TITLE OF THE INVENTION

SUBSTITUTED SPIROCYCLIC CGRP RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

CGRP (Calcitonin Gene-Related Peptide) is a naturally occurring 37-amino acid peptide that is generated by tissue-specific alternate processing of calcitonin messenger RNA and is widely distributed in the central and peripheral nervous system. CGRP is localized predominantly in sensory afferent and central neurons and mediates several biological actions, including vasodilation. CGRP is expressed in alpha- and beta-forms that vary by one and three amino acids in the rat and human, respectively. CGRP-alpha and CGRP-beta display similar biological properties. When released from the cell, CGRP initiates its biological responses by binding to specific cell surface receptors that are predominantly coupled to the activation of adenylyl cyclase. CGRP receptors have been identified and pharmacologically evaluated in several tissues and cells, including those of brain, cardiovascular, endothelial, and smooth muscle origin.

Based on pharmacological properties, these receptors are divided into at least two subtypes, denoted $CGRP_1$ and $CGRP_2$. Human α-CGRP-(8-37), a fragment of CGRP that lacks seven N-terminal amino acid residues, is a selective antagonist of $CGRP_1$, whereas the linear analogue of CGRP, diacetoamido methyl cysteine CGRP ([Cys(ACM)2,7]CGRP), is a selective agonist of $CGRP_2$. CGRP is a potent neuromodulator that has been implicated in the pathology of cerebrovascular disorders such as migraine and cluster headache. In clinical studies, elevated levels of CGRP in the jugular vein were found to occur during migraine attacks (Goadsby et al., Ann. Neurol., 1990, 28, 183-187), salivary levels of CGRP are elevated in migraine subjects between attacks (Bellamy et al., Headache, 2006, 46, 24-33), and CGRP itself has been shown to trigger migrainous headache (Lassen et al., Cephalalgia, 2002, 22, 54-61). In clinical trials, the CGRP antagonist BIBN4096BS has been shown to be effective in treating acute attacks of migraine (Olesen et al., New Engl. J. Med., 2004, 350, 1104-1110) and was able to prevent headache induced by CGRP infusion in a control group (Petersen et al., Clin. Pharmacol. Ther., 2005, 77, 202-213).

CGRP-mediated activation of the trigeminovascular system may play a key role in migraine pathogenesis. Additionally, CGRP activates receptors on the smooth muscle of intracranial vessels, leading to increased vasodilation, which is thought to contribute to headache pain during migraine attacks (Lance, Headache Pathogenesis: Monoamines, Neuropeptides, Purines and Nitric Oxide, Lippincott-Raven Publishers, 1997, 3-9). The middle meningeal artery, the principle artery in the dura mater, is innervated by sensory fibers from the trigeminal ganglion which contain several neuropeptides, including CGRP. Trigeminal ganglion stimulation in the cat resulted in increased levels of CGRP, and in humans, activation of the trigeminal

system caused facial flushing and increased levels of CGRP in the external jugular vein (Goadsby et al., Ann. Neurol., 1988, 23, 193-196). Electrical stimulation of the dura mater in rats increased the diameter of the middle meningeal artery, an effect that was blocked by prior administration of CGRP(8-37), a peptide CGRP antagonist (Williamson et al., Cephalalgia, 1997, 17, 525-531). Trigeminal ganglion stimulation increased facial blood flow in the rat, which was inhibited by CGRP(8-37) (Escott et al., Brain Res. 1995, 669, 93-99). Electrical stimulation of the trigeminal ganglion in marmoset produced an increase in facial blood flow that could be blocked by the non-peptide CGRP antagonist BIBN4096BS (Doods et al., Br. J. Pharmacol., 2000, 129, 420-423). Thus the vascular effects of CGRP may be attenuated, prevented or reversed by a CGRP antagonist.

CGRP-mediated vasodilation of rat middle meningeal artery was shown to sensitize neurons of the trigeminal nucleus caudalis (Williamson et al., The CGRP Family: Calcitonin Gene-Related Peptide (CGRP), Amylin, and Adrenomedullin, Landes Bioscience, 2000, 245-247). Similarly, distention of dural blood vessels during migraine headache may sensitize trigeminal neurons. Some of the associated symptoms of migraine, including extra-cranial pain and facial allodynia, may be the result of sensitized trigeminal neurons (Burstein et al., Ann. Neurol. 2000, 47, 614-624). A CGRP antagonist may be beneficial in attenuating, preventing or reversing the effects of neuronal sensitization.

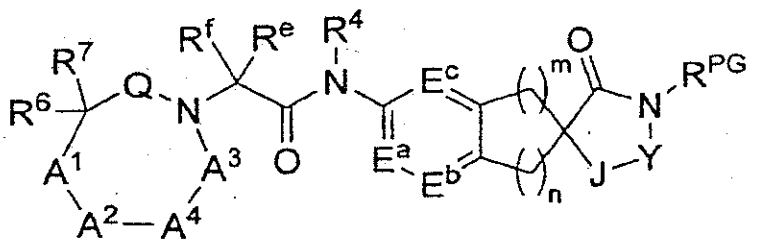
The ability of the compounds of the present invention to act as CGRP antagonists makes them useful pharmacological agents for disorders that involve CGRP in humans and animals, but particularly in humans. Such disorders include migraine and cluster headache (Doods, Curr Opin Inves Drugs, 2001, 2 (9), 1261-1268; Edvinsson et al., Cephalalgia, 1994, 14, 320-327); chronic tension type headache (Ashina et al., Neurology, 2000, 14, 1335-1340); pain (Yu et al., Eur. J. Pharm., 1998, 347, 275-282); chronic pain (Hulsebosch et al., Pain, 2000, 86, 163-175); neurogenic inflammation and inflammatory pain (Holzer, Neurosci., 1988, 24, 739-768; Delay-Goyet et al., Acta Physiol. Scanda. 1992, 146, 537-538; Salmon et al., Nature Neurosci., 2001, 4(4), 357-358); eye pain (May et al. Cephalalgia, 2002, 22, 195-196), tooth pain (Awawdeh et al., Int. Endocrin. J., 2002, 35, 30-36), non-insulin dependent diabetes mellitus (Molina et al., Diabetes, 1990, 39, 260-265); vascular disorders; inflammation (Zhang et al., Pain, 2001, 89, 265), arthritis, bronchial hyperreactivity, asthma, (Foster et al., Ann. NY Acad. Sci., 1992, 657, 397-404; Schini et al., Am. J. Physiol., 1994, 267, H2483-H2490; Zheng et al., J. Virol., 1993, 67, 5786-5791); shock, sepsis (Beer et al., Crit. Care Med., 2002, 30 (8), 1794-1798); opiate withdrawal syndrome (Salmon et al., Nature Neurosci., 2001, 4(4), 357-358); morphine tolerance (Menard et al., J. Neurosci., 1996, 16 (7), 2342-2351); hot flashes in men and women (Chen et al., Lancet, 1993, 342, 49; Spetz et al., J. Urology, 2001, 166, 1720-1723); allergic dermatitis (Wallengren, Contact Dermatitis, 2000, 43 (3), 137-143); psoriasis; encephalitis, brain trauma, ischaemia, stroke, epilepsy, and neurodegenerative diseases

(Rohrenbeck et al., Neurobiol. of Disease 1999, 6, 15-34); skin diseases (Geppetti and Holzer, Eds., Neurogenic Inflammation, 1996, CRC Press, Boca Raton, FL), neurogenic cutaneous redness, skin rosaceousness and erythema; tinnitus (Herzog et al., J. Membrane Biology, 2002, 189(3), 225); inflammatory bowel disease, irritable bowel syndrome, (Hoffman et al. Scandinavian Journal of Gastroenterology, 2002, 37(4) 414-422) and cystitis. Of particular importance is the acute or prophylactic treatment of headache, including migraine and cluster headache.

The present invention relates to compounds that are useful as ligands for CGRP receptors, in particular antagonists for CGRP receptors, processes for their preparation, their use in therapy, pharmaceutical compositions comprising them and methods of therapy using them.

SUMMARY

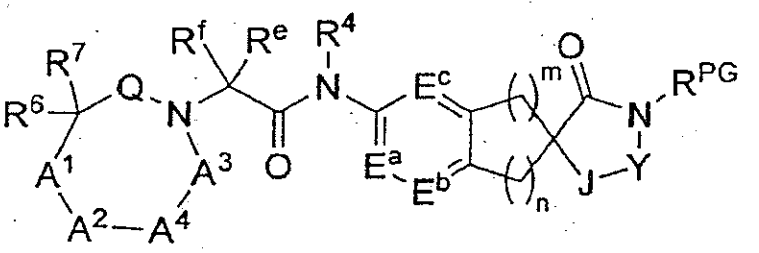
The disclosure is directed to compounds of the formula I:



(I)

(wherein variables A^1, A^2, A^3, A^4, m, n, J, Q, R^4, E^a, E^b, E^c, R^6, R^7, R^e, R^f, R^{PG} and Y are as described herein) which are antagonists of CGRP receptors and which are useful in the treatment or prevention of diseases in which CGRP is involved, such as migraine.

In a first aspect, there is provided a compound of the formula I:



I

wherein:

A^1 is selected from:

(1) -O-,
(2) -$S(O)_v$-,
(3) -$Si(OR^a)$-C_{1-4}alkyl-, where alkyl is unsubstituted or substituted with 1-5 halo,
(4) -$Si(C_{1-4}alkyl)_2$, where each alkyl is independently unsubstituted or substituted with 1-5 halo-,
(5) -CR^6R^7-,
(6) -$N(R^8)$-,
(7) -(C=O)-,
(8) -$C(R^8)(R^a)$-,
(9) -$C(N(R^b)$-$SO_2R^d)(R^a)$-,
(10) -$C(N(R^b)(C=O)R^a)(R^a)$-,
(11) -$C(N(R^b)(C=O)OR^a)(R^a)$-,
(12) -$CR^{10}R^{11}$-, and
(13) -$N(R^{11})$-;

A^2 is selected from:

(1) -CR^6R^7-,
(2) -$CR^{10}R^{11}$-, and
(3) -(C=O)-;

A^3 is selected from:

(1) $-CR^6R^7-$,
(2) $-N(R^8)-$,
(3) $-CR^{10}R^{11}-$, and
(4) $-N(R^{11})-$;

A^4 is selected from:
(1) $-CR^6R^7-$,
(2) $-(C=O)-$,
(3) $-N(R^8)-$,
(4) $-CR^{10}R^{11}-$,
(5) $-N(R^{11})-$, and
(6) a bond between A^2 and A^3;

E^a is selected from:
(1) $-C(R^{5a})=$,
(2) $-N=$, and
(3) $-(N^+-O^-)=$;

E^b is selected from:
(1) $-C(R^{5b})=$,
(2) $-N=$, and
(3) $-(N^+-O^-)=$;

E^c is selected from:
(1) $-C(R^{5c})=$,
(2) $-N=$, and
(3) $-(N^+-O^-)=$;

Q is selected from:
(1) $-(C=O)-$,
(2) $-SO_2-$,
(3) $-SO-$, and
(4) $-C(R^a)_2-$;

R^4 is selected from:
(1) hydrogen,
(2) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
  (a) halo,
  (b) $-C_{3-6}$cycloalkyl,
  (c) $-CF_3$, and
  (d) $-O-R^a$,
(3) $-C_{3-6}$cycloalkyl,

(4) benzyl, and

(5) phenyl;

R^{5a}, $R^{5b}$and R^{5c} are each independently selected from:

(1) hydrogen,

(2) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo,

(3) halo,

(4) -OR^a, and

(5) -CN;

R^6 and R^7 are each independently selected from:

(1) hydrogen,

(2) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,

(b) -OR^a,

(c) -C_{3-6}cycloalkyl,

(d) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl, indolyl, indazolyl, benzimidazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(i) halo,

(ii) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 halo,

(iii) -OR^a,

(iv) –NR^bR^c,

(v) –CN, and

(vi) oxo;

(e) -CO_2R^a,

(f) -$C(=O)NR^bR^c$,

(g) -$S(O)_vR^d$,

(h) -CN,

(i) -NR^bR^c,

(j) -$N(R^b)C(=O)R^a$,

(k) -$N(R^b)SO_2R^d$,

(l) -CF_3,

(m) -O-CO_2R^d,

(n) -O-(C=O)-NR^bR^c,

(o) -NR^b-(C=O)-NR^bR^c, and

(p) $-C(=O)R^a$,

(3) $-C_{3-8}$cycloalkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,

(b) -CN,

(c) $-C_{1-4}$alkyl, which is unsubstituted or substituted with 1-3 halo, and

(d) $-OR^a$,

(4) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,

(b) $-OR^a$,

(c) $-C_{3-6}$cycloalkyl,

(d) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

(i) halo,

(ii) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo, and

(iii) $-OR^a$,

(e) $-CO_2R^a$,

(f) $-C(=O)NR^bR^c$,

(g) $-S(O)_vR^d$,

(h) -CN,

(i) $-NR^bR^c$,

(j) $-N(R^b)C(=O)R^a$,

(k) $-N(R^b)SO_2R^d$,

(l) $-O-CO_2R^d$,

(m) $-O-(C=O)-NR^bR^c$,

(n) $-NR^b-(C=O)-NR^bR^c$,

(o) $-C(=O)R^a$,

(p) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo, and

(q) oxo;

(5) halo,

(6) $-OR^a$,

(7) -CN,

(8) $-CO_2R^a$

(9) $-N(R^b)C(=O)R^a$

(10) $-NR^bR^c$,
(11) $-C(=O)NR^bR^c$, and
(12) $-O(C=O)R^a$;

or R^6 and R^7 and the carbon atom or atoms to which they are attached join to form a ring selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, dioxolanyl, dioxanyl, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiapyranyl, oxetanyl, thietanyl and tetrahydrothienyl, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from:
  (i) halo,
  (ii) $-OR^a$,
  (iii) $-C_{3-6}$cycloalkyl,
  (iv) $-CO_2R^a$,
  (v) $-NR^bR^c$,
  (vi) $-S(O)_vR^d$,
  (vii) $-C(=O)NR^bR^c$, and
  (viii) phenyl,
(b) $-C_{3-6}$cycloalkyl, wherein the C_{3-6}cycloalkyl group is optionally fused to the ring, and which C_{3-6}cycloalkyl group is unsubstituted or substituted with 1-3 substituents each independently selected from:
  (i) halo,
  (ii) $-OR^a$,
  (iii) $-C_{3-6}$cycloalkyl,
  (iv) $-CO_2R^a$,
  (v) $-NR^bR^c$,
  (vi) $-S(O)_vR^d$,
  (vii) $-C(=O)NR^bR^c$, and
  (viii) phenyl,
(c) phenyl or heterocycle, wherein heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, imidazolyl, furanyl, tetrahydrofuranyl, thiazolyl and oxazolyl, wherein the phenyl or heterocycle is optionally fused to the ring,

and which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(i) halo,

(ii) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 halo,

(iii) -OR^a,

(iv) -CO_2R^a,

(v) -$O(C=O)R^a$,

(vi) -CN,

(vii) -NR^bR^c,

(viii) oxo,

(ix) -$C(=O)NR^bR^c$,

(x) -$N(R^b)C(=O)R^a$,

(xi) -$N(R^b)CO_2R^a$,

(xii) -$O(C=O)NR^bR^c$, and

(xiii) -$S(O)_vR^d$,

(d) -OR^a,

(e) -CO_2R^a,

(f) -$C(=O)NR^bR^c$,

(g) -$S(O)_vR^d$,

(h) -CN,

(i) halo,

(j) -NR^bR^c,

(k) -$N(R^b)C(=O)R^a$,

(l) -$N(R^b)SO_2R^d$,

(m) -O-CO_2R^d,

(n) -O-$(C=O)$-NR^bR^c,

(o) -NR^b-$(C=O)$-NR^bR^c,

(p) -$C(=O)R^a$, and

(q) oxo;

R^8 is independently selected from:

(1) hydrogen,

(2) -$C(=O)R^a$,

(3) -CO_2R^a,

(4) -$S(=O)R^d$,

(5) -SO_2R^d,

(6) -$C(=O)NR^bR^c$,

(7) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,

(b) -OR^a,

(c) -C_{3-6}cycloalkyl,

(d) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(i) halo,

(ii) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 halo, and

(iii) -OR^a,

(iv) -NR^bR^c,

(v) -$C(=O)R^a$,

(vi) -CO_2R^a, and

(vii) oxo,

(e) -CO_2R^a,

(f) -$C(=O)NR^bR^c$,

(g) -$S(O)_vR^d$,

(h) -CN,

(i) -NR^bR^c,

(j) -$N(R^b)C(=O)R^a$,

(k) -$N(R^b)SO_2R^d$,

(l) -CF_3,

(m) -O-CO_2R^d,

(n) -O-(C=O)-NR^bR^c,

(o) -NR^b-(C=O)-NR^bR^c, and

(p) -$C(=O)R^a$,

(8) -C_{3-6}cycloalkyl, which is unsubstituted or substituted with 1-6 substituents each independently selected from:

(a) halo,

(b) -CN,

(c) -OR^a, and

(d) C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo;

or R^7 and R^8 and the atoms to which they are attached join to form a 4-, 5-, 6- or 7-membered alkyl- or heteroalkyl-ring optionally containing an additional heteroatom selected from N, O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:

(a) halo,

(b) phenyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from: halo, OR^a, CN, and $-C(=O)OR^a$,

(c) $-OR^a$, and

(d) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo;

R^{10} is independently selected from:

(1) hydrogen,

(2) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,

(b) $-OR^a$,

(c) -CN,

(d) phenyl, and

(e) $-C_{3-6}$cycloalkyl, which is unsubstituted or substituted with 1-6 halo,

(3) $-C_{3-6}$cycloalkyl, which is unsubstituted or substituted with 1-6 halo;

R^{11} is independently selected from the group consisting of:

phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl, azepinyl, azepanyl, azetidinyl, benzimidazolyl, benzisoxazolyl, benzofuranyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, 1,3-benzodioxolyl, benzothiazolyl, benzothienyl, benzoxazolyl, benzopyrazolyl, benzotriazolyl, chromanyl, cinnolinyl, dibenzofuranyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, furanyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 4-oxonaphthyridinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxopyridyl, 2-oxoquinolinyl, piperidyl, piperazinyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyridinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuranyl, tetrahydrofuryl, tetrahydroimidazopyridinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, thienyl,

triazolyl, isoxazolyl, tetrahydrothienyl, tetrahydropyranyl, oxetanyl, tetrahydrothiapyranyl, and thietanyl, where R^{11} is unsubstituted or substituted with 1-5 substituents each independently selected from R^{12}, R^{13}, R^{14}, R^{15a} and R^{15b};

R^{12}, R^{13}, R^{14}, R^{15a} and R^{15b} are each independently selected from:

(1) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
  (a) halo,
  (b) -OR^a,
  (c) -C_{3-6}cycloalkyl,
  (d) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperdinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
    (i) halo,
    (ii) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 halo, and
    (iii) -OR^a,
  (e) -CO_2R^a,
  (f) -$C(=O)NR^bR^c$,
  (g) -$S(O)_vR^d$,
  (h) -CN,
  (i) -NR^bR^c,
  (j) -$N(R^b)C(=O)R^a$,
  (k) -$N(R^b)SO_2R^d$,
  (l) -CF_3,
  (m) -O-CO_2R^d,
  (n) -O-(C=O)-NR^bR^c,
  (o) -NR^b-(C=O)-NR^bR^c, and
  (p) -$C(=O)R^a$,

(2) -C_{1-6}cycloalkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
  (a) halo,
  (b) -CN,
  (c) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 halo,
  (d) -OR^a, and

(e) phenyl, which is unsubstituted or substituted with 1-5 substituents where the substituents are each independently selected from:

(i) $-OR^a$,

(ii) halo,

(iii) -CN, and

(iv) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 halo,

(3) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperdinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,

(b) $-OR^a$,

(c) $-C_{3-6}$cycloalkyl,

(d) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

(i) halo,

(ii) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo, and

(iii) $-OR^a$,

(e) $-CO_2R^a$,

(f) $-C(=O)NR^bR^c$,

(g) $-S(O)_vR^d$,

(h) -CN,

(i) $-NR^bR^c$,

(j) $-N(R^b)C(=O)R^a$,

(k) $-N(R^b)SO_2R^d$,

(l) $-O-CO_2R^d$,

(m) $-O-(C=O)-NR^bR^c$,

(n) $-NR^b-(C=O)-NR^bR^c$,

(o) $-C(=O)R^a$, and

(p) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo,

(4) halo,

(5) oxo,

(6) $-OR^a$,

(7) -CN,

(8) $-CO_2R^a$,

(9) $-C(=O)R^a$,

(10) $-NR^bR^c$,
(11) $-S(O)_vR^d$,
(12) $-C(=O)NR^bR^c$,
(13) $-O-CO_2R^d$,
(14) $-N(R^b)CO_2R^d$,
(15) $-O-(C=O)-NR^bR^c$,
(16) $-NR^b-(C=O)-NR^bR^c$,
(17) $-SO_2NR^bR^c$,
(18) $-N(R^b)SO_2R^d$,

or R^{15a} and R^{15b} and the atom(s) to which they are attached join to form a ring selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thietanyl and tetrahydrothienyl, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from:
  (i) halo,
  (ii) $-OR^a$,
  (iii) $-C_{3-6}$cycloalkyl,
  (iv) $-CO_2R^a$,
  (v) $-NR^bR^c$,
  (vi) $-S(O)_vR^d$,
  (vii) $-C(=O)NR^bR^c$, and
  (viii) phenyl,

(b) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
  (i) halo,
  (ii) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 halo, and
  (iii) $-OR^a$,

(c) $-OR^a$,

(d) halo,

(e) $-CO_2R^a$,

(f) $-C(=O)NR^bR^c$,

(g) $-S(O)_vR^d$,
(h) -CN,
(i) $-NR^bR^c$,
(j) $-N(R^b)C(=O)R^a$,
(k) $-N(R^b)SO_2R^d$,
(l) $-O-CO_2R^d$,
(m) $-O-(C=O)-NR^bR^c$,
(n) $-NR^b-(C=O)-NR^bR^c$, and
(o) $-C(=O)R^a$;

R^{PG} is independently selected from:

(1) hydrogen,
(2) $-C_{1-6}$alkyl which is unsubstituted or substituted with 1-5 halo,
(3) $-CH_2OR^a$,
(4) $-CH_2-O-CH_2CH_2Si(CH_3)_3$,
(5) $-CH_2OP(=O)(OR^c)_2$,
(6) $-(CH_2)_k$-phenyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from:
(a) halo,
(b) $-OR^a$,
(c) -CN, and
(d) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo;

J is independently selected from:

(1) $=C(R^{16a})-$,
(2) $-CR^{17}R^{18}-$,
(3) -C(=O)-, and
(4) $-N(R^b)-$;

Y is independently selected from:

(1) $=C(R^{16b})-$,
(2) $-CR^{17}R^{18}-$,
(3) -C(=O)-,
(4) =N-, and
(5) $-N(R^{16b})-$;

R^{17} and R^{18} are each independently selected from:

(1) hydrogen,
(2) halo,
(3) $-OR^a$,

(4) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-4 substituents each independently selected from:

(a) halo,

(b) -OR^a,

(c) -CN,

(d) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(i) -OR^a,

(ii) halo,

(iii) -CN,

(iv) -C_{1-6}alkyl which is unsubstituted or substituted with 1-6 halo,

(5) phenyl or heterocycle wherein heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,

(b) -CN,

(c) -OR^a,

(d) nitro,

(e) -C_{1-6}alkyl which is unsubstituted or substituted with 1-6 halo;

or R^{17} and R^{18} and the atom to which they are attached join to form a 4-, 5-, or 6-membered ring optionally containing a heteroatom selected from N, O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:

(a) halo,

(b) -OR^a,

(c) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo, and

(d) phenyl;

R^{16a} and R^{16b} are each independently selected from:

(1) hydrogen,

(2) -C_{1-4}alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,
(b) -OR^a,
(c) -C_{3-6}cycloalkyl,
(d) phenyl or heterocycle, wherein said heterocycle is selected from: imidazolyl, oxazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thiazolyl, thienyl, triazolyl, isoxazolyl and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
(i) halo,
(ii) -OR^a,
(iii) -CN, and
(iv) C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo,

(3) phenyl or heterocycle, wherein heterocycle is selected from: imidazolyl, oxazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, tetrahydrofuryl, piperidinyl, piperazinyl, pyrrolidinyl, azetidinyl, thiazolyl, thienyl, triazolyl, isoxazolyl and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
(a) halo,
(b) -OR^a,
(c) -C_{3-6}cycloalkyl,
(d) -C_{1-4}alkyl which is unsubstituted or substituted with 1-6 halo, and
(e) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
(i) halo,
(ii) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo, and
(iii) -OR^a,

(4) halo,
(5) -OR^a,
(6) -CN,
(7) -CO_2R^a,
(8) -NR^bR^c, and
(9) -$C(=O)NR^bR^c$;

or R^{16a} and R^{16b} and the atom(s) to which they are attached join to form a ring selected from cyclopentenyl, cyclohexenyl, phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, furanyl, dihydrofuranyl, dihydropyranyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl,

imidazolyl, triazolyl, thienyl, dihydrothienyl and dihydrothiopyranyl, which ring is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from:

(i) halo,

(ii) -OR^a,

(iii) -C_{3-6}cycloalkyl,

(iv) phenyl or heterocycle, wherein heterocycle is selected from pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(I) -OR^a,

(II) halo,

(III) -CN, and

(IV) -C_{1-6}alkyl which is unsubstituted or substituted with 1-6 halo,

(v) -CO_2R^a,

(vi) -NR^bR^c,

(vii) -$S(O)_vR^d$,

(viii) -$C(=O)NR^bR^c$,

(ix) -$N(R^b)CO_2R^a$, and

(x) -$N(R^b)SO_2R^d$,

(b) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, azetidinyl, piperazinyl, pyrrolidinyl, thienyl and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(v) halo,

(vi) -OR^a,

(vii) -CN, and

(viii) -C_{1-6}alkyl which is unsubstituted or substituted with 1-6 halo,

(c) halo,

(d) -$S(O)_vR^d$,

(e) -OR^a,

(f) -CN,

(g) -$C(=O)R^a$,

(h) $-NR^bR^c$,
(i) $-C(=O)NR^bR^c$,
(j) $-CO_2R^a$,
(k) $-(NR^b)CO_2R^a$,
(l) $-O-(C=O)-NR^bR^c$,
(m) $-(NR^b)-(C=O)-NR^bR^c$,
(n) oxido,
(o) oxo, and
(p) $-(NR^b)SO_2R^d$;

R^a is independently selected from:

(1) hydrogen,
(2) C_{1-6}alkyl, which is unsubstituted or substituted with 1-7 substituents each independently selected from:
  (a) halo,
  (b) $-O-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo,
  (c) hydroxyl,
  (d) -CN, and
  (e) phenyl or heterocycle wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
    (i) halo,
    (ii) $-O-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo,
    (iii) -CN,
    (iv) nitro,
    (v) hydroxyl, and
    (vi) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo,
(3) phenyl or heterocycle wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
  (a) halo,
  (b) -CN,
  (c) $-O-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo,

(d) nitro,

(e) hydroxyl, and

(f) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo, and

(4) -C_{3-6}cycloalkyl, which is unsubstituted or substituted with 1-6 halo;

R^b and R^c are independently selected from:

(1) hydrogen,

(2) C_{1-6}alkyl, which is unsubstituted or substituted with 1-7 substituents each independently selected from:

(a) halo,

(b) -OR^a,

(c) -CN,

(d) -CO_2R^a,

(e) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:

(i) halo,

(ii) -OR^a,

(iii) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo, and

(iv) nitro,

(3) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:

(a) halo,

(b) -OR^a,

(c) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo,

(d) -C_{3-6}cycloalkyl, which is unsubstituted or substituted with 1-6 halo,

(e) -CN, and

(f) -CO_2R^a,

(4) -C_{3-6}cycloalkyl, which is unsubstituted or substituted with 1-6 halo;

or R^b and R^c and the nitrogen to which they are attached join to form a 4-, 5-, or 6-membered ring optionally containing an additional heteroatom selected from N,

O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:

(a) halo,
(b) $-OR^a$, and
(c) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo, and
(d) phenyl;

R^d is independently selected from:

(1) C_{1-6}alkyl, which is unsubstituted or substituted with 1-4 substituents each independently selected from:
  (a) halo,
  (b) $-OR^a$,
  (c) $-CO_2R^a$,
  (d) -CN, and
  (e) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
    (i) halo,
    (ii) $-OR^a$,
    (iii) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo, and
    (iv) nitro,

(2) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
  (a) halo,
  (b) $-OR^a$,
  (c) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo,
  (d) $-C_{3-6}$cycloalkyl, which is unsubstituted or substituted with 1-6 halo
  (e) -CN, and
  (f) $-CO_2R^a$, and

(3) $-C_{3-6}$cycloalkyl, which is unsubstituted or substituted with 1-6 halo;

R^e and R^f are independently selected from:

(1) hydrogen,

(2) -C_{1-4}alkyl, which is unsubstituted or substituted with 1-6 halo,

(3) phenyl, and

(4) benzyl;

or where R^e and R^f and the atom to which they are attached join to form a 3-, 4-, 5-, or 6-membered ring optionally containing a heteroatom selected from N, O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:

(a) halo,

(b) -OR^a,

(c) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo, and

(d) phenyl;

m is 1, 2, or 3;

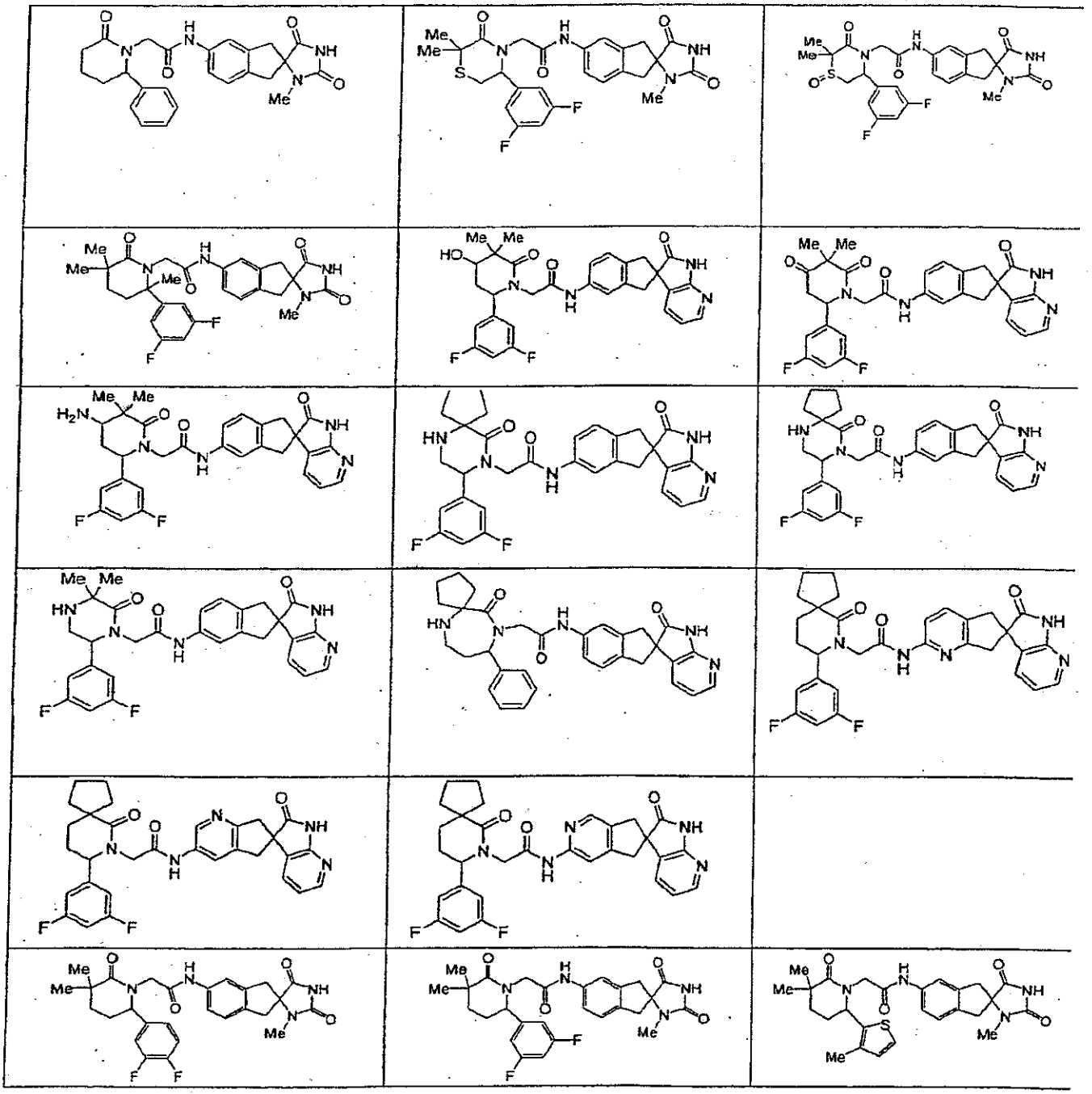
n is 1, 2, or 3;

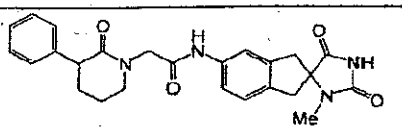
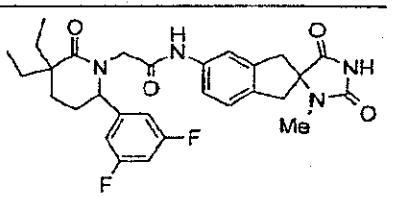
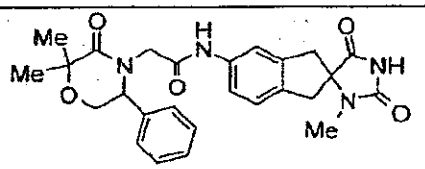
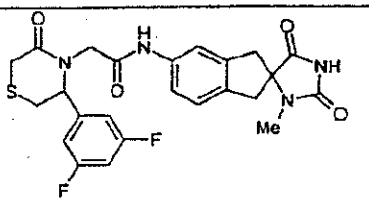
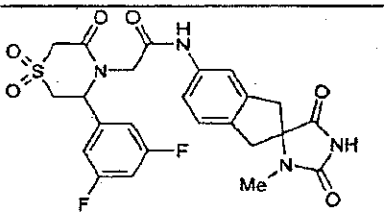
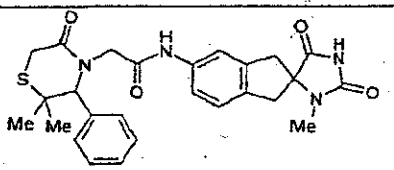
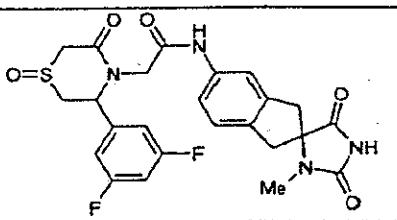
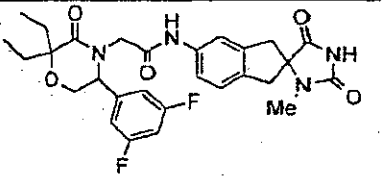
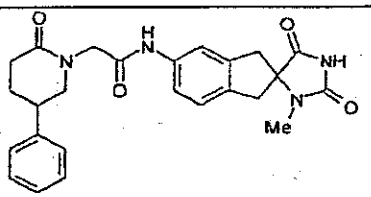
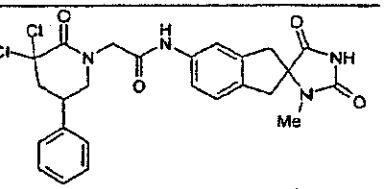
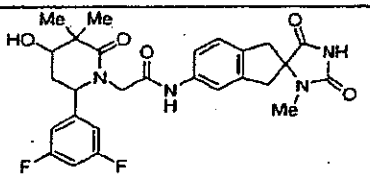
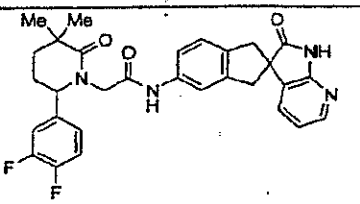
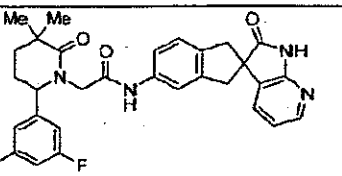
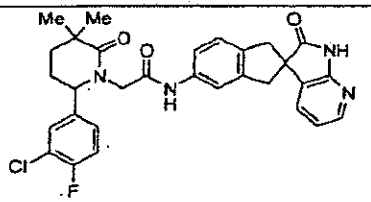
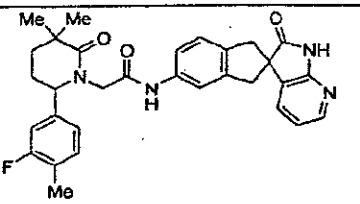
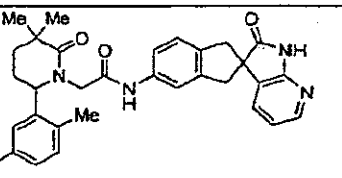
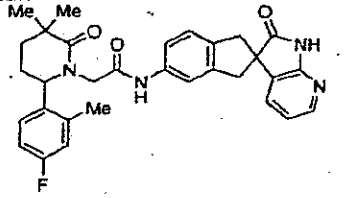
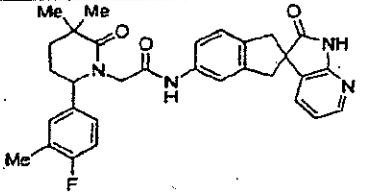
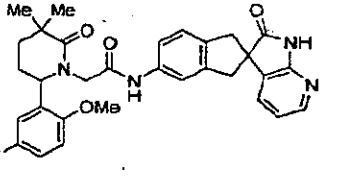
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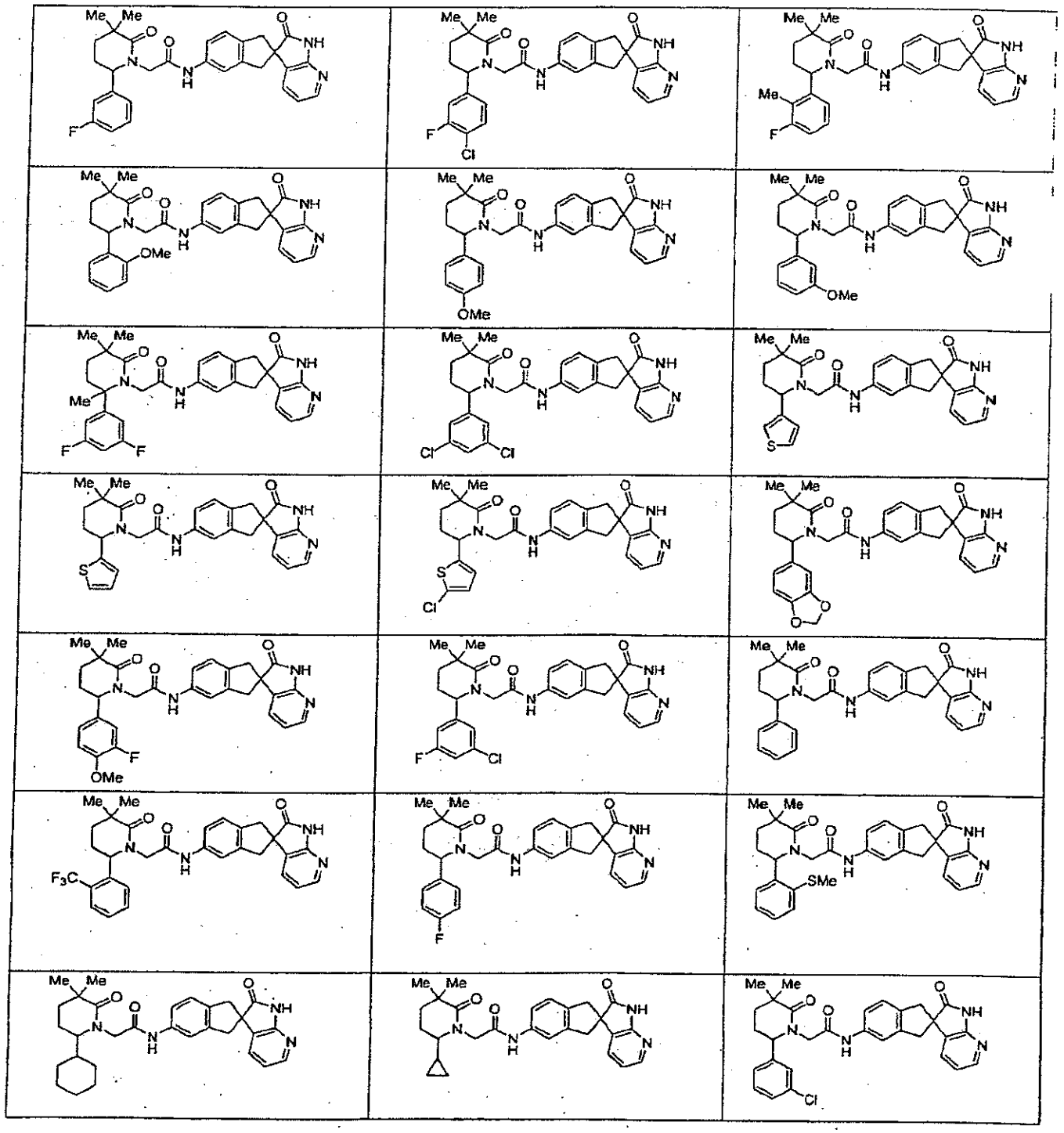
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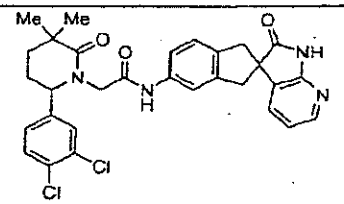
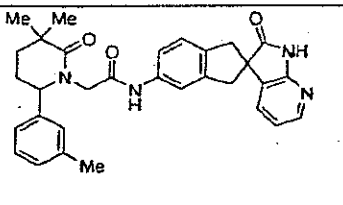
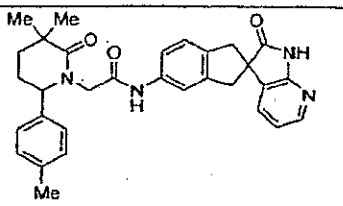
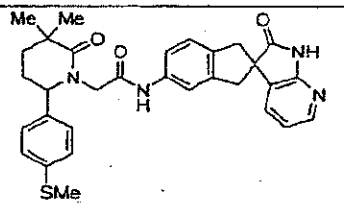
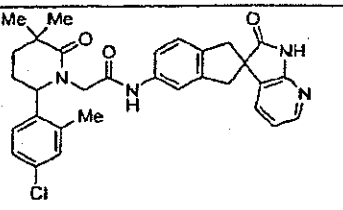
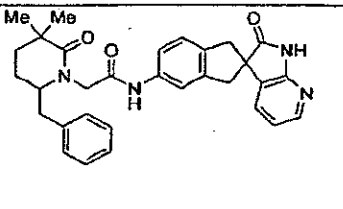
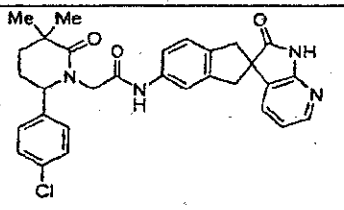
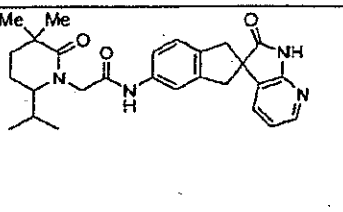
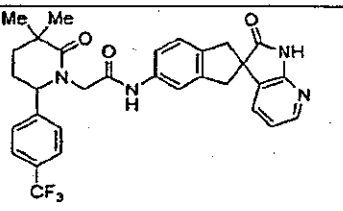
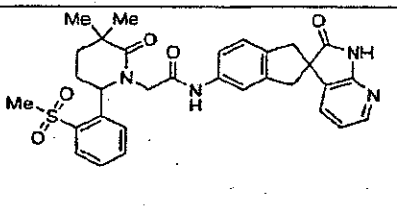
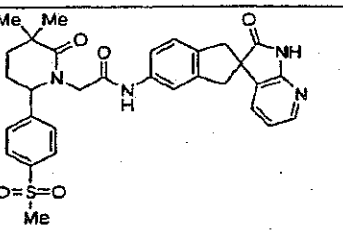
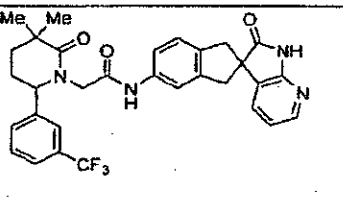
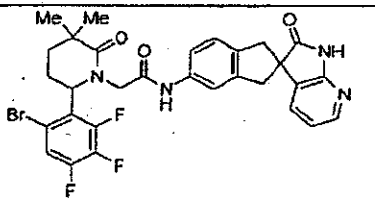
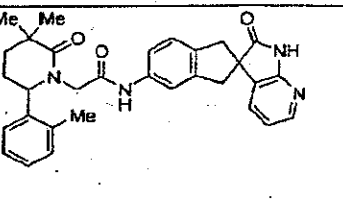
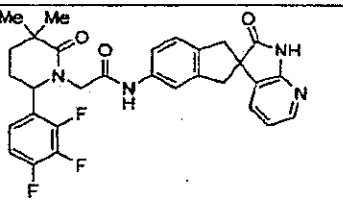
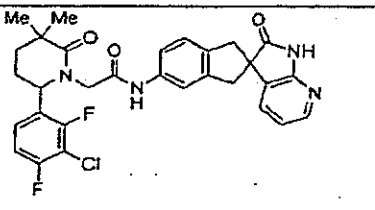
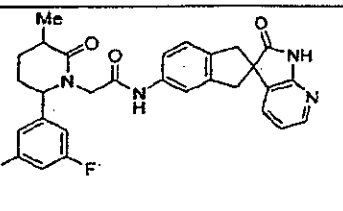
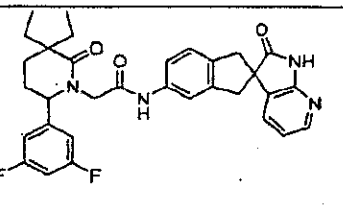
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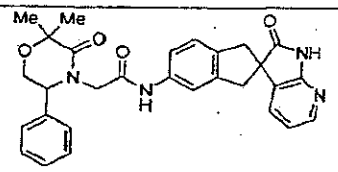
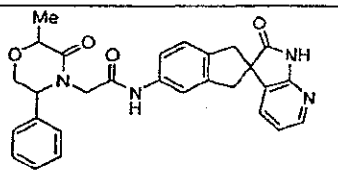
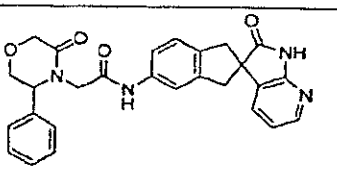
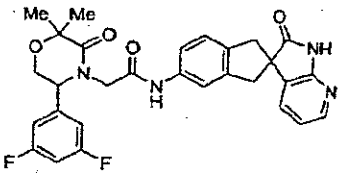
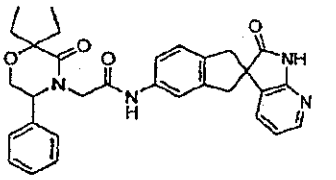
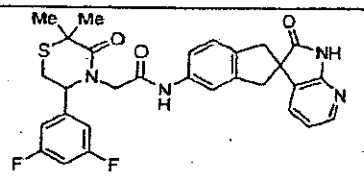
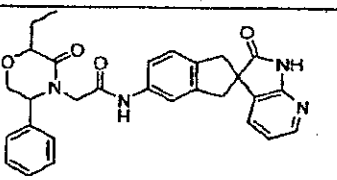
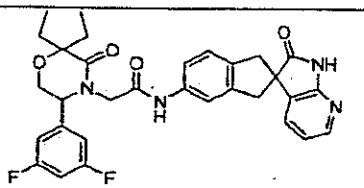
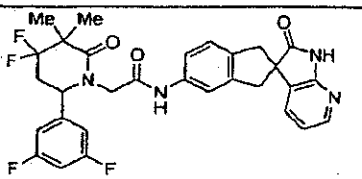
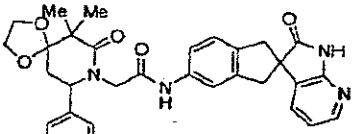
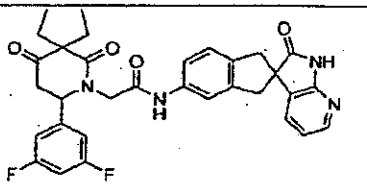
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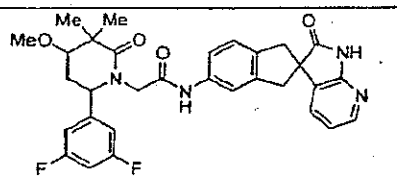
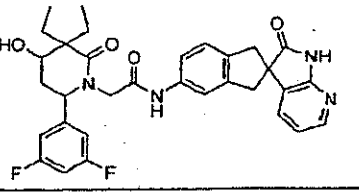
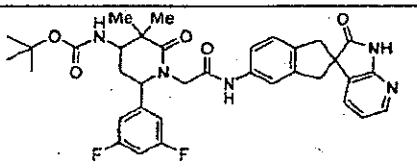
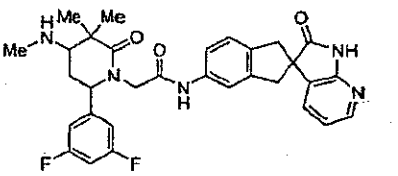
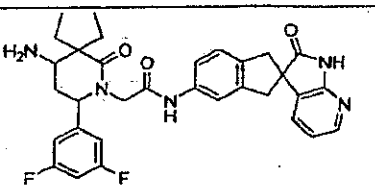
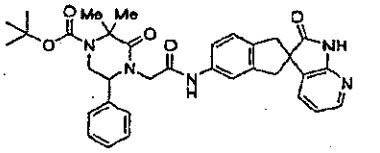
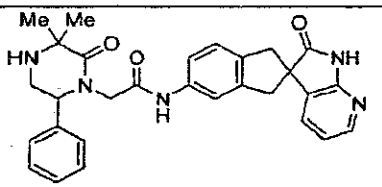
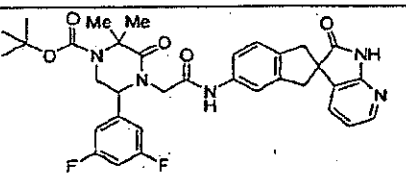
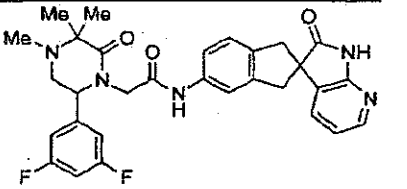


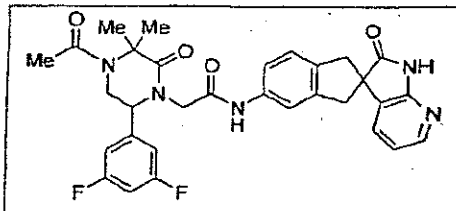
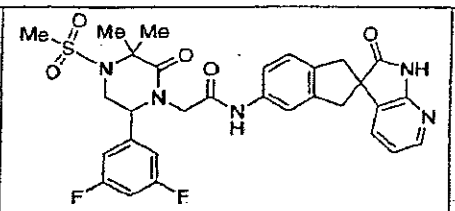
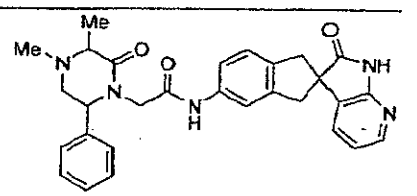
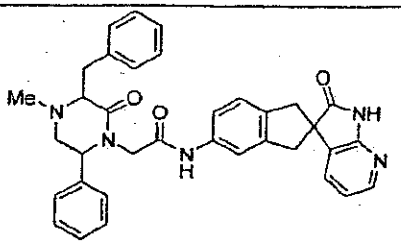
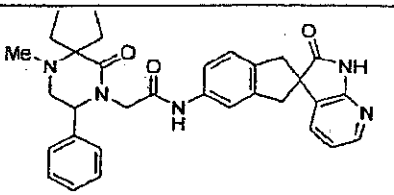
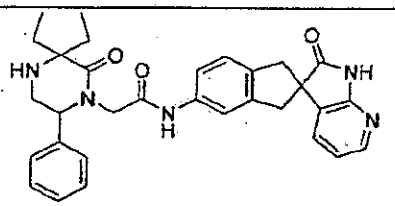
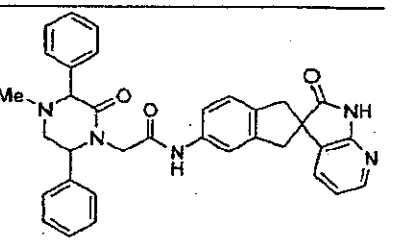
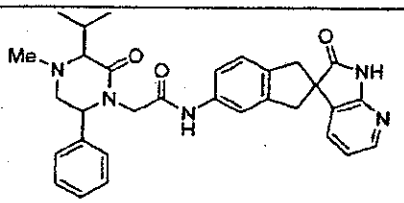
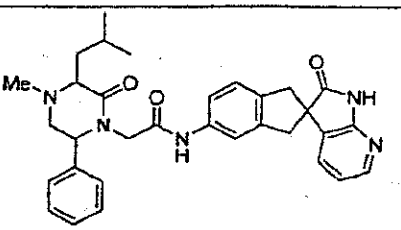
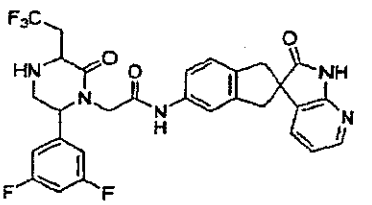
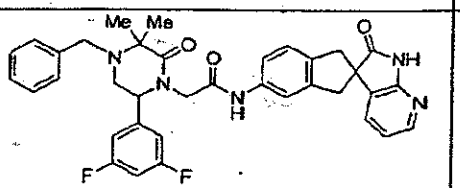
		
		
		
		
		
		
		

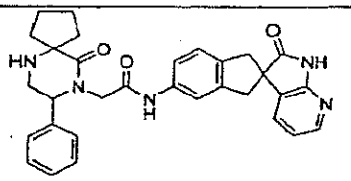
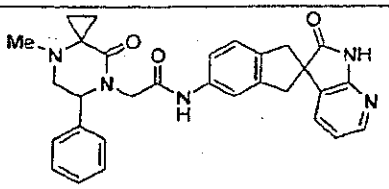
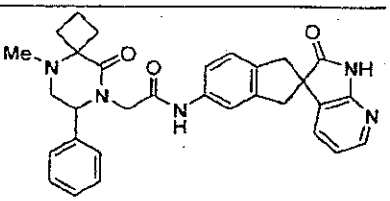
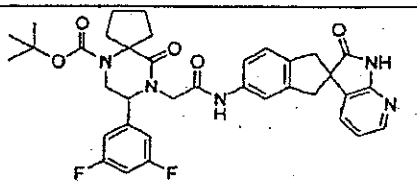
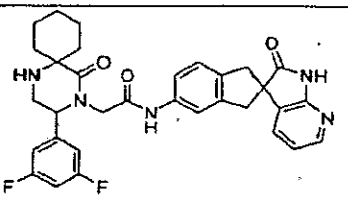
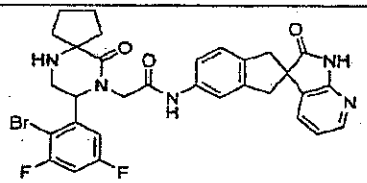
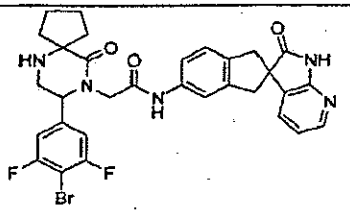
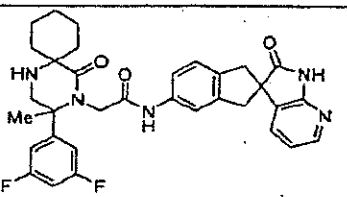
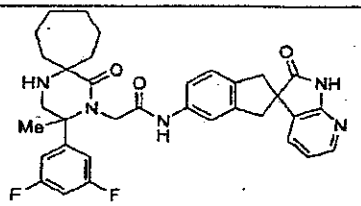
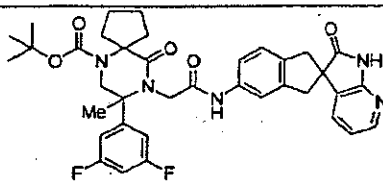
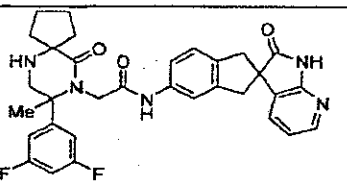


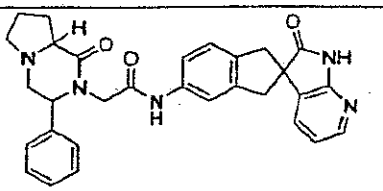
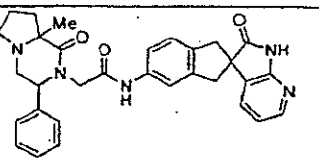
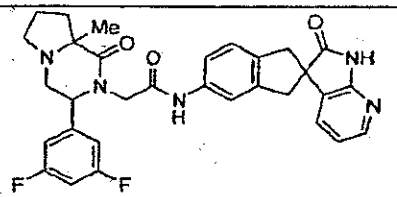
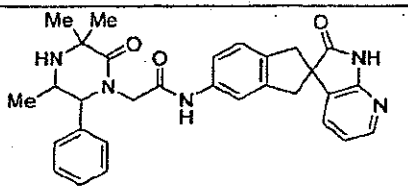
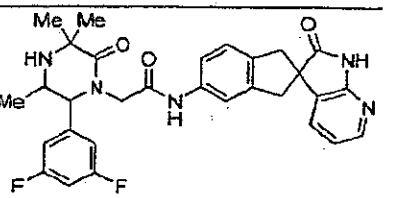
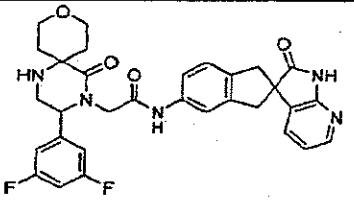
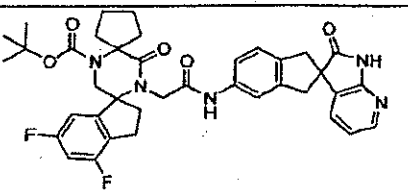
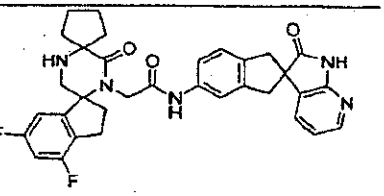
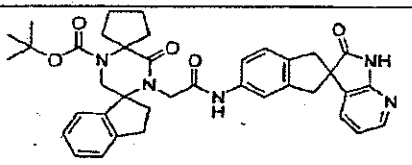
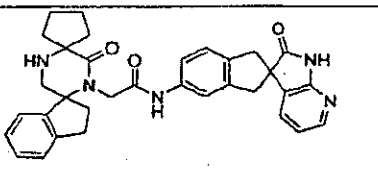
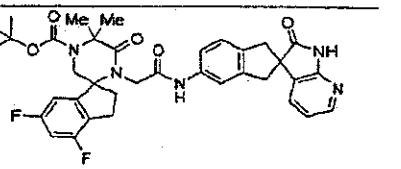
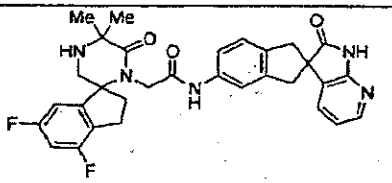
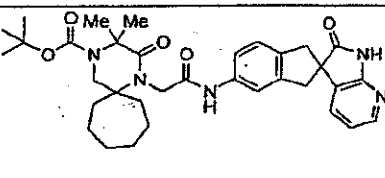
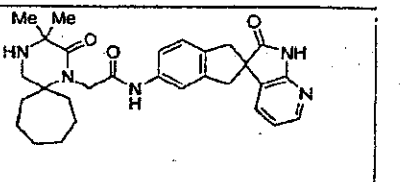
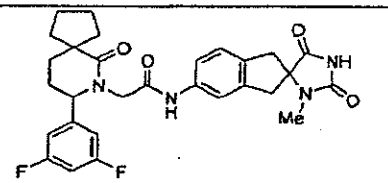
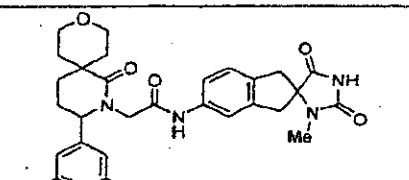
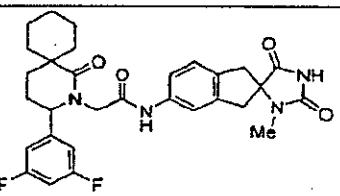
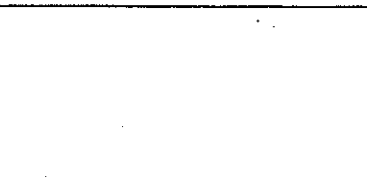
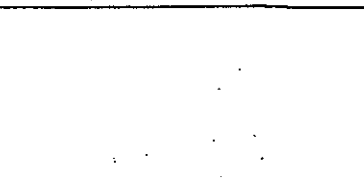
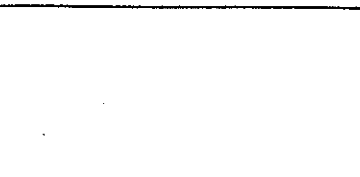
		
		
		
		
		
		

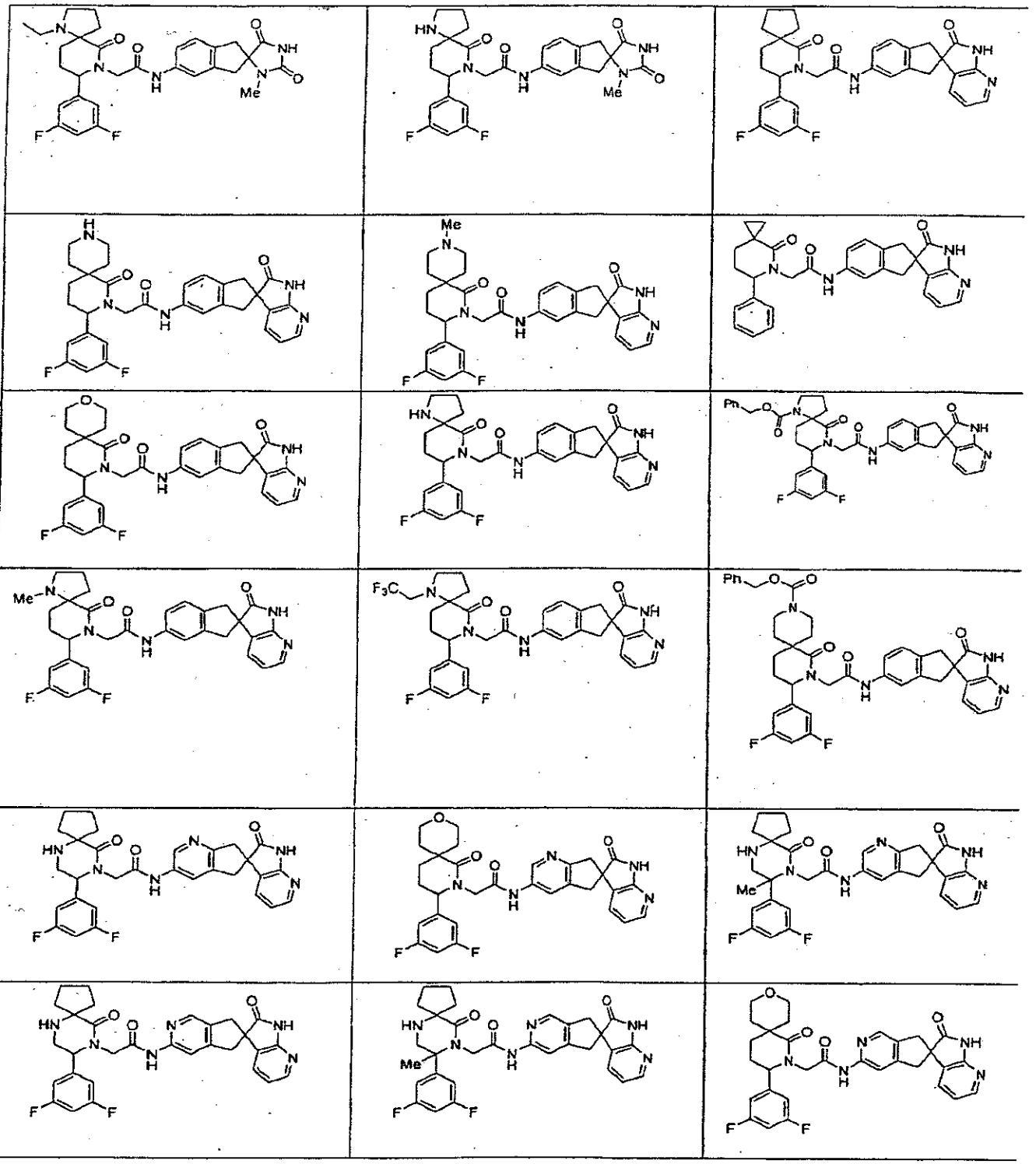
		
		
		
		
		



and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

The disclosure is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which CGRP is involved.

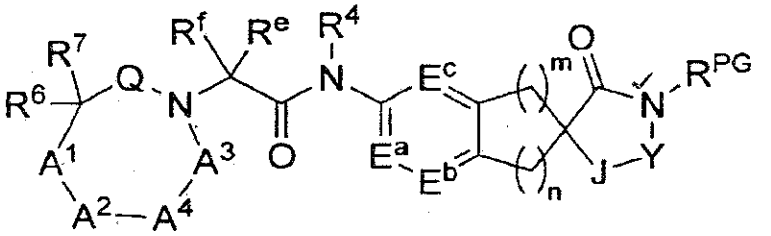
In a third aspect, there is provided a pharmaceutical composition which comprises an inert carrier and the compound as defined above.

In a fourth aspect, there is provided an effective amount of the compound as defined above for use in the antagonism of CGRP receptor activity in a mammal.

In a fifth aspect, there is provided the use of the compound as defined above in the manufacture of a medicament for treating, controlling, ameliorating or reducing the risk of headache, migraine or cluster headache in a mammalian patient.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of the formula I:



I

wherein:

A^1 is selected from:

(1) -O-,
(2) $-S(O)_v-$,
(3) $-Si(OR^a)-C_{1-4}$alkyl-, where alkyl is unsubstituted or substituted with 1-5 halo,
(4) $-Si(C_{1-4}alkyl)_2$, where each alkyl is independently unsubstituted or substituted with 1-5 halo-,
(5) $-CR^6R^7-$,
(6) $-N(R^8)-$,
(7) -(C=O)-,
(8) $-C(R^8)(R^a)-$,
(9) $-C(N(R^b)-SO_2R^d)(R^a)-$,
(10) $-C(N(R^b)(C=O)R^a)(R^a)-$,
(11) $-C(N(R^b)(C=O)OR^a)(R^a)-$,
(12) $-CR^{10}R^{11}-$, and
(13) $-N(R^{11})-$;

A^2 is selected from:

(1) $-CR^6R^7-$,
(2) $-CR^{10}R^{11}-$, and
(3) -(C=O)-;

A^3 is selected from:

(1) $-CR^6R^7-$,
(2) $-N(R^8)-$,
(3) $-CR^{10}R^{11}-$, and

(4) -N(R^{11})-;

A^4 is selected from:

(1) -CR^6R^7-,

(2) -(C=O)-,

(3) -N(R^8)-,

(4) -C$R^{10}R^{11}$-,

(5) -N(R^{11})-, and

(6) a bond between A^2 and A^3;

E^a is selected from:

(1) -C(R^{5a})=,

(2) -N=, and

(3) -(N^+-O^-)=;

E^b is selected from:

(1) -C(R^{5b})=,

(2) -N=, and

(3) -(N^+-O^-)=;

E^c is selected from:

(1) -C(R^{5c})=,

(2) -N=, and

(3) -(N^+-O^-)=;

Q is selected from:

(1) -(C=O)-,

(2) -SO_2-,

(3) -SO-, and

(4) -C(R^a)$_2$-;

R^4 is selected from:

(1) hydrogen,

(2) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,

(b) -C_{3-6}cycloalkyl,

(c) -CF_3, and

(d) -O-R^a,

(3) -C_{3-6}cycloalkyl,

(4) benzyl, and

(5) phenyl;

R^{5a}, R^{5b} and R^{5c} are each independently selected from:

(1) hydrogen,
(2) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo,
(3) halo,
(4) -OR^a, and
(5) -CN;

R^6 and R^7 are each independently selected from:
(1) hydrogen,
(2) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
(a) halo,
(b) -OR^a,
(c) -C_{3-6}cycloalkyl,
(d) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl, indolyl, indazolyl, benzimidazolyl, and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
(i) halo,
(ii) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 halo,
(iii) -OR^a,
(iv) –NR^bR^c,
(v) –CN, and
(vi) oxo;
(e) -CO_2R^a,
(f) -$C(=O)NR^bR^c$,
(g) -$S(O)_vR^d$,
(h) -CN,
(i) -NR^bR^c,
(j) -$N(R^b)C(=O)R^a$,
(k) -$N(R^b)SO_2R^d$,
(l) -CF_3,
(m) -O-CO_2R^d,
(n) -O-(C=O)-NR^bR^c,
(o) -NR^b-(C=O)-NR^bR^c, and
(p) -$C(=O)R^a$,
(3) -C_{3-8}cycloalkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,
(b) -CN,
(c) -C_{1-4}alkyl, which is unsubstituted or substituted with 1-3 halo, and
(d) -OR^a,

(4) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
(a) halo,
(b) -OR^a,
(c) -C_{3-6}cycloalkyl,
(d) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
(i) halo,
(ii) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo, and
(iii) -OR^a,
(e) -CO_2R^a,
(f) -$C(=O)NR^bR^c$,
(g) -$S(O)_vR^d$,
(h) -CN,
(i) -NR^bR^c,
(j) -$N(R^b)C(=O)R^a$,
(k) -$N(R^b)SO_2R^d$,
(l) -O-CO_2R^d,
(m) -O-$(C=O)$-NR^bR^c,
(n) -NR^b-$(C=O)$-NR^bR^c,
(o) -$C(=O)R^a$,
(p) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo, and
(q) oxo;

(5) halo,
(6) -OR^a,
(7) -CN,
(8) -CO_2R^a,
(9) -$N(R^b)C(=O)R^a$,
(10) -NR^bR^c,
(11) -$C(=O)NR^bR^c$, and
(12) -$O(C=O)R^a$;

or R^6 and R^7 and the carbon atom or atoms to which they are attached join to form a ring selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, dioxolanyl, dioxanyl, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiapyranyl, oxetanyl, thietanyl and tetrahydrothienyl, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from:
  (i) halo,
  (ii) $-OR^a$,
  (iii) $-C_{3-6}$cycloalkyl,
  (iv) $-CO_2R^a$,
  (v) $-NR^bR^c$,
  (vi) $-S(O)_vR^d$,
  (vii) $-C(=O)NR^bR^c$, and
  (viii) phenyl,

(b) $-C_{3-6}$cycloalkyl, wherein the C_{3-6}cycloalkyl group is optionally fused to the ring, and which C_{3-6}cycloalkyl group is unsubstituted or substituted with 1-3 substituents each independently selected from:
  (i) halo,
  (ii) $-OR^a$,
  (iii) $-C_{3-6}$cycloalkyl,
  (iv) $-CO_2R^a$,
  (v) $-NR^bR^c$,
  (vi) $-S(O)_vR^d$,
  (vii) $-C(=O)NR^bR^c$, and
  (viii) phenyl,

(c) phenyl or heterocycle, wherein heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, imidazolyl, furanyl, tetrahydrofuranyl, thiazolyl and oxazolyl, wherein the phenyl or heterocycle is optionally fused to the ring, and which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
  (i) halo,

(ii) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 halo,
(iii) -OR^a,
(iv) -CO_2R^a,
(v) -$O(C=O)R^a$,
(vi) -CN,
(vii) -NR^bR^c,
(viii) oxo,
(ix) -$C(=O)NR^bR^c$,
(x) -$N(R^b)C(=O)R^a$,
(xi) -$N(R^b)CO_2R^a$,
(xii) -$O(C=O)NR^bR^c$, and
(xiii) -$S(O)_vR^d$,

(d) -OR^a,
(e) -CO_2R^a,
(f) -$C(=O)NR^bR^c$,
(g) -$S(O)_vR^d$,
(h) -CN,
(i) halo,
(j) -NR^bR^c,
(k) -$N(R^b)C(=O)R^a$,
(l) -$N(R^b)SO_2R^d$,
(m) -O-CO_2R^d,
(n) -O-$(C=O)$-NR^bR^c,
(o) -NR^b-$(C=O)$-NR^bR^c,
(p) -$C(=O)R^a$, and
(q) oxo;

R^8 is independently selected from:

(1) hydrogen,
(2) -$C(=O)R^a$,
(3) -CO_2R^a,
(4) -$S(=O)R^d$,
(5) -SO_2R^d,
(6) -$C(=O)NR^bR^c$,
(7) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,
(b) -OR^a,

(c) -C_{3-6}cycloalkyl,

(d) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(i) halo,

(ii) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 halo, and

(iii) -OR^a,

(iv) -NR^bR^c,

(v) -$C(=O)R^a$,

(vi) -CO_2R^a, and

(vii) oxo,

(e) -CO_2R^a,

(f) -$C(=O)NR^bR^c$,

(g) -$S(O)_vR^d$,

(h) -CN,

(i) -NR^bR^c,

(j) -$N(R^b)C(=O)R^a$,

(k) -$N(R^b)SO_2R^d$,

(l) -CF_3,

(m) -O-CO_2R^d,

(n) -O-(C=O)-NR^bR^c,

(o) -NR^b-(C=O)-NR^bR^c, and

(p) -$C(=O)R^a$,

(8) -C_{3-6}cycloalkyl, which is unsubstituted or substituted with 1-6 substituents each independently selected from:

(a) halo,

(b) -CN,

(c) -OR^a, and

(d) C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo;

or R^7 and R^8 and the atoms to which they are attached join to form a 4-, 5-, 6- or 7-membered alkyl- or heteroalkyl-ring optionally containing an additional heteroatom selected from N, O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:

(a) halo,
(b) phenyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from: halo, OR^a, CN, and $-C(=O)OR^a$,
(c) $-OR^a$, and
(d) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo;

R^{10} is independently selected from:
(1) hydrogen,
(2) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
(a) halo,
(b) $-OR^a$,
(c) -CN,
(d) phenyl, and
(e) $-C_{3-6}$cycloalkyl, which is unsubstituted or substituted with 1-6 halo,
(3) $-C_{3-6}$cycloalkyl, which is unsubstituted or substituted with 1-6 halo;

R^{11} is independently selected from the group consisting of:
phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl, azepinyl, azepanyl, azetidinyl, benzimidazolyl, benzisoxazolyl, benzofuranyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, 1,3-benzodioxolyl, benzothiazolyl, benzothienyl, benzoxazolyl, benzopyrazolyl, benzotriazolyl, chromanyl, cinnolinyl, dibenzofuranyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, furanyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 4-oxonaphthyridinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxopyridyl, 2-oxoquinolinyl, piperidyl, piperazinyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyridinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuranyl, tetrahydrofuryl, tetrahydroimidazopyridinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, thienyl, triazolyl, isoxazolyl, tetrahydrothienyl, tetrahydropyranyl, oxetanyl, tetrahydrothiapyranyl, and thietanyl, where R^{11} is unsubstituted or substituted with 1-5 substituents each independently selected from R^{12}, R^{13}, R^{14}, R^{15a} and R^{15b};

R^{12}, R^{13}, R^{14}, R^{15a} and R^{15b} are each independently selected from:

(1) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
  (a) halo,
  (b) -OR^a,
  (c) -C_{3-6}cycloalkyl,
  (d) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperdinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
    (i) halo,
    (ii) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 halo, and
    (iii) -OR^a,
  (e) -CO_2R^a,
  (f) -$C(=O)NR^bR^c$,
  (g) -$S(O)_vR^d$,
  (h) -CN,
  (i) -NR^bR^c,
  (j) -$N(R^b)C(=O)R^a$,
  (k) -$N(R^b)SO_2R^d$,
  (l) -CF_3,
  (m) -O-CO_2R^d,
  (n) -O-(C=O)-NR^bR^c,
  (o) -NR^b-(C=O)-NR^bR^c, and
  (p) -$C(=O)R^a$,

(2) -C_{1-6}cycloalkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
  (a) halo,
  (b) -CN,
  (c) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 halo,
  (d) -OR^a, and
  (e) phenyl, which is unsubstituted or substituted with 1-5 substituents where the substituents are each independently selected from:
    (i) -OR^a,
    (ii) halo,
    (iii) -CN, and
    (iv) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5

halo,

(3) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperdinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,

(b) $-OR^a$,

(c) $-C_{3-6}$cycloalkyl,

(d) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

(i) halo,

(ii) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo, and

(iii) $-OR^a$,

(e) $-CO_2R^a$,

(f) $-C(=O)NR^bR^c$,

(g) $-S(O)_vR^d$,

(h) -CN,

(i) $-NR^bR^c$,

(j) $-N(R^b)C(=O)R^a$,

(k) $-N(R^b)SO_2R^d$,

(l) $-O-CO_2R^d$,

(m) $-O-(C=O)-NR^bR^c$,

(n) $-NR^b-(C=O)-NR^bR^c$,

(o) $-C(=O)R^a$, and

(p) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo,

(4) halo,

(5) oxo,

(6) $-OR^a$,

(7) -CN,

(8) $-CO_2R^a$,

(9) $-C(=O)R^a$,

(10) $-NR^bR^c$,

(11) $-S(O)_vR^d$,

(12) $-C(=O)NR^bR^c$,

(13) $-O-CO_2R^d$,

(14) $-N(R^b)CO_2R^d$,

(15) $-O-(C=O)-NR^bR^c$,

(16) - NR^b-(C=O)-NR^bR^c,
(17) -$SO_2NR^bR^c$,
(18) -$N(R^b)SO_2R^d$,

or R^{15a} and R^{15b} and the atom(s) to which they are attached join to form a ring selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thietanyl and tetrahydrothienyl, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from:
  (i) halo,
  (ii) -OR^a,
  (iii) -C_{3-6}cycloalkyl,
  (iv) -CO_2R^a,
  (v) -NR^bR^c,
  (vi) -$S(O)_vR^d$,
  (vii) -$C(=O)NR^bR^c$, and
  (viii) phenyl,
(b) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
  (i) halo,
  (ii) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 halo, and
  (iii) -OR^a,
(c) -OR^a,
(d) halo,
(e) -CO_2R^a,
(f) -$C(=O)NR^bR^c$,
(g) -$S(O)_vR^d$,
(h) -CN,
(i) -NR^bR^c,
(j) -$N(R^b)C(=O)R^a$,
(k) -$N(R^b)SO_2R^d$,
(l) -O-CO_2R^d,

(m) -O-(C=O)-NR^bR^c,

(n) -NR^b-(C=O)-NR^bR^c, and

(o) –C(=O)R^a;

R^{PG} is independently selected from:

(1) hydrogen,

(2) –C_{1-6}alkyl which is unsubstituted or substituted with 1-5 halo,

(3) -CH_2OR^a,

(4) -CH_2-O-$CH_2CH_2Si(CH_3)_3$,

(5) -$CH_2OP(=O)(OR^c)_2$,

(6) -$(CH_2)_k$-phenyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from:

(a) halo,

(b) -OR^a,

(c) -CN, and

(d) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo;

J is independently selected from:

(1) =$C(R^{16a})$-,

(2) -$CR^{17}R^{18}$-,

(3) -C(=O)-, and

(4) -$N(R^b)$-;

Y is independently selected from:

(1) =$C(R^{16b})$-,

(2) -$CR^{17}R^{18}$-,

(3) -C(=O)-,

(4) =N-, and

(5) -$N(R^{16b})$-;

R^{17} and R^{18} are each independently selected from:

(1) hydrogen,

(2) halo,

(3) -OR^a,

(4) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-4 substituents each independently selected from:

(a) halo,

(b) -OR^a,

(c) -CN,

(d) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, piperazinyl,

pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(i) $-OR^a$,

(ii) halo,

(iii) -CN,

(iv) $-C_{1-6}$alkyl which is unsubstituted or substituted with 1-6 halo,

(5) phenyl or heterocycle wherein heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,

(b) -CN,

(c) $-OR^a$,

(d) nitro,

(e) $-C_{1-6}$alkyl which is unsubstituted or substituted with 1-6 halo;

or R^{17} and R^{18} and the atom to which they are attached join to form a 4-, 5-, or 6-membered ring optionally containing a heteroatom selected from N, O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:

(a) halo,

(b) $-OR^a$,

(c) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo, and

(d) phenyl;

R^{16a} and R^{16b} are each independently selected from:

(1) hydrogen,

(2) $-C_{1-4}$alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,

(b) $-OR^a$,

(c) $-C_{3-6}$cycloalkyl,

(d) phenyl or heterocycle, wherein said heterocycle is selected from: imidazolyl, oxazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thiazolyl, thienyl, triazolyl,

isoxazolyl and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:

(i) halo,

(ii) $-OR^a$,

(iii) -CN, and

(iv) C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo,

(3) phenyl or heterocycle, wherein heterocycle is selected from: imidazolyl, oxazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, tetrahydrofuryl, piperidinyl, piperazinyl, pyrrolidinyl, azetidinyl, thiazolyl, thienyl, triazolyl, isoxazolyl and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:

(a) halo,

(b) $-OR^a$,

(c) $-C_{3-6}$cycloalkyl,

(d) $-C_{1-4}$alkyl which is unsubstituted or substituted with 1-6 halo, and

(e) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

(i) halo,

(ii) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo, and

(iii) $-OR^a$,

(4) halo,

(5) $-OR^a$,

(6) -CN,

(7) $-CO_2R^a$,

(8) $-NR^bR^c$, and

(9) $-C(=O)NR^bR^c$;

or R^{16a} and R^{16b} and the atom(s) to which they are attached join to form a ring selected from cyclopentenyl, cyclohexenyl, phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, furanyl, dihydrofuranyl, dihydropyranyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, thienyl, dihydrothienyl and dihydrothiopyranyl, which ring is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from:

(i) halo,

(ii) $-OR^a$,

(iii) $-C_{3-6}$cycloalkyl,

(iv) phenyl or heterocycle, wherein heterocycle is selected from pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(I) $-OR^a$,

(II) halo,

(III) -CN, and

(IV) $-C_{1-6}$alkyl which is unsubstituted or substituted with 1-6 halo,

(v) $-CO_2R^a$,

(vi) $-NR^bR^c$,

(vii) $-S(O)_vR^d$,

(viii) $-C(=O)NR^bR^c$,

(ix) $-N(R^b)CO_2R^a$, and

(x) $-N(R^b)SO_2R^d$,

(b) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, azetidinyl, piperazinyl, pyrrolidinyl, thienyl and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(i) halo,

(ii) $-OR^a$,

(iii) -CN, and

(iv) $-C_{1-6}$alkyl which is unsubstituted or substituted with 1-6 halo,

(c) halo,

(d) $-S(O)_vR^d$,

(e) $-OR^a$,

(f) -CN,

(g) $-C(=O)R^a$,

(h) $-NR^bR^c$,

(i) $-C(=O)NR^bR^c$,

(j) $-CO_2R^a$,

(k) $-(NR^b)CO_2R^a$,

(l) $-O-(C=O)-NR^bR^c$,

(m) $-(NR^b)-(C=O)-NR^bR^c$,

(n) oxido,

(o) oxo, and

(p) $-(NR^b)SO_2R^d$;

R^a is independently selected from:

(1) hydrogen,

(2) C_{1-6}alkyl, which is unsubstituted or substituted with 1-7 substituents each independently selected from:

(a) halo,

(b) $-O-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo,

(c) hydroxyl,

(d) -CN, and

(e) phenyl or heterocycle wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:

(i) halo,

(ii) $-O-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo,

(iii) -CN,

(iv) nitro,

(v) hydroxyl, and

(vi) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo,

(3) phenyl or heterocycle wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:

(a) halo,

(b) -CN,

(c) $-O-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo,

(d) nitro,

(e) hydroxyl, and

(f) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo, and

(4) $-C_{3-6}$cycloalkyl, which is unsubstituted or substituted with 1-6 halo;

R^b and R^c are independently selected from:

(1) hydrogen,

(2) C_{1-6}alkyl, which is unsubstituted or substituted with 1-7 substituents each independently selected from:
  (a) halo,
  (b) $-OR^a$,
  (c) -CN,
  (d) $-CO_2R^a$,
  (e) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
    (i) halo,
    (ii) $-OR^a$,
    (iii) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo, and
    (iv) nitro,

(3) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
  (a) halo,
  (b) $-OR^a$,
  (c) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo,
  (d) $-C_{3-6}$cycloalkyl, which is unsubstituted or substituted with 1-6 halo,
  (e) -CN, and
  (f) $-CO_2R^a$,

(4) $-C_{3-6}$cycloalkyl, which is unsubstituted or substituted with 1-6 halo;
or R^b and R^c and the nitrogen to which they are attached join to form a 4-, 5-, or 6-membered ring optionally containing an additional heteroatom selected from N, O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:
  (a) halo,
  (b) $-OR^a$, and
  (c) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo, and
  (d) phenyl;

R^d is independently selected from:

(1) C_{1-6}alkyl, which is unsubstituted or substituted with 1–4 substituents each independently selected from:
  (a) halo,
  (b) $-OR^a$,
  (c) $-CO_2R^a$,
  (d) -CN, and
  (e) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
    (i) halo,
    (ii) $-OR^a$,
    (iii) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo, and
    (iv) nitro,

(2) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
  (a) halo,
  (b) $-OR^a$,
  (c) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo,
  (d) $-C_{3-6}$cycloalkyl, which is unsubstituted or substituted with 1-6 halo
  (e) -CN, and
  (f) $-CO_2R^a$, and

(3) $-C_{3-6}$cycloalkyl, which is unsubstituted or substituted with 1-6 halo;

R^e and R^f are independently selected from:

(1) hydrogen,
(2) $-C_{1-4}$alkyl, which is unsubstituted or substituted with 1-6 halo,
(3) phenyl, and
(4) benzyl;

or where R^e and R^f and the atom to which they are attached join to form a 3-, 4-, 5-, or 6-membered ring optionally containing a heteroatom selected from N, O, and S, wherein

the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:

(a) halo,

(b) $-OR^a$,

(c) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo, and

(d) phenyl;

m is 1, 2, or 3;

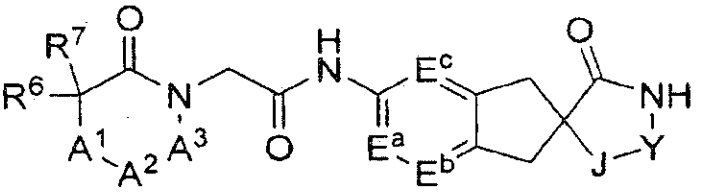
n is 1, 2, or 3;

v is 0, 1, or 2;

k is 0, 1, or 2;

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

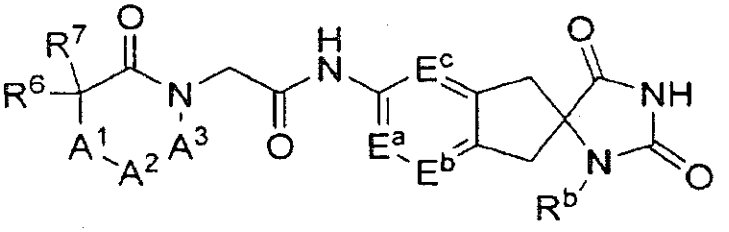
An embodiment of the invention includes compounds of formula Ia:



Ia

wherein A^1, A^2, A^3, J, Y, E^a, E^b, E^c, R^6, and R^7 are defined herein;
and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

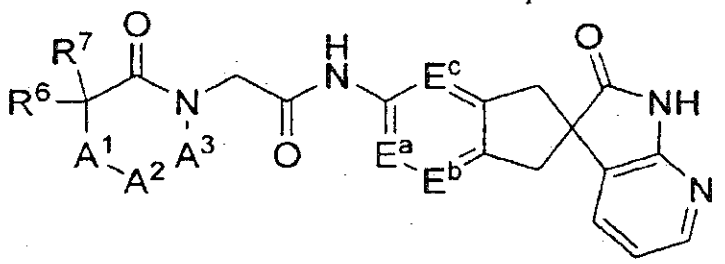
Another embodiment of the invention includes compounds of formula Ib:



Ib

wherein A^1, A^2, A^3, E^a, E^b, E^c, R^b , R^6, and R^7 are defined herein;
and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

Another embodiment of the invention includes compounds of formula Ic:



Ic

wherein A^1, A^2, A^3, E^a, E^b, E^c, R^6 and R^7 are defined herein;
and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

In an embodiment of the present invention A^1 is independently selected from:

(1) -O-,
(2) $-S(O)_v-$,
(3) $-CR^6R^7-$,
(4) $-N(R^8)-$,
(5) $-C(N(R^b)(C=O)OR^a)(R^a)-$,
(6) -(C=O)-, and
(7) $-N(R^{11})-$, wherein v, R^6, R^7, R^8, R^a, R^b, R^c and R^{11} are defined herein.

In an embodiment of the present invention A^1 is –O-.

In an embodiment of the present invention A^1 is $-S(O)_v-$, wherein v is defined herein.

In an embodiment of the present invention A^1 is $-CR^6R^7-$, wherein R^6 and R^7 are defined herein.

In an embodiment of the present invention A^1 is CH_2.

In an embodiment of the present invention A^1 is $-N(R^8)-$, wherein R^8 is defined herein.

In an embodiment of the present invention A^1 is –NH-.

In an embodiment of the present invention A^1 is $-C(OR^a)H-$, wherein R^a is defined herein.

In an embodiment of the present invention A^1 is –C(=O)-.

In an embodiment of the present invention A^1 is $-C(NR^bR^c)H-$, wherein R^b and R^c are defined herein.

In an embodiment of the present invention A^1 is $-C(N(R^b)(C=O)OR^a)H-$, wherein R^a and R^b are defined herein.

In an embodiment of the present invention A^2 is independently selected from:

(1) $-CR^6R^7-$,

(2) $-CR^{10}R^{11}-$, and

(3) -(C=O)-, wherein R^6, R^7, R^{10} and R^{11} are defined herein.

In an embodiment of the present invention A^2 is $-CR^6R^7-$, wherein R^6 and R^7 are defined herein.

In an embodiment of the present invention A^2 is $-CH_2-$.

In an embodiment of the present invention A^2 is –(C=O)-.

In an embodiment of the present invention A^3 is independently selected from:

(1) $-CR^6R^7-$,

(2) $-CR^{10}R^{11}-$, and

(3) $-N(R^{11})-$, wherein R^6, R^7, R^{10} and R^{11} are defined herein.

In an embodiment of the present invention A^3 is $-CR^6R^7-$, wherein R^6 and R^7 are defined herein.

In an embodiment of the present invention A^3 is $-CR^{10}R^{11}-$, wherein R^{10} and R^{11} are defined herein.

In an embodiment of the present invention A^4 is independently selected from:

(1) $-CR^6R^7-$,

(2) $-CR^{10}R^{11}-$,

(3) $-N(R^{11})-$,

(4) $-N(R^8)-$, and

(4) a bond between A^2 and A^3, wherein R^6, R^7, R^8, R^{10} and R^{11} are defined herein.

In an embodiment of the present invention A^4 is CH_2.

In an embodiment of the present invention A^4 is a bond between A^2 and A^3.

In an embodiment of the present invention E^a is $-C(R^{5a})=$, wherein R^{5a} is defined herein.

In an embodiment of the present invention E^a is –C(H)=.

In an embodiment of the present invention E^a is –N=.

In an embodiment of the present invention E^b is $-C(R^{5b})=$, wherein R^{5b} is defined herein.

In an embodiment of the present invention E^b is –C(H)=.

In an embodiment of the present invention E^b is –N=.

In an embodiment of the present invention E^c is $-C(R^{5c})=$, wherein R^{5c} is defined herein.

In an embodiment of the present invention E^c is –C(H)=.

In an embodiment of the present invention E^c is –N=.

In an embodiment of the present invention Q is –(C=O)-.

In an embodiment of the present invention R^4 is selected from: hydrogen and $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 fluoro.

In an embodiment of the present invention R^4 is hydrogen.

In an embodiment of the present invention R^{5a}, R^{5b} and R^{5c} are independently selected from hydrogen and halo.

In an embodiment of the present invention R^{5a}, R^{5b} and R^{5c} are hydrogen.

In an embodiment of the present invention R^6 and R^7 are independently selected from:

(1) hydrogen,

(2) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 substituents where the substitutents are each independently selected from: halo, phenyl, and $-OR^a$,

(3) $-C_{3-6}$cycloalkyl, which is unsubstituted or substituted with 1-5 fluoro,

(4) phenyl or heterocycle, which is unsubstituted or substituted with 1-5 halo, wherein heterocycle is defined herein,

(5) halo,

(6) $-OR^a$,

(7) $-NR^bR^c$, and

(8) $-O(C=O)R^a$, wherein R^a, R^b and R^c are defined herein.

In an embodiment of the present invention R^6 and R^7 are independently selected from hydrogen, OH and $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 fluoro.

In an embodiment of the present invention R^6 and R^7 are independently selected from hydrogen, $-NR^bR^c$ and $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 fluoro, wherein R^b and R^c are defined herein.

In an embodiment of the present invention R^6 and R^7 are independently selected from hydrogen and $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 fluoro.

In an embodiment of the present invention R^6 and R^7 are ethyl, which are unsubstituted or substituted with 1-5 fluoro.

In an embodiment of the present invention R^6 and R^7 are methyl, which are unsubstituted or substituted with 1-3 fluoro.

In an embodiment of the present invention R^6 and R^7 and the carbon atom or atoms to which they are attached join to form a ring selected from cyclopropyl, cyclobutyl, cyclopentyl, dioxolanyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, tetrahydropyranyl, pyrrolidinyl, and piperidinyl, which ring is unsubstituted or substituted with 1-6 substituents each independently selected from:

(1) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-3 substituents where the substitutents are each independently selected from: halo, and -OR^a,

(2) phenyl or pyridyl, wherein the phenyl or pyridyl is optionally fused to the ring, and which phenyl or pyridyl is unsubstituted or substituted with 1-3 substituents each independently selected from: halo, -OR^a, and -C_{1-4}alkyl, which is unsubstituted or substituted with 1-5 fluoro,

(3) halo, and

(4) -CO_2R^a,

wherein R^a is defined herein.

In an embodiment of the present invention R^8 is selected from: hydrogen, -$C(=O)R^a$, -CO_2R^a, -SO_2R^d, and –C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 fluoro, wherein R^a and R^d are defined herein.

In an embodiment of the present invention R^8 is selected from: hydrogen, and –C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 fluoro.

In an embodiment of the present invention R^8 is hydrogen.

In an embodiment of the present invention R^8 is methyl

In an embodiment of the present invention R^8 and R^7 and the atoms to which they are attached join to form a 4-, 5-, 6- or 7-membered alkyl- or heteroalkyl-ring optionally containing an additional heteroatom selected from N, O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:

(1) halo,

(2) phenyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from: halo, OR^a, CN, and –$C(=O)OR^a$,

(3) -OR^a, and

(4) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo, wherein R^a is defined herein.

In an embodiment of the present invention R^{10} is selected from: hydrogen, and –C_{1-6}alkyl, which is unsubstituted or substituted with fluoro.

In an embodiment of the present invention R^{10} is hydrogen.

In an embodiment of the present invention R^{11} is independently selected from the group consisting of:

phenyl, furanyl, pyrazinyl, pyridinyl, pyridyl, pyrimidinyl, pyrimidyl, tetrazolyl, thienyl, triazolyl,and isoxazolyl, where R^{11} is unsubstituted or substituted with 1-5 substituents each independently selected from R^{12}, R^{13}, R^{14}, R^{15a} and R^{15b}, wherein R^{12}, R^{13}, R^{14}, R^{15a} and R^{15b} are defined herein.

In an embodiment of the present invention R^{11} is phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from R^{12}, R^{13}, R^{14}, R^{15a} and R^{15b}, wherein R^{12}, R^{13}, R^{14}, R^{15a} and R^{15b} are defined herein.

In an embodiment of the present invention R^{PG} is selected from: hydrogen and -C_{1-6}alkyl, which is unsubstituted or substituted with 1-3 halo.

In an embodiment of the present invention R^{PG} is methyl.

In an embodiment of the present invention R^{PG} is hydrogen.

In an embodiment of the present invention J is $=C(R^{16a})-$, $-CR^{17}R^{18}-$ or $-N(R^b)-$, wherein R^{16a}, R^{17}, R^{18} and R^b are defined herein.

In an embodiment of the present invention J is $=C(R^{16a})-$, wherein R^{16a} is defined herein.

In an embodiment of the present invention J is $-CR^{17}R^{18}-$, wherein R^{17} and R^{18} are defined herein.

In an embodiment of the present invention J is $-CH_2-$.

In an embodiment of the present invention J is $-N(R^b)-$, wherein R^b is defined herein.

In an embodiment of the present invention J is $-N(CH_3)-$.

In an embodiment of the present invention Y is $=C(R^{16b})-$, $-CR^{17}R^{18}-$ or $-C(=O)-$, wherein R^{16b}, R^{17} and R^{18} are defined herein.

In an embodiment of the present invention Y is $=C(R^{16b})-$, wherein R^{16b} is defined herein.

In an embodiment of the present invention Y is $-C(=O)-$.

In an embodiment of the present invention R^{16a} and R^{16b} are independently selected from:

(1) hydrogen,

(2) -C_{1-4}alkyl, which is unsubstituted or substituted with 1-3 fluoro, and

(3) phenyl or heterocycle, wherein heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, thiazolyl, thienyl, triazolyl, isoxazolyl and morpholinyl.

In an embodiment of the present invention R^{16a} and R^{16b} and the atom(s) to which they are attached join to form a ring selected from phenyl, pyridyl, and pyrimidinyl, which ring is unsubstituted or substituted with 1-3 substituents each independently selected from: halo, OR^a and -C_{1-4}alkyl, which is unsubstituted or substituted with 1-3 fluoro, wherein R^a is defined herein.

In an embodiment of the present invention R^{16a} and R^{16b} and the atom(s) to which they are attached join to form a ring selected from pyridyl, and pyrimidinyl.

In an embodiment of the present invention m is 1.

In an embodiment of the present invention n is 1.

In an embodiment of the present invention n is 2.

It is to be understood that where one or more of the above recited structures or substructures recite multiple substituents having the same designation each such variable may be the same or different from each similarly designated variable. For example, if R^8 is recited multiple times in an embodiment of formula I, each instance of R^8 in formula I may independently be any of the substructures defined under R^8. The invention is not limited to structures and substructures wherein each R^8 must be the same for a given structure. The same is true with respect to any variable appearing multiple times in a structure or substructure.

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds.

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

The present invention includes compounds of formula I wherein one or more hydrogen atoms are replaced by deuterium.

Tautomers of compounds defined in Formula I are also included within the scope of the present invention. For example, compounds including carbonyl –$CH_2C(=O)$- groups (keto forms) may undergo tautomerism to form hydroxyl –CH=C(OH)- groups (enol forms). Both keto and enol forms are included within the scope of the present invention.

As will be appreciated by those of skill in the art, not all of the R^6 and R^7 substituents are capable of forming a ring structure. Moreover, even those substituents capable of ring formation may or may not form a ring structure.

Also as appreciated by those of skill in the art, halo or halogen as used herein are intended to include chloro, fluoro, bromo and iodo.

As used herein, "alkyl" is intended to mean linear, branched and cyclic structures having no carbon-to-carbon double or triple bonds. Thus C_{1-6}alkyl is defined to identify the group as having 1, 2, 3, 4, 5 or 6 carbons in a linear or branched arrangement. "Cycloalkyl" is an alkyl, part or all of which which forms a ring of three or more atoms. C_0 or C_0alkyl is defined to identify the presence of a direct covalent bond.

The term "alkenyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon double bond, wherein hydrogen may be replaced by an additional carbon-to-carbon double bond.

The term "alkynyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon triple bond.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. The term "heterocycle" or "heterocyclic", as used herein except where noted, represents a stable 4- to 8-membered monocyclic- or stable 8- to 12-membered bicyclic heterocyclic ring system which is either saturated or unsaturated, and which consists of carbon atoms and from one to six heteroatoms selected from the group consisting of N, O, S, P and Si, and wherein the nitrogen, sulfur and phosphorus heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic groups include, but are not limited to, azetidine, chroman, dihydrofuran, dihydropyran, dioxane, dioxolane, hexahydroazepine, imidazolidine, imidazolidinone, imidazoline, imidazolinone, indoline, isochroman, isoindoline, isothiazoline, isothiazolidine, isoxazoline, isoxazolidine, morpholine, morpholinone, oxazoline, oxazolidine, oxazolidinone, oxetane, 2-oxohexahydroazepin, 2-oxopiperazine, 2-oxopiperidine, 2-oxopyrrolidine, piperazine, piperidine, pyran, pyrazolidine, pyrazoline, pyrrolidine, pyrroline, quinuclidine, tetrahydrofuran, tetrahydropyran, thiamorpholine, thiazoline, thiazolidine, thiomorpholine and N-oxides thereof.

The term "heteroaryl", as used herein except where noted, represents a stable 5- to 7-membered monocyclic- or stable 9- to 10-membered fused bicyclic heterocyclic ring system which contains an aromatic ring, any ring of which may be saturated, such as piperidinyl, partially saturated, or unsaturated, such as pyridinyl, and which consists of carbon atoms and from one to six heteroatoms selected from the group consisting of N, O, S, P and Si, and wherein

the nitrogen, sulfur and phosphorus heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heteroaryl groups include, but are not limited to, benzimidazole, benzisothiazole, benzisoxazole, benzofuran, benzothiazole, benzothiophene, benzotriazole, benzoxazole, carboline, cinnoline, furan, furazan, imidazole, indazole, indole, indolizine, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, quinazoline, quinoline, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazine, triazole, and N-oxides thereof.

The term "alkoxy," as in C_1-C_6 alkoxy, is intended to refer to include alkoxy groups of from 1 to 6 carbon atoms of a straight, branched and cyclic configuration.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. In one aspect of the invention the salts are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric, and tartaric acids. It will be understood that,

as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Exemplifying the invention is the use of the compounds disclosed in the Examples and herein. Specific compounds within the present invention include a compound which is selected from the group consisting of the compounds disclosed in the following Examples and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

The subject compounds are useful in a method of antagonism of CGRP receptors in a patient such as a mammal in need of such antagonism comprising the administration of an effective amount of the compound. The present invention is directed to the use of the compounds disclosed herein as antagonists of CGRP receptors. In addition to primates, especially humans, a variety of other mammals can be treated according to the method of the present invention.

Another embodiment of the present invention is directed to a method for the treatment, control, amelioration, or reduction of risk of a disease or disorder in which the CGRP receptor is involved in a patient that comprises administering to the patient a therapeutically effective amount of a compound that is an antagonist of CGRP receptors.

The present invention is further directed to a method for the manufacture of a medicament for antagonism of CGRP receptors activity in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

The subject treated in the present methods is generally a mammal, for example a human being, male or female, in whom antagonism of CGRP receptor activity is desired. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. As used herein, the term "treatment" refers both to the treatment and to the prevention or prophylactic therapy of the mentioned conditions, particularly in a patient who is predisposed to such disease or disorder.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Such term in relation to pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient

must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the terms "administration of" or "administering a" compound shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

The utility of the compounds in accordance with the present invention as antagonists of CGRP receptor activity may be demonstrated by methodology known in the art. Inhibition of the binding of ^{125}I-CGRP to receptors and functional antagonism of CGRP receptors were determined as follows:

NATIVE RECEPTOR BINDING ASSAY: The binding of ^{125}I-CGRP to receptors in SK-N-MC cell membranes was carried out essentially as described (Edvinsson *et al.* (2001) *Eur. J. Pharmacol.* **415**, 39-44). Briefly, membranes (25 μg) were incubated in 1 mL of binding buffer [10 mM HEPES, pH 7.4, 5 mM $MgCl_2$ and 0.2% bovine serum albumin (BSA)] containing 10 pM ^{125}I-CGRP and antagonist. After incubation at room temperature for 3 h, the assay was terminated by filtration through GFB glass fibre filter plates (PerkinElmer) that had been blocked with 0.5% polyethyleneimine for 3 h. The filters were washed three times with ice-cold assay buffer (10 mM HEPES, pH 7.4 and 5 mM $MgCl_2$), then the plates were air dried. Scintillation fluid (50 μL) was added and the radioactivity was counted on a Topcount (Packard Instrument). Data analysis was carried out by using Prism and the K_i was determined by using the Cheng–Prusoff equation (Cheng & Prusoff (1973) *Biochem. Pharmacol.* **22**, 3099-3108).

RECOMBINANT RECEPTOR: Human CL receptor (Genbank accession number L76380) was subcloned into the expression vector pIREShyg2 (BD Biosciences Clontech) as a 5'NheI and 3' PmeI fragment. Human RAMP1 (Genbank accession number AJ001014) was subcloned into the expression vector pIRESpuro2 (BD Biosciences Clontech) as a 5'NheI and 3'NotI fragment. HEK 293 cells (human embryonic kidney cells; ATCC #CRL-1573) were cultured in DMEM with 4.5 g/L glucose, 1 mM sodium pyruvate and 2 mM glutamine supplemented with 10% fetal bovine serum (FBS), 100 units/mL penicillin and 100 μg/mL streptomycin, and maintained at 37 °C and 95% humidity. Cells were subcultured by

treatment with 0.25% trypsin with 0.1% EDTA in HBSS. Stable cell line generation was accomplished by co-transfecting 10 μg of DNA with 30 μg Lipofectamine 2000 (Invitrogen) in 75 cm^2 flasks. CL receptor and RAMP1 expression constructs were co-transfected in equal amounts. Twenty-four hours after transfection the cells were diluted and selective medium (growth medium + 300 μg/mL hygromycin and 1 μg/mL puromycin) was added the following day. A clonal cell line was generated by single cell deposition utilizing a FACS Vantage SE (Becton Dickinson). Growth medium was adjusted to 150 μg/mL hygromycin and 0.5 μg/mL puromycin for cell propagation.

RECOMBINANT RECEPTOR BINDING ASSAY: Cells expressing recombinant human CL receptor/RAMP1 were washed with PBS and harvested in harvest buffer containing 50 mM HEPES, 1 mM EDTA and Complete protease inhibitors (Roche). The cell suspension was disrupted with a laboratory homogenizer and centrifuged at 48,000 g to isolate membranes. The pellets were resuspended in harvest buffer plus 250 mM sucrose and stored at –70°C. For binding assays, 20 μg of membranes were incubated in 1 ml binding buffer (10 mM HEPES, pH 7.4, 5 mM $MgCl_2$, and 0.2% BSA) for 3 hours at room temperature containing 10 pM ^{125}I-hCGRP (GE Healthcare) and antagonist. The assay was terminated by filtration through 96-well GFB glass fiber filter plates (PerkinElmer) that had been blocked with 0.05% polyethyleneimine. The filters were washed 3 times with ice-cold assay buffer (10 mM HEPES, pH 7.4 and 5 mM $MgCl_2$). Scintillation fluid was added and the plates were counted on a Topcount (Packard). Non-specific binding was determined and the data analysis was carried out with the apparent dissociation constant (K_i) determined by using a non-linear least squares fitting the bound CPM data to the equation below:

$$Y_{obsd} = \frac{(Y_{max} - Y_{min})(\%I_{max} - \%I_{min} / 100) + Y_{min} + (Y_{max} - Y_{min})(100 - \%I_{max}/100)}{1 + ([Drug] / K_i (1 + [Radiolabel] / K_d)^{nH}}$$

Where Y is observed CPM bound, Y_{max} is total bound counts, Y_{min} is non specific bound counts, ($Y_{max} - Y_{min}$) is specific bound counts, % I_{max} is the maximum percent inhibition, % I min is the minimum percent inhibition, radiolabel is the probe, and the K_d is the apparent dissociation constant for the radioligand for the receptor as determined by Hot saturation experiments.

RECOMBINANT RECEPTOR FUNCTIONAL ASSAY: Cells were plated in complete growth medium at 85,000 cells/well in 96-well poly-D-lysine coated plates (Corning) and cultured for ~ 19 h before assay. Cells were washed with PBS and then incubated with inhibitor for 30 min at 37 °C and 95% humidity in Cellgro Complete Serum-Free/Low-Protein medium (Mediatech, Inc.) with L-glutamine and 1 g/L BSA. Isobutyl-methylxanthine was added to the cells at a concentration of 300 μM and incubated for 30 min at 37 °C. Human α-CGRP was added to the cells at a concentration of 0.3 nM and allowed to incubate at 37 °C for 5 min. After α-CGRP stimulation the cells were washed with PBS and processed for cAMP determination utilizing the two-stage assay procedure according to the manufacturer's

recommended protocol (cAMP SPA direct screening assay system; RPA 559; GE Healthcare). Dose response curves were plotted and IC_{50} values determined from a 4-parameter logistic fit as defined by the equation $y = ((a-d)/(1+(x/c)^b) + d$, where y = response, x = dose, a = max response, d = min response, c = inflection point and b = slope.

In particular, the compounds of the following examples had activity as antagonists of the CGRP receptor in the aforementioned assays, generally with a K_i or IC_{50} value of less than about 50 μM. Such a result is indicative of the intrinsic activity of the compounds in use as antagonists of CGRP receptors.

The ability of the compounds of the present invention to act as CGRP antagonists makes them useful pharmacological agents for disorders that involve CGRP in humans and animals, but particularly in humans.

The compounds of the present invention have utility in treating, preventing, ameliorating, controlling or reducing the risk of one or more of the following conditions or diseases: headache; migraine; cluster headache; chronic tension type headache; pain; chronic pain; neurogenic inflammation and inflammatory pain; neuropathic pain; eye pain; tooth pain; diabetes; non-insulin dependent diabetes mellitus; vascular disorders; inflammation; arthritis; bronchial hyperreactivity, asthma; shock; sepsis; opiate withdrawal syndrome; morphine tolerance; hot flashes in men and women; allergic dermatitis; psoriasis; encephalitis; brain trauma; epilepsy; neurodegenerative diseases; skin diseases; neurogenic cutaneous redness, skin rosaceousness and erythema; inflammatory bowel disease, irritable bowel syndrome, cystitis; and other conditions that may be treated or prevented by antagonism of CGRP receptors. Of particular importance is the acute or prophylactic treatment of headache, including migraine and cluster headache.

The subject compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the diseases, disorders and conditions noted herein.

The subject compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the aforementioned diseases, disorders and conditions in combination with other agents.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which compounds of Formula I or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical

composition in unit dosage form containing such other drugs and the compound of Formula I is preferred. However, the combination therapy may also include therapies in which the compound of Formula I and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of Formula I. Such combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active compounds. Likewise, compounds of the present invention may be used in combination with other drugs that are used in the prevention, treatment, control, amelioration, or reduction of risk of the diseases or conditions for which compounds of the present invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

The weight ratio of the compound of the compound of the present invention to the other active ingredient(s) may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000:1 to about 1:1000, or from about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

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

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants

and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals the compounds of the invention are effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, solutions, hard or soft capsules, or syrups or elixirs.

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

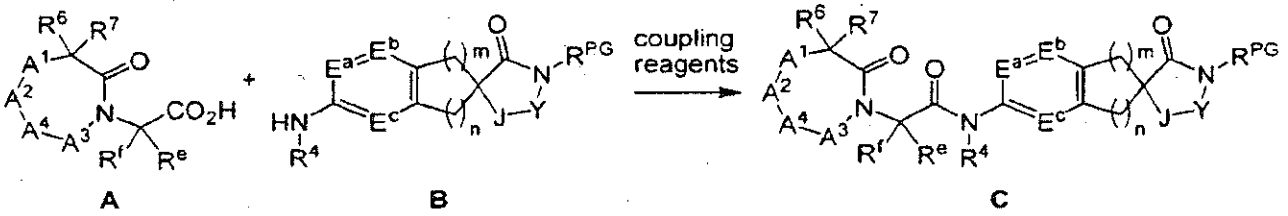
In the treatment, prevention, control, amelioration, or reduction of risk of conditions which require antagonism of CGRP receptor activity an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are may be provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0. 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, or may be administered once or twice per day.

When treating, preventing, controlling, ameliorating, or reducing the risk of headache, migraine, cluster headache, or other diseases for which compounds of the present invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body weight, given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligrams to about 1000 milligrams, or from about 1 milligrams to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

Several methods for preparing the compounds of this invention are illustrated in the following Examples. Starting materials are made according to procedures known in the art or as illustrated herein.

The compounds of the present invention can be prepared readily according to Scheme 1 and specific examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art but are not mentioned in greater detail.

SCHEME 1



Scheme 1 illustrates the general strategy for preparing the compounds of the present invention by coupling of a carboxylic acid intermediate (A) to an amine (B) to give the desired product amide **C**. Various carboxylic acid intermediates, such as those described herein (*vide infra*), may be coupled to a variety of amines to give the compounds of the present invention. There are many known strategies for effecting such coupling chemistry, including use of coupling reagents, such as EDC with HOBT, PyBOP, HATU, CDI and the like. Alternatively, the carboxylic acid **A** may be activated as an acid chloride or anhydride, for example, to facilitate reaction with the amine of interest. Activation of the amine **B**, for example as the corresponding aluminum amide which may be reacted with an ester derivative of carboxylic acid **A**, may also be a useful strategy in cases where the amine is relatively unreactive. In some cases, various protecting group strategies familiar to one skilled in the art of organic synthesis may be employed to allow preparation of a particular compound of the present invention.

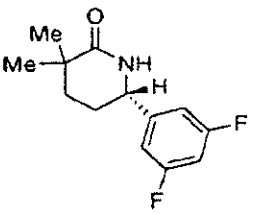
It is understood that alternative methodologies may also be employed in the synthesis of these key intermediates. For instance, racemic reaction sequences may be utilized, followed by chiral separations at appropriate steps to provide compounds of the present invention. The exact choice of reagents, solvents, temperatures, and other reaction conditions, depends upon the nature of the intended product. In some cases, appropriate protecting group strategies may be used.

In some cases the final product may be further modified, for example, by manipulation of substituents. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art.

In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. Additionally, various

protecting group strategies may be employed to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

INTERMEDIATE 1



(6*S*)-6-(3,5-Difluorophenyl)-3,3-dimethylpiperidin-2-one

Step A. Dimethyl 2,2-dimethylpentanedioate

To a solution of 3,3-dimethyldihydro-2*H*-pyran-2,6(3*H*)-dione (20.0 g, 141 mmol) in MeOH (140 mL), at ambient temperature and under a constant stream of nitrogen, was added TMSCl (7.64 g, 70.3 mmol). The reaction mixture was then heated to 60 °C for 3.25 h, before being cooled to ambient temperature. The reaction mixture was then concentrated *in vacuo* before being diluted with diethyl ether (200 mL) and water (100 mL). The organics were then washed with 100 mL, individually, of each of the following aqueous solutions: 1 M NaOH, 1 M HCl, water, half-saturated brine and saturated brine. The organics were then dried over sodium sulfate, filtered and concentrated *in vacuo* to give the title compound, which was used without further purification. MS: m/z = 189 (M + 1).

Step B. 5-Methoxy-4,4-dimethyl-5-oxopentanoic acid

To a solution of dimethyl 2,2-dimethylpentanedioate from Step A (25.4 g, 135 mol) in MeOH (150 mL), THF (100 mL) and water (100 mL), was added potassium carbonate (36.2 g, 262 mmol). This biphasic solution was allowed to stir for 68 h, at ambient temperature, after which time the reaction was about 50% complete. Solvents were carefully removed *in vacuo* such that the starting materials did not vaporize. The aqueous layer was diluted with water (266 mL) and then extracted with diethyl ether until no additional SM was detected in the aqueous layer. The aqueous layer was made acidic by the addition of 6 M HCl (95 mL), and was then saturated with NaCl. This aqueous layer was extracted once with diethyl ether (250 mL). This ethereal layer was washed with brine, then dryed over sodium sulfate, filtered and concentrated *in vacuo* to give the title compound. MS: m/z = 175 (M + 1).

Step C. Methyl 5-[methoxy(methyl)amino]-2,2-dimethyl-5-oxopentanoate

To a solution of 5-methoxy-4,4-dimethyl-5-oxopentanoic acid from Step B (7.00 g, 40.2 mmol), in DCM, was added DMF (0.1 mL), followed by the slow addition of oxalyl chloride (5.00 g, 39.4 mmol) over 33 minutes, during which time the reaction flask was maintained under a constant stream of dry nitrogen. Stirring was continued under a light stream of dry nitrogen for an additional hour, during which time the rate of carbon dioxide evolution diminished. This freshly formed acid chloride was then transferred via canula into a 500 mL round bottom flask, cooled to 0 °C, which already contained *N*-methoxymethanamine hydrochloride (5.76 g, 59.1 mmol) and triethylamine (15.9 g, 158 mmol). Fifteen minutes after complete addition of the acid chloride, the ice bath was removed and the reaction was allowed to warm to ambient temperature. After 1 h at ambient temperature, diethyl ether (100 mL) was added to precipitate some of the triethylamine hydrochloride, which was filtered and washed with more diethyl ether. The combined organics were then washed with 1M HCl (100 mL x 2), 1M NaOH (100 mL), water (100 mL), half-saturated brine (100 mL) and saturated brine (100 mL). The organics were then dried over sodium sulfate, filtered and concentrated *in vacuo* to provide the title compound which was used without further purification. MS: m/z = 218 (M + 1).

Step D. Methyl 5-(3,5-difluorophenyl)-2,2-dimethyl-5-oxopentanoate

To a solution of methyl 5-[methoxy(methyl)amino]-2,2-dimethyl-5-oxopentanoate from Step C (4.68 g, 21.6 mmol) in THF (46.8 mL), cooled to 0 °C, was added 3,5-difluorophenyl magnesium bromide (65 mL, 0.5 M in THF, 32.3 mmol) over 30 minutes. The reaction was allowed to stir at ambient temperature for 2 h, after which time no additional reaction progress was observed. Additional 3,5-difluorophenyl magnesium bromide (50 mL, 0.5 M in THF, 25.0 mmol) was added over 30 minutes. After 3 h at 0 °C, the reaction was quenched by the rapid addition of a cold (0 °C) solution of EtOH (71 mL) and conc. HCl (5.0 mL). The reaction was then diluted with water (200 mL) and diethyl ether (400 mL). The organics were washed with water (200 mL x 3) and brine (100 mL), then dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a residue. This residue was purified by silica gel chromatography, eluting with a gradient of CH_2Cl_2:hexanes – 50:50 to 100:0, to give the title compound. MS: m/z = 239 (M - 31(MeO^-)).

Step E. Methyl (5*S*)-5-{[(*S*)-*tert*-butylsulfinyl]amino}-5-(3,5-difluorophenyl)-2,2-dimethylpentanoate

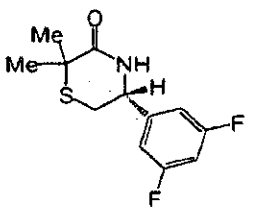
To a solution of methyl 5-(3,5-difluorophenyl)-2,2-dimethyl-5-oxopentanoate from Step D (500. mg, 1.85 mmol) and (*S*)-2-methylpropane-2-sulfinamide (336 mg, 2.78 mmol) in THF (6.5 mL), was added titanium tetraethoxide (616 mg, 2.52 mmol). The reaction vessel was quickly sealed and placed into a 60 °C bath for 3 hours. After cooling to ambient

temperature a septum and nitrogen inlet were attached prior to cooling to 0 °C. Sodium borohydride (191 mg, 5.05 mmol) was then added, and a complete reaction was observed after 15 minutes. Methyl alcohol was then slowly added until gas evolution had stopped. The reaction mixture was then diluted with saturated brine (6.5 mL) while experiencing rapid stirring. The resultant slurry was filtered through celite, washing with EtOAc as needed. The combined organics were then washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to give an oil. This oil was purified by silica gel chromatography, eluting with a gradient of EtOAc:Hexanes – 10:90 to 70:30, to give the title compound containing about 12% of the corresponding ethyl ester. MS: m/z = 376 (M + 1).

Step F. (6*S*)-6-(3,5-Difluorophenyl)-3,3-dimethylpiperidin-2-one

A solution of methyl (5*S*)-5-{[(*S*)-*tert*-butylsulfinyl]amino}-5-(3,5-difluorophenyl)-2,2-dimethylpentanoate from Step E (300. mg, 0.800 mmol) in MeOH (16 mL) was cooled to 0 °C. Hydrogen chloride gas (anhydrous) was bubbled through this cold solution for about 30 seconds, after which time the reaction vessel was sealed and allowed to sit in the ice bath for 15 minutes. Dry nitrogen was then bubbled through the solution for 30 minutes, prior to removal of solvent *in vacuo*. More MeOH (~50 mL) was added, and then removed *in vacuo*. After dissolving in a third volume of MeOH (16 mL), triethylamine (323 mg, 3.2 mmol) was introduced and the mixture was heated to 65 °C for 16 hours. After cooling to ambient temperature, the solvent was removed *in vacuo* and the residue was partitioned between diethyl ether (50 mL) and 1 M HCl (50 mL). The organics were washed with additional 1 M HCl (50 mL), water (50 mL) and saturated brine (50 mL). The ethereal solution was dried over sodium sulfate, filtered and then concentrated *in vacuo* to provide the title compound, which could be used without further purification. MS: m/z = 240 (M + 1).

INTERMEDIATE 2



(5*R*)-5-(3,5-Difluorophenyl)-2,2-dimethylthiomorpholin-3-one

Step A. 2-{[2-(3,5-Difluorophenyl)-2-oxoethyl]thio}-2-methylpropanoic acid

To a solution of 3,5-difluorophenacyl bromide (845 mg, 3.60 mmol) in THF (12 mL) and water (12 mL) was added sodium bicarbonate (317 mg, 3.78 mmol) and 2-mercaptoisobutryic acid (432 mg, 3.60 mmol). The reaction mixture was allowed to stir at ambient temperature for 1.0 h under a stream of nitrogen. The reaction mixture was diluted with diethyl ether (50 mL) and 1 M HCl (15 mL). The organic layer was then washed with 20 mL saturated brine. The organics were then dried over sodium sulfate, filtered and concentrated *in vacuo* to give the title compound, which was used without further purification. MS: *m/z* = 229 (M – CO_2H).

Step B. Methyl 2-{[2-(3,5-difluorophenyl)-2-oxoethyl]thio}-2-methylpropanoate

To a solution of 2-{[2-(3,5-difluorophenyl)-2-oxoethyl]thio}-2-methylpropanoic acid from Step A (400. mg, 1.46 mmol) in MeOH (3 mL), was added trimethylsilyldiazomethane (2 M in hexanes) until yellow color persists. The reaction mixture was stirred for an additional twenty minutes. The reaction mixture was diluted with ether (30 mL) and water (10 mL). The organics were washed with 5% sodium bicarbonate and then with saturated brine. The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a residue. This residue was purified by silica gel chromatography, eluting with a gradient of CH_2Cl_2:Hexanes – 40:60 to 90:10, to give the title compound. MS: *m/z* = 229 (M – CO_2Me).

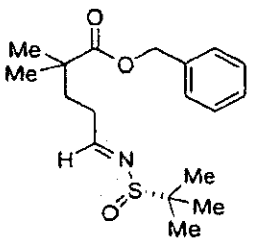
Step C. Ethyl 2-{[(2*R*)-2-[(*tert*-butylsulfinyl)amino]-2-(3,5-difluorophenyl)ethyl]thio}-2-methylpropanoate

To methyl 2-{[2-(3,5-difluorophenyl)-2-oxoethyl]thio}-2-methylpropanoate from Step B (500. mg, 1.74 mmol) was added (*R*)-(+)-2-methyl-2-propanesulfinamide (254 mg, 2.09 mmol) under a constant stream of nitrogen. The reagents were dissolved in THF (17 mL), and to the above mixture was added titanium ethoxide (796 mg, 3.49 mmol). The reaction was sealed and stirred at 60 °C for 15 hours. The reaction was complete as determined by LCMS analysis and transesterification was observed. The reaction was cooled gradually to 0 °C under nitrogen. To the reaction mixture was added sodium borohydride (132 mg, 3.49 mmol). The reaction was complete after fifteen minutes as indicated by LCMS analysis. The reaction was quenched after an additional twenty minutes of stirring with methanol until gas evolution ceased. Saturated brine (30 mL) was added with heavy stirring and the resulting slurry was filtered through celite and washed with aliquots of ethyl acetate. The organic layer was then washed with brine and dried over sodium sulfate. The solution was filtered and concentrated *in vacuo* to provide a residue that was purified by silica gel chromatography, eluting with a gradient of EtOAc:Hexanes – 20:80 to 75:25, to give the title compound (containing 10% of the undesired diastereomer). MS: *m/z* = 408 (M + 1).

Step D. (5*R*)-5-(3,5-Difluorophenyl)-2,2-dimethylthiomorpholin-3-one

To a solution of methyl 2-{[(2*R*)-2-[(*tert*-butylsulfinyl)amino]-2-(3,5-difluorophenyl)ethyl]thio}-2-methylpropanoate from Step C (428 mg, 1.09 mmol) in MeOH (20 mL), cooled to 0 °C, was added anhydrous HCl gas for 1 minute. The reaction was sealed and allowed to sit at 0 °C for fifteen minutes, after which nitrogen was bubbled through the reaction for twenty minutes. The reaction was concentrated *in vacuo*. Additional MeOH (30 mL) was added and it was again concentrated *in vacuo*. This was repeated with another addition of MeOH and triethylamine (440. mg, 4.35 mmol). To the resulting residue was added toluene (10 mL) and triethylamine (440. mg, 4.35 mmol). A reflux condenser was attached and the mixture stirred at 115 °C. After one week of stirring, the reaction was judged to be 90% complete by LCMS. The mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was diluted with diethyl ether (50 mL) and washed individually with 20 mL of each of the following aqueous solutions: 1 M HCl (twice), water, and saturated brine. The organic layer was then dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a residue that was purified by silica gel chromatography, eluting with a gradient of MeOH:CH_2Cl_2 – 1:99 to 5:95, to give the title compound. MS: *m/z* = 258 (M + 1).

INTERMEDIATE 3



Benzyl 5-{[(*S*)-*tert*-butylsulfinyl]imino}-2,2-dimethylpentanoate

Step A. Benzyl 2,2-dimethylpent-4-enoate

To a mixture of K_2CO_3 (1.58 g, 11.5 mmol), 2,2-dimethylpent-4-enoic acid (1.30 g, 10.1 mmol) and DMF (8.1 mL) was added benzyl bromide (1.40 g, 8.19 mmol) slowly over 15 minutes. After 4 hours the mixture was diluted with a mixture of water (80 mL) and diethylether (80 mL). The organic layer was separated and sequentially washed with 80 mL of 5% aqueous sodium bicarbonate, saturated copper sulfate, slightly acidic water, half-saturated brine, and then saturated brine. The organics were then dried over sodium sulfate, filtered and concentrated *in vacuo* to give the title compound which was used without further purification. MS: *m/z* = 219 (M + 1).

Step B. Benzyl 5-hydroxy-2,2-dimethylpentanoate

To a solution of benzyl 2,2-dimethylpent-4-enoate (5.74 g, 26.3 mmol, prepared according to Step A) in THF (100 mL) was added a solution of 9-BBN (63.1 mL, 31.6 mmol, 0.5 M in THF) over 20 minutes, while under nitrogen. The reaction was allowed to stir at ambient temperature for 17 hours. An aqueous solution of sodium acetate (7.3 g, 89 mmol, in 18 mL of water) was then added, followed by the slow addition of aqueous hydrogen peroxide (18 mL, 30% by weight solution) with occasional chilling in a 0 °C bath. This mixture was allowed to stir at ambient temperature for 1.5 hours, before being extracted with ethyl acetate. The combined organics were washed with saturated brine. The organics were then dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a residue that was purified by silica gel chromatography, eluting with a gradient of MeOH:DCM – 1:99 to 10:90, to give the title compound. MS: m/z = 237 (M + 1).

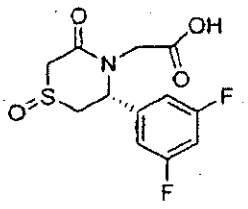
Step C. Benzyl 2,2-dimethyl-5-oxopentanoate

To a -78 °C solution of oxalyl chloride (4.80 g, 37.8 mmol) in DCM (200 mL) was add DMSO (5.91 g, 75.6 mmol) dropwise over 10 minutes. After 25 minutes of additional stirring, a -78 °C solution of benzyl 5-hydroxy-2,2-dimethylpentanoate (4.06 g, 17.2 mmol, Step B) in DCM (200 mL) was added via cannula over 75 minutes. After stirring for an additional 30 minutes, triethylamine (13.9 g, 137 mmol) was added slowly over 25 minutes. The cooling bath was allowed to warm, while the reaction stirred for an additional 18 hours. Reaction solvent was then removed *in vacuo*, and the residue was dissolved in a mixture of diethyl ether and water (containing enough HCl to remain acidic). The organics were then dried over sodium sulfated, filtered and concentrated *in vacuo* to give the title compound (3.67 g), which was used without further purification.

Step D. Benzyl 5-{[(*S*)-*tert*-butylsulfinyl]imino}-2,2-dimethylpentanoate

To a mixture of benzyl 2,2-dimethyl-5-oxopentanoate (1.06 g, 4.54 mmol, Step C) and anhydrous $CuSO_4$ (1.59 g, 9.98 mmol) in DCM (10 mL) was added (*S*)-2-methylpropane-2-sulfinamide (0.550 g, 4.54 mmol). This mixture was stirred for 22 hours, before being filtered through a pad of celite. Addditional DCM was used to wash the celite. The combined organics were concentrated *in vacuo* to give a residue that was purified by silica gel chromatography, eluting with a gradient of MeOH:DCM – 0.5:99.5 to 1.5:98.5, to give the title compound. MS: m/z = 338 (M + 1).

INTERMEDIATE 4



(major sulfoxide isomer)

[(3*R*)-3-(3,5-Difluorophenyl)-1-oxido-5-oxothiomorpholin-4-yl]acetic acid (major sulfoxide isomer)

Step A. Benzyl [(3*R*)-3-(3,5-difluorophenyl)-5-oxothiomorpholin-4-yl]acetate

To a 0 °C solution of (5*R*)-5-(3,5-difluorophenyl)thiomorpholin-3-one (247 mg, 1.08 mmol, prepared by analogy to Intermediate 2) in THF (8.0 mL) was added sodium hydride (38 mg, 1.5 mmol, 95% by weight). After 5 minutes, the ice bath was removed and the reaction was allowed to warm to ambient temperature. Once hydrogen gas evolution had ceased, as judged by an oil bubbler, the reaction mixture was cooled to 0 °C, prior to the introduction of benzyl acetate (272 mg, 1.19 mmol). After 5 minutes, the ice bath was removed and the reaction was stirred for15 hours. The bulk of the THF was removed under reduced pressure. The residue was then diluted with water and ether. The aqueous layer was extracted once with ether and the combined organics were washed with saturated brine. The organics were then dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a residue that was purified by silica gel chromatography, eluting with a gradient of MeOH:DCM – 0.5:99.5 to 5:95, to give the title compound. MS: *m/z* = 378 (M + 1).

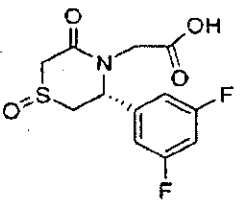
Step B. Benzyl [(3*R*)-3-(3,5-difluorophenyl)-1-oxido-5-oxothiomorpholin-4-yl]acetate

To a solution of benzyl [(3*R*)-3-(3,5-difluorophenyl)-5-oxothiomorpholin-4-yl]acetate (151 mg, 0.399 mmol, from Step A.) in MeOH (10 mL) was added aqueous hydrogen peroxide (30 drops, ~0.8 mL, 30% by weight), and aqueous HCl (5 drops, 3 M HCl). This mixture was then heated to 40 °C for 2.5 hours. After cooling to ambient temperature, the bulk of the MeOH was removed *in vacuo*, and the residue was partitioned between 50 mL of water and 100 mL of diethyl ether. The organics were washed with saturated brine, then dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a residue that was purified by silica gel chromatography eluting with a gradient of Hexanes:EtOAc – 1:1 to 100% EtOAc, to yield 24.5 mg of the minor sulfoxide isomer and 93.6 mg of the major sulfoxide isomer. MS: *m/z* = 394 (M + 1).

Step C. [(3*R*)-3-(3,5-Difluorophenyl)-1-oxido-5-oxothiomorpholin-4-yl]acetic acid (major sulfoxide isomer)

A solution of benzyl [(3*R*)-3-(3,5-difluorophenyl)-1-oxido-5-oxothiomorpholin-4-yl]acetate (93.6 mg, 0.238 mmol, major isomer, from Step B) in MeOH (5 mL) was purged with nitrogen. The septum sealing the reaction vessel was briefly removed to allow introduction of Pd/C (~18 mg, 10% Pd/C). The vessel was then purged with hydrogen from a balloon, before a fresh balloon of hydrogen was attached. After LCMS analysis indicated that the reaction had stalled at 60% conversion, the hydrogen atmosphere was replaced with nitrogen. The mixture was then filtered through a pad of celite, washing with MeOH as needed. The filtrate was concentrated *in vacuo* to provide a residue which was diluted with aqueous sodium bicarbonate (2%) and ether. The aqueous layer was extracted with ether (4 times) to remove un-reacted starting material. The aqueous layer was then made acidic by the addition of 3M HCl, and was then saturated with NaCl. This acidic aqueous layer was then extracted three times with DCM and three times with EtOAc. Both organics were dried over sodium sulfate, filtered and concentrated *in vacuo* to give the title compound. MS: *m/z* = 304 (M + 1).

INTERMEDIATE 5

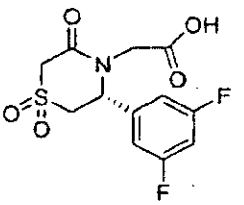


(minor sulfoxide isomer)

[(3*R*)-3-(3,5-Difluorophenyl)-1-oxido-5-oxothiomorpholin-4-yl]acetic acid (minor sulfoxide isomer)

A solution of benzyl [(3*R*)-3-(3,5-difluorophenyl)-1-oxido-5-oxothiomorpholin-4-yl]acetate (24.5 mg, 0.062 mmol, minor isomer, from the preparation of Intermediate 4, Step B) in MeOH (2 mL) was purged with nitrogen. The septum sealing the reaction vessel was briefly removed to allow introduction of Pd/C (~6 mg, 10% Pd/C). The vessel was then purged with hydrogen from a balloon, before a fresh balloon of hydrogen was attached. After LCMS analysis indicated that the reaction was progressing slowly, a suspension of 10% Pd/C was introduced via syringe. After 2.25 hours the hydrogen atmosphere was replaced with nitrogen. The mixture was then filtered through a pad of celite, washing with MeOH as needed. The filtrate was concentrated *in vacuo* to provide the title compound, which was used without further purification. MS: *m/z* = 304 (M + 1).

INTERMEDIATE 6



[(3*R*)-3-(3,5-Difluorophenyl)-1,1-dioxido-5-oxothiomorpholin-4-yl]acetic acid

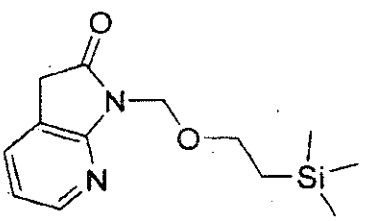
Step A. Benzyl [(3*R*)-3-(3,5-difluorophenyl)-1,1-dioxido-5-oxothiomorpholin-4-yl]acetate

To a solution of benzyl [(3*R*)-3-(3,5-difluorophenyl)-5-oxothiomorpholin-4-yl]acetate (65.9 mg, 0.175 mmol, from the preparation of Intermediate 4, Step A) in DCM (3 mL) was added *m*-CPBA (86.0 mg, 0.350 mmol, 70% by weight). After stirring for 17 hours at ambient temperature, the reaction mixture was applied to a silica gel column for purification, eluting with a gradient of Hexanes:EtOAc – 95:5 to 50:50, to give the title compound, which is 83% pure (balance being *m*-CPBA), and was used without further purification.

Step B. [(3*R*)-3-(3,5-Difluorophenyl)-1,1-dioxido-5-oxothiomorpholin-4-yl]acetic acid

A solution of benzyl [(3*R*)-3-(3,5-difluorophenyl)-1,1-dioxido-5-oxothiomorpholin-4-yl]acetate (71.7 mg, 0.145 mmol, 83%, from Step A) in MeOH (3 mL) was purged with nitrogen. The septum sealing the reaction vessel was briefly removed to allow introduction of Pd/C (~14 mg, 10% Pd/C). The vessel was then purged with hydrogen from a balloon, before a fresh balloon of hydrogen was attached. After 30 minutes the hydrogen atmosphere was replaced with nitrogen. The mixture was then filtered through a pad of celite, washing with MeOH as needed. The filtrate was concentrated *in vacuo* to provide the title compound. MS: *m/z* = 320 (M + 1).

INTERMEDIATE 7



1-{[2-(Trimethylsilyl)ethoxy]methyl}-1,3-dihydro-2*H*-pyrrolo[2,3-b]pyridin-2-one

Step A. 1-{[2-(Trimethylsilyl)ethoxy]methyl}-1*H*-pyrrolo[2,3-b]pyridine

Sodium hydride (60% dispersion in mineral oil; 16.2 g, 0.404 mol) was added in portions over 25 min to a solution of 7-azaindole (39.8 g, 0.337 mol) in DMF (200 mL) at 0 °C and the mixture was stirred for 1 h. 2-(Trimethylsilyl)ethoxymethyl chloride (71.8 mL, 0.404 mol) was then added slowly over 15 min, keeping the temperature of the reaction mixture below 10 °C. After 1 h, the reaction was quenched with water (500 mL) and the mixture was extracted with CH_2Cl_2 (5 × 300 mL). The combined organic layers were washed with saturated brine, dried over $MgSO_4$, filtered, concentrated and dried under high vacuum to give the title compound. MS: *m/z* = 249 (M + 1).

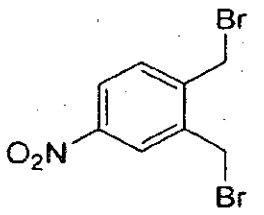
Step B. 3,3-Dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-dihydro-2*H*-pyrrolo[2,3-b]pyridin-2-one

A solution of 1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridine from Step A (43.1 g, 0.1735 mol) in dioxane (300 mL) was added dropwise over 30 min to a suspension of pyridine hydrobromide perbromide (277 g, 0.8677 mol) in dioxane (300 mL). The reaction was stirred at ambient temperature using an overhead mechanical stirrer to produce two layers. After 60 min, the reaction was quenched with water (300 mL) and extracted with EtOAc (500 mL). The aqueous layer was extracted further with EtOAc (2 × 300 mL) and the combined organic layers were washed with H_2O (4 × 300 mL; the final wash was pH 5-6), then brine (300 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was immediately dissolved in CH_2Cl_2 and the solution filtered through a plug of silica, eluting with CH_2Cl_2 until the dark red color had completely eluted from the plug. The filtrate was washed with saturated aqueous $NaHCO_3$ (400 mL), then brine (400 mL), dried over $MgSO_4$ filtered, and concentrated *in vacuo* to give the title compound. MS: *m/z* = 423 (M + 1).

Step C. 1-{[2-(Trimethylsilyl)ethoxy]methyl}-1,3-dihydro-2*H*-pyrrolo[2,3-b]pyridin-2-one

Zinc (100g, 1.54 mol) was added to a solution of 3,3-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (65 g, 0.154 mol) in THF (880 mL) and saturated aqueous NH_4Cl (220 mL). After 3 h, the reaction mixture was filtered and concentrated *in vacuo*. The residue was partitioned between EtOAc and H_2O which resulted in the formation of a white precipitate. Both layers were filtered through a Celite pad and the layers were separated. The aqueous layer was washed with EtOAc (2 × 500 mL) and the combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography, eluting with CH_2Cl_2:EtOAc – 90:10, to give the title compound. MS: *m/z* = 265 (M + 1).

INTERMEDIATE 8



1,2-*Bis*(bromomethyl)-4-nitrobenzene

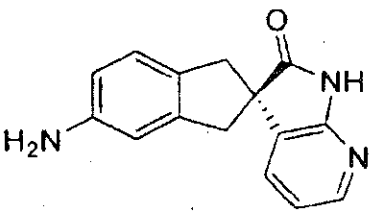
Step A. (4-Nitro-1,2-phenylene)dimethanol

A solution of 4-nitrophthalic acid (40 g, 189.5 mmol) in THF (500 mL) was added dropwise over 1.5 h to a solution of borane-THF complex (1 M, 490 mL, 490 mmol), keeping the reaction temperature between 0 °C and 5 °C. After the addition, the reaction mixture was allowed to warm slowly to ambient temperature and stirred for 18 h. MeOH (100 mL) was added carefully and the precipitated solid dissolved. The mixture was concentrated *in vacuo* to about 500 mL, cooled to 0 °C, and 10 N NaOH was added to adjust the pH to 10-11. This mixture was extracted with EtOAc (3 × 600 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the title compound. MS: *m/z* = 207 (M – OH + CH_3CN).

Step B. 1,2-*Bis*(bromomethyl)-4-nitrobenzene

Phosphorus tribromide (20.1 mL, 212 mmol) in Et_2O (250 mL) was added dropwise over 1.5 h to a solution of (4-nitro-1,2-phenylene)dimethanol from Step A (35.3 g, 193 mmol) in Et_2O (750 mL). After 18 h, the reaction mixture was cooled to 0 °C and quenched with H_2O (100 mL). The layers were separated and the organic layer was washed with H_2O (2 × 200 mL), then saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the title compound. MS: *m/z* = 309 (M + 1).

INTERMEDIATE 9



(*R*)-5-Amino-1,3-dihydrospiro[indene-2,3'-pyrrolo[2,3-b]pyridin]-2'(1'*H*)-one

Step A. (±)-5-Nitro-1'-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-dihydrospiro[indene-2,3'-pyrrolo[2,3-b]pyridin]-2'(1'*H*)-one

To a solution of 1,2-*bis*(bromomethyl)-4-nitrobenzene (40.9 g, 132 mmol, described in Intermediate 8) and 1-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (31.5 g, 119 mmol, described in Intermediate 7) in DMF (2 L) was added cesium carbonate (129 g, 397 mmol), portionwise, over 5 min. After 18 h, acetic acid (7.6 mL) was added and the mixture was concentrated to a volume of about 500 mL, then partitioned between EtOAc (1.5 L) and H_2O (1 L). The organic layer was washed with H_2O (1 L), then brine (500 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 100:0 to 0:100, to give the title compound. MS: *m/z* = 412 (M + 1).

Step B. (±)-5-Amino-1'-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-dihydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one

A mixture of 10% Pd/C (3 g) and (±)-5-nitro-1'-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-dihydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one from Step A (19.1 g, 46.4 mmol) was stirred vigorously in EtOH (400 mL) under an atmosphere of hydrogen (*ca.* 1 atm). After 18 h, the mixture was filtered through a pad of Celite, washing extensively with MeOH, and the filtrate was concentrated *in vacuo* to give the title compound. MS: *m/z* = 382 (M + 1).

Step C. *tert*-Butyl (*R*)-(2'-oxo-1'-{[2-(trimethylsilyl)ethoxy]methyl}-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-b]pyridin]-5-yl)carbamate

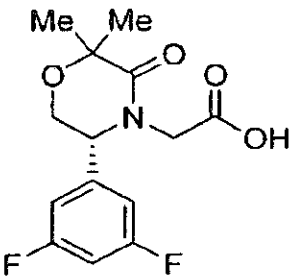
A solution of (±)-5-amino-1'-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-dihydrospiro[indene-2,3'-pyrrolo[2,3-b]pyridin]-2'(1'*H*)-one from Step B (104 g, 273 mmol) and di-*tert*-butyl dicarbonate (71.5 g, 328 mmol) in $CHCl_3$ (1 L) was heated to reflux for 17 h. The cooled mixture was concentrated *in vacuo* and the residue was purified by silica gel chromatography, eluting with hexane:EtOAc – 100:0 to 50:50, to give the racemic product. The enantiomers were resolved by HPLC, utilizing a ChiralPak AD column and eluting with EtOH. The first major peak to elute was *tert*-butyl (*S*)-(2'-oxo-1'-{[2-(trimethylsilyl)ethoxy]methyl}-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-5-yl)carbamate, and the second major peak to elute was *tert*-butyl (*R*)-(2'-oxo-1'-{[2-(trimethylsilyl)ethoxy]methyl}-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-5-yl)carbamate, the title compound. MS: *m/z* = 482 (M + 1).

Step D. (*R*)-5-Amino-1,3-dihydrospiro[indene-2,3'-pyrrolo[2,3-b]pyridin]-2'(1'*H*)-one

A solution of *tert*-butyl (*R*)-(2'-oxo-1'-{[2-(trimethylsilyl)ethoxy]methyl}-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-5-yl)carbamate from Step C (13.4 g, 27.8 mmol) in MeOH (300 mL) was saturated with HCl (g). The mixture was resaturated with

HCl (g) every 30 min until the starting material was consumed, and then concentrated *in vacuo*. The residue was dissolved in MeOH (150 mL) and treated with ethylenediamine (1.9 mL, 27.8 mmol) and 10 N sodium hydroxide (6 mL, 60 mmol) to adjust the mixture to pH 10. After 30 min, the mixture was diluted with H_2O (400 mL) and extracted with $CHCl_3$ (1 L). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was triturated with MeOH (35 mL) to give the title compound. MS: *m/z* = 252 (M + 1).

INTERMEDIATE 10



[(5*R*)-5-(3,5-Difluorophenyl)-2,2-dimethyl-3-oxomorpholin-4-yl]acetic acid

Step A. *N*-[(*S*S, 1*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(3,5-difluorophenyl)ethyl]-2-methylpropane-2-sulfinamide

To a stirred solution of (*S*S)-*N*-((1*E*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}ethylidene)-2-methylpropane-2-sulfinamide (5.00 g, 17.9 mmol) [Tang *et al.* (2001) *J. Org. Chem.*, **66**, 8772-8778] in THF (75 mL) at -78 °C was added 3,5-difluorophenylmagnesium bromide (71.6 mL of a 0.5 M solution in THF, 35.8 mmol) dropwise. The reaction mixture was stirred at -78 °C for 5 h, and then allowed to warm slowly to ambient temperature and stirring was continued for 18 h. The mixture was quenched with saturated aqueous NH_4Cl (25 mL) and extracted with EtOAc (3 × 75 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of CH_2Cl_2:EtOAc – 100:0 to 80:20, to give the title compound. MS: *m/z* = 392 (M + 1).

Step B. (2*R*)-2-Amino-2-(3,5-difluorophenyl)ethanol

To a solution of *N*-[(*S*S, 1*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-(3,5-difluorophenyl)ethyl]-2-methylpropane-2-sulfinamide from Step A (1.50 g, 3.81 mmol) in MeOH (40 mL) at 0 °C was added HCl (9.5 mL of a 2 M solution in Et_2O, 19 mmol). After 20 min, the reaction mixture was concentrated to dryness *in vacuo*. The residue was dissolved in H_2O (25 mL) and the mixture was extracted with EtOAc (2 × 50 mL) and these organic extracts were discarded. The aqueous phase was adjusted to pH 10 by addition of 1 N NaOH and

extracted with EtOAc (2 × 50 mL). These organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the title compound. MS: *m/z* = 174 (M + 1).

Step C. 2-Chloro-*N*-[(1*R*)-1-(3,5-difluorophenyl)-2-hydroxyethyl]acetamide

To a solution of (2*R*)-2-amino-2-(3,5-difluorophenyl)ethanol from Step B (630 mg, 3.64 mmol) and triethylamine (0.51 mL, 3.64 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added chloroacetyl chloride (0.29 mL, 3.64 mmol). After 20 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were washed with 10% citric acid, then brine, then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the title compound. MS: *m/z* = 250 (M + 1).

Step D. (5*R*)-5-(3,5-Difluorophenyl)morpholin-3-one

To a solution of 2-chloro-*N*-[(1*R*)-1-(3,5-difluorophenyl)-2-hydroxyethyl]acetamide from Step C (840 mg, 3.37 mmol) in THF (75 mL) at 0 °C was added NaH (291 mg of a 60% dispersion in oil, 7.28 mmol) and the mixture was stirred at ambient temperature for 1 h. Saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 75:25 to 25:75, to give the title compound. MS: *m/z* = 214 (M + 1).

Step E. *tert*-Butyl (3*R*)-3-(3,5-difluorophenyl)-5-oxomorpholine-4-carboxylate

A solution of (5*R*)-5-(3,5-difluorophenyl)morpholin-3-one from Step D (570 mg, 2.67 mmol), di-*tert*-butyl dicarbonate (584 mg, 2.67 mmol), and 4-dimethylaminopyridine (327 mg, 2.67 mmol) in CH_2Cl_2 (30 mL) was stirred at ambient temperature for 1 h. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 90:10 to 50:50, to give the title compound. MS: *m/z* = 377 (M + Na + CH_3CN).

Step F. *tert*-Butyl (5*R*)-5-(3,5-difluorophenyl)-2,2-dimethyl-3-oxomorpholine-4-carboxylate

To a 1 M solution of sodium *bis*(trimethylsilyl)amide in THF (1.60 mL, 1.60 mmol) at -78 °C was added dropwise a solution of *tert*-butyl (3*R*)-3-(3,5-difluorophenyl)-5-oxomorpholine-4-carboxylate from Step E (500 mg, 1.60 mmol) in DME (15 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 10 min then iodomethane (0.099 mL, 1.60 mmol) was added. After stirring at -78 °C for a further 1 h, the reaction mixture was slowly transferred via cannula into a 1 M solution of sodium *bis*(trimethylsilyl)amide in THF (1.60 mL, 1.60 mmol) at -78 °C. The resulting mixture was stirred at -78 °C for 10 min then a second equivalent of

iodomethane (0.099 mL, 1.60 mmol) was added. After stirring at -78 °C for a further 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (2 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 90:10 to 60:40, to give the title compound. MS: *m/z* = 286 ($M - C_4H_7$).

Step G. (5*R*)-5-(3,5-Difluorophenyl)-2,2-dimethylmorpholin-3-one

To a solution of *tert*-butyl (5*R*)-5-(3,5-difluorophenyl)-2,2-dimethyl-3-oxomorpholine-4-carboxylate from Step F (225 mg, 0.66 mmol) in CH_2Cl_2 (3 mL) at ambient temperature was added TFA (0.49 mL, 6.6 mmol). After stirring for 1 h, the reaction mixture was concentrated *in vacuo* to give the title compound. MS: *m/z* = 242 (M + 1).

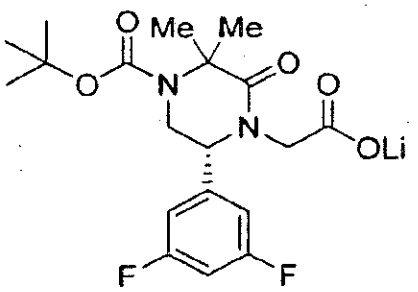
Step H. Ethyl [(5*R*)-5-(3,5-difluorophenyl)-2,2-dimethyl-3-oxomorpholin-4-yl]acetate

To a stirred solution of (5*R*)-5-(3,5-difluorophenyl)-2,2-dimethylmorpholin-3-one from Step G (150 mg, 0.62 mmol) in DMF (2 mL) at 0 °C was added NaH (27 mg of a 60% dispersion in oil, 0.68 mmol). After 10 min, ethyl bromoacetate (104 mg, 0.62 mmol) was added and the mixture was stirred at 0 °C for 30 min. Saturated aqueous $NaHCO_3$ (5 mL) was added and the mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 95:5 to 70:30, to give the title compound. MS: *m/z* = 328 (M + 1).

Step I. [(5*R*)-5-(3,5-Difluorophenyl)-2,2-dimethyl-3-oxomorpholin-4-yl]acetic acid

To a solution of ethyl [(5*R*)-5-(3,5-difluorophenyl)-2,2-dimethyl-3-oxomorpholin-4-yl]acetate from Step H (150 mg, 0.46 mmol) in THF (3 mL) and H_2O (3 mL) was added 1 N aqueous LiOH (0.55 mL, 0.55 mmol) and the resulting mixture was stirred at ambient temperature for 18 h. The reaction mixture was purified directly by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. Lyophilization provided the title compound. MS: *m/z* = 300 (M + 1).

INTERMEDIATE 13



Lithium [(6*R*)-4-(*tert*-butoxycarbonyl)-6-(3,5-difluorophenyl)-3,3-dimethyl-2-oxopiperazin-1-yl]acetate

Step A. Methyl 2-{[2-(3,5-difluorophenyl)-2-oxoethyl]amino}-2-methylpropanoate

A mixture of methyl α-aminoisobutyrate hydrochloride (10.3 g, 67.0 mmol), 3,5-difluorophenacyl bromide (15.0 g, 63.8 mmol), and K_2CO_3 (17.6 g, 128 mmol) in DMF (100 mL) was stirred at ambient temperature for 3 h. Saturated aqueous $NaHCO_3$ (400 mL) was added and the mixture was extracted with EtOAc (1 L). The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 100:0 to 0:100, to give the title compound. MS: *m/z* = 272 (M + 1).

Step B. (±)-Ethyl [6-(3,5-difluorophenyl)-3,3-dimethyl-2-oxopiperazin-1-yl]acetate

A mixture of methyl 2-{[2-(3,5-difluorophenyl)-2-oxoethyl]amino}-2-methylpropanoate from Step A (8.60 g, 31.7 mmol), glycine ethyl ester hydrochloride (44.3 g, 317 mmol), and AcOH (5.71 mL, 95 mmol) in MeOH (300 mL) was stirred at ambient temperature for 10 min. $NaCNBH_3$ (2.39 g, 38.0 mmol) was added and the pH of the mixture was checked and adjusted to pH ~ 5 as necessary. The reaction mixture was heated to 50 °C for 18 h. Additional AcOH (4 mL) was added and the reaction mixture was heated to 60 °C for 6 h then allowed to cool and concentrated *in vacuo* to a volume of *ca.* 150 mL. The resulting mixture was carefully quenched with saturated aqueous $NaHCO_3$ (300 mL) and then extracted with CH_2Cl_2 (1 L). The organic extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with hexane:EtOAc – 100:0 to 0:100, to give the title compound. MS: *m/z* = 327 (M + 1).

Step C. *tert*-Butyl (5*R*)-5-(3,5-difluorophenyl)-4-(2-ethoxy-2-oxoethyl)-2,2-dimethyl-3-oxopiperazine-1-carboxylate

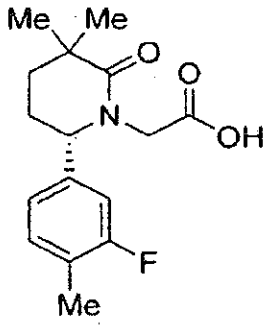
A solution of ethyl [8-(3,5-difluorophenyl)-10-oxo-6,9-diazaspiro[4.5]dec-9-yl]acetate from Step B (2.27 g, 6.96 mmol), *N*,*N*-diisopropylethylamine (0.607 mL, 3.48 mmol), and di-*tert*-butyl dicarbonate (15.2 g, 69.6 mmol) in acetonitrile (30 mL) was stirred at 60 °C for

18 h, then cooled and concentrated under reduced pressure. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 100:0 to 0:100, to give the racemic product. The enantiomers were separated by SFC, using a Chiralcel OD column and eluting with CO_2:MeOH – 80:20. The first major peak to elute was *tert*-butyl (5*S*)-5-(3,5-difluorophenyl)-4-(2-ethoxy-2-oxoethyl)-2,2-dimethyl-3-oxopiperazine-1-carboxylate and the second major peak to elute was *tert*-butyl (5*R*)-5-(3,5-difluorophenyl)-4-(2-ethoxy-2-oxoethyl)-2,2-dimethyl-3-oxopiperazine-1-carboxylate, the title compound. MS: *m/z* = 371 (M – C_4H_7).

Step D. Lithium [(6*R*)-4-(*tert*-butoxycarbonyl)-6-(3,5-difluorophenyl)-3,3-dimethyl-2-oxopiperazin-1-yl]acetate

To a solution of *tert*-butyl (5*R*)-5-(3,5-difluorophenyl)-4-(2-ethoxy-2-oxoethyl)-2,2-dimethyl-3-oxopiperazine-1-carboxylate from Step C (1.18 g, 2.77 mmol) in THF (18 mL) and H_2O (2 mL) was added 1 N aqueous LiOH (3.04 mL, 3.04 mmol) and the resulting mixture was stirred at ambient temperature for 5 h. The mixture was adjusted to pH 6 by addition of 1 N HCl and concentrated to dryness *in vacuo* to give the title compound. MS: *m/z* = 343 (M – C_4H_7).

INTERMEDIATE 14



(*S*)-[6-(3-Fluoro-4-methylphenyl)-3,3-dimethyl-2-oxopiperidin-1-yl]acetic acid

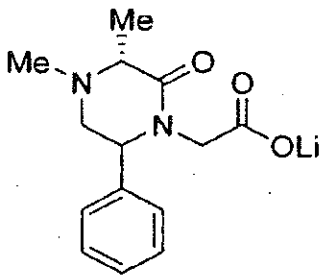
Step A. (*S*)-6-(3-Fluoro-4-methylphenyl)-3,3-dimethylpiperidin-2-one

To a stirred solution of benzyl (S_S)-5-[(*tert*-butylsulfinyl)imino]-2,2-dimethylpentanoate (1.00 g, 2.96 mmol, described in Intermediate 3) in toluene (28 mL) at -78 °C was added 3-fluoro-4-methylphenylmagnesium bromide (11.9 mL of a 0.5 M solution in THF, 5.93 mmol). The reaction mixture was warmed to ambient temperature for 2 h, and then heated at reflux for 2 h. The solvent was removed *in vacuo* and the crude solid dissolved in DMSO (5 mL). The crude product was purified by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. Lyophilization provided the title compound. MS: *m/z* = 236 (M + 1).

Step B. (*S*)-[6-(3-Fluoro-4-methylphenyl)-3,3-dimethyl-2-oxopiperidin-1-yl]acetic acid

To a stirred solution of (*S*)-6-(3-fluoro-4-methylphenyl)-3,3-dimethylpiperidin-2-one from Step A (80 mg, 0.340 mmol) in DMF (3 mL) at ambient temperature was added NaH (19 mg of a 60% dispersion in oil, 0.476 mmol). After 15 min, methyl bromoacetate (0.051 mL, 0.544 mmol) was added and the mixture was stirred for 16 h. Sodium hydroxide (0.061 mL of a 10 M solution, 0.612 mmol) was added and the mixture stirred for 2 h. The crude product was purified directly by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. The compound was further purified by SFC, utilizing a ChiralPak AD column and eluting with CO_2:MeOH – 91:9, to give the title compound. MS: *m/z* = 294 (M + 1).

INTERMEDIATE 19



Lithium [(3*R*)-3,4-dimethyl-2-oxo-6-phenylpiperazin-1-yl]acetate

Step A. Methyl (2*R*)-2-[(2-oxo-2-phenylethyl)amino]propanoate, TFA salt

A mixture of (*R*)-alanine methyl ester hydrochloride (1.00 g, 7.16 mmol), 2-bromoacetophenone (2.85 g, 14.3 mmol), and $NaHCO_3$ (1.20 g, 14.3 mmol) in DMF (20 mL) was stirred at ambient temperature for 6 h. The reaction mixture was quenched with 1 N aqueous HCl (25 mL) and the mixture was extracted with EtOAc (2 × 35 mL) and the organic phase was discarded. The aqueous phase was adjusted to pH 10 with saturated aqueous Na_2CO_3 and then extracted with EtOAc (3 × 75 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. Concentration of product-containing fractions *in vacuo* provided the title compound. MS: *m/z* = 222 (M + 1).

Step B. Methyl [(3*R*)-3,4-dimethyl-2-oxo-6-phenylpiperazin-1-yl]acetate

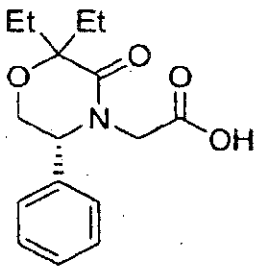
To a stirred mixture of methyl (2*R*)-2-[(2-oxo-2-phenylethyl)amino]propanoate, TFA salt, from Step A (152 mg, 0.452 mmol) and glycine methyl ester hydrochloride (85 mg,

0.678 mmol) in MeOH (1 mL) was added *N,N*-diisopropylethylamine (0.197 mL, 1.13 mmol), followed by AcOH (0.155 mL, 2.71 mmol). The resulting mixture was stirred at ambient temperature for 10 min, then $NaCNBH_3$ (34 mg, 0.54 mmol) was added. The reaction mixture was heated to 50 °C for 18 h then allowed to cool. Formaldehyde (0.067 mL of a 37% aqueous solution, 0.90 mmol) was added and the mixture was stirred at ambient temperature for 30 min. The reaction mixture was quenched with 1 N aqueous HCl (5 mL) and the mixture was extracted with EtOAc (2 × 10 mL) and the organic phase was discarded. The aqueous phase was adjusted to pH 10 with saturated aqueous Na_2CO_3 and then extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. The product-containing fractions were combined, basified with saturated aqueous NaHCO3, and extracted with EtOAc. The organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the title compound. MS: *m/z* = 277 (M + 1).

Step C. Lithium [(3*R*)-3,4-dimethyl-2-oxo-6-phenylpiperazin-1-yl]acetate

A solution of methyl [(3*R*)-3,4-dimethyl-2-oxo-6-phenylpiperazin-1-yl]acetate from Step B (50 mg, 0.18 mmol) in THF (1 mL) was added 1 N aqueous LiOH (0.20 mL, 0.20 mmol) and the resulting mixture was stirred at ambient temperature for 4 h. The mixture was adjusted to pH 6 by addition of 1 N HCl and concentrated to dryness *in vacuo* to give the title compound. MS: *m/z* = 263 (M + 1).

INTERMEDIATE 20



[(5*R*)-2,2-Diethyl-3-oxo-5-phenylmorpholin-4-yl]acetic acid

Step A. 2-Chloro-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]butanamide

To a solution of (*R*)-2-phenylglycinol (2.00 g, 14.6 mmol) and triethylamine (2.03 mL, 14.6 mmol) in CH_2Cl_2 (100 mL) at 0 °C was slowly added 2-chlorobutyryl chloride (1.66 mL, 14.6 mmol). After 30 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (2 × 75 mL). The combined organic extracts were

washed with 10% citric acid, then brine, then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 70:30 to 0:100, to give the title compound. MS: *m/z* = 242 (M + 1).

Step B. (2*R*,5*R*)-2-Ethyl-5-phenylmorpholin-3-one

To a solution of 2-chloro-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]butanamide from Step A (2.75 g, 11.4 mmol) in THF (200 mL) at 0 °C was added NaH (983 mg of a 60% dispersion in oil, 24.6 mmol) and the mixture was stirred at ambient temperature for 18 h. Saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture was extracted with EtOAc (3 × 40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 75:25 to 0:100, to give the title compound. MS: *m/z* = 206 (M + 1).

Step C. *tert*-Butyl (2*R*,5*R*)-2-ethyl-3-oxo-5-phenylmorpholine-4-carboxylate

A solution of (2*R*,5*R*)-2-ethyl-5-phenylmorpholin-3-one from Step B (900 mg, 4.41 mmol), di-*tert*-butyl dicarbonate (962 mg, 4.41 mmol), and 4-dimethylaminopyridine (538 mg, 4.41 mmol) in CH_2Cl_2 (50 mL) was stirred at ambient temperature for 4 h. The mixture was washed with 10% citric acid (35 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 95:5 to 60:40, to give the title compound. MS: *m/z* = 250 (M – C_4H_7).

Step D. *tert*-Butyl (5*R*)-2,2-diethyl-3-oxo-5-phenylmorpholine-4-carboxylate

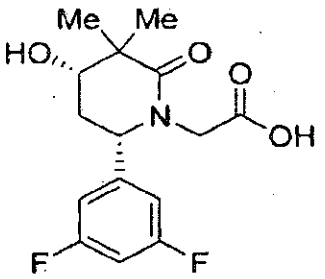
To a 1 M solution of sodium *bis*(trimethylsilyl)amide in THF (1.64 mL, 1.64 mmol) at -78 °C was added dropwise a solution of *tert*-butyl (2*R*,5*R*)-2-ethyl-3-oxo-5-phenylmorpholine-4-carboxylate from Step C (500 mg, 1.64 mmol) in DME (25 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 10 min then iodoethane (0.131 mL, 1.64 mmol) was added. After stirring at -78 °C for 30 min, then at -30 °C for 30 min, the reaction mixture was cooled to -78 °C and quenched with saturated aqueous NH_4Cl (20 mL) then extracted with EtOAc (2 × 40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 95:5 to 70:30, to give the title compound. MS: *m/z* = 278 (M – C_4H_7).

Step E. [(5*R*)-2,2-Diethyl-3-oxo-5-phenylmorpholin-4-yl]acetic acid

Essentially following the procedures described for Intermediate 10, but using *tert*-butyl (5*R*)-2,2-diethyl-3-oxo-5-phenylmorpholine-4-carboxylate in place of *tert*-butyl (5*R*)-5-

(3,5-difluorophenyl)-2,2-dimethyl-3-oxomorpholine-4-carboxylate, the title compound was prepared. MS: *m/z* = 292 (M + 1).

INTERMEDIATE 21



[(4*S*,6*S*)-6-(3,5-Difluorophenyl)-4-hydroxy-3,3-dimethyl-2-oxopiperidin-1-yl]acetic acid

Step A. 6-(3,5-Difluorophenyl)-3,3-dimethylpiperidine-2,4-dione

To a solution of 3,3-dimethylpyridine-2,4(1*H*,3*H*)-dione (978 mg, 7.03 mmol) [U.S. Patent 2,525,231] in benzene (10 mL) was added 3,5-difluorophenylmagnesium bromide (50 mL of a 0.5 M solution in THF, 25 mmol) and the resulting mixture was heated to reflux for 1.5 h. The mixture was cooled, quenched with 1 N aqueous HCl (10 mL), made basic with saturated $NaHCO_3$ solution (100 mL) and extracted with EtOAc (2 × 150 mL). The combined organic layers were washed with H_2O (50 mL), then brine (50 mL), and dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 100:0 to 60:40, to give the title compound. MS: *m/z* = 254 (M + 1).

Step B. *cis*-6-(3,5-Difluorophenyl)-4-hydroxy-3,3-dimethylpiperidin-2-one

To a solution of 6-(3,5-difluorophenyl)-3,3-dimethylpiperidine-2,4-dione from Step A (20.18 g, 80 mmol) in THF (600 mL) and CH_3OH (25 mL) at 0 °C was added $NaBH_4$ (4.57 g, 121 mmol). After 2.5 h, the reaction mixture was quenched with H_2O (200 mL) and concentrated *in vacuo*. The residue was partitioned between H_2O (600 mL), saturated aqueous $NaHCO_3$ (200 mL) and EtOAc (1 L). The organic layer was separated and the aqueous layer was extracted with EtOAc (600 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of CH_2Cl_2:CH_3OH – 100:0 to 88:12, to give the title compound, which contained approximately 20% of the corresponding *trans*-isomer. MS: *m/z* = 256 (M + 1).

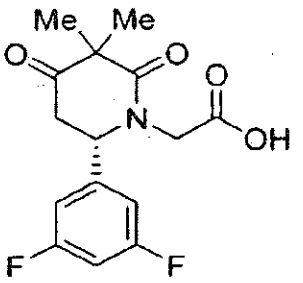
Step C. Ethyl [(4*S*,6*S*)-6-(3,5-difluorophenyl)-4-hydroxy-3,3-dimethyl-2-oxopiperidin-1-yl]acetate

To a solution of *cis*-6-(3,5-difluorophenyl)-4-hydroxy-3,3-dimethylpiperidin-2-one from Step B (17.1 g, 67.0 mmol) in THF (400 mL) at 0 °C was added NaH (60% dispersion in oil, 4.91 g, 73.7 mmol). After 30 min, ethyl bromoacetate (8.20 mL, 73.7 mmol) was added. After 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl (100 mL), diluted with H_2O (700 mL) and brine (100 mL) and extracted with EtOAc (700 mL). The organic extract was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 100:0 to 0:100, to give the alcohol as a mixture of four isomers. Additional purification was achieved by HPLC, using a ChiralPak AD column and eluting with hexane:EtOH:Et_2NH – 90:10:0.1. The first major peak to elute was a mixture of ethyl [(4*S*,6*S*)-6-(3,5-difluorophenyl)-4-hydroxy-3,3-dimethyl-2-oxopiperidin-1-yl]acetate and ethyl [(4*S*,6*R*)-6-(3,5-difluorophenyl)-4-hydroxy-3,3-dimethyl-2-oxopiperidin-1-yl]acetate (*ca.* 5:1). The second major peak to elute was a mixture of ethyl [(4*R*,6*R*)-6-(3,5-difluorophenyl)-4-hydroxy-3,3-dimethyl-2-oxopiperidin-1-yl]acetate and ethyl [(4*R*,6*S*)-6-(3,5-difluorophenyl)-4-hydroxy-3,3-dimethyl-2-oxopiperidin-1-yl]acetate (*ca.* 3:1). Further purification of the second major peak was achieved by SFC, using a ChiralPak AD column and eluting with CO_2:MeOH:Et_2NH – 90:10:0.1, to give ethyl [(4*R*,6*R*)-6-(3,5-difluorophenyl)-4-hydroxy-3,3-dimethyl-2-oxopiperidin-1-yl]acetate, which eluted first, and ethyl [(4*R*,6*S*)-6-(3,5-difluorophenyl)-4-hydroxy-3,3-dimethyl-2-oxopiperidin-1-yl]acetate, which eluted second. Further purification of the first major peak was achieved by SFC, using a ChiralPak AD column and eluting with CO_2:MeOH:Et_2NH – 90:10:0.1, to give ethyl [(4*S*,6*R*)-6-(3,5-difluorophenyl)-4-hydroxy-3,3-dimethyl-2-oxopiperidin-1-yl]acetate, which eluted first, and ethyl [(4*S*,6*S*)-6-(3,5-difluorophenyl)-4-hydroxy-3,3-dimethyl-2-oxopiperidin-1-yl]acetate, which eluted second, the title compound. MS: *m/z* = 342 (M + 1).

Step D. [(4*S*,6*S*)-6-(3,5-Difluorophenyl)-4-hydroxy-3,3-dimethyl-2-oxopiperidin-1-yl]acetic acid

To a solution of ethyl [(4*S*,6*S*)-6-(3,5-difluorophenyl)-4-hydroxy-3,3-dimethyl-2-oxopiperidin-1-yl]acetate from Step C (64 mg, 187 mmol) in THF (1 mL) and H_2O (0.5 mL) was added LiOH monohydrate (14 mg, 334 mmol) and the resulting mixture was stirred at ambient temperature for 1 h. The reaction mixture was quenched with 1 N HCl (0.40 mL, 400 mmol), concentrated *in vacuo* and dried to afford the title compound. MS: *m/z* = 314 (M + 1).

INTERMEDIATE 22



[(6*S*)-6-(3,5-Difluorophenyl)-3,3-dimethyl-2,4-dioxopiperidin-1-yl]acetic acid

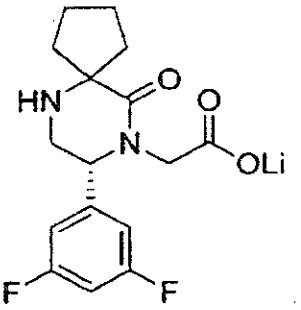
Step A. Ethyl [(6*S*)-6-(3,5-difluorophenyl)-3,3-dimethyl-2,4-dioxopiperidin-1-yl]acetate

To a solution of ethyl [(4*S*,6*S*)-6-(3,5-difluorophenyl)-4-hydroxy-3,3-dimethyl-2-oxopiperidin-1-yl]acetate (470 mg, 1.377 mmol, described in Intermediate 21) in acetone (24 mL) at 0 °C was added a solution of chromium (VI) trioxide (174 mg, 1.740 mmol) in H_2O (0.5 mL) and H_2SO_4 (0.147 mL, 2.75 mmol), in three portions over 5 min and the mixture was stirred at 0 °C for 30 min. Most of the acetone was removed by concentration *in vacuo*, and the residue was basified with saturated aqueous $NaHCO_3$ (75 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (40 mL) and dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of CH_2Cl_2:CH_3OH – 100:0 to 92:8, to give the title compound. MS: m/z = 340 (M + 1).

Step B. [(6*S*)-6-(3,5-Difluorophenyl)-3,3-dimethyl-2,4-dioxopiperidin-1-yl]acetic acid

To a solution of ethyl [(6*S*)-6-(3,5-difluorophenyl)-3,3-dimethyl-2,4-dioxopiperidin-1-yl]acetate from Step A (170 mg, 0.501 mmol) in THF (2 mL) and H_2O (1 mL) was added LiOH monohydrate (36 mg, 0.858 mmol) and the resulting mixture was stirred at ambient temperature for 18 h. The reaction mixture was quenched with 1 N HCl (1 mL, 1 mmol), concentrated *in vacuo* and dried to afford the title compound. MS: m/z = 312 (M + 1).

INTERMEDIATE 25



Lithium [(8*R*)-8-(3,5-difluorophenyl)-10-oxo-6,9-diazaspiro[4.5]dec-9-yl]acetate

Step A. Methyl 1-aminocyclopentanecarboxylate hydrochloride

A solution of 1-aminocyclopentanecarboxylic acid (2.00 g, 15.5 mmol) in MeOH (30 mL) was saturated with HCl (g). The resulting mixture was aged at ambient temperature for 2 h and concentrated *in vacuo* to provide the title compound. MS: m/z = 144 (M + 1).

Step B. Methyl 1-{[2-(3,5-difluorophenyl)-2-oxoethyl]amino}cyclopentanecarboxylate

A mixture of methyl 1-aminocyclopentanecarboxylate hydrochloride from Step A (1.50 g, 10.5 mmol), 3,5-difluorophenacyl bromide (3.20 g, 13.6 mmol), and $NaHCO_3$ (1.32 g, 15.7 mmol) in DMF (30 mL) was stirred at ambient temperature for 6 h. 1 N aqueous HCl (50 mL) was added and the mixture was extracted with EtOAc (75 mL) and this organic extract was discarded. The aqueous layer was adjusted to pH 10 by addition of saturated aqueous Na_2CO_3 (150 mL) and the mixture was extracted with EtOAc (3 × 75 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. The product-containing fractions were combined and concentrated to provide the title compound as the TFA salt. MS: m/z = 298 (M + 1).

Step C. Ethyl [(8*R*)-8-(3,5-difluorophenyl)-10-oxo-6,9-diazaspiro[4.5]dec-9-yl]acetate

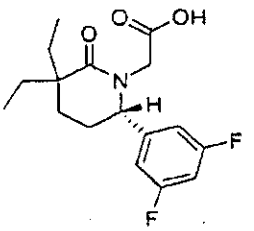
To a stirred mixture of methyl 1-{[2-(3,5-difluorophenyl)-2-oxoethyl]amino}cyclopentanecarboxylate, TFA salt, from Step B (1.10 g, 2.67 mmol) and glycine ethyl ester hydrochloride (560 mg, 4.01 mmol) in MeOH (7.5 mL) was added *N*,*N*-diisopropylethylamine (1.17 mL, 6.69 mmol), followed by AcOH (0.77 mL, 13.4 mmol). The resulting mixture was stirred at ambient temperature for 10 min, then $NaCNBH_3$ (252 mg, 4.01 mmol) was added. The reaction mixture was heated to 60 °C for 72 h then allowed to cool. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and then extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated

in vacuo. The crude product was purified by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. The product-containing fractions were combined, basified with saturated aqueous $NaHCO_3$, and extracted with EtOAc. The organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the racemic product. The enantiomers were separated by SFC, using a ChiralPak AD column and eluting with CO_2:MeOH – 90:10. The first major peak to elute was ethyl [(8*S*)-8-(3,5-difluorophenyl)-10-oxo-6,9-diazaspiro[4.5]dec-9-yl]acetate, and the second major peak to elute was ethyl [(8*R*)-8-(3,5-difluorophenyl)-10-oxo-6,9-diazaspiro[4.5]dec-9-yl]acetate, the title compound. MS: *m/z* = 353 (M + 1).

Step D. Lithium [(8*R*)-8-(3,5-difluorophenyl)-10-oxo-6,9-diazaspiro[4.5]dec-9-yl]acetate

To a solution of ethyl [(8*R*)-8-(3,5-difluorophenyl)-10-oxo-6,9-diazaspiro[4.5]dec-9-yl]acetate from Step C (90 mg, 0.26 mmol) in THF (3 mL) and H_2O (1 mL) was added 1 N aqueous LiOH (0.31 mL, 0.31 mmol) and the resulting mixture was stirred at ambient temperature for 1 h. The mixture was adjusted to pH 6 by addition of 1 N HCl and concentrated to dryness *in vacuo* to give the title compound. MS: *m/z* = 325 (M + 1).

INTERMEDIATE 26



[(6*S*)-6-(3,5-Difluorophenyl)-3,3-diethyl-2-oxopiperidin-1-yl]acetic acid

Step A. Ethyl (5*S*)-5-{[(*S*)-*tert*-butylsulfinyl]amino}-5-(3,5-difluorophenyl)pentanoate

To a solution of ethyl 5-(3,5-difluorophenyl)-5-oxovalerate (5.00 g, 19.5 mmol) and (*S*)-2-methylpropane-2-sulfinamide (2.88 g, 23.8 mmol) in THF (123 mL) was added titanium tetraethoxide (8.18 mL, 39.0 mmol). The reaction vessel was quickly sealed and placed into a 60 °C bath for 16 h. After cooling to ambient temperature a septum and nitrogen inlet were attached prior to cooling to 0 °C. Sodium borohydride (1.48 g, 39.0 mmol) was then added, and a complete reaction was observed after 1 h. Methyl alcohol was then slowly added until gas evolution had stopped. The reaction mixture was then diluted with brine (60 mL) while experiencing rapid stirring. The resultant slurry was filtered through celite, washing with EtOAc as needed. The combined organics were then washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to give an oil. This oil was purified by silica gel

chromatography, eluting with a gradient of EtOAc:Hexanes – 10:90 to 50:50, to give the title compound. MS: *m/z* = 362 (M + 1).

Step B. (6*S*)-6-(3,5-Difluorophenyl)-piperidin-2-one

A solution of ethyl (5*S*)-5-{[(*S*)-*tert*-butylsulfinyl]amino}-5-(3,5-difluorophenyl)pentanoate from Step A (4.42 g, 12.2 mmol) in MeOH (200 mL) was cooled to 0 °C. Hydrogen chloride gas (anhydrous) was bubbled through this cold solution for about 1 minute, after which time the reaction vessel was sealed and allowed to sit in the ice bath for 15 minutes. Dry nitrogen was then bubbled through the solution for 30 minutes, prior to removal of solvent *in vacuo*. More MeOH (~50 mL) was added, and then removed *in vacuo*. After dissolving in a third volume of MeOH (100 mL), triethylamine (6.78 mL, 48.9 mmol) was introduced and the mixture was heated to 65 °C for 3 hours. After cooling to ambient temperature, the solvent was removed *in vacuo* and the residue was partitioned between diethyl ether (100 mL) and 1 M HCl (50 mL). The organics were washed with additional 1 M HCl (50 mL), water (50 mL) and saturated brine (50 mL). The ethereal solution was dried over sodium sulfate, filtered and then concentrated *in vacuo* to provide the title compound, which could be used without further purification. MS: *m/z* = 212 (M + 1).

Step C. *tert*-Butyl (2*S*)-2-(3,5-difluorophenyl)-6-oxopiperidine-1-carboxylate

A solution of (6*S*)-6-(3,5-difluorophenyl)-piperidin-2-one from Step B (2.08 g, 9.85 mmol), di-*tert*-butyl dicarbonate (4.30 g, 19.7 mmol), and 4-dimethylaminopyridine (1.20 g, 9.85 mmol) in CH_2Cl_2 (50 mL) was stirred at ambient temperature for 20 h. An additional portion of di-*tert*-butyl dicarbonate (1.25 g, 5.73 mmol) was added and the solution stirred for a further 16 h. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 100:0 to 0:100, to give the title compound. MS: *m/z* = 256 (M - C_4H_7).

Step D. *tert*-Butyl (6*S*)-6-(3,5-difluorophenyl)-3,3-diethylpiperidin-2-one-1-carboxylate

To a solution of *tert*-butyl (2*S*)-2-(3,5-difluorophenyl)-6-oxopiperidine-1-carboxylate from Step C (1.53 g, 4.91 mmol) and iodoethane (0.993 mL, 12.3 mmol) in THF (15 mL) at -78 °C was added a 1 M solution of sodium *bis*(trimethylsilyl)amide in THF (10.8 mL, 10.8 mmol) dropwise over 15 min. The resulting mixture was stirred at -78 °C for 10 min and at 0 °C for 2 h, then quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 100:0 to 50:50, to give the title compound. MS: *m/z* = 312 (M – C_4H_7).

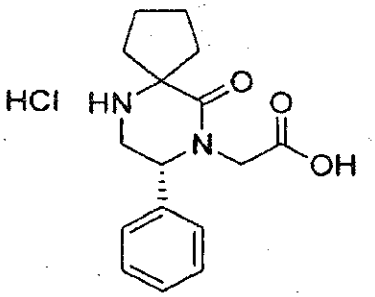
Step E. (6*S*)-6-(3,5-Difluorophenyl)-3,3-diethylpiperidin-2-one

To a solution of *tert*-butyl (6*S*)-6-(3,5-difluorophenyl)-3,3-diethylpiperidin-2-one-1-carboxylate from Step D (1.22 g, 3.32 mmol) in CH_2Cl_2 (7 mL) at ambient temperature was added TFA (3 mL). After stirring for 1.5 h, the reaction mixture was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (30 mL) and saturated $NaHCO_3$ (30 mL). The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (2 × 30 mL). The combined organics were dried over sodium sulfate, filtered and then concentrated *in vacuo* to provide the title compound, which could be used without further purification. MS: *m/z* = 268 (M + 1).

Step F. [(6*S*)-6-(3,5-Difluorophenyl)-3,3-diethyl-2-oxopiperidin-1-yl]acetic acid

To a stirred solution of (6*S*)-6-(3,5-difluorophenyl)-3,3-diethylpiperidin-2-one from Step E (850 mg, 3.18 mmol) in THF (15 mL) at ambient temperature was added NaH (178 mg of a 60% dispersion in oil, 4.45 mmol). After 15 min, methyl bromoacetate (0.469 mL, 5.09 mmol) was added and the mixture was stirred for 1 h. Sodium hydroxide (9.54 mL of a 1 M solution, 9.54 mmol) was added and the mixture stirred for an additional 16 h at 50 °C. The reaction mixture was poured onto 1 M HCl (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the title compound, which could be used without further purification. MS: *m/z* = 326 (M + 1).

INTERMEDIATE 28



[(8*R*)-10-Oxo-8-phenyl-6,9-diazaspiro[4.5]dec-9-yl]acetic acid hydrochloride

Step A. Methyl 1-[(2-oxo-2-phenylethyl)amino]cyclopentanecarboxylate

A mixture of methyl 1-aminocyclopentanecarboxylate hydrochloride (2.00 g, 11.1 mmol, described in Intermediate 25), 2-bromoacetophenone (2.44 g, 12.2 mmol), and $NaHCO_3$ (2.34 g, 27.9 mmol) in DMF (20 mL) was stirred at ambient temperature for 5 h. H_2O (25 mL) was added and the mixture was extracted with EtOAc (2 × 75 mL). The combined organic layers

were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. The product-containing fractions were combined, adjusted to pH 10 by addition of saturated aqueous Na_2CO_3 and extracted with EtOAc (2 × 75 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the title compound. MS: *m/z* = 262 (M + 1).

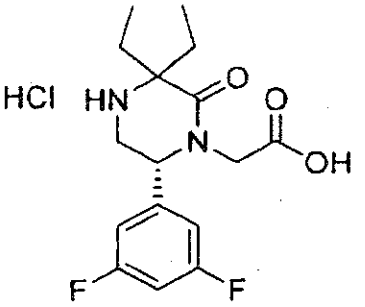
Step B. Ethyl [(8*R*)-10-oxo-8-phenyl-6,9-diazaspiro[4.5]dec-9-yl]acetate

To a stirred mixture of methyl 1-[(2-oxo-2-phenylethyl)amino]cyclopentanecarboxylate from Step A (1.10 g, 2.67 mmol) and glycine ethyl ester hydrochloride (881 mg, 6.31 mmol) in EtOH (10 mL) was added AcOH (0.72 mL, 12.6 mmol). The resulting mixture was stirred at ambient temperature for 5 min, then $NaCNBH_3$ (397 mg, 6.31 mmol) was added. The reaction mixture was heated to 70 °C for 3 h then allowed to cool. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and then extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. The product-containing fractions were combined, basified with saturated aqueous $NaHCO_3$, and extracted with EtOAc. The organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the racemic product. The enantiomers were separated by HPLC, using a Chiralcel OD column and eluting with hexane:EtOH – 60:40. The first major peak to elute was ethyl [(8*S*)-10-oxo-8-phenyl-6,9-diazaspiro[4.5]dec-9-yl]acetate and the second major peak to elute was ethyl [(8*R*)-10-oxo-8-phenyl-6,9-diazaspiro[4.5]dec-9-yl]acetate, the title compound. MS: *m/z* = 317 (M + 1).

Step C. [(8*R*)-10-Oxo-8-phenyl-6,9-diazaspiro[4.5]dec-9-yl]acetic acid hydrochloride

To a solution of ethyl [(8*R*)-10-oxo-8-phenyl-6,9-diazaspiro[4.5]dec-9-yl]acetate from Step B (407 mg, 1.29 mmol) in THF (8 mL) and H_2O (2 mL) was added 1 N aqueous LiOH (1.54 mL, 1.54 mmol) and the resulting mixture was stirred at ambient temperature for 4 h. The mixture was adjusted to pH 4 by addition of 1 N HCl and concentrated to dryness *in vacuo* to give the title compound. MS: *m/z* = 289 (M + 1).

INTERMEDIATE 29



[(6*R*)-6-(3,5-Difluorophenyl)-3,3-diethyl-2-oxopiperazin-1-yl]acetic acid hydrochloride

Step A. Methyl 2-amino-2-ethylbutanoate hydrochloride

A solution of 2-amino-2-ethylbutanoic acid (3.00 g, 22.9 mmol) in MeOH (200 mL) was saturated with HCl (g). The resulting mixture was heated at reflux for 24 h, during which time it was allowed to cool to ambient temperature and was again saturated with HCl (g) twice. After 24 h at reflux, the cooled mixture was concentrated *in vacuo* to provide the title compound. MS: *m/z* = 146 (M + 1).

Step B. Methyl 2-{[2-(3,5-difluorophenyl)-2-oxoethyl]amino}-2-ethylbutanoate

A mixture of methyl 2-amino-2-ethylbutanoate hydrochloride from Step A (2.10 g, 11.6 mmol), 3,5-difluorophenacyl bromide (2.99 g, 12.7 mmol), and $NaHCO_3$ (2.43 g, 28.9 mmol) in DMF (20 mL) was stirred at 45 °C for 1 h, and at ambient temperature for 2 h. 1 N aqueous HCl (50 mL) was added and the mixture was extracted with EtOAc (75 mL) and this organic extract was discarded. The aqueous layer was adjusted to pH 10 by addition of saturated aqueous Na_2CO_3 (150 mL) was added and the mixture was extracted with EtOAc (3 × 75 mL). The combined organic layers were treated with CF_3CO_2H (1.5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. The product-containing fractions were combined, basified with saturated aqueous $NaHCO_3$, and extracted with EtOAc. The organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the title compound. MS: *m/z* = 300 (M + 1).

Step C. Methyl [(6*R*)-6-(3,5-difluorophenyl)-3,3-diethyl-2-oxopiperazin-1-yl]acetate

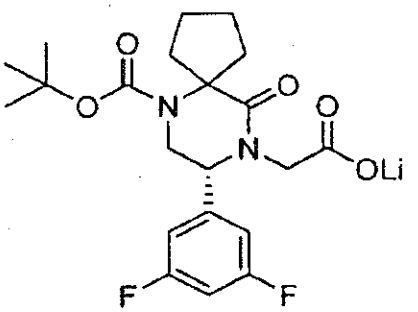
To a stirred mixture of methyl 2-{[2-(3,5-difluorophenyl)-2-oxoethyl]amino}-2-ethylbutanoate from Step B (475 mg, 1.59 mmol) and glycine ethyl ester hydrochloride (332 mg, 2.38 mmol) in MeOH (5 mL) were added titanium(IV) isopropoxide (1.16 mL, 3.97 mmol) and AcOH (0.273 mL, 4.76 mmol). The resulting mixture was stirred at ambient temperature for 15 min, then $NaCNBH_3$ (150 mg, 2.38 mmol) was added. The stirred reaction mixture was heated

at 50 °C for 18 h, then at 70 °C for 24 h, and allowed to cool. The mixture was quenched with saturated aqueous $NaHCO_3$ and then extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. The product-containing fractions were combined, basified with saturated aqueous $NaHCO_3$, and extracted with EtOAc. The organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the racemic product. The enantiomers were separated by HPLC, using a Chiralcel OD column and eluting with hexane:EtOH – 60:40. The first major peak to elute was methyl [(6*S*)-6-(3,5-difluorophenyl)-3,3-diethyl-2-oxopiperazin-1-yl]acetate and the second major peak to elute was methyl [(6*R*)-6-(3,5-difluorophenyl)-3,3-diethyl-2-oxopiperazin-1-yl]acetate, the title compound. MS: *m/z* = 341 (M + 1).

Step D. [(6*R*)-6-(3,5-Difluorophenyl)-3,3-diethyl-2-oxopiperazin-1-yl]acetic acid hydrochloride

To a solution of methyl [(6*R*)-6-(3,5-difluorophenyl)-3,3-diethyl-2-oxopiperazin-1-yl]acetate from Step C (43 mg, 0.126 mmol) in THF (0.75 mL) and H_2O (0.25 mL) was added 1 N aqueous LiOH (0.139 mL, 0.139 mmol) and the resulting mixture was stirred at ambient temperature for 1 h. The mixture was adjusted to pH 4 by addition of 1 N HCl and concentrated to dryness *in vacuo* to give the title compound. MS: *m/z* = 327 (M + 1).

INTERMEDIATE 32



Lithium [(8*R*)-6-(*tert*-butoxycarbonyl)-8-(3,5-difluorophenyl)-10-oxo-6,9-diazaspiro[4.5]dec-9-yl]acetate

Step A. Methyl 1-{[2-(3,5-difluorophenyl)-2-oxoethyl]amino}cyclopentanecarboxylate

A mixture of methyl 1-aminocyclopentanecarboxylate hydrochloride (10.0 g, 55.7 mmol, described in Intermediate 25), 3,5-difluorophenacyl bromide (14.4 g, 61.2 mmol), and Na_3PO_4 (22.8 g, 139 mmol) in DMF (100 mL) was stirred at ambient temperature for 3.5 h. The reaction mixture was acidified with 1 N aqueous HCl and the mixture was extracted with EtOAc

(200 mL) and this organic extract was discarded. The aqueous layer was adjusted to pH 8-9 by addition of saturated aqueous $NaHCO_3$ and the mixture was extracted with EtOAc (3 × 250 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 90:10 to 50:50, to give the title compound. MS: m/z = 298 (M + 1).

Step B. Ethyl [8-(3,5-difluorophenyl)-10-oxo-6,9-diazaspiro[4.5]dec-9-yl]acetate

A mixture of methyl 1-{[2-(3,5-difluorophenyl)-2-oxoethyl]amino}cyclopentanecarboxylate from Step A (10.0 g, 33.6 mmol), glycine ethyl ester hydrochloride (46.9 g, 336 mmol), and AcOH (5.78 mL, 101 mmol) in MeOH (300 mL) was stirred at ambient temperature for 10 min. $NaCNBH_3$ (2.54 g, 40.4 mmol) was added and the pH of the mixture was checked and adjusted to pH ~ 5 as necessary by addition of AcOH. The reaction mixture was heated to 50 °C for 18 h then allowed to cool. The reaction mixture was carefully quenched with saturated aqueous $NaHCO_3$ (250 mL) and then extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with hexane:EtOAc – 100:0 to 0:100, to give the title compound. MS: m/z = 353 (M + 1).

Step C. *tert*-Butyl (8*R*)-8-(3,5-difluorophenyl)-9-(2-ethoxy-2-oxoethyl)-10-oxo-6,9-diazaspiro[4.5]decane-6-carboxylate

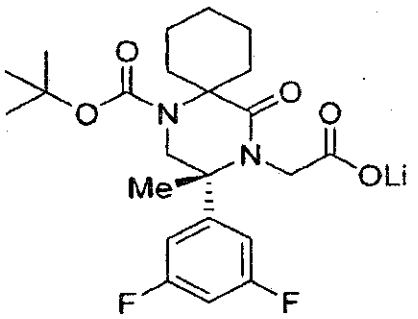
A solution of ethyl [8-(3,5-difluorophenyl)-10-oxo-6,9-diazaspiro[4.5]dec-9-yl]acetate from Step B (3.00 g, 8.51 mmol), *N*,*N*-diisopropylethylamine (0.743 mL, 4.26 mmol), and di-*tert*-butyl dicarbonate (9.29 g, 42.6 mmol) in acetonitrile (25 mL) was stirred at 60 °C for 6 h, then cooled and concentrated under reduced pressure. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 95:5 to 50:50, to give the racemic product. The enantiomers were separated by HPLC, using a Chiralcel OD column and eluting with hexane:*i*-PrOH:Et_2NH – 60:40:0.1. The first major peak to elute was *tert*-butyl (8*S*)-8-(3,5-difluorophenyl)-9-(2-ethoxy-2-oxoethyl)-10-oxo-6,9-diazaspiro[4.5]decane-6-carboxylate and the second major peak to elute was *tert*-butyl (8*R*)-8-(3,5-difluorophenyl)-9-(2-ethoxy-2-oxoethyl)-10-oxo-6,9-diazaspiro[4.5]decane-6-carboxylate, the title compound. MS: m/z = 397 (M – C_4H_7).

Step D. Lithium [(8*R*)-6-(*tert*-butoxycarbonyl)-8-(3,5-difluorophenyl)-10-oxo-6,9-diazaspiro[4.5]dec-9-yl]acetate

To a solution of *tert*-butyl (8*R*)-8-(3,5-difluorophenyl)-9-(2-ethoxy-2-oxoethyl)-10-oxo-6,9-diazaspiro[4.5]decane-6-carboxylate from Step C (50 mg, 0.11 mmol) in THF (0.75

mL) and H_2O (0.25 mL) was added 1 N aqueous LiOH (0.12 mL, 0.12 mmol) and the resulting mixture was stirred at ambient temperature for 6 h. The mixture was adjusted to pH 7 by addition of 1 N HCl and concentrated to dryness *in vacuo* to give the title compound. MS: *m/z* = 369 ($M - C_4H_7$).

INTERMEDIATE 33



Lithium [(3*R*)-1-(*tert*-butoxycarbonyl)-3-(3,5-difluorophenyl)-3-methyl-5-oxo-1,4-diazaspiro[5.5]undec-4-yl]acetate

Step A. Di-*tert*-butyl [1-(3,5-difluorophenyl)ethyl]imidodicarbonate

To a solution of [1-(3,5-difluorophenyl)ethyl]amine (10.0 g, 63.6 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added di-*tert*-butyl dicarbonate (13.9 g, 63.6 mmol) and the resulting mixture was stirred at ambient temperature for 18 h. The solvent was removed under reduced pressure. To the residue was added di-*tert*-butyl dicarbonate (20.8 g, 95.4 mmol) and DMAP (7.78 g, 63.6 mmol) and the reaction mixture was heated at 80 °C for 2 h. The mixture was allowed to cool and additional di-*tert*-butyl dicarbonate (69.4 g, 318 mmol) was added. The reaction mixture was heated at 80 °C for 2 h, allowed to cool, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 98:2 to 90:10, to give the title compound. MS: *m/z* = 421 ($M + Na + CH_3CN$).

Step B. *tert*-Butyl 2-[(*tert*-butoxycarbonyl)amino]-2-(3,5-difluorophenyl)propanoate

To a stirred suspension of potassium *tert*-butoxide in THF (300 mL) at -78 °C was added a solution of di-*tert*-butyl [1-(3,5-difluorophenyl)ethyl]imidodicarbonate from Step A (22.0 g, 61.6 mmol) in THF (200 mL), dropwise, over 45 min. The reaction mixture was allowed to warm to ambient temperature and stirring was continued for 3 h. The reaction mixture was cooled to -78 °C and quenched with 1 N aqueous HCl (300 mL), warmed to 0 °C, and poured into Et_2O (300 mL). The organic layer was extracted and the aqueous layer was extracted further with Et_2O (300 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel

chromatography, eluting with hexane:EtOAc – 95:5 to 80:20, to give the title compound. MS: m/z = 421 (M + Na + CH_3CN).

Step C. *tert*-Butyl [1-(3,5-difluorophenyl)-1-methyl-2-oxoethyl]carbamate

To a stirred solution of *tert*-butyl 2-[(*tert*-butoxycarbonyl)amino]-2-(3,5-difluorophenyl)propanoate from Step B (2.00 g, 5.60 mmol) in THF (20 mL) at -78 °C was added $LiAlH_4$ (5.60 mL of a 1 M solution in THF, 5.60 mmol), dropwise. The reaction mixture was stirred at -78 °C for 6 h, then quenched with EtOAc (5.6 mL), then H_2O (15.6 mL), then 1 N aqueous NaOH (5.6 mL), then EtOAc (17 mL). The reaction mixture was warmed to ambient temperature, stirred for 1 h, filtered, and extracted with EtOAc (2 × 40 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the title compound in sufficient purity for use in the next step. MS: m/z = 186 (M – $CO_2C_4H_7$).

Step D. Methyl 1-aminocyclohexanecarboxylate hydrochloride

Essentially following the procedures described in Intermediate 25 for methyl 1-aminocyclopentanecarboxylate hydrochloride, but using 1-aminocyclohexanecarboxylic acid in place of 1-aminocyclopentanecarboxylic acid, the title compound was obtained. MS: m/z = 158 (M + 1).

Step E. Methyl 1-{[2-[(*tert*-butoxycarbonyl)amino]-2-(3,5-difluorophenyl)propyl]amino}cyclohexanecarboxylate

A mixture of *tert*-butyl [1-(3,5-difluorophenyl)-1-methyl-2-oxoethyl]carbamate from Step C (500 mg, 1.75 mmol), methyl 1-aminocyclohexanecarboxylate hydrochloride from Step D (1.38 g, 8.76 mmol), and AcOH (0.301 mL, 5.26 mmol) in MeOH (15 mL) was stirred at ambient temperature for 30 min. $NaCNBH_3$ (165 mg, 2.63 mmol) was added and the pH of the mixture was checked and adjusted to pH ~ 5 as necessary by addition of AcOH. The reaction mixture was stirred at ambient temperature for 1 h, then quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with hexane:EtOAc – 100:0 to 80:20, to give the title compound. MS: m/z = 427 (M + 1).

Step F. Methyl 1-{[2-amino-2-(3,5-difluorophenyl)propyl]amino}cyclohexanecarboxylate

A solution of methyl 1-{[2-[(*tert*-butoxycarbonyl)amino]-2-(3,5-difluorophenyl)propyl]amino}cyclohexanecarboxylate from Step E (280 mg, 0.657 mmol) in EtOAc (5 mL) at 0 °C was saturated with HCl (g). The reaction mixture was aged at 0 °C for 30 min, then poured carefully into saturated aqueous $NaHCO_3$ (10 mL). The resulting mixture was

extracted with EtOAc (2 × 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the title compound. MS: *m/z* = 327 (M + 1).

Step G. (3*R*)-3-(3,5-Difluorophenyl)-3-methyl-1,4-diazaspiro[5.5]undecan-5-one

A solution of methyl 1-{[2-amino-2-(3,5-difluorophenyl)propyl]amino}cyclohexanecarboxylate from Step F (205 mg, 0.628 mmol), and AcOH (0.36 mL, 6.28 mmol) in xylenes (5 mL) was heated at 80 °C for 3 h, allowed to cool, then poured into saturated aqueous $NaHCO_3$ (5 mL). The resulting mixture was extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography, eluting with a gradient of EtOAc:MeOH – 100:0 to 92:8, to give the racemic product. The enantiomers were separated by HPLC, using a ChiralPak AD column and eluting with hexane:EtOH:Et_2NH – 40:60:0.1. The first major peak to elute was (3*R*)-3-(3,5-difluorophenyl)-3-methyl-1,4-diazaspiro[5.5]undecan-5-one, the title compound, and the second major peak to elute was (3*S*)-3-(3,5-difluorophenyl)-3-methyl-1,4-diazaspiro[5.5]undecan-5-one. MS: *m/z* = 295 (M + 1).

Step H. *tert*-Butyl (3*R*)-3-(3,5-difluorophenyl)-3-methyl-5-oxo-1,4-diazaspiro[5.5]undecane-1-carboxylate

A solution of (3*R*)-3-(3,5-difluorophenyl)-3-methyl-1,4-diazaspiro[5.5]undecan-5-one from Step G (90 mg, 0.306 mmol), *N*,*N*-diisopropylethylamine (0.027 mL, 0.153 mmol), and di-*tert*-butyl dicarbonate (667 mg, 3.06 mmol) in acetonitrile (2 mL) was stirred at 60 °C for 8 h, then cooled and concentrated under reduced pressure. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 95:5 to 50:50, to give the title compound. MS: *m/z* = 339 (M – C_4H_7).

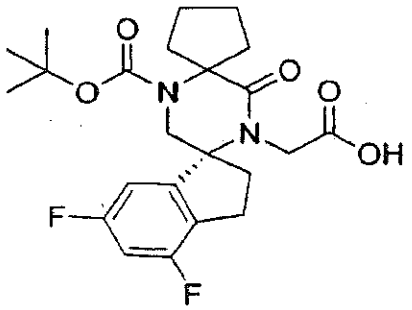
Step I. *tert*-Butyl (3*R*)-3-(3,5-difluorophenyl)-4-(2-ethoxy-2-oxoethyl)-3-methyl-5-oxo-1,4-diazaspiro[5.5]undecane-1-carboxylate

To a stirred solution of *tert*-butyl (3*R*)-3-(3,5-difluorophenyl)-3-methyl-5-oxo-1,4-diazaspiro[5.5]undecane-1-carboxylate from Step H (60 mg, 0.152 mmol) in THF (0.5 mL) at 0 °C was added NaH (12 mg of a 60% dispersion in oil, 0.30 mmol). After 5 min, ethyl bromoacetate (437 mg, 2.62 mmol) was added and the mixture was allowed to warm to ambient temperature and stirring was continued for 1 h. Saturated aqueous $NaHCO_3$ (2 mL) was added and the mixture was extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 95:5 to 60:40, to give the title compound. MS: *m/z* = 425 (M – C_4H_7).

Step J. Lithium [(3*R*)-1-(*tert*-butoxycarbonyl)-3-(3,5-difluorophenyl)-3-methyl-5-oxo-1,4-diazaspiro[5.5]undec-4-yl]acetate

To a solution of *tert*-butyl (3*R*)-3-(3,5-difluorophenyl)-4-(2-ethoxy-2-oxoethyl)-3-methyl-5-oxo-1,4-diazaspiro[5.5]undecane-1-carboxylate from Step I (65 mg, 0.135 mmol) in THF (1.5 mL) and H_2O (0.5 mL) was added 1 N aqueous LiOH (0.14 mL, 0.14 mmol) and the resulting mixture was stirred at ambient temperature for 1 h. The mixture was adjusted to pH 7 by addition of 1 N HCl and concentrated to dryness *in vacuo* to give the title compound. MS: *m/z* = 397 (M – C_4H_7).

INTERMEDIATE 34



[(5"*R*)-1'-(*tert*-Butoxycarbonyl)-4",6"-difluoro-3'-oxo-2",3"-dihydro-4'*H*-dispiro[cyclopentane-1,2'-piperazine-5',1"-inden]-4'-yl]acetic acid

Step A. 4',6'-Difluoro-2',3'-dihydro-2*H*,5*H*-spiro[imidazolidine-4,1'-indene]-2,5-dione

A mixture of 4,6-difluoroindan-1-one [Musso *et al.* (2003) *J. Med. Chem.*, **46**, 399-408] (14.5 g, 86 mmol), NaCN (12.9 g, 262 mmol), and $(NH_4)_2CO_3$ (16.8 g, 175 mmol) in H_2O (150 mL) and EtOH (150 mL) was heated at 70 °C for 3 h. Additional $(NH_4)_2CO_3$ (16.8 g, 175 mmol) was added and heating at 70 °C was continued for 4 h. The mixture was concentrated to dryness under reduced pressure. To the residue was added H_2O (200 mL) and the precipitate was isolated by filtration, washed with H_2O, and dried to give the title compound. MS: *m/z* = 280 (M + 1 + CH_3CN).

Step B. 1-Amino-4,6-difluoroindane-1-carboxylic acid hydrochloride

A mixture of 4',6'-difluoro-2',3'-dihydro-2*H*,5*H*-spiro[imidazolidine-4,1'-indene]-2,5-dione from Step A (16.7 g, 70.1 mmol) and conc. HCl (90 mL) in a high pressure reactor was heated at 180 °C for 5 h. The mixture was cooled to 0 °C, vented carefully, and concentrated to dryness *in vacuo* to afford the title compound. MS: *m/z* = 214 (M + 1).

Step C. Methyl 1-amino-4,6-difluoroindane-1-carboxylate hydrochloride

A solution of 1-amino-4,6-difluoroindane-1-carboxylic acid hydrochloride (2.00 g, 15.5 mmol) in MeOH (100 mL) was saturated with HCl (g). The resulting mixture was heated at reflux for 20 h and concentrated *in vacuo* to provide the title compound. MS: m/z = 228 (M + 1).

Step D. Methyl 1-[(*tert*-butoxycarbonyl)amino]-4,6-difluoroindane-1-carboxylate

A solution of methyl 1-amino-4,6-difluoroindane-1-carboxylate hydrochloride from Step C (3.82 g, 14.5 mmol), *N*,*N*-diisopropylethylamine (5.62 g, 43.5 mmol), and di-*tert*-butyl dicarbonate (15.8 g, 72.5 mmol) in acetonitrile (40 mL) was stirred at 60 °C for 3 h, then cooled and concentrated under reduced pressure. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 100:0 to 40:60, to give the title compound. MS: m/z = 228 (M – $CO_2C_4H_7$).

Step E. *tert*-Butyl [4,6-difluoro-1-(hydroxymethyl)-2,3-dihydro-1*H*-inden-1-yl]carbamate

To a stirred solution of methyl 1-[(*tert*-butoxycarbonyl)amino]-4,6-difluoroindane-1-carboxylate from Step D (2.80 g, 8.55 mmol) in THF (30 mL) at -78 °C was added $LiAlH_4$ (18.0 mL of a 1 M solution in THF, 18.0 mmol), dropwise, over 30 min. The reaction mixture was stirred at -78 °C for 2 h, then quenched with H_2O (1 mL), then 1 N aqueous NaOH (2 mL), then H_2O (2 mL), then EtOAc (2 mL). The reaction mixture was warmed to ambient temperature, saturated aqueous $NaHCO_3$ (150 mL) was added, and the mixture was extracted with EtOAc (200 mL). The organic extract was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 100:0 to 50:50, to give the title compound. MS: m/z = 244 (M – C_4H_7).

Step F. *tert*-Butyl (4,6-difluoro-1-formyl-2,3-dihydro-1*H*-inden-1-yl)carbamate

To a stirred solution of oxalyl chloride (0.91 mL, 10.4 mmol) in CH_2Cl_2 (40 mL) at -78 °C was added DMSO (1.48 mL, 20.9 mmol), dropwise, over 5 min. The reaction mixture was stirred for 30 min, during which time it warmed to -60 °C, then a solution of *tert*-butyl [4,6-difluoro-1-(hydroxymethyl)-2,3-dihydro-1*H*-inden-1-yl]carbamate from Step E (2.08 g, 6.95 mmol) in CH_2Cl_2 (22 mL) was added, dropwise, over 30 min. During the addition, the reaction temperature rose to -45 °C and it was stirred at this temperature for an additional 15 min. To the resulting mixture was added *N*,*N*-diisopropylethylamine (7.28 mL, 41.7 mmol), dropwise, over 2 min. The mixture was allowed to warm to 0 °C, stirred for 15 min then poured into ice (60 mL) and 1 N aqueous HCl (30 mL). The resulting mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed with H_2O (30 mL), then brine (50 mL), then dried

over Na_2SO_4, filtered, and concentrated *in vacuo* to give the title compound. MS: *m/z* = 224 (M – OC_4H_9).

Step G. Methyl 1-[({1-[(*tert*-butoxycarbonyl)amino]-4,6-difluoro-2,3-dihydro-1*H*-inden-1-yl}methyl)amino]cyclopentanecarboxylate

A mixture of *tert*-butyl (4,6-difluoro-1-formyl-2,3-dihydro-1*H*-inden-1-yl)carbamate from Step F (890 mg, 2.99 mmol), methyl 1-aminocyclopentanecarboxylate (4.25 g, 29.7 mmol, described in Intermediate 25), and AcOH (2.10 mL, 36.7 mmol) in MeOH (32 mL) was stirred at ambient temperature for 20 min. $NaCNBH_3$ (405 mg, 6.44 mmol) was added and the pH of the mixture was checked and adjusted to pH ~ 5 as necessary by addition of AcOH. The reaction mixture was stirred at ambient temperature for 23 h, then quenched with saturated aqueous $NaHCO_3$ (80 mL) and extracted with EtOAc (200 mL). The organic extract was washed with H_2O (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with hexane:EtOAc – 100:0 to 30:70, to give the title compound. MS: *m/z* = 425 (M + 1).

Step H. Methyl 1-{[(1-amino-4,6-difluoro-2,3-dihydro-1*H*-inden-1-yl)methyl]amino}cyclopentanecarboxylate hydrochloride

A solution of methyl 1-[({1-[(*tert*-butoxycarbonyl)amino]-4,6-difluoro-2,3-dihydro-1*H*-inden-1-yl}methyl)amino]cyclopentanecarboxylate from Step G (753 mg, 1.77 mmol) in EtOAc (40 mL) at 0 °C was saturated with HCl (g). The reaction mixture was aged at 0 °C for 45 min then concentrated *in vacuo* to give the title compound. MS: *m/z* = 325 (M + 1).

Step I. 4",6"-Difluoro-2",3"-dihydro-3'*H*-dispiro[cyclopentane-1,2'-piperazine-5',1"-inden]-3'-one

A solution of methyl 1-{[(1-amino-4,6-difluoro-2,3-dihydro-1*H*-inden-1-yl)methyl]amino}cyclopentanecarboxylate hydrochloride from Step H (741 mg, 2.05 mmol), and AcOH (5.0 mL, 6.28 mmol) in xylenes (50 mL) was heated at 150 °C for 24 h, allowed to cool, and concentrated to dryness under reduced pressure. The residue was partitioned between saturated aqueous $NaHCO_3$ (80 mL) and EtOAc (100 mL). The organic extract was washed with H_2O (60 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound. MS: *m/z* = 293 (M + 1).

Step J. *tert*-Butyl (5"*R*)-4",6"-difluoro-3'-oxo-2",3"-dihydro-1'*H*-dispiro[cyclopentane-1,2'-piperazine-5',1"-indene]-1'-carboxylate

A solution of 4",6"-difluoro-2",3"-dihydro-3'*H*-dispiro[cyclopentane-1,2'-piperazine-5',1"-inden]-3'-one from Step I (453 mg, 1.55 mmol), *N*,*N*-diisopropylethylamine (0.135 mL, 0.78 mmol), and di-*tert*-butyl dicarbonate (3.45 g, 15.8 mmol) in acetonitrile (6 mL)

was stirred at 50 °C for 18 h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (40 mL) and EtOAc (60 mL). The organic extract was dried over Na_2SO_4, filtered, and concentrated under reduced pressure The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 100:0 to 50:50, to give the racemic product. The enantiomers were separated by HPLC, using a ChiralPak AD column and eluting with hexane:EtOH:Et_2NH – 40:60:0.1. The first major peak to elute was *tert*-butyl (5"*R*)-4",6"-difluoro-3'-oxo-2",3"-dihydro-1'*H*-dispiro[cyclopentane-1,2'-piperazine-5',1"-indene]-1'-carboxylate, the title compound, and the second major peak to elute was *tert*-butyl (5"*S*)-4",6"-difluoro-3'-oxo-2",3"-dihydro-1'*H*-dispiro[cyclopentane-1,2'-piperazine-5',1"-indene]-1'-carboxylate. MS: *m/z* = 337 (M – C_4H_7).

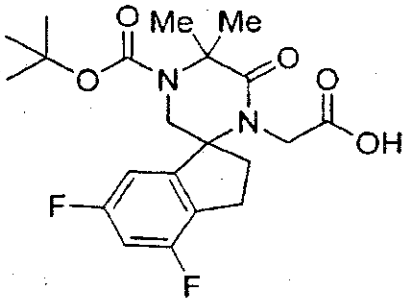
Step K. *tert*-Butyl (5"*R*)-4'-(2-ethoxy-2-oxoethyl)-4",6"-difluoro-3'-oxo-2",3"-dihydro-1'*H*-dispiro[cyclopentane-1,2'-piperazine-5',1"-indene]-1'-carboxylate

To a stirred solution of *tert*-butyl (5"*R*)-4",6"-difluoro-3'-oxo-2",3"-dihydro-1'*H*-dispiro[cyclopentane-1,2'-piperazine-5',1"-indene]-1'-carboxylate from Step J (217 mg, 0.553 mmol) in THF (4 mL) at ambient temperature was added NaH (44 mg of a 60% dispersion in oil, 1.11 mmol). After 15 min, ethyl bromoacetate (185 mg, 1.11 mmol) was added and the mixture was allowed to warm to ambient temperature and stirring was continued for 3 h. Saturated aqueous $NaHCO_3$ (25 mL) was added and the mixture was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 100:0 to 50:50, to give the title compound. MS: *m/z* = 479 (M + 1).

Step L. [(5"*R*)-1'-(*tert*-Butoxycarbonyl)-4",6"-difluoro-3'-oxo-2",3"-dihydro-4'*H*-dispiro[cyclopentane-1,2'-piperazine-5',1"-inden]-4'-yl]acetic acid

To a solution of *tert*-butyl (5"*R*)-4'-(2-ethoxy-2-oxoethyl)-4",6"-difluoro-3'-oxo-2",3"-dihydro-1'*H*-dispiro[cyclopentane-1,2'-piperazine-5',1"-indene]-1'-carboxylate from Step K (258 mg, 0.539 mmol) in THF (3 mL) was added 1 N aqueous LiOH (0.65 mL, 0.65 mmol) and the resulting mixture was stirred at ambient temperature for 20 h. To the reaction mixture was added THF (3 mL), EtOH (0.2 mL), and 1 N aqueous LiOH (0.20 mL, 0.20 mmol) and the resulting mixture was stirred at ambient temperature for 16 h. The mixture was acidified by addition of 1 N aqueous HCl (0.9 mL, 0.9 mmol) and concentrated to dryness *in vacuo* to give the title compound. MS: *m/z* = 451 (M + 1).

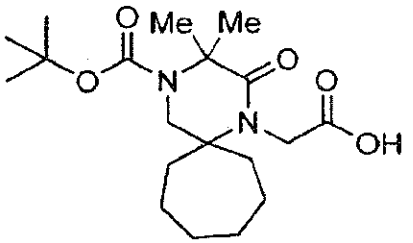
INTERMEDIATE 35



(±)-[4'-(*tert*-Butoxycarbonyl)-4,6-difluoro-5',5'-dimethyl-6'-oxo-2,3-dihydro-1'*H*-spiro[indene-1,2'-piperazin]-1'-yl]acetic acid

Essentially following the procedures described in Intermediate 34, but using methyl α-aminoisobutyrate in place of methyl 1-aminocyclopentanecarboxylate, the title compound was obtained. MS: *m/z* = 425 (M + 1).

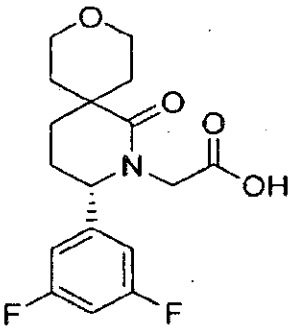
INTERMEDIATE 36



[4-(*tert*-Butoxycarbonyl)-3,3-dimethyl-2-oxo-1,4-diazaspiro[5.6]dodec-1-yl]acetic acid

Essentially following the procedures described in Intermediate 34, but using methyl α-aminoisobutyrate in place of methyl 1-aminocyclopentanecarboxylate, and using methyl 1-aminocycloheptanecarboxylate hydrochloride in place of methyl 1-amino-4,6-difluoroindane-1-carboxylate hydrochloride, the title compound was obtained. MS: *m/z* = 369 (M + 1).

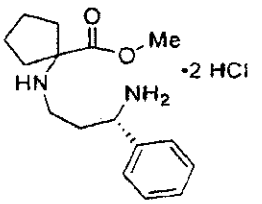
INTERMEDIATE 37



[(3*S*)-3-(3,5-Difluorophenyl)-1-oxo-9-oxa-2-azaspiro[5.5]undec-2-yl]acetic acid

Essentially following the procedures described in Intermediate 26, but using 2-iodoethyl ether in place of iodoethane, the title compound was obtained. MS: *m/z* = 340 (M + 1).

INTERMEDIATE 38



Methyl 1-{[(3*S*)-3-amino-3-phenylpropyl]amino}cyclopentanecarboxylate bis-hydrochloride

Step A. Ethyl (3*S*)-3-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanoate

To a solution of (*S*)-3-amino-3-phenylpropanoic acid ethyl ester hydrochloride (2.50 g, 10.9 mmol) and Boc-anhydride (2.38 g, 10.9 mmol) in CH_2Cl_2 (16.3 mL) was slowly added triethylamine (3.03 mL, 21.8 mmol). After 4.5 hours, the reaction mixture was applied to the top of a silica gel column, and following elution with a gradient of EtOAc:hexanes – 5:95 to 40:60 the title compound was obtained. MS: *m/z* = 294 (M + 1).

Step B. *tert*-Butyl [(1*S*)-3-oxo-1-phenylpropyl]carbamate

To a dry, cooled (-78 °C) solution of ethyl (3*S*)-3-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanoate from Step A (1.00 g, 3.41 mmol) was added a solution of DiBAl-H (6.82 mL, 6.82 mmol, 1 M in CH_2Cl_2) slowly over 30 min. After an additional 30 min of stirring at -78 °C, the reaction was quenched by the rapid addition of saturated aqueous Rochelle's salt (32 mL). The cooling bath was then removed and the reaction was allowed to rapidly stir until a noticeable decrease in the amount of emulsion was observed. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). Combined organics were dried over

sodium sulfate, filtered and concentrated *in vacuo* to give an oil. This oil was purified by silica gel chromatography, eluting with a gradient of EtOAc:hexanes 5:95 to 40:60, to give the title compound. MS: *m/z* = 150 (M – $CO_2C_4H_7$).

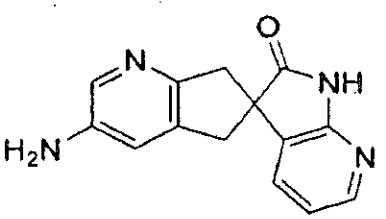
Step C. Methyl 1-({(3*S*)-3-[(*tert*-butoxycarbonyl)amino]-3-phenylpropyl}amino)cyclopentanecarboxylate

To a solution of *tert*-butyl [(1*S*)-3-oxo-1-phenylpropyl]carbamate from Step B (0.820 g, 3.29 mmol) and methyl 1-aminocyclopentanecarboxylate hydrochloride (0.591 g, 3.29 mmol) in chloroform (33 mL) was added Hunig's base (0.574 mL, 3.29 mmol). After stirring at ambient temperature for 20 min, $NaHB(OAc)_3$ (1.74 g, 8.22 mmol) was added as a solid. Upon completion of the reaction, saturated aqueous $NaHCO_3$ (3 mL) was added and the mixture was allowed to stir for at least 2 h. Water (5 mL) and additional saturated $NaHCO_3$ (3 mL) was then added to form two layers. The aqueous layer was extracted once with chloroform (50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give an oil. This oil was purified by silica gel chromatography, eluting with a gradient of MeOH:DCM 1:99 to 6:94, to give the title compound. MS: *m/z* = 377 (M + 1).

Step D. Methyl 1-{[(3*S*)-3-amino-3-phenylpropyl]amino}cyclopentanecarboxylate bis-hydrochloride

To a cooled (0 °C) solution of methyl 1-({(3*S*)-3-[(*tert*-butoxycarbonyl)amino]-3-phenylpropyl}amino)cyclopentanecarboxylate from Step C (0.920 g, 2.44 mmol) in MeOH (49 mL) was added excess anhydrous hydrogen chloride gas. After 30 min the solution was purged with dry nitrogen for about 40 min. The solvent was then removed *in vacuo* to provide a solid/oil mix. Additional MeOH (50 mL) was then added and subsequently removed *in vacuo* to provide the title compound. MS: *m/z* = 277 (M + 1).

INTERMEDIATE 41



3-Amino-5,7-dihydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one, isomer A

Step A. (±)-1'-{[2-(Trimethylsilyl)ethoxy]methyl}-3*H*-spiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-2',3(1'*H*)-dione

To a solution of 1-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (2.50 g, 9.46 mmol, described in Intermediate 7) and cesium carbonate (6.78 g, 20.8 mmol) in DMF (45 mL) was added dropwise a solution of 1,4-dibromobutan-2-one [Meijere *et al.* (2001) *Eur. J. Org. Chem.* **20**, 3789-3795] (1.59 g, 12.3 mmol) in DMF (45 mL). After 68 h, the mixture was partitioned between Et_2O (200 mL) and H_2O (200 mL). The organic layer was separated and the aqueous layer was further extracted with Et_2O (2 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 100:0 to 75:25, to give the title compound. MS: *m/z* = 333 (M + 1).

Step B. (±)-3-Nitro-1'-{[2-(trimethylsilyl)ethoxy]methyl}-5,7-dihydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one

A mixture of (±)-1'-{[2-(trimethylsilyl)ethoxy]methyl}-3*H*-spiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-2',3(1'*H*)-dione from Step A (230 mg, 0.692 mmol) and 1-methyl-3,5-dinitropyridin-2(1*H*)-one [Tohda *et al.* (1990) *Bull. Chem. Soc. Japan* ***63***, 2820-2827] (173 mg, 0.869 mmol) in 2 M ammonia in MeOH (3.5 mL) was heated to reflux for 18 h. The mixture was concentrated *in vacuo* and purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 100:0 to 50:50, to give the title compound. MS: *m/z* = 413 (M + 1).

Step C. (±)-3-Amino-1'-{[2-(trimethylsilyl)ethoxy]methyl}-5,7-dihydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one

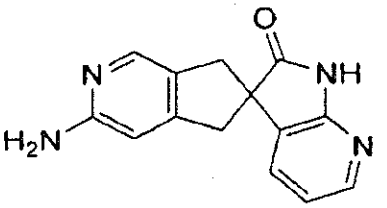
A mixture of 10% Pd/C (20 mg) and (±)-3-nitro-1'-{[2-(trimethylsilyl)ethoxy]methyl}-5,7-dihydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one from Step B (117 mg, 0.284 mmol) was stirred vigorously in MeOH (5 mL) under an atmosphere of hydrogen (*ca.* 1 atm). After 4.5 h, the mixture was filtered through a pad of Celite, washing extensively with MeOH, and the filtrate was concentrated *in vacuo* to give the title compound. MS: *m/z* = 383 (M + 1).

Step D. 3-Amino-5,7-dihydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one, isomer A

A solution of (±)-3-amino-1'-{[2-(trimethylsilyl)ethoxy]methyl}-5,7-dihydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one from Step C (117 mg, 0.306 mmol) in MeOH (5 mL) was saturated with HCl (g). The mixture was stirred for 30 min and then concentrated *in vacuo*. The residue was dissolved in MeOH (3 mL) and treated with

ethylenediamine (0.020 mL, 0.306 mmol) and 10 N sodium hydroxide to adjust the mixture to pH 10. After 1 h, the reaction mixture was purified directly by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. Lyophilization provided the racemic title compound as the TFA salt. The enantiomers were resolved by HPLC, utilizing a ChiralPak AD column and eluting with EtOH. The first major peak to elute was 3-amino-5,7-dihydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one, isomer A, the title compound, and the second major peak to elute was 3-amino-5,7-dihydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one, isomer B. MS: *m/z* = 253 (M + 1).

INTERMEDIATE 42



3-Amino-5,7-dihydrospiro[cyclopenta[*c*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one, isomer A

Step A. 4,5-*Bis*(hydroxymethyl)pyridine-2-carbonitrile

To a solution of dimethyl 6-cyanopyridine-3,4-dicarboxylate [Hashimoto *et al.* (1997) *Heterocycles* **46**, 581] (2.00 g, 9.08 mmol) in EtOH (50 mL) was added lithium borohydride (4.54 mL of a 2 M solution in THF, 9.08 mmol) dropwise. The reaction mixture was stirred at ambient temperature for 3 h, and then cooled to 0 °C. Saturated aqueous $NaHCO_3$ (20 mL) was added slowly and the quenched mixture was extracted with EtOAc (9 × 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of CH_2Cl_2:MeOH – 100:0 to 85:15, to give the title compound. MS: *m/z* = 165 (M + 1).

Step B. 4,5-*Bis*(bromomethyl)pyridine-2-carbonitrile

To a solution of 4,5-*bis*(hydroxymethyl)pyridine-2-carbonitrile from Step A (750 mg, 4.57 mmol) in THF (15 mL) was added phosphorus tribromide (1.61 g, 5.94 mmol) in THF (5 mL) dropwise. The reaction mixture was stirred at ambient temperature for 2 h, and then cooled to 0 °C. Saturated aqueous $NaHCO_3$ (5 mL) was added slowly and the quenched mixture was extracted with $CHCl_3$ (2 × 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel

chromatography, eluting with a gradient of hexane:EtOAc – 100:0 to 25:75, to give the title compound. MS: *m/z* = 291 (M + 1).

Step C. (±)-2'-Oxo-1',2',5,7-tetrahydrospiro[cyclopenta[*c*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridine]-3-carbonitrile

To a solution of 4,5-*bis*(bromomethyl)pyridine-2-carbonitrile from Step B (2.56 g, 8.83 mmol) and 1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one [Marfat & Carta (1987) *Tetrahedron Lett.* **28**, 4027] (1.18 g, 8.83 mmol) in THF (120 mL) and H_2O (60 mL) was added lithium hydroxide monohydrate (1.11 g, 26.5 mmol). After 20 min, the reaction mixture was poured onto water (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of CH_2Cl_2:MeOH: NH_4OH – 100:0:0 to 95:5:1, to give the title compound. MS: *m/z* = 263 (M + 1).

Step D. (±)-Sodium 2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[*c*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxylate

To a solution of (±)-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[*c*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridine]-3-carbonitrile from Step C (1.53 g, 5.83 mmol) in EtOH (20 mL) was added 5 M aqueous NaOH (3.50 mL). The mixture was heated at reflux for 72 h, with additional 5 M aqueous NaOH (2.00 mL) added at 6 h. The reaction mixture was allowed to cool and was concentrated to dryness *in vacuo* to afford the title compound in sufficient purity for use in subsequent steps. MS: *m/z* = 282 (M + 1).

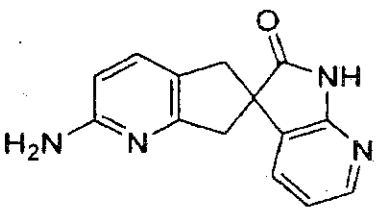
Step E. (±)-*tert*-Butyl (2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[*c*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-3-yl)carbamate

To a suspension of (±)-sodium 2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[*c*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxylate from Step D (1.64 g, 5.83 mmol) and triethylamine (1.62 mL, 11.7 mmol) in *tert*-butanol (50 mL) was added diphenylphosphoryl azide (1.89 mL, 8.75 mmol) and the mixture was heated at reflux for 72 h. Additional diphenylphosphoryl azide (1.89 mL, 8.75 mmol) was added after 24 h and 56 h. The reaction mixture was concentrated *in vacuo* and then partitioned between CH_2Cl_2 (75 mL) and saturated $NaHCO_3$ (100 mL). The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of CH_2Cl_2:MeOH: NH_4OH – 100:0:0 to 95:5:1, to give the title compound. MS: *m/z* = 353 (M + 1).

Step F. 3-Amino-5,7-dihydrospiro[cyclopenta[*c*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one, isomer A

A solution of (±)-*tert*-butyl (2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[*c*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-3-yl)carbamate from Step E (1.39 g, 3.94 mmol) was stirred in CH_2Cl_2 (10 mL) and TFA (3 mL) for 18 h and then concentrated *in vacuo* to provide the racemic title compound as the TFA salt. The enantiomers were resolved by HPLC, utilizing a ChiralPak AD column and eluting with MeOH. The first major peak to elute was 3-amino-5,7-dihydrospiro[cyclopenta[*c*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one, isomer A, the title compound, and the second major peak to elute was 3-amino-5,7-dihydrospiro[cyclopenta[*c*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one, isomer B. MS: *m/z* = 253 (M + 1).

INTERMEDIATE 43



(±)-2-Amino-5,7-dihydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one

Step A. Dimethyl 6-cyanopyridine-2,3-dicarboxylate

To a solution of dimethyl pyridine-2,3-dicarboxylate 1-oxide [Niiyami *et al.* (2002) *Bioorg. Med. Chem. Lett.* **12**, 3041] (15.3 g, 72.5 mmol) and trimethylsilyl cyanide (15.7 mL, 117 mmol) in DME (161 mL) was added dimethylcarbamoyl chloride (10.5 mL, 114 mmol). The reaction mixture was heated at reflux for 72 h, and then cooled to 0 °C. Saturated aqueous $NaHCO_3$ (800 mL) was added slowly and the quenched mixture was extracted with EtOAc (2 × 1 L). The combined organic extracts were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 100:0 to 50:50, to give the title compound. MS: *m/z* = 221 (M + 1).

Step B. 5,6-*Bis*(hydroxymethyl)pyridine-2-carbonitrile

To a solution of dimethyl 6-cyanopyridine-2,3-dicarboxylate from Step A (13.0 g, 59.0 mmol) in EtOH (295 mL) was added lithium borohydride (29.5 mL of a 2 M solution in THF, 59.0 mmol) dropwise. The reaction mixture was stirred at ambient temperature for 4 h, and then cooled to 0 °C. Saturated aqueous $NaHCO_3$ (200 mL) was added slowly and the

quenched mixture was extracted with EtOAc (9 × 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of CH_2Cl_2:MeOH – 100:0 to 85:15, to give the title compound. MS: *m/z* = 165 (M + 1).

Step C. 5,6-*Bis*(bromomethyl)pyridine-2-carbonitrile

To a solution of 5,6-*bis*(hydroxymethyl)pyridine-2-carbonitrile from Step B (2.50 g, 15.2 mmol) in THF (76 mL) was added phosphorus tribromide (5.36 g, 19.8 mmol) in THF (20 mL) dropwise. The reaction mixture was stirred at ambient temperature for 2 h, and then cooled to 0 °C. Saturated aqueous $NaHCO_3$ (20 mL) was added slowly and the quenched mixture was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 100:0 to 30:70, to give the title compound. MS: *m/z* = 291 (M + 1).

Step D. (±)-2'-Oxo-1'-{[2-(trimethylsilyl)ethoxy]methyl}-1',2',5,7-tetrahydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridine]-2-carbonitrile

To a solution of 5,6-*bis*(bromomethyl)pyridine-2-carbonitrile from Step C (1.80 g, 6.21 mmol) and 1-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (1.64 g, 6.21 mmol, described in Intermediate 7) in DMF (207 mL) was added cesium carbonate (6.07 g, 18.6 mmol), portionwise, over 5 min. After 18 h, the mixture was partitioned between CH_2Cl_2 (100 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (200 mL). The organic layer was removed and the aqueous layer was extracted further with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 100:0 to 10:90, to give the title compound. MS: *m/z* = 393 (M + 1).

Step E. (±)-2'-Oxo-1',2',5,7-tetrahydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridine]-2-carboxylic acid

To a solution of (±)-2'-oxo-1'-{[2-(trimethylsilyl)ethoxy]methyl}-1',2',5,7-tetrahydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridine]-2-carbonitrile from Step D (690 mg, 1.76 mmol) in THF (5 mL) was added 3 N aqueous HCl (36 mL). The mixture was heated at reflux for 18 h, allowed to cool and concentrated to dryness *in vacuo*. The reaction mixture was dissolved in water (12 mL) and purified directly by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 95:5:0.1 to 5:95:0.1. Lyophilization of the product-containing fractions provided the title compound. MS: *m/z* = 282 (M + 1).

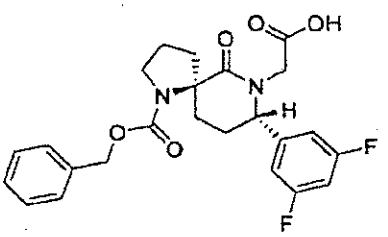
Step F. (±)-*tert*-Butyl (2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-2-yl)carbamate

To a suspension of (±)-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridine]-2-carboxylic acid from Step E (224 mg, 0.796 mmol) and triethylamine (0.333 mL, 2.39 mmol) in *tert*-butanol (5 mL) was added diphenylphosphoryl azide (0.258 mL, 1.20 mmol) and the mixture was heated at reflux for 1 h. The reaction mixture was concentrated *in vacuo* and then partitioned between CH_2Cl_2 (20 mL) and saturated $NaHCO_3$ (20 mL). The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of CH_2Cl_2:MeOH: NH_4OH – 100:0:0 to 95:5:1, to give the title compound. MS: *m/z* = 353 (M + 1).

Step G. (±)-2-Amino-5,7-dihydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one

A solution of (±)-*tert*-butyl (2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-2-yl)carbamate from Step F (147 mg, 0.417 mmol) was stirred in CH_2Cl_2 (6 mL) and TFA (1 mL) for 3 h and then concentrated *in vacuo* to provide the title compound as the TFA salt. MS: *m/z* = 253 (M + 1).

INTERMEDIATE 44



[(5*R*,8*S*)-1-[(Benzyloxy)carbonyl]-8-(3,5-difluorophenyl)-6-oxo-1,7-diazaspiro[4.5]dec-7-yl]acetic acid

Step A. 1-Benzyl 2-methyl (2*R*)-2-(3-oxopropyl)pyrrolidine-1,2-dicarboxylate

To a solution of DMSO (5.11 mL, 72.1 mmol) in CH_2Cl_2 (25 mL) at -78 °C was added a solution of oxalyl chloride (3.15 mL, 36.0 mmol) in CH_2Cl_2 (25 mL) dropwise. After 10 min of additional stirring, a solution of 1-benzyl 2-methyl (2*R*)-2-(3-hydroxypropyl)pyrrolidine-1,2-dicarboxylate [Cox and Lectka (1998) *J. Am. Chem. Soc.* **120**, 10660-10668] (7.72 g, 24.0 mmol) in CH_2Cl_2 (50 mL) at -78 °C was added dropwise. After stirring for an additional 1 h,

triethylamine (16.7 mL, 120 mmol) was added slowly. The reaction mixture was stirred for 1 h at -78 °C and 2.5 h at ambient temperature. Water (100 mL) was added slowly and the quenched mixture was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with 10% HCl (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 90:10 to 0:100, to give the title compound. MS: *m/z* = 320 (M + 1).

Step B. 1-Benzyl 2-methyl (2*R*)-2-((3*E*)-3-{[(*S*)-tert-butylsulfinyl]imino}propyl)pyrrolidine-1,2-dicarboxylate

To a mixture of 1-benzyl 2-methyl (2*R*)-2-(3-oxopropyl)pyrrolidine-1,2-dicarboxylate from Step A (1.69 g, 5.29 mmol) and anhydrous $CuSO_4$ (2.36 g, 10.6 mmol) in CH_2Cl_2 (10 mL) was added (*S*)-2-methylpropane-2-sulfinamide (0.641 g, 5.29 mmol). This mixture was stirred for 25 h before being filtered through a pad of celite. Additional CH_2Cl_2 was used to wash the celite. The combined organics were concentrated *in vacuo* to give a residue that was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 95:5 to 0:100, to give the title compound. MS: *m/z* = 423 (M + 1).

Step C. 1-Benzyl 2-methyl (2*R*)-2-[(3*S*)-3-{[(*S*)-tert-butylsulfinyl]amino}-3-(3,5-difluorophenyl)propyl]pyrrolidine-1,2-dicarboxylate

To a stirred solution of 1-benzyl 2-methyl (2*R*)-2-((3*E*)-3-{[(*S*)-tert-butylsulfinyl]imino}propyl)pyrrolidine-1,2-dicarboxylate from Step B (1.56 g, 3.70 mmol) in toluene (30 mL) at -78 °C was added 3,5-difluorophenylmagnesium bromide (14.8 mL of a 0.5 M solution in THF, 7.41 mmol) dropwise. The reaction mixture was stirred for 30 min at -78 °C, 3.5 h at -10 °C, and then at ambient temperature for 1.5 h. The mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 95:5 to 0:100, to give the title compound. MS: *m/z* = 537 (M + 1).

Step D. Benzyl (5*R*,8*S*)-8-(3,5-difluorophenyl)-6-oxo-1,7-diazaspiro[4.5]decane-1-carboxylate

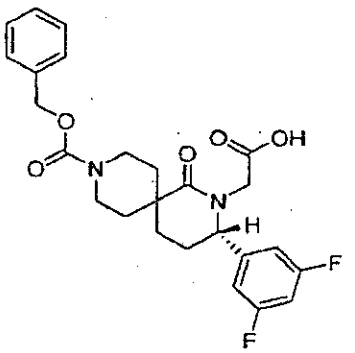
HCl (g) was bubbled through a solution of 1-benzyl 2-methyl (2*R*)-2-[(3*S*)-3-{[(*S*)-*tert*-butylsulfinyl]amino}-3-(3,5-difluorophenyl)propyl]pyrrolidine-1,2-dicarboxylate from Step C (1.02 g, 1.90 mmol) in MeOH (25 mL) at 0 °C for 1 min. After stirring for 1 h, the reaction mixture was concentrated to dryness *in vacuo*. To the crude product suspended in toluene (25 mL) was added triethylamine (2.12 mL, 15.2 mmol), and the reaction mixture was heated to reflux for 66 h. The reaction mixture was concentrated *in vacuo* and the crude product

was purified by silica gel chromatography, eluting with a gradient of CH_2Cl_2:MeOH: NH_4OH – 100:0:0 to 95:5:1, to give the title compound. MS: *m/z* = 401 (M + 1).

Step E. [(5*R*,8*S*)-1-[(Benzyloxy)carbonyl]-8-(3,5-difluorophenyl)-6-oxo-1,7-diazaspiro[4.5]dec-7-yl]acetic acid

To a stirred solution of benzyl (5*R*,8*S*)-8-(3,5-difluorophenyl)-6-oxo-1,7-diazaspiro[4.5]decane-1-carboxylate from Step D (541 mg, 1.35 mmol) in THF (3 mL) at ambient temperature was added NaH (81 mg of a 60% dispersion in oil, 2.03 mmol). After 30 min, ethyl bromoacetate (0.196 mL, 1.76 mmol) was added and the mixture was stirred for 30 min. Sodium hydroxide (8.11 mL of a 1 M solution, 8.11 mmol) was added and the mixture stirred for 16 h. The reaction mixture was poured onto 1 M HCl (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1 to give the title compound. MS: *m/z* = 459 (M + 1).

INTERMEDIATE 45



[(3*S*)-9-[(Benzyloxy)carbonyl]-3-(3,5-difluorophenyl)-1-oxo-2,9-diazaspiro[5.5]undec-2-yl]acetic acid

Step A. Methyl 4-allylpiperidine-4-carboxylate

HCl (g) was bubbled through a solution of 4-allyl-1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid [Jiang *et al.* (2004) *Bioorg. Med. Chem. Lett.* **14**, 3675-3678] (6.50 g, 24.1 mmol,) in MeOH (200 mL). The solution was heated at reflux for 16 h and then concentrated *in vacuo* to give the title compound as the hydrochloride salt. MS: *m/z* = 184 (M + 1).

Step B. 1-Benzyl 4-methyl 4-allylpiperidine-1,4-dicarboxylate

A mixture of methyl 4-allylpiperidine-4-carboxylate from Step A (5.30 g, 24.2 mmol), *N*-(benzyloxycarbonyloxy)succinimide (7.25 g, 29.1 mmol), and *N,N*-diisopropylethylamine (12.7 mL, 72.7 mmol) in CH_3CN (61 mL) was stirred for 16 h. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc (100 mL) and saturated $NaHCO_3$ (100 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (2 × 100 mL).The combined organic extracts were concentrated *in vacuo* to give a residue that was purified by silica gel chromatography, eluting with a gradient of hexane:EtOAc – 100:0 to 40:60, to give the title compound. MS: *m/z* = 318 (M + 1).

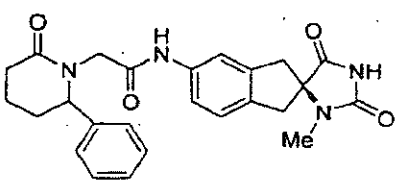
Step C. 1-Benzyl 4-methyl 4-(2-oxoethyl)piperidine-1,4-dicarboxylate

To a solution of 1-benzyl 4-methyl 4-allylpiperidine-1,4-dicarboxylate from Step B (4.45 g, 14.0 mmol) in THF (70 mL) at 0 °C was added borane-methyl sulfide complex (28.0 mL of a 2M solution in THF, 56.1 mmol). The reaction mixture was slowly warmed to ambient temperature and stirred for 16 h, then quenched with water and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (140 mL) and added drop wise to a solution of PCC (6.65 g. 30.8 mmol) and 4Å molecular sieves (6.65 g) in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was warmed to ambient temperature and stirred for 16 h, then diluted with ether (200 mL) and filtered through a pad of celite. Additional ether was used to wash the celite. The combined organics were concentrated *in vacuo* to give a residue that was purified by silica gel chromatography, eluting with a gradient of CH_2Cl_2:MeOH – 100:0 to 95:5, to give the title compound. MS: *m/z* = 356 (M + Na).

[(3*S*)-9-[(Benzyloxy)carbonyl]-3-(3,5-difluorophenyl)-1-oxo-2,9-diazaspiro[5.5]undec-2-yl]acetic acid

Essentially following the procedures described for Intermediate 44, but using 1-benzyl 4-methyl 4-(2-oxoethyl)piperidine-1,4-dicarboxylate in place of 1-benzyl 2-methyl (2*R*)-2-(3-oxopropyl)pyrrolidine-1,2-dicarboxylate, the title compound was prepared. MS: *m/z* = 473 (M + 1).

EXAMPLE 1



N-[(4*S*)-3-Methyl-2,5-dioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-5'-yl]-2-((6±)-2-oxo-6-phenylpiperidin-1-yl)acetamide

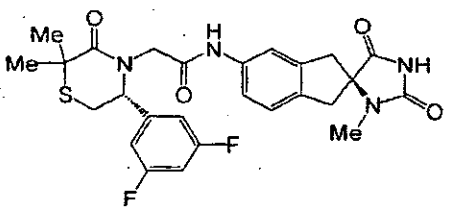
Step A. (±)-(2-Oxo-6-phenylpiperidin-1-yl)acetic acid

To a stirred solution of (±)-6-phenylpiperidin-2-one (155 mg, 0.885 mmol) in THF (10 mL), cooled to 0 °C, was added NaH (30.0 mg, 1.24 mmol). The ice bath was removed and the reaction was allowed to warm to ambient temperature. After 1 h at ambient temperature, the reaction was cooled to 0 °C prior to the introduction of methyl bromoacetate (149 mg, 0.973 mmol). After 40 minutes, the ice bath was removed and the reaction was stirred under nitrogen for 12 h. Additional quantities of NaH and methyl bromoacetate were then added in parts to nearly consume the lactam, as judged by LCMS analysis. After sufficient lactam was consumed, 1 M aqueous sodium hydroxide was added (1 mL, 1 mmol). After a majority of the methyl ester was saponified (~3 h), the reaction was quenched with 1 M hydrochloric acid (5 mL), and EtOAc (50 mL). The organics were washed with saturated brine (twice), dried over sodium sulfate, filtered and concentrated *in vacuo*, to yield a residue which was used without further purification. MS: m/z = 234 (M + 1).

Step B. *N*-[(4*S*)-3-Methyl-2,5-dioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-5'-yl]-2-((6±)-2-oxo-6-phenylpiperidin-1-yl)acetamide

To a solution of (±)-(2-oxo-6-phenylpiperidin-1-yl)acetic acid from Step A (100. mg, 0.429 mmol), HOAt (29.0 mg, 0.214 mmol) and (4*S*)-5'-amino-3-methyl-1',3'-dihydro-2*H*,5*H*-spiro[imidazolidine-4,2'-indene]-2,5-dione (109 mg, 0.472 mmol, prepared according to Bell, I. M., *et al.*, PCT Int. Appl., WO 2004082605 A2) in DMF (5.0 mL) was added EDCI (115 mg, 0.600 mmol). This solution was stirred at ambient temperature for 15 h. The reaction was then quenched by the addition of 1 M HCl (10 mL) and EtOAc (50 mL). The organics were further washed with an additional aliquot of 1M HCl (10 mL), then saturated brine (20 mL x2), followed by drying over sodium sulfate. The organics were then filtered , concentrated *in vacuo*, and applied to a silica gel column for purification, eluting with a gradient of CH_2Cl_2:MeOH – 99.5:0.5 to 95:5. Clean product-containing fractions were pooled and concentrated *in vacuo* to give the title compound. MS: m/z = 447 (M + 1). HRMS: m/z = 447.2013; calculated m/z = 447.2027 for $C_{25}H_{27}N_4O_4$.

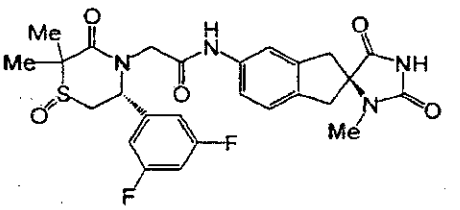
EXAMPLE 2



2-[(5*R*)-5-(3,5-Difluorophenyl)-2,2-dimethyl-3-oxo-4-thiomorpholinyl]-*N*-[(4*S*)-3-methyl-2,5-dioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-5'-yl]acetamide

Starting from (5*R*)-5-(3,5-difluorophenyl)-2,2-dimethylthiomorpholin-3-one (Intermediate 2), the compound in Example 2 was prepared following analogous procedures for the preparation of Example 1, to provide the title compound. MS: *m/z* = 551 (M + Na). HRMS: *m/z* = 529.1734; calculated *m/z* = 529.1716 for $C_{26}H_{26}F_2N_4O_4S$.

EXAMPLE 3

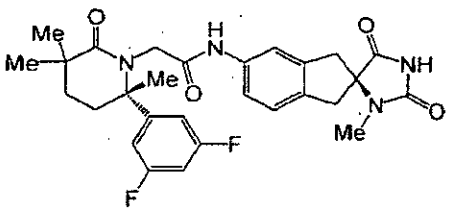


2-[(5*R*)-5-(3,5-Difluorophenyl)-2,2-dimethyl-1-oxido-3-oxo-4-thiomorpholinyl]-*N*-[(4*S*)-3-methyl-2,5-dioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-5'-yl]acetamide

Step A. (5*R*)-5-(3,5-Difluorophenyl)-2,2-dimethylthiomorpholin-3-one

To a solution of 2-[(5*R*)-5-(3,5-difluorophenyl)-2,2-dimethyl-3-oxo-4-thiomorpholinyl]-*N*-[(4*S*)-3-methyl-2,5-dioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-5'-yl]acetamide (Example 2) in 1.5 mL chloroform at 0 °C, was added 3-chloroperoxybenzoic acid (21 mg with a purity of 77%, 0.121 mmol). An LCMS of the reaction mixture after two hours showed that all starting material was consumed. Calcium hydroxide (14 mg, 0.185 mmol) was added to the reaction and stirred for fourty minutes. The mixture was then vacuum filtered through filter paper and the solid was washed with chloroform (3x 10 mL). The filtrate was concentrated *in vacuo* to give a residue that was purified by silica gel chromatography, eluting with a gradient of MeOH:CH_2Cl_2 – 1:99 to 5:95, to give the title compound. MS: *m/z* = 545 (M + H). HRMS: *m/z* = 545.1653; calculated *m/z* = 545.1665 for $C_{26}H_{26}F_2N_4O_5S$.

EXAMPLE 4



2-[(2*S*)-2-(3,5-Difluorophenyl)-2,5,5-trimethyl-6-oxo-1-piperidinyl]-*N*-[(4*S*)-3-methyl-2,5-dioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-5'-yl]acetamide

Step A. Methyl (5E)-5-[(*tert*-butylsulfinyl)imino]-5-(3,5-difluorophenyl)-2,2-dimethylpentanoate

To a solution of methyl 5-(3,5-difluorophenyl)-2,2-dimethyl-5-oxopentanoate from Intermediate 1, Step D (500 mg of 85% purity, 1.85 mmol) and (*S*)-2-methylpropane-2-sulfinamide (336 mg, 2.78 mmol) in THF (9.5 mL), was added titanium tetraethoxide (904 mg, 3.70 mmol). The reaction vessel was quickly sealed and placed into a 60 °C bath for 2 hours. After cooling to ambient temperature the reaction mixture was then diluted with saturated brine (9.5 mL) while experiencing rapid stirring. The resultant slurry was filtered through celite, washing with EtOAc, as needed. The combined organics were then washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to give an oil. This oil was purified by silica gel chromatography, eluting with a gradient of MeOH:CH_2Cl_2 – 0.5:99.5 to 3:97, to give the title compound. MS: *m/z* = 374 (M + 1).

Step B. Methyl (5*S*)-5-[(*tert*-butylsulfinyl)amino]-5-(3,5-difluorophenyl)-2,2-dimethylhexanoate

To a solution of methyl (5E)-5-[(*tert*-butylsulfinyl)imino]-5-(3,5-difluorophenyl)-2,2-dimethylpentanoate (342 mg, 0.920 mmol) in CH_2Cl_2 (6 mL) at 0°C, was added dropwise over five minutes methyl magnesium bromide as a 3M solution in diethyl ether (0.61 mL, 1.83 mmol). After 15 minutes the reaction was determined to be complete by LCMS analysis. The reaction was quenched by the dropwise addition of 1M HCl (5 mL), followed by 5 mL of water. The aqueous layer was extracted once with CH_2Cl_2 (10 mL) and the organics were combined and washed once with brine (15 mL). The organics were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a residue that was purified by silica gel chromatography, eluting with a gradient of EtOAc:Hexanes – 10:90 to 55:45, to give the title compound. MS: *m/z* = 390 (M + 1).

Step C. (6*S*)-6-(3,5-Difluorophenyl)-3,3,6-trimethylpiperidin-2-one

To a solution of methyl (5*S*)-5-[(*tert*-butylsulfinyl)amino]-5-(3,5-difluorophenyl)-2,2-dimethylhexanoate (1.14 g, 2.93 mmol) in MeOH (60 mL), cooled to 0 °C, was added anhydrous HCl gas for 1 minute. The reaction was sealed and allowed to sit at 0°C for fifteen minutes at which point the reaction was complete by LCMS analysis. Nitrogen was bubbled

through the reaction for twenty minutes. The reaction was concentrated *in vacuo*. Additional MeOH (50 mL) was added and it was again concentrated *in vacuo*. This was repeated with another addition of MeOH and triethylamine (1.18 g, 11.7 mmol). To the resulting residue was added toluene (50 mL) and triethylamine (1.18 g, 11.7 mmol). A reflux condenser was attached and the mixture stirred at 110°C. After five days of stirring at relux, the reaction was judged to be complete by LCMS. The mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was diluted with diethyl ether (75 mL) and washed individually with 30 mL of each of the following aqueous solutions: 1M HCl (twice), water, saturated brine. The organic layer was then dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a residue that was purified by silica gel chromatography, eluting with a gradient of MeOH:CH_2Cl_2 – 1:99 to 5.5:94.5, to give the title compound. MS: *m/z* = 254 (M + 1).

Step D. Methyl [(2*S*)-2-(3,5-difluorophenyl)-2,5,5-trimethyl-6-oxopiperidin-1-yl]acetate

To a solution of (6S)-6-(3,5-difluorophenyl)-3,3,6-trimethylpiperidin-2-one (540. mg, 2.13 mmol) in THF (20 mL), chilled to 0°C was added potassium hydride (approximately 86 mg, 2.13 mmol, as a 30% suspension in oil) under a constant stream of nitrogen. The reaction was allowed to stir for 30 minutes at which time methyl bromoacetate (391 mg, 2.56 mmol) was added at 0°C. An LCMS after one hour indicated that the reaction was incomplete, thus more potassium hydride was added (approximately 43 mg, 1.06 mmol, as a 30% suspension in oil) at 0°C. The reaction was sealed well and was stirred for an additional 16 hours, during which time the bath temperature warmed to ambient temperature. The reaction was judged to be 46% complete by LCMS analysis. The reaction was chilled to 0°C and saturated aqueous ammonium chloride (5 mL) was added to quench the potassium hydride. To the reaction was added 1M aqueous HCl (5 mL) and the reaction was diluted with ethyl acetate. The organic layer was washed once with brine and then dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a residue that was purified by silica gel chromatography, eluting with a gradient of EtOAc:Hexanes – 10:90 to 75:25, to give the title compound. MS: *m/z* = 326 (M + 1).

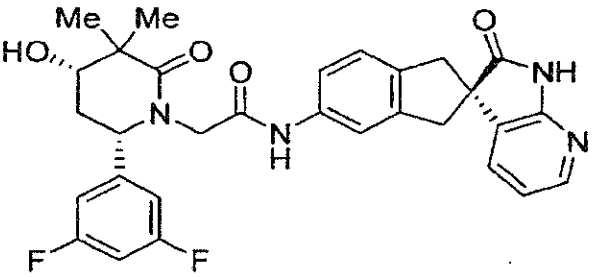
Step E. Potassium [(2*S*)-2-(3,5-difluorophenyl)-2,5,5-trimethyl-6-oxopiperidin-1-yl]acetate

To a solution of methyl [(2*S*)-2-(3,5-difluorophenyl)-2,5,5-trimethyl-6-oxopiperidin-1-yl]acetate from Step D (298 mg, 0.916 mmol) in THF (9 mL) at ambient temperature was added potassium trimethylsilanolate (147 mg, 1.14 mmol). The reaction was stirred for 24 hours and found to be incomplete by LCMS analysis. Additional quantities of potassium trimethylsilanolate were added as needed. The reaction was concentrated *in vacuo* to give a residue that required no further purification. MS: *m/z* = 312 (M + 1 for parent acid).

Step F. 2-[(2*S*)-2-(3,5-Difluorophenyl)-2,5,5-trimethyl-6-oxo-1-piperidinyl]-*N*-[(4S)-3-methyl-2,5-dioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-5'-yl]acetamide

Starting from potassium [(2*S*)-2-(3,5-difluorophenyl)-2,5,5-trimethyl-6-oxopiperidin-1-yl]acetate (182 mg, 0.522 mmol), Example 4 was prepared following the analogous procedure for the preparation of Example 1, Step B, to provide the title compound. MS: *m/z* = 525 (M + 1). HRMS: *m/z* = 525.2326; calculated *m/z* = 525.2308 for $C_{28}H_{30}F_2N_4O_4$.

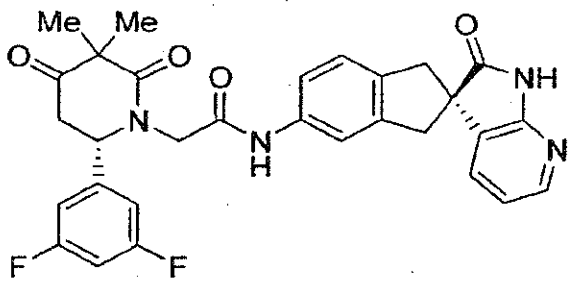
EXAMPLE 6



2-[(4*S*,6*S*)-6-(3,5-Difluorophenyl)-4-hydroxy-3,3-dimethyl-2-oxopiperidin-1-yl]-*N*-[(2*R*)-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-b]pyridin]-5-yl]acetamide

A mixture of [(4*S*,6*S*)-6-(3,5-difluorophenyl)-4-hydroxy-3,3-dimethyl-2-oxopiperidin-1-yl]acetic acid (130 mg, 0.415 mmol, described in Intermediate 21), (*R*)-5-amino-1,3-dihydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one (140 mg, 0.557 mmol, described in Intermediate 9), HOBT (82 mg, 0.535 mmol), and EDC (95 mg, 0.498 mmol) in DMF (2 mL) was stirred at ambient temperature for 6 h. The reaction mixture was partitioned between H_2O (50 mL), saturated aqueous $NaHCO_3$ (30 mL) and EtOAc (100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of CH_2Cl_2:CH_3OH – 100:0 to 90:10, to give the title compound. MS: m/z = 547 (M + 1). HRMS: *m/z* = 547.2169; calculated *m/z* = 547.2151 for $C_{30}H_{29}F_2N_4O_4$.

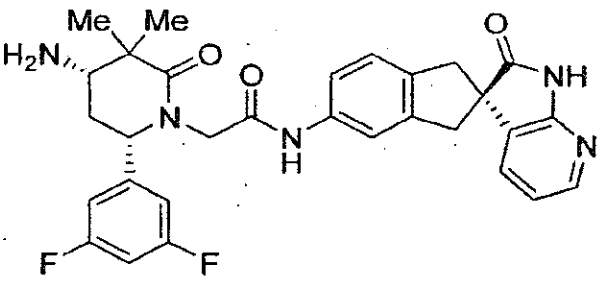
EXAMPLE 7



2-[(6*S*)-6-(3,5-Difluorophenyl)-3,3-dimethyl-2,4-dioxopiperidin-1-yl]-*N*-[(2*R*)-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-b]pyridin]-5-yl]acetamide

A mixture of [(6*S*)-6-(3,5-difluorophenyl)-3,3-dimethyl-2,4-dioxopiperidin-1-yl]acetic acid (156 mg, 0.501 mmol, described in Intermediate 22), (*R*)-5-amino-1,3-dihydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one (145 mg, 0.577 mmol, described in Intermediate 9), HOBT (95 mg, 0.620 mmol), and EDC (123 mg, 0.642 mmol) in DMF (2 mL) was stirred at ambient temperature for 16 h. The reaction mixture was partitioned between H_2O (60 mL) and EtOAc (100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of CH_2Cl_2:CH_3OH – 100:0 to 90:10, to give the title compound. MS: m/z = 545 (M + 1). HRMS: *m/z* = 545.2025; calculated *m/z* = 545.1995 for $C_{30}H_{27}F_2N_4O_4$.

EXAMPLE 8

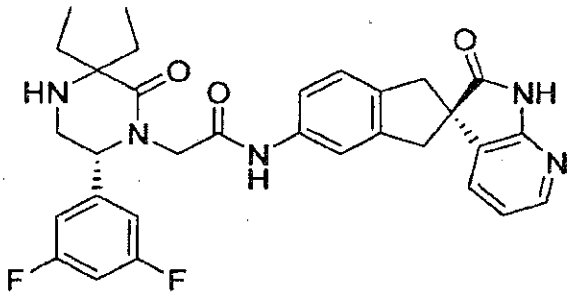


2-[(4*S*,6*S*)-4-Amino-6-(3,5-difluorophenyl)-3,3-dimethyl-2-oxopiperidin-1-yl]-*N*-[(2*R*)-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-5-yl]acetamide

A mixture of 2-[(6*S*)-6-(3,5-difluorophenyl)-3,3-dimethyl-2,4-dioxopiperidin-1-yl]-*N*-[(2*R*)-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-b]pyridin]-5-yl]acetamide (380 mg, 0.698 mmol, described in Example 7) and NH_4OAc (571 mg, 7.41 mmol) in CH_3OH (2 mL) was stirred at ambient temperature for 20 min. $NaCNBH_3$ (498 mg, 7.92 mmol) was added and stirring was continued at ambient temperature for 12 h. The reaction mixture was diluted with H_2O (40 mL) and aqueous $NaHCO_3$ (70 mL) and extracted with EtOAc (2 × 100 mL). The

combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with a gradient of CH_2Cl_2:CH_3OH – 100:0 to 80:20, to give 2-[(4*R*,6*S*)-4-amino-6-(3,5-difluorophenyl)-3,3-dimethyl-2-oxopiperidin-1-yl]-*N*-[(2*R*)-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-5-yl]acetamide, which eluted first, and 2-[(4*S*,6*S*)-4-amino-6-(3,5-difluorophenyl)-3,3-dimethyl-2-oxopiperidin-1-yl]-*N*-[(2*R*)-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-5-yl]acetamide, which eluted second, the title compound. MS: m/z = 546 (M + 1). HRMS: *m/z* = 546.2287; calculated *m/z* = 546.2311 for $C_{30}H_{30}F_2N_5O_3$.

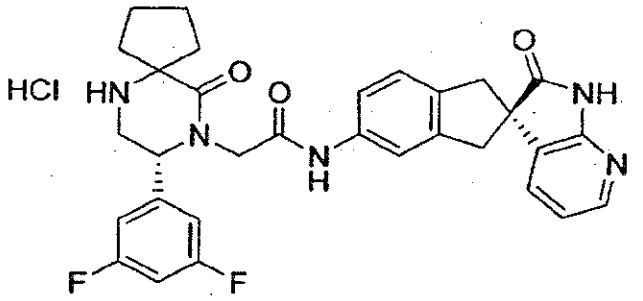
EXAMPLE 10



2-[(6*R*)-6-(3,5-Difluorophenyl)-3,3-diethyl-2-oxopiperazin-1-yl]-*N*-[(2*R*)-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-5-yl]acetamide

A mixture of [(6*R*)-6-(3,5-difluorophenyl)-3,3-diethyl-2-oxopiperazin-1-yl]acetic acid hydrochloride (43 mg, 0.119 mmol, described in Intermediate 29), (*R*)-5-amino-1,3-dihydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one (30 mg, 0.119 mmol, described in Intermediate 9), HOBT (27 mg, 0.179 mmol), and EDC (34 mg, 0.179 mmol) in DMF (0.5 mL) was stirred at ambient temperature for 18 h. The reaction mixture was purified directly by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. The pure, product-containing fractions were combined, basified with saturated aqueous $NaHCO_3$, and extracted with EtOAc. The organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the title compound. MS: *m/z* = 560 (M + 1). HRMS: *m/z* = 560.2469; calculated *m/z* = 560.2468 for $C_{31}H_{32}F_2N_5O_3$.

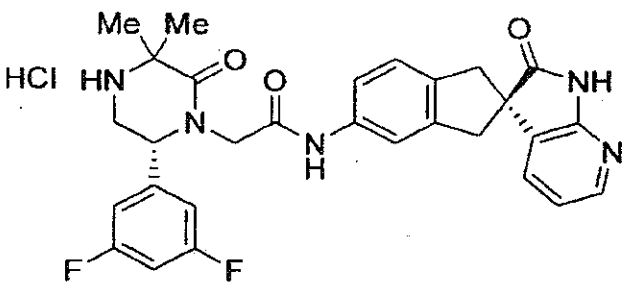
EXAMPLE 12



2-[(8*R*)-8-(3,5-Difluorophenyl)-10-oxo-6,9-diazaspiro[4.5]dec-9-yl]-*N*-[(2*R*)-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-5-yl]acetamide hydrochloride

A mixture of lithium [(8*R*)-6-(*tert*-butoxycarbonyl)-8-(3,5-difluorophenyl)-10-oxo-6,9-diazaspiro[4.5]dec-9-yl]acetate (30 mg, 0.070 mmol, described in Intermediate 32), (*R*)-5-amino-1,3-dihydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one (20 mg, 0.079 mmol, described in Intermediate 9), HOBT (14 mg, 0.092 mmol), and EDC (18 mg, 0.092 mmol) in DMF (0.5 mL) was stirred at ambient temperature for 18 h. The reaction mixture was diluted with EtOAc (5 mL) and washed successively with 10% citric acid (2 mL), H_2O (2 mL), saturated aqueous $NaHCO_3$ (2 mL), and brine (2 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography, eluting with CH_2Cl_2:EtOAc – 100:0 to 0:100, to give the Boc-protected product. The Boc-protected product was dissolved in EtOAc (3 mL), the solution was cooled to 0 °C, and HCl (g) was bubbled in for 1 min. The mixture was aged at 0 °C for 15 min and the title compound was isolated by filtration. MS: *m/z* = 558 (M + 1). HRMS: *m/z* = 558.2300; calculated *m/z* = 558.2311 for $C_{31}H_{30}F_2N_5O_3$.

EXAMPLE 13

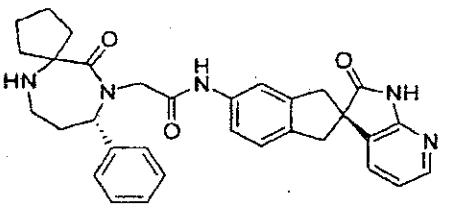


2-[(6*R*)-6-(3,5-Difluorophenyl)-3,3-dimethyl-2-oxopiperazin-1-yl]-*N*-[(2*R*)-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-5-yl]acetamide hydrochloride

To a mixture of lithium [(6*R*)-4-(*tert*-butoxycarbonyl)-6-(3,5-difluorophenyl)-3,3-dimethyl-2-oxopiperazin-1-yl]acetate (1.12 g, 2.77 mmol, described in Intermediate 13), (*R*)-5-

amino-1,3-dihydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one (835 mg, 3.32 mmol, described in Intermediate 9), and HATU (1.26 g, 3.32 mmol) in DMF (12 mL) was added *N*-methylmorpholine (0.61 mL, 5.54 mmol) and the resulting mixture was stirred at ambient temperature for 90 min. The reaction mixture was diluted with EtOAc (500 mL) and washed successively with 10% citric acid (100 mL), H_2O (100 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine (100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography, eluting with CH_2Cl_2:MeOH – 100:0 to 90:10, to give the Boc-protected product. The Boc-protected product was dissolved in EtOAc (75 mL), the solution was cooled to 0 °C, and HCl (g) was bubbled in for 2 min. After 15 min, additional HCl (g) was bubbled in for 1 min. The mixture was aged at 0 °C for 30 min and concentrated *in vacuo* to provide the title compound. MS: *m/z* = 532 (M + 1). HRMS: *m/z* = 532.2172; calculated *m/z* = 532.2155 for $C_{29}H_{28}F_2N_5O_3$.

EXAMPLE 15



2-[(9*S*)-11-Oxo-9-phenyl-6,10-diazaspiro[4.6]undec-10-yl]-*N*-[(2*R*)-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-5-yl]acetamide

Step A. Methyl 1-({(3*S*)-3-[(2-oxo-2-{[(2*R*)-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-5-yl]amino}ethyl)amino]-3-phenylpropyl}amino)cyclopentanecarboxylate

To a cooled (0 °C) solution of (2*R*)-5-amino-1,3-dihydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one (0.100 g, 0.398 mmol, Intermediate 9) and triethylamine (100. µL, 0.716 mmol) in THF (8 mL) was added bromoacetyl bromide (46.0 µL, 0.523 mmol). After allowing the reaction to warm to ambient temperature, triethylamine (0.230 mL, 1.67 mmol) and methyl 1-{[(3*S*)-3-amino-3-phenylpropyl]amino}cyclopentanecarboxylate bis-hydrochloride (0.139 g, 0.398 mmol, Intermediate 38) were added, prior to heating the reaction to 50 °C for 17 h. After cooling to ambient temperature, the reaction mixture was diluted with chloroform and saturated aqueous sodium bicarbonate. The aqueous layer was extracted twice with additional chloroform. The combined organics were dried over sodium sulfate, filtered and concentrated *in vacuo* to give an oil. This oil was purified by silica gel chromatography, eluting with a gradient

of CH_2Cl_2:MeOH:NH_4OH – 99:1:0.1 to 92:8:0.8, to give the title compound. MS: *m/z* = 568 (M + 1).

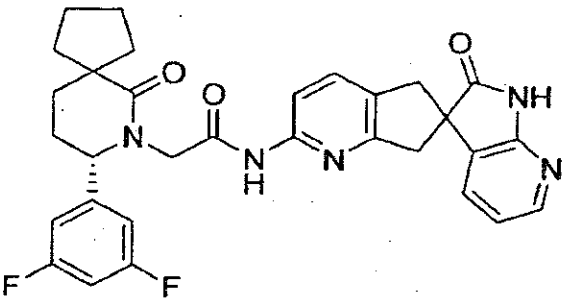
Step B. Potassium 1-({(3*S*)-3-[(2-oxo-2-{[(2*R*)-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-5-yl]amino}ethyl)amino]-3-phenylpropyl}amino)cyclopentanecarboxylate

To a stirred solution of methyl 1-({(3*S*)-3-[(2-oxo-2-{[(2*R*)-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-5-yl]amino}ethyl)amino]-3-phenylpropyl}amino)cyclopentanecarboxylate from Step A (0.141 g, 0.249 mmol) in dry THF (5 mL) was added KOTMS (64.0 mg, 0.498 mmol) and the reaction mixture was heated to 40 °C, at which point the desired product began to precipitate. Two additional quantities of KOTMS (~60 mg × 2) were added over the next 2 h resulting in a complete consumption of starting material. The mixture was then allowed to cool to ambient temperature. The THF, which contained only traces of product, was then decanted away from the precipitated product. This solid was then washed with two additional quantities of anhydrous THF (5 mL × 2), to provide the title compound. MS: *m/z* = 554 (M + 1).

Step C. 2-[(9*S*)-11-Oxo-9-phenyl-6,10-diazaspiro[4.6]undec-10-yl]-*N*-[(2*R*)-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-5-yl]acetamide

To a stirred solution of potassium 1-({(3*S*)-3-[(2-oxo-2-{[(2*R*)-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-*b*]pyridin]-5-yl]amino}ethyl)amino]-3-phenylpropyl}amino)cyclopentanecarboxylate from Step B (0.147 g, 0.249 mmol) in DMF (8.3 mL) was added EDCI (0.0720 g, 0.374 mmol) and HOAt (0.0340 g, 0.249 mmol). The reaction mixture was then heated to 40 °C. After 1 h, additional EDCI (0.0350 mg) was added and the reaction temperature was increased to 50 °C, for 15 h. The reaction was allowed to cool to ambient temperature before being diluted with 5% aqueous sodium bicarbonate (100 mL) and chloroform (100 mL). The organics were washed successively with water (100 mL) and saturated brine (100 mL). The combined organics were dried over sodium sulfate, filtered and concentrated *in vacuo* to give an oil. This oil was purified by silica gel chromatography, eluting with a gradient of CH_2Cl_2:MeOH – 99:1 to 91:9, to give the title compound. MS: *m/z* = 536 (M + 1). HRMS: *m/z* = 536.2694; calculated *m/z* = 536.2656 for $C_{32}H_{34}N_5O_3$.

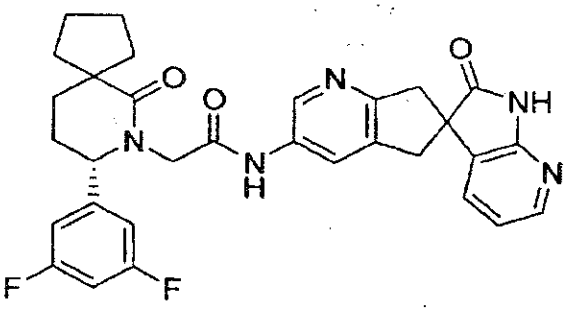
EXAMPLE 19



2-[(8*S*)-8-(3,5-Difluorophenyl)-6-oxo-7-azaspiro[4.5]dec-7-yl]-*N*-(2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-2-yl)acetamide

A mixture of [(8*S*)-8-(3,5-difluorophenyl)-6-oxo-7-azaspiro[4.5]dec-7-yl]acetic acid (21 mg, 0.067 mmol, described in Intermediate 86), (±)-2-amino-5,7-dihydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one (17 mg, 0.067 mmol, described in Intermediate 43), PyClu (28 mg, 0.080 mmol), and *N,N N*-diisopropylethylamine (0.058 mL, 0.33 mmol) in THF (1 mL) was stirred at ambient temperature for 16 h. The reaction mixture was purified directly by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. Lyophilization provided the title compound as the TFA salt. MS: *m/z* = 558 (M + 1). HRMS: *m/z* = 558.2313; calculated *m/z* = 558.2311 for $C_{31}H_{30}F_2N_5O_3$.

EXAMPLE 20

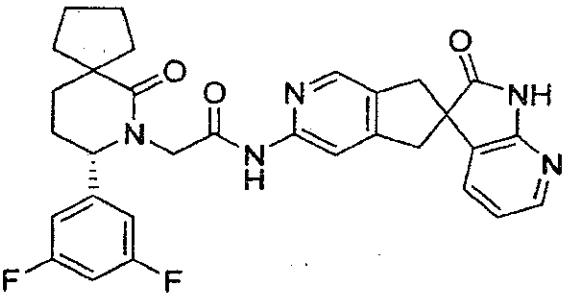


2-[(8*S*)-8-(3,5-Difluorophenyl)-6-oxo-7-azaspiro[4.5]dec-7-yl]-*N*-(2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-3-yl)acetamide, isomer A

A mixture of [(8*S*)-8-(3,5-difluorophenyl)-6-oxo-7-azaspiro[4.5]dec-7-yl]acetic acid (50 mg, 0.16 mmol, described in Intermediate 86), 3-amino-5,7-dihydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one, isomer A (39 mg, 0.16 mmol, described in Intermediate 41), HATU (88 mg, 0.23 mmol), and *N,N N*-diisopropylethylamine (0.135 mL, 0.77 mmol) in DMF (1 mL) was stirred at ambient

temperature for 16 h. NH_4OH (10 drops) was added and the reaction mixture was purified directly by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. Lyophilization provided the title compound as the TFA salt. MS: *m/z* = 558 (M + 1). HRMS: *m/z* = 558.2301; calculated *m/z* = 558.2311 for $C_{31}H_{30}F_2N_5O_3$.

EXAMPLE 21



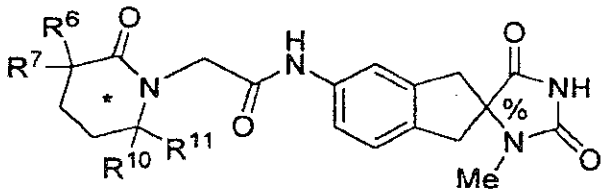
2-[(8*S*)-8-(3,5-Difluorophenyl)-6-oxo-7-azaspiro[4.5]dec-7-yl]-*N*-(2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[*c*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-3-yl)acetamide, isomer A

A mixture of [(8*S*)-8-(3,5-difluorophenyl)-6-oxo-7-azaspiro[4.5]dec-7-yl]acetic acid (128 mg, 0.395 mmol, described in Intermediate 86), 3-amino-5,7-dihydrospiro[cyclopenta[*c*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one, isomer A (66.5 mg, 0.264 mmol, described in Intermediate 42), HATU (160 mg, 0.422 mmol), and *N*-methylmorpholine (0.087 mL, 0.791 mmol) in DMF (1 mL) was stirred at ambient temperature for 18 h. The reaction mixture was purified directly by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. Lyophilization provided the title compound as the TFA salt. MS: *m/z* = 558 (M + 1). HRMS: *m/z* = 558.2334; calculated *m/z* = 558.2311 for $C_{31}H_{30}F_2N_5O_3$.

The examples appearing in the following tables were prepared by analogy to the above examples and intermediates, as described or prepared as a result of similar transformations with modifications known to those skilled in the art. The requisite starting materials and intermediates were described herein (*vide supra*), commercially available, known in the literature, or readily synthesized by one skilled in the art. In some cases, additional synthetic transformations that are well known to those skilled in the art were utilized after the key amide coupling to provide other products of interest. Straightforward protecting group strategies were applied in some routes. Some of the examples described in the tables were synthesized as

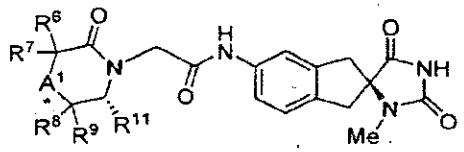
mixtures of stereoisomers and subsequently purified to give individual isomers. In some cases, relevant experimental procedures are indicated in the tables.

TABLE 12



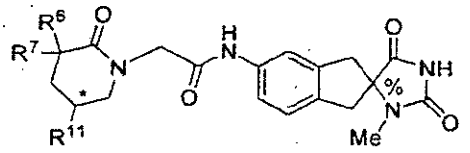
Example	R^6	R^7	R^{10}	R^{11}	*	%	LCMS (M+1)
22	H	H	H	phenyl	±	S	447
23	Me	Me	H	3,4-difluorophenyl	±	S	511
24	Me	Me	H	3,4-difluorophenyl	S	S	511
25	Me	Me	H	3,4-difluorophenyl	R	S	511
26	Me	Me	H	3,5-difluorophenyl	S	S	511
27	Me	Me	H	3-methyl-2-thienyl	R	S	495
28	Me	Me	H	3-methyl-2-thienyl	S	S	495
29	Me	Me	Me	3,5-difluorophenyl	S	S	525
30	H	Ph	H	H	±	S	447
31	H	Ph	H	H	±	R	447
32	Et	Et	H	3,5-difluorophenyl	S	S	539

TABLE 13



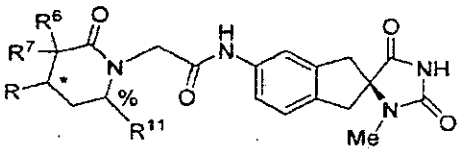
Example	R^6	R^7	R^8	R^9	A^1	R^{11}	*	LCMS (M+1)
33	Me	Me	H	H	O	phenyl		477
34	H	H	H	H	S	3,5-difluorophenyl		501
35	H	H	H	H	SO_2	3,5-difluorophenyl		533
36	H	H	Me	Me	S	phenyl		493
37	H	H	H	H	SO	3,5-difluorophenyl	minor	517
38	H	H	H	H	SO	3,5-difluorophenyl	major	517
39	Me	Me	H	H	SO	3,5-difluorophenyl	minor	545
40	Et	Et	H	H	O	3,5-difluorophenyl		541

TABLE 14



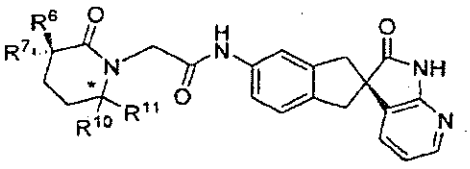
Example	R^6	R^7	R^{11}	*	%	LCMS (M+1)
41	H	H	phenyl	±	S	447
42	H	H	phenyl	±	R	447
43	Cl	Cl	phenyl	±	S	515
44	Cl	Cl	phenyl	±	R	515

TABLE 15



Example	R^6	R^7	R	R^{11}	*	%	LCMS (M+1)	Relevant experimental procedures
45	Me	Me	OH	3,5-difluorophenyl	S	S	527	Ex. 6

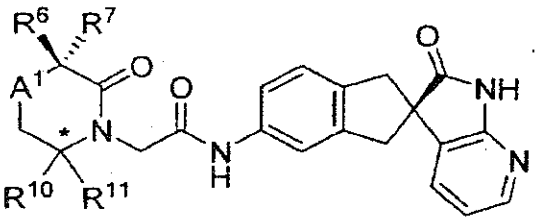
TABLE 16



Example	R^6	R^7	R^{10}	R^{11}	*	LCMS (M+1)	Relevant experimental procedures
46	Me	Me	H	3,4-difluorophenyl	±	531	Ex. 10
47	Me	Me	H	3,4-difluorophenyl	R	531	Ex. 46
48	Me	Me	H	3,4-difluorophenyl	S	531	Ex. 46
49	Me	Me	H	3,5-difluorophenyl	S	531	Ex. 10
50	Me	Me	H	3-chloro-4-fluorophenyl	S	547	Ex. 10
51	Me	Me	H	3-fluoro-4-methylphenyl	S	527	Ex. 10
52	Me	Me	H	5-fluoro-2-methylphenyl	S	527	Ex. 10
53	Me	Me	H	4-fluoro-2-methylphenyl	S	527	Ex. 10
54	Me	Me	H	4-fluoro-3-methylphenyl	S	527	Ex. 10

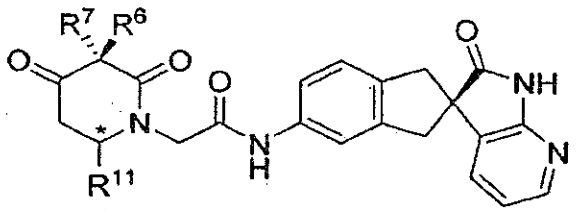
55	Me	Me	H	5-fluoro-2-methoxyphenyl	S	543	Ex. 10
56	Me	Me	H	3-fluorophenyl	S	513	Ex. 10
57	Me	Me	H	4-chloro-3-fluorophenyl	S	547	Ex. 10
58	Me	Me	H	3-fluoro-2-methylphenyl	S	527	Ex. 10
59	Me	Me	H	2-methoxyphenyl	S	525	Ex. 10
60	Me	Me	H	4-methoxyphenyl	S	525	Ex. 10
61	Me	Me	H	3-methoxyphenyl	S	525	Ex. 10
62	Me	Me	Me	3,5-difluorophenyl	S	545	Ex. 10
63	Me	Me	H	3,5-dichlorophenyl	S	563	Ex. 10
64	Me	Me	H	3-thienyl	S	501	Ex. 10
65	Me	Me	H	2-thienyl	S	501	Ex. 10
66	Me	Me	H	5-chloro-2-thienyl	S	535	Ex. 10
67	Me	Me	H	1,3-benzodioxol-5-yl	S	539	Ex. 10
68	Me	Me	H	3-fluoro-4-methoxyphenyl	S	543	Ex. 10
69	Me	Me	H	3-chloro-5-fluorophenyl	S	547	Ex. 10
70	Me	Me	H	phenyl	S	495	Ex. 10
71	Me	Me	H	2-trifluoromethylphenyl	S	563	Ex. 10
72	Me	Me	H	4-fluorophenyl	S	513	Ex. 10
73	Me	Me	H	2-(methylthio)phenyl	S	541	Ex. 10
74	Me	Me	H	cyclohexyl	S	501	Ex. 10
75	Me	Me	H	cyclopropyl	S	459	Ex. 10
76	Me	Me	H	3-chlorophenyl	S	529	Ex. 10
77	Me	Me	H	3,4-dichlorophenyl	S	563	Ex. 10
78	Me	Me	H	3-methylphenyl	S	509	Ex. 10
79	Me	Me	H	4-methylphenyl	S	509	Ex. 10
80	Me	Me	H	4-(methylthio)phenyl	S	541	Ex. 10
81	Me	Me	H	4-chloro-2-methylphenyl	S	543	Ex. 10
82	Me	Me	H	benzyl	S	509	Ex. 10
83	Me	Me	H	4-chlorophenyl	S	529	Ex. 10
84	Me	Me	H	isopropyl	S	461	Ex. 10
85	Me	Me	H	4-trifluoromethylphenyl		563	Ex. 10
86	Me	Me	H	2-(methylsulfonyl)phenyl	S	573	Ex. 73
87	Me	Me	H	4-(methylsulfonyl)phenyl	S	573	Ex. 80
88	Me	Me	H	3-trifluoromethylphenyl	±	563	Ex. 10
89	Me	Me	H	6-bromo-2,3,4-trifluorophenyl		627	Ex. 10
90	Me	Me	H	2-methylphenyl	S	509	Ex. 10
91	Me	Me	H	2,3,4-trifluorophenyl		549	Ex. 10
92	Me	Me	H	3-chloro-2,4-difluorophenyl		565	Ex. 10
93	Me	H	H	3,5-difluorophenyl	S	517	Ex. 10
94	Et	Et	H	3,5-difluorophenyl	S	559	Ex. 10

TABLE 17



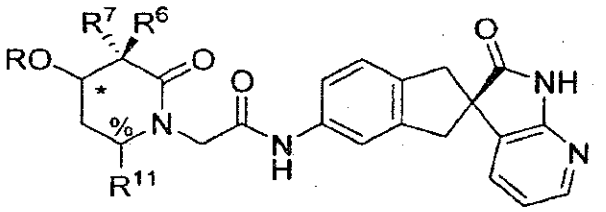
Example	R^6	R^7	A^1	R^{10}	R^{11}	*	LCMS (M+1)	Relevant experimental procedures
95	Me	Me	O	H	phenyl	R	497	Ex. 6
96	Me	H	O	H	phenyl	R	483	Ex. 6
97	H	H	O	H	phenyl	R	469	Ex. 6
98	Me	Me	O	H	3,5-difluorophenyl	R	533	Ex. 6
99	Et	Et	O	H	phenyl	R	525	Ex. 6
100	H	Me	O	H	phenyl	R	483	Ex. 6
101	Me	Me	O	H	3,5-difluorophenyl	S	533	Ex. 6
102	Me	Me	S	H	3,5-difluorophenyl	R	549	Ex. 2
103	H	Et	O	H	phenyl	R	497	Ex. 6
104	Et	Et	O	H	3,5-difluorophenyl	R	561	Ex. 6
105	Me	Me	CF_2	H	3,5-difluorophenyl	S	567	Ex. 7
106	Me	Me	1,3-dioxolan-2-yl	H	3,5-difluorophenyl	S	589	Ex. 7

TABLE 18



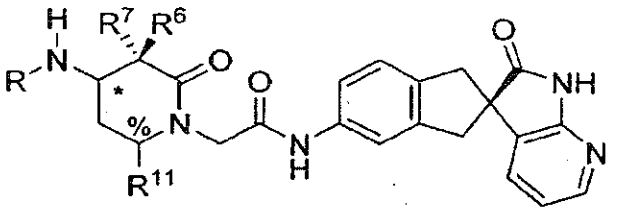
Example	R^6	R^7	R^{11}	*	LCMS (M+1)	Relevant experimental procedures
107	Me	Me	3,5-difluorophenyl	R	545	Ex. 7
108	Et	Et	3,5-difluorophenyl	S	573	Ex. 7
109	Et	Et	3,5-difluorophenyl	R	573	Ex. 7

TABLE 19



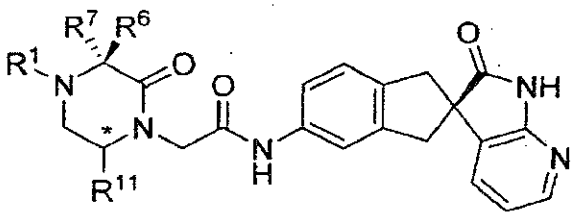
Example	R^6	R^7	R	*	R^{11}	%	LCMS (M+1)	Relevant experimental procedures
110	Me	Me	H	R	3,5-difluorophenyl	R	547	Ex. 6
111	Me	Me	H	R	3,5-difluorophenyl	S	547	Ex. 6
112	Me	Me	H	S	3,5-difluorophenyl	R	547	Ex. 6
113	Me	Me	Me	S	3,5-difluorophenyl	S	561	Ex. 6
114	Et	Et	H	S	3,5-difluorophenyl	S	575	Ex. 6
115	Et	Et	H	R	3,5-difluorophenyl	R	575	Ex. 6
116	Et	Et	H	R	3,5-difluorophenyl	S	575	Ex. 8
117	Me	Me	Me	R	3,5-difluorophenyl	R	561	Ex. 6

TABLE 20



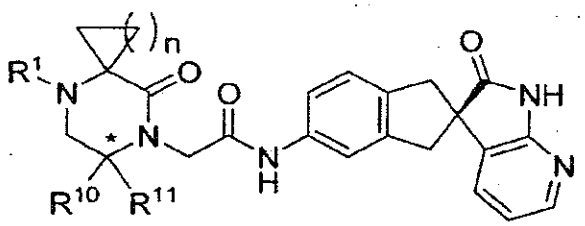
Example	R^6	R^7	R	*	R^{11}	%	LCMS (M+1)	Relevant experimental procedures
118	Me	Me	*tert*-butoxycarbonyl	±	3,5-difluorophenyl	S	646	Ex. 8
119	Me	Me	H	±	3,5-difluorophenyl	S	546	Ex. 8
120	Me	Me	Me	S	3,5-difluorophenyl	S	560	Ex. 8
121	Me	Me	H	S	3,5-difluorophenyl	S	546	Ex. 8
122	Me	Me	H	R	3,5-difluorophenyl	S	546	Ex. 8
123	Et	Et	H	S	3,5-difluorophenyl	S	574	Ex. 8
124	Et	Et	H	R	3,5-difluorophenyl	S	574	Ex. 8

TABLE 21



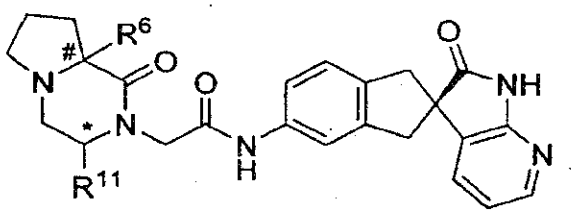
Example	R^6	R^7	R^1	R^{11}	*	LCMS (M+1)	Relevant experimental procedures
125	Me	Me	*tert*-butoxycarbonyl	phenyl	±	596	Ex. 12
126	Me	Me	H	phenyl	±	496	Ex. 12
127	Me	Me	*tert*-butoxycarbonyl	phenyl	S	596	Ex. 12
128	Me	Me	*tert*-butoxycarbonyl	phenyl	R	596	Ex. 12
129	Me	Me	H	phenyl	R	496	Ex. 12
130	Me	Me	*tert*-butoxycarbonyl	3,5-difluorophenyl	S	632	Ex. 13
131	Me	Me	*tert*-butoxycarbonyl	3,5-difluorophenyl	R	632	Ex. 13
132	Me	Me	Me	3,5-difluorophenyl	R	546	Ex. 13
133	Me	Me	acetyl	3,5-difluorophenyl	R	574	Ex. 13
134	Me	Me	methylsulfonyl	3,5-difluorophenyl	R	610	Ex. 13
135	H	Me	Me	phenyl	±	496	Ex. 10
136	Me	H	Me	phenyl	±	496	Ex. 10
137	H	Bn	Me	phenyl	S	572	Ex. 10
138	H	Bn	Me	phenyl	R	572	Ex. 10
139	Et	Et	Me	phenyl	±	524	Ex. 10
140	Et	Et	H	phenyl	±	538	Ex. 10
141	Et	Et	H	3,5-difluorophenyl	S	560	Ex. 10
142	H	Ph	Me	phenyl	S	558	Ex. 10
143	H	Ph	Me	phenyl	R	558	Ex. 10
144	H	*i*-Pr	Me	phenyl	S	524	Ex. 10
145	H	*i*-Pr	Me	phenyl	R	524	Ex. 10
146	H	*i*-Bu	Me	phenyl	S	538	Ex. 10
147	H	*i*-Bu	Me	phenyl	R	538	Ex. 10
148	*i*-Bu	H	Me	phenyl	S	538	Ex. 10
149	*i*-Bu	H	Me	phenyl	R	538	Ex. 10
150	CH_2CF_3	H	H	3,5-difluorophenyl	R	586	Ex. 10
151	CH_2CF_3	H	H	3,5-difluorophenyl	S	586	Ex. 10
152	H	CH_2CF_3	H	3,5-difluorophenyl	R	586	Ex. 10
153	Me	Me	$PhCH_2$	3,5-difluorophenyl	R	622	Ex. 13
154	Me	Me	CF_3CH_2	3,5-difluorophenyl	R	614	Ex. 13
155	Me	Me	H	3,5-difluorophenyl	S	532	Ex. 13

TABLE 22



Example	R^1	n	R^{10}	R^{11}	*	LCMS (M+1)	Relevant experimental procedures
156	H	3	H	phenyl	R	522	Ex. 10
157	H	3	H	phenyl	S	522	Ex. 10
158	Me	1	H	phenyl	±	508	Ex. 10
159	Me	2	H	phenyl	±	522	Ex. 10
160	*tert*-butoxycarbonyl	3	H	3,5-difluorophenyl	R	658	Ex. 12
161	H	3	H	3,5-difluorophenyl	S	558	Ex. 12
162	H	4	H	3,5-difluorophenyl	R	572	Ex. 12
163	H	4	H	3,5-difluorophenyl	S	572	Ex. 12
164	H	3	H	2-bromo-3,5-difluorophenyl	R	636	Ex. 10
165	H	3	H	4-bromo-3,5-difluorophenyl	R	636	Ex. 10
166	H	4	Me	3,5-difluorophenyl	R	586	Ex. 13
167	H	4	Me	3,5-difluorophenyl	S	586	Ex. 13
168	H	5	Me	3,5-difluorophenyl	R	600	Ex. 13
169	H	5	Me	3,5-difluorophenyl	S	600	Ex. 13
170	*tert*-butoxycarbonyl	3	Me	3,5-difluorophenyl	R	672	Ex. 12
171	*tert*-butoxycarbonyl	3	Me	3,5-difluorophenyl	S	672	Ex. 12
172	H	3	Me	3,5-difluorophenyl	R	572	Ex. 12
173	H	3	Me	3,5-difluorophenyl	S	572	Ex. 12
174	*tert*-butoxycarbonyl	3	H	3,5-difluorophenyl	S	658	Ex. 12

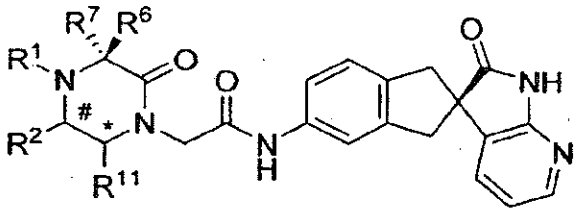
TABLE 23



Example	R^6	#	R^{11}	*	LCMS (M+1)	Relevant experimental procedures
175	H	S	phenyl	R	508	Ex. 10
176	H	S	phenyl	S	508	Ex. 10
177	H	R	phenyl	R	508	Ex. 10
178	H	R	phenyl	S	508	Ex. 10
179	Me	S	phenyl	R	522	Ex. 10
180	Me	S	phenyl	S	522	Ex. 10

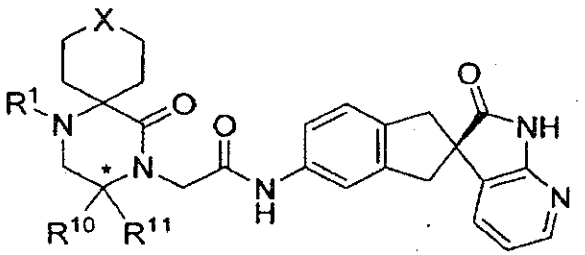
181	Me	S	3,5-difluorophenyl	R	558	Ex. 10
182	Me	S	3,5-difluorophenyl	S	558	Ex. 10

TABLE 24



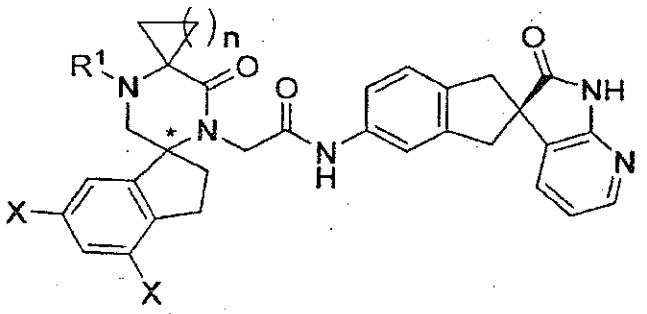
Example	R^6	R^7	R^1	R^2	#	R^{11}	*	LCMS (M+1)	Relevant experimental procedures
183	Me	Me	H	Me	R	phenyl	R	510	Ex. 10
184	Me	Me	H	Me	S	phenyl	S	510	Ex. 10
185	Me	Me	H	Me	R	3,5-difluorophenyl	R	546	Ex. 10
186	Me	Me	H	Me	S	3,5-difluorophenyl	S	546	Ex. 10

TABLE 25



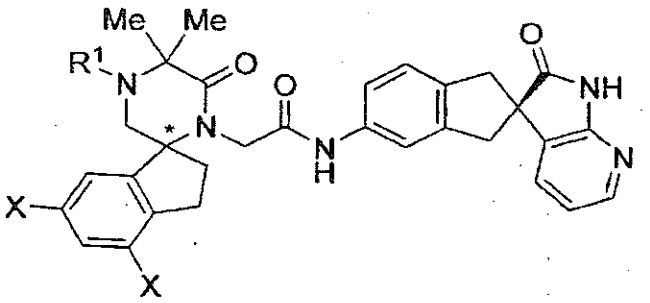
Example	R^1	X	R^{10}	R^{11}	*	LCMS (M+1)	Relevant experimental procedures
187	H	O	H	3,5-difluorophenyl	R	574	Ex. 10
188	H	O	H	3,5-difluorophenyl	S	574	Ex. 10

TABLE 26



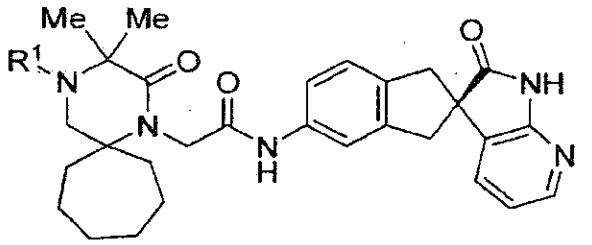
Example	R^1	n	X	*	LCMS (M+1)	Relevant experimental procedures
189	*tert*-butoxycarbonyl	3	F	R	684	Ex. 13
190	*tert*-butoxycarbonyl	3	F	S	684	Ex. 13
191	H	3	F	R	584	Ex. 13
192	H	3	F	S	584	Ex. 13
193	*tert*-butoxycarbonyl	3	H	±	648	Ex. 13
194	H	3	H	±	548	Ex. 13

TABLE 27



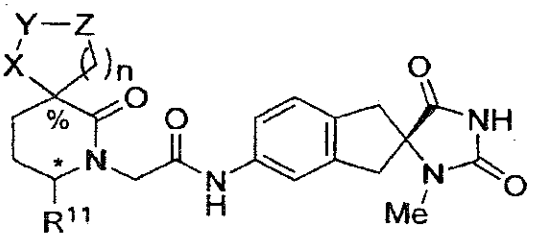
Example	R^1	n	X	*	LCMS (M+1)	Relevant experimental procedures
195	*tert*-butoxycarbonyl	3	F	±	658	Ex. 13
196	H	3	F	±	558	Ex. 13

TABLE 28



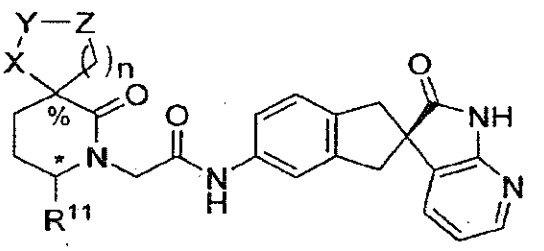
Example	R^1	LCMS (M+1)	Relevant experimental procedures
197	*tert*-butoxycarbonyl	602	Ex. 13
198	H	502	Ex. 13

TABLE 29



Example	X	Y	Z	n	R^{11}	*	%	LCMS (M+1)	Relevant experimental procedures
199	CH_2	CH_2	CH_2	1	3,5-difluorophenyl	S		537	Ex. 10
200	CH_2	CH_2	O	2	3,5-difluorophenyl	S		553	Ex. 10
201	CH_2	CH_2	CH_2	2	3,5-difluorophenyl	S		551	Ex. 10
202	NEt	CH_2	CH_2	1	3,5-difluorophenyl	S	R	566	Ex. 10
203	NH	CH_2	CH_2	1	3,5-difluorophenyl	S	R	538	Ex. 10

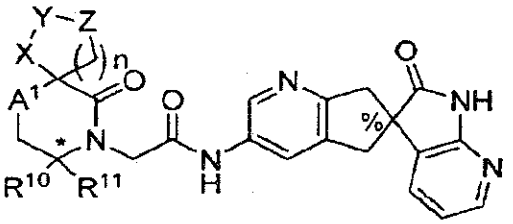
TABLE 30



Example	X	Y	Z	n	R^{11}	*	%	LCMS (M+1)	Relevant experimental procedures

204	CH_2	CH_2	CH_2	1	3,5-difluorophenyl	S		557	Ex. 10
205	CH_2	CH_2	NH	2	3,5-difluorophenyl	S		572	Ex. 10
206	CH_2	CH_2	NMe	2	3,5-difluorophenyl	S		586	Ex. 10
207	CH_2	bond	bond	1	phenyl	±		493	Ex. 10
208	CH_2	CH_2	O	2	3,5-difluorophenyl	S		573	Ex. 10
209	NH	CH_2	CH_2	1	3,5-difluorophenyl	S	R	558	Ex. 10
210	NCO_2CH_2Ph	CH_2	CH_2	1	3,5-difluorophenyl	S	R	692	Ex. 10
211	NMe	CH_2	CH_2	1	3,5-difluorophenyl	S	R	572	Ex. 10
212	NCH_2CF_3	CH_2	CH_2	1	3,5-difluorophenyl	S	R	640	Ex. 10
213	CH_2	CH_2	NCO_2CH_2Ph	2	3,5-difluorophenyl	S		706	Ex. 10

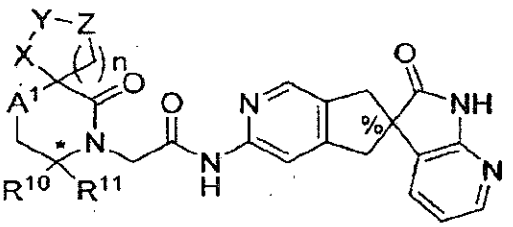
TABLE 31



5

Example	X	Y	Z	A^1	n	R^{10}	R^{11}	*	%	LCMS (M+1)	Relevant experimenta procedures
214	CH_2	CH_2	CH_2	CH_2	1	H	3,5-difluorophenyl	S	±	558	Ex. 20
215	CH_2	CH_2	CH_2	CH_2	1	H	3,5-difluorophenyl	S	Isomer B	558	Ex. 20
216	CH_2	CH_2	CH_2	NH	1	H	3,5-difluorophenyl	R	Isomer A	559	Ex. 20
217	CH_2	CH_2	O	CH_2	2	H	3,5-difluorophenyl	S	Isomer A	574	Ex. 20
218	CH_2	CH_2	CH_2	NH	1	Me	3,5-difluorophenyl	R	Isomer A	573	Ex. 20

TABLE 32



10

Example	X	Y	Z	A^1	n	R^{10}	R^{11}	*	%	LCMS (M+1)	Relevant experimenta procedures
219	CH_2	CH_2	CH_2	CH_2	1	H	3,5-difluorophenyl	S	Isomer B	558	Ex. 21
220	CH_2	CH_2	CH_2	NH	1	H	3,5-difluorophenyl	R	Isomer A	559	Ex. 21
221	CH_2	CH_2	CH_2	NH	1	H	3,5-difluorophenyl	R	Isomer B	559	Ex. 21
222	CH_2	CH_2	CH_2	NH	1	H	3,5-difluorophenyl	R	±	559	Ex. 21
223	CH_2	CH_2	O	CH_2	2	H	3,5-difluorophenyl	S	Isomer A	574	Ex. 21

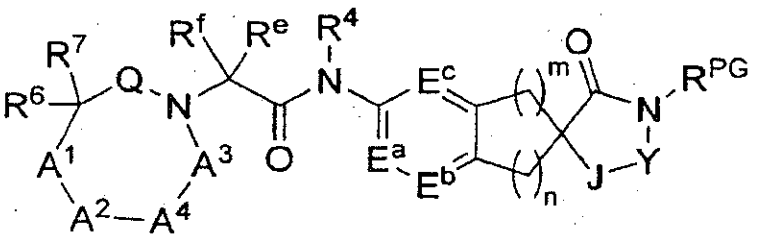
224	CH_2	CH_2	CH_2	NH	1	Me	3,5-difluorophenyl	R	Isomer A	573	Ex. 21

Although specific enantiomers and diastereomers appear in the above Examples and Intermediates, it is well understood by those skilled in the art that modifications to reaction conditions and reagents (for example, but not limited to: using the opposite chirality for starting materials; different catalysts; using the opposite chirality for reagents; choosing to use a different enantiomer or diastereomer subsequent to a chiral resolution) will provide alternative enantiomers and diastereomers, all of which are included in the spirit and scope of the invention. It is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of the formula I:



I

wherein:

A^1 is selected from:

(1) -O-,
(2) $-S(O)_v-$,
(3) $-Si(OR^a)-C_{1-4}$alkyl-, where alkyl is unsubstituted or substituted with 1-5 halo,
(4) $-Si(C_{1-4}alkyl)_2$, where each alkyl is independently unsubstituted or substituted with 1-5 halo-,
(5) $-CR^6R^7-$,
(6) $-N(R^8)-$,
(7) -(C=O)-,
(8) $-C(R^8)(R^a)-$,
(9) $-C(N(R^b)-SO_2R^d)(R^a)-$,
(10) $-C(N(R^b)(C=O)R^a)(R^a)-$,
(11) $-C(N(R^b)(C=O)OR^a)(R^a)-$,
(12) $-CR^{10}R^{11}-$, and
(13) $-N(R^{11})-$;

A^2 is selected from:

(1) $-CR^6R^7-$,
(2) $-CR^{10}R^{11}-$, and
(3) -(C=O)-;

A^3 is selected from:

(1) $-CR^6R^7-$,
(2) $-N(R^8)-$,
(3) $-CR^{10}R^{11}-$, and
(4) $-N(R^{11})-$;

A^4 is selected from:
(1) $-CR^6R^7-$,
(2) $-(C=O)-$,
(3) $-N(R^8)-$,
(4) $-CR^{10}R^{11}-$,
(5) $-N(R^{11})-$, and
(6) a bond between A^2 and A^3;

E^a is selected from:
(1) $-C(R^{5a})=$,
(2) $-N=$, and
(3) $-(N^+-O^-)=$;

E^b is selected from:
(1) $-C(R^{5b})=$,
(2) $-N=$, and
(3) $-(N^+-O^-)=$;

E^c is selected from:
(1) $-C(R^{5c})=$,
(2) $-N=$, and
(3) $-(N^+-O^-)=$;

Q is selected from:
(1) $-(C=O)-$,
(2) $-SO_2-$,
(3) $-SO-$, and
(4) $-C(R^a)_2-$;

R^4 is selected from:
(1) hydrogen,
(2) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
(a) halo,
(b) $-C_{3-6}$cycloalkyl,
(c) $-CF_3$, and
(d) $-O-R^a$,
(3) $-C_{3-6}$cycloalkyl,

(4) benzyl, and

(5) phenyl;

R^{5a}, $R^{5b}$and R^{5c} are each independently selected from:

(1) hydrogen,

(2) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo,

(3) halo,

(4) -OR^a, and

(5) -CN;

R^6 and R^7 are each independently selected from:

(1) hydrogen,

(2) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,

(b) -OR^a,

(c) -C_{3-6}cycloalkyl,

(d) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl, indolyl, indazolyl, benzimidazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(i) halo,

(ii) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 halo,

(iii) -OR^a,

(iv) –NR^bR^c,

(v) –CN, and

(vi) oxo;

(e) -CO_2R^a,

(f) -$C(=O)NR^bR^c$,

(g) -$S(O)_vR^d$,

(h) -CN,

(i) -NR^bR^c,

(j) -$N(R^b)C(=O)R^a$,

(k) -$N(R^b)SO_2R^d$,

(l) -CF_3,

(m) -O-CO_2R^d,

(n) -O-(C=O)-NR^bR^c,

(o) -NR^b-(C=O)-NR^bR^c, and

(p) $-C(=O)R^a$,

(3) $-C_{3-8}$cycloalkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,

(b) -CN,

(c) $-C_{1-4}$alkyl, which is unsubstituted or substituted with 1-3 halo, and

(d) $-OR^a$,

(4) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,

(b) $-OR^a$,

(c) $-C_{3-6}$cycloalkyl,

(d) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

(i) halo,

(ii) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo, and

(iii) $-OR^a$,

(e) $-CO_2R^a$,

(f) $-C(=O)NR^bR^c$,

(g) $-S(O)_vR^d$,

(h) -CN,

(i) $-NR^bR^c$,

(j) $-N(R^b)C(=O)R^a$,

(k) $-N(R^b)SO_2R^d$,

(l) $-O-CO_2R^d$,

(m) $-O-(C=O)-NR^bR^c$,

(n) $-NR^b-(C=O)-NR^bR^c$,

(o) $-C(=O)R^a$,

(p) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo, and

(q) oxo;

(5) halo,

(6) $-OR^a$,

(7) -CN,

(8) $-CO_2R^a$

(9) $-N(R^b)C(=O)R^a$

(10) $-NR^bR^c$,
(11) $-C(=O)NR^bR^c$, and
(12) $-O(C=O)R^a$;

or R^6 and R^7 and the carbon atom or atoms to which they are attached join to form a ring selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, dioxolanyl, dioxanyl, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiapyranyl, oxetanyl, thietanyl and tetrahydrothienyl, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from:
  (i) halo,
  (ii) $-OR^a$,
  (iii) $-C_{3-6}$cycloalkyl,
  (iv) $-CO_2R^a$,
  (v) $-NR^bR^c$,
  (vi) $-S(O)_vR^d$,
  (vii) $-C(=O)NR^bR^c$, and
  (viii) phenyl,
(b) $-C_{3-6}$cycloalkyl, wherein the C_{3-6}cycloalkyl group is optionally fused to the ring, and which C_{3-6}cycloalkyl group is unsubstituted or substituted with 1-3 substituents each independently selected from:
  (i) halo,
  (ii) $-OR^a$,
  (iii) $-C_{3-6}$cycloalkyl,
  (iv) $-CO_2R^a$,
  (v) $-NR^bR^c$,
  (vi) $-S(O)_vR^d$,
  (vii) $-C(=O)NR^bR^c$; and
  (viii) phenyl,
(c) phenyl or heterocycle, wherein heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, imidazolyl, furanyl, tetrahydrofuranyl, thiazolyl and oxazolyl, wherein the phenyl or heterocycle is optionally fused to the ring,

and which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(i) halo,
(ii) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 halo,
(iii) -OR^a,
(iv) -CO_2R^a,
(v) -$O(C=O)R^a$,
(vi) -CN,
(vii) -NR^bR^c,
(viii) oxo,
(ix) -$C(=O)NR^bR^c$,
(x) -$N(R^b)C(=O)R^a$,
(xi) -$N(R^b)CO_2R^a$,
(xii) -$O(C=O)NR^bR^c$, and
(xiii) -$S(O)_vR^d$,

(d) -OR^a,
(e) -CO_2R^a,
(f) -$C(=O)NR^bR^c$,
(g) -$S(O)_vR^d$,
(h) -CN,
(i) halo,
(j) -NR^bR^c,
(k) -$N(R^b)C(=O)R^a$,
(l) -$N(R^b)SO_2R^d$,
(m) -O-CO_2R^d,
(n) -O-$(C=O)$-NR^bR^c,
(o) -NR^b-$(C=O)$-NR^bR^c,
(p) -$C(=O)R^a$, and
(q) oxo;

R^8 is independently selected from:

(1) hydrogen,
(2) -$C(=O)R^a$,
(3) -CO_2R^a,
(4) -$S(=O)R^d$,
(5) -SO_2R^d,
(6) -$C(=O)NR^bR^c$,

(7) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,

(b) -OR^a,

(c) -C_{3-6}cycloalkyl,

(d) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(i) halo,

(ii) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 halo, and

(iii) -OR^a,

(iv) -NR^bR^c,

(v) -$C(=O)R^a$,

(vi) -CO_2R^a, and

(vii) oxo,

(e) -CO_2R^a,

(f) -$C(=O)NR^bR^c$,

(g) -$S(O)_vR^d$,

(h) -CN,

(i) -NR^bR^c,

(j) -$N(R^b)C(=O)R^a$,

(k) -$N(R^b)SO_2R^d$,

(l) -CF_3,

(m) -O-CO_2R^d,

(n) -O-(C=O)-NR^bR^c,

(o) -NR^b-(C=O)-NR^bR^c, and

(p) -$C(=O)R^a$,

(8) -C_{3-6}cycloalkyl, which is unsubstituted or substituted with 1-6 substituents each independently selected from:

(a) halo,

(b) -CN,

(c) -OR^a, and

(d) C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo;

or R^7 and R^8 and the atoms to which they are attached join to form a 4-, 5-, 6- or 7-membered alkyl- or heteroalkyl-ring optionally containing an additional heteroatom selected from N, O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:

(a) halo,

(b) phenyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from: halo, OR^a, CN, and $-C(=O)OR^a$,

(c) $-OR^a$, and

(d) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo;

R^{10} is independently selected from:

(1) hydrogen,

(2) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,

(b) $-OR^a$,

(c) -CN,

(d) phenyl, and

(e) $-C_{3-6}$cycloalkyl, which is unsubstituted or substituted with 1-6 halo,

(3) $-C_{3-6}$cycloalkyl, which is unsubstituted or substituted with 1-6 halo;

R^{11} is independently selected from the group consisting of:

phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl, azepinyl, azepanyl, azetidinyl, benzimidazolyl, benzisoxazolyl, benzofuranyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, 1,3-benzodioxolyl, benzothiazolyl, benzothienyl, benzoxazolyl, benzopyrazolyl, benzotriazolyl, chromanyl, cinnolinyl, dibenzofuranyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, furanyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 4-oxonaphthyridinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxopyridyl, 2-oxoquinolinyl, piperidyl, piperazinyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyridinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuranyl, tetrahydrofuryl, tetrahydroimidazopyridinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, thienyl,

triazolyl, isoxazolyl, tetrahydrothienyl, tetrahydropyranyl, oxetanyl, tetrahydrothiapyranyl, and thietanyl, where R^{11} is unsubstituted or substituted with 1-5 substituents each independently selected from R^{12}, R^{13}, R^{14}, R^{15a} and R^{15b};

R^{12}, R^{13}, R^{14}, R^{15a} and R^{15b} are each independently selected from:

(1) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
  (a) halo,
  (b) -OR^a,
  (c) -C_{3-6}cycloalkyl,
  (d) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperdinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
    (i) halo,
    (ii) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 halo, and
    (iii) -OR^a,
  (e) -CO_2R^a,
  (f) -$C(=O)NR^bR^c$,
  (g) -$S(O)_vR^d$,
  (h) -CN,
  (i) -NR^bR^c,
  (j) -$N(R^b)C(=O)R^a$,
  (k) -$N(R^b)SO_2R^d$,
  (l) -CF_3,
  (m) -O-CO_2R^d,
  (n) -O-(C=O)-NR^bR^c,
  (o) -NR^b-(C=O)-NR^bR^c, and
  (p) -$C(=O)R^a$,

(2) -C_{1-6}cycloalkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
  (a) halo,
  (b) -CN,
  (c) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 halo,
  (d) -OR^a, and

(e) phenyl, which is unsubstituted or substituted with 1-5 substituents where the substituents are each independently selected from:

(i) $-OR^a$,

(ii) halo,

(iii) -CN, and

(iv) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 halo,

(3) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperdinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,

(b) $-OR^a$,

(c) $-C_{3-6}$cycloalkyl,

(d) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

(i) halo,

(ii) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo, and

(iii) $-OR^a$,

(e) $-CO_2R^a$,

(f) $-C(=O)NR^bR^c$,

(g) $-S(O)_vR^d$,

(h) -CN,

(i) $-NR^bR^c$,

(j) $-N(R^b)C(=O)R^a$,

(k) $-N(R^b)SO_2R^d$,

(l) $-O-CO_2R^d$,

(m) $-O-(C=O)-NR^bR^c$,

(n) $-NR^b-(C=O)-NR^bR^c$,

(o) $-C(=O)R^a$, and

(p) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo,

(4) halo,

(5) oxo,

(6) $-OR^a$,

(7) -CN,

(8) $-CO_2R^a$,

(9) $-C(=O)R^a$,

(10) $-NR^bR^c$,
(11) $-S(O)_vR^d$,
(12) $-C(=O)NR^bR^c$,
(13) $-O-CO_2R^d$,
(14) $-N(R^b)CO_2R^d$,
(15) $-O-(C=O)-NR^bR^c$,
(16) $-NR^b-(C=O)-NR^bR^c$,
(17) $-SO_2NR^bR^c$,
(18) $-N(R^b)SO_2R^d$,

or R^{15a} and R^{15b} and the atom(s) to which they are attached join to form a ring selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thietanyl and tetrahydrothienyl, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from:
  (i) halo,
  (ii) $-OR^a$,
  (iii) $-C_{3-6}$cycloalkyl,
  (iv) $-CO_2R^a$,
  (v) $-NR^bR^c$,
  (vi) $-S(O)_vR^d$,
  (vii) $-C(=O)NR^bR^c$, and
  (viii) phenyl,
(b) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
  (i) halo,
  (ii) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 halo, and
  (iii) $-OR^a$,
(c) $-OR^a$,
(d) halo,
(e) $-CO_2R^a$,
(f) $-C(=O)NR^bR^c$,

(g) $-S(O)_vR^d$,
(h) -CN,
(i) $-NR^bR^c$,
(j) $-N(R^b)C(=O)R^a$,
(k) $-N(R^b)SO_2R^d$,
(l) $-O-CO_2R^d$,
(m) $-O-(C=O)-NR^bR^c$,
(n) $-NR^b-(C=O)-NR^bR^c$, and
(o) $-C(=O)R^a$;

R^{PG} is independently selected from:
(1) hydrogen,
(2) $-C_{1-6}$alkyl which is unsubstituted or substituted with 1-5 halo,
(3) $-CH_2OR^a$,
(4) $-CH_2-O-CH_2CH_2Si(CH_3)_3$,
(5) $-CH_2OP(=O)(OR^c)_2$,
(6) $-(CH_2)_k$-phenyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from:
(a) halo,
(b) $-OR^a$,
(c) -CN, and
(d) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo;

J is independently selected from:
(1) $=C(R^{16a})-$,
(2) $-CR^{17}R^{18}-$,
(3) -C(=O)-, and
(4) $-N(R^b)-$;

Y is independently selected from:
(1) $=C(R^{16b})-$,
(2) $-CR^{17}R^{18}-$,
(3) -C(=O)-,
(4) =N-, and
(5) $-N(R^{16b})-$;

R^{17} and R^{18} are each independently selected from:
(1) hydrogen,
(2) halo,
(3) $-OR^a$,

(4) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-4 substituents each independently selected from:

(a) halo,

(b) -OR^a,

(c) -CN,

(d) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(i) -OR^a,

(ii) halo,

(iii) -CN,

(iv) -C_{1-6}alkyl which is unsubstituted or substituted with 1-6 halo,

(5) phenyl or heterocycle wherein heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,

(b) -CN,

(c) -OR^a,

(d) nitro,

(e) -C_{1-6}alkyl which is unsubstituted or substituted with 1-6 halo;

or R^{17} and R^{18} and the atom to which they are attached join to form a 4-, 5-, or 6-membered ring optionally containing a heteroatom selected from N, O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:

(a) halo,

(b) -OR^a,

(c) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo, and

(d) phenyl;

R^{16a} and R^{16b} are each independently selected from:

(1) hydrogen,

(2) -C_{1-4}alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) halo,
(b) -OR^a,
(c) -C_{3-6}cycloalkyl,
(d) phenyl or heterocycle, wherein said heterocycle is selected from: imidazolyl, oxazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thiazolyl, thienyl, triazolyl, isoxazolyl and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
(i) halo,
(ii) -OR^a,
(iii) -CN, and
(iv) C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo,

(3) phenyl or heterocycle, wherein heterocycle is selected from: imidazolyl, oxazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, tetrahydrofuryl, piperidinyl, piperazinyl, pyrrolidinyl, azetidinyl, thiazolyl, thienyl, triazolyl, isoxazolyl and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
(a) halo,
(b) -OR^a,
(c) -C_{3-6}cycloalkyl,
(d) -C_{1-4}alkyl which is unsubstituted or substituted with 1-6 halo, and
(e) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
(i) halo,
(ii) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo, and
(iii) -OR^a,

(4) halo,
(5) -OR^a,
(6) -CN,
(7) -CO_2R^a,
(8) -NR^bR^c, and
(9) -$C(=O)NR^bR^c$;

or R^{16a} and R^{16b} and the atom(s) to which they are attached join to form a ring selected from cyclopentenyl, cyclohexenyl, phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, furanyl, dihydrofuranyl, dihydropyranyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl,

imidazolyl, triazolyl, thienyl, dihydrothienyl and dihydrothiopyranyl, which ring is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from:

(i) halo,

(ii) -OR^a,

(iii) -C_{3-6}cycloalkyl,

(iv) phenyl or heterocycle, wherein heterocycle is selected from pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(I) -OR^a,

(II) halo,

(III) -CN, and

(IV) -C_{1-6}alkyl which is unsubstituted or substituted with 1-6 halo,

(v) -CO_2R^a,

(vi) -NR^bR^c,

(vii) -$S(O)_vR^d$,

(viii) -$C(=O)NR^bR^c$,

(ix) -$N(R^b)CO_2R^a$, and

(x) -$N(R^b)SO_2R^d$,

(b) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, azetidinyl, piperazinyl, pyrrolidinyl, thienyl and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

(v) halo,

(vi) -OR^a,

(vii) -CN, and

(viii) -C_{1-6}alkyl which is unsubstituted or substituted with 1-6 halo,

(c) halo,

(d) -$S(O)_vR^d$,

(e) -OR^a,

(f) -CN,

(g) -$C(=O)R^a$,

(h) $-NR^bR^c$,
(i) $-C(=O)NR^bR^c$,
(j) $-CO_2R^a$,
(k) $-(NR^b)CO_2R^a$,
(l) $-O-(C=O)-NR^bR^c$,
(m) $-(NR^b)-(C=O)-NR^bR^c$,
(n) oxido,
(o) oxo, and
(p) $-(NR^b)SO_2R^d$;

R^a is independently selected from:

(1) hydrogen,
(2) C_{1-6}alkyl, which is unsubstituted or substituted with 1-7 substituents each independently selected from:
(a) halo,
(b) $-O-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo,
(c) hydroxyl,
(d) -CN, and
(e) phenyl or heterocycle wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
(i) halo,
(ii) $-O-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo,
(iii) -CN,
(iv) nitro,
(v) hydroxyl, and
(vi) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo,
(3) phenyl or heterocycle wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
(a) halo,
(b) -CN,
(c) $-O-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo,

(d) nitro,
(e) hydroxyl, and
(f) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo, and

(4) -C_{3-6}cycloalkyl, which is unsubstituted or substituted with 1-6 halo;

R^b and R^c are independently selected from:

(1) hydrogen,

(2) C_{1-6}alkyl, which is unsubstituted or substituted with 1-7 substituents each independently selected from:

(a) halo,
(b) -OR^a,
(c) -CN,
(d) -CO_2R^a,
(e) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:

(i) halo,
(ii) -OR^a,
(iii) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo, and
(iv) nitro,

(3) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:

(a) halo,
(b) -OR^a,
(c) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo,
(d) -C_{3-6}cycloalkyl, which is unsubstituted or substituted with 1-6 halo,
(e) -CN, and
(f) -CO_2R^a,

(4) -C_{3-6}cycloalkyl, which is unsubstituted or substituted with 1-6 halo;

or R^b and R^c and the nitrogen to which they are attached join to form a 4-, 5-, or 6-membered ring optionally containing an additional heteroatom selected from N,

O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:

(a) halo,

(b) $-OR^a$, and

(c) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo, and

(d) phenyl;

R^d is independently selected from:

(1) C_{1-6}alkyl, which is unsubstituted or substituted with 1-4 substituents each independently selected from:

(a) halo,

(b) $-OR^a$,

(c) $-CO_2R^a$,

(d) -CN, and

(e) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:

(i) halo,

(ii) $-OR^a$,

(iii) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo, and

(iv) nitro,

(2) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidinyl, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:

(a) halo,

(b) $-OR^a$,

(c) $-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-6 halo,

(d) $-C_{3-6}$cycloalkyl, which is unsubstituted or substituted with 1-6 halo

(e) -CN, and

(f) $-CO_2R^a$, and

(3) $-C_{3-6}$cycloalkyl, which is unsubstituted or substituted with 1-6 halo;

R^e and R^f are independently selected from:

(1) hydrogen,

(2) -C_{1-4}alkyl, which is unsubstituted or substituted with 1-6 halo,

(3) phenyl, and

(4) benzyl;

or where R^e and R^f and the atom to which they are attached join to form a 3-, 4-, 5-, or 6-membered ring optionally containing a heteroatom selected from N, O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:

(a) halo,

(b) -OR^a,

(c) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo, and

(d) phenyl;

m is 1, 2, or 3;

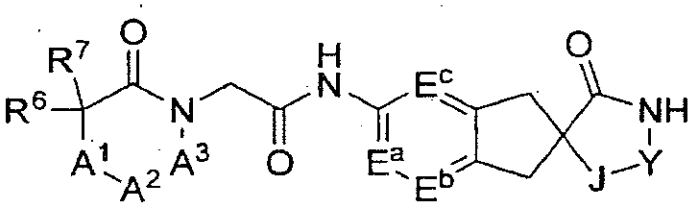
n is 1, 2, or 3;

v is 0, 1, or 2;

k is 0, 1, or 2;

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

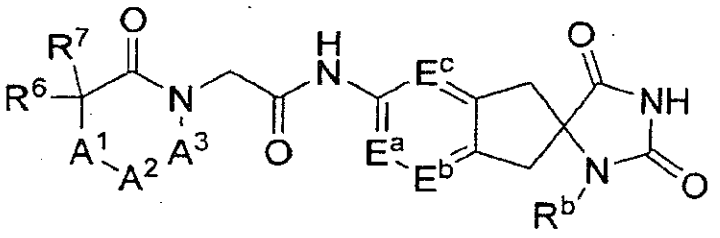
2. The compound of claim 1 having the formula Ia:



Ia

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

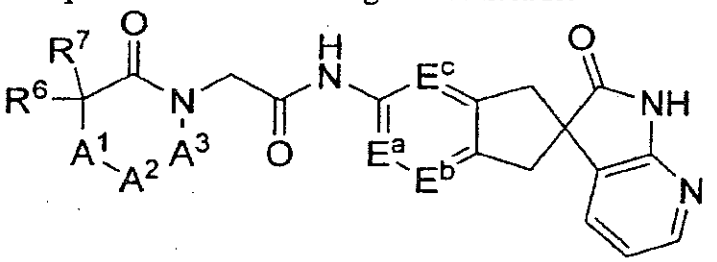
3. The compound of claim 1 having the formula Ib:



Ib

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

4. The compound of claim 1 having the formula Ic:



Ic

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

5. The compound of claim 1, wherein A^1 is selected from:

(1) -O-,
(2) $-S(O)_v-$,
(3) $-CR^6R^7-$,
(4) $-N(R^8)-$,
(5) $-C(N(R^b)(C=O)OR^a)(R^a)-$,
(6) -(C=O)-, and
(7) $-N(R^{11})-$.

6. The compound of claim 1, wherein A^2 is independently selected from $-CR^6R^7-$, $-CR^{10}R^{11}-$, and -(C=O)-, or wherein A^3 is independently selected from $-CR^6R^7-$, $-CR^{10}R^{11}-$, and $-N(R^{11})-$; or wherein A^4 is independently selected from $-CR^6R^7-$, $-CR^{10}R^{11}-$, $-N(R^{11})-$, $-N(R^8)-$, and a bond between A^2 and A^3.

7. The compound of claim 1, wherein E^a is independently selected from -$C(R^{5a})$=, -N=, and -(N^+-O^-)=; or wherein E^b is independently selected from -$C(R^{5b})$=, -N=, and -(N^+-O^-)=; or wherein E^c is independently selected from -$C(R^{5c})$=, -N=, and -(N^+-O^-)=.

8. The compound of claim 1, wherein Q is –C(=O)-.

9. The compound of claim 1, wherein R^4 is selected from: hydrogen and –C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 fluoro.

10. The compound of claim 1, wherein R^{5a}, R^{5b} and R^{5c} are independently selected from hydrogen and halo.

11. The compound of claim 1, wherein R^6 and R^7 are independently selected from:

(1) hydrogen,

(2) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 substituents where the substitutents are each independently selected from: halo, phenyl, and -OR^a,

(3) phenyl or heterocycle, which is unsubstituted or substituted with 1-5 halo,

(4) halo,

(5) -OR^a, and

(6) -NR^bR^c.

12. The compound of claim 1, wherein R^6 and R^7 and the carbon atom or atoms to which they are attached join to form a ring selected from cyclopropyl, cyclobutyl, cyclopentyl, dioxolanyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, tetrahydropyranyl, pyrrolidinyl, and piperidinyl, which ring is unsubstituted or substituted with 1-6 substituents each independently selected from:

(1) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-3 substituents where the substitutents are each independently selected from: halo, and -OR^a,

(2) phenyl or pyridyl, wherein the phenyl or pyridyl is optionally fused to the ring, and which phenyl or pyridyl is unsubstituted or substituted with 1-3 substituents each independently selected from: halo, -OR^a, and -C_{1-4}alkyl, which is unsubstituted or substituted with 1-5 fluoro,

(3) halo, and

(4) -CO_2R^a.

13. The compound of claim 1, wherein R^8 is selected from: hydrogen, -C(=O)R^a, -CO_2R^a, -SO_2R^d, and –C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 fluoro.

14. The compound of claim 1, wherein R^8 and R^7 and the atoms to which they are attached join to form a 4-, 5-, 6- or 7-membered alkyl- or heteroalkyl-ring optionally containing an additional heteroatom selected from N, O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:

(1) halo,

(2) phenyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from: halo, OR^a, CN, and –C(=O)OR^a,

(3) -OR^a, and

(4) -C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 halo.

15. The compound of claim 1, wherein R^{10} is selected from: hydrogen, and –C_{1-6}alkyl, which is unsubstituted or substituted with fluoro.

16. The compound of claim 1, wherein R^{11} is independently selected from the group consisting of:

phenyl, furanyl, pyrazinyl, pyridinyl, pyridyl, pyrimidinyl, pyrimidyl, tetrazolyl, thienyl, triazolyl,and isoxazolyl, where R^{11} is unsubstituted or substituted with 1-5 substituents each independently selected from R^{12}, R^{13}, R^{14}, R^{15a} and R^{15b}.

17. The compound of claim 1, wherein R^{PG} is selected from hydrogen, and -C_{1-6}alkyl, which is unsubstituted or substituted with 1-3 halo.

18. The compound of claim 1, wherein J is =C(R^{16a})-, -C$R^{17}R^{18}$- or –N(R^b)-; and wherein Y is =C(R^{16b})-, -C$R^{17}R^{18}$- or –C(=O)-.

19. The compound of claim 1, wherein R^{16a} and R^{16b} are independently selected from:

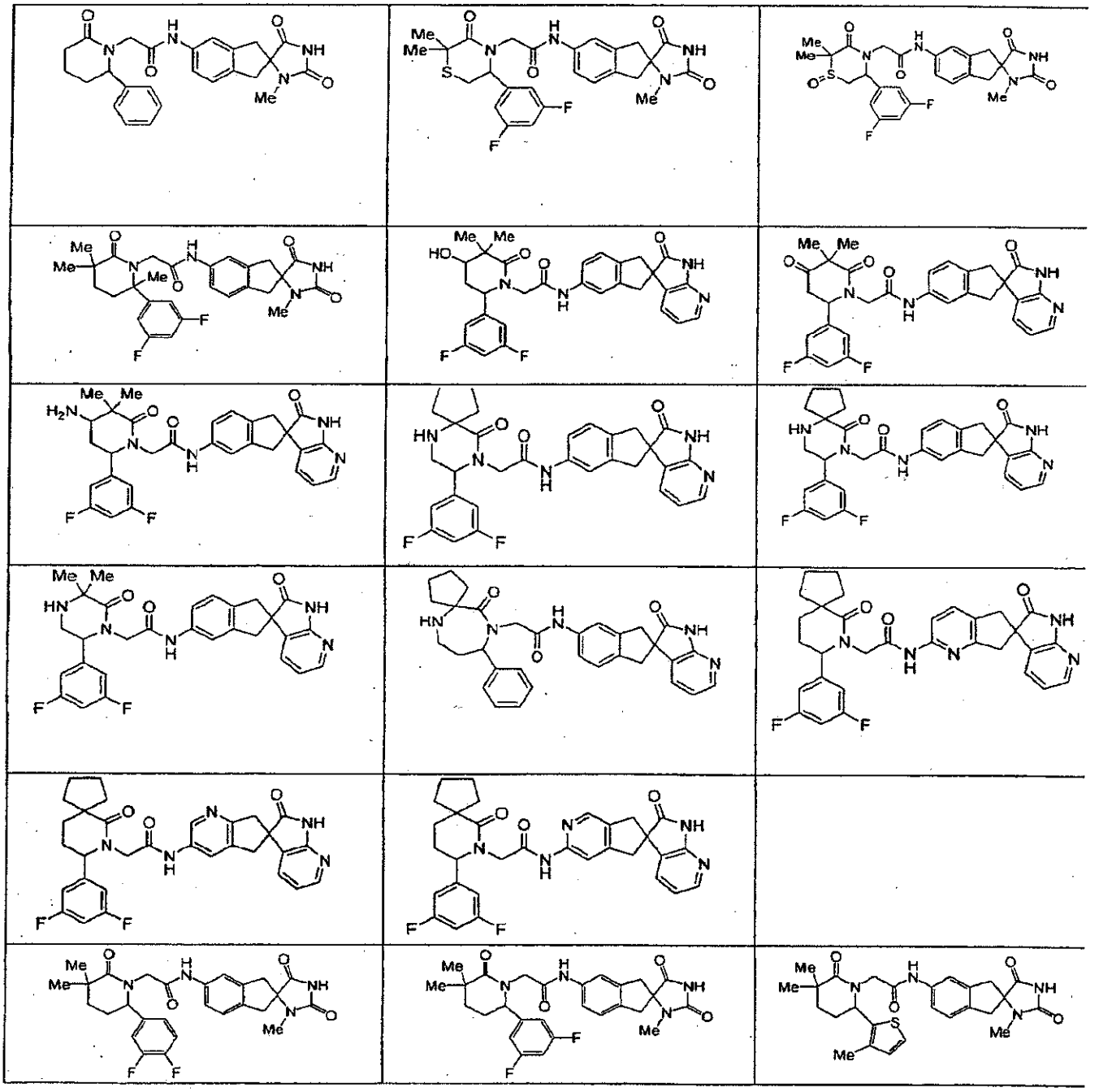
(1) hydrogen,

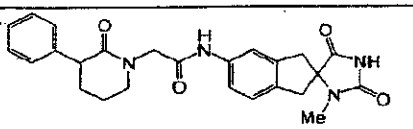
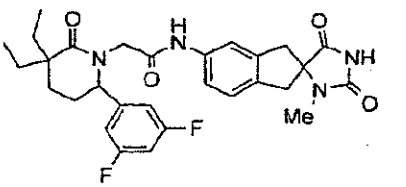
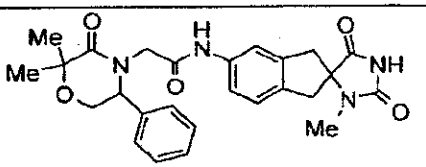
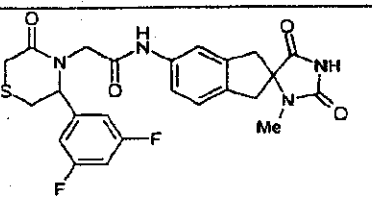
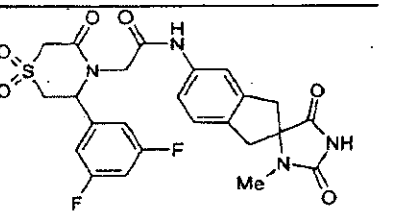
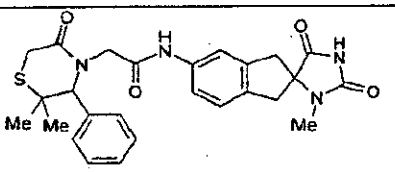
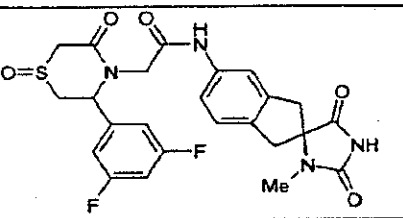
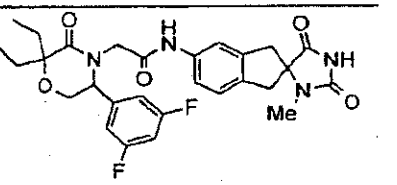
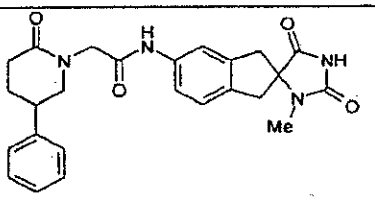
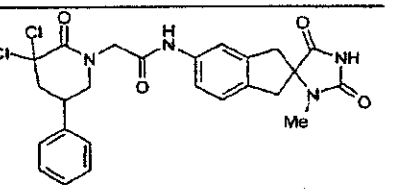
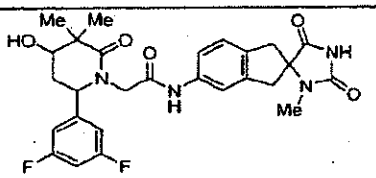
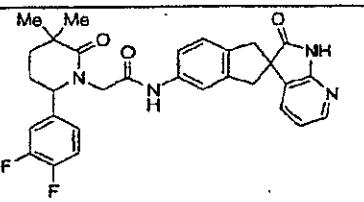
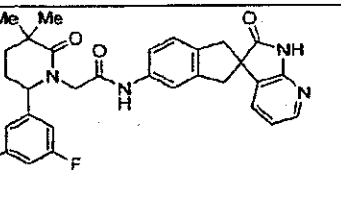
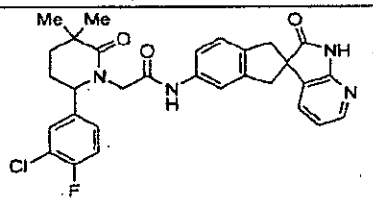
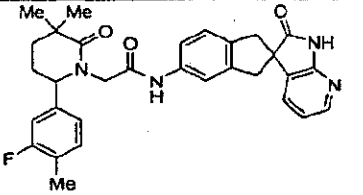
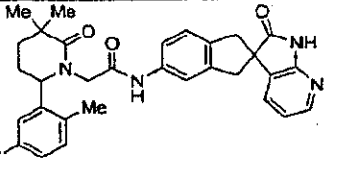
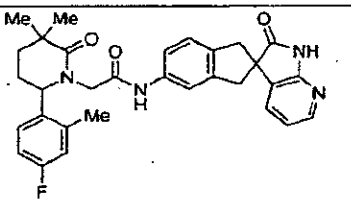
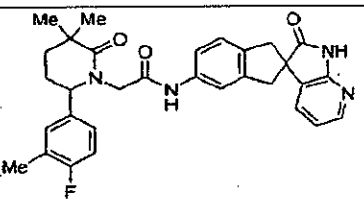
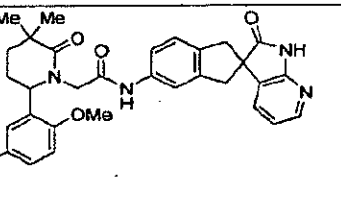
(2) -C_{1-4}alkyl, which is unsubstituted or substituted with 1-3 fluoro, and

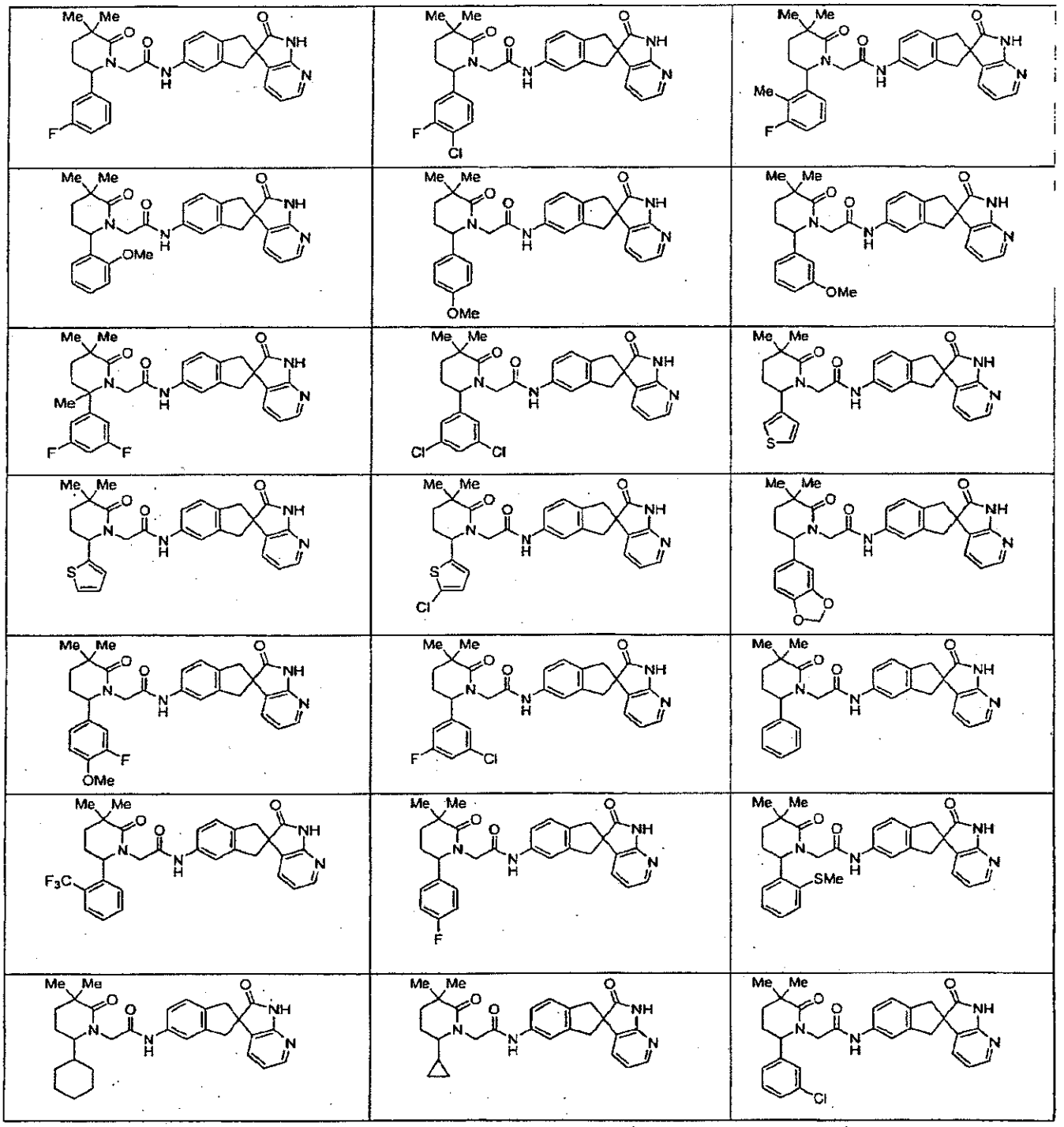
(3) phenyl or heterocycle, wherein heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, thiazolyl, thienyl, triazolyl, isoxazolyl and morpholinyl.

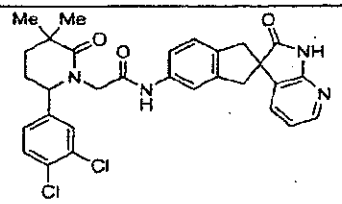
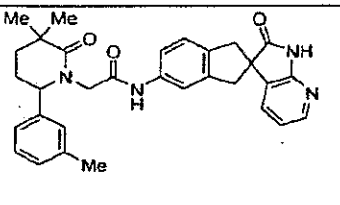
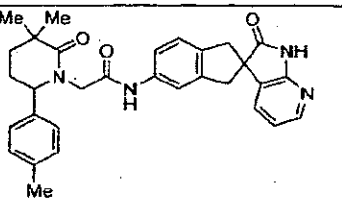
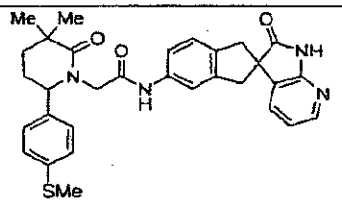
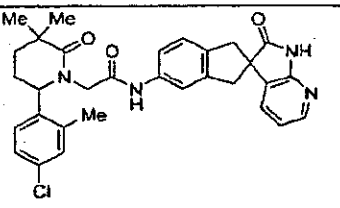
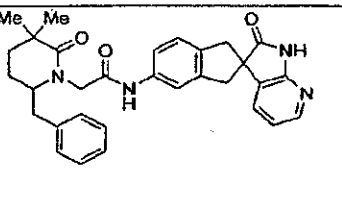
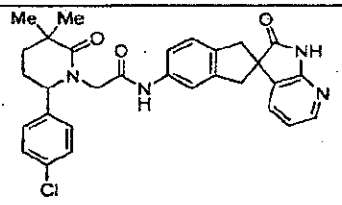
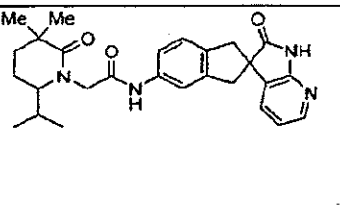
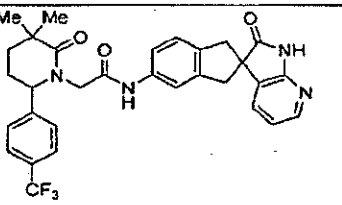
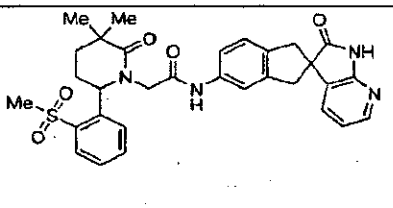
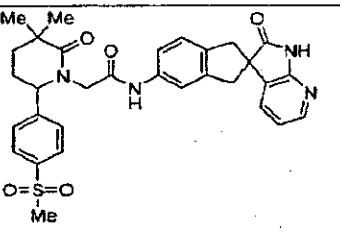
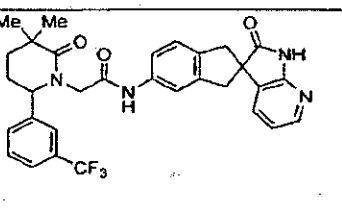
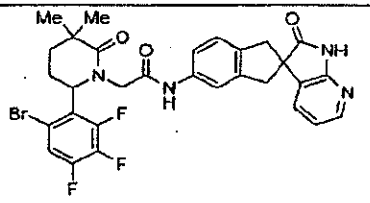
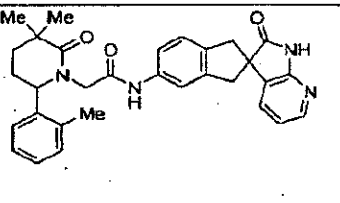
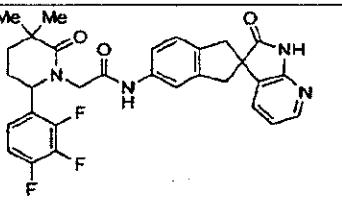
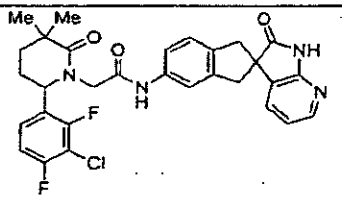
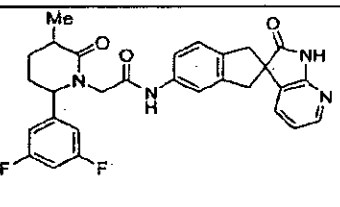
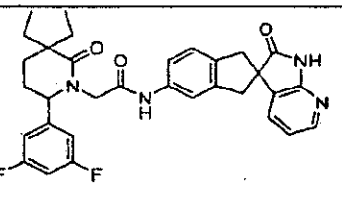
20. The compound of claim 1, wherein R^{16a} and R^{16b} and the atom(s) to which they are attached join to form a ring selected from phenyl, pyridyl and pyrimidinyl, which ring is unsubstituted or substituted with 1-3 substituents each independently selected from: halo, OR^a, and $-C_{1-4}$alkyl, which is unsubstituted or substituted with 1-3 fluoro.

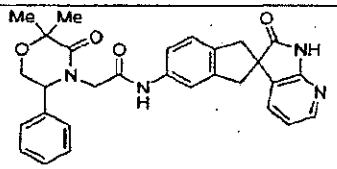
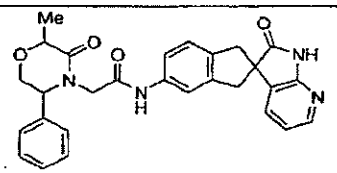
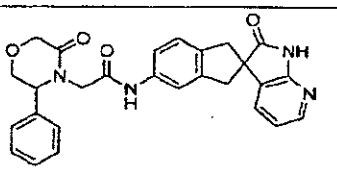
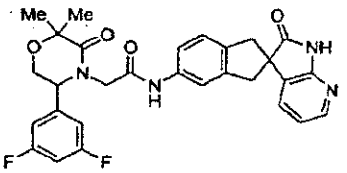
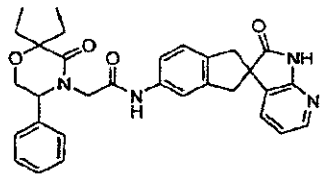
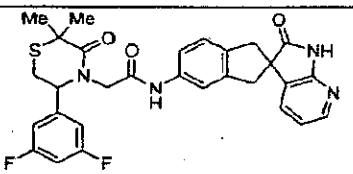
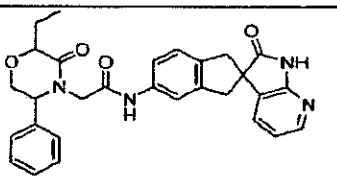
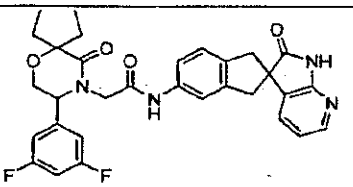
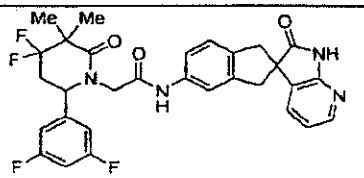
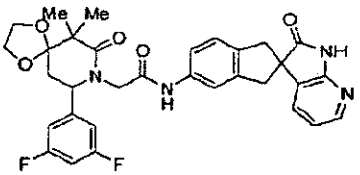
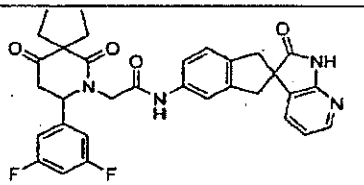
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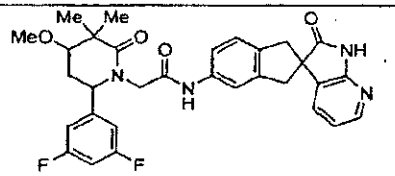
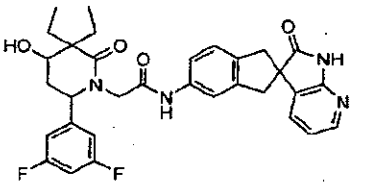
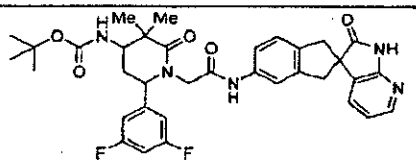
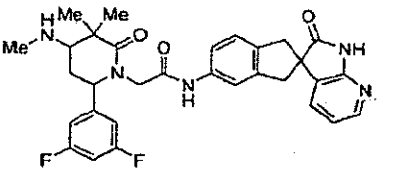
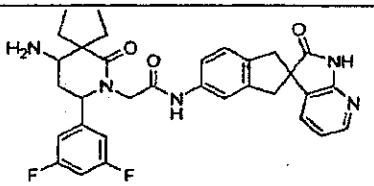
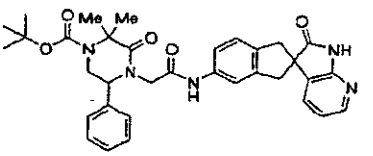
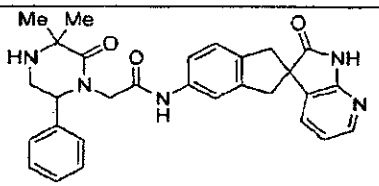
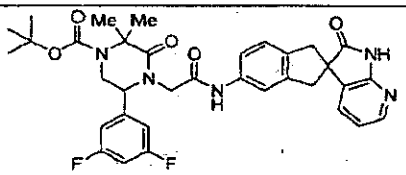
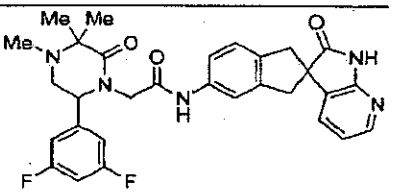


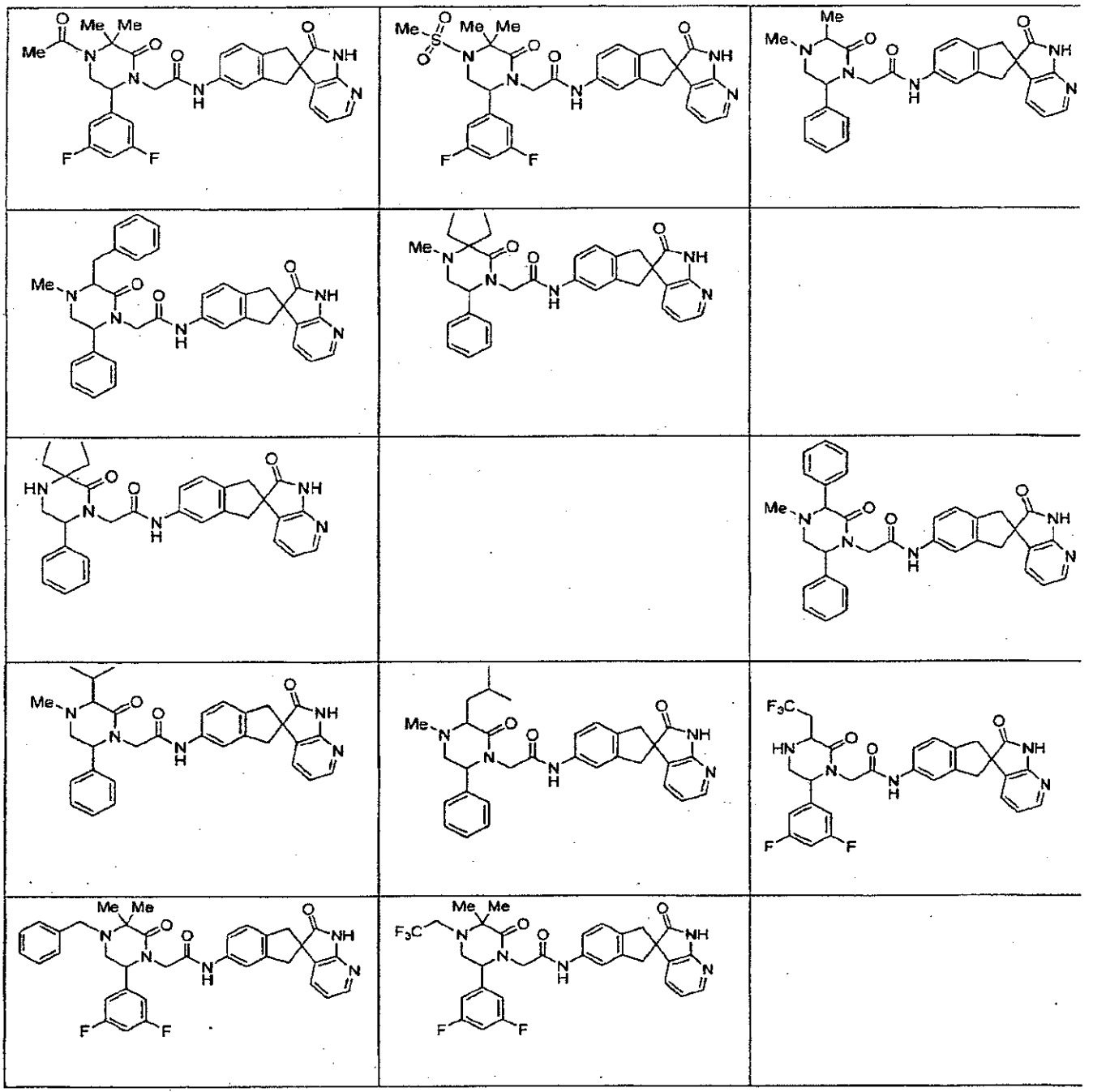
		
		
		
		
		
		
		

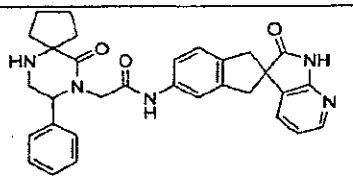
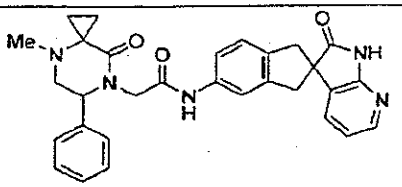
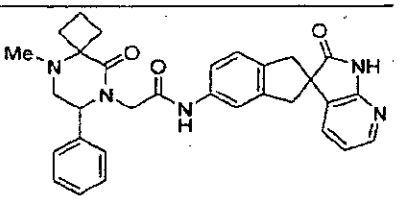
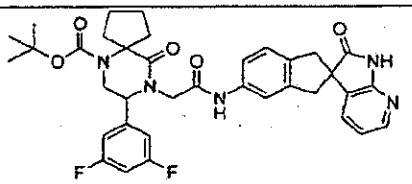
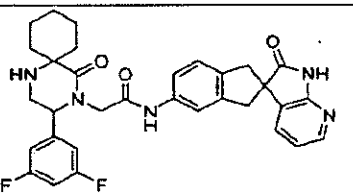
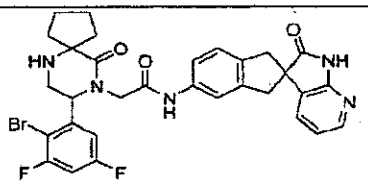
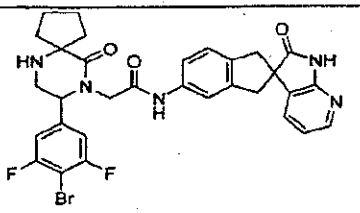
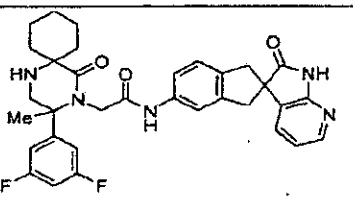
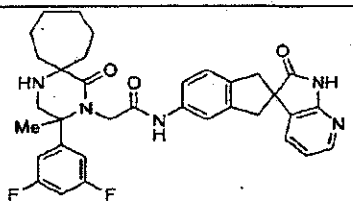
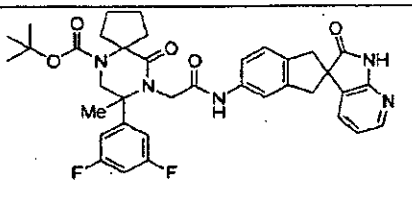
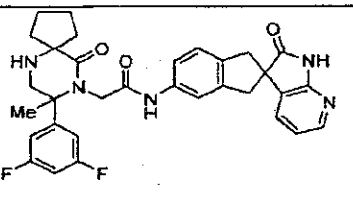


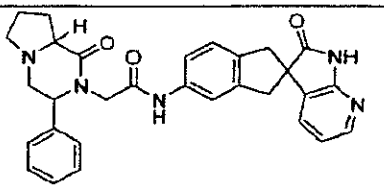
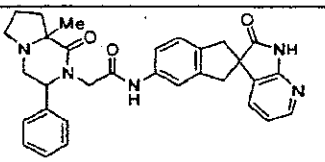
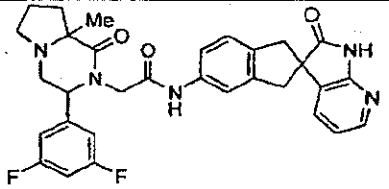
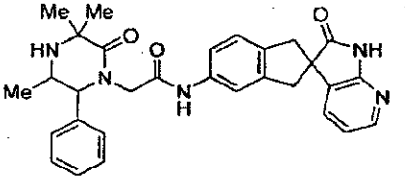
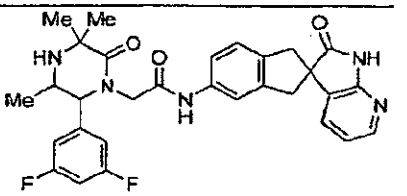
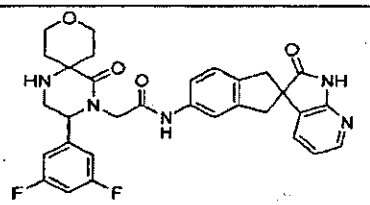
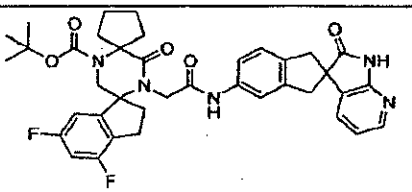
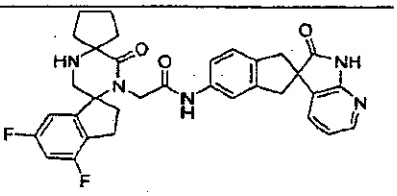
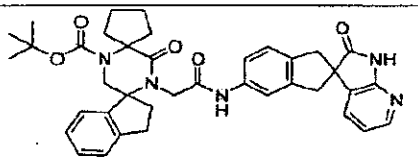
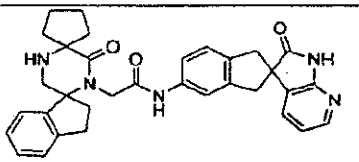
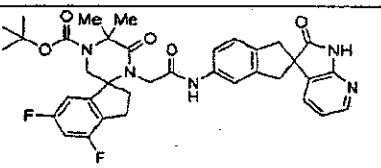
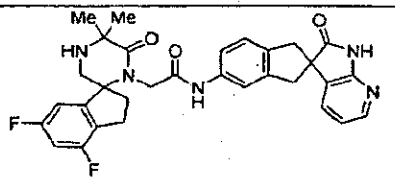
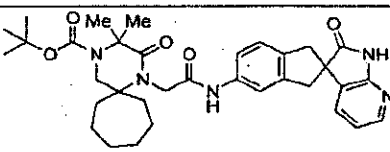
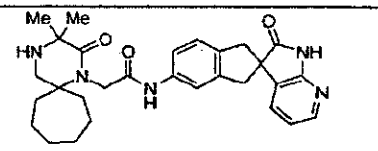
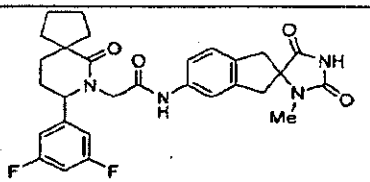
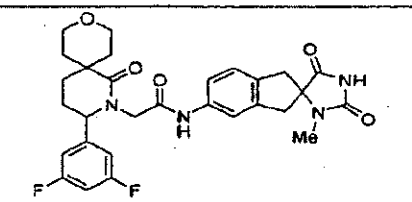
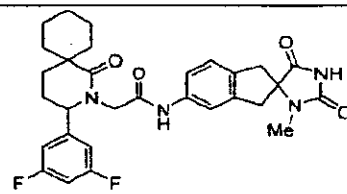
		
		
		
		
		
		

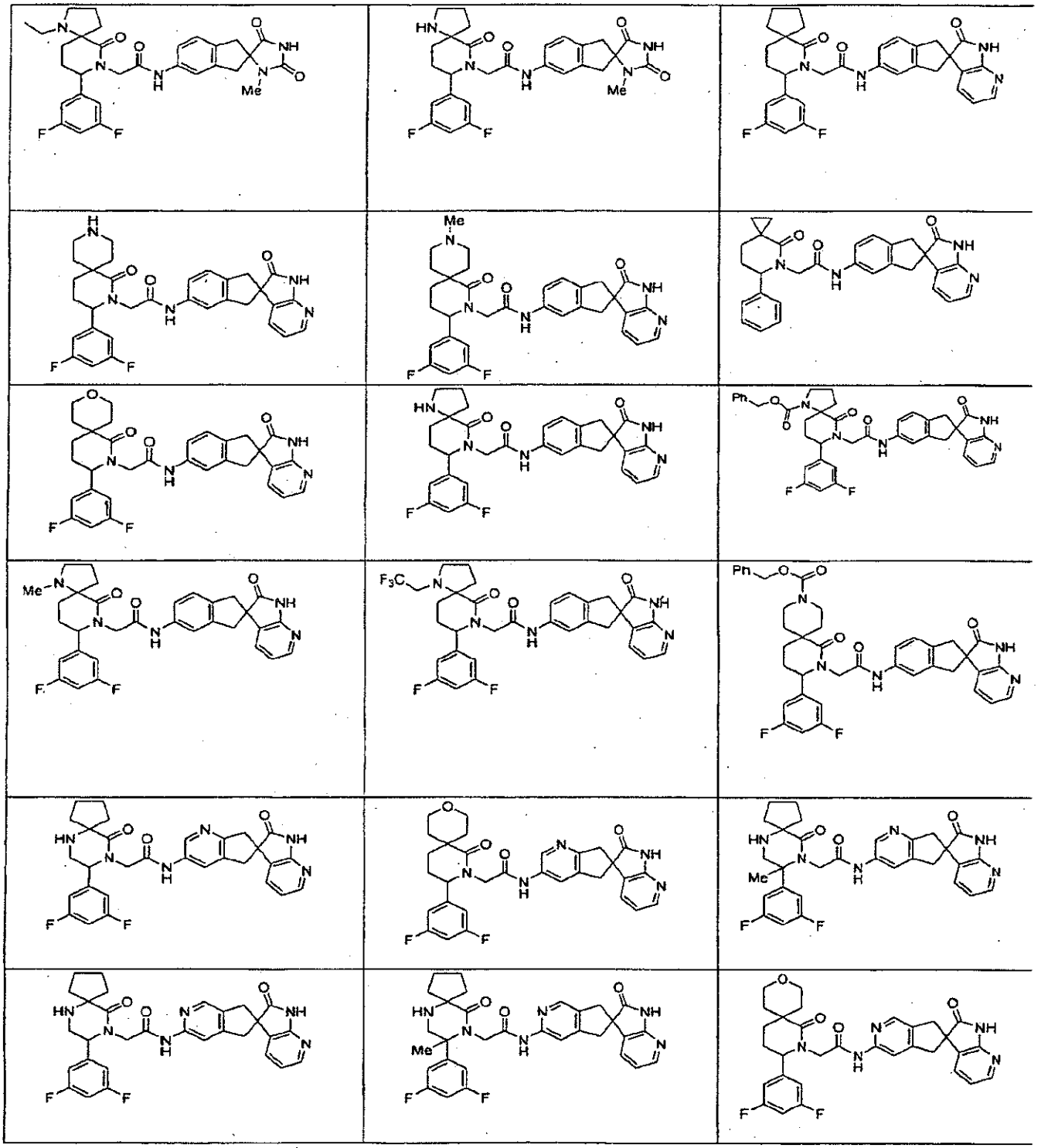
		
		
		
		
		





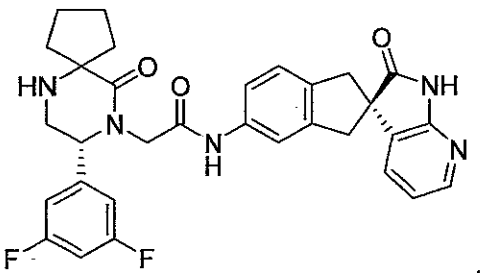
and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

22. A pharmaceutical composition which comprises an inert carrier and the compound of claim 1.

23. An effective amount of the compound of claim 1 for use in the antagonism of CGRP receptor activity in a mammal.

24. Use of the compound of claim 1 in the manufacture of a medicament for treating, controlling, ameliorating or reducing the risk of headache, migraine or cluster headache in a mammalian patient.

25. The compound of claim 1 having the formula:



26. The compound of claim 1 having the formula:

