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(54) Title: MGLUR5 MODULATORS II

(57) Abstract: The present invention is directed to novel compounds, to a process for their preparation, their use in therapy and pharmaceutical compositions comprising the novel compounds.



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MGLUR5 MODULATORS II

Field of the invention

- 5 The present invention is directed to novel compounds, their use in therapy and pharmaceutical compositions comprising said novel compounds.

Background of the invention

- 10 Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system (CNS). Glutamate produces its effects on central neurons by binding to and thereby activating cell surface receptors. These receptors have been divided into two major classes, the ionotropic and metabotropic glutamate receptors, based on the structural features of the
15 receptor proteins, the means by which the receptors transduce signals into the cell, and pharmacological profiles.

The metabotropic glutamate receptors (mGluRs) are G protein-coupled receptors that activate a variety of intracellular second messenger systems following the binding of glutamate.

- 20 Activation of mGluRs in intact mammalian neurons elicits one or more of the following responses: activation of phospholipase C; increases in phosphoinositide (PI) hydrolysis; intracellular calcium release; activation of phospholipase D; activation or inhibition of adenylyl cyclase; increases or decreases in the formation of cyclic adenosine monophosphate (cAMP); activation of guanylyl cyclase; increases in the formation of cyclic guanosine monophosphate
25 (cGMP); activation of phospholipase A₂; increases in arachidonic acid release; and increases or decreases in the activity of voltage- and ligand-gated ion channels. Schoepp *et al.*, *Trends Pharmacol. Sci.* 14:13 (1993), Schoepp, *Neurochem. Int.* 24:439 (1994), Pin *et al.*, *Neuropharmacology* 34:1 (1995), Bordi and Ugolini, *Prog. Neurobiol.* 59:55 (1999).

Molecular cloning has identified eight distinct mGluR subtypes, termed mGluR1 through mGluR8. Nakanishi, *Neuron* 13:1031 (1994), Pin *et al.*, *Neuropharmacology* 34:1 (1995), Knopfel *et al.*, *J. Med. Chem.* 38:1417 (1995). Further receptor diversity occurs via expression of alternatively spliced forms of certain mGluR subtypes. Pin *et al.*, *PNAS* 89:10331 (1992), Minakami *et al.*, *BBRC* 199:1136 (1994), Joly *et al.*, *J. Neurosci.* 15:3970 (1995).

Metabotropic glutamate receptor subtypes may be subdivided into three groups, Group I, Group II, and Group III mGluRs, based on amino acid sequence homology, the second messenger systems utilized by the receptors, and by their pharmacological characteristics. Group I mGluR comprises mGluR1, mGluR5 and their alternatively spliced variants. The binding of agonists to these receptors results in the activation of phospholipase C and the subsequent mobilization of intracellular calcium.

Neurological, psychiatric and pain disorders

Attempts at elucidating the physiological roles of Group I mGluRs suggest that activation of these receptors elicits neuronal excitation. Various studies have demonstrated that Group I mGluR agonists can produce postsynaptic excitation upon application to neurons in the hippocampus, cerebral cortex, cerebellum, and thalamus, as well as other CNS regions. Evidence indicates that this excitation is due to direct activation of postsynaptic mGluRs, but it also has been suggested that activation of presynaptic mGluRs occurs, resulting in increased neurotransmitter release. Baskys, *Trends Pharmacol. Sci.* 15:92 (1992), Schoepp, *Neurochem. Int.* 24:439 (1994), Pin *et al.*, *Neuropharmacology* 34:1(1995), Watkins *et al.*, *Trends Pharmacol. Sci.* 15:33 (1994).

Metabotropic glutamate receptors have been implicated in a number of normal processes in the mammalian CNS. Activation of mGluRs has been shown to be required for induction of hippocampal long-term potentiation and cerebellar long-term depression. Bashir *et al.*,

Nature 363:347 (1993), Bortolotto *et al.*, *Nature* 368:740 (1994), Aiba *et al.*, *Cell* 79:365 (1994), Aiba *et al.*, *Cell* 79:377 (1994). A role for mGluR activation in nociception and analgesia also has been demonstrated, Meller *et al.*, *Neuroreport* 4: 879 (1993), Bordi and Ugolini, *Brain Res.* 871:223 (1999). In addition, mGluR activation has been suggested to
5 play a modulatory role in a variety of other normal processes including synaptic transmission, neuronal development, apoptotic neuronal death, synaptic plasticity, spatial learning, olfactory memory, central control of cardiac activity, waking, motor control and control of the vestibulo-ocular reflex. Nakanishi, *Neuron* 13: 1031 (1994), Pin *et al.*, *Neuropharmacology* 34:1, Knopfel *et al.*, *J. Med. Chem.* 38:1417 (1995).

10 Further, Group I metabotropic glutamate receptors and mGluR5 in particular, have been suggested to play roles in a variety of pathophysiological processes and disorders affecting the CNS. These include stroke, head trauma, anoxic and ischemic injuries, hypoglycemia, epilepsy, neurodegenerative disorders such as Alzheimer's disease and pain. Schoepp *et al.*,
15 *Trends Pharmacol. Sci.* 14:13 (1993), Cunningham *et al.*, *Life Sci.* 54:135 (1994), Hollman *et al.*, *Ann. Rev. Neurosci.* 17:31 (1994), Pin *et al.*, *Neuropharmacology* 34:1 (1995), Knopfel *et al.*, *J. Med. Chem.* 38:1417 (1995), Spooren *et al.*, *Trends Pharmacol. Sci.* 22:331 (2001), Gasparini *et al.* *Curr. Opin. Pharmacol.* 2:43 (2002), Neugebauer *Pain* 98:1 (2002). Much of the pathology in these conditions is thought to be due to excessive glutamate-induced
20 excitation of CNS neurons. Because Group I mGluRs appear to increase glutamate-mediated neuronal excitation via postsynaptic mechanisms and enhanced presynaptic glutamate release, their activation probably contributes to the pathology. Accordingly, selective antagonists of Group I mGluR receptors could be therapeutically beneficial, specifically as neuroprotective agents, analgesics or anticonvulsants.

25 Recent advances in the elucidation of the neurophysiological roles of metabotropic glutamate receptors generally and Group I in particular, have established these receptors as promising drug targets in the therapy of acute and chronic neurological and psychiatric disorders and chronic and acute pain disorders.

Gastrointestinal disorders

The lower esophageal sphincter (LES) is prone to relaxing intermittently. As a consequence, fluid from the stomach can pass into the esophagus since the mechanical barrier is temporarily lost at such times, an event hereinafter referred to as “reflux”.

Gastro-esophageal reflux disease (GERD) is the most prevalent upper gastrointestinal tract disease. Current pharmacotherapy aims at reducing gastric acid secretion, or at neutralizing acid in the esophagus. The major mechanism behind reflux has been considered to depend on a hypotonic lower esophageal sphincter. However, e.g. *Holloway & Dent (1990) Gastroenterol. Clin. N. Amer. 19, pp. 517-535*, has shown that most reflux episodes occur during transient lower esophageal sphincter relaxations (TLESRs), i.e. relaxations not triggered by swallows. It has also been shown that gastric acid secretion usually is normal in patients with GERD.

The novel compounds according to the present invention are assumed to be useful for the inhibition of transient lower esophageal sphincter relaxations (TLESRs) and thus for treatment of gastro-esophageal reflux disorder (GERD).

It is well known that certain compounds may cause undesirable effects on cardiac repolarisation in man, observed as a prolongation of the QT interval on electrocardiograms (ECG). In extreme circumstances, this drug-induced prolongation of the QT interval can lead to a type of cardiac arrhythmia called Torsades de Pointes (TdP; Vandenberg et al. hERG K⁺ channels: friend and foe. Trends Pharmacol Sci 2001; 22: 240-246), leading ultimately to ventricular fibrillation and sudden death. The primary event in this syndrome is inhibition of the rapid component of the delayed rectifying potassium current (IKr) by these compounds. The compounds bind to the aperture-forming alpha sub-units of the channel protein carrying this current – sub-units that are encoded by the human ether-a-go-go-related gene (hERG).

Since IKr plays a key role in repolarisation of the cardiac action potential, its inhibition slows repolarisation and this is manifested as a prolongation of the QT interval. Whilst QT interval prolongation is not a safety concern per se, it carries a risk of cardiovascular adverse effects and in a small percentage of people it can lead to TdP and degeneration into ventricular
5 fibrillation.

Generally, compounds of the present invention have low activity against the hERG-encoded potassium channel. In this regard, low activity against hERG *in vitro* is indicative of low activity *in vivo*.

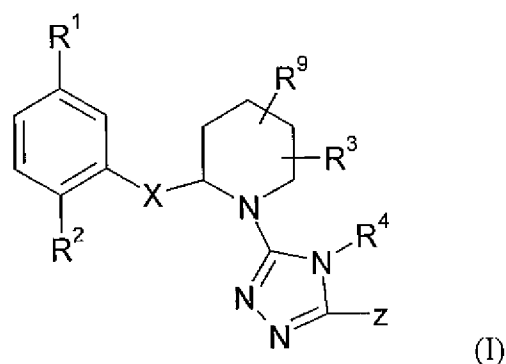
10 It is also desirable for drugs to possess good metabolic stability in order to enhance drug efficacy. Stability against human microsomal metabolism *in vitro* is indicative of stability towards metabolism *in vivo*.

15 Because of their physiological and pathophysiological significance, there is a need for new potent mGluR agonists and antagonists that display a high selectivity for mGluR subtypes, particularly the Group I receptor subtype, most particularly the mGluR5.

20 The object of the present invention is to provide compounds exhibiting an activity at metabotropic glutamate receptors (mGluRs), especially at the mGluR5 receptor. In particular, the compounds according to the present invention are predominantly peripherally acting, i.e. have a limited ability of passing the blood-brain barrier.

DESCRIPTION OF THE INVENTION

The present invention relates to a compound of formula I:



5 wherein

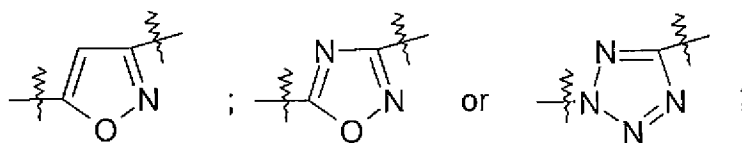
R^1 is methyl, halogen or cyano;

R^2 is hydrogen or fluoro;

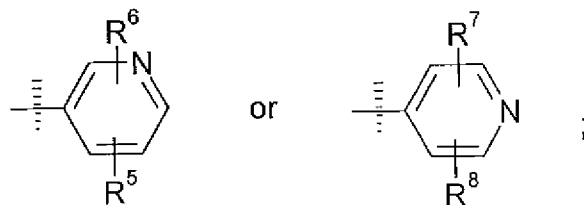
R^3 is hydrogen, fluoro or C_1 - C_3 alkyl;

R^4 is C_1 - C_3 alkyl or cyclopropyl;

10 X is



and Z is



wherein

15 R^5 is hydrogen, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, C_1 - C_3 alkoxy; C_1 - C_3 haloalkoxy or halogen;

R^6 is hydrogen, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, C_1 - C_3 alkoxy; C_1 - C_3 haloalkoxy or halogen;

R^7 is C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, C_1 - C_3 alkoxy; C_1 - C_3 haloalkoxy or halogen;

R^8 is hydrogen, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, C_1 - C_3 alkoxy; C_1 - C_3 haloalkoxy or halogen;

R⁹ is hydrogen, fluoro or C₁-C₃ alkyl;

as well as pharmaceutically acceptable salts, hydrates, isoforms, tautomers and/or enantiomers thereof.

5 In one embodiment, R¹ is halogen or cyano.

In a further embodiment, R¹ is chloro. In a further embodiment, R¹ is cyano.

In a further embodiment, R² is hydrogen.

10

In a further embodiment, R³ is hydrogen or fluoro.

In a further embodiment, R⁴ is C₁-C₂ alkyl.

15 In a further embodiment, R⁴ is methyl.

In a further embodiment, R⁵ is hydrogen, C₁-C₂ alkyl or C₁-C₂ alkoxy.

In a further embodiment, R⁶ is hydrogen, C₁-C₂ alkyl or C₁-C₂ alkoxy.

20

In a further embodiment, R⁷ is C₁-C₂ alkyl or C₁-C₂ alkoxy.

In a further embodiment, R⁸ is hydrogen, C₁-C₂ alkyl or C₁-C₂ alkoxy.

25 In a further embodiment, R⁹ is hydrogen or fluoro.

Another embodiment is a pharmaceutical composition comprising as active ingredient a therapeutically effective amount of the compound according to formula I, in association with one or more pharmaceutically acceptable diluents, excipients and/or inert carriers.

5 Other embodiments, as described in more detail below, relate to a compound according to formula I for use in therapy, in treatment of mGluR5 mediated disorders, in the manufacture of a medicament for the treatment of mGluR5 mediated disorders.

Still other embodiments relate to a method of treatment of mGluR5 mediated disorders,
10 comprising administering to a mammal a therapeutically effective amount of the compound according according to formula I.

In another embodiment, there is provided a method for inhibiting activation of mGluR5 receptors, comprising treating a cell containing said receptor with an effective amount of the
15 compound according to formula I.

The compounds of the present invention are useful in therapy, in particular for the treatment of neurological, psychiatric, pain, and gastrointestinal disorders.

20 It will also be understood by those of skill in the art that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the compounds of formula I.

25 Within the scope of the invention are also salts of the compounds of formula I. Generally, pharmaceutically acceptable salts of compounds of the present invention are obtained using standard procedures well known in the art, for example, by reacting a sufficiently basic compound, for example an alkyl amine with a suitable acid, for example, HCl, acetic acid or a methanesulfonic acid, to afford a salt with a physiologically acceptable anion. It is also
30 possible to make a corresponding alkali metal (such as sodium, potassium, or lithium) or an

alkaline earth metal (such as a calcium) salt by treating a compound of the present invention having a suitably acidic proton, such as a carboxylic acid or a phenol, with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a suitably basic organic amine (such as choline or meglumine) in an aqueous medium, followed by conventional purification techniques. Additionally, quaternary ammonium salts can be prepared by the addition of alkylating agents, for example, to neutral amines.

In one embodiment of the present invention, the compound of formula I may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

The general terms used in the definition of formula I have the following meanings:

Halogen as used herein is selected from chlorine, fluorine, bromine or iodine.

C₁-C₃ alkyl is a straight or branched alkyl group, having from 1 to 3 carbon atoms, for example methyl, ethyl, n-propyl or isopropyl.

C₁-C₃ alkoxy is an alkoxy group having 1 to 3 carbon atoms, for example methoxy, ethoxy, isopropoxy or n-propoxy.

C₁-C₃ haloalkoxy is an alkoxy group having 1 to 3 carbon atoms, for example methoxy, ethoxy or n-propoxy wherein at least one of the carbon atoms is substituted by a halogen atom.

All chemical names were generated using a software known as AutoNom accessed through ISIS draw.

In formula I above, X may be present in any of the two possible orientations.

5 Pharmaceutical Composition

The compounds of the present invention may be formulated into conventional pharmaceutical compositions comprising a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, in association with a pharmaceutically acceptable carrier or excipient. The
10 pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents, flavoring
15 agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents. A solid carrier can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the active component is
20 mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by,
25 for example, stirring. The molten homogeneous mixture is then poured into convenient sized moulds and allowed to cool and solidify.

Suitable carriers include, but are not limited to, magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium
30 carboxymethyl cellulose, low-melting wax, cocoa butter, and the like.

The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it.

5 Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

10 Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or water propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

15 Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other
20 suspending agents known to the pharmaceutical formulation art. Exemplary compositions intended for oral use may contain one or more coloring, sweetening, flavoring and/or preservative agents.

Depending on the mode of administration, the pharmaceutical composition will include from
25 about 0.05%w (percent by weight) to about 99%w, or from about 0.10%w to 50%w, of a compound of the invention, all percentages by weight being based on the total weight of the composition.

A therapeutically effective amount for the practice of the present invention can be determined
30 by one of ordinary skill in the art using known criteria including the age, weight and response

of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented.

5 Medical use

The compounds according to the present invention are useful in the treatment of conditions associated with excitatory activation of mGluR5 and for inhibiting neuronal damage caused by excitatory activation of mGluR5. The compounds may be used to produce an inhibitory
10 effect of mGluR5 in mammals, including man.

The Group I mGluR receptors including mGluR5 are highly expressed in the central and peripheral nervous system and in other tissues. Thus, it is expected that the compounds of the invention are well suited for the treatment of mGluR5-mediated disorders such as acute and
15 chronic neurological and psychiatric disorders, gastrointestinal disorders, and chronic and acute pain disorders.

The invention relates to compounds of formula I, as defined hereinbefore, for use in therapy.

20 The invention relates to compounds of formula I, as defined hereinbefore, for use in treatment of mGluR5-mediated disorders.

The invention relates to compounds of formula I, as defined hereinbefore, for use in treatment of Alzheimer's disease senile dementia, AIDS-induced dementia, Parkinson's disease,
25 amyotrophic lateral sclerosis, Huntington's Chorea, migraine, epilepsy, schizophrenia, depression, anxiety, acute anxiety, ophthalmological disorders such as retinopathies, diabetic retinopathies, glaucoma, auditory neuropathic disorders such as tinnitus, chemotherapy induced neuropathies, post-herpetic neuralgia and trigeminal neuralgia, tolerance, dependency, Fragile X, autism, mental retardation, schizophrenia and Down's Syndrome.

The invention relates to compounds of formula I, as defined above, for use in treatment of pain related to migraine, inflammatory pain, neuropathic pain disorders such as diabetic neuropathies, arthritis and rheumatoid diseases, low back pain, post-operative pain and pain associated with various conditions including cancer, angina, renal or biliary colic,
5 menstruation, migraine and gout.

The invention relates to compounds of formula I as defined hereinbefore, for use in treatment of stroke, head trauma, anoxic and ischemic injuries, hypoglycemia, cardiovascular diseases and epilepsy.

10 The present invention relates also to the use of a compound of formula I as defined hereinbefore, in the manufacture of a medicament for the treatment of mGluR Group I receptor-mediated disorders and any disorder listed above.

15 One embodiment of the invention relates to the use of a compound according to formula I in the treatment of gastrointestinal disorders.

Another embodiment of the invention relates to the use of a formula I compound for the manufacture of a medicament for inhibition of transient lower esophageal sphincter
20 relaxations, for the treatment of GERD, for the prevention of gastroesophageal reflux, for the treatment regurgitation, for treatment of asthma, for treatment of laryngitis, for treatment of lung disease, for the management of failure to thrive, for the treatment of irritable bowel disease (IBS) and for the treatment of functional dyspepsia (FD).

25 Another embodiment of the present invention relates to the use of a compound of formula I for treatment of overactive bladder or urinary incontinence.

The wording "TLESR", transient lower esophageal sphincter relaxations, is herein defined in accordance with *Mittal, R.K., Holloway, R.H., Penagini, R., Blackshaw, L.A., Dent, J., 1995; Transient lower esophageal sphincter relaxation. Gastroenterology 109, pp. 601-610.*
30

The wording "reflux" is herein defined as fluid from the stomach being able to pass into the esophagus, since the mechanical barrier is temporarily lost at such times.

- 5 The wording "GERD", gastro-esophageal reflux disease, is herein defined in accordance with *van Heerwarden, M.A., Smout A.J.P.M., 2000; Diagnosis of reflux disease. Baillière's Clin. Gastroenterol. 14, pp. 759-774.*

10 The compounds of formula I above are useful for the treatment or prevention of obesity or overweight, (e.g., promotion of weight loss and maintenance of weight loss), prevention or reversal of weight gain (e.g., rebound, medication-induced or subsequent to cessation of smoking), for modulation of appetite and/or satiety, eating disorders (e.g. binge eating, anorexia, bulimia and compulsive) and cravings (for drugs, tobacco, alcohol, any appetizing macronutrients or non-essential food items).

15

The invention also provides a method of treatment of mGluR5-mediated disorders and any disorder listed above, in a patient suffering from, or at risk of, said condition, which comprises administering to the patient an effective amount of a compound of formula I, as hereinbefore defined.

20

The dose required for the therapeutic or preventive treatment of a particular disorder will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated.

- 25 In the context of the present specification, the term "therapy" and "treatment" includes prevention or prophylaxis, unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

In this specification, unless stated otherwise, the term “antagonist” and “inhibitor” shall mean a compound that by any means, partly or completely, blocks the transduction pathway leading to the production of a response by the ligand.

- 5 The term “disorder”, unless stated otherwise, means any condition and disease associated with metabotropic glutamate receptor activity.

One embodiment of the present invention is a combination of a compound of formula I and an acid secretion inhibiting agent. A “combination” according to the invention may be
10 present as a “fix combination” or as a “kit of parts combination”. A “fix combination” is defined as a combination wherein the (i) at least one acid secretion inhibiting agent; and (ii) at least one compound of formula I are present in one unit. A “kit of parts combination” is defined as a combination wherein the (i) at least one acid secretion inhibiting agent; and (ii) at least one compound of formula I are present in more than one unit. The components of the
15 “kit of parts combination” may be administered simultaneously, sequentially or separately. The molar ratio of the acid secretion inhibiting agent to the compound of formula I used according to the invention is within the range of from 1:100 to 100:1, such as from 1:50 to 50:1 or from 1:20 to 20:1 or from 1:10 to 10:1. The two drugs may be administered separately in the same ratio. Examples of acid secretion inhibiting agents are H₂ blocking
20 agents, such as cimetidine, ranitidine; as well as proton pump inhibitors such as pyridinylmethylsulfinyl benzimidazoles such as omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole or related substances such as leminoprazole.

Non- Medical use

25

In addition to their use in therapeutic medicine, the compounds of formula I, as well as salts and hydrates of such compounds, are useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of mGluR related activity in laboratory animals such as cats, dogs, rabbits,
30 monkeys, rats and mice, as part of the search for new therapeutic agents.

Methods of Preparation

5 Another aspect of the present invention provides processes for preparing compounds of formula I, or salts or hydrates thereof. Processes for the preparation of the compounds in the present invention are described herein.

Throughout the following description of such processes it is to be understood that, where
10 appropriate, suitable protecting groups will be added to, and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in "Protective Groups in Organic Synthesis", T.W. Green, P.G.M. Wuts, Wiley-Interscience, New York,
15 (1999). It is also to be understood that a transformation of a group or substituent into another group or substituent by chemical manipulation can be conducted on any intermediate or final product on the synthetic path toward the final product, in which the possible type of transformation is limited only by inherent incompatibility of other functionalities carried by the molecule at that stage to the conditions or reagents employed in the transformation. Such
20 inherent incompatibilities, and ways to circumvent them by carrying out appropriate transformations and synthetic steps in a suitable order, will be readily understood to the one skilled in the art of organic synthesis. Examples of transformations are given below, and it is to be understood that the described transformations are not limited only to the generic groups or substituents for which the transformations are exemplified. References and descriptions on
25 other suitable transformations are given in "Comprehensive Organic Transformations – A Guide to Functional Group Preparations" R. C. Larock, VHC Publishers, Inc. (1989). References and descriptions of other suitable reactions are described in textbooks of organic chemistry, for example, "Advanced Organic Chemistry", March, 4th ed. McGraw Hill (1992) or, "Organic Synthesis", Smith, McGraw Hill, (1994). Techniques for purification of
30 intermediates and final products include for example, straight and reversed phase

chromatography on column or rotating plate, recrystallisation, distillation and liquid-liquid or solid-liquid extraction, which will be readily understood by the one skilled in the art. The definitions of substituents and groups are as in formula I except where defined differently.

The term "room temperature" and "ambient temperature" shall mean, unless otherwise specified, a temperature between 16 and 25 °C.

The term "reflux" shall mean, unless otherwise stated, in reference to an employed solvent a temperature at or above the boiling point of named solvent.

Abbreviations

10	atm	Atmosphere
	aq.	Aqueous
	BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
	Boc	<i>tert</i> -butoxycarbonyl
	CDI	N,N'-Carbonyldiimidazole
15	DCC	N,N-Dicyclohexylcarbodiimide
	DCM	Dichloromethane
	DBU	Diaza(1,3)bicyclo[5.4.0]undecane
	DEA	N,N-Diisopropyl ethylamine
	DIBAL-H	Diisobutylaluminium hydride
20	DIC	N,N'-Diisopropylcarbodiimide
	DMAP	N,N-Dimethyl-4-aminopyridine
	DMF	Dimethylformamide
	DMSO	Dimethylsulfoxide
	DPPF	Diphenylphosphinoferrocene
25	EA	Ethyl acetate
	EDCI	N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride
	EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
	Et ₂ O	Diethylether
	EtOAc	Ethyl acetate
30	EtOH	Ethanol

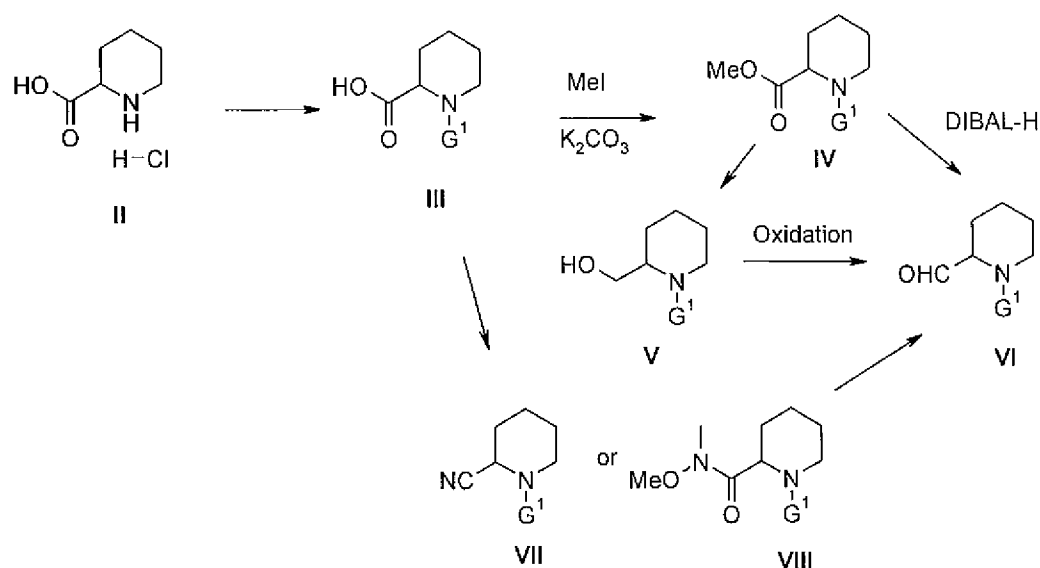
	EtI	Iodoethane
	Et	Ethyl
	Fmoc	9-fluorenylmethyloxycarbonyl
	h	hour(s)
5	HetAr	Heteroaryl
	HOBt	N-Hydroxybenzotriazole
	HBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
	HPLC	High performance liquid chromatography
	LAH	Lithium aluminium hydride
10	LCMS	HPLC mass spec
	MCPBA	<i>m</i> -Chlorbenzoic acid
	MeCN	Acetonitrile
	MeOH	Methanol
	min	Minutes
15	MeI	Iodomethane
	MeMgCl	Methyl magnesium chloride
	Me	Methyl
	<i>n</i> -BuLi	1-Butyllithium
	NaOAc	Sodium acetate
20	NMR	Nuclear magnetic resonance
	NMP	N-Methyl pyrrolidinone
	<i>n</i> BuLi	1-Butyl lithium
	o.n.	Over night
	RT, rt, r.t.	Room temperature
25	TEA	Triethylamine
	THF	Tetrahydrofurane
	<i>n</i> Bu	normal Butyl
	OMs	Mesylate or methane sulfonate ester
	OTs	Tosylate, toluene sulfonate or 4-methylbenzene sulfonate ester
30	PCC	Pyridinium chlorochromate

PPTS	Pyridinium <i>p</i> -toluenesulfonate
TBAF	Tetrabutylammonium fluoride
pTsOH	<i>p</i> -Toluenesulfonic acid
SPE	Solid phase extraction (usually containing silica gel for mini-chromatography)
5 sat.	Saturated

Preparation of intermediates

- 10 The intermediates provided in synthetic paths given below, are useful for further preparation of compounds of formula **I**. Other starting materials are either commercially available or can be prepared via methods described in the literature. The synthetic pathways described below are non-limiting examples of preparations that can be used. One of skill in the art would understand other pathways might be used.

Synthesis of Isoxazoles



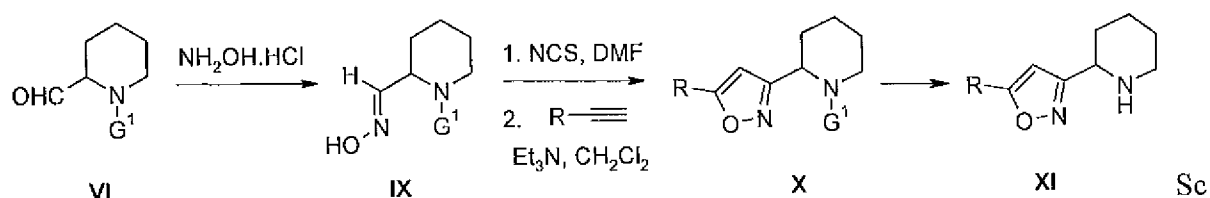
Scheme 1

5

Aldehydes of formula VI may be used in the preparation of isoxazoles. Commercially available acid derivatives of formula II wherein N-G¹ (G¹ is a protecting group) may undergo N-protection to yield compounds of formula III wherein G¹ is a protecting group such as Boc or Fmoc using methods well known in the art. The acid moiety in compounds of formula III may be transformed into an alkyl ester of formula IV, such as for example the methyl or ethyl ester, which may be transformed to aldehydes of formula VI using a mild reducing agent such as DIBAL-H in a solvent such as toluene at low temperature, for example -78 °C. Higher temperatures or stronger reducing agents may result in formation of the primary alcohols of formula V, either exclusively or as a mixture with the aldehydes of formula VI. Other functional groups such as the primary alcohol in compounds of formula V, the nitrile in compounds of formula VII and Weinreb amide moiety in compounds of formula VIII may be transformed into aldehydes of formula VI utilizing procedures established in the art. Additionally, acids of formula II may be converted into nitriles of formula VII by methods known in the art, for example by conversion of the acid to the primary amide followed by dehydration to the nitrile.

20

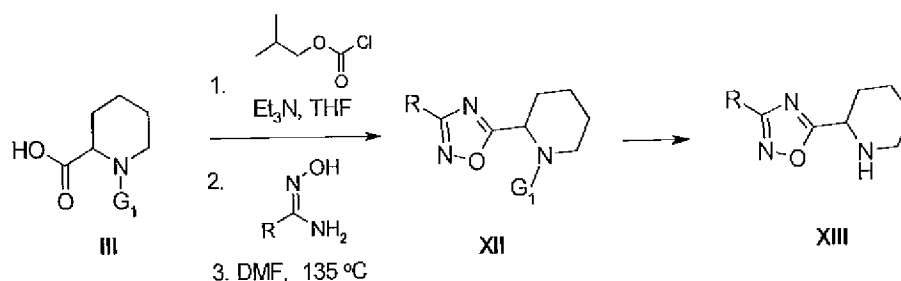
Aldehydes of formula **VI** may be converted to oximes of formula **IX** by treatment with hydroxylamine, in a solvent such as pyridine, at a temperature between 0 °C to room temperature. Isoxazoles of formula **X** may be prepared by chlorination of oximes of formula **IX** using a reagent such as N-chlorosuccinimide (NCS), followed by 1,3-dipolar cycloaddition with the appropriately R-substituted acetylenes, wherein R may be an aryl, substituted aryl or a masking group (eg. alkyl stannane) (Steven, R. V. et al. *J. Am. Chem. Soc.* 1986, 108, 1039). The isoxazole intermediate **X** can subsequently be deprotected to give **XI** by standard methods.



heme 2

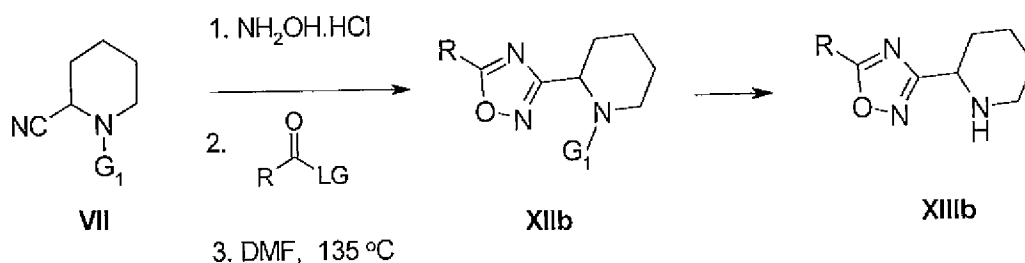
Isoxazoles of formula **X** wherein R is a masking group may be prepared in this manner and the masking group transformed into the desired R group by cross-coupling reactions. For example, the use of trialkylstannylacetylenes would result in a trialkylstannyl isoxazole, which may undergo reactions such as for example Stille type cross coupling to introduce aryl substituents by coupling to an appropriate aryl halide.

Synthesis of [1,2,4]-Oxadiazoles



Scheme 3

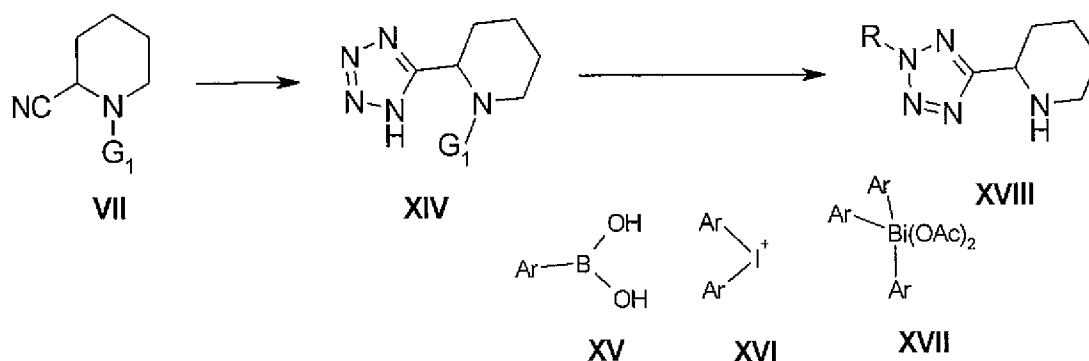
Carboxylic acids of formula **III** may be used in the preparation of the corresponding 3-R substituted [1,2,4]oxadiazoles of formula **XII** by activation of the acid moiety, addition of a suitable R-substituted hydroxyamidine to form an ester, followed by cyclization to the oxadiazole **XIII**. [See Tetrahedron Lett., 2001, 42, 1495-98, Tetrahedron Lett., 2001, 42, 1441-43, and Bioorg. Med. Chem. Lett. 1999, 9, 1869-74]. The acid may be activated as the mixed anhydride using an alkyl chloroformate such as isobutyl chloroformate, in the presence of a base such as triethylamine in a suitable solvent such as THF. Alternatively, other well known methods of activating the acid may be employed, including *in situ* activation of the acid using a reagent such as EDCI, DCC, DIC or HBTU, with or without the presence of co-reagents such as HOBt or DMAP, in suitable solvents such as DMF, DCM, THF, or MeCN at a temperature from -20 to 100 °C. The cyclization may be accomplished by heating in a solvent such as pyridine or DMF, under microwave irradiation or by employing catalysts such as TBAF. R-substituted hydroxyamidines are available from nitriles by addition of hydroxylamine hydrochloride in the presence of a base such as NaOH, NaHCO₃ or Na₂CO₃, to generate the free hydroxylamine, in a solvent such as ethanol or methanol or the like, at temperatures between room temperature and 100 °C.



Scheme 4

5-R substituted [1,2,4]oxadiazoles of formula **XIIIb** may be prepared from nitriles of formula **VII** by effectively reversing the substituents attached to the [1,2,4]-oxadiazole. Nitriles of formula **VII** react with hydroxylamine as described above to provide the intermediate hydroxyamidine, and may be converted to the [1,2,4]oxadiazoles of formula **XIIIb** using an acylating agent containing the R group using the method described above for conversion of compounds of formula **III** to compounds of formula **XII**.

Synthesis of Tetrazoles



Scheme 5

Nitriles of formula **VII** may be used in the preparation of the corresponding tetrazoles of formula **XVIII** by treatment with an azide, such as NaN_3 , LiN_3 , trialkyltinazide or trimethylsilylazide, preferably with a catalyst such as dibutyltin oxide or $ZnBr_2$, in solvents such as DMF, water or toluene at a temperature of 50 to 200 °C by conventional heating or microwave irradiation [See J. Org. Chem. 2001, 7945-7950; J. Org. Chem. 2000, 7984-7989 or J. Org. Chem. 1993, 4139-4141].

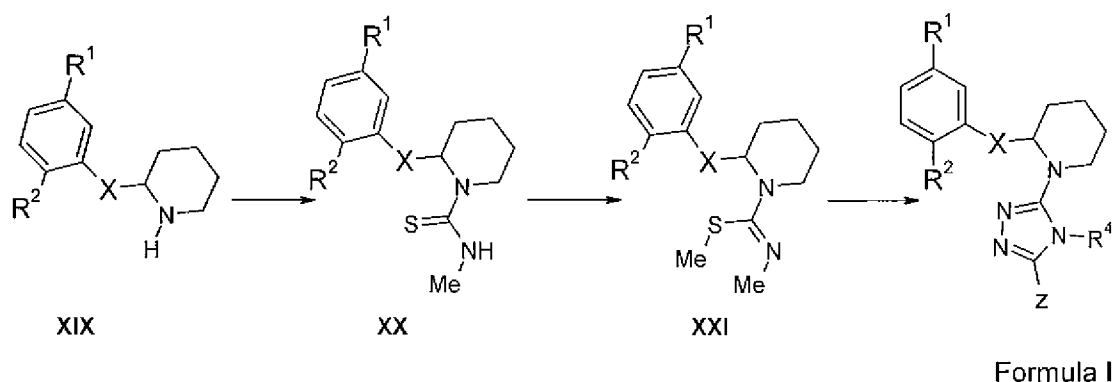
N2-arylation of 5-substituted tetrazoles have been reported in the literature using a variety of coupling partners. Compounds of formula **XVIII** wherein R is an aryl group may be prepared using for example boronic acids of formula **XV** [with the $B(OH)_2$ moiety], or the corresponding iodonium salts of formula **XVII** [with the I^+-Ar moiety], or the corresponding triarylbismuth diacetates [with the $Bi(OAc)_2Ar_2$ moiety], as arylating agents mediated by transition metals [See Tetrahedron Lett. 2002, 6221-6223; Tetrahedron Lett. 1998, 2941-2944; Tetrahedron Lett. 1999, 2747-2748]. With boronic acids, stoichiometric amounts of Cu(II)acetate and pyridine are used in solvents such as dichloromethane, DMF, dioxane or THF at a temperature of room temperature to 100 °C. With iodonium salts, catalytic amounts of Pd(II)-compounds, such as $Pd(OAc)_2$ or a Pd(0) complex such as $Pd(dba)_2$ or, together with catalytic amounts of Cu(II)-carboxylates, such as Cu(II)-phenylcyclopropylcarboxylate, and bidentate ligands, such as BINAP or DPPF, are used in solvents such as *t*-BuOH at a

temperature of 50 to 100 °C. With triarylbismuth diacetates, catalytic amounts of cupric acetate may be employed in the presence of N,N,N',N'-tetramethylguanidine in a suitable solvent such as THF with heating at a temperature of 40-60 °C. Iodonium salts of formula **XVI** may be obtained from, for example, the respective boronic acids by treatment with

5 hypervalent iodine substituted aromatics, such as hydroxyl(tosyloxy)iodobenzene or $\text{PhI}(\text{OAc})_2 \cdot 2\text{TfOH}$, in dichloromethane or the like [See Tetrahedron Lett. 2000, 5393-5396]. Triarylbismuth diacetates may be prepared from aryl magnesium bromides with bismuth trichloride in a suitable solvent such as refluxing THF to give the triarylbismuthane, which is then oxidized to the diacetate using an oxidizing agent such as sodium perborate in acetic

10 acid [Synth. Commun. 1996, 4569-75].

Synthesis of Amino-Triazoles



Scheme 6

5

The deprotected amines of formula **XI**, **XIII**, **XVIII** and **XIX** may be subjected to a sequence of thiourea formation, methylation and triazole formation to deliver compounds of formula **I** wherein the R1 and/or R2 are defined as in formula **I**. Thioureas of formula **XX** are available from well established methods using for example an isothiocyanate R⁴SCN (MeNCS shown in Scheme 6), or 1,1-thiocarbonyl-diimidazole in the presence of RNH₂, in a solvent such as methanol, ethanol and the like, at a temperature between room temperature and 100 °C, and are typically carried out at 60 °C. Alkylation of the thiourea intermediates can be performed using an alkylating agents such as iodomethane (shown in Scheme 6) or iodoethane, in a solvent such as DMF, acetone, CH₂Cl₂, at room temperature or elevated temperatures to give the isothiourethane of formula **XXI**. When an iodoalkane is employed, the product may be isolated as the hydroiodide salt [see Synth.Comm. 1998, 28, 741-746]. Compounds of formula **XXI** may react with an acyl hydrazine or with hydrazine followed by an acylating agent to form an intermediate which may be cyclized to the 3-aminotriazoles of formula **I** by heating at 0 to 150 °C in a suitable solvent such as pyridine or DMF.

20

Examples

The invention will now be illustrated by the following non-limiting examples.

General methods

All starting materials are commercially available or earlier described in the literature.

The ^1H and ^{13}C NMR spectra were recorded either on Bruker 300, Bruker DPX400 or Varian +400 spectrometers operating at 300, 400 and 400 MHz for ^1H NMR respectively, using

5 TMS or the residual solvent signal as reference, in deuterated chloroform as solvent unless otherwise indicated. All reported chemical shifts are in ppm on the delta-scale, and the fine splitting of the signals as appearing in the recordings (s: singlet, br s: broad singlet, d: doublet, t: triplet, q: quartet, m: multiplet).

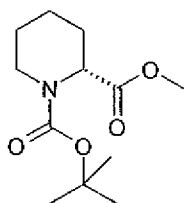
Analytical in line liquid chromatography separations followed by mass spectra detections,
10 were recorded on a Waters LCMS consisting of an Alliance 2795 (LC) and a ZQ single quadrupole mass spectrometer. The mass spectrometer was equipped with an electrospray ion source operated in a positive and/or negative ion mode. The ion spray voltage was ± 3 kV and the mass spectrometer was scanned from m/z 100-700 at a scan time of 0.8 s. To the column, X-Terra MS, Waters, C8, 2.1 x 50 mm, 3.5 mm, was applied a linear gradient from 5 % to
15 100 % acetonitrile in 10 mM ammonium acetate (aq.), or in 0.1 % TFA (aq.).

Preparative reversed phase chromatography was run on a Gilson autopreparative HPLC with a diode array detector using an XTerra MS C8, 19 x 300mm, 7mm as column.

Purification by a chromatotron was performed on rotating silica gel / gypsum (Merck, 60 PF-254 with calcium sulphate) coated glass sheets, with coating layer of 1, 2, or 4 mm using a
20 TC Research 7924T chromatotron. Purification of products were also done by flash chromatography in silica-filled glass columns.

Microwave heating was performed in a Smith Synthesizer Single-mode microwave cavity producing continuous irradiation at 2450 MHz (Personal Chemistry AB, Uppsala, Sweden).

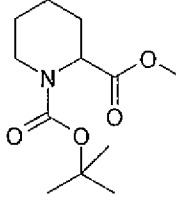
Example 1.1: (R)-Piperidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester



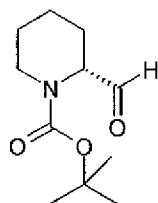
To (R)-Piperidine-1,2-dicarboxylic acid 1-tert-butyl ester (5.1 g, 22.2 mmol) in DMF (60 mL) were added K_2CO_3 (12.3 g, 88.8 mmol) and MeI (1.7 mL, 26.6 mmol). After stirring at room temperature overnight, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with water (6 times) and brine, dried over anhydrous Na_2SO_4 , filtered and concentrated to give the title product (5.4 g, 99 %).

1H NMR (300 MHz, $CDCl_3$): δ 4.82 (m, 1H), 3.99 (m, 1H), 3.75 (s, 3H), 2.95 (m, 1H), 2.21 (m, 1H), 2.45 (m, 14H).

In a similar manner the following compound was synthesized:

1.2		Piperidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester	98 % 5.2 g Colorless oil
1H NMR	(300 MHz, $CDCl_3$): δ 4.82 (m, 1H), 3.99 (m, 1H), 3.75 (s, 3H), 2.95 (m, 1H), 2.21 (m, 1H), 2.45 (m, 14H)		

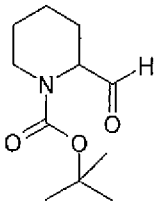
Example 2.1: (R)-2-Formyl-piperidine-1-carboxylic acid tert-butyl ester



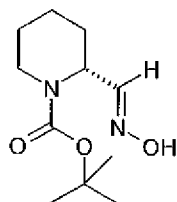
To the title compound of Example 1.1 (5.4 g, 22.1 mmol) in toluene (50 mL) at $-78^\circ C$ was added 1.5 M DIBAL in toluene (33.8 mL, 50.7 mmol) drop-wise over 40 minutes. Methanol (120 mL) was then added drop-wise at $-78^\circ C$ over 10 minutes. The reaction mixture was moved to an ice-bath where 10 % wt citric acid (500 mL) was added and then the mixture was stirred for an additional 1 hour. After the resulting mixture was extracted with ethyl acetate (2 times), the organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 , filtered and concentrated to give the title product as a colorless oil (3.0 g, 64 %).

1H NMR (300 MHz, $CDCl_3$): δ 9.61 (s, 1H), 4.60 (m, 1H), 4.96 (m, 1H), 2.91 (m, 1H), 2.19 (m, 1H), 1.49 (m, 14H)

In a similar manner the following compounds were synthesized:

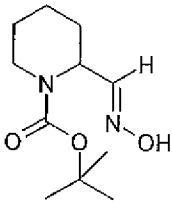
2.2		2-Formyl-piperidine-1-carboxylic acid tert-butyl ester	95 % 4.3 g colorless liquid
¹H NMR	(300 MHz, CDCl ₃): δ 9.61 (s, 1H), 4.60 (m, 1H), 4.96 (m, 1H), 2.91 (m, 1H), 2.19 (m, 1H), 1.49 (m, 14H)		

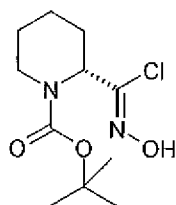
Example 3.1: (R)-2-(Hydroxyimino-methyl)-piperidine-1-carboxylic acid tert-butyl ester



To the title compound of Example 2.1 (3.0 g, 14.1 mmol) in MeOH/H₂O (30 mL / 30 mL) in an ice-bath was added Na₂CO₃ (895 mg, 8.4 mmol) and hydroxylamine hydrochloride (1.2 g, 16.9 mmol). After stirring for 30 minutes, the reaction mixture was warmed to room temperature and stirred for an additional 4 hours. The reaction mixture was concentrated to half volume and then extracted with ethyl acetate (2 times), washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give the title product as a colorless oil (3.1 g, 97 %).

In a similar manner the following compounds were synthesized:

3.2		2-(Hydroxyimino-methyl)-piperidine-1-carboxylic acid tert-butyl ester	100 % 4.7 g
¹H NMR	(300 MHz, CDCl ₃): δ 7.40 (bs, 1H), 6.88 (d, 1H), 4.31 (m, 1H), 4.10 (m, 1H), 2.90 (m, 1H), 2.00 (m, 1H), 1.59 (m, 14H)		

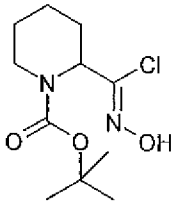
Example 4.1: tert-Butyl (2R)-2-[chloro(hydroxyimino)methyl]piperidine-1-carboxylate

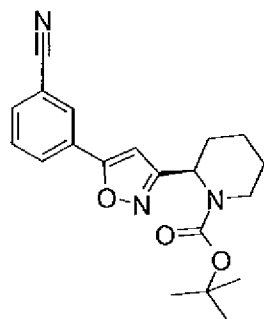
To the title compound of example 3.1 (3.1 g, 13.7 mmol) in DMF (30 mL) at 40 °C was added N-chlorosuccinimide (2.0 g, 15.1 mmol) in 3 portions. After stirring for 1 hour, the reaction mixture was diluted with ethyl acetate and then the organic layer was washed with water (3 times) and brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give the title product (3.1 g, 85 %).

¹H NMR (300 MHz, CDCl₃): δ 8.79 (bs, 1H), 4.31 (m, 1H), 3.99 (m, 1H), 2.90 (m, 1H), 2.28 (m, 1H), 1.59 (m, 14H).

10

In a similar manner the following compound was synthesized:

4.2		tert-Butyl 2-[chloro(hydroxyimino)methyl]piperidine-1-carboxylate	93 % 5.1 g
¹H NMR	(300 MHz, CDCl ₃): δ 8.79 (bs, 1H), 4.31 (m, 1H), 3.99 (m, 1H), 2.90 (m, 1H), 2.28 (m, 1H), 1.59 (m, 14H)		

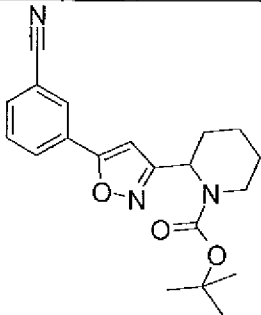
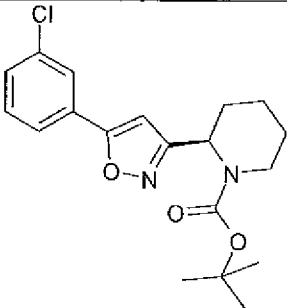
Example 5.1: (R)-2-[5-(3-Cyano-phenyl)-isoxazol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester

15

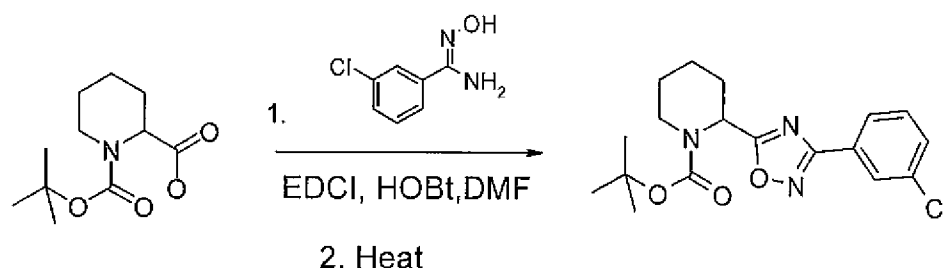
To the title compound of Example 4.1 (500 mg, 1.9 mmol) and 3-ethynylbenzonitrile (532 mg, 4.2 mmol) in DCM (10 mL) at 0 °C, was added Et₃N (0.530 mL, 3.8 mmol). After 30 minutes, the reaction mixture was warmed to room temperature and stirred for an additional 3 days. The reaction mixture was concentrated and then diluted with ethyl acetate. The organic was washed with water (3 times) and brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography eluted with hexanes to 20 % ethyl acetate in hexanes to give the title product as yellow oil (194 mg, 29 %).

¹H NMR (300 MHz, CDCl₃): δ 8.04 (m, 1H), 8.00 (m, 1H), 7.74 (m, 1H), 7.63 (t, 1H), 6.44 (s, 1H), 5.54 (m, 1H), 4.11 (m, 1H), 2.81 (m, 1H), 2.29 (m, 1H), 1.66 (m, 5H), 1.51 (s, 9H).

In a similar manner the following compounds were synthesized:

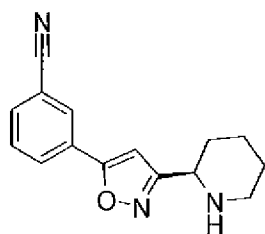
5.2		2-[5-(3-Cyano-phenyl)-isoxazol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester	67 % 611 mg Colorless oil
¹H NMR	(300 MHz, CDCl ₃): δ 8.05 (m, 1H), 8.00 (m, 1H), 7.74 (m, 1H), 7.63 (t, 1H), 6.45 (s, 1H), 5.54 (m, 1H), 4.11 (m, 1H), 2.81 (m, 1H), 2.29 (m, 1H), 1.66 (m, 5H), 1.53 (s, 9H)		
5.3		(R)-2-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester	50 %
¹H NMR	(300 MHz, CDCl ₃): δ 7.75 (m, 1H), 7.65 (m, 1H), 7.41 (m, 2H), 6.36 (s, 1H), 5.51 (s br, 1H), 4.06 (m, 1H), 2.80 (m, 1H), 2.36 (m, 1H), 2.06 (m, 1H), 1.58-1.72 (m, 4H), 1.52 (s, 9H)		

Example 5.4: 2-[3-(3-Chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidine-1-carboxylic acid tert-butyl ester. A general procedure for synthesis of 1,2,4 Oxadiazole-Piperidine intermediates



- 5 A solution of (R)-N-Boc-piperidine-2-carboxylic acid (0.81 g, 3.5 mmol), EDCI (745 mg, 3.9 mmol), HOBT (0.52 g, 3.9 mmol) and 3-chloro-N'-hydroxybenzenecarboxyimide (0.66 g, 3.9 mmol) in DMF (5 mL), was stirred at room temperature (RT) overnight. The reaction mixture was diluted with ethyl acetate, washed with water (2 x 30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, filtered and then concentrated in vacuo. The
- 10 amidoxime coupled intermediate was then taken up in DMF and heated to 127 °C. The reaction was judged complete by TLC after ~2 hours. The mixture was then cooled to RT and extracted into 100 mL ethyl acetate, washed with water (3 x 20 mL) and brine (20 mL). Dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford 918 mg of the title compound (72 % yield).
- 15 ¹H NMR (300 MHz, CDCl₃): δ 8.10 (d, 1H), 7.98 (dd, 1H), 7.50 (m, 2H), 5.70 (s br, 1H), 4.12 (m, 1H), 3.01 (m, 1H), 2.38 (m, 1H), 2.06 (m, 1H), 1.58-1.72 (m, 4H), 1.52 (s, 9H)

Example 6.1: 3-((R)-3-Piperidin-2-yl-isoxazol-5-yl)-benzonitrile



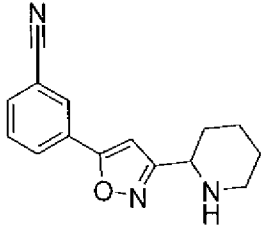
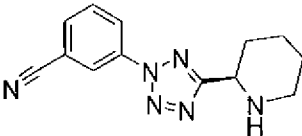
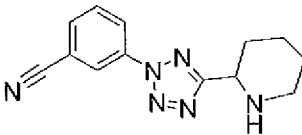
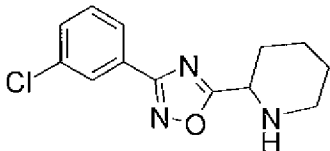
- 20 To the title compound of Example 5.1 (194 mg, 0.56 mmol) in DCM (2.1 mL) at 0 °C was added TFA (1.1 mL). After 1 hour, the reaction mixture was warmed to room temperature and stirred for an additional 1 hour. The reaction mixture was diluted with saturated

NaHCO₃ and then extracted with DCM. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to give the title product (119 mg, 86 %).

¹H NMR (300 MHz, CDCl₃): δ 8.04 (s, 1H), 7.99 (d, 1H), 7.71 (d, 1H), 7.62 (t, 1H), 6.67 (s, 1H), 3.96 (d, 1H), 3.20 (m, 1H), 2.85 (t, 1H), 1.91 (m, 2H), 1.62 (m, 5H)

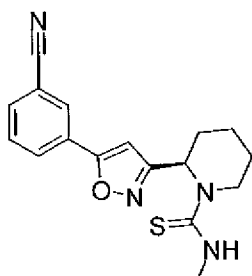
5

In a similar manner the following compounds were synthesized:

6.2		3-(3-Piperidin-2-yl-isoxazol-5-yl)-benzonitrile	95 % 411 mg off-white solid
¹H NMR	(300 MHz, CDCl ₃): δ 8.06 (s, 1H), 8.00 (d, 1H), 7.72 (d, 1H), 7.62 (t, 1H), 6.68 (s, 1H), 3.96 (d, 1H), 3.20 (m, 1H), 2.85 (t, 1H), 1.91 (m, 2H), 1.62 (m, 5H)		
6.3		3-((R)-5-Piperidin-2-yl-tetrazol-2-yl)-benzonitrile	95 % 186 mg Brown oil
¹H NMR	(300 MHz, CDCl ₃): δ 8.43 (m, 2H), 7.72 (m, 2H), 4.19 (dd, 1H), 3.24 (d, 1H), 2.88 (m, 1H), 2.2 (m, 2H), 1.71 (m, 5H)		
6.4		3-(5-Piperidin-2-yl-2H-tetrazol-2-yl)benzonitrile	100 %
¹H NMR	(300 MHz, CDCl ₃): δ 8.43 (m, 2H), 7.72 (m, 2H), 4.19 (dd, 1H), 3.24 (d, 1H), 2.88 (m, 1H), 2.2 (m, 2H), 1.71 (m, 5H)		
6.5		2-[3-(3-Chlorophenyl)-1,2,4-oxadiazol-5-yl]piperidine	95 %
¹H NMR	(300 MHz, CDCl ₃): δ 8.12 (m, 1H), 8.00 (dd, 1H), 7.47 (m, 2H), 4.15 (dd, 1H), 3.22 (m, 1H), 2.85 (m, 1H), 2.2 - 1.71 (m, 7H)		

The following compounds were synthesised according to the procedure in Example 73 in WO 2005/080386.

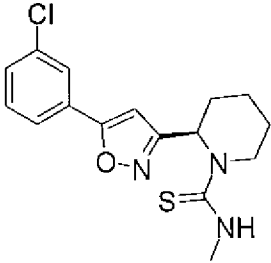
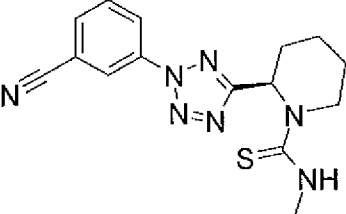
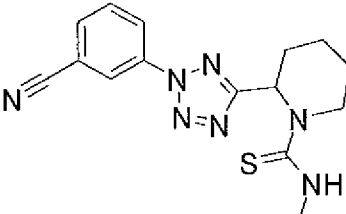
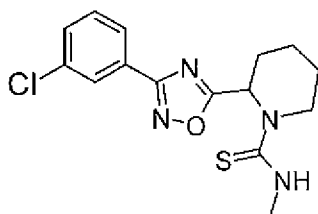
Example 7.1: (R)-2-[5-(3-Cyano-phenyl)-isoxazol-3-yl]-piperidine-1-carbothioic acid methylamide



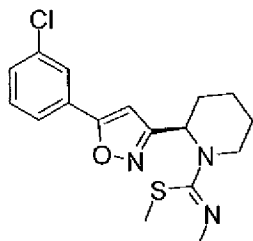
- 5 To the title compound of Example 6.1 (119 mg, 0.47 mmol) in CHCl_3 (3 mL) at room temperature was added CH_3NCS (0.037 mL, 0.54 mmol) and then stirred overnight. The reaction mixture was concentrated and the residue was triturated with 50 % diethyl ether/hexanes, filtered and dried to give the title product (153 mg, quantitative).
- ^1H NMR (300 MHz, CDCl_3): δ 8.05 (s, 1H), 8.00 (d, 1H), 7.73 (d, 1H), 7.61 (t, 1H), 6.88 (m, 1H), 6.60 (s, 1H), 5.92 (m, 1H), 4.00 (m, 1H), 3.20 (m, 4H), 2.38 (m, 1H), 2.04 (m, 1H), 1.79 (m, 2H), 1.59 (m, 2H).
- 10

In a similar manner the following compounds were synthesized:

<u>7.2</u>		2-[5-(3-Cyano-phenyl)-isoxazol-3-yl]-piperidine-1-carbothioic acid methylamide	93 % 485 mg Light brown solid
^1H NMR	(300 MHz, CDCl_3): δ 8.05 (s, 1H), 8.00 (d, 1H), 7.73 (d, 1H), 7.61 (t, 1H), 6.88 (m, 1H), 6.61 (s, 1H), 5.84 (m, 1H), 4.00 (m, 1H), 3.20 (m, 4H), 2.38 (m, 1H), 2.04 (m, 1H), 1.79 (m, 2H), 1.59 (m, 2H)		

<u>7.3</u>		(R)-2-[5-(3-Chlorophenyl)-isoxazol-3-yl]-piperidine-1-carbothioic acid methylamide	Quantitative yield
¹ H NMR	(300 MHz, CDCl ₃): δ 7.73 (s, 1H), 7.63 (m, 1H), 7.39 (m, 2H), 6.78 (d, 1H), 6.50 (s, 1H), 5.94 (d, 1H), 4.06 (d, 1H), 3.21 (d, 3H), 3.14 (m, 1H), 2.35 (d, 1H), 1.72-1.98 (m, 5H)		
<u>7.4</u>		(R)-2-[2-(3-Cyanophenyl)-2H-tetrazol-5-yl]-piperidine-1-carbothioic acid methylamide	98 % Yellow oil,
¹ H NMR	(300 MHz, CDCl ₃): δ 8.42 (m, 2H), 7.74 (m, 2H), 7.05 (br, 1H), 6.01 (br, 1H), 4.15 (m, 1H), 3.37 (td, 1H), 3.25 (d, 3H), 2.48 (m, 1H), 2.14 (m, 1H), 1.82 (m, 2H), 1.6 (m, 2H)		
<u>7.5</u>		2-[2-(3-Cyanophenyl)-2H-tetrazol-5-yl]-piperidine-1-carbothioic acid methylamide	85 % Yellow oil
¹ H NMR	(300 MHz, CDCl ₃): δ 8.42 (m, 2H), 7.74 (m, 2H), 7.05 (br, 1H), 6.01 (br, 1H), 4.15 (m, 1H), 3.37 (td, 1H), 3.25 (d, 3H), 2.48 (m, 1H), 2.14 (m, 1H), 1.82 (m, 2H), 1.6 (m, 2H)		
<u>7.6</u>		2-[3-(3-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-N-methylpiperidine-1-carbothioamide	84 % White solid
¹ H NMR	(300 MHz, CDCl ₃): δ 8.08 (m, 1H), 7.98 (dd, 1H), 7.47 (m, 2H), 7.05 (br, 1H), 6.00 (br, 1H), 4.10 (m, 1H), 3.39 (td, 1H), 3.24 (d, 3H), 2.48 (m, 1H), 2.14 (m, 1H), 1.82 (m, 2H), 1.6 (m, 2H)		

Example 8.1: (R)-2-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-N-methyl-piperidine-1-carboximidothioic acid methyl ester

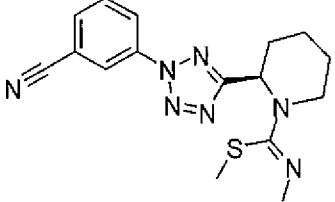
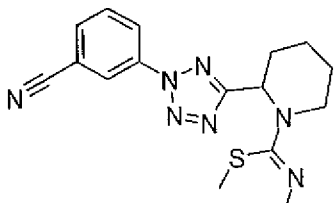
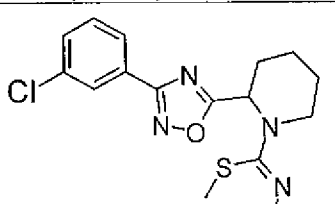


To the title compound of Example 7.3 (153 mg, 0.47 mmol) in THF (2 mL) at room temperature were added sodium tert-butoxide (45 mg, 0.47 mmol) and CH₃I (0.044 mL, 0.70 mmol). After stirring the reaction mixture for 1 hour, the reaction mixture was diluted with water and then extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give the title product as a light yellow solid (150 mg, 94 %).

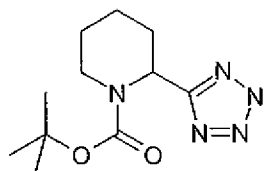
¹H NMR (300 MHz, CDCl₃): δ 8.04 (s, 1H), 8.00 (d, 1H), 7.92 (d, 1H), 7.60 (t, 1H), 6.51 (s, 1H), 5.46 (m, 1H), 3.86 (m, 1H), 3.27 (s, 3H), 3.04 (m, 1H), 2.36 (m, 4H), 1.96 (m, 1H), 1.76 (m, 2H), 1.66 (m, 2H).

In a similar manner the following compounds were synthesized:

<u>8.2</u>		2-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-N-methyl-piperidine-1-carboximidothioic acid methyl ester	97 % 490 mg Off-white solid
¹H NMR	(300 MHz, CDCl ₃): δ 8.04 (s, 1H), 8.00 (d, 1H), 7.92 (d, 1H), 7.60 (t, 1H), 6.51 (s, 1H), 5.46 (m, 1H), 3.86 (m, 1H), 3.27 (s, 3H), 3.04 (m, 1H), 2.36 (m, 4H), 1.96 (m, 1H), 1.76 (m, 2H), 1.66 (m, 2H)		

8.3		(R)-2-[2-(3-Cyano-phenyl)-2H-tetrazol-5-yl]-N-methyl-piperidine-1-carboximidothioic acid methyl ester	82 % 220 mg Brown oil
¹H NMR	(300 MHz, CDCl ₃): δ 8.42 (m, 2H), 7.75 (m, 2H), 5.76 (br, 1H), 3.85 (br, 1H), 3.25 (m, 1H), 3.2 (td, 3H), 2.41 (d, 3H), 2.3 (m, 1H), 2.09 (m, 1H), 1.68 (m, 4H)		
8.4		2-[2-(3-Cyano-phenyl)-2H-tetrazol-5-yl]-N-methyl-piperidine-1-carboximidothioic acid methyl ester	80 % Yellow oil
¹H NMR	(300 MHz, CDCl ₃): δ 8.42 (m, 2H), 7.75 (m, 2H), 5.76 (br, 1H), 3.85 (br, 1H), 3.25 (m, 1H), 3.2 (td, 3H), 2.41 (d, 3H), 2.3 (m, 1H), 2.09 (m, 1H), 1.68 (m, 4H)		
8.5		Methyl 2-[3-(3-chlorophenyl)-1,2,4-oxadiazol-5-yl]-N-methylpiperidine-1-carbimidothioate	72 %
¹H NMR	(300 MHz, CDCl ₃): δ 8.10 (m, 1H), 7.98 (dd, 1H), 7.45 (m, 2H), 5.48 (dd, 1H), 3.75 (m, 1H), 3.45 (m, 1H), 3.16 (s, 3H), 2.40 (s, 3H), 2.3 (m, 1H), 2.09 (m, 1H), 1.68 (m, 4H)		

Example 9.1: 2-(2H-Tetrazol-5-yl)-piperidine-1-carboxylic acid tert-butyl ester

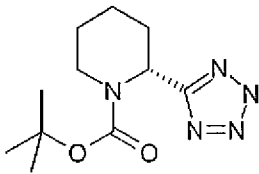


2-Cyano-piperidine-1-carboxylic acid tert-butyl ester (2.1 g, 10mmol) was mixed with sodium azide (0.715 g, 11 mmol) and ammonium chloride (0.588 g, 11 mmol) in N,N-dimethylformamide (7.5 mL). The reaction mixture was heated at 100 °C for overnight. The reaction mixture was cooled to room temperature and diluted with water. The product was

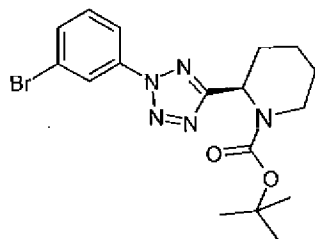
extracted using ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude yellow oil gave a white solid after trituration with ethyl acetate, as the title product (1.23 g, 48.6 %).

¹H NMR (300 MHz, CDCl₃): δ 5.63 (br, 1H), 4.02 (m, 1H), 2.76 (td, 1H), 2.43 (m, 1H), 1.96 (m, 2H), 1.8 (m, 2H), 1.55 (m, 2H), 1.49 (s, 9H).

In a similar manner the following compound was synthesized:

9.2		(R)-2-(2H-Tetrazol-5-yl)-piperidine-1-carboxylic acid tert-butyl ester	86 % White solid
¹ H NMR	(300 MHz, CDCl ₃): δ 5.63 (br, 1H), 4.02 (m, 1H), 2.76 (td, 1H), 2.43 (m, 1H), 1.96 (m, 2H), 1.8 (m, 2H), 1.55 (m, 2H), 1.49 (s, 9H)		

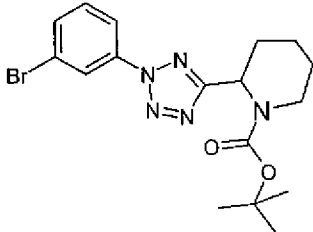
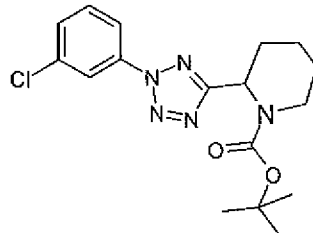
Example 10.1: (R)-2-[2-(3-Bromo-phenyl)-2H-tetrazol-5-yl]-piperidine-1-carboxylic acid tert-butyl ester



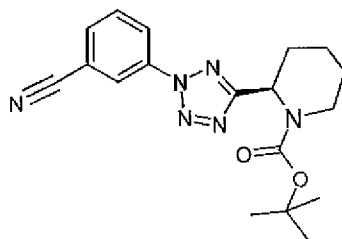
(R)-2-(2H-Tetrazol-5-yl)-piperidine-1-carboxylic acid tert-butyl ester (1.025 g, 4.046 mmol) was dissolved in tert-BuOH (25 mL). Argon was bubbled through for 10 min. and the title compound of Example 13.2, (2.34 g, 4.45 mmol), sodium tert-butoxide (428 mg, 4.45 mmol), BINAP (99.6 mg, 0.16 mmol), Pd₂(dba)₃ (36.6 mg, 0.04 mmol), copper 2-phenylpropane carboxylate (30.8 mg, 0.08 mmol) in t-BuOH (25 mL) was stirred at 90 °C for 12 h. The reaction mixture was concentrated on silica gel and purified by column chromatography using ethyl acetate: hexane = 10 % : 90 % to afford the title product as a yellow oil (1.11 g, 67 %).

¹H NMR (300 MHz, CDCl₃): δ 8.30 (s, 1H), 8.08 (d, 1H), 7.63 (d, 1H), 7.43 (t, 1H), 5.74 (br, 1H), 4.13 (br, 1H), 3.03 (br, 1H), 2.44 (br, 1H), 2.06 (m, 1H), 1.68 (m, 2H), 1.55 (m, 2H), 1.53 (s, 9H).

5 In a similar manner the following compound was synthesized:

10.2		2-[2-(3-Bromo-phenyl)-2H-tetrazol-5-yl]-piperidine-1-carboxylic acid tert-butyl ester	71 % 803 mg Yellow oil
¹H NMR	(300 MHz, CDCl ₃): δ 8.30 (s, 1H), 8.08 (d, 1H), 7.63 (d, 1H), 7.43 (t, 1H), 5.74 (br, 1H), 4.13 (br, 1H), 3.03 (br, 1H), 2.44 (br, 1H), 2.06 (m, 1H), 1.68 (m, 2H), 1.55 (m, 2H), 1.53 (s, 9H)		
10.3		2-[2-(3-Chloro-phenyl)-2H-tetrazol-5-yl]-piperidine-1-carboxylic acid tert-butyl ester	Synthesis previously described in Example 22 of WO 2005/080386
¹H NMR	(300 MHz, CDCl ₃): δ 8.14 (d, 1H), 8.03 (d, 1H), 7.46 (m, 2H), 5.75 (br, 1H), 4.10 (br, 1H), 3.05 (m, 1H), 2.43 (m, 1H), 1.99 (m, 1H), 1.68 (m, 2H), 1.55 (m, 2H), 1.53 (s, 9H)		

Example 11.1: (R)-2-[2-(3-Cyano-phenyl)-2H-tetrazol-5-yl]-piperidine-1-carboxylic acid tert-butyl ester

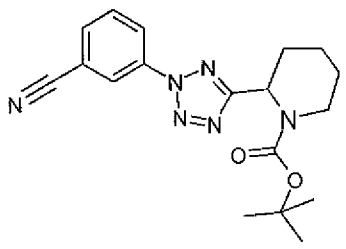


10 The title compound of Example 10.1 (340 mg, 0.832 mmol), dppf (69.3 mg, 0.125 mmol), zinc cyanide (146.7 mg, 1.25 mmol), Pd₂(dba)₃ (38 mg, 0.0416 mmol), zinc acetate (10.5 mg,

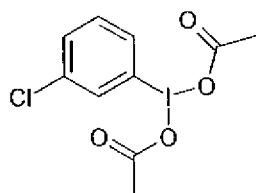
0.066 mmol) and Zn dust (4.31 mg, 0.066 mmol) were stirred in DMF (10 mL) and water (0.5 mL) for 3 h at 90 °C. The reaction mixture was partitioned between ethyl acetate and water. The organic extracts were dried over sodium sulphate, filtered and concentrated and purified by column chromatography using ethyl acetate: hexane = 20 % : 80 % to afford the title product (272 mg, 92 %).

¹H NMR (300 MHz, CDCl₃): δ 8.41 (m, 2H), 7.77 (m, 2H), 5.74 (br, 1H), 4.1 (br, 1H), 3.01 (br, 1H), 2.4 (br, 1H), 1.98 (m, 1H), 1.69 (m, 2H), 1.54 (m, 2H), 1.51 (s, 9H).

In a similar manner the following compound was synthesized:

11.2		2-[2-(3-Cyano-phenyl)-2H-tetrazol-5-yl]-piperidine-1-carboxylic acid tert-butyl ester	71 % 803 mg Yellow oil
¹H NMR	(300 MHz, CDCl ₃): δ 8.41 (m, 2H), 7.77 (m, 2H), 5.74 (br, 1H), 4.1 (br, 1H), 3.01 (br, 1H), 2.4 (br, 1H), 1.98 (m, 1H), 1.69 (m, 2H), 1.54 (m, 2H), 1.51 (s, 9H)		

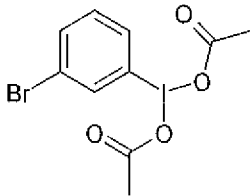
Example 12.1: m-Chlorophenyl iodine diacetate

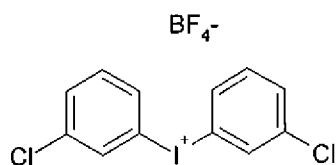


1-Chloro-3-iodobenzene (5.0 g, 21 mmol) was stirred at 30 °C. Peracetic acid (40 %, 8.35 mL, 50.3 mmol) was added drop wise to the solution and the reaction was allowed to stir for 12 h. The white solid that formed was filtered, washed 1 time with 10 % acetic acid, and 3 times with hexanes and dried in vacuo to afford the title product (27.5 g, 92 %) as a white solid.

¹H NMR (300 MHz, CDCl₃): δ (ppm) 8.10 (s, 1H), 7.99 (d, 1H), 7.57 (d, 1H), 7.46 (t, 1H), 2.04 (s, 6H).

In a similar manner the following compound was synthesized:

<u>12.2</u>		m-Bromophenyliodine diacetate	58 %
¹H NMR	(300 MHz, CDCl ₃): δ 8.24 (t, 1H), 7.72 (dd, 1H), 7.39 (t, 1H), 7.02 (d, 1H), 2.05 (s, 6H)		

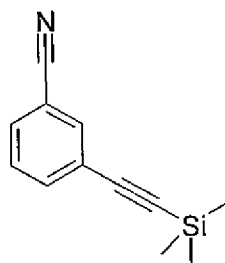
Example 13.1: Bis(3-chlorophenyl)iodonium tetrafluoroborate

Borontrifluoride diethyl etherate (16.51 g, 116.3 mmol) was added slowly to 3-chlorophenyl
 boronic acid (17.37 g, 111.0 mmol) in DCM (170 mL) at -5°C , while stirring. After 15
 minutes, the title compound of Example 12.1 (37.71 g, 105.8 mmol) in DCM (150 mL) was
 added slowly. The reaction stirred for 1 h at 0°C and sodium tetrafluoroborate (225 g in 300
 mL water) was added and stirred for 1 h. The organic layer was separated, dried over sodium
 sulphate, filtered and concentrated and triturated with ether to afford the title product (31.6 g,
 68 %) as a light brown solid.

^1H NMR (300 MHz, $(\text{CD}_3)_2\text{SO}$): δ (ppm) 8.50 (s, 2H), 8.26 (dd, 2H), 7.74 (dd, 2H), 7.60 (t, 2H).

In a similar manner the following compounds were synthesized:

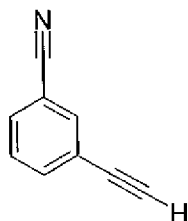
13.2		Bis(3-bromophenyl)iodonium tetrafluoroborate	55 %
^1H NMR	(300 MHz, CDCl_3): δ 7.72 (t, 2H), 7.88 (dd, 2H), 7.830 (dd, 2H), 8.62 (t, 2H)		

Example 14: 3-Trimethylsilyl-ethynyl-benzonitrile

3-Iodo-benzonitrile (10.0 g, 43.7 mmol), trimethylsilane acetylene (5.57 g, 56.8 mmol), palladium tetrakis triphenylphosphine (2.02 g, 1.75 mmol), and copper iodide (1.0 g, 5.24 mmol) in triethylamine (120 mL) was stirred for 12 h. The reaction was concentrated and purified by column chromatography to afford the title product (9.35 g, quantitative yield) as a brown oil.

^1H NMR (300 MHz, CDCl_3): δ (ppm) 7.76 (t, 1H), 7.71 (dd, 1H), 7.63 (dd, 1H), 7.28 (t, 1H), 0.26 (s, 9H).

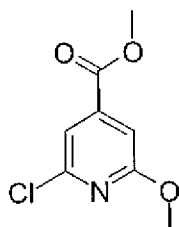
Example 15: 3-Ethynyl-benzonitrile



The title compound of Example 14 (9.35 g, 47.0 mmol) and potassium carbonate (32.0 g, 235.0 mmol) was stirred in MeOH (120 mL) at RT for 15 minutes. The reaction was partitioned between water and hexanes. The organic extracts were washed with water, dried over sodium sulphate, filtered and concentrated. The reaction mixture was purified by column chromatography to afford the title product (1.45 g, 56 %) as a white solid.

^1H NMR (300 MHz, CDCl_3): δ (ppm) 3.21 (s, 1H), 7.49 (t, 1H), 7.65 (dd, 1H), 7.71 (dd, 1H), 7.78 (t, 1H).

Example 16.1: 2-Chloro-6-methoxy-isonicotinic acid methyl ester



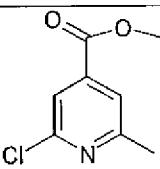
To 2-chloro-6-methoxy-isonicotinic acid (16 g, 85.3 mmol) in DMF (220 mL) were added K_2CO_3 (47 g, 341 mmol) and MeI (6.37 mL, 102.3 mmol). After stirring overnight, the reaction mixture was filtered and then concentrated. The residue was dissolved in ethyl

acetate, washed with water (3 times) and brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. Purification by flash column chromatography eluted with 10 - 30 % ethyl acetate in hexanes gave the title product (15 g, 87 %).

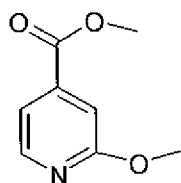
^1H NMR (300 MHz, CDCl_3): δ 7.45 (s, 1H), 7.23 (s, 1H), 3.98 (s, 3H), 3.95 (s, 3H).

5

In a similar manner the following compound was synthesized:

16.2		2-Chloro-6-methyl-isonicotinic acid methyl ester	92 % Light brown solid
NMR	(300 MHz, CDCl_3): δ 7.71 (s, 1H), 7.65 (s, 1H), 3.97 (s, 3H), 2.63 (s, 3H)		

Example 17.1: 2-Methoxy-isonicotinic acid methyl ester



10

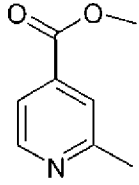
The title compound of Example 16.1 (15 g, 75 mmol) was mixed with Pd/C (7.4 g, 82 mmol) in ethanol (350 mL). The reaction mixture was flushed and filled with hydrogen, and then stirred at room temperature for overnight. The reaction mixture was filtered through Celite ® pad and concentrated in vacuo. The residue was dissolved in dichloromethane and washed with twice with water and brine. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give light yellow oil as product (9.5 g, 75 %).

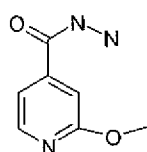
15

^1H NMR (300 MHz, CDCl_3): δ 8.29 (d, 1H), 7.41 (d, 1H), 7.32 (s, 1H), 3.98 (s, 3H), 3.95 (s, 3H).

20

In a similar manner the following compounds were synthesized:

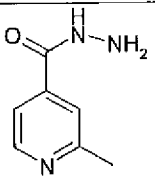
17.2		2-Methyl-isonicotinic acid methyl ester	75 % Colorless oil
¹H NMR	(300 MHz, CDCl ₃): δ 8.67 (d, 1H), 7.74 (s, 1H), 7.65 (d, 1H), 3.97 (s, 3H), 2.66 (s, 3H)		

Example 18.1: 2-Methoxy-isonicotinic acid hydrazide

To the title compound of Example 17.1 (9.51 mg, 56.9 mmol) in ethanol (100 mL) was added hydrazine hydrate (3.45 mL, 71.2 mmol) and then heated at 78 °C overnight. The reaction mixture was cooled and concentrated in vacuo. The residue was triturated with ethyl acetate, filtered and dried to give the title product as a white solid (6.69 mg, 70.3 %).

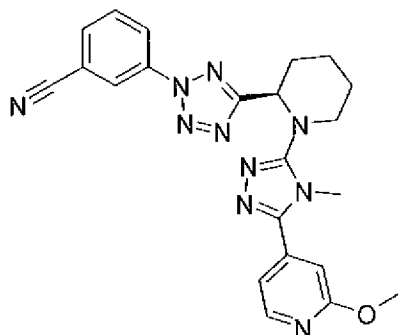
¹H NMR (300 MHz, (CD₃)₂SO): δ 10.04 (br, 1H), 8.27 (d, 1H), 7.32 (d, 1H), 7.15 (s, 1H), 4.62 (br, 2H), 3.88 (s, 3H).

In a similar manner the following compound was synthesized:

18.2		2-Methyl-isonicotinic acid hydrazide	88 % White solid
¹H NMR	(300 MHz, (CD ₃) ₂ SO): δ 8.54 (d, 1H), 7.6 (s, 1H), 7.51 (d, 1H), 2.5 (s, 3H)		

NB: Nicotinic Hydrazide and Isonicotinic Hydrazide were commercially available

Example 19.1: 3-(5-((R)-1-[5-(2-Methoxy-pyridin-4-yl)-4-methyl-4H-[1,2,4]triazol-3-yl]-piperidin-2-yl)-tetrazol-2-yl)-benzonitrile

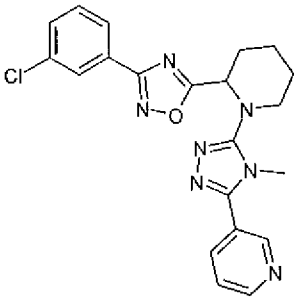
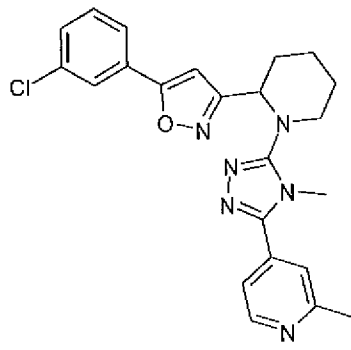
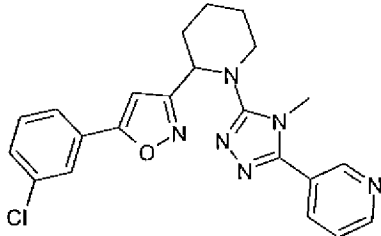
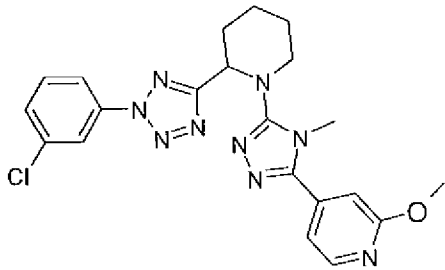


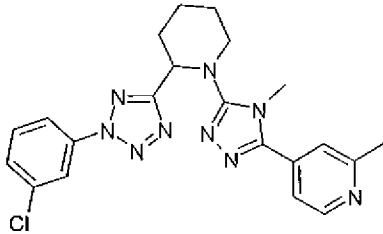
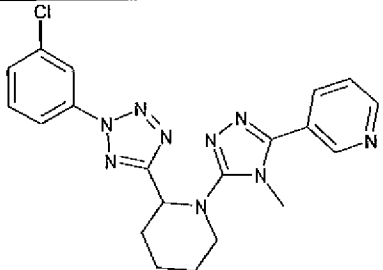
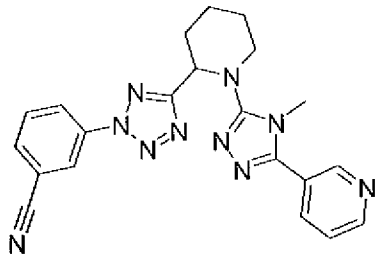
The title compound of Example 18.1 (122 mg, 0.73 mmol) and the title compound of Example 8.3 (100 mg, 0.29 mmol) were mixed in isopropanol (5 mL), the mixture was heated at 95°C for over night. The reaction mixture was cooled to room temperature, and concentrated in vacuo. The residue was diluted with ethyl acetate (20 mL), and water (20 mL) was added. The organic phase was separated and washed with brine (4 times 25 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude residue was purified on silica gel using ethyl acetate: hexane = 60 % : 40 % then methanol : hexane : ethyl acetate = 5 % : 15 % : 80 % to give the title product as yellow oil (86 mg, 67 %).

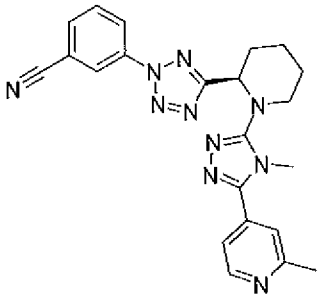
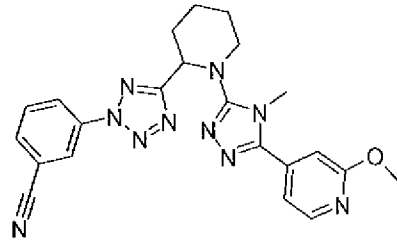
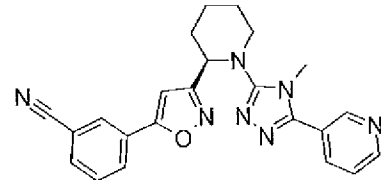
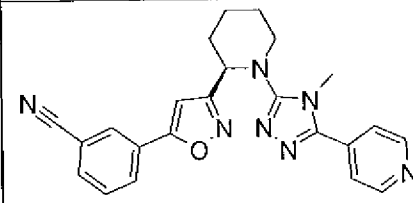
¹H NMR (300 MHz, CDCl₃): δ 8.36 (m, 2H), 8.27 (d, 1H), 7.75 (d, 1H), 7.67 (t, 1H), 7.22 (d, 1H), 6.99 (s, 1H), 5.13 (m, 1H), 3.95 (s, 3H), 3.72 (s, 3H), 3.52 (m, 1H), 3.28 (m, 1H), 2.29 (m, 1H), 2.14 (m, 1H), 1.92 (m, 4H).

In a similar manner the following compounds were synthesized:

19.2		4-(5-{2-[3-(3-Chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-4-methyl-4H-[1,2,4]triazol-3-yl)-2-methyl-pyridine	33 % Off-white solid
¹H NMR	(300 MHz, CDCl ₃): δ 8.65 (d, 1H), 8.02 (s, 1H), 7.92 (d, 1H), 7.38 (m, 4H), 5.10 (m, 1H), 3.72 (s, 3H), 3.56 (m, 1H), 3.28 (m, 1H), 2.64 (s, 3H), 2.35 (m, 1H), 2.13 (m, 1H), 1.85 (m, 4H)		

19.3		3-(5-{2-[3-(3-Chlorophenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-4-methyl-4H-[1,2,4]triazol-3-yl)-pyridine	52 % White solid
¹H NMR	(300 MHz, CDCl ₃): δ 8.90 (s, 1H), 8.73 (d, 1H), 8.04 (m, 2H), 7.93 (dd, 1H), 7.43 (m, 3H), 5.10 (m, 1H), 3.70 (s, 3H), 3.55 (m, 1H), 3.29 (m, 1H), 2.38 (m, 1H), 2.16 (m, 1H), 1.87 (m, 4H)		
19.4		4-(5-{2-[5-(3-Chlorophenyl)-isoxazol-3-yl]-piperidin-1-yl}-4-methyl-4H-[1,2,4]triazol-3-yl)-2-methyl-pyridine	54 % White solid
¹H NMR	(300 MHz, CDCl ₃): δ 8.62 (d, 1H), 7.71 (s, 1H), 7.70 (m, 1H), 7.49 (s, 1H), 7.36 (m, 3H), 6.54 (s, 1H), 4.79 (t, 1H), 3.62 (s, 3H), 3.34 (m, 2H), 2.62 (s, 3H), 2.21 (q, 2H), 1.85 (m, 4H)		
19.5		3-(5-{2-[5-(3-Chlorophenyl)-isoxazol-3-yl]-piperidin-1-yl}-4-methyl-4H-[1,2,4]triazol-3-yl)-pyridine	51 % White solid
¹H NMR	(300 MHz, CDCl ₃): δ 8.88 (s, 1H), 8.71 (d, 1H), 8.03 (dd, 1H), 7.71 (s, 1H), 7.59 (m, 1H), 7.37 (m, 3H), 6.56 (s, 1H), 4.80 (t, 1H), 3.61 (s, 3H), 3.35 (m, 2H), 2.23 (q, 2H), 1.85 (m, 4H)		
19.6		4-(5-{2-[2-(3-Chlorophenyl)-2H-tetrazol-5-yl]-piperidin-1-yl}-4-methyl-4H-[1,2,4]triazol-3-yl)-2-methoxy-pyridine	39 % White solid

¹H NMR	(300 MHz, CDCl ₃): δ 8.28 (d, 1H), 8.08 (s, 1H), 7.97 (m, 1H), 7.46 (m, 2H), 7.24 (d, 1H), 7.01 (s, 1H), 5.12 (m, 1H), 3.99 (s, 3H), 3.71 (s, 3H), 3.49 (m, 1H), 3.30 (m, 1H), 2.30~1.64 (m, 6H)		
<u>19.7</u>		4-(5-{2-[2-(3-Chlorophenyl)-2H-tetrazol-5-yl]-piperidin-1-yl}-4-methyl-4H-[1,2,4]triazol-3-yl)-2-methyl-pyridine	41 % Off-white solid
¹H NMR	(300 MHz, CDCl ₃): δ 8.60 (d, 1H), 8.06 (s, 1H), 7.95 (m, 1H), 7.40 (m, 4H), 5.09 (m, 1H), 3.71 (s, 3H), 3.48 (m, 1H), 3.28 (m, 1H), 2.60 (s, 3H), 2.28-1.80 (m, 6H)		
<u>19.8</u>		3-(5-{2-[2-(3-Chlorophenyl)-2H-tetrazol-5-yl]-piperidin-1-yl}-4-methyl-4H-[1,2,4]triazol-3-yl)-pyridine	47 % Yellow solid
¹H NMR	(300 MHz, CDCl ₃): δ 8.87 (s, 1H), 8.68 (d, 1H), 8.03 (m, 3H), 7.42 (m, 3H), 5.09 (m, 1H), 3.68 (s, 3H), 3.46 (m, 1H), 3.28 (m, 1H), 2.80-1.76 (m, 6H)		
<u>19.9</u>		3-{5-[1-(4-Methyl-5-pyridin-3-yl-4H-[1,2,4]triazol-3-yl)-piperidin-2-yl]-tetrazol-2-yl}-benzonitrile	58 % Pale yellow solid
¹H NMR	(300 MHz, CDCl ₃): δ 8.89 (s, 1H), 8.75 (d, 1H), 8.38 (m, 2H), 8.03 (dd, 1H), 7.72 (m, 2H), 7.43 (m, 1H), 5.14 (m, 1H), 3.72 (s, 3H), 3.51 (m, 1H), 3.28 (m, 1H), 2.06~1.63 (m, 6H)		

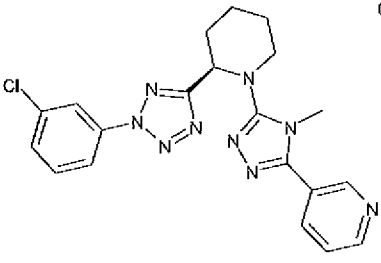
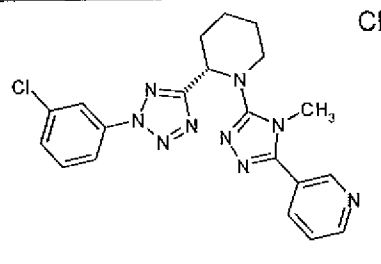
19.10		3-(5-((R)-1-[4-Methyl-5-(2-methylpyridin-4-yl)-4H-[1,2,4]triazol-3-yl]-piperidin-2-yl)-tetrazol-2-yl)-benzonitrile	67 % Clear oil
¹H NMR	(300 MHz, CDCl ₃): δ 8.60 (d, 1H), 8.35 (m, 2H), 7.73 (m, 2H), 7.49 (s, 1H), 7.36 (d, 1H), 5.13 (m, 1H), 3.73 (s, 3H), 3.50 (m, 1H), 3.27 (m, 1H), 2.61 (s, 3H), 2.28 (m, 1H), 2.14 (m, 1H), 1.92 (m, 4H)		
19.11		3-(5-{1-[5-(2-Methoxy-pyridin-4-yl)-4-methyl-4H-[1,2,4]triazol-3-yl]-piperidin-2-yl}-tetrazol-2-yl)-benzonitrile	74 % Off-white solid
¹H NMR	(300 MHz, CDCl ₃): δ 8.62 (d, 1H), 8.38 (m, 2H), 7.75 (m, 2H), 7.51 (s, 1H), 7.38 (d, 1H), 5.14 (m, 1H), 3.74 (s, 3H), 3.51 (m, 1H), 3.28 (m, 1H), 2.64 (s, 3H), 2.30~1.75 (m, 6H)		
19.12		3-{3-[(2R)-1-(4-methyl-5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)piperidin-2-yl]isoxazol-5-yl}benzonitrile	41 % Yellow foam solid
¹H NMR	(300 MHz, CDCl ₃): δ 8.86 (s, 1H), 8.67 (d, 1H), 8.01 (m, 3H), 7.66 (d, 1H), 7.57 (t, 1H), 7.4 (dd, 1H), 6.65 (s, 1H), 4.8 (t, 1H), 3.63 (s, 3H), 3.35 (m, 1H), 3.24 (m, 1H), 2.18 (m, 2H), 1.82 (m, 4H)		
19.13		3-{3-[(2R)-1-(4-Methyl-5-pyridin-4-yl-4H-1,2,4-triazol-3-yl)piperidin-2-yl]isoxazol-5-yl}benzonitrile	47 % Yellow foam solid
¹H NMR	(300 MHz, CDCl ₃): δ 8.72 (d, 2H), 7.96 (m, 2H), 7.38 (m, 4H), 6.65 (s, 1H), 4.82 (t, 1H), 3.67 (s, 3H), 3.3 (m, 2H), 2.18 (m, 2H), 1.82 (m, 4H).		

Example 20: The following compounds were obtained from separation of racemic compound using chiral HPLC.

Chiral separation using Chiralpak AD 250 x 20 mm, particle size 10 µm. Mobile phase MeCN:TEA 100 / 0.1, Flow 18 mL / min, Detection 260 nm, Temp 40 °C.

5

In a similar manner the following compounds were isolated:

<u>20.1</u>		3-(5-{(R)-2-[2-(3-Chloro-phenyl)-2H-tetrazol-5-yl]-piperidin-1-yl}-4-methyl-4H-[1,2,4]triazol-3-yl)-pyridine	Chiral separation
¹H NMR	(400 MHz, CDCl ₃) 8.85 (s, 1 H), 8.66 (d, 1 H), 8.05 (s, 1 H), 7.99 (d, 1 H), 7.94 (d, 1 H), 7.45-7.35 (m, 3 H), 5.07 (m, 1 H), 3.66 (s, 3 H), 3.46 (m, 1 H), 3.26 (m, 1 H), 2.27 (m, 1 H), 2.10 (m, 1 H), 1.96-1.73 (m, 4 H)		
<u>20.2</u>		3-(5-{(S)-2-[2-(3-Chloro-phenyl)-2H-tetrazol-5-yl]-piperidin-1-yl}-4-methyl-4H-[1,2,4]triazol-3-yl)-pyridine	Chiral separation
¹H NMR	(400 MHz, CDCl ₃) 8.85 (s, 1 H), 8.66 (d, 1 H), 8.05 (s, 1 H), 7.99 (d, 1 H), 7.94 (d, 1 H), 7.45-7.35 (m, 3 H), 5.07 (m, 1 H), 3.66 (s, 3 H), 3.46 (m, 1 H), 3.26 (m, 1 H), 2.27 (m, 1 H), 2.10 (m, 1 H), 1.96-1.73 (m, 4 H)		

Biological evaluation

10

Functional assessment of mGluR5 antagonism in cell lines expressing mGluR5D

The properties of the compounds of the invention can be analyzed using standard assays for pharmacological activity. Examples of glutamate receptor assays are well known in the art as described in for example Aramori *et al.*, *Neuron* 8:757 (1992), Tanabe *et al.*, *Neuron* 8:169 (1992), Miller *et al.*, *J. Neuroscience* 15: 6103 (1995), Balazs, *et al.*, *J. Neurochemistry*

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69:151 (1997). The methodology described in these publications is incorporated herein by reference. Conveniently, the compounds of the invention can be studied by means of an assay (FLIPR) that measures the mobilization of intracellular calcium, $[Ca^{2+}]_i$ in cells expressing mGluR5 or another assay (IP3) that measures inositol phosphate turnover.

5

FLIPR Assay

Cells expressing human mGluR5d as described in WO97/05252 are seeded at a density of 100,000 cells per well on collagen coated clear bottom 96-well plates with black sides and experiments are done 24 h following seeding. All assays are done in a buffer containing 127 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 0.7 mM NaH_2PO_4 , 2 mM $CaCl_2$, 0.422 mg/ml $NaHCO_3$, 2.4 mg/ml HEPES, 1.8 mg/ml glucose and 1 mg/ml BSA Fraction IV (pH 7.4). Cell cultures in the 96-well plates are loaded for 60 minutes in the above mentioned buffer containing 4 μM of the acetoxymethyl ester form of the fluorescent calcium indicator fluo-3 (Molecular Probes, Eugene, Oregon) in 0.01% pluronic acid (a proprietary, non-ionic surfactant polyol – CAS Number 9003-11-6). Following the loading period the fluo-3 buffer is removed and replaced with fresh assay buffer. FLIPR experiments are done using a laser setting of 0.800 W and a 0.4 second CCD camera shutter speed with excitation and emission wavelengths of 488 nm and 562 nm, respectively. Each experiment is initiated with 160 μl of buffer present in each well of the cell plate. A 40 μl addition from the antagonist plate was followed by a 50 μL addition from the agonist plate. A 90 second interval separates the antagonist and agonist additions. The fluorescence signal is sampled 50 times at 1 second intervals followed by 3 samples at 5 second intervals immediately after each of the two additions. Responses are measured as the difference between the peak height of the response to agonist, less the background fluorescence within the sample period. IC_{50} determinations are made using a linear least squares fitting program.

25

IP3 Assay

An additional functional assay for mGluR5d is described in WO97/05252 and is based on phosphatidylinositol turnover. Receptor activation stimulates phospholipase C activity and leads to increased formation of inositol 1,4,5-triphosphate (IP₃).

GHEK stably expressing the human mGluR5d are seeded onto 24 well poly-L-lysine coated plates at 40×10^4 cells /well in media containing 1 μ Ci/well [3H] myo-inositol. Cells were incubated overnight (16 h), then washed three times and incubated for 1 h at 37°C in HEPES buffered saline (146 mM NaCl, 4.2 mM KCl, 0.5 mM MgCl₂, 0.1% glucose, 20 mM HEPES, pH 7.4) supplemented with 1 unit/ml glutamate pyruvate transaminase and 2 mM pyruvate. Cells are washed once in HEPES buffered saline and pre-incubated for 10 min in HEPES buffered saline containing 10 mM LiCl. Compounds are incubated in duplicate at 37°C for 15 min, then either glutamate (80 μ M) or DHPG (30 μ M) is added and incubated for an additional 30 min. The reaction is terminated by the addition of 0.5 ml perchloric acid (5%) on ice, with incubation at 4°C for at least 30 min. Samples are collected in 15 ml polypropylene tubes and inositol phosphates are separated using ion-exchange resin (Dowex AG1-X8 formate form, 200-400 mesh, BIORAD) columns. Inositol phosphate separation was done by first eluting glycerophosphatidyl inositol with 8 ml 30 mM ammonium formate. Next, total inositol phosphates is eluted with 8 ml 700 mM ammonium formate / 100 mM formic acid and collected in scintillation vials. This eluate is then mixed with 8 ml of scintillant and [3H] inositol incorporation is determined by scintillation counting. The dpm counts from the duplicate samples are plotted and IC₅₀ determinations are generated using a linear least squares fitting program.

Abbreviations

BSA	Bovine Serum Albumin
CCD	Charge Coupled Device
CRC	Concentration Response Curve
DHPG	3,5-dihydroxyphenylglycine
DPM	Disintegrations per Minute
EDTA	Ethylene Diamine Tetraacetic Acid

FLIPR	Fluorometric Imaging Plate reader
GHEK	GLAST-containing Human Embryonic Kidney
GLAST	glutamate/aspartate transporter
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (buffer)
5 IP ₃	inositol triphosphate

Generally, the compounds were active in the assay above with IC₅₀ values less than 10 000 nM. In one aspect of the invention, the IC₅₀ value is less than 1000 nM. In a further aspect of the invention, the IC₅₀ value is less than 100 nM.

10

Determination of Brain to Plasma Ratio in Rat

Brain to plasma ratios are estimated in female Sprague Dawley rats. The compound is dissolved in water or another appropriate vehicle. For determination of brain to plasma ratio the compound is administrated as a subcutaneous, or an intravenous bolus injection, or an intravenous infusion, or an oral administration. At a predetermined time point after the administration a blood sample is taken with cardiac puncture. The rat is terminated by cutting the heart open, and the brain is immediately retained. The blood samples are collected in heparinized tubes and centrifuged within 30 minutes, in order to separate the plasma from the blood cells. The plasma is transferred to 96-well plates and stored at -20°C until analysis. The brains are divided in half, and each half is placed in a pre-tarred tube and stored at -20°C until analysis. Prior to the analysis, the brain samples are thawed and 3 ml/g brain tissue of distilled water is added to the tubes. The brain samples are sonicated in an ice bath until the samples are homogenized. Both brain and plasma samples are precipitated with acetonitrile. After centrifugation, the supernatant is diluted with 0.2 % formic acid. Analysis is performed on a short reversed-phase HPLC column with rapid gradient elution and MSMS detection using a triple quadrupole instrument with electrospray ionisation and Selected Reaction Monitoring (SRM) acquisition. Liquid-liquid extraction may be used as an alternative sample

clean-up. The samples are extracted, by shaking, to an organic solvent after addition of a suitable buffer. An aliquot of the organic layer is transferred to a new vial and evaporated to dryness under a stream of nitrogen. After reconstitution of the residuals the samples are ready for injection onto the HPLC column.

Generally, the compounds according to the present invention are peripherally restricted with a drug in brain over drug in plasma ratio in the rat of < 0.5 . In one embodiment, the ratio is less than 0.15.

Determination of in vitro Stability

Rat liver microsomes are prepared from Sprague-Dawley rats liver samples. Human liver microsomes are either prepared from human liver samples or acquired from BD Gentest. The compounds are incubated at 37 °C at a total microsome protein concentration of 0.5 mg/mL in a 0.1 mol/L potassium phosphate buffer at pH 7.4, in the presence of the cofactor, NADPH (1.0 mmol/L). The initial concentration of compound is 1.0 μ mol/L. Samples are taken for analysis at 5 time points, 0, 7, 15, 20 and 30 minutes after the start of the incubation. The enzymatic activity in the collected sample is immediately stopped by adding a 3.5 times volume of acetonitrile. The concentration of compound remaining in each of the collected samples is determined by means of LC-MS. The elimination rate constant (k) of the mGluR5 inhibitor is calculated as the slope of the plot of $\ln[\text{mGluR5 inhibitor}]$ against incubation time (minutes). The elimination rate constant is then used to calculate the half-life ($T_{1/2}$) of the mGluR5 inhibitor, which is subsequently used to calculate the intrinsic clearance (CL_{int}) of the mGluR5 inhibitor in liver microsomes as:

$$CL_{int} = (\ln 2 \times \text{incubation volume}) / (T_{1/2} \times \text{protein concentration}) = \mu\text{l}/\text{min}/\text{mg}$$

Screening for compounds active against TLESR

Adult Labrador retrievers of both genders, trained to stand in a Pavlov sling, are used. Mucosa-to-skin esophagostomies are formed and the dogs are allowed to recover completely before any experiments are done.

Motility measurement

In brief, after fasting for approximately 17 h with free supply of water, a multilumen sleeve/sidehole assembly (Dentsleeve, Adelaide, South Australia) is introduced through the esophagostomy to measure gastric, lower esophageal sphincter (LES) and esophageal pressures. The assembly is perfused with water using a low-compliance manometric perfusion pump (Dentsleeve, Adelaide, South Australia). An air-perfused tube is passed in the oral direction to measure swallows, and an antimony electrode monitored pH, 3 cm above the LES. All signals are amplified and acquired on a personal computer at 10 Hz.

When a baseline measurement free from fasting gastric/LES phase III motor activity has been obtained, placebo (0.9% NaCl) or test compound is administered intravenously (i.v., 0.5 ml/kg) in a foreleg vein. Ten min after i.v. administration, a nutrient meal (10% peptone, 5% D-glucose, 5% Intralipid, pH 3.0) is infused into the stomach through the central lumen of the assembly at 100 ml/min to a final volume of 30 ml/kg. The infusion of the nutrient meal is followed by air infusion at a rate of 500 ml/min until an intragastric pressure of 10 ± 1 mmHg is obtained. The pressure is then maintained at this level throughout the experiment using the infusion pump for further air infusion or for venting air from the stomach. The experimental time from start of nutrient infusion to end of air insufflation is 45 min. The procedure has been validated as a reliable means of triggering TLESRs.

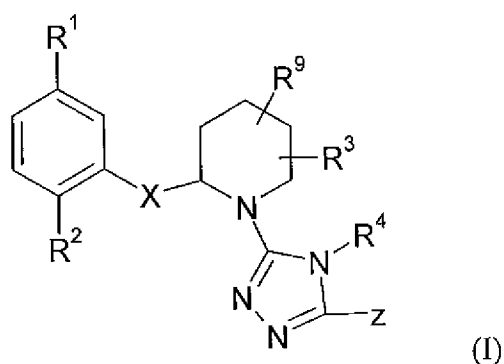
TLESRs is defined as a decrease in lower esophageal sphincter pressure (with reference to intragastric pressure) at a rate of >1 mmHg/s. The relaxation should not be preceded by a pharyngeal signal ≤ 2 s before its onset in which case the relaxation is classified as swallow-induced. The pressure difference between the LES and the stomach should be less than 2 mmHg, and the duration of the complete relaxation longer than 1 s.

Specimen results are shown in the following Table:

Example	FLIPR hmGluR5d (nM)	Brain / Plasma Ratio of compound in Rat
19.11	110	0.06
20.2	193	0.085

Claims

1. A compound of formula (I)



wherein

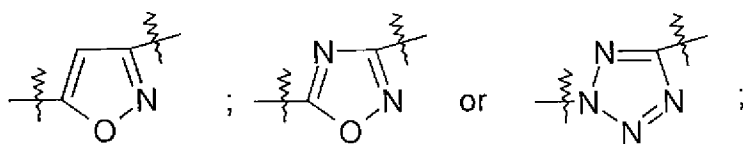
R^1 is methyl, halogen or cyano;

R^2 is hydrogen or fluoro;

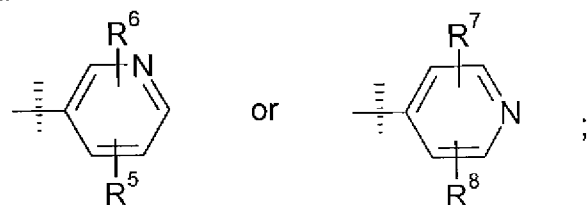
10 R^3 is hydrogen, fluoro or C_1 - C_3 alkyl;

R^4 is C_1 - C_3 alkyl or cyclopropyl;

X is



and Z is



15 wherein

R^5 is hydrogen, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, C_1 - C_3 alkoxy; C_1 - C_3 haloalkoxy or halogen;

R^6 is hydrogen, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, C_1 - C_3 alkoxy; C_1 - C_3 haloalkoxy or halogen;

R⁷ is C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy; C₁-C₃ haloalkoxy or halogen;
R⁸ is hydrogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy; C₁-C₃ haloalkoxy or halogen;
R⁹ is hydrogen, fluoro or C₁-C₃ alkyl;
as well as pharmaceutically acceptable salts, hydrates, isoforms, tautomers and/or
5 enantiomers thereof.

2. A compound according to claim 1, wherein R¹ is halogen or cyano.

3. A compound according to claim 2, wherein R¹ is chloro.

10 4. A compound according to claim 2, wherein R¹ is cyano.

5. A compound according to any one of claims 1-4, wherein R² is hydrogen.

15 6. A compound according to any one of claims 1-5, wherein R³ is hydrogen or fluoro.

7. A compound according to any one of claims 1-6, wherein R⁴ is C₁-C₂ alkyl.

8. A compound according to claim 7, wherein R⁴ is methyl.

20 9. A compound according to any one of claims 1-8, wherein R⁵ is hydrogen, C₁-C₂ alkyl or
C₁-C₂ alkoxy.

10. A compound according to any one of claims 1-9, wherein R⁶ is hydrogen, C₁-C₂ alkyl or
25 C₁-C₂ alkoxy.

11. A compound according to any one of claims 1-10, wherein R⁷ is C₁-C₂ alkyl or C₁-C₂
alkoxy.

12. A compound according to any one of claims 1-11, wherein R⁸ is hydrogen, C₁-C₂ alkyl or C₁-C₂ alkoxy.

13. A compound according to any one of claims 1-12, wherein R⁹ is hydrogen or fluoro.

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14. A compound selected from

3-(5-{(R)-1-[5-(2-Methoxy-pyridin-4-yl)-4-methyl-4H-[1,2,4]triazol-3-yl]-piperidin-2-yl}-tetrazol-2-yl)-benzonitrile;

4-(5-{2-[3-(3-Chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-4-methyl-4H-[1,2,4]triazol-3-yl)-2-methyl-pyridine;

3-(5-{2-[3-(3-Chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-4-methyl-4H-[1,2,4]triazol-3-yl)-pyridine;

4-(5-{2-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-piperidin-1-yl}-4-methyl-4H-[1,2,4]triazol-3-yl)-2-methyl-pyridine;

3-(5-{2-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-piperidin-1-yl}-4-methyl-4H-[1,2,4]triazol-3-yl)-pyridine;

4-(5-{2-[2-(3-Chloro-phenyl)-2H-tetrazol-5-yl]-piperidin-1-yl}-4-methyl-4H-[1,2,4]triazol-3-yl)-2-methoxy-pyridine;

4-(5-{2-[2-(3-Chloro-phenyl)-2H-tetrazol-5-yl]-piperidin-1-yl}-4-methyl-4H-[1,2,4]triazol-3-yl)-2-methyl-pyridine;

3-(5-{2-[2-(3-Chloro-phenyl)-2H-tetrazol-5-yl]-piperidin-1-yl}-4-methyl-4H-[1,2,4]triazol-3-yl)-pyridine;

3-{5-[1-(4-Methyl-5-pyridin-3-yl)-4H-[1,2,4]triazol-3-yl]-piperidin-2-yl}-tetrazol-2-yl}-benzonitrile;

3-(5-{(R)-1-[4-Methyl-5-(2-methyl-pyridin-4-yl)-4H-[1,2,4]triazol-3-yl]-piperidin-2-yl}-tetrazol-2-yl)-benzonitrile;

3-(5-{1-[5-(2-Methoxy-pyridin-4-yl)-4-methyl-4H-[1,2,4]triazol-3-yl]-piperidin-2-yl}-tetrazol-2-yl)-benzonitrile;

3-(5-{(R)-2-[2-(3-Chloro-phenyl)-2H-tetrazol-5-yl]-piperidin-1-yl}-4-methyl-4H-[1,2,4]triazol-3-yl)-pyridine; and

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3-(5-{{(S)-2-[2-(3-Chloro-phenyl)-2H-tetrazol-5-yl]-piperidin-1-yl}-4-methyl-4H-[1,2,4]triazol-3-yl)-pyridine
as well as pharmaceutically acceptable salts, hydrates, isoforms, tautomers and/or enantiomers thereof.

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15. A compound according to any one of claims 1-14 for use in therapy.

16. A pharmaceutical composition comprising a compound according to any one of claims 1-14 as an active ingredient, together with a pharmacologically and pharmaceutically acceptable carrier.

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17. Use of a compound according to any one of claims 1-14, or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for the inhibition of transient lower esophageal sphincter relaxations.

15

18. Use of a compound according to any one of claims 1-14, or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for treatment or prevention of gastroesophageal reflux disease.

20

19. Use of a compound according to any one of claims 1-14, or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for treatment or prevention of pain.

25

20. Use of a compound according to any one of claims 1-14, or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for treatment or prevention of anxiety.

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21. Use of a compound according to any one of claims 1-14, or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for treatment or prevention of irritable bowel syndrome (IBS).

22. A method for the inhibition of transient lower esophageal sphincter relaxations whereby an effective amount of a compound according to any one of claims 1-14 is administered to a subject in need of such inhibition.

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23. A method for the treatment or prevention of gastroesophageal reflux disease, whereby an effective amount of a compound according to any one of claims 1-14 is administered to a subject in need of such treatment or prevention.

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24. A method for the treatment or prevention of pain, whereby an effective amount of a compound according to any one of claims 1-14 is administered to a subject in need of such treatment or prevention.

15

25. A method for the treatment or prevention of anxiety, whereby an effective amount of a compound according to any one of claims 1-14 is administered to a subject in need of such treatment or prevention.

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26. A method for the treatment or prevention of irritable bowel syndrome (IBS), whereby an effective amount of a compound according to any one of claims 1-14 is administered to a subject in need of such treatment or prevention.

27. A combination comprising (i) at least one compound according to any one of claims 1-14 and (ii) at least one acid secretion inhibiting agent.

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28. A combination according to claim 27 wherein the acid secretion inhibiting agent is selected from cimetidine, ranitidine, omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole or leminoprazole.

29. A compound selected from

(R)-2-[5-(3-Cyano-phenyl)-isoxazol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester;
 3-((R)-3-Piperidin-2-yl-isoxazol-5-yl)-benzonitrile;
 (R)-2-[2-(3-Bromo-phenyl)-2H-tetrazol-5-yl]-piperidine-1-carboxylic acid tert-butyl
 ester;

5 2-[2-(3-Bromo-phenyl)-2H-tetrazol-5-yl]-piperidine-1-carboxylic acid tert-butyl ester;
 (R)-2-[2-(3-Cyano-phenyl)-2H-tetrazol-5-yl]-piperidine-1-carboxylic acid tert-butyl ester;
 2-[2-(3-Cyano-phenyl)-2H-tetrazol-5-yl]-piperidine-1-carboxylic acid tert-butyl ester;
 2-[5-(3-Cyano-phenyl)-isoxazol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester;
 (R)-2-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester;

10 3-(3-Piperidin-2-yl-isoxazol-5-yl)-benzonitrile;
 3-((R)-3-Piperidin-2-yl-isoxazol-5-yl)-benzonitrile;
 3-((R)-5-Piperidin-2-yl-tetrazol-2-yl)-benzonitrile;
 3-(5-piperidin-2-yl-2H-tetrazol-2-yl)benzonitrile;

(R)-2-[5-(3-Cyano-phenyl)-isoxazol-3-yl]-piperidine-1-carbothioic acid methylamide;
 15 2-[5-(3-Cyano-phenyl)-isoxazol-3-yl]-piperidine-1-carbothioic acid methylamide;
 (R)-2-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-piperidine-1-carbothioic acid methylamide;
 (R)-2-[2-(3-Cyano-phenyl)-2H-tetrazol-5-yl]-piperidine-1-carbothioic acid methylamide;
 2-[2-(3-Cyano-phenyl)-2H-tetrazol-5-yl]-piperidine-1-carbothioic acid methylamide;
 (R)-2-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-N-methyl-piperidine-1-carboximidothioic acid
 20 methyl ester;

(R)-2-[2-(3-Cyano-phenyl)-2H-tetrazol-5-yl]-N-methyl-piperidine-1-carboximidothioic
 acid methyl ester;
 2-[2-(3-Cyano-phenyl)-2H-tetrazol-5-yl]-N-methyl-piperidine-1-carboximidothioic acid
 methyl ester;

25 (R)-2-(Hydroxyimino-methyl)-piperidine-1-carboxylic acid tert-butyl ester;
 tert-Butyl (2R)-2-[chloro(hydroxyimino)methyl]piperidine-1-carboxylate;
 tert-Butyl 2-[chloro(hydroxyimino) methyl]piperidine-1-carboxylate;
 2-[3-(3-Chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidine-1-carboxylic

acid tert-butyl ester;

2-[3-(3-Chlorophenyl)-1,2,4-oxadiazol-5-yl]piperidine;

2-[3-(3-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-N-methylpiperidine-1-carbothioamide;

Methyl 2-[3-(3-chlorophenyl)-1,2,4-oxadiazol-5-yl]-N-methylpiperidine-1-

5 carbimidothioate;

(R)-2-[2-(3-Cyano-phenyl)-2H-tetrazol-5-yl]-piperidine-1-carboxylic acid tert-butyl ester;

2-[2-(3-Cyano-phenyl)-2H-tetrazol-5-yl]-piperidine-1-carboxylic acid tert-butyl ester; and

(R)-2-(2H-Tetrazol-5-yl)-piperidine-1-carboxylic acid tert-butyl ester.