

TITLE

Novel Heterocyclic Compounds as mGlu5 Antagonists

DESCRIPTION

5

Field of the Invention

This invention relates to novel heterocyclic compounds having selective affinity for the mGlu5 subtype of metabotropic receptors and to pharmaceutical compositions including such compounds.

10

Background of the Invention

Lower urinary tract disorders encompass an assortment of syndromes that affect normal micturition. Lower urinary tract disorders may develop through combination of pathological and/or age-related changes of the urogenital system, or other etiology, *e.g.*,
15 neurological disorders. Individuals suffering from lower urinary tract disorders suffer from impaired quality of life, including embarrassment, poor self-perception, and a general reduction in emotional well-being, social function, and general health. Lower urinary tract disorders, moreover, may be associated with other physical ailments, including cellulitis, pressure ulcers, urinary tract infections, falls with fractures, sleep deprivation, social
20 withdrawal, depression, and sexual dysfunction. Older individuals suffering from lower urinary tract disorders may require more care from care providers, both family and profession, which may be a factor in decisions to place them in institutions.

According to the U.S. National Institutes of Health (NIH), up to 35 million Americans are estimated to suffer lower urinary tract disorders. Lower urinary tract
25 disorders are more common among women than men (2:1) until age 80, after which men and women are equally affected. The prevalence of lower urinary tract disorders increases with age. By the age 65, lower urinary tract disorders affect 15% to 30% of all individuals and approximately 50% of individuals in long-term care.

Agents with various modes of action have been used to treat lower urinary tract
30 disorders. These include agents that act directly on the lower urinary tract, *e.g.*, antimuscarinics and alpha 1 antagonists, and agents that act through the central nervous system, *e.g.*, serotonin and/or noradrenaline reuptake inhibitors. According to the NIH, however, while some progress has been made in the diagnosis, management, and treatment of lower urinary tract disorders, these disorders frequently remain intractable. Thus, there is

a continued need for improved agents, formulations and therapies to treat lower urinary tract disorders.

Glutamic acid, an excitatory amino acid, is present at synapses throughout the central nervous system and is known to act on at least two types of receptors: ionotropic and
5 metabotropic glutamate receptors.

The principle function of ionotropic glutamate receptors is that their activation forms ligand-gated ion channels and, thereby, directly mediates electrical signaling of nerve cells, producing rapid and relatively large conductance changes in the post-synaptic membranes. Metabotropic glutamate receptors (mGluRs) regulate electrical signaling
10 indirectly, by influencing intracellular metabolic processes via G-proteins. Changes in the post-synaptic cell that are mediated through mGluRs are consequently relatively slow over time and are not linked to rapid and large changes in neuronal membrane conductance.

Three subtypes of ionotropic glutamate receptors have been described, *i.e.*, the NMDA, AMPA and kainate subtypes.

Eight subtypes of metabotropic glutamate receptors have been cloned. The subtypes
15 are classified into three groups on the basis of sequence similarities, and pharmacological and biochemical properties (Spooren et al., *Trends Pharmacol. Sci.* 22: 331-337, 2001): Group I mGlu receptors (mGlu1 and mGlu5), Group II mGlu receptors (mGlu2 and mGlu3) and Group III mGlu receptors (mGlu4, mGlu6, mGlu7 and mGlu8).

Group I receptor mGlu5 (either human or rat) is known to comprise at least two
20 subtypes, "a" and "b". Subtype "b" is longer than subtype "a", because of an alternative splicing of a 32-amino-acid stretch in the C-terminal (intracellular) domain, 50 residues downstream of the beginning of the domain. The human mGlu5b is 1212 amino acids long, while the "a" form lacks the amino acids from 877 to 908 (n. 828 being the first of the
25 intracellular domain). The rat mGlu5b is 1203 amino acids long, while the "a" form lacks the amino acids from 876 to 907 (n. 827 being the first of the intracellular domain). (Hermans and Challis, *Biochem. J.* 359: 465-484, 2001).

The mGlu receptors, belonging to family 3 of GPCRs, are characterized by two
30 distinct topological domains: a large extracellular N-terminal domain containing a Venus fly-trap module responsible for agonist binding and the 7-TM domain plus intracellular C-terminal domain that is involved in receptor activation and G-protein coupling.

The 7-TMD of mGlu I receptors has been shown to form a binding pocket for positive and negative allosteric modulators; the negative ones have been identified thanks to high throughput screening technologies and act as non-competitive antagonists, having no

effect on agonist binding. The most interesting property of these molecules, in addition to their high potency, is their remarkable subtype selectivity.

The 7-TM binding region is located in a pocket-lined by TM-III, TM-V, TM-VI and TM-VII; this site corresponds to the retinal binding pocket in rhodopsin.

5 Allosteric modulators of mGlu5 represent an exciting advance in demonstrating the potentiality for developing novel research tools and therapeutic agents that regulate activity of specific mGluR subtypes.

The compounds of the instant invention are always reported as mGlu5 antagonist but actually are negative allosteric modulators acting at the 7-TM binding region.

10 WO 00/63166 discloses tricyclic carbamic acid derivatives useful for the treatment of different diseases, including urinary incontinence. The derivatives are disclosed to be agonists or antagonists of Group I mGlu receptors with specificity for the mGlu1 receptor.

15 WO 01/32632 discloses pyrimidine derivatives useful for the treatment of different diseases, including urinary incontinence. The derivatives are disclosed as selective antagonists of the mGlu 1 receptor with at least 10-fold selectivity for the mGlu1 receptor over the mGlu 5 receptor.

WO 01/27070 discloses new bisarylacetamides useful for the treatment of urinary incontinence, among other conditions. The molecules are disclosed to be agonists or antagonists selective for the mGlu 1 receptor.

20 US 6,369,222 discloses heterocycloazepinyl pyrimidine derivatives useful for the treatment of urinary incontinence, among other conditions. The derivatives are disclosed to be antagonists of the mGlu 1 receptor.

25 The aforementioned applications and patent, therefore, disclose mGlu1 receptor antagonists as useful for treating urinary incontinence. None of the references, however, provide experimental support for treatment of urinary incontinence, either in human patients or in an animal model for lower urinary tract disease.

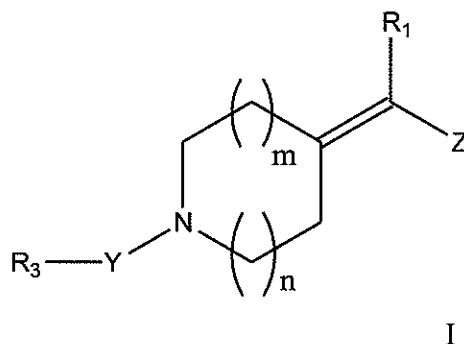
30 We have tested the activity of selective mGlu1 and selective mGlu5 antagonists, in a rat model useful to detect activity on the lower urinary tract. Surprisingly, good activity was found for antagonists selective for the mGlu5 receptor, whereas two commercially available antagonists selective for mGlu1 receptor failed to exhibit an effect. An antagonist selective for Group II mGluR receptors also failed to exhibit an effect in the rat model. Given these results, selective mGlu5 antagonists can be an effective means to treat lower urinary tract disorders.

Accordingly, the present inventors have unexpectedly found that administration of negative allosteric modulators of the glutamate mGlu5 receptor, in this document called mGlu5 antagonists, provide a potent inhibition of the micturition reflex. These modulators are thus useful for treatment of lower urinary tract disorders and symptoms thereof,

International Patent Application WO04/067002 (Recordati).

Description of the Invention

The invention provides compounds having the general formula I



wherein

Z represents a group of the formula $-\text{C}\equiv\text{C}-\text{R}_2$ or $-\text{CH}=\text{CH}-\text{R}_2$;

R_1 represents

- a hydrogen or halogen atom, or
- a hydroxy, cyano, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkylcarbonyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ alkoxy carbonyl, $\text{C}_1\text{-C}_6$ alkylcarbonyloxy, $\text{C}_1\text{-C}_6$ alkoxy carbonyloxy, $\text{C}_1\text{-C}_6$ alkylthio, di- $(\text{C}_1\text{-C}_6)$ amino or $\text{C}_3\text{-C}_{14}$ cycloalkyl group:

R_2 represents

- an optionally substituted mono- or bicyclic $\text{C}_1\text{-C}_9$ heterocyclic group containing from 1 to 3 heteroatoms chosen from nitrogen, oxygen and sulphur,
- an optionally substituted mono-, bi- or tricyclic $\text{C}_6\text{-C}_{14}$ aryl group,
- an optionally substituted $\text{C}_1\text{-C}_6$ alkyl group,
- an optionally substituted $\text{C}_2\text{-C}_6$ alkenyl group, or
- an optionally substituted $\text{C}_3\text{-C}_6$ cycloalkyl group,

or R_2 represents a group $-\text{C}(\text{O})-\text{R}_{2A}$ wherein R_{2A} is defined as R_2 above;

R_3 represents

- a hydrogen atom,
- an optionally substituted $\text{C}_1\text{-C}_6$ alkyl group,

- an optionally substituted mono-, bi- or tricyclic C₁-C₁₄ heterocyclic group containing 1 to 3 heteroatoms chosen from nitrogen, oxygen and sulphur,
- an optionally substituted mono, bi or tricyclic C₆-C₁₄ aryl group,
- an optionally substituted C₃-C₆ cycloalkyl group, or
- 5 • an optionally substituted C₃-C₆ cycloalkenyl group,

Y represents a group of the formula -C(O)-, -C(S)-, -NH-C(O)-, -N(C₁-C₆ alkyl)-C(O)-, -O-C(O)-, -NH-C(S)-, -N(C₁-C₆ alkyl)-C(S)-, -O-C(S)- or -SO₂- or is absent.

m is 0, 1 or 2;

n is 0, 1 or 2;

10

the substituents for each optionally substituted group being

- a halogen atom or an oxo, nitro, cyano, hydroxy, carbamoyl, C₁-C₆ alkylsulphonyl, C₁-C₆ alkylthio, C₁-C₆ alkylcarbonyl or C₁-C₆ alkylcarbonyl-(C₁-C₆)alkyl group or a group of the formula -NR*R* wherein each R* independently represents a hydrogen atom or a
- 15 C₁-C₆ alkyl, C₁-C₆ alkylcarbonyl, phenyl or benzyl group, or
- a C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or C₁-C₆ alkoxy group, each of which may optionally bear from 1 to 8 independently selected oxo, halo, cyano, nitro, amino, hydroxy or phenyl substituents,
- a C₃-C₉ mono- or bicycloalkyl group optionally bearing from 1 to 3 independently
- 20 selected C₁-C₆ alkyl, oxo, halo, cyano, nitro, amino, hydroxy or phenyl substituents, or
- a group of the formula -A, -O-A, -C(O)-A, -(CH₂)_q-A, -NR**-A, -C(O)NR**-A, -NR**C(O)-A or -OC(O)-A,

wherein A represents a phenyl group or a C₁-C₈ heterocyclic group containing from 1 to 3 heteroatoms chosen from nitrogen, oxygen and sulphur, each of which groups A may

25 optionally bear from 1 to 3 independently selected halo, hydroxy, cyano, nitro and C₁-C₆ alkyl substituents,

each R** independently represents a hydrogen atom or a C₁-C₆ alkyl group, and

q is 0 or an integer from 1 to 6;

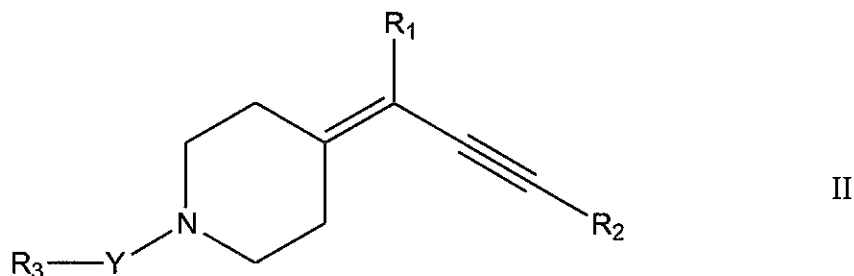
30

with the proviso that if Z represents a group of the formula -C=C-R₂ then R₁ represents a halogen atom and oxo and hydroxy are excluded from the optional substituents.

Enantiomers, diastereomers, N-oxides and pharmaceutically acceptable salts of the compounds I are included within the invention.

Preferred compounds according to the invention are those in which Z represents a group of the formula $-\text{C}\equiv\text{C}-\text{R}_2$.

Also preferred are compounds in which m is 1 and n is 1. Combining these preferences with the preferred group Z, one has the following compounds II



as most preferred.

The compounds of the invention are mGlu5 antagonists useful in the treatment of neuromuscular dysfunction of the lower urinary tract, migraine and in gastroesophageal reflux disease (GERD) in mammals. In jurisdictions in which methods of treatment of humans and animals are considered patentable, the invention extends to methods for the treatment of neuromuscular dysfunction of the lower urinary tract, for the treatment of migraine and for the treatment of gastroesophageal reflux disease (GERD) in mammals.

Y preferably represents a group of the formula $-\text{C}(\text{O})-$, $-\text{NH}-\text{C}(\text{O})-$, $-\text{N}(\text{C}_1-\text{C}_6 \text{ alkyl})-\text{C}(\text{O})-$, $-\text{O}-\text{C}(\text{O})-$, $-\text{NH}-\text{C}(\text{S})-$ or $-\text{SO}_2-$ or is absent.

R_1 preferably represents a hydrogen or fluorine atom or a methyl, phenyl, hydroxy, methoxy, methoxycarbonyloxy, dimethylamino or piperidino group. When Z represents a group of the formula $-\text{C}=\text{C}-\text{R}_2$, R_1 preferably represents a hydrogen or fluorine atom or a methyl group.

R_2 preferably represents

- an optionally substituted mono or bicyclic C_1-C_9 heterocyclic group containing from 1 to 3 heteroatoms chosen from nitrogen, oxygen and sulphur,
 - an optionally substituted phenyl group,
 - an optionally substituted C_1-C_6 alkyl group,
 - an optionally substituted C_2-C_6 alkenyl group,
 - an optionally substituted C_3-C_6 cycloalkyl group,
- or a group $-\text{C}(\text{O})-\text{R}_{2\text{A}}$ wherein $\text{R}_{2\text{A}}$ is as defined as R_2 above.

More preferably, R_2 represents an optionally substituted pyrrolidinyl, thiazolyl, pyridyl, quinolyl, quinoxalinyll or phenyl group, the substituents for each optionally

substituted group being a fluorine, chlorine or bromine atom or an oxo, nitro, cyano, cyanomethyl, acetyl, methyl, methoxy, ethoxy, isopropoxy, trifluoromethyl, trifluoromethoxy, acetamino, 2,2-dimethylpropanoylamino, 3,3-dimethyl-2-oxo-1-azetidiny, 1-pyrrolidinylmethyl, 1H-pyrazol-1-yl, 3-methyl-1,2,4-oxadiazol-5-yl or morpholino group. Particularly preferred amongst this group are compounds in which R₂ represents a pyridyl or phenyl group substituted with a fluorine atom and/or a methyl group, further substituents being optional.

Most preferably, R₂ represents a 6-methyl-2-pyridyl, 5-cyano-2-pyridyl, 3-fluorophenyl, 2,5-difluorophenyl group or 3,5-difluorophenyl group.

10 R₃ preferably represents

- a C₁-C₆ alkyl group substituted with an optionally substituted group A,
- an optionally substituted mono- or bicyclic C₁-C₉ heterocyclic group containing 1 to 3 heteroatoms chosen from nitrogen, oxygen and sulphur,
- an optionally substituted phenyl group,
- 15 • an optionally substituted C₃-C₆ cycloalkyl group, or
- an optionally substituted C₃-C₆ cycloalkenyl group.

More preferably R₃ represents a mono- or bicyclic C₁-C₉ heterocyclic group containing 1 to 3 heteroatoms chosen from nitrogen, oxygen and sulphur and at least 2 adjacent carbon atoms, one of which is bonded to the nitrogen atom of the illustrated nitrogen containing ring (Y being absent) and the other of which bears a cyano or nitro substituent, further substituents being optional.

Alternatively R₃ may represent an optionally substituted pyrrolidinyl, pyrazolyl, imidazolyl, 1,2,4-triazolyl, isoxazolyl, furyl, thienyl, pyridyl, piperidyl, pyrazinyl, pyrimidinyl, morpholinyl, imidazo[2,1-b]thiazolyl, indolyl, isoindolyl, imidazo[1,2-a]pyridyl, 1,2,3-benzotriazolyl, quinolyl, isoquinolyl, quinoxaliny, pyrido[2,3-b]pyrazinyl, 1,4-benzoxazinyl or phenyl group, the substituents for each optionally substituted group being a fluorine, chlorine, bromine or iodine atom or a methyl, isopropyl, methoxy, ethoxy, propoxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, acetyl, acetamino, phenyl, benzyloxy, phenylcarbamoyl, 4-fluorophenyl, 3-fluoro-4-methylphenyl, 2-furyl, 2-thienyl, 4-pyridyl, piperidino, 2-pyrimidinyl, 2-pyrimidinylloxy, 1,3-thiazol-2-yl, 2-methyl-1,3-thiazol-4-yl, 2-oxo-pyrrolidin-1-yl, 5-methyl-1,2,4-oxadiazol-3-yl, 2,5-dimethyl-1H-pyrrol-1-yl group.

Most preferably R₃ represents a 6-methyl-3-nitro-2-pyridyl, 6-methyl-3-cyano-2-pyridyl, 4-methoxy-3-cyano-2-pyridyl, 3-cyano-2-thienyl, or 3-cyano-2-pyrazinyl group.

The most preferred compounds according to the invention are those prepared in the Examples hereinbelow.

The selectivity of the compounds of the invention may be measured by

- (a) individually measuring the binding affinity of a test compound for the mGlu5 receptor, mGlu1 receptor and Group II mGlu receptors;
- (b) identifying those test compounds that:
 - (1) bind to a mGlu5 receptor with an affinity of at least 10^{-6} M, and
 - (2) bind to a mGlu5 receptor with an affinity at least 10-fold stronger than the affinity for the mGlu1 receptor and Group II mGlu receptors.
- (c) individually measuring the ability of each of the compounds identified in step (b) to act as an antagonist or inverse agonist at the mGlu5 receptor.

Preferably, the activity of compounds identified in steps (a), (b), and (c) above is confirmed by evaluating the activity of the compound in treatment of lower urinary tract disease in humans or an animal model system. More preferably the compounds identified exhibit activity in increasing bladder volume capacity in conscious rats.

The term "salts" can include acid addition salts or addition salts of free bases. Preferably, the salts are pharmaceutically acceptable. Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include, but are not limited to, salts derived from nontoxic inorganic acids such as nitric, phosphoric, sulphuric, or hydrobromic, hydroiodic, hydrofluoric, phosphorous, as well as salts derived from nontoxic organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxyl alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulphonic acids, and acetic, maleic, succinic, or citric acids. Non-limiting examples of such salts include napadisylate, besylate, sulphate, pyrosulphate, bisulphate, sulphite, bisulphite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulphonate, toluenesulphonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulphonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge, *et al.* "Pharmaceutical Salts," *J. Pharm. Sci.* 1977;66:1).

Typically, a pharmaceutically acceptable salt of a compound I may be readily prepared by using a desired acid or base as appropriate. The salt may precipitate from

solution and be collected by filtration or may be recovered by evaporation of the solvent. For example, an aqueous solution of an acid such as hydrochloric acid may be added to an aqueous suspension of a compound I and the resulting mixture evaporated to dryness (lyophilized) to obtain the acid addition salt as a solid. Alternatively, a compound I may be dissolved in a suitable solvent, for example an alcohol such as isopropanol, and the acid may be added in the same solvent or another suitable solvent. The resulting acid addition salt may then be precipitated directly, or by addition of a less polar solvent such as diisopropyl ether or hexane, and isolated by filtration.

The acid addition salts of the compounds I may be prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine.

The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid.

Compounds of the invention may have both a basic and an acidic center and therefore be in the form of zwitterions.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates of the compound of the invention are within the scope of the invention. The salts of the compounds I may form solvates (*e.g.*, hydrates) and the invention also includes all such solvates. The meaning of the word "solvates" is well known to those skilled in the art as a compound formed by interaction of a solvent and a solute (*i.e.*, solvation). Techniques for the preparation of solvates are well

established in the art (see, for example, Brittain. *Polymorphism in Pharmaceutical solids*. Marcel Decker, New York, 1999.).

Compounds I can exist in racemic mixtures or in any other combination. Racemic mixtures can be subjected to methods for enantiomeric enrichment, to yield compositions enriched in a particular enantiomer, or resolved to a composition comprising a single enantiomer.

Purification of complex mixtures of diastereomers into enantiomers typically requires two steps. In a first step, the mixture of diastereomers is resolved into enantiomeric pairs. In a second step, enantiomeric pairs are further purified into compositions enriched for one or the other enantiomer or, more preferably resolved into compositions comprising pure enantiomers. Resolution of enantiomers typically requires reaction or molecular interaction with a chiral agent, *e.g.*, solvent or column matrix. Resolution may be achieved, for example, by converting the mixture of enantiomers, *e.g.*, a racemic mixture, into a mixture of diastereomers by reaction with a pure enantiomer of a second agent, *i.e.*, a resolving agent. The two resulting diasteromeric products can then be separated. The separated diastereomers are then reconverted to the pure enantiomers by reversing the initial chemical transformation.

Resolution of enantiomers can also be accomplished by differences in their non-covalent binding to a chiral substance, *e.g.*, by chromatography on homochiral adsorbants. The noncovalent binding between enantiomers and the chromatographic adsorbant establishes diastereomeric complexes, leading to differential partitioning in the mobile and bound states in the chromatographic system. The two enantiomers therefore move through the chromatographic system, *e.g.*, column, at different rates, allowing for their separation.

Chiral resolving columns are well known in the art and are commercially available (*e.g.*, from MetaChem Technologies Inc., a division of ANSYS Technologies, Inc., Lake Forest, CA). Enantiomers can be analyzed and purified using, for example, chiral stationary phases (CSPs) for HPLC. Chiral HPLC columns typically contain one form of an enantiomeric compound immobilized to the surface of a silica packing material.

D-phenylglycine and L-leucine are examples of Type I CSPs and use combinations of π - π interactions, hydrogen bonds, dipole-dipole interactions, and steric interactions to achieve chiral recognition. To be resolved on a Type I column, analyte enantiomers must contain functionality complementary to that of the CSP so that the analyte undergoes essential interactions with the CSP. The sample should preferably contain one of the following functional groups: π -acid or π -base, hydrogen bond donor and/or acceptor, or an

amide dipole. Derivatization is sometimes used to add the interactive sites to those compounds lacking them. The most common derivatives involve the formation of amides from amines and carboxylic acids.

The MetaChiral ODM™ is an example of a type II CSP. The primary mechanisms for the formation of solute-CSP complexes is through attractive interactions, but inclusion complexes also play an important role. Hydrogen bonding, π - π interactions, and dipole stacking are important for chiral resolution on the MetaChiral™ ODM. Derivatization maybe necessary when the solute molecule does not contain the groups required for solute-column interactions. Derivatization, usually to benzylamides, may be required for some strongly polar molecules like amines and carboxylic acids, which would otherwise interact strongly with the stationary phase through non-specific-stereo interactions.

Compounds of formula I can be separated into diastereomeric pairs by, for example, separation by column chromatography or TLC on silica gel. These diastereomeric pairs are referred to herein as diastereomer with upper TLC Rf; and diastereomer with lower TLC Rf. The diastereomers can further be enriched for a particular enantiomer or resolved into a single enantiomer using methods well known in the art, such as those described herein.

The relative configuration of the diastereomeric pairs can be deduced by the application of theoretical models or rules (*e.g.*, Cram's rule, the Felkin-Ahn model) or using more reliable three-dimensional models generated by computational chemistry programs. In many instances, these methods are able to predict which diastereomer is the energetically favored product of a chemical transformation. As an alternative, the relative configuration of the diastereomeric pairs can be indirectly determined by discovering the absolute configurations of a single enantiomer in one (or both) of the diastereomeric pair(s).

The absolute configuration of the stereocenters can be determined by very well known method to those skilled in the art (*e.g.*, X-Ray diffraction, circular dichroism). Determination of the absolute configuration can be useful also to confirm the predictability of theoretical models and can be helpful to extend the use of these models to similar molecules prepared by reactions with analogous mechanisms (*e.g.*, ketone reductions and reductive amination of ketones by hydrides).

The present invention also encompasses stereoisomers of the syn-anti type, and mixtures thereof encountered when is a double bond and R₂ is an alkyl group and/or m is not 1. The group of highest Cahn-Ingold-Prelog priority attached to one of the terminal doubly bonded atoms of the oxime, is compared with hydroxyl group of the oxime. The stereoisomer is designated as *Z* (*zusammen* = together) or *Syn* if the oxime hydroxyl lies on

the same side of a reference plane passing through the C=N double bond as the group of highest priority; the other stereoisomer is designated as *E* (*entgegen* = opposite) or *Anti*.

The invention also encompasses pro-drugs of the compounds I, *i.e.*, compounds which release an active parent drug according to formula I *in vivo* when administered to a mammalian subject. A pro-drug is a pharmacologically active or more typically an inactive compound that is converted into a pharmacologically active agent by a metabolic transformation. Pro-drugs of compounds I are prepared by modifying functional groups present in the compounds I in such a way that the modifications may be cleaved *in vivo* to release the parent compound. *In vivo*, a pro-drug readily undergoes chemical changes under physiological conditions [*e.g.*, are acted on by naturally occurring enzyme(s)] resulting in liberation of the pharmacologically active agent. Pro-drugs include compounds I wherein a hydroxy, amino, or carboxy group is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxy, amino or carboxy group, respectively. Examples of pro-drugs include, but are not limited to esters (*e.g.*, acetate, formate, and benzoate derivatives) of compounds I or any other derivative which upon being brought to the physiological pH or through enzyme action is converted to the active parent drug. Conventional procedures for the selection and preparation of suitable pro-drug derivatives are described in the art (see, for example, Bundgaard. Design of Pro-drugs. Elsevier, 1985).

Pro-drugs may be administered in the same manner as the active ingredient to which they convert or they may be delivered in a reservoir form, *e.g.*, a transdermal patch or other reservoir which is adapted to permit (by provision of an enzyme or other appropriate reagent) conversion of a pro-drug to the active ingredient slowly over time, and delivery of the active ingredient to the patient.

The present invention also encompasses metabolites. "Metabolite" of a compound disclosed herein is a derivative of a compound which is formed when the compound is metabolised. The term "active metabolite" refers to a biologically active derivative of a compound which is formed when the compound is metabolised. The term "metabolised" refers to the sum of the processes by which a particular substance is changed in the living body. In brief, all compounds present in the body are manipulated by enzymes within the body in order to derive energy and/or to remove them from the body. Specific enzymes produce specific structural alterations to the compound. For example, cytochrome P450 catalyses a variety of oxidative and reductive reactions while uridine diphosphate glucuronyltransferases catalyse the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulphhydryl groups.

Further information on metabolism may be obtained from *The Pharmacological Basis of Therapeutics*, 9th Edition, McGraw-Hill (1996), pages 11-17.

Metabolites of the compounds disclosed herein can be identified either by administration of compounds to a host and analysis of tissue samples from the host, or by
5 incubation of compounds with hepatic cells *in vitro* and analysis of the resulting compounds. Both methods are well known in the art.

Brief Description of the Drawings

Figure 1 is a plot showing the time course of the effect on rat bladder volume
10 capacity of the compound of Example 1, administered at 1 and 3 mg/kg, orally, vs vehicle treated controls.

Figure 2 is a plot showing the time course of the effect on rat bladder volume capacity of the compound of Example 10, administered at 0.3 and 1 mg/kg, orally, vs vehicle treated controls.

15 Figure 3 is a plot showing the time course of the effect on rat bladder volume capacity of the reference compound, MTEP, administered at 1 and 3 mg/kg, orally, vs vehicle treated controls.

Lower-Urinary Tract Disorders

20 The nomenclature of lower urinary tract symptoms and pathologies used herein is set forth in Abrams et al., *Neurol. and Urodyn.* 21:167-178 (2002) and Andersson et al., *Pharmacol. Rev.* 56:581-631 (2004).

Voiding dysfunctions can be roughly classified as disturbances of storage or emptying. Storage symptoms are experienced during the storage phase of the bladder, and
25 include increased daytime frequency, nocturia (the waking at night one or more times to void), urgency (a sudden, compelling desire to pass urine that is difficult to defer), and urinary incontinence (the any involuntary leakage of urine). Urinary incontinence may be further characterized according to symptoms. Stress urinary incontinence is the involuntary leakage on effort or exertion, or on sneezing or coughing. Urge urinary incontinence is the
30 involuntary leakage of urine accompanied by or immediately preceded by urgency. Mixed urinary incontinence is the involuntary leakage of urine associated with urgency and also with exertion, effort, sneezing or coughing. Overflow incontinence is the involuntary leakage of urine occurring after the bladder capacity has been exceeded, *e.g.*, from a failure

to empty. Enuresis also refers to any involuntary loss of urine. Nocturnal enuresis is the loss of urine occurring during sleep.

Voiding symptoms include slow stream, splitting or spraying of the urine stream, intermittent stream (intermittency, *i.e.*, the stopping and restarting of urine flow during micturition, hesitancy (difficulty in initiating micturition resulting in a delay in the onset of voiding after the individual is ready to pass urine), straining and terminal dribble (a prolonged final part of micturition, when the flow has slowed to a trickle/dribble).

Lower urinary tract disorders may further be categorized by a constellation of symptoms (*i.e.*, a syndrome) or by etiology. Individuals suffering from overactive bladder (OAB) syndrome, *e.g.*, typically suffer from symptoms of urgency, urge incontinence, increased daytime frequency or nocturia. OAB occurs as a result of detrusor muscle overactivity referred to as detrusor muscle instability. Detrusor muscle instability can arise from non-neurological abnormalities, such as bladder stones, muscle disease, urinary tract infection or drug side effects or can be idiopathic.

Neurogenic overactive bladder (or neurogenic bladder) is a type of overactive bladder which occurs as a result of detrusor muscle overactivity referred to as detrusor hyperreflexia, secondary to known neurological disorders. Patients with neurological disorders, such as stroke, Parkinson's disease, diabetes, multiple sclerosis, peripheral neuropathy, or spinal cord lesions often suffer from neurogenic overactive bladder.

Cystitis (including interstitial cystitis) is a lower urinary tract disorder of unknown etiology that predominantly affects young and middle-aged females, although men and children can also be affected. Symptoms of interstitial cystitis can include voiding symptoms, increased daytime frequency, urgency, nocturia or suprapubic or pelvic pain related to and relieved by voiding. Many interstitial cystitis patients also experience headaches as well as gastrointestinal and skin problems. In some cases, interstitial cystitis can also be associated with ulcers or scars of the bladder.

Prostatitis and prostatic dysuria are other lower urinary tract disorders that have been suggested to affect approximately 2-9% of the adult male population. Prostatitis is an inflammation of the prostate, and includes bacterial prostatitis (acute and chronic) and non-bacterial prostatitis. Acute and chronic bacterial prostatitis are characterized by inflammation of the prostate and bacterial infection of the prostate gland, usually associated with symptoms of pain, increased daytime frequency and/or urgency. Chronic bacterial prostatitis is distinguished from acute bacterial prostatitis based on the recurrent nature of the disorder. Chronic non-bacterial prostatitis is characterized by inflammation of the

prostate which is of unknown etiology accompanied by the presence of an excessive amount of inflammatory cells in prostatic secretions not currently associated with bacterial infection of the prostate gland, and usually associated with symptoms of pain, increased daytime frequency and/or urgency. Prostadynia is a disorder which mimics the symptoms of prostatitis absent inflammation of the prostate, bacterial infection of the prostate and elevated levels inflammatory cells in prostatic secretions. Prostadynia can be associated with symptoms of pain, increased daytime frequency and/or urgency.

Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate that is very common in men over 40 years of age. BPH is thought to be due to excessive cellular growth of both glandular and stromal elements of the prostate. Symptoms of BPH can include increased frequency, urgency, urge incontinence, nocturia, and voiding symptoms, including slow stream, splitting or spraying of the urine stream, intermittency, hesitancy, straining and terminal dribble.

Effective amounts of a compound I may be used for treating lower urinary tract disorders in a patient in need of such treatment. Treatment of lower urinary tract disorders includes treatment of storage symptoms or voiding symptoms. Treatment of lower urinary tract disorders also includes treatment of increased daytime frequency, nocturia, urgency, urinary incontinence, including urge incontinence, stress incontinence, mixed incontinence and overflow incontinence, enuresis, including nocturnal enuresis, slow stream, splitting or spraying of the urine stream, intermittency, hesitancy, straining and terminal dribble.

Treatment of lower urinary tract disorders also includes treatment of OAB syndrome, including treatment of one or more symptoms of urgency, urge incontinence, daytime frequency or nocturia.

Treatment of lower urinary tract disorders further encompasses treatment of any of the aforementioned conditions, symptoms and/or syndromes when caused by or associated with cystitis, including interstitial cystitis, prostatitis, BPH, neurological disorders, decreased urinary compliance (*i.e.*, decreased bladder storage capacity).

A compound I may be used to treat the involuntary passage of urine, *i.e.*, urinary incontinence, *e.g.*, urge incontinence, stress incontinence, mixed incontinence or overflow incontinence. Such urinary incontinence may be caused by and/or associated with OAB or BPH.

Pharmaceutical compositions

While it is possible that a compound I may be administered as the bulk substance, it is preferable to present the active ingredient in a pharmaceutical formulation, *e.g.*, wherein the agent is in admixture with a pharmaceutically acceptable carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

Accordingly, in one aspect, the invention also provides a pharmaceutical composition comprising a compound I, or an enantiomer, diastereomer, N-oxide or pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable carrier..

Compounds I may be used in combination with other therapies and/or active agents. Accordingly the invention provides, in a further aspect, a pharmaceutical composition comprising at least one compound I or a pharmaceutically acceptable derivative thereof, a second active agent and, optionally, a pharmaceutically acceptable carrier.

When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

The term "carrier" refers to a diluent, excipient, and/or vehicle with which an active compound is administered. The pharmaceutical compositions of the invention may contain combinations of more than one carrier. Such pharmaceutical carriers can be sterile liquids, such as water, saline solutions, aqueous dextrose solutions, aqueous glycerol solutions, and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or aqueous solution saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin, 18th Edition.

The compounds of the invention may be formulated for administration in any convenient way for use in human or veterinary medicine and the invention therefore includes within its scope pharmaceutical compositions comprising a compound of the invention adapted for use in human or veterinary medicine. Such compositions may be presented for use in a conventional manner with the aid of one or more suitable carriers. Acceptable carriers for therapeutic use are well-known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985). The choice of pharmaceutical carrier can be selected with regard to

the intended route of administration and standard pharmaceutical practice. The pharmaceutical compositions may comprise as, in addition to, the carrier any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), and/or solubilizing agent(s).

5 Preservatives, stabilizers, dyes and even flavoring agents may be provided in the pharmaceutical composition. Examples of preservatives include sodium benzoate, ascorbic acid and esters of p-hydroxybenzoic acid. Antioxidants and suspending agents may be also used.

10 The compounds of the invention may be milled using known milling procedures such as wet milling to obtain a particle size appropriate for tablet formation and for other formulation types. Finely divided (nanoparticulate) preparations of the compounds of the invention may be prepared by processes known in the art, for example see WO 02/00196 (SmithKline Beecham).

Routes of Administration and Unit Dosage Forms

15 The routes for administration (delivery) include, but are not limited to, one or more of: oral (*e.g.*, as a tablet, capsule, or as an ingestible solution), topical, mucosal (*e.g.*, as a nasal spray or aerosol for inhalation), nasal, parenteral (*e.g.*, by an injectable form), gastrointestinal, intraspinal, intraperitoneal, intramuscular, intravenous, intrauterine, intraocular, intradermal, intracranial, intratracheal, intravaginal, intracerebroventricular, 20 intracerebral, subcutaneous, ophthalmic (including intravitreal or intracameral), transdermal, rectal, buccal, epidural and sublingual.

 Therefore, the compositions of the invention include those in a form especially formulated for, *e.g.*, parenteral, oral, buccal, rectal, topical, implant, ophthalmic, nasal or genito-urinary use. In preferred embodiments, the pharmaceutical compositions of the 25 invention are formulated in a form that is suitable for oral delivery.

 There may be different composition/formulation requirements depending on the different delivery systems. It is to be understood that not all of the compounds need to be administered by the same route. Likewise, if the composition comprises more than one active component, then those components may be administered by different routes. By way 30 of example, the pharmaceutical composition of the present invention may be formulated to be delivered using a mini-pump or by a mucosal route, for example, as a nasal spray or aerosol for inhalation or ingestible solution, or parenterally in which the composition is formulated by an injectable form, for delivery, by, for example, an intravenous,

intramuscular or subcutaneous route. Alternatively, the formulation may be designed to be delivered by multiple routes.

Where the agent is to be delivered mucosally through the gastrointestinal mucosa, it should be able to remain stable during transit through the gastrointestinal tract; for example, it should be resistant to proteolytic degradation, stable at acid pH and resistant to the detergent effects of bile. For example, a compound I may be coated with an enteric coating layer. The enteric coating layer material may be dispersed or dissolved in either water or in a suitable organic solvent. As enteric coating layer polymers, one or more, separately or in combination, of the following can be used; *e.g.*, solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, cellulose acetate butyrate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating layer polymer(s). For environmental reasons, an aqueous coating process may be preferred. In such aqueous processes methacrylic acid copolymers are most preferred.

Where appropriate, the pharmaceutical compositions can be administered by inhalation, in the form of a suppository or pessary, topically in the form of a lotion, solution, cream, ointment or dusting powder, by use of a skin patch, orally in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavoring or coloring agents, or they can be injected parenterally, for example intravenously, intramuscularly or subcutaneously. For buccal or sublingual administration the compositions may be administered in the form of tablets or lozenges, which can be formulated in a conventional manner.

Pharmaceutical compositions of the present invention can be administered parenterally, *e.g.*, by infusion or injection. Where the composition of the invention is to be administered parenterally, such administration includes one or more of: intravenously, intraarterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or subcutaneously administering the agent; and/or by using infusion techniques. Pharmaceutical compositions suitable for injection or infusion may be in the form of a sterile aqueous solution, a dispersion or a sterile powder that contains the active ingredient, adjusted, if necessary, for preparation of such a sterile solution or dispersion suitable for infusion or injection. This preparation may optionally be encapsulated into liposomes. In all cases, the final preparation must be sterile, liquid, and

stable under production and storage conditions. To improve storage stability, such preparations may also contain a preservative to prevent the growth of microorganisms. Prevention of the action of micro-organisms can be achieved by the addition of various antibacterial and antifungal agents, *e.g.*, paraben, chlorobutanol, or ascorbic acid. In many cases isotonic substances are recommended, *e.g.*, sugars, buffers and sodium chloride to assure osmotic pressure similar to those of body fluids, particularly blood. Prolonged absorption of such injectable mixtures can be achieved by introduction of absorption-delaying agents, such as aluminium monostearate or gelatin.

Dispersions can be prepared in a liquid carrier or intermediate, such as glycerin, liquid polyethylene glycols, triacetin oils, and mixtures thereof. The liquid carrier or intermediate can be a solvent or liquid dispersive medium that contains, for example, water, ethanol, a polyol (*e.g.*, glycerol, propylene glycol or the like), vegetable oils, non-toxic glycerine esters and suitable mixtures thereof. Suitable flowability may be maintained, by generation of liposomes, administration of a suitable particle size in the case of dispersions, or by the addition of surfactants.

For parenteral administration, the compound is best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

Sterile injectable solutions can be prepared by mixing a compound of formulas I, II, or III with an appropriate solvent and one or more of the aforementioned carriers, followed by sterile filtering. In the case of sterile powders suitable for use in the preparation of sterile injectable solutions, preferable preparation methods include drying in vacuum and lyophilization, which provide powdery mixtures of the aldosterone receptor antagonists and desired excipients for subsequent preparation of sterile solutions.

The compounds according to the invention may be formulated for use in human or veterinary medicine by injection (*e.g.*, by intravenous bolus injection or infusion or via intramuscular, subcutaneous or intrathecal routes) and may be presented in unit dose form, in ampoules, or other unit-dose containers, or in multi-dose containers, if necessary with an added preservative. The compositions for injection may be in the form of suspensions, solutions, or emulsions, in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing, solubilizing and/or dispersing agents. Alternatively the

active ingredient may be in sterile powder form for reconstitution with a suitable vehicle, *e.g.*, sterile, pyrogen-free water, before use.

The compounds of the invention can be administered (*e.g.*, orally or topically) in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain
5 flavoring or coloring agents, for immediate-, delayed-, modified-, sustained-, pulsed-or controlled-release applications.

The compounds of the invention may also be presented for human or veterinary use in a form suitable for oral or buccal administration, for example in the form of solutions, gels, syrups, mouth washes or suspensions, or a dry powder for constitution with water or
10 other suitable vehicle before use, optionally with flavoring and coloring agents. Solid compositions such as tablets, capsules, lozenges, pastilles, pills, boluses, powder, pastes, granules, bullets or premix preparations may also be used. Solid and liquid compositions for oral use may be prepared according to methods well-known in the art. Such compositions may also contain one or more pharmaceutically acceptable carriers and
15 excipients which may be in solid or liquid form.

The tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycolate, croscarmellose sodium and certain complex silicates, and granulation binders such as
20 polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia.

Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

The compositions may be administered orally, in the form of rapid or controlled
25 release tablets, microparticles, mini tablets, capsules, sachets, and oral solutions or suspensions, or powders for the preparation thereof. In addition to the new solid-state forms of pantoprazole of the present invention as the active substance, oral preparations may optionally include various standard pharmaceutical carriers and excipients, such as binders, fillers, buffers, lubricants, glidants, dyes, disintegrants, odorants, sweeteners, surfactants,
30 mold release agents, antiadhesive agents and coatings. Some excipients may have multiple roles in the compositions, *e.g.*, act as both binders and disintegrants.

Examples of pharmaceutically acceptable disintegrants for oral compositions useful in the present invention include, but are not limited to, starch, pre-gelatinized starch, sodium starch glycolate, sodium carboxymethylcellulose, croscarmellose sodium, microcrystalline

cellulose, alginates, resins, surfactants, effervescent compositions, aqueous aluminum silicates and cross-linked polyvinylpyrrolidone.

Examples of pharmaceutically acceptable binders for oral compositions useful herein include, but are not limited to, acacia; cellulose derivatives, such as methylcellulose, carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose or hydroxyethylcellulose; gelatin, glucose, dextrose, xylitol, polymethacrylates, polyvinylpyrrolidone, sorbitol, starch, pre-gelatinized starch, tragacanth, xanthane resin, alginates, magnesium–aluminum silicate, polyethylene glycol or bentonite.

Examples of pharmaceutically acceptable fillers for oral compositions include, but are not limited to, lactose, anhydrolactose, lactose monohydrate, sucrose, dextrose, mannitol, sorbitol, starch, cellulose (particularly microcrystalline cellulose), dihydro- or anhydro-calcium phosphate, calcium carbonate and calcium sulphate.

Examples of pharmaceutically acceptable lubricants useful in the compositions of the invention include, but are not limited to, magnesium stearate, talc, polyethylene glycol, polymers of ethylene oxide, sodium lauryl sulphate, magnesium lauryl sulphate, sodium oleate, sodium stearyl fumarate, and colloidal silicon dioxide.

Examples of suitable pharmaceutically acceptable odorants for the oral compositions include, but are not limited to, synthetic aromas and natural aromatic oils such as extracts of oils, flowers, fruits (*e.g.*, banana, apple, sour cherry, peach) and combinations thereof, and similar aromas. Their use depends on many factors, the most important being the organoleptic acceptability for the population that will be taking the pharmaceutical compositions.

Examples of suitable pharmaceutically acceptable dyes for the oral compositions include, but are not limited to, synthetic and natural dyes such as titanium dioxide, beta-carotene and extracts of grapefruit peel.

Examples of useful pharmaceutically acceptable coatings for the oral compositions, typically used to facilitate swallowing, modify the release properties, improve the appearance, and/or mask the taste of the compositions include, but are not limited to, hydroxypropylmethylcellulose, hydroxypropylcellulose and acrylate-methacrylate copolymers.

Suitable examples of pharmaceutically acceptable sweeteners for the oral compositions include, but are not limited to, aspartame, saccharin, saccharin sodium, sodium cyclamate, xylitol, mannitol, sorbitol, lactose and sucrose.

Suitable examples of pharmaceutically acceptable buffers include, but are not limited to, citric acid, sodium citrate, sodium bicarbonate, dibasic sodium phosphate, magnesium oxide, calcium carbonate and magnesium hydroxide.

5 Suitable examples of pharmaceutically acceptable surfactants include, but are not limited to, sodium lauryl sulphate and polysorbates.

10 Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the agent may be combined with various sweetening or flavoring agents, coloring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

The compounds of the invention may also, for example, be formulated as suppositories *e.g.*, containing conventional suppository bases for use in human or veterinary medicine or as pessaries *e.g.*, containing conventional pessary bases.

15 The compounds according to the invention may be formulated for topical administration, for use in human and veterinary medicine, in the form of ointments, creams, gels, hydrogels, lotions, solutions, shampoos, powders (including spray or dusting powders), pessaries, tampons, sprays, dips, aerosols, drops (*e.g.*, eye ear or nose drops) or pour-ons.

20 For application topically to the skin, the agent of the present invention can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate
25 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, and water. Such compositions may also contain other pharmaceutically acceptable excipients, such as polymers, oils, liquid carriers, surfactants, buffers, preservatives, stabilizers, antioxidants, moisturizers, emollients, colorants, and odorants.

30 Examples of pharmaceutically acceptable polymers suitable for such topical compositions include, but are not limited to, acrylic polymers; cellulose derivatives, such as carboxymethylcellulose sodium, methylcellulose or hydroxypropylcellulose; natural polymers, such as alginates, tragacanth, pectin, xanthan and cytosan.

Examples of suitable pharmaceutically acceptable oils which are so useful include but are not limited to, mineral oils, silicone oils, fatty acids, alcohols, and glycols.

Examples of suitable pharmaceutically acceptable liquid carriers include, but are not limited to, water, alcohols or glycols such as ethanol, isopropanol, propylene glycol, hexylene glycol, glycerol and polyethylene glycol, or mixtures thereof in which the pseudopolymorph is dissolved or dispersed, optionally with the addition of non-toxic anionic, cationic or non-ionic surfactants, and inorganic or organic buffers.

Suitable examples of pharmaceutically acceptable preservatives include, but are not limited to, various antibacterial and antifungal agents such as solvents, for example ethanol, propylene glycol, benzyl alcohol, chlorobutanol, quaternary ammonium salts, and parabens (such as methyl paraben, ethyl paraben, propyl paraben, etc.).

Suitable examples of pharmaceutically acceptable stabilizers and antioxidants include, but are not limited to, ethylenediaminetetraacetic acid (EDTA), thiourea, tocopherol and butyl hydroxyanisole.

Suitable examples of pharmaceutically acceptable moisturizers include, but are not limited to, glycerine, sorbitol, urea and polyethylene glycol.

Suitable examples of pharmaceutically acceptable emollients include, but are not limited to, mineral oils, isopropyl myristate, and isopropyl palmitate.

The compounds may also be dermally or transdermally administered, for example, by use of a skin patch.

For ophthalmic use, the compounds can be formulated as micronized suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride.

As indicated, the compounds of the present invention can be administered intranasally or by inhalation and is conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurized container, pump, spray or nebulizer with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134AT) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA), carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container, pump, spray or nebulizer may contain a solution or suspension of the active compound, *e.g.*, using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, *e.g.*, sorbitan trioleate.

Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound and a suitable powder base such as lactose or starch.

5 For topical administration by inhalation the compounds according to the invention may be delivered for use in human or veterinary medicine via a nebulizer.

The pharmaceutical compositions of the invention may contain from 0.01 to 99% weight per volume of the active material. For topical administration, for example, the composition will generally contain from 0.01-10%, more preferably 0.01-1% of the active material.

10 The active agents can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

15 The pharmaceutical composition or unit dosage forms comprising an effective amount of the present invention may be administered to an animal, preferably a human, in need of treatment of neuromuscular dysfunction of the lower urinary tract described by E. J. McGuire in "Campbell's UROLOGY", 5th Ed., 616-638, 1986, W.B. Saunders Company.

20 As used herein, the term "effective amount" refers to an amount that results in measurable amelioration of at least one symptom or parameter of a specific disorder. In a preferred embodiment, the compound treats disorders of the urinary tract, such as urinary urgency, overactive bladder, increased urinary frequency, reduced urinary compliance (reduced bladder storage capacity), cystitis (including interstitial cystitis), incontinence, urine leakage, enuresis, dysuria, urinary hesitancy and difficulty in emptying the bladder. In another preferred embodiment the compound treats migraine. In other preferred
25 embodiment the compound is used to treat GERD.

The pharmaceutical composition or unit dosage form of the present invention may be administered according to a dosage and administration regimen defined by routine testing in the light of the guidelines given above in order to obtain optimal activity while minimizing toxicity or side effects for a particular patient. However, such fine tuning of the
30 therapeutic regimen is routine in the light of the guidelines given herein.

The dosage of the active agents of the present invention may vary according to a variety of factors such as underlying disease conditions, the individual's condition, weight, sex and age, and the mode of administration. An effective amount for treating a disorder can easily be determined by empirical methods known to those of ordinary skill in the art,

for example by establishing a matrix of dosages and frequencies of administration and comparing a group of experimental units or subjects at each point in the matrix. The exact amount to be administered to a patient will vary depending on the state and severity of the disorder and the physical condition of the patient. A measurable amelioration of any symptom or parameter can be determined by a person skilled in the art or reported by the patient to the physician. It will be understood that any clinically or statistically significant attenuation or amelioration of any symptom or parameter of urinary tract disorders is within the scope of the invention. Clinically significant attenuation or amelioration means perceptible to the patient and/or to the physician.

For example, a single patient may suffer from several symptoms of dysuria simultaneously, such as, for example, urgency and excessive frequency of urination or both, and these may be reduced using the methods of the present invention. In the case of incontinence, any reduction in the frequency or volume of unwanted passage of urine is considered a beneficial effect of the present method of treatment.

The amount of the agent to be administered can range between about 0.01 and about 25 mg/kg/day, preferably between about 0.1 and about 10 mg/kg/day and most preferably between 0.2 and about 5 mg/kg/day. It will be understood that the pharmaceutical formulations of the present invention need not necessarily contain the entire amount of the agent that is effective in treating the disorder, as such effective amounts can be reached by administration of a plurality of doses of such pharmaceutical formulations.

In a preferred embodiment of the present invention, the compounds I are formulated in capsules or tablets, preferably containing 10 to 200 mg of the compounds of the invention, and are preferably administered to a patient at a total daily dose of 10 to 300 mg, preferably 20 to 150 mg and most preferably about 50 mg, for relief of urinary incontinence and other dysfunctions.

A pharmaceutical composition for parenteral administration contains from about 0.01% to about 100% by weight of the active agents of the present invention, based upon 100% weight of total pharmaceutical composition.

Generally, transdermal dosage forms contain from about 0.01% to about 100% by weight of the active agents versus 100% total weight of the dosage form.

For treatment of lower urinary tract disorders, a compound I may be administered in combination with at least one compound of an additional class of therapeutic agents. Such additional class could be that of antimuscarinic drugs such as, without limitation, oxybutynin, tolterodine, darifenacin, solifenacin, trospium, fesoterodine and temiverine.

Combination therapy with at least one compound I may further include treatment with a selective or non selective COX inhibitor. Examples of COX inhibitors include, without limitations, ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, piroprofen, carprofen, tioxaprofen, suprofen, tiaprofenic acid, fluprofen, indomethacin, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, ibufenac, acetyl salicylic acid, piroxicam, tenoxicam, nabumetone, ketorolac, azapropazone, mefenamic acid, tolfenamic acid, diflunisal, acemetacin, fentiazac, clidanac, meclofenamic acid, flufenamic acid, niflumic acid, flufenisal, sudoxicam, etodolac, salicylic acid, benorylate, isoxicam, 2-fluoro- α -methyl[1,1'-biphenyl]-4-acetic acid 4-(nitrooxy)butyl ester (see Wenk et al. Europ. J. Pharmacol. 453, 319-324 (2002)), meloxicam, parecoxib, nimesulide.

Combination therapy with at least one compound I may further include treatment with an α 1-adrenergic antagonist. Preferred α 1-adrenergic antagonists suitable for administration in combination with mGlu5 antagonists are, for example, and without limitation, prazosin, doxazosin, terazosin, alfuzosin, silodosin, and tamsulosin. Additional α 1-adrenergic antagonists suitable for administration in combination with mGlu5 antagonists are described in US 5990114, US 6306861, US 6365591, US 6387909 and US 6403594.

Combination therapy with at least one compound I may further include treatment with a serotonin and/or noradrenaline reuptake inhibitor. Examples of serotonin and/or noradrenaline reuptake inhibitors include, without limitation, duloxetine, milnacipran, amoxapine, venlafaxine, des-venlafaxine, sibutramine, tesofensine and des-methylsibutramine.

In certain embodiments, a serotonin and/or noradrenaline reuptake inhibitor suitable for administration in combination with mGlu5 antagonists is a selective serotonin reuptake inhibitor (*i.e.*, an SSRI). In certain embodiments, a serotonin and/or noradrenaline reuptake inhibitors suitable for administration in combination with mGlu5 antagonists is a selective noradrenaline reuptake inhibitor (*i.e.*, a NARI).

The pharmaceutical composition or unit dosage form may be administered in a single daily dose, or the total daily dosage may be administered in divided doses. In addition, co-administration or sequential administration of another compound for the treatment of the disorder may be desirable. To this purpose, the combined active principles are formulated into a simple dosage unit.

For combination treatment where the compounds are in separate dosage formulations, the compounds can be administered concurrently, or each can be administered at staggered intervals. For example, the compound of the invention may be administered in the morning and the antimuscarinic compound may be administered in the evening, or vice versa. Additional compounds may be administered at specific intervals too. The order of administration will depend upon a variety of factors including age, weight, sex and medical condition of the patient; the severity and aetiology of the disorders to be treated, the route of administration, the renal and hepatic function of the patient, the treatment history of the patient, and the responsiveness of the patient. Determination of the order of administration may be fine-tuned and such fine-tuning is routine in the light of the guidelines given herein.

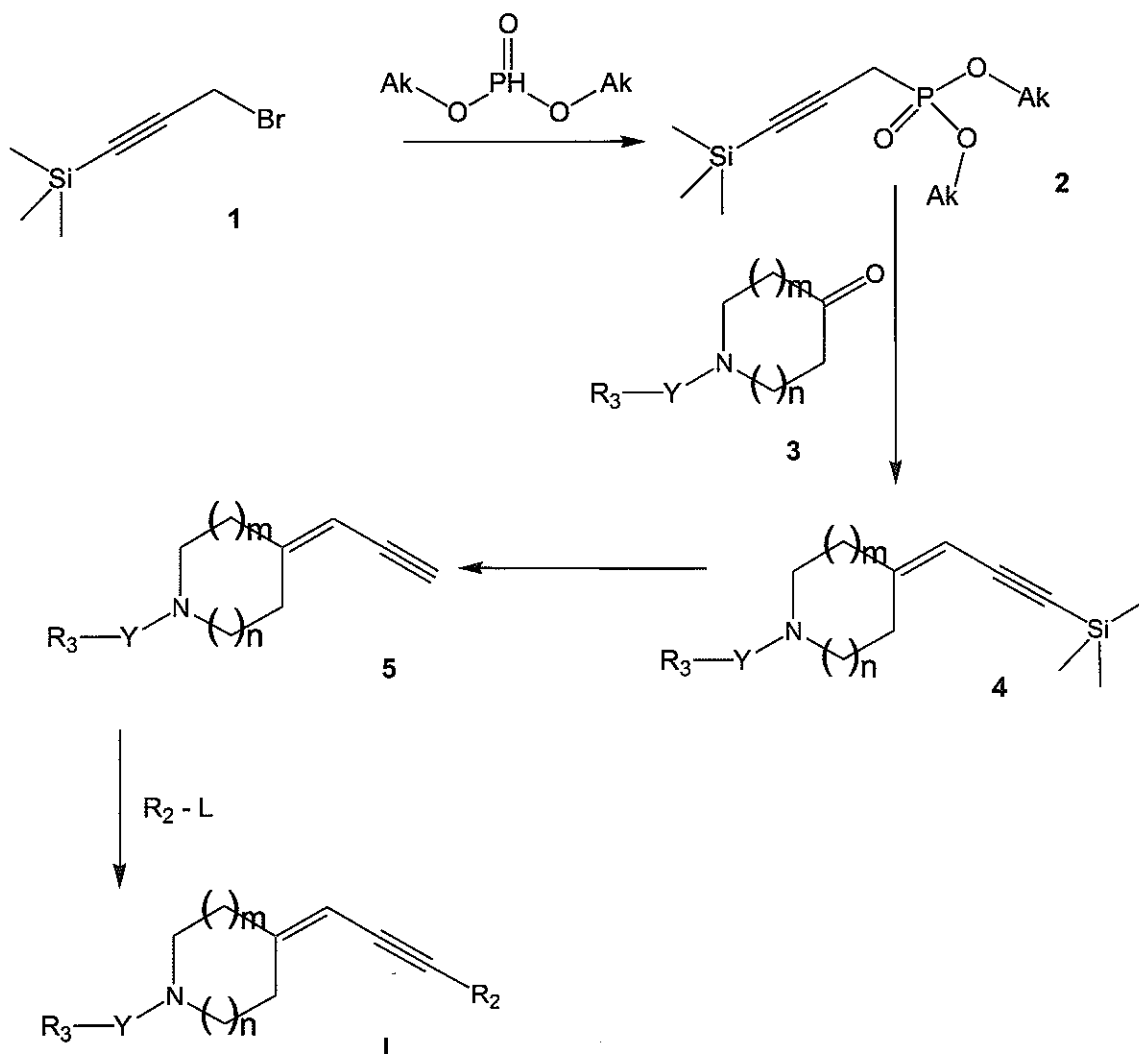
Synthesis of the Compounds of the Invention

It will be appreciated by those skilled in the art that it may be desirable to use protected derivatives of intermediates used in the preparation of the compounds I. Protection and deprotection of functional groups may be performed by methods known in the art (see, for example, Green and Wuts *Protective Groups in Organic Synthesis*. John Wiley and Sons, New York, 1999.). Hydroxy or amino groups may be protected with any hydroxy or amino protecting group. The amino protecting groups may be removed by conventional techniques. For example, acyl groups, such as alkanoyl, alkoxycarbonyl and aroyl groups, may be removed by solvolysis, *e.g.*, by hydrolysis under acidic or basic conditions. Arylmethoxycarbonyl groups (*e.g.*, benzyloxycarbonyl) may be cleaved by hydrogenolysis in the presence of a catalyst such as palladium-on-charcoal.

The synthesis of the target compounds is completed by removing any protecting groups which may be present in the penultimate intermediates using standard techniques, which are well-known to those skilled in the art. The deprotected final products are then purified, as necessary, using standard techniques such as silica gel chromatography, HPLC on silica gel and the like, or by recrystallization.

The compounds of the invention where R_1 is H are generally prepared according to the following schemes:

Scheme 1



In Scheme 1, Ak represents an alkyl group, L represents a leaving group and the remaining variables are as defined for the general formula I.

- 5 3-Bromo-1-trimethylsilyl-1-propyne (1) is added at a temperature of -10°C to 25°C to a solution of the pre-formed phosphanion generated in situ from an appropriate dialkyl phosphite (*e.g.* diethyl phosphite) treating with a base, preferably sodium or lithium *bis*-trimethylsilylamide, in an aprotic solvent, preferably THF or DME at a temperature between -50°C and 0°C. This procedure affords compound 2 (see also Gibson, A. W.;
 10 Humphrey, G. R.; Kennedy, D. J.; Wright, S. H. B.; *Synthesis* 1991 (5), 414).

- Compound 2 is then converted to the corresponding stabilized ylide by reaction with a base, preferably sodium or lithium *bis*-trimethylsilylamide (LiHMDS), in an aprotic solvent, preferably THF or DME at a temperature between -78°C and 0°C. This ylide is then reacted with the piperidones 3 in the same reaction vessel at -60 - 0°C affording
 15 compounds 4 (Gibson, A. W.; Humphrey, G. R.; Kennedy, D. J.; Wright, S. H. B.;

Synthesis 1991 (5), 414 or Boehmer, J.; Schobert, R.; J Chem Res, Synop, 1998, (7), 372-373).

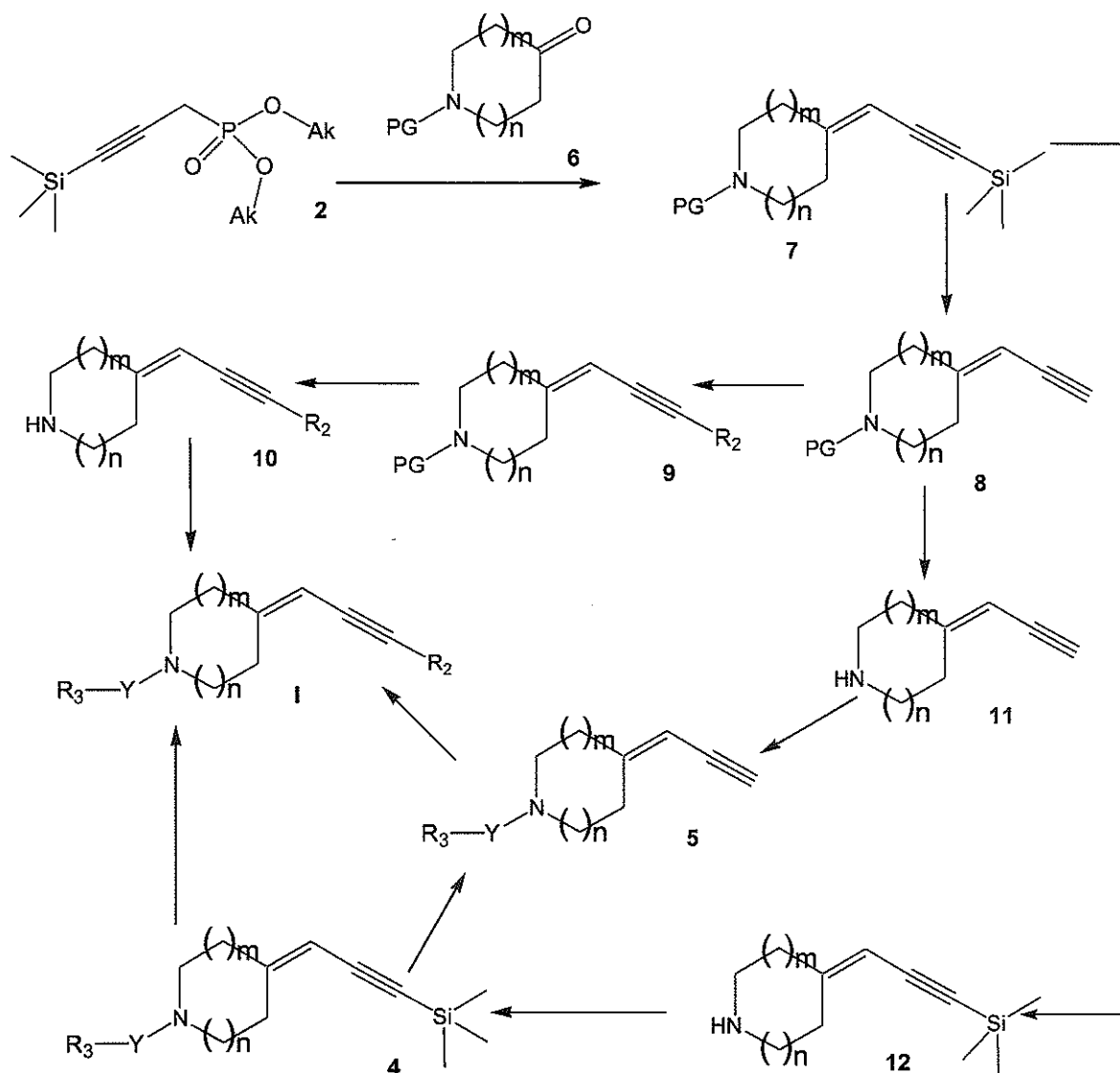
The acetylenic compounds **4** could be alternatively obtained by reacting the piperidones **3** with the ylide obtained from (3-trimethylsilyl-2-propynyl)-triphenylphosphonium bromide and *e.g.* BuLi in THF (Hann, M. M.; Sammes, P. G.; Kennewell, P. D.; Taylor, J. B.; J Chem Soc, Perkin Trans 1, 1982, 307 or Nicolaou, K. C.; Webber, S. E.; J Am Chem Soc 1984, 106, 5734) and reacting it in a similar way as above. Another suitable procedure consists in using (3-2-propynyl)triphenylarsonium bromide (Shen, Yanchang; Liao, Quimu; J. Organomet. Chem.; 346; 1988; 181-184) and generating the arsenic ylide with BuLi or other suitable base and reacting it with piperidones **3**.

The silyl protecting group of **4** is then removed by treatment with tetrabutylammonium fluoride in THF at a temperature in the range from ambient temperature to reflux or by hydrolysis with base (K_2CO_3 or KOH in MeOH) or other suitable method chosen from those reported in Greene-Wuts (Greene's Protective Groups in Organic Synthesis, 3rd Edition, Peter G. M. Wuts, Theodora W. Greene 1999, Wiley Interscience page 654-659) and well known by those skilled in the art. The so-obtained acetylenic compounds **5** are then transformed into compounds **I** by reacting them with R_2-L following the well known Sonogashira procedure (Science of Synthesis, H. Heaney and S. Christie, October 2003, Vol. 3, Page 402 and following), that uses cuprous iodide and a palladium complex chosen from $(Ph_3P)_2PdCl_2$, $(Ph_3P)_2Pd(OAc)_2$, $(Ph_3P)_4Pd$ (which can also be generated in situ *e.g.* from triphenylphosphine and $Pd(OAc)_2$) and all the other palladium complexes cited in the literature and used for this kind of reaction, in the presence of a base such as TEA, DEA, DIPEA, TMA, butylamine, piperidine. Solvents are chosen among THF, DME, DMF, DMA, EtOAc, DMSO, toluene and others suitable for the purpose of the reaction; or the same base in excess can be used as the reaction solvent. If one carries out the reaction in DMF or DME, the isolation of compounds **5** can be avoided by adding the tetrabutylammonium fluoride or tetrabutylammonium chloride directly to the reaction medium containing **4**, before the coupling (Sorensen, U.S., Pombo-Villar, E. Tetrahedron 2005, 61, 2697-2703). The R_2 substituents are introduced using aryl or heteroaryl halides (preferred in decreasing order iodide, bromide, chloride), aryl or heteroaryl triflates, alkyl halogenides or acyl chlorides, aroyl chlorides, heteroaroyl chlorides. Triflates are synthesized using very well known method to people who have skills in the art, *e.g.* from phenols or hydroxyaryls (heteroaryls) using trifluoromethanesulphonic anhydride in a chlorinated solvent or using N-phenyltriflimide in toluene or a chlorinated solvent in the

presence or not of a base (e.g. TEA). Both processes can be accelerated with the aid of microwaves performing the reaction in a microwave oven. Other suitable leaving groups L for R_2-L are nonaflates, tosylates and potassium trifluoroborates.

Piperidones **3** are commercially available or can be easily prepared from piperidones, with the keto group free or protected as ketal, following easy procedures of acylation, (thio)carbamoylation, reductive amination, alkylation, arylation at the basic nitrogen very well known to those skilled in the art and well documented in the literature.

Scheme 2



Scheme 2 represents a feasible and possible alternative to Scheme 1 for the obtention of compound I with $R_1 = H$. In Scheme 2, Ak represents an alkyl group, PG represents a protecting group and the remaining variables are as defined for the general formula I.

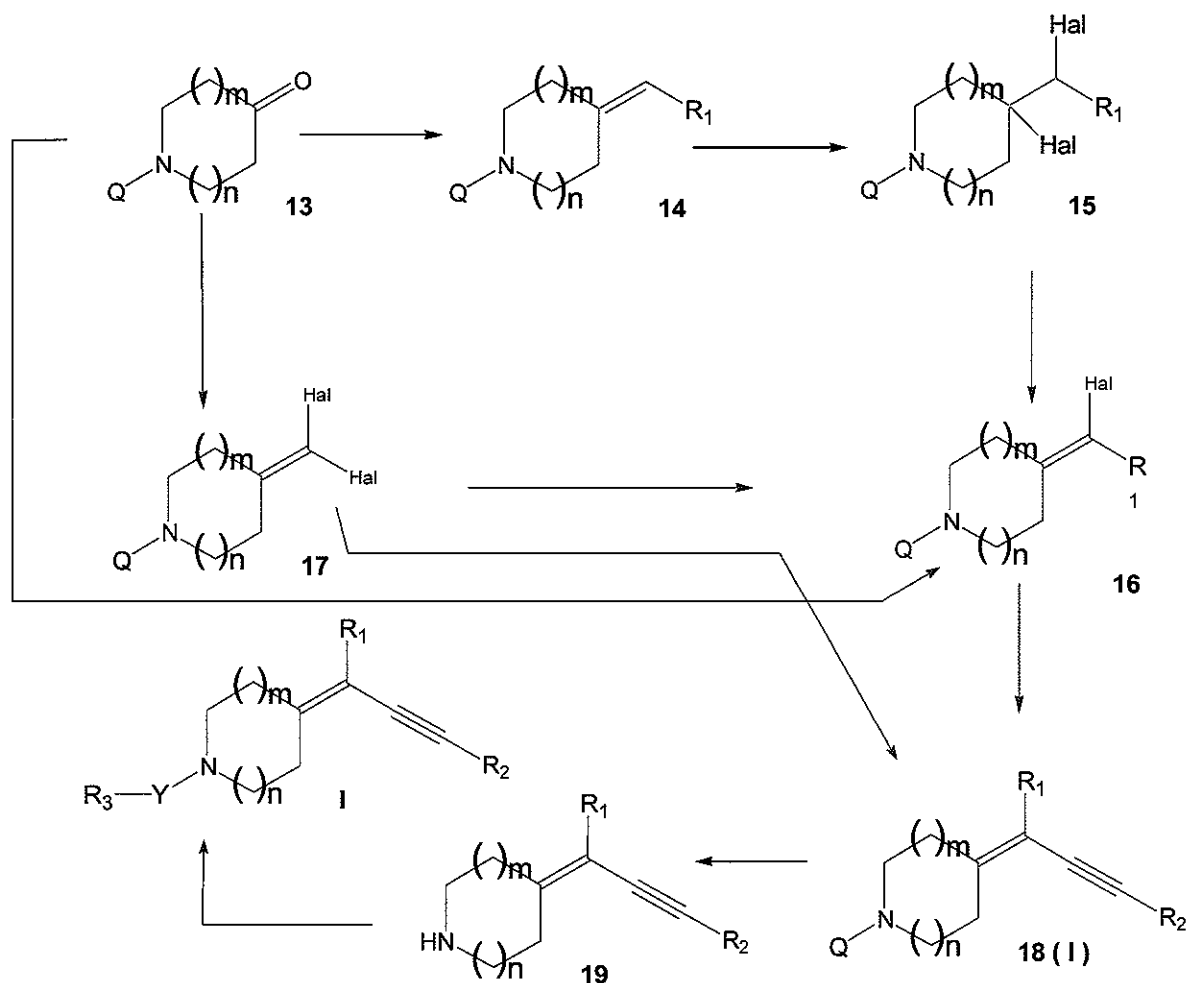
This synthetic path makes use of N-protected piperidones (commercially available or easily prepared by standard procedures), where PG is an appropriately chosen protective group such as t-butoxycarbonyl (Boc), fluorenylmethoxycarbonyl (Fmoc), benzyl (Bn), benzyloxycarbonyl (Z), trityl (Tr), arylsulphonyl or other. The protected piperidones **6** are
5 reacted by the same methods described for compounds **3** to afford compounds **7**, well designed derivatives provided with orthogonal protection. So, compounds **7** can be sequentially converted, as described above for Scheme 1, to compounds **8** and **9** and deprotected to **10**, following standard deprotection procedures chosen from those reported in Greene-Wuts (Greene's Protective Groups in Organic Synthesis, 3rd Edition, Peter G. M.
10 Wuts, Theodora W. Greene 1999, Wiley Interscience page 654-659). **10** are synthons useful for synthesizing by simple reaction procedures compounds **I** with a previously determined and fixed R₂ substituent.

Alternatively, compounds **8** can be further N-deprotected by known procedures to afford compounds **11**, which, on turn, are sequentially N-derivatized and subjected to the
15 acetylenic CH derivatization as described above for **5** in scheme 1.

Alternatively, selective deprotection of the N-PG groups of **7** leads to compounds **12**, which can be reacted as described above to provide compounds **4**, further derivatizable following scheme 1 to afford compounds **I**.

The compounds **I** of the invention where R₁ is as described in the general formula I
20 (H also included) can be generally prepared according to the following scheme 3:

Scheme 3



In Scheme 3, Q represents a protecting group or a group R₃-Y-, Hal represents a halogen atom and the remaining variables are as defined for the general formula I.

- 5 Compounds **14** can be obtained from **13** using standard olefination conditions such as Wittig, Horner-Hemmons, Petersen or arsenic based methodologies. Some general reviews of these methodologies and directions are contained in the following references: 'The Wittig reaction and related methods', N. J. Lawrence in Preparation of Alkenes, J. M. J. Williams, Ed., Oxford University Press, Oxford (1996); pp 19-58;
- 10 Phosphorus Ylides, O. I. Kolodiazhnyi, Wiley, N.Y. (1999); A. W. Johnson, Ylides and Imines of Phosphorus, Wiley, N.Y. (1993); Ager, D. J. *Org. React.* **1990**, 38, 1-223.

- When the reaction is conducted using a triphenylphosphonium salt, butyl lithium or LDA (lithium diisopropylamide) or LHMDS (lithium hexamethyldisilylamide) can be used to generate the phosphorus ylide in THF or other aprotic solvent (*e.g.* DME) and the ylide is
- 15 reacted with the proper piperidone to provide the desired product. The phosphinate, phosphine oxide or phosphonate based reagents could be used with similar bases or with

sodium or potassium methoxide or ethoxide in alcoholic solvents or with sodium hydride in aprotic solvents.

Compounds **14** are then easily converted to compounds **16**, usually without isolation of the intermediate dihaloderivatives **15**, carrying out first a dihalogenation of the olefinic bond (Br_2 , NCS, NBS or other reagents in a suitable solvent *e.g.* AcOH or a chlorinated solvent) then by dehydrohalogenation of compounds **15** by using a base (K_2CO_3 , DBU, DMAP or alike).

If one carries out on **13** the same olefination reactions as above using CHBr_3 or CBr_4 or CH_2Br_2 or CFBr_3 and triphenylphosphine (or other triarylphosphine bounded or not to a polymeric resin) in the presence or not of a catalyst like ZnBr_2 or diethylzinc, compounds **17** are easily obtained. Use of CBr_4 leads to the obtention of the 1,1-dibromovinyl derivative **17**, which can be reacted on turn with an organometallic species *e.g.* methylmagnesium bromide to give the derivative **16** ($\text{R}_1 = \text{Alkyl, Phenyl}$) or reacted with a strong organic base (*e.g.* BuLi or NaHMDS or alike) to generate the carbanion, which is on turn reacted with an electrophile (*e.g.* CH_3I) to afford **16** ($\text{R}_1 = \text{Alkyl, Phenyl}$).

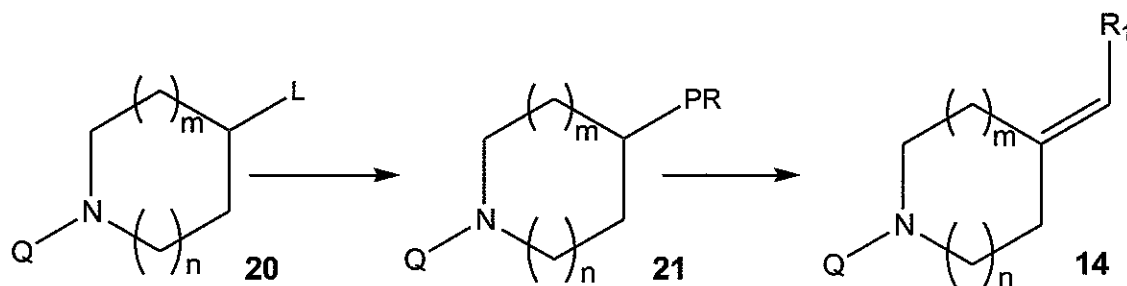
The use of an halomethylphosphorous reagent (*e.g.* chloromethyltriphenyl phosphonium chloride or diphenylchloromethylphenylphosphonate) leads, using the same methodologies described above for the Horner reaction, directly to compounds **16** starting from Compounds **13**.

An alternative methodology useful for executing the conversion of **13** to **17** concerns the use of CH_2Br_2 or CH_2I_2 or CH_2Cl_2 or CHI_3 in the presence of TiCl_4 and Magnesium or in the presence of a Titanium complex or with CrCl_2 .

Compounds **16** (or Compounds **17** where (Hal, Hal is fluorine plus iodide or fluorine plus bromide) are then reacted in a Sonogashira fashion (see above) to give Compounds **18** (**I**) with $\text{R}_1 = \text{F}$.

Compounds **18**, where Q is equal to PG (Protecting Group), must be submitted to a further deprotection step leading to Compounds **19**, as described above in Scheme 2. Compounds **19** can be properly converted into Compounds **I** with the standard procedures described above.

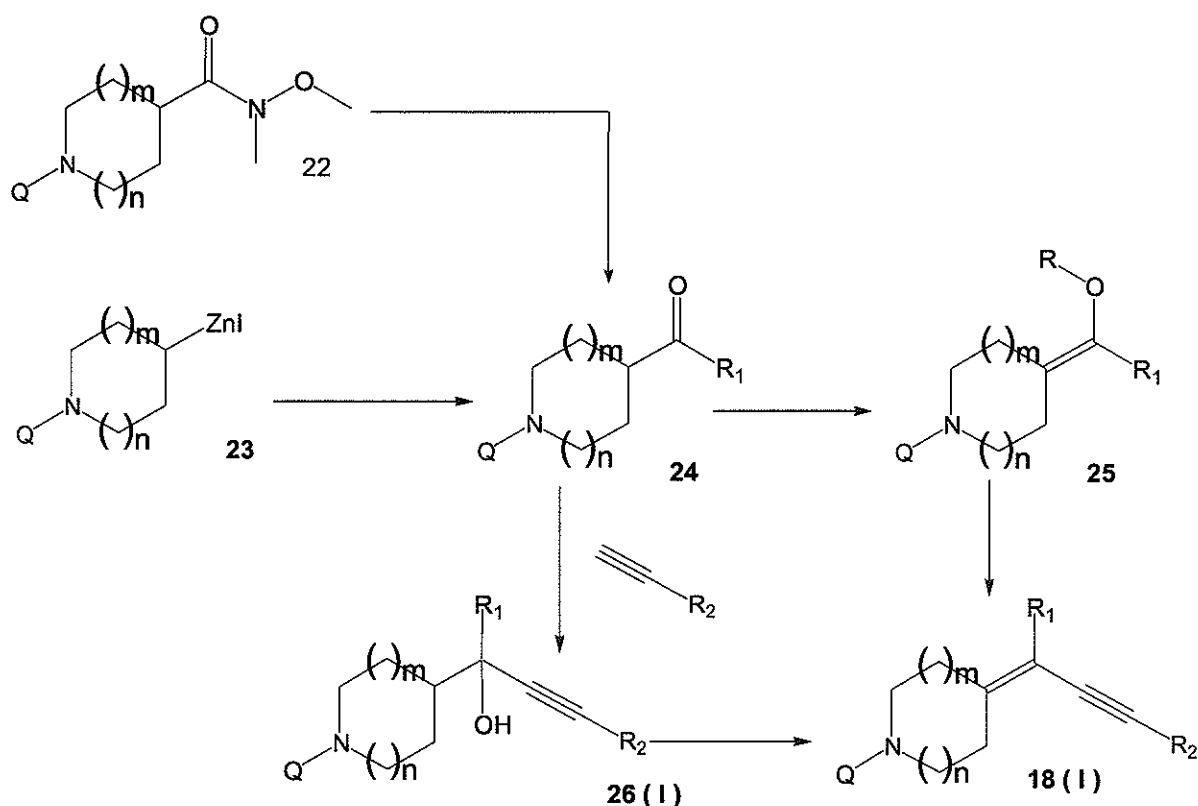
Scheme 4



In Scheme 4, L represents an appropriate leaving group (halogen, mesylate, tosylate or other), PR represents a Phosphorous containing residue (e.g. dialkoxyposphoryl or diphenoxyposphoryl or triphenylphosphinyl or triphenylarsinyl), Q represents a protecting group or a group R₃-Y-, R₁ represents an alkyl or phenyl group and the remaining variables are as defined for the general formula I.

Scheme 4 describes an alternative procedure for preparing compounds **14** with R₁ = alkyl or phenyl. In this method, compounds **20** (which are commercially available or easily prepared by standard procedures well known to those skilled in the art), are reacted following the Arbuzov procedure or other suitable method to generate phosphonium salts or phosphonates or other phosphorous intermediates, which in turn can be coupled with an alkyl aldehyde or benzaldehyde by a Wittig-Horner procedure to afford compounds **14** (R₁ = alkyl or phenyl).

Scheme 5



Scheme 5, in which PG represents a protecting group, Q represents a protecting group or a group R₃-Y- and the remaining variables are as defined for the general formula I, shows another synthetic opportunity to obtain compounds **18 (I)**. Easily prepared Weinreb's amides **22** (L. De Luca, G. Giacomelli, M. Taddei, *J. Org. Chem.*, 2001, 66, 2535-2537) can be reacted according to the well known methods, with Grignard's reagents or lithium reagents to afford ketones **24**. In the case where R₁=H compounds **24** are commercially available or are very easily synthesized from commercially available starting materials. The facile conversion to enol triflates or enol sulphonates **25** (R = CF₃SO₂, p-MePhSO₂) guarantees a good starting material for the following conversion to compounds **18 (I)** by Sonogashira coupling described above.

Alternatively compounds **23** (Corley, E. G. et al., *J Org Chem*, 69, (15), 2004, 5120-5123) can be reacted in a Palladium-catalyzed coupling with acyl chlorides to afford compounds **24**.

Compounds **24** can be also condensated with acetylenic compounds $R_2C\equiv CH$ using Lewis' acid methodologies or Aldol type reactions by the use of bases to afford compounds **26 (I)**, which can be on turn dehydrated to give Compounds **18 (I)**.

Compounds **18** and **26**, where Q is equal to PG (Protecting Group), must be submitted to a further deprotection step leading to N-deprotected compounds, as described above in Scheme 2. The so-obtained compounds can be properly N-derivatized to Compounds **I** with the standard procedures described above.

5

The syntheses of other compounds of the invention included in the Examples, which are not currently described in this general description of the synthesis of the compounds of the invention are well documented inside the experimental part of this invention.

10 The free bases of formula **I**, their diastereomers or enantiomers can be converted to the corresponding pharmaceutically acceptable salts under standard conditions well known in the art. For example, the free base is dissolved in a suitable organic solvent, such as methanol, treated with, for example one equivalent of maleic or oxalic acid, one or two equivalents of hydrochloric acid or methanesulphonic acid, and then concentrated under vacuum to provide the corresponding pharmaceutically acceptable salt. The residue can
15 then be purified by recrystallization from a suitable organic solvent or organic solvent mixture, such as methanol/diethyl ether.

The N-oxides of compounds of formula **I** can be synthesized by simple oxidation procedures well known to those skilled in the art.

20 Examples of the Invention.

The following examples illustrate the invention.

Example 1

1-(3-nitro-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

25

Diethyl (3-trimethylsilylprop-2-ynyl)phosphonate (Compound 1a)

Into a solution of LiHMDS (1M in THF, 63.8 ml, 63.8 mmol) in anhydrous THF (162 ml) was added dropwise under stirring at -10°C in nitrogen atmosphere diethyl phosphite (7.4 ml, 63.8 mmol). The obtained solution was stirred at the same temperature for 20 min..
30 Afterwards, 3-bromo-1-trimethylsilyl-1-propyne (10 ml, 63.8 mmol) was dropped into and the reaction mixture was stirred at -10°C for 2 h., then quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness *in vacuo* to afford 14.86 g of the title product. ¹H-NMR (CDCl₃, δ): conform to Feringa, Ben L. et al., Org. Biomol. Chem., Volume 3 (14), 2005, 2524-2533

MS: $[M+NH_4]^+ = 266.15$

1-(3-nitro-2-pyridyl)-4-(3-trimethylsilyl-prop-2-ynylidene)-piperidine (Compound 1b)

Into a solution of Compound 1a (0.68 g, 2.74 mmol) in anhydrous THF (15 ml) stirred at –
 5 60°C under N₂ stream, was dropped a solution of LiHMDS (1M in THF, 2.74 ml, 2.74
 mmol) and the mixture was stirred at –60°C for 15 min.. To the resulting solution was
 added dropwise a solution of 1-(3-nitro-2-pyridyl)-4-oxo-piperidine (0.55 g, 2.49 mmol) in
 anhydrous THF(12 ml). The reaction mixture was stirred at –60° for 15 min., then it was
 allowed to warm up to ambient temperature over 2 h.. Afterwards, it was quenched with
 10 water and extracted with EtOAc. The combined organic layers were washed with brine,
 dried on Na₂SO₄ and evaporated to dryness *in vacuo* to afford 0.79 g of the title product.
 The crude was pure enough to be used in the following step without any further purification
MS: $[M+H]^+ = 316.16$

15 1-(3-nitro-2-pyridyl)-4-(prop-2-ynylidene)-piperidine (Compound 1c)

A solution of Compound 1b (0.57 g, 1.81 mmol), tetra-*n*-butylammonium fluoride hydrate
 (0.57 g, 2.03 mmol) in 38 ml of THF was stirred at ambient temperature for 2 h. The
 reaction mixture was poured into water and extracted with EtOAc. The combined organic
 layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness *in vacuo* to
 20 afford a residue, which was purified by flash chromatography (EtOAc – Petroleum Ether 1 :
 9) giving the title product (0.21 g).

MS: $[M+H]^+ = 244.13$

1-(3-nitro-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

25 A mixture of Compound 1c (0.21 g, 0.86 mmol), 2-bromo-6-methylpyridine (0.11 ml, 0.95
 mmol), *tetrakis*(triphenylphosphine)palladium(0) (70 mg, 0.06 mmol), CuI (16 mg, 0.09
 mmol) in anhydrous and degassed triethylamine (10 ml) was heated at 80°C under a
 nitrogen atmosphere for 2 h in sealed vessel. The reaction mixture was cooled, poured into
 water and extracted with EtOAc. The combined organic layers were washed with brine,
 30 dried on Na₂SO₄ and evaporated to dryness *in vacuo* to afford a residue, which was purified
 by flash chromatography (EtOAc – Petroleum Ether 3.5 : 6.5) affording the title product
 (0.20 g).

¹H-NMR (CDCl₃δ): 2.48-2.55 (m, 2H), 2.61 (s, 3H), 2.80-2.85 (m, 2H), 3.50-3.58 (m, 4H), 5.66 (s, 1H), 6.75-6.80 (m, 1H), 7.09 (d, 1H, J = 7.46 Hz), 7.24-7.29 (m, 1H), 7.55 (t, 1H, J = 7.46 Hz), 8.14-8.19 (m, 1H), 8.35-8.38 (m, 1H)

MS: [M+H]⁺ = 335.12

5

Example 2

1-(t-butoxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

1-(t-butoxycarbonyl)-4-(3-trimethylsilyl-prop-2-ynylidene)-piperidine (Compound 2a)

10 The title compound was obtained following the procedure described for Compound 1b but using 1-(t-butoxycarbonyl)-4-oxo-piperidine instead of 1-(3-nitro-2-pyridyl)-4-oxo-piperidine. After the usual work-up procedure, evaporation of the combined EtOAc extracts afforded a crude which was enough pure to be used in the next step without further purification.

15 ¹H-NMR (CDCl₃δ): 0.21 (s, 9H), 1.50 (s, 9H), 2.21-2.27 (m, 2H), 2.48-2.53 (m, 2H), 3.40-3.51 (m, 4H), 5.40 (s, 1H)

MS: [M+H]⁺ = 294.29

1-(t-butoxycarbonyl)-4-(prop-2-ynylidene)-piperidine (Compound 2b)

20 The title compound was obtained following the procedure described for Compound 1c but using Compound 2a instead of Compound 1b. After the usual work-up procedure, evaporation of the combined EtOAc extracts afforded a crude which was pure enough to be used in the next step without further purification.

25 ¹H-NMR (CDCl₃δ): 1.50 (s, 9H), 2.20-2.27 (m, 2H), 2.48-2.53 (m, 2H), 3.02 (s, 1H), 3.40-3.51 (m, 4H), 5.48 (s, 1H)

MS: [M+H]⁺ = 222.23

1-(t-butoxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

30 The title compound was obtained following the procedure described for the Compound of Example 1, but starting from Compound 2b instead of Compound 1c. After the usual work-up procedure, evaporation of the combined EtOAc extracts afforded a crude which was purified by flash chromatography (EtOAc – Petroleum Ether 3.5 : 6.5) affording the title product.

¹H-NMR (*CDCl*₃δ): 1.50 (s, 9H), 2.29-2.35 (m, 2H), 2.58 (s, 3H), 2.59-2.65 (m, 2H), 3.45-3.55 (m, 4H), 5.60 (s, 1H), 7.09 (d, 1H, J = 7.51 Hz), 7.26(d, 1H, 7.51 Hz), 7.55 (t, 1H, J = 7.51 Hz)

MS: [M+H]⁺ = 313.27

5

Example 3

4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

To a solution of the compound of Example 2 (17 g, 54.4 mmol) in *CHCl*₃ (840 ml) was added trifluoroacetic acid (60 ml, 779 mmol) and the reaction mixture was then stirred at 10 70°C for 15 min. until the complete conversion of the reagent was observed by LC-MS. After cooling to ambient temperature, water was added followed by aq. NaOH (2N) to make alkaline the pH. Separation of the organic layer and extraction of the aqueous layer with *CH*₂*Cl*₂, washing with brine and drying over Na₂SO₄ afforded the title compound (11.6 g).

¹H-NMR (*CDCl*₃δ): 2.29-2.35 (m, 2H), 2.58 (s, 3H), 2.59-2.65 (m, 2H), 2.91-2.99 (m, 4H), 15 5.52 (s, 1H), 7.07 (d, 1H, J = 7.54 Hz), 7.24(d, 2H, 7.54 Hz), 7.53 (t, 1H, J = 7.54 Hz)

MS: [M+H]⁺ = 213.25

Example 4

1-(2-nitrophenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

20 A well homogenised mixture of the Compound of Example 3 (20 mg, 0.09 mmol) and 1-bromo-2-nitrobenzene (22.8 mg, 0.11 mmol) was stirred at 90°C for 0.5 h, then at 110°C for 1 h. The reaction crude was purified by flash chromatography (EtOAc – Petroleum Ether gradient from 3 : 7 to 4 : 6) affording the title product (8.3 mg).

¹H-NMR (*CDCl*₃δ): 2.50-2.55 (m, 2H), 2.61 (s, 3H), 2.82-2.87 (m, 2H), 3.11-3.16 (m, 2H), 25 3.16-3.21 (m, 2H), 5.62 (s, 1H), 7.03-7.16 (m, 2H), 7.19 (d, 1H, J = 7.51 Hz), 7.26-7.30 (m, 1H), 7.48 (t, 1H, J = 7.51 Hz), 7.52-7.64 (m, 1H), 7.81 (d, 1H)

MS: [M+H]⁺ = 334.30

Example 5

1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

30 A well homogenised mixture of the Compound of Example 3 (23 mg, 0.11 mmol) and 2-chloro-6-methyl-3-nitropyridine (26.2 mg, 0.15 mmol) was stirred at 120°C for 0.5 h. The

reaction crude was purified by flash chromatography (EtOAc – Petroleum Ether gradient from 3 : 7 to 4 : 6) affording the title product (21 mg).

¹H-NMR (*CDCl*₃δ): 2.48 (s, 3H), 2.49-2.53 (m, 2H), 2.67 (s, 3H), 2.81-2.86 (m, 2H), 3.49-3.55 (m, 2H), 3.56-3.60 (m, 2H), 5.66 (s, 1H), 6.61 (d, 1H, J=8.2Hz), 7.13-7.18 (m, 1H), 7.29-7.35 (m, 1H), 7.60-7.70 (m, 1H), 8.09 (d, 1H, J = 8.2Hz)

MS: [M+H]⁺ = 349.41

Example 6

1-(6-methoxy-3-nitro-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

A well homogenised mixture of the Compound of Example 3 (23 mg, 0.11 mmol) and 2-chloro-5-methoxy-3-nitropyridine (24.4 mg, 0.13 mmol) was stirred at 120°C for 0.5 h. The reaction crude was purified by flash chromatography (EtOAc – Petroleum Ether gradient from 2 : 8 to 3 : 7) affording the title product (24 mg).

¹H-NMR (*CDCl*₃δ): 2.50-2.55 (m, 2H), 2.66 (s, 3H), 2.85-2.90 (m, 2H), 3.50-3.55 (m, 2H), 3.60-3.65 (m, 2H), 3.97 (s, 3H), 5.68 (s, 1H), 6.17 (d, 1H, J=8.76Hz), 7.13-7.18 (m, 1H), 7.29-7.35 (m, 1H), 7.60-7.70 (m, 1H), 8.25 (d, 1H, J=8.76Hz)

MS: [M+H]⁺ = 365.36

Example 7

1-(5-methyl-2-nitrophenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

A well homogenised mixture of the Compound of Example 3 (19 mg, 0.89 mmol) and 3-fluoro-4-nitrotoluene (20.2 mg, 0.13 mmol) was stirred at 120°C for 0.5 h. The reaction crude was purified by flash chromatography (EtOAc – Petroleum Ether gradient from 2 : 8 to 3 : 7) affording the title product (18 mg).

¹H-NMR (*CDCl*₃δ): 2.40 (s, 3H), 2.52-2.57 (m, 2H), 2.68 (s, 3H), 2.85-2.92 (m, 2H), 3.10-3.15 (m, 2H), 3.17-3.22 (m, 2H), 5.64 (s, 1H), 6.85 (d, 1H, J=8.19Hz), 6.93 (s, 1H), 7.13-7.20 (m, 1H), 7.30-7.37 (m, 1H), 7.60-7.72 (m, 1H), 7.78 (d, 1H, J=8.19Hz)

MS: [M+H]⁺ = 348.36

Example 8

1-(5-methoxy-2-nitrophenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

A well homogenised mixture of the Compound of Example 3 (20 mg, 0.93 mmol) and 2-fluoro-4-methoxynitrobenzene (21.3 mg, 0.12 mmol) was stirred at 120°C for 0.5 h. The

reaction crude was purified by flash chromatography (EtOAc – Petroleum Ether 1 : 1) affording the title product (21 mg).

¹H-NMR (CDCl₃δ): 2.55-2.62 (m, 2H), 2.80 (s, 3H), 2.93-3.02 (m, 2H), 3.10-3.18 (m, 2H), 3.22-3.28 (m, 2H), 3.88 (s, 3H), 5.66 (s, 1H), 6.51-6.59 (m, 2H), 7.19-7.31 (m, 1H), 7.36-7.46 (m, 1H), 7.73-7.87 (m, 1H), 8.05 (d, 1H)

MS: [M+H]⁺ = 364.31

Example 9

1-(3-nitro-2-pyridyl)-4-[3-(2-pyridyl)-prop-2-ynylidene]-piperidine

The title compound was obtained as described for the Compound of Example 1, reacting Compound 1c with 2-iodopyridine instead of 2-bromo-6-methylpyridine. The crude was purified by flash chromatography (EtOAc – Petroleum Ether 1 : 1) affording the title compound.

¹H-NMR (CDCl₃δ): 2.50-2.55 (m, 2H), 2.80-2.85(m, 2H), 3.50-3.60 (m, 4H), 5.68 (s, 1H), 6.78 (dd, 1H, J=4.6 and 7.8Hz), 7.27-7.32 (m, 1H), 7.48 (d, 1H, J=7.84Hz), 7.81 (t, 1H, J = 4.2 Hz), 8.16 (dd, 1H, J= 7.8 Hz and 1.7Hz), 8.36 (dd, 1H, J=1.7 Hz and 4.2 Hz), 8.60-8.65 (m, 1H)

MS: [M+H]⁺ = 321.10

Example 10

1-(3-nitro-2-pyridyl)-4-(3-phenyl-prop-2-ynylidene)-piperidine

The title compound was obtained as described for the Compound of Example 1, reacting Compound 1c with iodobenzene instead of 2-bromo-6-methylpyridine. Purification by flash chromatography with Petroleum Ether - EtOAc 65:35 afforded the title product.

¹H-NMR (CDCl₃δ): 2.50-2.55 (m, 2H), 2.76-2.81(m, 2H), 3.52-3.60 (m, 4H), 5.65 (s, 1H), 6.80 (dd, 1H, J=4.6 and 7.8Hz), 7.30-7.36 (m, 3H), 7.43-7.47 (m, 2H), 8.19 (d, 1H, J= 7.8 Hz), 8.38 (d, 1H, J=4.2 Hz)

MS: [M+H]⁺ = 320.24

Example 11

1-(3-nitro-2-pyridyl)-4-[3-(3-pyridyl)-prop-2-ynylidene]-piperidine

The title compound was obtained as described for the Compound of Example 1, reacting Compound 1c with 3-iodopyridine instead of 2-bromo-6-methylpyridine. Purification by

flash chromatography with Petroleum Ether – EtOAc 6 : 4 afforded the compound of Example 11.

¹H-NMR (CDCl₃δ): 2.52-2.57 (m, 2H), 2.74-2.79(m, 2H), 3.50-3.60 (m, 4H), 5.67 (s, 1H), 6.82 (dd, 1H, J=4.4 and 7.8Hz), 7.66-7.74 (m, 1H), 8.13-8.21 (m, 2H), 8.38 (dd, 1H), 8.58-8.63 (m, 1H), 8.72-8.77 (m, 1H).

MS: [M+H]⁺ = 321.30

Example 12

1-phenylcarbamoyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

To a solution of the Compound of Example 3 (0.11 g, 0.52 mmol) in CH₂Cl₂ (10 ml) was added phenylisocyanate (0.06 ml, 0.54 mmol) and the reaction mixture was stirred overnight at ambient temperature. Evaporation and purification of the crude by automated flash liquid chromatography (HorizonTM – Biotage) eluting with a gradient Petroleum Ether – EtOAc from 87 : 13 to 0 : 100 gave the title product (154 mg).

¹H-NMR (CDCl₃δ): 2.41-2.46 (m, 2H), 2.64 (m, 3H), 2.74-2.79 (m, 2H), 3.57-3.62 (m, 4H), 5.65 (s, 1H), 6.58 (s, 1H), 7.05 (t, 1H, J = 7.52 Hz), 7.14 (d, 1H, J = 7.88 Hz), 7.28-7.34 (m, 3H), 7.38-7.42 (m, 2H), 7.63 (t, 1H, J = 7.88 Hz)

MS: [M+H]⁺ = 332.4

Examples 13-26 (Table I)

These compounds were synthesized following the procedure described in Example 12 substituting reagent B (see table I below) for phenylisocyanate. Purification was carried out by automated flash liquid chromatography (HorizonTM – Biotage) eluting with a gradient Petroleum Ether – EtOAc from 100:0 to 20:80. The compounds of Example 17 and 18 were further purified by preparative RP LC-MS chromatography, using MS-C18 XTerra column 30x50 mm eluting with ammonium bicarbonate 20 mM pH 8 buffer – acetonitrile gradient.

TABLE I

Ex.	Structure	Reagent B	LC-MS [M+H] ⁺	¹ H-NMR
13			326.4	2.34-2.40 (m, 2H), 2.60 (s, 3H), 2.65-2.72 (m, 2H), 3.27-3.40 (m, 8H), 3.68-3.75 (m, 4H), 5.62 (s, 1H), 7.11 (d, 1H, J = 7.6 Hz), 7.28 (d, 1H, J = 7.6 Hz), 7.59 (t, 1H)
14			317.3	2.25-2.54 (m, 2H), 2.63 (s, 3H), 2.65-2.82 (m, 2H), 3.38-3.86 (m, 4H), 5.66 (s, 1H), 7.11-7.17 (m, 1H), 7.25-7.33 (m, 1H), 7.40-7.47 (m, 5H), 7.57-7.66 (m, 1H)
15			328.29	0.96 (t, 3H), 1.40 (sextet, 2H), 1.63 (quintet, 2H), 2.44- 2.49 (m, 2H), 2.58 (s, 3H), 2.71-2.77 (m, 2H), 3.66-3.72 (m, 2H), 3.85-3.90 (m, 2H), 3.92-3.97 (m, 2H), 5.63 (s, 1H), 5.74 (br, 1H), 7.10 (d, 1H, J = 7.6 Hz), 7.26 (d, 1H, J = 7.6 Hz), 7.57 (t, 1H)
16			300.31	1.26 (t, 3H), 2.44- 2.49 (m, 2H), 2.61 (s, 3H), 2.74-2.79 (m, 2H), 3.70-3.78 (m, 2H), 3.86-3.90 (m, 2H), 3.94-3.98 (m, 2H), 5.63 (s, 1H), 5.70 (br, 1H), 7.12 (d, 1H, J = 7.6 Hz), 7.26 (d, 1H, J = 7.6 Hz), 7.60 (t, 1H, 7.6 Hz)
17			312.27	1.38 (s, 9H), 2.34- 2.38 (m, 2H), 2.63 (s, 3H), 2.66 -2.72 (m, 2H), 3.39-3.45 (m, 4H), 4.38 (br, 1H), 5.61 (s, 1H), 7.10-7.17 (m, 1H), 7.27-7.33 (m, 1H), 7.56-7.67 (m, 1H)
18			377.3	2.41-2.49 (m, 2H), 2.58 (s, 3H), 2.70-2.77 (m, 2H), 3.59-3.63 (m, 4H), 5.66 (s, 1H), 6.93 (s, 1H), 7.09-7.14 (m, 1H), 7.25-7.33 (m, 1H), 7.46 (t, 1H), 7.58 (t, 1H), (d, 1H), 7.89 (d, 1H), 8.26 (s, 1H).
19			362.3	2.27-2.89 (m, 4H), 2.58 (s, 3H), 3.40-3.58 (m, 2H), 3.76-3.97 (m, 2H), 5.68 (s, 1H), 7.09-7.14 (m, 1H), 7.18-7.31 (m, 1H), 7.56 (t, 1H), 7.65 (t, 1H), 7.80 (d, 1H), 8.30-8.36 (m, 2H).
20			285.27	1.29 (t, 3H), 2.29- 2.37 (m, 2H), 2.59 (s, 3H), 2.60-2.66 (m, 2H), 3.50-3.59 (m, 4H), 4.18 (q, 2H), 5.61 (s, 1H), 7.10 (d, 1H, J = 7.6 Hz), 7.26 (d, 1H, J = 7.6 Hz), 7.57 (t, 1H, 7.6 Hz)

21			354.3	1.12-1.26 (m, 3H), 1.37-1.52 (m, 2H), 1.59-1.77 (m, 3H), 2.10-2.19 (m, 2H), 2.45- 2.52 (m, 2H), 2.62 (s, 3H), 2.75-2.81 (m, 2H), 3.83-3.88 (m, 2H), 3.91-3.96 (m, 2H), 4.32-4.43 (m, 1H), 5.42, (brd, 1H), 5.65 (s, 1H), 7.13 (d, 1H, J = 7.6 Hz), 7.26 (d,
22			348.3	2.45- 2.52 (m, 2H), 2.56 (s, 3H), 2.75-2.81 (m, 2H), 3.83-3.88 (m, 2H), 3.91-3.96 (m, 2H), 5.65 (s, 1H), 7.09 (d, 1H, J = 7.6 Hz), 7.15-7.21 (m, 3H), 7.26 (d, 1H, J = 7.6 Hz), 7.31-7.42 (m, 3H), 7.54 (t, 1H, 7.6 Hz)
23			360.3	1.52 (d, 3H), 2.32-2.38 (m, 2H), 2.58 (s, 3H), 2.62-2.69 (m, 2H), 3.42-3.49 (m, 4H), 4.76 (d, 1H), 5.05 (quintet, 1H), 5.60 (s, 1H), 7.09 (d, 1H), 7.23-7.29 (m, 2H), 7.33-7.38 (m, 4H), 7.56 (t, 1H)
24			283.2	1.00 (t, 3H), 1.70 (sextet, 2H), 2.31-2.39 (m, 4H), 2.57 (s, 3H), 2.59-2.68 (m, 2H), 3.48-3.56 (m, 2H), 3.64-3.71 (m, 2H), 5.62 (s, 1H), 7.08 (d, 1H, J = 7.6 Hz), 7.22-7.29 (m, 1H), 7.54 (t, 1H, 7.6 Hz)
25			312.3	0.95 (t, 3H), 1.35 (sextet, 2H), 1.53 (quintet, 2H), 2.35- 2.39 (m, 2H), 2.69 (s, 3H), 2.60-2.80 (m, 2H), 3.26 (t, 2H), 3.42-3.52 (m, 4H), 4.52 (br, 1H), 5.61 (s, 1H), 7.17 (d, 1H), 7.34 (d, 1H), 7.65-7.71 (br, 1H)
26			284.4	1.18 (t, 3H), 2.33- 2.40 (m, 2H), 2.64 (s, 3H), 2.65-2.73 (m, 2H), 3.32 (q, 2H), 3.42-3.52 (m, 4H), 4.48 (br, 1H), 5.61 (s, 1H), 7.13 (d, 1H), 7.29 (d, 1H), 7.55-7.70 (m, 1H)

Example 27

1-benzyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

A mixture of the compound of Example 3 (0.22 g, 1.04 mmol), benzaldehyde (0.13 ml, 1.25 mmol), sodium triacetoxyborohydride (0.33 g, 1.56 mmol) and 15 ml of CH₂Cl₂ was stirred overnight at ambient temperature. Afterwards, it was diluted with water, the organic layer was separated, washed with brine (2 x 15 ml), dried (Na₂SO₄) and evaporated to dryness *in vacuo* the give a crude, which was purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with a gradient Petroleum Ether – EtOAc from 85:15 to 0:100 affording the title compound, which was further purified by preparative RP LC-MS

chromatography, using MS-C18 XTerra column 30x50 mm eluting with ammonium bicarbonate 20 mM pH 8 buffer – acetonitrile gradient (0.12 g).

¹H-NMR (CDCl₃δ): 2.34-2.80 (m, 11H), 3.57-3.74 (m, 2H), 5.54 (s, 1H), 7.07 (d, 1H, J = 7.65Hz), 7.23 (d, 1H, J = 7.65Hz), 7.29-7.43 (m, 5H), 7.52 (t, 1H, J = 7.65Hz).

5 MS: [M+H]⁺ = 303.3

Example 28

1-butyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

10 The title compound was prepared following the procedure described for the compound of Example 27, but substituting butyraldehyde for benzaldehyde. After the usual work-up procedure, the crude was purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with a gradient Petroleum Ether – (EtOAc + 1.4 N methanolic ammonia 1 : 0.1) from 90 : 10 to 30 : 70 affording the title compound.

¹H-NMR (CDCl₃δ): 0.96 (t, 3H), 1.35 (sextet, 2H), 1.62 (br, 2H), 2.4-2.9 (m, 13H), 5.56 (s, 1H), 7.07 (d, 1H, J = 7.65Hz), 7.25 (d, 1H, J = 7.65Hz), 7.54 (t, 1H, J = 7.65Hz).

15 MS: [M+H]⁺ = 269.3

Example 29

1-(3-nitro-2-pyridyl)-4-[3-(4-pyridyl)-prop-2-ynylidene]-piperidine

20 The title compound was obtained as described for the Compound of Example 1, but reacting Compound 1c with 4-iodopyridine instead of 2-bromo-6-methylpyridine. Purification by flash chromatography with Petroleum Ether – EtOAc 6.5 : 3.5 afforded the compound of Example 29.

¹H-NMR (CDCl₃δ): 2.52-2.57 (m, 2H), 2.75-2.80(m, 2H), 3.50-3.60 (m, 4H), 5.68 (s, 1H), 6.79-6.84 (m, 1H), 7.44-7.48 (m, 2H), 8.18 (d, 1H), 8.36-8.39 (m, 1H), 8.48-8.82 (m, 2H).

25 MS: [M+H]⁺ = 321.29

Example 30

1-(3-nitro-2-pyridyl)-4-[3-(3-quinolyl)-prop-2-ynylidene]-piperidine

30 A well homogenised mixture of the Compound 1c (50 mg, 0.21 mmol), 3-bromoquinoline (0.039 ml, 0.21 mmol), *bis*-(triphenylphosphine)palladium dichloride (5 mg, 0.007 mmol) and *tetra*-butylammonium fluoride (215 mg, 0.82 mmol) was stirred at 80°C for 1 h in a sealed vessel. The reaction mixture was cooled, poured into water and extracted with

EtOAc. The combined organic layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness *in vacuo* to afford a residue, which was purified by flash chromatography (EtOAc – Petroleum Ether gradient from 2 : 8 to 4 : 6) affording the title product (0.51 g).

5 ¹H-NMR (CDCl₃δ): 2.52-2.58 (m, 2H), 2.79-2.80 (m, 2H), 3.52-3.62 (m, 4H), 5.71 (s, 1H), 6.78-6.84 (m, 1H), 7.68-7.74 (m, 1H), 7.82-7.92 (m, 2H), 8.16-8.21 (m, 1H), 8.36-8.49 (m, 3H), 8.98 (s, 1H).

MS: [M+H]⁺ = 371.38

10 Example 31

1-(3-nitro-2-pyridyl)-4-[3-(6-morpholino-3-pyridyl)-prop-2-ynylidene]-piperidine

The title compound was obtained as described for the Compound of Example 31, but reacting Compound 1c with 5-iodo-2-morpholino-pyridine instead of 3-bromoquinoline. Purification by flash chromatography with Petroleum Ether – EtOAc 6 : 4 afforded the
15 compound of Example 31.

¹H-NMR (CDCl₃δ): 2.48-2.52 (m, 2H), 2.71-2.76 (m, 2H), 3.50-3.58 (m, 4H), 3.66-3.78 (m, 4H), 3.81-3.92 (m, 4H), 5.62 (s, 1H), 6.68-6.70 (m, 1H), 6.77-6.81 (m, 1H), 7.60-7.66 (m, 1H), 8.14-8.18 (m, 1H), 8.32 (s, 1H), 8.31-8.38 (m, 1H).

MS: [M+H]⁺ = 406.28

20

Example 32

1-(3-nitro-2-pyridyl)-4-[3-(6-fluoro-3-pyridyl)-prop-2-ynylidene]-piperidine

The title compound was obtained as described for the Compound of Example 31, but using 5-bromo-2-fluoropyridine instead of 3-bromoquinoline in the coupling with Compound 1c.

25 Purification by flash chromatography with Petroleum Ether – EtOAc 6 : 4 afforded the compound of Example 32.

¹H-NMR (CDCl₃δ): 2.50-2.54 (m, 2H), 2.74-2.78 (m, 2H), 3.52-3.59 (m, 4H), 5.64 (s, 1H), 6.80-6.84 (m, 1H), 6.90-6.95 (m, 1H), 7.80-7.85 (m, 1H), 8.19 (d, 1H), 8.31 (s, 1H), 8.39-8.41 (m, 1H).

30 MS: [M+H]⁺ = 339.14

Example 33

1-(3-nitro-2-pyridyl)-4-[3-(6-acetyl-2-pyridyl)-prop-2-ynylidene]-piperidine

The title compound was obtained as described for the Compound of Example 30, but using 2-acetyl-6-bromopyridine instead of 3-bromoquinoline in the coupling with Compound 1c.

- 5 Purification by flash chromatography with Petroleum Ether – EtOAc 6 : 4 afforded the title compound.

¹H-NMR (CDCl₃δ): 2.53-2.58 (m, 2H), 2.77 (s, 3H), 2.81-2.86 (m, 2H), 3.55-3.61 (m, 4H), 5.70 (s, 1H), 6.80-6.84 (m, 1H), 7.58-7.62 (m, 1H), 7.78-7.84 (m, 1H), 7.95-7.99 (m, 1H), 8.18-8.22 (m, 1H), 8.38-8.41 (m, 1H).

- 10 MS: [M+H]⁺ = 363.28

Example 34

1-(3-nitro-2-pyridyl)-4-[3-(6-isopropoxy-3-pyridyl)-prop-2-ynylidene]-piperidine

The title compound was obtained as described for the Compound of Example 31, but using 5-iodo-2-isopropoxypyridine instead of 3-bromoquinoline in the coupling with Compound 1c. Purification by flash chromatography with Petroleum Ether – EtOAc 3.5 : 6.5 afforded the title compound.

- 15 ¹H-NMR (CDCl₃δ): 1.40 (s, 6H), 2.48-2.52 (m, 2H), 2.72-2.77 (m, 2H), 3.51-3.58 (m, 4H), 5.32-5.42 (m, 1H), 5.63 (s, 1H), 6.73 (d, 1H), 6.78-6.82 (m, 1H), 7.65-7.70 (m, 1H), 8.16-8.19 (m, 1H), 8.29 (m, 1H), 8.37-8.41 (m, 1H).

MS: [M+H]⁺ = 379.30

Example 35

1-(3-nitro-2-pyridyl)-4-[3-(3-methoxy-2-pyridyl)-prop-2-ynylidene]-piperidine

- 25 The title compound was obtained as described for the Compound of Example 31, but using 2-iodo-3-methoxypyridine instead of 3-bromoquinoline. Purification by flash chromatography with Petroleum Ether – EtOAc 1 : 1 afforded the compound of Example 35.

- ¹H-NMR (CDCl₃δ): 2.50-2.56 (m, 2H), 2.86-2.92 (m, 2H), 3.52-3.60 (m, 4H), 3.98 (s, 3H), 5.75 (m, 1H), 6.76-6.81 (m, 1H), , 7.35-7.38 (m, 2H), 8.16-8.19 (m, 1H), 8.23-8.31 (m, 1H), 8.35-8.41 (m, 1H).

MS: [M+H]⁺ = 351.24

Example 36

1-phenyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

A mixture of the compound of Example 3 (0.22 g, 1.04 mmol), bromobenzene (0.17 g, 1.04 mmol), cesium carbonate (0.68 g, 2.1 mmol), BINAP (0.031g, 0.05 mmol),
 5 palladium(II)acetate (0.01 mg, 0.05 mmol), in anhydrous and degassed toluene (10 ml) was heated at 110°C under a nitrogen atmosphere for 12 h in a sealed vessel. The reaction mixture was cooled, poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness *in vacuo* to afford a residue, which was purified by flash chromatography (EtOAc – Petroleum Ether 2 :
 10 8) affording the title product (0.30 g). ¹H-NMR (CDCl₃δ): 2.40-2.65 (m, 5H), 2.86 (brd, 2H), 3.38 (brd, 4H), 5.63 (s, 1H), 6.8-7.20 (m, 6H), 7.32(d, 1H, J = 7.65Hz), 7.58 (t, 1H, J = 7.65Hz).

MS: [M+H]⁺ = 289.3

15 Example 37

1-(2-cyanophenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

The title compound was prepared following the procedure described for the compound of Example 36, but substituting 2-bromobenzonitrile for bromobenzene. Purification by flash chromatography (EtOAc – Petroleum Ether 3 : 7) affording the title product.
 20 ¹H-NMR (CDCl₃δ): 2.55-2.65 (m, 5H), 2.91 (brd, 2H), 3.25-3.35 (m, 4H), 5.65 (s, 1H), 6.80-7.08 (m, 2H), 7.14 (d, 1H, J = 7.65Hz), 7.31 (d, 1H, J = 7.65Hz), 7.48 (t, 1H, J = 7.65Hz), 7.55-7.65 (m, 2H).

MS: [M+H]⁺ = 314.3

25 Example 38

1-(4-methoxy-2-nitrophenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

The title compound was prepared following the procedure described for the compound of Example 36, but substituting 4-bromo-3-nitroanisole for bromobenzene. Purification by flash chromatography (EtOAc – Petroleum Ether 3 : 7) affording the title product.
 30 ¹H-NMR (CDCl₃δ): 2.45-2.55 (m, 2H), 2.61 (s, 3H), 2.75-2.85 (m, 2H), 3.00-3.15 (m, 4H), 3.84 (s, 3H), 5.60 (s, 1H), 7.05-7.20 (m, 3H), 7.24-7.35 (m, 2H) 7.59 (t, 1H, J = 7.65Hz).

MS: [M+H]⁺ = 364.3

Example 39

1-(t-butoxycarbonyl)-4-[3-(5-cyano-3-pyridyl)-prop-2-ynylidene]-piperidine

A mixture of Compound 2b (0.5 g, 2.26 mmol), 5-bromonicotinonitrile (0.511 g, 2.26 mmol), *bis*(triphenylphosphine)palladium(II)dichloride (80 mg, 0.05 mmol), CuI (43.1 mg, 0.1 mmol) in anhydrous and degassed triethylamine (12.6 ml) was heated at 80°C under a nitrogen atmosphere for 2 h in a sealed vessel. The reaction mixture was cooled, filtered on Celite, poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness *in vacuo* to afford a residue, which was purified by flash chromatography (EtOAc – Petroleum Ether gradient from 4 :96 to 30:70) affording the title product (0.731 g).

MS: [M+H]⁺ = 324.2

Example 40

1-(t-butoxycarbonyl)-4-[3-(6-cyano-3-pyridyl)-prop-2-ynylidene]-piperidine

The title compound was prepared following the procedure described for the compound of Example 39, but substituting 5-bromo-2-cyanopyridine for 5-bromonicotinonitrile. Purification by flash chromatography (EtOAc – Petroleum Ether gradient from 5 : 95 to 40 : 60) afforded the title product.

MS: [M+H]⁺ = 324.2

Examples 41 and 42

1-(3-nitro-2-pyridyl)-4-[3-(5-cyano-3-pyridyl)-prop-2-ynylidene]-piperidine

1-(3-nitro-2-pyridyl)-4-[3-(6-cyano-3-pyridyl)-prop-2-ynylidene]-piperidine

4-[3-(5-cyano-3-pyridyl)-prop-2-ynylidene]-piperidine (Compound 41a)

4-[3-(6-cyano-3-pyridyl)-prop-2-ynylidene]-piperidine (Compound 42a)

The title compounds were prepared following the procedure described for the compound of Example 3 but starting respectively from the compounds of Example 39 and 40 instead of the compound of Example 2. The crudes were used in the next step without further purification.

MS: [M+H]⁺ = 224.3

MS: [M+H]⁺ = 224.3

1-(3-nitro-2-pyridyl)-4-[3-(5-cyano-3-pyridyl)-prop-2-ynylidene]-piperidine (Compound 41)

1-(3-nitro-2-pyridyl)-4-[3-(6-cyano-3-pyridyl)-prop-2-ynylidene]-piperidine (Compound 42)

5

Using 2-bromo-3-nitropyridine instead of 1-bromo-2-nitrobenzene and carrying out the reaction as described in Example 4, but stirring overnight at ambient temperature in N,N-dimethylacetamide in the presence of a molar equivalent of TEA the title products were easily synthesized.

10 **MS:** $[M+H]^+ = 346.2$

MS: $[M+H]^+ = 346.2$

Example 43

1-(t-butoxycarbonyl)-4-[3-(2-methyl-1,3-thiazol-4-yl)-prop-2-ynylidene]-piperidine

15

1-(t-butoxycarbonyl)-4-bromomethylene-piperidine (Compound 43a)

Lithium bis-trimethylsilylamide (1 M in THF, 7.38 ml, 7.38 mmol) was dropped into a suspension of bromomethyltriphenylphosphonium bromide (3.22 g, 7.38 mmol) at -15°C under nitrogen atmosphere. After 15 min. under stirring at the same temperature, N-Boc piperidone (1.4 g, 7.03 mmol) dissolved in THF (10 ml) was added. Stirring was maintained and after 2 h at ambient temperature, the reaction mixture was quenched with water and with EtOAc. The combined extracts were washed, dried over Na_2SO_4 and evaporated to dryness. The crude residue was purified by flash chromatography (EtOAc – Petroleum Ether 98 : 2) affording the title product (1.27 g).

25 **MS:** $[M+H]^+ = 276.2$

1-(t-butoxycarbonyl)-4-[3-(2-methyl-1,3-thiazol-4-yl)-prop-2-ynylidene]-piperidine

A solution of tetrabutylammonium fluoride hydrate (818 mg, 2.93 mmol) in DMF (8 ml) was dropped into a solution of 2-methyl-4-trimethylsilylthiazole (Yasuyoshi et al., J. Med. Chem., 49, 3, 2006, 1080 - 1100, 0.52 g, 2.66 mmol) in DMF (7 ml). After 2 h under stirring, was added bis(triphenylphosphine)palladium(II)dichloride (93 mg, 0.13 mmol), CuI (51 mg, 0.27 mmol), anhydrous and degassed triethylamine (1 ml) and Compound 43a. The mixture was heated at 80°C under a nitrogen atmosphere for 2 h in sealed vessel. The reaction mixture was cooled, poured into water and extracted with

30

EtOAc. The combined organic layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness *in vacuo* to afford a residue, which was purified by flash chromatography (EtOAc – Petroleum Ether gradient from 4 :96 to 30:70) affording the title product (0.847 g).

5 MS: [M+H]⁺ = 319.2

Example 44

4-[3-(2-methyl-1,3-thiazol-4-yl)-prop-2-ynylidene]-piperidine

10 The title product was synthesized according to Example 3 but starting from the Compound of Example 43 instead of the Compound of Example 2.

MS: [M+H]⁺ = 219.2

Example 45

1-(3-nitro-2-pyridyl)-4-[3-(2-methyl-1,3-thiazol-4-yl)-prop-2-ynylidene]-piperidine

15 The title product was synthesized according to Example 41 but starting from the Compound of Example 44, instead of Compound 41a. After the usual work-up procedure, the crude was purified by flash chromatography (EtOAc – Petroleum Ether gradient from 8 : 92 to 40 : 60) affording the title product.

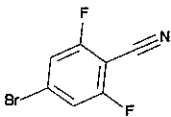
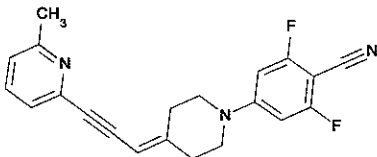
MS: [M+H]⁺ = 341.1

20

Examples 46 to 52 (Table II)

These compounds were synthesized following the procedure described in Example 37, but substituting Reagent B (Table II) for bromobenzene. Purification was carried out by automated flash liquid chromatography (HorizonTM – Biotage) eluting with Petroleum Ether – EtOAc gradient from 95 :5 to 30 : 70.

TABLE II

Ex.	Reagent B	Structure	Compound Name	LC-MS M/Z
46			1-(4-cyano-3,5-difluorophenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	350.21

47			1-(5-cyano-2-methoxyphenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	344.25
48			1-(5-bromo-2-cyano-3-fluorophenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	410.01
49			1-(4-fluoro-2-nitrophenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	352.25
50			1-(4-cyano-2-nitrophenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	359.16
51			1-[2-(2,5-dimethyl-1H-pyrrazol-1-yl)-5-pyrimidinyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	384.2
52			1-(6-quinoxaliny)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	341.3

Example 53**1-(2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine**

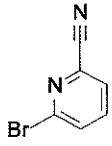
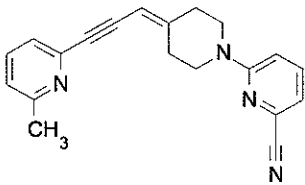
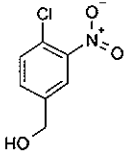
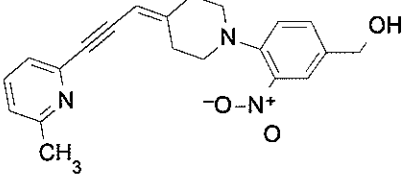
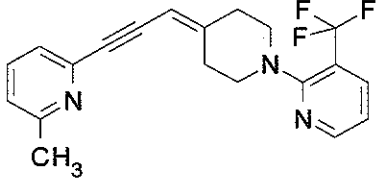
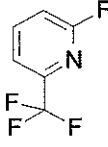
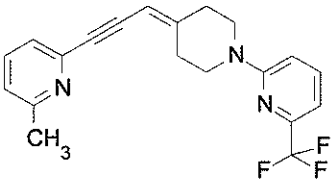
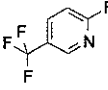
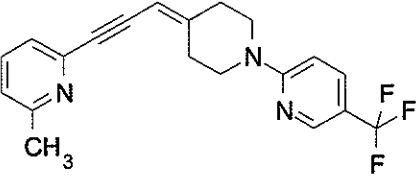
A solution of the Compound of Example 3 (100 mg, 0.47 mmol), 2-fluoropyridine (45.5 μ l, 0.52 mmol), TEA (102 μ l) in N-methylpyrrolidone was heated in a microwave oven at 160°C for 20 min.. Afterwards, the reaction mixture was cooled, poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness *in vacuo* to afford a residue, which was purified by flash chromatography (EtOAc – Petroleum Ether gradient from 7 : 93 to 40 : 60) affording the title product (0.02 g).

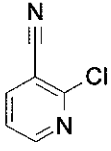
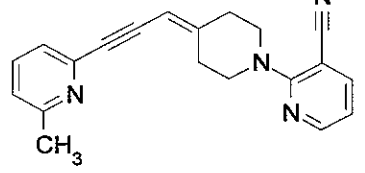
MS: $[M+H]^+ = 290.34$

Examples 54 to 59 (Table III)

These compounds were synthesized following the procedure described in Example 54 substituting Reagent B for 2-fluoropyridine. Purification was carried out by automated flash liquid chromatography (Horizon™ – Biotage) eluting with Petroleum Ether – EtOAc gradient from 95 : 5 to 30 : 70.

TABLE III

Ex.	Reagent B	Structure	Compound Name	LC-MS M/Z
54			1-(6-cyano-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	315.4
55			1-(4-hydroxymethyl-2-nitrophenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	364.3
56			1-(3-trifluoromethyl-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	358.2
57			1-(6-trifluoromethyl-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	358.2
58			1-(5-trifluoromethyl-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	358.2

59			1-(3-cyano-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	315.2
----	---	---	--	-------

Example 60**1-(t-butoxycarbonyl)-4-[1-fluoro-3-phenyl-prop-2-ynylidene]-piperidine****5 1-(t-butoxycarbonyl)-4-[bromo(fluoro)methylene]-piperidine (Compound 60a)**

To a solution of 1-(t-butoxycarbonyl)-4-oxo-piperidine (500 mg, 2.52 mmol), triphenylphosphine (808 mg, 3.02 mmol) and tribromofluoromethane (818 mg, 3.02 mmol) in 50 ml of anhydrous THF was added dropwise a solution of diethylzinc (1 M in hexane, 3.02 ml, 3.02 mmol) stirring at ambient temperature. After 2.5h, the reaction mixture was

10 quenched with MeOH (10 ml), stirred for 30 min., evaporated to dryness *in vacuo*. Purification was carried out by automated flash liquid chromatography (Horizon™ – Biotage) eluting with Petroleum Ether – EtOAc gradient from 95 :5:0 to 90 : 10 to afford the title compound (326 mg).

MS: $[M+H]^+ = 295.16$

15

1-(t-butoxycarbonyl)-4-[1-fluoro-3-phenyl-prop-2-ynylidene]-piperidine

The title product was prepared following the procedure reported for the Compound of Example 39 but using phenylacetylene instead of instead of Compound 2b and Compound 60a instead of 5-bromonicotinonitrile. The residue coming from the usual work-up

20 procedure was purified by flash chromatography (EtOAc – Petroleum Ether gradient from 5 :95 to 10:90).

MS: $[M+H]^+ = 316.22$

Example 61**25 1-(3-nitro-2-pyridyl)-4-[1-fluoro-3-phenyl-prop-2-ynylidene]-piperidine****4-(1-fluoro-3-phenyl-prop-2-ynylidene)-piperidine (Compound 61a)**

The title product was synthesized following the procedure reported for Example 3 but starting from the Compound of Example 60 instead of the compound of Example 2.

30 **MS:** $[M+H]^+ = 216.22$

1-(3-nitro-2-pyridyl)-4-[1-fluoro-3-phenyl-prop-2-ynylidene]-piperidine

The title compound was prepared following the procedure described for the Compound of Example 41, but replacing Compound 41a with Compound 61a. The crude was purified by
5 flash chromatography (EtOAc – Petroleum Ether 1 : 9).

MS: $[M+H]^+ = 338.22$

Example 62

1-(2-methoxyethoxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

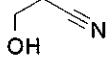
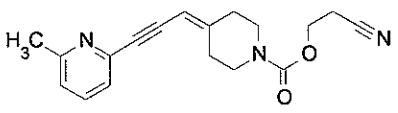
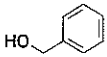
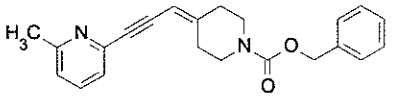
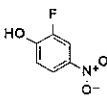
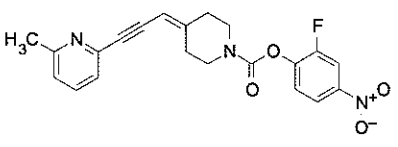
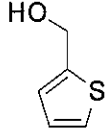
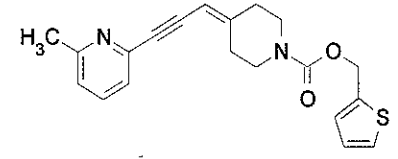
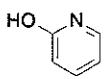
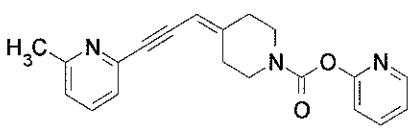
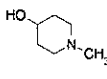
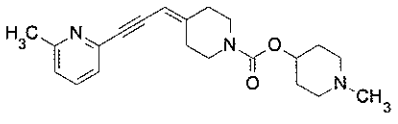
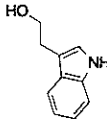
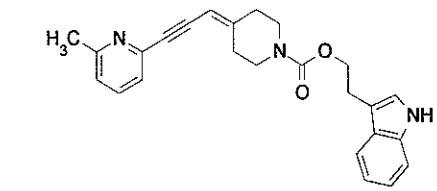
10 To a solution of 2-methoxyethanol (26.9 μ l, 0.34 mmol) and ditrichloromethyl carbonate (37.2 mg, 0.125 mmol) in CH_2Cl_2 (1.5 ml) stirred at ambient temperature, was added dropwise a solution of DEA (139 μ l, 0.814 mmol) in 1.5 ml of CH_2Cl_2 over 30'. After 40 min., was added a solution of the Compound of Example 3 (72 mg, 0.339 mmol) and 70 μ l of DEA in 0.8 ml of CH_2Cl_2 . After 24h, the reaction mixture was evaporated to dryness *in*
15 *vacuo* and the residue was purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with Petroleum Ether – EtOAc gradient from 7 : 3 to 3 : 7 to afford the title compound (57 mg).

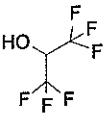
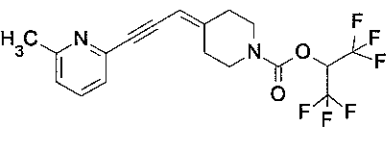
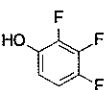
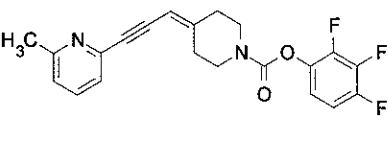
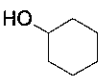
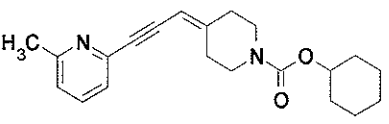
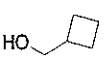
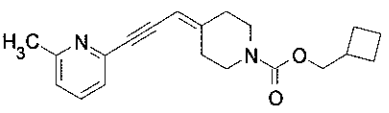
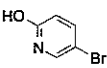
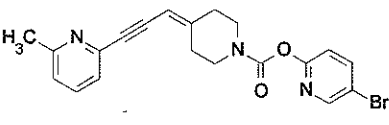
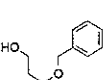
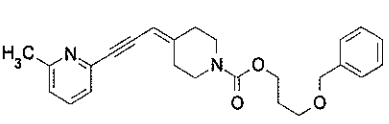
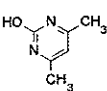
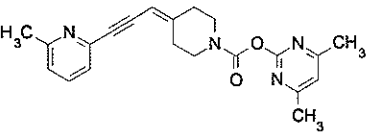
MS: $[M+H]^+ = 315.17$

20 Examples 63 to 76 (Table IV)

These compounds were synthesized following the procedure described in Example 62, but substituting reagent B (see table IV below; commercially available) for 2-methoxyethanol. Purification was carried out by automated flash liquid chromatography (HorizonTM – Biotage) eluting with Petroleum Ether – EtOAc gradient from 100:0 to 20:80 or CH_2Cl_2 –
25 EtOAc from 100:0 to 20:80. The compound of Example 76 was further purified by preparative RP LC-MS chromatography, using MS-C18 XTerra column 30x50 mm eluting with ammonium bicarbonate 20 mM pH 8 buffer – acetonitrile gradient.

TABLE IV

Ex.	Reagent B	Structure	Compound Name	LC-MS M/Z
63			1-(2-cyanoethoxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	310.20
64			1-benzoyloxycarbonyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	346.09
65			1-(2-fluoro-4-nitrophenoxy)carbonyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	396.09
66			1-(2-thienylmethoxy)carbonyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	353.20
67			1-(2-pyridyloxy)carbonyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	334.12
68			1-(1-methyl-4-piperidinylmethoxy)carbonyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	354.19
69			1-[2-(1H-indol-3-yl)ethoxy]carbonyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	400.15

70			1-(2,2,2-trifluoro-1-ethoxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	407.08
71			1-(2,3,4-trifluorophenoxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	387.07
72			1-(cyclohexyloxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	339.23
73			1-(cyclobutylmethoxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	325.17
74			1-(5-bromo-2-pyridyloxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	414.00
75			1-(3-phenoxypropoxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	405.19
76			1-(4,6-dimethylpyrimidin-2-yloxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	363.15

Example 77

1-(N-methyl-N-phenylcarbamoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

- 5 To a solution of ditrichloromethyl carbonate (43.6 mg, 0.147 mmol) in CH₂Cl₂ (1 ml) stirred at ambient temperature, was added dropwise a solution of N-methylaniline (48.2 μl, 0.445 mmol) and DEA (168 μl, 0.98 mmol) in 1.5 ml of CH₂Cl₂ over 30'. After 40 min.,

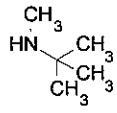
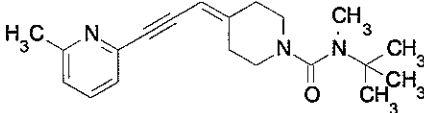
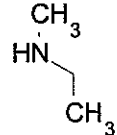
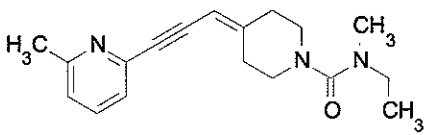
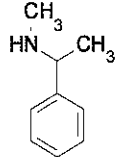
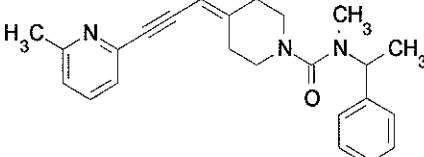
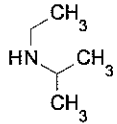
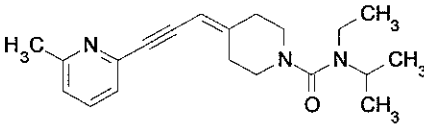
was added a solution of the Compound of Example 3 (94.4 mg, 0.445 mmol) and 168 μ l of DEA in 2 ml di CH_2Cl_2 . After 24h, the reaction mixture was evaporated to dryness *in vacuo*, taken up with water and extracted with EtOAc. The residue from extraction was purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with Petroleum Ether – EtOAc gradient from 4 :6 to 2 : 8 to afford the title compound (123 mg).
MS: $[\text{M}+\text{H}]^+ = 346.22$

Examples 78 to 85 (Table V)

These compounds were synthesized following the procedure described in Example 77 but substituting reagent B (see table V below; commercially available) for N-methylaniline. Purification was carried out by automated flash liquid chromatography (HorizonTM – Biotage) eluting with Petroleum Ether – EtOAc gradient from 100:0 to 20:80 or CH_2Cl_2 – EtOAc from 100:0 to 20:80.

TABLE V

Ex.	Reagent B	Structure	Compound Name	LC-MS M/Z
78			1-(N,N-diethylcarbamoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	312.23
79			1-(N,N-dimethylcarbamoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	284.25
80			1-(N-methyl-N-(3-nitrophenylcarbamoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	391.2
81			1-(N-methyl-N-butylcarbamoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	326.22

82			1-[N-methyl-N-(t-butyl)-carbamoyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	326.22
83			1-(N-methyl-N-ethylcarbamoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	298.17
84			1-[N-methyl-N-(1-phenylethyl)-carbamoyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	374.2
85			1-(N-ethyl-N-isopropylcarbamoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	326.29

Example 86

1-(p-tolylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

A solution of the Compound of Example 3 (60 mg, 0.283 mmol), p-toluenesulphonyl chloride (80.9 mg, 0.425 mmol) and TEA (0.425 mmol) in 5 ml of CHCl_3 was stirred at ambient temperature for 1 h. The chloroform solution was washed with NaOH 0.1 N, water, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. Purification by flash chromatography (EtOAc - Petroleum Ether 1:1), afforded 67 mg of the title product.

MS: $[\text{M}+\text{H}]^+ = 367.13$

10

Examples 87 to 109 (Table VI)

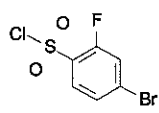
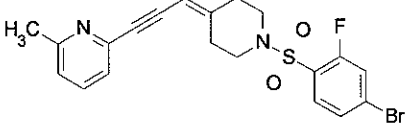
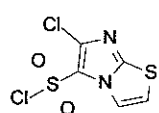
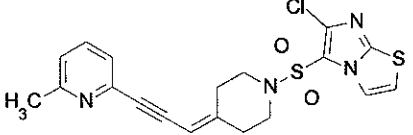
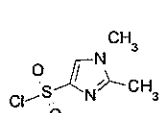
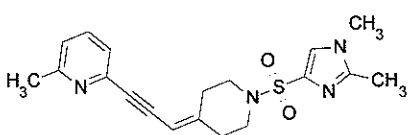
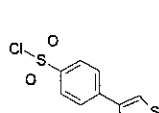
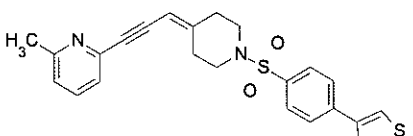
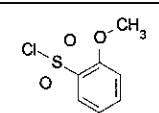
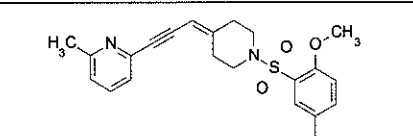
These compounds were synthesized following the procedure described in Example 86 but substituting reagent B (see table VI below; commercially available) for p-toluenesulphonyl chloride. Purification was carried out by flash chromatography eluting with Petroleum Ether – EtOAc.

15

TABLE VI

Ex.	Reagent B	Structure	Compound Name	LC-MS M/Z
87			1-(2-nitrophenylsulfonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	398.10
88			1-phenylsulphonyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	353.20
89			1-[5-(2-oxo-1-pyrrolidinyl)-2-methyl-phenylsulfonyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	450.17
90			1-(4-methoxyphenylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	383.15
91			1-(4-bromo-2,5-difluorophenylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	468.99
92			1-benzylsulphonyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	353.20
93			1-ethylsulphonyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	305.22
94			1-(2-chloro-4-cyanophenylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	412.04

95		1-(3-fluorobenzylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	385.18
96		1-(cyclohexylmethylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	373.28
97		1-(4-methyl-3-nitrophenylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	412.11
98		1-(2,2,2-trifluoroethylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	359.23
99		1-(4-isopropylphenylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	395.18
100		1-(4-cyanophenylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	378.18
101		1-(5-chloro-2-methoxy-4-methylphenylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	431.07
102		1-(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-ylmethylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	427.15
103		1-[3-(4-methoxyphenoxy)propylsulphonyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	441.14
104		1-(3-bromophenylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	433.03

105			1-(4-bromo-2-fluorophenylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	451.99
106			1-(6-chloro-imidazo[2,1-b]thiazol-5-ylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	433.03
107			1-(1,2-dimethyl-1H-imidazol-4-ylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	371.19
108			1-[4-(1,2,3-thiadiazol-4-yl)-phenylsulphonyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	437.09
109			1-[5-(t-butyl)-2-methoxyphenylsulphonyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	439.12

Example 110

1-(2-nitrobenzoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

- 5 To a solution 2-nitrobenzoic acid (42.6mg, 0.25 mmol) in CH_2Cl_2 (2 ml) and DMF (0.5 ml) stirred at 0-5°C, was added 1-hydroxybenzotriazole (50 mg, 0.322 mmol) and, after 30', 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (62 mg, 0.323 mmol). Afterwards, the Compound of Example 3 (53 mg, 0.25 mmol) was added. The reaction mixture was stirred at ambient temperature for 2 h and kept overnight at the same temperature. After dilution
- 10 with water and 1 N NaOH, the organic layer was separated and washed with water, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. Purification by flash chromatography (CHCl_3 - 1.4 N MeOH/ NH_3 100:0.1) yielded the title compound (82 mg).

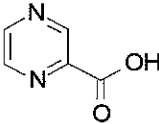
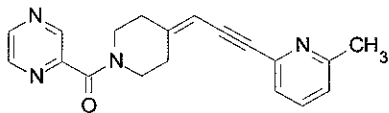
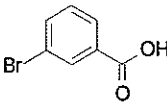
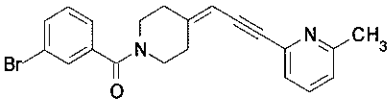
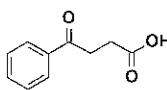
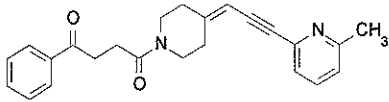
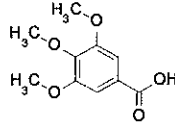
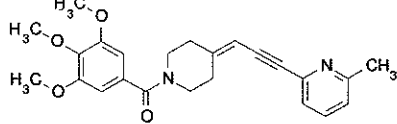
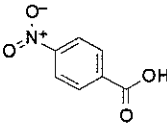
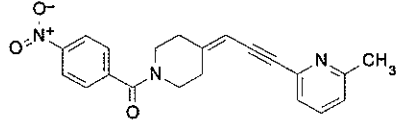
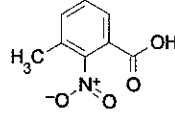
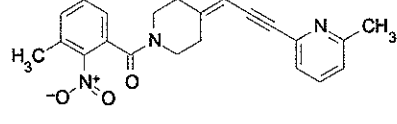
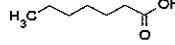
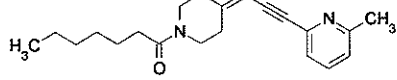
Examples 111 to 156 (Table VII)

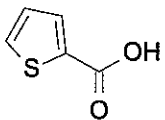
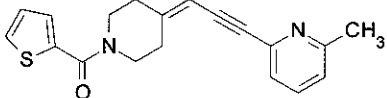
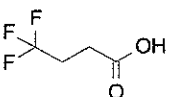
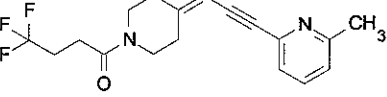
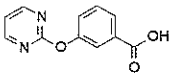
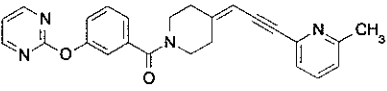
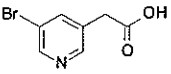
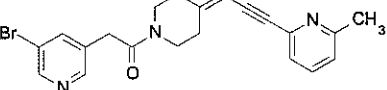
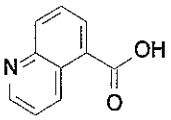
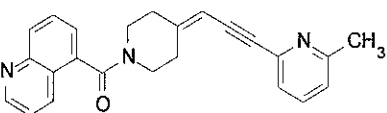
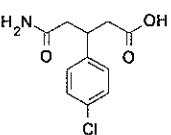
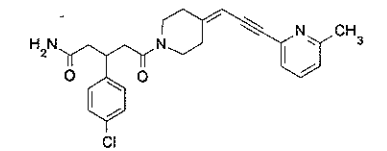
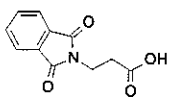
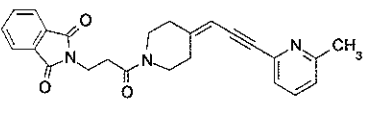
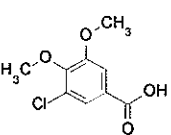
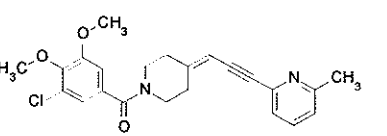
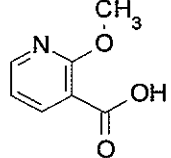
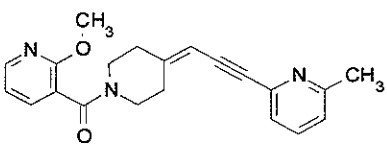
- 15 These compounds were synthesized following the procedure described in Example 110 but substituting reagent B (see table VII below; commercially available) for 2-nitrobenzoic acid. Purification was carried out by automated flash liquid chromatography (HorizonTM –

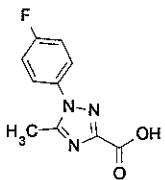
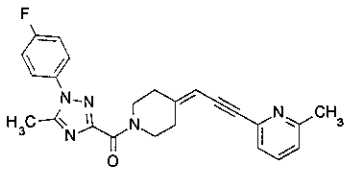
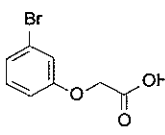
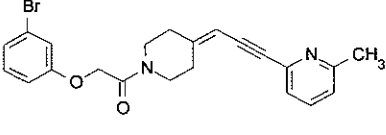
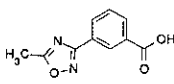
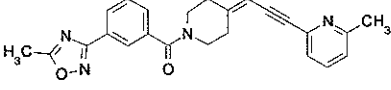
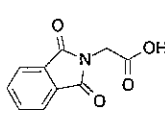
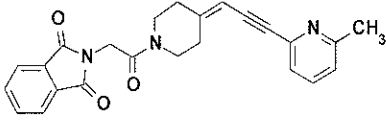
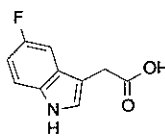
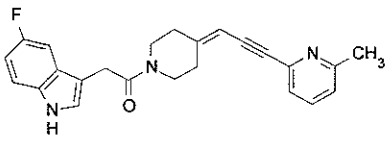
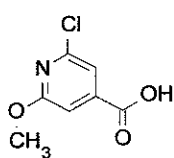
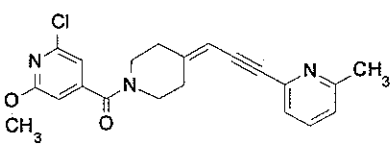
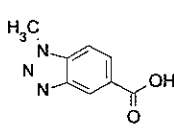
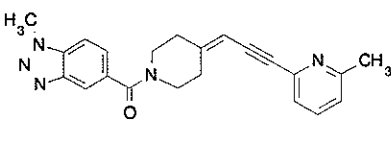
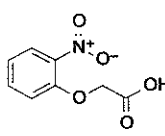
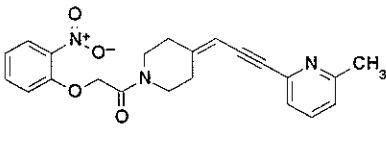
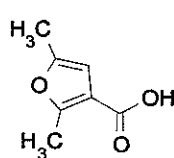
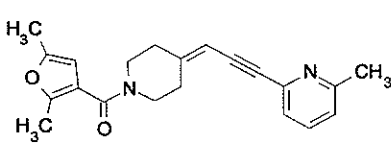
Biotage) eluting with Petroleum Ether – EtOAc gradient from 100:0 to 20:80 or CH₂Cl₂ – EtOAc from 100:0 to 20:80.

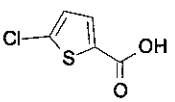
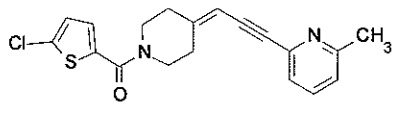
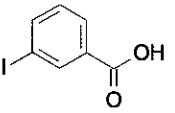
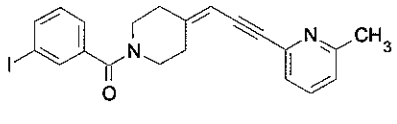
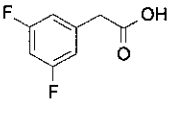
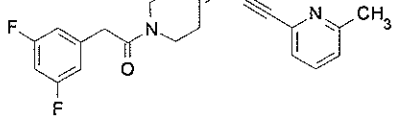
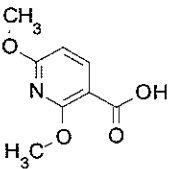
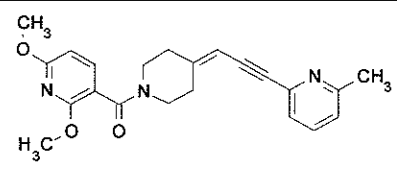
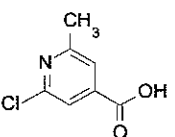
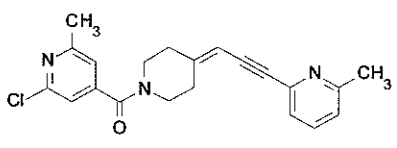
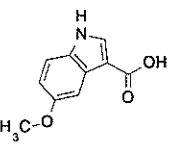
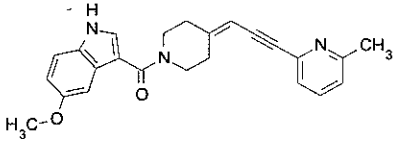
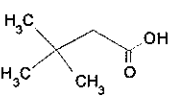
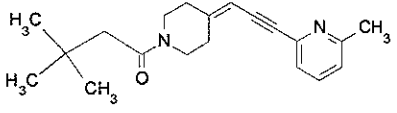
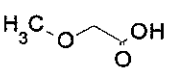
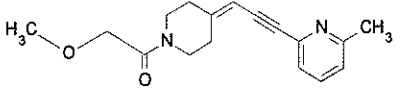
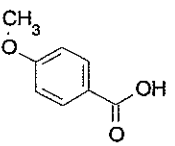
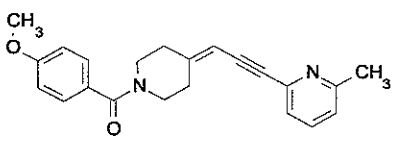
TABLE VII

5

Ex.	Reagent B	Structure	Compound Name	LC-MS M/Z
111			1-(2-pyrazinylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	319.1 5
112			1-(3-bromobenzoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	395.0 4
113			1-(4-phenyl-4-oxobutyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	373.2 2
114			1-(3,4,5-trimethoxybenzoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	407.1 5
115			1-(4-nitrobenzoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	362.2 4
116			1-(3-methyl-2-nitrobenzoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	376.2 3
117			1-heptanoyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	325.3 8

118			1-(2-thienylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	323.1 4
119			1-(4,4,4-trifluorobutyryl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	337.2 7
120			1-[3-(2-pyrimidin-2-yloxy)benzoyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	411.1 3
121			1-(5-bromo-3-pyridylacetyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	412.0 4
122			1-(5-quinolylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	368.1 8
123			1-[5-amino-5-oxo-3-(4-chlorophenyl)pentanoyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	436.0 4
124			1-(3-phthalimidopropionyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	414.4 1
125			1-(3-chloro-4,5-dimethoxybenzoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	411.2
126			1-(2-methoxy-3-pyridylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	348.1 8

127			1-[5-methyl-1-(4-fluorophenyl)-1H-1,2,4-triazol-3-ylcarbonyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	416.2 4
128			1-(3-bromophenoxyacetyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	424.9 8
129			1-[3-(5-methyl-1,2,4-oxadiazol-3-yl)-benzoyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	399.1 7
130			1-phthalimidoacetyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	400.0 8
131			1-(5-fluoro-1H-indol-3-ylacetyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	388.0 5
132			1-(2-chloro-6-methoxy-4-pyridylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	382.2 4
133			1-(1-methyl-1H-1,2,3-benzotriazol-5-ylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	372.1 7
134			1-(2-nitrophenoxyacetyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	392.2 5
135			1-(2,5-dimethyl-3-furylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	335.1 7

136			1-(5-chloro-2-thienylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	357.06
137			1-(3-iodobenzoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	443.12
138			1-(3,5-difluorophenylacetyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	367.23
139			1-(2,6-dimethoxy-3-pyridylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	378.07
140			1-(2-chloro-6-methyl-4-pyridylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	366.35
141			1-(5-methoxy-1H-indol-3-ylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	386.2
142			1-(3,3-dimethylbutyryl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	311.2
143			1-methoxyacetyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	285.2
144			1-(4-methoxybenzoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	347.1

145			1-(3-methoxybenzoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	347.1 8
146			1-(2-methoxybenzoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	347
147			1-(2-methoxy-3-pyridylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	362
148			1-[1-(4-pyridyl)-4-piperidinylcarbonyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	401
149			1-[3(4H)-oxo-2H-1,4-benzoxazin-6-ylcarbonyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	388
150			1-[3-(3-fluorophenoxy)-propionyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	379.4 5
151			1-(2-piperidino-5-pyrimidinylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	402.0 9
152			1-[1-(3-fluoro-4-methylphenyl)-2-oxo-pyrrolidin-4-ylcarbonyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	432.2
153			1-(4-acetamido-2-methylbenzoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	388.1 7

154			1-(3-chlorobenzoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	351.2 2
155			1-(3-phenylbenzoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	393.1 5
156			1-(2-furoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	307.3 3

Example 157**1-phenylacetyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine**

To a solution of phenylacetic acid (61.5 mg, 0.452 mmol) in 10 ml of CH₂Cl₂ was added
 5 PS-carbodiimide 1,25 mmol/g (480 mg, 0.6 mmol), while gently stirring at ambient temperature. After 20 min., the Compound of Example 3 (64 mg, 0.301 mmol) was added. A very slow stirring was maintained overnight. Filtration, followed by washing the resin with CH₂Cl₂ and evaporation afforded a crude which was purified by flash chromatography (CHCl₃ – 1.4 N MeOH/NH₃ 100 : 0.2) yielding the title product (80 mg).

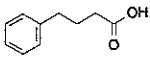
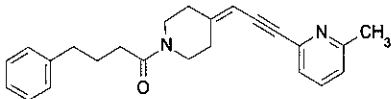
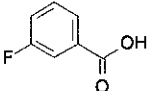
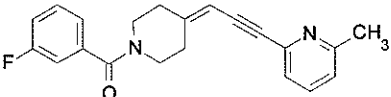
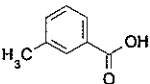
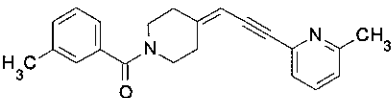
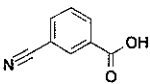
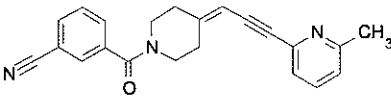
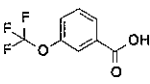
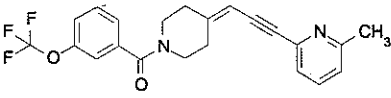
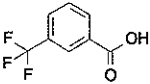
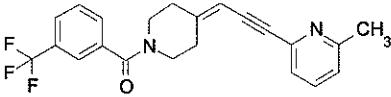
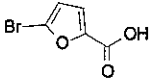
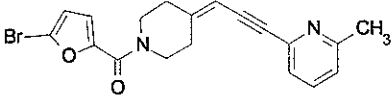
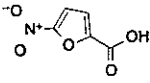
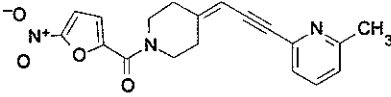
10

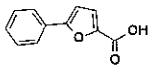
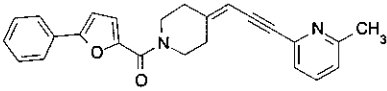
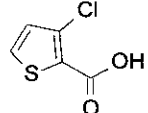
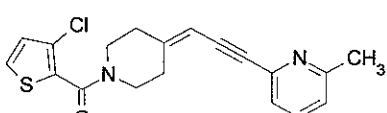
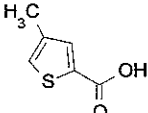
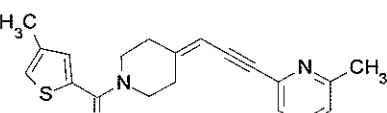
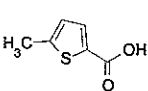
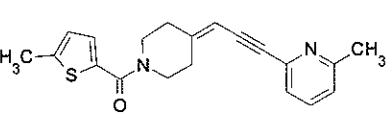
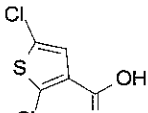
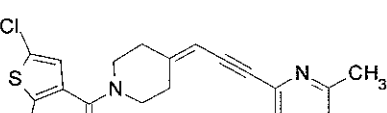
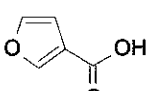
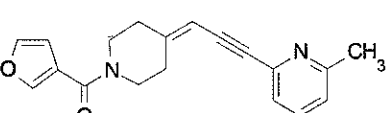
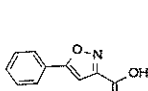
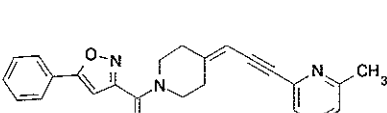
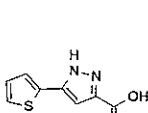
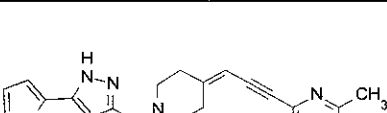
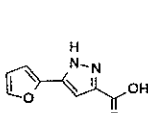
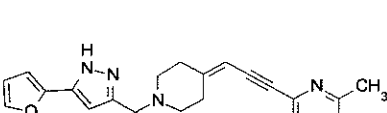
Examples 158 to 183 (Table VIII)

These compounds were synthesized following the procedure described in Example 157 but substituting reagent B (see table VIII below; commercially available) for phenylacetic acid. Purification was carried out by automated flash liquid chromatography (HorizonTM –
 15 Biotage) eluting with Petroleum Ether – EtOAc gradient from 100 : 0 to 20 : 80 or CH₂Cl₂ – EtOAc from 100 : 0 to 20 : 80.

20

TABLE VIII

Ex.	Reagent B	Structure	Compound Name	LC-MS M/Z
158			1-(4-phenylbutyryl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	359.27
159			1-(3-fluorobenzoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	335.34
160			1-(3-methylbenzoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	331.42
161			1-(3-cyanobenzoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	342.28
162			1-(3-(trifluoromethoxy)benzoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	401.41
163			1-(3-(trifluoromethyl)benzoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	385.05
164			1-(5-bromo-2-furoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	386.14
165			1-(5-nitro-2-furoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	352.19

166			1-(5-phenyl-2-furoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	383.24
167			1-(3-chloro-2-thienylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	357.09
168			1-(4-methyl-2-thienylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	337.16
169			1-(5-methyl-2-thienylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	337.14
170			1-(2,5-dichloro-3-thienylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	392.31
171			1-(3-furoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	307.24
172			1-(5-phenyl-3-isoxazolylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	384.71
173			1-[5-(2-thienyl)-1H-pyrazol-3-yl-carbonyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	389.06
174			1-[5-(2-furyl)-1H-pyrazol-3-yl-carbonyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	373.32

175			1-(5-nitro-2-thienylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	368.25
176			1-benzyloxybenzoyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	422.04
177			1-(3-methyl-2-furoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	321.06
178			1-(3-ethoxy-2-thienylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	367.18
179			1-(5-acetyl-2-thienylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	365.22
180			1-(5-phenyl-2-thienylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	399.31
181			1-[3-(2-methyl-1,3-thiazol-4-yl)-benzoyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	414.21
182			1-(5-chloro-4-methoxy-3-thienylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	387.4
183			1-(5-methylthio-2-thienylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	369.25

Example 184

1-(3-chloro-4-methyl-2-thienylcarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

To a solution of the Compound of Example 3 (64 mg, 0.301 mmol) and TEA (70 μ l) in CH₂Cl₂ (8 ml) stirred at ambient temperature was added 3-chloro-4-methylthienyl chloride (66.6 mg, 0.331 mmol) in 2 ml of CH₂Cl₂. The reaction mixture was stirred for 6 h at ambient temperature. After dilution with water and 1 N NaOH, the organic layer was separated and washed with water, dried over Na₂SO₄ and evaporated to dryness *in vacuo*. Purification by flash chromatography (CHCl₃) yielded the title compound (112 mg).

10 **MS:** [M+H]⁺ = 371.86

By the same method the following compounds were obtained using the appropriate commercial acid chlorides:

15 Example 185

1-[3-(1,3-thiazol-2-yl)-benzoyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

MS: [M+H]⁺ = 400.70

Example 186

1-[3-(2-pyrimidinyl)-benzoyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

20 **MS:** [M+H]⁺ = 395.51

Example 187

1-(3-nitro-2-pyridyl)-4-(4-oxo-pent-2-ynylidene)-piperidine

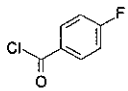
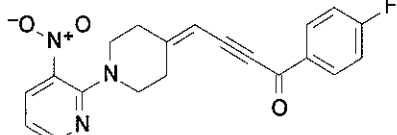
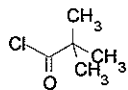
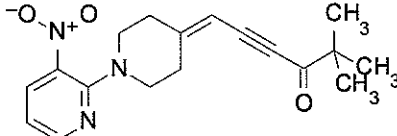
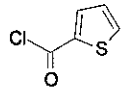
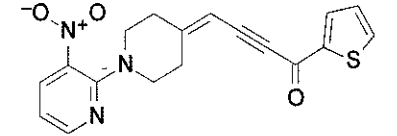
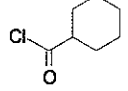
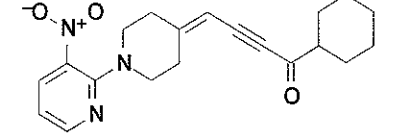
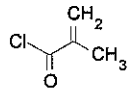
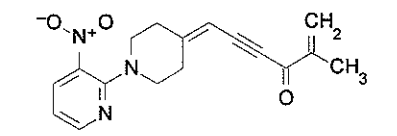
To a solution of Compound 1c (52 mg; 0.213 mmol), acetyl chloride (46 μ l, 0.647 mmol), *bis*(triphenyl)palladium(II)dichloride (4.49 mg, 0.0064 mmol) and copper (I) iodide (1.62 mg, 0.085 mmol) in anhydrous THF (5 ml), was added triethylamine (85 μ l, 0.61 mmol) and the reaction mixture was stirred, in a closed vessel, at 60°C for 5 h, cooled to ambient temperature poured into water and extracted with EtOAc. The combined extracts were washed with NaOH 0.1N, water, dried over Na₂SO₄ and evaporated to dryness *in vacuo*. Purification by flash chromatography (EtOAc - Petroleum Ether 25 : 75), afforded 17.5 mg of the title product.

30 **MS:** [M+H]⁺ = 286.10

Examples 188 to 192 (Table IX)

These compounds were synthesized following the procedure described in Example 193 but substituting reagent B (see table IX below; commercially available) for acetyl chloride. Purification was carried out by automated flash liquid chromatography (Horizon™ – Biotage) eluting with Petroleum Ether – EtOAc gradient from 100:0 to 20:80 or CH₂Cl₂ – EtOAc from 100:0 to 20:80.

TABLE IX

Ex.	Reagent B	Structure	Compound Name	LC-MS M/Z
188			1-(3-nitro-2-pyridyl)-4-[4-(4-fluorophenyl)-4-oxo-but-2-ynylidene]-piperidine	366.15
189			1-(3-nitro-2-pyridyl)-4-(5,5-dimethyl-4-oxohex-2-ynylidene)-piperidine	328.24
190			1-(3-nitro-2-pyridyl)-4-[4-(2-thienyl)-4-oxo-but-2-ynylidene]-piperidine	354.19
191			1-(3-nitro-2-pyridyl)-4-(4-cyclohexyl-4-oxo-but-2-ynylidene)-piperidine	354.26
192			1-(3-nitro-2-pyridyl)-4-(5-methyl-4-oxohex-5-en-2-ynylidene)-piperidine	312.23

Example 1931-(3-nitro-2-pyridyl)-4-[3-(3,5-difluoro-4-methoxyphenyl)-prop-2-ynylidene]-piperidine

A mixture of Compound 1c (50 mg, 0.206 mmol), 4-bromo-2,6-difluoroanisole (45.9 ml, 0.206 mmol), *bis*(triphenylphosphine)palladium(II)dichloride (7.23 mg, 0.012 mmol), CuI (3.92 mg, 0.206 mmol) in anhydrous and degassed triethylamine (3 ml) was heated at 80°C under a nitrogen atmosphere for 2 h in a sealed vessel. The reaction mixture was cooled, filtered on Celite, poured into water and extracted with EtOAc. The combined organic

layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness *in vacuo* to afford a residue, which was purified by flash chromatography (EtOAc – Petroleum Ether 10:90) affording the title product (22 mg).

MS: [M+H]⁺ = 386.52

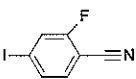
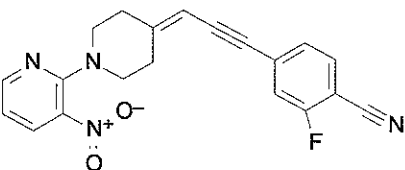
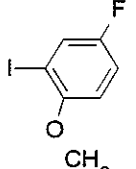
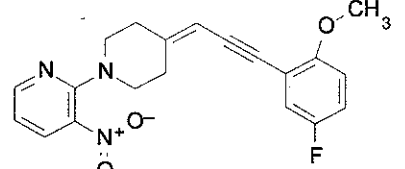
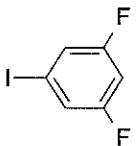
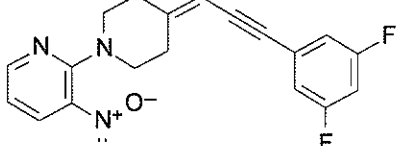
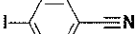
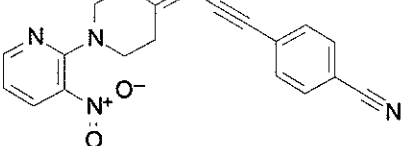
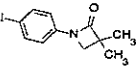
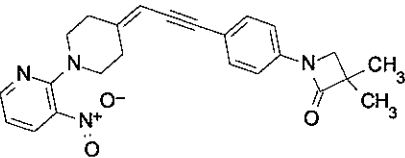
5

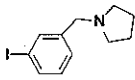
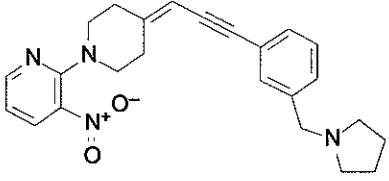
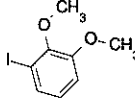
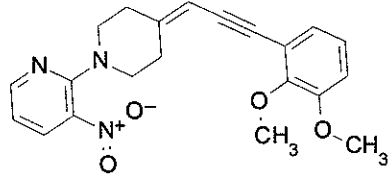
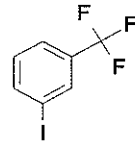
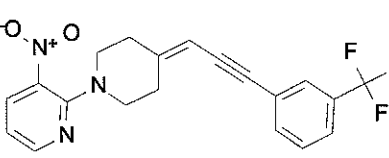
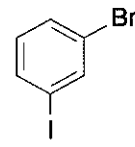
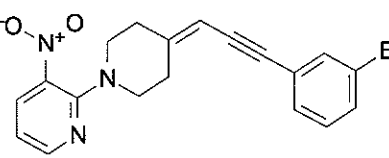
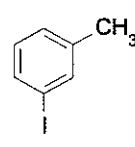
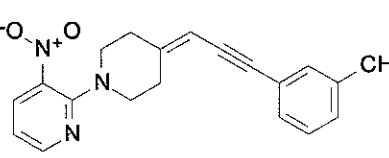
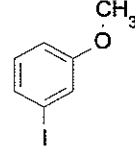
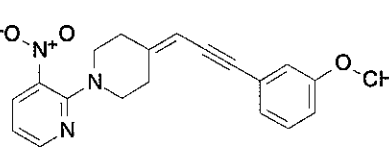
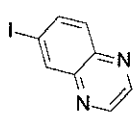
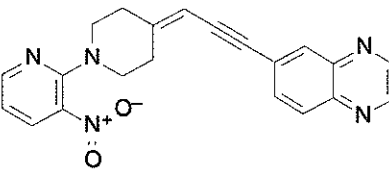
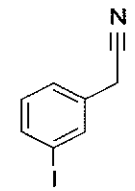
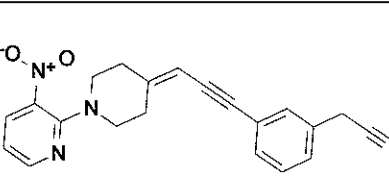
Examples 194 to 209 (Table X)

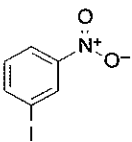
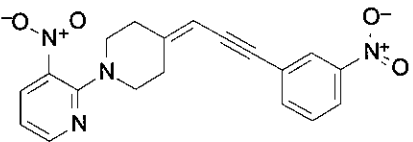
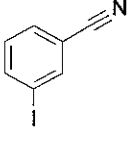
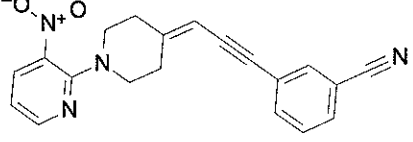
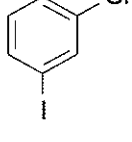
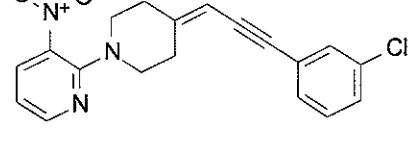
These compounds were synthesized following the procedure described in Example 193 but substituting reagent B (see table X below; commercially available) for 4-bromo-2,6-difluoroanisole. Purification was carried out by automated flash liquid chromatography (HorizonTM – Biotage) eluting with Petroleum Ether – EtOAc gradient from 100:0 to 20:80.

10

TABLE X

Ex.	Reagent B	Structure	Compound Name	LC-MS M/Z
194			1-(3-nitro-2-pyridyl)-4-[3-(4-cyano-3-fluorophenyl)-prop-2-ynylidene]-piperidine	363.3
195			1-(3-nitro-2-pyridyl)-4-[3-(5-fluoro-2-methoxyphenyl)-prop-2-ynylidene]-piperidine	368.4
196			1-(3-nitro-2-pyridyl)-4-[3-(3,5-difluorophenyl)-prop-2-ynylidene]-piperidine	356.3
197			1-(3-nitro-2-pyridyl)-4-[3-(4-cyanophenyl)-prop-2-ynylidene]-piperidine	345.4
198			1-(3-nitro-2-pyridyl)-4-[3-{4-[3-(3,3-dimethyl-2-oxo-1-azetidinyl)-phenyl]-prop-2-ynylidene}-piperidine	417.5

199			1-(3-nitro-2-pyridyl)-4-{3-[4-(1-pyrrolidinylmethyl)-phenyl]-prop-2-ynylidene}-piperidine	403.5
200			1-(3-nitro-2-pyridyl)-4-[3-(2,3-dimethoxyphenyl)-prop-2-ynylidene]-piperidine	380.4
201			1-(3-nitro-2-pyridyl)-4-[3-(3-(trifluoromethyl)phenyl)-prop-2-ynylidene]-piperidine	388.3
202			1-(3-nitro-2-pyridyl)-4-[3-(3-bromophenyl)-prop-2-ynylidene]-piperidine	399.3
203			1-(3-nitro-2-pyridyl)-4-[3-(3-methylphenyl)-prop-2-ynylidene]-piperidine	334.4
204			1-(3-nitro-2-pyridyl)-4-[3-(3-methoxyphenyl)-prop-2-ynylidene]-piperidine	350.4
205			1-(3-nitro-2-pyridyl)-4-[3-(6-quinolyl)-prop-2-ynylidene]-piperidine	372.4
206			1-(3-nitro-2-pyridyl)-4-[3-(3-cyanomethylphenyl)-prop-2-ynylidene]-piperidine	359.4

207			1-(3-nitro-2-pyridyl)-4-[3-(3-nitrophenyl)-prop-2-ynylidene]-piperidine	365.4
208			1-(3-nitro-2-pyridyl)-4-[3-(3-cyanophenyl)-prop-2-ynylidene]-piperidine	345.4
209			1-(3-nitro-2-pyridyl)-4-[3-(3-chlorophenyl)-prop-2-ynylidene]-piperidine	354.8

Example 210

1-(t-butoxycarbonyl)-4-(hept-2-ynylidene)-piperidine

A mixture of palladium tetrakis(triphenylphosphine) (21 mg, 0.018 mmol), butylamine (2.5 ml) and Compound 43a (200 mg, 0.724 mmol) were stirred at room temperature for 45 minutes. Copper iodide (10.3 mg, 0.05 mmol) was then added, followed by hex-1-yne (41.6 μ l, 0.362 mmol). The solution was heated for 3-5 hours at 70°C till change in colour to depth blue. The reaction was quenched with ammonium chloride, extracted with diethyl ether, washed with brine, dried over magnesium sulphate, filtered, concentrated to dryness and purified by preparative HPLC-MS e affording the title product (78 mg).

MS: $[M+H]^+ = 278.4$

Examples 211 to 219

These compounds were synthesized following the procedure described below (method A or method B, Table XI) using commercially available starting materials. Purification was carried out by automated flash liquid chromatography (HorizonTM – Biotage) eluting with Petroleum Ether – EtOAc gradient from 100:0 to 20:80 or by classical flash chromatography (Petroleum Ether – EtOAc mixtures).

Method A: A mixture of Compound 1c (36 mg; 0.148 mmol), Reagent B (0.296 mmol), bis(triphenylphosphine)palladium(II)dichloride (3.60 mg, 0.0051 mmol) and tetrabutylammonium fluoride (155 mg, 0.593 mmol) was heated in a sealed vessel at 80°C

and the melted mixture was stirred at 80°C for 1.5 hours, cooled to ambient temperature and rinsed with EtOAc. The EtOAc solution was washed with water, dried over Na₂SO₄ and evaporated to dryness *in vacuo*. Purification by flash chromatography (EtOAc-ETP 15:85), afforded the title products.

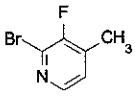
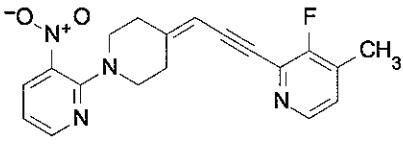
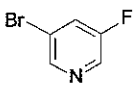
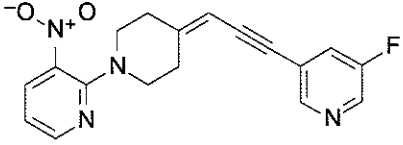
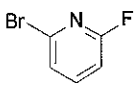
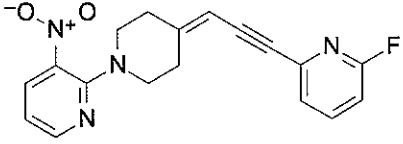
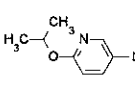
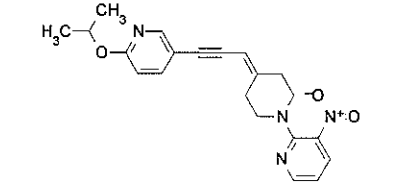
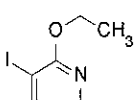
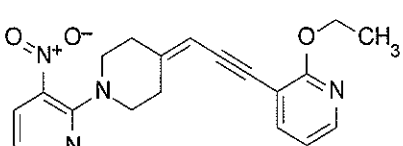
5

Method B: A solution of Compound 1c (23 mg; 0.946 mmol), Reagent B (0.253 mmol), *tetrakis*(triphenylphosphine)palladium(0) (8 mg, 0.0069 mmol) and copper(I) iodide (2 mg, 0.0105 mmol) in triethylamine (4 ml), in a sealed vessel, was stirred at 90°C for 2 h, cooled to ambient temperature, poured into water and extracted with EtOAc. The EtOAc solution was washed with water, dried over Na₂SO₄ and evaporated to dryness *in vacuo*. Purification by flash chromatography (EtOAc-ETP 2:8), afforded the title products.

10

TABLE XI

Ex.	Reagent B	Structure	Compound Name	LC-MS M/Z	Method
211			1-(3-nitro-2-pyridyl)-4-[3-(6-trifluoromethyl-3-pyridyl)-prop-2-ynylidene]-piperidine	389.10	A
212			1-(3-nitro-2-pyridyl)-4-[3-(2-fluoro-6-methyl-3-pyridyl)-prop-2-ynylidene]-piperidine	353.14	B
213			1-(3-nitro-2-pyridyl)-4-[3-(3-bromo-2-chloro-4-pyridyl)-prop-2-ynylidene]-piperidine	434.99	B
214			1-(3-nitro-2-pyridyl)-4-[3-(3-bromo-2-fluoro-4-pyridyl)-prop-2-ynylidene]-piperidine	418.97	B

215			1-(3-nitro-2-pyridyl)-4-[3-(3-fluoro-4-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine	353.14	A
216			1-(3-nitro-2-pyridyl)-4-[3-(5-fluoro-3-pyridyl)-prop-2-ynylidene]-piperidine	339.16	A
217			1-(3-nitro-2-pyridyl)-4-[3-(6-fluoro-2-pyridyl)-prop-2-ynylidene]-piperidine	339.16	A
218			1-(3-nitro-2-pyridyl)-4-[3-(6-isopropoxy-3-pyridyl)-prop-2-ynylidene]-piperidine	379.23	B
219			1-(3-nitro-2-pyridyl)-4-[3-(2-ethoxy-3-pyridyl)-prop-2-ynylidene]-piperidine	365.11	B

Example 220

1-(5-nitro-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

The title compound was prepared following the procedure described for the compound of Example 53, but substituting NMP with N,N-dimethylacetamide and substituting 2-fluoropyridine with 2-bromo-5-nitropyridine. Purification was carried out by automated flash liquid chromatography (HorizonTM – Biotage) eluting with CHCl₃ - 1.4 N MeOH NH₃ 100 : 0.5.

¹H-NMR (CDCl₃, δ): 2.42 - 2.54 (m, 2H), 2.67 (s, 3H); 2.75 - 2.90 (m, 2H), 3.83 - 3.95 (m, 4H), 5.70 (s, 1H), 6.60 - 6.70 (m, 1H), 7.12 - 7.20 (m, 1H); 7.28 - 7.38 (m, 1H); 7.60 - 7.70 (m, 1H); 8.20 - 8.30 (m, 1H); 9.08 (d, J = 4 Hz, 1H).

MS: [M+H]⁺ = 335.17

Example 221

1-(6-methoxy-3-nitro-2-pyridyl)-4-[3-(3,5-difluorophenyl)-prop-2-ynylidene]-piperidine

1-(t-butoxycarbonyl)-4-[3-(3,5-difluorophenyl)-prop-2-ynylidene]-piperidine (Compound

5 221a)

A mixture of the Compound 43a (0.110 g, 0.40 mmol), palladium *tetrakis*(triphenylphosphine) (0.023 g, 0.02 mmol), copper(I) iodide (0.0078 g, 0.04 mmol) and 1-ethynyl-3,5-difluorobenzene (49 μ L, 0.4 mmol) and TEA (2.5 ml) was heated for 3 h at 80°C. Afterwards, the reaction mixture was cooled, poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness in vacuo to afford a residue (0.062 g.), used in the next step without further purification.

¹H-NMR (CDCl₃, δ): 1.50 (s, 9H), 2.27-2.37 (m, 2H), 2.52-2.60 (m, 2H), 3.45-3.55 (m, 4H), 5.56 (s, 1H), 6.74-6.82 (m, 1H), 6.91-6.98 (m, 2H).

15 MS: [M+H]⁺ = 334.15

4-[3-(3,5-difluorophenyl)-prop-2-ynylidene]-piperidine (Compound 221b)

To a solution of Compound 221a (0.090 g, 0.27 mmol) in CHCl₃ (1 ml) was added trifluoroacetic acid (0.42 ml, 5.4 mmol) and the reaction mixture was then stirred at 70°C for 15 min. until the complete conversion of the reagent was observed by LC-MS. After cooling to ambient temperature, water was added and the solution was alkalized by addition of 2 N NaOH. The solution was extracted with CH₂Cl₂, the organic layer washed with brine and dried over Na₂SO₄ affording the title compound (0.051 g).

¹H-NMR (CDCl₃, δ): 1.85 (s, 1H, broad), 2.27-2.38 (m, 2H), 2.52-2.62 (m, 2H), 2.90-3.00 (m, 4H), 5.49 (s, 1H), 6.72-6.81 (m, 1H), 6.90-6.98 (m, 2H).

25 MS: [M+H]⁺ = 234.26

1-(6-methoxy-3-nitro-2-pyridyl)-4-[3-(3,5-difluorophenyl)-prop-2-ynylidene]-piperidine

A solution of Compound 221b (0.046 mg, 0.197 mmol), 2-chloro-6-methoxy-3-nitropyridine (34.6 mg, 0.18 mmol), potassium carbonate (50.3 mg, 0.36 mmol) in N,N-dimethylacetamide was heated in a microwave oven at 165°C for 3 min. Afterwards, the reaction mixture was cooled, poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness in vacuo

to afford a residue, which was purified by flash chromatography (EtOAc – Petroleum Ether 5 : 95) affording the title product (0.058 g).

MS: $[M+H]^+ = 386.16$

5 Example 222

1-(5-bromo-2-pyrimidinyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

The title compound was prepared following the procedure described for the compound of Example 53, but substituting NMP with N,N-dimethylacetamide and substituting 2-fluoropyridine with 5-bromo-2-iodopyrimidine and reacting the mixture at ambient
10 temperature. Purification was carried out by automated flash liquid chromatography (HorizonTM – Biotage) eluting with CHCl₃ - 1.4 N MeOH NH₃ 100 : 0.5. White solid. Yield: 64.1%.

¹H-NMR (CDCl₃, δ): 2.35 - 2.45 (m, 2H), 2.59 (s, 3H); 2.63 - 2.75 (m, 2H), 3.83 - 3.95 (m, 4H), 5.65 (s, 1H), 7.04 - 7.14 (m, 1H), 7.22 - 7.30 (m, 1H); 7.50 - 7.60 (m, 1H); 8.32 (s, 2H).
15

MS: $[M+H]^+ = 370.10$

Example 223

1-(3-methyl-5-nitro-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

20 The title compound was prepared following the procedure described for the compound of Example 53, but substituting N,N-dimethylacetamide for NMP and substituting 2-bromo-3-methyl-5-nitropyridine for 2-fluoropyridine. Purification was carried out by automated flash liquid chromatography (HorizonTM – Biotage) eluting with CHCl₃ - 1.4 N MeOH NH₃ 100 : 0.25. Yellow solid. Yield: 97.3%.

25 **¹H-NMR** (CDCl₃, δ): 2.39 (s, 3H), 2.46 - 2.56 (m, 2H), 2.59 (s, 3H); 2.74 - 2.85 (m, 2H), 3.51 - 3.61 (m, 4H), 5.66 (s, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H); 7.56 (t, J = 8.0 Hz, 1H); 8.15 (s, 1H), 8.98 (s, 1H).

MS: $[M+H]^+ = 349.23$

30 Example 224

1-(5-cyano-3-methyl-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

The title compound was prepared following the procedure described for the compound of Example 53, but substituting N,N-dimethylacetamide for NMP and substituting 5-cyano-2-fluoro-3-methylpyridine for 2-fluoropyridine. Purification was carried out by automated

flash liquid chromatography (HorizonTM – Biotage) eluting with EtOAc – Petroleum Ether 2:8. Yellowish solid. Yield: 81.3%.

¹H-NMR (CDCl₃, δ): 2.33 (s, 3H), 2.45 - 2.56 (m, 2H), 2.66 (s, 3H); 2.77 – 2.88 (m, 2H), 3.40 - 3.51 (m, 4H), 5.65 (s, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H); 7.57 (s, 1H); 7.58 – 7.75 (m, 1H), 8.40 (s, 1H).

MS: [M+H]⁺ = 329.22

Example 225

1-(6-cyano-3-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

A mixture of the compound of Example 3 (0.102 g, 0.48 mmol), 5-bromo-2-cyanopyridine (0.073 g, 0.40 mmol), cesium carbonate (0.658 g, 2 mmol), 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (8.8 mg, 0.05 mmol), palladium(II) acetate (0.0046 mg, 0.05 mmol), in anhydrous and degassed THF (3 ml) was heated in a microwave oven at 110°C for 15 min in a sealed vessel. The reaction mixture was cooled, poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness *in vacuo* to afford a residue, which was purified by flash chromatography (EtOAc – Petroleum Ether 1:1) affording the title product (0.013 g).

¹H-NMR (CDCl₃, δ): 2.45 - 2.54 (m, 2H), 2.61 (s, 3H), 2.72 – 2.90 (m, 2H), 3.48 - 3.60 (m, 4H), 5.68 (s, 1H), 7.05 – 7.20 (m, 2H), 7.22 – 7.35 (m, 1H); 7.50 – 7.70 (m, 2H); 8.35 (s, 1H).

MS: [M+H]⁺ = 315.17

Example 226

1-(4-methyl-3-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

A mixture of the compound of Example 3 (0.102 g, 0.48 mmol), 3-bromo-4-methylpyridine (0.046 g, 0.40 mmol), cesium carbonate (0.658 g, 2 mmol), 2-(dicyclohexylphosphino)biphenyl (8.8 mg, 0.024 mmol), palladium(II) acetate (0.0027 mg, 0.012 mmol), in anhydrous and degassed toluene (3 ml) was heated in a microwave oven at 150°C for 15 min in a sealed vessel. The reaction mixture was cooled, poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness *in vacuo* to afford a residue, which was purified by flash chromatography (CHCl₃ – 1.4 N MeOH NH₃ 100 : 0.25) affording the title product (0.008 g).

¹H-NMR (*CDCl*₃, δ): 2.38 (s, 3H), 2.47 - 2.54 (m, 2H), 2.58 (s, 3H), 2.77 - 2.87 (m, 2H), 3.04 - 3.12 (m, 4H), 5.63 (s, 1H), 7.05 - 7.12 (m, 1H), 7.13 - 7.20 (m, 1H), 7.25 - 7.30 (m, 1H); 7.50 - 7.60 (m, 1H); 8.20 - 8.30 (m, 2H).

MS: $[M+H]^+ = 304.19$

5

Example 227

1-(4-isoquinolyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

A mixture of the compound of Example 3 (0.076 g, 0.36 mmol), 4-bromoisoquinoline (0.064 g, 0.30 mmol), cesium carbonate (0.494 g, 1.5 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (0.011 g, 0.024 mmol), palladium(II) acetate (0.0027 mg, 0.012 mmol) in anhydrous and degassed toluene (3 ml) was heated at reflux under a nitrogen atmosphere for 18 h. The reaction mixture was cooled, poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness *in vacuo* to afford a residue, which was purified by flash chromatography (CHCl₃ - 1.4 N MeOH NH₃ 100 : 0.25) affording the title product (0.061 g).

15

¹H-NMR (*CDCl*₃, δ): 2.59 (s, 3H), 2.62 - 2.73 (m, 2H), 2.91 - 3.02 (m, 2H), 3.23 - 3.36 (m, 4H), 5.70 (s, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H); 7.75 (t, J = 8.0 Hz, 1H); 7.89 (t, J = 8.0 Hz, 1H); 8.10 (d, J = 8.0 Hz, 1H); 8.15 (s, 1H); 8.23 (d, J = 8.0 Hz, 1H); 9.04 (s, 1H).

20

MS: $[M+H]^+ = 340.21$

Example 228

1-(4-methyl-5-oxo-cyclopentenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

A mixture of the Compound of Example 3 (500 mg, 2.36 mmol), 3-methyl-1,2-cyclopentanedione (350 mg, 3.11 mmol), acetic acid (0.18 ml, 3.11 mmol) in ethanol (10 ml) was refluxed for 8 h. The reaction mixture was evaporated, poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness *in vacuo* to afford a residue, which was purified by automated flash liquid chromatography (HorizonTM - Biotage) eluting with Petroleum Ether - EtOAc 85 : 15, affording the title product as a brown solid.

30

MS: $[M+H]^+ = 307.61$

Example 229

1-(3-nitro-2-thienyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

A well homogenised mixture of Compound 3 (0.86 mmol), 2-chloro-3-nitrothiophen (0.95 mmol) and triethylamine (249 μ l, 1.74 mmol) in N,N-dimethylacetamide (15 ml) was stirred at ambient temperature for 4 h. Afterwards, the reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness *in vacuo* to afford a residue, which was purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with Petroleum Ether- EtOAc 1:1 affording the title product as a yellow solid.

MS: [M+H]⁺ = 340.45

Example 230

1-(5-nitro-2-furyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

A suspension of the Compound of Example 3 (100 mg, 0.47 mmol), 2-bromo-5-nitrofuran (98 mg, 0.51 mmol) and potassium carbonate (72 mg, 0.52 mmol) in DMF (2 ml) was stirred at ambient temperature for 4 h. Afterwards, the reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness *in vacuo* to afford a residue, which was purified by flash chromatography eluting with Petroleum Ether - EtOAc 6 : 4 affording the title product (94 mg) as a yellow solid.

MS: [M+H]⁺ = 324.33

Example 231

1-(5-phenylcarbamoyl-2-furyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

A well homogenised mixture of the Compound of Example 3 (100 mg, 0.47 mmol) and N-phenyl-5-bromofuran-2-carboxamide (125 mg, 0.47 mmol) was stirred at 120°C for 8 h. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness *in vacuo* to afford a residue, which was purified by flash chromatography eluting with Petroleum Ether - EtOAc 7 : 3, affording the title product (36 mg) as a brown solid.

MS: [M+H]⁺ = 398.51

Example 2321-(2-methyl-4-nitro-1H-5-imidazolyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

A well homogenised mixture of the Compound of Example 3 (100 mg, 0.47 mmol), 5-bromo-2-methyl-4-nitro-1H-imidazole (97 mg, 0.47 mmol) and potassium bicarbonate was stirred at 120°C for 8 h. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness *in vacuo* to afford a residue, which was purified by automated flash liquid chromatography (HorizonTM – Biotage), eluting with Petroleum Ether - EtOAc 7 : 3, affording the title product as a brown solid.

MS: [M+H]⁺ = 338.40

Example 2331-(t-butoxycarbonyl)-(3E)-3-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-pyrrolidine

15

1-(t-butoxycarbonyl)-(3E)-3-(3-trimethylsilyl-prop-2-ynylidene)-pyrrolidine (Compound 233a)

The title compound was prepared following the procedure described for Compound 1b using N-boc-3-pyrrolidinone instead of 1-(3-nitro-2-pyridyl)-4-oxo-piperidine. The crude was purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with Petroleum Ether - EtOAc 85 : 15, affording the title product as a colorless oil.

MS: [M+H]⁺ = 280.52

1-(t-butoxycarbonyl)-(3E)-3-(-prop-2-ynylidene)-pyrrolidine (Compound 233b)

The title compound was prepared following the procedure described for Compound 1c using Compound 233a instead of Compound 1b. The crude was purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with Petroleum Ether - EtOAc 95 : 5, affording the title product as a colorless oil.

MS: [M+H]⁺ = 208.74

30

1-(t-butoxycarbonyl)-(3E)-3-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-pyrrolidine

The title compound was obtained as described for the Compound of Example 1, but using in the last step Compound 233b instead of Compound 1c. The crude was purified by

automated flash liquid chromatography (HorizonTM – Biotage) eluting with Petroleum Ether - EtOAc 7 : 3, affording the title product as a brownish oil.

MS: $[M+H]^+ = 299.40$

5 Example 234

1-(3-nitro-2-pyridyl)-4-(4-phenyl-but-3-yn-2-ylidene)-piperidine

1-(t-butoxycarbonyl)-4-(2-hydroxy-4-phenyl-but-3-yn-2-yl)-piperidine (Compound 234a)

10 Into a solution of 1-(t-butoxycarbonyl)-4-acetylpiperidine (0.67 g, 2.95 mmol), prepared as described in WO 2004/041777, in THF (20 ml) cooled at -10°C was dropped a 1M solution of phenylethynylmagnesium bromide in THF (4.5 ml, 4.5 mmol). The reaction mixture was stirred at room temperature overnight. Afterwards, it was quenched with a saturated aq. solution of ammonium chloride and extracted with EtOAc. The combined organic layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness *in vacuo* to afford a residue, which was purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with Petroleum Ether - EtOAc 7:3, affording the title product as a pale yellow oil.

MS: $[M+H]^+ = 330.54$

20 1-(t-butoxycarbonyl)-4-(4-phenyl-but-3-yn-2-ylidene)-piperidine (Compound 234b)

1-(t-butoxycarbonyl)-4-(4-phenyl-but-3-yn-1-en-2-yl)-piperidine (Compound 234c)

A well homogenised mixture of Compound 235a (0.3 g, 0.911 mmol) and Burgess' reagent (Methyl N-(triethylammoniumsulphonyl)carbamate) (0.35 g, 1.49 mmol) was heated at 60°C for 2 h. Afterwards, the reaction mixture was cooled, poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness *in vacuo* to afford a residue, which was purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with Petroleum Ether - EtOAc 95:5, affording the title products as an oily mixture.

MS: $[M+H]^+ = 312.54$

30

4-(4-phenyl-but-3-yn-2-ylidene)-piperidine (Compound 234d)

4-(4-phenyl-but-3-yn-1-en-2-yl)-piperidine (Compound 234e)

The title compounds were prepared following the procedure described for the compound of Example 3, but using the mixture of Compounds 234b and 234c instead of the Compound

of Example 2 . After the usual work-up procedure, the crude was used for the next step without further purification.

MS: $[M+H]^+ = 212.32$

5 1-(3-nitro-2-pyridyl)-4-(4-phenyl-but-3-yn-2-ylidene)-piperidine

The title compound was prepared following the procedure described for the compound of Example 229, but using the mixture of Compounds 234d and 234e instead of Compound 3 and 2-chloro-3-nitropyridine instead of 2-chloro-3-nitrothiophen. The crude was purified by preparative RP LC-MS chromatography, using MS-C18 XTerra column 30x50 mm eluting
10 with ammonium bicarbonate 20 mM pH 8 buffer – acetonitrile gradient affording the title product and 1-(3-nitro-2-pyridyl)-4-(4-phenyl-but-3-yn-1-en-2-yl)-piperidine.

MS $[M+H]^+ = 333.35$

¹H-NMR (CDCl₃δ): 1.97 (s, 3H), 2.57-2.60 (m, 2H), 2.83-2.86 (m, 2H), 3.50-3.56 (m, 4H),
6.73-6.76 (m, 1H), 7.28-7.35 (m, 3H), 7.44-7.46 (m, 2H), 8.13-8.17 (m, 1H), 8.36-8.37 (m,
15 1H)

Example 235

1-(3-nitro-2-pyridyl)-4-[(2E)-3-phenyl-prop-2-enylidene]-piperidine

20 1-(t-butoxycarbonyl)-4-[(2E)-3-phenyl-prop-2-enylidene]-piperidine (Compound 235a)

Lithium bis(trimethylsilyl)amide (1M sol. in THF, 2.63 ml, 2.63 mmol) was added at -60°C under nitrogen atmosphere to a solution of diethyl cinnamylphosphonate (0.629 ml, 2.64 mmol). After 15 min. under stirring at the same temperature, N-Boc-4-piperidone (500 mg, 2.51 mmol) dissolved in THF (5 ml) was added. Stirring and cooling was maintained for 30
25 min and, after 2 h, the reaction mixture was quenched with water and with EtOAc. The combined extracts were washed, dried over Na₂SO₄ and evaporated to dryness affording the title product (752 mg), that was used in the next step without further purification.

MS: $[M+H]^+ = 300.25$

30 4-[(2E)-3-phenyl-prop-2-enylidene]-piperidine (Compound 235b)

To a solution of Compound 235a (752 mg, 2.51 mmol) in CHCl₃ (15 ml) was added trifluoroacetic acid (0.967 ml, 12.6 mmol) and the reaction mixture was stirred at 25°C for 24 h, until the complete conversion of the reagent was observed by LC-MS. Water was added followed by aq. NaOH (2 N) to give alkaline pH. Separation of the organic layer and

extraction of the aqueous layer with CH₂Cl₂, washing with brine and drying over Na₂SO₄ the combined organic layers, afforded the title compound. The crude was purified by flash chromatography (CHCl₃ - 1.6 M methanolic ammonia 100:5) affording the title product (359 mg).

5 **MS:** [M+H]⁺ = 200.22

1-(3-nitro-2-pyridyl)-4-[(2E)-3-phenyl-prop-2-enylidene]-piperidine

10 A well homogenised mixture of Compound 235b (175 mg, 0.878 mmol), 2-chloro-3-nitropyridine (153 mg, 0.966 mmol) and triethylamine (0.139 ml, 0.97 mmol) was stirred at 25°C for 24 h. The reaction crude was purified by flash chromatography (EtOAc – Petroleum Ether 8:2) affording the title product (270 mg).

MS: [M+H]⁺ = 322.20

¹H-NMR (CDCl₃δ): 2.45-2.50 (m, 2H), 2.65-2.70 (m, 2H), 3.50-3.60 (m, 4H), 6.14 (d, 1H), 6.56 (d, 1H), 6.70-6.80 (m, 1H), 6.95-7.15 (m, 1H) 7.20-7.45 (m, 5H), 8.16 (d, 1H), 8.37
15 (d, 1H).

Example 236

1-(3-nitro-imidazo[1,2-a]pyridin-2-yl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

20 A well homogenised mixture of the Compound of Example 3 (150 mg, 0.71 mmol), 2-chloro-3-nitroimidazo[1,2-a]pyridine (154 mg, 0.778 mmol) and triethylamine (0.152 ml, 1.06 mmol) was stirred at 25°C for 24 h. The reaction crude was purified by flash chromatography (EtOAc – Petroleum Ether 1:1) affording the title product (146 mg).

MS: [M+H]⁺ = 374.22

25 ¹H-NMR (CDCl₃δ): 2.50-2.70 (m, 5H), 2.85-2.90 (m, 2H), 2.78-2.87 (m, 1H), 3.75-3.85 (m, 4H), 5.68 (s, 1H), 7.25-7.30 (m, 1H), 7.45-7.65 (m, 3H), 9.50 (d, 2H).

Example 237

1-(3-nitro-2-pyridyl)-4-[3-(3-trifluoromethoxyphenyl)-prop-2-ynylidene]-piperidine

30 A mixture of Compound 1c (60 mg, 0.25 mmol), 3-trifluoromethoxy-iodobenzene (41,6 µl, 0.26 mmol), bis(triphenylphosphine)palladium(II)dichloride (8.65 mg, 0.01 mmol), CuI (4.69 mg, 0.1 mmol) in anhydrous and degassed triethylamine (3 ml) was heated at 80°C under a nitrogen atmosphere for 2 h in a sealed vessel. The reaction mixture was cooled,

filtered on Celite, poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried on Na₂SO₄ and evaporated to dryness *in vacuo* to afford a residue, which was purified by flash chromatography (EtOAc – Petroleum Ether 5 : 95) affording the title product (57 mg).

5 **MS:** [M+H]⁺ = 404.35

¹H-NMR (CDCl₃δ): 2.50-2.53 (m, 2H), 2.75-2.78 (m, 2H), 3.53-3.58 (m, 4H), 5.64 (s, 1H), 6.78-6.81 (m, 1H), 7.17-7.19 (m, 1H), 7.28-7.30 (m, 1H) 7.34-7.37 (m, 2H), 8.17-8.19 (m, 1H), 8.37-8.38 (m, 1H).

10 Example 238

1-(3-nitro-2-pyridyl)-4-[3-(2-oxo-1-pyrrolidinyl)-prop-2-ynylidene]-piperidine

1-(3-nitro-2-pyridyl)-4-(3-bromo-prop-2-ynylidene)-piperidine (Compound 238a)

A mixture of Compound 1c (200 mg, 0.82 mmol), CBr₄ (0.54 mg, 1.65 mmol), potassium hydroxide (0.138 mg, 2.46 mmol), 18-C-6 crown ether (21.8 mg, 0.823 mmol) and 10 ml of benzene was stirred at 65°C for 11 h. The reaction mixture was cooled to ambient temperature, diluted with EtOAc, washed with water, dried over Na₂SO₄ and evaporated to dryness *in vacuo*. The crude residue was purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with PE - EtOAc gradient from 98:2 to 80:20, affording the title product (111 mg) as a mixture with the starting material (77:23 Compound 238a : Compound 1c) and used as it was in the next reaction step.

1-(3-nitro-2-pyridyl)-4-[3-(2-oxo-1-pyrrolidinyl)-prop-2-ynylidene]-piperidine

A mixture of Compound 238a (111 mg, 0.345 mmol), cupric sulphate (11 mg, 0.69 mmol), 1,10-phenantroline (24.9 mg, 0.138 mmol), K₂CO₃ (95.4 mg, 0.69 mmol), 2-pyrrolidone (39.7 µl, 0.518 mmol) and 5 ml of toluene was stirred at 80 °C for 12 h. The reaction mixture was cooled to ambient temperature, diluted with EtOAc, washed with water, dried over Na₂SO₄ and evaporated to dryness *in vacuo*. The crude residue was purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with PE - EtOAc gradient from 98:2 to 0:10, giving the title product (2 mg)

MS: [M+H]⁺ = 327.15

¹H-NMR (CDCl₃, δ): 2.10-2.20 (m, 2H), 2.41-2.53 (m, 4H), 2.65-2.70 (m, 2H), 3.40-3.52 (m, 4H), 3.72-3.76 (m, 2H), 5.60 (s, 1H), 6.75-6.78 (m, 1H), 8.14-8.17 (m, 1H), 8.35 (s, 1H)

Example 239

1-(5-trifluoromethyl-3-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

A vial was filled with a mixture of the compound of Example 3 (84.9 mg, 0.4 mmol), 3-bromo-5-(trifluoromethyl)-pyridine (93 mg, 0.4 mmol), DIPEA (140 μ L, 0.8 mmol), 1 ml of anhydrous N-methylpyrrolidone and sealed. The vial was heated in a microwave oven at 160°C (200 W) for 2 h. The reaction mixture was then cooled to ambient temperature, diluted with EtOAc, washed with water, dried over Na₂SO₄ and evaporated to dryness *in vacuo*. The crude black oily residue was purified by preparative RP LC-MS chromatography, using MS-C18 XTerra column 30x50 mm eluting with ammonium bicarbonate 20 mM pH 8 buffer – acetonitrile gradient affording 1.8 mg of the title compound.

MS: [M+H]⁺ = 358.4

¹H-NMR (CDCl₃, δ): 2.42-2.53 (m, 2H), 2.59 (s, 3H), 2.79-2.82 (m, 2H), 3.43-3.47 (m, 4H), 5.67 (s, 1H), 7.10 (d, 1H, J = 8.0), 7.27 (d, 1H, J = 8.0 Hz), 7.35 (s, 1H), 7.56 (t, 1H, J = 8.0 Hz), 8.33 (s, 1H), 8.50 (s, 1H).

Example 240

1-(3-cyano-5-phenyl-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

Following the procedure reported above for the compound of Example 240 but replacing 5-(trifluoromethyl)-pyridine with 2-chloro-5-phenylnicotinonitrile the title product was synthesized. After the reaction work-up, the residue was purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with PE - EtOAc gradient from 9:1 to 4:6, affording the title product (10 %).

MS: [M+H]⁺ = 391.35

¹H-NMR (CDCl₃, δ): 2.52-2.57 (m, 2H), 2.62 (s, 3H), 2.75-2.80 (m, 2H), 3.85-3.95 (m, 4H), 5.68 (s, 1H), 7.08-7.15 (m, 1H), 7.25-7.70 (m, 7H), 8.00 (s, 1H), 8.61 (s, 1H).

MS: [M+H]⁺ = 391.35

Example 241

1-(2-propoxy-3-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

Into a flamed flask flushed with nitrogen a mixture of CuI (19.4 mg, 0.1 mmol), K₃PO₄ (425 mg, 2 mmol), ethylene glycol (112 μ L), 3-iodo-2-propoxypyridine (263 mg, 1 mmol) in 1 ml of *n*-Butanol were added 255 mg of the compound of Example 3 dissolved in 1 ml of *n*-Butanol. The suspension was heated at 100°C for 5 h. The reaction mixture was then

cooled to ambient temperature, diluted with EtOAc, washed with aq. NaHCO₃ and water, dried over Na₂SO₄ and evaporated to dryness *in vacuo*. After the work-up the residue was purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with PE - EtOAc 8:2. affording the title product (32 mg, 10 %).

5 **MS:** [M+H]⁺ = 348.43

¹H-NMR (CDCl₃, δ): 1.10 (t, J = 8.0 Hz, 3H); 1.85 - 1.92 (m, 2H); 2.53 - 2.56 (m, 2H); 2.58 (s, 3H); 2.83 - 2.85 (m, 2H); 3.14 - 3.19 (m, 4H); 4.35 (t, J = 8.0 Hz, 2H); 5.60 (s, 1H); 6.82 - 6.85 (m, 1H); 7.08 - 7.10 (m, 2H); 7.26 - 7.28 (m, 1H); 7.55 (t, J = 8.0 Hz, 1H); 7.80 (d, J = 8.0 Hz, 1H).

10

Example 242

1-(pyrido[2,3-b]pyrazin-7-yl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

Following the procedure reported for the compound Example 227 and using 7-bromopyrido[2,3-b]pyrazine instead of 4-bromoisoquinoline the title compound was prepared. Purification was done by automated flash liquid chromatography (HorizonTM-Biotage) eluting with CHCl₃ – 1.4 N NH₃ sol. in MeOH 100 : 0.25. Yield: 16 %.

15 **MS:** [M+H]⁺ = 342.41

¹H-NMR (CDCl₃, δ): 2.50 - 2.70 (m, 5H); 2.85 - 2.88 (m, 2H); 3.60 - 3.64 (m, 4H); 5.70 (s, 1H); 7.11 (d, J = 8.0 Hz, 1H); 7.28 (d, J = 8.0 Hz, 1H); 7.54 - 7.58 (m, 2H); 8.80 (m, 20 2H); 9.95 (d, J = 4.0 Hz, 1H).

Example 243

1-(3-cyano-2-thienyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

Following the procedure reported for the compound of Example 227 and using 2-bromo-3-cyanothiophene instead of 4-bromoisoquinoline the title compound was prepared. Purification was by RP LC-MS chromatography, using MS-C18 XTerra column 30x50 mm eluting with ammonium bicarbonate 20 mM pH 8 buffer – acetonitrile gradient affording the compound of the title. Yield: 22 %.

MS: [M+H]⁺ = 320.36

30 **¹H-NMR** (CDCl₃, δ): 2.53 - 2.58 (m, 5H); 2.83 - 2.85 (m, 2H); 3.58 - 3.60 (m, 4H); 5.66 (s, 1H); 6.51 (d, J = 8.0 Hz, 1H); 6.90 (d, J = 8.0 Hz, 1H); 7.10 (d, J = 8.0 Hz, 1H); 7.27 (d, J = 8.0 Hz, 1H); 7.56 (t, J = 8.0 Hz, 1H).

Example 244

1-(6-ethoxy-3-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

Following the procedure reported for the compound of Example 227 and using 5-bromo-2-ethoxypyridine instead of 4-bromoisoquinoline and tol-BINAP (2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl) instead of BINAP the title compound was prepared. After the work-up, the residue was purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with PE - EtOAc 8:2. affording the title product as a yellow oil. Yield: 10%.

MS: $[M+H]^+ = 334.19$

¹H-NMR (CDCl₃, δ): 1.40 (t, J = 8.0 Hz, 3H); 2.45 – 2.56 (m, 2H); 2.59 (s, 3H); 2.75 – 2.87 (m, 2H); 3.10 – 3.30 (m, 4H); 4.32 (q, J = 8.0 Hz, 2H); 5.61 (s, 1H); 6.69 (d, J = 8.0 Hz, 1H); 7.10 (d, J = 8.0 Hz, 1H); 7.27 (d, J = 8.0 Hz, 1H); 7.30 – 7.40 (m, 1H); 7.56 (t, J = 8.0 Hz, 1H); 7.83 (s, 1H).

Example 245

1-(3-nitro-2-pyridyl)-4-[3-(2,6-difluorophenyl)-prop-2-ynylidene]-piperidine

1-t-(butoxycarbonyl)-4-(prop-2-ynyl)-piperidine(Compound 245a)

Method A: The title compound was synthesized following the methodology described in U.S. Patent 6,265,434 (Caldwell *et al.*, July 24, 2001).

Method B: The title compound was synthesized following the methodology described for Compound 1c but using 1-(t-butoxycarbonyl)-4-(3-trimethylsilylprop-2-ynyl)-piperidine (Tatsunori S. et Al. Heterocycles 54(2), 747-755, 2001) instead of Compound 1b.

Traditional work-up procedure followed by flash column chromatography (EtOAc – Petroleum Ether 0.5 : 9.5) gave the title product as a colourless oil.

Method C: Into a solution of trimethylsilyldiazomethane (1.65 ml, 3.3 mmol) in THF (5 ml) cooled at -78°C was dropped BuLi (2.5 N in *n*-hexane, 1.14 ml, 2.86 mmol). The reaction mixture was kept at the same temperature for 30 min., then 1-Boc-4-oxoethylpiperidine (0.5 g, 2.2 mmol) dissolved in THF (25 ml) was dropped and stirring was continued at the same temperature for 1 h. After having allowed the reaction to reach spontaneously ambient temperature, it was quenched with a saturated aq. solution of ammonium chloride and extracted with EtOAc. The combined organic layers were washed with brine, dried on

Na₂SO₄ and evaporated to dryness *in vacuo* to afford a residue, which was purified by flash chromatography (EtOAc – Petroleum Ether 1.5 : 8.5) affording the title product (0.19 g).

¹H-NMR (CDCl₃δ): 1.17-1.33 (m, 2H), 1.47 (s, 9H), 1.60-1.71 (m, 1H), 1.73-1.82 (m, 2H), 2.12-2.14 (dd, 1H), 2.18-2.21 (dd, 2H), 2.69-2.74 (m, 2H), 4.12-4.20 (m 2H)

5 MS: [M+H]⁺ = 224.4

1-(t-butoxycarbonyl)-4-[3-(3,5-difluorophenyl)-prop-2-ynyl]-piperidine (Compound 245b)

The title compound was obtained as described for the Compound of Example 1, but using in the last step Compound 245a instead of Compound 1c and 3,5-difluoro-iodobenzene instead
10 of 2-bromo-6-methylpyridine. The crude was purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with Petroleum Ether - EtOAc 85 :15, affording the title product as a colorless oil.

MS: [M+H]⁺ = 336.98

15 4-[3-(3,5-difluorophenyl)-prop-2-ynyl]-piperidine (Compound 245c)

The title compound was prepared following the procedure described for the the Compound of Example 3, using the Compound of Example 246b instead of the Compound of Example 2. After the usual work-up procedure, the crude was used for the next step without further purification.

20 MS: [M+H]⁺ =236.32

The title compound was prepared as described for the compound of Example 229 but starting from Compound 245c instead of compound 3 and using diisopropylethylamine (DIPEA) instead of triethylamine and 2-chloro-3-nitropyridine instead of 2-chloro-3-
25 nitrothiophen. After the work-up, the residue was purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with PE – EtOAc gradient from 9:1 to 7:3 affording the title product. Yellow oil. Yield: 55%.

MS: [M+H]⁺ = 356.34

¹H-NMR (CDCl₃, δ): 2.5-2.6 (m, 2H), 2.8 (m, 2H), 3.5-3.6 (m, 4H), 5.7 (m, 1H), 6.75-6.85
30 (m, 1H), 6.9-7.0 (m, 2H), 7.2-7.3 (m, 1H), 8.15-8.20 (m, 1H), 8.35-8.40 (m, 1H)

Examples 246 to 249 (Table XII)

These compounds (see table XII) were prepared following the procedure described in Example 193 but substituting reagent B for 4-bromo-2,6-difluoroanisole. Purification was

carried out by automated flash liquid chromatography (HorizonTM – Biotage) eluting with Petroleum Ether – EtOAc gradient from 100:0 to 20:80.

TABLE XII

5

Example	Reagent B (Note)	Chem. Name	LC-MS M/Z	¹ H-NMR (CDCl ₃ , δ)
246	1-(3-iodobenzyl)-1H-pyrazole	1-(3-nitro-2-pyridyl)-4-{3-[3-(1H-pyrazol-1-ylmethyl)-phenyl]-prop-2-ynylidene}-piperidine	400.45	2.45-2.55 (m, 2H), 2.7-2.8 (m, 2H), 3.45-3.55 (m, 4H), 5.3 (m, 2H), 5.6 (m, 1H), 6.25-6.35 (m, 1H), 6.75-6.85 (m, 1H), 7.15-7.25 (m, 1H), 7.3 (m, 2H), 7.4 (m, 2H), 7.6 (m, 1H), 8.15-8.20 (m, 1H), 8.35-8.40 (m, 1H)
247	N-(3-iodo-2-pyridyl)-pivalamide; THF as co-solvent; ambient temperature	1-(3-nitro-2-pyridyl)-4-{3-[2-(2,2-dimethylpropionylamino)-3-pyridyl]-prop-2-ynylidene}-piperidine	420.48	1.4 (s, 9H), 2.45-2.55 (m, 2H), 2.7-2.8 (m, 2H), 3.5-3.6 (m, 4H), 5.7 (m, 1H), 6.8 (m, 1H), 7.25 (m, 1H), 7.9-8.0 (m, 1H), 8.2 (m, 1H), 8.4 (m, 1H), 8.5 (m, 1H), 9.2 (s, 1H)
248	1-(3-iodobenzyl)-4-methylpiperazine	1-(3-nitro-2-pyridyl)-4-{3-[3-(4-methylpiperazin-1-ylmethyl)-phenyl]-prop-2-ynylidene}-piperidine	432.54	
259	3-acetyl-iodobenzene	1-(3-nitro-2-pyridyl)-4-[3-(3-acetylphenyl)-prop-2-ynylidene]-piperidine	362.40	2.45-2.55 (m, 2H), 2.6 (s, 3H), 2.7-2.8 (m, 2H), 3.45-3.55 (m, 4H), 5.65 (m, 1H), 6.8 (m, 1H), 7.4-7.5 (m, 1H), 7.6-7.7 (d, 1H), 7.9 (d, 1H), 8.0 (s, 1H), 8.2 (d, 1H), 8.4 (m, 1H)

Example 250

1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(4-fluoro-2-pyridyl)-prop-2-ynylidene]-piperidine

10 1-(*t*-butoxycarbonyl)-4-[3-(4-fluoro-2-pyridyl)-prop-2-ynylidene]-piperidine (Compound 250a)

The title compound was prepared following the procedure described for the Compound of Example 193, but using Compound 2b instead of Compound 1c and 2-chloro-4-fluoropyridine instead of 4-bromo-2,6-difluoroanisole. After the usual work-up procedure, purification was carried out by automated flash liquid chromatography (HorizonTM – Biotage) eluting with PE – EtOAc gradient from 95:5 to 60:40. Yield: 38.5 %.

MS: [M+H]⁺ = 317.2

4-[3-(4-fluoro-2-pyridyl)-prop-2-ynylidene]-piperidine (Compound 250b)

Compound 250a was converted into the title compound by using the procedure described for Compound 221b. Compound 250b was used in the next step without further purification.

5 Yield: 76 %

MS: $[M+H]^+ = 217.2$

1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(4-fluoro-2-pyridyl)-prop-2-ynylidene]-piperidine

10 The title product was prepared following the method described above for the Compound of Example 229 but replacing Compound 3 with compound 250b, replacing 2-chloro-3-nitrothiophen with 2-chloro-6-methyl-3-nitropyridine and using N-methylpyrrolidone instead of N,N-dimethylacetamide. Purification by automated flash liquid chromatography (HorizonTM – Biotage) eluting with a PE - EtOAc gradient from 95:5 to 60:40 afforded the title compound as a yellow solid. Yield: 36%.

15 MS: $[M+H]^+ = 353.2$

¹H-NMR (CDCl₃, δ): 2.49 (s, 3H), 2.50-2.57 (m, 2H), 2.75-2.85(m, 2H), 3.45-3.60 (m, 4H), 5.65 (s, 1H), 6.63 (d, J=8Hz, 1H), 6.95-7.05 (m, 1H), 7.17 (d, J=8Hz, 1H), 8.10 (d, J=8Hz, 1H), 8.52-8.60 (m, 1H).

20 Example 251

1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(3,5-difluorophenyl)-prop-2-ynylidene]-piperidine

4-(3-trimethylsilyl-prop-2-ynylidene)-piperidine (Compound 251a)

25 The title compound was synthesized following the procedure described for the compound of Example 3 starting from Compound 2a instead of the Compound of Example 2.

An alternative procedure that can be utilized to carry out the reaction includes stirring at ambient temperature (instead at 70°C) for 4 h and overnight resting.

The reaction mixture was washed with water and aq. K₂CO₃, dried on anhydrous Na₂SO₄ and evaporated to dryness *in vacuo* and used in the next step without further purification.

30 MS: $[M+H]^+ = 194.24$

1-(6-methyl-3-nitro-2-pyridyl)-4-(3-trimethylsilyl-prop-2-ynylidene)-piperidine (Compound 251b)

Method A: The title compound was synthesized following the procedure described for the Compound of Example 250, but replacing Compound 250b with Compound 251a. The crude residue obtained from a standard work-up procedure was used in the next step without further purification.

Method B: The title compound was prepared starting from 1-(6-methyl-3-nitro-2-pyridyl)-4-piperidone instead of 1-(3-nitro-2-pyridyl)-4-piperidone and following the procedure described for Compound 1b. The crude residue was used as an intermediate without further purification.

MS: $[M+H]^+ = 330.27$

1-(6-methyl-3-nitro-2-pyridyl)-4-(prop-2-ynylidene)-piperidine (Compound 251c)

The title compound was synthesized following the procedure described for Compound 1c, but using Compound 251b instead of Compound 1b. Purification by automated flash liquid chromatography (HorizonTM – Biotage) eluting with a PE - Acetone gradient from 97:3 to 9:1 afforded the title compound. Yield: 29%.

MS: $[M+H]^+ = 258.08$

1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(3,5-difluorophenyl)-prop-2-ynylidene]-piperidine

To a suspension of Compound 251c (70 mg, 0.27 mmol), sodium acetate trihydrate (74.2 mg, 0.55 mmol) and 1-bromo-3,5-difluorobenzene (33.5 μ l, 0.27 mmol) in 2.05 ml of DMF flushed with nitrogen was added *tetrakis*(triphenylphosphine)palladium(0) (15.8 mg, 0.014 mmol) and the reaction mixture was put into a microwave oven (Biotage) at 120°C for 10 min. Dilution with EtOAc, washing with H₂O and drying over Na₂SO₄ followed by evaporation and purification of the residue by automated flash liquid chromatography (HorizonTM – Biotage) (PE-CH₂Cl₂ 6:4) afforded 74 mg (73.7%) of the title compound.

MS: $[M+H]^+ = 370.27$

¹H-NMR (CDCl₃, δ): 2.49-2.53 (s and m, 5H), 2.72-2.78 (m, 2H), 3.51-3.59 (m, 4H), 5.61 (s, 1H), 6.64 (d, 1H, J = 8Hz), 6.75-6.82 (m, 1H), 6.94-6.98 (m, 2H), 8.11 (d, 1H, J=8Hz)

The following compounds were prepared in the same way as the Compound of Example 251 but substituting 1-bromo-3,5-difluorobenzene respectively with the shown halo derivatives:

Example 252

1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(3-fluorophenyl)-prop-2-ynylidene]-piperidine

From 1-bromo-3-fluorobenzene. Purification by automated flash chromatography (HorizonTM – Biotage) PE - EtOAc gradient from 97.5:2.5 to 9:1. Orange solid. Yield: 82

5 %

MS: $[M+H]^+ = 352.49$

¹H-NMR (CDCl₃, δ): 2.48-2.51 (m, 5H), 2.74-2.77 (m, 2H), 3.51-3.58 (m, 4H), 5.62 (s, 1H), 6.62 (d, 1H, J = 8Hz), 6.98-7.07 (m, 1H), 7.14 (d, 1H, J = 8Hz), 7.22 (m, 1H), 7.27-7.33 (m, 1H), 8.11 (d, 1H, J=8Hz)

10

Example 253

1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(2-pyridyl)-prop-2-ynylidene]-piperidine

From 2-bromopyridine. Purification by automated flash chromatography (HorizonTM – Biotage) PE - EtOAc gradient from 9:1 to 7:3. Yellow solid. Yield: 42 %

15 **MS:** $[M+H]^+ = 335.34$

¹H-NMR (CDCl₃, δ): 2.48-2.53 (s and m, 5H), 2.78-2.83 (m, 2H), 3.49-3.59 (m, 4H), 5.65 (s, 1H), 6.62 (d, 1H, J = 8Hz), 7.21-7.26 (m, 1H), 7.43-7.47 (dd, 1H), 7.66-7.71 (m, 1H), 8.10 (d, 1H, J=8Hz), 8.59-8.63 (dd, 1H)

20 Example 254

1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(6-fluoro-2-pyridyl)-prop-2-ynylidene]-piperidine

From 2-bromo-6-fluoropyridine. Purification by automated flash chromatography (HorizonTM – Biotage) PE - EtOAc gradient from 95: 5 to 9:1. Yellow oil. Yield: 68 %

MS: $[M+H]^+ = 353.33$

25 **¹H-NMR** (CDCl₃, δ): 2.49-2.54 (s and m, 5H), 2.77-2.82 (m, 2H), 3.51-3.59 (m, 4H), 5.64 (s, 1H), 6.64 (d, 1H, J = 8Hz), 6.86-6.91 (dd, 1H), 7.27-7.34 (dd, 1H), 7.73-7.80 (m, 1H), 8.12 (d, 1H, J=8Hz)

Example 255

30 1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(6-fluoro-3-pyridyl)-prop-2-ynylidene]-piperidine

From 5-bromo-2-fluoropyridine. Purification by automated flash chromatography (HorizonTM – Biotage) PE - EtOAc gradient from 95: 5 to 8:2. Yellow solid. Yield: 54 %

MS: $[M+H]^+ = 353.33$

¹H-NMR (CDCl₃, δ): 2.49-2.53 (s and m, 5H), 2.73-2.78 (m, 2H), 3.51-3.59 (m, 4H), 5.62 (s, 1H), 6.64 (d, 1H, J = 8Hz), 6.90-6.95 (dd, 1H), 7.79-7.85 (dd, 1H), 8.11 (d, 1H, J=8Hz), 8.31 (s, 1H)

5 Example 256

1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(2-fluoro-4-pyridyl)-prop-2-ynylidene]-piperidine

From 4-iodo-2-fluoropyridine. Purification by automated flash chromatography (HorizonTM – Biotage) PE - EtOAc gradient from 9: 1 to 8:2. Yellow solid. Yield: 60 %

MS: [M+H]⁺ = 353.33

10 ¹H-NMR (CDCl₃, δ): 2.51-2.55 (s and m, 5H), 2.74-2.79 (m, 2H), 3.52-3.60 (m, 4H), 5.64 (s, 1H), 6.65 (d, 1H, J = 8Hz), 6.94 (s, 1H), 7.16-7.19 (dd, 1H), 8.12 (d, 1H, J=8Hz), 8.185 (d, 1H, J = 4Hz)

Example 257

15 1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(5-fluoro-3-pyridyl)-prop-2-ynylidene]-piperidine

From 3-bromo-5-fluoropyridine. Purification by automated flash chromatography (HorizonTM – Biotage) PE - EtOAc gradient from 93: 7 to 7:3. Yellow solid. Yield: 56 %

MS: [M+H]⁺ = 353.33

20 ¹H-NMR (CDCl₃, δ): 2.49-2.54 (s and m, 5H), 2.73-2.78 (m, 2H), 3.51-3.60 (m, 4H), 5.64 (s, 1H), 6.64 (d, 1H, J = 8Hz), 6.45-6.49 (m, 1H), 8.11 (d, 1H, J=8Hz), 8.41 (s, 1H), 8.50 (s, 1H)

Example 258

1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(5-cyano-3-pyridyl)-prop-2-ynylidene]-piperidine

25 From 5-bromonicotinonitrile. Purification by automated flash chromatography (HorizonTM – Biotage) PE - EtOAc gradient from 9: 1 to 7:3. Yellow solid. Yield: 73 %

MS: [M+H]⁺ = 360.33

30 ¹H-NMR (CDCl₃, δ): 2.51-2.55 (s and m, 5H), 2.74-2.79 (m, 2H), 3.52-3.61 (m, 4H), 5.65 (s, 1H), 6.65 (d, 1H, J = 8Hz), 7.97 (s, 1H), 8.12 (d, 1H, J=8Hz), 8.77 (s, 1H), 8.84 (s, 1H).

Example 259

1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(2,5-difluorophenyl)-prop-2-ynylidene]-piperidine

From 2,5-difluoro-iodobenzene. Purification by automated flash chromatography (HorizonTM – Biotage) PE - EtOAc 97.5: 2.5. Yellow solid. Yield: 63 %.

MS: $[M+H]^+ = 370.34$

¹H-NMR (CDCl₃, δ): 2.49-2.53 (s and m, 5H), 2.75-2.80 (m, 2H), 3.51-3.59 (m, 4H), 5.65 (s, 1H), 6.63 (d, 1H, J = 8Hz), 6.96-7.08 (m, 2H), 7.09-7.15 (m, 1H), 8.11 (d, 1H, J=8Hz).

5 Example 260

1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(3,5-difluorophenyl)-prop-2-ynylidene]-piperidine

The title compound was synthesized following the procedure reported for the compound of Example 53 replacing the compound of Example 3, 2-fluoropyridine and TEA respectively with Compound 221b, 2-chloro-6-methylnicotinonitrile and potassium carbonate.

10 Purification by automated flash chromatography (HorizonTM – Biotage) eluting with PE - EtOAc 95: 5. Yellow solid. Yield: 61 %

MS: $[M+H]^+ = 350.11$

¹H-NMR (CDCl₃, δ): 2.40 – 2.55 (m, 5H); 2.70 – 2.80 (m, 2H); 3.75 – 3.88 (m, 4H); 5.60 (s, 1H); 6.63 (d, J = 8.0 Hz, 1H); 6.70 – 6.88 (m, 1H); 6.90 – 7.00 (m, 2H); 7.68 (d, J = 8.0
15 Hz, 1H).

Example 261

1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(3-fluorophenyl)-prop-2-ynylidene]-piperidine

20 1-(3-cyano-6-methyl-2-pyridyl)-4-(3-trimethylsilyl-prop-2-ynylidene)-piperidine
(Compound 261a)

The title compound was prepared by refluxing a solution of DIPEA and Compound 251a in MeCN for 20 h with 2-chloro-6-methylnicotinonitrile. After the usual work-up, the crude residue was purified by automated flash chromatography (HorizonTM – Biotage) eluting with

25 PE - EtOAc 98:2. Yield: 51 %.

The purified product contained an amount of the corresponding desilylated alkyne, but was used as an intermediate without further purification.

1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(3-fluorophenyl)-prop-2-ynylidene]-piperidine

30 The title compound was prepared in the same way as the Compound of Example 251 but replacing 1-bromo-3,5-difluorobenzene with 1-fluoro-3-iodobenzene and Compound 251c with Compound 261a. The residue from the work-up procedure was purified by preparative RP LC-MS chromatography, using MS-C18 XTerra column 30x50 mm eluting with ammonium bicarbonate 20 mM pH 8 buffer – acetonitrile gradient affording the title
35 compound as a colourless oil. Yield: 20.4 %

MS: $[M+H]^+ = 332.40$

¹H-NMR (CDCl₃, δ): 2.45 – 2.55 (m, 5H); 2.72 – 2.82 (m, 2H); 3.78 – 3.90 (m, 4H); 5.62 (s, 1H); 6.63 (d, J = 8.0 Hz, 1H); 6.98 – 7.06 (m, 1H); 7.12 – 7.18 (m, 1H); 7.21 – 7.26 (m, 1H); 7.26 – 7.34 (m, 1H); 7.68 (d, J = 8.0 Hz, 1H).

5

The following compounds were prepared in the same way as the Compound of Example 261 but substituting respectively the shown haloderivatives for 1-fluoro-3-iodobenzene:

Example 262

10 1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(4-pyridyl)-prop-2-ynylidene]-piperidine

From 4-iodopyridine. Purification by automated flash chromatography (Horizon™ – Biotage) PE - EtOAc 7: 3. Beige solid. Yield: 84.7 %.

MS: $[M+H]^+ = 315.25$

15 **¹H-NMR** (CDCl₃, δ): 2.47 (s, 3H); 2.51 – 2.55 (m, 2H); 2.72 – 2.83 (m, 2H); 3.78 – 3.90 (m, 4H); 5.65 (s, 1H); 6.64 (d, J = 8.0 Hz, 1H); 7.36 (d, J = 8.0 Hz, 2H); 7.68 (d, J = 8.0 Hz, 1H); 8.59 (d, J = 8.0 Hz, 2H).

Example 263

1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(6-fluoro-2-pyridyl)-prop-2-ynylidene]-piperidine

20 From 2-bromo-6-fluoropyridine.. Purification by automated flash chromatography (Horizon™ – Biotage) PE - EtOAc 9: 1. Pale yellow oil. Yield: 81.7 %

MS: $[M+H]^+ = 333.38$

25 **¹H-NMR** (CDCl₃, δ): 2.47 (s, 3H); 2.48 – 2.55 (m, 2H); 2.75 – 2.85 (m, 2H); 3.77 – 3.90 (m, 4H); 5.63 (s, 1H); 6.63 (d, J = 8.0 Hz, 1H); 6.85 – 6.93 (m, 1H); 7.30 – 7.35 (m, 1H); 7.67 (d, J = 8.0 Hz, 1H); 7.70 – 7.80 (m, 1H).

Example 264

1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(5-cyano-3-pyridyl)-prop-2-ynylidene]-piperidine

30 From 5-bromonicotinonitrile. Purification by automated flash chromatography (Horizon™ – Biotage) PE - EtOAc 9: 1. White solid. Yield: 65.1 %

MS: $[M+H]^+ = 340.38$

¹H-NMR (CDCl₃, δ): 2.50 (s, 3H); 2.50 – 2.60 (m, 2H); 2.72 – 2.83 (m, 2H); 3.79 – 3.92 (m, 4H); 5.64 (s, 1H); 6.66 (d, J = 8.0 Hz, 1H); 7.70 (d, J = 8.0 Hz, 1H); 7.98 (s, 1H); 8.78 (s, 1H); 8.84 (s, 1H).

Example 265

1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(2-fluoro-4-pyridyl)-prop-2-ynylidene]-piperidine

From 2-fluoro-4-iodopyridine. Purification by automated flash chromatography (Horizon™ – Biotage) PE - EtOAc 95: 5. White solid. Yield: 62.2 %

5 **MS:** $[M+H]^+ = 332.45$

¹H-NMR (CDCl₃, δ): 2.50 (s, 3H); 2.50 – 2.60 (m, 2H); 2.73 – 2.83 (m, 2H); 3.79 – 3.92 (m, 4H); 5.64 (s, 1H); 6.66 (d, J = 8.0 Hz, 1H); 6.95 (s, 1H); 7.19 (d, J = 4.0 Hz, 1H); 7.71 (d, J = 8.0 Hz, 1H); 8.19 (d, J = 4.0 Hz, 1H).

10 Example 266

1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(2-pyridyl)-prop-2-ynylidene]-piperidine

From 2-iodopyridine. Purification by automated flash chromatography (Horizon™ – Biotage) PE - EtOAc 72: 28. Orange oil. Yield: 76.2 %

MS: $[M+H]^+ = 315.46$

15 **¹H-NMR** (CDCl₃, δ): 2.46 (s, 3H); 2.47 – 2.57 (m, 2H); 2.77 – 2.88 (m, 2H); 3.77 – 3.92 (m, 4H); 5.65 (s, 1H); 6.62 (d, J = 8.0 Hz, 1H); 7.22 – 7.30 (m, 1H); 7.42 – 7.53 (m, 1H); 7.61–7.77 (m, 1H); 8.60 – 7.65 (m, 1H).

Example 267

20 1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(2,5-difluorophenyl)-prop-2-ynylidene]-piperidine

From 2,5-difluoro-iodobenzene. Purification by automated flash chromatography (Horizon™ – Biotage) PE - Et₂O 85: 15. Orange solid. Yield: 96.2 %

MS: $[M+H]^+ = 350.46$

25 **¹H-NMR** (CDCl₃, δ): 2.50 (s, 3H); 2.51 – 2.57 (m, 2H); 2.74 – 2.85 (m, 2H); 3.79 – 3.92 (m, 4H); 5.65 (s, 1H); 6.64 (d, J = 8.0 Hz, 1H); 6.95 – 7.08 (m, 2H); 7.09 – 7.16 (m, 1H); 7.70 (d, J = 8.0 Hz, 1H).

Example 268

1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(5-cyano-2-pyridyl)-prop-2-ynylidene]-piperidine

30 From 2-chloro-5-cyanopyridine. Purification by automated flash chromatography (Horizon™ – Biotage) PE - Et₂O 6: 4. Yellow solid. Yield: 45.2 %

MS: $[M+H]^+ = 340.38$

¹H-NMR (CDCl₃, δ): 2.52 (s, 3H); 2.53 – 2.60 (m, 2H); 2.78 – 2.89 (m, 2H); 3.81 – 3.93 (m, 4H); 5.68 (s, 1H); 6.66 (d, J = 8.0 Hz, 1H); 7.52 (d, J = 8.0 Hz, 1H); 7.72 (d, J = 8.0 Hz, 1H); 7.92 (d, J = 8.0 Hz, 1H); 8.85 (s, 1H).

5 Example 269

1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(6-fluoro-3-pyridyl)-prop-2-ynylidene]-piperidine

From 5-bromo-2-fluoropyridine. Purification by automated flash chromatography (HorizonTM – Biotage) PE-EtOAc 95: 5. Brownish oil. Yield: 54.8 %

MS: [M+H]⁺ = 333.31

10 ¹H-NMR (CDCl₃, δ): 2.50 (s, 3H); 2.50 – 2.57 (m, 2H); 2.72 – 2.82 (m, 2H); 3.79 – 3.92 (m, 4H); 5.62 (s, 1H); 6.65 (d, J = 8.0 Hz, 1H); 6.88 – 6.98 (m, 1H); 7.70 (d, J = 8.0 Hz, 1H); 7.77 – 7.89 (m, 1H); 8.31 (s, 1H).

Example 270

15 1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(5-fluoro-3-pyridyl)-prop-2-ynylidene]-piperidine

From 3-bromo-5-fluoropyridine. Purification by automated flash chromatography (HorizonTM – Biotage) PE - EtOAc 85:15. Yellowish solid. Yield: 42.8 %

MS: [M+H]⁺ = 333.38

20 ¹H-NMR (CDCl₃, δ): 2.48 (s, 3H); 2.49 – 2.58 (m, 2H); 2.72 – 2.83 (m, 2H); 3.79 – 3.92 (m, 4H); 5.63 (s, 1H); 6.64 (d, J = 8.0 Hz, 1H); 7.42 – 7.50 (m, 1H); 7.69 (d, J = 8.0 Hz, 1H); 8.41 (s broad, 1H); 8.50 (s broad, 1H).

Example 271

1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(3-fluorophenyl)-prop-2-ynylidene]-piperidine

25

1-(3-cyano-4-methoxy-2-pyridyl)-4-(3-trimethylsilyl-prop-2-ynylidene)-piperidine
(Compound 271a)

The title compound was synthesized following the procedure described for the Compound of Example 239, but replacing 3-bromo-5-(trifluoromethyl)-pyridine with 2-chloro-4-methoxynicotinonitrile, the compound of Example 3 with compound 251a and stirring at 135° C. Purification by automated flash chromatography (HorizonTM – Biotage) PE - EtOAc 100:30 afforded an ivory solid. Yield: 35 %.

30 MS: [M+H]⁺ = 326.31

1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(3-fluorophenyl)-prop-2-ynylidene]-piperidine

The title compound was prepared in the same way as the Compound of Example 251 but replacing Compound 251c with Compound 271a and 1-bromo-3,5-difluorobenzene with 1-fluoro-3-iodobenzene and adding 1 molar equivalent of tetrabutylammonium fluoride monohydrate to the starting reaction mixture.. Purification by automated flash chromatography (HorizonTM – Biotage) PE - EtOAc 100:30, then by CHCl₃ followed by a final purification by preparative RP LC-MS chromatography, using MS-C18 XTerra column 30x50 mm eluting with ammonium bicarbonate 20 mM pH 8 buffer – acetonitrile gradient afforded a colourless oil. Yield: 20.4 %. LCPREP. Colourless oil. Yield: 20.4 %

10 **MS:** [M+H]⁺ = 348.43

¹H-NMR (CDCl₃, δ): 2.51-2.54 (m, 2H), 2.77-2.79 (m, 2H), 3.81-3.87 (m, 4H), 3.99 (s, 3H), 5.62 (s, 1H), 6.39 (d, 1H, J 8Hz), 7.00-7.05 (m, 1H), 7.13-7.16 (m, 1H), 7.22-7.24 (m, 1H), 7.27-7.32 (m, 1H), 8.23 (d, 1H, J 4Hz)

15 The following compounds were prepared in the same way as the Compound of Example 271 but substituting 1-fluoro-3-iodobenzene respectively with the shown haloderivatives:

Example 272

1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(3,5-difluorophenyl)-prop-2-ynylidene]-piperidine

20 From 3,5-difluoro-bromobenzene. Purification by automated flash chromatography (HorizonTM – Biotage) CHCl₃ - MeOH/NH₃ 100:0.1. Ochre yellow solid. Yield: 65 %

MS: [M+H]⁺ = 366.35

¹H-NMR (CDCl₃, δ): 2.50-2.53 (m, 2H), 2.74-2.77 (m, 2H), 3.79-3.85 (m, 4H), 3.98 (s, 3H), 5.60 (s, 1H), 6.37 (d, 1H, J 4Hz), 6.76-6.81 (m, 1H), 6.95-6.97 (m, 2H), 8.22 (d, 1H, J 8Hz)

Example 273

1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(2,5-difluorophenyl)-prop-2-ynylidene]-piperidine

30 From 2,5-difluoro-iodobenzene. Purification by automated flash chromatography (HorizonTM – Biotage) CHCl₃ - MeOH/NH₃ 100:0.07. Ivory solid. Yield: 84 %

MS: [M+H]⁺ = 366.35

¹H-NMR (CDCl₃, δ): 2.51-2.53 (m, 2H), 2.77-2.80 (m, 2H), 3.80-3.85 (m, 4H), 3.98 (s, 3H), 5.64 (s, 1H), 6.37 (d, 1H, J 4Hz), 6.97-7.07 (m, 2H), 7.10-7.15 (m, 1H), 8.22 (d, 1H, J 8Hz).

Example 274

1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(2-pyridyl)-prop-2-ynylidene]-piperidine

From 2-bromopyridine. Purification by automated flash chromatography (HorizonTM – Biotage) CHCl₃ - MeOH/NH₃ 100:0.05. Pale yellow oil. Yield: 25 %

5 **MS:** [M+H]⁺ = 331.35

¹H-NMR (CDCl₃, δ): 2.51-2.54 (m, 2H), 2.81-2.84 (m, 2H), 3.79-3.84 (m, 4H), 3.97 (s, 3H), 5.66 (s, 1H), 6.37 (d, 1H, J 4Hz), 7.24-7.27 (m, 1H), 7.46-7.48 (m, 1H), 7.69-7.73 (m, 1H), 8.22 (d, 1H, J 4Hz), 8.61-8.62(m, 1H).

10 Example 275

1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(6-fluoro-2-pyridyl)-prop-2-ynylidene]-piperidine

From 2-bromo-6-fluoropyridine. Purification by automated flash chromatography (HorizonTM – Biotage) CHCl₃ - MeOH/NH₃ 100:0.05. Vitreous yellow solid. Yield: 47 %

MS: [M+H]⁺ = 349.41

15 ¹H-NMR (CDCl₃, δ): 2.51-2.53 (m, 2H), 2.78-2.81 (m, 2H), 3.79-3.84 (m, 4H), 3.98 (s, 3H), 5.63 (s, 1H), 6.37 (d, 1H, J 4Hz), 6.87-6.89 (m, 1H), 7.28-7.33 (m, 1H), 7.72-7.78 (m, 1H), 8.22 (d, 1H, J 4Hz).

Example 276

20 1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(6-fluoro-3-pyridyl)-prop-2-ynylidene]-piperidine

From 5-bromo-2-fluoropyridine. Purification by automated flash chromatography (HorizonTM – Biotage) CHCl₃ - MeOH/NH₃ 100:0.05. Ivory solid. Yield: 40 %

¹H-NMR (CDCl₃, δ): 2.51-2.53 (m, 2H), 2.75-2.78 (m, 2H), 3.80-3.85 (m, 4H), 3.98 (s, 3H), 5.62 (s, 1H), 6.38 (d, 1H, J 4Hz), 6.91-6.94 (m, 1H), 7.80-7.85 (m, 1H), 8.22 (d, 1H, J 4Hz), 8.31 (s, 1H)

MS: [M+H]⁺ = 349.41

Example 277

1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(2-fluoro-4-pyridyl)-prop-2-ynylidene]-piperidine

30 From 2-fluoro-4-iodopyridine. Purification by automated flash chromatography (HorizonTM – Biotage) PE – EtOAc 10:3. Hazel-brown solid. Yield: 97 %

MS: [M+H]⁺ = 349.41

¹H-NMR (CDCl₃, δ): 2.52-2.55 (m, 2H), 2.75-2.78 (m, 2H), 3.80-3.85 (m, 4H), 3.98 (s, 3H), 5.63 (s, 1H), 6.38 (d, 1H, J 4Hz), 6.95 (s, 1H), 7.17-7.19 (m, 1H), 8.18 (d, 1H, J 4Hz), 8.22 (d, 1H, J 4Hz)

5 Example 278

1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(5-fluoro-3-pyridyl)-prop-2-ynylidene]-piperidine

From 3-bromo-5-fluoropyridine. Purification by automated flash chromatography (HorizonTM – Biotage) PE – EtOAc 10:3. Ivory solid. Yield: 76 %

MS: [M+H]⁺ = 349.41

10 **¹H-NMR** (CDCl₃, δ): 2.51-2.54 (m, 2H), 2.75-2.78 (m, 2H), 3.80-3.85 (m, 4H), 3.98 (s, 3H), 5.63 (s, 1H), 6.38 (d, 1H, J 8Hz), 7.43-7.46 (m, 1H), 8.22 (d, 1H, J 4Hz), 8.41 (s, 1H), 8.50 (s, 1H).

Example 279

15 1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(5-cyano-3-pyridyl)-prop-2-ynylidene]-piperidine

From 3-bromo-5-cyanopyridine. Purification by automated flash chromatography (HorizonTM – Biotage) PE – EtOAc 10:3. Vitreous rosy solid. Yield: 71 %

MS: [M+H]⁺ = 356.41

20 **¹H-NMR** (CDCl₃, δ): 2.52-2.55 (m, 2H), 2.76-2.78 (m, 2H), 3.81-3.85 (m, 4H), 3.99 (s, 3H), 5.64(s, 1H), 6.39 (d, 1H, J 4Hz), 7.98 (s, 1H), 8.22 (d, 1H, J 4Hz), 8.77 (s, 1H), 8.84 (s, 1H)

Example 280

1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(5-cyano-2-pyridyl)-prop-2-ynylidene]-piperidine

25 From 2-chloro-5-cyanopyridine. Purification by automated flash chromatography (HorizonTM – Biotage) PE – EtOAc 10:3. Vitreous yellow solid. Yield: 7 %

MS: [M+H]⁺ = 356.48

30 **¹H-NMR** (CDCl₃, δ): 2.52-2.55 (m, 2H), 2.80-2.82 (m, 2H), 3.81-3.85 (m, 4H), 3.98 (s, 3H), 5.67(s, 1H), 6.39 (d, 1H, J 4Hz), 7.52 (d, 1H, J 4Hz), 7.92 (d, 1H, J 4Hz), 8.22 (d, 1H, J 4Hz), 8.85 (s, 1H).

Example 281

1-(3-cyano-6-methyl-2-pyridyl)-4-(4-phenyl-but-3-yn-2-ylidene)-piperidine

The title compound was synthesized following the procedure described for the Compound of Example 239 replacing 3-bromo-5-(trifluoromethyl)-pyridine with 2-chloro-6-methylnicotinonitrile and the compound of Example 3 with Compound 234d. Purification by automated flash chromatography (HorizonTM – Biotage) PE - EtOAc 9:1 afforded a colorless oil. Yield: 35 %.

MS: $[M+H]^+ = 328.51$

¹H-NMR (CDCl₃, δ): 1.98 (s, 3H), 2.48 (s, 3H), 2.57-2.60 (m, 2H), 2.84-2.87 (m, 2H), 3.83-3.88 (m, 4H), 4.18 (s, 3H), 6.59-6.61 (m, 1H), 7.34-7.36 (m, 3H), 7.45-7.47 (m, 2H), 7.68-7.70 (m, 1H).

Example 282

1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(6-bromo-2-pyridyl)-prop-2-ynylidene]-piperidine

Method A:

The title compound was prepared in the same way as the Compound of Example 251 but substituting 1-bromo-3,5-difluorobenzene with 2,6-dibromopyridine. Purification by automated flash chromatography (HorizonTM – Biotage) PE – EtOAc gradient from 1:0 to 8:2.

Yellow solid. Yield: 30 %

MS: $[M+H]^+ : 413.2$

¹H-NMR (CDCl₃, δ): 2.45-2.60 (m, 5H), 2.72-2.85 (m, 2H), 3.45-3.60 (m, 4H), 5.65 (s, 1H), 6.63 (d, J=8Hz, 1H) 7.25-7.58 (m, 3H), 8.11 (d, J=8Hz, 1H).

Method B:

1-(*t*-butoxycarbonyl)-4-[3-(6-bromo-2-pyridyl)-prop-2-ynylidene]-piperidine (Compound 282a)

The title compound was prepared from Compound 2a (in place of Compound 251c) following the procedure described for the compound of Example 251, using 2,6-dibromopyridine instead of 1-bromo-3,5-difluorobenzene and adding 1 molar equivalent of tetrabutylammonium fluoride monohydrate to the starting reaction mixture. After the work-up, the residue was purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with PE – EtOAc gradient from 10:0 to 8:2 affording the title product. White solid. Yield: 68%.

4-[3-(6-bromo-2-pyridyl)-prop-2-ynylidene]-piperidine (Compound 282b)

The title product was prepared following the method described for the Compound of Example 3 but using as starting material Compound 282a instead of the Compound of Example 2 and stirring at ambient temperature for 3 days. The reaction mixture was
5 evaporated to dryness in vacuo, taking up the residue several times with chloroform to remove excess trifluoroacetic acid.

1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(6-bromo-2-pyridyl)-prop-2-ynylidene]-piperidine

The title compound was prepared as described for the compound of Example 229 but
10 starting from Compound 282b instead of compound 3 and 2-chloro-6-methyl-3-nitropyridine instead of 2-chloro-3-nitrothiophen. An additional equivalent of TEA was used.. After the work-up, the residue was purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with PE – EtOAc gradient from PE:EtAc 95:5 to 6:4 affording the title product. Yellow oil. Yield: 95%.

Example 283

1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(3-ethoxyphenyl)-prop-2-ynylidene]-piperidine

The title Compound was prepared from Compound 251c following the procedure described for the compound of Example 251 but using 3-ethoxybromobenzene instead of 1-bromo-
20 3,5-difluorobenzene and adding 1 molar equivalent of tetrabutylammonium fluoride monohydrate to the starting reaction mixture.. After the work-up, the residue was purified by automated flash liquid chromatography (SP1TM – Biotage) eluting with PE – EtOAc gradient from PE:EtAc 1:0 to 8:2 affording the title product. Yellow solid. Yield: 46 %.

MS: [M+H]⁺ 378.44

¹H-NMR (CDCl₃, δ): 1.4-1.5 (m, 3H), 2.5-2.6 (m, 5H), 2.8 (m, 2H), 3.5-3.6 (m, 4H), 4.0-4.1 (m, 2H), 5.6 (m, 1H), 6.6 (d, 1H), 6.85-6.9 (d, 1H), 6.95-7.0 (s, 1H), 7.1 (d, 1H), 7.2-7.3 (m, 1H), 8.10-8.15 (d, 1H)

Example 284

1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(3-acetylphenyl)-prop-2-ynylidene]-piperidine

The title compound was prepared in the same way as the Compound of Example 193 but substituting Compound 251c for Compound 1c and 3-acetyl-iodobenzene for 4-bromo-2,6-difluoranisole. After the work-up, the residue was purified by automated flash liquid

chromatography (SP1TM – Biotage) eluting with PE – EtOAc gradient from 9:1 to 8:2 affording the title product. Yellow oil. Yield: 84.3 %.

MS: [M+H]⁺ 376.43

5 Example 285

1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(3-acetamidophenyl)-prop-2-ynylidene]-piperidine

The title Compound was prepared from Compound 251c following the procedure described for the compound of Example 251 using 3-bromoacetanilide instead of 1-bromo-3,5-difluorobenzene and adding 1 molar equivalent of tetrabutylammonium fluoride monohydrate to the starting reaction mixture. After the work-up, the residue was purified by automated flash liquid chromatography (SP1TM – Biotage) eluting with PE – EtOAc gradient from 7:3 to 4:6 affording the title product. Orange oil. Yield: 54%.

MS: [M+H]⁺ 391.44

¹H-NMR (CDCl₃, δ): 2.2 (s,3H), 2.5-2.6 (m, 2H), 2.8 (m, 2H), 3.5-3.6 (m, 4H), 5.6 (m,1H), 6.6 (d,1H), 7.05-7.15 (s,1H), 7.18-7.22 (d, 1H), 7.25-7.35 (m, 1H), 7.45-7.55 (d, 1H), 7.6 (s, 1H), 8.10-8.15 (d, 1H).

Example 286

1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(3-acetylphenyl)-prop-2-ynylidene]-piperidine

The title Compound was prepared from Compound 251c following the procedure described for the compound of Example 251 using 3-bromophenylacetone instead of 1-bromo-3,5-difluorobenzene and adding 1 molar equivalent of tetrabutylammonium fluoride monohydrate to the starting reaction mixture. After the work-up, the residue was purified by automated flash liquid chromatography (SP1TM – Biotage) eluting with PE – EtOAc gradient from 9:1 to 7:3 affording the title product. Orange oil. Yield: 41%.

MS: [M+H]⁺ 390.45

¹H-NMR (CDCl₃, δ): 2.2 (s,3H), 2.5-2.6 (s, 5H), 2.8 (m, 2H), 3.5-3.6 (m, 4H), 3.7 (s,2H), 5.6 (m,1H), 6.6 (d,1H), 7.1-7.2 (m,1H), 7.25 (m, 1H), 7.35 (m, 1H), 7.5 (d, 1H), 8.10-8.15 (d, 1H).

Examples 287 and 288

1-(6-methyl-3-nitro-2-pyridyl)-3-(3Z)-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

1-(6-methyl-3-nitro-2-pyridyl)-3-(3E)-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

1-(t-butoxycarbonyl)-3-(3Z)-[3-(3-trimethylsilyl-prop-2-ynylidene)-piperidine
(Compound 287a)

1-(t-butoxycarbonyl)-3-(3E)-[3-(3-trimethylsilyl-prop-2-ynylidene)-piperidine
(Compound 288a)

- 5 The title compounds were synthesized following the procedure described for Compound 1b but using 1-(t-butoxycarbonyl)-piperidin-3-one instead of 1-(3-nitro-2-pyridyl)-piperidin-4-one. After the work-up, the residue was purified by automated flash liquid chromatography (SP1TM – Biotage) eluting with PE – EtOAc gradient from PE - EtOAc 95:5 to 8:2 affording the title product. The less polar collected fractions corresponded to Compound 310a (9.5
10 %). The last eluted collected fractions were attributed to Compound 311a (10.3%).

Compound 287a MS: [M+H]⁺ 294.24

Compound 288a MS: [M+H]⁺ 294.26

1-(t-butoxycarbonyl)-3-(3Z)-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine
15 Compound 287b)

1-(t-butoxycarbonyl)-3-(3E)-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine
Compound 288b)

- Starting respectively from compounds 287a and 288a the title compounds were prepared following the procedure reported for the compound of example 251 but replacing 1-bromo-
20 3,5-difluorobenzene with 2-bromo-6-methylpyridine. After the work-up, the residue was purified by automated flash liquid chromatography (SP1TM – Biotage) eluting with PE – EtOAc gradient from PE - EtOAc 85:15 to 5:5 affording the title products. Compound 310b: 61 %. Compound 311b: 47%

Compound 287b MS: [M+H]⁺ 313.35

- 25 Compound 288b MS: [M+H]⁺ 313.33

3-(3Z)-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine (Compound 287c)
3-(3E)-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine (Compound 288c)

- The title compounds were obtained following the procedure described for the compound of
30 Example 3 and replacing respectively the Compound of Example 2 with Compound 287b or 288b and used without further purification in the next step.

Compound 287c MS: [M+H]⁺ 213.33

Compound 288c MS: [M+H]⁺ 213.41

1-(6-methyl-3-nitro-2-pyridyl)-3-(3Z)-(3-(6-methyl-2-pyridyl)-prop-2-ynylidene)-piperidine

1-(6-methyl-3-nitro-2-pyridyl)-3-(3E)-(3-(6-methyl-2-pyridyl)-prop-2-ynylidene)-piperidine

The title compounds were prepared as described for the compound of Example 229 but starting from Compound 287c or 288c instead of compound 3 and using 2-chloro-6-methyl-3-nitropyridine instead of 2-chloro-3-nitrothiophen. After the work-up, the residue was purified by automated flash liquid chromatography (SP1™ – Biotage) eluting with PE – EtOAc gradient from PE - EtOAc 7:3 to 6:4 affording the title products. Example 287: 18 %. Example 288: 11%

Compound 287MS: [M+H]⁺ 349.41

¹H-NMR (CDCl₃, δ): 1.87 (s, 2H), 2.46-2.53 (m, 5H), 2.60 (s, 3H), 3.61 (s, 2H), 4.35 (s, 2H), 5.62 (s, 1H), 6.57-6.59 (d, 1H), 7.11-7.13 (m, 1H), 7.35-7.37 (s, 1H), 7.61 (bs, 1H), 8.06-8.08 (d, 1H)

Compound 288 MS: [M+H]⁺ 349.34

¹H-NMR (CDCl₃, δ): 1.86-1.92 (m, 2H), 2.46 (s, 3H), 2.62 (s, 3H) 2.75-2.78 (m, 2H), 3.46-3.49 (m, 2H), 4.30 (s, 2H), 5.69 (s, 1H), 6.59-6.61 (d, 1H), 7.11-7.13 (m, 2H), 7.56-7.69 (s, 1H), 8.08-8.10 (d, 1H)

Example 289

1-(6-methyl-3-nitro-2-pyridyl)-4-(4-phenyl-but-3-yn-2-ylidene)-piperidine

The title compound was prepared as described for the compound of Example 229 but starting from Compound 234d instead of Compound 3 and 2-chloro-6-methyl-3-nitropyridine instead of 2-chloro-3-nitrothiophen. After the work-up, the residue was purified by automated flash liquid chromatography (Horizon™ – Biotage) eluting with PE – EtOAc 9:1 affording the title products as yellow oil. Yield: 87%.

MS: [M+H]⁺ = 348.52

¹H-NMR (CDCl₃, δ): 1.97 (s, 3H), 2.51 (s, 3H), 2.56-2.59 (m, 2H), 2.83-2.86 (m, 2H), 3.52-3.56 (m, 4H), 6.59-6.61 (m, 1H), 7.31-7.35 (m, 3H), 7.44-7.46 (m, 2H), 8.09-8.11 (m, 1H).

Example 290

1-(1-methyl-4-nitro-1H-imidazol-5-yl)-4-(4-phenyl-but-3-yn-2-ylidene)-piperidine

The title compound was prepared as described for the compound of Example 229 but starting from Compound 234d instead of compound 3 and using 5-chloro-1-methyl-4-nitroimidazole instead of 2-chloro-3-nitrothiophen. After the work-up, the residue was

purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with CH₂Cl₂ - MeOH 98:2; affording the title product as a pale yellow oil. Yield: 36.6 %.

MS: [M+H]⁺ = 337.41

¹H-NMR (CDCl₃, δ): 2.00 (s, 3H), 2.55-2.57 (m, 2H), 2.83-2.84 (m, 2H), 3.20-3.26 (m, 4H), 3.63 (s, 3H), 6.59-6.61 (m, 1H), 7.28-7.36 (m, 4H), 7.45-7.47 (m, 2H).

Example 291

1-(1-methyl-4-nitro-1H-imidazol-5-yl)-4-[3-(3,5-difluorophenyl)-prop-2-ynylidene]-piperidine

1-(1-methyl-4-nitro-1H-imidazol-5-yl)-4-(3-trimethylsilyl-prop-2-ynylidene)-piperidine
(Compound 291a)

A mixture of Compound 251a (600 mg, 3.01 mmol), 5-chloro-1-methyl-4-nitroimidazole (752 mg, 4.68 mmol) and DIPEA (1.1 ml, 6.2 mmol) in 20 ml of DMF was stirred at 135°C for 5h. After the usual work-up procedure, the residue was purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with EtOAc - MeOH gradient from 98:2 to 90:10; affording 250 mg of the title compound as mixture with the corresponding desilylated product.

MS: [M+H]⁺ 319.38

1-(1-methyl-4-nitro-1H-imidazol-5-yl)-4-[3-(3,5-difluorophenyl)-prop-2-ynylidene]-piperidine

The title compound was prepared according to the final two steps described for the compound of Example 251 but using Compound 291a instead of Compound 251b. After the usual work-up procedure, the residue was purified by automated flash liquid chromatography (HorizonTM – Biotage) eluting with EtOAc - MeOH gradient from 1:0 to 92:8; affording the title compound. Yield: 53%.

¹H-NMR (CDCl₃, δ): 2.51-2.54 (m, 2H); 2.75-2.77 (m, 2H); 3.24-3.29 (m, 4H); 3.63 (s, 3H); 5.63 (s, 1H); 6.67-6.81 (m, 1H); 6.95-6.97 (m, 2H); 7.28 (s, 1H)

MS: [M+H]⁺ 359.35

Example 292

1-(1-methyl-4-nitro-1H-imidazol-5-yl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

The title compound was prepared according to the final two steps described for the compound of Example 251 using Compound 291a instead of Compound 251b and 2-bromo-6-methylpyridine instead of 1-bromo-3,5-difluorobenzene. After the usual work-up procedure, the residue was purified by automated flash liquid chromatography (Horizon™ – Biotage) eluting with EtOAc - MeOH gradient from 1:0 to 92:8; affording the title compound. Yield: 50%.

MS: $[M+H]^+$ 338.42

¹H-NMR (CDCl₃, δ): 2.51-2.54 (m, 2H); 2.62 (s, 3H) 2.84 (bs, 2H); 3.24-3.29 (m, 4H); 3.63 (s, 3H); 5.68 (s, 1H); 7.12-7.14 (m, 1H); 7.28 (s, 1H); 7.32 (s, 1H); 7.60 (bs, 1H).

Example 293

1-(4-nitro-1H-imidazol-5-yl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

To a solution of 1,4-dinitroimidazole (207 mg, 1.31 mmol) and sodium hydrogen carbonate (242 mg, 2.88 mmol) in 4 ml of water and 0.16 ml of acetone was added drop wise a solution of the compound of Example 3 (278 mg, 1.31 mmol) in acetone. The reaction mixture was refluxed for 2 h, poured into water and extracted with EtOAc. The crude residue was purified by automated flash liquid chromatography (Horizon™ – Biotage) eluting with EtOAc - MeOH gradient from 1:0 to 92:8; affording the title compound not enough pure. So, it was purified again by preparative RP LC-MS chromatography, using MS-C18 XTerra column 30x50 mm eluting with ammonium bicarbonate 20 mM pH 8 buffer – acetonitrile gradient affording 4 mg of the title compound.

MS: $[M+H]^+$ 324.42

¹H-NMR (CDCl₃, δ): 2.52 (bs, 2H); 2.60 (s, 3H); 2.75 (bs, 2H); 3.73 (bs, 4H); 5.63 (s, 1H); 7.12-7.14 (d, 1H); 7.43-7.47 (s, 1H); 7.55 (s, 1H); 7.58-7.62 (s, 1H); 7.0-7.50 (bs, 1H).

Example 294

1-(3-cyano-2-thienyl)-4-[3-(2,5-difluorophenyl)-prop-2-ynylidene]-piperidine

1-(3-cyano-2-thienyl)-4-(3-trimethylsilyl-prop-2-ynylidene)-piperidine (Compound 294a)

The title compound was prepared following the procedure reported for the compound of Example 36 replacing 2-bromobenzene with 2-bromothiophene-3-carbonitrile,

palladium(II)acetate with tris(dibenzylideneacetone)dipalladium(0), and the compound of Example 3 with Compound 251a. After the work-up, the residue was purified by automated flash liquid chromatography (SP1TM – Biotage) eluting with PE – Diethyl Ether 95:5 affording the title product. Yellowish oil. Yield: 89%.

5 **MS:** $[M+H]^+ = 301.37$

¹H-NMR (CDCl₃, δ): 0.23 (s, 9H); 2.43-2.51 (m, 2H); 2.69-2.78 (m, 2H); 3.49-3.62 (m, 4H); 5.45 (s, 1H); 6.47 - 6.53 (m, 1H); 6.86 – 6.92 (m, 1H).

1-(3-cyano-2-thienyl)-4-[3-(2,5-difluorophenyl)-prop-2-ynylidene]-piperidine

10 The title Compound was prepared from Compound 294a following the procedure described for the compound of Example 251 using 2,5-difluoro-iodobenzene instead of 1-bromo-3,5-difluorobenzene and adding 1 molar equivalent of tetrabutylammonium fluoride monohydrate to the starting reaction mixture. After the work-up, the residue was purified by automated flash liquid chromatography (SP1TM – Biotage) eluting with PE – EtOAc 98:2
15 affording the title product. Yellow solid. Yield: 66%.

MS: $[M+H]^+ = 341.43$

¹H-NMR (CDCl₃, δ): 2.51-2.62 (m, 2H); 2.77-2.88 (m, 2H); 3.55-3.78 (m, 4H); 5.67 (s, 1H); 6.47 – 6.57 (m, 1H); 6.92 – 6.95 (m, 1H); 6.96 -7.18 (m, 3H).

20 Example 295

1-(6-methyl-3-nitro-2-pyridyl)-4-{3-[3-(3-methyl-1,2,4-oxadiazol-5-yl)-phenyl]-prop-2-ynylidene-piperidine

The title Compound was prepared from Compound 251c following the procedure described for the compound of Example 251 using 5-(3-bromophenyl)-3-methyl-1,2,4-oxadiazole
25 instead of 1-bromo-3,5-difluorobenzene and adding 1 molar equivalent of tetrabutylammonium fluoride monohydrate to the starting reaction mixture.. After the work-up, the residue was purified by automated flash liquid chromatography (SP1TM – Biotage) eluting with PE – EtOAc gradient from 9:1 to 7:3 affording the title product. Yellow oil. Yield: 61%.

30 **MS:** $[M+H]^+ = 416.45$

¹H-NMR (CDCl₃, δ): 2.45-2.55 (m, 8H); 2.75-2.85 (m, 2H); 3.45-3.55 (m, 2H); 3.55-3.65 (m, 2H); 5.63 (s, 1H); 6.6 (d, 1H); 7.45-7.55 (m, 1H); 7.65 (d, 1H); 8.00-8.05 (d, 1H); 8.10 (d, 1H); 8.2 (s, 1H).

Example 296

1-(2-cyano-3-pyrazinyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine

The title compound was prepared as reported for the compound of Example 229 but using 2-chloro-3-cyanopyrazine instead of 2-chloro-3-nitrothiophen. After the work-up, the residue was purified by automated flash liquid chromatography (SP1™ – Biotage) eluting with PE – EtOAc gradient from 7:3 affording the title product. Yellowish solid. Yield: 81%.

MS: $[M+H]^+ = 316.51$

¹H-NMR (CDCl₃, δ): 2.52-2.55 (m, 2H); 2.60 (s, 3H); 2.81-2.84 (m, 2H); 3.87-3.93 (m, 4H); 5.69 (s, 1H); 7.11 (d, 1H, J 8Hz); 7.27-7.29 (bs, 1H); 7.56-7.59 (m, 1H); 8.04 (s, 1H); 8.28 (s, 1H).

Example 297

Affinity of Selected Antagonists for mGlu5 Receptor Subtype

Radioligand Binding Assay at metabotropic glutamate receptor 5 in rat brain.

Methods

a) Membrane preparation: male Sprague Dawley rats (200-300g, Charles River, Italy) were killed by cervical dislocation and the forebrain (cortex, striatum and hippocampus) was homogenized (2x20 sec) in 50 vols of cold 50 mM Tris buffer pH 7.4, using a Politron homogenizer (Kinematica). Homogenates were centrifuged at 48000xg for 15 min, resuspended in 50 vols of the same buffer, incubated at 37°C for 15 min and centrifuged and resuspended two more times. The final pellets were frozen and stored at -80°C until use.

b) Binding assay: pellets from rat forebrain were resuspended in 100 vols of 20mM HEPES, 2 mM MgCl₂, 2mM CaCl₂, pH 7.4. The membranes were incubated in a final volume of 1 ml for 60 min at 25°C with 4 nM [³H]MPEP in the absence or presence of competing drugs. Non-specific binding was determined in the presence of 10 μM MPEP (Spooren W. *et al.*, Trends Pharmacol Sci. 22, 331-337, 2001). The incubation was stopped by the addition of cold Tris buffer pH 7.4 and rapid filtration through 0.5% polyethyleneimine pretreated Filtermat 1204-401 (Wallac) filters. The filters were then washed with cold buffer and the radioactivity retained on the filters was counted by liquid scintillation spectrometry.

c) Data Analysis: the inhibition of specific binding of the radioligands by the tested compounds was analyzed to estimate the inhibitory concentration 50% (IC₅₀) value by

using the non-linear curve-fitting software Prism 4.0 (Graphpad, San Diego, CA). The IC₅₀ value was converted to an affinity constant (K_i) by the equation of Cheng & Prusoff (Cheng, Y.C.& Prusoff, W.H. Biochem. Pharmacol. 22, 3099-3108, 1973).

Results

- 5 The affinity (K_i) of the compounds of the instant invention for mGlu5 receptor is between 0.1 and 1000 nM. For instance, Compound of Example 1 has a K_i of 0.37 nM.

Example 298

Affinity of Selected Antagonists for mGlu1 Receptor Subtype

- 10 Radioligand Binding Assay at metabotropic glutamate receptor 1 in rat brain.

Methods

- a) Membrane preparation: male Sprague Dawley rats (200-300g, Charles River, Italy) were killed by cervical dislocation and the cerebella were homogenized (2x20 sec) in 50 vols of cold 50 mM Tris buffer pH 7.4, using a Polotron homogenizer (Kinematica).
- 15 Homogenates were centrifuged at 48000xg for 15 min, resuspended in 50 vols of the same buffer, incubated at 37°C for 15 min and centrifuged and resuspended two more times. The final pellets were frozen and stored at -80°C until use.
- b) Binding assay: pellets from rat cerebellum were resuspended in 50 mM Tris, 1.2 mM MgCl₂, 2mM CaCl₂, pH 7.4; membranes were incubated in a final volume of 1 ml for
- 20 30 min at 0°C with 1.5 nM [³H] R214127 in absence or presence of competing drugs. Non-specific binding was determined in the presence of 1 μM R214127 (Lavreysen H et al Mol. Pharmacol. 63:1082-1093, 2003). The incubation was stopped by the addition of cold Tris buffer pH 7.4 and rapid filtration through 0.5% polyethyleneimine pretreated Filtermat 1204-401 (Wallac) filters. The filters were then washed with cold buffer and the
- 25 radioactivity retained on the filters was counted by liquid scintillation spectrometry.
- c) Data Analysis: the inhibition of specific binding of the radioligands by the tested compounds was analyzed to estimate the inhibitory concentration 50% (IC₅₀) value by using the non-linear curve-fitting software Prism 4.0 (Graphpad, San Diego, CA). The IC₅₀ value was converted to an affinity constant (K_i) by the equation of Cheng & Prusoff
- 30 (Cheng, Y.C.& Prusoff, W.H. Biochem. Pharmacol. 22, 3099-3108, 1973).

Results

The affinity of the compounds of the instant invention for mGlu1 receptor is at least 10 times lower than their affinity for mGlu5 receptor.

Example 299

Affinity of Selected Antagonists for Group II (mGlu2+ mGlu3) Receptor Subtypes

Radioligand Binding Assay at Group II metabotropic glutamate receptors in rat brain.

Methods

- 5 a) Membrane preparation: male Sprague Dawley rats (200-300g, Charles River, Italy) were killed by cervical dislocation and the forebrain (cortex, striatum and hippocampus) was homogenized (2x20 sec) in 50 vols of cold 50 mM Tris buffer pH 7.4, using a Politron homogenizer (Kinematica). Homogenates were centrifuged at 48000xg for 15 min, resuspended in 50 vols of the same buffer, incubated at 37°C for 15 min and centrifuged
10 and resuspended two more times. The final pellets were frozen and stored at -80°C until use.
- b) Binding assay: pellets of rat forebrain were washed three times with ice-cold assay buffer (10 mM potassium phosphate + 100 nM potassium bromide, pH 7.6). Final pellets were resuspended in 200 vols of the assay buffer and membranes incubated in a final
15 volume of 1 ml for 30 min at 0°C with 1 nM [³H]LY341495 in the absence or presence of competing drugs. Non-specific binding was determined in the presence of 1 mM L-glutamate (Wright R.A. et al. J. Pharmacol. Exp. Ther. 298:453-460, 2001; Mutel V et al. J. Neurochem. 75, 2590-2601, 2000). The incubation was stopped by the addition of cold Tris buffer pH 7.4 and rapid filtration through 0.5% polyethyleneimine pretreated Filtermat
20 1204-401 (Wallac) filters. The filters were then washed with cold buffer and the radioactivity retained on the filters was counted by liquid scintillation spectrometry.
- c) Data Analysis: the inhibition of specific binding of the radioligands by the tested compounds was analyzed to estimate the inhibitory concentration 50% (IC₅₀) value by using the non-linear curve-fitting software Prism 4.0 (Graphpad, San Diego, CA). The
25 IC₅₀ value was converted to an affinity constant (K_i) by the equation of Cheng & Prusoff (Cheng, Y.C. & Prusoff, W.H. Biochem. Pharmacol. 22, 3099-3108, 1973).

Results

The compounds of the instant invention did not affect [³H]LY341495 binding to Group II (mGlu2+ mGlu3) metabotropic glutamate receptors up to 1000 nM.

Example 300

Determination of Functional Activity at mGlu5 receptor as Accumulation of Inositol Phosphate

To determine the mode of action (agonist, antagonist or inverse agonist) of the test compounds at mGlu5 receptor, the concentration dependence of the stimulation of inositol phosphate production in response to the agonist (glutamate or quisqualic acid) was compared in the absence and presence of different concentrations of the test compounds themselves, measured in cells expressing mGlu5 receptor.

The cells were preincubated with the glutamate-degrading enzyme (1U/ml glutamate pyruvate transaminase) and 2 mM pyruvate to avoid the possible action of glutamate released from the cells. The stimulation was then conducted in a medium containing 10 mM LiCl, and different concentrations of the agonist (glutamate or quisqualic acid) or compounds to be tested for agonistic activity.

When antagonist activity was studied, test compounds were added to cell cultures 20 min prior to the addition of the agonist and further incubated in the presence of the agonist.

The incubation was stopped adding ice cold perchloric acid then samples were neutralized, centrifuged and the supernatant utilized for the determination of inositol phosphate (IP) accumulation using the The Biotrak D-*myo*-Inositol 1,4,5-trisphosphate assay system from Amersham Biosciences. D-*myo*-Inositol 1,4,5-trisphosphate (IP₃) may be measured in the range 0.19-25 pmol (0.08-10.5 ng) per tube. In the assay, unlabelled IP₃ competes with a fixed amount of [³H]-labelled IP₃ for a limited number of bovine adrenal IP₃ binding proteins. The bound IP₃ is then separated from the free IP₃ by centrifugation, which brings the binding protein to the bottom of the tube. The free IP₃ in the supernatant can then be discarded by simple decantation, leaving the bound fraction adhering to the tube.

Measurement of the radioactivity in the tube enables the amount of unlabelled IP₃ in the sample to be determined by interpolation from a standard curve.

EC₅₀/IC₅₀ were determined by nonlinear regression analysis using the software Prism 4.0 (Graphpad, San Diego, CA).

Results

The compounds of the instant invention showed antagonistic activity.

Example 301

Effect on Cystometry in Conscious Rats

Methods:

Male Sprague-Dawley rats [CrI: CD[®] (SD) IGS BR] of 300-400g b.w. supplied by Charles River Italia were used. The animals were housed with free access to food and water and maintained on a forced 12-hour-light/12-hour-dark cycle at 22-24°C of temperature, except during the experiment. To quantify urodynamic parameters in conscious rats, cystometrographic studies were performed according to the procedure previously reported (Guarneri et al., Pharmacol. Res. 24: 175, 1991).

Briefly, the rats were anaesthetised by intraperitoneal administration of 3 ml/kg of Equithensin solution (pentobarbital 30 mg/kg and chloral hydrate 125 mg/kg) and placed in a supine position. An approximately 10mm long midline incision was made in the shaved and cleaned abdominal wall. The urinary bladder was gently freed from adhering tissues, emptied and then cannulated via an incision in the bladder body, using a polyethylene cannula (0.58mm internal diameter, 0.96mm external diameter) which was permanently sutured with silk thread. The cannula was exteriorised through a subcutaneous tunnel in the retroscapular area, where it was connected to a plastic adapter in order to avoid the risk of removal by the animal. For drug testing, the rats were utilised one day after implantation.

On the day of the experiment, the rats were placed in modified Bollman cages, *i.e.*, restraining cages that were large enough to permit the rats to adopt a normal crouched posture, but narrow enough to prevent turning around. After a stabilisation period of about 20 minutes, the free tip of the bladder cannula was connected through a T-shaped tube to a pressure transducer (Statham P23XL) and to a peristaltic pump (Gilson Minipuls 2) for continuous infusion of a warm (37°C) saline solution into the urinary bladder, at a constant rate of 0.1 ml/minute. The intraluminal-pressure signal during infusion of saline into the bladder (cystometrogram) was continuously recorded on a polygraph (Rectigraph-8K San-ei with BM614/2 amplifier from Biomedica Mangoni) or stored on PC by data acquisition system (PowerLab, Chart 4 software, AD Instruments). From the cystometrogram, bladder volume capacity (BVC) was evaluated. BVC (in ml) is defined as the volume of saline infused into the bladder necessary to induce detrusor contraction followed by micturition. Basal BVC value was evaluated as the mean of the values observed in the cystometrograms recorded in an initial period of 30-60 minutes. At this point in the assay, the infusion was interrupted and the test compounds were administered orally by a stomach tube. The bladder infusion restarted and changes in BVC were evaluated from the mean values

obtained in the cystometrograms observed during 1, 2, and 3 hours after treatment. The compounds were administered in a volume of 2 ml/kg. Groups of control animals received the same amount of vehicle corresponding to a solution 0.5% methocel in water.

Under the given test conditions, measurement of BVC is equivalent to measurement of interval time between micturitions.

Statistical Analysis

Each experimental group was composed of 4-11 animals. All data were expressed as mean $\pm$ standard error. The percent change of BVC *versus* the basal value, as well as Δ value (difference in ml) of BVC (BVC at time "x" minus basal value), were also evaluated for each rat/time. In the figures, data are reported as % change *versus* the basal value.

Statistical analysis on BVC values, as well as on Δ values, was performed by S.A.S./STAT software, version 6.12. The difference between vehicle and active treatment effect was evaluated on Δ values of BVC, whereas the difference between the values at different times *versus* the basal values was evaluated on original BVC data.

Results

The time course of the effects of the orally administered doses of Example 1 is shown in Figure 1. The compound administered at 1 and 3 mg/kg p.o. proved effective in increasing the bladder volume capacity (Figure 1).

The time course of the effects of the orally administered doses of Example 10 is shown in Figure 2. The administration of 0.3 mg/kg slightly increased the bladder volume capacity (not statistical significant); the dose of 1 mg/kg proved effective in increasing bladder volume capacity (effect statistically significant after 2 and 3 hours from treatment).

The same results were obtained with Example 5 and 6.

The time course of the effect of the reference compound MTEP, orally administered at 1 and 3 mg/kg, is shown in Figure 3. The dose of 1 mg/kg showed only a slight increase of bladder volume capacity, whereas the dose of 3 mg/kg induced a sustained increase of this parameter, that resulted statistically significant from the vehicle group after 3 hours from treatment.

The activity of compounds of the invention and reference standard expressed as MED (*i.e.* Minimal Effective Dose that induces statistically significant increase of bladder volume capacity) is given in Table XIII.

TABLE XIII

Examples	"In vivo" cystometry MED (mg/kg os)
Example 1	3
Example 5	0.1
Example 6	1
Example 9	1
Example 10	1
Example 32	3
Example 37	3
Example 49	0.3
Example 50	1
Example 61	1
Example 196	3
Example 202	0.3
MTEP	3

Example 302

5 Plasma Extravasation in the Dura Mater of Rats Induced by Electrical Stimulation of the Trigeminal Ganglion

Electrical stimulation of the trigeminal ganglion induces inflammation in the dura mater which causes plasma extravasation. This animal model is widely accepted for testing drugs useful in migraine.

- 10 Male Wistar rats weighing 175-190 g are anaesthetised with 50 mg/kg i.p. of pentobarbital and the jugular vein is cannulated for injection of drugs. The animals are placed in a stereotaxic frame. Symmetrical boreholes are drilled 3.0 mm laterally and 3.2 mm posteriorly from bregma and the electrodes are lowered 9.5 mm from dura mater. The test compound or control-vehicle solution are administered intravenously 10 min prior to
- 15 electrical stimulation of the right trigeminal ganglion (5 min; 2.0 mA, 5 Hz, 5 ms duration and Evans blue (30 mg/kg i.v.), is given 5 min prior to electrical stimulation as a marker of plasma protein extravasation. 15 minutes after the end of the stimulation period the animals are perfused with 50 ml saline via the left cardiac ventricle to remove intravascular Evans blue. The dura mater is removed, blotted dry and weighed. Tissue Evans blue is extracted
- 20 in 0.3 ml formamide at 50° C. for 24 h. Dye concentrations are measured with a spectrophotometer at 620 nm wavelength, interpolated on a standard curve and expressed as ng Evans blue content per mg tissue weight.

Extravasation is expressed as the quotient calculated by dividing the Evan's blue content of the stimulated side by the Evan's blue content of the unstimulated side.

Example 303

5 GERD model in dogs

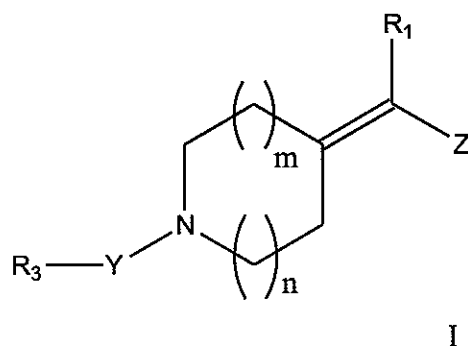
Beagle dogs are equipped with a chronic esophagostomy to allow passage of a manometric catheter and a pH probe along the esophagus and the stomach.

Following recording of the basal pressure of the Lower Esophageal Sphincter and the stomach, compounds under evaluation and vehicle for control are administered by
10 intravenous route.

Transient Lower Esophageal Sphincter Relaxations (TLESRs) and acid reflux are induced by infusion of an acidified meal followed by stomach distension using a peristaltic pump infusing air at 40 ml/min, in accordance to Stakeberg J. and Lehmann A., (Neurogastroenterol. Mot. (1999) 11: 125-132). Active compounds reduce dose-
15 dependently the frequency of TLESRs and TLESRs associated with acid reflux. The activity is determined as % inhibition of both parameters as compared to vehicle control.

CLAIMS

1. A compound having the general formula I



wherein

Z represents a group of the formula $-\text{C}\equiv\text{C}-\text{R}_2$ or $-\text{CH}=\text{CH}-\text{R}_2$;

R_1 represents

- a hydrogen or halogen atom, or
- a hydroxy, cyano, phenyl, C_1 - C_6 alkyl, C_1 - C_6 alkylcarbonyl, C_1 - C_6 alkoxy, C_1 - C_6 alkoxycarbonyl, C_1 - C_6 alkylcarbonyloxy, C_1 - C_6 alkoxycarbonyloxy, C_1 - C_6 alkylthio, di- $(\text{C}_1$ - C_6 alkyl)-amino or C_3 - C_{14} cycloalkyl group;

R_2 represents

- an optionally substituted mono- or bicyclic C_1 - C_9 heterocyclic group containing from 1 to 3 heteroatoms chosen from nitrogen, oxygen and sulphur,
- an optionally substituted mono-, bi- or tricyclic C_6 - C_{14} aryl group,
- an optionally substituted C_1 - C_6 alkyl group,
- an optionally substituted C_2 - C_6 alkenyl group, or
- an optionally substituted C_3 - C_6 cycloalkyl group,

or R_2 represents a group $-\text{C}(\text{O})-\text{R}_{2\text{A}}$ wherein $\text{R}_{2\text{A}}$ is defined as R_2 above;

R_3 represents

- a hydrogen atom,
- an optionally substituted C_1 - C_6 alkyl group,
- an optionally substituted mono-, bi- or tricyclic C_1 - C_{14} heterocyclic group containing 1 to 3 heteroatoms chosen from nitrogen, oxygen and sulphur,
- an optionally substituted mono, bi or tricyclic C_6 - C_{14} aryl group,
- an optionally substituted C_3 - C_6 cycloalkyl group, or
- an optionally substituted C_3 - C_6 cycloalkenyl group,

Y represents a group of the formula -C(O)-, -C(S)-, -NH-C(O)-, -N(C₁-C₆ alkyl)-C(O)-, -O-C(O)-, -NH-C(S)-, -N(C₁-C₆ alkyl)-C(S)-, -O-C(S)- or -SO₂- or is absent.

m is 0, 1 or 2;

n is 0, 1 or 2;

the substituents for each optionally substituted group being

- a halogen atom or an oxo, nitro, cyano, hydroxy, carbamoyl, C₁-C₆ alkylsulphonyl, C₁-C₆ alkylthio, C₁-C₆ alkylcarbonyl or C₁-C₆ alkylcarbonyl-(C₁-C₆)alkyl group or a group of the formula -NR^{*}R^{*} wherein each R^{*} independently represents a hydrogen atom or a C₁-C₆ alkyl, C₁-C₆ alkylcarbonyl, phenyl or benzyl group, or
- a C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or C₁-C₆ alkoxy group, each of which may optionally bear from 1 to 8 independently selected oxo, halo, cyano, nitro, amino, hydroxy or phenyl substituents,
- a C₃-C₉ mono- or bicycloalkyl group optionally bearing from 1 to 3 independently selected C₁-C₆ alkyl, oxo, halo, cyano, nitro, amino, hydroxy or phenyl substituents, or
- a group of the formula -A, -O-A, -C(O)-A, -(CH₂)_q-A, -NR^{**}-A, -C(O)NR^{**}-A, -NR^{**}C(O)-A or -OC(O)-A,

wherein A represents a phenyl group or a C₁-C₈ heterocyclic group containing from 1 to 3 heteroatoms chosen from nitrogen, oxygen and sulphur, each of which groups A may optionally bear from 1 to 3 independently selected halo, hydroxy, cyano, nitro and C₁-C₆ alkyl substituents,

each R^{**} independently represents a hydrogen atom or a C₁-C₆ alkyl group, and

q is 0 or an integer from 1 to 6;

with the provisos that if Z represents a group of the formula -CH=CH-R₂ then R₁ represents a hydrogen atom and oxo and hydroxy are excluded from the optional substituents;

or an enantiomer, diastereomer, N-oxide or pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 in which Z represents a group of the formula -C≡C-R₂ wherein R₂ is as defined in claim 1.

3. A compound according to claim 2 in which R_1 represents a hydrogen or fluorine atom or a methyl group.
4. A compound according to any preceding claim in which m is 1 and n is 1.
5. A compound according to any preceding claim in which Y represents a group of the formula $-C(O)-$, $-NH-C(O)-$, $-N(C_1-C_6 \text{ alkyl})-C(O)-$, $-O-C(O)-$, $-NH-C(S)-$ or $-SO_2-$ or is absent.
6. A compound according to any preceding claim in which R_2 represents
 - an optionally substituted mono or bicyclic C_1-C_9 heterocyclic group containing from 1 to 3 heteroatoms chosen from nitrogen, oxygen and sulphur,
 - an optionally substituted phenyl group,
 - an optionally substituted C_1-C_6 alkyl group,
 - an optionally substituted C_2-C_6 alkenyl group,
 - an optionally substituted C_3-C_6 cycloalkyl group,or R_2 represents a group $-C(O)-R_{2A}$ wherein R_{2A} is defined as R_2 in this claim.
7. A compound according to claim 6 in which R_2 represents an optionally substituted pyrrolidinyl, thiazolyl, pyridyl, quinolyl, quinoxalinyll or phenyl group, the substituents for each optionally substituted group being a fluorine, chlorine or bromine atom or an oxo, nitro, cyano, cyanomethyl, acetyl, methyl, methoxy, ethoxy, isopropoxy, trifluoromethyl, trifluoromethoxy, acetamino, 2,2-dimethylpropanoylamino, 3,3-dimethyl-2-oxo-1-azetidinyll, 1-pyrrolidinylmethyl, 1H-pyrazol-1-yl, 3-methyl-1,2,4-oxadiazol-5-yl or morpholino group.
8. A compound according to claim 7 in which R_2 represents a pyridyl or phenyl group substituted with a fluorine atom and/or a methyl group, further substituents being optional.
9. A compound according to claim 7 in which R_2 represents a 6-methyl-2-pyridyl, 5-cyano-2-pyridyl, 3-fluorophenyl, 2,5-difluorophenyl group or 3,5-difluorophenyl group.
10. A compound according to any preceding claim in which R_3 represents

- a C₁-C₆ alkyl group substituted with an optionally substituted group A,
 - an optionally substituted mono- or bicyclic C₁-C₉ heterocyclic group containing 1 to 3 heteroatoms chosen from nitrogen, oxygen and sulphur,
 - an optionally substituted phenyl group,
 - an optionally substituted C₃-C₆ cycloalkyl group, or
 - an optionally substituted C₃-C₆ cycloalkenyl group.
11. A compound according to claim 10 in which R₃ represents a mono- or bicyclic C₁-C₉ heterocyclic group containing 1 to 3 heteroatoms chosen from nitrogen, oxygen and sulphur and at least 2 adjacent carbon atoms, one of which is bonded to the nitrogen atom of the illustrated nitrogen containing ring (Y being absent) and the other of which bears a cyano or nitro substituent, further substituents being optional.
12. A compound according to claim 10 in which R₃ represents an optionally substituted pyrrolidinyl, pyrazolyl, imidazolyl, 1,2,4-triazolyl, isoxazolyl, furyl, thienyl, pyridyl, piperidyl, pyrazinyl, pyrimidinyl, morpholinyl, imidazo[2,1-b]thiazolyl, indolyl, isoindolyl, imidazo[1,2-a]pyridyl, 1,2,3-benzotriazolyl, quinolyl, isoquinolyl, quinoxalinyl, pyrido[2,3-b]pyrazinyl, 1,4-benzoxazinyl or phenyl group, the substituents for each optionally substituted group being a fluorine, chlorine, bromine or iodine atom or a methyl, isopropyl, methoxy, ethoxy, propoxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, acetyl, acetamino, phenyl, benzyloxy, phenylcarbamoyl, 4-fluorophenyl, 3-fluoro-4-methylphenyl, 2-furyl, 2-thienyl, 4-pyridyl, piperidino, 2-pyrimidinyl, 2-pyrimidinylloxy, 1,3-thiazol-2-yl, 2-methyl-1,3-thiazol-4-yl, 2-oxo-pyrrolidin-1-yl, 5-methyl-1,2,4-oxadiazol-3-yl, 2,5-dimethyl-1H-pyrrol-1-yl group.
13. A compound according to claim 10 in which R₃ represents a 6-methyl-3-nitro-2-pyridyl, 6-methyl-3-cyano-2-pyridyl, 4-methoxy-3-cyano-2-pyridyl, 3-cyano-2-thienyl, or 3-cyano-2-pyrazinyl group.
14. Any one of the following compounds according to claim 1, or an enantiomer, diastereomer, N-oxide or pharmaceutically acceptable salt thereof, namely:
- 1-(3-nitro-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
 - 1-(t-butoxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,

- 4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(2-nitrophenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methoxy-3-nitro-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(5-methyl-2-nitrophenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(5-methoxy-2-nitrophenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-(3-phenyl-prop-2-ynylidene)-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-phenylcarbamoyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-morpholinocarbonyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-benzoyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-butylaminothiocarbonyl-3-nitro-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-ethylaminothiocarbonyl-3-nitro-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(t-butylcarbamoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitrophenylcarbamoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitrobenzoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-ethoxycarbonyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-cyclohexylaminothiocarbonyl-3-nitro-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-phenylaminothiocarbonyl-3-nitro-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(1-phenylethyl-carbamoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-butyryl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-butylcarbamoyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-ethylcarbamoyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-benzyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-butyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,

- 1-(3-nitro-2-pyridyl)-4-[3-(4-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(3-quinolyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(6-morpholino-3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(6-fluoro-3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(6-acetyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(6-isopropoxy-3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(3-methoxy-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-phenyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(2-cyanophenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(4-methoxy-2-nitrophenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(t-butoxycarbonyl)-4-[3-(5-cyano-3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(t-butoxycarbonyl)-4-[3-(6-cyano-3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(5-cyano-3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(6-cyano-3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(t-butoxycarbonyl)-4-[3-(2-methyl-1,3-thiazol-4-yl)-prop-2-ynylidene]-piperidine,
- 4-[3-(2-methyl-1,3-thiazol-4-yl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(2-methyl-1,3-thiazol-4-yl)-prop-2-ynylidene]-piperidine,
- 1-(4-cyano-3,5-difluorophenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(5-cyano-2-methoxyphenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(5-bromo-2-cyano-3-fluorophenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(4-fluoro-2-nitrophenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(4-cyano-2-nitrophenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-[2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-pyrimidinyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(6-quinoxaliny)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(6-cyano-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(4-hydroxymethyl-2-nitrophenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,

- 1-(3-trifluoromethyl-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(6-trifluoromethyl-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(5-trifluoromethyl-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(t-butoxycarbonyl)-4-[1-fluoro-3-phenyl-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[1-fluoro-3-phenyl-prop-2-ynylidene]-piperidine,
- 1-(2-methoxyethoxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(2-cyanoethoxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-benzyloxycarbonyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(2-fluoro-4-nitro-phenoxy carbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(2-thienyl-methoxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(2-pyridyloxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(1-methyl-4-piperidinyloxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-[2-(1H-indol-3yl)-ethoxycarbonyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(2,2,2-trifluoro-1-trifluoromethyl-ethoxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(2,3,4-trifluorophenoxy carbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(cyclohexyloxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(cyclobutylmethoxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(5-bromo-2-pyridyloxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-phenoxypropoxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,

- 1-(4,6-dimethyl-pyrimidinylloxycarbonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(N-methyl-N-phenylcarbamoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(N,N-diethylcarbamoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(N,N-dimethylcarbamoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(N-methyl-N-3-nitrophenylcarbamoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(N-methyl-N-butylcarbamoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-[N-methyl-N-(t-butyl)-carbamoyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(N-methyl-N-ethylcarbamoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-[N-methyl-N-(1-phenylethyl)-carbamoyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(N-ethyl-N-isopropylcarbamoyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(p-tolylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(2-nitrophenylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-phenylsulphonyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-[5-(2-oxo-1-pyrrolidinyl)-2-methyl-phenylsulphonyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(4-methoxyphenylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(4-bromo-2,5-difluorophenylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-benzylsulphonyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-ethylsulphonyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(2-chloro-4-cyanophenylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-fluorobenzylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,

- 1-cyclohexylmethylsulphonyl-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(4-methyl-3-nitrophenylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(2,2,2-trifluoroethylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(4-isopropylphenylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(4-cyanophenylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(5-chloro-2-methoxy-4-methylphenylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-ylmethylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-[3-(4-methoxyphenoxy)-propylsulphonyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-bromophenylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(4-bromo-2-fluorophenylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(6-chloro-imidazo[2,1-b]thiazol-5-ylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(1,2-dimethyl-1H-imidazol-4-ylsulphonyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-[4-(1,2,3-thiadiazol-4-yl)-phenylsulphonyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-[5-(t-butyl)-2-methoxyphenylsulphonyl]-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-(4-oxo-pent-2-ynylidene)-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[4-(4-fluorophenyl)-4-oxo-but-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-(5,5-dimethyl-4-oxo-hex-2-ynylidene)-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[4-(2-thienyl)-4-oxo-but-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-(4-cyclohexyl-4-oxo-but-2-ynylidene)-piperidine,
- 1-(3-nitro-2-pyridyl)-4-(5-methyl-4-oxo-hex-5-en-2-ynylidene)-piperidine,

- 1-(3-nitro-2-pyridyl)-4-[3-(3,5-difluoro-4-methoxyphenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(4-cyano-3-fluorophenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(5-fluoro-2-methoxyphenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(3,5-difluorophenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(4-cyanophenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-{3-[4-(3,3-dimethyl-2-oxo-1-azetidiny)-phenyl]-prop-2-ynylidene}-piperidine,
- 1-(3-nitro-2-pyridyl)-4-{3-[4-(1-pyrrolidinylmethyl)-phenyl]-prop-2-ynylidene}-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(2,3-dimethoxyphenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(3-trifluoromethylphenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(3-bromophenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(3-methylphenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(3-methoxyphenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(6-quinoxaliny)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(3-cyanomethylphenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(3-nitrophenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(3-cyanophenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(3-chlorophenyl)-prop-2-ynylidene]-piperidine,
- 1-(t-butoxycarbonyl)-4-(hept-2-ynylidene)-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(6-trifluoromethyl-3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(2-fluoro-6-methyl-3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(3-bromo-2-chloro-4-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(3-bromo-2-fluoro-4-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(3-fluoro-4-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(5-fluoro-3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(6-fluoro-2-pyridyl)-prop-2-ynylidene]-piperidine,

- 1-(3-nitro-2-pyridyl)-4-[3-(6-isopropoxy-3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(2-ethoxy-3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(5-nitro-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methoxy-3-nitro-2-pyridyl)-4-[3-(3,5-difluorophenyl)-prop-2-ynylidene]-piperidine,
- 1-(5-bromo-2-pyrimidinyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-methyl-5-nitro-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(5-cyano-3-methyl-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(6-cyano-3-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(4-methyl-3-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(4-isoquinolyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(4-methyl-5-oxo-cyclopentenyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-thienyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(5-nitro-2-furyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(5-phenylcarbamoyl-2-furyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(2-methyl-4-nitro-1H-5-imidazolyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(t-butoxycarbonyl)-(3E)-3-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-pyrrolidine,
- 1-(3-nitro-2-pyridyl)-4-(4-phenyl-but-3-yn-2-ylidene)-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[(2E)-3-phenyl-prop-2-enylidene]-piperidine,
- 1-(3-nitro-imidazo[1,2-a]pyridin-2-yl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(3-trifluoromethoxyphenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(2-oxo-1-pyrrolidinyl)-prop-2-ynylidene]-piperidine,
- 1-(5-trifluoromethyl-3-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-5-phenyl-2-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(2-propoxy-3-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,

- 1-(pyrido[2,3-b]pyrazin-7-yl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-2-thienyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(6-ethoxy-3-pyridyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(2,6-difluorophenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-nitro-2-pyridyl)-4-{3-[3-(1H-pyrazol-1-ylmethyl)-phenyl]-prop-2-ynylidene}-piperidine,
- 1-(3-nitro-2-pyridyl)-4-{3-[2-(2,2-dimethyl-propionylamino)-3-pyridyl]-prop-2-ynylidene}-piperidine,
- 1-(3-nitro-2-pyridyl)-4-{3-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-prop-2-ynylidene}-piperidine,
- 1-(3-nitro-2-pyridyl)-4-[3-(3-acetylphenyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(4-fluoro-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(3,5-difluorophenyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(3-fluorophenyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(6-fluoro-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(6-fluoro-3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(2-fluoro-4-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(5-fluoro-3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(5-cyano-3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(2,5-difluorophenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(3,5-difluorophenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(3-fluorophenyl)-prop-2-ynylidene]-piperidine,

- 1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(4-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(6-fluoro-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(5-cyano-3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(2-fluoro-4-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(2,5-difluorophenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(5-cyano-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(6-fluoro-3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-6-methyl-2-pyridyl)-4-[3-(5-fluoro-3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(3-fluorophenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(3,5-difluorophenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(2,5-difluorophenyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(6-fluoro-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(6-fluoro-3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(2-fluoro-4-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(5-fluoro-3-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(5-cyano-3-pyridyl)-prop-2-ynylidene]-piperidine,

- 1-(3-cyano-4-methoxy-2-pyridyl)-4-[3-(5-cyano-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-6-methyl-2-pyridyl)-4-(4-phenyl-but-3-yn-2-ylidene)-piperidine,
- 1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(6-bromo-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(3-ethoxyphenyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(3-acetylphenyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(3-acetamidophenyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methyl-3-nitro-2-pyridyl)-4-[3-(3-acetonylphenyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methyl-3-nitro-2-pyridyl)-3-(3Z)-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methyl-3-nitro-2-pyridyl)-3-(3E)-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methyl-3-nitro-2-pyridyl)-4-(4-phenyl-but-3-yn-2-ylidene)-piperidine,
- 1-(1-methyl-4-nitro-1H-imidazol-5-yl)-4-(4-phenyl-but-3-yn-2-ylidene)-piperidine,
- 1-(1-methyl-4-nitro-1H-imidazol-5-yl)-4-[3-(3,5-difluorophenyl)-prop-2-ynylidene]-piperidine,
- 1-(1-methyl-4-nitro-1H-imidazol-5-yl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(4-nitro-1H-imidazol-5-yl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine,
- 1-(3-cyano-2-thienyl)-4-[3-(2,5-difluorophenyl)-prop-2-ynylidene]-piperidine,
- 1-(6-methyl-3-nitro-2-pyridyl)-4-{3-[3-(3-methyl-1,2,4-oxadiazol-5-yl)-phenyl]-prop-2-ynylidene-piperidine, or
- 1-(2-cyano-3-pyrazinyl)-4-[3-(6-methyl-2-pyridyl)-prop-2-ynylidene]-piperidine.

15. A pharmaceutical composition comprising a compound according to any preceding claim, or an enantiomer, diastereomer, N-oxide or pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable diluent or carrier.