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(54) Title: SUBSTITUTED AMINO-AZA-CYCLOHEXANES

(57) Abstract: The invention relates to novel amino-aza-cyclohexane derivatives and related compounds and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as inhibitors of plasmepsin II.

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SUBSTITUTED AMINO-AZA-CYCLOHEXANES

The invention relates to novel compounds which are substituted amino-aza-cyclohexane derivatives of the general formula I. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of general formula I and especially their use as inhibitors of the plasmodium falciparum protease plasmepsin II for the treatment or prevention of malaria. Furthermore, these compounds can be regarded as inhibitors of other aspartyl proteases and might, therefore, be useful as inhibitors of plasmepsin I, plasmepsin IV or histo-aspartic protease (HAP) to treat malaria and as inhibitors of *Candida albicans* secreted aspartyl proteases to treat fungal infections.

Background of the invention:

Malaria is one of the most serious and complex health problems affecting humanity in the 21st century. The disease affects about 300 million people worldwide, killing 1 to 1.5 million people every year. Malaria is an infectious disease caused by four species of the protozoan parasite Plasmodium, P. falciparum being the most severe of the four. All attempts to develop vaccines against P. falciparum have failed so far. Therefore, therapies and preventive measures against malaria are confined to drugs. However, resistance to many of the currently available antimalarial drugs is spreading rapidly and new drugs are needed.

P. falciparum enters the human body by way of bites of the female anophelino mosquito. The plasmodium parasite initially populates the liver, and during later stages of the infectious cycle reproduces in red blood cells. During this stage, the parasite degrades hemoglobin and uses the degradation products as nutrients for growth [1]. Hemoglobin degradation is mediated by serine proteases, metalloproteases and aspartic proteases.

Aspartic proteases have been shown to be indispensable to parasite growth. A non-selective inhibitor of aspartic proteases, Pepstatin, inhibits the growth of P. falciparum in red blood cells in vitro. The same results have been obtained with analogs of pepstatin [2], [3]. These results show that inhibition of parasite aspartic proteases interferes with the life cycle of P. falciparum. Consequently, aspartic proteases are targets for antimalarial drug development.

The present invention relates to the identification of low molecular weight, non-peptidic inhibitors of the plasmodium falciparum protease plasmepsin II or other related aspartic proteases such as plasmepsin I, plasmepsin IV or Histo-Aspartic-Protease (HAP) to treat and/or prevent malaria.

Prior Art:

To date several classes of plasmepsin II inhibitors have been described in the literature. To the best of our knowledge, none of these compounds has entered clinical development so far. Research efforts within different structural classes of plasmepsin II inhibitors have recently been summarized and published [C. Boss et al.; *Curr. Med. Chem.* **2003**, *10*, 883-907 and references cited there]. Plasmepsin inhibitors based on a peptidomimetic or a substrate-analogue approach are described in the following patents: US-05734054 (Pharmacopeia Inc), US-05892038 (Pharmacopeia Inc.), WO-00114331 (University of California, Berkley), WO-02074719 (Johns Hopkins University), and publications: D. Nöteberg, E. Hamelink, J. Hulten, M. Wahlgren, L. Vrang, B. Samuelsson, A. Hallberg, *J. Med. Chem.*, **2003**, *46*, 734-746. K. Oscarsson, S. Oscarson, L. Vrang, E. Hamelink, A. Hallberg, B. Samuelsson, *Bioorg. Med. Chem.*, **2003**, *11*, 1235-1246. A. Dahlgren, I. Kvarnström, L. Vrang, E. Hamelink, A. Hallberg, A. Rosenquist, B. Samuelsson, *Bioorg. Med. Chem.*, **2003**, *11*, 827-841. Non-peptidomimetic plasmepsin II inhibitors are described in the following patents: WO-00224649 (Actelion Phramaceuticals Ltd.), WO-00238543 (Actelion Phramaceuticals Ltd.) and WO-09912532 (F.

Hoffmann-LaRoche Ltd.). Only three publications were found so far that describe non-peptidomimetic, rationally designed plasmepsin II inhibitors: Carcache, D. A.; Hörtner, S. R.; Bertogg A.; Binkert, C.; Bur, D.; Märki, H.-P.; Dorn, A.; Diederich, F.; *ChemBioChem*, **2002**, *11*, 1137. Carcache, D. A.; Hörtner, S. R.; Seiler, P.; Diederich, F.; Dorn, A.; Märki, H.-P.; Binkert, C.; Bur, D.; *Helv. Chim. Acta*, **2003**, *86*, 2173. Carcache, D. A.; Hörtner, S. R.; Bertogg, A.; Diederich, F.; Dorn, A.; Märki, H.-P.; Binkert, C.; Bur, D.; *Helv. Chim. Acta*, **2003**, *86*, 2192.

The compounds of general formula I were tested against plasmepsin II, HIV-protease, human cathepsin D, human cathepsin E and human renin in order to determine their biological activity and their selectivity profile.

In vitro Assays:

The fluorescence resonance energy transfer (FRET) assay for HIV, plasmepsin II, human cathepsin D and human cathepsin E.

The assay conditions were selected according to reports in the literature [4 - 7]. The FRET assay was performed in white polysorp plates (Fluoronunc, cat n° 437842 A). The assay buffer consisted of 50 mM sodium acetate pH 5, 12,5% glycerol, 0.1% BSA + 392 mM NaCl (for HIV-protease).

The incubates per well were composed of:

- 160 µl buffer
- 10 µl inhibitor (in DMSO)
- 10 µl of the corresponding substrate in DMSO (see table A) to a final concentration of 1 µM
- 20 µl of enzyme to a final amount of x ng per assay tube (x = 10 ng/assay tube plasmepsin II, x = 100 ng/assay tube HIV-protease, x = 10 ng/assay tube human cathepsin E and x = 20 ng/assay tube human cathepsin D)

The reactions were initiated by addition of the enzyme. The assay was incubated at 37°C for 30 min (for human cathepsin E), 40 min (for plasmepsin II and HIV-protease) or 120 min (for human cathepsin D). The reactions were stopped by adding 10% (v/v) of a 1 M solution of Tris-base. Product-accumulation was monitored by measuring the fluorescence at 460 nm.

Auto-fluorescence of all the test substances is determined in assay buffer in the absence of substrate and enzyme and this value was subtracted from the final signal.

Aspartyl protease	**substrate**		**enzyme concentration** ng/at (nM)	**Buffer**	**pH**	**incubation time** minutes
	sequence	substrate concentration µM				
HIV	Dabcyl-Abu-SQNY:PIVN-EDANS	1	100 (22.5)	50 mM Na acetate ; 12,5 % glycerol ; 0.1 % BSA 392 mM NaCl	5	40
Plasmepsin II	Dabcyl-ERNleF:LSFP-EDANS	1	10 (1.25)	50 mM Na acetate ; 12,5 % glycerol ; 0.1% BSA	5	40
h Cathepsin D	Dabcyl-ERNleF:LSFP-EDANS	1	20 (2.5)	50 mM Na acetate ; 12,5 % glycerol ; 0.1% BSA	5	120
h Cathepsin E	Dabcyl-ERNleF:LSFP-EDANS	1	10 (1.25)	50 mM Na acetate ; 12,5 % glycerol ; 0.1% BSA	5	30

Table A: Summary of the conditions used for the aspartyl proteases fluorescent assays. (at = assay tube)

Activities of the compounds are evident from the following IC_{50} values on plasmepsin II (PMII) of selected Examples:

Example No:	IC_{50} (PMII) in nM:
Example 1	49
Example 2	58
Example 3	69
Example 4	69
Example 5	80
Example 6	106
Example 7	277
Example 8	560
Example 9	275
Example 12	90
Example 13	147
Example 14	175
Example 19	382
Example 25	96
Example 26	459
Example 31	308
Example 33	327
Example 41	376
Example 42	401
Example 47	160
Example 50	338
Example 59	550
Example 60	487

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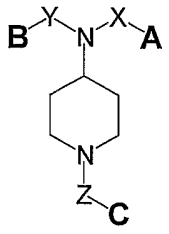
The present invention relates to novel, low molecular weight organic compounds, which are substituted amino-aza-cyclohexanes of the **general formula I**:



General Formula I

wherein

X represents $-(CH_2)_n-$;

Y represents $-(CH_2)_n-$; -(C=O)-; $-(SO_2)-$; -(C=O)-NH-;

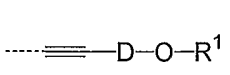
Z represents a bond; $-(CH_2)_n-$;

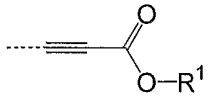
C represents hydrogen; lower alkyl; lower alkenyl; lower alkynyl; aryl; heteroaryl; cycloalkyl; cycloalkenyl; heterocyclyl; or lower alkyl substituted by hydroxy, carboxy or lower alkoxycarbonyl;

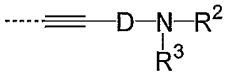
n represents the whole numbers 1, 2, 3 or 4;

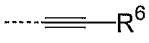
A and **B** represent aryl; heteroaryl; heterocyclyl; cycloalkyl; with the proviso that at least one of **A** and **B** represents aryl or heteroaryl substituted by an alkynyl group Q which is represented by the following groups:

- alkynyl containing two to six carbon atoms; and









wherein

D represents $-(CH_2)_n-$;

R^1 represents hydrogen; methyl; ethyl; propyl; butyl; tert.-butyl; iso-propyl; aryl; heteroaryl;

R^2 represents hydrogen; methyl; ethyl; propyl; butyl; tert.-butyl; iso-propyl; $-(CH_2)_m$-aryl; $-(CH_2)_m$-heteroaryl; $-(CH_2)_m$-cycloalkyl; $-(C=O)-R^4$; $-(C=O)-NH-R^4$; $-(C=O)-O-R^4$;

R^3 represents hydrogen; methyl; ethyl; propyl; butyl; $-(CH_2)_m$-aryl; $-(CH_2)_m$-heteroaryl; $-(CH_2)_m$-cycloalkyl;

R^4 represents lower alkyl; $-(CH_2)_m$-aryl; $-(CH_2)_m$-heteroaryl; $-(CH_2)_m$-cycloalkyl;

R^6 represents aryl, heteroaryl or lower alkyl optionally substituted by OR^1 and/or any of aryl and heteroaryl;

m represents the whole numbers 0 (zero), 1, 2 or 3;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes, morphological forms and prodrugs of any of these compounds.

In the definitions of general formula **I** – if not otherwise stated – the term **lower alkyl**, alone or in combination with other groups, means saturated, straight and branched chain groups with one to eight carbon atoms, preferably one to five carbon atoms that can be optionally substituted by halogens. Examples of lower alkyl groups are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and heptyl.

The term **lower alkoxy** refers to a R-O group, wherein R is a lower alkyl. Examples of lower alkoxy groups are methoxy, ethoxy, propoxy, iso-propoxy, iso-butoxy, sec-butoxy and tert-butoxy.

The term **lower alkenyl**, alone or in combination with other groups, means straight and branched chain groups comprising an olefinic bond and two to eight carbon atoms, preferably two to five carbon atoms, that can be optionally substituted by halogens. Examples of lower alkenyl are vinyl, propenyl, butenyl or pentenyl.

The term **lower alkynyl**, alone or in combination with other groups, means straight and branched chain groups comprising a triple bond and two to eight carbon atoms, preferably two to five carbon atoms, that can be optionally substituted by halogens. Examples of lower alkynyl are ethynyl, propynyl or butynyl.

The term **lower alkylene**, alone or in combination with other groups, means straight and branched divalent chain groups with one to eight carbon atoms, preferably one to five carbon atoms that can be optionally substituted by halogens. Examples of lower alkylene are ethylene, propylene or butylene.

The term **lower alkenylene**, alone or in combination with other groups, means straight and branched divalent chain groups comprising an olefinic bond and two to eight carbon atoms, preferably two to five carbon atoms, that can be optionally substituted by halogens. Examples of lower alkenylene are vinylene, propenylene and butenylene.

The term **lower alkylenedioxy**, refers to a lower alkylene substituted at each end by an oxygen atom. Examples of lower alkylenedioxy groups are preferably methylenedioxy and ethylenedioxy.

The term **lower alkylenoxy** refers to a lower alkylene substituted at one end by an oxygen atom. Examples of lower alkylenoxy groups are preferably ethylenoxy and propylenoxy.

The term **halogen** means fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine and bromine.

The term **cycloalkyl** alone or in combination, means a saturated cyclic hydrocarbon ring system with 3 to 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, which can be optionally mono-, di-, or trisubstituted independently by lower alkyl, lower alkenyl, lower alkenylene, lower alkoxy, lower alkylenoxy, lower alkylenedioxy, hydroxy, halogen, $-CF_3$, $-NR^1R^2$, $-NR^1C(O)R^4$, $-NR^1S(O)_2R^4$, $-C(O)NR^1R^2$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-SO_2NR^1R^2$, whereby R1, R2 and R4 are defined as in formula I above.

The term **cycloalkenyl** has analogous meaning to cycloalkyl, except that it is unsaturated (but not aromatic).

The term **aryl**, alone or in combination, relates to the phenyl, the naphthyl or the indanyl group, preferably the phenyl group, which can be optionally mono-, di-, tri-, tetra- or pentasubstituted independently by lower alkyl, lower alkenyl, lower alkinyl, lower alkenylene or lower alkylene forming with the aryl ring a five- or six-membered ring, lower alkoxy, lower alkylenedioxy, lower alkylenoxy, hydroxy, hydroxy-lower alkyl, halogen, cyano, $-CF_3$, $-OCF_3$, $-NR^1R^2$, $-NR^1C(O)R^4$, $-NR^1S(O)_2R^4$, $-C(O)NR^1R^2$, $-NO_2$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-S(O)R^1$, $-S(O)_2R^1$, $-SO_2NR^1R^2$, (R1, R2 and R4 being defined as in formula I above) or by benzyloxy or phenoxy. Phenyl groups can also be substituted by phenyl, which latter can be substituted as defined above under phenyl. Preferred substituents are lower alkynyl, lower alkoxy, lower alkyl and 4-methoxy-biphenyl.

The term **aryloxy** refers to an Ar-O group, wherein Ar is an aryl. An example of aryloxy groups is phenoxy.

The term **heterocyclyl**, alone or in combination, means saturated or unsaturated (but not aromatic) five-, six- or seven-membered rings containing one or two nitrogen, oxygen or sulfur atoms which may be the same or different and which rings can be optionally substituted with lower alkyl, hydroxy, lower alkoxy and halogen. The nitrogen atoms, if present, can be substituted by a $COOR^2$ group. Examples of such rings are piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, 1,4-dioxanyl, pyrrolidinyl, tetrahydrofuranyl, dihydropyrrolyl, imidazolidinyl, dihydropyrazolyl, dihydroquinolinyl, tetrahydroquinolinyl, tetrahydro-isoquinolinyl.

The term **heteroaryl**, alone or in combination, means six-membered aromatic rings containing one to four nitrogenatoms; benzofused six-membered aromatic rings containing one to three nitrogen atoms; five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; benzofused five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; five-membered aromatic rings containing one oxygen and one nitrogen atom and benzofused derivatives thereof; five-membered aromatic rings containing a sulfur and a nitrogen or an oxygen atom and benzofused derivatives thereof; five-membered aromatic rings containing two nitrogen atoms and benzofused derivatives thereof; five-membered aromatic rings containing three nitrogen atoms and benzofused derivatives thereof, or a tetrazolyl ring. Examples of such ring systems are furanyl, thiophenyl, pyrrolyl, pyridinyl, pyrimidinyl, indolyl, quinolinyl, isoquinolinyl, imidazolyl, triazinyl, thiazinyl, thiazolyl, isothiazolyl, pyridazinyl, pyrazolyl, oxazolyl, isoxazolyl, coumarinyl, benzothiophenyl, quinazolinyl, quinoxalinyl. Such rings may be adequatly substituted with lower alkyl, lower alkenyl, lower alkinyl, lower alkylene, lower alkenylene, lower alkylenedioxy, lower alkyleneoxy, hydroxy-lower alkyl, lower alkoxy, hydroxy, halogen, cyano, $-CF_3$, $-OCF_3$, $-NR^1R^2$, $-N(R^1)COR^2$, $-N(R^1)SO_2R^2$, $-CONR^1R^2$, $-NO_2$,

lower alkylcarbonyl, -$COOR^1$, -SR^1, -$S(O)R^1$, -$S(O)_2R^1$, -$SO_2NR^1R^2$ (R1, R2 and R4 being defined as in formula I above) or by another aryl, another heteroaryl or another heterocyclyl, and the like.

The term **heteroaryloxy** refers to a Het-O group, wherein Het is a heteroaryl.

It is understoood that the substituents outlined relative to the expressions cycloalkyl, heterocyclyl, heteroaryl and aryl have been omitted in the definitions of the **general formula I** and the following formulae II to VII and in claims 1 to 15 for clarity reasons but the definitions in **general formula I** and the following formulae II to VII and in claims 1 to 15 should be read as if they are included therein.

The expression **pharmaceutically acceptable** salts encompasses either salts with inorganic acids or organic acids like hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic acid, and the like that are non toxic to living organisms or in case the compound of formula **I** is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide and the like.

The compounds of the general formula **I** can contain one or more asymmetric carbon atoms and may be prepared in form of optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form and pharmaceutically acceptable salts therof. The present invention encompasses all these forms. Mixtures may be separated in a manner known *per se*, i.e. by column chromatography, thin layer chromatography, HPLC or crystallization.

The compounds of general formula **I,** and their pharmaceutically acceptable salts may be used as therapeutics e.g. in form of pharmaceutical

compositions. They may especially be used in the treatment and/or prophylaxis of malaria and other protozoal diseases.

In addition, the invention relates to the use of compounds as defined above for the preparation of medicaments for the treatment and/or prophylaxis of diseases, which are associated with the inhibition of plasmepsin II and other, related protozoal aspartic proteases. These medicaments may be prepared in a manner known per se by mixing one or more of the compounds of formulae I to VII with inert excipients.

The compounds of formula I may also be used in combination with one or more other therapeutically useful substances.

All forms of prodrugs leading to an active component comprised in general formula I are included in the present invention.

The compounds of formula I and their pharmaceutically acceptable acid addition salts can be used as medicaments, e. g. in the form of pharmaceutical preparations for enteral, parenteral, or topical administration. They can be administered, for example, perorally, e. g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e. g. in the form of suppositories, parenterally, e. g. in the form of injection solutions or infusion solutions, or topically, e. g. in the form of ointments, creams or oils.

The production of pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula I and their pharmaceutically acceptable acid addition salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials (excipients) and, if desired, usual pharmaceutical adjuvants in a manner known per se.

Suitable carrier materials are not only inorganic carrier materials (excipients), but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers are, however, required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injections are, for example, water, alcohols, polyols, glycerols and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

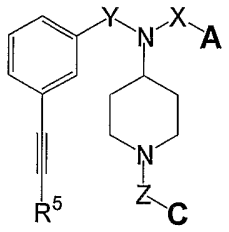
Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of compounds of formula I can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 mg to about 1000 mg, especially about 50 mg to about 500 mg, comes into consideration. For children the dosage has to be adapted to the body weight and age.

The pharmaceutical preparations conveniently contain about 1 - 500 mg, preferably 5 - 200 mg of a compound of formula I.

The compounds of general formula **I** can be manufactured by the methods given below, by the methods given in the examples of an earlier application filed by the applicant (WO 02/24649) or by analogous methods.

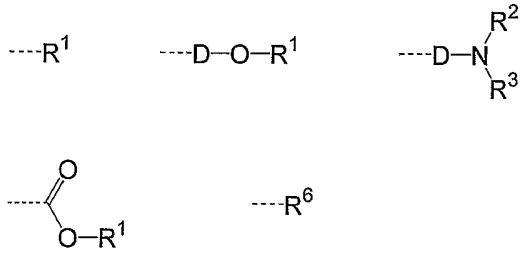
Preferred compounds are compounds of the **formula II**



Formula II

wherein

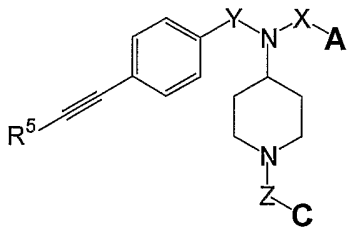
A, **C**, **X**, **Y** and **Z** are as defined in **general formula I** above and R^5 represents one of the groups



wherein R^1, R^2, R^3, R^6 and **D** are as defined in **general formula I** above and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms. A group of especially preferred compounds according to formula II are compounds wherein **A**, **C**, **X** and **Z** are as defined in **general formula I** above, and wherein **Y** represents $-(CH_2)-$ and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

Another group of especially preferred compounds according to formula II are compounds wherein **A**, **C**, **X** and **Z** are as defined in **general formula I** above, and wherein **Y** represents –(C=O)- and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

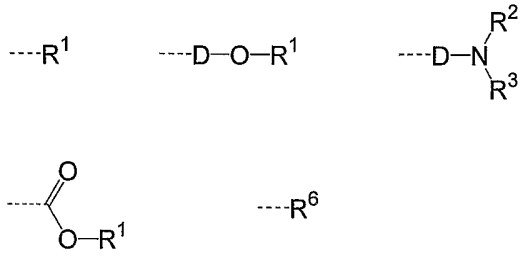
Preferred compounds are compounds of the **formula III**



Formula III

wherein

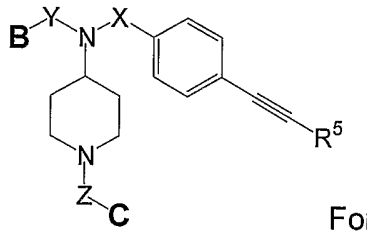
A, **C**, **X**, **Y** and **Z** are as defined in **general formula I** above and R^5 represents one of the groups



wherein R^1, R^2, R^3, R^6 and **D** are as defined in **general formula I** above and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms. A group of especially preferred compounds according to formula III are compounds wherein **A**, **C**, **X** and **Z** are as defined in **general formula I** above, and wherein **Y** represents $-(CH_2)-$ and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes

and morphological forms. Another group of especially preferred compounds according to formula III are compounds wherein **A**, **C**, **X** and **Z** are as defined in **general formula I** above, and wherein **Y** represents –(C=O)- and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

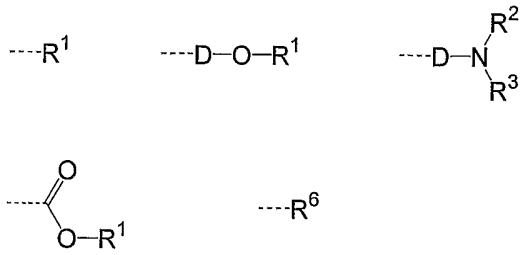
Preferred compounds are compounds of the **formula IV**



Formula IV

wherein

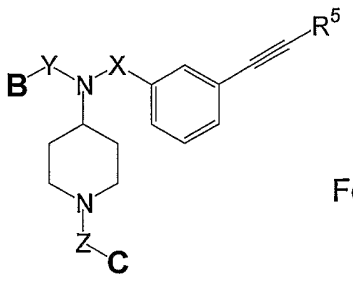
B, **C**, **X**, **Y** and **Z** are as defined in **general formula I** above and R^5 represents one of the groups



wherein R^1, R^2, R^3, R^6 and **D** are as defined in **general formula I** above and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms. A group of especially preferred compounds according to formula IV are compounds wherein **B**, **C**, **X** and **Z** are as defined in **general formula I** above, and wherein **Y** represents $-(CH_2)-$ and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms. Another group of especially preferred compounds according to formula IV are compounds wherein **B**, **C**, **X** and **Z** are as defined in **general formula I** above, and wherein **Y** represents –(C=O)- and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as

pharmaceutically acceptable salts, solvent complexes and morphological forms.

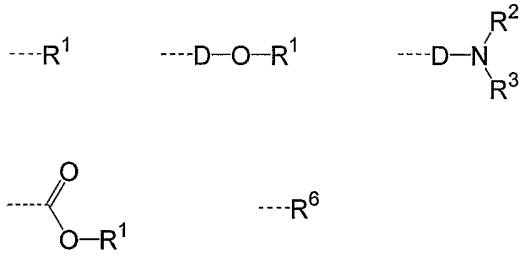
Preferred compounds are compounds of the **formula V**



Formula V

wherein

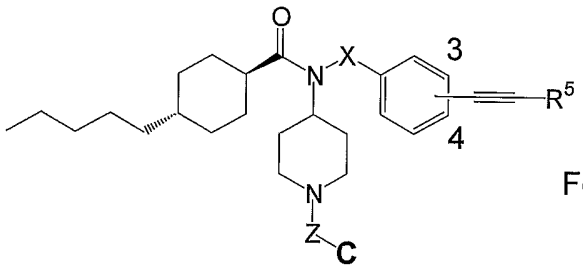
B, **C**, **X**, **Y** and **Z** are as defined in **general formula I** above and R^5 represents one of the groups



wherein R^1, R^2, R^3, R^6 and **D** are as defined in **general formula I** above and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms. A group of especially preferred compounds according to formula V are compounds wherein **B**, **C**, **X** and **Z** are as defined in **general formula I** above, and wherein **Y** represents $-(CH_2)-$ and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms. Another group of especially preferred compounds according to formula V are compounds wherein **B**, **C**, **X** and **Z** are as defined in **general formula I** above, and wherein **Y** represents –(C=O)- and optically pure enantiomers, mixtures of enantiomers such as racemates,

diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

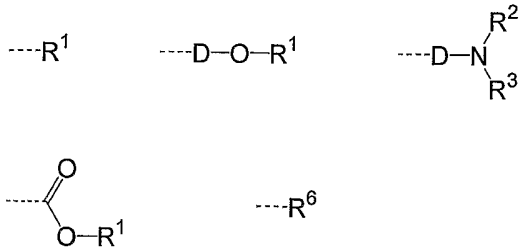
Preferred compounds are compounds of the **formula VI**



Formula VI

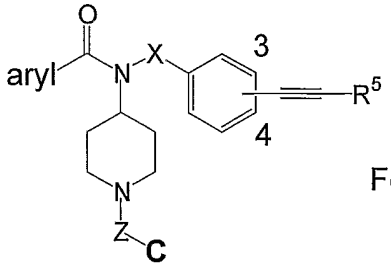
wherein

C, **X** and **Z** are as defined in **general formula I** above, the alkyne unit is attached to the phenyl ring at position 3 or position 4, and $\mathbf{R^5}$ represents one of the groups



wherein $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$ R^6 and **D** are as defined in **general formula I** above and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

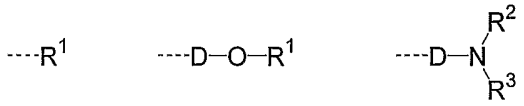
Preferred compounds are compounds of the **formula VII**

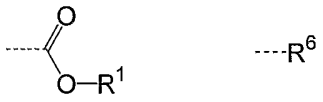


Formula VII

wherein

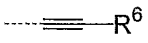
C, **X** and **Z** are as defined in **general formula I** above, the alkyne unit is attached to the phenyl ring at position 3 or position 4, and $\mathbf{R^5}$ represents one of the groups



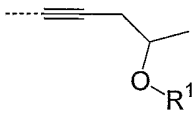


wherein $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$,R^6 and **D** are as defined in **general formula I** above and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

In a subgroup of compounds of formula I the group



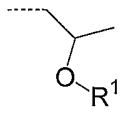
represents the group



in which R^1 is as in claim 1,

and C in formula I represents hydrogen; lower alkyl; lower alkenyl; lower alkynyl; aryl; heteroaryl; cycloalkyl; cycloalkenyl;or heterocyclyl.

In subgroups of compounds of formulas II-VII the group R^6 represents the group



in which R^1 is as in claim 1,

and C in formulas II-VII represents hydrogen; lower alkyl; lower alkenyl; lower alkynyl; aryl; heteroaryl; cycloalkyl; cycloalkenyl;or heterocyclyl.

Preferred compounds are:

N-[3-(3-Hydroxy-prop-1-ynyl)-benzyl]-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide;

N-[3-(4-Hydroxy-pent-1-ynyl)-benzyl]-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide;

N-[3-(3-Methoxy-prop-1-ynyl)-benzyl]-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide;

N-[3-(3,3-Dimethyl-but-1-ynyl)-benzyl]-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide;

N-[3-(4-Hydroxy-but-1-ynyl)-benzyl]-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide;

N-[1-(3-Methyl-butyl)-piperidin-4-yl]-4-pentyl-N-(3-pent-1-ynyl-benzyl)-benzamide;

N-[4-(3-Hydroxy-prop-1-ynyl)-benzyl]-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide;

N-[4-(4-Hydroxy-pent-1-ynyl)-benzyl]-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide;

N-[4-(4-Hydroxy-but-1-ynyl)-benzyl]-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide;

N-[1-(3-Methyl-butyl)-piperidin-4-yl]-4-pentyl-N-(4-pent-1-ynyl-benzyl)-benzamide;

N-[4-(3,3-Dimethyl-but-1-ynyl)-benzyl]-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide;

(4-{(4'-Methoxy-biphenyl-4-ylmethyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-carbamoyl}-phenyl)-propynoic acid methyl ester;

N-(4'-Methoxy-biphenyl-4-ylmethyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pent-1-ynyl-benzamide;

4-Hex-1-ynyl-N-(4'-methoxy-biphenyl-4-ylmethyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-benzamide;

4-(3,3-Dimethyl-but-1-ynyl)-N-(4'-methoxy-biphenyl-4-ylmethyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-benzamide;

N-(4'-Methoxy-biphenyl-4-ylmethyl)-4-(3-methoxy-prop-1-ynyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-benzamide;

N-(4'-Methoxy-biphenyl-4-ylmethyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-phenylethynyl-benzamide;

N-(4'-Methoxy-biphenyl-4-ylmethyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pyridin-2-ylethynyl-benzamide;

3-Hex-1-ynyl-N-(4'-methoxy-biphenyl-4-ylmethyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-benzamide;

N-(4'-Methoxy-biphenyl-4-ylmethyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-3-phenylethynyl-benzamide;

3-(3,3-Dimethyl-but-1-ynyl)-N-(4'-methoxy-biphenyl-4-ylmethyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-benzamide;

N-(4'-Methoxy-biphenyl-4-ylmethyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-3-pent-1-ynyl-benzamide;

N-(4'-Methoxy-biphenyl-4-ylmethyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-3-pyridin-2-ylethynyl-benzamide;

N-(4'-Methoxy-biphenyl-4-ylmethyl)-3-(3-methoxy-prop-1-ynyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-benzamide;

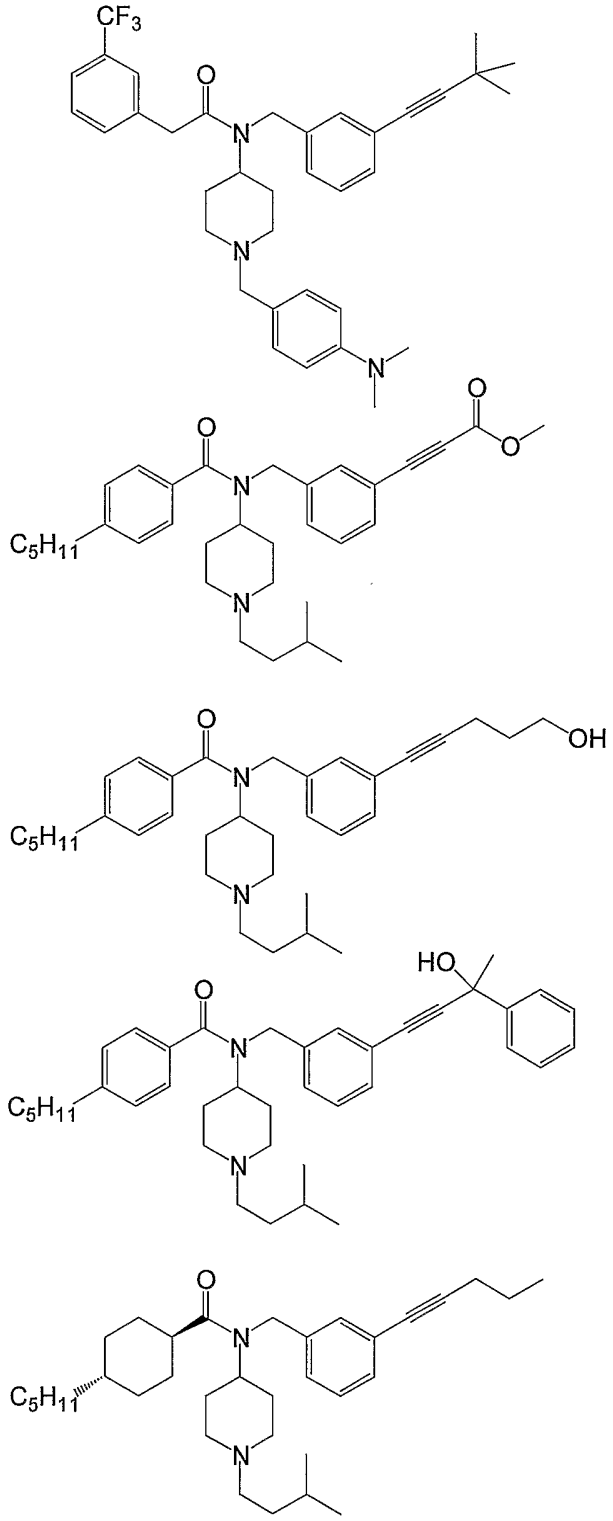
4-Pentyl-cyclohexanecarboxylic acid [1-(3-methyl-butyl)-piperidin-4-yl]-(4-pent-1-ynyl-benzyl)-amide;

4-Pentyl-cyclohexanecarboxylic acid (1-benzyl-piperidin-4-yl)-(4-pent-1-ynyl-benzyl)-amide;

4-Pentyl-cyclohexanecarboxylic acid (1-furan-3-ylmethyl-piperidin-4-yl)-(4-pent-1-ynyl-benzyl)-amide;

4-Pentyl-cyclohexanecarboxylic acid (4-pent-1-ynyl-benzyl)-(1-pyridin-4-ylmethyl-piperidin-4-yl)-amide;

4-Pentyl-cyclohexanecarboxylic acid [1-(1H-imidazol-4-ylmethyl)-piperidin-4-yl]-(4-pent-1-ynyl-benzyl)-amide; and also compounds represented by the following formulae:



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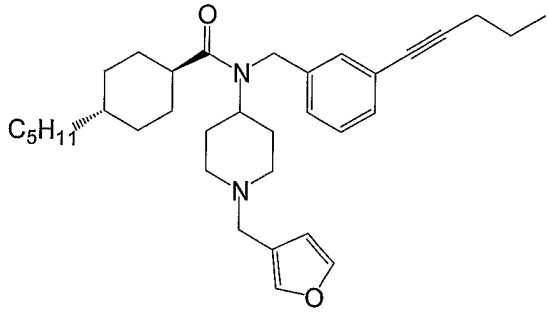
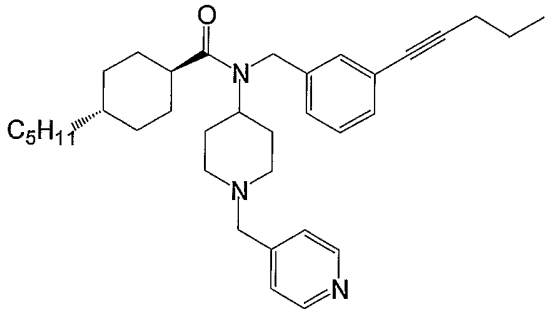
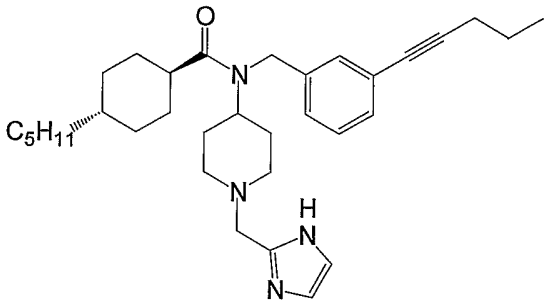
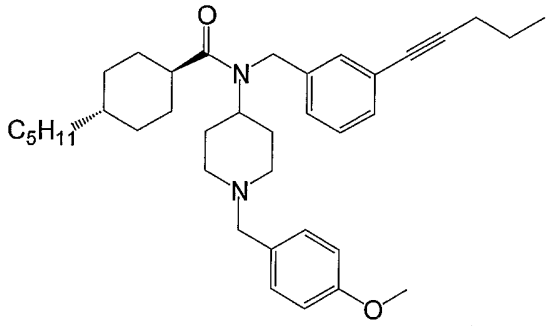
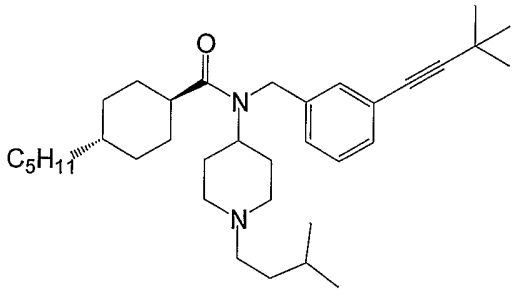
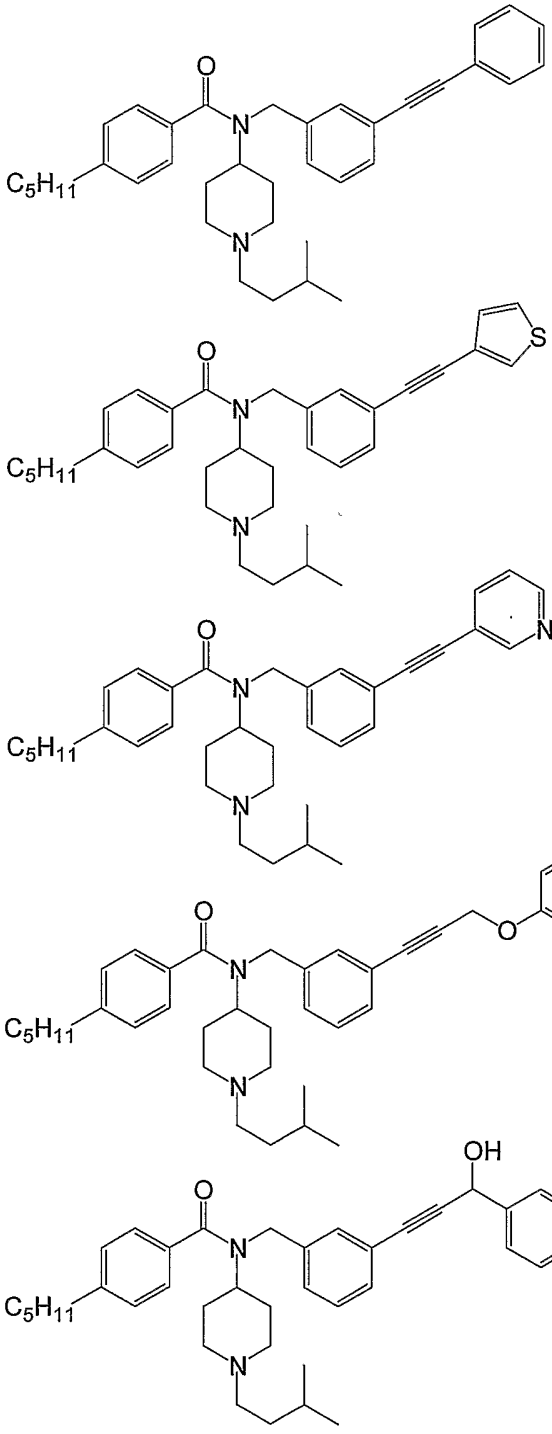


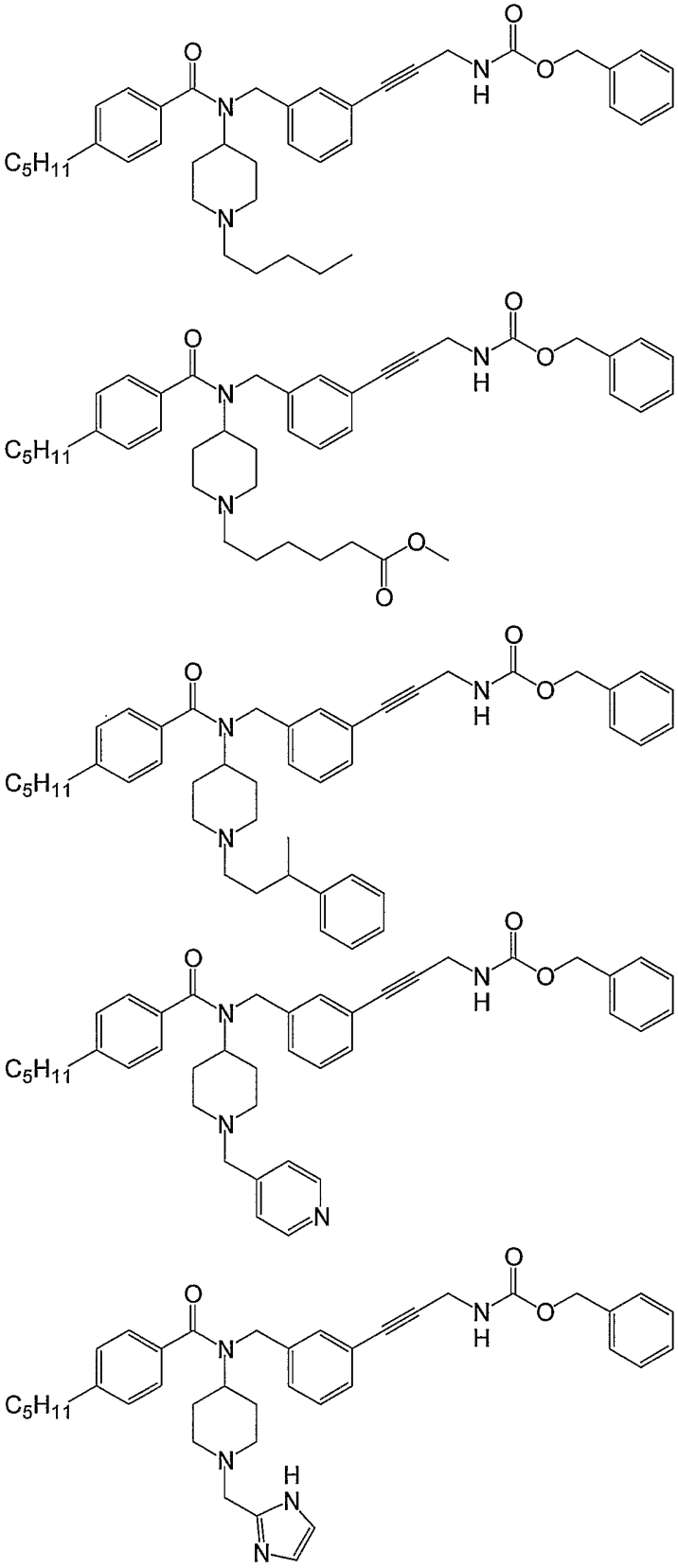


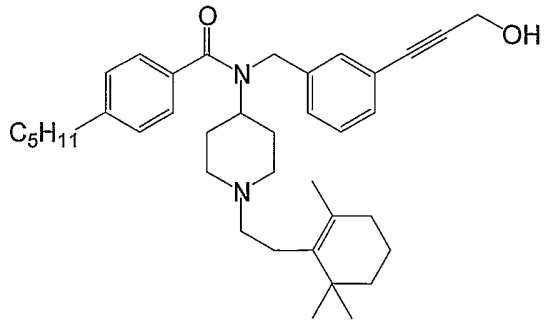


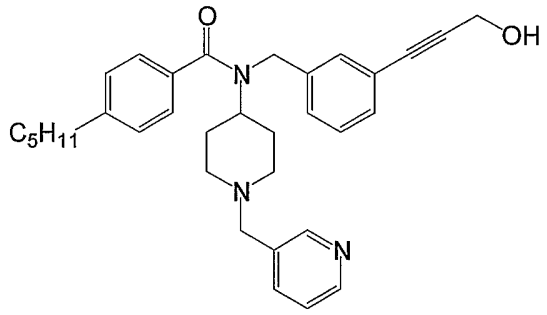


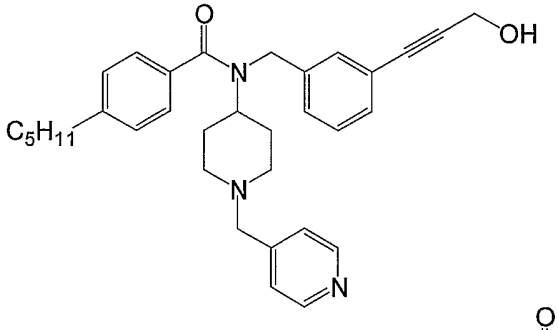


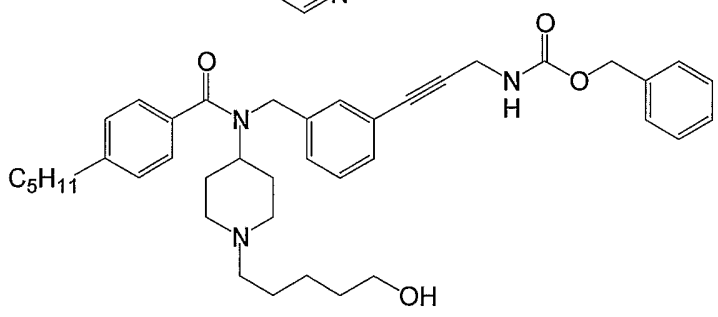


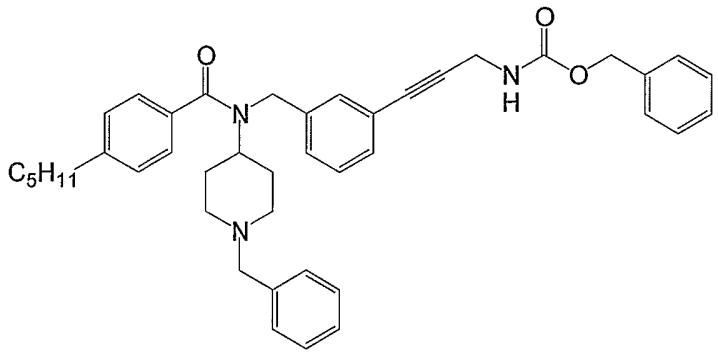


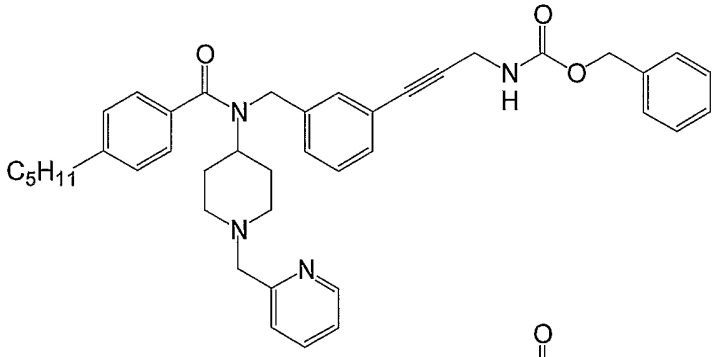


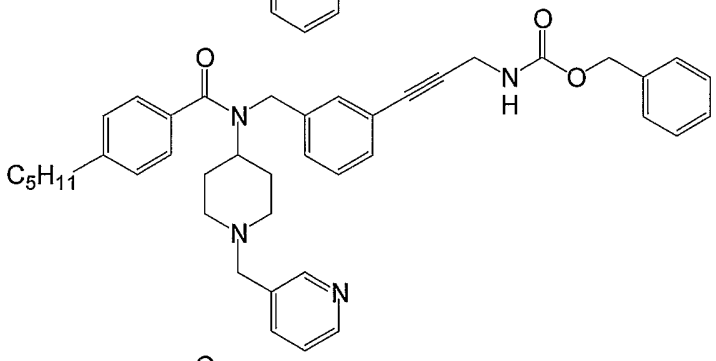


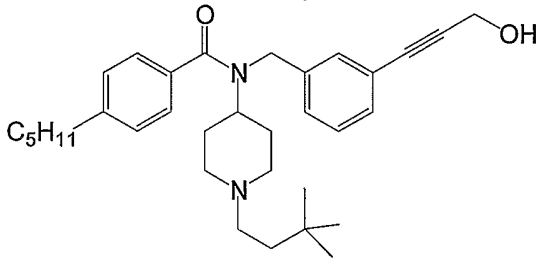


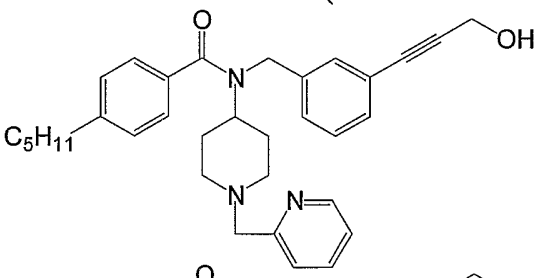


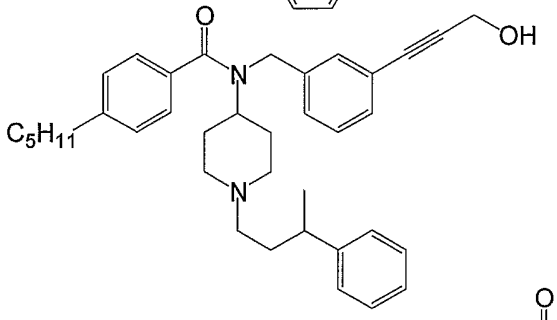


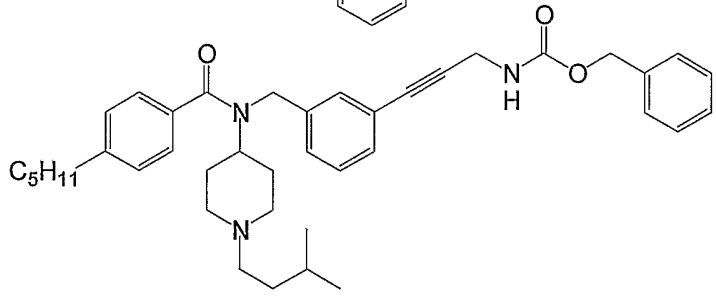








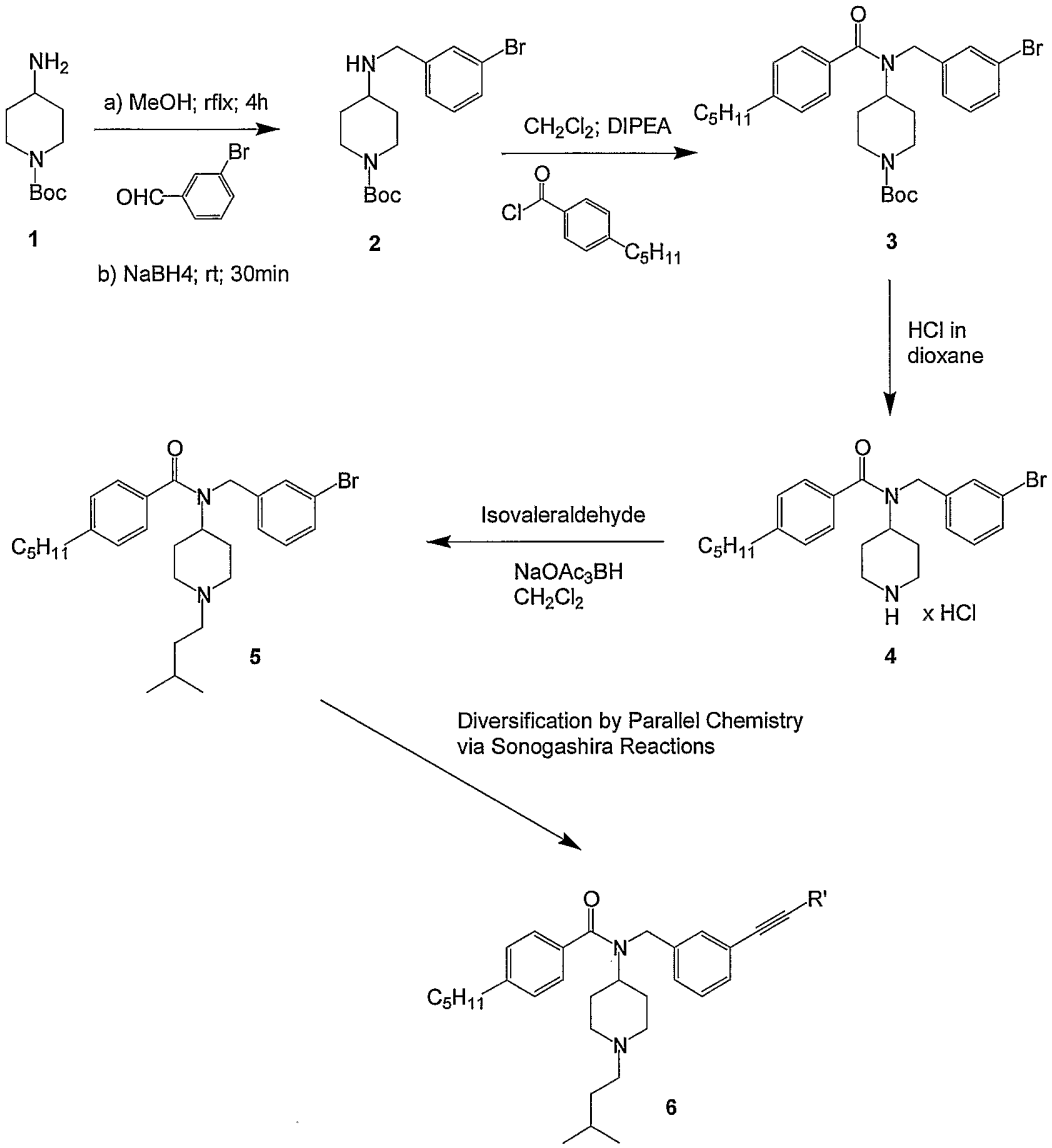




The compounds of the **general formula I** of the present invention may be prepared according to the procedures and sequences of reactions outlined below. For simplicity and clarity reasons, only parts of the synthetic possibilities which lead to compounds of the formulae I to VII are described. For general methods of the necessary steps see Typical Procedures A to M and / or WO 02/24649 and C. Boss et al; *Curr. Med. Chem.*, **2003**, *10*, 883-907.

Scheme 1: Synthesis of compounds of the **General Formula I**:

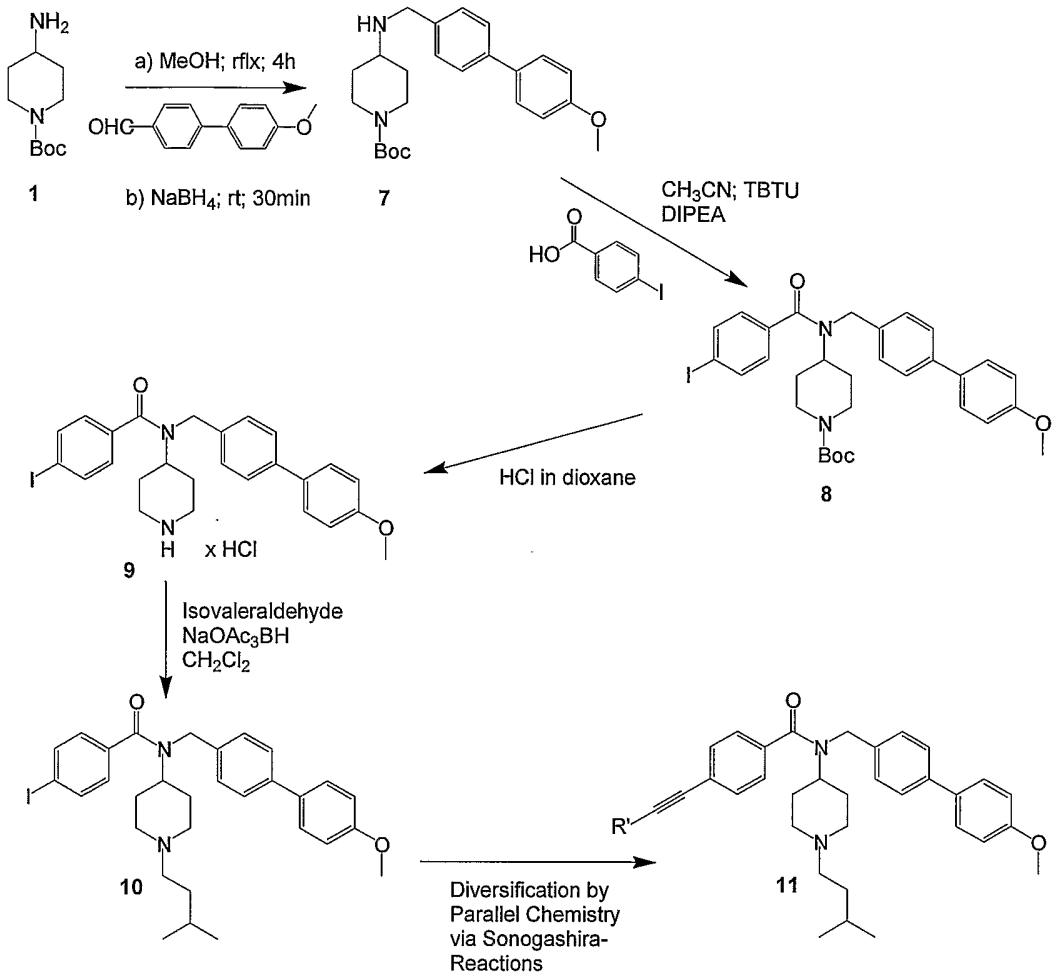
Pathway A) Alkyne-Substituent in group A:



The reactions were performed according to the descriptions given in the Typical Procedures. Scheme 1, for simplicity and clarity reasons, describes only limited structural diversity which is not meant to restrict the invention.

Scheme 1 (continued): Synthesis of compounds of the **General Formula I**:

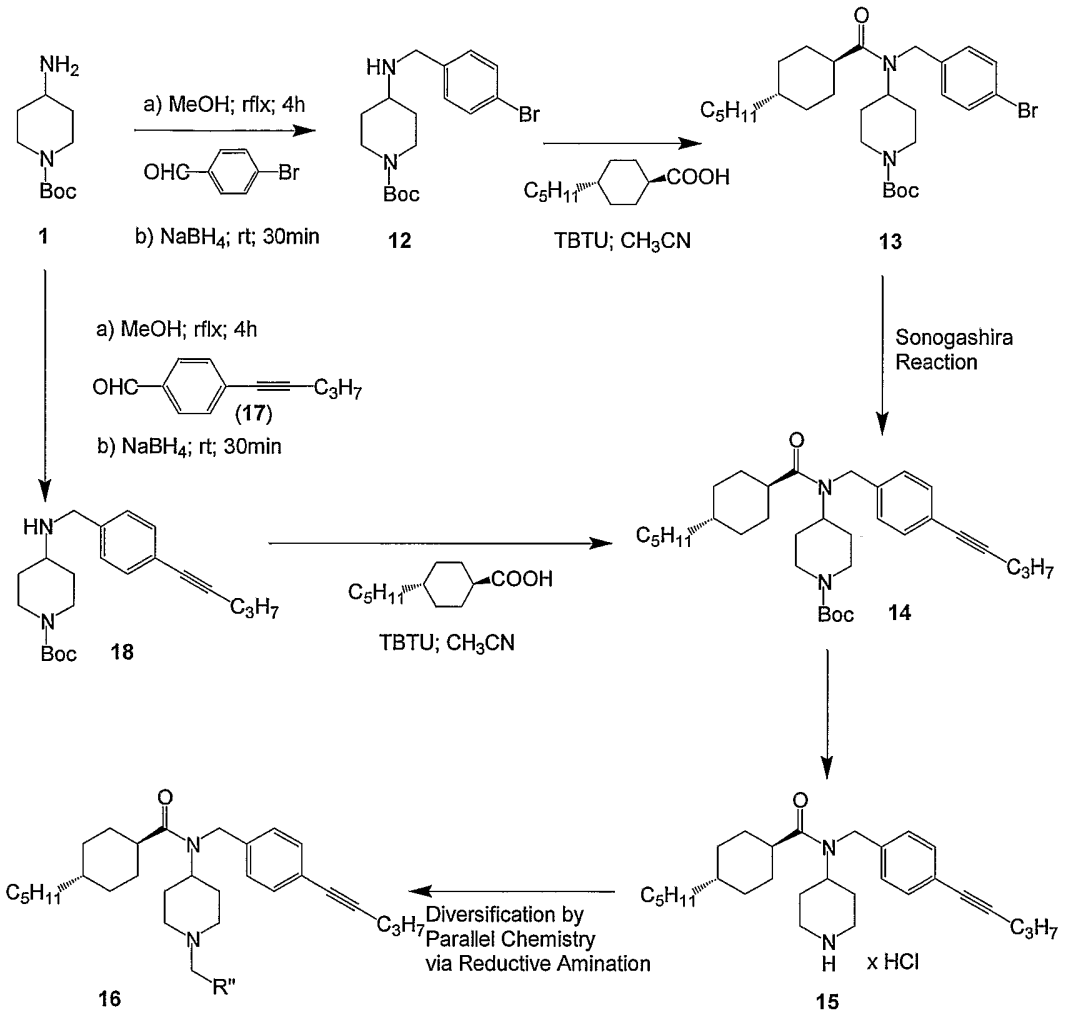
Pathway B) Alkyne-Substituent in group B:



The reactions were performed according to the descriptions given in the Typical Procedures. Scheme 1, for simplicity and clarity reasons, describes only limited structural diversity which is not meant to restrict the invention.

Scheme 1 (continued): Synthesis of compounds of the **General Formula I**:

Pathway C) Alkyne-Substituent in group A and variations of group C by parallel chemistry:



The reactions were performed according to the descriptions given in the Typical Procedures. Scheme 1, for simplicity and clarity reasons, describes only limited structural diversity which is not meant to restrict the invention.

The following examples illustrate the invention but do not limit the scope thereof. All temperatures are stated in °C.

List of abbreviations:

Boc_2O	di-tert.-butyl-di-carbonat
Boc or boc	tert.-butyloxycarbonyl
BSA	bovine serum albumine
Cbz	benzyloxycarbonyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene(1,5-5)
DCC	N,N'-dicyclohexylcarbodiimide
DCM	dichloromethane
DIPEA	Hünig's base
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EDC	N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide
EtOAc	ethyl acetate
HATU	O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HBTU	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HCl	hydrogen chloride
HV	high vacuum
LAH	lithium aluminium hydride
M	molar
NMM	N-methylmorpholine
PG	protecting group
PyBOP	Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate
Rt or rt	room temperature
TBTU	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TEA	triethylamine
TFA	trifluoroacetic acid

THF	tetrahydrofuran
tR or t_R	retention time

General Procedures and Examples:

The following compounds were prepared according to the procedures described for the synthesis of compounds encompassed by the general formulae hereinbefore. All compounds were characterized by ^{1}H-NMR (300MHz) and occasionally by ^{13}C-NMR (75MHz) (Varian Oxford, 300MHz; chemical shifts are given in ppm relative to the solvent used; multiplicities: s = singlet, d = doublet, t = triplet; m = multiplet), by LC-MS: **A**: 2 min < t_R < 10 min; (Waters Micromass; ZMD-platform with ESI-probe with Alliance 2790 HT; Colum: 2x30mm, Gromsil ODS4, 3□m, 120A; Gradient: 0 – 100% acetonitril in water, 6 min, with 0.05% formic acid, flow: 0.45ml/min; t_R is given in min.), **B**: 0.1 min < t_R < 1.5 min; (Finnigan AQA with ESI-probe with HP 110 DAD and HP110 binary pump; column: Develosil RP-AQUEOUS, 5□m, 4.6 mm x 50 mm; gradient: 5 - 95% acetonitril in water (0.04% TFA), 1 min., 95% acetonitril in water (0.04% TFA) 0.4 min., 4.5 ml/min.), by TLC (TLC-plates from Merck, Silica gel 60 F_{254}) and occasionally by melting point.

a) General Procedures:

(for additional descriptions see also: WO 02/24649 and WO 02/38534)

Typical Procedure A) for the reductive amination:

The amine and the aldehyde (1.5 eq.) (which are used as starting materials, are known compounds or the synthesis is described in the *Reference Examples*), are mixed in anhydrous methanol and refluxed for 4 h. The mixture is cooled to rt and then treated with sodium borohydride (1.5 eq.) and again stirred for 2 h at reflux temperature. The reaction mixture is concentrated in vacuo and water is slowly added followed by extraction with DCM (3x). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude compound is purified by column chromatography on silica gel by an appropriate mixture of EtOAc / hexane

containing 1% TEA or by recrystallization from a suitable solvent. Further experimental details on reductive aminations can be found in the literature: A. F. Abdel-Magid et al; *J. Org. Chem.*; **1996**, *61*, 3849 - 3862; K. A. Neidigh et al; *J. Chem. Soc. Perkin Trans. 1*; **1998**, 2527 - 2531; B. J. Lavey et al; *J. Org. Chem.*; **1996**, *61*, 7633 - 7636.

Typical Procedure B) for the acylation (with acid chlorides or sulfonylchlorides):

To a solution of the secondary amine in anhydrous DCM is added Hünig's base (DIPEA; 10 eq) or another suitable base followed by the addition of the carboxylic acid chloride or the sulfonylchloride (1.5 eq.). The reaction mixture is stirred for 4 to 12 h at rt. Then saturated sodium carbonate solution was added and the mixture was exctracted with DCM (3x). The combined organic layers were washed with 1 N HCl and brine, dried over magnesium sulfate, filtered and evaporated. The crude compound is purified by column chromatography on silica gel by an appropriate mixture of EtOAc / hexane or by recrystallization from a suitable solvent to give the pure amide intermediates.

Typical Procedure C) for the reaction with isocyanates:

To a solution of the secondary amine in DCM was added the isocyanate (1.5 eq) and the reaction mixture was stirred at rt for 4 to 12 h. The reaction mixture was directly concentrated in vacuo and the crude material was purified by column chromatography on silica gel by an appropriate mixture of EtOAc / hexane or by recrystallization from a suitable solvent to give the pure urea intermediates.

Typical Procedure D) for the second reductive amination with aldehydes:

To a solution of the secondary amine in DCM was added the aldehyde (1.5 eq) and sodium triacetoxy borohydride (4 eq). Stirring was continued for 6 to

12 h. Water was added and the mixture was extracted with DCM (3x). The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo and the crude material was purified by column chromatography on silica gel by an appropriate mixture of EtOAc / hexane or by recrystallization from a suitable solvent to give the pure tertiary amine intermediates.

Typical Procedure E) for the acylation with carboxylic acids:

To a solution of the secondary amine in acetonitrile was added the respective carboxylic acid (1 eq.) and a coupling reagent like HATU (1.05 eq) (or TBTU or PyBOP or HBTU and the like) followed by slow addition of DIPEA (2.1 eq). Stirring was continued for 10 h at rt followed by the addition of EtOAc. The mixture was extracted with 2M HCl-solution, saturated $NaHCO_3$-solution and brine, dried over $MgSO_4$ and evaporated. The crude products were purified by HPLC.

Typical Procedure F) for the Boc-deprotection:

To a solution of the Boc-protected amine in dioxane at rt was added a solution of 4 M HCl in dioxane (commercially available from Aldrich). Stirring was continued for 1 to 5 h. The mixture was evaporated and dried at HV to give the pure HCl salt of the secondary amine, which were used without further purification. [see also: P. J. Kocienski, *Protecting Groups*, Thieme, **1994**; T. W. Greene, P. G. M. Wuts; *Protective Groups in Organic Synthesis*, John Wiley & sons; **1991**.]

Typical Procedure G) for the Suzuki coupling with arylbromides:

To a solution of arylbromide in toluene is added the boronic acid (1.1 eq.) in isopropanol and a 2M aqueous solution of potassium carbonate (5 eq.). The mixture is purged with nitrogen for 10 min and tetrakis(triphenylphosphine) palladium (0.03 eq.) is added. After heating under reflux for 6 h, water is added to the cooled reaction mixture and the product is extracted with ethyl acetate. The organic phase is washed with brine and dried over sodium sulfate. The solvent is evaporated to give the crude aldehyde, which is purified by flash chromatography (EtOAc/heptane gradient).

Typical Procedure H) for the Suzuki coupling with arylchlorides:

The arylchloride, the boronic acid (1.5 eq) and potassium phosphate (K3PO4; 3 eq)) were added subsequently to dioxane (5 ml / mmol arylchloride). While heating to 100°C, nitrogen is bubbled through the mixture. Then a solution of 2'-(dimethylamino)-2-biphenylyl-palladium(II)-chloride dinorbornylphosphine-complex (from Solvias or Fluka 36037; 0.01 eq)) was added to the hot reaction mixture and stirring was continued for 6 to 18 h. The reaction mixture is cooled to rt, water is added and the product extracted with EtOAc. The combined organic layers were dried with magnesium sulfate, filtered and concentrated in vacuo. The crude product is purified by flash chromatography (EtOAc/heptane gradient).

[References for *Suzuki*-couplings: A. F. Littke, G. C. Fu, *Angew. Chem.*, **1998**, *110*, 3586-3587. J. P. Gardner et al., *WO 01/90055* to EliLilly and Co. A. Giroux et al, *Tetrahedron Lett.*, **1997**, *38*, 3841-3844. A. Suzuki, *J. Organometallic Chem.*, **1999**, *576*, 147-168. A. R. Martin et al, *Acta. Chem. Scand.*, **1993**, *47*, 221-230. N. Miyaura et al, *Chem. Rev.*, **1995**, *95*, 2457-2483. A. F. Littke, G. C. Fu, *Angew. Chem.*, **2002**, *114*, 4350-4386. J. Hassan et al; *Chem. Rev.*, **2002**, *102*, 1359-1469.]

Typical Procedure I) for the Sonogashira coupling of terminal acetylenes with aryliodides:

Stephan Thorand, Norbert Krause, *J. Org. Chem.*, **1998**, *63*, 8551-8553.

D. Trachsel, *Helv. Chim. Acta.*, **2003**, in press.

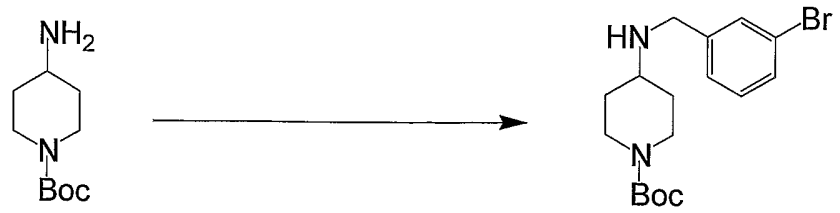
Typical Procedure K) for the Sonogashira coupling of terminal acetylenes with arylbromides:

G. Reginato, A. Mordini, M. Caracciolo; *J. Org. Chem.*; **1997**, *62*, 6187-6192.

Typical Procedure L) for the preparation of alkyl substituted aryl- and heteroaryl units:

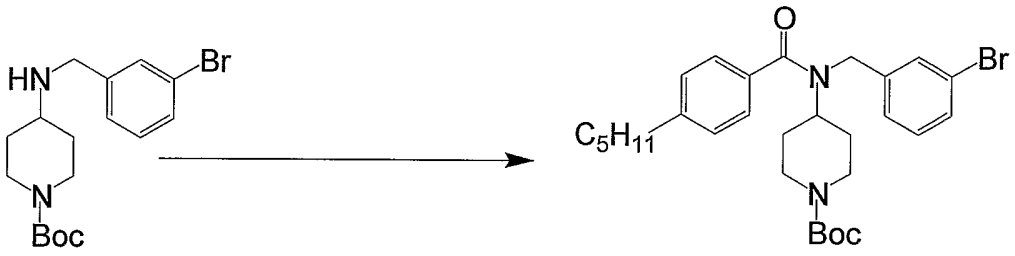
A. Fürstner, A. Leitner, M. Mendez, H. Krause; *J. Am. Chem. Soc.*; **2002**, *124*, 13856-13863.

Example 1:



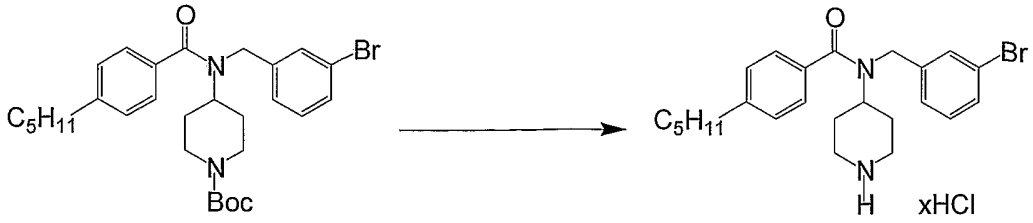
4-(3-Bromo-benzylamino)-piperidine-1-carboxylic acid *tert*-butyl ester

According to Typical Procedure A, 4-(3-bromo-benzylamino)-piperidine-1-carboxylic acid tert-butyl ester (1.67 g) was prepared from N-Boc-4-amino-piperidine (1.18 g; commercially available from Neosystem) and 3-bromobenzaldehyde (0.88 g). LC-MS: tR : 0.75 min.; $[M+H]^+$: 371.26.



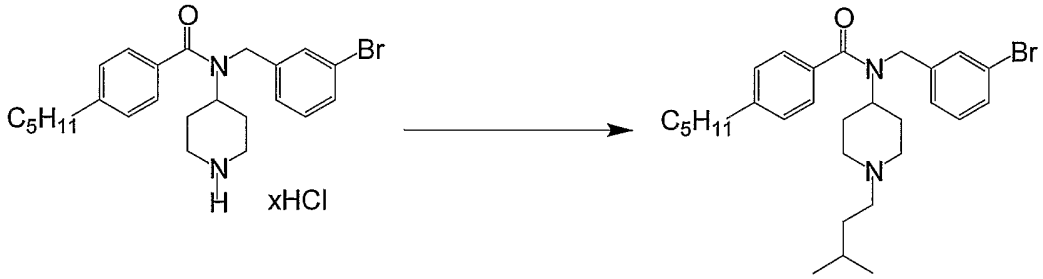
4-[(3-Bromo-benzyl)-(4-pentyl-benzoyl)-amino]-piperidine-1-carboxylic acid *tert*-butyl ester

According to Typical Procedure B, 4-[(3-Bromo-benzyl)-(4-pentyl-benzoyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (2.7 g) was prepared form 4-(3-bromo-benzylamino)-piperidine-1-carboxylic acid tert-butyl ester (2.2 g) and 4-pentyl-benzoylchloride (1.51 g). LC-MS: tR : 1.18 min.; $[M+H]^+$: 545.1.



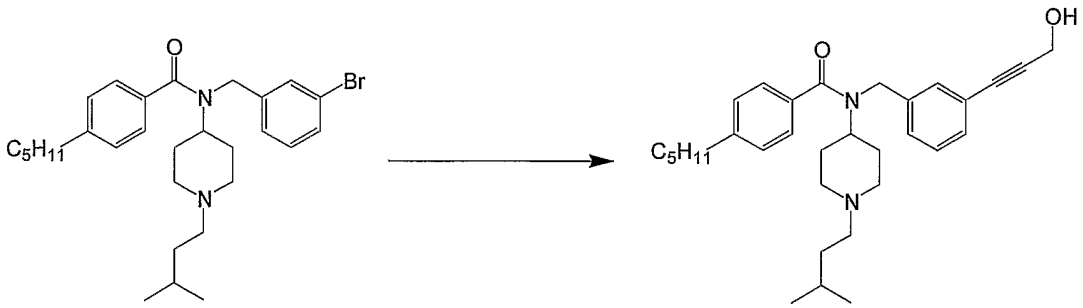
N-(3-Bromo-benzyl)-4-pentyl-*N*-piperidin-4-yl-benzamide Hydrochloride

According to Typical Procedure F, N-(3-Bromo-benzyl)-4-pentyl-N-piperidin-4-yl-benzamide hydrochloride (2.17 g) was prepared from 4-[(3-Bromo-benzyl)-(4-pentyl-benzoyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (2.5 g). LC-MS: tR : 0.88 min.; $[M+H]^+$: 443.1.



N-(3-Bromo-benzyl)-*N*-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide

According to the Typical Procedure D, N-(3-Bromo-benzyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide (2.22 g) was prepared from N-(3-Bromo-benzyl)-4-pentyl-N-piperidin-4-yl-benzamide hydrochloride (2.17 g) and isovaleraldehyde (0.59 g). LC-MS: tR : 0.97 min.; $[M+H]^+$: 513.2.

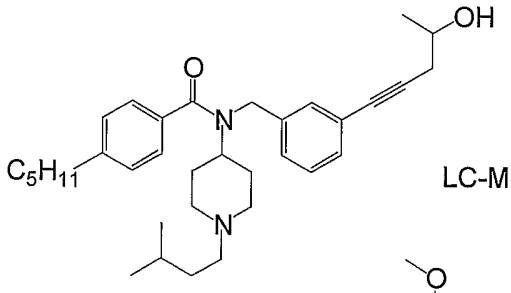


N-[3-(3-Hydroxy-prop-1-ynyl)-benzyl]-*N*-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide

According to the Typical Procedure K adapted to a parallel chemistry setting, N-[3-(3-Hydroxy-prop-1-ynyl)-benzyl]-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide (0.02 g) was prepared from N-(3-Bromo-benzyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide (0.05 g) and propargyl alcohol. LC-MS: tR : 0.92 min.; $[M+H]^+$: 489.48.

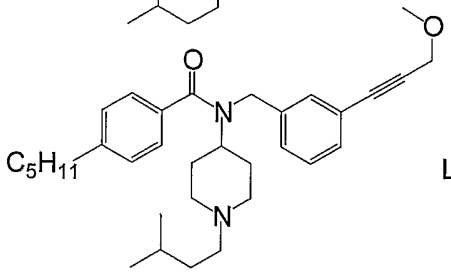
The following Examples 2 to 6 were prepared in analogy to the preparation described for Example 1. No nomenclature is given! This is not a mistake but would be better in addition to the formulae (see also following examples).

Example 2



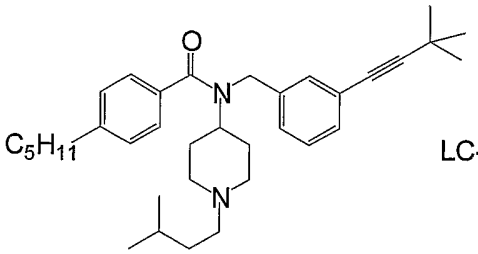
LC-MS: tR = 0.94 ; $[M+H]^+$ = 517.48

Example 3



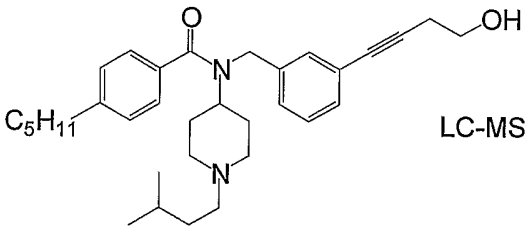
LC-MS: tR = 0.98 ; $[M+H]^+$ = 503.49

Example 4



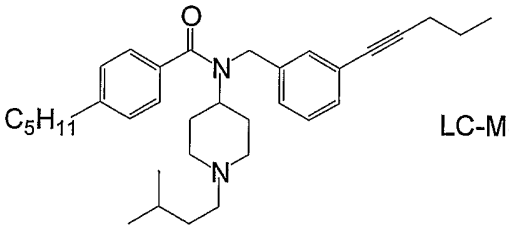
LC-MS: tR = 1.04 ; $[M+H]^+$ = 515.50

Example 5



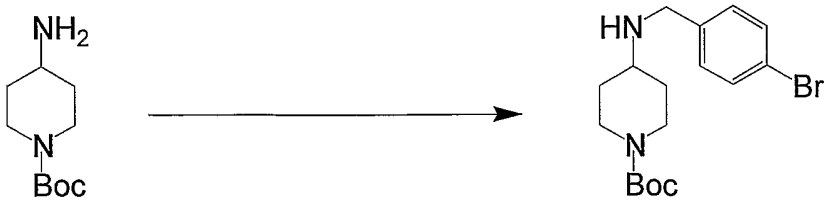
LC-MS: tR = 0.93 ; $[M+H]^+$ = 503.49

Example 6



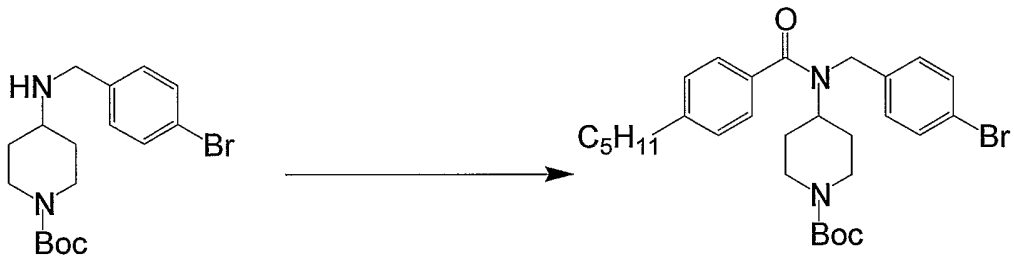
LC-MS: tR = 1.03 ; $[M+H]^+$ = 501.51

Example 7:



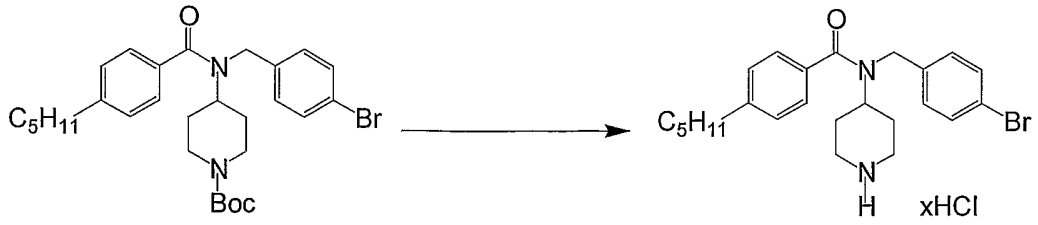
4-(4-Bromo-benzylamino)-piperidine-1-carboxylic acid *tert*-butyl ester

According to Typical Procedure A, 4-(4-bromo-benzylamino)-piperidine-1-carboxylic acid tert-butyl ester (9.62 g) was prepared from N-Boc-4-amino-piperidine hydrochloride (5.0 g; commercially available from Neosystem) and 4-bromobenzaldehyde (6.39 g). LC-MS: tR : 0.76 min.; $[M+H]^+$: 371.13.



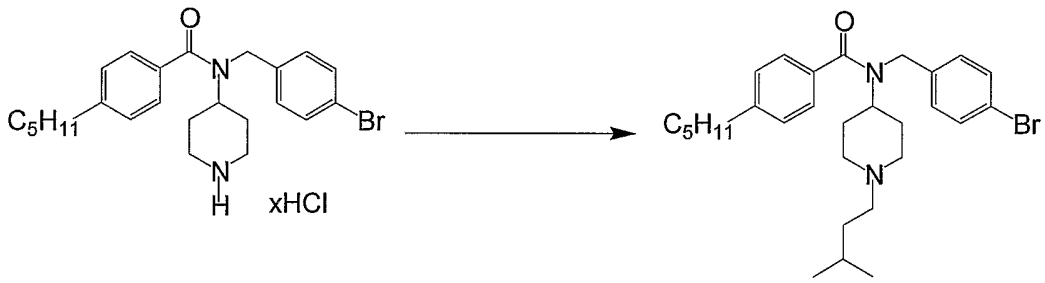
4-[(4-Bromo-benzyl)-(4-pentyl-benzoyl)-amino]-piperidine-1-carboxylic acid *tert*-butyl ester

According to Typical Procedure B, 4-[(4-Bromo-benzyl)-(4-pentyl-benzoyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (3.63 g) was prepared form 4-(4-bromo-benzylamino)-piperidine-1-carboxylic acid tert-butyl ester (3.0 g) and 4-pentyl-benzoylchloride (2.05 g). LC-MS: tR : 1.16 min.; $[M+H]^+$: 545.17.



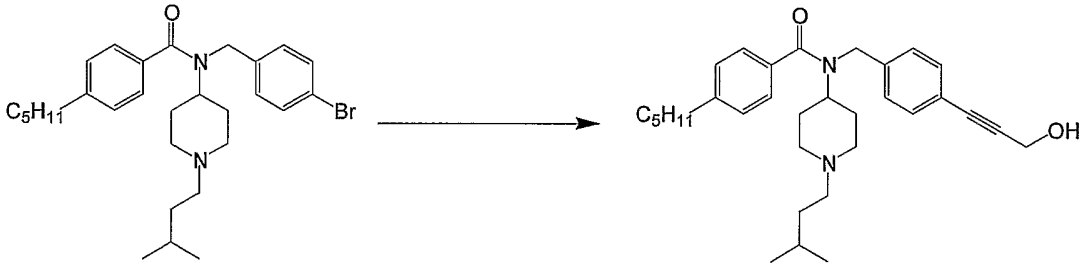
N-(4-Bromo-benzyl)-4-pentyl-*N*-piperidin-4-yl-benzamide Hydrochloride

According to Typical Procedure F, N-(4-Bromo-benzyl)-4-pentyl-N-piperidin-4-yl-benzamide Hydrochloride (2.05 g) was prepared from 4-[(4-Bromo-benzyl)-(4-pentyl-benzoyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (2.5 g). LC-MS: tR : 0.88 min.; $[M+H]^+$: 443.1.



N-(4-Bromo-benzyl)-*N*-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide

According to the Typical Procedure D, N-(4-Bromo-benzyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide (1.05 g) was prepared from N-(4-Bromo-benzyl)-4-pentyl-N-piperidin-4-yl-benzamide Hydrochloride (1.61 g) and isovaleraldehyde (0.29 g). LC-MS: tR : 0.97 min.; $[M+H]^+$: 515.2.

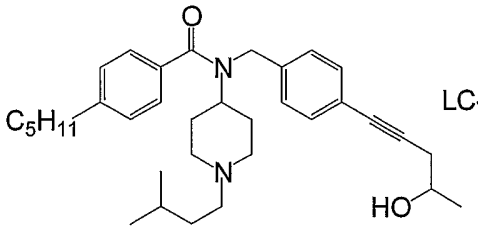


N-[4-(3-Hydroxy-prop-1-ynyl)-benzyl]-*N*-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide

According to the Typical Procedure K adapted to a parallel chemistry setting, N-[4-(3-Hydroxy-prop-1-ynyl)-benzyl]-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide (0.02 g) was prepared from N-(4-Bromo-benzyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide (0.05 g) and propargyl alcohol. LC-MS: tR : 0.92 min.; $[M+H]^+$: 489.51.

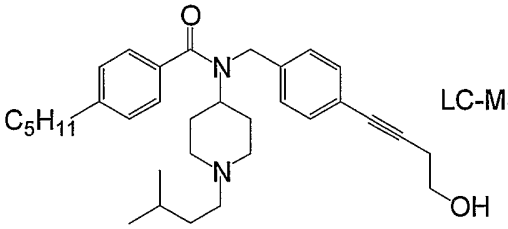
The following Examples 8 to 11 were prepared in analogy to the preparation described for Example 7.

Example 8



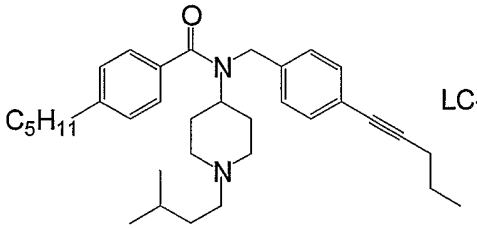
LC-MS: tR = 0.94 ; $[M+H]^+$ = 517.49

Example 9



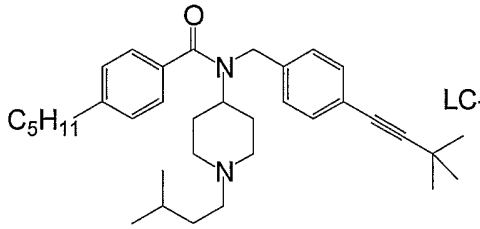
LC-MS: tR = 0.93 ; $[M+H]^+$ = 503.51

Example 10



LC-MS: tR = 1.03 ; $[M+H]^+$ = 501.50

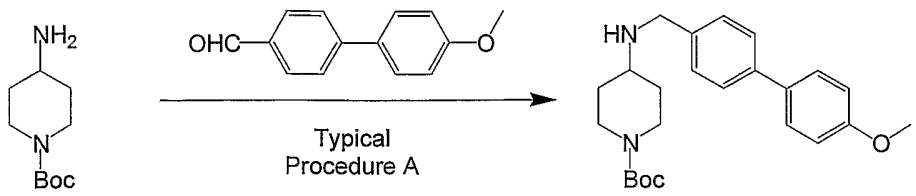
Example 11



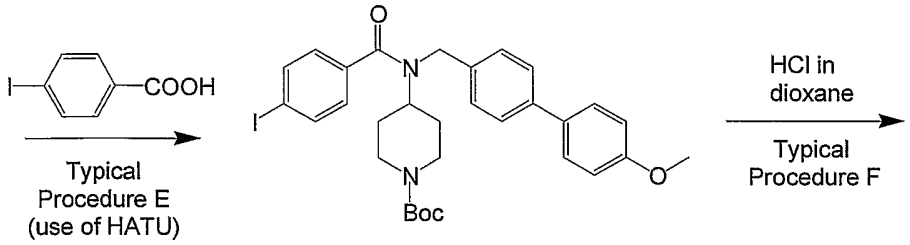
LC-MS: tR = 1.04 ; $[M+H]^+$ = 515.50

Example 12:

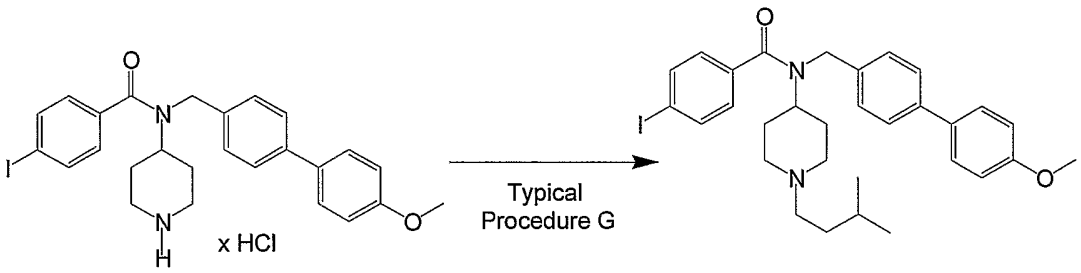
Prepared as described in WO 02/24649



LC-MS: tR = 0.83;
$[M+H]^+$ = 397.31



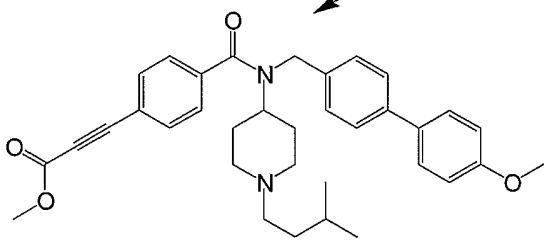
LC-MS: tR = 1.13;
$[M+H]^+$ = 627.09



LC-MS: tR = 0.85;
$[M+H]^+$ = 527.07

LC-MS: tR = 0.92;
$[M+H]^+$ = 597.13

Typical Procedure K

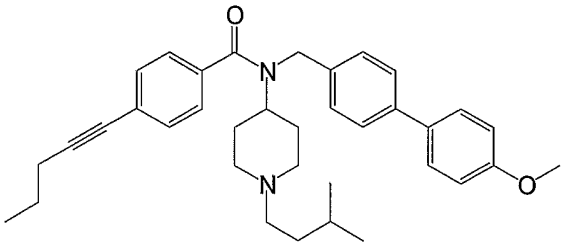


Example 12

LC-MS: tR = 0.94;
$[M+H]^+$ = 553.32

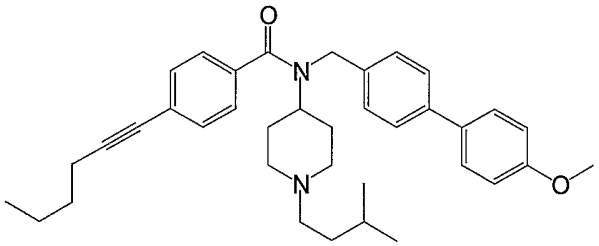
The following Examples 13 to 18 were prepared in analogy to the preparation described for Example 12.

Example 13



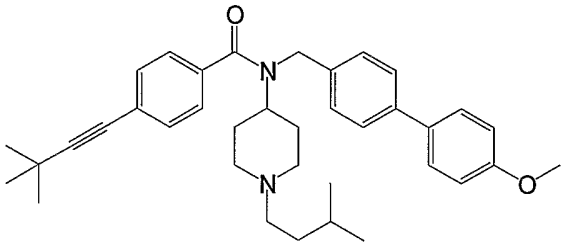
LC-MS: tR = 0.99; $[M+H]^+$ = 537.30

Example 14



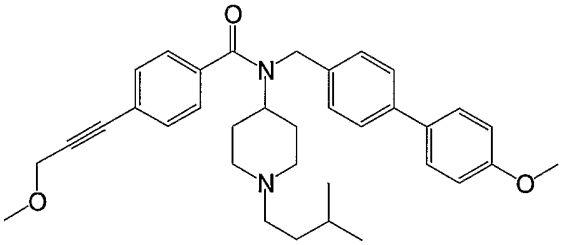
LC-MS: tR = 1.00; $[M+H]^+$ = 551.28

Example 15



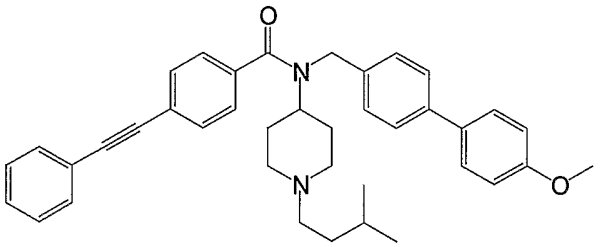
LC-MS: tR = 0.99; $[M+H]^+$ = 551.37

Example 16



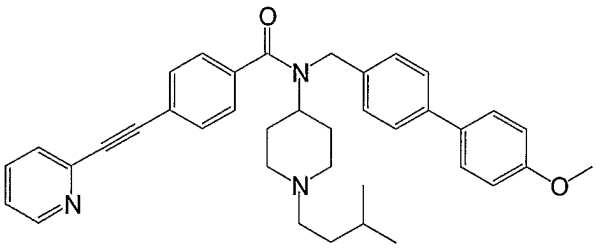
LC-MS: tR = 0.93; $[M+H]^+$ = 539.25

Example 17



LC-MS: tR = 1.00; $[M+H]^+$ = 571.27

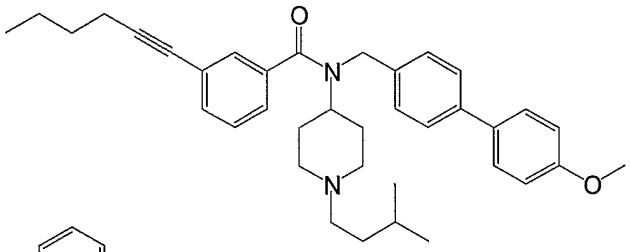
Example 18



LC-MS: tR = 0.92; $[M+H]^+$ = 572.27

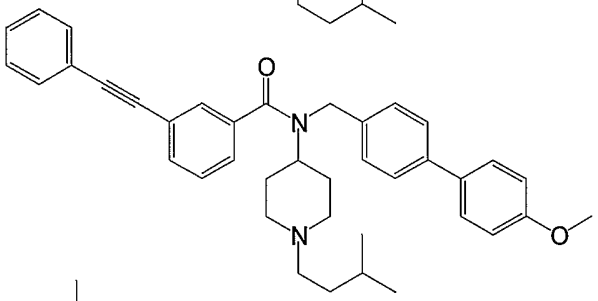
The following Examples 19 to 24 were prepared in analogy to the preparation described for Example 12.

Example 19



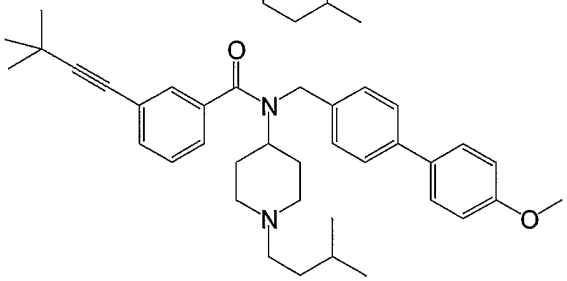
LC-MS: tR = 1.00;
$[M+H]^+$ = 551.28

Example 20



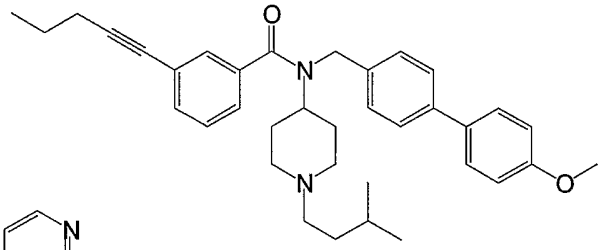
LC-MS: tR = 0.99;
$[M+H]^+$ = 571.26

Example 21



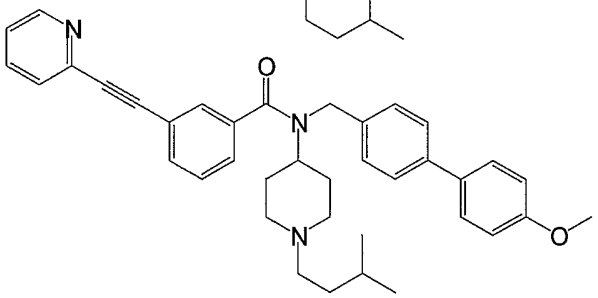
LC-MS: tR = 1.00;
$[M+H]^+$ = 551.30

Example 22



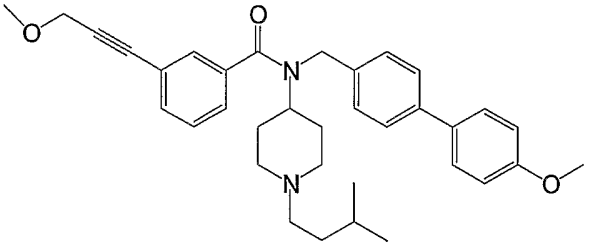
LC-MS: tR = 0.99;
$[M+H]^+$ = 537.30

Example 23



LC-MS: tR = 0.91;
$[M+H]^+$ = 572.24

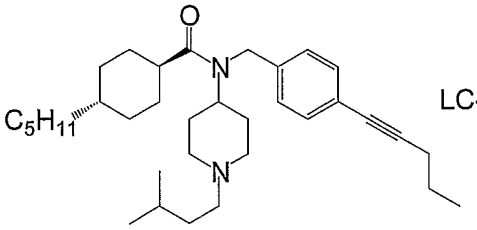
Example 24



LC-MS: tR = 0.93;
$[M+H]^+$ = 539.29

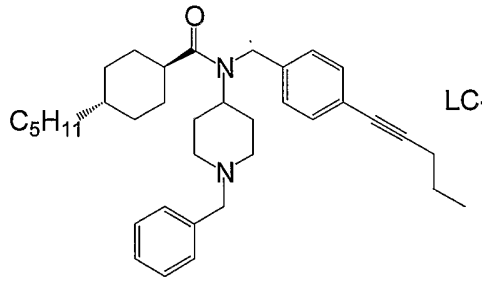
The following Examples 25 to 29 were prepared in analogy to the Typical Procedures and to the procedures described for the preparation of the Examples 1 to 24.

Example 25



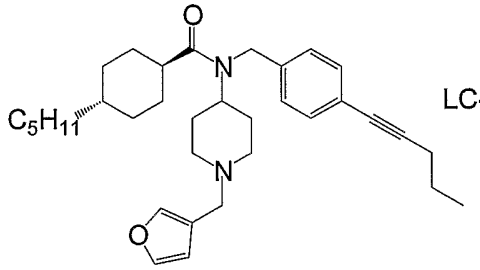
LC-MS: tR = 1.05 ; $[M+H]^+$ = 507.59

Example 26



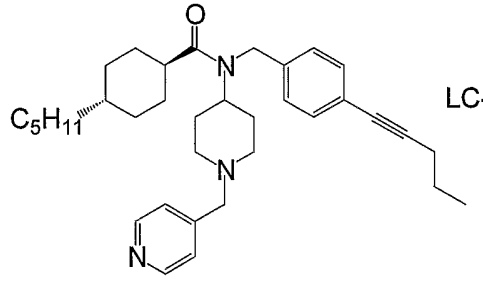
LC-MS: tR = 1.05 ; $[M+H]^+$ = 527.54

Example 27



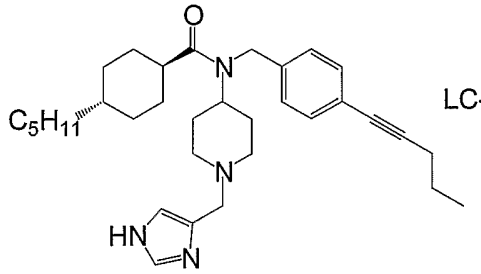
LC-MS: tR = 1.03 ; $[M+H]^+$ = 517.51

Example 28



LC-MS: tR = 0.96 ; $[M+H]^+$ = 528.53

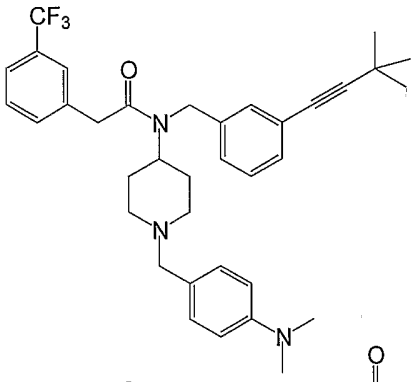
Example 29



LC-MS: tR = 0.97 ; $[M+H]^+$ = 517.52

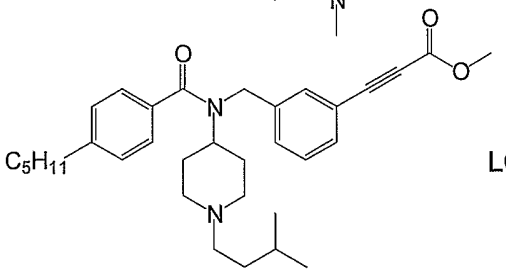
According to the procedures described above the following examples were prepared:

Example 30



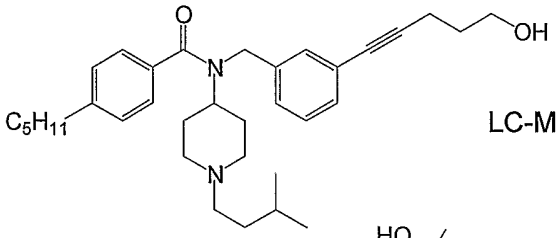
LC-MS: tR = 0.99; $[M+H]^+$= 590.49

Example 31



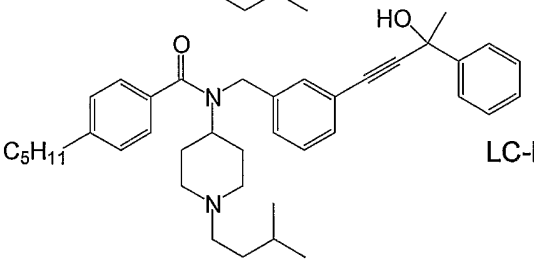
LC-MS: tR = 0.98; $[M+H]^+$= 517.5

Example 32



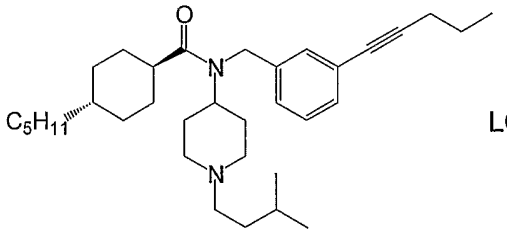
LC-MS: tR = 0.93; $[M+H]^+$= 517.61

Example 33



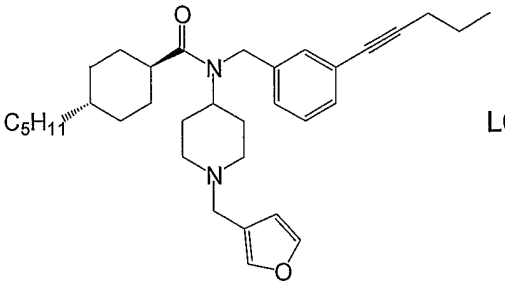
LC-MS: tR = 0.99; $[M+H]^+$= 579.58

Example 34



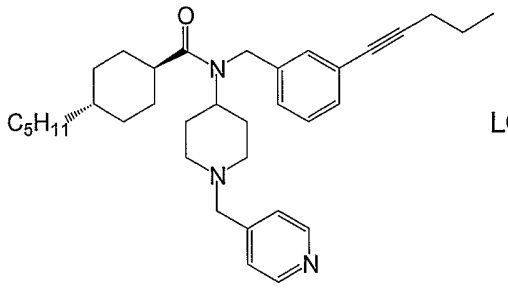
LC-MS: tR = 1.06; $[M+H]^+$= 507.47

Example 35



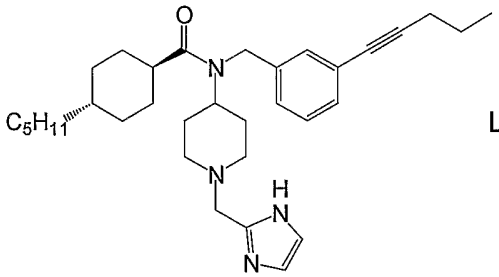
LC-MS: tR = 1.03; $[M+H]^+$= 517.37

Example 36



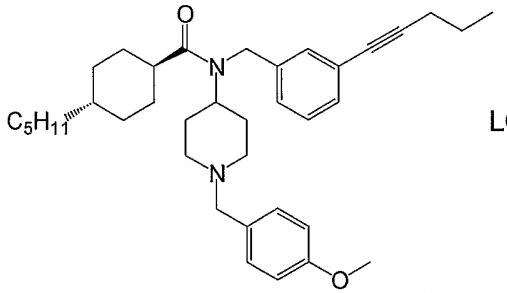
LC-MS: tR = 0.96; $[M+H]^+$= 528.40

Example 37



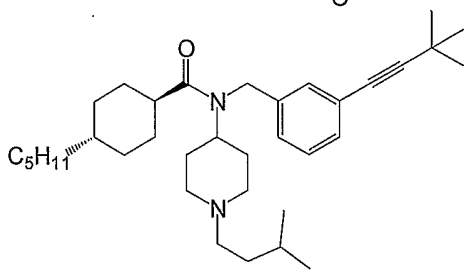
LC-MS: tR = 0.95; $[M+H]^+$= 517.40

Example 38

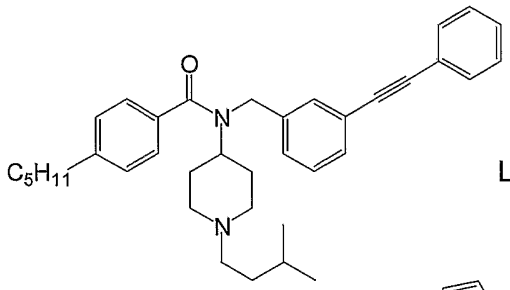


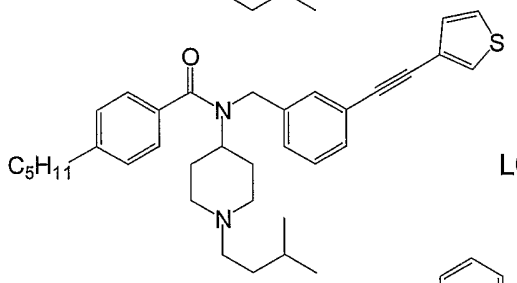
LC-MS: tR = 1.05; $[M+H]^+$= 557.42

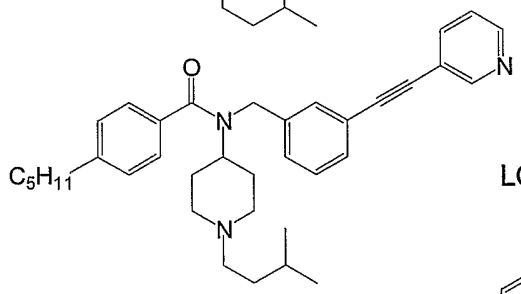
Example 39

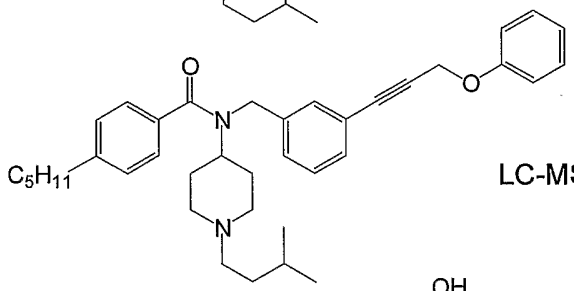


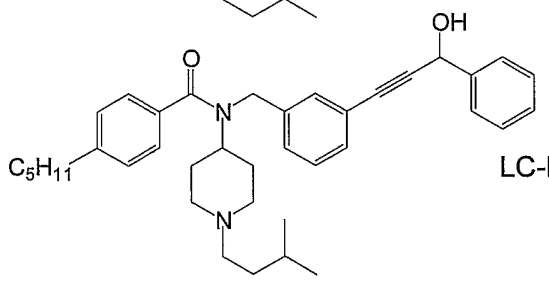
LC-MS: tR = 1.07; $[M+H]^+$= 521.46

Example 40  LC-MS: tR = 1.03; $[M+H]^+$= 535.2

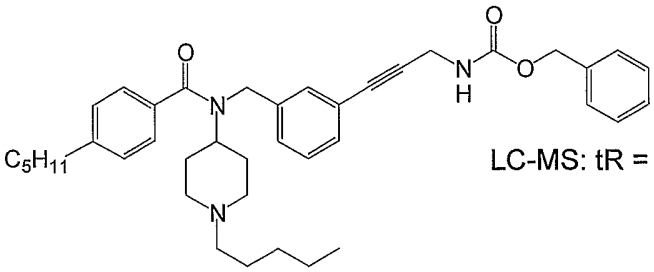
Example 41  LC-MS: tR = 1.02; $[M+H]^+$= 541.2

Example 42  LC-MS: tR = 0.98; $[M+H]^+$= 536.2

Example 43  LC-MS: tR = 1.02; $[M+H]^+$= 565.2

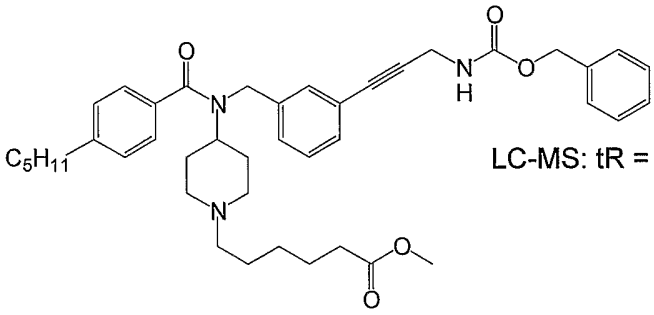
Example 44  LC-MS: tR = 0.97; $[M+H]^+$= 565.2

Example 45



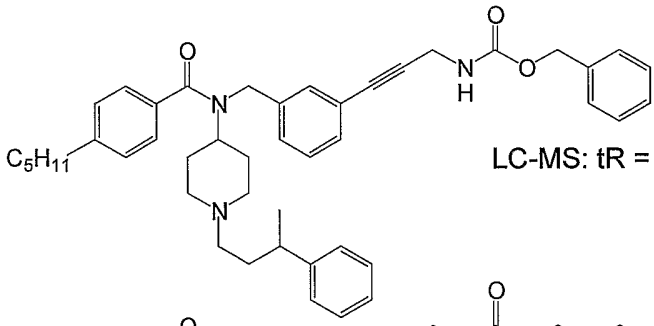
LC-MS: tR = 1.01; $[M+H]^+$= 622.3

Example 46



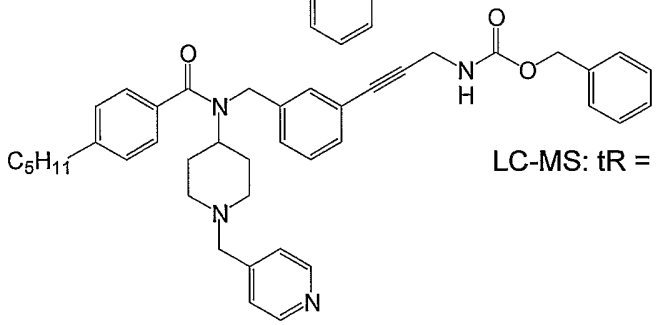
LC-MS: tR = 0.99; $[M+H]^+$= 680.24

Example 47



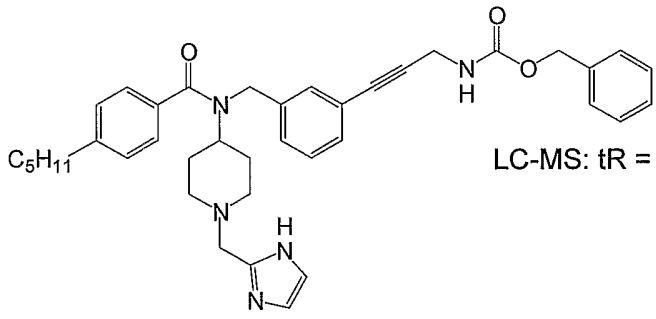
LC-MS: tR = 1.03; $[M+H]^+$= 684.26

Example 48



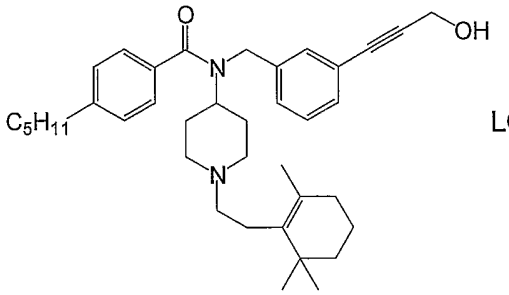
LC-MS: tR = 0.91; $[M+H]^+$= 643.20

Example 49



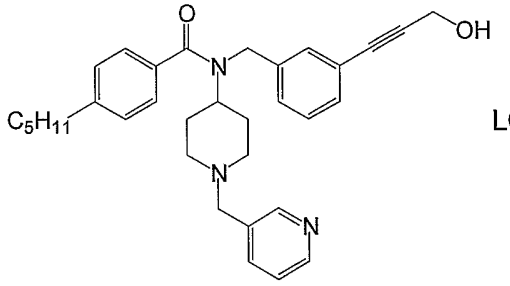
LC-MS: tR = 0.90; $[M+H]^+$= 632.20

Example 50



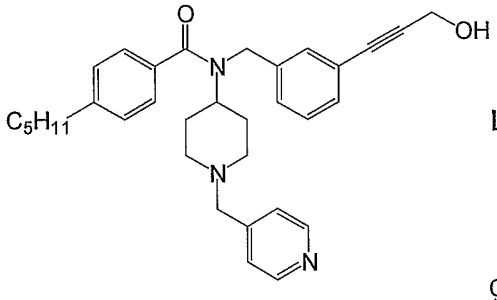
LC-MS: tR = 1.00; $[M+H]^+$= 569.30

Example 51



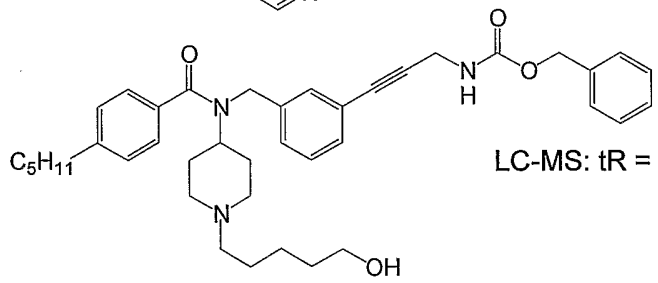
LC-MS: tR = 0.81; $[M+H]^+$= 510.30

Example 52



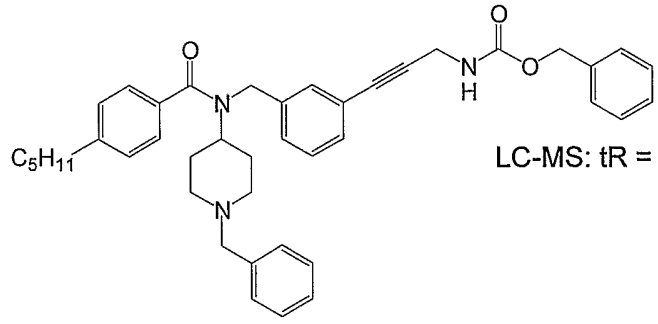
LC-MS: tR = 0.80; $[M+H]^+$= 510.20

Example 53

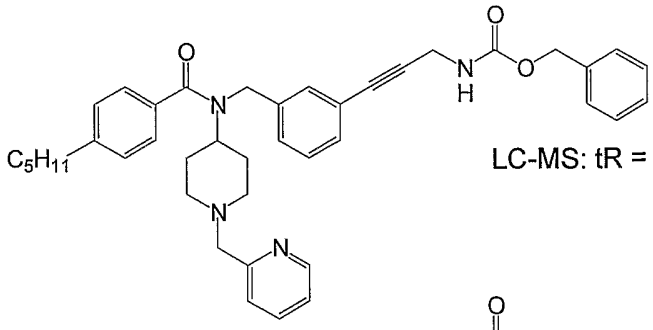


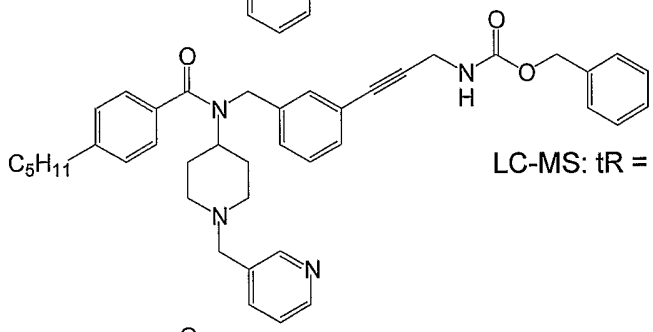
LC-MS: tR = 0.94; $[M+H]^+$= 638.28

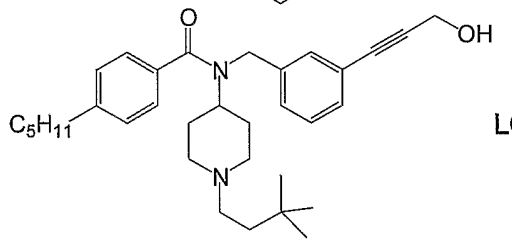
Example 54

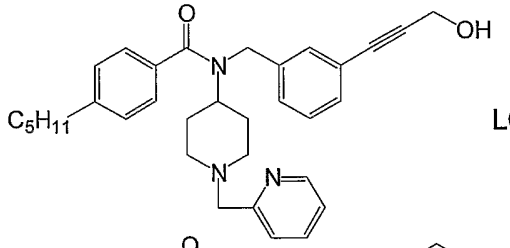


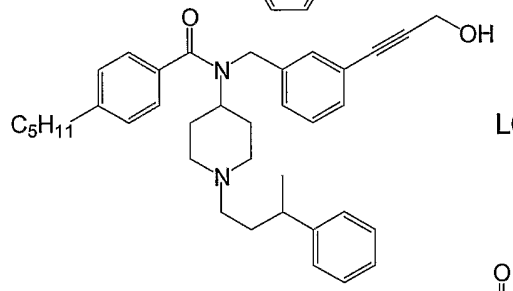
LC-MS: tR = 1.00; $[M+H]^+$= 642.20

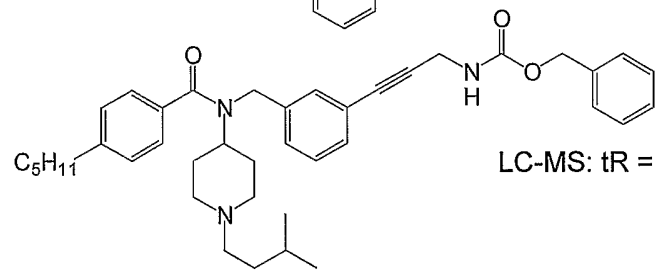
Example 55  LC-MS: tR = 0.96; $[M+H]^+$= 643.20

Example 56  LC-MS: tR = 0.92; $[M+H]^+$= 643.20

Example 57  LC-MS: tR = 0.93; $[M+H]^+$= 503.20

Example 58  LC-MS: tR = 0.87; $[M+H]^+$= 510.2

Example 59  LC-MS: tR = 0.95; $[M+H]^+$= 551.2

Example 60  LC-MS: tR = 1.03; $[M+H]^+$= 593.2

Example A

Active ingredients can be formulated according to methods known per se to give pharmaceutical preparations of the following composition:

1. 500 mg tablets

Active ingredient	500 mg
Lactose powder	149 mg
Polyvinylpyrrolidone	15 mg
Dioctyl sodiumsulphosuccinate	1 mg
Na carboxymethylstarch	30 mg
Magnesium stearate	5 mg
	700 mg

2. 50 mg tablets

Active ingredient	50 mg
Lactose powder	50 mg
Microcrystalline cellulose	82 mg
Na carboxymethylstarch	15 mg

3. 100 mg capsules

Active ingredient	100.0 mg
Lactose powder	104.7 mg
Corn starch	70.0 mg
Hydroxypropylmenthyl cellulose	10.0 mg
Dioctyl sodiumsulphosuccinate	0.3 mg
Talc	12.0 mg
Magnesium stearate	3.0 mg

4. 500 mg suppositories

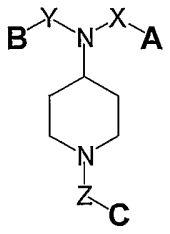
Active ingredient	500 mg
Suppository mass	ad 2000 mg

5. 100 mg suppository

Active ingredient	100 mg
Medium chain triglyceride	300 mg
	400 mg

Claims:

1. Compounds of the **general formula I**:



General Formula I

wherein

X represents $-(CH_2)_n-$;

Y represents $-(CH_2)_n-$; -(C=O)-; $-(SO_2)-$; -(C=O)-NH-;

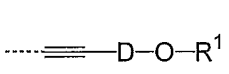
Z represents a bond; $-(CH_2)_n-$;

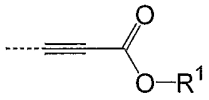
C represents hydrogen; lower alkyl; lower alkenyl; lower alkynyl; aryl; heteroaryl; cycloalkyl; cycloalkenyl; heterocyclyl; or lower alkyl substituted by hydroxy, carboxy or lower alkoxycarbonyl;

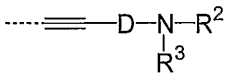
n represents the whole numbers 1, 2, 3 or 4;

A and **B** represent aryl; heteroaryl; heterocyclyl; cycloalkyl; with the proviso that at least one of **A** and **B** represents aryl or heteroaryl substituted by an alkynyl group Q which is represented by the following groups:

- alkynyl containing two to six carbon atoms;and







wherein

D represents $-(CH_2)_n-$;

R^1 represents hydrogen; methyl; ethyl; propyl; butyl; tert.-butyl; iso-propyl; aryl; heteroaryl;

R^2 represents hydrogen; methyl; ethyl; propyl; butyl; tert.-butyl; iso-propyl; $-(CH_2)_m$-aryl; $-(CH_2)_m$-heteroaryl; $-(CH_2)_m$-cycloalkyl; $-(C=O)-R^4$; $-(C=O)-NH-R^4$; $-(C=O)-O-R^4$;

R^3 represents hydrogen; methyl; ethyl; propyl; butyl; $-(CH_2)_m$-aryl; $-(CH_2)_m$-heteroaryl; $-(CH_2)_m$-cycloalkyl;

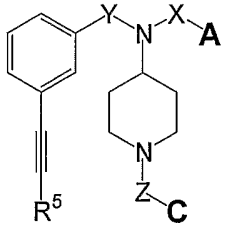
R^4 represents lower alkyl; $-(CH_2)_m$-aryl; $-(CH_2)_m$-heteroaryl; $-(CH_2)_m$-cycloalkyl;

R^6 represents aryl, heteroaryl or lower alkyl optionally substituted by OR^1 and/or any of aryl and heteroaryl;

m represents the whole numbers 0 (zero), 1, 2 or 3;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes, morphological forms and prodrugs of any of these compounds.

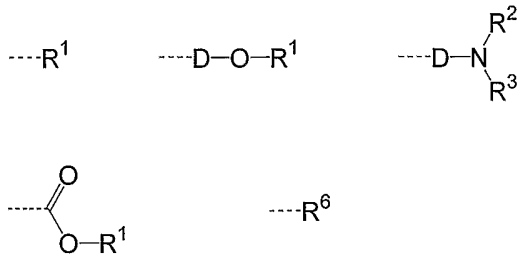
2. Compounds of the **formula II**



Formula II

wherein

A, **C**, **X**, **Y** and **Z** are as defined in **general formula I** above and $\mathbf{R^5}$ represents one of the groups

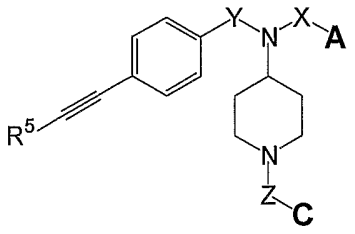


wherein $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, R^6 and **D** are as defined in **general formula I** above and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

3. Compounds according to **formula II** wherein **A**, **C**, **X** and **Z** are as defined in **general formula I** above, and wherein **Y** represents $-(CH_2)-$ and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

4. Compounds according to **formula II** wherein **A**, **C**, **X** and **Z** are as defined in **general formula I** above, and wherein **Y** represents $-(C=O)-$ and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

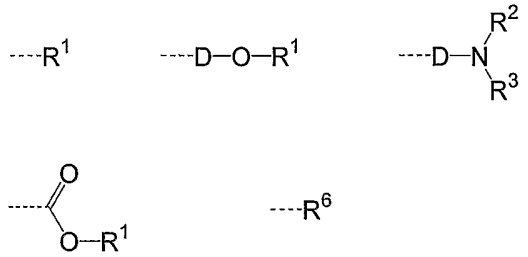
5. Compounds of the **formula III**:



Formula III

wherein

A, **C**, **X**, **Y** and **Z** are as defined in **general formula I** above and R^5 represents one of the groups

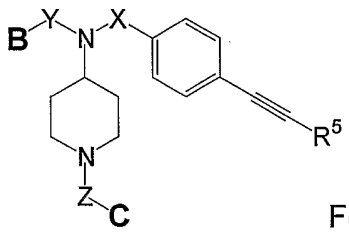


wherein R^1, R^2, R^3, $R^6$and **D** are as defined in **general formula I** above and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

6. Compounds according to **formula III** wherein **A**, **C**, **X** and **Z** are as defined in **general formula I** above, and wherein **Y** represents $-(CH_2)-$ and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

7. Compounds according to **formula III** wherein **A**, **C**, **X** and **Z** are as defined in **general formula I** above, and wherein **Y** represents –(C=O)- and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

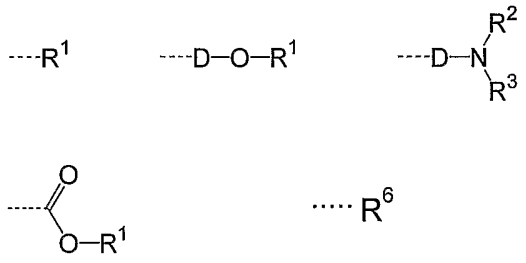
8. Compounds of the **formula IV**



Formula IV

wherein

B, **C**, **X**, **Y** and **Z** are as defined in **general formula I** above and R^5 represents one of the groups

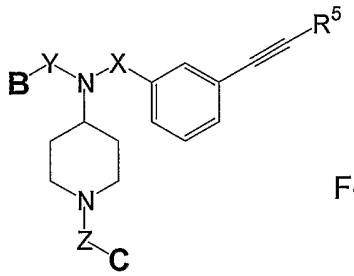


wherein R^1, R^2, R^3, $R^6$and **D** are as defined in **general formula I** above and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

9. Compounds according to **formula IV** wherein **B**, **C**, **X** and **Z** are as defined in **general formula I** above, and wherein **Y** represents $-(CH_2)-$ and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

10. Compounds according to **formula IV** wherein **B**, **C**, **X** and **Z** are as defined in **general formula I** above, and wherein **Y** represents $-(C=O)-$ and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

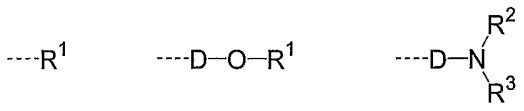
11. Compounds of the **formula V**

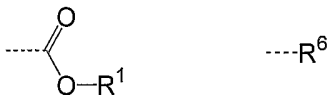


Formula V

wherein

B, **C**, **X**, **Y** and **Z** are as defined in **general formula I** above and R^5 represents one of the groups



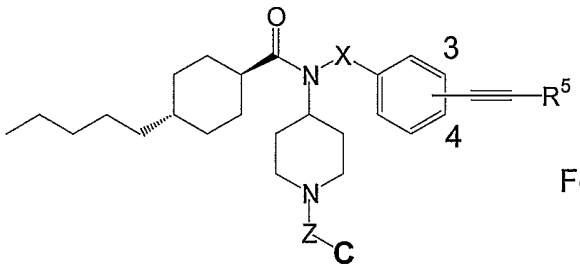


wherein R^1, R^2, R^3,$R^6$and **D** are as defined in **general formula I** above and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

12. Compounds according to **formula V** wherein **B**, **C**, **X** and **Z** are as defined in **general formula I** above, and wherein **Y** represents $-(CH_2)-$ and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

13. Compounds according to **formula V** wherein **B**, **C**, **X** and **Z** are as defined in **general formula I** above, and wherein **Y** represents –(C=O)- and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

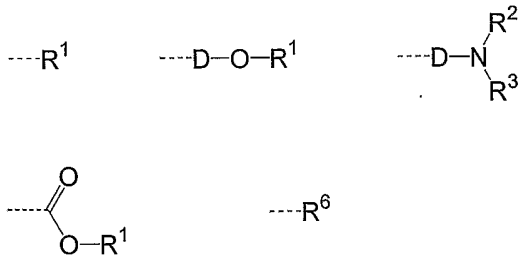
14. Compounds of the **formula VI**



Formula VI

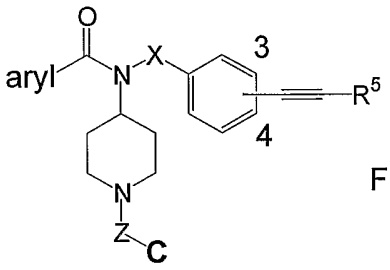
wherein

C, **X** and **Z** are as defined in **general formula I** above, the alkyne group is attached to the phenyl ring at position 3 or position 4, and $\mathbf{R^5}$ represents one of the groups



wherein $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, R^6 and **D** are as defined in **general formula I** above and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

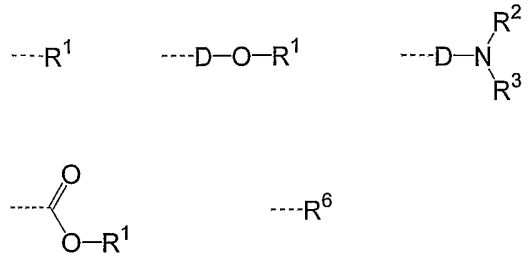
15. Compounds of the **formula VII**



Formula VII

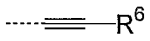
wherein

C, **X** and **Z** are as defined in **general formula I** above, the alkyne group is attached to the phenyl ring at position 3 or position 4, and $\mathbf{R^5}$ represents one of the groups

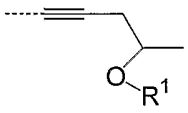


wherein **R**^{1}, **R**^{2}, **R**^{3}, R^6 and **D** are as defined in **general formula I** above and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

16. compounds according to any one of claims 1-15, in which the group



in claim 1 represents the group



in which R^1 is as in claim 1;
and C in formula I represents hydrogen; lower alkyl; lower alkenyl; lower alkynyl; aryl; heteroaryl; cycloalkyl; cycloalkenyl;or heterocyclyl.

17. A compound according to any one of the claims 1 to 16 selected from the group consisting of:

N-[3-(3-Hydroxy-prop-1-ynyl)-benzyl]-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide;

N-[3-(4-Hydroxy-pent-1-ynyl)-benzyl]-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide;

N-[3-(3-Methoxy-prop-1-ynyl)-benzyl]-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide;

N-[3-(3,3-Dimethyl-but-1-ynyl)-benzyl]-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide;

N-[3-(4-Hydroxy-but-1-ynyl)-benzyl]-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide;

N-[1-(3-Methyl-butyl)-piperidin-4-yl]-4-pentyl-N-(3-pent-1-ynyl-benzyl)-benzamide;

N-[4-(3-Hydroxy-prop-1-ynyl)-benzyl]-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide;

N-[4-(4-Hydroxy-pent-1-ynyl)-benzyl]-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide;

N-[4-(4-Hydroxy-but-1-ynyl)-benzyl]-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide;

N-[1-(3-Methyl-butyl)-piperidin-4-yl]-4-pentyl-N-(4-pent-1-ynyl-benzyl)-benzamide;

N-[4-(3,3-Dimethyl-but-1-ynyl)-benzyl]-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pentyl-benzamide;

(4-{(4'-Methoxy-biphenyl-4-ylmethyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-carbamoyl}-phenyl)-propynoic acid methyl ester;

N-(4'-Methoxy-biphenyl-4-ylmethyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pent-1-ynyl-benzamide;

4-Hex-1-ynyl-N-(4'-methoxy-biphenyl-4-ylmethyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-benzamide;

4-(3,3-Dimethyl-but-1-ynyl)-N-(4'-methoxy-biphenyl-4-ylmethyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-benzamide;

N-(4'-Methoxy-biphenyl-4-ylmethyl)-4-(3-methoxy-prop-1-ynyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-benzamide;

N-(4'-Methoxy-biphenyl-4-ylmethyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-phenylethynyl-benzamide;

N-(4'-Methoxy-biphenyl-4-ylmethyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-4-pyridin-2-ylethynyl-benzamide;

3-Hex-1-ynyl-N-(4'-methoxy-biphenyl-4-ylmethyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-benzamide;

N-(4'-Methoxy-biphenyl-4-ylmethyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-3-phenylethynyl-benzamide;

3-(3,3-Dimethyl-but-1-ynyl)-N-(4'-methoxy-biphenyl-4-ylmethyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-benzamide;

N-(4'-Methoxy-biphenyl-4-ylmethyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-3-pent-1-ynyl-benzamide;

N-(4'-Methoxy-biphenyl-4-ylmethyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-3-pyridin-2-ylethynyl-benzamide;

N-(4'-Methoxy-biphenyl-4-ylmethyl)-3-(3-methoxy-prop-1-ynyl)-N-[1-(3-methyl-butyl)-piperidin-4-yl]-benzamide;

4-Pentyl-cyclohexanecarboxylic acid [1-(3-methyl-butyl)-piperidin-4-yl]-(4-pent-1-ynyl-benzyl)-amide;

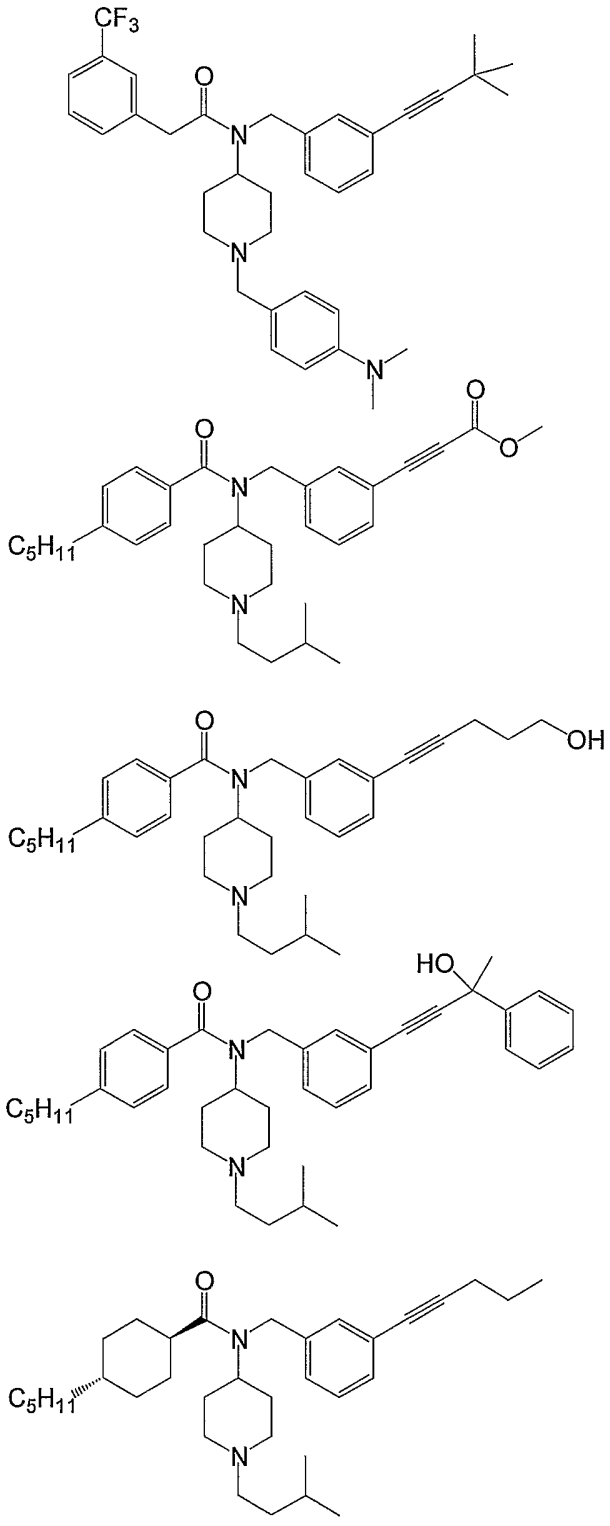
4-Pentyl-cyclohexanecarboxylic acid (1-benzyl-piperidin-4-yl)-(4-pent-1-ynyl-benzyl)-amide;

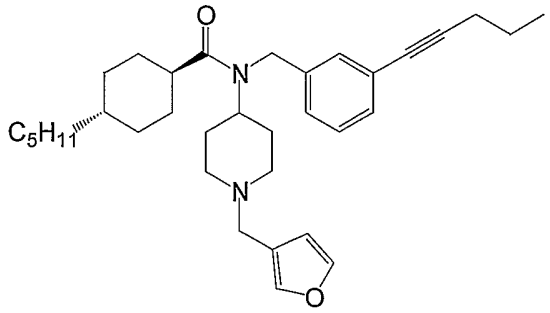
4-Pentyl-cyclohexanecarboxylic acid (1-furan-3-ylmethyl-piperidin-4-yl)-(4-pent-1-ynyl-benzyl)-amide;

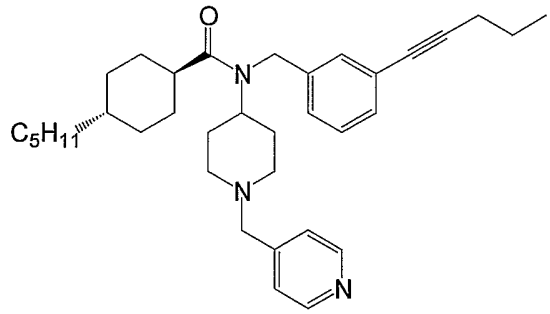
4-Pentyl-cyclohexanecarboxylic acid (4-pent-1-ynyl-benzyl)-(1-pyridin-4-ylmethyl-piperidin-4-yl)-amide;

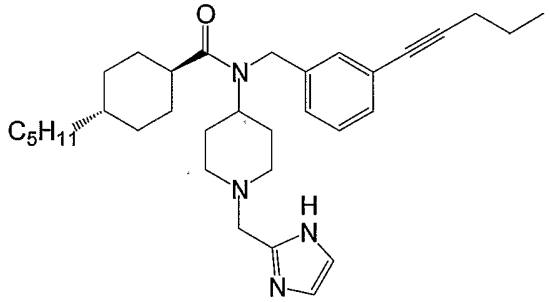
4-Pentyl-cyclohexanecarboxylic acid [1-(1H-imidazol-4-ylmethyl)-piperidin-4-yl]-(4-pent-1-ynyl-benzyl)-amide.

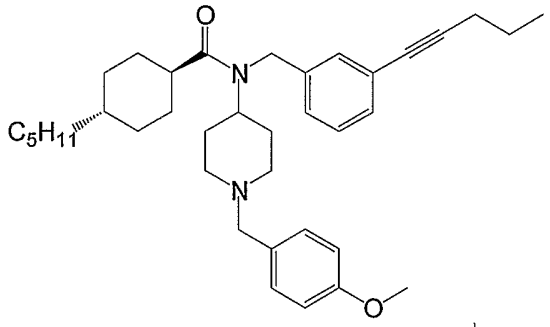
18. A compound according to claim 1 selected from the group consisting of:

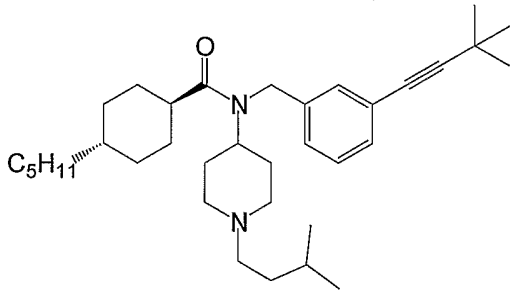


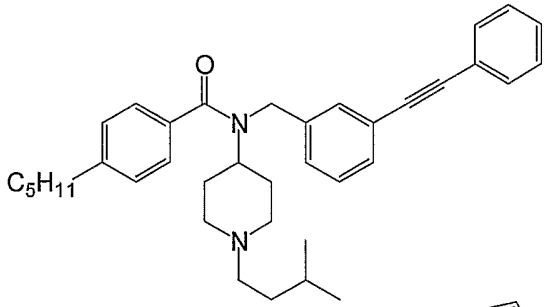


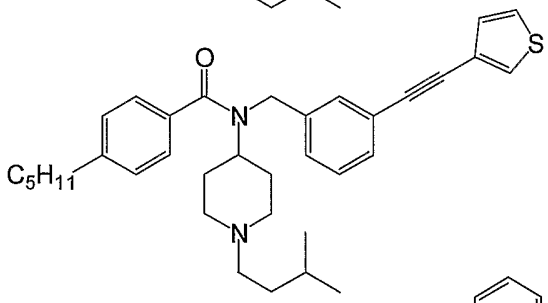


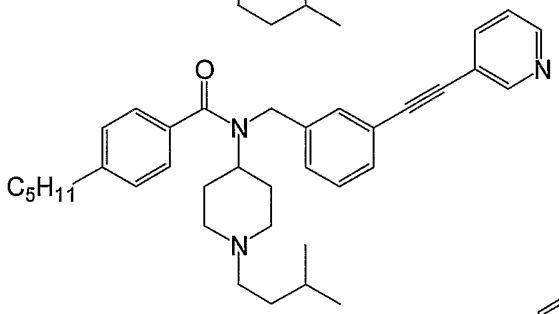


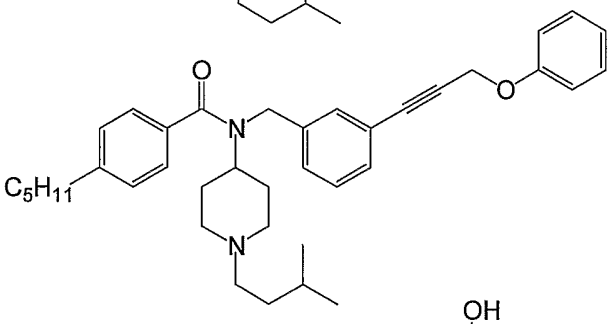


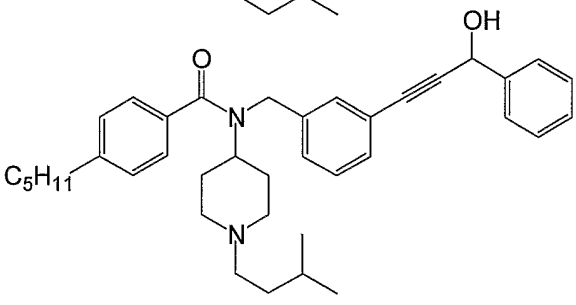


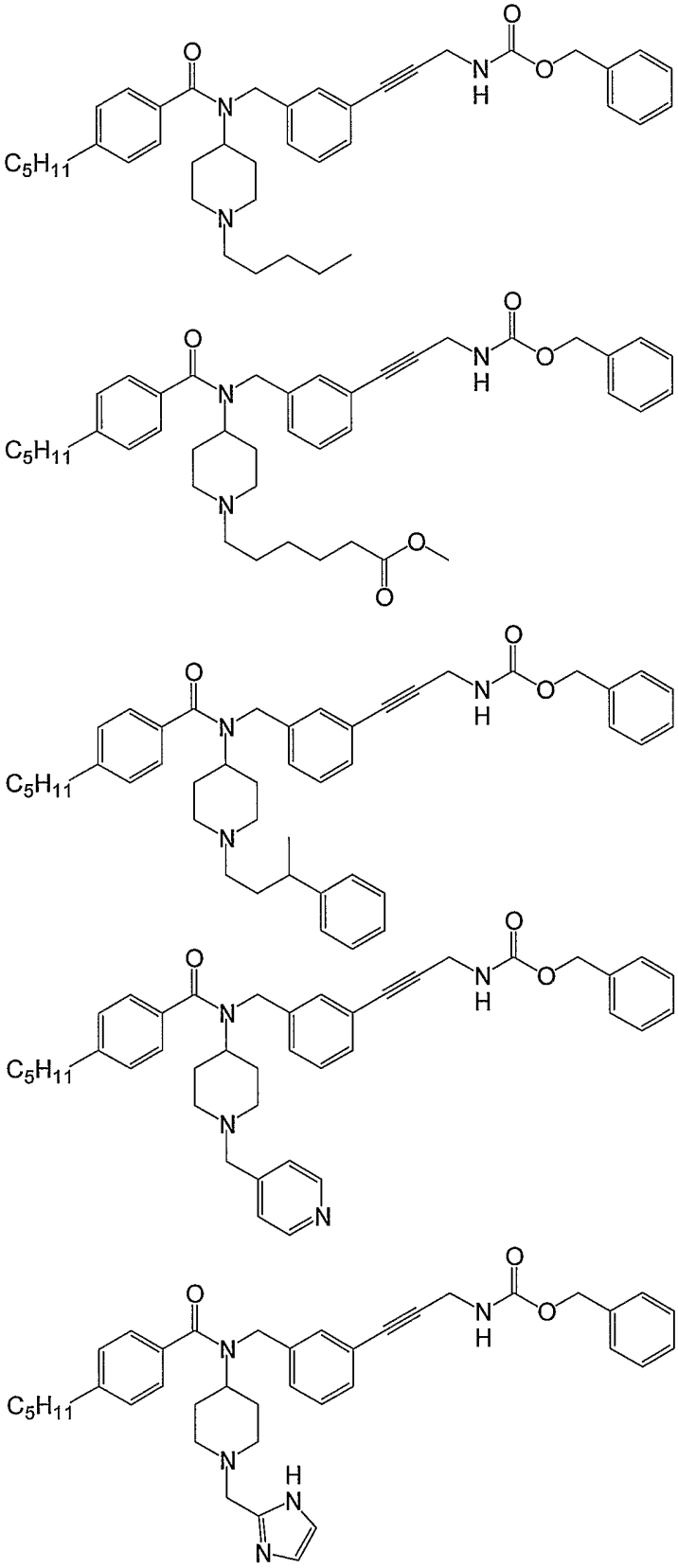


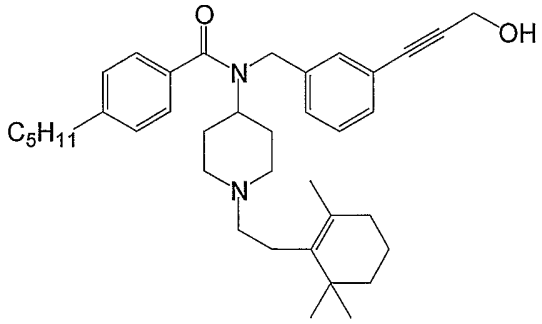


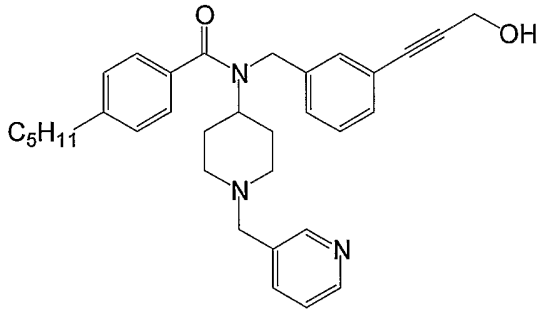


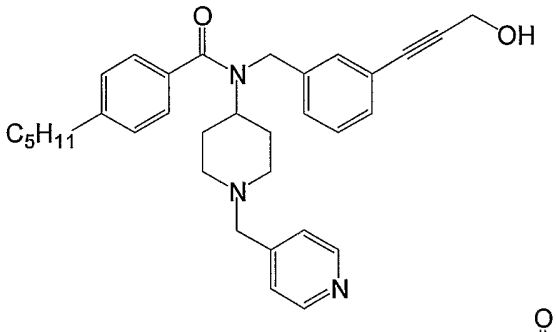


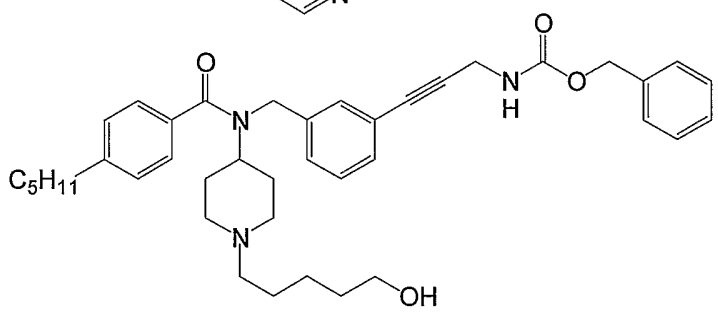


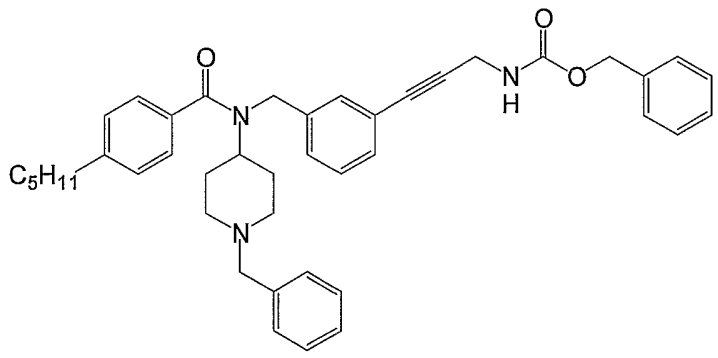


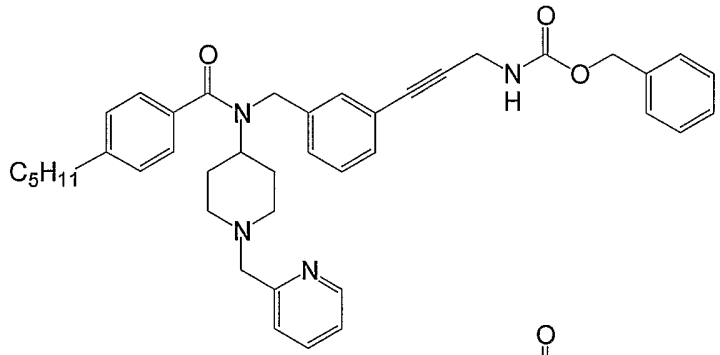


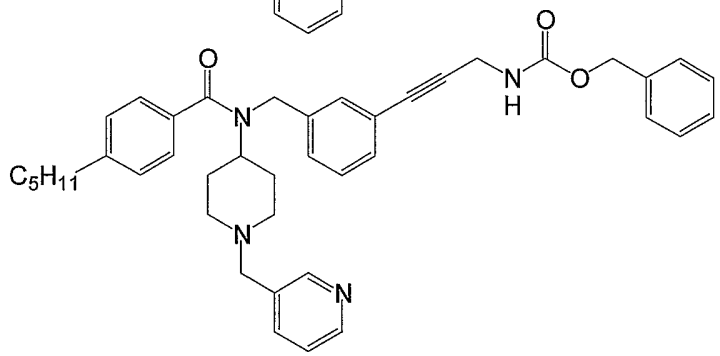


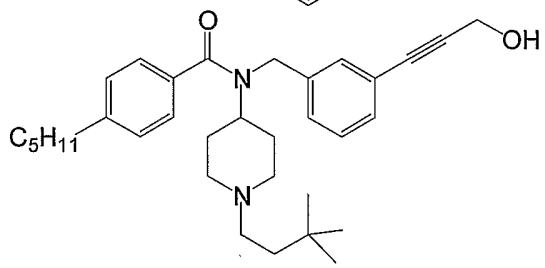


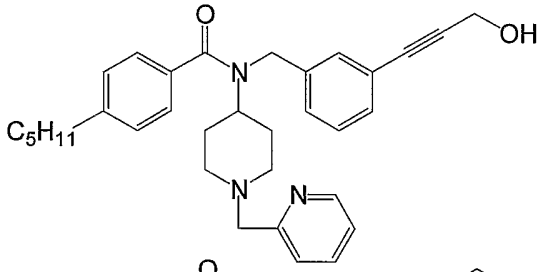


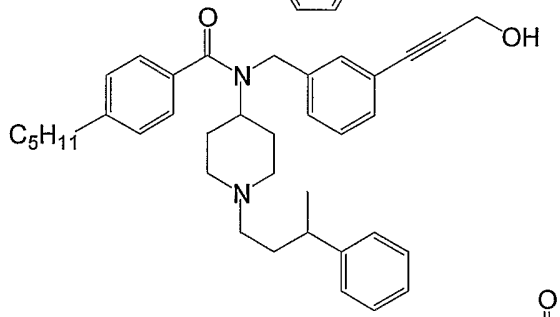


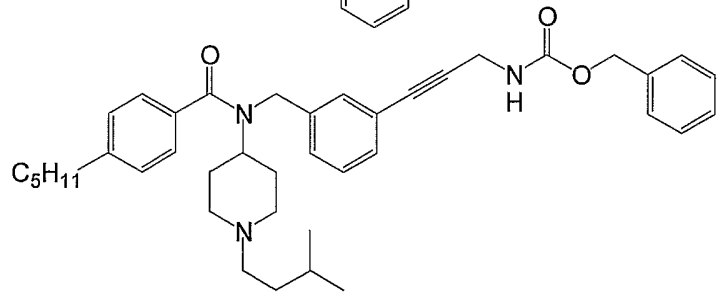












19. Pharmaceutical compositions containing one or more compounds as claimed in any one of claims 1 to 18 and inert excipients.

20. Pharmaceutical compositions according to claim 19 containing one or more compounds as claimed in any one of claims 1 to 18 for treatment of diseases demanding the inhibition of parasitic aspartic proteases.

21. Pharmaceutical compositions according to claim 19 containing one or more compounds as claimed in any one of claims 1 to 18 for treatment of disorders associated with the role of plasmepsin II and which require inhibition of plasmepsin II for treatment.

22. Pharmaceutical compositions according to claim 19 containing one or more compounds as claimed in any one of claims 1 to 18 for treatment or prevention of malaria.

23. Pharmaceutical compositions according to claim 19 containing one or more compounds as claimed in any one of claims 1 to 18 for treatment or prevention of diseases caused by protozoal infection.

24. Pharmaceutical compositions according to claim 19 containing one or more compounds as claimed in any one of claims 1 to 18 which contain aside of one or more compounds of the general formula I a known plasmepsin II inhibitor, a known antimalarial or a known HIV protease inhibitor.

25. Use of pharmaceutical compositions according to any one of claims 19 to 24 for treatment of diseases demanding the inhibition of parasitic aspartic proteases

26. Use of pharmaceutical compositions according to any one of claims 19 to 24 for treatment or prevention of malaria.

27. Use of pharmaceutical compositions according to any one of claims 19 to 24 for treatment or prevention of protozoal infections.

28. Use of pharmaceutical compositions according to any one of claims 19 to 24 for treatment or prevention of diseases in combination with a known plasmepsin II inhibitor, a known antimalarial or a known HIV protease inhibitor or another known anti-HIV treatment.

29. A method of treating a patient suffering from a disease requiring the inhibition of parasitic aspartic proteases by administering a pharmaceutical composition according to any one of claims 19 to 24.

30. A method according to claim 29 by administering a dose of the parasitic aspartic protease inhibitor of the general formula I between 1 mg and 1000 mg per day.

31. A method according to claim 29 by administering a dose of the parasitic aspartic protease inhibitor of the general formula I between 1 mg and 500 mg per day.

32. A method according to claim 29 by administering a dose of the parasitic aspartic protease inhibitor of the general formula I between 5 mg and 200 mg per day.

33. A process for the preparation of a pharmaceutical composition according to any one of the claims 19 to 24, characterized by mixing one or more active ingredients according to claims 1 to 18 with inert excipients in a manner known per se.

34. The use of a compound according to any one of claims 1 to 18 in the preparation of a medicament for the treatment or prevention of malaria or protozoal infections.

35. A compound according to any one of claims 1 to 18 for use in the treatment or prevention of malaria or protozoal infections.

36. The new compounds, intermediates, processes and pharmaceutical compositions as described hereinbefore.

37. A process for the manufacture of the compounds of claim 1, which comprises

a) reacting a compound of formula I, in which the alkynyl group Q is replaced by bromine of iodine , with an alcohol QOH, in which Q is as in claim 1; or

b) subjecting a compound of formula I, in which the group –Z-C is replaced by hydrogen, to reductive amination with an aldehyde yielding the group –Z-C; or

c) converting a compound of formula I into a pharmaceutically acceptable salt thereof.

38. Compounds of formula I in claim I and their pharmaceutically acceptable salts, whenever prepared by the process according to claim 37 or by an obvious chemical equivalent thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/009010

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/58 C07D405/06 C07D401/06 C07D409/12 A61K31/44 A61P33/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/24649 A (WELLER THOMAS ; BOSS CHRISTOPH (CH); FISCHLI WALTER (CH); ACTELION PHA) 28 March 2002 (2002-03-28) the whole document	1-38
Y	BOSS C ET AL: "INHIBITORS OF THE PLASMODIUM FALCIPARUM PARASITE ASPARTIC PROTEASE PLASMEPSIN II AS POTENTIAL ANTIMALARIAL AGENTS" CURRENT MEDICINAL CHEMISTRY, BENTHAM SCIENCE PUBLISHERS BV, BE, vol. 10, no. 11, 2003, pages 883-907, XP009036752 ISSN: 0929-8673 pages 894-896	1-38

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
8 November 2004	15/11/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Lauro, P

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/009010

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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