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(54) Title: HETEROCYCLIC COMPOUNDS WHICH MODULATE THE CB2 RECEPTOR

(57) Abstract: Compounds which modulate the CB2 receptor are disclosed. Compounds according to the invention bind to and are agonists of the CB2 receptor, and are useful for treating inflammation. Those compounds which are agonists are additionally useful for treating pain.

Heterocyclic Compounds Which Modulate The CB2 Receptor

APPLICATION DATA

This application claims benefit to US provisional application serial no. 61/153,333 filed February 18, 2009.

BACKGROUND OF THE INVENTION

1. TECHNICAL FIELD

The present invention relates to novel compounds which modulate the CB2 receptor and their use as medicaments.

2. BACKGROUND INFORMATION

Cannabinoids are a group of about 60 distinct compounds found in *Cannabis sativa* (also know as marijuana) with cannabinol, cannabidiol and Δ^9-tetrahydrocannabinol (THC) being the most representative molecules. The therapeutic usage of *Cannabis* can be dated back to ancient dynasties of China and includes applications for various illnesses ranging from lack of appetite, emesis, cramps, menstrual pain, spasticity to rheumatism. The long history of *Cannabis* use has led to the development of several pharmaceutical drugs. For example, Marinol and Cesamet which are based on THC and its analogous nabilone, respectively, are used as anti-emetic and appetite stimulant. Despite of the clinical benefits, the therapeutic usage of cannabis is limited by its psychoactive effects including hallucination, addiction and dependence. Mechoulam R, ed. *Cannabinoids as Therapeutic Agents*, Boca Raton, FL; CRC Press, 1986 provides a review of the medicinal use of cannabis.

The physiological effects of cannabinoids are mediated by at least two G-protein coupled receptors, CB1 and CB2. Autoradiographic studies have demonstrated that CB1 receptors are expressed primarily in the central nervous system, specifically in the cerebral cortex, hippocampus, basal ganglia and cerebellum. They are also found to a lesser degree in the

reproductive system and other peripheral tissues including that of the immune system. CB1 receptors regulate the release of neurotransmitters from the pre-synaptic neurons and are believed to mediate most of the euphoric and other central nervous system effects of cannabis, such as THC-induced ring-catalepsy, hypomobility, and hypothermia, which were found to be completely absent in mice with a deletion of the CB1 gene (Zimmer et al., Increased mortality, hypoactivity, and hypoalgesia in cannabinoid CB1 receptor knockout mice. Proc Natl Acad Sci U S A. (1999) 96:5780-5785.)

CB2 receptors are almost exclusively found in the immune system, with the greatest density in the spleen. It is estimated that the expression level of CB2 in the immune cells is about 10 to 100 times higher than CB1. Within the immune system, CB2 is found in various cell types, includung B cells, NK cells, monocytes, microglial cells, neutrophils, T cells, dentritic cells and mast cells, suggesting that a wide range of immune functions can be regulated through CB2 modulators (Klein et al., The cannabinoid system and immune system. J Leukoc Biol (2003) 74:.486-496). This is supported by the finding that the immunomodulatory effect of THC is absent in CB2 deficient mice mice (Bicklet et al., Immunomodulation by cannabinoid is absent in mice deficient for the cannabinoid CB2 receptor. Eur J Pharmacol (2000) 396:141-149). CB2 selective ligands have been developed and tested for their effects in various imflammatory settings. For example, in animal models of inflammation, CB2 selective agonists, inverse agonists and antagonists have been shown to be effective in suppressing inflammation (Hanus et al., HU-308: a specific agonist for CB(2), a peripheral cannabinoid receptor. Proc Natl Acad Sci U S A. (1999) 96:14228-14233, Ueda et al., Involvement of cannabinoid CB(2) receptor-mediated response and efficacy of cannabinoid CB(2) receptor inverse agonist, JTE-907, in cutaneous inflammation in mice. Eur J Pharmacol. (2005) 520:164-171 and Smith et al., The anti-inflammatory activities of cannabinoid receptor ligands in mouse peritonitis models Eur J Pharmacol. (2001) 432:107-119.). Furthermore, CB2 selective agonists inhibit disease severity and spasticity in animal models for multiple sclerosis (Baker et al., Cannabinoids control spasticity and tremor in a multiple sclerosis model. Nature (2000) 404:84-87.Arevalo-Martin et al., Therapeutic action of cannabinoids in

a murine model of multiple sclerosis J Neurosci. (2003) 23:2511-2516.). Taken together, these results support the notion that CB2 receptor modulators can be employed for the treatment of medical conditions having an inflammatory component.

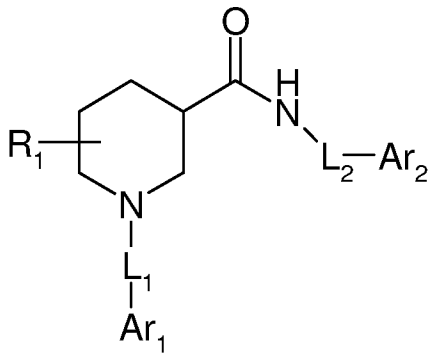
In addition to inflammation, CB2 agonists have been shown to inhibit pain and emesis. For instance, CB2 selective agonists blunt the pain response induced by thermal or other stimuli (Malan et al., CB2 cannabinoid receptor-mediated peripheral antinociception. Pain. (2001) 93:239-45 and Nackley et al., Selective activation of cannabinoid CB(2) receptors suppresses spinal fos protein expression and pain behavior in a rat model of inflammation. Neuroscience (2003) 119:747-57.) CB2 activation has also been demonstrated to inhibit neuropathic pain response (Ibrahim et al., Activation of CB2 cannabinoid receptors by AM1241 inhibits experimental neuropathic pain: pain inhibition by receptors not present in the CNS. Proc Natl Acad Sci U S A. (2003) 100:10529-33.) Finally, in contrast to the earlier data which did not find CB2 in the brain, a recent article demonstrated the expression of CB2 in the brain, at about 1.5 % of the level in the spleen. CB2 activation is shown by this article to be responsible for the anti-emetic effect of endocannabinoid (Van Sickle et al., Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science. 2005 310:329-332.) The foregoing results confirm that CB2 agonists can be used for the treatment of inflammatory and neuropathic pain as well as emesis.

BRIEF SUMMARY OF THE INVENTION

The present invention provides novel compounds which bind to and modulate the CB2 receptor. The invention also provides a method and pharmaceutical compositions for treating inflammation by way of the administration of therapeutic amounts of these compounds. Lastly, the invention provides a method and pharmaceutical compositions for treating pain by way of the administration of therapeutic amounts of the new compounds which are CB2 agonists.

DETAILED DESCRIPTION OF THE INVENTION

In one generic aspect of the invention there is provided a compound of the formula (IA)



(IA)

wherein:

Ar_1 is chosen from carbocycle, heterocyclyl and heteroaryl each optionally substituted by 1-3 C_{1-10} alkyl which is optionally substituted by halogens, C_{1-10} alkoxy, CN, halogen, NO_2, -$S(O)_m$-C_{1-10} alkyl, -CO_2- C_{1-10} alkyl, -NH(C_{1-5} alkyl)-CO_2-C_{1-10} alkyl, -C(O)-NH(C_{1-5} alkyl), -C(O)-N(C_{1-5} alkyl)$_2$, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)-C(O)-C_{1-10} alkyl, -N(C_{1-5} alkyl)-$S(O)_m$-C_{1-10} alkyl, carbocycle and heterocyclyl;

Ar_2 is chosen from carbocycle, heterocyclyl and heteroaryl each optionally substituted by 1-3 C_{1-10} alkyl which is optionally substituted by halogens, C_{3-10} cycloalkyl, carbocycle, C_{1-10} alkylcarbocycle, heteroaryl, CN or halogen, wherein the C_{1-10} alkyl and carbocycle may be additionally optionally substituted by hydroxyl, C_{1-5} alkoxycarbonyl or C_{1-5} alkoxy;

L_1 and **L_2** are each independently chosen from a bond or C_{1-10} alkyl chain wherein each -CH_2- of said chain is optionally replaced by -O-, C(O), or $S(O)_m$;

wherein each **L_1** and **L_2** where possible is optionally substituted by halogen or C_{1-3} alkyl;

R_1 is chosen from hydrogen, oxo (=O) and OH;

m is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The compound according to the embodiment described immediately above and wherein:

Ar_1 is chosen from phenyl, C_{3-6} cycloalkyl, dioxanyl, tetrahydrofuranyl, tetrahydropyranyl, thiomorpholinyl, 1,1-Dioxo-1λ^6-thiomorpholinyl, morpholinyl and pyridinyl, each optionally substituted by 1-3 C_{1-6} alkyl which is optionally substuituted with halogens, or halogen,

Ar_2 is chosen from oxazolyl, isoxazolyl, thiazoyl, thiadiazoyl, benzothiazoyl, triazoyl, isothiazoyl, phenyl, pyrimidinyl, pyridizinyl, pyrazinyl and pyridinyl, each optionally substituted by 1-3 C_{1-6} alkyl which is optionally substituted by halogens, phenyl, halogen or C_{3-8} cycloalkyl;

R_1 is hydrogen;

L_1 is a bond, or C_{1-3}alkyl chain wherein each -CH_2- of said chain is optionally replaced by C(O) or $S(O)_m$;

L_2 is a bond

The compound according to the embodiment described immediately above and wherein:

Ar_1 is chosen from phenyl, C_{3-6} cycloalkyl, tetrahydropyranyl, 1-Dioxo-1λ^6-thiomorpholinyl, morpholinyl and pyridinyl, each optionally substituted by 1-3 C_{1-6} alkyl, trifluoromethyl or halogen;

Ar_2 is chosen from isoxazolyl, pyridinyl, each optionally substituted by C_{1-6} alkyl or trifluoromethyl;

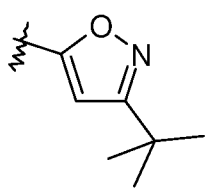
L_1 is a bond, -CH_2-, C(O) or $S(O)_2$;

The compound according to the embodiment described immediately above and wherein:

Ar_1 is chosen from phenyl, cyclohexyl, tetrahydropyranyl, 1-Dioxo-1λ^6-thiomorpholinyl, morpholinyl and pyridinyl, each optionally substituted by 1-3 C_{1-3} alkyl, trifluoromethyl or halogen;

The compound according to the embodiment described immediately above and wherein:

Ar_2 is chosen from



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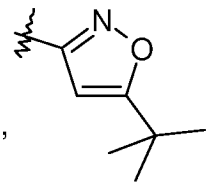
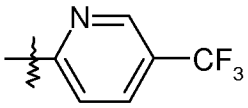


and


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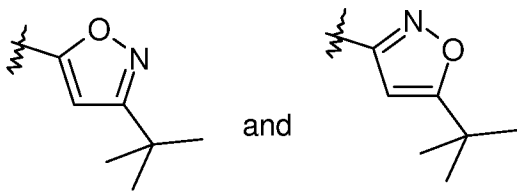
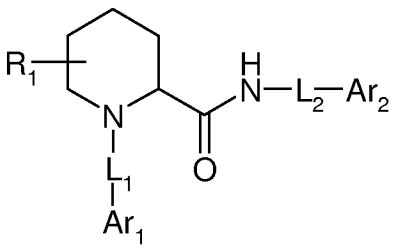
The compound according to the embodiment described immediately above and wherein:

Ar_2 is chosen from



In another generic aspect of the invention there is provided a compound of the formula (IIA)



(IIA)

wherein

Ar_1 is chosen from C_{1-6} alkyl which is optionally substituted by halogens,, C_{1-6} alkoxy, carbocycle, heterocyclyl and heteroaryl each optionally substituted by 1-3 C_{1-10} alkyl which is optionally substituted by halogens, C_{1-10} alkoxy, CN, halogen, NO_2, $-S(O)_m-C_{1-10}$ alkyl, $-C(O)-C_{1-10}$ alkyl, $-CO_2-C_{1-10}$ alkyl, C_{1-10} acyl, oxo (=O),$-NH(C_{1-5}$ alkyl)$-CO_2-C_{1-10}$ alkyl, $-C(O)-NH(C_{1-5}$ alkyl), $-C(O)-N(C_{1-5}$ alkyl$)_2$, $-NH(C_{1-5}$ alkyl), $-N(C_{1-5}$ alkyl$)-C(O)-C_{1-10}$ alkyl, $-N(C_{1-5}$ alkyl$)-S(O)_m-C_{1-10}$ alkyl and heterocyclyl the heterocyclyl being further optionally substituted by C_{1-5} alkyl;

Ar_2 is chosen from C_{1-6} alkyl, carbocycle, heterocyclyl and heteroaryl each optionally substituted by 1-3 C_{1-10} alkyl which is optionally substituted by halogens alkoxy or hydroxy,

carbocycle optionally substituted by C_{1-3} alkyl , aryl which is optionally substituted by halogen, heteroaryl, CN, halogen, C_{1-10} acyl or oxo (=O), wherein the C_{1-6} alkyl and carbocycle may be additionally optionally substituted by hydroxyl,;

L_1 and **L_2** are each independently chosen from a bond or C_{1-10} alkyl chain wherein each $-CH_2-$ of said chain is optionally replaced by -O-, C(O), $S(O)_m$ or -NH-;

R_1 is chosen from hydrogen, hydroxyl and oxo (=O);

m is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The compound according to the embodiment described immediately above and wherein:

Ar_1 is chosen from C_{1-6} alkyl which is optionally substituted by halogens, C_{1-6} alkoxyl, phenyl, C_{3-8} cycloalkyl, dioxanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyran-1,1-dioxide, tetrahydrothiofuranyl, tetrahydrothiofuran-1,1-dioxide, thiomorpholinyl, 1-Oxo-$1\lambda^4$-thiomorpholinyl, 1,1-Dioxo-$1\lambda^6$-thiomorpholinyl, morpholinyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolidinyl, piperidinyl and piperazinyl, each optionally substituted by 1-3 C_{1-6} alkyl which is optionally substituted by halogens, C_{1-6} alkoxy, CN, halogen, oxo, $-C(O)-C_{1-10}$ alkyl, $-S(O)_2-C_{1-3}$ alkyl or $-CO_2-C_{1-4}$ alkyl;

Ar_2 is chosen from C_{1-6} alkyl, cyclohexyl, phenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, imidazolyl, thienyl, thiadiazolyl, triazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl,

benzofuranyl and benzothienyl, each optionally substituted by 1-3 C_{1-6} alkyl which is optionally substituted by halogen, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, phenyl optionally substituted by halogens, CN, halogens, C_{1-6} alkoxy or hydroxy;

R_1 is hydrogen, hydroxyl and oxo (=O);

L_1 is bond or C_{1-3} alkyl chain wherein each $-CH_2-$ of said chain is optionally replaced by C(O) or $S(O)_m$;

L_2 is chosen bond or C_{1-5} alkyl chain wherein each $-CH_2-$ of said chain is optionally replaced by -O- or $S(O)_m$;

The compound according to the embodiment described immediately above and wherein:

Ar_1 is chosen from C_{1-6} alkyl which is optionally substituted by halogens, C_{1-6} alkoxyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyran-1,1-dioxide, tetrahydrothiofuranyl, tetrahydrothiofuran-1,1-dioxide, thiomorpholinyl, 1-Oxo-$1\lambda^4$-thiomorpholinyl, 1,1-Dioxo-$1\lambda^6$-thiomorpholinyl, morpholinyl, pyridinyl, pyrrolidinyl, piperidinyl and piperazinyl, each optionally substituted by 1-3 C_{1-6} alkyl, trifluoromethyl, C_{1-2} alkoxy, CN, halogen, oxo, $-C(O)-C_{1-10}$ alkyl, $-S(O)_2-C_{1-3}$ alkyl or $-CO_2-C_{1-4}$ alkyl;

Ar_2 is chosen from C_{1-6} alkyl, cyclohexyl, phenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, triazolyl and pyridinyl, each optionally substituted by 1-3 C_{1-6} alkyl, trifluoromethyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl optionally substituted by halogens, CN, halogen, C_{1-6} alkoxy or C_{1-6} hydroxy;

L_1 is bond or C_{1-3} alkyl chain wherein each $-CH_2-$ of said chain is optionally replaced by C(O) or SO_2;

L_2 is chosen bond or C_{1-5} alkyl chain wherein each $-CH_2-$ of said chain is optionally replaced by -O- or S;

The compound according to the embodiment described immediately above and wherein:

Ar_1 is chosen from phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyran-1,1-dioxide, tetrahydrothiofuranyl, tetrahydrothiofuran-1,1-dioxide, thiomorpholinyl, 1-oxo-$1\lambda^4$-thiomorpholinyl, 1,1-dioxo-$1\lambda^6$-thiomorpholinyl, pyridinyl, pyrrolidinyl, piperidinyl and piperazinyl, each optionally substituted by 1-3 C_{1-6} alkyl, trifluoromethyl, C_{1-2} alkoxy, halogen, oxo, $-C(O)-C_{1-10}$ alkyl, $-S(O)_2-C_{1-3}$ alkyl or $-CO_2-C_{1-4}$ alkyl;

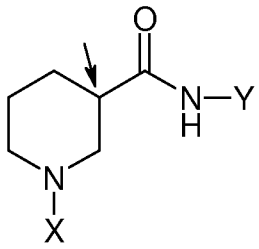
Ar_2 is chosen from cyclohexyl, phenyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, isothiazolyl, thiadiazolyl, triazolyl and pyridinyl, each optionally substituted by 1-3 C_{1-6} alkyl, trifluoromethyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl optionally substituted by halogens, CN, halogen or C_{1-6} alkoxy;

R_1 is hydrogen or oxo;

L_2 is chosen bond or C_{1-3} alkyl chain wherein each $-CH_2-$ of said chain is optionally replaced by S;

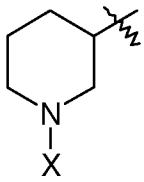
The compound according to the embodiment described immediately above and wherein:
R_1 is hydrogen;

In another generic aspect of the invention there is provided a compound of the formula (IIIA)

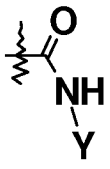


(IIIA)

wherein

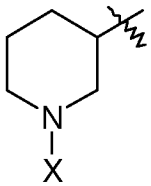
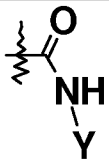


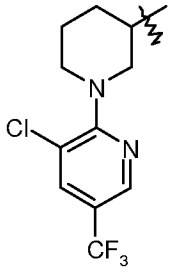
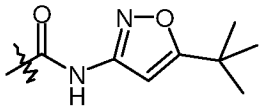
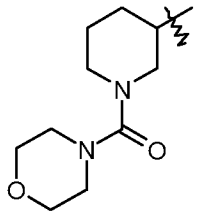
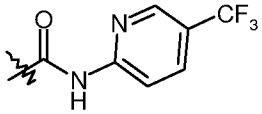
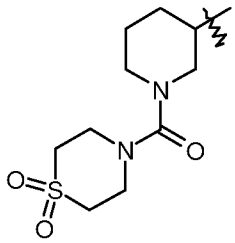
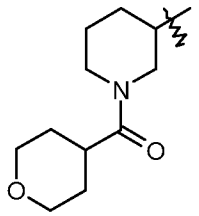
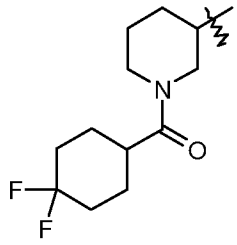
of the formula (IIIA) is chosen from A1 – A9 of Table I, and

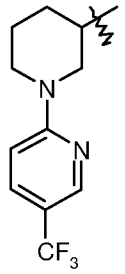
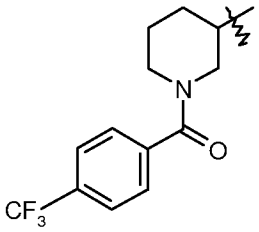
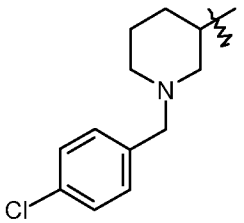
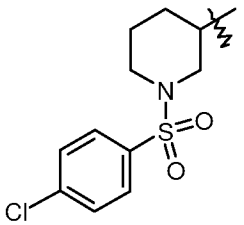


of the formula (IIIA) is chosen from B1 – B2 of Table I,

Table I

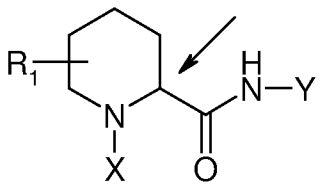
A1		B1	
A2		B2	
A3			
A4			
A5			

A6			
A7			
A8			
A9			

or a pharmaceutically acceptable salt thereof;

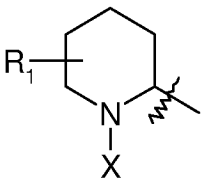
In another embodiment of the invention, the compounds in Table I, the stereogenic carbon indicated with an arrow is in the (R) configuration.

In another generic aspect of the invention there is provided a compound of the formula (IVA)

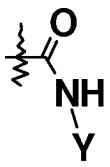


(IVA)

wherein

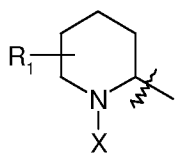
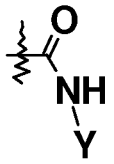


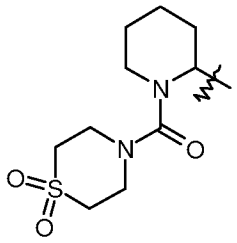
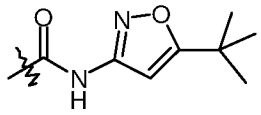
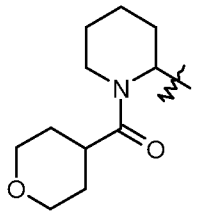
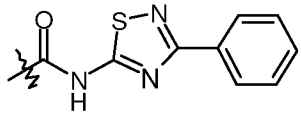
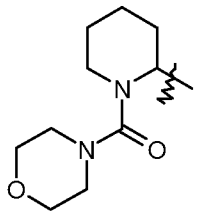
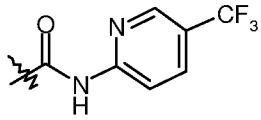
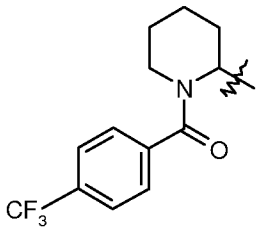
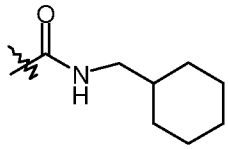
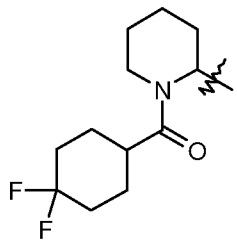
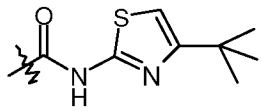
of the formula (IVA) is chosen from A1 – A53 of Table II, and

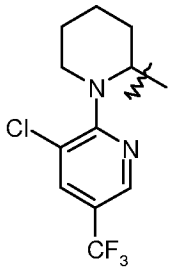
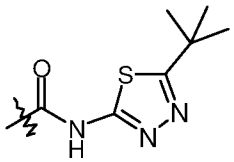
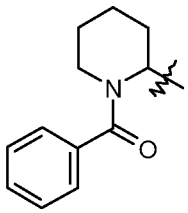
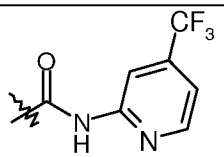
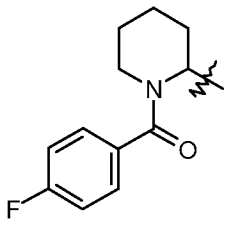
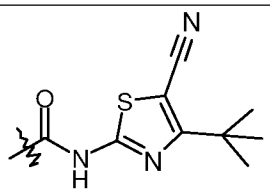
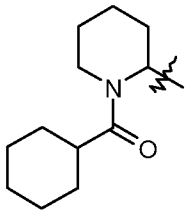
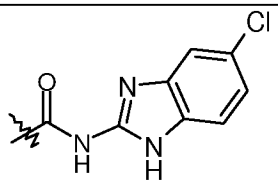
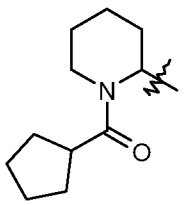
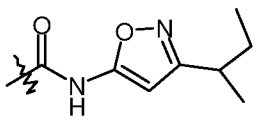
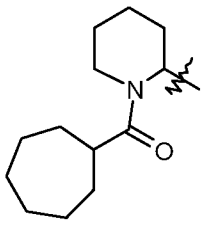
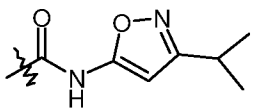


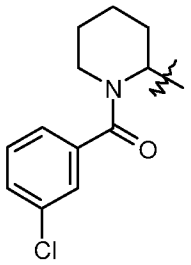
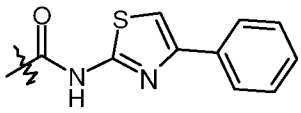
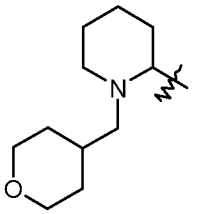
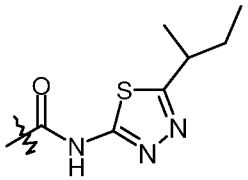
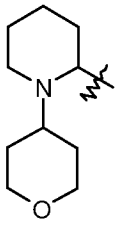
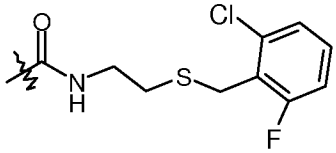
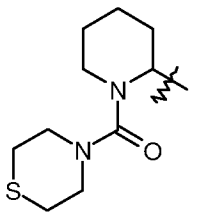
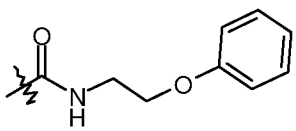
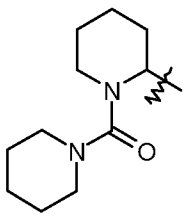
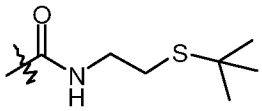
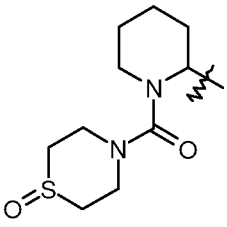
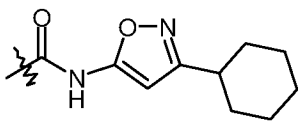
of the formula (IVA) is chosen from B1 – B40 of Table II,

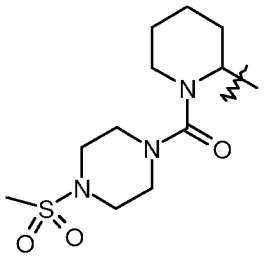
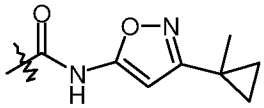
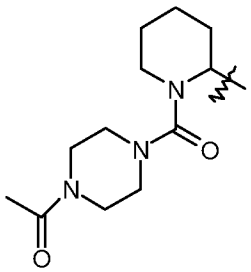
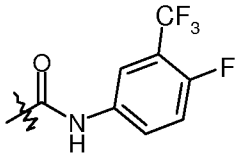
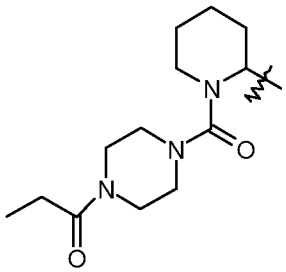
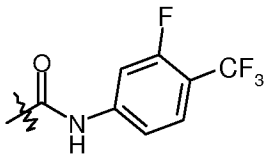
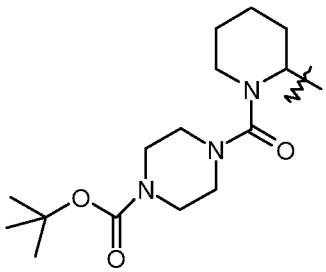
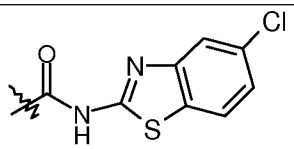
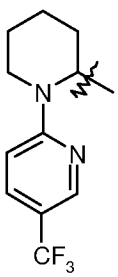
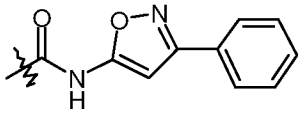
Table II

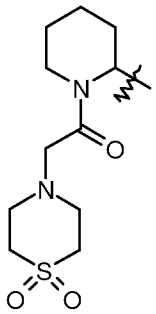
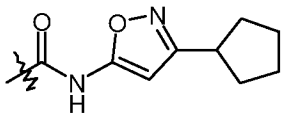
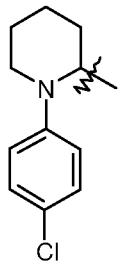
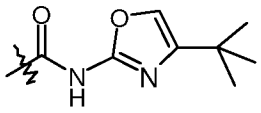
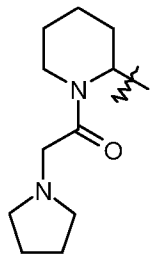
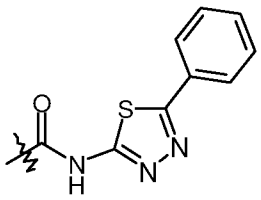
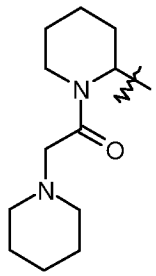
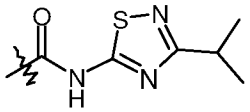
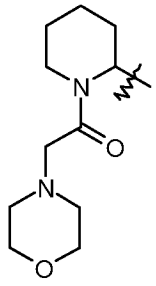
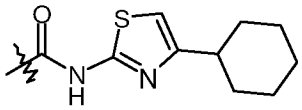
			

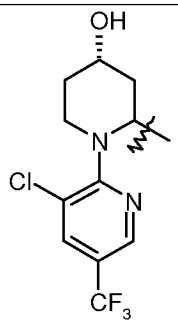
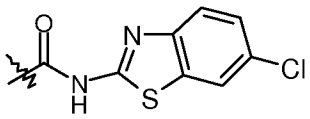
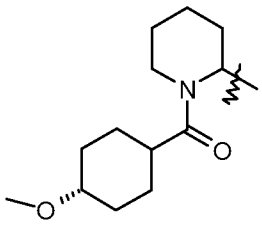
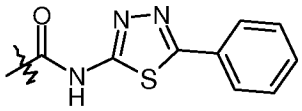
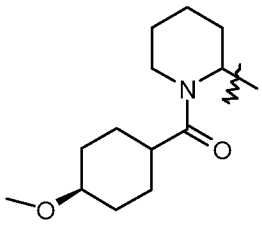
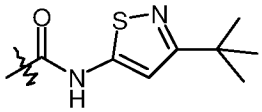
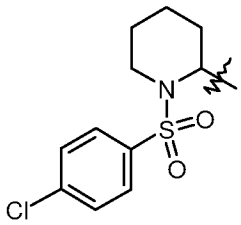
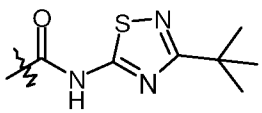
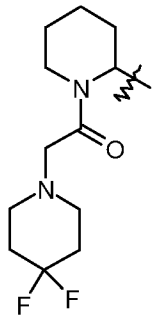
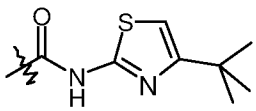
A1		B1	
A2		B2	
A3		B3	
A4		B4	
A5		B5	

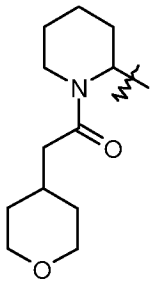
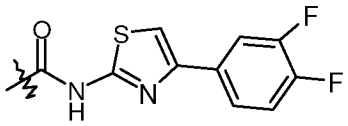
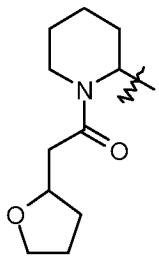
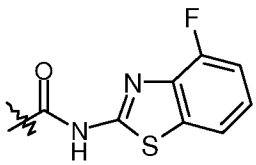
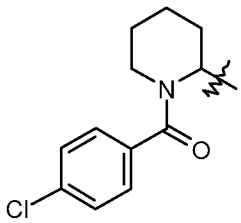
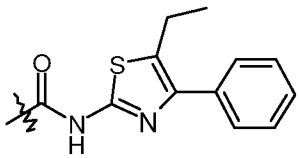
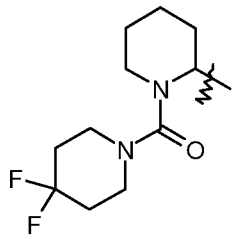
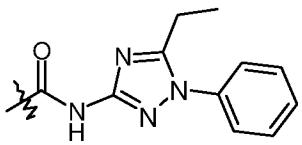
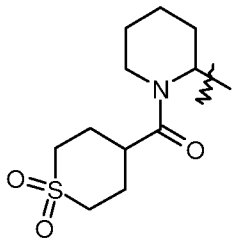
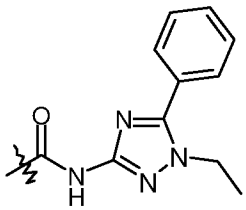
A6		B6	
A7		B7	
A8		B8	
A9		B9	
A10		B10	
A11		B11	

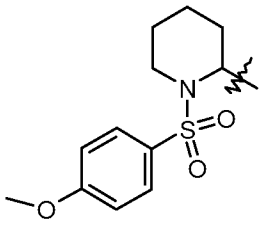
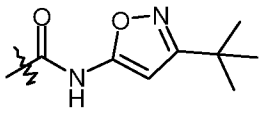
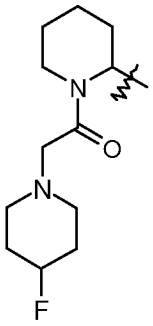
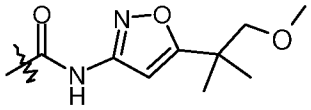
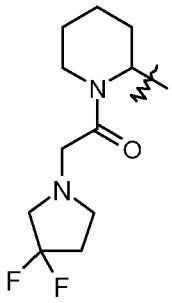
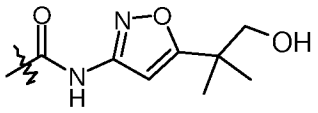
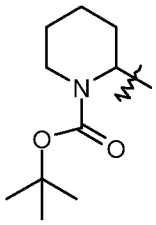
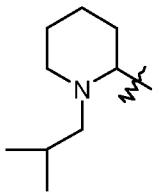
A12		B12	
A13		B13	
A14		B14	
A15		B15	
A16		B16	
A17		B17	

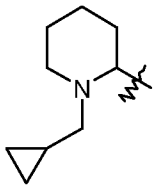
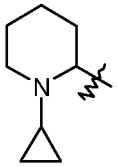
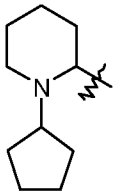
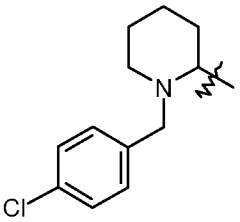
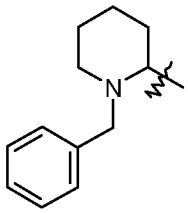
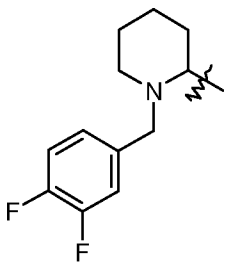
A18		B18	
A19		B19	
A20		B20	
A21		B21	
A22		B22	

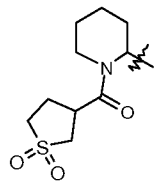
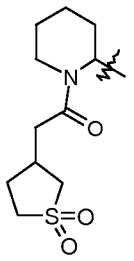
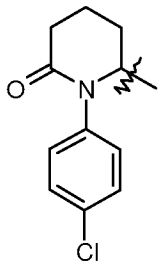
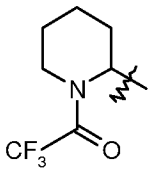
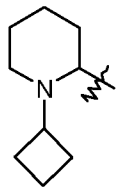
A23		B23	
A24		B24	
A25		B25	
A26		B26	
A27		B27	

A28		B28	
A29		B29	
A30		B30	
A31		B31	
A32		B32	

A33		B33	
A34		B34	
A35		B35	
A36		B36	
A37		B37	

A38		B38	
A39		B39	
A40		B40	
A41			
A42			

A43			
A44			
A45			
A46			
A47			
A48			

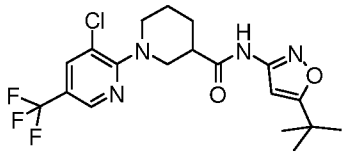
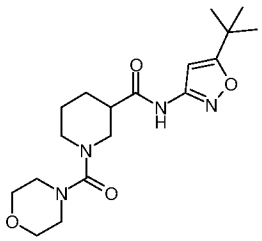
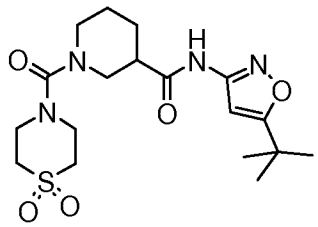
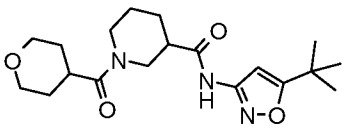
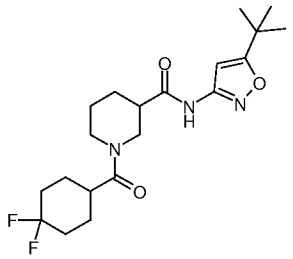
A49			
A50			
A51			
A52			
A53			

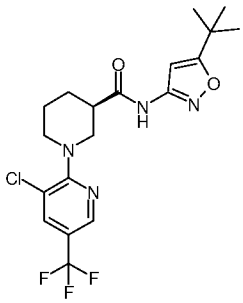
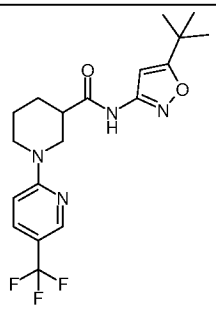
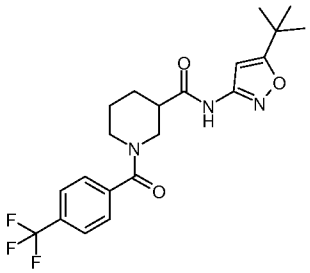
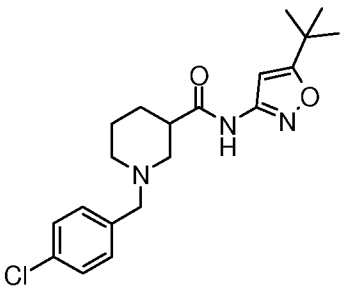
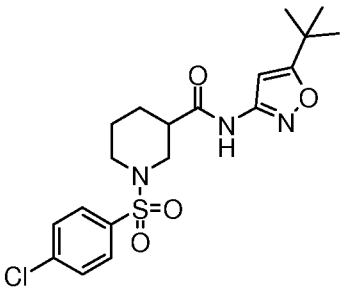
or a pharmaceutically acceptable salt thereof.

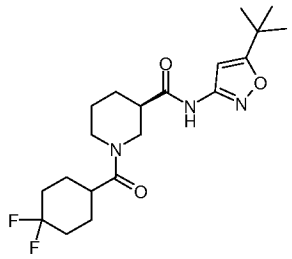
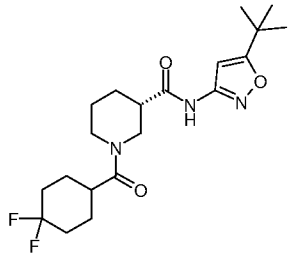
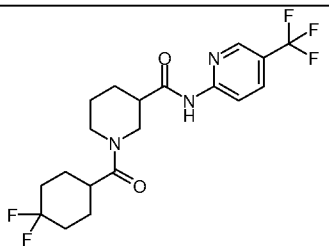
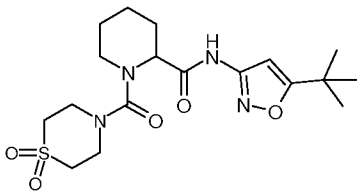
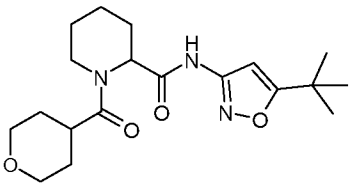
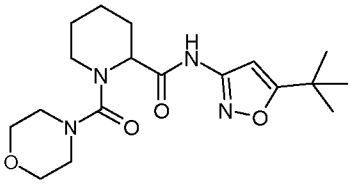
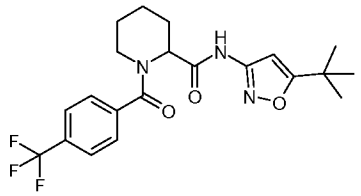
In another embodiment of the invention, the compounds in Table II, the stereogenic carbon indicated with an arrow is in the (S) configuration.

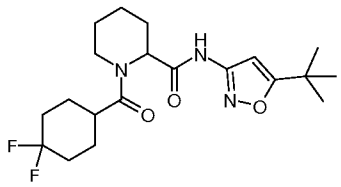
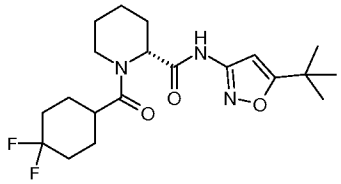
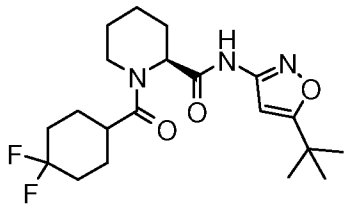
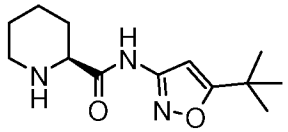
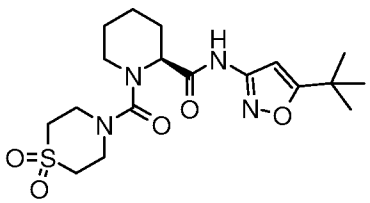
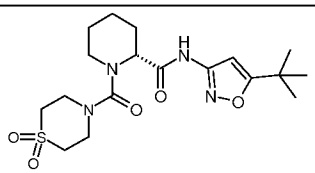
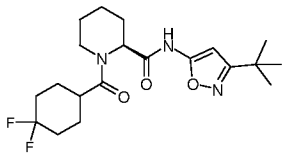
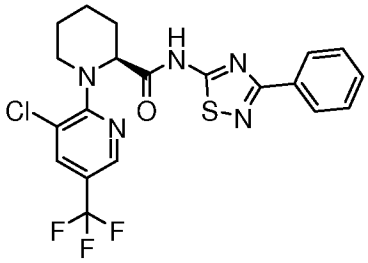
In another embodiment of the invention, there is provided compounds in Table III, which can be made by the methods and examples shown herein and methods known in the art.

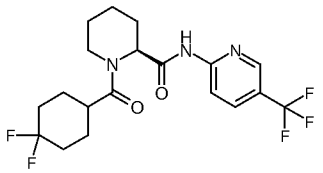
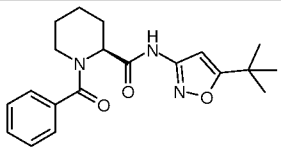
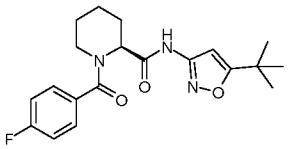
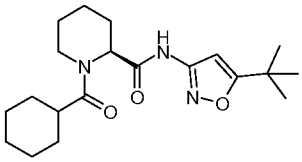
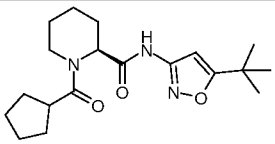
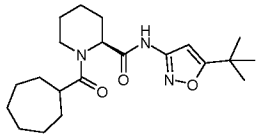
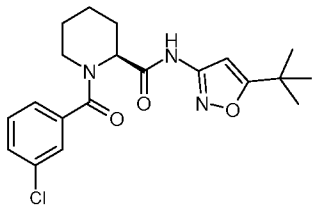
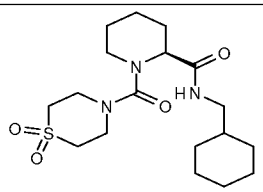
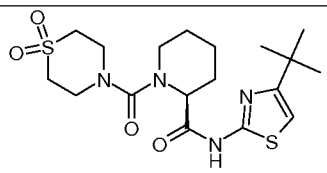
Table III

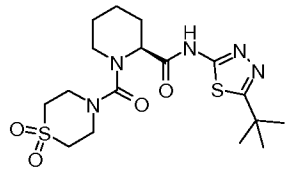
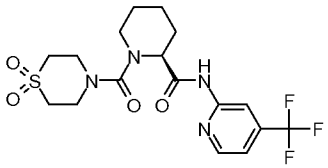
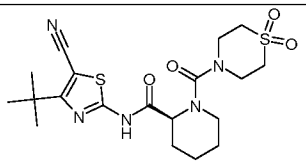
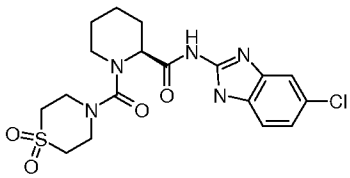
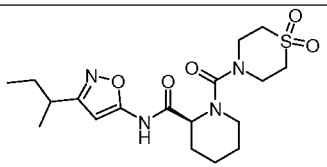
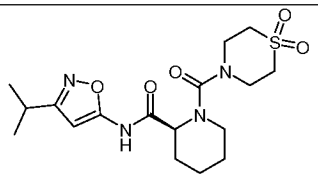
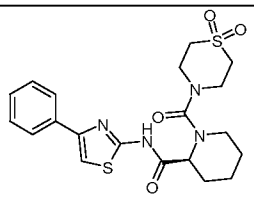
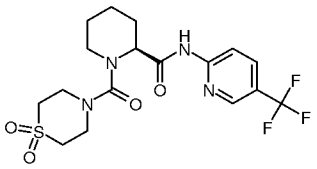
Structure	Name
	3'-Chloro-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide
	1-(Morpholine-4-carbonyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide
	1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide
	1-(Tetrahydro-pyran-4-carbonyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide
	1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide

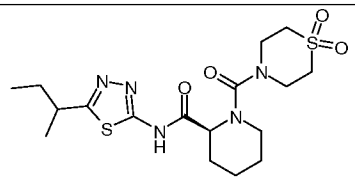
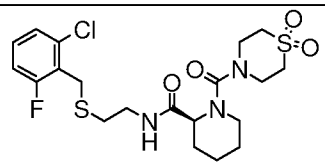
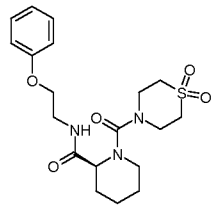
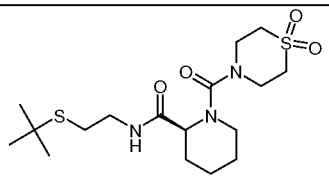
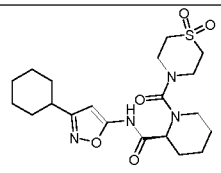
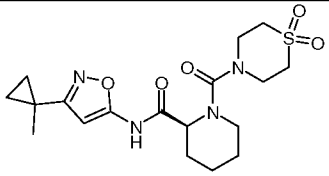
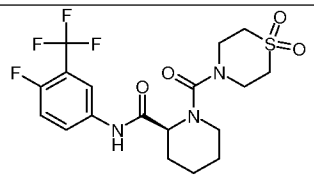
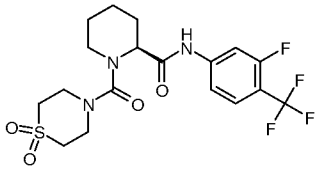
	(R)-3'-Chloro-5'-trifluoromethyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide
	5'-Trifluoromethyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide
	1-(4-Trifluoromethyl-benzoyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide
	1-(4-Chloro-benzyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide
	1-(4-Chloro-benzenesulfonyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide

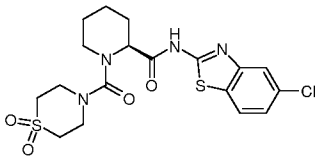
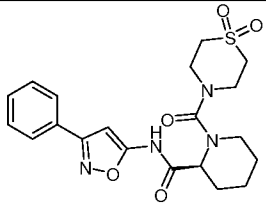
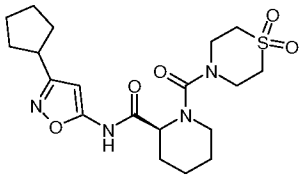
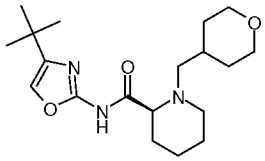
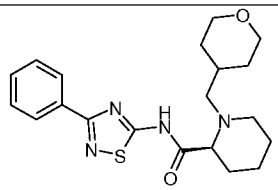
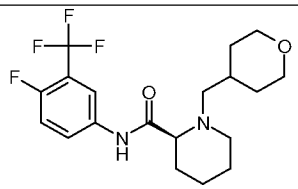
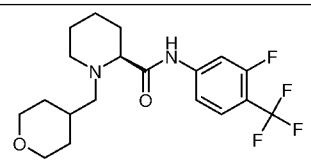
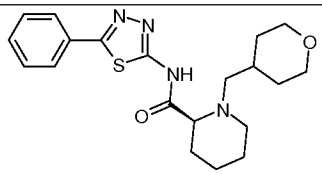
	(R)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide
	(S)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide
	1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-3-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide
	1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	1-(Tetrahydro-pyran-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	1-(4-Trifluoromethyl-benzoyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide

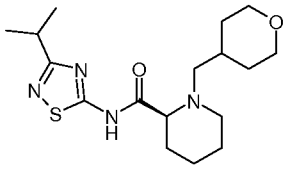
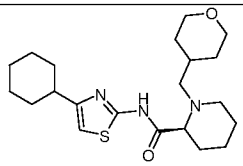
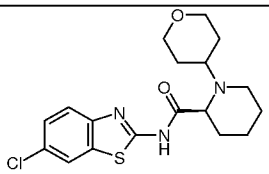
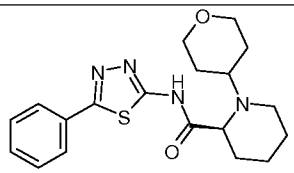
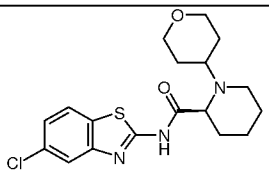
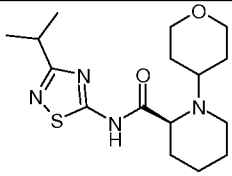
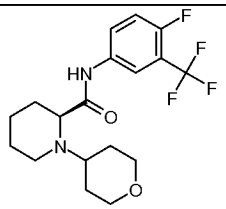
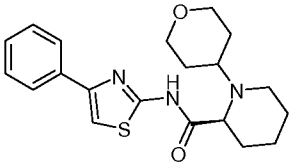
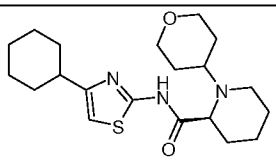
	1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(R)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-Piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(R)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide
	(S)-3'-Chloro-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-1,2'-bipyridinyl-2-carboxylic acid (3-phenyl-1,2,4-thiadiazol-5-yl)-amide

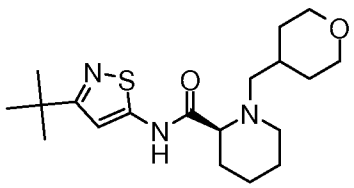
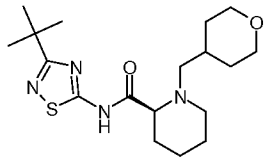
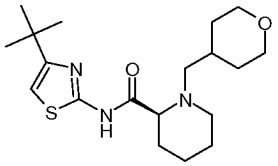
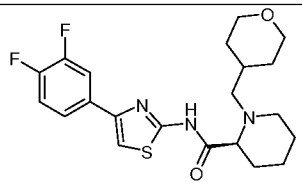
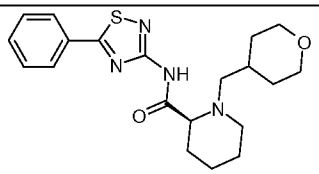
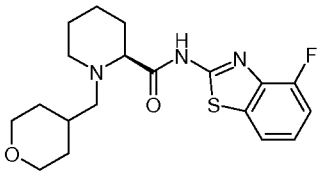
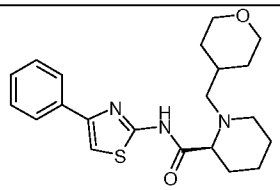
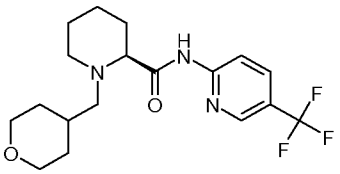
	(S)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide
	(S)-1-Benzoyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(4-Fluoro-benzoyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	S)-1-Cyclohexanecarbonyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-Cyclopentanecarbonyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-Cycloheptanecarbonyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(3-Chloro-benzoyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid cyclohexylmethyl-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (4-tert-butyl-thiazol-2-yl)-amide

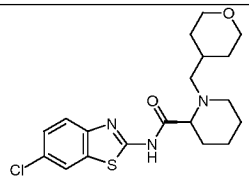
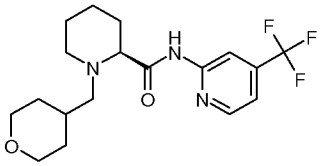
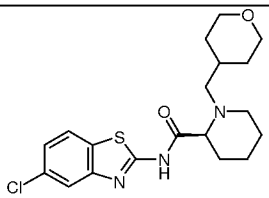
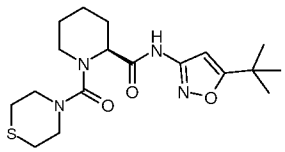
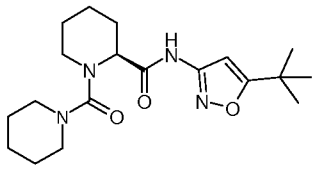
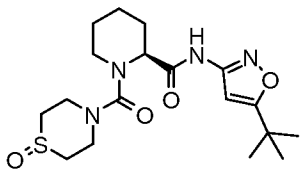
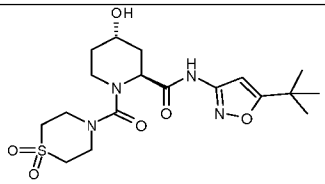
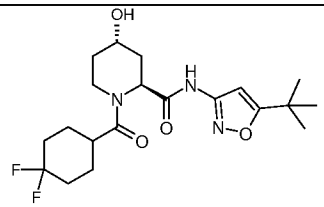
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (4-trifluoromethyl-pyridin-2-yl)-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (4-tert-butyl-5-cyano-thiazol-2-yl)-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-chloro-1H-benzimidazol-2-yl)-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-sec-butyl-isoxazol-5-yl)-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-isopropyl-isoxazol-5-yl)-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (4-phenyl-thiazol-2-yl)-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide

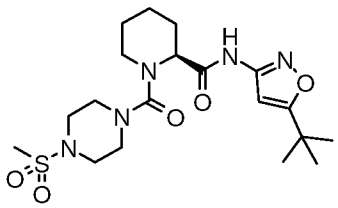
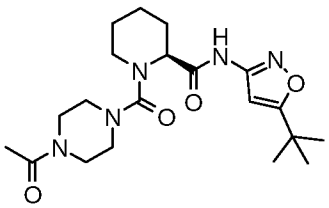
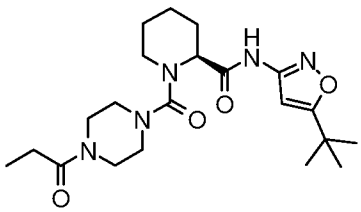
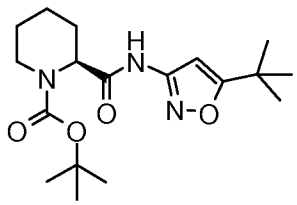
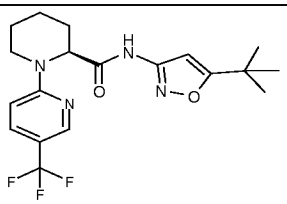
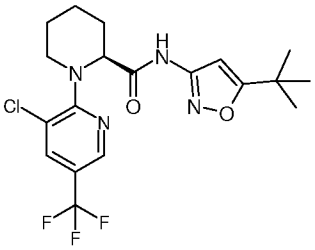
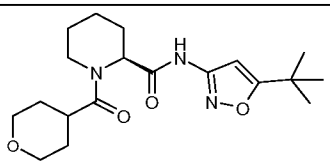
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-sec-butyl-1,3,4-thiadiazol-2-yl)-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [2-(2-chloro-6-fluoro-benzylsulfanyl)-ethyl]-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (2-phenoxy-ethyl)-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (2-tert-butylsulfanyl-ethyl)-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-cyclohexyl-isoxazol-5-yl)-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [3-(1-methyl-cyclopropyl)-isoxazol-5-yl]-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (4-fluoro-3-trifluoromethyl-phenyl)-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-fluoro-4-trifluoromethyl-phenyl)-amide

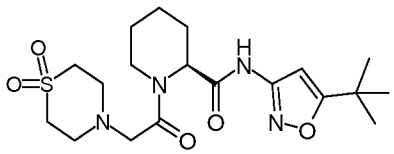
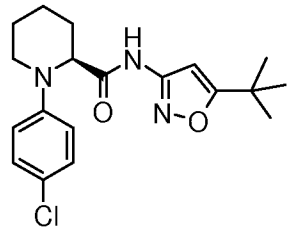
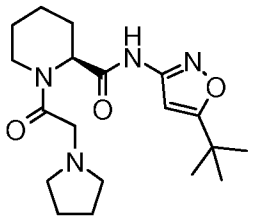
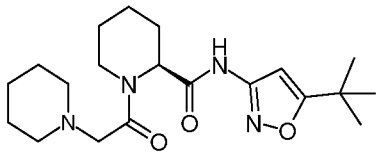
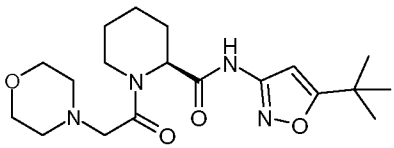
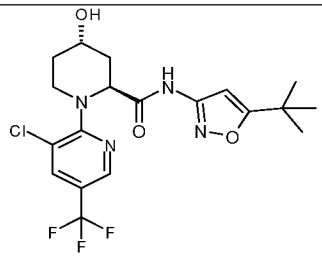
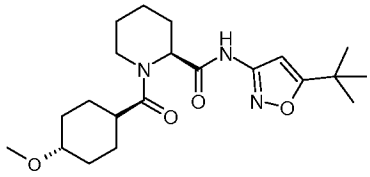
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-chloro-benzothiazol-2-yl)-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-phenyl-isoxazol-5-yl)-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-cyclopentyl-isoxazol-5-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-tert-butyl-oxazol-2-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-phenyl-1,2,4-thiadiazol-5-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-fluoro-3-trifluoromethyl-phenyl)-amide
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-fluoro-4-trifluoromethyl-phenyl)-amide
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-phenyl-1,3,4-thiadiazol-2-yl)-amide

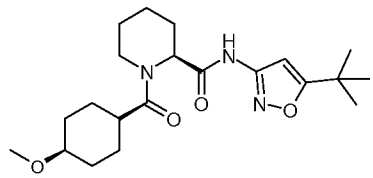
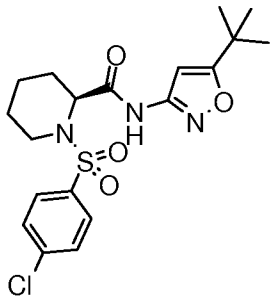
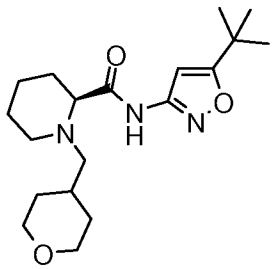
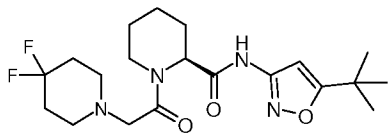
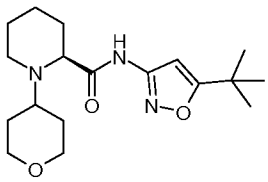
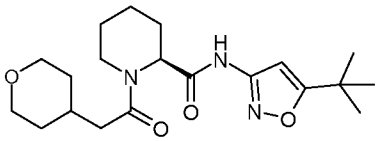
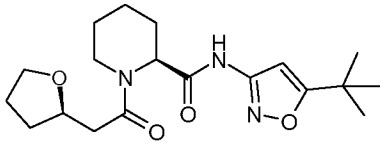
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-isopropyl-1,2,4-thiadiazol-5-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-cyclohexyl-thiazol-2-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (6-chloro-benzothiazol-2-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (5-phenyl-1,3,4-thiadiazol-2-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (5-chloro-benzothiazol-2-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (3-isopropyl-1,2,4-thiadiazol-5-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (4-fluoro-3-trifluoromethyl-phenyl)-amide
	(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (4-phenyl-thiazol-2-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (4-cyclohexyl-thiazol-2-yl)-amide

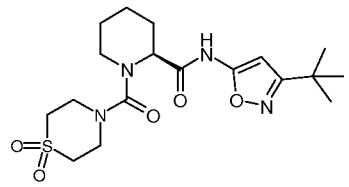
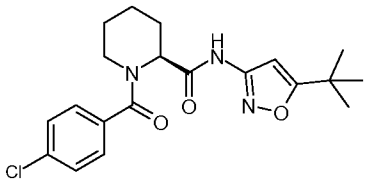
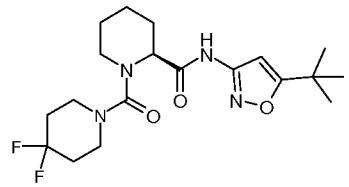
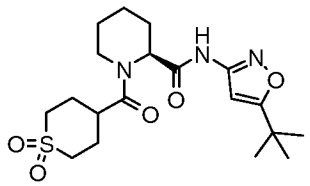
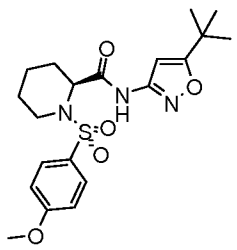
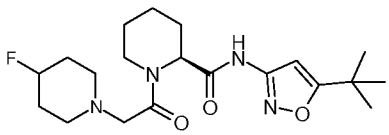
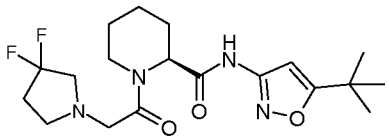
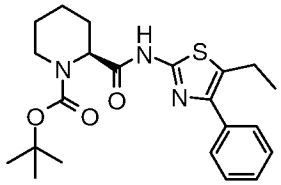
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-tert-butyl-isothiazol-5-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-tert-butyl-1,2,4-thiadiazol-5-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-tert-butyl-thiazol-2-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid [4-(3,4-difluoro-phenyl)-thiazol-2-yl]-amide
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-phenyl-1,2,4-thiadiazol-3-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-fluoro-benzothiazol-2-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-phenyl-thiazol-2-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide

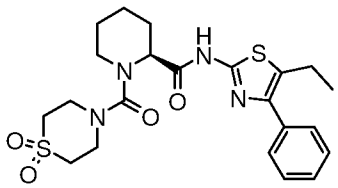
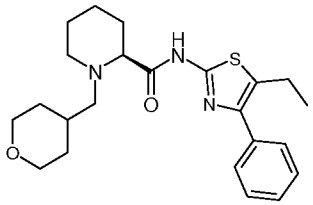
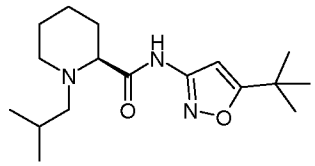
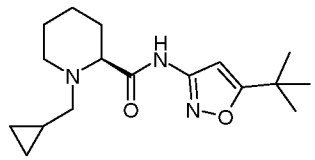
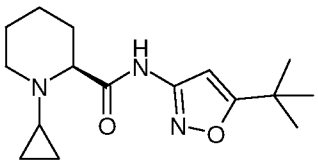
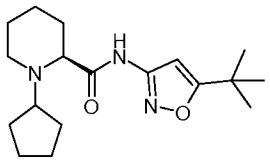
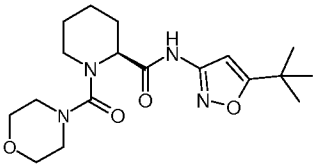
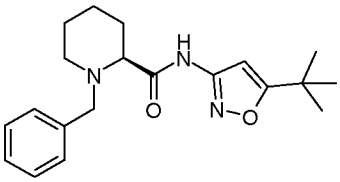
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (6-chloro-benzothiazol-2-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-trifluoromethyl-pyridin-2-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-chloro-benzothiazol-2-yl)-amide
	(S)-1-(Thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(Piperidine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(1-Oxo-1λ4-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(2S,4S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-4-hydroxy-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(2S,4S)-1-(4,4-Difluoro-cyclohexanecarbonyl)-4-hydroxy-piperidine-2-carboxylic acid (5-tert-butyl isoxazol-3-yl)-amide

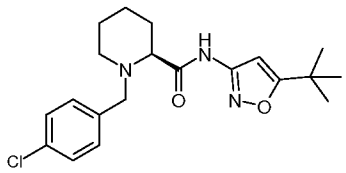
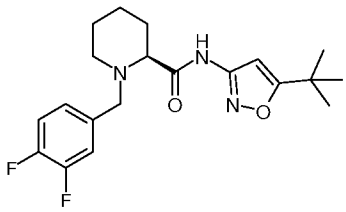
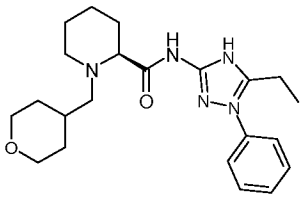
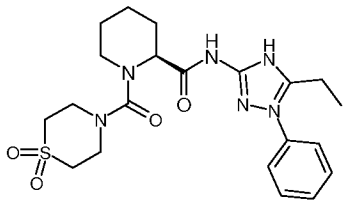
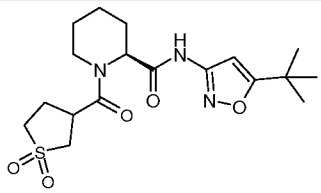
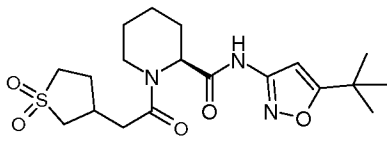
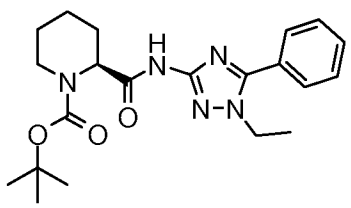
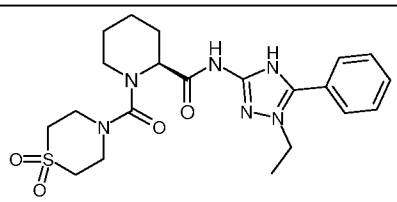
	(S)-1-(4-Methanesulfonyl-piperazine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(4-Acetyl-piperazine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(4-Propionyl-piperazine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-2-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester
	(S)-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-3'-Chloro-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide

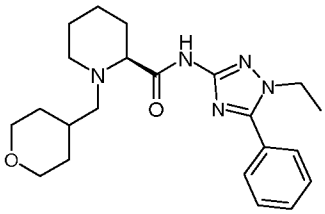
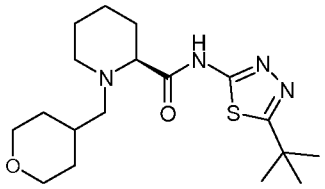
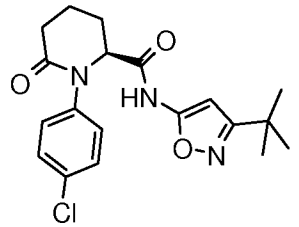
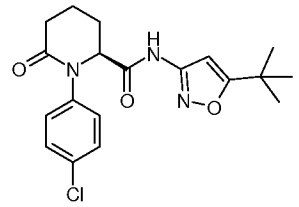
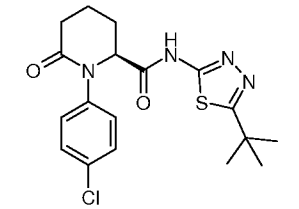
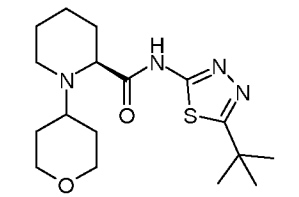
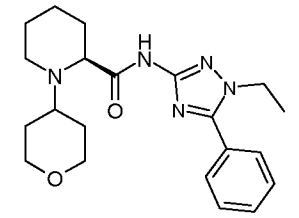
	(S)-1-[2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-acetyl]-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(4-Chloro-phenyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(2-Pyrrolidin-1-yl-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(2-Piperidinyl-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(2-Morpholin-4-yl-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(2S,4S)-3'-Chloro-4-hydroxy-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(4-trans-Methoxy-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide

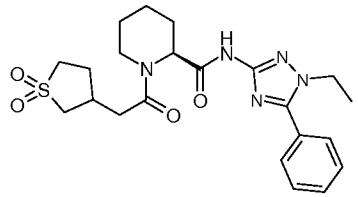
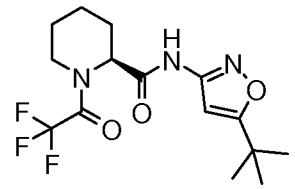
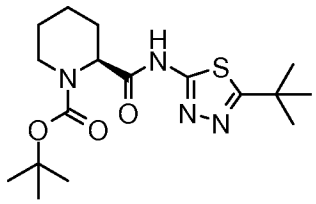
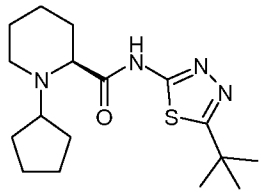
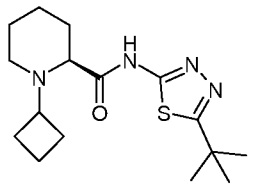
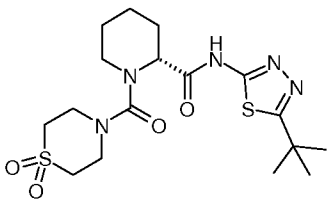
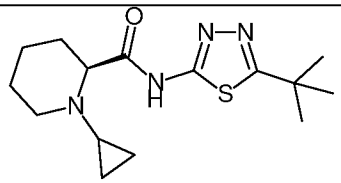
	(S)-1-(4-cis-Methoxy-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(4-Chloro-benzenesulfonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-[2-(4,4-Difluoro-piperidin-1-yl)-acetyl]-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(2-Tetrahydro-pyran-4-yl-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-((R)-2-Tetrahydro-furan-2-yl-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide

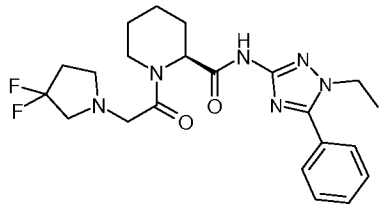
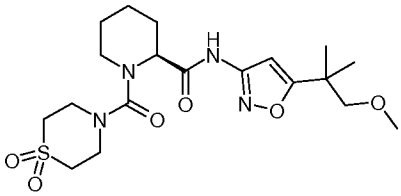
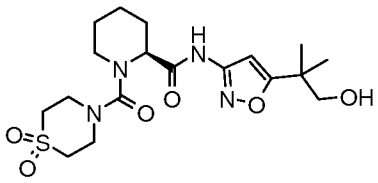
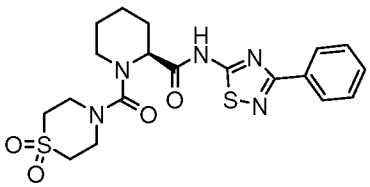
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide
	(S)-1-(4-Chloro-benzoyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(4,4-Difluoro-piperidine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(1,1-Dioxo-hexahydro-1λ6-thiopyran-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(4-Methoxy-benzenesulfonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-[2-(4-Fluoro-piperidin-1-yl)-acetyl]-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-[2-(3,3-Difluoro-pyrrolidin-1-yl)-acetyl]-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-2-(5-Ethyl-4-phenyl-thiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester

	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-ethyl-4-phenyl-thiazol-2-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-ethyl-4-phenyl-thiazol-2-yl)-amide
	(S)-1-Isobutyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-Cyclopropylmethyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-Cyclopropyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-Cyclopentyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(Morpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(benzyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide

	(S)-1-(4-Chloro-benzyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(3,4-Difluoro-benzyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-ethyl-1-phenyl-1H-1,2,4-triazol-3-yl)-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-ethyl-1-phenyl-1H-1,2,4-triazol-3-yl)-amide
	(S)-1-(1,1-Dioxo-tetrahydro-1λ6-thiophene-3-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-[2-(1,1-Dioxo-tetrahydro-1λ6-thiophen-3-yl)-acetyl]-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-2-(1-Ethyl-5-phenyl-1H-1,2,4-triazol-3-ylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (1-ethyl-5-phenyl-1H-1,2,4-triazol-3-yl)-amide

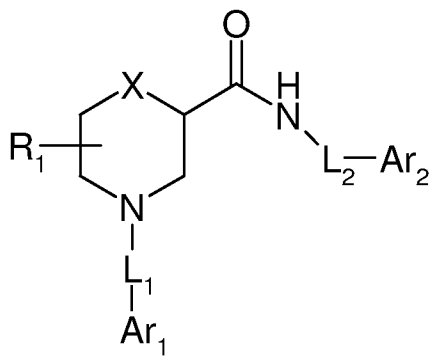
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (1-ethyl-5-phenyl-1H-1,2,4-triazol-3-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide
	(S)-1-(4-Chloro-phenyl)-6-oxo-piperidine-2-carboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide
	(S)-1-(4-Chloro-phenyl)-6-oxo-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-1-(4-Chloro-phenyl)-6-oxo-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (1-ethyl-5-phenyl-1H-1,2,4-triazol-3-yl)-amide

	(S)-1-[2-(1,1-Dioxo-tetrahydro-1λ6-thiophen-3-yl)-acetyl]-piperidine-2-carboxylic acid (1-ethyl-5-phenyl-1H-1,2,4-triazol-3-yl)-amide
	(S)-1-(2,2,2-Trifluoro-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
	(S)-2-(5-tert-Butyl-1,3,4-thiadiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester
	(S)-1-Cyclopentyl-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide
	(S)-1-Cyclobutyl-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide
	(R)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide
	(S)-1-Cyclopropyl-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide

	(S)-1-[2-(3,3-Difluoro-pyrrolidin-1-yl)-acetyl]-piperidine-2-carboxylic acid (1-ethyl-5-phenyl-1H-1,2,4-triazol-3-yl)-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [5-(2-methoxy-1,1-dimethyl-ethyl)-isoxazol-3-yl]-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [5-(2-hydroxy-1,1-dimethyl-ethyl)-isoxazol-3-yl]-amide
	(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-phenyl-1,2,4-thiadiazol-5-yl)-amide

or a pharmaceutically acceptable salt thereof.

In another generic aspect of the invention there is provided a compound of the formula (IB)



(IB)

wherein:

X is O, S, -S(O)- or $-SO_2$;

Ar_1 is chosen from carbocycle, heterocyclyl and heteroaryl each optionally substituted by 1-3 C_{1-10} alkyl which is optionally substituted by halogens, C_{1-10} alkoxy, CN, halogen, NO_2, -$S(O)_m$-C_{1-10} alkyl, -CO_2- C_{1-10} alkyl, -NH(C_{1-5} alkyl)-CO_2-C_{1-10} alkyl, -C(O)-NH(C_{1-5} alkyl), -C(O)-N(C_{1-5} alkyl)$_2$, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)-C(O)-C_{1-10} alkyl, -N(C_{1-5} alkyl)-$S(O)_m$-C_{1-10} alkyl, carbocycle or heterocyclyl;

Ar_2 is chosen from carbocycle, heterocyclyl and heteroaryl each optionally substituted by 1-3 C_{1-10} alkyl which is optionally substituted by halogens, C_{3-10} cycloalkyl, carbocycle, C_{1-10} alkylcarbocycle, heteroaryl, CN or halogen, wherein the C_{1-10} alkyl and carbocycle may be additionally optionally substituted by hydroxyl, C_{1-5} alkoxycarbonyl or C_{1-5} alkoxy;

L_1 and **L_2** are each independently chosen from a bond or C_{1-10} alkyl chain wherein each -CH_2- of said chain is optionally replaced by -O-, C(O), or $S(O)_m$;

wherein each **L_1** and **L_2** where possible is optionally substituted by halogen or C_{1-3} alkyl;

R_1 is chosen from hydrogen, oxo (=O) and OH;

m is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The compound according to the embodiment described immediately above and wherein:

X is O

Ar_1 is chosen from phenyl, C_{3-6} cycloalkyl, tetrahydrofuranyl, tetrahydropyranyl, and pyridinyl, each optionally substituted by 1-3 C_{1-6} alkyl which is optionally substituted by halogens, or halogen;

Ar_2 is chosen from oxazolyl, isoxazolyl and pyridinyl, each optionally substituted by 1-3 C_{1-6} alkyl which is optionally substituted by halogens, or halogen.

The compound according to the embodiment described immediately above and wherein:

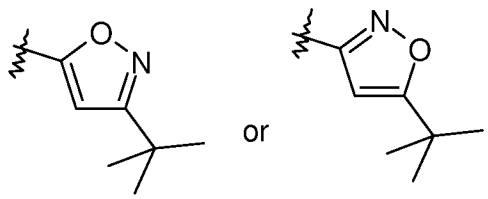
Ar_1 is chosen from phenyl, cyclohexyl, tetrahydropyranyl and pyridinyl, each optionally substituted by 1-3 C_{1-6} alkyl, halogen or trifluoromethyl;

Ar_2 is chosen from isoxazolyl substituted by C_{1-6} alkyl;

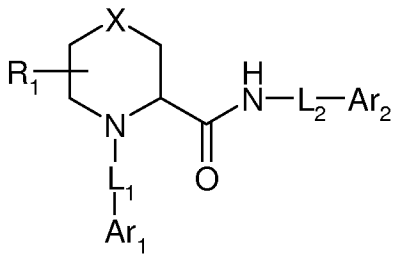
L_1 is a bond or C(O);

The compound according to the embodiment described immediately above and wherein:

Ar_2 is chosen from



In another generic aspect of the invention there is provided a compound of the formula (IIB)



(IIB)

wherein

X is O, S, -S(O)- or $-SO_2$;

Ar_1 is chosen from C_{1-6} alkyl which is optionally substituted by halogens, C_{1-6} alkoxy, carbocycle, heterocyclyl and heteroaryl each optionally substituted by 1-3 C_{1-10} alkyl which is optionally substituted by halogens, C_{1-10} alkoxy, CN, halogen, NO_2, $-S(O)_m-C_{1-10}$ alkyl, $-C(O)-C_{1-10}$ alkyl, $-CO_2-C_{1-10}$ alkyl, C_{1-10} acyl, oxo (=O),$-NH(C_{1-5}$ alkyl)$-CO_2-C_{1-10}$ alkyl, $-C(O)-NH(C_{1-5}$ alkyl), $-C(O)-N(C_{1-5}$ alkyl$)_2$, $-NH(C_{1-5}$ alkyl), $-N(C_{1-5}$ alkyl$)-C(O)-C_{1-10}$ alkyl, $-N(C_{1-5}$ alkyl$)-S(O)_m-C_{1-10}$ alkyl or heterocyclyl the heterocyclyl being further optionally substituted by C_{1-5} alkyl;

Ar_2 is chosen from C_{1-6} alkyl, carbocycle, heterocyclyl and heteroaryl each optionally substituted by halogen, 1-3 C_{1-10} alkyl which is optionally substituted by halogens, alkoxy or hydroxy, carbocycle optionally substituted by C_{1-3} alkyl, aryl which is optionally substituted by halogen, heteroaryl, CN, halogen, C_{1-10} acyl or oxo (=O);

L_1 and **L_2** are each independently chosen from a bond or C_{1-10} alkyl chain wherein each $-CH_2-$ of said chain is optionally replaced by -O-, C(O), $S(O)_m$ or -NH-;

R_1 is chosen from hydrogen, hydroxyl and oxo (=O);

m is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The compound according to the embodiment described immediately above and wherein:

X is O;

Ar_1 is chosen from phenyl, C_{3-6} cycloalkyl, tetrahydrofuranyl, tetrahydropyranyl, and pyridinyl, each optionally substituted by 1-3 C_{1-6} alkyl which is optionally substuituted with halogens, or halogen;

Ar_2 is chosen from oxazolyl, isoxazolyl and pyridinyl, each optionally substituted by 1-3 C_{1-6} alkyl which is optionally substituted by halogens or halogen;

R_1 is hydrogen;

L_1 is a bond, C(O) or $S(O)_2$;

L_2 is a bond.

The compound according to the embodiment described immediately above and wherein:

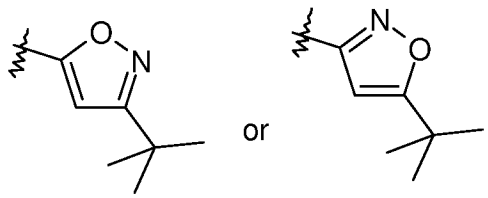
Ar_1 is chosen from phenyl or cyclohexyl, each optionally substituted by 1-3 C_{1-6} alkyl or halogen;

Ar_2 is chosen from isoxazolyl substituted by C_{1-6} alkyl;

L_1 is C(O) or SO_2;

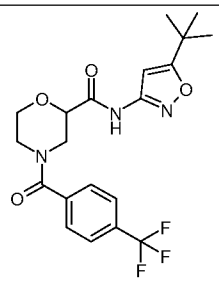
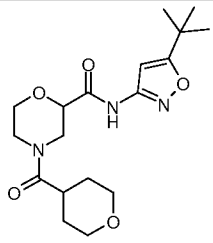
The compound according to the embodiment described immediately above and wherein:

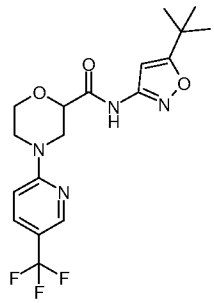
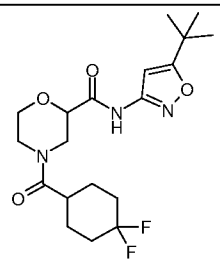
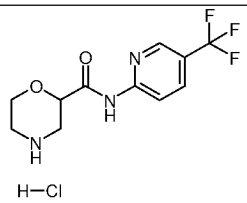
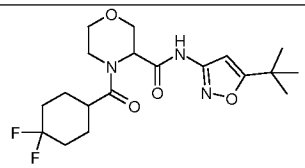
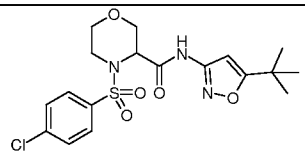
Ar_2 is chosen from



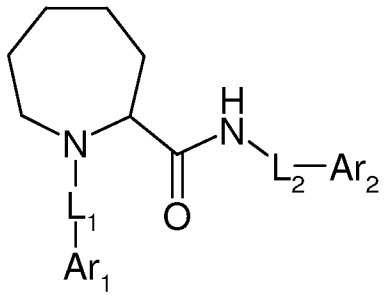
In another embodiment of the invention, there is provided compounds in Table IV, which can be made by the methods and examples shown herein and methods known in the art.

Table IV

Structure	Name
	4-(4-Trifluoromethyl-benzoyl)-morpholine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide
	4-(Tetrahydro-pyran-4-carbonyl)-morpholine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide

	4-(5-Trifluoromethyl-pyridin-2-yl)-morpholine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide
	4-(4,4-Difluoro-cyclohexanecarbonyl)-morpholine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide
	Morpholine-2-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide; hydrochloride
	4-(4,4-Difluoro-cyclohexanecarbonyl)-morpholine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide
	4-(4-Chloro-benzenesulfonyl)-morpholine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide

In another generic aspect of the invention there is provided a compound of the formula (IC)



(IC)

wherein

Ar_1 is chosen from C_{1-6} alkyl which is optionally substituted by halogens, C_{1-6} alkoxy, carbocycle, heterocyclyl and heteroaryl each optionally substituted by 1-3 C_{1-10} alkyl which is optionally substituted by halogens, C_{1-10} alkoxy, CN, halogen, NO_2, $-S(O)_m-C_{1-10}$ alkyl, $-C(O)-C_{1-10}$ alkyl, $-CO_2-C_{1-10}$ alkyl, C_{1-10} acyl, oxo (=O), $-NH(C_{1-5}$ alkyl$)-CO_2-C_{1-10}$ alkyl, $-C(O)-NH(C_{1-5}$ alkyl), $-C(O)-N(C_{1-5}$ alkyl$)_2$, $-NH(C_{1-5}$ alkyl), $-N(C_{1-5}$ alkyl$)-C(O)-C_{1-10}$ alkyl, $-N(C_{1-5}$ alkyl$)-S(O)_m-$ C_{1-10} alkyl and heterocyclyl the heterocyclyl being further optionally substituted by C_{1-5} alkyl;

Ar_2 is chosen from C_{1-6} alkyl, carbocycle, heterocyclyl and heteroaryl each optionally substituted by 1-3 C_{1-10} alkyl which is optionally substituted by halogens, alkoxy or hydroxy, carbocycle which is optionally substituted by C_{1-3} alkyl, aryl which is optionally substituted by halogen, heteroaryl, CN, halogen, C_{1-10} acyl or oxo (=O), wherein the C_{1-6} alkyl and carbocycle may be additionally optionally substituted by hydroxyl;

L_1 and **L_2** are each independently chosen from a bond or C_{1-10} alkyl chain wherein each $-CH_2-$ of said chain is optionally replaced by -O-, C(O), $S(O)_m$ or -NH-;

m is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The compound according to the embodiment described immediately above and wherein:

Ar_1 is chosen from C_{1-6} alkyl which is optionally substituted by halogens, C_{1-6} alkoxyl, phenyl, C_{3-8} cycloalkyl, dioxanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyran-1,1-dioxide, tetrahydrothiofuranyl, tetrahydrothiofuran-1,1-dioxide, thiomorpholinyl, 1-oxo-1λ^4-thiomorpholinyl, 1,1-dioxo-1λ^6-thiomorpholinyl, morpholinyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolidinyl, piperidinyl and piperazinyl, each optionally substituted by 1-3 C_{1-6} alkyl which is optionally substituted by halogens, C_{1-6} alkoxy, CN, halogen, oxo, -C(O)-C_{1-10} alkyl, -$S(O)_2$-C_{1-3} alkyl or -CO_2-C_{1-4} alkyl;

Ar_2 is chosen from C_{1-6} alkyl, cyclohexyl, phenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, imidazolyl, thienyl, thiadiazolyl, triazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, benzofuranyl and benzothienyl, each optionally substituted by 1-3 C_{1-6} alkyl which is optionally substituted by halogen, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, phenyl optionally substituted by halogens, CN, halogens, C_{1-6} alkoxy or hydroxy;

L_1 is a bond or C_{1-3} alkyl chain wherein each -CH_2- of said chain is optionally replaced by C(O) or $S(O)_m$;

L_2 is a bond or C_{1-5} alkyl chain wherein each -CH_2- of said chain is optionally replaced by -O- or $S(O)_m$.

The compound according to any of the embodiments described above and wherein:

Ar_1 is chosen from phenyl, tetrahydropyranyl, thiomorpholinyl, 1-Oxo-1λ^4-thiomorpholinyl, and 1,1-dioxo-1λ^6-thiomorpholinyl, each optionally substituted halogen.

The compound according to any of the embodiments described above and wherein:

Ar_2 is isoxazolyl substituted by 1-3 C_{1-6} alkyl group.

The compound according to any of the embodiments described above and wherein:

L_1 is a bond or C_{1-3} alkyl chain wherein each $-CH_2-$ of said chain is optionally replaced by C(O);

L_2 is a bond.

The compound according to any of the embodiments described above and wherein:

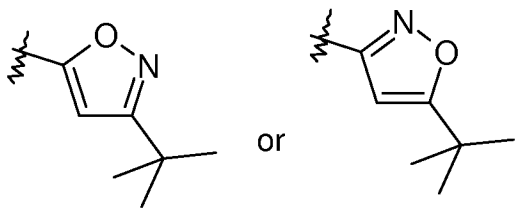
Ar_1 is chosen from phenyl, tetrahydropyranyl, thiomorpholinyl, 1-Oxo-1λ^4-thiomorpholinyl, and 1,1-dioxo-1λ^6-thiomorpholinyl, each optionally substituted chloro;

Ar_2 is isoxazolyl substituted by 1-3 C_{1-6} alkyl group;

L_1 is a bond or C_{1-2} alkyl chain wherein each $-CH_2-$ of said chain is optionally replaced by C(O);

L_2 is a bond.

The compound according to any of the embodiments described above and wherein:
Ar_2 is



The compound according to any of the embodiments described above and wherein:

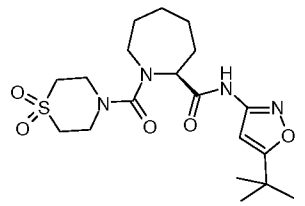
Ar_1 is chosen from phenyl optionally substituted chloro, tetrahydropyranyl, and 1,1-dioxo-1λ^6-thiomorpholinyl;

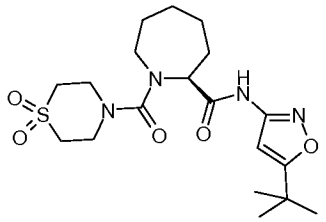
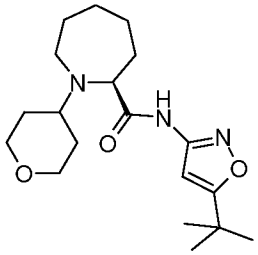
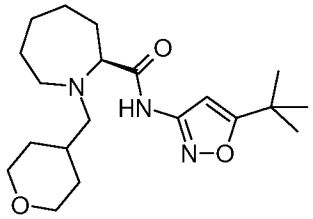
L_1 is a bond or -CH_2-;

L_2 is a bond.

In another embodiment of the invention, there is provided compounds in Table V, which can be made by the methods and examples shown herein and methods known in the art.

Table V

Structure	Name
	(S)-1-(4-Chloro-phenyl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide

	(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-yl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide
	(S)-1-(Tetrahydro-pyran-4-ylmethyl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide

Of the above compounds, the following are preferred CB2 agonists:

Table VI

Compound	***CB2 CAMP @ EC50 nM (mean)***
3'-Chloro-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	113
1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	215
1-(Tetrahydro-pyran-4-carbonyl)-piperidine-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	205
1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	23

(R)-3'-Chloro-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	54
1-(4-Trifluoromethyl-benzoyl)-piperidine-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	16
1-(4-Chloro-benzyl)-piperidine-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	2.7
1-(4-Chloro-benzenesulfonyl)-piperidine-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	12
(R)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	42
(S)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	119
1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	18
1-(Tetrahydro-pyran-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	274
1-(4-Trifluoromethyl-benzoyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	395
1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	11
(R)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	64
(S)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	4.6
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	7.9
(R)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	60
(S)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide	1

(S)-3'-Chloro-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-1,2'-bipyridinyl-2-carboxylic acid (3-phenyl-1,2,4-thiadiazol-5-yl)-amide	11
(S)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide	282
(S)-1-Benzoyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	47
(S)-1-(4-Fluoro-benzoyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	2.2
S)-1-Cyclohexanecarbonyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	15
(S)-1-Cyclopentanecarbonyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	14
S)-1-Cycloheptanecarbonyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	8.2
(S)-1-(3-Chloro-benzoyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	44
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide	53
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-chloro-1H-benzimidazol-2-yl)-amide	77
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-sec-butyl-isoxazol-5-yl)-amide	105
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-isopropyl-isoxazol-5-yl)-amide	170
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (4-phenyl-thiazol-2-yl)-amide	17
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [2-(2-chloro-6-fluoro-benzylsulfanyl)-ethyl]-amide	130
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-cyclohexyl-isoxazol-5-yl)-amide	59

(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [3-(1-methyl-cyclopropyl)-isoxazol-5-yl]-amide	9.8
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-chloro-benzothiazol-2-yl)-amide	23
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-cyclopentyl-isoxazol-5-yl)-amide	42
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-tert-butyl-oxazol-2-yl)-amide	2.4
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-phenyl-1,2,4-thiadiazol-5-yl)-amide	1.2
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-fluoro-3-trifluoromethyl-phenyl)-amide	26
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-fluoro-4-trifluoromethyl-phenyl)-amide	1.8
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-isopropyl-1,2,4-thiadiazol-5-yl)-amide	208
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-cyclohexyl-thiazol-2-yl)-amide	9
(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (5-chloro-benzothiazol-2-yl)-amide	206
(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (4-cyclohexyl-thiazol-2-yl)-amide	65
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-tert-butyl-isothiazol-5-yl)-amide	0.3
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-tert-butyl-1,2,4-thiadiazol-5-yl)-amide	12
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-tert-butyl-thiazol-2-yl)-amide	13
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid [4-(3,4-difluoro-phenyl)-thiazol-2-yl]-amide	3.6

(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-phenyl-1,2,4-thiadiazol-3-yl)-amide	14
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-fluoro-benzothiazol-2-yl)-amide	1.3
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-phenyl-thiazol-2-yl)-amide	9.9
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide	69
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (6-chloro-benzothiazol-2-yl)-amide	131
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-trifluoromethyl-pyridin-2-yl)-amide	290
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-chloro-benzothiazol-2-yl)-amide	0.2
(S)-1-(Thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	7
(S)-1-(Piperidine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	22
(S)-1-(1-Oxo-1λ^4-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	151
(S)-1-(4-Acetyl-piperazine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	460
(S)-1-(4-Propionyl-piperazine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	332
(S)-2-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester	279
(S)-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	0.093
(S)-3'-Chloro-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	0.18

(S)-1-(Tetrahydro-pyran-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	83
(S)-1-[2-(1,1-Dioxo-1λ^6-thiomorpholin-4-yl)-acetyl]-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	161
(S)-1-(4-Chloro-phenyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	0.19
(S)-1-(2-Pyrrolidin-1-yl-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	431
(S)-1-(2-Morpholin-4-yl-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	188
(2S,4S)-3'-Chloro-4-hydroxy-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	0.3
(S)-1-(4-cis-Methoxy-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	43
(S)-1-(4-Chloro-benzenesulfonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	21
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	0.41
(S)-1-[2-(4,4-Difluoro-piperidin-1-yl)-acetyl]-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	34
(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	33
(S)-1-(2-Tetrahydro-pyran-4-yl-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	17
(S)-1-((R)-2-Tetrahydro-furan-2-yl-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	94
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide	18
(S)-1-(4-Chloro-benzoyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	334

(S)-1-(4,4-Difluoro-piperidine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	3.7
(S)-1-(1,1-Dioxo-hexahydro-1λ6-thiopyran-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	301
(S)-1-(4-Methoxy-benzenesulfonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	27
(S)-1-[2-(4-Fluoro-piperidin-1-yl)-acetyl]-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	75
(S)-1-[2-(3,3-Difluoro-pyrrolidin-1-yl)-acetyl]-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	2.9
(S)-2-(5-Ethyl-4-phenyl-thiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester	180
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-ethyl-4-phenyl-thiazol-2-yl)-amide	5.2
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-ethyl-4-phenyl-thiazol-2-yl)-amide	0.55
(S)-1-Isobutyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	1.5
(S)-1-Cyclopropylmethyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	0.94
(S)-1-Cyclopropyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	8.5
(S)-1-Cyclopentyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	9.4
(S)-1-(Morpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	132
(S)-1-(benzyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	1.9
(S)-1-(4-Chloro-benzyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	1.7

(S)-1-(3,4-Difluoro-benzyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	0.58
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-ethyl-1-phenyl-1H-1,2,4-triazol-3-yl)-amide	19
(S)-1-(1,1-Dioxo-tetrahydro-1λ^6-thiophene-3-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	17
(S)-1-[2-(1,1-Dioxo-tetrahydro-1λ^6-thiophen-3-yl)-acetyl]-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	7.7
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (1-ethyl-5-phenyl-1H-1,2,4-triazol-3-yl)-amide	135
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (1-ethyl-5-phenyl-1H-1,2,4-triazol-3-yl)-amide	8.6
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide	1.6
(S)-1-(4-Chloro-phenyl)-6-oxo-piperidine-2-carboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide	181
(S)-1-[2-(1,1-Dioxo-tetrahydro-1λ^6-thiophen-3-yl)-acetyl]-piperidine-2-carboxylic acid (1-ethyl-5-phenyl-1H-1,2,4-triazol-3-yl)-amide	365
(S)-1-(2,2,2-Trifluoro-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	48
(S)-2-(5-tert-Butyl-1,3,4-thiadiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester	495
(S)-1-Cyclobutyl-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide	140
(S)-1-Cyclopropyl-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide	485
(S)-1-[2-(3,3-Difluoro-pyrrolidin-1-yl)-acetyl]-piperidine-2-carboxylic acid (1-ethyl-5-phenyl-1H-1,2,4-triazol-3-yl)-amide	262
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [5-(2-methoxy-1,1-dimethyl-ethyl)-isoxazol-3-yl]-amide	162

(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-phenyl-1,2,4-thiadiazol-5-yl)-amide	28
4-(4-Trifluoromethyl-benzoyl)-morpholine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	85
4-(4-Chloro-benzenesulfonyl)-morpholine-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	34
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [3-(4-methoxy-phenyl)-[1,2,4]thiadiazol-5-yl]-amide	20
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [3-(4-fluoro-phenyl)-[1,2,4]thiadiazol-5-yl]-amide	22
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-fluoro-benzothiazol-2-yl)-amide	56
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5,6-difluoro-benzothiazol-2-yl)-amide	448
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (4-chloro-benzothiazol-2-yl)-amide	27
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [4-(4-chloro-phenyl)-thiazol-2-yl]-amide	9.9
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [4-(3,4-difluoro-phenyl)-thiazol-2-yl]-amide	26
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [4-(2,4-difluoro-phenyl)-thiazol-2-yl]-amide	22
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [4-(4-fluoro-phenyl)-thiazol-2-yl]-amide	38
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (4-fluoro-benzothiazol-2-yl)-amide	59
(S)-1-(4-Chloro-phenyl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	0.4
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	15

(S)-1-(Tetrahydro-pyran-4-yl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	0.18
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	0.03

In all the compounds disclosed hereinabove in this application, in the event the nomenclature is in conflict with the structure, it shall be understood that the compound is defined by the structure.

The invention also relates to pharmaceutical preparations, containing as active substance one or more compounds of the invention, or the pharmaceutically acceptable derivatives thereof, optionally combined with conventional excipients and/or carriers.

Compounds of the invention also include their isotopically-labelled forms. An isotopically-labelled form of an active agent of a combination of the present invention is identical to said active agent but for the fact that one or more atoms of said active agent have been replaced by an atom or atoms having an atomic mass or mass number different from the atomic mass or mass number of said atom which is usually found in nature. Examples of isotopes which are readily available commercially and which can be incorporated into an active agent of a combination of the present invention in accordance with well established procedures, include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, *e.g.*, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. An active agent of a combination of the present invention, a prodrug thereof, or a pharmaceutically acceptable salt of either which contains one or more of the above-mentioned isotopes and/or other isotopes of other atoms is contemplated to be within the scope of the present invention.

The invention includes the use of any compounds of described above containing one or more asymmetric carbon atoms may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Isomers shall be defined as being

enantiomers and diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be in the R or S configuration, or a combination of configurations.

Some of the compounds of the invention can exist in more than one tautomeric form. The invention includes methods using all such tautomers.

All terms as used herein in this specification, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. For example, "C_{1-4}alkoxy" is a C_{1-4}alkyl with a terminal oxygen, such as methoxy, ethoxy, propoxy, butoxy. All alkyl, alkenyl and alkynyl groups shall be understood as being branched or unbranched where structurally possible and unless otherwise specified. Other more specific definitions are as follows:

Carbocyclic or cycloalkyl groups include hydrocarbon rings containing from three to twelve carbon atoms. These carbocyclic or cycloalkyl groups may be either aromatic or non-aromatic ring systems. The non-aromatic ring systems may be mono- or polyunsaturated. Preferred carbocycles include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptanyl, cycloheptenyl, phenyl, indanyl, indenyl, benzocyclobutanyl, dihydronaphthyl, tetrahydronaphthyl, naphthyl, decahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl. Certain terms for cycloalkyl such as cyclobutanyl and cyclobutyl shall be used interchangeably.

The term "heterocycle" refers to a stable nonaromatic 4-8 membered (but preferably, 5 or 6 membered) monocyclic or nonaromatic 8-11 membered bicyclic or spirocyclic heterocycle radical which may be either saturated or unsaturated. Each heterocycle consists of carbon atoms and one or more, preferably from 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulfur. The heterocycle may be attached by any atom of the cycle, which results in the creation of a stable structure.

The term "heteroaryl" shall be understood to mean an aromatic 5-8 membered monocyclic or 8-11 membered bicyclic ring containing 1-4 heteroatoms such as N,O and S.

Unless otherwise stated, heterocycles and heteroaryl include but are not limited to, for example furanyl, pyranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, tetrahydropyranyl, dioxanyl, tetrahydrofuranyl, tetrahydrothiopyranyl, tetrahydrothienyl, tetrahydrothiopyranyl 1,1-dioxide, tetrahydrothienyl 1,1-dioxide, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, thiazolyl, pyrazolyl, pyrrolyl, imidazolyl, thienyl, thiadiazolyl, thiomorpholinyl, 1,1-dioxo-$1\lambda^6$-thiomorpholinyl, morpholinyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolidinyl, piperidinyl, piperazinyl, quinolinyl, Dihydro-2H-quinolinyl, isoquinolinyl, quinazolinyl, indazolyl, indolyl, isoindolyl, benzofuranyl, benzopyranyl and benzodioxolyl.

The term "heteroatom" as used herein shall be understood to mean atoms other than carbon such as O, N, S and P.

In all alkyl groups or carbon chains one or more carbon atoms can be optionally replaced by heteroatoms: O, S or N, it shall be understood that if N is not substituted then it is NH, it shall also be understood that the heteroatoms may replace either terminal carbon atoms or internal carbon atoms within a branched or unbranched carbon chain. Such groups can be substituted as herein above described by groups such as oxo to result in definitions such as but not limited to: alkoxycarbonyl, acyl, amido and thioxo.

The term "aryl" as used herein shall be understood to mean aromatic carbocycle as defined herein. Each aryl unless otherwise specified includes it's partially or fully hydrogenated derivative. For example, naphthyl may include its hydrogenated derivatives such as tetrahydranaphthyl. Other partially or fully hydrogenated derivatives of the aryl compounds described herein will be apparent to one of ordinary skill in the art.

As used herein, "nitrogen" and "sulfur" include any oxidized form of nitrogen and sulfur and the quaternized form of any basic nitrogen. For example, for an -S-C_{1-6} alkyl radical, unless otherwise specified, this shall be understood to include -S(O)-C_{1-6} alkyl and -$S(O)_2$-C_{1-6} alkyl.

The term "alkyl" refers to a saturated aliphatic radical containing from one to ten carbon atoms or a mono- or polyunsaturated aliphatic hydrocarbon radical containing from two to twelve carbon atoms. The mono- or polyunsaturated aliphatic hydrocarbon radical containing at least one double or triple bond, respectively. "Alkyl" refers to both branched and unbranched alkyl groups. It should be understood that any combination term using an "alk" or "alkyl" prefix refers to analogs according to the above definition of "alkyl". For example, terms such as "alkoxy", "alkythio" refer to alkyl groups linked to a second group via an oxygen or sulfur atom. "Alkanoyl" refers to an alkyl group linked to a carbonyl group (C=O).

The term "halogen" as used in the present specification shall be understood to mean bromine, chlorine, fluorine or iodine, preferably fluorine. The definitions "halogenated", "partially or fully halogenated"; partially or fully fluorinated; "substituted by one or more halogen atoms", includes for example, mono, di or tri halo derivatives on one or more carbon atoms. For alkyl, a nonlimiting example would be -CH_2CHF_2, -CF_3 etc.

Each alkyl, carbocycle, heterocycle or heteroaryl, or the analogs thereof, described herein shall be understood to be optionally partially or fully halogenated.

The compounds of the invention are only those which are contemplated to be 'chemically stable' as will be appreciated by those skilled in the art. For example, a compound which would have a 'dangling valency', or a 'carbanion' are not compounds contemplated by the inventive methods disclosed herein.

The invention includes pharmaceutically acceptable derivatives of compounds of the invention. A "pharmaceutically acceptable derivative" refers to any pharmaceutically acceptable salt or ester, or any other compound which, upon administration to a patient, is capable of providing (directly or indirectly) a compound useful for the invention, or a pharmacologically active metabolite or pharmacologically active residue thereof. A pharmacologically active metabolite shall be understood to mean any compound of the invention capable of being metabolized enzymatically or chemically. This includes, for example, hydroxylated or oxidized derivative compounds of the invention.

Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfuric, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfuric and benzenesulfonic acids. Other acids, such as oxalic acid, while not themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (*e.g.*, sodium), alkaline earth metal (*e.g.*, magnesium), ammonium and N-$(C_1$-C_4 alkyl$)_4^+$ salts.

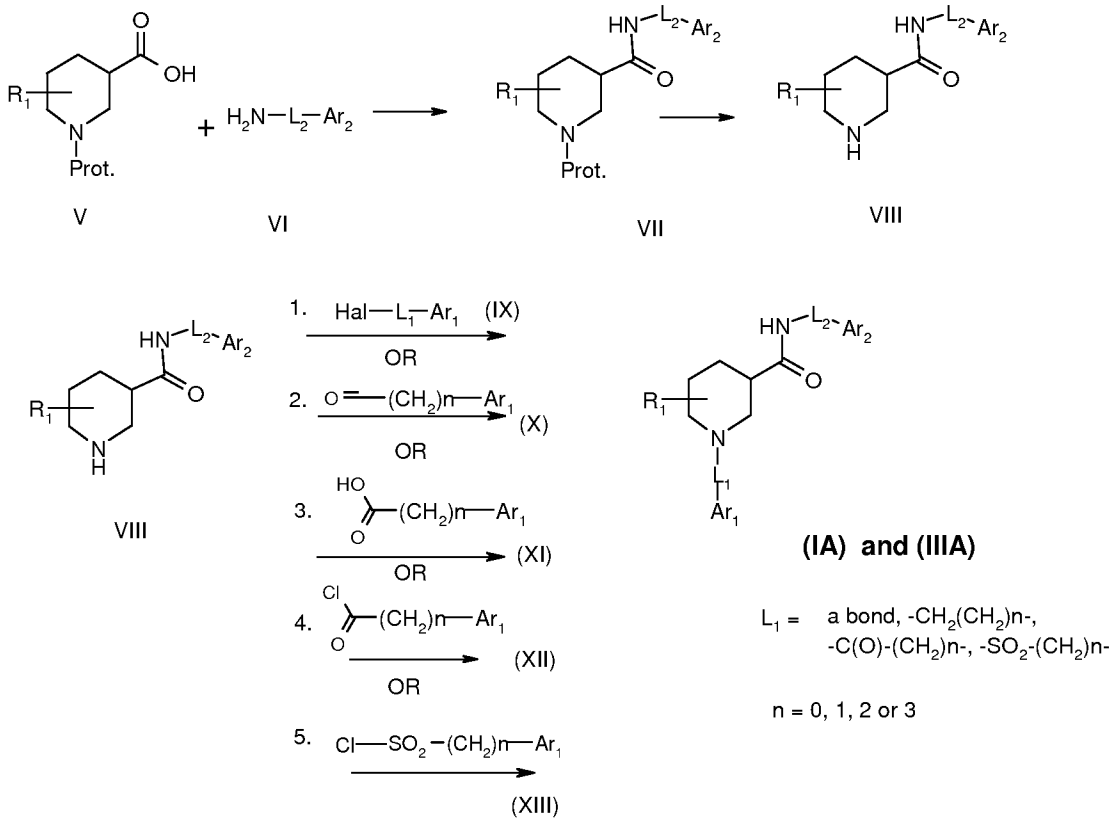
In addition, within the scope of the invention is use of prodrugs of compounds of the invention. Prodrugs include those compounds that, upon simple chemical transformation, are modified to produce compounds of the invention. Simple chemical transformations include hydrolysis, oxidation and reduction. Specifically, when a prodrug is administered to a patient, the prodrug may be transformed into a compound disclosed hereinabove, thereby imparting the desired pharmacological effect.

The compounds of the invention may be made using the general synthetic methods described below, which also constitute part of the invention.

GENERAL SYNTHETIC METHODS

The invention also provides processes for making compounds of Formula (IA), (IIA), (IIIA), (IVA), (IB), (IIB) and (IC). In all Schemes, unless specified otherwise, R_1, L_1, L_2, Ar_1, Ar_2 and X in the Formulas below shall have the meaning of R_1, L_1, L_2, Ar_1, Ar_2 and X in Formula (IA), (IIA), (IIIA), (IVA), (IB), (IIB) and (IC) of the invention described herein above.
Optimum reaction conditions and reaction times may vary depending on the particular reactants used. Unless otherwise specified, solvents, temperatures, pressures, and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Synthetic Examples section. Typically, reaction progress may be monitored by thin layer chromatography (TLC), if desired, and intermediates and products may be purified by chromatography on silica gel and/or by recrystallization.
The examples which follow are illustrative and, as recognized by one skilled in the art, particular reagents or conditions could be modified as needed for individual compounds without undue experimentation. Starting materials and intermediates used, in the Schemes below, are either commercially available or easily prepared from commercially available materials by those skilled in the art.

Compounds of Formula (IA) and (IIIA) may be synthesized by the method outlined in scheme 1.



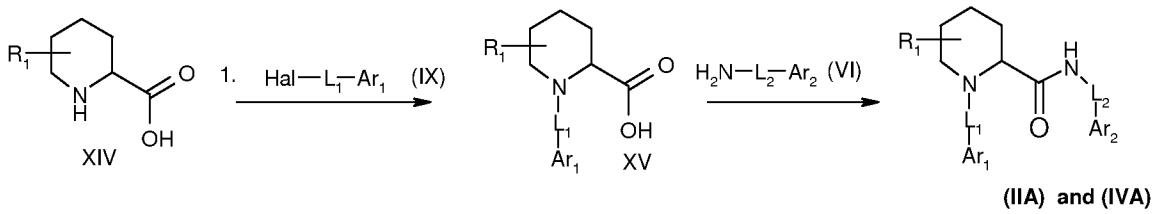
Scheme1

As illustrated in scheme 1, reaction of an appropriately substituted piperidine-3-carboxylic acid (V) with an amine of formula (VI), under standard coupling conditions and as described in the examples, provides an amide of formula (VII). Prot. = amine protecting group, such as BOC. Reaction of the intermediate (VII) with an acid such as hydrochloric acid, in a suitable solvent, provides the deprotected amine intermediate (VIII). Reaction of the intermediate (VIII) with a suitable halide Hal-L_1 –Ar_1 (IX), wherein Hal = F, Cl, Br or I, in a suitable solvent, in the presence of a suitable base, provides a compound of Formula (I). Intermediate (VIII) may also be reacted with a carbonyl compound of formula (X) under reductive amination conditions, to provide a compound of Formula (IA).

Alternatively, reaction of the intermediate (VIII) with an acid of formula (XI) under standard coupling conditions, provides a compound of Formula (I). Reaction of intermediate (VIII)

with an acid chloride of formula (XII) or a sulfonyl chloride of formula (XIII), under standard reaction conditions, provides the corresponding compound of Formula (IA).
Compounds of Formula (IIA) and (IVA) may be synthesized using the procedure outlined in scheme 1, and as described in the examples, by using the appropriate piperidine -2- carboxylic acid staring material instead of the piperidine -3- carboxylic acid starting material (V).

Compounds of Formula (IIA) and (IVA) may be prepared according to scheme 2.

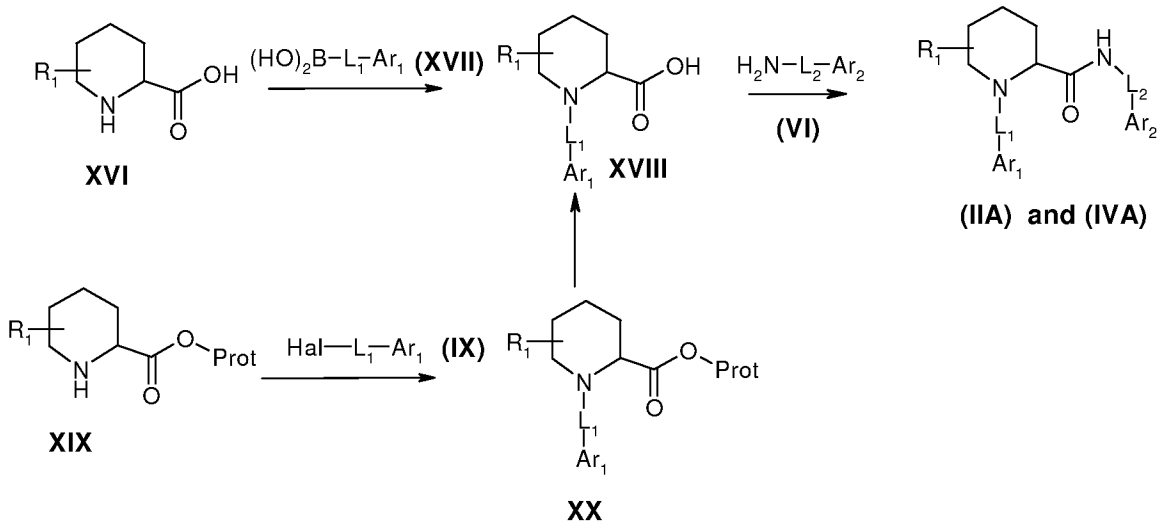


Scheme 2

As outlined in scheme 2, reaction of the piperidine-2 carboxylic acid starting material of formula (XIV) with a suitable halide Hal-L_1 –Ar_1 (IX), wherein Hal = F, Cl, Br or I, in a suitable solvent, in the presence of a suitable base, provides a compound of formula (XV). Reaction of intermediate (XV) with an amine of formula (VI), under standard coupling conditions and as described in coupling methods in examples, provides a compound of Formula (IIA).

Compounds of Formula (IA) and (IIIA) may be synthesized using the procedure outlined in scheme 2, by using the appropriate piperidine -3 carboxylic acid staring material instead of the piperidine -2 carboxylic acid starting material (XIV).

Compounds of Formula (IIA) and (IVA) may be made according to scheme 3.

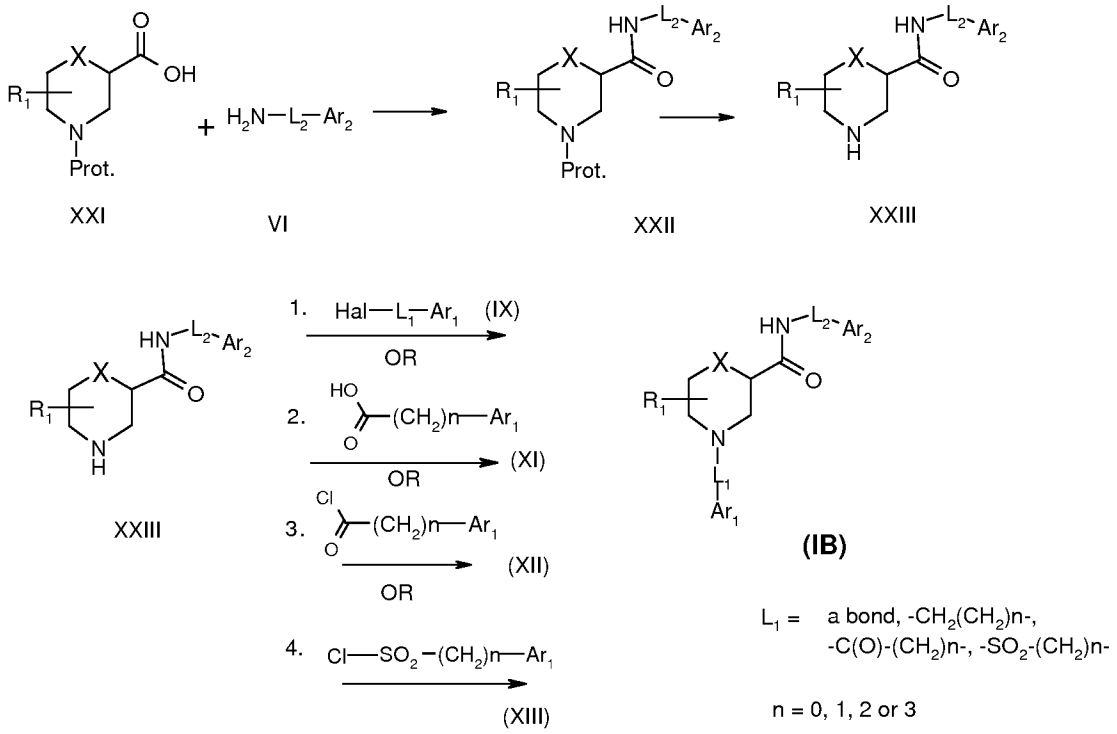


Scheme 3

As illustrated in scheme 3, reaction of an appropriately substituted piperidine -2 carboxylic acid (XVI) with a boronic acid or ester of formula (XVII), under standard arylation conditions, provides an acid of formula (XVIII). Alternately, the intermediate of formula (XVIII) can be prepared by reacting a compound of formula (XIX) with a suitable halide Hal-L_1-Ar_1 (IX), wherein Hal = F, Cl, Br or I, in a suitable solvent, to afford ester of formula (XX). Prot = acid protecting group, such as tert-butyl ester. Hydrolysis of the compound of formula (XX) under standard conditions, provides an acid of formula (XVIII). Reaction of acid (XVIII) with an amine of formula (VI), under standard coupling conditions provides a compound of Formula (IIA).

Compounds of Formula (IVA) may also be prepared by scheme 3 by using the appropriately substituted starting material (XVI).

Compounds of Formula (IB) may be synthesized by the method outlined in scheme 4.

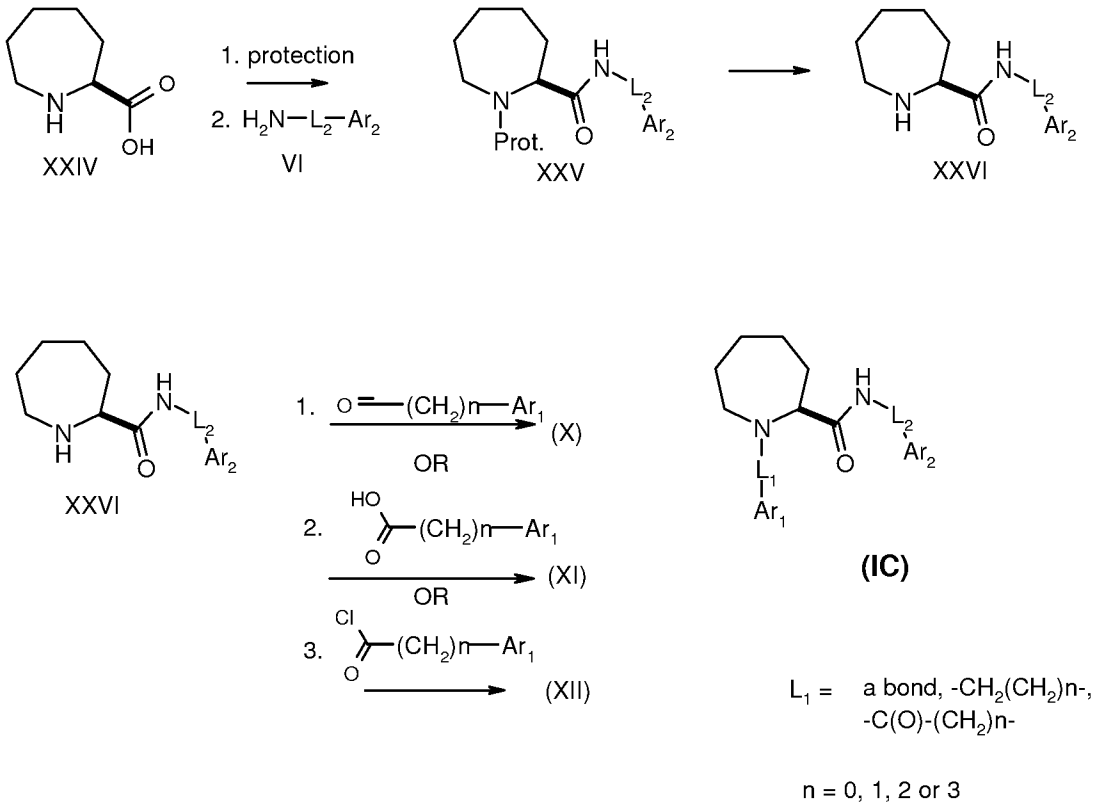


Scheme 4

As illustrated in scheme 4, reaction of an appropriately substituted morpholine-2-carboxylic acid (XXI) with an amine of formula (VI), under standard coupling conditions and as described in the examples, provides an amide of formula (XXII). Prot. = amine protecting group, such as BOC. Reaction of the intermediate (XXII) with an acid such as hydrochloric acid, in a suitable solvent, provides the deprotected amine intermediate (XXIII). Reaction of the intermediate (XXIII) with a suitable halide Hal-L_1 –Ar_1 (IX), wherein Hal = F, Cl, Br or I, in a suitable solvent, in the presence of a suitable base, provides a compound of Formula (IB). Alternatively, reaction of the intermediate (XXIII) with an acid of formula (XI) under standard coupling conditions, provides a compound of Formula (IB). Reaction of intermediate (XXIII) with an acid chloride of formula (XII) or a sulfonyl chloride of formula (XIII), under standard reaction conditions, provides the corresponding compound of Formula (IB).

Compounds of Formula (IIB) may be synthesized using the procedure outlined in scheme 4, and as described in the examples, by using the appropriate morpholine -3- carboxylic acid staring material instead of the morpholine -2- carboxylic acid starting material (XXI).

Compounds of Formula IC may be prepared by the method outlined in scheme 5



Scheme 5

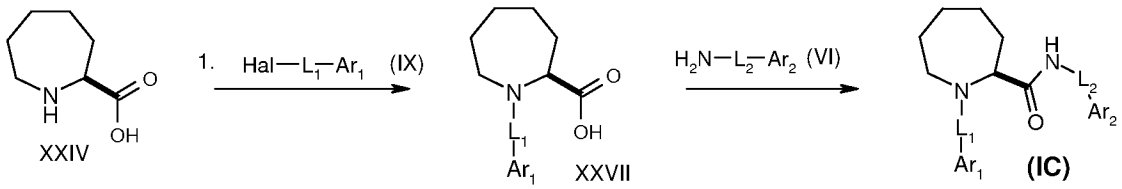
Starting acid of formula XXIV is prepared by adaptation of the following literature:

Dutton,F. E.; Lee, B. H.; Johnson,S. S.;Coscarelli, E. M.;Lee, P. H. *J. Med. Chem.* **2003,** *46,* 2057-2073

As illustrated in scheme 5, reaction of an azepine carboxylic acid of formula (XXIV), after protection of the nitrogen with standard groups, a with an amine of formula (VI), under

standard coupling conditions and as described in the examples, provides an amide of formula (XXV). Prot. = amine protecting group, such as BOC. Reaction of the intermediate (XXV) with an acid such as hydrochloric acid, in a suitable solvent, provides the deprotected amine intermediate (XXVI). Reaction of the intermediate (XXVI) with a carbonyl compound of formula (X) under reductive amination conditions, provides a compound of Formula (IC). Alternatively, reaction of the intermediate (XXVI) with an acid of formula (XI) under standard coupling conditions, provides a compound of Formula (IC). Reaction of intermediate (XXVI) with an acid chloride of formula (XII), under standard reaction conditions, provides the corresponding compound of Formula (IC).

Compounds of Formula (IIA) and (IVA) may be prepared according to scheme 2.



Scheme 6

As outlined in scheme 6, reaction of the azepine carboxylic acid starting material of formula (XXIV) with a suitable halide Hal-L_1 –Ar_1 (IX), wherein Hal = F, Cl, Br or I, in a suitable solvent, in the presence of a suitable base, provides a compound of formula (XXVII). Reaction of intermediate (XXVII) with an amine of formula (VI), under standard coupling conditions provides a compound of Formula (IC)

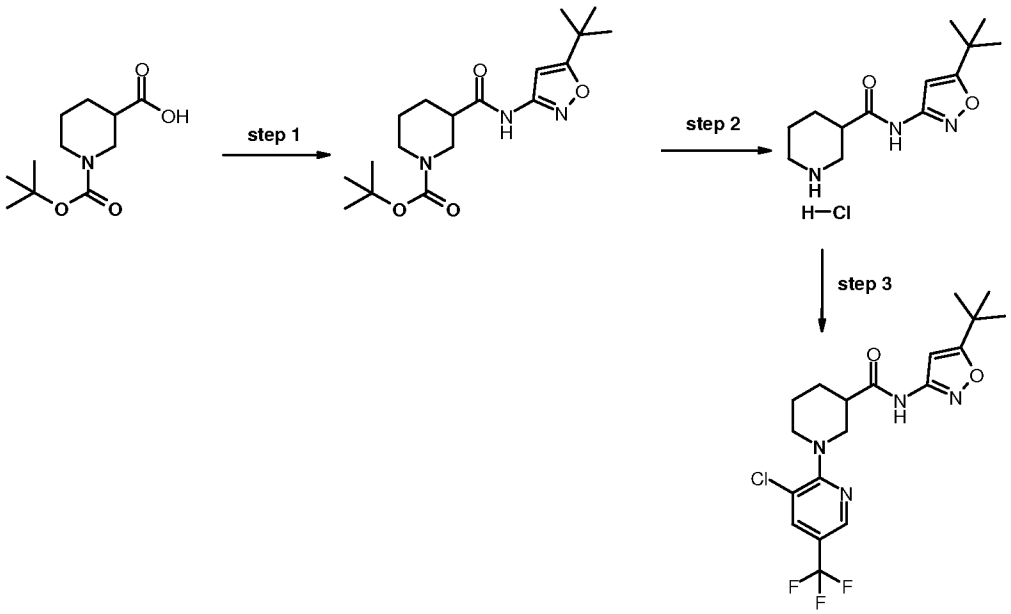
Further modification of the initial product of Formula (IA), (IIA), (IIIA), (IVA), (IB), (IIB) and (IC) by methods known to one skilled in the art and illustrated in the examples below, provides additional compounds of this invention.

EXAMPLES

Compounds of Formula (IA) and (IIIA)

Method A

Synthesis of 3'-Chloro-5'-trifluoromethyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide (Example 1)



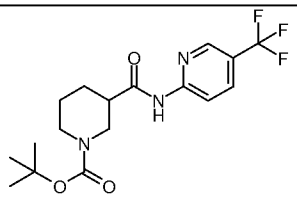
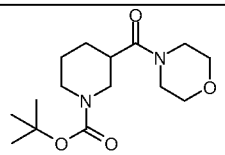
Step 1: Synthesis of 3-(5-*tert*-Butyl-isoxazol-3-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester

To a cold (5°C) solution of piperidine-1,3-dicarboxylic acid 1-*tert*-butyl ester (1g; 4.362mmol) and 3-amino-5-t-butylisoxazole (589mg; 4.2mmol) in anhydrous pyridine (12mL) is added phosphorus oxychloride (0.393mL; 4.362mmol). The reaction mixture is stirred at room temperature for 30 minutes. The mixture is quenched with saturated NH4Cl aqueous solution and extracted with ethyl acetate 3 times. The organics are combined and washed with brine, dried over Na2SO4, filtered and concentrated *in vacuo*. Purification by

flash chromatography on silica using methanol/methylene chloride provides the title compound, m/z 352 [M+H$^+$].

Amide intermediates in Table 1 are made in a similar manner.

Table 1

Structure	Name	m/z [M+H$^+$]
	3-(5-Trifluoromethyl-pyridin-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	374
	3-(Morpholine-4-carbonyl)-piperidine-1-carboxylic acid *tert*-butyl ester	299

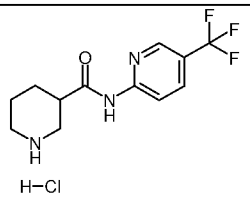
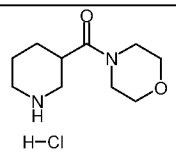
Step 2: Synthesis of piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide; hydrochloride

To a solution of 3-(5-*tert*-Butyl-isoxazol-3-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester (620mg; 1.764mmol) in methylene chloride (20mL) is added 4N HCl in dioxanes (1.8mL; 7.2mmol). The reaction mixture is left stirring at room temperature for 1 hour. The mixture is concentrated *in vacuo* to provide the title compound, m/z 252 [M+H$^+$].

Intermediates in Table 2 are made in a similar manner.

Table 2

Structure	Name	m/z [M+H$^+$]

	Piperidine-3-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide; hydrochloride	274
	Morpholin-4-yl-piperidin-3-yl-methanone; hydrochloride	199

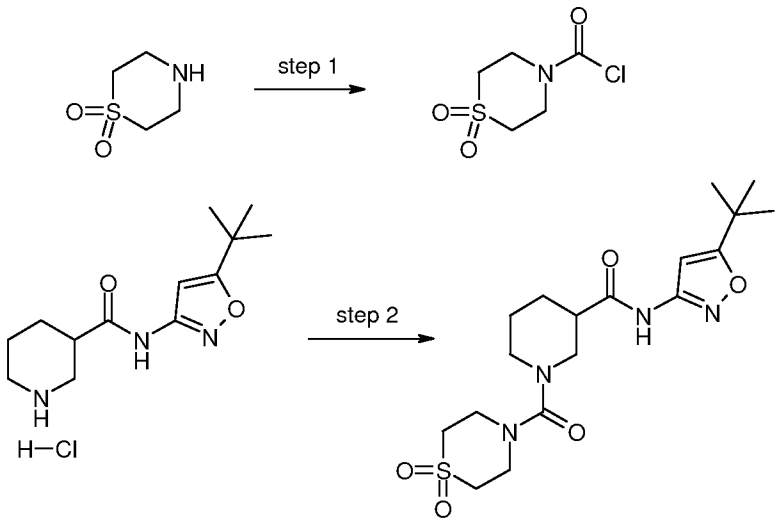
Step 3: Synthesis of 3'-Chloro-5'-trifluoromethyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide

A microwave reaction vial is charged with piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide; hydrochloride (94mg; 0.327mmol), 3-chloro-2-fluoro-5-trifluoromethylpyridine (0.043mL; 0.33mmol), triethylamine (0.092mL; 0.66mmol) and t-butanol (0.5mL). The vial is heated in microwave at 175°C for 1 hour then left standing at room temperature overnight. The reaction mixture is concentrated *in vacuo*. Purification by flash chromatography on silica using methanol/methylene chloride then recrystallization from hot methanol provides the title compound, m/z 431 [M+H$^+$].

Compounds found in Table 3 Method A are prepared in a similar manner.

Method B

Synthesis of 1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide (Example 3):



Step 1: Synthesis of 1,1-dioxo-1λ^6-thiomorpholine-4-carbonyl chloride

Thiomorpholine 1,1-dioxide (1g; 7.397mmolline) is dispersed in THF (50mL). Triethylamine (1.238mL; 8.88mmol) is added, followed by 20% phosgene in toluene (11.743mL; 22.2 mmol). The reaction mixture is stirred at room temperature for 18 hours. The reaction mixture is diluted with diethyl ether and filtered through Celite®. The Celite® is washed with diethyl ether several times and the combined filtrates are concentrated *in vacuo* to afford the title compound. H NMR (400MHz, CDCl3): δ 3.1-3.2 (m; 4H), 4.1-4.3 (d, 4H).

Step 2: Synthesis of 1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide

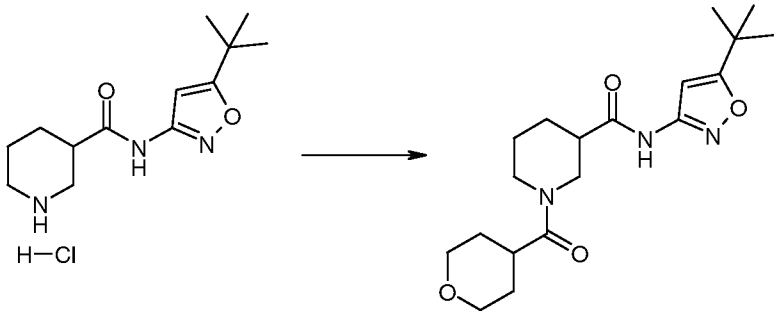
To a solution of piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide; hydrochloride (100mg; 0.347mmol) in anhydrous THF (1mL) is added triethylamine (0.098mL; 0.7mmol) and 1,1-dioxo-1λ^6-thiomorpholine-4-carbonyl chloride (71.15mg; 0.36mmol). The reaction mixture is left stirring at room temperature overnight. The reaction mixture is diluted with water and extracted with ethyl acetate 3 times. The organics are combined and washed with brine, dried over Na2SO4, filtered and concentrated *in vacuo*.

Purification by flash chromatography on silica using methanol/methylene chloride then trituration from diethyl ether provides the title compound, m/z 412 [M+H$^+$].

Compounds found in Table 3 Method B are prepared in a similar manner.

Method C:

Synthesis of 1-(Tetrahydro-pyran-4-carbonyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide (Example 4)

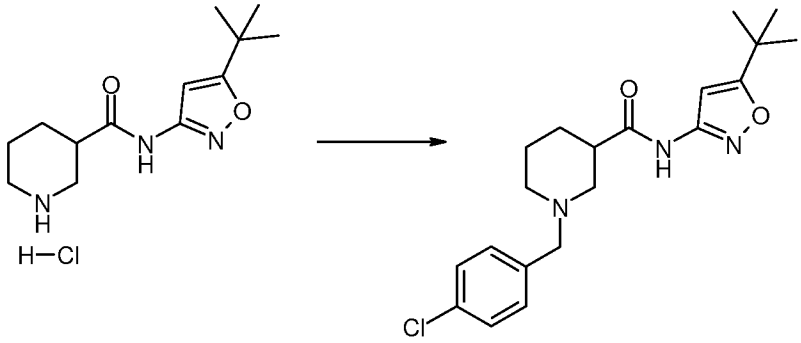


To a solution of tetrahydro-pyran-4-carboxylic acid (54.66mg; 0.42mmol) and 1-hydroxybenzotriazole hydrate (56.76mg; 0.42mmol) in anhydrous DMF (1.5mL) is added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (80.52mg; 0.42mmol) and the reaction mixture is stirred at room temperature for 15 minutes. After this time, piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide; hydrochloride (90mg; 0.313mmol), triethylamine (0.044mL; 0.313mmol) and 4-dimethylaminopyridine (4.1mg; 0.034mmol) are added. The reaction mixture is stirred at room temperature for 18 hours. The mixture is diluted with ethyl acetate and then washed with water, saturated NaHCO3 aqueous solution then brine, dried over Na2SO4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica using methanol/methylene chloride then recrystallization from hot ethyl acetate provides the title compound, m/z 364 [M+H$^+$].

Compounds found in Table 3 Method C are prepared in a similar manner.

Method D:

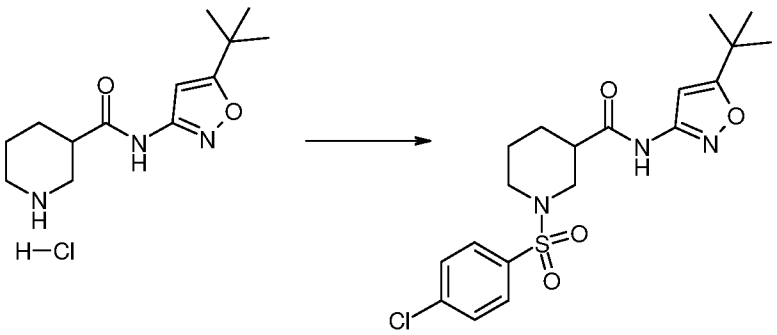
Synthesis 1-(4-Chloro-benzyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide (Example 9):



To a solution of 4-chlorobenzyl chloride (134mg; 0.832mmol) in DMF (3mL) is added piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide; hydrochloride (238.86mg; 0.83mmol) and N,N-diisopropylethylamine (0.331mL; 1.9mmol). The reaction mixture is left stirring at room temperature for 18 hours in the presence of catalytic amount of 4-dimethylaminopyridine (1mg). The mixture is diluted with ethyl acetate and washed with water 3 times then brine, dried over Na2SO4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica using methanol/methylene chloride provides the title compound, m/z 376/378 [$M+H^+$].

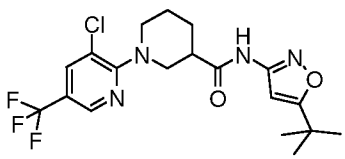
Method E:

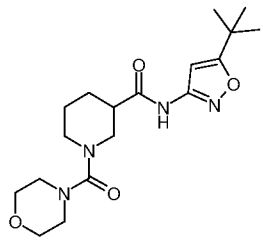
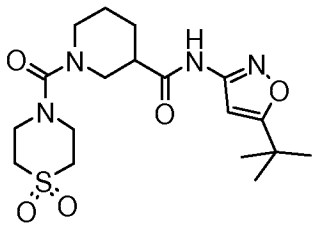
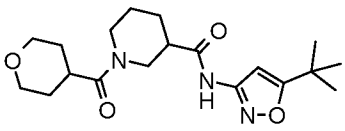
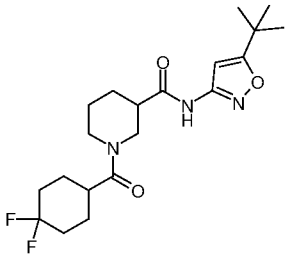
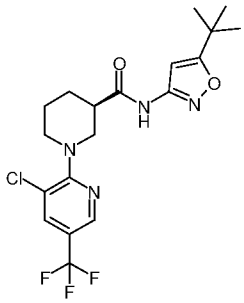
Synthesis of 1-(4-Chloro-benzenesulfonyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide (Example 10):

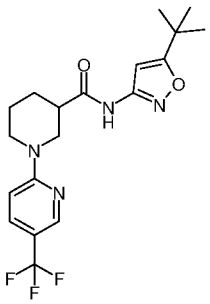
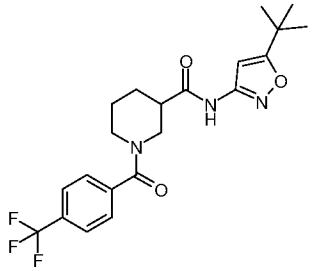
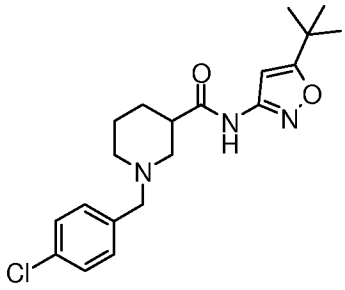
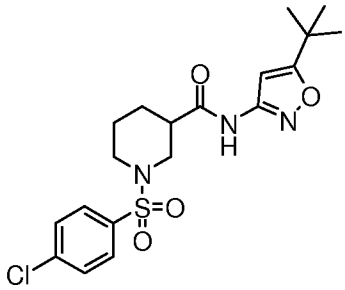
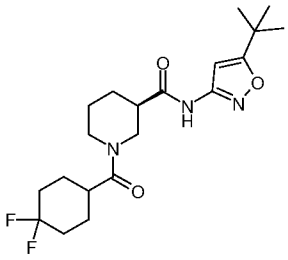


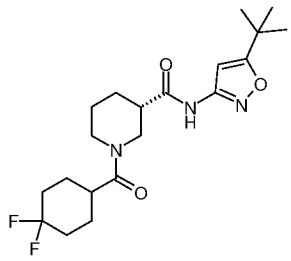
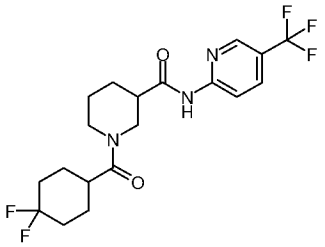
To a solution of 4-chlorophenylsulfonyl chloride (117.35mg; 0.556mmol) in DMF (2mL) is added piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide; hydrochloride (160mg; 0.556mmol), N,N-diisopropylethylamine (0.261mL; 1.5mmol) and 4-dimethylaminopyridine (2mg, 0.016mmol). The reaction mixture is left stirring at room temperature for 18 hours. After this time, the mixture is diluted with ethyl acetate and washed with water 3 times, then brine, dried over Na2SO4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica using methanol/methylene chloride provides the title compound, m/z 426/428 [M+H$^+$].

Table 3: Examples

Example	Structure	Name	m/z [M+H$^+$]	Patent Method
1		3'-Chloro-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	431	A

2		1-(Morpholine-4-carbonyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	365	B
3		1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	412	B
4		1-(Tetrahydro-pyran-4-carbonyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	365	C
5		1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	398	C
6		(R)-3'-Chloro-5'-trifluoromethyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	431	A

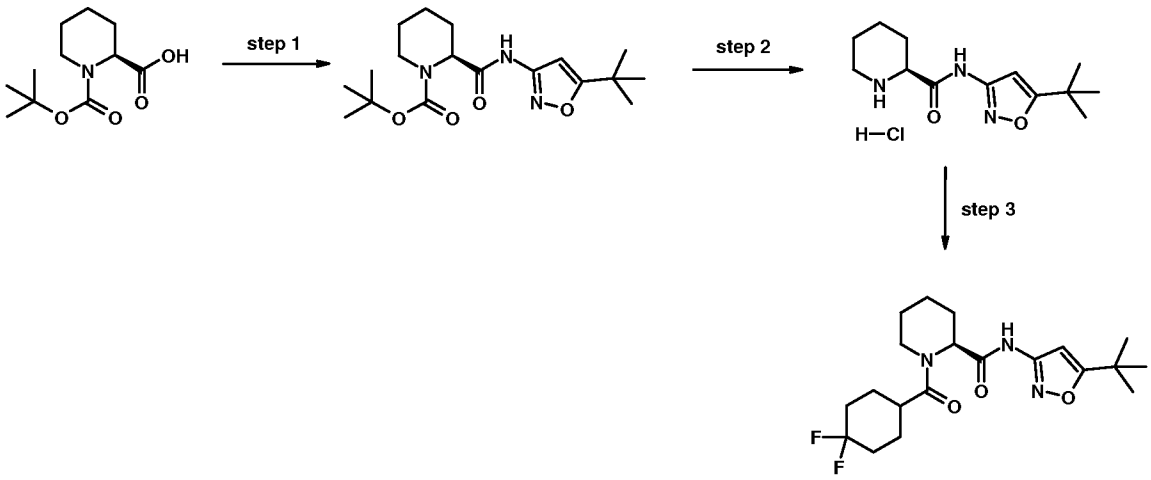
7		5'-Trifluoromethyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	397	A
8		1-(4-Trifluoromethyl-benzoyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	424	C
9		1-(4-Chloro-benzyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	376/ 378	D
10		1-(4-Chloro-benzenesulfonyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	426/ 428	E
11		(R)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	398	C

12		(S)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	398	C
13		1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-3-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide	420	C

Compounds of Formula (IIA) and (IVA)

Method F

Synthesis of (S)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide (Example 18)



Step 1:

Five different amide coupling procedures can be used for step 1. Amide intermediates and the coupling procedures 1 - 5 to synthesize them are listed in Table 4.

Amide coupling procedure 1: Synthesis of (S)-2-(5-*tert*-Butyl-isoxazol-3-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester

To a cold (5°C) solution of (S)-piperidine-2-carboxylic acid (480mg; 2.094mmol) and 3-amino-5-t-butylisoxazole (300mg; 2.14mmol) in anhydrous pyridine (5mL) is added phosphorus chloride (0.198mL; 2.2mmol). The reaction mixture is left stirring and allowed to warm to room temperature overnight. The reaction mixture is quenched with water and extracted with ethyl acetate twice. The combined organics are washed with brine, dried over Na2SO4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica using methanol/methylene chloride provides the title compound, m/z 352 [$M+H^+$].

Amide coupling procedure 2:Synthesis of (S)-2-(3-*tert*-Butyl-isoxazol-5-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester

2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (445mg; 1.8mmol) is added to a solution of (S)-piperidine-2-carboxylic acid (300mg; 1.308mmol) and 5-amino-3-t-butylisoxazole

(183.4mg; 1.308mmol) in toluene (4.2mL) at room temperature and the mixture is stirred for 18 hours. After this time, the mixture is concentrated *in vacuo*. Purification by flash chromatography on silica gel using methanol/methylene chloride provides the title compound, m/z 352 [M+H$^+$].

Amide coupling procedure 3: Synthesis of (S)-2-(5-*tert*-Butyl-isoxazol-3-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester

To solution of the (S)-piperidine-2-carboxylic acid (5g; 21.808mmol), 3-amino-5-t-butylisoxazole (3.084g; 22mmol), and N,N-diisopropylethylamine (3.799mL; 21.808mmol) in anhydrous toluene (80mL) is added 2-chloro-1-methylpyridinium iodide (6.132g; 24mmol). The mixture is left stirring for 2 hours at 75°C. After cooling to room temperature, the reaction mixture is diluted with ethyl acetate and washed with water twice then brine, dried over Na2SO4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel using ethyl acetate/Hexanes provides the title compound, m/z 352 [M+H$^+$].

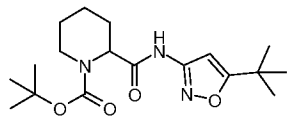
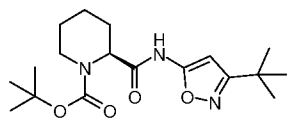
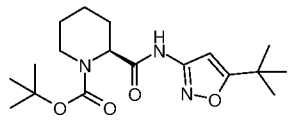
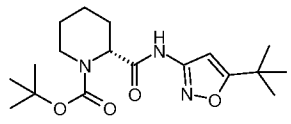
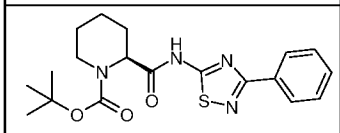
Amide coupling procedure 4: Synthesis of (S)-2-(5-*tert*-Butyl-1,3,4-thiadiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester

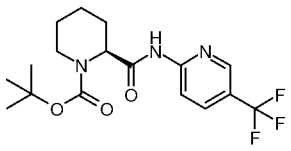
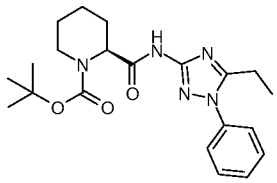
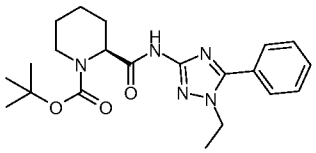
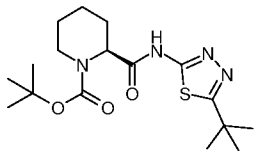
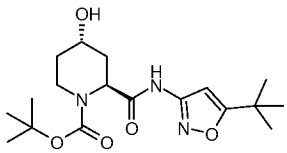
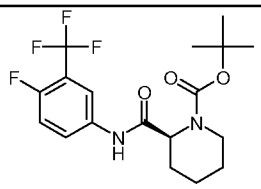
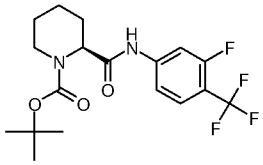
To a suspension of (S)-piperidine-2-carboxylic acid (0.4g; 1.745mmol) in THF (5mL) is added N,N-diisopropylethylamine (0.608mL; 3.49mmol) and 3-(diethoxyphosphoryloxy)-1,2,3-benzotrizin-4(3*H*)-one (1.044g; 3.49mmol) at room temperature. After 30 minutes of stirring, 2-amino-5-t-butyl-1,3,4-thiadiazole (0.274g; 1.745mmol) is added and the reaction is stirred at room temperature for 18 hours. The reaction is quenched with saturated NH4Cl aqueous solution and extracted with ethyl acetate 3 times. The organics are combined and washed with water, then brine, dried over Na2SO4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel using ethyl acetate/Hexanes provides the title compound, m/z 369 [M+H$^+$].

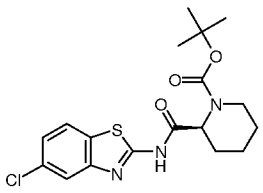
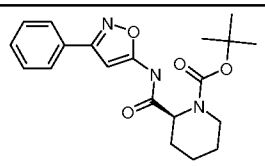
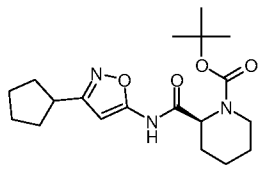
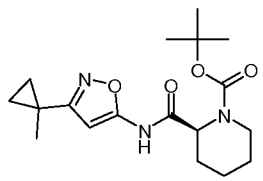
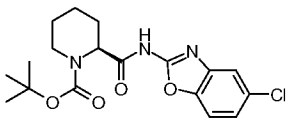
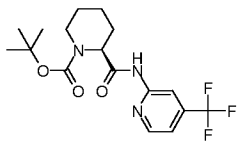
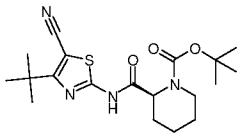
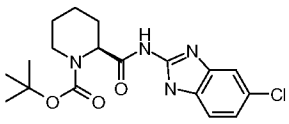
Amide coupling procedure 5: Synthesis of (S)-2-(5-*tert*-Butyl-1,3,4-thiadiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester

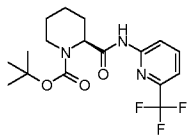
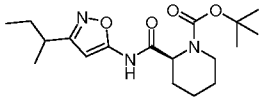
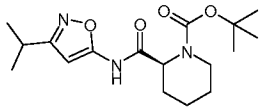
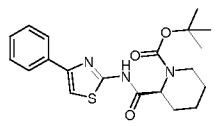
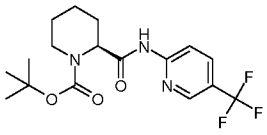
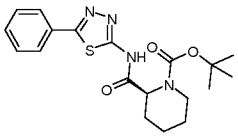
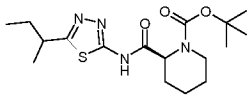
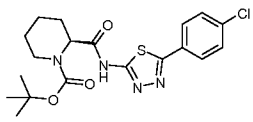
To a solution of (S)-piperidine-2-carboxylic acid (1g; 4.362mmol) and 2-amino-5-t-butyl-1,3,4-thiadiazole (0.686g; 4.362mmol) in dichloromethane (35mL) is added 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (1.304mL; 4.5mmol). The mixture is stirred at room temperature for 2.5 hours. The reaction mixture was concentrated in vacuo. Purification by flash chromatography on silica gel using ethyl acetate/Hexanes provides the title compound, m/z 369 [M+H$^+$].

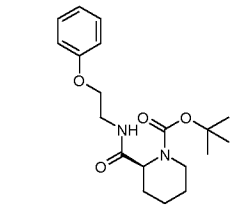
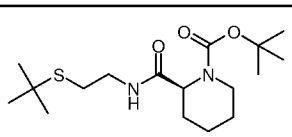
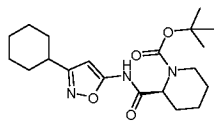
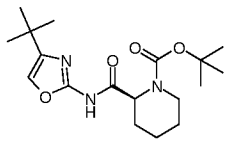
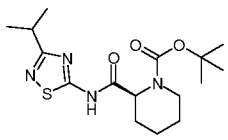
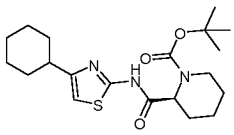
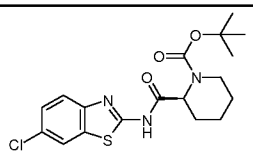
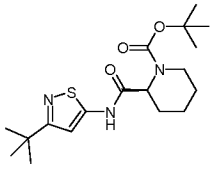
Table 4: Amide intermediates

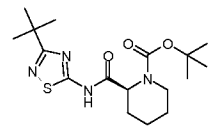
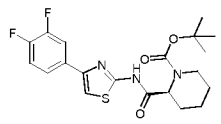
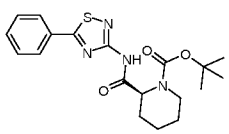
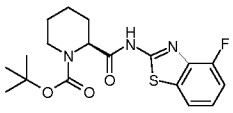
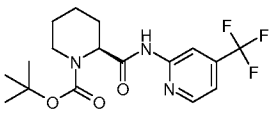
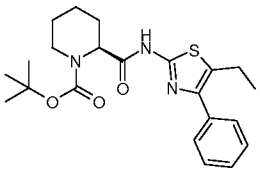
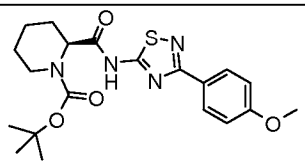
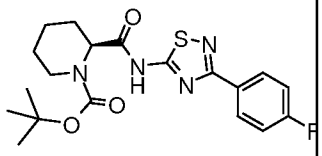
Structure	Name	m/z [M+H$^+$]	Coupling procedure
	2-(5-*tert*-Butyl-isoxazol-3-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	352	1
	(S)-2-(3-*tert*-Butyl-isoxazol-5-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	352	2
	(S)-2-(5-*tert*-Butyl-isoxazol-3-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	352	1, 2 and 3
	(R)-2-(5-*tert*-Butyl-isoxazol-3-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	352	1
	(S)-2-(3-Phenyl-1,2,4-thiadiazol-5-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	389	2

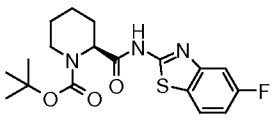
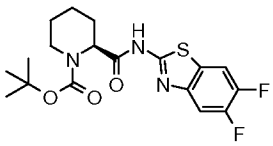
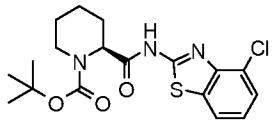
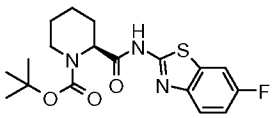
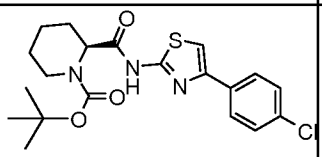
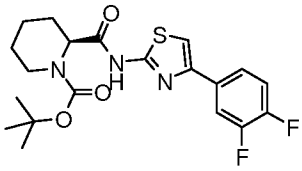
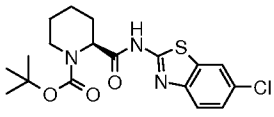
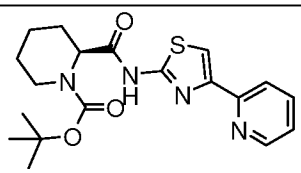
	(S)-2-(5-Trifluoromethyl-pyridin-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	374	2
	(S)-2-(5-Ethyl-1-phenyl-1*H*-1,2,4-triazol-3-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	400	1
	(S)-2-(1-Ethyl-5-phenyl-1*H*-1,2,4-triazol-3-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	400	1 and 2
	(S)-2-(5-*tert*-Butyl-1,3,4-thiadiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	369	1, 4 and 5
	(2S,4S)-2-(5-*tert*-Butyl-isoxazol-3-ylcarbamoyl)-4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester	368	2
	(S)-2-(4-Fluoro-3-trifluoromethyl-phenylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	391	1
	(S)-2-(3-Fluoro-4-trifluoromethyl-phenylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	391	1

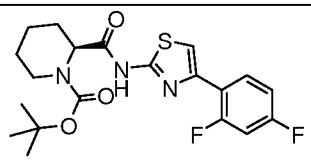
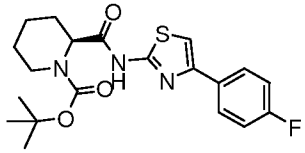
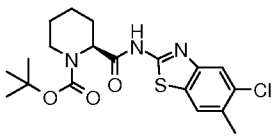
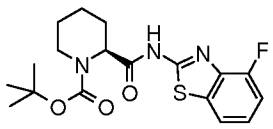
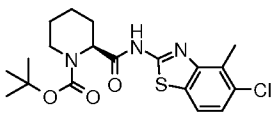
	(S)-2-(5-Chloro-benzothiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	396	1
	(S)-2-(3-Phenyl-isoxazol-5-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	372	1
	(S)-2-(3-Cyclopentyl-isoxazol-5-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	364	1
	(S)-2-[3-(1-Methyl-cyclopropyl)-isoxazol-5-ylcarbamoyl]-piperidine-1-carboxylic acid *tert*-butyl ester	350	1 and 2
	(S)-2-(5-Chloro-benzoxazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	380	2
	(S)-2-(4-Trifluoromethyl-pyridin-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	374	2
	(S)-2-(4-*tert*-Butyl-5-cyano-thiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	393	2
	(S)-2-(5-Chloro-1*H*-benzimidazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	379	2

	(S)-2-(6-Trifluoromethyl-pyridin-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	374	2
	(S)-2-(3-*sec*-Butyl-isoxazol-5-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	352	2
	(S)-2-(3-Isopropyl-isoxazol-5-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	338	2
	(S)-2-(4-Phenyl-thiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	388	2
	(S)-2-(5-Trifluoromethyl-pyridin-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	374	2
	(S)-2-(5-Phenyl-1,3,4-thiadiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	389	2
	(S)-2-(5-*sec*-Butyl-1,3,4-thiadiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	369	2
	(S)-2-[5-(4-Chloro-phenyl)-1,3,4-thiadiazol-2-ylcarbamoyl]-piperidine-1-carboxylic acid *tert*-butyl ester	423	2

	(S)-2-(2-Phenoxy-ethylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	349	2
	(S)-2-(2-*tert*-Butylsulfanyl-ethylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	345	2
	(S)-2-(3-Cyclohexyl-isoxazol-5-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	378	2
	(S)-2-(4-*tert*-Butyl-oxazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	352	2
	(S)-2-(3-Isopropyl-1,2,4-thiadiazol-5-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	355	2
	(S)-2-(4-Cyclohexyl-thiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	394	2
	(S)-2-(6-Chloro-benzothiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	396	2
	(S)-2-(3-*tert*-Butyl-isothiazol-5-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	368	2

	(S)-2-(3-*tert*-Butyl-1,2,4-thiadiazol-5-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	369	2
	(S)-2-[4-(3,4-Difluoro-phenyl)-thiazol-2-ylcarbamoyl]-piperidine-1-carboxylic acid *tert*-butyl ester	424	2
	(S)-2-(5-Phenyl-1,2,4-thiadiazol-3-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	389	2
	(S)-2-(4-Fluoro-benzothiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	380	2
	(S)-2-(4-Trifluoromethyl-pyridin-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	374	2
	(S)-2-(5-Ethyl-4-phenyl-thiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	416	2
	(S)-2-[3-(4-Methoxy-phenyl)-[1,2,4]thiadiazol-5-ylcarbamoyl]-piperidine-1-carboxylic acid *tert*-butyl ester	419	4
	(S)-2-[3-(4-Fluoro-phenyl)-[1,2,4]thiadiazol-5-ylcarbamoyl]-piperidine-1-carboxylic acid *tert*-butyl ester	407	4

	(S)-2-(5-Fluoro-benzothiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester	380	4
	(S)-2-(5,6-Difluoro-benzothiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	398	4
	(S)-2-(4-Chloro-benzothiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	396	4
	(S)-2-(6-Fluoro-benzothiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	380	4
	(S)-2-[4-(4-Chloro-phenyl)-thiazol-2-ylcarbamoyl]-piperidine-1-carboxylic acid *tert*-butyl ester	422	4
	(S)-2-[4-(3,4-Difluoro-phenyl)-thiazol-2-ylcarbamoyl]-piperidine-1-carboxylic acid *tert*-butyl ester	424	4
	(S)-2-(6-Chloro-benzothiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	396	4
	(S)-2-(4-Pyridin-2-yl-thiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	389	4

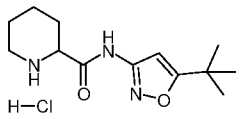
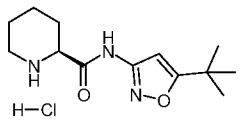
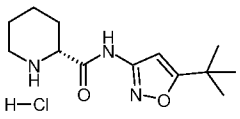
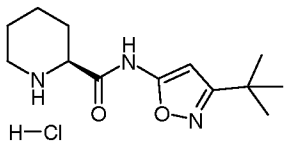
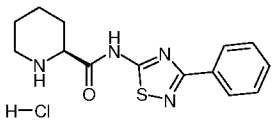
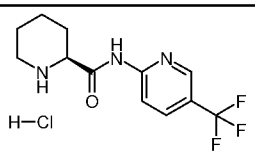
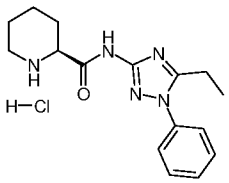
	(S)-2-[4-(2,4-Difluoro-phenyl)-thiazol-2-ylcarbamoyl]-piperidine-1-carboxylic acid *tert*-butyl ester	424	4
	(S)-2-[4-(4-Fluoro-phenyl)-thiazol-2-ylcarbamoyl]-piperidine-1-carboxylic acid *tert*-butyl ester	406	4
	(S)-2-(5-Chloro-6-methyl-benzothiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	410	4
	(*S*)-2-(4-Fluoro-benzothiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	380	4
	(S)-2-(5-Chloro-4-methyl-benzothiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester	410	4

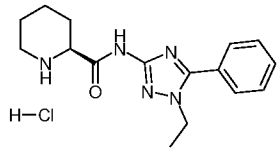
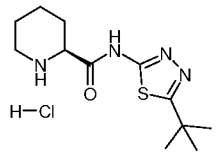
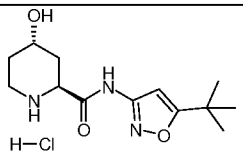
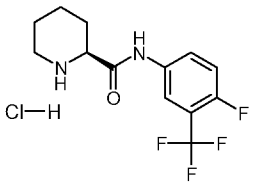
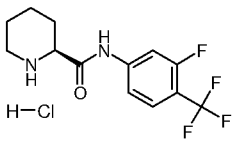
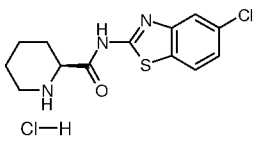
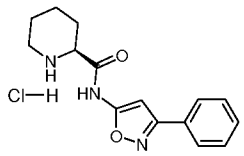
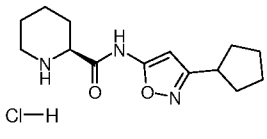
Step 2: Synthesis of (S)-Piperidine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl) amide; hydrochloride

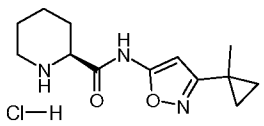
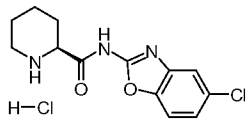
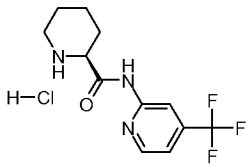
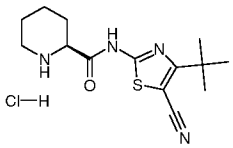
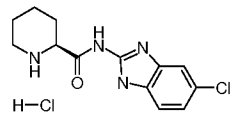
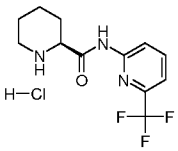
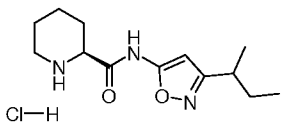
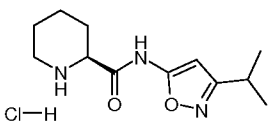
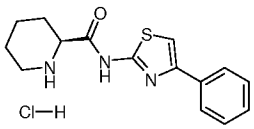
4N HCl in dioxanes (0.675mL; 2.7mmol) is added to a solution of (S)-2-(5-*tert*-Butyl-isoxazol-3-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester (235mg; 0.669mmol) in dichloromethane (5mL). The reaction mixture is stirred at room temperature for 18 hour. The reaction is concentrated *in vacuo* to provide the title compound, m/z 252 [M+H$^+$].

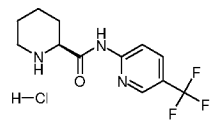
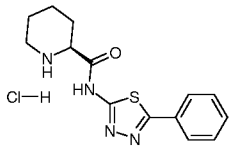
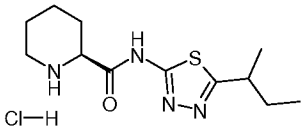
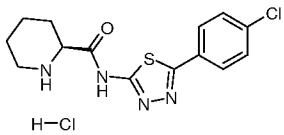
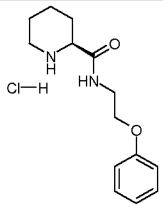
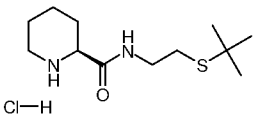
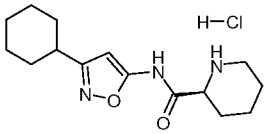
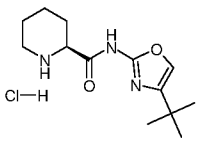
Intermediates listed in Table 5 are made in a similar manner.

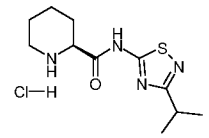
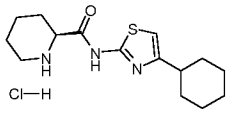
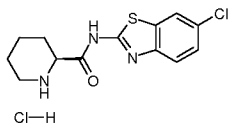
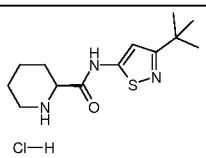
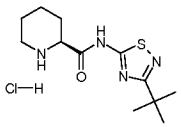
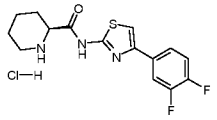
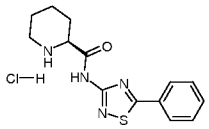
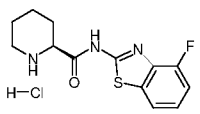
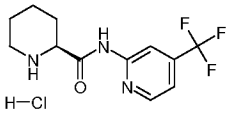
Table 5

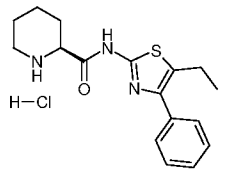
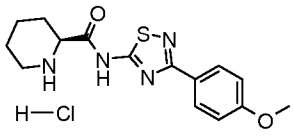
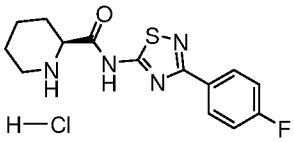
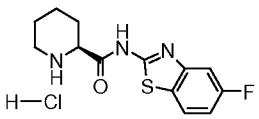
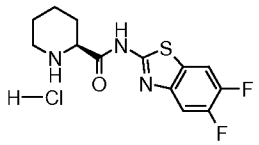
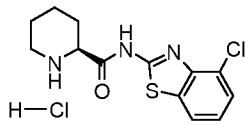
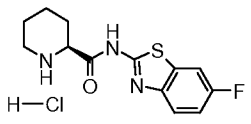
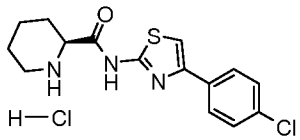
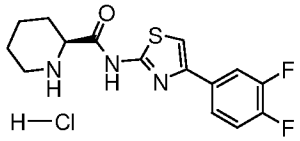
Structure	Name	m/z [M+H$^+$]
	Piperidine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide; hydrochloride	252
	(S)-Piperidine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide; hydrochloride	252
	(R)-Piperidine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide; hydrochloride	252
	(S)-Piperidine-2-carboxylic acid (3-*tert*-butyl-isoxazol-5-yl)-amide; hydrochloride	252
	(S)-Piperidine-2-carboxylic acid (3-phenyl-1,2,4-thiadiazol-5-yl)-amide; hydrochloride	289
	(S)-Piperidine-2-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide; hydrochloride	274
	(S)-Piperidine-2-carboxylic acid (5-ethyl-1-phenyl-1*H*-1,2,4-triazol-3-yl)-amide; hydrochloride	300

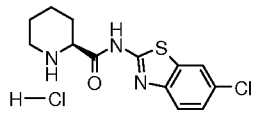
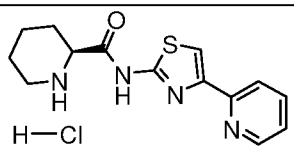
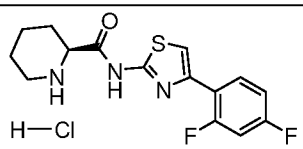
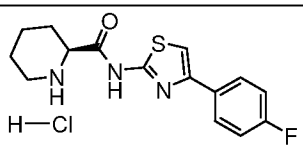
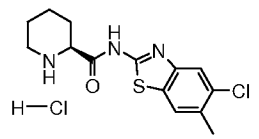
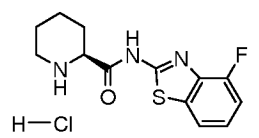
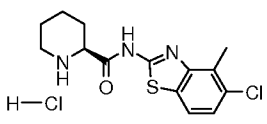
	(S)-Piperidine-2-carboxylic acid (1-ethyl-5-phenyl-1*H*-1,2,4-triazol-3-yl)-amide; hydrochloride	300
	(S)-Piperidine-2-carboxylic acid (5-*tert*-butyl-1,3,4-thiadiazol-2-yl)-amide; hydrochloride	269
	(2S,4S)-4-Hydroxy-piperidine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide; hydrochloride	268
	(S)-Piperidine-2-carboxylic acid (4-fluoro-3-trifluoromethyl-phenyl)-amide; hydrochloride	291
	(S)-Piperidine-2-carboxylic acid (3-fluoro-4-trifluoromethyl-phenyl)-amide; hydrochloride	291
	(S)-Piperidine-2-carboxylic acid (5-chloro-benzothiazol-2-yl)-amide; hydrochloride	296
	(S)-Piperidine-2-carboxylic acid (3-phenyl-isoxazol-5-yl)-amide; hydrochloride	272
	(S)-Piperidine-2-carboxylic acid (3-cyclopentyl-isoxazol-5-yl)-amide; hydrochloride	264

	(S)-Piperidine-2-carboxylic acid [3-(1-methyl-cyclopropyl)-isoxazol-5-yl]-amide; hydrochloride	250
	(S)-Piperidine-2-carboxylic acid (5-chloro-benzoxazol-2-yl)-amide; hydrochloride	280
	(S)-Piperidine-2-carboxylic acid (4-trifluoromethyl-pyridin-2-yl)-amide; hydrochloride	274
	(S)-Piperidine-2-carboxylic acid (4-*tert*-butyl-5-cyano-thiazol-2-yl)-amide; hydrochloride	293
	(S)-Piperidine-2-carboxylic acid (5-chloro-1*H*-benzimidazol-2-yl)-amide; hydrochloride	279
	(S)-Piperidine-2-carboxylic acid (6-trifluoromethyl-pyridin-2-yl)-amide; hydrochloride	274
	(S)-Piperidine-2-carboxylic acid (3-*sec*-butyl-isoxazol-5-yl)-amide; hydrochloride	252
	(S)-Piperidine-2-carboxylic acid (3-isopropyl-isoxazol-5-yl)-amide; hydrochloride	238
	(S)-Piperidine-2-carboxylic acid (4-phenyl-thiazol-2-yl)-amide; hydrochloride	288

	(S)-Piperidine-2-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide; hydrochloride	274
	(S)-Piperidine-2-carboxylic acid (5-phenyl-1,3,4-thiadiazol-2-yl)-amide; hydrochloride	289
	(S)-Piperidine-2-carboxylic acid (5-*sec*-butyl-1,3,4-thiadiazol-2-yl)-amide; hydrochloride	269
	(S)-Piperidine-2-carboxylic acid [5-(4-chloro-phenyl)-1,3,4-thiadiazol-2-yl]-amide; hydrochloride	323
	(S)-Piperidine-2-carboxylic acid (2-phenoxy-ethyl)-amide; hydrochloride	249
	(S)-Piperidine-2-carboxylic acid (2-*tert*-butylsulfanyl-ethyl)-amide; hydrochloride	245
	(S)-Piperidine-2-carboxylic acid (3-cyclohexyl-isoxazol-5-yl)-amide; hydrochloride	278
	(S)-Piperidine-2-carboxylic acid (4-*tert*-butyl-oxazol-2-yl)-amide; hydrochloride	252

	(S)-Piperidine-2-carboxylic acid (3-isopropyl-1,2,4-thiadiazol-5-yl)-amide; hydrochloride	255
	(S)-Piperidine-2-carboxylic acid (4-cyclohexyl-thiazol-2-yl)-amide; hydrochloride	294
	(S)-Piperidine-2-carboxylic acid (6-chloro-benzothiazol-2-yl)-amide; hydrochloride	296
	(S)-Piperidine-2-carboxylic acid (3-*tert*-butyl-isothiazol-5-yl)-amide; hydrochloride	268
	(S)-Piperidine-2-carboxylic acid (3-*tert*-butyl-1,2,4-thiadiazol-5-yl)-amide; hydrochloride	269
	(S)-Piperidine-2-carboxylic acid [4-(3,4-difluoro-phenyl)-thiazol-2-yl]-amide; hydrochloride	324
	(S)-Piperidine-2-carboxylic acid (5-phenyl-1,2,4-thiadiazol-3-yl)-amide; hydrochloride	289
	(S)-Piperidine-2-carboxylic acid (4-fluoro-benzothiazol-2-yl)-amide; hydrochloride	280
	(S)-Piperidine-2-carboxylic acid (4-trifluoromethyl-pyridin-2-yl)-amide; hydrochloride	274

	(S)-Piperidine-2-carboxylic acid (5-ethyl-4-phenyl-thiazol-2-yl)-amide; hydrochloride	316
	(S)-Piperidine-2-carboxylic acid [3-(4-methoxy-phenyl)-[1,2,4]thiadiazol-5-yl]-amide; hydrochloride	not obtained
	(S)-Piperidine-2-carboxylic acid [3-(4-fluoro-phenyl)-[1,2,4]thiadiazol-5-yl]-amide; hydrochloride	not obtained
	(S)-Piperidine-2-carboxylic acid (5-fluoro-benzothiazol-2-yl)-amide; hydrochloride	not obtained
	(S)-Piperidine-2-carboxylic acid (5,6-difluoro-benzothiazol-2-yl)-amide; hydrochloride	not obtained
	(S)-Piperidine-2-carboxylic acid (4-chloro-benzothiazol-2-yl)-amide; hydrochloride	not obtained
	(S)-Piperidine-2-carboxylic acid (6-fluoro-benzothiazol-2-yl)-amide; hydrochloride	not obtained
	(S)-Piperidine-2-carboxylic acid [4-(4-chloro-phenyl)-thiazol-2-yl]-amide; hydrochloride	not obtained
	(S)-Piperidine-2-carboxylic acid [4-(3,4-difluoro-phenyl)-thiazol-2-yl]-amide; hydrochloride	not obtained

	(S)-Piperidine-2-carboxylic acid (6-chloro-benzothiazol-2-yl)-amide; hydrochloride	not obtained
	(S)-Piperidine-2-carboxylic acid (4-pyridin-2-yl-thiazol-2-yl)-amide; hydrochloride	not obtained
	(S)-Piperidine-2-carboxylic acid [4-(2,4-difluoro-phenyl)-thiazol-2-yl]-amide; hydrochloride	not obtained
	(S)-Piperidine-2-carboxylic acid [4-(4-fluoro-phenyl)-thiazol-2-yl]-amide; hydrochloride	not obtained
	(S)-Piperidine-2-carboxylic acid (5-chloro-6-methyl-benzothiazol-2-yl)-amide; hydrochloride	not obtained
	(S)-Piperidine-2-carboxylic acid (4-fluoro-benzothiazol-2-yl)-amide; hydrochloride	not obtained
	(S)-Piperidine-2-carboxylic acid (5-chloro-4-methyl-benzothiazol-2-yl)-amide; hydrochloride	not obtained

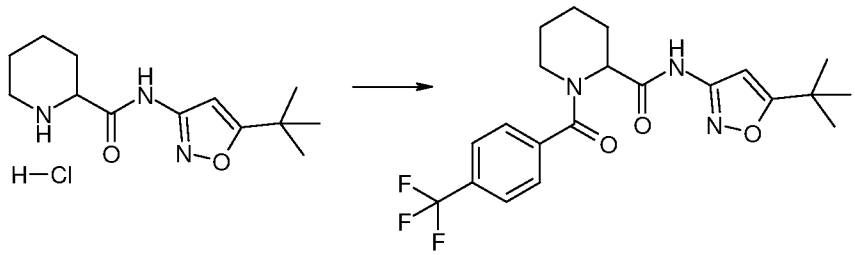
Step 3: Two amide coupling procedures can be used.

<u>Amide coupling procedure 1</u>: Synthesis of (S)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide (Example 18)

To a solution of 4,4-difluorocyclohexanecarboxylic acid (118.2mg; 0.72mmol) and 1-hydroxybenzotriazole hydrate (97.3mg; 0.72mmol) in DMF (2mL) is added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (138mg; 0.72mmol). After 15 minutes of stirring, (S)-Piperidine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl) amide; hydrochloride (190mg; 0.66mmol) is added, followed by triethylamine (0.093mL; 0.67mmol) and 4-dimethylaminopyridine (4mg; 0.033mmol). The reaction mixture is stirred at room temperature for 18 hours. The reaction mixture is quenched with water and the crude product is collected by filtration. Purification by flash chromatography on silica gel using methanol/methylene chloride provides the title compound, m/z 398 [M+H$^+$].

Compounds in Table 7 Method F1 are prepared in a similar manner.

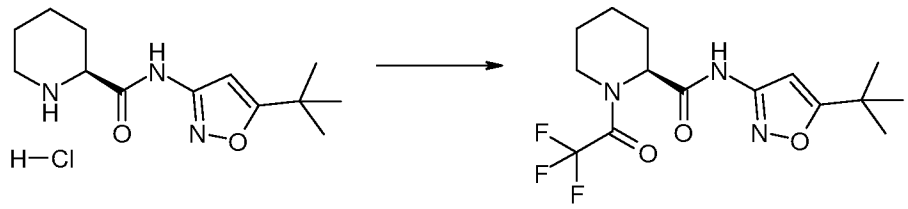
<u>Amide coupling procedure 2</u>: Synthesis of 1-(4-Trifluoromethyl-benzoyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide (Example 17)



To a solution of piperidine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl) amide; hydrochloride (100mg; 0.347mmol) and 4-(trifluoromethyl)benzoic acid (66mg; 0.347mmol) in pyridine (1mL) at 0°C is added phosphorous oxychloride (0.032mL; 0.347mmol) and the reaction mixture is left stirring at room temperature for 3 hours. After this time, the reaction mixture is quenched with saturated NH4Cl aqueous solution and extracted with ethyl acetate 3 times. The combined organics are washed with brine, dried over Na2SO4, filtered and concentrated in *vacuo*. Purification by flash chromatography on silica gel using methanol/methylene chloride provides the title compound, m/z 424 [M+H$^+$].

Compounds in Table 7 Method F2 are prepared in a similar manner.

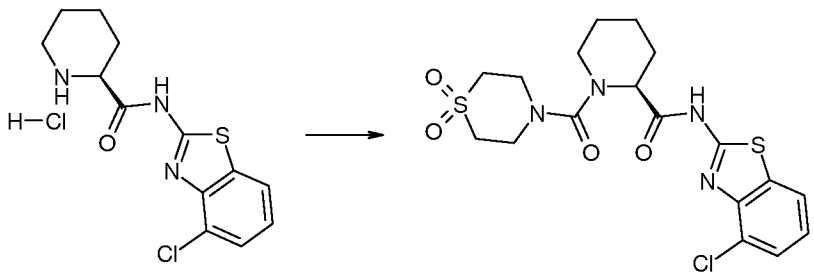
Amide coupling procedure 3: Synthesis of (S)-1-(2,2,2-Trifluoro-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide (Example 137)



To a solution of (S)-Piperidine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl) amide; hydrochloride (126mg; 0.438mmol) in DMF (2mL) is added N,N-diisopropylethylamine (0.153mL; 0.876mmol), followed by trifluoroacetic anhydride (0.061mL; 0.438mmol). The reaction mixture is stirred at room temperature for 48 hours. The mixture is diluted with ethyl acetate and washed with water twice then brine, dried over Na2SO4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel using ethyl acetate/Hexanes provides the title compound, m/z 348 [$M+H^+$].

Compounds in Table 7 Method F3 are prepared in a similar manner.

Amide coupling procedure 4: Synthesis of Synthesis of (S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (4-chloro-benzothiazol-2-yl)-amide (Example 158)



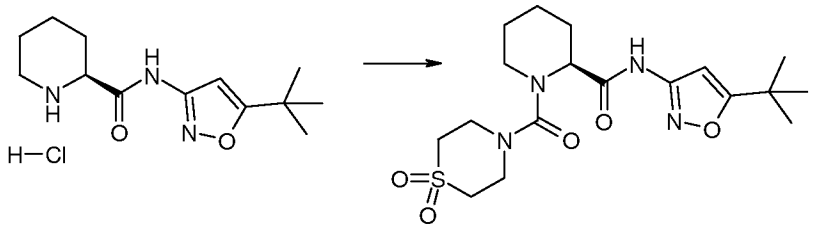
To the thiomorpholine dioxide carbonyl chloride (75 mg, 0.38 mmol) is added the amine (83 mg, 0.25 mmol) and N-methyl morpholine (139 μL, 1.27 mmol) in dichloromethane (1 mL).

The reaction is shaken at room temperature for 16 hours then concentrated under reduced pressure. Purification by preparative HPLC provides the desired final compound (19 mg, 0.04 mmol, 17% yield).

Compounds in Table 7 Method F4 are prepared in a similar manner

Method G:

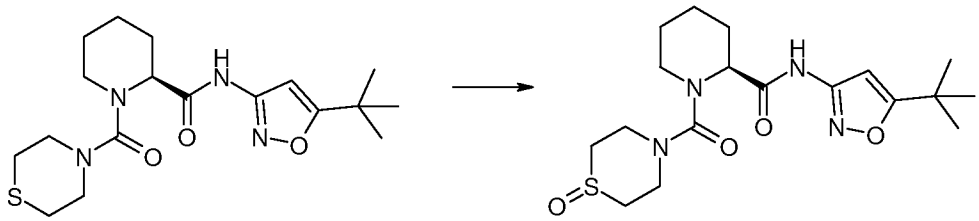
Synthesis of (S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide (Example 22):



To a suspension of (S)-Piperidine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl) amide hydrochloride (150mg; 0.521mmol) in THF (6mL) is added 1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl chloride (102.97mg; 0.521mmol) and N,N-diisopropylethylamine (0.186mL; 1.07mmol). The reaction mixture is stirred at room temperature for 4 hours. The reaction mixture is quenched with water and extracted with methylene chloride twice. The combined organics were washed with brine, dried over Na2SO4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel using methanol/methylene chloride provides the title compound, m/z 413 [M+H$^+$].

Compounds found in Table 7 Method G are prepared in a similar manner.

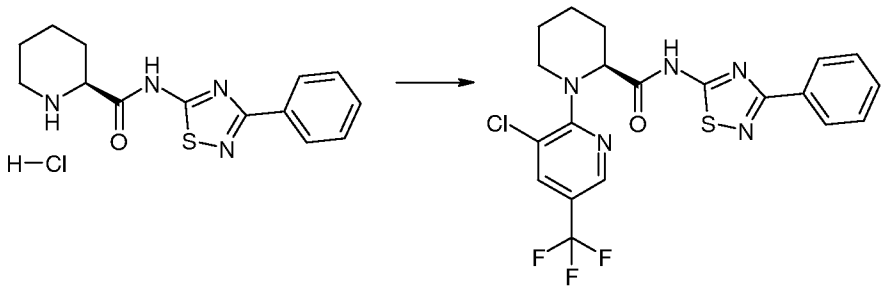
Synthesis of (S)-1-(1-Oxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide (Example 81):



To a solution of (S)-1-(Thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide (150mg; 0.394mmol) in 50% methylene chloride in methanol (4mL) is added oxone (122.8mg; 0.2mmol) and water (0.1mL). The reaction mixture is stirred at room temperature for 2 hours. The mixture is quenched with water and extracted with dichloromethane 3 times. The organics are combined and dried over Na2SO4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel using methanol/methylene chloride provides the title compound, m/z 397 [M+H$^+$].

Method H:

Synthesis of (S)-3'-Chloro-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-1,2'-bipyridinyl-2-carboxylic acid (3-phenyl-1,2,4-thiadiazol-5-yl)-amide (Example 25):

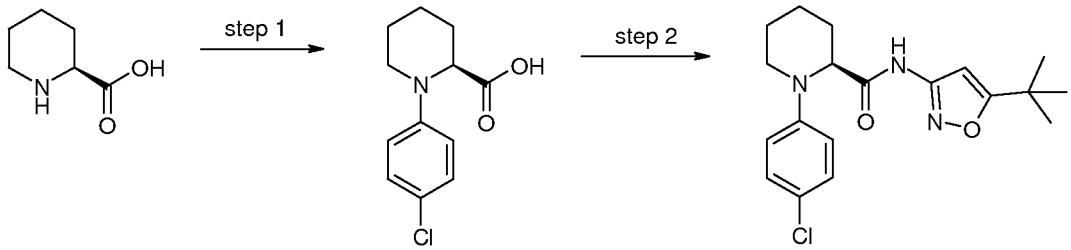


To a stirred solution of (S)-Piperidine-2-carboxylic acid (3-phenyl-1,2,4-thiadiazol-5-yl)-amide; hydrochloride (70mg; 0.215mmol) and N,N-diisopropylethylamine (0.037mL; 0.215mmol) in DMSO (1mL) is added 3-chloro-2-fluoro-5-trifluoromethylpyridine (42.9mg; 0.215mmol). The reaction mixture is heated at 100°C for 4 hours. Purification by flash chromatography on silica gel using methanol/methylene chloride provides the title compound, m/z 468 [M+H$^+$].

Compounds in Table 7 Method H are prepared in a similar manner.

Method I:

Synthesis of (S)-1-(4-Chloro-phenyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide (Example 92):



Step 1: Synthesis of (S)-1-(4-Chloro-phenyl)-piperidine-2-carboxylic acid

A reaction vessel containing L-(S)-pipecolic acid (200mg; 1.549mmol), 4-bromochlorobenzene (296.56mg; 1.549mmol), potassium carbonate (324.79mg; 2.35mmol) and copper iodide (29.5mg; 0.155mmol) is evacuated and purged with Argon several times. Dimethylacetamide (3mL) is added and the mixture is heated at 100°C for 3 days in a sealed vessel. After this time, the mixture is cooled to room temperature and diluted with ethyl acetate and water. The two layers are separated and the aqueous later is acidified to PH ~ 1 by adding 1N HCl aqueous solution and extracted with ethyl acetate twice. The organics are combined and dried over Na2SO4, filtered and concentrated. Purification by flash chromatography on silica gel using ethyl acetate/Hexanes provides the title compound, m/z 240 [M+H$^+$].

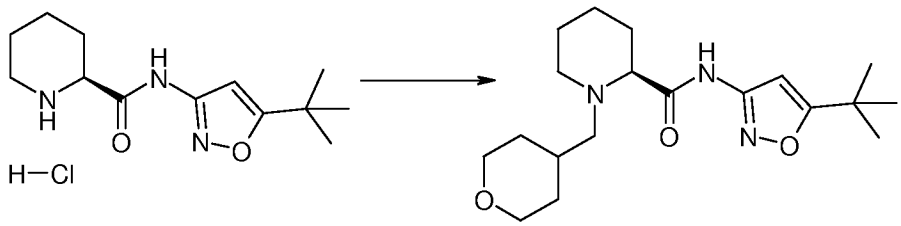
Step 2: Synthesis of (S)-1-(4-Chloro-phenyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide

Amide bond coupling method described in Example 1 coupling method A is used to synthesize the title compound, m/z 362 [M+H$^+$].

Method J:

Three different reductive amination procedures can be used

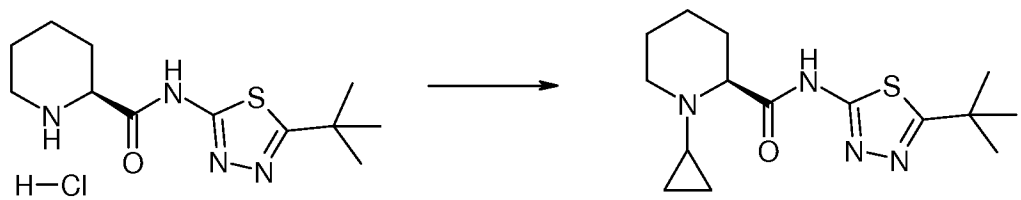
Reductive amination procedure 1: Synthesis of (S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide (Example 100):



To a solution of (S)-Piperidine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl) amide; hydrochloride (110mg; 0.382mmol) in DMF (1.5mL) is added tetrahydro-pyran-4-carbaldehyde (87.2mg; 0.764mmol), acetic acid (0.022mL; 0.382mmol) and sodium sulfate (5-10 equivalents). The mixture is stirred at room temperature for 30 minutes before adding sodium cyanoborohydride (24mg; 0.382mmol). The mixture is stirred at room temperature for 18 hours. The mixture is diluted with dichloromethane and washed with saturated NaHCO3 aqueous solution. The organic layer is dried over Na2SO4, filtered and concentrated *in vacuo*. Crude product is purified by preparative HPLC. Product fractions are pooled and concentrated *in vacuo* to afford the title compound, m/z 350 [$M+H^+$].

Compounds in Table 7 Method J1 are prepared in a similar manner.

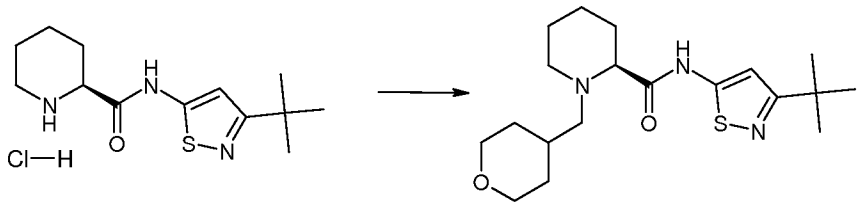
Reductive amination procedure 2: Synthesis of (S)-1-Cyclopropyl-piperidine-2-carboxylic acid (5-*tert*-butyl-1,3,4-thiadiazol-2-yl)-amide (Example 142):



To a solution of (S)-Piperidine-2-carboxylic acid (5-*tert*-butyl-1,3,4-thiadiazol-2-yl)-amide; hydrochloride (125mg; 0.41mmol) in methanol (3mL) is added acetic acid (0.235mL; 4.1mmol), [(1-ethoxycyclopropyl)oxy]trimethylsilane (0.48mL; 2.4mmol) and sodium cyanoborohydride (116.25mg; 1.85mmol). The reaction mixture is heated at reflux for 5 hours. After cooling, the mixture is diluted with ethyl acetate and washed with saturated NaHCO3 aqueous solution then brine, dried over Na2SO4, filtered and concentrated *in vacuo*. Purification by preparative HPLC affords the title compound, m/z 309 [M+H$^+$].

Compounds in Table 7 Method J2 are prepared in a similar manner.

<u>Reductive amination procedure 3:</u> Synthesis of (S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-*tert*-butyl-isothiazol-5-yl)-amide (Example 68):

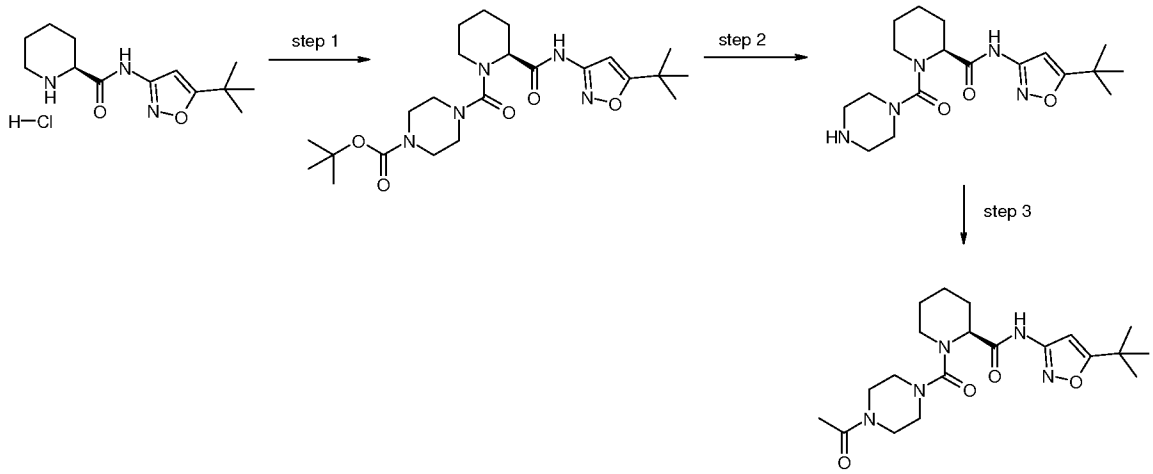


To a solution of (S)-Piperidine-2-carboxylic acid (3-*tert*-butyl-isothiazol-5-yl)-amide; hydrochloride (40.4mg; 0.11mmol) in DMF (1mL) is added acetic acid (0.05mL; 0.87mmol) and a solution of tetrahydropyranyl-4-carboxaldehyde (37.7mg; 0.33mmol) in DMF (1mL). The reaction is shaken for 4 hours. To the mixture is added a solution of sodium triacetoxyborohydride (93.2mg; 0.44mmol) in DMF (0.4mL). The reaction mixture is shaken for 16 hours at room temperature. After this time, the reaction is quenched with water (0.1mL) and the mixture is concentrated *in vacuo*. Purification by preparative HPLC provides the title compound, m/z 366 [M+H$^+$].

Compounds in Table 7 Method J3 are prepared in a similar manner.

<u>Method K:</u>

Synthesis of (S)-1-(4-Acetyl-piperazine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide (Example 85):



Step 1: Synthesis 4-[(S)-2-(5-*tert*-Butyl-isoxazol-3-ylcarbamoyl)-piperidine-1-carbonyl]-piperazine-1-carboxylic acid *tert*-butyl ester

To a solution of (S)-Piperidine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl) amide; hydrochloride (675mg; 2.345mmol) in THF (18mL) is added N,N-diisopropylethylamine (0.81mL; 4.65mmol) and 4-chlorocarbonyl-piperazine-1-carboxylic acid *tert*-butyl ester (609mg; 2.45mmol). The reaction mixture is left stirring at room temperature for 18 hours. After this time, the reaction mixture is diluted with ethyl acetate and washed with water then brine, dried over Na2SO4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel using ethyl acetate/Hexanes provides the title compound, m/z 464 [$M+H^+$].

Step 2: Synthesis of (S)-1-(Piperazine-1-carbonyl)-piperidine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide

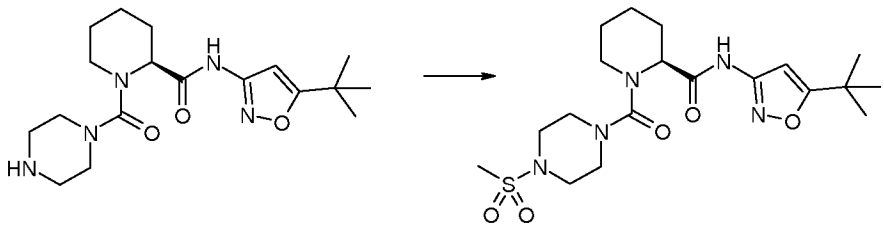
To a solution of 4-[(S)-2-(5-*tert*-Butyl-isoxazol-3-ylcarbamoyl)-piperidine-1-carbonyl]-piperazine-1-carboxylic acid *tert*-butyl ester (655mg; 1.413mmol) in dichloromethane (100mL) is added 4N hydrochloric acid in dioxane (1.25mL; 5mmol) and the reaction mixture is stirred at room temperature for 3 hours. More 4N hydrochloric acid in dioxane (1.25mL; 5mmol) is added and the stirring is continued for another 3 hours. After this time, the reaction

mixture is concentrated to afford the product. The product is taken up in the mixture of ethyl acetate and saturated NaHCO3 aqueous solution to free base the product. The aqueous layer is extracted with ethyl acetate twice. The combined organics are washed with brine, dried over Na2SO4, filtered and concentrated to afford the title compound, m/z 364 [M+H$^+$].

Step 3: Synthesis of (S)-1-(4-Acetyl-piperazine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide (Example 85):

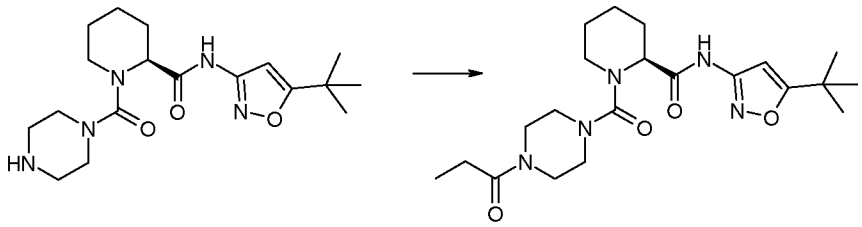
To a solution of (S)-Piperidine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl) amide (60mg; 0.165mmol) in THF (1mL) is added acetic anhydride (0.016mL; 0.17mmol), followed by N,N-diisopropylethylamine (0.03mL; 0.17mmol) and 4-dimethylaminopyridine (4mg; 0.033mmol). The reaction mixture is stirred at room temperature for 18 hours. The mixture is diluted with ethyl acetate and water. The layers are separated and the organic layer is concentrated *in vacuo*. Purification by flash chromatography on silica gel using ethyl acetate/Hexanes provides the title compound, m/z 406 [M+H$^+$].

Synthesis of (S)-1-(4-Methanesulfonyl-piperazine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide (Example 84):



To a solution of (S)-1-(Piperazine-1-carbonyl)-piperidine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide (60mg; 0.165mmol) in THF (1mL) is added methane sulfonyl chloride (0.013mL; 0.17mmol), followed by N,N-diisopropylethylamine (0.03mL; 0.17mmol). The mixture is stirred at room temperature for 18 hours. The mixture is diluted with ethyl acetate and water. The layers are separated and the organic layer is concentrated *in vacuo*. Purification by flash chromatography on silica gel using ethyl acetate/Hexanes provides the title compound, m/z 442 [M+H$^+$].

Synthesis of (S)-1-(4-Propionyl-piperazine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide (Example 86):

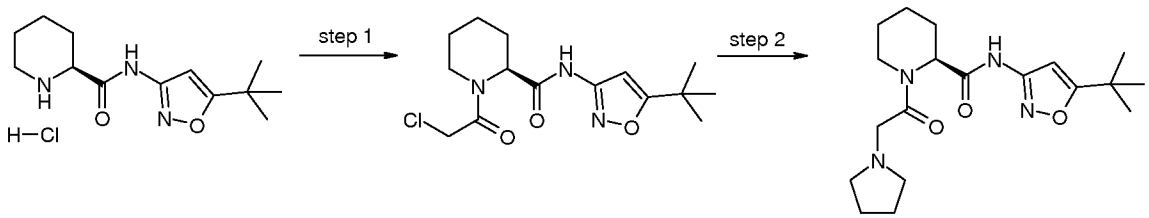


To a solution of (S)-1-(Piperazine-1-carbonyl)-piperidine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide (60mg; 0.165mmol) in THF (1mL) is added propionyl chloride (0.015mL; 0.17mmol), followed by N,N-diisopropylethylamine (0.03mL; 0.17mmol). The mixture is stirred at room temperature for 18 hours. The mixture is diluted with ethyl acetate and water. The layers are separated and the organic layer is concentrated *in vacuo*. Purification by flash chromatography on silica gel using ethyl acetate/Hexanes provides the title compound, m/z 420 [$M+H^+$].

Compounds in Table 7 Method K are prepared in a similar manner.

Method L:

Synthesis of (S)-1-(2-Pyrrolidin-1-yl-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide (Example 93):



Step 1: Synthesis of (S)-1-(2-Chloro-acetyl)-piperidine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide

To a solution of (S)-Piperidine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl) amide; hydrochloride (611mg; 2.123mmol) in THF (15mL) is added N,N-diisopropylethylamine (0.74mL; 4.246mmol), followed by alpha-chloroacetyl chloride (0.17mL; 2.134mmol). The reaction mixture is stirred at room temperature for 18 hours.
The reaction mixture is diluted with ethyl acetate and washed with water then brine, dried over Na2SO4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel using ethyl acetate/Hexanes provides the title compound, m/z 328 [$M+H^+$].

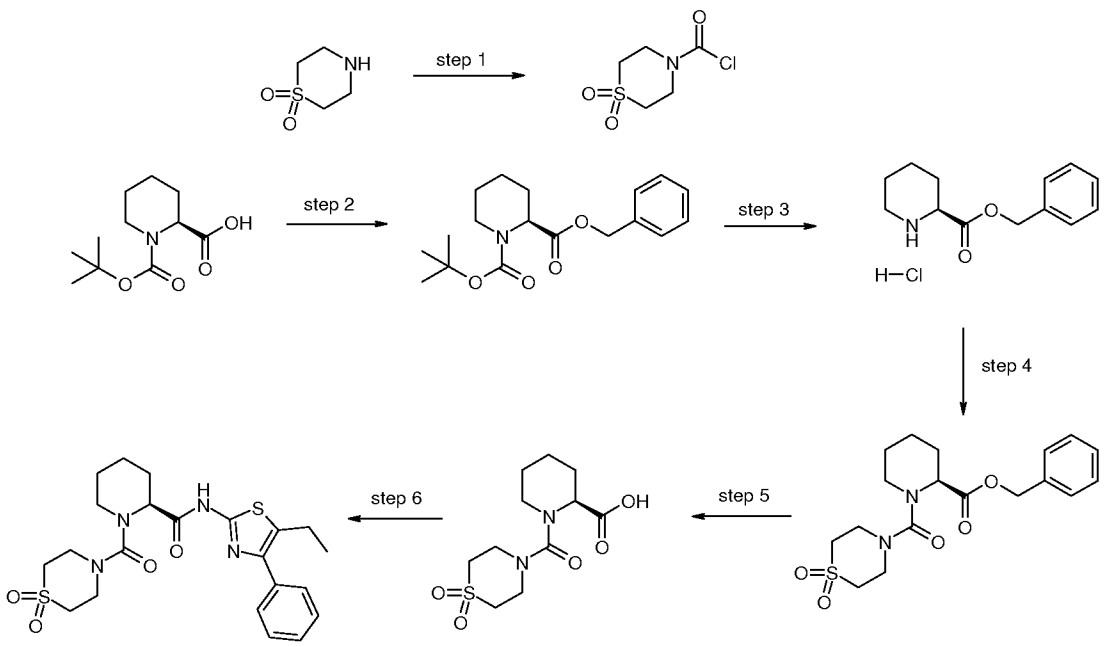
Step 2: Synthesis of (S)-1-(2-Pyrrolidin-1-yl-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide

A mixture of pyrrolidine (33.43mg; 0.47mmol) and 4-dimethylaminopyridine (2mg; 0.016mmol) in DMF (1mL) is added to (S)-1-(2-Chloro-acetyl)-piperidine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide (77mg; 0.235mmol). The reaction mixture is heated at 60°C for 18 hours. Purification by preparative HPLC provides the title compound, m/z 363 [$M+H^+$].

Compounds in Table7 Method L are prepared in a similar manner.

Method M:

Synthesis of (S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-ethyl-4-phenyl-thiazol-2-yl)-amide (Example 113):



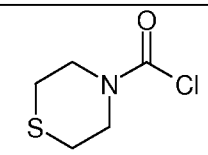
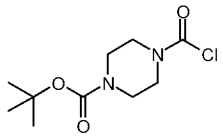
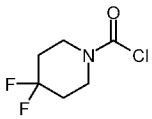
Step 1: Synthesis of 1,1-dioxo-1λ^6-thiomorpholine-4-carbonyl chloride

Thiomorpholine 1,1-dioxide (3g; 22.192mmol) is dissolved in THF (70mL) and cooled to 0 °C. Triethylamine (3.708mL; 26.6mmol) is added, followed by 20% phosgene in toluene (35.229mL; 66.6mmol). The reaction mixture is stirred at room temperature for 18 hours. After this time, the reaction mixture is poured into ethyl ether (200mL), then filtered through Celite®. The Celite® is washed with ethyl ether several times and the combined filtrates are concentrated *in vacuo* to afford the title compound as a white solid. ^{1}H NMR (400MHz, d-$CDCl_3$): δ 3.1-3.2 (m; 4H), 4.1-4.3 (d, 4H).

Intermediates in Table 6 are made in a similar manner.

Table 6:

Structure	Name

	Thiomorpholine-4-carbonyl chloride
	4-Chlorocarbonyl-piperazine-1-carboxylic acid *tert*-butyl ester
	4,4-Difluoro-piperidine-1-carbonyl chloride

Step 2: Synthesis of (S)-Piperidine-1,2-dicarboxylic acid 2-benzyl ester 1-*tert*-butyl ester

To a suspension of (S)-piperidine-2-carboxylic acid (5.159g; 22.5mmol) in acetonitrile (50mL) at 0 oC is added benzyl bromide (2.5mL; 21.019mmol), followed by 1,5-diazabicyclo[4.3.0]non-5-ene (2.6mL; 21.04mmol). The reaction mixture is left stirring and slowly warm to room temperature overnight. The reaction mixture is diluted with ethyl acetate and washed with water, saturated NH4Cl aqueous solution then brine, dried over Na2SO4, filtered and concentrated *in vacuo* to afford the title compound, m/z 320 [$M+H^+$].

Step 3 is the same as Method F step 2.

Step 4 is the same as Method G.

Step 5: Synthesis of (S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid

To a solution of (S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid benzyl ester (1.53g; 4.021mmol) in ethyl acetate (100mL) is added 10% palladium on carbon (500mg) and the reaction mixture is placed under an atmosphere of hydrogen and stirred at room temperature overnight. After this time, the mixture is filtered through Celite®.

The Celite® is washed with 50% ethyl acetate in ethanol then ethanol and the combined filtrates are concentrated *in vacuo* to afford the title compound as a white solid, m/z 291 [M+H$^+$].

Step 6: Various amide coupling procedures can be used

Amide coupling procedure 1: is the same as Method F, step 1, amide coupling procedure 2.

Synthesis of (S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-ethyl-4-phenyl-thiazol-2-yl)-amide

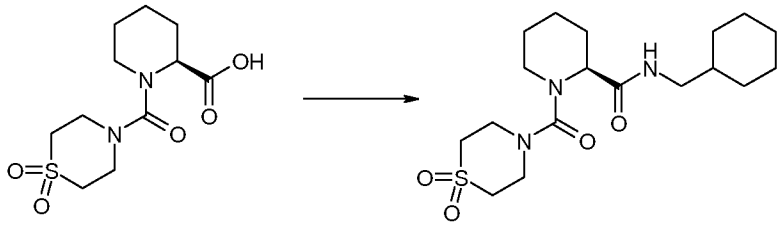
To a solution of (S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (92mg; 0.317mmol) and 2-amino-5-ethyl-4-phenyl-1,3-thiazole (64.8mg; 0.317mmol) in dichloromethane (4mL) is added 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (79.1mg; 0.32mmol). The reaction mixture is left stirring at room temperature for 18 hours. The reaction mixture is directly purified by preparative HPLC provides the title compound, m/z 477 [M+H$^+$].

Compounds in Table 7 Method M1 are prepared in a similar manner.

Amide coupling procedure 2: is the same as Method F, step 1, coupling procedure 4:

Compounds in Table 7 Method M2 are prepared in a similar manner.

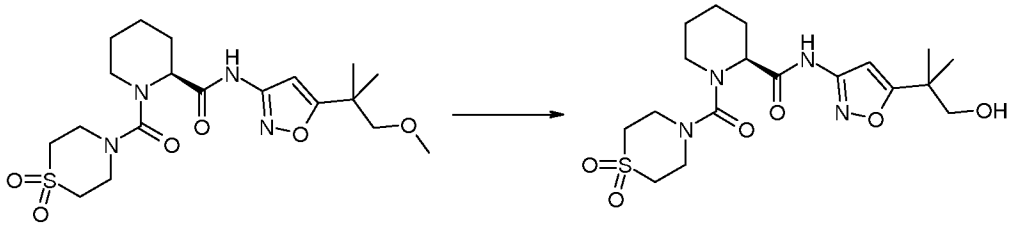
Amide coupling procedure 3: Synthesis of (S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid cyclohexylmethyl-amide (Example 33):



To a solution of (S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (58.07mg; 0.2mmol), N,N-diisopropylethylamine (142mg; 1.1mmol) and cyclohexanemethylamine (33.96mg; 0.3mmol) in dichloromethane (0.4mL) at room temperature is added bromotripyrrolidinophosphonium hexafluorophosphate (279.7mg; 0.6mmol). The reaction mixture is shaken on an orbital shaker for 16 hours. The reaction mixture is concentrated *in vacuo*. Purification by preparative HPLC affords the title compound, m/z 386 [M+H$^+$].

Compounds in Table 7 Method M3 are prepared in a similar manner.

Synthesis of (S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [5-(2-hydroxy-1,1-dimethyl-ethyl)-isoxazol-3-yl]-amide (Example 145):

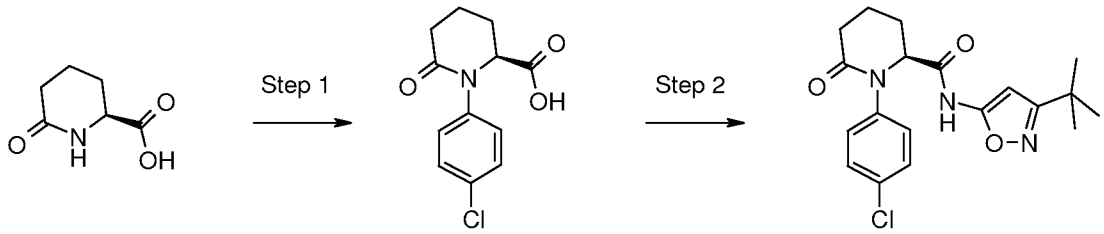


(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [5-(2-methoxy-1,1-dimethyl-ethyl)-isoxazol-3-yl]-amide (110mg; 0.249mmol) is dissolved in ethanethiol (2mL) and cooled to 0°C. Aluminum chloride (498mg; 3.735mmol) is added to the solution and the reaction mixture is stirred at room temperature for 2 hours. The mixture is quenched with water (10mL) and 3 drops of concentrated HCl aqueous solution and extracted with ethyl acetate 3 times. The organics are combined and washed with brine, dried over

Na2SO4, filtered and concentrated. Purification by preparative HPLC affords title compound, m/z 429 [M+H$^+$].

Method N:

Synthesis of (S)-1-(4-Chloro-phenyl)-6-oxo-piperidine-2-carboxylic acid (3-*tert*-butyl-isoxazol-5-yl)-amide (Example 131):



Step 1: Synthesis of (S)-1-(4-Chloro-phenyl)-6-oxo-piperidine-2-carboxylic acid

To a stirred suspension of (S)-1-(4-chloro-phenyl)-6-oxo-piperidine-2-carboxylic acid (1.368g, 9.558mmol) in 1,2-dichloroethane (35 mL) 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) (3.1mL, 20.854mmol) is added at room temperature. After 10 min di-μ-hydroxy-bis[N,N,N',N'-tetramethylenediamine)-copper (II) chloride (Cu-TMEDA) (1.614g, 3.476mmol) is added to the clear solution. The mixture is stirred for 10 min and 4-chlorophenylboronic acid (1.495g, 9.558mmol) is added. After 20 h solvent is evaporated *in vacuo*, the concentrate taken up in saturated sodium bicarbonate solution (150mL) and the aqueous layer is washed with ethyl acetate (3X100mL). The aqueous layer is treated with 1 N hydrochloric acid to pH 2 and extracted with ethyl acetate (3X100mL). Combined organic extracts washed with brine (2X50mL), dried over anhydrous sodium sulfate and solvent removed *in vacuo* to give the title compound as an off-white solid, m/z 254 [M+H$^+$].

Step 2: Synthesis of (S)-1-(4-Chloro-phenyl)-6-oxo-piperidine-2-carboxylic acid (3-*tert*-butyl-isoxazol-5-yl)-amide

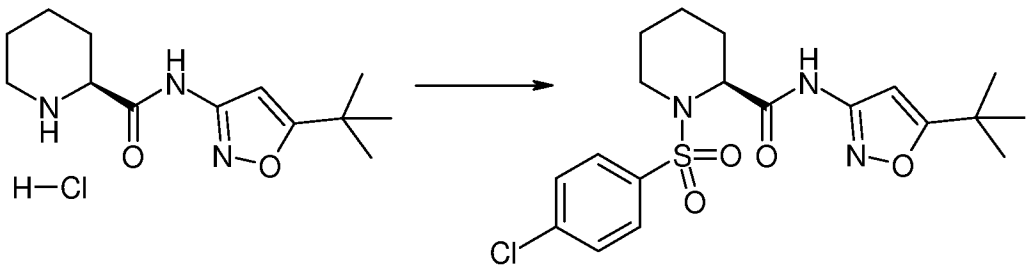
To a cold slurry of (S)-1-(4-Chloro-phenyl)-6-oxo-piperidine-2-carboxylic acid (0.2g; 0.788mmol) and 5-amino-3-tert-butylisoxazole (0.110g; 0.788mmol) in pyridine (0.956mL;

11.820mmol) is added phosphorous oxychloride (0.088mL; 0.946mmol). The mixture is stirred at 0°C for 30 minutes and then diluted with water and extracted with ethyl acetate several times. The organics are combined and washed with water and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by preparative HPLC affords title compound, m/z 376 [$M+H^+$].

Compounds in Table7 Method N are prepared in a similar manner.

Method O:

Synthesis of (S)-1-(4-chloro-benzenesulfonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide (Example 99)

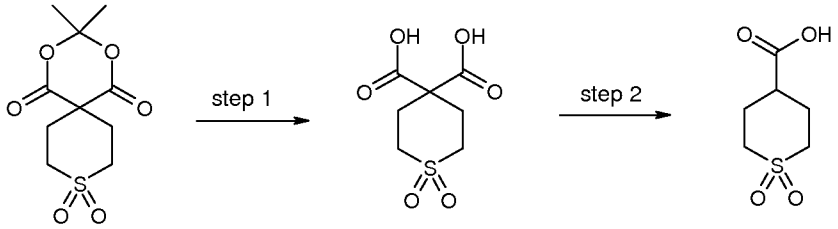


To a solution of (S)-Piperidine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl) amide; hydrochloride (110mg; 0.382mmol) in DMF (1.5mL) is added 4-chlorobenzenesulfonyl chloride (80.6mg; 0.382mmol) and N,N-diisopropylethylamine (0.133mL; 0.764mmol). The reaction mixture is left stirring at room temperature for 18 hours in the presence of catalytic amount of 4-dimethylaminopyridine. The reaction mixture is quenched with water and extracted with ethyl acetate twice. The combined organics are washed with water then brine, dried over Na2SO4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel using ethyl acetate/Hexanes provides the title compound, m/z 426 [$M+H^+$].

Compounds in Table7 Method O are prepared in a similar manner.

Synthesis of intermediates:

Synthesis of (S)-1-(1,1-Dioxo-hexahydro-1λ^6-thiopyran-4-carbonyl)-piperidine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide (Intermediate for Example 108):



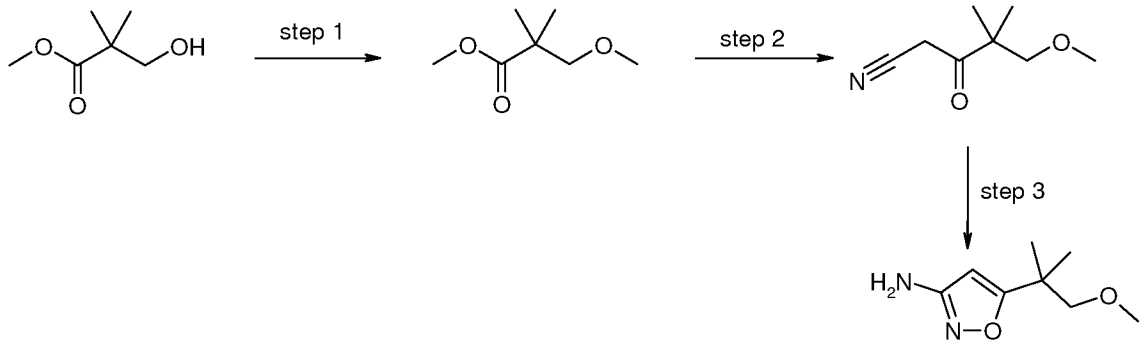
Step 1: Synthesis of 1,1-Dioxo-tetrahydro-1λ^6-thiopyran-4,4-dicarboxylic acid

3,3-Dimethyl-9,9-dioxo-2,4-dioxa-9λ^6-thia-spiro[5.5]undecane-1,5-dione (200mg; 0.763mmol) is dispersed in 2M HCl aqueous solution (2mL) and the vial is placed into microwave oven for 23 minutes at 100°C. After cooling, the reaction mixture is extracted with diethyl ether once. The aqueous layer is saturated with solid sodium chloride and extracted with 50% THF in ethyl acetate three times. The organics are combined and dried over Na2SO4, filtered and concentrated *in vacuo* to afford the title compound.

Step 2: Synthesis of 1,1-Dioxo-hexahydro-1λ^6-thiopyran-4-carboxylic acid

In a microwave vial is added 1,1-Dioxo-tetrahydro-1λ^6-thiopyran-4,4-dicarboxylic acid (112mg; 0.504mmol), 2% cross-linked poly-4-vinylpyridine (225mg) and DMF (2.1mL). The vial is sealed and placed into microwave oven for 10 minutes at 95°C. After cooling, the mixture is filtered through filter paper and washed the paper with diethyl ether. The filtrate is concentrated *in vacuo* to afford the title compound.

Synthesis of 5-(2-Methoxy-1,1-dimethyl-ethyl)-isoxazol-3-ylamine (Intermediate for Example 144)



Step 1: Synthesis of 3-Methoxy-2,2-dimethyl-propionic acid methyl ester

Powdered potassium hydroxide (3.519g; 62.712mmol) is stirred in DMSO (30mL) for 5 minutes before adding hydroxypivalic acid methyl eater (2mL; 15.678mmol) and methyl iodide (3.904mL; 62.712mmol). The reaction mixture is stirred at room temperature for 30 minutes. The mixture is quenched with water and extracted with dichloromethane 3 times. The organics are combined and washed with water twice then brine, dried over Na2SO4, filtered and concentrated *in vacuo* to provide the title compound.

Step 2: Synthesis of 5-Methoxy-4,4-dimethyl-3-oxo-pentanenitrile

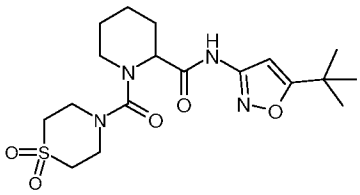
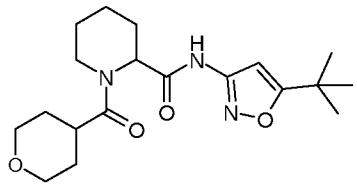
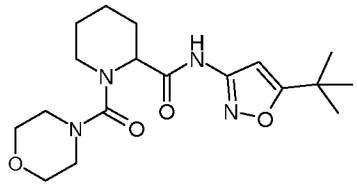
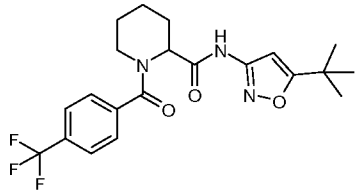
60% sodium hydride in mineral oil (667.2mg, 16.68mmol) in toluene (15mL) is heated to reflux. A solution of 3-methoxy-2,2-dimethyl-propionic acid methyl ester (1.742g, 11.916mmol) and acetonitrile (0.878mL, 16.68mmol) in toluene (5mL) is added dropwise through an additional funnel into the NaH suspension in toluene. After the addition, the reaction is stirred at reflux for 3 hours. After cooling, the reaction mixture is neutralized to PH ~7 by adding 1N HCl aqueous solution. The mixture is extracted with ethyl acetate 3 times. The organics are combined and washed with brine, dried over Na2SO4, filtered and concentrated *in vacuo* to afford the title compound.

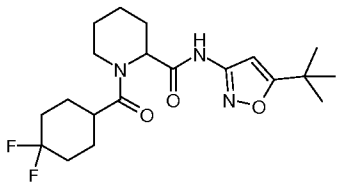
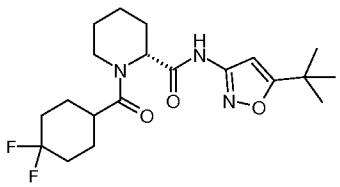
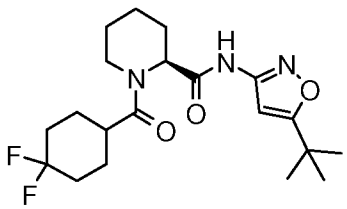
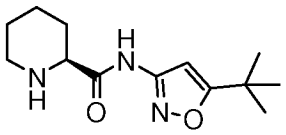
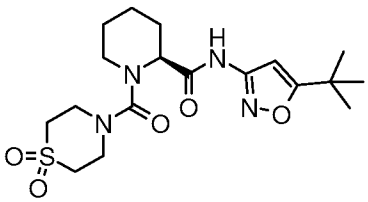
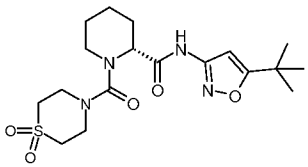
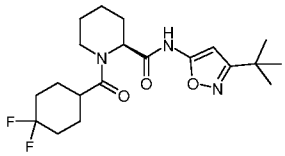
Step 3: Synthesis of 5-(2-Methoxy-1,1-dimethyl-ethyl)-isoxazol-3-ylamine

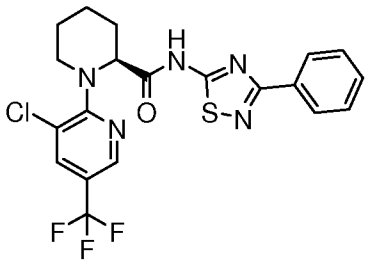
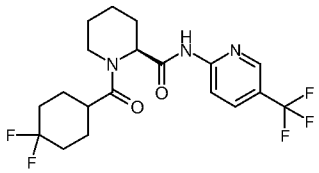
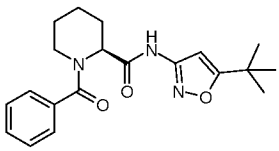
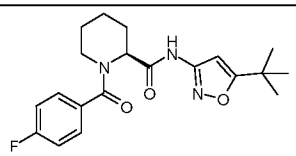
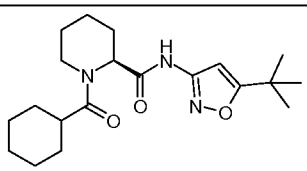
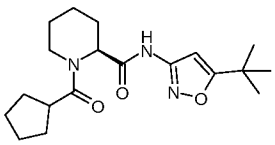
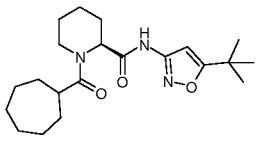
A solution of hydroxylamine sulfate (976mg; 5.947mmol) in water (4mL) is added to a stirred solution of 5-methoxy-4,4-dimethyl-3-oxo-pentanenitrile (1.678g; 10.812mmol) and sodium

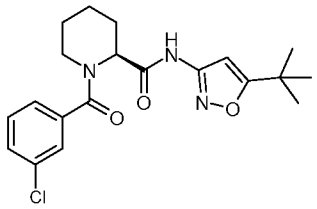
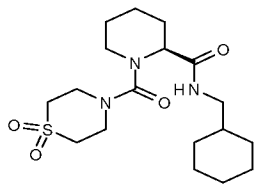
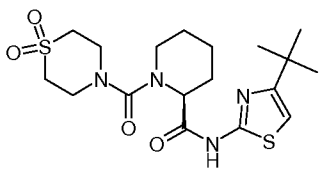
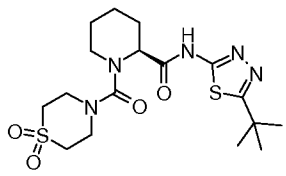
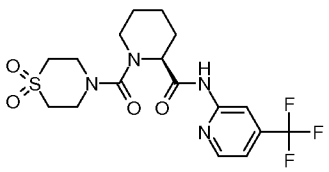
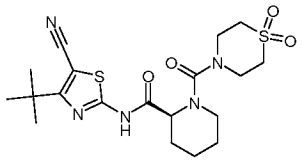
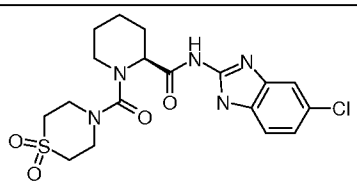
hydroxide (490.3mg; 11.89mmol) in water (13mL). The reaction mixture is heated to reflux over 30 minutes and kept at reflux for 1 hour. After cooling, 37% HCl aqueous solution (0.8mL; 9.73mmol) is added and the mixture is heated to reflux for 20 minutes. After cooling, the mixture's pH is adjusted to ~ 12 by adding 40% sodium hydroxide aqueous solution. The mixture is extracted with methylene chloride 3 times. The organics are combined and washed with brine, dried over Na2SO4, filtered and concentrated *in vacuo* to afford the title compound, m/z 171 [M+H$^+$].

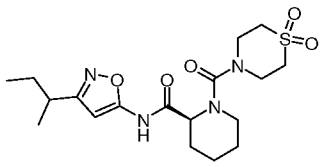
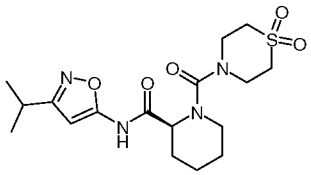
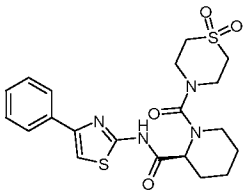
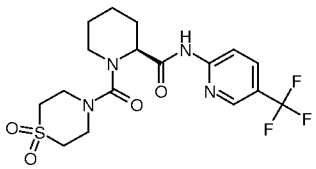
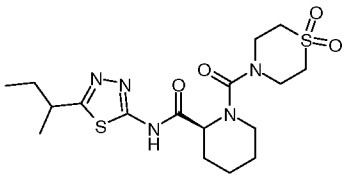
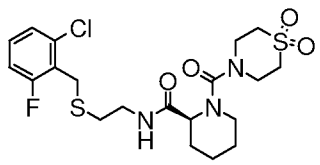
Table 7: Examples

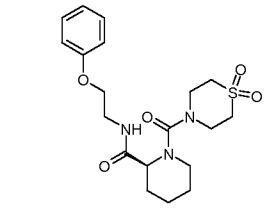
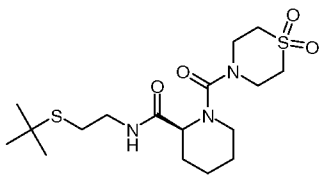
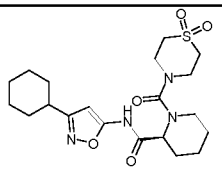
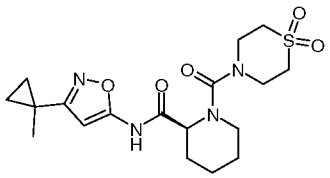
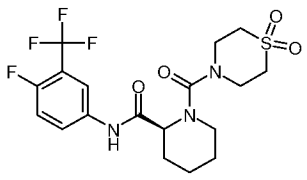
Example	Structure	Name	m/z [M+H$^+$]	Method
14		1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	413	G
15		1-(Tetrahydro-pyran-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	364	F1
16		1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	413	G
17		1-(4-Trifluoromethyl-benzoyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	424	F2

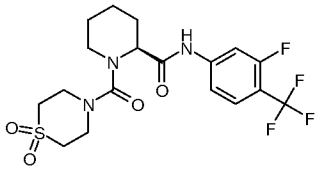
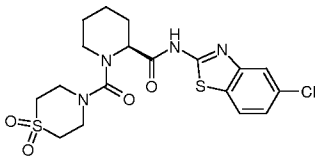
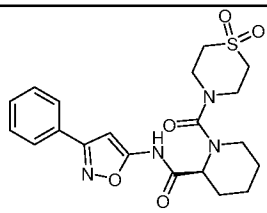
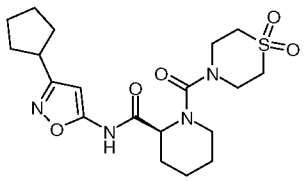
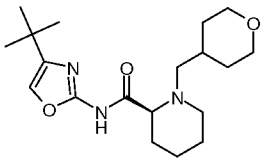
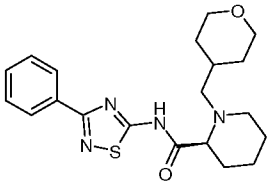
18		1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	398	F2
19		(R)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	398	F1
20		(S)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	398	F1
21		(S)-Piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	252	F
22		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	413	G
23		(R)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	413	G
24		(S)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide	398	F1

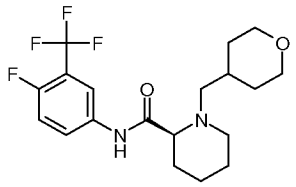
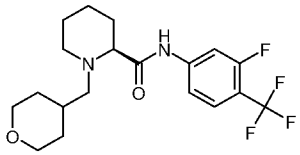
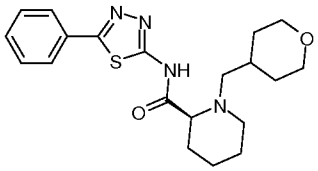
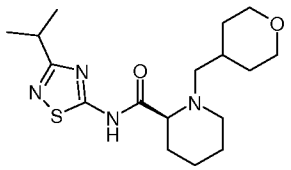
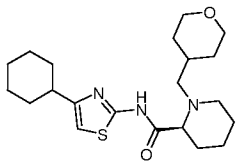
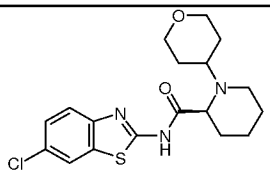
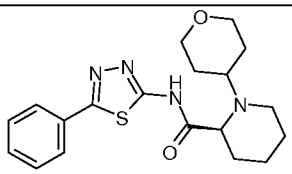
25		(S)-3'-Chloro-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-1,2'-bipyridinyl-2-carboxylic acid (3-phenyl-1,2,4-thiadiazol-5-yl)-amide	468	H
26		(S)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide	420	F1
27		(S)-1-Benzoyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	356	F1
28		(S)-1-(4-Fluoro-benzoyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	374	F1
29		S)-1-Cyclohexanecarbonyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	362	F1
30		(S)-1-Cyclopentanecarbonyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	348	F1
31		(S)-1-Cycloheptanecarbonyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	376	F1

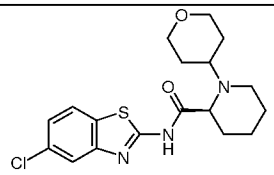
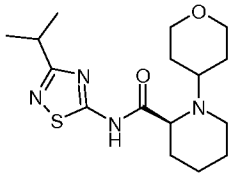
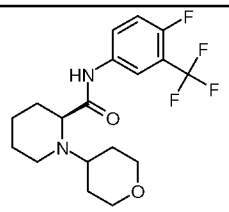
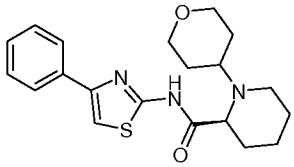
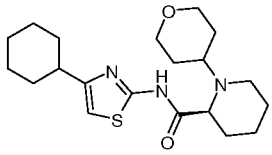
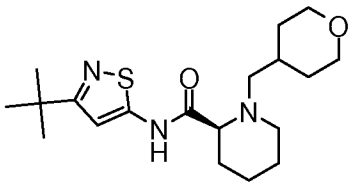
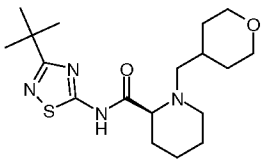
32		(S)-1-(3-Chloro-benzoyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	390/ 392	F1
33		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid cyclohexylmethyl-amide	386	M 3
34		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (4-tert-butyl-thiazol-2-yl)-amide	429	M 3
35		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide	430	M 3
36		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (4-trifluoromethyl-pyridin-2-yl)-amide	435	G
37		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (4-tert-butyl-5-cyano-thiazol-2-yl)-amide	454	G
38		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-	440	G

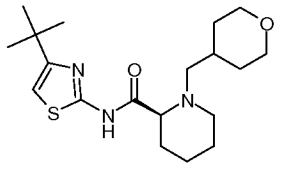
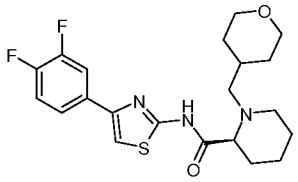
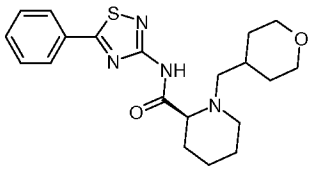
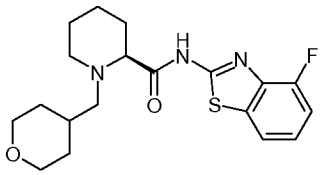
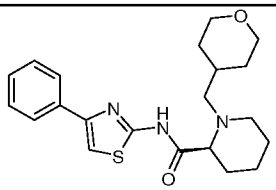
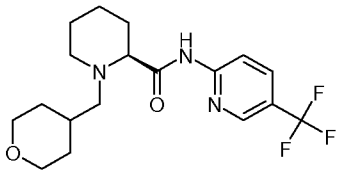
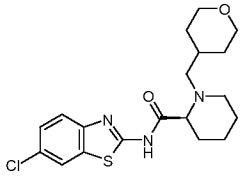
		chloro-1H-benzimidazol-2-yl)-amide		
39		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-sec-butyl-isoxazol-5-yl)-amide	413	G
40		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-isopropyl-isoxazol-5-yl)-amide	399	G
41		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (4-phenyl-thiazol-2-yl)-amide	449	G
42		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide	435	G
43		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-sec-butyl-1,3,4-thiadiazol-2-yl)-amide	430	G
44		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [2-(2-chloro-6-fluoro-benzylsulfanyl)-	493	M 1

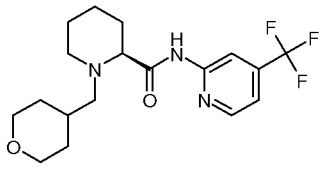
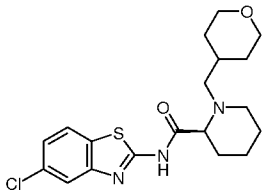
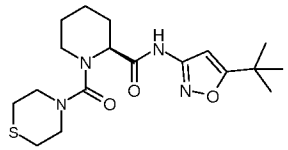
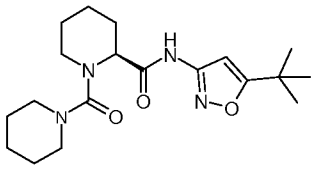
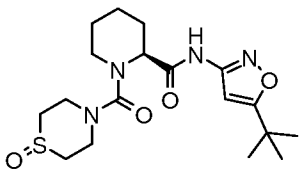
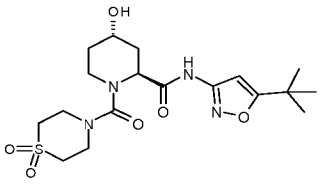
		ethyl]-amide		
45		(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (2-phenoxy-ethyl)-amide	410	G
46		(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (2-tert-butylsulfanyl-ethyl)-amide	406	G
47		(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-cyclohexyl-isoxazol-5-yl)-amide	439	G
48		(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [3-(1-methyl-cyclopropyl)-isoxazol-5-yl]-amide	411	G
49		(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (4-fluoro-3-trifluoromethyl-phenyl)-amide	452	G

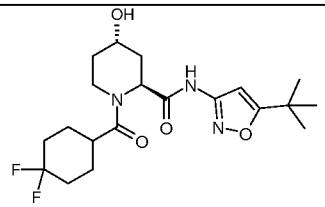
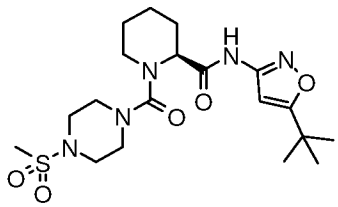
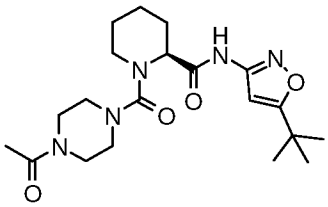
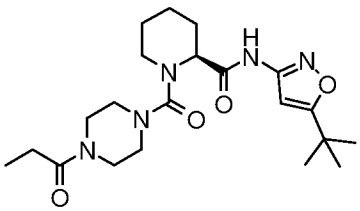
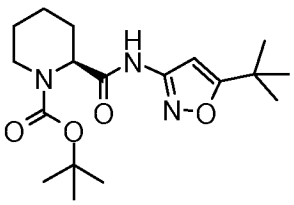
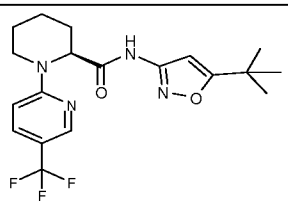
50		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-fluoro-4-trifluoromethyl-phenyl)-amide	452	G
51		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-chloro-benzothiazol-2-yl)-amide	457	G
52		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-phenyl-isoxazol-5-yl)-amide	433	G
53		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-cyclopentyl-isoxazol-5-yl)-amide	425	G
54		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-tert-butyl-oxazol-2-yl)-amide	350	J1
55		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-phenyl-1,2,4-thiadiazol-5-yl)-amide	387	J1

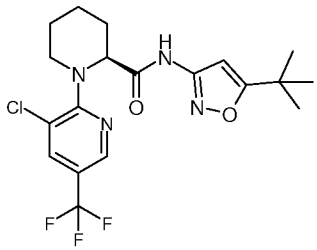
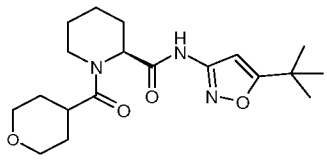
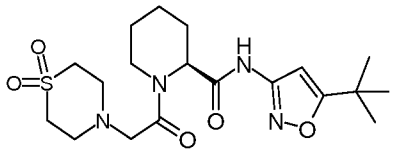
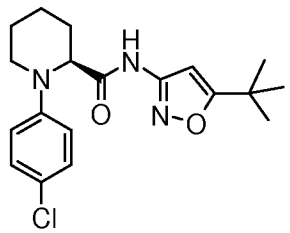
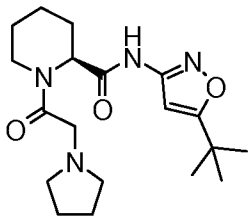
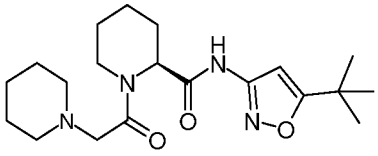
56		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-fluoro-3-trifluoromethyl-phenyl)-amide	389	J1
57		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-fluoro-4-trifluoromethyl-phenyl)-amide	389	J1
58		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-phenyl-1,3,4-thiadiazol-2-yl)-amide	387	J1
59		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-isopropyl-1,2,4-thiadiazol-5-yl)-amide	353	J1
60		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-cyclohexyl-thiazol-2-yl)-amide	392	J1
61		(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (6-chloro-benzothiazol-2-yl)-amide	380	J1
62		(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (5-phenyl-1,3,4-thiadiazol-2-yl)-amide	373	J1

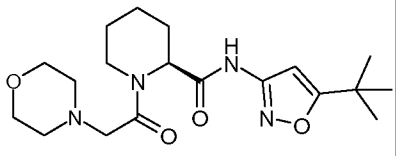
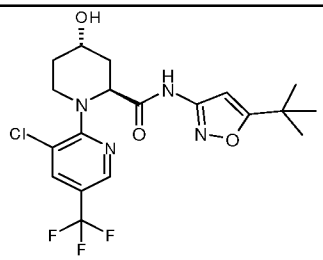
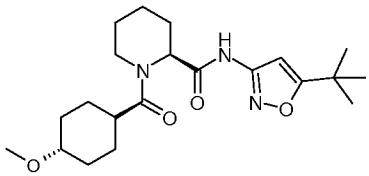
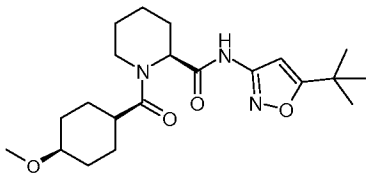
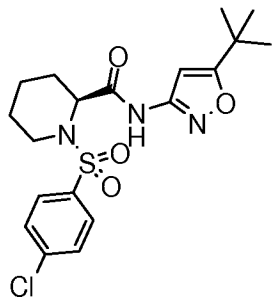
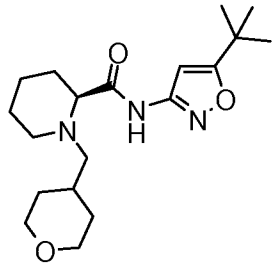
63		(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (5-chloro-benzothiazol-2-yl)-amide	380	J1
64		(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (3-isopropyl-1,2,4-thiadiazol-5-yl)-amide	339	J1
65		(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (4-fluoro-3-trifluoromethyl-phenyl)-amide	375	J3
66		(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (4-phenyl-thiazol-2-yl)-amide	372	J3
67		(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (4-cyclohexyl-thiazol-2-yl)-amide	378	J3
68		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-tert-butyl-isothiazol-5-yl)-amide	366	J3
69		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-tert-butyl-1,2,4-thiadiazol-5-yl)-amide	367	J3

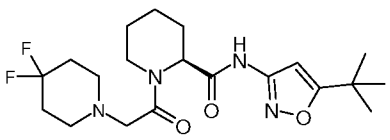
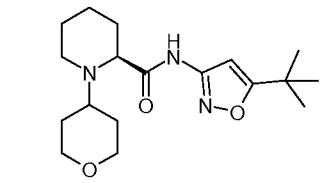
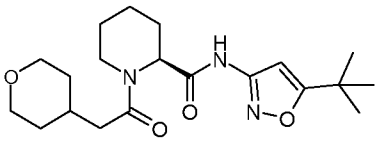
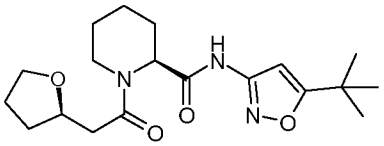
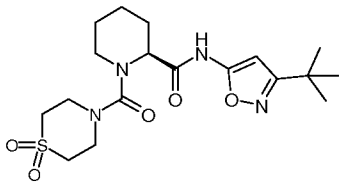
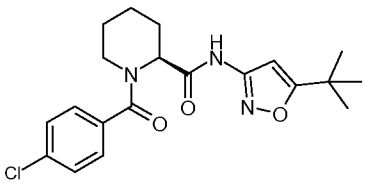
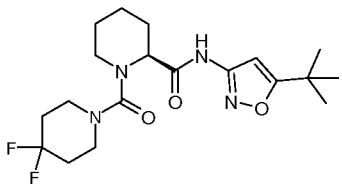
70		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-tert-butyl-thiazol-2-yl)-amide	366	J3
71		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid [4-(3,4-difluoro-phenyl)-thiazol-2-yl]-amide	422	J3
72		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-phenyl-1,2,4-thiadiazol-3-yl)-amide	387	J3
73		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-fluoro-benzothiazol-2-yl)-amide	378	J3
74		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-phenyl-thiazol-2-yl)-amide	386	J3
75		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide	372	J3
76		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (6-chloro-benzothiazol-2-yl)-amide	394	J3

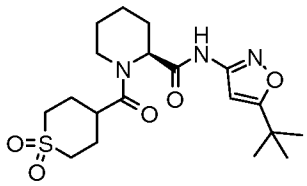
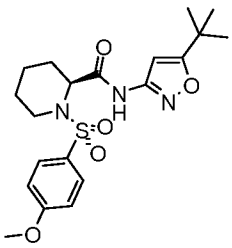
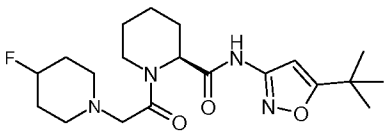
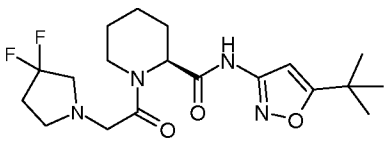
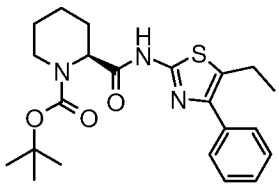
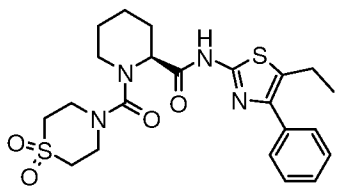
77		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-trifluoromethyl-pyridin-2-yl)-amide	372	J3
78		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-chloro-benzothiazol-2-yl)-amide	394	J3
79		(S)-1-(Thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	381	G
80		(S)-1-(Piperidine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	363	G
81		(S)-1-(1-Oxo-1l4-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	397	G
82		(2S,4S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-4-hydroxy-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	429	G

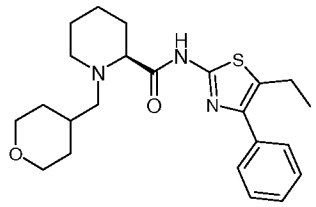
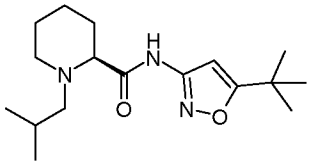
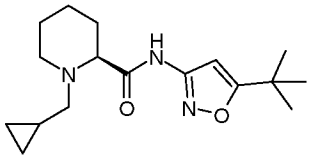
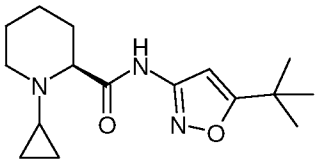
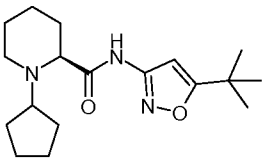
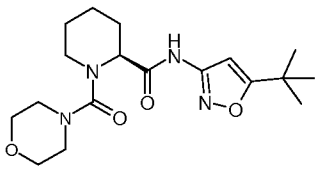
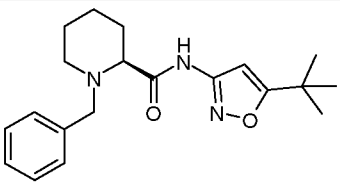
83		(2S,4S)-1-(4,4-Difluoro-cyclohexanecarbonyl)-4-hydroxy-piperidine-2-carboxylic acid (5-tert-butyl isoxazol-3-yl)-amide	414	F1
84		(S)-1-(4-Methanesulfonyl-piperazine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	442	K
85		(S)-1-(4-Acetyl-piperazine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	406	K
86		(S)-1-(4-Propionyl-piperazine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	420	K
87		(S)-2-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester	352	F
88		(S)-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	397	H

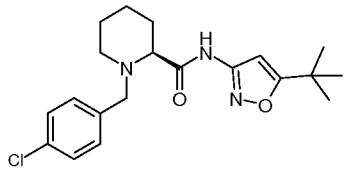
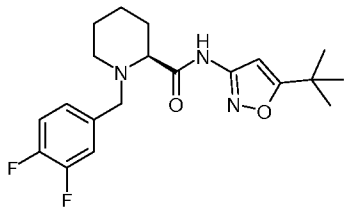
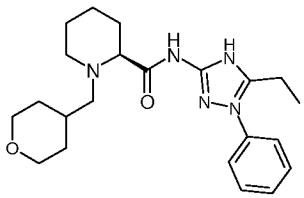
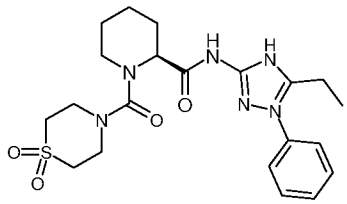
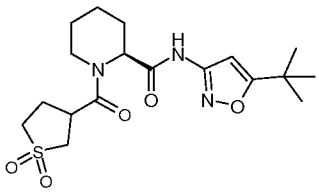
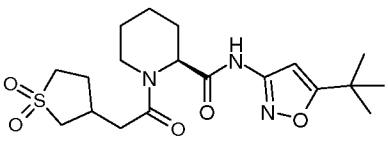
89		(S)-3'-Chloro-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	431	H
90		(S)-1-(Tetrahydro-pyran-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	364	F1
91		(S)-1-[2-(1,1-Dioxo-1λ^6-thiomorpholin-4-yl)-acetyl]-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	427	F1
92		(S)-1-(4-Chloro-phenyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	362	I
93		(S)-1-(2-Pyrrolidin-1-yl-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	363	L
94		(S)-1-(2-Piperidinyl-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	377	L

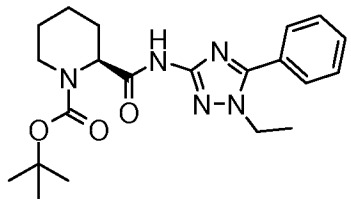
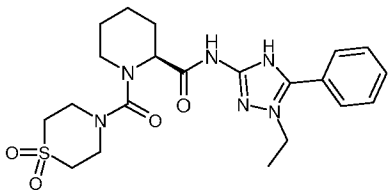
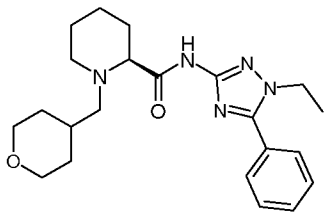
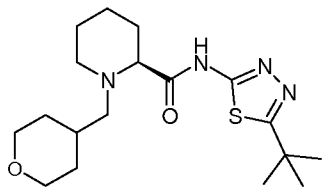
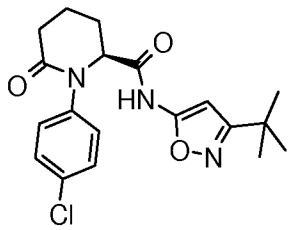
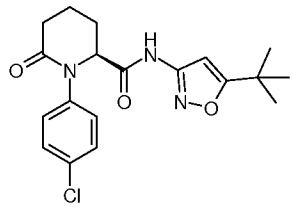
95		(S)-1-(2-Morpholin-4-yl-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	379	L
96		(2S,4S)-3'-Chloro-4-hydroxy-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	447/ 449	H
97		(S)-1-(4-trans-Methoxy-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	392	F1
98		(S)-1-(4-cis-Methoxy-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	392	F1
99		(S)-1-(4-Chloro-benzenesulfonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	426	O
100		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	350	J1

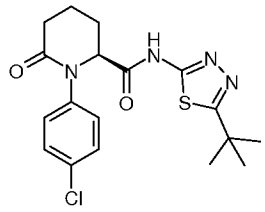
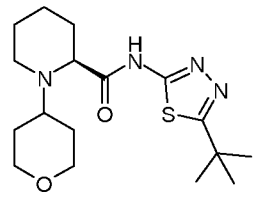
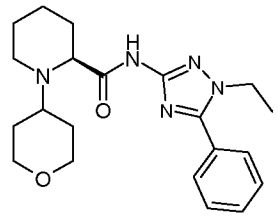
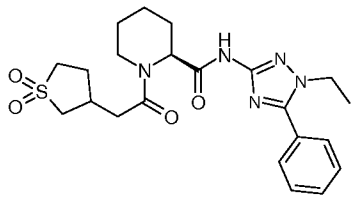
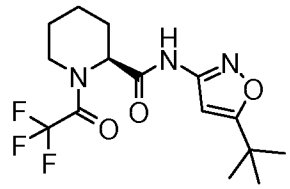
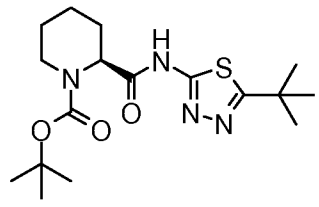
101		(S)-1-[2-(4,4-Difluoro-piperidin-1-yl)-acetyl]-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	413	L
102		(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	336	J1
103		(S)-1-(2-Tetrahydro-pyran-4-yl-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	378	F1
104		(S)-1-((R)-2-Tetrahydro-furan-2-yl-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	364	F1
105		(S)-1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide	413	G
106		(S)-1-(4-Chloro-benzoyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	390	F1
107		(S)-1-(4,4-Difluoro-piperidine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	399	G

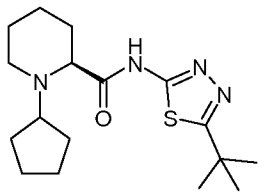
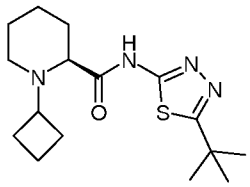
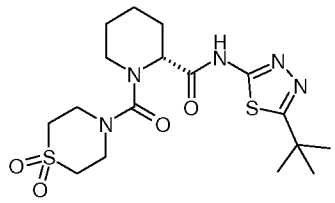
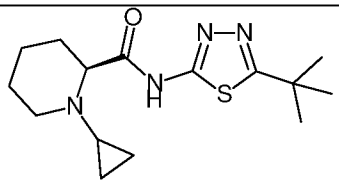
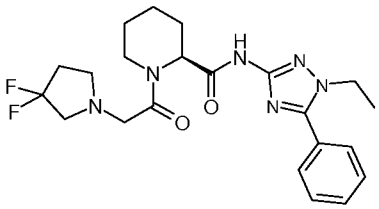
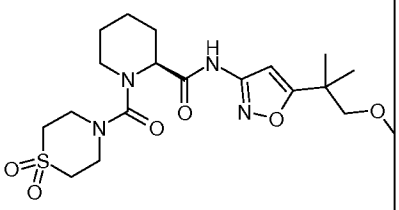
108		(S)-1-(1,1-Dioxo-hexahydro-1λ^6-thiopyran-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	412	F1
109		(S)-1-(4-Methoxy-benzenesulfonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	442	O
110		(S)-1-[2-(4-Fluoro-piperidin-1-yl)-acetyl]-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	395	L
111		(S)-1-[2-(3,3-Difluoro-pyrrolidin-1-yl)-acetyl]-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	399	L
112		(S)-2-(5-Ethyl-4-phenyl-thiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester	416	F
113		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-ethyl-4-phenyl-thiazol-2-yl)-amide	477	M 1

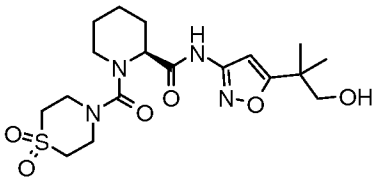
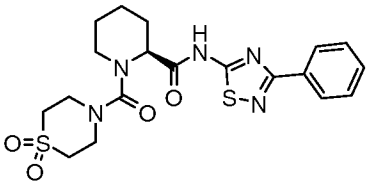
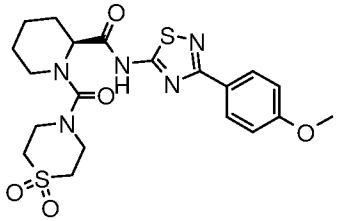
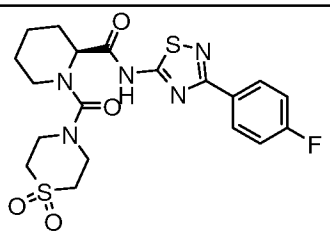
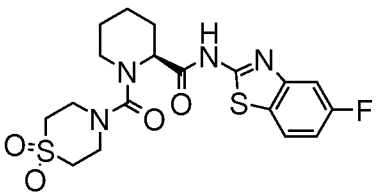
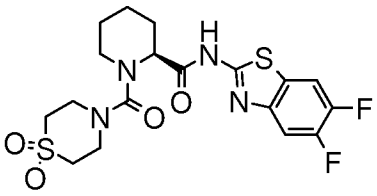
114		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-ethyl-4-phenyl-thiazol-2-yl)-amide	414	J1
115		(S)-1-Isobutyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	308	J1
116		(S)-1-Cyclopropylmethyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	306	J1
117		(S)-1-Cyclopropyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	292	J2
118		(S)-1-Cyclopentyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	320	J1
119		(S)-1-(Morpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	365	G
120		(S)-1-(benzyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	342	J1

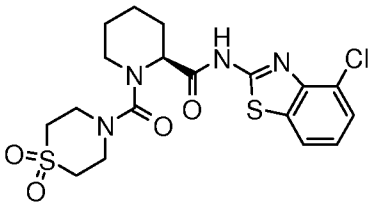
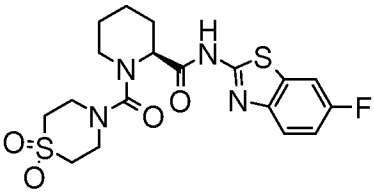
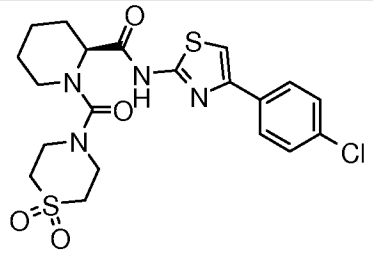
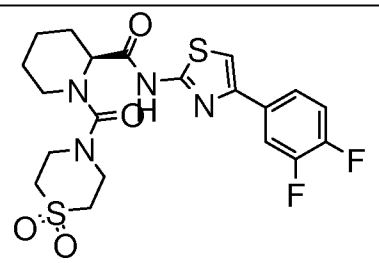
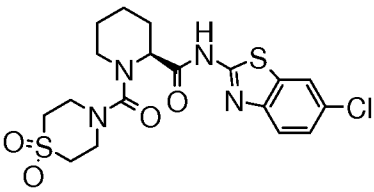
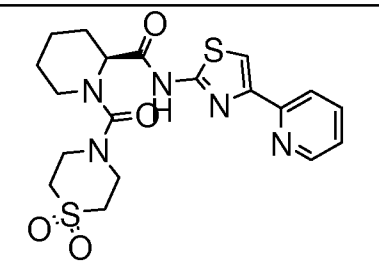
121		(S)-1-(4-Chloro-benzyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	376/ 378	J1
122		(S)-1-(3,4-Difluoro-benzyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	378	J1
123		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-ethyl-1-phenyl-1H-1,2,4-triazol-3-yl)-amide	398	J1
124		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-ethyl-1-phenyl-1H-1,2,4-triazol-3-yl)-amide	461	G
125		(S)-1-(1,1-Dioxo-tetrahydro-1λ6-thiophene-3-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	398	F1
126		(S)-1-[2-(1,1-Dioxo-tetrahydro-1λ^6-thiophen-3-yl)-acetyl]-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	412	F1

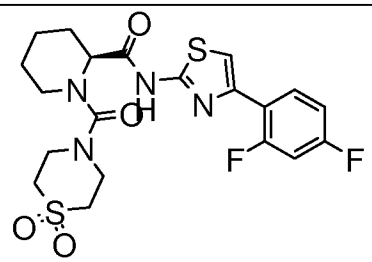
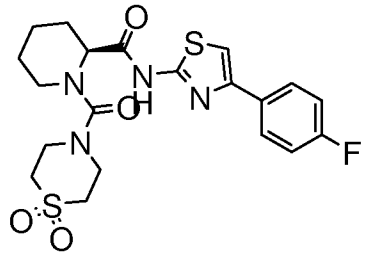
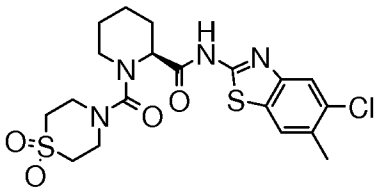
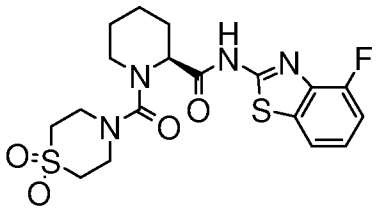
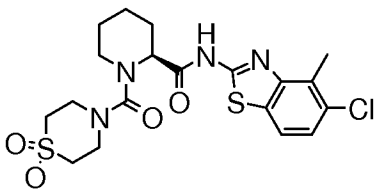
127		(S)-2-(1-Ethyl-5-phenyl-1H-1,2,4-triazol-3-ylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester	400	F
128		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (1-ethyl-5-phenyl-1H-1,2,4-triazol-3-yl)-amide	461	G
129		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (1-ethyl-5-phenyl-1H-1,2,4-triazol-3-yl)-amide	398	J1
130		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide	367	J1
131		(S)-1-(4-Chloro-phenyl)-6-oxo-piperidine-2-carboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide	376/ 378	N
132		(S)-1-(4-Chloro-phenyl)-6-oxo-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	376/ 378	N

133		(S)-1-(4-Chloro-phenyl)-6-oxo-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide	393/ 395	N
134		(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide	353	J1
135		(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (1-ethyl-5-phenyl-1H-1,2,4-triazol-3-yl)-amide	384	J1
136		(S)-1-[2-(1,1-Dioxo-tetrahydro-1λ^6-thiophen-3-yl)-acetyl]-piperidine-2-carboxylic acid (1-ethyl-5-phenyl-1H-1,2,4-triazol-3-yl)-amide	460	F1
137		(S)-1-(2,2,2-Trifluoro-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	348	F3
138		(S)-2-(5-tert-Butyl-1,3,4-thiadiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester	369	F

139		(S)-1-Cyclopentyl-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide	337	J1
140		(S)-1-Cyclobutyl-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide	323	J1
141		(R)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide	430	G
142		(S)-1-Cyclopropyl-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide	309	J2
143		(S)-1-[2-(3,3-Difluoro-pyrrolidin-1-yl)-acetyl]-piperidine-2-carboxylic acid (1-ethyl-5-phenyl-1H-1,2,4-triazol-3-yl)-amide	447	L
144		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [5-(2-methoxy-1,1-dimethyl-ethyl)-isoxazol-3-yl]-amide	443	M 2

145		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [5-(2-hydroxy-1,1-dimethyl-ethyl)-isoxazol-3-yl]-amide	429	M 2
146		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-phenyl-1,2,4-thiadiazol-5-yl)-amide	450	G
154		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [3-(4-methoxy-phenyl)-[1,2,4]thiadiazol-5-yl]-amide	480	F4
155		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [3-(4-fluoro-phenyl)-[1,2,4]thiadiazol-5-yl]-amide	468	F4
156		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-fluoro-benzothiazol-2-yl)-amide	441	F4
157		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5,6-difluoro-benzothiazol-2-yl)-amide	459	F4

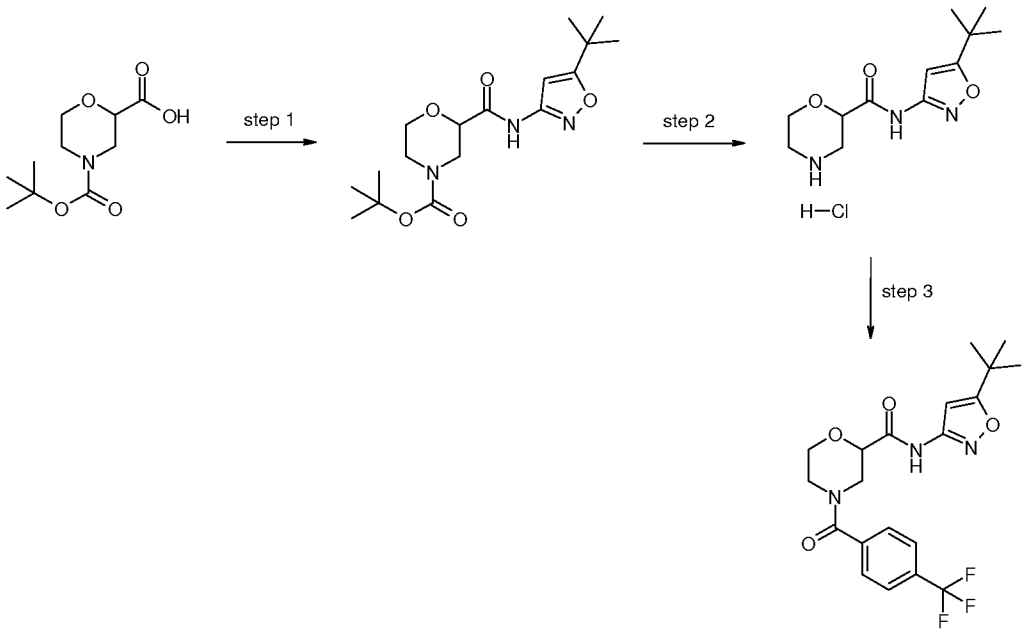
158		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (4-chloro-benzothiazol-2-yl)-amide	457	F4
159		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (6-fluoro-benzothiazol-2-yl)-amide	441	F4
160		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [4-(4-chloro-phenyl)-thiazol-2-yl]-amide	483	F4
161		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [4-(3,4-difluoro-phenyl)-thiazol-2-yl]-amide	485	F4
162		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (6-chloro-benzothiazol-2-yl)-amide	457	F4
163		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (4-pyridin-2-yl-thiazol-2-yl)-amide	451	F4

164		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [4-(2,4-difluoro-phenyl)-thiazol-2-yl]-amide	485	F4
165		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [4-(4-fluoro-phenyl)-thiazol-2-yl]-amide	467	F4
166		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-chloro-6-methyl-benzothiazol-2-yl)-amide	471	F4
167		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (4-fluoro-benzothiazol-2-yl)-amide	441	F4
168		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-chloro-4-methyl-benzothiazol-2-yl)-amide	471	F4

Compounds of Formula (IB)

Method P:

Synthesis of 4-(4-Trifluoromethyl-benzoyl)-morpholine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide (Example 147)

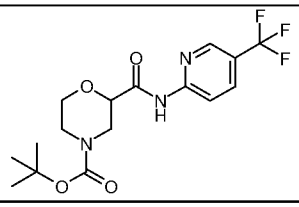


Step 1: Synthesis of 2-(5-*tert*-Butyl-isoxazol-3-ylcarbamoyl)-morpholine-4-carboxylic acid *tert*-butyl ester

To a cold (0°C) solution of morpholine-2,4-dicarboxylic acid 4-*tert*-butyl ester (1g; 4.424mmol) and 3-amino-5-t-butylisoxazole (606mg; 4.324mmol) and N,N-diisopropylethylamine (1.521mL; 8.732mmol) in anhydrous acetonitrile (12mL) is added phosphorous oxychloride (0.39mL; 4.424mmol). The reaction mixture is stirred at room temperature for 18 hours. After this time, the reaction mixture is quenched with saturated NH4Cl aqueous solution and extracted with ethyl acetate twice. The organics are combined and washed with brine, dried over Na2SO4, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel using ethyl acetate/Hexanes provides the title compound, m/z 354 [$M+H^+$].

Amide intermediate in Table 8 is made in a similar manner.

Table 8

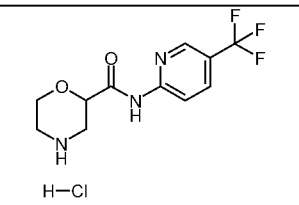
Structure	Name	m/z [M+H$^+$]
	2-(5-Trifluoromethyl-pyridin-2-ylcarbamoyl)-morpholine-4-carboxylic acid *tert*-butyl ester	376

Step 2: Synthesis of Morpholine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide; hydrochloride

To a solution of 2-(5-*tert*-Butyl-isoxazol-3-ylcarbamoyl)-morpholine-4-carboxylic acid *tert*-butyl ester (1.143g; 3.234mmol) in methylene chloride (10mL) is added 4N HCl in dioxanes (4mL; 16mmol). The reaction mixture is left stirring at room temperature for 18 hours. After this time, the reaction mixture is concentrated *in vacuo* to provide the title compound, m/z 254 [M+H$^+$].

Intermediate in Table 9 is made in a similar manner.

Table 9

Structure	Name	m/z [M+H$^+$]
	Morpholine-2-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide; hydrochloride	276

Step 3: Synthesis of 4-(4-Trifluoromethyl-benzoyl)-morpholine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide

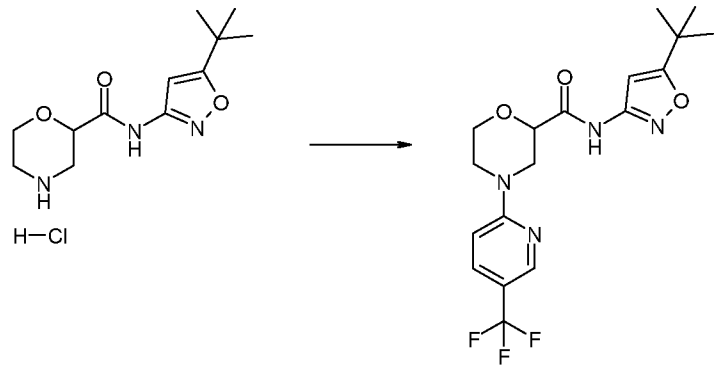
To a cold (0^{o}C) solution of morpholine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide; hydrochloride (75mg; 0.259mmol), 4-(trifluoromethyl)benzoic acid (49.2mg; 0.259mmol) and N,N-diisopropylethylamine (0.099mL; 0.57mmol) in anhydrous acetonitrile (2mL) is added phosphorous oxychloride (0.023mL; 0.259mmol). The reaction mixture is left stirring at room temperature for 3.5 hours. After this time, the reaction mixture is quenched with saturated NH4Cl aqueous solution and extracted with ethyl acetate twice. The organics are combined

and washed with brine, dried over Na2SO4, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel using methanol/methylene chloride then trituation from hot methanol provides the title compound, m/z 426 [M+H$^+$].

Compounds in Table10 Method P are prepared in a similar manner.

Method Q:

Synthesis of 4-(5-Trifluoromethyl-pyridin-2-yl)-morpholine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide (Example 149)

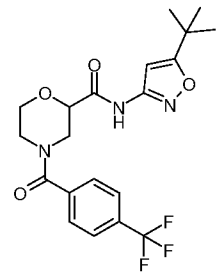
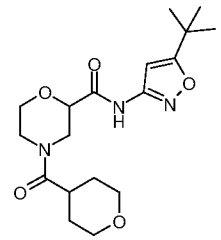
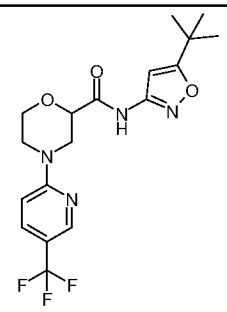
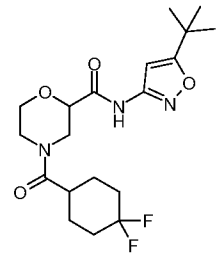
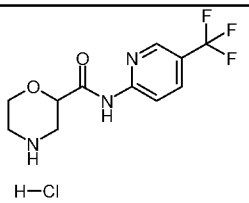


A microwave vial is charged with morpholine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide; hydrochloride (75mg; 0.259mmol), 2-bromo-5-trifluoromethylpyridine (58.8mg; 0.26mmol), triethylamine (0.072mL; 0.52mmol) and t-butanol (0.5mL). The vial is heated in microwave at 175^{o}C for 1 hour then left standing at room temperature for 18 hours. After this time, the reaction mixture is concentrated in vacuo. Purification by flash chromatography using methanol/methylene chloride provides the title compound, m/z 399 [M+H$^+$].

Compounds in Table10 Method Q are prepared in a similar manner.

Table 10: Examples

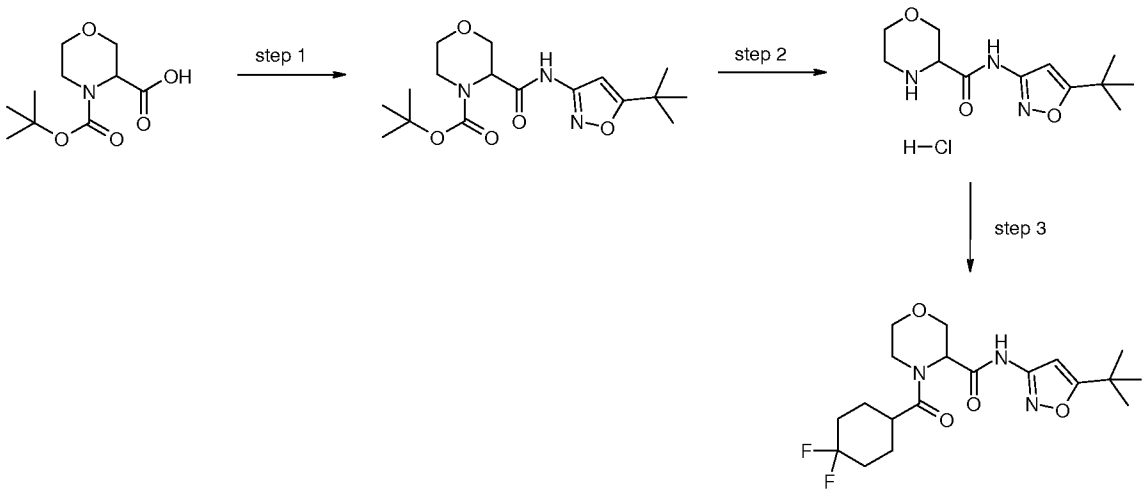
Example	Structure	Name	m/z [M+H$^+$]	Patent Method

147		4-(4-Trifluoromethyl-benzoyl)-morpholine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	426	P
148		4-(Tetrahydro-pyran-4-carbonyl)-morpholine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	366	P
149		4-(5-Trifluoromethyl-pyridin-2-yl)-morpholine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	399	Q
150		4-(4,4-Difluoro-cyclohexanecarbonyl)-morpholine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	400	P
151		Morpholine-2-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide; hydrochloride	276	P

Compounds of Formula (IIB)

Method R:

Synthesis of 4-(4,4-Difluoro-cyclohexanecarbonyl)-morpholine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide (Example 152)



Step 1: Synthesis of 3-(5-*tert*-Butyl-isoxazol-3-ylcarbamoyl)-morpholine-4-carboxylic acid *tert*-butyl ester

To a cold (0°C) solution of morpholine-3,4-dicarboxylic acid 4-*tert*-butyl ester (100mg; 0.432mmol) and 3-amino-5-t-butylisoxazole (58.9mg; 0.42mmol) in anhydrous pyridine (1.2mL) is added phosphorous oxychloride (0.039mL; 0.432mmol). The reaction mixture is left stirring at room temperature for 1 hour. After this time, the reaction mixture is quenched with saturated NH4Cl aqueous solution and extracted with ethyl acetate twice. The organics are combined and washed with brine, dried over Na2SO4, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel using methanol/methylene chloride provides the title compound, m/z 354 [$M+H^+$].

Step 2: Synthesis of Morpholine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide; hydrochloride

To a solution of 3-(5-*tert*-butyl-isoxazol-3-ylcarbamoyl)-morpholine-4-carboxylic acid *tert*-butyl ester (87mg; 0.246mmol) in methylene chloride (2mL) is added 4N HCl in dioxanes (0.615mL; 2.46mmol). The reaction mixture is left stirring at room temperature for 18 hours.

After this time, the reaction mixture is concentrated *in vacuo* to provide the title compound, m/z 254 [M+H$^+$].

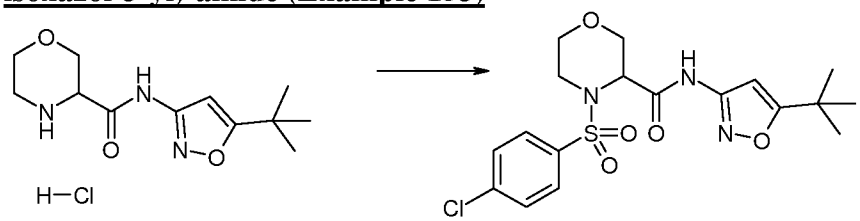
Step 3: Synthesis of 4-(4,4-Difluoro-cyclohexanecarbonyl)-morpholine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide

To a cold (0°C) solution of morpholine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide; hydrochloride (50mg; 0.115mmol), 4,4-difluorocyclohexanecarboxylic acid (18.9mg, 0.115mmol) and N,N-diisopropylethylamine (0.052mL; 0.3mmol) in anhydrous acetonitrile (2mL) is added phosphorous oxychloride (0.01mL; 0.115mmol). The reaction mixture is left stirring at room temperature for 18 hours. After this time, the reaction mixture is quenched with saturated NH4Cl aqueous solution and extracted with ethyl acetate twice. The organics are combined and washed with brine, dried over Na2SO4, filtered and concentrated under reduced pressure. Purification by preparative LC-MS provides the title compound, m/z 400 [M+H$^+$].

Compounds in Table 11 Method R are prepared in a similar manner.

Method S:

Synthesis of 4-(4-Chloro-benzenesulfonyl)-morpholine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide (Example 153)

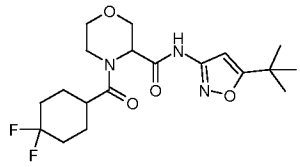
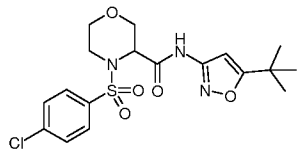


To a solution of morpholine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide; hydrochloride (55mg; 0.19mmol) in anhydrous DMF (1mL) is added 4-chlorobenzenesulfonyl chloride (40.1mg; 0.19mmol) and N,N-diisopropylethylamine (0.089mL; 0.513mmol). The reaction mixture is left stirring at room temparture for 18 hours in the presence of catalytic amount of 4-dimethylaminopyridine. After this time, the reaction mixture is diluted with ethyl

acetate and washed with eater 3 times, then brine, dried over Na2SO4, filtered and concentrated *in vacuo*. Recrystallization from hot methanol provides the title compound, m/z 428 [M+H$^+$].

Compounds in Table11 Method S are prepared in a similar manner.

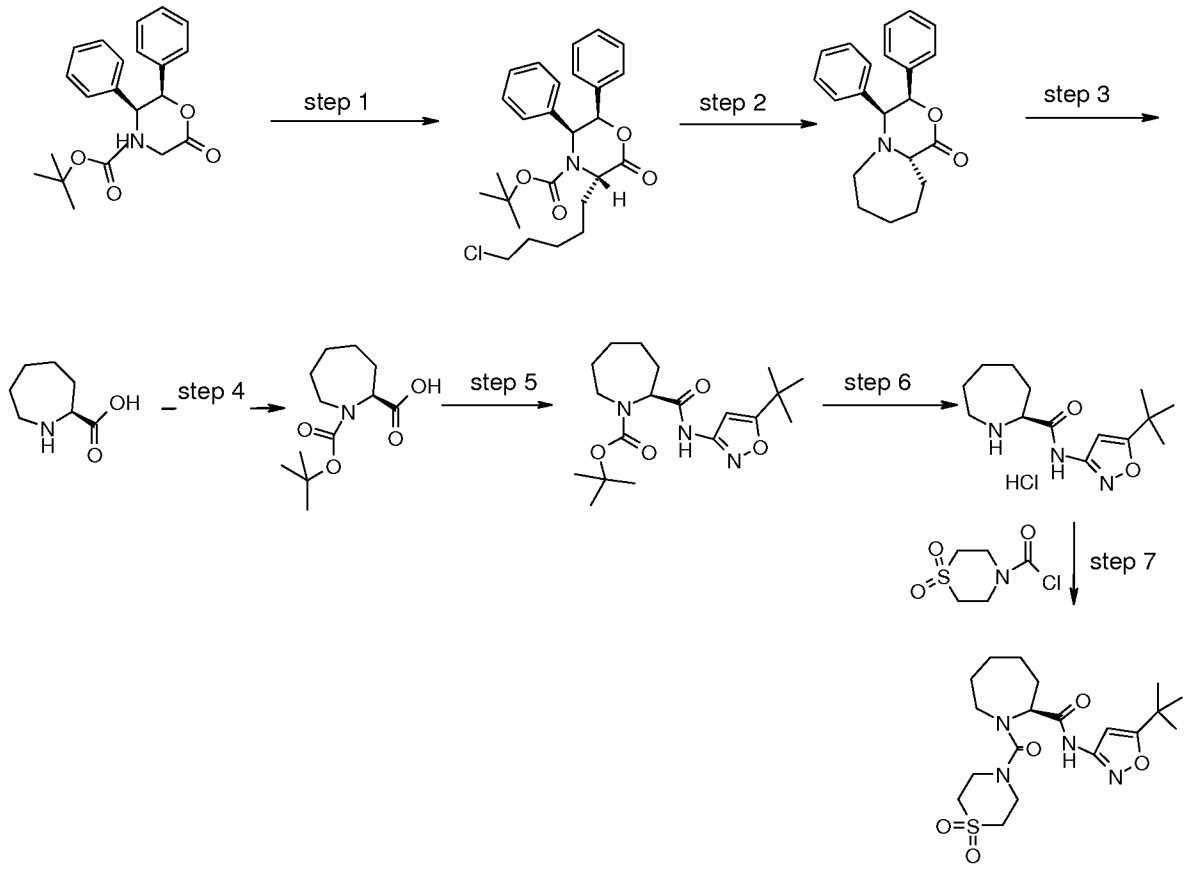
Table 11: Examples

Example	Structure	Name	m/z [M+H$^+$]	Patent Method
152		4-(4,4-Difluoro-cyclohexanecarbonyl)-morpholine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	400	R
153		4-(4-Chloro-benzenesulfonyl)-morpholine-3-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	428	S

Compounds of Formula (IC)

Method T

Synthesis of 1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-perhydro-azepine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide (Example 170)



Step 1: Synthesis of (3S,5S,6R)-3-(5-Chloro-pentyl)-2-oxo-5,6-diphenyl-morpholine-4-carboxylic acid tert-butyl ester

A 1.0M solution of sodium bis(trimethylsilyl)amide in THF (55.0 mL, 55.2 mmol) is added at -78°C to a solution of (5S,6R)-5,6-diphenyl-4-tert-butoxycarbonyl-morpholin-2-one (13.0 g, 36.8 mmol), 1-chloro-5-iodo-pentane (25.0 g, 108.0 mmol) and HMPA (55.0 mL) in THF (200.0 mL). The reaction mixture is stirred at -78°C for 2 hours and at room temperature for 1 hour. The reaction mixture is diluted with EtOAc, washed with water and brine. After drying the organic phase over anhydrous Na_2SO_4, the solvent is removed under reduced pressure to afford the crude product that is purified by silica gel column chromatography to afford the title compound; m/z 358 [M-Boc + H].

Step 2: Synthesis of (3R,4S,9aS)-3,4-Diphenyl-octahydro-2-oxa-4a-aza-benzocyclohepten-1-one

A solution of TFA in DCM (20%, 60mL) is added at 0°C to (3S,5S,6R)-3-(5-chloro-pentyl)-2-oxo-5,6-diphenyl-morpholine-4-carboxylic acid tert-butyl ester (8.0 g, 17.5 mmol). The reaction mixture is slowly warmed up to room temperature and stirred for 4 hours. The reaction mixture is poured into a saturated K_2CO_3 solution, the two phases are separated and the water phase is extracted with DCM twice. The combined organic phases are dried over anhydrous Na_2SO_4 and removal of the solvent under reduced pressure affords 6.0 g of (3S,5S,6R)-3-(5-Chloro-pentyl)-5,6-diphenyl-morpholin-2-one trifluoroacetate.

A solution of the above crude, K_2CO_3 (2.89 g, 20.0 mmol) and KI (3.46 g, 20.9 mmol) in ACN (100.0 mL) is stirred under refluxing conditions for 24 hours. The reaction mixture is diluted with EtOAc and washed with water and brine. The organic phase is dried over anhydrous Na_2SO_4, and removal of the solvent under reduced pressure affords the crude that is purified via silica gel column chromatography to afford the title compound; m/z 322 [M + H].

Step 3: Synthesis of (S)-Perhydro-azepine-2-carboxylic acid

Palladium (II) chloride (800 mg, 4.51 mmol) is added to a solution of (3R,4S,9aS)-3,4-diphenyl-octahydro-2-oxa-4a-aza-benzocyclohepten-1-one (4.5 g, 14.0 mmol) in THF (140 mL) and EtOH (160 mL). The reaction mixture is stirred for 12 hours under H_2 atmosphere at 50 psi, then filtered through celite that is washed with EtOH. Removal of the solvent under reduced pressure affords the title compound m/z 144 [M + H].

Step 4: Synthesis of (S)-Perhydro-azepine-1,2-dicarboxylic acid 1-*tert*-butyl ester

Triethylamine (3.46 g, 34.3 mmol) and di-tert-butyl dicarbonate (3.74 g, 17.2 mmol) are added in sequence at 0°C to a solution of (S)-perhydro-azepine-2-carboxylic acid in THF (105 mL) and water (46 mL). After stirring at room temperature for 12 hours, the reaction mixture is extracted with diethyl ether. The water phase is acidified with 1N HCl and then extracted with diethyl ether. The combined organic layer is dried over anhydrous Na_2SO_4, filtered and

concentrated under reduced pressure to afford the title compound that is used in the next step without further purification; m/z 242 [M- H].

Step 5: Synthesis of (S)-2-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-perhydro-azepine-1-carboxylic acid tert-butyl ester

Phosphorus oxychloride (0.88 g, 5.73 mmol) is added drop wise at 0°C to a solution of perhydro-azepine-1,2-dicarboxylic acid 1-*tert*-butyl ester (0.93 g, 3.82 mmol) and 5-*tert*-butyl-isoxazol-3-ylamine (0.54g, 3.82 mol) in pyridine (10.0 mL). The reaction mixture is slowly warmed up to room temperature and stirred for three hours. The mixture is diluted with EtOAc and washed twice with saturated NH_4Cl solution. The organic phase is washed with 1N HCl , and after drying over anhydrous Na_2SO_4 the solvent is removed under reduced pressure to afford the crude product that is used in the next step without further purification; m/z 366 [$M+H^+$].

Step 6: Synthesis of (S)-Perhydro-azepine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide hydrochloride

HCl in dioxane (10.0 mL) is added slowly at 0°C to a solution of (S)-2-(5-*tert*-butyl-isoxazol-3-ylcarbamoyl)-perhydro-azepine-1-carboxylic acid *tert*-butyl ester (0.70 g, 1.90 mmol) in DCM (15.0 mL). After stirring the reaction mixture at 0°C for 3 hours, the solvent is removed under reduced pressure to afford the title product that is used in the next step without further purification.

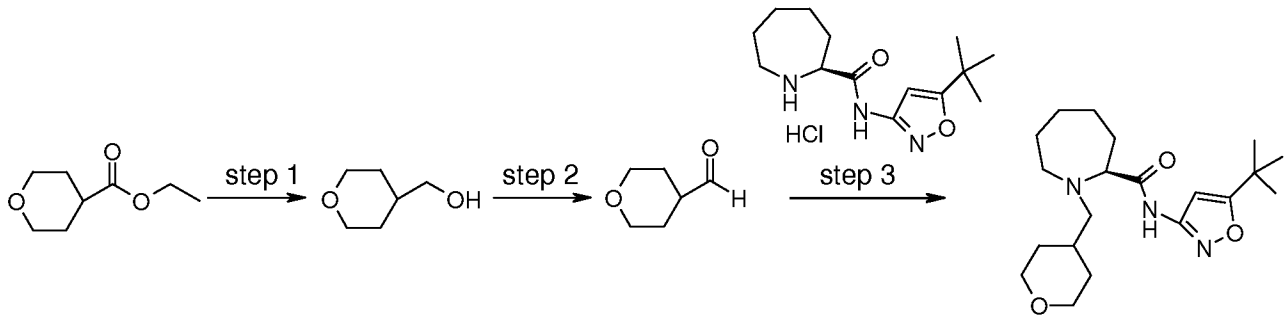
Step 7: Synthesis of (S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-perhydro-azepine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide

A solution of (S)-perhydro-azepine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide hydrochloride (0.30 g, 1.13 mmol), DIPEA (0.32 g, 2.48 mmol) and DMAP (16.0 mg, 0.13 mmol) is stirred at room temperature for 15 minutes. 1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl chloride (0.27 g, 1.35 mmol) (prepared according to method M step 1) is added drop

wise at 0°C to the reaction mixture that is slowly warmed up to room temperature and stirred for 14 hours. The reaction mixture is diluted with EtOAc, washed with water and brine. After drying the organic phase over anhydrous Na_2SO_4, removal of the solvent under reduced pressured affords the crude product that is purified by prep TLC to afford the title product; m/z 427 [$M+H^+$].

Method U

Synthesis of (S)-1-(Tetrahydro-pyran-4-ylmethyl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide (Example 172)



Step 1: Synthesis of (Tetrahydro-pyran-4-yl)-methanol

$LiAlH_4$ (1M in THF) (100.0 mL, mmol) is added at 0°C to a solution of tetrahydro-pyran-4-carboxylic acid ethyl ester (25.0 g, 173.6 mmol) is THF (500.0 mL). The reaction mixture is warmed up to room temperature and stirred under reflux for five hours. The reaction mixture is cooled to room temperature and then 5.0 mL of water, 5.0 mL of 5N NaOH and 20.0 mL of water are added and the precipitated salts are filtered through a celite pad and washed with 1:1 Et_2O: MeOH. The filtrate is concentrated under reduced pressure to afford the title product.

Step 2: Synthesis of tetrahydro-pyran-4-carbaldehyde

Pyridinium chlorochromate (37.8 g, 175.0 mmol) is added to a solution of (tetrahydro-pyran-4-yl)-methanol (13.6 g, 117.0 mmol) in DCM (50.0 mL) at 0°C. The reaction mixture is stirred at room temperature for 12 hours. The reaction mixture is filtered through a pad of celite that

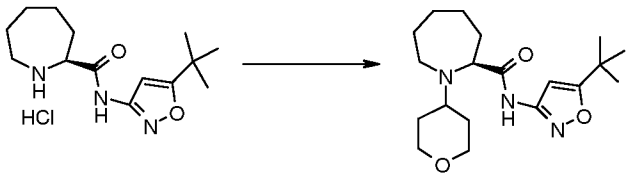
is washed with diethyl ether. The filtrate is concentrated under reduced pressure to afford the title compound.

Step 3: Synthesis of (S)-1-(Tetrahydro-pyran-4-ylmethyl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide

Sodium cyanoborohydride (0.19 g, 3.02 mmol) and tetrahydro-pyran-4-carbaldehyde (0.26 g, 2.26 mmol) is added to a solution of (S)-perhydro-azepine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide hydrochloride (prepared according to Method T, step 6) (0.4 g, 1.51 mmol) in DMF (5.0 mL). After stirring for four hours, the reaction mixture is diluted with EtOAc and washed twice with water. The organic phase is dried over anhydrous Na_2SO_4 and after removal of the solvent under reduced pressure, the crude is purified by prep TLC to afford the title compound; m/z 364 [M+H].

Method V

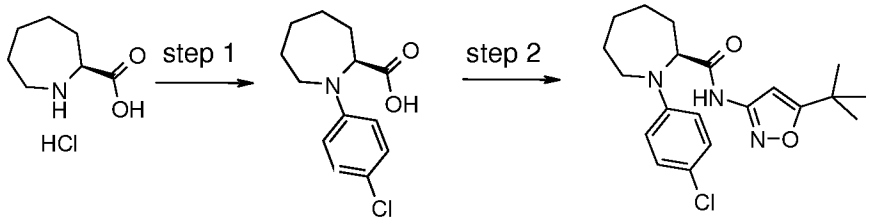
Synthesis of (S)-1-(tetrahydro-pyran-4-yl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide (Example 171)



Sodium cyanoborohydride (71 mg, 1.13 mmol) and tetrahydro-pyran-4-one (75 mg, 0.75 mmol) are added to a solution of (S)-perhydro-azepine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide hydrochloride (prepared according to Method T, step 6) (0.2 g, 0.75 mmol) in DCM (8.0 mL). After stirring for four hours, the reaction mixture is diluted with EtOAc and washed twice with water. The organic phase is dried over anhydrous Na_2SO_4 and after removal of the solvent under reduced pressure, the crude is purified by prep TLC to afford the title compound; m/z 350 [M+H].

Method Z

Synthesis of (S)-1-(4-Chloro-phenyl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide (Example 169)



Step 1: Synthesis of (S)-1-(4-Chloro-phenyl)-azepane-2-carboxylic acid

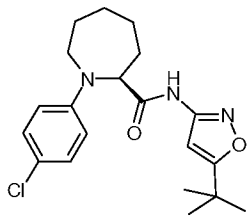
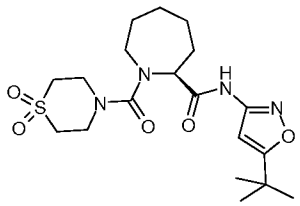
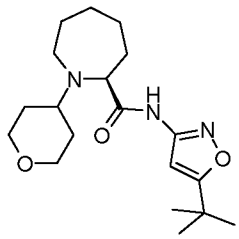
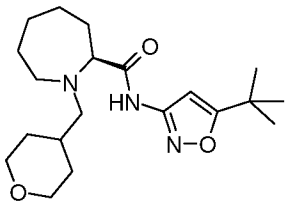
A solution of (S)-perhydro-azepine-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide hydrochloride (prepared according to Method T, step 6) (0.60 g, 4.20 mmol), 1-Bromo-4-chloro-benzene (0.80 g, 4.20 mmol), potassium carbonate (0.87 g, 6.29 mmol) and copper (I) iodide (0.08 g, 0.42 mmol) in DMA (10.0 mL), is heated at 100°C in a sealed tube for 48 hours. The reaction mixture is diluted with EtOAc and washed with water. The water phase is acidified with 1N HCl and then extracted with EtOAc. The organic layers are combined, and after drying over anhydrous Na_2SO_4, removal of the solvent affords the title product that is used in the next step without any further purification. m/z 254 [M + H].

Step 2: Synthesis of (S)-1-(4-Chloro-phenyl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide

Phosphorus oxychloride (0.21 g, 1.38 mmol) is added drop wise at 0°C to a solution of (S)-1-(4-chloro-phenyl)-azepane-2-carboxylic acid (0.23 g, 0.92 mmol) and 5-*tert*-butyl-isoxazol-3-ylamine (0.19g, 1.38 mol) in pyridine. The reaction mixture is slowly warmed up to room temperature and stirred for three hours. The mixture is diluted with EtOAc and washed twice with saturated NH_4Cl solution. The organic phase is washed with 1N HCl , and after drying

over anhydrous Na_2SO_4 the solvent is removed under reduced pressure to afford the crude product that is purified by prep TLC to afford the title compound; m/z 376 [$M+H^+$].

Table 12: Examples

Example	Structure	Name	m/z [$M+H^+$]	Patent Method
169		(S)-1-(4-Chloro-phenyl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	376	Z
170		(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	427	T
171		(S)-1-(Tetrahydro-pyran-4-yl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	350	V
172		(S)-1-(Tetrahydro-pyran-4-ylmethyl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide	364	U

Assessment of Biological Properties

The biological properties of the compounds of the invention were assessed using the assays described below.

A. Human CB1 and CB2 Receptor Binding:

Experimental Method:

CB2 membranes were purchased and made from HEK293 EBNA cells stably transfected with human CB2 receptor cDNA (Perkin Elmer Life and Analytical Sciences). CB1 membranes were isolated from HEK cells stably co-transfected with human CB1 receptor and Gα16 cDNA's. The membrane preparation was bound to scintillation beads (Ysi-Poly-L-lysine SPA beads, GE Healthcare) for 4 hours at room temperature in assay buffer containing 50mM Tris, pH 7.5, 2.5mM EDTA, 5mM $MgCl_2$, 0.8% fatty acid free Bovine Serum Albumin. Unbound membrane was removed by washing in assay buffer. Membrane–bead mixture was added to 96-well assay plates in the amounts of 15ug membrane per well (CB2) or 2.5ug per well (CB1) and 1mg SPA bead per well. Compounds were added to the membrane–bead mixture in dose-response concentrations ranging from 1x 10^{-5} M to 1x10^{-10} M with 0.25% DMSO, final. The competition reaction was initiated with the addition of ^{3}H-CP55940 (Perkin Elmer Life and Analytical Sciences) at a final concentration of 1.5nM (CB2) or 2.5nM (CB1). The reaction was incubated at room temperature for 18hours and read on TopCount NXT plate reader. Total and non-specific binding was determined in the absence and presence of 1.25uM Win 55212 (Sigma). IC50 values for each compound were calculated as the concentration of compound that inhibits the specific binding of the radioactively labeled ligand to the receptor by 50% using the XLFit 4.1 four parameter logistic model. IC50 values were converted to inhibition constant (Ki) values using Cheng-Prusoff equation.

B. CB2R mediated modulation of cAMP synthesis:

Compounds of the invention were evaluated for their CB2 agonist or inverse agonistic activity in accordance with the following experimental method. Compounds which were shown to bind to CB2 by the binding assay described above but which were not shown to exhibit CB2R-mediated modulation of cAMP synthesis by this assay were presumed to be CB2 antagonists.

Experimental Method:

CHO cells expressing human CB2R (Euroscreen) were plated at a density of 5000 cells per well in 384 well plates and incubated overnight at 37°C. After removing the media, the cells were treated with test compounds diluted in stimulation buffer containing 1mM IBMX, 0.25% BSA and 10uM Forskolin. The assay was incubated for 30 minutes at 37°C. Cells were lysed and the cAMP concentration was measured using DiscoverX –XS cAMP kit, following the manufacturer's protocol. In this setting, agonists will decrease forskolin induced production of cAMP while inverse agonists will further increase forskolin induced production of cAMP. EC50 of agonists were calculated as follows. The maximal amount of cAMP produced by forskolin compared to the level of cAMP inhibited by 1uM CP55940 is defined as 100%. The EC50 value of each test compound was determined as the concentration at which 50% of the forskolin-stimulated cAMP synthesis was inhibited. Data was analyzed using a four-parameter logistic model. (Model 205 of XLfit 4.0).

C. CB1R mediated modulation of cAMP synthesis:

Compounds of the invention were evaluated for their CB1 agonist or inverse agonistic activity in accordance with the following experimental method. Compounds which were shown to bind to CB1 by the binding assay described above but which were not shown to exhibit CB1R-mediated modulation of cAMP synthesis by this assay were presumed to be CB1 antagonists.

Experimental Method:

CHO cells expressing human CB1R (Euroscreen) were plated at a density of 5000 cells per well in 384 well plates and incubated overnight at 37°C. After removing the media, the cells were treated with test compounds diluted in stimulation buffer containing 1mM IBMX, 0.25% BSA and 10uM Forskolin. The assay was incubated for 30 minutes at 37°C. Cells were lysed and the cAMP concentration was measured using DiscoverX –XS cAMP kit, following the manufacturer's protocol. In this setting, agonists will decrease forskolin induced production

of cAMP while inverse agonists will further increase forskolin induced production of cAMP. EC50 of agonists were calculated as follows. The maximal amount of cAMP produced by forskolin compared to the level of cAMP inhibited by 1uM CP55940 is defined as 100%. The EC50 value of each test compound was determined as the concentration at which 50% of the forskolin-stimulated cAMP synthesis was inhibited. Data was analyzed using a four-parameter logistic model. (Model 205 of XLfit 4.0).

Compounds Having Agonist Activity

Through the use of the above described assays compounds were found to exhibit agonistic activity and thus to be particularly well suited for the treatment of pain as well as for the treatment of inflammation. Preferred compounds had EC 50 values <500 nM.

Therapeutic Use

As can be demonstrated by the assays described above, the compounds of the invention are useful in modulating the CB2 receptor function. By virtue of this fact, these compounds have therapeutic use in treating disease-states and conditions mediated by the CB2 receptor function or that would benefit from modulation of the CB2 receptor function.

As the compounds of the invention modulate the CB2 receptor function, they have very useful anti-inflammatory and immune-suppressive activity and they can be used in patients as drugs, particularly in the form of pharmaceutical compositions as set forth below, for the treatment of disease-states and conditions.

As noted before, those compounds which are CB2 agonists can also be employed for the treatment of pain.

The agonist compounds according to the invention can be used in patients as drugs for the treatment of the following disease-states or indications that are accompanied by inflammatory processes:

(i) Lung diseases: e.g. asthma, bronchitis, allergic rhinitis, emphysema, adult respiratory distress syndrome (ARDS), pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease (COPD), asthma including allergic asthma (atopic or non-atopic) as well as exercise-induced bronchoconstriction, occupational asthma, viral- or bacterial exacerbation of asthma, other non-allergic asthmas and "wheezy-infant syndrome", pneumoconiosis, including aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis;

(ii) Rheumatic diseases or autoimmune diseases or musculoskeletal diseases: all forms of rheumatic diseases, especially rheumatoid arthritis, acute rheumatic fever, and polymyalgia rheumatica; reactive arthritis; rheumatic soft tissue diseases; inflammatory soft tissue diseases of other genesis; arthritic symptoms in degenerative joint diseases (arthroses); tendinitis, bursitis, osteoarthritis, traumatic arthritis; collagenoses of any genesis, e.g., systemic lupus erythematosus, scleroderma, polymyositis, dermatomyositis, Sjögren syndrome, Still disease, Felty syndrome; and osteoporosis and other bone resorption diseases;

(iii) Allergic diseases: all forms of allergic reactions, e.g., angioneurotic edema, hay fever, insect bites, allergic reactions to drugs, blood derivatives, contrast agents, etc., anaphylactic shock (anaphylaxis), urticaria, angioneurotic edema, and contact dermatitis;

(iv) Vascular diseases: panarteritis nodosa, polyarteritis nodosa, periarteritis nodosa, arteritis temporalis, Wegner granulomatosis, giant cell arthritis, atherosclerosis, reperfusion injury and erythema nodosum;

(v) Dermatological diseases: e.g. dermatitis, psoriasis; sunburn, burns, eczema;

(vi) Renal diseases: e.g. nephrotic syndrome; and all types of nephritis, e.g., glomerulonephritis; pancreatits;

(vii) Hepatic diseases: e.g. acute liver cell disintegration; acute hepatitis of various genesis, e.g., viral, toxic, drug-induced; and chronically aggressive and/or chronically intermittent hepatitis;

(viii) Gastrointestinal diseases: e.g. inflammatory bowel diseases, irritable bowel syndrome, regional enteritis (Crohns disease), colitis ulcerosa; gastritis; aphthous ulcer, celiac disease, regional ileitis, gastroesophageal reflux disease;

(ix) Neuroprotection: e.g. in the treatment of neurodegeneration following stroke; cardiac arrest; pulmonary bypass; traumatic brain injury; spinal cord injury or the like;

(x) Eye diseases: allergic keratitis, uveitis, or iritis; conjunctivitis; blepharitis; neuritis nervi optici; choroiditis; glaucoma and sympathetic ophthalmia;

(xi) Diseases of the ear, nose, and throat (ENT) area: e.g. tinnitus; allergic rhinitis or hay fever; otitis externa; caused by contact eczema, infection, etc.; and otitis media;

(xii) Neurological diseases: e.g. brain edema, particularly tumor-related brain edema; multiple sclerosis; acute encephalomyelitis; meningitis; acute spinal cord injury; trauma; dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease; Parkinson's disease and Creutzfeldt-Jacob disease; Huntington's chorea, Pick's disease; motor neuron disease), vascular dementia (including multi-infarct dementia) as well as dementia associated with intracranial space occupying lesions; infections and related conditions (including HIV infection); Guillain-Barre syndrome; myasthenia gravis, stroke; and various forms of seizures, e.g., nodding spasms;

(xiii) Blood diseases: acquired hemolytic anemia; aplastic anemia, and idiopathic thrombocytopenia;

(xiv) Tumor diseases: acute lymphatic leukemia; Hodgkin's disease, malignant lymphoma; lymphogranulomatoses; lymphosarcoma; solid malignant tumors; extensive metastases,;

(xv) Endocrine diseases: endocrine ophthalmopathy; endocrine orbitopathia; thyrotoxic crisis; Thyroiditis de Quervain; Hashimoto thyroiditis; Morbus Basedow; granulomatous thyroiditis; struma lymphomatosa; and Graves disease; type I diabetes (insulin-dependent diabetes);

(xvi) Organ and tissue transplantations and graft-versus-host diseases;

(xvii) Severe states of shock, e.g., septic shock, anaphylactic shock, and systemic inflammatory response syndrome (SIRS);

(xviii) Acute pain such as dental pain, perioperative, post-operative pain, traumatic pain, muscle pain, pain in burned skin, sun burn, trigeminal neuralgia, sun burn; spasm of the gastrointestinal tract or uterus, colics;

(xix) Visceral pain such as pain associated with chronic pelvic pain, pancreatitis, peptic ulcer, interstitial cystitis, renal colic, angina, dysmenorrhoea, menstruation, gynaecological pain, irritable bowel syndrome (IBS), non-ulcer dyspepsia, non-cardiac chest pain, myocardial ischemia;

(xx) Neuropathic pain such as low back pain, non-herpetic neuralgia, post herpetic neuralgia, diabetic neuropathy, nerve injury, acquired immune deficiency syndrome (AIDS) related neuropathic pain, head trauma, painful traumatic mononeuropathy, toxin and chemotherapy induced pain, phantom limb pain, painful polyneuropathy, thalamic pain syndrome, post-stroke pain, central nervous system injury, post surgical pain, stump pain, repetitive motion pain, pain induced by post mastectomy syndrome, multiple sclerosis, root avulsions, postthoracotomy syndrome, neuropathic pain associated hyperalgesia and allodynia.

(xxi) Inflammatory/nociceptive pain induced by or associated with disorders such as osteoarthritis, rheumatoid arthritis, rheumatic disease, teno-synovitis, gout, vulvodynia, myofascial pain (muscular injury, fibromyalgia), tendonitis, osteoarthritis, juvenile arthritis, spondylitis, gouty arthritis, psoriatic arthritis, muscoskeletal pain, fibromyalgia, sprains and strains, sympathetically maintained pain, myositis, pain

associated with migraine, toothache, influenza and other viral infections such as the common cold, rheumatic fever, systemic lupus erythematosus;

(xxii) Cancer pain induced by or associated with tumors such as lymphatic leukemia; Hodgkin's disease, malignant lymphoma; lymphogranulomatoses; lymphosarcoma; solid malignant tumors; extensive metastases;

(xxiii) Headache such as cluster headache, migraine with and without aura, tension type headache, headache with different origins, headache disorders including prophylactic and acute use;

(xxiv) various other disease-states or conditions including, restenosis following percutaneous transluminal coronary angioplasty, acute and chronic pain, atherosclerosis, reperfusion injury, congestive heart failure, myocardial infarction, thermal injury, multiple organ injury secondary to trauma, necrotizing enterocolitis and syndromes associated with hemodialysis, leukopheresis, and granulocyte transfusion, sarcoidosis, gingivitis, pyrexia. edema resulting from trauma associated with bums, sprains or fracture, cerebral oedema and angioedema, Diabetes such as diabetic vasculopathy, diabetic neuropathy, diabetic retinopathy, post capillary resistance or diabetic symptoms associated with insulitis (e.g. hypergiycemia, diuresis, proteinuria and increased nitrite and kallikrein urinary excretion).

Other indications include: epilepsy, septic shock e.g. as antihypovolemic and/or antihypotensive agents, cancer, sepsis, osteoporosis, benign prostatic hyperplasia and hyperactive bladder, pruritis, vitiligo, general gastrointestinal disorders, disturbances of visceral motility at respiratory, genitourinary, gastrointestinal or vascular regions, wounds, burns, tissue damage and postoperative fever, syndromes associated with itching.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like.

For treatment of the above-described diseases and conditions, a therapeutically effective dose will generally be in the range from about 0.01 mg to about 100 mg/kg of body weight per dosage of a compound of the invention; preferably, from about 0.1 mg to about 20 mg/kg of body weight per dosage. For example, for administration to a 70 kg person, the dosage range would be from about 0.7 mg to about 7000 mg per dosage of a compound of the invention, preferably from about 7.0 mg to about 1400 mg per dosage. Some degree of routine dose optimization may be required to determine an optimal dosing level and pattern. The active ingredient may be administered from 1 to 6 times a day.

General Administration and Pharmaceutical Compositions

When used as pharmaceuticals, the compounds of the invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared using procedures well known in the pharmaceutical art and comprise at least one compound of the invention. The compounds of the invention may also be administered alone or in combination with adjuvants that enhance stability of the compounds of the invention, facilitate administration of pharmaceutical compositions containing them in certain embodiments, provide increased dissolution or dispersion, increased inhibitory activity, provide adjunct therapy, and the like. The compounds according to the invention may be used on their own or in conjunction with other active substances according to the invention, optionally also in conjunction with other pharmacologically active substances. In general, the compounds of this invention are administered in a therapeutically or pharmaceutically effective amount, but may be administered in lower amounts for diagnostic or other purposes.

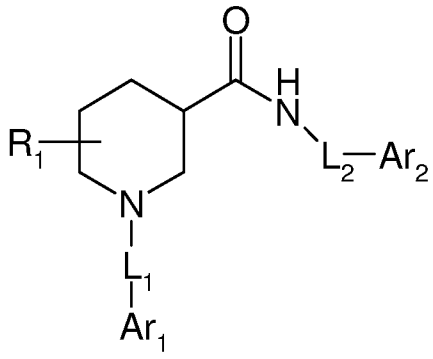
Administration of the compounds of the invention, in pure form or in an appropriate pharmaceutical composition, can be carried out using any of the accepted modes of administration of pharmaceutical compositions. Thus, administration can be, for example, orally, buccally (e.g., sublingually), nasally, parenterally, topically, transdermally, vaginally,

or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as, for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The pharmaceutical compositions will generally include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents, vehicles, or combinations thereof. Such pharmaceutically acceptable excipients, carriers, or additives as well as methods of making pharmaceutical compositions for various modes or administration are well-known to those of skill in the art. The state of the art is evidenced, e.g., by *Remington: The Science and Practice of Pharmacy*, 20th Edition, A. Gennaro (ed.), Lippincott Williams & Wilkins, 2000; *Handbook of Pharmaceutical Additives*, Michael & Irene Ash (eds.), Gower, 1995; *Handbook of Pharmaceutical Excipients*, A.H. Kibbe (ed.), American Pharmaceutical Ass'n, 2000; H.C. Ansel and N.G. Popovish, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5th ed., Lea and Febiger, 1990; each of which is incorporated herein by reference in their entireties to better describe the state of the art.

As one of skill in the art would expect, the forms of the compounds of the invention utilized in a particular pharmaceutical formulation will be selected (e.g., salts) that possess suitable physical characteristics (e.g., water solubility) that is required for the formulation to be efficacious.

CLAIMS

1. A compound of the formula (IA)



(IA)

wherein:

Ar_1 is chosen from carbocycle, heterocyclyl and heteroaryl each optionally substituted by 1-3 C_{1-10} alkyl which is optionally substituted by halogens, C_{1-10} alkoxy, CN, halogen, NO_2, -$S(O)_m$-C_{1-10} alkyl, -CO_2- C_{1-10} alkyl, -NH(C_{1-5} alkyl)-CO_2-C_{1-10} alkyl, -C(O)-NH(C_{1-5} alkyl), -C(O)-N(C_{1-5} alkyl)$_2$, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)-C(O)-C_{1-10} alkyl, -N(C_{1-5} alkyl)-$S(O)_m$-C_{1-10} alkyl, carbocycle and heterocyclyl;

Ar_2 is chosen from carbocycle, heterocyclyl and heteroaryl each optionally substituted by 1-3 C_{1-10} alkyl which is optionally substituted by halogens, C_{3-10} cycloalkyl, carbocycle, C_{1-10} alkylcarbocycle, heteroaryl, CN or halogen, wherein the C_{1-10} alkyl and carbocycle may be additionally optionally substituted by hydroxyl, C_{1-5} alkoxycarbonyl or C_{1-5} alkoxy;

L_1 and **L_2** are each independently chosen from a bond or C_{1-10} alkyl chain wherein each -CH_2- of said chain is optionally replaced by -O-, C(O), or $S(O)_m$;

wherein each **L_1** and **L_2** where possible is optionally substituted by halogen or C_{1-3} alkyl;

R_1 is chosen from hydrogen, oxo (=O) and OH;

m is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 and wherein:

Ar_1 is chosen from phenyl, C_{3-6} cycloalkyl, dioxanyl, tetrahydrofuranyl, tetrahydropyranyl, thiomorpholinyl, 1,1-Dioxo-1λ^6-thiomorpholinyl, morpholinyl and pyridinyl, each optionally substituted by 1-3 C_{1-6} alkyl which is optionally substuituted with halogens, or halogen,

Ar_2 is chosen from oxazolyl, isoxazolyl, thiazoyl, thiadiazoyl, benzothiazoyl, triazoyl, isothiazoyl, phenyl, pyrimidinyl, pyridizinyl, pyrazinyl and pyridinyl, each optionally substituted by 1-3 C_{1-6} alkyl which is optionally substituted by halogens, phenyl, halogen or C_{3-8} cycloalkyl;

R_1 is hydrogen;

L_1 is a bond, or C_{1-3}alkyl chain wherein each -CH_2- of said chain is optionally replaced by C(O) or $S(O)_m$;

L_2 is a bond.

3. The compound according to the claim 2 and wherein:

Ar_1 is chosen from phenyl, C_{3-6} cycloalkyl, tetrahydropyranyl, 1-Dioxo-1λ^6-thiomorpholinyl, morpholinyl and pyridinyl, each optionally substituted by 1-3 C_{1-6} alkyl, trifluoromethyl or halogen;

Ar_2 is chosen from isoxazolyl, pyridinyl, each optionally substituted by C_{1-6} alkyl or trifluoromethyl;

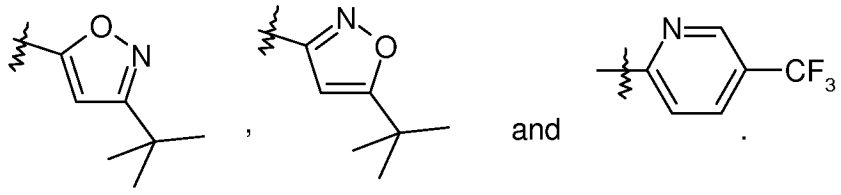
L_1 is a bond, -CH_2-, C(O) or $S(O)_2$.

4. The compound according to claim 3 and wherein:

Ar_1 is chosen from phenyl, cyclohexyl, tetrahydropyranyl, 1-Dioxo-1λ^6-thiomorpholinyl, morpholinyl and pyridinyl, each optionally substituted by 1-3 C_{1-3} alkyl, trifluoromethyl or halogen.

5. The compound according to claim 4 and wherein:

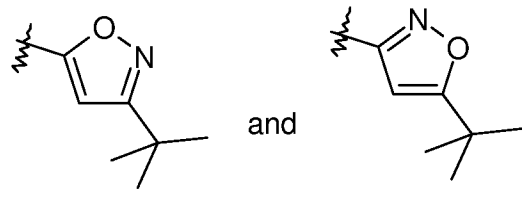
Ar_2 is chosen from



and .

6. The compound according to claim 5 and wherein:

Ar_2 is chosen from



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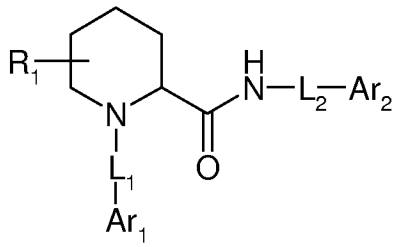
7. A compound of the formula (IIA)



(IIA)

wherein

Ar_1 is chosen from C_{1-6} alkyl which is optionally substituted by halogens,, C_{1-6} alkoxy, carbocycle, heterocyclyl and heteroaryl each optionally substituted by 1-3 C_{1-10} alkyl which is optionally substituted by halogens, C_{1-10} alkoxy, CN, halogen, NO_2, $-S(O)_m-C_{1-10}$ alkyl, $-C(O)-C_{1-10}$ alkyl, $-CO_2-C_{1-10}$ alkyl, C_{1-10} acyl, oxo (=O),$-NH(C_{1-5}$ alkyl)$-CO_2-C_{1-10}$ alkyl, $-C(O)-NH(C_{1-5}$ alkyl), $-C(O)-N(C_{1-5}$ alkyl$)_2$, $-NH(C_{1-5}$ alkyl), $-N(C_{1-5}$ alkyl$)-C(O)-C_{1-10}$ alkyl, $-N(C_{1-5}$ alkyl$)-S(O)_m-C_{1-10}$ alkyl and heterocyclyl the heterocyclyl being further optionally substituted by C_{1-5} alkyl;

Ar_2 is chosen from C_{1-6} alkyl, carbocycle, heterocyclyl and heteroaryl each optionally substituted by 1-3 C_{1-10} alkyl which is optionally substituted by halogens alkoxy or hydroxy, carbocycle optionally substituted by C_{1-3} alkyl , aryl which is optionally substituted by halogen,

heteroaryl, CN, halogen, C_{1-10} acyl or oxo (=O), wherein the C_{1-6} alkyl and carbocycle may be additionally optionally substituted by hydroxyl;

L_1 and **L_2** are each independently chosen from a bond or C_{1-10} alkyl chain wherein each $-CH_2-$ of said chain is optionally replaced by -O-, C(O), $S(O)_m$ or -NH-;

R_1 is chosen from hydrogen, hydroxyl and oxo (=O);

m is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

8. The compound according to claim 7 and wherein:

Ar_1 is chosen from C_{1-6} alkyl which is optionally substituted by halogens, C_{1-6} alkoxyl, phenyl, C_{3-8} cycloalkyl, dioxanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyran-1,1-dioxide, tetrahydrothiofuranyl, tetrahydrothiofuran-1,1-dioxide, thiomorpholinyl, 1-Oxo-$1\lambda^4$-thiomorpholinyl, 1,1-Dioxo-$1\lambda^6$-thiomorpholinyl, morpholinyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolidinyl, piperidinyl and piperazinyl, each optionally substituted by 1-3 C_{1-6} alkyl which is optionally substituted by halogens, C_{1-6} alkoxy, CN, halogen, oxo, $-C(O)-C_{1-10}$ alkyl, $-S(O)_2-C_{1-3}$ alkyl or $-CO_2-C_{1-4}$ alkyl;

Ar_2 is chosen from C_{1-6} alkyl, cyclohexyl, phenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, imidazolyl, thienyl, thiadiazolyl, triazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, benzofuranyl and benzothienyl, each optionally substituted by 1-3 C_{1-6} alkyl which is

optionally substituted by halogen, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, phenyl optionally substituted by halogens, CN, halogens, C_{1-6} alkoxy or hydroxy;

R_1 is hydrogen, hydroxyl and oxo (=O);

L_1 is bond or C_{1-3} alkyl chain wherein each $-CH_2-$ of said chain is optionally replaced by C(O) or $S(O)_m$;

L_2 is chosen bond or C_{1-5} alkyl chain wherein each $-CH_2-$ of said chain is optionally replaced by -O- or $S(O)_m$.

9. The compound according to claim 8 and wherein:

Ar_1 is chosen from C_{1-6} alkyl which is optionally substituted by halogens, C_{1-6} alkoxyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyran-1,1-dioxide, tetrahydrothiofuranyl, tetrahydrothiofuran-1,1-dioxide, thiomorpholinyl, 1-Oxo-$1\lambda^4$-thiomorpholinyl, 1,1-Dioxo-$1\lambda^6$-thiomorpholinyl, morpholinyl, pyridinyl, pyrrolidinyl, piperidinyl and piperazinyl, each optionally substituted by 1-3 C_{1-6} alkyl, trifluoromethyl, C_{1-2} alkoxy, CN, halogen, oxo, $-C(O)-C_{1-10}$ alkyl, $-S(O)_2-C_{1-3}$ alkyl or $-CO_2-C_{1-4}$ alkyl;

Ar_2 is chosen from C_{1-6} alkyl, cyclohexyl, phenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, triazolyl and pyridinyl, each optionally substituted by 1-3 C_{1-6} alkyl, trifluoromethyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl optionally substituted by halogens, CN, halogen, C_{1-6} alkoxy or C_{1-6} hydroxy;

L_1 is bond or C_{1-3} alkyl chain wherein each -CH_2- of said chain is optionally replaced by C(O) or SO_2;

L_2 is chosen bond or C_{1-5} alkyl chain wherein each -CH_2- of said chain is optionally replaced by -O- or S.

10. The compound according to claim 9 and wherein:

Ar_1 is chosen from phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyran-1,1-dioxide, tetrahydrothiofuranyl, tetrahydrothiofuran-1,1-dioxide, thiomorpholinyl, 1-oxo-1λ^4-thiomorpholinyl, 1,1-dioxo-1λ^6-thiomorpholinyl, pyridinyl, pyrrolidinyl, piperidinyl and piperazinyl, each optionally substituted by 1-3 C_{1-6} alkyl, trifluoromethyl, C_{1-2} alkoxy, halogen, oxo, -C(O)-C_{1-10} alkyl, -$S(O)_2$-C_{1-3} alkyl or -CO_2-C_{1-4} alkyl;

Ar_2 is chosen from cyclohexyl, phenyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, isothiazolyl, thiadiazolyl, triazolyl and pyridinyl, each optionally substituted by 1-3 C_{1-6} alkyl, trifluoromethyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl optionally substituted by halogens, CN, halogen or C_{1-6} alkoxy;

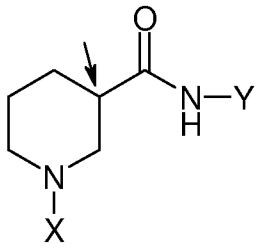
R_1 is hydrogen or oxo;

L_2 is chosen bond or C_{1-3} alkyl chain wherein each -CH_2- of said chain is optionally replaced by S.

11. The compound according to claim 10 and wherein:

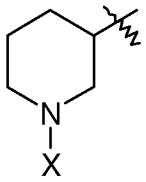
$\mathbf{R_1}$ is hydrogen.

12. A compound of the formula (IIIA)

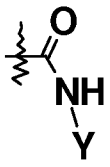


(IIIA)

wherein

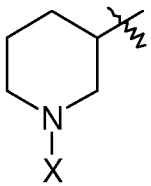
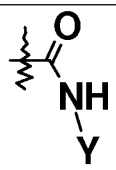


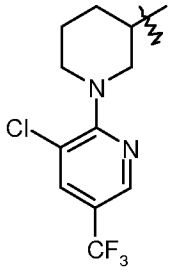
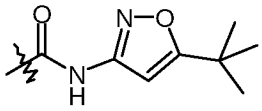
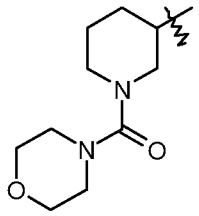
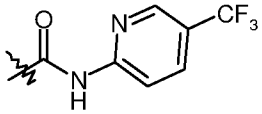
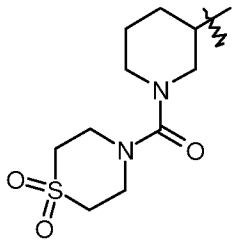
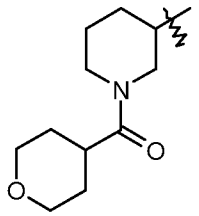
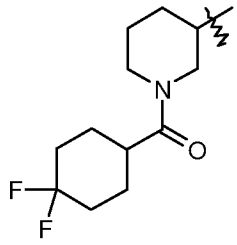
of the formula (IIIA) is chosen from A1 – A9 of Table I, and

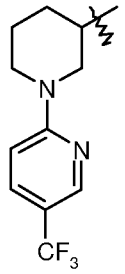
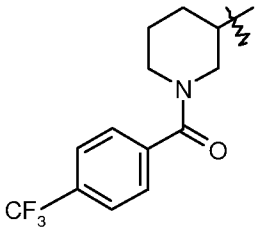
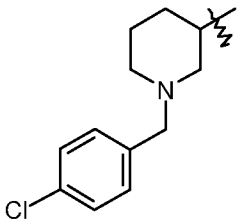
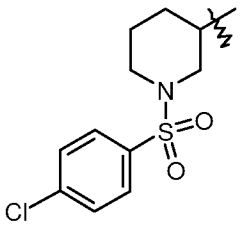


of the formula (IIIA) is chosen from B1 – B2 of Table I,

Table I

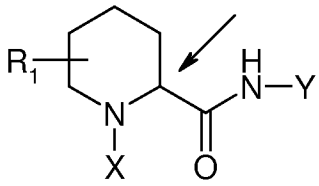
A1		B1	
A2		B2	
A3			
A4			
A5			

A6			
A7			
A8			
A9			

or a pharmaceutically acceptable salt thereof.

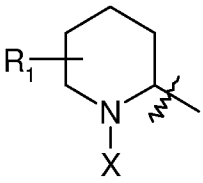
13. The compound according to claim 12 wherein the stereogenic carbon indicated with an arrow is in the (R) configuration.

14. A compound of the formula (IVA)

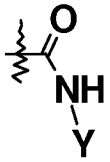


(IVA)

wherein

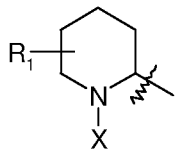
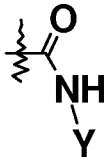
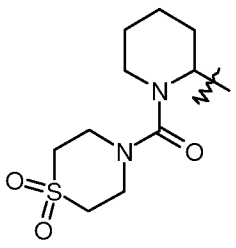
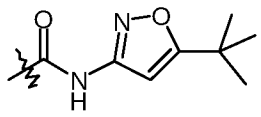


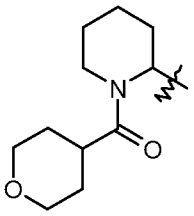
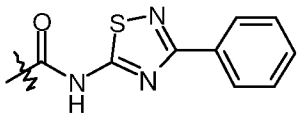
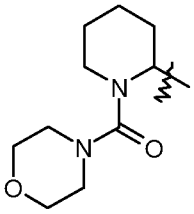
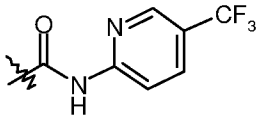
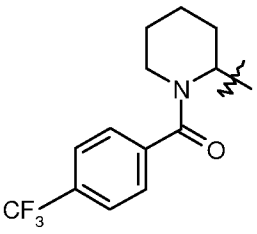
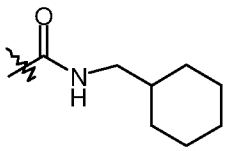
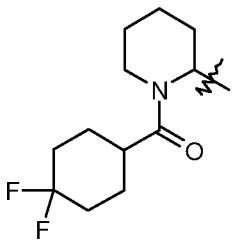
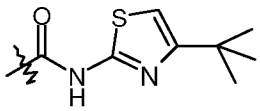
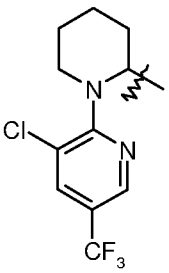
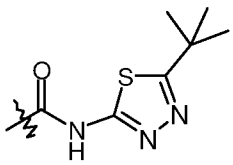
of the formula (IVA) is chosen from A1 – A53 of Table II, and

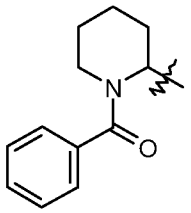
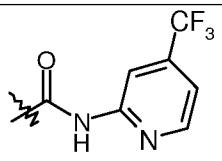
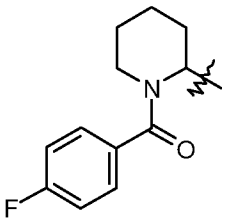
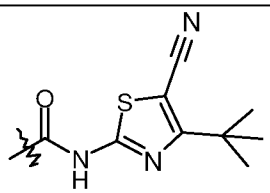
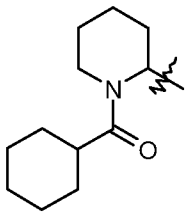
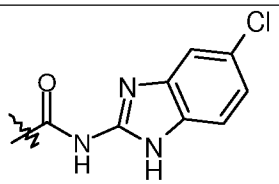
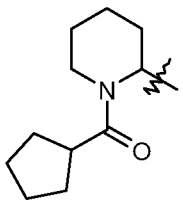
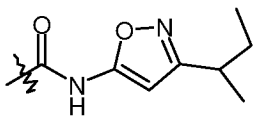
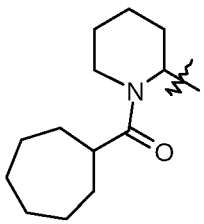
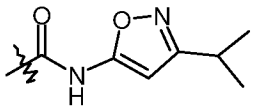
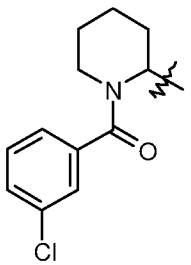
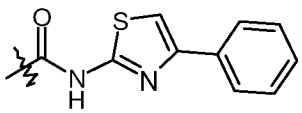


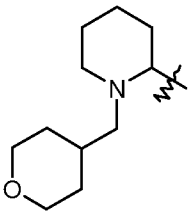
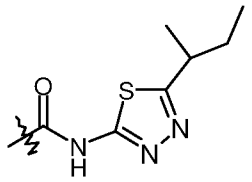
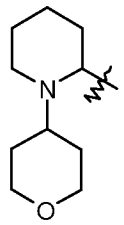
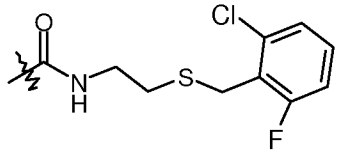
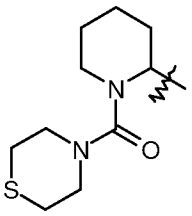
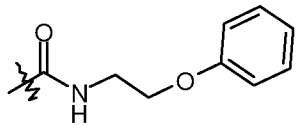
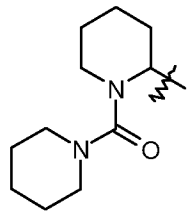
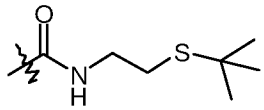
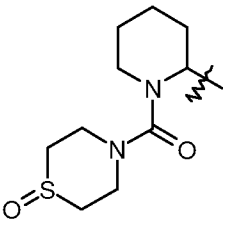
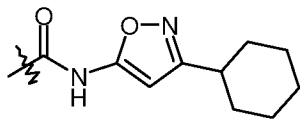
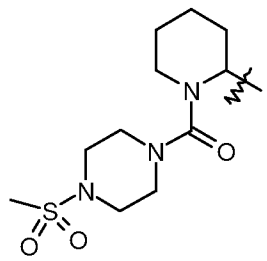
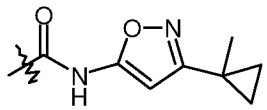
of the formula (IVA) is chosen from B1 – B40 of Table II,

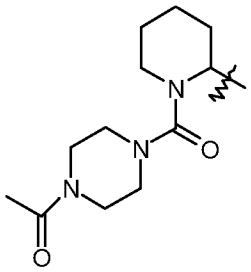
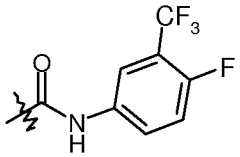
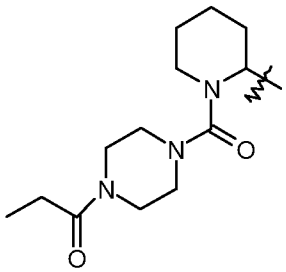
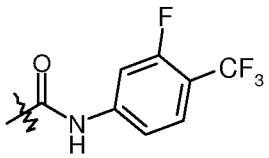
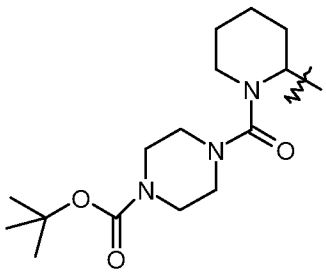
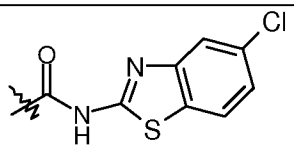
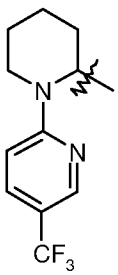
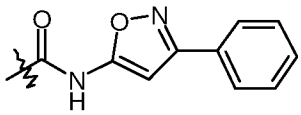
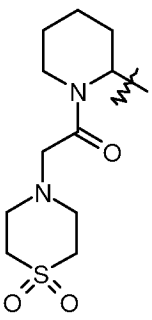
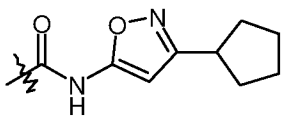
Table II

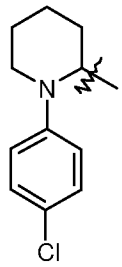
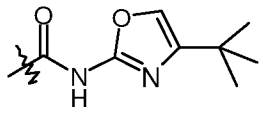
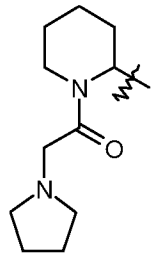
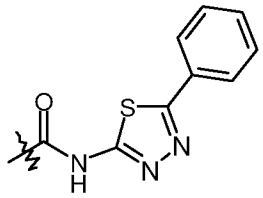
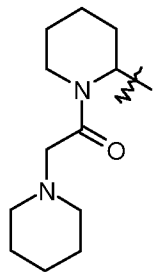
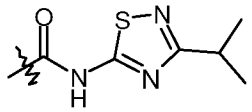
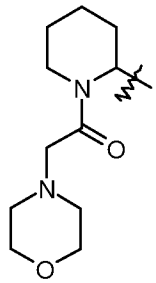
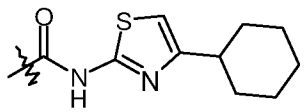
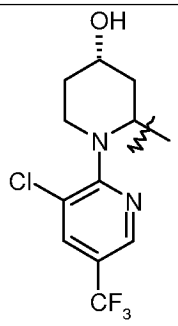
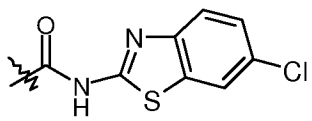
			
A1		B1	

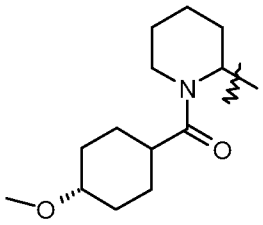
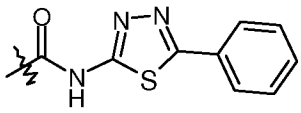
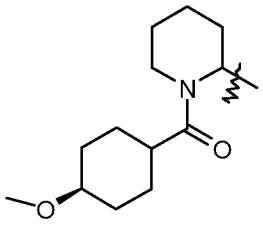
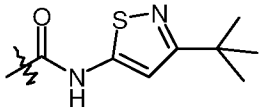
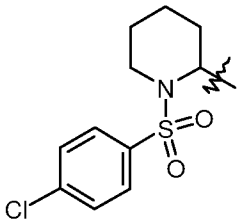
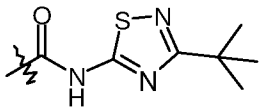
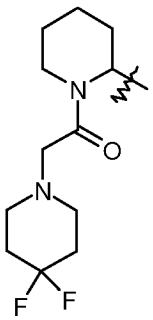
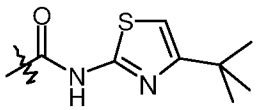
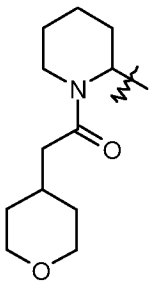
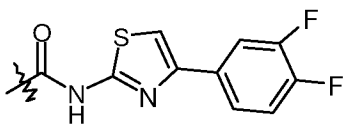
A2		B2	
A3		B3	
A4		B4	
A5		B5	
A6		B6	

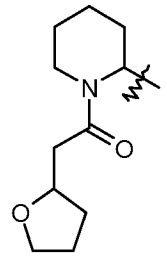
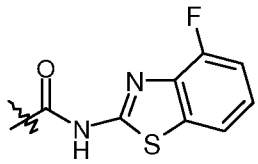
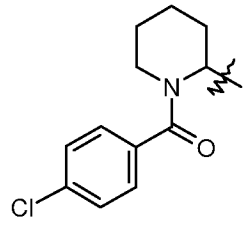
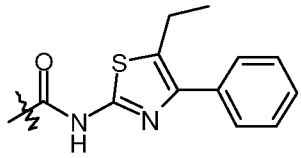
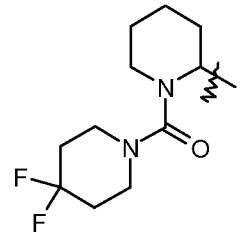
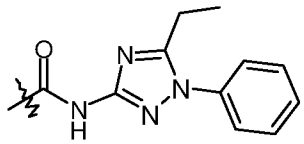
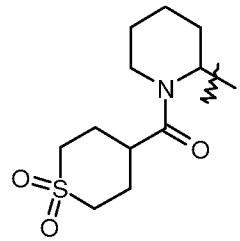
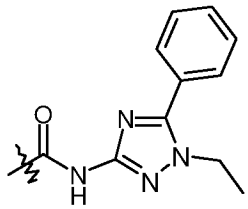
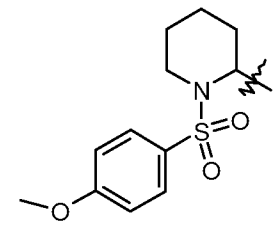
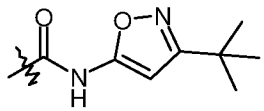
A7		B7	
A8		B8	
A9		B9	
A10		B10	
A11		B11	
A12		B12	

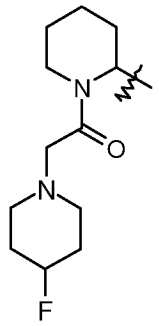
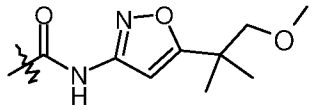
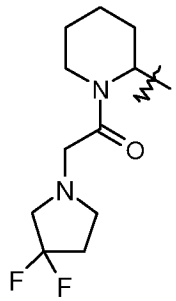
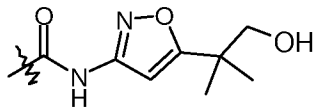
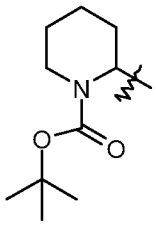
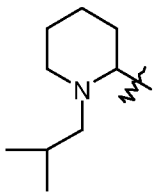
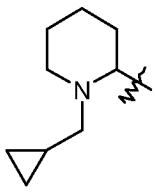
A13		B13	
A14		B14	
A15		B15	
A16		B16	
A17		B17	
A18		B18	

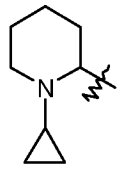
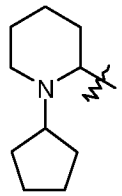
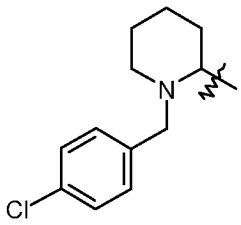
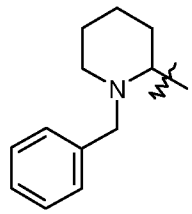
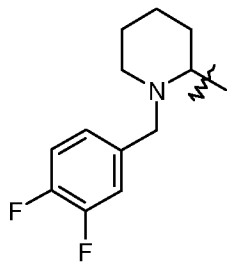
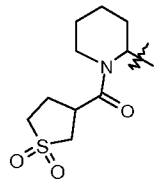
A19		B19	
A20		B20	
A21		B21	
A22		B22	
A23		B23	

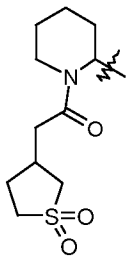
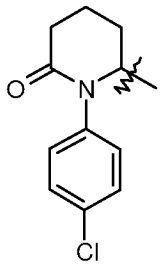
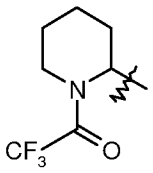
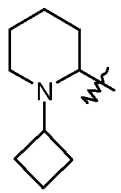
A24		B24	
A25		B25	
A26		B26	
A27		B27	
A28		B28	

A29		B29	
A30		B30	
A31		B31	
A32		B32	
A33		B33	

A34		B34	
A35		B35	
A36		B36	
A37		B37	
A38		B38	

A39		B39	
A40		B40	
A41			
A42			
A43			

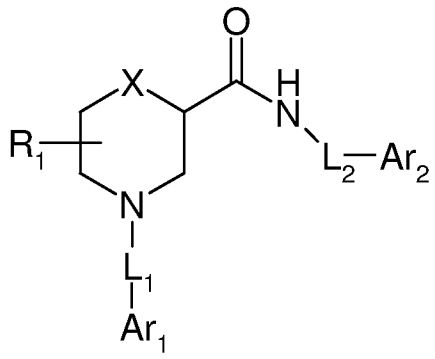
A44			
A45			
A46			
A47			
A48			
A49			

A50			
A51			
A52			
A53			

or a pharmaceutically acceptable salt thereof.

15. The compounds according to claim 14 wherein the stereogenic carbon indicated with an arrow is in the (S) configuration.

16. A compound of the formula (IB)



(IB)

wherein:

X is O, S, -S(O)- or $-SO_2$;

Ar_1 is chosen from carbocycle, heterocyclyl and heteroaryl each optionally substituted by 1-3 C_{1-10} alkyl which is optionally substituted by halogens, C_{1-10} alkoxy, CN, halogen, NO_2, -$S(O)_m$-C_{1-10} alkyl, -CO_2- C_{1-10} alkyl, -NH(C_{1-5} alkyl)-CO_2-C_{1-10} alkyl, -C(O)-NH(C_{1-5} alkyl), -C(O)-N(C_{1-5} alkyl)$_2$, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)-C(O)-C_{1-10} alkyl, -N(C_{1-5} alkyl)-$S(O)_m$-C_{1-10} alkyl, carbocycle or heterocyclyl;

Ar_2 is chosen from carbocycle, heterocyclyl and heteroaryl each optionally substituted by 1-3 C_{1-10} alkyl which is optionally substituted by halogens, C_{3-10} cycloalkyl, carbocycle, C_{1-10} alkylcarbocycle, heteroaryl, CN or halogen, wherein the C_{1-10} alkyl and carbocycle may be additionally optionally substituted by hydroxyl, C_{1-5} alkoxycarbonyl or C_{1-5} alkoxy;

L_1 and **L_2** are each independently chosen from a bond or C_{1-10} alkyl chain wherein each -CH_2- of said chain is optionally replaced by -O-, C(O), or $S(O)_m$;

wherein each **L_1** and **L_2** where possible is optionally substituted by halogen or C_{1-3} alkyl;

R_1 is chosen from hydrogen, oxo (=O) and OH;

m is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

17. The compound according to claim 16 and wherein:

X is O;

Ar_1 is chosen from phenyl, C_{3-6} cycloalkyl, tetrahydrofuranyl, tetrahydropyranyl, and pyridinyl, each optionally substituted by 1-3 C_{1-6} alkyl which is optionally substituted by halogens, or halogen;

Ar_2 is chosen from oxazolyl, isoxazolyl and pyridinyl, each optionally substituted by 1-3 C_{1-6} alkyl which is optionally substituted by halogens, or halogen.

18. The compound according to claim 17 and wherein:

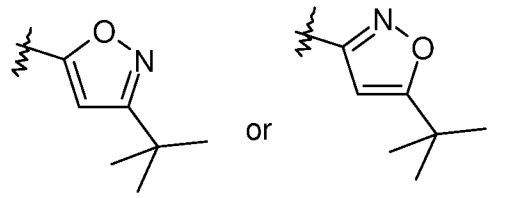
Ar_1 is chosen from phenyl, cyclohexyl, tetrahydropyranyl and pyridinyl, each optionally substituted by 1-3 C_{1-6} alkyl, halogen or trifluoromethyl;

Ar_2 is chosen from isoxazolyl substituted by C_{1-6} alkyl;

L_1 is a bond or C(O).

19. The compound according to claim 18 and wherein:

Ar_2 is chosen from



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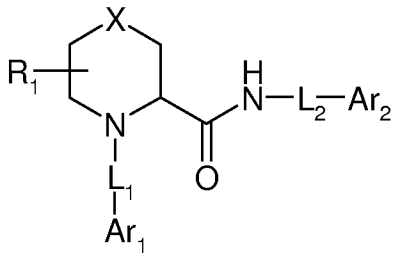
20. A compound of the formula (IIB)



(IIB)

wherein

X is O, S, -S(O)- or $-SO_2$;

Ar_1 is chosen from C_{1-6} alkyl which is optionally substituted by halogens, C_{1-6} alkoxy, carbocycle, heterocyclyl and heteroaryl each optionally substituted by 1-3 C_{1-10} alkyl which is optionally substituted by halogens, C_{1-10} alkoxy, CN, halogen, NO_2, $-S(O)_m-C_{1-10}$ alkyl, $-C(O)-C_{1-10}$ alkyl, $-CO_2-C_{1-10}$ alkyl, C_{1-10} acyl, oxo (=O),$-NH(C_{1-5}$ alkyl)$-CO_2-C_{1-10}$ alkyl, $-C(O)-NH(C_{1-5}$ alkyl), $-C(O)-N(C_{1-5}$ alkyl$)_2$, $-NH(C_{1-5}$ alkyl), $-N(C_{1-5}$ alkyl$)-C(O)-C_{1-10}$ alkyl, $-N(C_{1-5}$ alkyl$)-S(O)_m-C_{1-10}$ alkyl or heterocyclyl the heterocyclyl being further optionally substituted by C_{1-5} alkyl;

Ar_2 is chosen from C_{1-6} alkyl, carbocycle, heterocyclyl and heteroaryl each optionally substituted by halogen, 1-3 C_{1-10} alkyl which is optionally substituted by halogens, alkoxy or

hydroxy, carbocycle optionally substituted by C_{1-3} alkyl, aryl which is optionally substituted by halogen, heteroaryl, CN, halogen, C_{1-10} acyl or oxo (=O);

L_1 and **L_2** are each independently chosen from a bond or C_{1-10} alkyl chain wherein each $-CH_2-$ of said chain is optionally replaced by -O-, C(O), $S(O)_m$ or -NH-;

R_1 is chosen from hydrogen, hydroxyl and oxo (=O);

m is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

21. The compound according to claim 20 and wherein:

X is O;

Ar_1 is chosen from phenyl, C_{3-6} cycloalkyl, tetrahydrofuranyl, tetrahydropyranyl, and pyridinyl, each optionally substituted by 1-3 C_{1-6} alkyl which is optionally substuituted with halogens, or halogen;

Ar_2 is chosen from oxazolyl, isoxazolyl and pyridinyl, each optionally substituted by 1-3 C_{1-6} alkyl which is optionally substituted by halogens or halogen;

R_1 is hydrogen;

L_1 is a bond, C(O) or $S(O)_2$;

L_2 is a bond.

The compound according to the embodiment described immediately above and wherein:

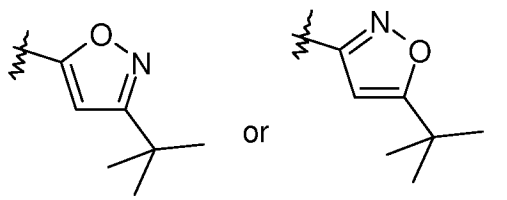
Ar_1 is chosen from phenyl or cyclohexyl, each optionally substituted by 1-3 C_{1-6} alkyl or halogen;

Ar_2 is chosen from isoxazolyl substituted by C_{1-6} alkyl;

L_1 is C(O) or SO_2;

22. The compound according to claim 21 and wherein:

Ar_2 is chosen from



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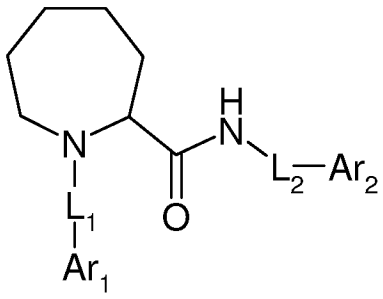
23. A compound of the formula (IC)



(IC)

wherein

Ar_1 is chosen from C_{1-6} alkyl which is optionally substituted by halogens, C_{1-6} alkoxy, carbocycle, heterocyclyl and heteroaryl each optionally substituted by 1-3 C_{1-10} alkyl which is optionally substituted by halogens, C_{1-10} alkoxy, CN, halogen, NO_2, $-S(O)_m-C_{1-10}$ alkyl, $-C(O)-C_{1-10}$ alkyl, $-CO_2-C_{1-10}$ alkyl, C_{1-10} acyl, oxo (=O), $-NH(C_{1-5}$ alkyl$)-CO_2-C_{1-10}$ alkyl, $-C(O)-NH(C_{1-5}$ alkyl), $-C(O)-N(C_{1-5}$ alkyl$)_2$, $-NH(C_{1-5}$ alkyl), $-N(C_{1-5}$ alkyl$)-C(O)-C_{1-10}$ alkyl, $-N(C_{1-5}$ alkyl$)-S(O)_m-$ C_{1-10} alkyl and heterocyclyl the heterocyclyl being further optionally substituted by C_{1-5} alkyl;

Ar_2 is chosen from C_{1-6} alkyl, carbocycle, heterocyclyl and heteroaryl each optionally substituted by 1-3 C_{1-10} alkyl which is optionally substituted by halogens, alkoxy or hydroxy, carbocycle which is optionally substituted by C_{1-3} alkyl, aryl which is optionally substituted by halogen, heteroaryl, CN, halogen, C_{1-10} acyl or oxo (=O), wherein the C_{1-6} alkyl and carbocycle may be additionally optionally substituted by hydroxyl;

L_1 and **L_2** are each independently chosen from a bond or C_{1-10} alkyl chain wherein each $-CH_2-$ of said chain is optionally replaced by -O-, C(O), $S(O)_m$ or -NH-;

m is 0, 1 or 2;
or a pharmaceutically acceptable salt thereof.

24. The compound according to claim 23 and wherein:

Ar_1 is chosen from C_{1-6} alkyl which is optionally substituted by halogens, C_{1-6} alkoxyl, phenyl, C_{3-8} cycloalkyl, dioxanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl,

tetrahydrothiopyran-1,1-dioxide, tetrahydrothiofuranyl, tetrahydrothiofuran-1,1-dioxide, thiomorpholinyl, 1-oxo-1λ^4-thiomorpholinyl, 1,1-dioxo-1λ^6-thiomorpholinyl, morpholinyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolidinyl, piperidinyl and piperazinyl, each optionally substituted by 1-3 C_{1-6} alkyl which is optionally substituted by halogens, C_{1-6} alkoxy, CN, halogen, oxo, -C(O)-C_{1-10} alkyl, -$S(O)_2$-C_{1-3} alkyl or -CO_2-C_{1-4} alkyl;

Ar_2 is chosen from C_{1-6} alkyl, cyclohexyl, phenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, imidazolyl, thienyl, thiadiazolyl, triazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, benzofuranyl and benzothienyl, each optionally substituted by 1-3 C_{1-6} alkyl which is optionally substituted by halogen, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, phenyl optionally substituted by halogens, CN, halogens, C_{1-6} alkoxy or hydroxy;

L_1 is a bond or C_{1-3} alkyl chain wherein each -CH_2- of said chain is optionally replaced by C(O) or $S(O)_m$;

L_2 is a bond or C_{1-5} alkyl chain wherein each -CH_2- of said chain is optionally replaced by -O- or $S(O)_m$.

25. The compound according to claim 24 and wherein:

Ar_1 is chosen from phenyl, tetrahydropyranyl, thiomorpholinyl, 1-Oxo-1λ^4-thiomorpholinyl, and 1,1-dioxo-1λ^6-thiomorpholinyl, each optionally substituted halogen.

26. The compound according to any one of the claims 1, 7, 16, 20 or 23 and wherein:

Ar_2 is isoxazolyl substituted by 1-3 C_{1-6} alkyl group.

27. The compound according to any one of claims 1, 7, 16, 20 or 23 and wherein:

L_1 is a bond or C_{1-3} alkyl chain wherein each -CH_2- of said chain is optionally replaced by C(O);

L_2 is a bond.

28. The compound according to any one of claims 1, 7, 16, 20 or 23 and wherein:

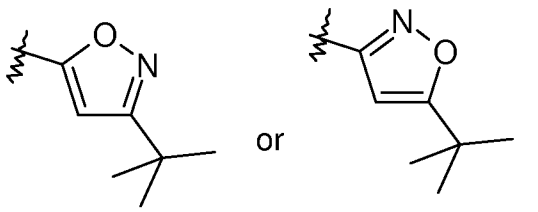
Ar_1 is chosen from phenyl, tetrahydropyranyl, thiomorpholinyl, 1-Oxo-1λ^4-thiomorpholinyl, and 1,1-dioxo-1λ^6-thiomorpholinyl, each optionally substituted chloro;

Ar_2 is isoxazolyl substituted by 1-3 C_{1-6} alkyl group;

L_1 is a bond or C_{1-2} alkyl chain wherein each -CH_2- of said chain is optionally replaced by C(O);

L_2 is a bond.

29. The compound according to any one of claims 1, 7, 16, 20 or 23 and wherein:
Ar_2 is



30. The compound according to any one of claims 1, 7, 16, 20 or 23 and wherein:

Ar_1 is chosen from phenyl optionally substituted chloro, tetrahydropyranyl, and 1,1-dioxo-1λ^6-thiomorpholinyl;

L_1 is a bond or -CH_2-;

L_2 is a bond.

31. A compound chosen from

3'-Chloro-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
1-(1,1-Dioxo-1λ6-thiomorpholine-4-carbonyl)-piperidine-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
1-(Tetrahydro-pyran-4-carbonyl)-piperidine-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(R)-3'-Chloro-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
1-(4-Trifluoromethyl-benzoyl)-piperidine-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide

1-(4-Chloro-benzyl)-piperidine-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
1-(4-Chloro-benzenesulfonyl)-piperidine-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(R)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
1-(Tetrahydro-pyran-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
1-(4-Trifluoromethyl-benzoyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(R)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(R)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide
(S)-3'-Chloro-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-1,2'-bipyridinyl-2-carboxylic acid (3-phenyl-1,2,4-thiadiazol-5-yl)-amide
(S)-1-(4,4-Difluoro-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide

(S)-1-Benzoyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(4-Fluoro-benzoyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
S)-1-Cyclohexanecarbonyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-Cyclopentanecarbonyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
S)-1-Cycloheptanecarbonyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(3-Chloro-benzoyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-chloro-1H-benzimidazol-2-yl)-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-sec-butyl-isoxazol-5-yl)-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-isopropyl-isoxazol-5-yl)-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (4-phenyl-thiazol-2-yl)-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [2-(2-chloro-6-fluoro-benzylsulfanyl)-ethyl]-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-cyclohexyl-isoxazol-5-yl)-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [3-(1-methyl-cyclopropyl)-isoxazol-5-yl]-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-chloro-benzothiazol-2-yl)-amide

(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-cyclopentyl-isoxazol-5-yl)-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-tert-butyl-oxazol-2-yl)-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-phenyl-1,2,4-thiadiazol-5-yl)-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-fluoro-3-trifluoromethyl-phenyl)-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-fluoro-4-trifluoromethyl-phenyl)-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-isopropyl-1,2,4-thiadiazol-5-yl)-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-cyclohexyl-thiazol-2-yl)-amide
(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (5-chloro-benzothiazol-2-yl)-amide
(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (4-cyclohexyl-thiazol-2-yl)-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-tert-butyl-isothiazol-5-yl)-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (3-tert-butyl-1,2,4-thiadiazol-5-yl)-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-tert-butyl-thiazol-2-yl)-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid [4-(3,4-difluoro-phenyl)-thiazol-2-yl]-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-phenyl-1,2,4-thiadiazol-3-yl)-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-fluoro-benzothiazol-2-yl)-amide

(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-phenyl-thiazol-2-yl)-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (6-chloro-benzothiazol-2-yl)-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (4-trifluoromethyl-pyridin-2-yl)-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-chloro-benzothiazol-2-yl)-amide
(S)-1-(Thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(Piperidine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(1-Oxo-1λ^4-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(4-Acetyl-piperazine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(4-Propionyl-piperazine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-2-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester
(S)-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-3'-Chloro-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(Tetrahydro-pyran-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-[2-(1,1-Dioxo-1λ^6-thiomorpholin-4-yl)-acetyl]-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide

(S)-1-(4-Chloro-phenyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(2-Pyrrolidin-1-yl-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(2-Morpholin-4-yl-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(2S,4S)-3'-Chloro-4-hydroxy-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(4-cis-Methoxy-cyclohexanecarbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(4-Chloro-benzenesulfonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-[2-(4,4-Difluoro-piperidin-1-yl)-acetyl]-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(Tetrahydro-pyran-4-yl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(2-Tetrahydro-pyran-4-yl-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-((R)-2-Tetrahydro-furan-2-yl-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide
(S)-1-(4-Chloro-benzoyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(4,4-Difluoro-piperidine-1-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(1,1-Dioxo-hexahydro-1λ6-thiopyran-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide

(S)-1-(4-Methoxy-benzenesulfonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-[2-(4-Fluoro-piperidin-1-yl)-acetyl]-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-[2-(3,3-Difluoro-pyrrolidin-1-yl)-acetyl]-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-2-(5-Ethyl-4-phenyl-thiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-ethyl-4-phenyl-thiazol-2-yl)-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-ethyl-4-phenyl-thiazol-2-yl)-amide
(S)-1-Isobutyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-Cyclopropylmethyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-Cyclopropyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-Cyclopentyl-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(Morpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(benzyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(4-Chloro-benzyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(3,4-Difluoro-benzyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-ethyl-1-phenyl-1H-1,2,4-triazol-3-yl)-amide

(S)-1-(1,1-Dioxo-tetrahydro-1λ^6-thiophene-3-carbonyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-[2-(1,1-Dioxo-tetrahydro-1λ^6-thiophen-3-yl)-acetyl]-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (1-ethyl-5-phenyl-1H-1,2,4-triazol-3-yl)-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (1-ethyl-5-phenyl-1H-1,2,4-triazol-3-yl)-amide
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide
(S)-1-(4-Chloro-phenyl)-6-oxo-piperidine-2-carboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide
(S)-1-[2-(1,1-Dioxo-tetrahydro-1λ^6-thiophen-3-yl)-acetyl]-piperidine-2-carboxylic acid (1-ethyl-5-phenyl-1H-1,2,4-triazol-3-yl)-amide
(S)-1-(2,2,2-Trifluoro-acetyl)-piperidine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-2-(5-tert-Butyl-1,3,4-thiadiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester
(S)-1-Cyclobutyl-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide
(S)-1-Cyclopropyl-piperidine-2-carboxylic acid (5-tert-butyl-1,3,4-thiadiazol-2-yl)-amide
(S)-1-[2-(3,3-Difluoro-pyrrolidin-1-yl)-acetyl]-piperidine-2-carboxylic acid (1-ethyl-5-phenyl-1H-1,2,4-triazol-3-yl)-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [5-(2-methoxy-1,1-dimethyl-ethyl)-isoxazol-3-yl]-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (3-phenyl-1,2,4-thiadiazol-5-yl)-amide
4-(4-Trifluoromethyl-benzoyl)-morpholine-2-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide

4-(4-Chloro-benzenesulfonyl)-morpholine-3-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [3-(4-methoxy-phenyl)-[1,2,4]thiadiazol-5-yl]-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [3-(4-fluoro-phenyl)-[1,2,4]thiadiazol-5-yl]-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5-fluoro-benzothiazol-2-yl)-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (5,6-difluoro-benzothiazol-2-yl)-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (4-chloro-benzothiazol-2-yl)-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [4-(4-chloro-phenyl)-thiazol-2-yl]-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [4-(3,4-difluoro-phenyl)-thiazol-2-yl]-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [4-(2,4-difluoro-phenyl)-thiazol-2-yl]-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid [4-(4-fluoro-phenyl)-thiazol-2-yl]-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-piperidine-2-carboxylic acid (4-fluoro-benzothiazol-2-yl)-amide
(S)-1-(4-Chloro-phenyl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide
(S)-1-(1,1-Dioxo-1λ^6-thiomorpholine-4-carbonyl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide
(S)-1-(Tetrahydro-pyran-4-yl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide and
(S)-1-(Tetrahydro-pyran-4-ylmethyl)-azepane-2-carboxylic acid (5-*tert*-butyl-isoxazol-3-yl)-amide

or a pharmaceutically acceptable salt thereof.

32. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1, 7, 16, 20, 23 or 31 and one or more pharmaceutically acceptable carriers and/or adjuvants.

33. A method of treating pain comprising administering a therapeutically effective amount of a compound according to any one of claims 1, 7, 16, 20, 23 or 31.

34. A method of treating a disease or condition chosen from a lung disease, a rheumatic disease, an autoimmune disease, a musculoskeletal disease, an allergic disease, an allergic reaction, a vascular disease, a dermatological disease, a renal disease, a hepatic disease, a gastrointestinal disease, neurodegeneration eye disease, diseases of the ear, nose, and throat, neurological disease blood disease, tumors, endocrine diseases, organ and tissue transplantations and graft-versus-host diseases, severe states of shock, acute pain, visceral pain, spasm of the gastrointestinal tract or uterus, colics, neuropathic pain, inflammatory and nociceptive pain, cancer pain, headache, restenosis, atherosclerosis, reperfusion injury, congestive heart failure, myocardial infarction, thermal injury, multiple organ injury secondary to trauma, necrotizing enterocolitis and syndromes associated with hemodialysis, leukopheresis, and granulocyte transfusion, sarcoidosis, gingivitis and pyrexia comprising administering a therapeutically effective amount of a compound according to any one of claims 1, 7, 16, 20, 23 or 31.