DMSO-d₆) δ 10.68 (1H, s), 7.49 (2H, s), 7.20 (2H, m), 7.09 (2H, m), 6.76 (1H, s), 6.70 (1H, m), 6.59 (1H, s),

25

4.49 (2H, d, *J* 13.2), 4.13 (1H, m), 3.73 (3H, s), 3.71 (3H, s), 2.94 (2H, t, *J* 126), 2.38 (3H, s), 2.26 (6H, s), 1.75 (4H, m). MS: 527.22 (M+H).

F. 3-(1-(4-(4-Hydroxy-3,5-dimethylbenzoyl)pyridine-2-yl)piperidine-4-yl)-3,4-dihydroquinazolin-2(1H)-one



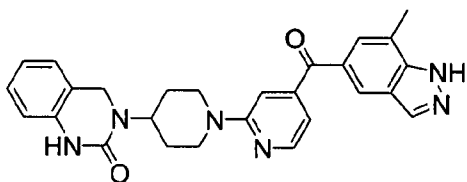
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To a solution of 2-chloropyridine-4-carbonyl chloride (352 mg, 2 mmol) and aluminum trichloride (266 mg, 2 mmol) in dichloroethane (10 mL) at 0 °C is added dropwise a solution of 2,6-dimethyl phenol (244 mg, 2 mmol) in dichloroethane (5 mL). The reaction is allowed to stir an additional 10 min at 0 °C and then poured over ice. The resulting slurry is extracted with EtOAc (60 mL), the organic layer is dried over sodium sulfate and evaporated under vacuum to afford (2-chloropyridin-4-yl)(4-hydroxy-3,5-dimethylphenyl)methanone as an orange solid.

In a 5 mL reaction vial, 100 mg (0.4 mmol) of the above orange solid is combined with 3-(piperidine-4-yl)-3,4-dihydroquinazolin-2(1H)-one (139 mg, 0.6 mmol). The mixture is melted at 140 °C for 2h. The resulting solid is dissolved in MeOH and the product partially purified by PTLC eluting with a mixture of EtOAc, MeOH, and TEA (20:2:1). The resulting impure product band ($R_f = 0.8$) is collected and further purified by PTLC eluting with 5/95 MeOH / methylene chloride to afford the title compound as a yellow solid. ¹H NMR (CDCl₃) 8.29(d,1H), 7.58 (s, 2H), 7.26 (s, 1H), 7.15 (t, 1H), 7.03 (d, 1H), 6.95 (t, 1H), 6.90 (s, 1H), 6.75 (d, 1H), 6.70 (d,1H), 4.68 (m, 1H), 4.50 (bd, 2H), 4.32 (s, 2H), 3.02 (bm, 2H), 2.30 (s, 6H), 1.85, (bm, 4H). MS: 457 (M+H).

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G. 3-(1-(4-((7-methyl-1H-indazol-5-yl)carbonyl)pyridine-2-yl)piperidine-4-yl)-3,4-dihydroquinazolin-2(1H)-one



To a flask containing 10mL toluene and 10mL saturated sodium bicarbonate is added 2-chloroisonicotinic acid (4g, 25 mmol) followed by isobutyl chloroformate (3.8 g, 27 mmol) in portions. The mixture is stirred at rt for 16 h and diluted with diethyl ether (20 mL). The

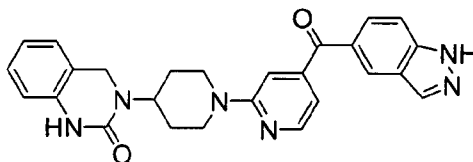
25

organic fraction is dried over sodium sulfate and the solvent evaporated under reduced pressure. A portion of the resulting mixed anhydride is used in the next step without further purification.

To a solution of 5-bromo-7-methyl-1H-indazole (350 mg, 1.7 mmol) in THF (10 mL) at -78 °C is added t-butyl lithium (3 mL of a 1.7M pentane solution). The mixture is allowed to stir at -78 °C for 10 min. A solution of the above mixed anhydride (315 mg, 2.0mmol) in THF (5 mL) is added drop wise. The reaction mixture is allowed to slowly warm to rt over 3h. The solvent is removed under reduced pressure. The crude reaction mixture is suspended in EtOAc(5 mL), filtered through celite and diluted with hexanes (1-2 mL) until a precipitate of (2-chloropyridin-4-yl) (7-methyl-1H-indazol-5-yl)methanone appears. This product is collected by filtration as a white crystalline powder and used without further purification.

To a 5 mL reaction vial containing the above biaryl ketone (75 mg, 0.3 mmol) and the TFA salt of 3-(piperidine-4-yl)-3,4-dihydroquinazolin-2(1H)-one (110 mg, 0.32 mmol) is added potassium carbonate (50 mg) and DMF (0.2 mL). The reaction mixture is heated at 150 °C for 3h. Without workup, the product is partially purified by PTLC eluting with 10% MeOH / methylene chloride. The product is further purified by PTLC eluting with 5/95 MeOH / methylene chloride to afford the title product as a clear film. ¹H NMR (CDCl₃) 8.35(d,1H), 8.20 (s, 1H), 8.10 (s, 1H), 7.80 (s, 1H), 7.19 (t, 1H), 7.10 (s, 1H), 7.05 (d, 1H), 6.95 (m, 1H), 6.80 (d, 1H), 6.69 (d, 1H), 4.70 (m, 1H), 4.55 (d, 2H), 4.34 (s, 2H), 3.05 (m, 2H), 2.62, (s, 3H), 1.80, (bs, 4H). MS: 467 (M+H).

H. 3-(1-(4-(1H-indazol-5-ylcarbonyl)pyridine-2-yl)piperidine-4-yl)-3,4-dihydroquinazolin-2(1H)-one



To a flask containing 10 mL toluene and 10 mL saturated sodium bicarbonate is added 2-chloroisonicotinic acid (4 g, 25 mmol) followed by isobutyl chloroformate (3.8 g, 27 mmol) in portions. The mixture is stirred at rt for 16 h and diluted with diethyl ether (20 mL). The organic fraction is dried over sodium sulfate and the solvent evaporated under reduced pressure. A portion of the mixed anhydride is used without further purification.

To a solution of 5-bromo-1H-indazole (300 mg, 1.5 mmol) in THF (5 mL) at -78 °C is added t-butyl lithium solution (2 mL of a 1.7M pentane solution). The reaction mixture is stirred 10 min at -78 °C. A solution of the above mixed anhydride (392 mg, 1.5 mmol) in THF (3 mL) is added dropwise. The reaction is stirred for 3 h, allowing it to slowly warm to rt. The solvent is

removed under reduced pressure. The resulting solid is triturated with methanol to afford (2-chloropyridin-4-yl) (1H-indazol-5-yl)methanone as a yellow crystalline powder.

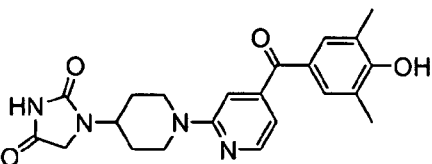
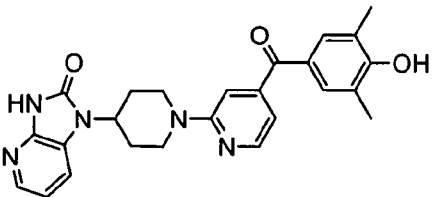
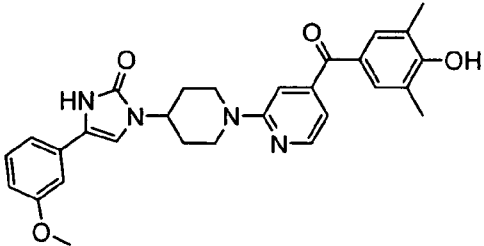
To a 5 mL reaction vial containing the above ketone (35 mg) and the hydrochloride salt of 3-(piperidine-4-yl)-3,4-dihydroquinazolin-2(1H)-one (45 mg) is added potassium carbonate (50 mg) and DMF (0.2 mL). The reaction mixture is heated at 150 °C for 3h. Upon cooling, the reaction is diluted with EtOAc (2 mL) and washed with water (2 mL). The organic phase is filtered through celite and concentrated under reduced pressure. The residue is separated by PTLC eluting with 9/1 MeOH / methylene chloride. The impure product is further purified by PTLC eluting with 4/6 THF / methylene chloride to afford the title compound as a yellow solid.

MS: 453 (M+H).

EXAMPLE 3. ADDITIONAL REPRESENTATIVE BIARYL KETONE-SUBSTITUTED PIPERIDINES

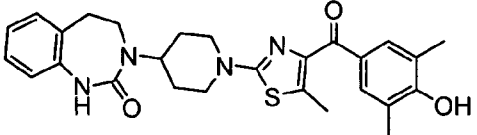
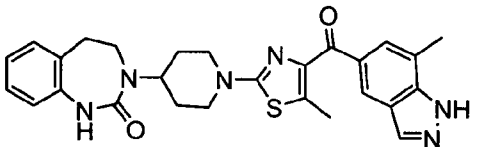
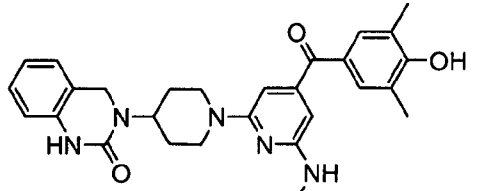
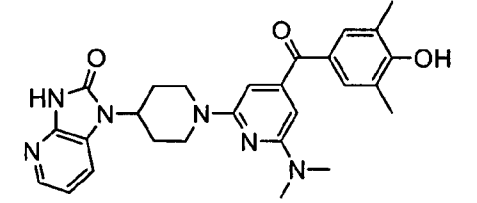
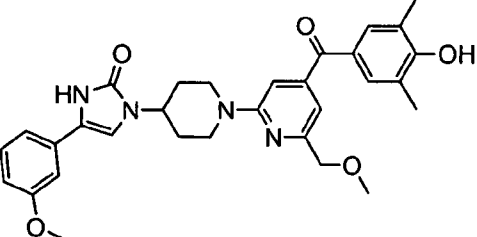
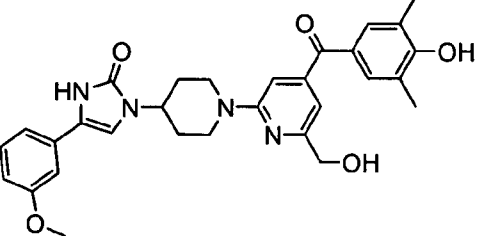
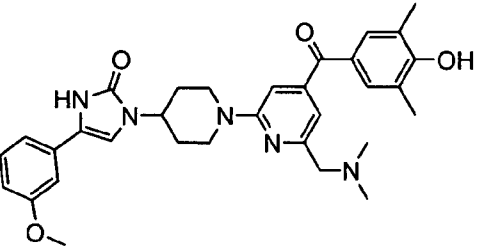
Using routine modifications, the starting materials may be varied and additional steps employed to produce other compounds provided herein. Compounds listed in Table I are prepared using such methods. Compounds provided in Table I with a "*" in the column headed "IC₅₀" exhibit an IC₅₀ (determined as described in Example 5) that is 2 micromolar or less. Mass spectroscopy data is provided as M+1 in the column headed "MS," with the retention times ("Ret Time") given in minutes.

Table I
Representative Biaryl Ketone-Substituted Piperidines

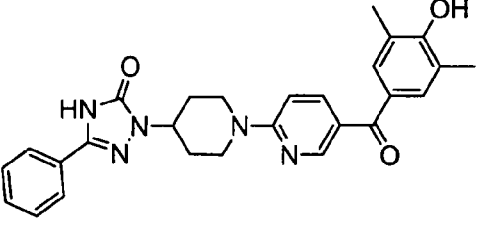
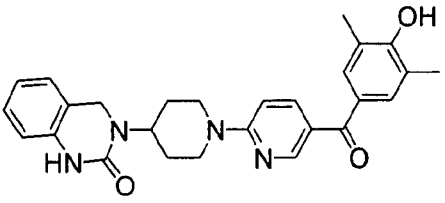
	COMPOUND	NAME	MS	Ret Time	IC ₅₀
1		1-(1-(4-(4-hydroxy-3,5-dimethylbenzoyl)pyridin-2-yl)piperidin-4-yl)imidazolidine-2,4-dione	409.15	1.6	
2		1-(1-(4-(4-hydroxy-3,5-dimethylbenzoyl)pyridin-2-yl)piperidin-4-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	444.14	1.71	
3		1-(1-(4-(4-hydroxy-3,5-dimethylbenzoyl)pyridin-2-yl)piperidin-4-yl)-4-(3-methoxyphenyl)-1H-imidazol-2(3H)-one	499.15	1.78	

	COMPOUND	NAME	MS	Ret Time	IC ₅₀
4		4-(1-(4-(4-hydroxy-3,5-dimethylbenzoyl)pyridin-2-yl)piperidin-4-yl)-2-phenyl-1,2-dihydropyrazol-5-one			
5		3-(1-(4-(4-hydroxy-3,5-dimethylbenzoyl)pyridin-2-yl)piperidin-4-yl)quinolin-2(1H)-one	454.14	1.76	
6		1-[4-(4-hydroxy-3,5-dimethylbenzoyl)pyridin-2-yl]-1'H-spiro[piperidine-4,4'-quinazolin]-2'(3'H)-one	443.14	1.74	
7		1-(1-(4-(4-hydroxy-3,5-dimethylbenzoyl)pyridin-2-yl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one			
8		8-fluoro-3-(1-(4-(4-hydroxy-3,5-dimethylbenzoyl)pyridin-2-yl)piperidin-4-yl)-3,4-dihydroquinazolin-2(1H)-one			
9		1-(1-(4-(4-hydroxy-3,5-dimethylbenzoyl)-6-methylpyridin-2-yl)piperidin-4-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one			
10		3-(1-(4-(4-hydroxy-3,5-dimethylbenzoyl)-6-methylpyridin-2-yl)piperidin-4-yl)-3,4-dihydroquinazolin-2(1H)-one			
11		3-(1-(4-(4-hydroxy-3-methyl-5-(trifluoromethyl)benzoyl)-6-methylpyridin-2-yl)piperidin-4-yl)-3,4-dihydroquinazolin-2(1H)-one			

	<u>COMPOUND</u>	<u>NAME</u>	<u>MS</u>	<u>Ret</u> <u>Time</u>	<u>IC₅₀</u>
12		3-(1-(4-(3-chloro-4-hydroxy-5-methylbenzoyl)-6-methylpyridin-2-yl)piperidin-4-yl)-3,4-dihydroquinazolin-2(1H)-one			
13		3-(1-(4-(3-bromo-4-hydroxy-5-methylbenzoyl)-6-methylpyridin-2-yl)piperidin-4-yl)-3,4-dihydroquinazolin-2(1H)-one			
14		1-(1-(5-(4-hydroxy-3,5-dimethylbenzoyl)pyridin-2-yl)piperidin-4-yl)-4-(3-methoxyphenyl)-1H-imidazol-2(3H)-one	499.20	2.81	
15		1-(1-(5-(4-hydroxy-3,5-dimethylbenzoyl)pyridin-2-yl)piperidin-4-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	444.13	2.57	
16		1-(1-(4-(4-hydroxy-3,5-dimethylbenzoyl)-5-methylthiazol-2-yl)piperidin-4-yl)imidazolidine-2,4-dione			
17		3-(1-(4-(4-hydroxy-3,5-dimethylbenzoyl)-5-methylthiazol-2-yl)piperidin-4-yl)-3,4-dihydroquinazolin-2(1H)-one			
18		1-(1-(4-(4-hydroxy-3,5-dimethylbenzoyl)-5-methylthiazol-2-yl)piperidin-4-yl)-4-(3-methoxyphenyl)-1H-imidazol-2(3H)-one			

	COMPOUND	NAME	MS	Ret Time	IC ₅₀
19		3-(1-(4-(4-hydroxy-3,5-dimethylbenzoyl)-5-methylthiazol-2-yl)piperidin-4-yl)-4,5-dihydro-1H-benzo[d][1,3]diazepin-2(3H)-one			
20		3-(1-(5-methyl-4-(7-methyl-1H-indazole-5-carbonyl)thiazol-2-yl)piperidin-4-yl)-4,5-dihydro-1H-benzo[d][1,3]diazepin-2(3H)-one			
21		3-(1-(4-(4-hydroxy-3,5-dimethylbenzoyl)-6-(methylamino)pyridin-2-yl)piperidin-4-yl)-3,4-dihydroquinazolin-2(1H)-one			
22		1-(1-(6-(dimethylamino)-4-(4-hydroxy-3,5-dimethylbenzoyl)pyridin-2-yl)piperidin-4-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one			
23		1-(1-(4-(4-hydroxy-3,5-dimethylbenzoyl)-6-(methoxymethyl)pyridin-2-yl)piperidin-4-yl)-4-(3-methoxyphenyl)-1H-imidazol-2(3H)-one			
24		1-(1-(4-(4-hydroxy-3,5-dimethylbenzoyl)-6-(hydroxymethyl)pyridin-2-yl)piperidin-4-yl)-4-(3-methoxyphenyl)-1H-imidazol-2(3H)-one			
25		1-(1-(6-((dimethylamino)methyl)-4-(4-hydroxy-3,5-dimethylbenzoyl)pyridin-2-yl)piperidin-4-yl)-4-(3-methoxyphenyl)-1H-imidazol-2(3H)-one			

	COMPOUND	NAME	MS	Ret Time	IC ₅₀
26		2-(1-(4-(4-hydroxy-3,5-dimethylbenzoyl)pyridin-2-yl)piperidin-4-yl)-5-(3-methoxyphenyl)-2H-1,2,4-triazol-3(4H)-one			
27		2-(1-(4-(4-hydroxy-3,5-dimethylbenzoyl)-6-methylpyridin-2-yl)piperidin-4-yl)-5-(3-methoxyphenyl)-2H-1,2,4-triazol-3(4H)-one			
28		2-(1-(6-(dimethylamino)-4-(4-hydroxy-3,5-dimethylbenzoyl)pyridin-2-yl)piperidin-4-yl)-5-(3-methoxyphenyl)-2H-1,2,4-triazol-3(4H)-one			
29		2-(1-(4-(4-hydroxy-3,5-dimethylbenzoyl)pyridin-2-yl)piperidin-4-yl)-5-phenyl-2H-1,2,4-triazol-3(4H)-one			
30		2-(1-(4-(4-hydroxy-3,5-dimethylbenzoyl)-6-methylpyridin-2-yl)piperidin-4-yl)-5-phenyl-2H-1,2,4-triazol-3(4H)-one			
31		2-(1-(6-(dimethylamino)-4-(4-hydroxy-3,5-dimethylbenzoyl)pyridin-2-yl)piperidin-4-yl)-5-phenyl-2H-1,2,4-triazol-3(4H)-one			
32		2-(1-(5-(4-hydroxy-3,5-dimethylbenzoyl)pyridin-2-yl)piperidin-4-yl)-5-(3-methoxyphenyl)-2H-1,2,4-triazol-3(4H)-one	500.14	1.79	

	<u>COMPOUND</u>	<u>NAME</u>	<u>MS</u>	<u>Ret Time</u>	<u>IC₅₀</u>
33		2-(1-(5-(4-hydroxy-3,5-dimethylbenzoyl)pyridin-2-yl)piperidin-4-yl)-5-phenyl-2H-1,2,4-triazol-3(4H)-one			
34		3-{1-[5-(4-hydroxy-3,5-dimethylbenzoyl)pyridin-2-yl]piperidin-4-yl}-3,4-dihydroquinazolin-2(1H)-one	457.17	1.24	

EXAMPLE 4. PREPARATION OF CGRP RECEPTOR-TRANSFECTED CELLS

This Example illustrates the preparation of CGRP receptor-transfected cells for use in CGRP receptor calcium mobilization assays (Example 5).

- 5 Complementary DNAs encoding the human receptor activity-modify protein 1 (hRAMP-1; GenBank #NM_005855) and human calcitonin receptor-like receptor (hCRLR; GenBank #NM_005795) are cloned in the pCDNA3 IRES mammalian expression vector (Invitrogen Corporation, Carlsbad, CA). The hCRLR is subcloned into the plasmid 5' of the IRES element and the hRAMP-1 is subcloned into the plasmid 3' of the IRES element. This plasmid is
- 10 transfected into HEK293 cells that stably express recombinant rat olfactory cyclic nucleotide gated channel subunit 1 (GenBank # X55519) and rat olfactory cyclic nucleotide gated channel subunit 2 (GenBank #U12623), thus generating cells that take up extracellular calcium via the rat olfactory cyclic nucleotide gated channel in response to increased intracellular cyclic AMP. A clonal cell line stably expressing human CGRP receptor is selected by neomycin resistance and
- 15 by a calcium mobilization assay using calcium sensitive fluorescent dye as detailed below.

EXAMPLE 5. CALCIUM MOBILIZATION ASSAY

This Example illustrates representative calcium mobilization assays for use in evaluating test compounds for agonist and antagonist activity at CGRP receptor.

- 20 The day prior to the experiment, cells expressing CGRP receptor are plated at a density of 25,000 cells/well in 384 well PDL coated BD Falcon plates. On the day of the experiment, the media is removed and 25 μ L of 2.3 μ M Fluo-4 AM dye (TEF Labs, Inc., Austin, TX) in KRH buffer (5 mM KCl, 115 mM NaCl, 960 μ M MgH_2PO_4 , 1 mM MgSO_4 , 2 mM CaCl_2 , 5 mM glucose, 25 mM HEPES, 1 mM probenecid) is added. Plates are incubated at 37 $^\circ\text{C}$, 5% CO_2 for

1 hour. Wells are then washed with 50 μ L KRH buffer. Wash buffer is removed and 25 μ L fresh KRH is added to each well. Plates are incubated for 1 hour at room temperature, after which 25 μ L of KRH and test compound (100X final concentration) in DMSO or KRH and DMSO is transferred into the appropriate wells. Test compounds are tested in serial dilutions from 10 μ M, 4 μ M, 1 μ M, or 0.1 μ M stocks; for positive control cells, no test compound is added. The plates are incubated for an additional 1 hour at room temperature, and then transferred to a FLIPR384 instrument (Molecular Devices, Sunnyvale, CA) for calcium mobilization analysis.

For determination of antagonist activity, activating agonist (25 μ L of KRH containing CGRP) is transferred using the FLIPR into the plate, such that the final CGRP concentration is the EC_{50} for the CGRP-mediated response in these cells (1.6 nM CGRP). In negative control cells, 25 μ L of KRH without CGRP is added at this stage. Fluorescence is monitored for at least 4 minutes. The data is analyzed as follows. First, the average maximum relative fluorescent unit (RFU) response from the negative control wells (no CGRP) is subtracted from the maximum response detected for each of the other experimental wells. Second, average maximum RFU response is calculated for the agonist response to CGRP in the positive control wells (agonist wells). Then, percent inhibition for each compound tested is calculated using the equation:

$$\% \text{ inhibition} = \left[1 - \frac{(\text{agonist RFU response} + \text{compound RFU response})}{(\text{agonist RFU response})} \right] \times 100$$

The % inhibition data is plotted as a function of test compound concentration and test compound IC_{50} is determined using, for example, KALEIDAGRAPH software (Synergy Software, Reading, PA) best fit of the data to the equation:

$$y = m_1 * (1 / (1 + (m_2 / m_0)^{m_3}))$$

where y is the percent inhibition, m_0 is the concentration of the agonist (CGRP), m_1 is the maximum RFU, m_2 corresponds to the test compound IC_{50} (the concentration required to provide a 50% decrease, relative to the response observed in the presence of CGRP and without antagonist) and m_3 is the Hill coefficient. Antagonists of the CGRP receptor decrease the response induced by CGRP alone (in the absence of test compound) by at least about 20%, preferably by at least about 50%, and most preferably by at least 80%, at a concentration of 10 micromolar or less, preferably 4 micromolar or less, and more preferably 1 micromolar or less. The IC_{50} such antagonists is preferably below 1 micromolar, 100 nanomolar, 10 nanomolar or 1 nanomolar.

Similar assays are performed in the absence of added CGRP for the determination of agonist activity of the test compounds. Within such assays, the ability of a test compound to act

as an agonist of CGRP receptor is determined by measuring the fluorescence response elicited by the test compound as a function of compound concentration. CGRP receptor antagonists that exhibit no detectable agonist activity elicit no detectable fluorescence at concentrations of 100 nanomolar, or 1, 4 or 10 micromolar.

5

EXAMPLE 6. MDCK CYTOTOXICITY ASSAY

This Example illustrates the evaluation of compound toxicity using a Madin Darby canine kidney (MDCK) cell cytotoxicity assay.

1 μ L of test compound is added to each well of a clear bottom 96-well plate (Packard, Meriden, CT) to give final concentration of compound in the assay of 10 μ M, 100 μ M or 200 μ M. Solvent without test compound is added to control wells.

MDCK cells, ATCC no. CCL-34 (American Type Culture Collection, Manassas, VA), are maintained in sterile conditions following the instructions in the ATCC production information sheet. Confluent MDCK cells are trypsinized, harvested, and diluted to a concentration of 0.1×10^6 cells/mL with warm (37°C) medium (VITACELL Minimum Essential Medium Eagle, ATCC catalog # 30-2003). 100 μ L of diluted cells is added to each well, except for five standard curve control wells that contain 100 μ L of warm medium without cells. The plate is then incubated at 37°C under 95% O₂, 5% CO₂ for 2 hours with constant shaking. After incubation, 50 μ L of mammalian cell lysis solution (from the Packard ATP-LITE-M Luminescent ATP detection kit) is added per well, the wells are covered with PACKARD TOPSEAL stickers, and plates are shaken at approximately 700 rpm on a suitable shaker for 2 min.

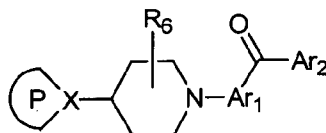
Compounds causing toxicity will decrease ATP production, relative to untreated cells. The ATP-LITE-M Luminescent ATP detection kit is generally used according to the manufacturer's instructions to measure ATP production in treated and untreated MDCK cells. PACKARD ATP LITE-M reagents are allowed to equilibrate to room temperature. Once equilibrated, the lyophilized substrate solution is reconstituted in 5.5 mL of substrate buffer solution (from kit). Lyophilized ATP standard solution is reconstituted in deionized water to give a 10 mM stock. For the five control wells, 10 μ L of serially diluted PACKARD standard is added to each of the standard curve control wells to yield a final concentration in each subsequent well of 200 nM, 100 nM, 50 nM, 25 nM, and 12.5 nM. PACKARD substrate solution (50 μ L) is added to all wells, which are then covered, and the plates are shaken at approximately 700 rpm on a suitable shaker for 2 min. A white PACKARD sticker is attached to the bottom of each plate and samples are dark adapted by wrapping plates in foil and placing in

the dark for 10 min. Luminescence is then measured at 22°C using a luminescence counter (*e.g.*, PACKARD TOPCOUNT Microplate Scintillation and Luminescence Counter or TECAN SPECTRAFLUOR PLUS), and ATP levels calculated from the standard curve. ATP levels in cells treated with test compound(s) are compared to the levels determined for untreated cells.

- 5 Cells treated with 10 μ M of a preferred test compound exhibit ATP levels that are at least 80%, preferably at least 90%, of the untreated cells. When a 100 μ M concentration of the test compound is used, cells treated with preferred test compounds exhibit ATP levels that are at least 50%, preferably at least 80%, of the ATP levels detected in untreated cells.

What is Claimed:

1. A compound of formula:



5 or a pharmaceutically acceptable salt or hydrate thereof, wherein:



is a 5- or 6-membered heterocyclic ring, wherein X is C, CH, or N, such that the heterocyclic ring:

(a) comprises at least one ring nitrogen atom;

(b) is substituted with oxo;

10 (c) is optionally substituted with C₁-C₄alkyl; and

(d) is:

(i) substituted with a phenyl or 5- or 6-membered heteroaryl substituent; or

(ii) fused to a phenyl or 5- or 6-membered heterocyclic ring;

each of which (i) and (ii) is substituted with from 0 to 4 substituents

15 independently chosen from halogen, hydroxy, cyano, amino, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₆alkoxy, and mono- or di-(C₁-C₆alkyl)aminoC₀-C₄alkyl;

Ar₁ is phenyl or a 5- or 6-membered heteroaryl, each of which is substituted with from 0 to 3 substituents independently chosen from R_A;

20 Each R_A is independently chosen from:

(i) halogen, hydroxy, cyano and amino;

(ii) C₁-C₆alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, and (4- to 7-membered heterocycle)C₀-C₄alkyl; each of which is substituted with from 0 to 2 substituents

25 independently chosen from halogen, hydroxy, amino, C₁-C₄alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl and (4- to 10-membered heterocycle)C₀-C₄alkyl; and

(iii) substituents that are taken together to form a fused 5- to 7-membered carbocycle or heterocycle that is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, C₁-C₆alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, and (4- to 7-membered heterocycle)C₀-C₄alkyl;

30

Ar₂ is phenyl or a 5- or 6-membered heteroaryl, each of which is substituted with from 0 to 5 substituents independently chosen from:

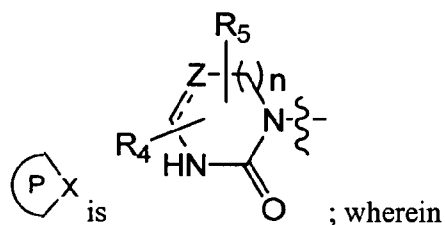
(i) halogen, hydroxy, cyano, amino, aminocarbonyl and aminosulfonyl;

(ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈haloalkyl, C₁-C₈hydroxyalkyl, C₂-C₈alkyl ether, C₁-C₈alkoxy, C₁-C₈alkoxycarbonyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, mono- or di-(C₁-C₈alkyl)aminoC₀-C₄alkyl, phenylC₀-C₄alkyl and (4- to 12-membered heterocycle)C₀-C₄alkyl; each of which is substituted with from 0 to 6 substituents independently chosen from hydroxy, oxo, halogen, amino, aminocarbonyl, aminosulfonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkylthio, C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl, C₁-C₆alkylsulfinyl, C₁-C₆alkoxycarbonyl, mono- or di-(C₁-C₆alkyl)aminocarbonyl, and mono- or di-(C₁-C₆alkyl)aminosulfonyl; and

(iii) substituents that are taken together to form a fused 5- to 7-membered carbocycle or heterocycle that is substituted with from 0 to 4 substituents independently chosen from C₁-C₆alkyl; and

R₆ represents from 0 to 4 substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy and C₁-C₆alkyl ether.

2. The compound or salt of hydrate thereof according to claim 1 wherein:



X is N;

Z is C, CH, CH₂, N or NH;

n is 0, 1 or 2;

R₄ represents zero substituents or:

(i) oxo;

(ii) a phenyl or 5- or 6-membered heteroaryl substituent; or

(iii) a fused phenyl or 5- or 6-membered heterocyclic ring;

each of which (ii) and (iii) is substituted with from 0 to 4 substituents independently chosen from:

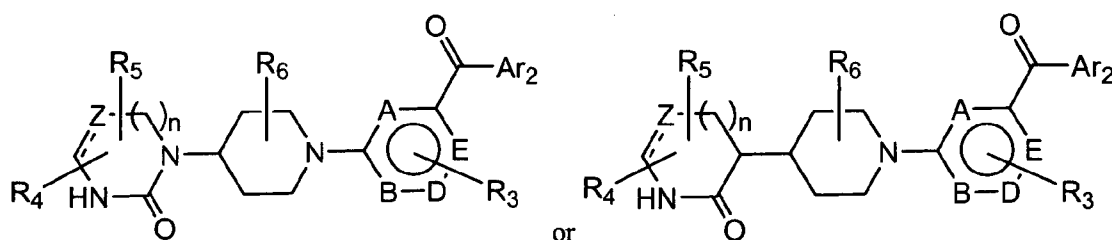
(a) halogen, hydroxy, cyano, amino and oxo; and

- (b) C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, mono- or di-(C₁-C₆alkyl)aminoC₀-C₄alkyl, and (4- to 10-membered heterocycle)C₀-C₄alkyl; each of which is substituted with from 0 to 4 substituents independently chosen from hydroxy, oxo, halogen, amino, aminocarbonyl, aminosulfonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkylthio, C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl, C₁-C₆alkylsulfinyl, C₁-C₆alkoxycarbonyl, mono- or di-(C₁-C₆alkyl)aminocarbonyl, and mono- or di-(C₁-C₆alkyl)aminosulfonyl; and
- 10 R₅ represents from 0 to 4 substituents independently chosen from C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, and (C₃-C₈cycloalkyl)C₀-C₄alkyl.

3. The compound or salt or hydrate thereof according to claim 1, wherein Ar₁ is a 6-membered heteroaryl that is substituted with from 0 to 3 substituents independently chosen from R_A.

4. The compound or salt or hydrate thereof according to claim 3, wherein Ar₁ is pyridyl or pyrimidyl, each of which is substituted with from 0 to 3 substituents independently chosen from R_A.

5. The compound or salt or hydrate thereof according to claim 3, wherein the compound has the formula:



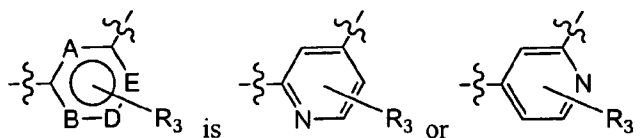
wherein:

A, B, D and E are each C, CH or N, such that exactly one or two of A, B, D and E are N; and R₃ represents from 0 to 3 substituents independently chosen from:

- (i) halogen, hydroxy, cyano and amino; and
- (ii) C₁-C₆alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, and (4- to 7-membered heterocycle)C₀-C₄alkyl; each of which is substituted with from 0 to 2 substituents

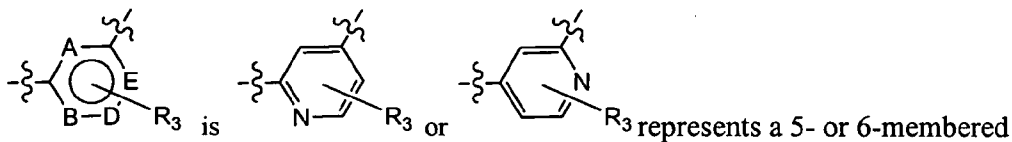
independently chosen from halogen, hydroxy, amino, C₁-C₄alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl and (4- to 10-membered heterocycle)C₀-C₄alkyl;
 or two substituents represented by R₃ are taken together to form a fused 5- to 7-membered carbocycle or heterocycle that is substituted with from 0 to 3 substituents independently
 5 chosen from halogen, hydroxy, amino, C₁-C₆alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, and (4- to 7-membered heterocycle)C₀-C₄alkyl;

6. The compound or salt or hydrate thereof according to claim 5, wherein:



10 7. The compound or salt or hydrate thereof according to claim 5 or claim 6, wherein R₃ represents from 0 to 2 substituents independently chosen from halogen, C₁-C₄alkyl, C₁-C₄alkoxy, C₂-C₄alkyl ether and mono- or di-(C₁-C₄alkyl)amino.

8. The compound or salt or hydrate thereof according to claim 6, wherein:

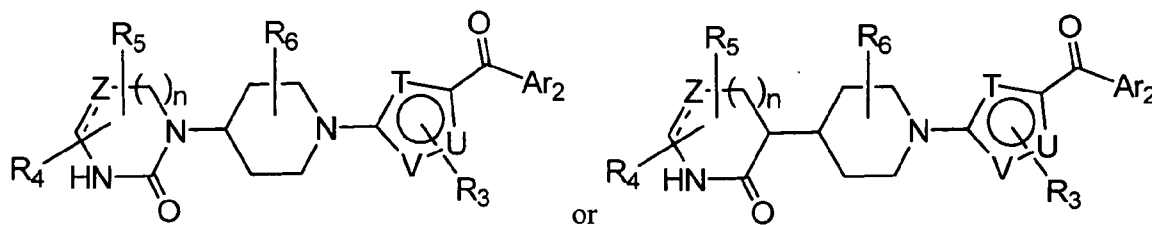


15 carbocycle or heterocycle, each of which is substituted with from 0 to 4 substituents independently chosen from halogen, hydroxy, amino, C₁-C₆alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, and (4- to 7-membered heterocycle)C₀-C₄alkyl.

20 9. The compound or salt or hydrate thereof according to claim 1, wherein Ar₁ is a 5-membered heteroaryl that is substituted with from 0 to 2 substituents independently chosen from R_A.

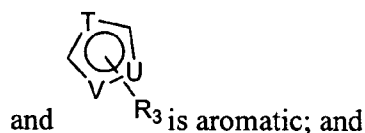
10. The compound or salt or hydrate thereof according to claim 9, wherein Ar₁ is thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl or triazolyl, each of which is substituted with from 0 to 2 substituents independently chosen from R_A.

11. The compound or salt or hydrate thereof according to claim 9, wherein the compound has the formula:



wherein:

- 5 T, U and V are independently C, CH, N, NH, S and O, such that at least one of T, U and V is N;



R_3 represents from 0 to 2 substituents independently chosen from:

- (i) halogen, hydroxy, cyano and amino; and
- (ii) C_1 - C_6 alkyl, $(\text{C}_3$ - C_8 carbocycle) C_0 - C_4 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkyl ether, mono- or di- $(\text{C}_1$ - C_6 alkyl)amino C_0 - C_2 alkyl, and (4- to 7-membered heterocycle) C_0 - C_4 alkyl; each of which is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, amino, C_1 - C_4 alkyl, $(\text{C}_3$ - C_8 carbocycle) C_0 - C_4 alkyl and (4- to 10-membered heterocycle) C_0 - C_4 alkyl;
- or two substituents represented by R_3 are taken together to form a fused 5- to 7-membered carbocycle or heterocycle that is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, C_1 - C_6 alkyl, $(\text{C}_3$ - C_8 carbocycle) C_0 - C_4 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkyl ether, mono- or di- $(\text{C}_1$ - C_6 alkyl)amino C_0 - C_2 alkyl, and (4- to 7-membered heterocycle) C_0 - C_4 alkyl.

12. The compound or salt or hydrate thereof according to claim 11, wherein exactly one of T, U and V is CH.

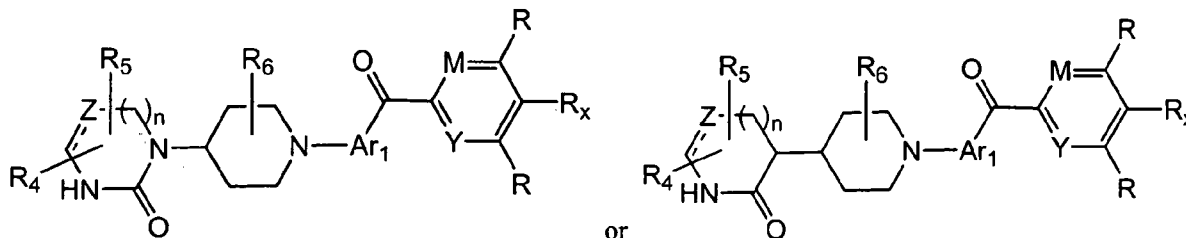
13. The compound or salt or hydrate thereof according to claim 11 or claim 12, wherein R_3 represents from 0 to 2 substituents independently chosen from halogen, C_1 - C_4 alkyl, C_2 - C_4 alkyl ether and mono- or di- $(\text{C}_1$ - C_4 alkyl)amino.

14. The compound or salt or hydrate thereof according to any one of claims 1-13, wherein Ar_2 is phenyl, pyridyl or pyrimidinyl, each of which is substituted with from 0 to 5 substituents independently chosen from:

- (i) halogen, hydroxy, cyano, amino, aminocarbonyl and aminosulfonyl;
 (ii) C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, mono- or di-(C₁-C₆alkyl)aminoC₀-C₄alkyl, phenyl, and 4- to 7-membered heterocycle; each of which is substituted with from 0 to 4 substituents independently chosen from hydroxy, oxo, halogen, amino, aminocarbonyl, aminosulfonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkylthio, C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl, C₁-C₆alkylsulfinyl, C₁-C₆alkoxycarbonyl, mono- or di-(C₁-C₆alkyl)aminocarbonyl, and mono- or di-(C₁-C₆alkyl)aminosulfonyl; and
 (iii) substituents that are taken together to form a fused 5- or 6-membered carbocycle or heterocycle.

15. The compound or salt or hydrate thereof according to claim 14, wherein Ar₂ is optionally substituted phenyl, pyridyl, pyrimidinyl, naphthyl, indanyl, indenyl, indolyl, indazolyl, benzimidazolyl, quinolinyl, quinazolinyl or naphthyridinyl.

16. The compound or salt or hydrate thereof according to claim 14, wherein the compound has the formula:



wherein:

M and Y are independently CH or N;

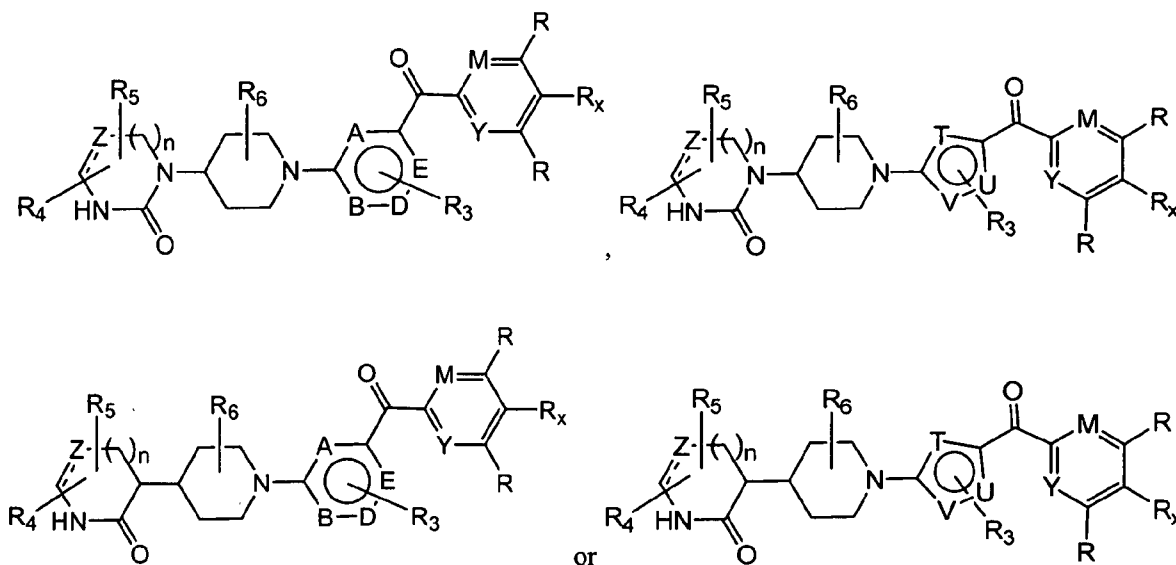
R_x is (i) halogen, hydroxy, cyano, amino, aminocarbonyl and aminosulfonyl; or (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈haloalkyl, C₁-C₈hydroxyalkyl, C₂-C₈alkyl ether, C₁-C₈alkoxy, C₁-C₈alkoxycarbonyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, mono- or di-(C₁-C₈alkyl)aminoC₀-C₄alkyl, phenylC₀-C₄alkyl and (4- to 12-membered heterocycle)C₀-C₄alkyl; each of which is substituted with from 0 to 6 substituents independently chosen from hydroxy, oxo, halogen, amino, aminocarbonyl, aminosulfonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkylthio, C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl, C₁-C₆alkylsulfinyl, C₁-C₆alkoxycarbonyl, mono- or di-(C₁-C₆alkyl)aminocarbonyl, and mono- or di-(C₁-C₆alkyl)aminosulfonyl; and

each R is independently (i) hydrogen, halogen, hydroxy, cyano, amino, aminocarbonyl and aminosulfonyl; or (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈haloalkyl, C₁-C₈hydroxyalkyl, C₂-C₈alkyl ether, C₁-C₈alkoxy, C₁-C₈alkoxycarbonyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, mono- or di-(C₁-C₈alkyl)aminoC₀-C₄alkyl, phenylC₀-C₄alkyl and (4- to 12-membered heterocycle)C₀-C₄alkyl; each of which is substituted with from 0 to 6 substituents independently chosen from hydroxy, oxo, halogen, amino, aminocarbonyl, aminosulfonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkylthio, C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl, C₁-C₆alkylsulfinyl, C₁-C₆alkoxycarbonyl, mono- or di-(C₁-C₆alkyl)aminocarbonyl, and mono- or di-(C₁-C₆alkyl)aminosulfonyl.

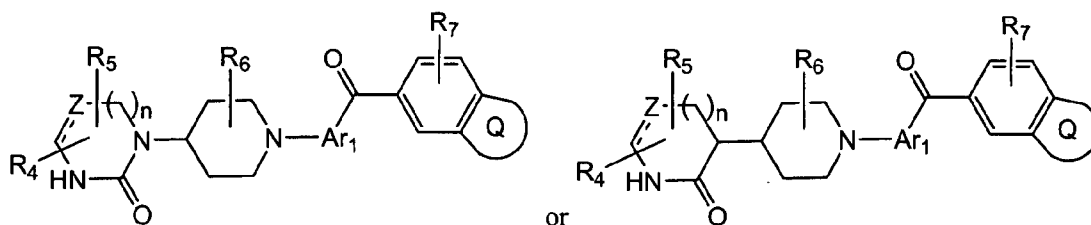
17. The compound or salt or hydrate thereof according to claim 16, wherein R_x is halogen, hydroxy, cyano, amino, aminocarbonyl and aminosulfonyl C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈haloalkyl, C₁-C₈hydroxyalkyl, C₂-C₈alkyl ether, C₁-C₈alkoxy, C₁-C₈alkoxycarbonyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, or mono- or di-(C₁-C₈alkyl)aminoC₀-C₄alkyl.

18. The compound or salt or hydrate thereof according to claim 17, wherein R_x is hydroxy or C₁-C₈alkoxy and each R is C₁-C₆alkyl.

19. The compound or salt or hydrate thereof according to claim 16, wherein the compound has the formula:



20. The compound or salt or hydrate thereof according to claim 14, wherein the compound has the formula:



wherein:

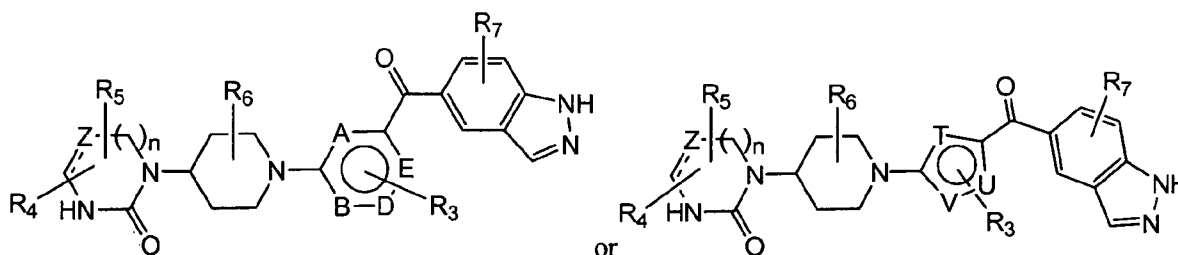
R₇ represents from 0 to 3 substituents independently chosen from:

- (i) halogen, hydroxy and amino; and
- 5 (ii) C₁-C₆alkyl, C₁-C₆alkoxy, mono- or di-(C₁-C₆alkyl)amino, C₁-C₆alkoxycarbonyl, C₂-C₆alkyl ether, phenyl and 4- to 7-membered heterocycle, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, amino, oxo, C₁-C₄alkyl, C₁-C₄alkoxy and mono- or di-(C₁-C₄alkyl)amino; and



is a 5- or 6-membered heterocycle that is optionally substituted with C₁-C₄alkyl.

- 10 21. The compound or salt or hydrate thereof according to claim 20, wherein the compound has the formula:



wherein:

A, B, D and E are each C, CH or N, such that exactly one or two of A, B, D and E are N;

- 15 T, U and V are independently CH, N, NH, S and O, such that at least one of T, U and V is N;



exactly one of T, U and V is CH; and is aromatic; and

R₃ represents from 0 to 3 substituents independently chosen from:

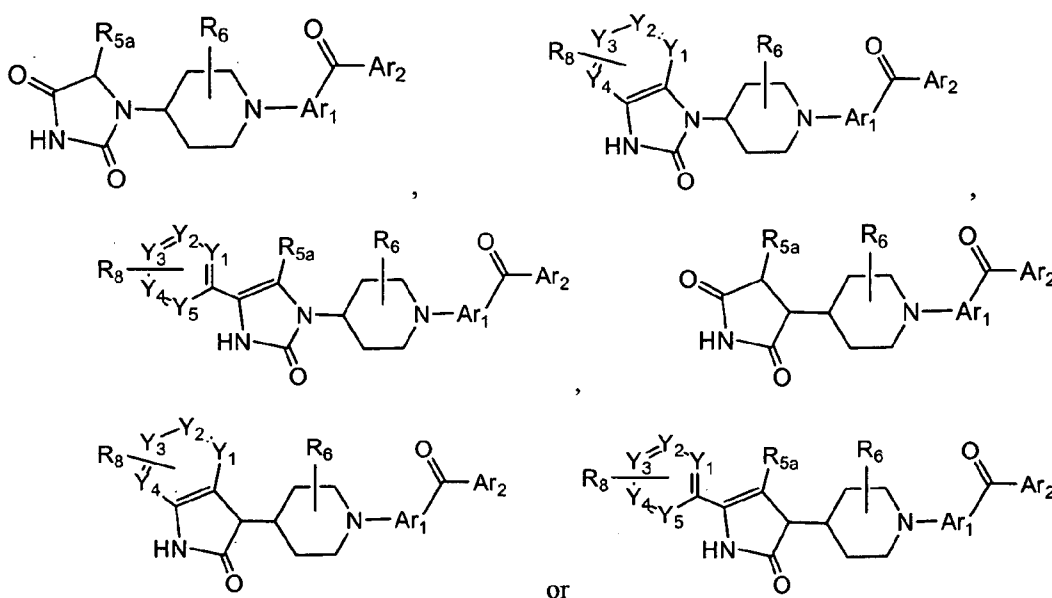
- (i) halogen, hydroxy, cyano and amino; and
- 20 (ii) C₁-C₆alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, and (4- to 7-membered heterocycle)C₀-C₄alkyl; each of which is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, amino, C₁-C₄alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl and (4- to 10-membered heterocycle)C₀-C₄alkyl;

or two substituents represented by R_3 are taken together to form a fused 5- to 7-membered carbocycle or heterocycle that is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, C_1 - C_6 alkyl, (C_3 - C_8 carbocycle) C_0 - C_4 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkyl ether, mono- or di-(C_1 - C_6 alkyl)amino C_0 - C_2 alkyl, and (4- to 7-membered heterocycle) C_0 - C_4 alkyl.

22. The compound or salt or hydrate thereof according to claim 20 or claim 21, wherein R_7 represents one or two methyl substituents.

23. The compound or salt or hydrate thereof according to any one of claims 2-22, wherein n is 0.

24. The compound or salt or hydrate thereof according to claim 23, wherein the compound has the formula:



wherein:

Y_1, Y_2, Y_3, Y_4 and Y_5 are independently C, N, or CH;

R_{5a} is hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl or (C_3 - C_8 cycloalkyl) C_0 - C_4 alkyl; and

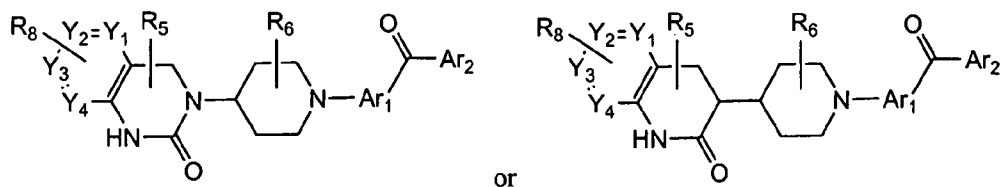
R_8 represents from 0 to 4 substituents independently chosen from halogen, hydroxy, cyano,

amino, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, (C_3 - C_8 cycloalkyl) C_0 - C_4 alkyl, C_1 -

C_6 alkoxy, and mono- or di-(C_1 - C_6 alkyl)amino C_0 - C_4 alkyl.

25. The compound or salt or hydrate thereof according to any one of claims 2-22, wherein n is 1.

26. The compound or salt or hydrate thereof according to claim 25, wherein the compound has the formula:

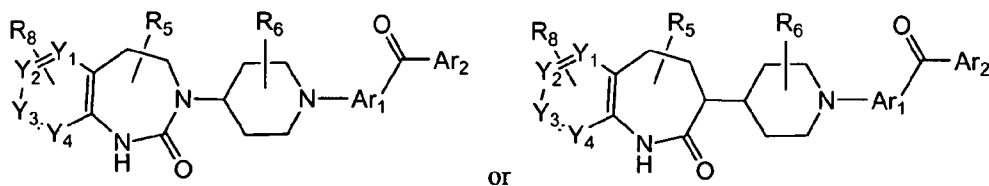


wherein:

- 5 Y_1, Y_2, Y_3 and Y_4 are independently C, N or CH; and
 R_8 represents from 0 to 4 substituents independently chosen from halogen, hydroxy, cyano, amino, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $(C_3$ - C_8 cycloalkyl) C_0 - C_4 alkyl, C_1 - C_6 alkoxy, and mono- or di- $(C_1$ - C_6 alkyl)amino C_0 - C_4 alkyl.

27. The compound or salt or hydrate thereof according to any one of claims 2-22, wherein n
 10 is 2.

28. The compound or salt or hydrate thereof according to claim 27, wherein the compound has the formula:

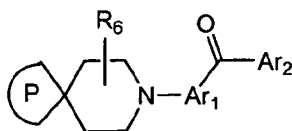


wherein:

- 15 Y_1, Y_2, Y_3 and Y_4 are independently C, N or CH; and
 R_8 represents from 0 to 4 substituents independently chosen from halogen, hydroxy, cyano, amino, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $(C_3$ - C_8 cycloalkyl) C_0 - C_4 alkyl, C_1 - C_6 alkoxy, and mono- or di- $(C_1$ - C_6 alkyl)amino C_0 - C_4 alkyl.

29. The compound or salt or hydrate thereof according to any one of claims 1-27, wherein R_5
 20 and R_6 each represent 0 substituents.

30. A compound of the formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:



is a 5- or 6-membered heterocycle that:

- (a) comprises at least one ring nitrogen atom;
- (b) is substituted with oxo;
- (c) is optionally substituted with C₁-C₄alkyl; and
- (d) is:

- (i) substituted with a phenyl or 5- or 6-membered heteroaryl substituent; or
- (ii) fused to a phenyl or 5- or 6-membered heterocyclic ring;

each of which (i) and (ii) is substituted with from 0 to 4 substituents

independently chosen from halogen, hydroxy, cyano, amino, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₆alkoxy, and mono- or di-(C₁-C₆alkyl)aminoC₀-C₄alkyl;

Ar₁ is phenyl or a 5- or 6-membered heteroaryl, each of which is substituted with from 0 to 3 substituents independently chosen from R_A;

Each R_A is independently chosen from:

- (i) halogen, hydroxy, cyano and amino;
- (ii) C₁-C₆alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, and (4- to 7-membered heterocycle)C₀-C₄alkyl; each of which is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, amino, C₁-C₄alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl and (4- to 10-membered heterocycle)C₀-C₄alkyl; and
- (iii) substituents that are taken together to form a fused 5- to 7-membered carbocycle or heterocycle that is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, C₁-C₆alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, and (4- to 7-membered heterocycle)C₀-C₄alkyl;

Ar₂ is phenyl or a 5- or 6-membered heteroaryl, each of which is substituted with from 0 to 5 substituents independently chosen from:

- (i) halogen, hydroxy, cyano, amino, aminocarbonyl and aminosulfonyl;
- (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈haloalkyl, C₁-C₈hydroxyalkyl, C₂-C₈alkyl ether, C₁-C₈alkoxy, C₁-C₈alkoxycarbonyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, mono- or di-(C₁-C₈alkyl)aminoC₀-C₄alkyl, phenylC₀-C₄alkyl and (4- to 12-membered heterocycle)C₀-C₄alkyl; each of which is substituted with from 0 to 6 substituents independently chosen from hydroxy, oxo, halogen, amino,

aminocarbonyl, aminosulfonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkylthio, C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl, C₁-C₆alkylsulfinyl, C₁-C₆alkoxycarbonyl, mono- or di-(C₁-C₆alkyl)aminocarbonyl, and mono- or di-(C₁-C₆alkyl)aminosulfonyl; and

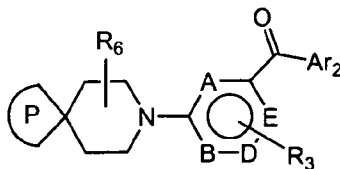
- 5 (iii) substituents that are taken together to form a fused 5- to 7-membered carbocycle or heterocycle that is substituted with from 0 to 4 substituents independently chosen from C₁-C₆alkyl; and

R₆ represents from 0 to 4 substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy and C₁-C₆alkyl ether.

- 10 31. The compound or salt or hydrate thereof according to claim 30, wherein Ar₁ is a 6-membered heteroaryl that is substituted with from 0 to 3 substituents independently chosen from R_A.

32. The compound or salt or hydrate thereof according to claim 31, wherein Ar₁ is pyridyl or pyrimidyl, each of which is substituted with from 0 to 3 substituents independently chosen from R_A.

33. The compound or salt or hydrate thereof according to claim 32, wherein the compound has the formula:



wherein:

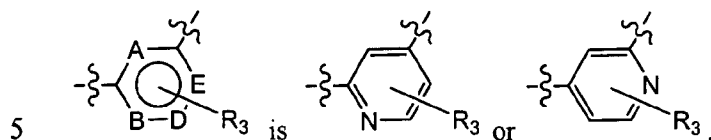
- 20 A, B, D and E are each CH or N, such that exactly one or two of A, B, D and E are N; and R₃ represents from 0 to 3 substituents independently chosen from:

(i) halogen, hydroxy, cyano and amino; and

- (ii) C₁-C₆alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, and (4- to 7-membered heterocycle)C₀-C₄alkyl; each of which is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, amino, C₁-C₄alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl and (4- to 10-membered heterocycle)C₀-C₄alkyl; or two substituents represented by R₃ are taken together to form a fused 5- to 7-membered carbocycle or heterocycle that is substituted with from 0 to 3 substituents independently

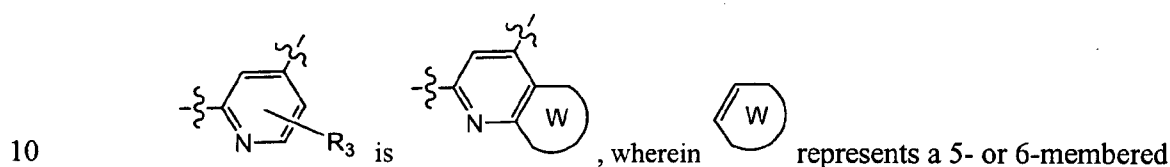
chosen from halogen, hydroxy, amino, C₁-C₆alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, and (4- to 7-membered heterocycle)C₀-C₄alkyl.

34. The compound or salt or hydrate thereof according to claim 33, wherein:



35. The compound or salt or hydrate thereof according to any one of claims 30-34, wherein R₃ represents from 0 to 2 substituents independently chosen from halogen, C₁-C₄alkyl, C₁-C₄alkoxy, C₂-C₄alkyl ether and mono- or di-(C₁-C₄alkyl)amino.

36. The compound or salt or hydrate thereof according to claim 34, wherein:

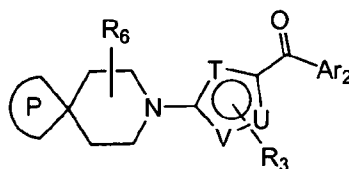


carbocycle or heterocycle, each of which is substituted with from 0 to 4 substituents independently chosen from halogen, hydroxy, amino, C₁-C₆alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, and (4- to 7-membered heterocycle)C₀-C₄alkyl.

15 37. The compound or salt or hydrate thereof according to claim 30, wherein Ar₁ is a 5-membered heteroaryl that is substituted with from 0 to 2 substituents independently chosen from R_A.

20 38. The compound or salt or hydrate thereof according to claim 37, wherein Ar₁ is thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl or triazolyl, each of which is substituted with from 0 to 2 substituents independently chosen from R_A.

39. The compound or salt or hydrate thereof according to claim 38, wherein the compound has the formula:



wherein

T, U and V are independently CH, N, NH, S and O, such that at least one of T, U and V is N;



exactly one of T, U and V is CH; and R_3 is aromatic; and

5 R_3 represents from 0 to 2 substituents independently chosen from:

(i) halogen, hydroxy, cyano and amino; and

(ii) C_1 - C_6 alkyl, (C_3 - C_8 carbocycle) C_0 - C_4 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkyl ether, mono- or di- $(C_1$ - C_6 alkyl)amino C_0 - C_2 alkyl, and (4- to 7-membered heterocycle) C_0 - C_4 alkyl; each of which is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, amino, C_1 - C_4 alkyl, (C_3 - C_8 carbocycle) C_0 - C_4 alkyl and (4- to 10-membered heterocycle) C_0 - C_4 alkyl;

or two substituents represented by R_3 are taken together to form a fused 5- to 7-membered carbocycle or heterocycle that is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, C_1 - C_6 alkyl, (C_3 - C_8 carbocycle) C_0 - C_4 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkyl ether, mono- or di- $(C_1$ - C_6 alkyl)amino C_0 - C_2 alkyl, and (4- to 7-membered heterocycle) C_0 - C_4 alkyl.

40. The compound or salt or hydrate thereof according to claim 39, wherein exactly one of T, U and V is CH.

41. The compound or salt or hydrate thereof according to any one of claims 33, 34, 40 and 39, wherein R_3 represents from 0 to 2 substituents independently chosen from halogen, C_1 - C_4 alkyl, C_2 - C_4 alkyl ether and mono- or di- $(C_1$ - C_4 alkyl)amino.

42. The compound or salt or hydrate thereof according to any one of claims 29-40, wherein Ar_2 is phenyl, pyridyl or pyrimidinyl, each of which is substituted with from 0 to 5 substituents independently chosen from:

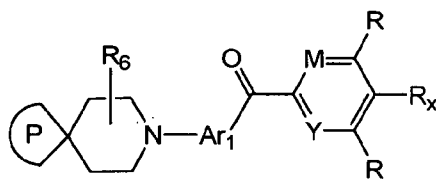
(i) halogen, hydroxy, cyano, amino, aminocarbonyl and aminosulfonyl;

(ii) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkyl ether, C_1 - C_6 alkoxy, C_1 - C_6 alkoxycarbonyl, (C_3 - C_8 cycloalkyl) C_0 - C_4 alkyl,

mono- or di-(C₁-C₆alkyl)aminoC₀-C₄alkyl, phenyl and 4- to 7-membered heterocycle; each of which is substituted with from 0 to 4 substituents independently chosen from hydroxy, oxo, halogen, amino, aminocarbonyl, aminosulfonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkylthio, C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl, C₁-C₆alkylsulfinyl, C₁-C₆alkoxycarbonyl, mono- or di-(C₁-C₆alkyl)aminocarbonyl, and mono- or di-(C₁-C₆alkyl)aminosulfonyl; and (iii) substituents that are taken together to form a fused 5- or 6-membered carbocycle or heterocycle.

43. The compound or salt or hydrate thereof according to claim 42, wherein Ar₂ is optionally substituted phenyl, pyridyl, pyrimidinyl, naphthyl, indanyl, indenyl, indolyl, indazolyl, benzimidazolyl, quinolinyl, quinazolinyl or naphthyridinyl.

44. The compound or salt or hydrate thereof according to claim 43, wherein the compound has the formula:



wherein:

M and Y are independently CH or N;

R_x is (i) halogen, hydroxy, cyano, amino, aminocarbonyl and aminosulfonyl; or (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈haloalkyl, C₁-C₈hydroxyalkyl, C₂-C₈alkyl ether, C₁-C₈alkoxy, C₁-C₈alkoxycarbonyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, mono- or di-(C₁-C₈alkyl)aminoC₀-C₄alkyl, phenylC₀-C₄alkyl and (4- to 12-membered heterocycle)C₀-C₄alkyl; each of which is substituted with from 0 to 6 substituents independently chosen from hydroxy, oxo, halogen, amino, aminocarbonyl, aminosulfonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkylthio, C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl, C₁-C₆alkylsulfinyl, C₁-C₆alkoxycarbonyl, mono- or di-(C₁-C₆alkyl)aminocarbonyl, and mono- or di-(C₁-C₆alkyl)aminosulfonyl; and

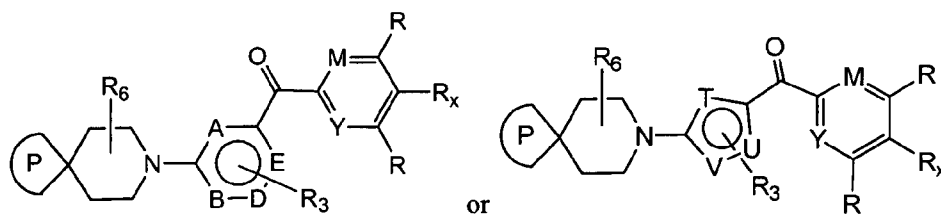
each R is independently (i) hydrogen, halogen, hydroxy, cyano, amino, aminocarbonyl and aminosulfonyl; or (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈haloalkyl, C₁-C₈hydroxyalkyl, C₂-C₈alkyl ether, C₁-C₈alkoxy, C₁-C₈alkoxycarbonyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, mono- or di-(C₁-C₈alkyl)aminoC₀-C₄alkyl, phenylC₀-C₄alkyl and (4- to 12-membered heterocycle)C₀-C₄alkyl; each of which is substituted with from 0

to 6 substituents independently chosen from hydroxy, oxo, halogen, amino, aminocarbonyl, aminosulfonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkylthio, C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl, C₁-C₆alkylsulfinyl, C₁-C₆alkoxycarbonyl, mono- or di-(C₁-C₆alkyl)aminocarbonyl, and mono- or di-(C₁-C₆alkyl)aminosulfonyl.

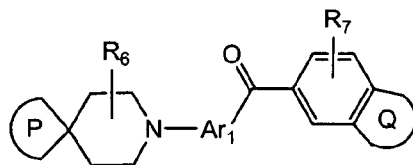
- 5 45. The compound or salt or hydrate thereof according to claim 44, wherein R_x is halogen, hydroxy, cyano, amino, aminocarbonyl and aminosulfonyl C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈haloalkyl, C₁-C₈hydroxyalkyl, C₂-C₈alkyl ether, C₁-C₈alkoxy, C₁-C₈alkoxycarbonyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, or mono- or di-(C₁-C₈alkyl)aminoC₀-C₄alkyl.

- 10 46. The compound or salt or hydrate thereof according to claim 45, wherein R_x is hydroxy or C₁-C₈alkoxy and each R is C₁-C₆alkyl.

47. The compound or salt or hydrate thereof according to claim 44, wherein the compound has the formula:



- 15 48. The compound or salt or hydrate thereof according to claim 43, wherein the compound has the formula:



wherein:

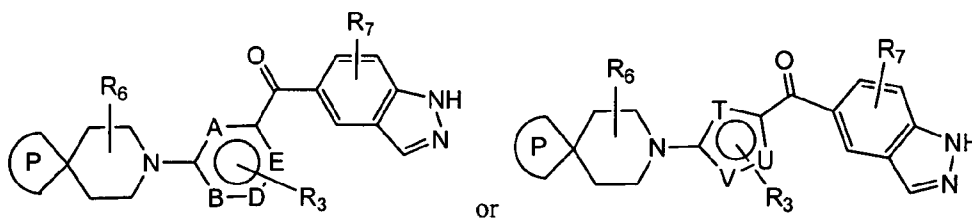
R₇ represents from 0 to 3 substituents independently chosen from:

- 20 (i) halogen, hydroxy and amino; and
 (ii) C₁-C₆alkyl, C₁-C₆alkoxy, mono- or di-(C₁-C₆alkyl)amino, C₁-C₆alkoxycarbonyl, C₂-C₆alkyl ether, phenyl and 4- to 7-membered heterocycle, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, amino, oxo, C₁-C₄alkyl, C₁-C₄alkoxy and mono- or di-(C₁-C₄alkyl)amino; and



is a 5- or 6-membered heterocycle that is optionally substituted with C₁-C₄alkyl.

49. The compound or salt or hydrate thereof according to claim 48, wherein the compound has the formula:



5 wherein:

A, B, D and E are each CH or N, such that exactly one or two of A, B, D and E are N;
T, U and V are independently CH, N, NH, S and O, such that at least one of T, U and V is N;



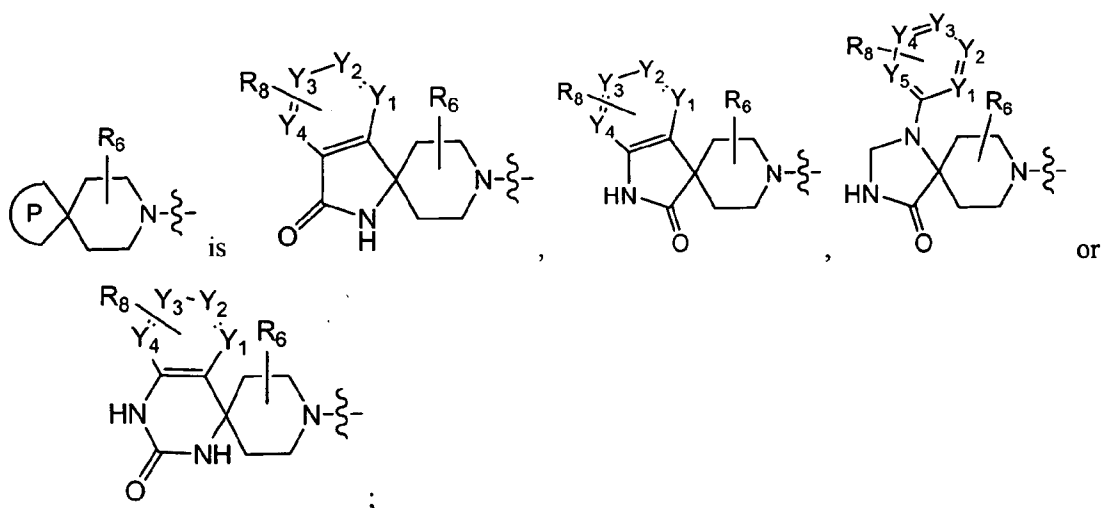
exactly one of T, U and V is CH; and R_3 is aromatic; and

R_3 represents from 0 to 3 substituents independently chosen from:

- 10 (i) halogen, hydroxy, cyano and amino; and
(ii) C₁-C₆alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, and (4- to 7-membered heterocycle)C₀-C₄alkyl; each of which is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, amino, C₁-C₄alkyl, (C₃-
15 C₈carbocycle)C₀-C₄alkyl and (4- to 10-membered heterocycle)C₀-C₄alkyl;
or two substituents represented by R_3 are taken together to form a fused 5- to 7-membered carbocycle or heterocycle that is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, C₁-C₆alkyl, (C₃-C₈carbocycle)C₀-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl,
20 and (4- to 7-membered heterocycle)C₀-C₄alkyl.

50. The compound or salt or hydrate thereof according to claim 48 or claim 49, wherein R_7 represents one or two methyl substituents.

51. The compound or salt or hydrate thereof according to any one of claims 30-50, wherein:



wherein:

Y₁, Y₂, Y₃, Y₄ and Y₅ are independently C, N or CH; and

- 5 R₈ represents from 0 to 4 substituents independently chosen from halogen, hydroxy, cyano, amino, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₆alkoxy, and mono- or di-(C₁-C₆alkyl)aminoC₀-C₄alkyl.

52. The compound or salt or hydrate thereof according to claim 51, wherein R₈ represents 0 substituents.

- 10 53. The compound or salt or hydrate thereof according to any one of claims 30-52, wherein R₆ represents 0 substituents.

54. A pharmaceutical composition, comprising at least one compound or salt or hydrate thereof according to any one of claims 1-53, in combination with a physiologically acceptable carrier or excipient.

- 15 55. The pharmaceutical composition according to claim 54, wherein the composition is formulated as an injectible fluid, an aerosol, a cream, a gel, a pill, a capsule, a syrup or a transdermal patch.

56. A method for inhibiting ligand-induced CGRP receptor activity *in vitro*, the method comprising contacting a CGRP receptor with at least one compound or salt or hydrate thereof according to any one of claims 1-53, under conditions and in an amount sufficient to detectably inhibit ligand-induced CGRP receptor activity.
- 20

57. A method for inhibiting induction of ligand-induced CGRP receptor activity in a patient, comprising contacting cells expressing a CGRP receptor with at least one compound or salt or hydrate thereof according to any one of claims 1-53, in an amount sufficient to detectably inhibit ligand-induced CGRP receptor activity in cells expressing a cloned CGRP receptor *in vitro*, and thereby inhibiting ligand-induced CGRP activity in the patient.

58. A method according to claim 56, wherein the patient is a human.

59. A method for treating a condition responsive to CGRP receptor modulation in a patient, comprising administering to the patient a therapeutically effective amount of at least one compound or salt or hydrate thereof according to any one of claims 1-53, and thereby alleviating the condition in the patient.

60. The method according to claim 59, wherein the condition is headache, migraine, inflammation, neurogenic vasodilation, thermal injury, shock or hot flashes.

61. A method for treating migraine in a patient, comprising administering to a patient suffering from migraine a therapeutically effective amount of at least one compound or salt or hydrate thereof according to any one of claims 1-53, and thereby alleviating migraine in the patient.

62. A method for treating headache in a patient, comprising administering to a patient suffering from headache a therapeutically effective amount of at least one compound or salt or hydrate thereof according to any one of claims 1-53, and thereby alleviating headache in the patient.

63. The method according to claim 62, wherein the patient is suffering from cluster headache or tension headache.

64. The method according to claim 62 or claim 63, wherein the patient is a human.

65. A compound or salt or hydrate thereof according to claim 1 or claim 30, wherein the compound is radiolabeled.

66. A method for determining the presence or absence of CGRP receptor in a sample, comprising the steps of:

- 5 (a) contacting a sample with a compound or salt or hydrate thereof according to any one of claims 1-53, under conditions that permit binding of the compound to CGRP receptor; and
- (b) detecting a signal indicative of a level of the compound bound to CGRP receptor, and therefrom determining the presence or absence of CGRP receptor in the sample.

10 67. The method according to claim 66, wherein the compound is radiolabeled, and wherein the step of detection comprises the steps of:

- (i) separating unbound compound from bound compound; and
- (ii) detecting the presence or absence of bound radiolabel in the sample.

68. A packaged pharmaceutical preparation, comprising:

- 15 (a) a pharmaceutical composition according to claim 54 in a container; and
- (b) instructions for using the composition to treat a condition responsive to CGRP receptor modulation.

69. The packaged pharmaceutical preparation according to claim 68, wherein the condition responsive to CGRP receptor modulation is migraine or headache.

20 70. The use of a compound or salt or hydrate thereof according to any one of claims 1-53 for the manufacture of a medicament for the treatment of a condition responsive to CGRP receptor modulation.

71. The use according to claim 70, wherein the condition is migraine or headache.