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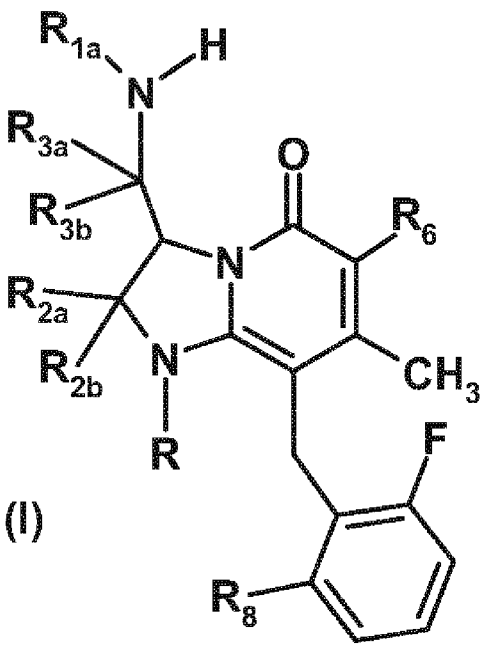
(54) Title: PYRIDINONE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS THEREOF



(I)

(57) Abstract: The present application relates to imidazopyridinone derivatives of the formula (I) as gonadotropin-releasing hormone (GnRH) receptor antagonists. Further aspects of the invention are a process for their preparation and their use for the manufacture of medicaments for the treatment and/or prophylaxis of diseases, especially sex-hormone-related conditions in both men and women. For example, such conditions include endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, gonadal steroid-dependent neoplasia such as cancers of the prostate, breast and ovary, gonadotrope pituitary adenomas, sleep apnea, irritable bowel syndrome, premenstrual syndrome, benign prostatic hypertrophy, contraception and infertility (e.g., assisted reproductive therapy such as in vitro fertilization).

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Pyridinone derivatives and pharmaceutical compositions thereof.

TECHNICAL FIELD

The present invention refers generally to pyridinone derivatives as gonadotropin-releasing hormone (GnRH) receptor antagonists, pharmaceutical compositions containing a pyridinone derivative according to the invention and methods of treating disorders by administration of a pyridinone derivative according to invention to a mammal, particularly a human, in need thereof.

BACKGROUND ART

Gonadotropin-releasing hormone (GnRH) is a decapeptide (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2) released from the hypothalamus, also known as luteinizing hormone-releasing hormone (LHRH). GnRH acts on the pituitary gland to stimulate the biosynthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH released from the pituitary gland is responsible for the regulation of gonadal steroid production in both genders and late ovarian follicle development and ovulation in female mammals, FSH regulates spermatogenesis in males and early follicular development in females. Thus GnRH plays a key role in human reproduction.
As a consequence of its biological significance, synthetic antagonists and agonists to GnRH have been the center of several research activities, particularly in the field of endometriosis, uterine leiomyoma (fibroids), prostate cancer, breast cancer, ovarian cancer, prostatic hyperplasia, assisted reproductive therapy and precocious puberty.

For example, peptidic GnRH agonists, such as leuprorelin (pGlu-His-Trp-Ser-Tyr-d-Leu-Leu-Arg-Pro-NHEt), are described for the use in the treatment of such conditions (*The Lancet* **2001**, *358*, 1793 – 1803; *Mol. Cell. Endo.* **2000**, *166*, 9 – 14). Said agonists initially induce the synthesis and release of gonadotropins, by binding to the GnRH receptor on the pituitary gonadotrophic cells ('flare-up'). However, chronic administration of GnRH agonists reduces gonadotropin release from the pituitary and results in the down-regulation of the receptor, with the consequence of suppressing sex steroidal hormone production after some period of treatment.

GnRH antagonists, on the contrary, are supposed to suppress gonadotropins from the onset, offering several advantages, in particular a lack of side effects associated with the flare up seen under GnRH superagonist treatment. Several peptidic antagonists with low histamine

release potential are known in the art. Said peptidic products show low oral bioavailability which limits their clinical use.

A number of nonpeptidic compounds have also been described for use as GnRH receptor antagonists, for example:

- Thieno [2,3-b]pyridin-4-ones (*Cho et al., J. Med. Chem.* **1998**, *41*, 4190 – 4195);
- substituted indoles (US 5,780, 437, US 5,849, 764, WO97/21704, WO98/55479, WO98/55470, WO98/55116, WO98/55119, WO 97/21707, WO97/21703 and WO97/21435);
- tricyclic diazepines (WO 96/38438) and phenyl-substituted fused nitrogen-containing bicyclic compounds WO99/33831;
- quinoline and thienopyridine derivatives (W097/14682, WO97/14697 and WO99/09033);
- substituted quinolin-2-ones (WO97/44037, WO97/44041, WO97/44321 and WO97/44339);
- indole derivatives and novel bicyclic and tricyclic pyrrolidine (WO02/066459 and WO02/11732).

Other compounds with a heterocyclic structure and their use as GnRH antagonists are included in WO00/69859, WO01/29044, WO01/55119, WO03/013528, WO03/011870, WO03/011841, WO03/011839, WO03/011293 and WO05/007164.

Nevertheless, effective small molecule GnRH receptor antagonists are still highly required in art as well as pharmaceutical compositions containing such GnRH receptor antagonists and methods relating to the use thereof to treat, for example, sex-hormone-related conditions in particular for the treatment of leiomyoma.

The pyridinone derivatives according to the present invention meets these needs, and provide at the same time further related advantages.

Pyridinone derivatives are known in the art as pharmaceutical active ingredients but their activity as GnRH receptor antagonists has not been described as state of the art, for example:

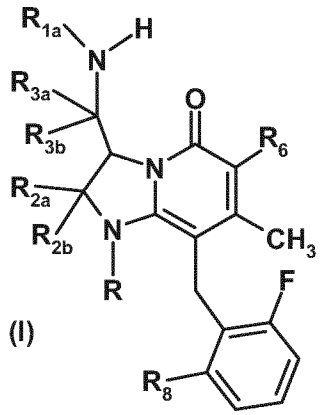
Almqvist et al., in “Synthesis and evaluation of dihydroimidazolo and dihydrooxazolo ring-fused 2-pyridones-targeting pilus biogenesis in uropathogenic bacteria” *Tetrahedron* **2008**, *64*, 9368 - 9376, describes a one-pot process that allowed synthesis of dihydrooxazolo ring-

fused 2-pyridones starting from acylated serine derivatives. After hydrolysis to their corresponding carboxylic acids and lithium carboxylates, biological evaluation revealed that the sulfur could be replaced by an oxygen atom and still maintains the ability to inhibit pilus assembly in uropathogenic E. coli. However, introducing a secondary amine instead of oxygen resulted in a substantial decrease in biological activity.

WO2009/134203 relates to pyrazol ring-fused 2-pyridones, and pharmaceutical compositions containing them, and their use in the treatment of amyloid diseases, especially AB amyloid disease, such as observed in Alzheimer's disease, infectious diseases, PAI-I related disease, and in the manufacture of medicaments for such treatment.

DISCLOSURE OF THE INVENTION

The aim of the present invention is to provide gonadotropin-releasing hormone (GnRH) receptor antagonists, as well as the methods for their preparation and use, and pharmaceutical compositions containing the same.
In particular, the present invention relates to compounds of formula **(I)**:



(I)

in which

R_{1a} represent a hydrogen atom, a
C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_3-C_8-cycloalkyl-, aryl-, heteroaryl-, -C_1-C_6-alkylene-aryl, -C_1-C_6-alkylene-heteroaryl, -C_1-C_6-alkylene-C_3-C_{10}-cycloalkyl, -C_1-C_6-alkylene-(3- to 10-membered heterocycloalkyl), -C(=O)-C_1-C_6-alkyl, -C(=O)-C_1-C_6-alkylene-aryl, -C(=O)-C_1-C_6-alkylene-heteroaryl, -$S(=O)_2R^9$ group;
wherein said groups are optionally substituted one to three times, in the same

way or differently, with a substituent selected from :
halo-, hydroxy-, oxo, cyano-, C_1-C_6-alkyl-,
halo-C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-,
C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-,
aryl-, -C_1-C_6-alkylene-aryl, heteroaryl-, -C(=O)OH,
-C(=O)O-C_1-C_6-alkyl, -OC(=O)-C_1-C_6-alkyl,
-N(H)C(=O)R^9, -C(=O)NR^9R^{10}, -N(C_1-C_6-alkyl)C(=O)OR^9,
-N(C_1-C_6-alkyl)C(=O)NR^9R^{10},
-SR^9, -S(=O)R^9, -S(=O)$_2$OH, -S(=O)$_2R^9$, -NR^9R^{10} , and wherein
R^9 and R^{10} represent, independently of one another, a hydrogen atom, a
C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-,
halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_{10}-cycloalkyl-, aryl-, heteroaryl-,
or
R^9 and R^{10} joined, and taken together with the atom to which they are attached,
form a 3- to 10-membered heterocycloalkyl-, optionally substituted one or two
times, in the same way or differently, with a substituent selected from the
group consisting of halo-, hydroxyl-, cyano-, oxo, C_1-C_6-alkyl-,
halo-C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, C_1-C_6-alkoxy-C_1-C_6-alkyl-,
halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, -C(=O)OH,

R_{2a} and R_{2b} are both a hydrogen atom or a methyl group;

R_{3a} is a phenyl group optionally substituted one to three times with a halogen atom, cyano, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy or halo-C_1-C_6-alkoxy;

R_{3b} is hydrogen or C_1-C_6-alkyl;

R represent a hydrogen atom, a
C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, -C(=O)R^9, -C(=O)OR^9,
-C(=O)NR^9R^{10}, or -S(=O)$_2R^9$ group,
R^9 and R^{10} represent, independently of one another, a hydrogen atom, a
C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-,
halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-,
C_3-C_{10}-cycloalkyl-, aryl-, -C_1-C_6-alkylene-aryl, heteroaryl-,
or
R^9 and R^{10} joined, and taken together with the atom to which they are attached,
form a

3- to 10-membered heterocycloalkyl-, optionally substituted one or two times, in the same way or differently, with a substituent selected from the group consisting of halo-, hydroxyl-, cyano-, oxo, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, -C(=O)OH,

R_6 represents an aryl-, a heteroaryl-, a benzo[1,3]dioxolyl- or 2,3-dihydro-1,4-benzodioxinyl group wherein said group is optionally substituted one to three times, in the same way or differently, with a substituent R_{11} selected from : hydrogen, halogen, hydroxy, cyano, nitro, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-hydroxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkyl-C(=O)OH, -C(=O)OH, -C(=O)C_1-C_6-alkyl;

R_8 is selected from the group consisting of a hydrogen atom, a fluorine atom or a fluorinated C_1-C_6-alkyl group, in particular a -CF_3;

Compounds of the invention are the compounds of the formula **(I)** and the salts, solvates and solvates of the salts thereof, the compounds which are encompassed by formula **(I)** and are of the formulae mentioned hereinafter, and the salts, solvates and solvates of the salts thereof, and the compounds which are encompassed by formula **(I)** and are mentioned hereinafter as exemplary embodiments, and the salts, solvates and solvates of the salts thereof, insofar as the compounds encompassed by formula **(I)** and mentioned hereinafter are not already salts, solvates and solvates of the salts.

Hydrates of the compounds of the invention or their salts are stoichiometric compositions of the compounds with water, such as, for example, hemi-, mono-, or dihydrates.
Solvates of the compounds of the invention or their salts are stoichiometric compositions of the compounds with solvents.

Solvates which are preferred for the purposes of the present invention are hydrates.

Salts for the purposes of the present invention are preferably pharmaceutically acceptable salts of the compounds according to the invention (for example, see S. M. Berge et al., "Pharmaceutical Salts", *J. Pharm. Sci.* **1977**, *66*, 1-19).
Pharmaceutically acceptable salts include acid addition salts of mineral acids, carboxylic acids and sulfonic acids, for example salts of hydrochloric acid, hydrobromic acid, sulfuric

acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, benzenesulfonic acid, naphthalenedisulfonic acid, maleic, fumaric, benzoic, ascorbic, succinic, acetic, trifluoroacetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, mandelic, cinnamic, aspartic, stearic, palmitic, glycolic, and glutamic acid.

Pharmaceutically acceptable salts also include salts of customary bases, such as for example and preferably alkali metal salts (for example sodium, lithium and potassium salts), alkaline earth metal salts (for example calcium and magnesium salts), and ammonium salts derived from ammonia or organic amines, such as illustratively and preferably ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, benzylamine, dibenzylamine, N-methylmorpholine, N-methylpiperidine, dihydroabietyl- amine, arginine, lysine, and ethylenediamine.

Also encompassed are salts which are themselves unsuitable for pharmaceutical uses but can be used for example for isolating or purifying the compounds of the invention.

The present invention additionally encompasses prodrugs of the compounds of the invention. The term "prodrugs" encompasses compounds which themselves may be biologically active or inactive, but are converted during their residence time in the body into compounds of the invention (for example by metabolism or hydrolysis).

Furthermore, the compounds of this invention may, either by nature of asymmetric centers or by restricted rotation, be present in the form of isomers (enantiomers, diastereomers). Any isomer may be present in which the asymmetric center is in the (*R*)-, (*S*)-, or (*R,S*)-configuration.

It will also be appreciated that when two or more asymmetric centers are present in the compounds of the invention, several diastereomers and enantiomers of the exemplified structures will often be possible, and that pure diastereomers and pure enantiomers represent preferred embodiments. It is intended that pure stereoisomers, pure diastereomers, pure enantiomers, and mixtures thereof, are within the scope of the invention.

Geometric isomers by nature of substituents about a double bond or a ring may be present in cis (= *Z*-) or trans (= *E*-) form, and both isomeric forms are encompassed within the scope of this invention.

All isomers, whether separated, pure, partially pure, or in racemic mixture, of the compounds of this invention are encompassed within the scope of this invention. The purification of said isomers and the separation of said isomeric mixtures may be accomplished by standard techniques known in the art. For example, diastereomeric mixtures can be separated into the individual isomers by chromatographic processes or crystallization, and racemates can be separated into the respective enantiomers either by chromatographic processes on chiral phases or by resolution.

If the compounds of the invention may occur in tautomeric forms, the present invention encompasses all tautomeric forms.

Unless otherwise stated, the following definitions apply for the substituents and residues used throughout this specification and claims. The particularly named chemical groups and atoms (for example fluorine, methyl, methyloxy and so on) should be considered as particular forms of embodiment for the respective groups in compounds according to the invention.

The term "halogen atom" or "halo" is to be understood as meaning a fluorine, chlorine, bromine or iodine atom.

The term "C_1-C_6-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent hydrocarbon group having 1, 2, 3, 4, 5 or 6 carbon atoms, *e.g.* a methyl, ethyl, propyl, butyl, pentyl, hexyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl, iso-pentyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, neo-pentyl, 1,1-dimethylpropyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 2-ethylbutyl, 1-ethylbutyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 2,3-dimethylbutyl, 1,3-dimethylbutyl, or 1,2-dimethylbutyl group, or an isomer thereof. Particularly, said group has 1, 2 or 3 carbon atoms ("C_1-C_3-alkyl"), methyl, ethyl, n-propyl- or iso-propyl.

The term "halo-C_1-C_6-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent hydrocarbon group in which the term "C_1-C_6-alkyl" is defined *supra*, and in which one or more hydrogen atoms is replaced by a halogen atom, in the same way or differently, *i.e.* one halogen atom being independent from another.
Particularly, said halogen atom is F. Said halo-C_1-C_6-alkyl group is, in particular $-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2CF_3$, $-CF_2CH_3$, or $-CH_2CF_3$.

The term "C_1-C_6-alkoxy" is to be understood as preferably meaning a linear or branched, saturated, monovalent, hydrocarbon group of formula –O-alkyl, in which the term "alkyl" is defined *supra*, *e.g.* a methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, tert-butoxy, sec-butoxy, pentoxy, iso-pentoxy, or n-hexoxy group, or an isomer thereof.

The term "halo-C_1-C_6-alkoxy" is to be understood as preferably meaning a linear or branched, saturated, monovalent C_1-C_6-alkoxy group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, in the same way or differently, by a halogen atom. Particularly, said halogen atom is F. Said halo-C_1-C_6-alkoxy group is, for example, $–OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OCF_2CF_3$, or $-OCH_2CF_3$.

The term "C_1-C_6-alkoxy-C_1-C_6-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent alkyl group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, in the same way or differently, by a C_1-C_6-alkoxy group, as defined *supra*, *e.g.* methoxyalkyl, ethoxyalkyl, propyloxyalkyl, iso-propoxyalkyl, butoxyalkyl, iso-butoxyalkyl, tert-butoxyalkyl, sec-butoxyalkyl, pentyloxyalkyl, iso-pentyloxyalkyl, hexyloxyalkyl group, in which the term "C_1-C_6-alkyl" is defined *supra*, or an isomer thereof.

The term "halo-C_1-C_6-alkoxy-C_1-C_6-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent C_1-C_6-alkoxy-C_1-C_6-alkyl group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, in the same way or differently, by a halogen atom.
Particularly, said halogen atom is F. Said halo-C_1-C_6-alkoxy-C_1-C_6-alkyl group is, for example, $–CH_2CH_2OCF_3$, $-CH_2CH_2OCHF_2$, $-CH_2CH_2OCH_2F$, $-CH_2CH_2OCF_2CF_3$, or $-CH_2CH_2OCH_2CF_3$.

Alkylcarbonyl in general represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms which is bonded via a carbonyl group to the rest of the molecule. Non-limiting examples include acetyl, n-propionyl, n-butyryl, isobutyryl, pivaloyl.

Alkoxycarbonylamino illustratively and preferably represents methoxycarbonylamino, ethoxy-carbonylamino, n-propoxycarbonylamino, isopropoxycarbonylamino, n-butoxycarbonylamino and tert.-butoxycarbonylamino.

Alkoxycarbonyl illustratively and preferably represents methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, iso-propoxycarbonyl, n-butoxycarbonyl and tert.-butoxycarbonyl.

Alkylsulfonyl in general represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms which is bonded via a sulfonyl (-SO_2-) group to the rest of the molecule. Non-limiting examples include methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, tert.-butylsulfonyl.

S-Alkylsulfonimidoyl in general represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms which is bonded via a sulfonimidoyl [-S(=O)(=NH)-] group to the rest of the molecule and which is attached to the sulfur atom of that group. Non-limiting examples include S-methylsulfonimidoyl, S-ethylsulfonimidoyl, S-n-propylsulfonimidoyl, S-isopropylsulfonimidoyl, S-n-butylsulfonimidoyl, S-tert.-butylsulfonimidoyl. Monoalkylamino in general represents an amino radical having one alkyl residue attached to the nitrogen atom. Non-limiting examples include methylamino, ethylamino, n-propylamino, iso-propylamino, n-butylamino, tert-butylamino. The same applies to radicals such as monoalkyl- aminocarbonyl.

Dialkylamino in general represents an amino radical having two independently selected alkyl residues attached to the nitrogen atom. Non-limiting examples include *N,N*-dimethylamino, *N,N*-diethylamino, *N,N*-diisopropylamino, *N*-ethyl-*N*-methylamino, *N*-methyl-*N*-n-propylamino, *N*-iso-propyl-*N*-n-propylamino, *N*-tert.-butyl-*N*-methylamino. The same applies to radicals such as di-alkylaminocarbonyl.

Monoalkylaminocarbonyl illustratively and preferably represents methylaminocarbonyl, ethyl-aminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, n-butylaminocarbonyl and tert-butylaminocarbonyl.

Dialkylaminocarbonyl illustratively and preferably represents *N,N*-dimethylaminocarbonyl, *N,N*-diethylaminocarbonyl, *N,N*-diisopropylaminocarbonyl, *N*-ethyl-*N*-methylaminocarbonyl, *N*-methyl-*N*-n-propylaminocarbonyl, *N*-isopropyl-*N*-n-propylaminocarbonyl and *N*-tert-butyl-*N*-methyl-aminocarbonyl.

Alkylcarbonylamino in general represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms which is bonded via a carbonylamino (-C(=O)-NH-) group to the rest of the molecule and which is attached to the carbon atom of that group. Non-limiting examples include acetyl- amino, n-propionylamino, n-butyrylamino, isobutyrylamino, pivaloylamino.

The term "C_2-C_6-alkenyl" is to be understood as preferably meaning a linear or branched, monovalent hydrocarbon group, which contains one or more double bonds, and which has 2,

3, 4, 5, 6 carbon atoms, particularly 2 or 3 carbon atoms ("C_2-C_3-alkenyl"), it being understood that in the case in which said alkenyl group contains more than one double bond, then said double bonds may be isolated from, or conjugated with, each other.
Said alkenyl group is, for example, a vinyl, allyl, (*E*)-2-methylvinyl, (*Z*)-2-methylvinyl, homoallyl, (*E*)-but-2-enyl, (*Z*)-but-2-enyl, (*E*)-but-1-enyl, (*Z*)-but-1-enyl, pent-4-enyl, (*E*)-pent-3-enyl, (*Z*)-pent-3-enyl, (*E*)-pent-2-enyl, (*Z*)-pent-2-enyl, (*E*)-pent-1-enyl, (*Z*)-pent-1-enyl, hex-5-enyl, (*E*)-hex-4-enyl, (*Z*)-hex-4-enyl, (*E*)-hex-3-enyl, (*Z*)-hex-3-enyl, (*E*)-hex-2-enyl, (*Z*)-hex-2-enyl, (*E*)-hex-1-enyl, (*Z*)-hex-1-enyl, isopropenyl, 2-methylprop-2-enyl, 1-methylprop-2-enyl, 2-methylprop-1-enyl, (*E*)-1-methylprop-1-enyl, (*Z*)-1-methylprop-1-enyl, 3-methylbut-3-enyl, 2-methylbut-3-enyl, 1-methylbut-3-enyl, 3-methylbut-2-enyl, (*E*)-2-methylbut-2-enyl, (*Z*)-2-methylbut-2-enyl, (*E*)-1-methylbut-2-enyl, (*Z*)-1-methylbut-2-enyl, (*E*)-3-methylbut-1-enyl, (*Z*)-3-methylbut-1-enyl, (*E*)-2-methylbut-1-enyl, (*Z*)-2-methylbut-1-enyl, (*E*)-1-methylbut-1-enyl, (*Z*)-1-methylbut-1-enyl, 1,1-dimethylprop-2-enyl, 1-ethylprop-1-enyl, 1-propylvinyl, 1-isopropylvinyl, 4-methylpent-4-enyl, 3-methylpent-4-enyl, 2-methylpent-4-enyl, 1-methylpent-4-enyl, 4-methylpent-3-enyl, (*E*)-3-methylpent-3-enyl, (*Z*)-3-methylpent-3-enyl, (*E*)-2-methylpent-3-enyl, (*Z*)-2-methylpent-3-enyl, (*E*)-1-methylpent-3-enyl, (*Z*)-1-methylpent-3-enyl, (*E*)-4-methylpent-2-enyl, (*Z*)-4-methylpent-2-enyl, (*E*)-3-methylpent-2-enyl, (*Z*)-3-methylpent-2-enyl, (*E*)-2-methylpent-2-enyl, (*Z*)-2-methylpent-2-enyl, (*E*)-1-methylpent-2-enyl, (*Z*)-1-methylpent-2-enyl, (*E*)-4-methylpent-1-enyl, (*Z*)-4-methylpent-1-enyl, (*E*)-3-methylpent-1-enyl, (*Z*)-3-methylpent-1-enyl, (*E*)-2-methylpent-1-enyl, (*Z*)-2-methylpent-1-enyl, (*E*)-1-methylpent-1-enyl, (*Z*)-1-methylpent-1-enyl, 3-ethylbut-3-enyl, 2-ethylbut-3-enyl, 1-ethylbut-3-enyl, (*E*)-3-ethylbut-2-enyl, (*Z*)-3-ethylbut-2-enyl, (*E*)-2-ethylbut-2-enyl, (*Z*)-2-ethylbut-2-enyl, (*E*)-1-ethylbut-2-enyl, (*Z*)-1-ethylbut-2-enyl, (*E*)-3-ethylbut-1-enyl, (*Z*)-3-ethylbut-1-enyl, 2-ethylbut-1-enyl, (*E*)-1-ethylbut-1-enyl, (*Z*)-1-ethylbut-1-enyl, 2-propylprop-2-enyl, 1-propylprop-2-enyl, 2-isopropylprop-2-enyl, 1-isopropylprop-2-enyl, (*E*)-2-propylprop-1-enyl, (*Z*)-2-propylprop-1-enyl, (*E*)-1-propylprop-1-enyl, (*Z*)-1-propylprop-1-enyl, (*E*)-2-isopropylprop-1-enyl, (*Z*)-2-isopropylprop-1-enyl, (*E*)-1-isopropylprop-1-enyl, (*Z*)-1-isopropylprop-1-enyl, (*E*)-3,3-dimethylprop-1-enyl, (*Z*)-3,3-dimethylprop-1-enyl, 1-(1,1-dimethylethyl)ethenyl, buta-1,3-dienyl, penta-1,4-dienyl, hexa-1,5-dienyl, or methylhexadienyl group. Particularly, said group is vinyl or allyl.

The term "C_2-C_6-alkynyl" is to be understood as preferably meaning a linear or branched, monovalent hydrocarbon group which contains one or more triple bonds, and which contains 2, 3, 4, 5, 6 carbon atoms, particularly 2 or 3 carbon atoms ("C_2-C_3-alkynyl").

Said C_2-C_{10}-alkynyl group is, for example, ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, but-3-ynyl, pent-1-ynyl, pent-2-ynyl, pent-3-ynyl, pent-4-ynyl, hex-1-ynyl, hex-2-inyl, hex-3-inyl, hex-4-ynyl, hex-5-ynyl, 1-methylprop-2-ynyl, 2-methylbut-3-ynyl, 1-methylbut-3-ynyl, 1-methylbut-2-ynyl, 3-methylbut-1-ynyl, 1-ethylprop-2-ynyl, 3-methylpent-4-ynyl, 2-methylpent-4-ynyl, 1-methylpent-4-ynyl, 2-methylpent-3-ynyl, 1-methylpent-3-ynyl, 4-methylpent-2-ynyl, 1-methylpent-2-ynyl, 4-methylpent-1-ynyl, 3-methylpent-1-ynyl, 2-ethylbut-3-ynyl, 1-ethylbut-3-ynyl, 1-ethylbut-2-ynyl, 1-propylprop-2-ynyl, 1-isopropylprop-2-ynyl, 2,2-dimethylbut-3-inyl, 1,1-dimethylbut-3-ynyl, 1,1-dimethylbut-2-ynyl, or 3,3-dimethylbut-1-ynyl group. Particularly, said alkynyl group is ethynyl, prop-1-ynyl, or prop-2-ynyl.

The term "C_3-C_{10}-cycloalkyl" is to be understood as preferably meaning a saturated, monovalent, mono-, or bicyclic hydrocarbon ring which contains 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms, particularly 3, 4, 5, or 6 carbon atoms ("C_3-C_6-cycloalkyl"). Said C_3-C_{10}-cycloalkyl group is for example, a monocyclic hydrocarbon ring, *e.g.* a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl group, or a bicyclic hydrocarbon ring, *e.g.* a perhydropentalenylene or decalin ring. Said cycloalkyl ring can optionally contain one or more double bonds *e.g.* cycloalkenyl, such as a cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl, or cyclodecenyl group, wherein the bond between said ring with the rest of the molecule may be to any carbon atom of said ring, be it saturated or unsaturated.

The term "3- to 10-membered heterocycloalkyl" is to be understood as preferably meaning a saturated or partially unsaturated, monovalent, mono- or bicyclic hydrocarbon ring which contains 2, 3, 4, 5, 6, 7, 8, or 9 carbon atoms, and one or more heteroatom-containing groups selected from C(=O), O, S, S(=O), $S(=O)_2$, NH, NR', wherein R' represents a C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_3-C_6 heterocycloalkyl, $C(=O)R^9$, $C(=O)NR^{10}R^{11}$, $-S(=O)_2R^9$, $-S(=O)_2NR^{10}R^{11}$ group as defined *supra*, it being understood that when said R' represents a C_3-C_6 heterocycloalkyl group, then said C_3-C_6 heterocycloalkyl group is present only once. Particularly, said ring can contain 2, 3, 4, or 5 carbon atoms, and one or more of the above-mentioned heteroatom-containing groups (a "3- to 6-membered heterocycloalkyl"), more particularly said ring can contain 4 or 5 carbon atoms, and one or more of the above-mentioned heteroatom-containing groups (a "5- to 6-membered heterocycloalkyl"). Non-limiting examples include aziridinyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, pyrazolidinyl, tetrahydrofuranyl, thiolanyl, sulfolanyl, 1,3-dioxolanyl, 1,3-oxazolidinyl, 1,3-thiazolidinyl, piperidinyl, piperazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,3-dioxanyl,1,4-dioxanyl, morpholinyl, thiomorpholinyl, 1,1-dioxidothiomorpholinyl,

perhydro-azepinyl, perhydro-1,4-diazepinyl, perhydro-1,4-oxazepinyl, perhydroazocinyl, octahydropyrrolo-[3,4-b]pyrrolyl, octahydroisoindolyl, octahydropyrrolo[3,4-b]pyridyl, octahydropyrrolo[1,2-a]pyrazinyl, decahydroisochinolinyl, 7-azabicyclo[2.2.1]heptyl, 3-azabicyclo[3.2.0]heptyl, 7-azabicyclo-[4.1.0]heptyl, 2,5-diazabicyclo[2.2.1]heptyl, 2-oxa-5-azabicyclo[2.2.1]heptyl, 2-azabicyclo-[2.2.2]octyl, 3-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]octyl, 8-oxa-3-azabicyclo[3.2.1]octyl, 3-oxa-9-azabicyclo[3.3.1]nonyl. Particular preference is given to 5- to 7-membered monocyclic heterocycloalkyl radicals having up to 2 heteroatoms selected from the group consisting of N, O and S, such as illustratively and preferably tetrahydrofuranyl, 1,3-dioxolanyl, pyrrolidinyl, tetrahydropyranyl, 1,4-dioxanyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, perhydro- azepinyl, perhydro-1,4-diazepinyl and perhydro-1,4-oxazepinyl.

The term “aryl” is to be understood as preferably meaning a monovalent, aromatic or partially aromatic, mono-, or bi- or tricyclic hydrocarbon ring having 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms (a “C_6-C_{14}-aryl” group), particularly a ring having 6 carbon atoms (a “C_6-aryl” group), *e.g.* a phenyl group, or a biphenyl group, or a ring having 9 carbon atoms (a “C_9-aryl” group), *e.g.* an indanyl or indenyl group, or a ring having 10 carbon atoms (a “C_{10}-aryl” group), *e.g.* a tetralinyl, dihydronaphthyl, or naphthyl group, or a ring having 13 carbon atoms, (a “C_{13}-aryl” group), *e.g.* a fluorenyl group, or a ring having 14 carbon atoms, (a “C_{14}-aryl” group), *e.g.* an anthranyl group.

The term “heteroaryl” is understood as preferably meaning a monovalent, aromatic, mono- or bicyclic aromatic ring system having 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 ring atoms (a “5- to 14-membered heteroaryl” group), particularly 5 or 6 or 9 or 10 atoms, and which contains at least one heteroatom which may be identical or different, said heteroatom being such as oxygen, nitrogen or sulfur, and can be monocyclic, bicyclic, or tricyclic, and in addition in each case can be benzocondensed. Preference is given to 6-membered heteroaryl radicals having up to 2 nitrogen atoms, and to 5-membered heteroaryl radicals having up to 3 heteroatoms. Particularly, heteroaryl is selected from thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, thia-4H-pyrazolyl, tetrazolyl and benzo derivatives thereof, such as, for example, benzofuranyl, benzothienyl, benzoxazolyl, benzisoxazolyl, benzimidazolyl, benzotriazolyl, indazolyl, indolyl, isoindolyl,; or pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, *etc.*, and benzo derivatives thereof, such as, for example, quinolinyl, quinazolinyl, isoquinolinyl, *etc.*; or azocinyl, indolizinyl, purinyl and benzo derivatives thereof; or cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthpyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl,

phenothiazinyl, phenoxazinyl, xanthenyl, or oxepinyl. More particularly, heteroaryl is selected from thienyl, oxazolyl, thiazolyl, 1*H*-tetrazol-5-yl, pyridyl, benzothienyl, or furanyl.

The term "alkylene" is understood as preferably meaning an optionally substituted hydrocarbon chain (or "tether") having 1, 2, 3, 4, 5, or 6 carbon atoms, *i.e.* an optionally substituted $-CH_2-$ ("methylene" or "single membered tether" or, for example $-C(Me)_2-$), $-CH_2-CH_2-$ ("ethylene", "dimethylene", or "two-membered tether"), $-CH_2-CH_2-CH_2-$ ("propylene", "trimethylene", or "three-membered tether"), $-CH_2-CH_2-CH_2-CH_2-$ ("butylene", "tetramethylene", or "four-membered tether"), $-CH_2-CH_2-CH_2-CH_2-CH_2-$ ("pentylene", "pentamethylene" or "five-membered ether"), or $-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-$ ("hexylene", "hexamethylene", or six-membered tether") group. Particularly, said alkylene tether has 1, 2, 3, 4, or 5 carbon atoms, more particularly 1 or 2 carbon atoms.

The term "alkylenedioxy" is understood as preferably meaning $-O-C_1-C_6$alkylene-O- in particular methylenedioxy and ethylenedioxy as in the below exemplified formula:

The term "C_1-C_6", as used throughout this text, *e.g.* in the context of the definition of "C_1-C_6-alkyl", "C_1-C_6-haloalkyl", "C_1-C_6-alkoxy", or "C_1-C_6-haloalkoxy" is to be understood as meaning an alkyl group having a finite number of carbon atoms of 1 to 6, *i.e.* 1, 2, 3, 4, 5, or 6 carbon atoms. It is to be understood further that said term "C_1-C_6" is to be interpreted as any sub-range comprised therein, *e.g.* C_1-C_6, C_2-C_5, C_3-C_4, C_1-C_2, C_1-C_3, C_1-C_4, C_1-C_5, C_1-C_6; particularly C_1-C_2, C_1-C_3, C_1-C_4, C_1-C_5, C_1-C_6; more particularly C_1-C_4; in the case of "C_1-C_6-haloalkyl" or "C_1-C_6-haloalkoxy" even more particularly C_1-C_2.

Similarly, as used herein, the term "C_2-C_6", as used throughout this text, *e.g.* in the context of the definitions of "C_2-C_6-alkenyl" and "C_2-C_6-alkynyl", is to be understood as meaning an alkenyl group or an alkynyl group having a finite number of carbon atoms of 2 to 6, *i.e.* 2, 3, 4, 5, or 6 carbon atoms. It is to be understood further that said term "C_2-C_6" is to be interpreted as any sub-range comprised therein, *e.g.* C_2-C_6, C_3-C_5, C_3-C_4, C_2-C_3, C_2-C_4, C_2-C_5; particularly C_2-C_3.

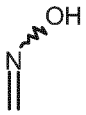
Further, as used herein, the term "C_3-C_{10}", as used throughout this text, *e.g.* in the context of the definition of "C_3-C_{10}-cycloalkyl", is to be understood as meaning a cycloalkyl group having a finite number of carbon atoms of 3 to 10, *i.e.* 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms, particularly 3, 4, 5 or 6 carbon atoms. It is to be understood further that said term "C_3-C_{10}" is to be interpreted as any sub-range comprised therein, *e.g.* C_3-C_{10}, C_4-C_9, C_5-C_8, C_6-C_7; particularly C_3-C_6.

Oxo represents a double-bonded oxygen atom.

As used herein, the term "one or more times", *e.g.* in the definition of the substituents of the compounds of the general formulae of the present invention, is understood as meaning "one, two, three, four or five times, particularly one, two, three or four times, more particularly one, two or three times, even more particularly one or two times".

Throughout this document, for the sake of simplicity, the use of singular language is given preference over plural language, but is generally meant to include the plural language if not otherwise stated. E.g., the expression "A method of treating a disease in a patient, comprising administering to a patient an effective amount of a compound of formula **(I)**" is meant to include the simultaneous treatment of more than one disease as well as the administration of more than one compound of formula **(I)**

 indicates a non-specified sp^2- or sp^3-stereobond or a mixture of stereoisomers, for example, the group



represents a *E*- or *Z*-isomer, or a mixture thereof.

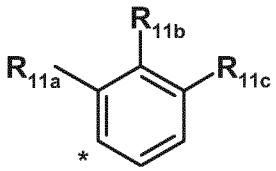
* indicates the point of attachment to of a given group, for example a ring, to general formula in which said group is reported.

Particular forms of embodiment of compounds of the general formula **(I)** as described above are going to be illustrated in the following.

A further detailed embodiment, in conjunction with any of the above or below embodiments, refers to compounds in which R_6 is phenyl, pyridyl or pyridazyl group wherein said group is optionally substituted one to three times, in the same way or differently, with a substituent R_{11}

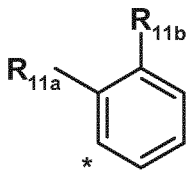
selected from an hydrogen or an halogen, particularly a fluorine atom, and a -O-C_1-C_6-alkyl or -O-C_1-C_6-haloalkyl group, particularly -OCH_3 , -OCF_2H or -OCF_3.

A further detailed embodiment, in conjunction with any of the above or below embodiments, refers to compounds according to formula **(I)** in which R_6 is any one of the following groups:



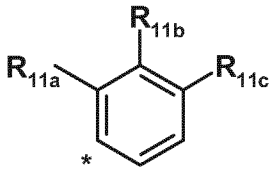
in which R_{11a}, R_{11b} and R_{11c} have the meaning as given with any of the above or below embodiments and definitions.

A further detailed embodiment, in conjunction with any of the above or below embodiments, refers to compounds according to formula **(I)** in which R_6 is



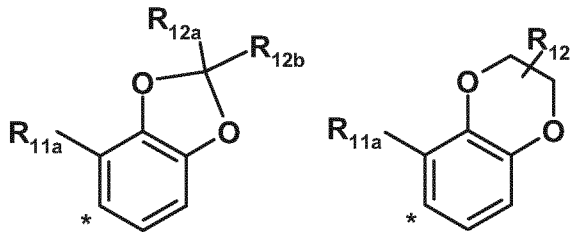
wherein R_{11a} is an hydrogen or an halogen, particularly a fluorine atom, and R_{11b} is a -O-C_1-C_6-alkyl or -O-C_1-C_6-haloalkylgroup, particularly -OCH_3 , -OCF_2H or -OCF_3.

A further detailed embodiment, in conjunction with any of the above or below embodiments, refers to compounds according to formula **(I)** in which R_6 is



and in which R_{11a} is an halogen, particularly a fluorine atom, R_{11b} is a hydrogen and R_{11c} is a -O-C_1-C_6-alkyl or -O-C_1-C_6-haloalkylgroup, particularly -OCH_3 , -OCF_2H or -OCF_3.

In a further embodiment, in conjunction with any of the above or below embodiments, compounds according to formula **(I)** are in particular those in which R_6 is any one of the following groups:



More particularly, further forms of embodiment, in conjunction with any of the above or below embodiments, refer to compounds according to the invention comprising any one of the following groups with the following meaning:

R_{1a} represent a hydrogen atom, a
C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_3-C_8-cycloalkyl-,
aryl-, heteroaryl-, -C_1-C_6-alkylene-aryl, -C_1-C_6-alkylene-heteroaryl,
-C_1-C_6-alkylene-C_3-C_{10}-cycloalkyl,
-C_1-C_6-alkylene-(3- to 10-membered heterocycloalkyl),
-C(=O)-C_1-C_6-alkyl, -C(=O)-C_1-C_6-alkylene-aryl,
-C(=O)-C_1-C_6-alkylene-heteroaryl, -S(=O)$_2$$R^9$ group;
wherein said groups are optionally substituted one to three times, in the same way or differently, with a substituent selected from :
halo-, hydroxy-, oxo, cyano-, C_1-C_6-alkyl-,
halo-C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-,
C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-,
aryl-, -C_1-C_6-alkylene-aryl, heteroaryl-, -C(=O)OH,
-C(=O)O-C_1-C_6-alkyl, -OC(=O)-C_1-C_6-alkyl,
-N(H)C(=O)R^9, -C(=O)N$R^9$$R^{10}$, -N($C_1$-$C_6$-alkyl)C(=O)O$R^9$,
-N(C_1-C_6-alkyl)C(=O)N$R^9$$R^{10}$,
-SR^9, -S(=O)R^9, -S(=O)$_2$OH, -S(=O)$_2$$R^9$, -N$R^9$$R^{10}$

More particularly R_{1a} is selected from the group consisting of a hydrogen atom, a
C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, -C_1-C_6-alkenyl-, aryl-, heteroaryl-,
-C_1-C_6-alkylene-aryl, -C_1-C_6-alkylene-heteroaryl, -C(=O)-C_1-C_6-alkyl,
optionally substituted one to three times times, in the same way or differently, with a substituent selected from : halo-, hydroxy-, cyano-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-,

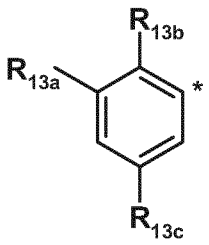
-C(=O)OH, -C(=O)NH_2, -$S(=O)_2$OH, -N(H)C(=O)NH_2,
-N(H)C(=NH)NH_2, -C(=O)O-C_1-C_6-alkyl, -NH_2

More specifically, R_{1a} is a –CH_2-CH_2-CH_2-C(=O)O-CH_2-CH_3 ,
–CH_2-CH_2-O-CH_2-C(=O)O-CH_3 , –CH_2-CH_2-O-CH_2-C(=O)O-CH_2-CH_3 ,
–CH_2-CH_2-CH_2-C(=O)OH, –CH_2-CH_2-O-CH_2-C(=O)OH.

R_{2a} and R_{2b} are both a hydrogen atom or a methyl group; and more particularly R_{2a} and R_{2b} are both an hydrogen

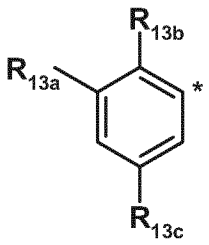
R_{3a} is a phenyl group optionally substituted one to three times with a halogen atom, cyano, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy or halo-C_1-C_6-alkoxy;

In particular R_{3a} is



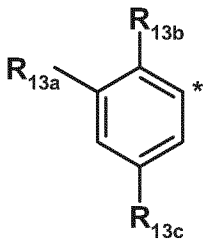
wherein R_{13a} and R_{13c} is an hydrogen or an halogen, particularly a fluorine atom, and R_{13b} is an hydrogen or an halogen, particularly a fluorine atom.

Furthermore, R_{3a} is more particularly



wherein R_{13a}, R_{13b} and R_{13c} is an hydrogen.

In a specific form R_{3a} is further



wherein R_{13a} and R_{13c} is an hydrogen and R_{13b} is a fluorine atom or R_{13b} is an hydrogen and R_{13a} and R_{13c} is a fluorine atom.

R_{3b} is hydrogen or C_1-C_6-alkyl, more specifically and hydrogen

R represent a hydrogen atom, a C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)NR^9R^{10}$, or $-S(=O)_2R^9$ group,

R_8 is selected from the group consisting of a hydrogen atom, particularly a fluorine atom or a fluorinated C_1-C_6-alkyl group, in particular a $-CF_3$,

More particularly, R_8 is a fluorine atom or a $-CF_3$.

R^9 and R^{10} joined, and taken together with the atom to which they are attached, form a 5- to 6-membered heterocycloalkyl-, optionally substituted one or two times, in the same way or differently, with a substituent selected from the group consisting of halo-, hydroxyl-, cyano-, oxo, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, $-C(=O)OH$,

Specifically R^9 and R^{10} joined, and taken together with the atom to which they are attached, form a 5- to 6-membered heterocycloalkyl-, optionally substituted one or two times, in the same way or differently, with a substituent selected from the group consisting of: of halo-, hydroxyl-, cyano-, oxo, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-.

Furthermore, R^9 and R^{10} represent, independently of one another, a hydrogen atom, a C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_{10}-cycloalkyl-, aryl-, -C_1-C_6-alkylene-aryl, heteroaryl-, or specifically

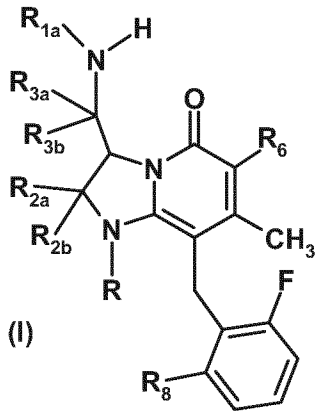
R^9 and R^{10} are independently selected from the group consisting of hydrogen, hydroxyl, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy

R_{11} , R_{11a} , R_{11b} and R_{11c} are independently of one another hydrogen, halogen, hydroxy, cyano, nitro, C_1-C_6-alkyl, -C(=O)C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy with halogen, preferably fluorine atom.

R_{12} , R_{12a} and R_{12b} are an hydrogen or an halogen atom, preferably a fluorine atom.

R_{13a} , R_{13b} and R_{13c} is an hydrogen or an halogen, particularly a fluorine atom.

More particularly the present invention refers to a compound of formula **(I)**



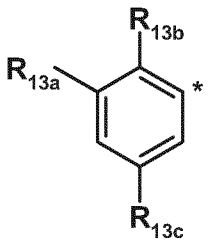
(I)

in which

R_{1a} represent a hydrogen atom, a C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, -C_1-C_6-alkenyl-, aryl-, heteroaryl-, -C_1-C_6-alkylene-aryl, -C_1-C_6-alkylene-heteroaryl, -C(=O)-C_1-C_6-alkyl, optionally substituted one to three times times, in the same way or differently, with a substituent selected from : halo-, hydroxy-, cyano-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, -C(=O)OH, -C(=O)NH_2, -S(=O)$_2$OH, -N(H)C(=O)NH_2, -N(H)C(=NH)NH_2, -C(=O)O-C_1-C_6-alkyl, -NH_2,

R_{2a} and R_{2b} are both a hydrogen;

R_{3a} is



wherein R_{13a}, R_{13b} and R_{13c} is an hydrogen;

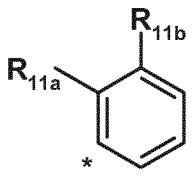
R_{3b} is hydrogen;

R represent a hydrogen atom, a C_1-C_6-alkyl-, -C(=O)R^9, -C(=O)OR^9, or -S(=O)$_2R^9$ group, wherein R^9 is a hydrogen atom, a C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_{10}-cycloalkyl-, aryl-, -C_1-C_6-alkylene-aryl, heteroaryl-;

R_8 is -CF_3;

R_6 represents an aryl-, a heteroaryl-, a benzo[1,3]dioxolyl- or 2,3-dihydro-1,4-benzodioxinyl group wherein said group is optionally substituted one to three times, in the same way or differently, with a substituent R_{11} selected from : hydrogen, halogen, hydroxy, cyano, nitro, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-hydroxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkyl-C(=O)OH, -C(=O)OH, -C(=O)C_1-C_6-alkyl; or

R_6 is



wherein R_{11a} is an hydrogen or an halogen, particularly a fluorine atom, and R_{11b} is a -O-C_1-C_6-alkyl or -O-C_1-C_6-haloalkylgroup, particularly -OCH_3 , -OCF_2H or -OCF_3

Compounds according to the invention are:

{3*R*-[3*R*(R*)*]}-benzyl 3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*S*-[3*R*(R*)*]}-benzyl 3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*R*-[3*R*(S*)*]}-benzyl 3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*S*-[3*R*(S*)*]}-benzyl 3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*R*-[3*R*(R*)*]}-3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1*H*)-one

{3*S*-[3*R*(R*)*]}-3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1*H*)-one

{3*R*-[3*R*(S*)*]}-3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1*H*)-one

{3*S*-[3*R*(S*)*]}-3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1*H*)-one

{3*R*-[3*R*(R*)*]}-benzyl 3-{[(4-ethoxy-4-oxobutyl)amino](phenyl)methyl}-6-(2-fluoro-3-methoxy phenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyri-dine-1(5*H*)-carboxylate

{3*S*-[3*R*(R*)*]}-benzyl 3-{[(4-ethoxy-4-oxobutyl)amino](phenyl)methyl}-6-(2-fluoro-3-methoxy phenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyri-dine-1(5*H*)-carboxylate

{3*R*-[3*R*(S*)*]}-benzyl 3-{[(4-ethoxy-4-oxobutyl)amino](phenyl)methyl}-6-(2-fluoro-3-methoxy phenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyri-dine-1(5*H*)-carboxylate

{3*S*-[3*R*(S*)*]}-benzyl 3-{[(4-ethoxy-4-oxobutyl)amino](phenyl)methyl}-6-(2-fluoro-3-methoxy phenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyri-dine-1(5*H*)-carboxylate

{3*R*-[3*R**(*R**)]}-benzyl 3-[{[2-(2-ethoxy-2-oxoethoxy)ethyl] amino}(phenyl)methyl]-6-(2-fluoro-3-methoxy phenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a] pyridine-1(5*H*)-carboxylate

{3*S*-[3*R**(*R**)]}-benzyl 3-[{[2-(2-ethoxy-2-oxoethoxy)ethyl] amino}(phenyl)methyl]-6-(2-fluoro-3-methoxy phenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a] pyridine-1(5*H*)-carboxylate

{3*R*-[3*R**(*S**)]}-benzyl 3-[{[2-(2-ethoxy-2-oxoethoxy)ethyl] amino}(phenyl)methyl]-6-(2-fluoro-3-methoxy phenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a] pyridine-1(5*H*)-carboxylate

{3*S*-[3*R**(*S**)]}-benzyl 3-[{[2-(2-ethoxy-2-oxoethoxy)ethyl] amino}(phenyl)methyl]-6-(2-fluoro-3-methoxy phenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a] pyridine-1(5*H*)-carboxylate

{3*R*-[3*R**(*R**)]}-benzyl 6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-{[(2-methoxyethyl)amino](phenyl)methyl}-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*S*-[3*R**(*R**)]}-benzyl 6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-{[(2-methoxyethyl)amino](phenyl)methyl}-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*S*-[3*R**(*R**)]}-benzyl 6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-{[(2-methoxyethyl)amino](phenyl)methyl}-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*S*-[3*R**(*S**)]}-benzyl 6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-{[(2-methoxyethyl)amino](phenyl)methyl}-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*R*-[3*R**(*R**)]}-benzyl 3-{[(cyanomethyl)amino](phenyl)methyl}-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*S*-[3*R**(*R**)]}-benzyl 3-{[(cyanomethyl)amino](phenyl)methyl}-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*R*-[3*R**(*S**)]}-benzyl 3-{[(cyanomethyl)amino](phenyl)methyl}-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*S*-[3*R**(*S**)]}-benzyl 3-{[(cyanomethyl)amino](phenyl)methyl}-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*R*-[3*R**(*R**)]}-ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate

{3*S*-[3*R**(*R**)]}-ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate

{3*R*-[3*R**(*S**)]}-ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate

{3*S*-[3*R**(*S**)]}-ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate

{3*R*-[3*R**(*R**)]}-ethyl (2-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl} (phenyl)methyl]amino} ethoxy)acetate

{3*S*-[3*R**(*R**)]}-ethyl (2-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl} (phenyl)methyl]amino} ethoxy)acetate

{3*R*-[3*R**(*S**)]}-ethyl (2-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl} (phenyl)methyl]amino} ethoxy)acetate

{3*S*-[3*R**(*S**)]}-ethyl (2-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl} (phenyl)methyl]amino} ethoxy)acetate

{3*R*-[3*R**(*R**)]}-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-{[(2-methoxyethyl)amino](phenyl)methyl}-7-methyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one

{3*S*-[3*R**(*R**)]}-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-{[(2-methoxyethyl)amino](phenyl)methyl}-7-methyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one

{3*R*-[3*R**(*S**)]}-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-{[(2-methoxyethyl)amino](phenyl)methyl}-7-methyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one

{3*S*-[3*R**(*S**)]}-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-{[(2-methoxyethyl)amino](phenyl)methyl}-7-methyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one

{3*R*-[3*R**(*R**)]}-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}acetonitrile

{3*S*-[3*R**(*R**)]}-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}acetonitrile

{3*R*-[3*R**(*S**)]}-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}acetonitrile

{3*S*-[3*R**(*S**)]}-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}acetonitrile

{3*R*-[3*R**(*R**)]}-ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl](methyl)amino} butanoate

{3*S*-[3*R**(*R**)]}-ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl](methyl)amino} butanoate

{3*R*-[3*R**(*S**)]}-ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl](methyl)amino} butanoate

{3*S*-[3*R**(*S**)]}-ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl](methyl)amino} butanoate

{3*R*-[3*R**(*R**)]}-4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoic acid

{3*S*-[3*R**(*R**)]}-4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoic acid

{3*R*-[3*R**(*S**)]}-4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoic acid

{3*S*-[3*R**(*S**)]}-4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoic acid

{3*R*-[3*R*(R*)*]}-sodium 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate

{3*S*-[3*R*(R*)*]}-sodium 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate

{3*R*-[3*R*(S*)*]}-sodium 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate

{3*S*-[3*R*(S*)*]}-sodium 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate

{3*R*-[3*R*(R*)*]}-sodium (2-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}ethoxy)acetate

{3*S*-[3*R*(R*)*]}-sodium (2-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}ethoxy)acetate

{3*R*-[3*R*(S*)*]}-sodium (2-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}ethoxy)acetate

{3*S*-[3*R*(S*)*]}-sodium (2-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}ethoxy)acetate

Another embodiment of the present invention provides compounds according to general formula **(I)** and related specific embodiments for use as a medicament.

In another embodiment, the present invention provides a method of treating GnRH related disorder in a patient in need of such treatment, comprising administering to the patient an effective amount of a compound according to the invention as defined above.

In still another aspect, the invention provides use of a compound according to the invention as defined above for manufacturing a pharmaceutical composition for the treatment or prevention of GnRH related disorders.

The term "treating" or "treatment" as stated throughout this document is used conventionally, e.g., the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of a disease or disorder, such as for example endometriosis and uterine fibroids.

The term "subject" or "patient" includes organisms which are capable of suffering from a disorder or who could otherwise benefit from the administration of a compound of the invention, such as human and non-human animals. Preferred humans include human patients suffering from or prone to suffering from disorders, such as for example endometriosis and uterine fibroids. The term "non-human animals" includes vertebrates, e.g., mammals, such as non-human primates, sheep, cow, dog, cat and rodents, e.g., mice, and non-mammals, such as chickens, amphibians, reptiles, etc.

In another aspect, the invention provides a pharmaceutical composition comprising a compound according to the invention, together with a pharmaceutically acceptable carrier.

In still another aspect, the invention provides a process for preparing a pharmaceutical composition. The process includes the step of combining at least one compound according to the invention as defined above with at least one pharmaceutically acceptable carrier, and bringing the resulting combination into a suitable administration form.

The compounds according to general formula **(I)** are used as a medicament. In particular, said compounds are used to treat sex-hormone-related conditions in both men and women, as well as a mammal in general (also referred to herein as a "subject"). For example, such conditions include endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, gonadal steroid-dependent neoplasia such as cancers of the prostate, breast and ovary, gonadotrope pituitary adenomas, sleep apnea, irritable bowel syndrome, premenstrual syndrome, benign prostatic hypertrophy, contraception and infertility (e.g., assisted reproductive therapy such as in vitro fertilization).
The compounds of this invention are also useful as an adjunct to treatment of growth hormone deficiency and short stature, and for the treatment of systemic lupus erythematosus.
According to a further embodiment of the present invention the compounds according to general formula **(I)** are also useful and can be used in combination with androgens, estrogens, progestins, SERMs, antiestrogens and antiprogestins for the treatment of endometriosis, fibroids, and in contraception, as well as in combination with an angiotensin-

converting enzyme inhibitor, an angiotensin II-receptor antagonist, or a renin inhibitor for the treatment of uterine fibroids.

A combination of compounds according to general formula **(I)** with bisphosphonates and other agents for the treatment and/or prevention of disturbances of calcium, phosphate and bone metabolism, and in combination with estrogens, SERMs, progestins and/or androgens for the prevention or treatment of bone loss or hypogonadal symptoms such as hot flushes during therapy with a GnRH antagonist is also part of the present invention.

The methods of this invention include administering an effective amount of a GnRH receptor antagonist, preferably in the form of a pharmaceutical composition, to a mammal in need thereof. Thus, in still a further embodiment, pharmaceutical compositions are disclosed containing one or more GnRH receptor antagonists of this invention in combination with a pharmaceutically acceptable carrier and/or diluent.

These and other aspects of the invention will be apparent upon reference to the following detailed description. To this end, various references are set forth herein which describe in more detail certain background information, procedures, compounds and/or compositions, and are each hereby incorporated by reference in their entirety.

The compounds of the present invention may generally be utilized as the free acid or free base. Alternatively, the compounds of this invention may be used in the form of acid or base addition salts.

Thus, the term "pharmaceutically acceptable salt" of compounds of general formula **(I)** is intended to encompass any and all acceptable salt forms.

In addition, prodrugs are also included within the context of this invention. Prodrugs are any covalently bonded carriers that release a compound of general formula **(I)** *in vivo* when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or *in vivo*, yielding the parent compound.

Prodrugs include, for example, compounds of this invention wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a patient, cleaves to form the hydroxy, amine or sulfhydryl groups. Thus, representative examples of prodrugs include (but are not limited to) acetate, formate and benzoate derivatives of alcohol and amine functional groups of the compounds of general formula **(I)**. Further, in the case of a

carboxylic acid (-COOH), esters may be employed, such as methyl esters, ethyl esters, and the like.

With regard to stereoisomers, the compounds of general formula **(I)** may have chiral centers and may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof. Furthermore, some of the crystalline forms of the compounds of general formula **(I)** may exist as polymorphs, which are included in the present invention. In addition, some of the compounds of general formula **(I)** may also form solvates with water or other organic solvents. Such solvates are similarly included within the scope of this invention.

The effectiveness of a compound as a GnRH receptor antagonist may be determined by various assay techniques. Assay techniques well known in the field include the use of cultured pituitary cells for measuring GnRH activity (*Vale et al., Endocrinology* **1972**, *91*, 562 - 572) and the measurement of radioligand binding to rat pituitary membranes (*Perrin et al., Mol. Pharmacol.* **1983**, *23*, 44 - 51) or to membranes from cells expressing cloned receptors as described below. Other assay techniques include (but are not limited to) measurement of the effects of GnRH receptor antagonists on the inhibition of GnRH-stimulated calcium flux, modulation of phosphoinositol hydrolysis, and the circulating concentrations of gonadotropins in the castrate animal. Descriptions of these techniques, the synthesis of radiolabelled ligand, the employment of radiolabelled ligand in radioimmunoassay, and the measurement of the effectiveness of a compound as a GnRH receptor antagonist follow.

In another embodiment of the invention, pharmaceutical compositions containing one or more GnRH receptor antagonists are disclosed. For the purposes of administration, the compounds of the present invention may be formulated as pharmaceutical compositions.

Pharmaceutical compositions of the present invention comprise a GnRH receptor antagonist of the present invention and a pharmaceutically acceptable carrier and/or diluent. The GnRH receptor antagonist is present in the composition in an amount which is effective to treat a particular disorder that is, in an amount sufficient to achieve GnRH receptor antagonist activity, and preferably with acceptable toxicity to the patient. Typically, the pharmaceutical compositions of the present invention may include a GnRH receptor antagonist in an amount from 0.1 mg to 500 mg per day dosage depending upon the route of administration, and more typically from 0.5 mg to 150 mg per day. Appropriate concentrations and dosages can be readily determined by one skilled in the art.

Determination of a therapeutically effective amount or a prophylactically effective amount of the compounds of the invention can be readily made by the physician or veterinarian (the "attending clinician"), as one skilled in the art, by the use of known techniques and by observing results obtained under analogous circumstances. The dosages may be varied depending upon the requirements of the patient in the judgment of the attending clinician; the severity of the condition being treated and the particular compound being employed. In determining the therapeutically effective amount or dose, and the prophylactically effective amount or dose, a number of factors are considered by the attending clinician, including, but not limited to: the specific GnRH mediated disorder involved; pharmacodynamic characteristics of the particular agent and its mode and route of administration; the desired time course of treatment; the species of mammal; its size, age, and general health; the specific disease involved; the degree of or involvement or the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the kind of concurrent treatment (i.e., the interaction of the compound of the invention with other coadministered therapeutics); and other relevant circumstances.

Treatment can be initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage may be increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

Pharmaceutically acceptable carrier and/or diluents are familiar to those skilled in the art. For compositions formulated as liquid solutions, acceptable carriers and/or diluents include saline and sterile water, and may optionally include antioxidants, buffers, bacteriostats and other common additives. The compositions can also be formulated as pills, capsules, granules, or tablets which contain, in addition to a GnRH receptor antagonist, diluents, dispersing and surface active agents, binders, and lubricants. One skilled in this art may further formulate the GnRH receptor antagonist in an appropriate manner, and in accordance with accepted practices, such as those disclosed in *Remington's Pharmaceutical Sciences, Gennaro, Ed.* , Mack Publishing Co., Easton, PA 1990.

In another embodiment, the present invention provides a method for treating sex-hormone-related conditions as discussed above. Such methods include administering of a compound of the present invention to a warm-blooded animal in an amount sufficient to treat the condition. In this context, "treat" includes prophylactic administration. Such methods include systemic administration of a GnRH receptor antagonist of this invention, preferably in the

form of a pharmaceutical composition as discussed above. As used herein, systemic administration includes oral and parenteral methods of administration. For oral administration, suitable pharmaceutical compositions of GnRH receptor antagonists include powders, granules, pills, tablets, and capsules as well as liquids, syrups, suspensions, and emulsions. These compositions may also include flavorants, preservatives, suspending, thickening and emulsifying agents, and other pharmaceutically acceptable additives. For parental administration, the compounds of the present invention can be prepared in aqueous injection solutions which may contain, in addition to the GnRH receptor antagonist, buffers, antioxidants, bacteriostats, and other additives commonly employed in such solutions.

MODE(S) FOR CARRYING OUT THE INVENTION

The following examples are provided for purposes of illustration, not limitation. In summary, the GnRH receptor antagonists of this invention may be assayed by the general methods disclosed above, while the following examples disclose the synthesis of representative compounds of this invention.

EXPERIMENTAL DETAILS AND GENERAL PROCESSES

The following table lists the abbreviations used in this paragraph and in the examples section as far as they are not explained within the text body.

Abbreviation	Meaning
Ac	acetyl
br	broad
CI	chemical ionisation
d	doublet
dd	doublet of doublet
ddd	doublet of doublet of doublet
dt	doublet of triplet
dq	doublet of quartet
DCM	dichloromethane
DIPEA	N,N-diisopropylethyl amine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
eq.	equivalent
EI	electron impact
ESI	electrospray ionization
GP	general procedure
HPLC	high performance liquid chromatography
LCMS	liquid chromatography mass spectrometry
LG	leaving group
m	multiplet
mc	centred multiplet
MS	mass spectrometry
NMR	nuclear magnetic resonance spectroscopy: chemical shifts (δ) are given in ppm
Pg	protecting group
R_f	retardation factor or retention factor
R_T	retention time

r.t. or rt or room temp.	room temperature
s	singlet
sept	septet
t or tr	triplet
TBAF	tetra-N-butylammonium fluoride
TEA	triethylamine
TLC	thin layer chromatography
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Ts	para-toluenesulfonyl
UPLC-MS	ultra performance liquid chromatography mass spectrometry

NMR peak forms are stated as they appear in the spectra, possible higher order effects have not been considered. Chemical shifts are given in ppm; all spectra were calibrated to solvent residual peak. Integrals are given in integers, except for those cases atropisomerism was observed. Then non integer numbers were used; signals are marked with an asterisk (*), for example (0.5H*).

Ultra performance liquid chromatography / liquid chromatography mass spectrometry – methods:

The term “UPLC-MS (ESI+)” refers to the following condition:
Instrument: Waters Acquity UPLC-MS SQD 3001; column: Acquity UPLC BEH C18 1.7 50x2.1mm; eluent A: water + 0.1% formic acid, eluent B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow 0.8 ml/min; temperature: 60 °C; injection: 2 µl; DAD scan: 210-400 nm; or
Instrument: Waters Acquity UPLC-MS SQD 3001; column: Acquity UPLC BEH C18 1.7 50x2.1mm; Eluent A: water + 0.2% ammonia, eluent B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow 0.8 ml/min; temperature: 60 °C; injection: 2 µl; DAD scan: 210-400 nm
The term “UPLC_MS (ESI+)” refers to the following condition:
Waters HPLC-MS: Micromass ZQ, PDA 2996 (210-350 nm), column: Waters XBridge 4.6x50 mm C18 3.5 µm (20 °C), gradient: 0-8 min. 1-99% acetonitrile in water (0.1% formic acid), flow 2 mL/min.

Chemical names were generated according to the IUPAC rules [ACD/Name Batch ver. 12.00] or using AutoNom2000 as implemented in MDL ISIS Draw [MDL Information Systems Inc. (Elsevier MDL)]. In some cases generally accepted names of commercially available

reagents were used in place of IUPAC names or AutoNom2000 generated names. Stereodescriptors are used according to chemical abstracts.

In the case of formation of new stereogenic centers during the chemical synthesis pure diastereomers or mixtures may be obtained. Within the meaning of the present invention the term diastereomer 1 refers to the less polar (apolar) diastereomer under standard TLC conditions (silica gel TLC / organic solvent, e.g. hexanes / ethyl acetate or DCM / methanol or alcohol), i.e. the less polar (apolar) diastereomer has the greater R_f under standard TLC conditions and elutes from the flash column before the more polar counterpart. The term diasteromer 2 refers to the more polar diastereomer under standard TLC conditions (silica gel TLC / organic solvent, e.g. hexanes / ethyl acetate or DCM / methanol or alcohol), i.e. the polar diastereomer has the smaller R_f under standard TLC conditions and elutes from the flash column after the apolar counterpart.
The term enantiomer 1 used in the present invention refers to the enantiomer of an racemic mixture which elutes in the chiral HPLC / preparative HPLC before its counterpart enantiomer 2, i.e. enantiomer 1 has the smaller R_T in chiral HPLC.

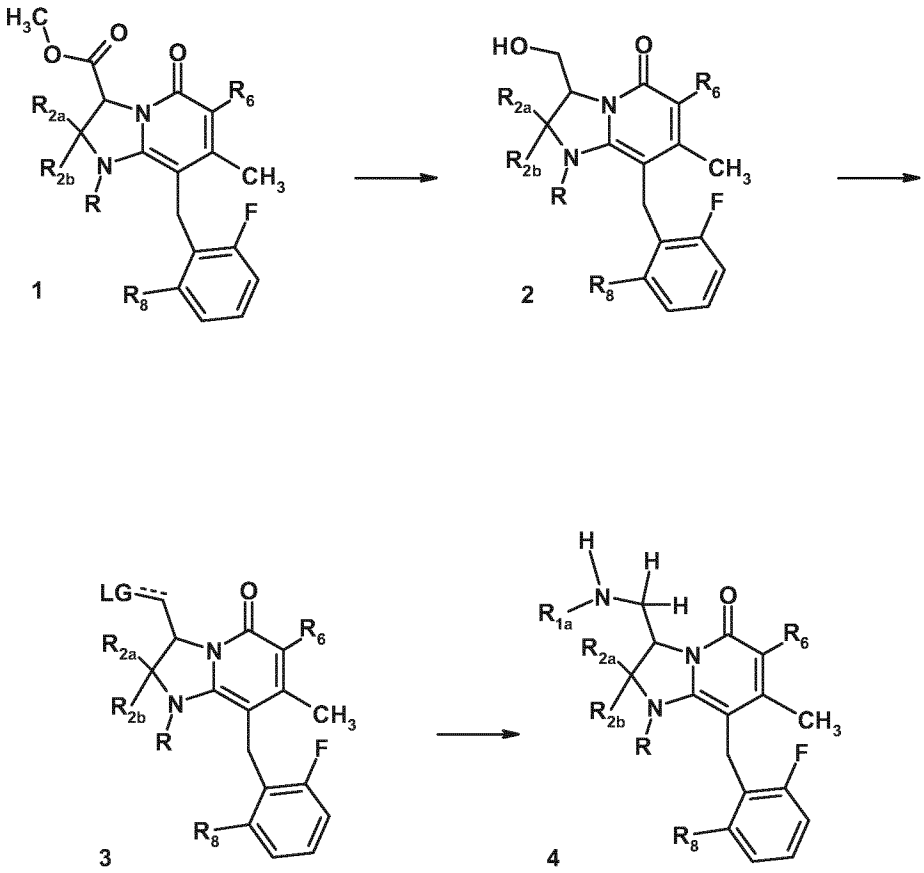
Reactions employing microwave irradiation may be run with a Biotage Initiator® microwave oven optionally equipped with a robotic unit. The reported reaction times employing microwave heating are intended to be understood as fixed reaction times after reaching the indicated reaction temperature.

The compounds and intermediates produced according to the methods of the invention may require purification. Purification of organic compounds is well known to the person skilled in the art and there may be several ways of purifying the same compound. In some cases, no purification may be necessary. In some cases, the compounds may be purified by crystallization. In some cases, impurities may be stirred out using a suitable solvent. In some cases, the compounds may be purified by chromatography, particularly flash column chromatography, using for example prepacked silica gel cartridges, e.g. from Separtis such as Isolute® Flash silica gel or Isolute® Flash NH_2 silica gel in combination with a Flashmaster II autopurifier (Argonaut/Biotage) and eluents such as gradients of hexane/ethyl acetate or DCM/ethanol. In some cases, the compounds may be purified by preparative HPLC using for example a Waters autopurifier equipped with a diode array detector and/or on-line electrospray ionization mass spectrometer in combination with a suitable prepacked reverse phase column and eluents such as gradients of water and acetonitrile which may contain additives such as trifluoroacetic acid or aqueous ammonia.

In some cases, purification methods as described above can provide those compounds of the present invention which possess a sufficiently basic or acidic functionality in the form of a salt, such as, in the case of a compound of the present invention which is sufficiently basic, a trifluoroacetate or formate salt for example, or, in the case of a compound of the present invention which is sufficiently acidic, an ammonium salt for example. A salt of this type can either be transformed into its free base or free acid form, respectively, by various methods known to the persion skilled in the art, or be used as salts in subsequent biological assays. It is to be understood that the specific form (e.g. salt, free base etc.) of a compound of the present invention as isolated as described herein is not necessarily the only form in which said compound can be applied to a biological assay in order to quantify the specific biological activity.

The following schemes and general procedures illustrate general synthetic routes to the compounds of general formula **(I)** of the invention and are not intended to be limiting. It is obvious to the person skilled in the art that the order of transformations as exemplified in Schemes 1 to 3 can be modified in various ways. The order of transformations exemplified in Schemes 1 to 3 is therefore not intended to be limiting. In addition, interconversion of substituents, for example of residues R, R_{1a}, R_{2a}, R_{2b}, R_{3a}, R_{3b}, R_6, and R_8 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example *T.W. Greene and P.G.M. Wuts*, *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999).

Scheme 1



Scheme 1 General procedures for the preparation of a compound of general formula **4** starting from an ester of general formula **1**, R, R_{1a}, R_{2a}, R_{2b}, R_6, and R_8 are as defined in the description and claims of this invention. The procedure is favourable for the synthesis of compounds of general formula **(I)** wherein R_{3a} and R_{3b} comprises Hydrogen.

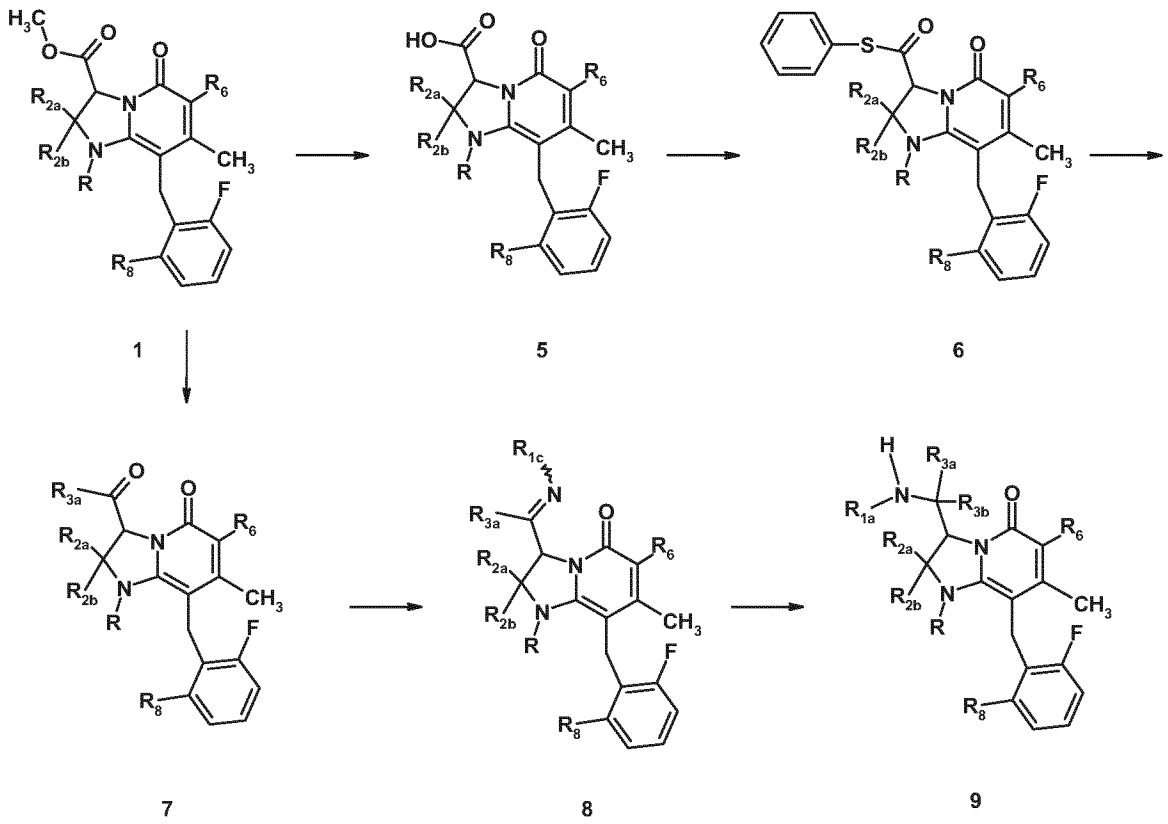
A compound of general formula **4** can be synthesized according to the procedure depicted in Scheme 1 from a suitably functionalized activated precursor **3**, wherein LG is an appropriate leaving group, such as, for example, a p-toluenesulfonyloxy (LG is OTs) or chlorine (LG is Cl), in aprotic polar solvents, such as, for example, THF or DMF, with an appropriate amine, $HNR_{1a}R_{1b}$, at temperatures between 0°C and the boiling point of the solvent, preferably at 60°C. Further in situ activation of the chlorine precursor **3** (LG is Cl), according to standard Finkelstein´s procedure (*S. D. Bowers Jr., J. M. Sturtevant, J. Am. Chem. Soc.* **1955**, *77*, 4903 - 4907; *M. Yonovich-Weiss, Y. Sasson, Synthesis* **1984**, 34 - 35) may be necessary. The activated precursor **3**, is obtainable from the suitably functionalized alcohol **2** by reacting, for example, with p-toluenesulfonic anhydride and *N,N*-dimethylaminopyridine or p-toluenesulfonic acid chloride, a catalytic amount of *N,N*-dimethylaminopyridine and an appropriate base, such as, for example, Hünig´s base or triethylamine in an aprotic polar

solvent, such as, for example, dichloromethane at temperatures between -20°C and the boiling point of the solvent, preferably at room temperature.

Alternatively LG may comprise the Oxygen of an aldehyde moiety, i.e. a compound of general formula **4** can be synthesized by reductive amination of a suitably functionalized aldehyde **3** (LG is O) with an appropriate amine, $HNR_{1a}R_{1b}$, employing all methods available to the person skilled in the art. For example, a suitably functionalized aldehyde **3** (LG is O) can be reacted with an appropriate amine in the presence of an reducing reagent, such as, for example, sodium trisacetoxyborohydride in an appropriate solvent, such as, for example, toluene at temperatures between 0°C and the boiling point of the solvent, preferably at room temperature. The required suitably functionalized aldehyde can be obtained from an alcohol of general formula **2** by standard oxidation procedures, such as, for example Dess-Martin-oxidation (*J. Prakt. Chem.* **1996**, *338*, 588 - 590) or Swern-oxidation (*Synthesis* **1981**, 165 - 185) protocols.

A alcohol of general formula **2** can be obtained from corresponding suitably functionalized ester **1** by reduction with an appropriate reducing reagent, such as, for example, lithium aluminum hydride or lithium borohydride in an aprotic polar solvent, such as, for example, THF at temperatures between -20°C and the boiling point of the solvent, preferably at room temperature.

Scheme 2



Scheme 2 General procedures for the preparation of a compound of the general formula **9** from an ester of general formula **1**, R, R_{1a}, R_{2a}, R_{2b}, R_{3a}, R_{3b}, R_6, and R_8 are as defined in the description and claims of this invention. The procedure is favourable for the synthesis of compounds of general formula **(I)** wherein at least R_{3a} or R_{3b} are different from Hydogen.

A compound of general formula **9** can be synthesized according to the procedure depicted in Scheme 2 from a suitably functionalized imine and/or oxime **8**. Since the process disclosed in scheme 2 can optionally deliver a compound of the general formula **9** wherein R_{1a} of general formula **9** comprises hydrogen, the latter compound may act as a precursor for the introduction of further substituents R_{1a} different from hydrogen. The transformation primary amine (R_{1a} of general formula **9** comprises hydrogen) to secondary or tertiary amine, amide, sulphonamide etc. can be achieved by any of the transformations known to a person skilled in the art. For example: reductive amination and/or alkylation introduces further substituents R_{1a} different from hydrogen of general formula **9**.

A primary amine of general formula **9** wherein R_{1a} of general formula **9** comprises hydrogen, can be synthesized in analogy to the method described by *Kano et al.* (*Synthesis* **1980**, 695 – 697) from a suitably functionalized oxime **8** wherein R_{1c} is hydroxy or O-methyl by reduction with an appropriate reducing reagent, such as, for example lithium borohydride, in

the presence of a lewis acid, such as, for example titanium tetrachloride, in a polar aprotic solvent, such as, for example, dimethoxyethane at temperatures between -78°C and room temperature and the boiling point of the solvent, preferably at 0°C.

A primary amine of the general formula **9** wherein R_{1a} of general formula **9** comprises Hydrogen and R_{3b} is different from hydrogen or deuterium, can be synthesized in analogy to the method described by *Kano et al.* (*Synthesis* **1980**, 695 – 697) from a suitably functionalized oxime **8** wherein R_{1c} comprises hydroxyl or O-methyl by addition of an appropriate Grignard reagent, such as, for example, methyl magnesium chloride in the presence of a lewis acid, such as for example titanium tetrachloride, in a polar aprotic solvent, such as, for example, dimethoxyethane at temperatures between -78°C and room temperature and the boiling point of the solvent, preferably at 0°C.

Alternatively, a primary amine of the general formula **9** wherein R_{1a} of general formula **9** comprises hydrogen and R_{3b} is different from Hydrogen or deuterium, can be synthesized from a suitably functionalized secondary amine **9** (R_{1a} is allyl) by deallylation using an appropriate catalyst, such as, for example, palladium on charcoal in an protic solvent, such as, for example, ethanol at temperatures between room temperature and the boiling point of the solvent, preferably at 80°C.

A secondary amine of the general formula **9** wherein R_{1a} is different from hydrogen can – besides the formation from a primary amine (see above) – be synthesized in analogy to the method described by *Kano et al.* (*Synthesis* **1980**, 695 – 697) from a suitably functionalized imine **8** wherein R_{1c} comprises allyl by reduction with an appropriate reducing reagent, such as, for example, lithium borohydride, in a polar aprotic solvent, such as, for example, dimethoxyethane, at temperatures between -78°C and room temperature and the boiling point of the solvent, preferably at room temperature.

The imine or oxime **8**, is obtainable from the suitably functionalized ketone **7** by reacting with an appropriate amine, $H_2N\text{-}R_{1c}$, such as, for example, hydroxylamine hydrochloride or O-methylhydroxylamine or allylamine in a polar solvent, such as, for example, glacial acetic acid, alcohol or toluene or mixtures thereof at temperatures between room temperature and the boiling point of the solvent, preferably at 60°C. The addition of a suitable base, such as, for example, pyridine or triethylamine may be necessary. Some reactions may need the employment of a Dean-Stark apparatus and/or the addition of a suitable Lewis acid, such as, for example, titanium alkoxides. Ketone **7** can be synthesized in three different ways starting from suitably functionalized ester **1**:

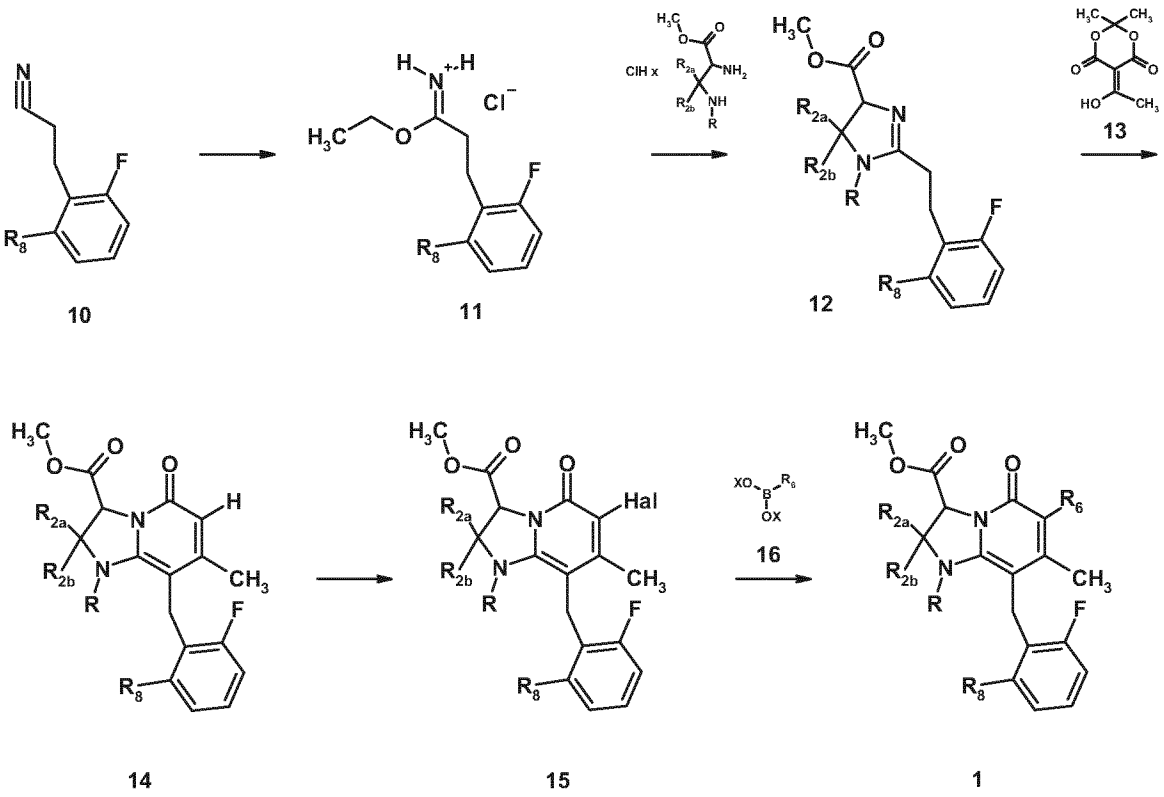
1.) Suitably functionalized thioester **6** can be reacted with an appropriate (hetero)aryl boronic acid in the presence of an appropriate catalytic system, such as, for example, as described by *Liebeskind et al.* (*J. Am. Chem. Soc.* **2000**, 122, 11260 - 11261; and *Org. Lett.*, **2000**, 2, 3229 - 3231) tris-(dibenzylidenaceton)-dipalladium (0) / 2-

thiophenecarboxylic acid, copper(I) salt / phosphorous acid triethyl ester in an aprotic polar solvent, such as, for example, THF, at temperatures between room temperature and the boiling point of the solvent, preferably at 60°C. Furthermore an appropriate (hetero)aryl stannane in the presence of an appropriate catalytic system can be used instead of the boronic acid as described recently (*Liebeskind et al., Org. Lett.* **2003**, *5*, 3033 - 3035). Thioester **6** can be prepared from a suitably functionalized acid **5** by, however, all processes that are known for thioester formation to the person skilled in the art. The acid of general formula **5**, which can be obtained from the corresponding ester of general formula **1** by saponification, can be reacted, for example, with thiophenol in an aprotic polar solvent, such as, for example, DMF, via an activated acid derivative, which is obtainable, for example, with hydroxybenzotriazole and a carbodiimide, such as, for example, *N*-ethyl-*N'*,*N'*-dimethylaminopropylcarbodiimide / *N,N*-dimethylaminopyridine, at temperatures between 0°C and the boiling point of the solvent, preferably at room temperature.

2.) Suitably functionalized ester **1** can be directly transformed into ketone **7** in aprotic non-polar solvents, such as, for example, toluene, at temperatures between -78°C and the boiling point of the solvent, preferably at -70°C, by reacting with an appropriate metallated (hetero)aryl, which is commercially available or is obtainable, for example, from (hetero)aryl halide by halogen-metal-exchange or direct metallation of an (hetero)aromat, by employing, for example butyllithium or lithium metal in an aprotic solvent at temperatures between -100°C and the boiling point of the solvent, preferably at -20°C temperature. The addition of an Lewis acid, such as, for example borontrifluoride diethylether complex, may be necessary.

3.) Furthermore suitably functionalized thioester **6** can also act as appropriate starting material for the above [bullet point 2.)] described transformation.

Scheme 3

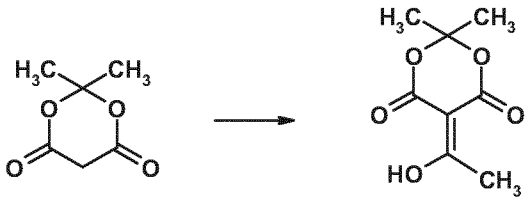


Scheme 3 General procedures for the preparation of an ester of general formula **1** from an propionitrile of general formula **10**, R, R_{2a}, R_{2b}, R_6,and R_8 are as defined in the description and claims of this invention.

An ester of general formula **1** can be synthesized according to the procedure depicted in Scheme 3 from a suitably functionalized 6-halo-pyridinone **15** and a suitable functionalized benzo[1,3]dioxolyl-, 2,3-dihydro-1,4-benzodioxinyl or (hetero)aryl boronic acid **16** (X is H) or an ester thereof. For carbon-carbon-bond formation, however, all methods that are known for Suzuki coupling to the person skilled in the art are available. For example, a suitably functionalized 6-iodo-pyridinone **15** (Hal is I) can be reacted with a suitable functionalized benzo[1,3]dioxolyl-, 2,3-dihydro-1,4-benzodioxinyl or (hetero)aryl boronic acid **16** in the presence of an appropriate catalyst and base, such as, for example, dichlor(1,1'-bis(diphenylphosphin)ferrocene) palladium dichloromethane complex and aqueous potassium carbonate, respectively, in an appropriate solvent, such as, for example, dioxane, at temperatures between room temperature and the boiling point as well as above the boiling point of the solvent, preferably at 130°C temperature employing a microwave reactor. The synthesis of 6-halo-pyridinone **15** starts from corresponding suitably functionalized 6-H-pyridinone **14** in analogy to *Almqvist et al.* (*J. Org. Chem.* **2004**, *69*, 7830 - 7835). N-iodosuccinimide and bromine, respectively, in a polar protic solvent, such as, for example,

glacial acetic acid at temperatures between -20°C and the boiling point of the solvent, preferably at room temperature, can be used to introduce the desired halide at position C-6 of the pyridinone core. A pyridinone of general formula **14** can be synthesized starting from a suitably functionalized dihydroimidazole **12** and a suitably functionalized Meldrum´s acid derivative **13** according to a method developed by *Almqvist et al.* (*Tetrahedron* **2008**, *64*, 9368 - 9376). Dihydroimidazole of general formula **12** can be synthesized via suitably functionalized iminoether **11** and readily available methyl 2,3-diaminopropanoate hydrochloride (*J. Med. Chem.* **1980**, *23*, 1232 – 1235; *ibid.* **1999**, *42*, 95 – 108; *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5211 – 5217, *ibid.* **2008**, *18*, 3183 – 3187) and derivatives thereof starting from a suitably functionalized propionitrile **10**.

Scheme 4

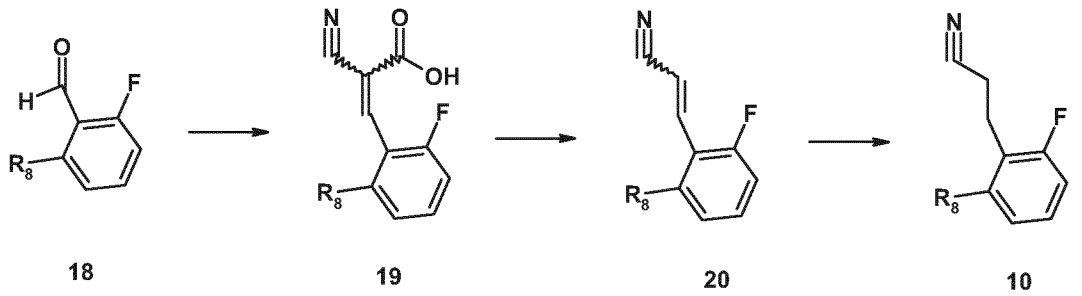


17 **13**

Scheme 4 General procedure for the preparation of an Meldrum´s acid of general formula **14** from Meldrum´s acid **17**.

The Meldrum´s acid derivative **13** can either be purchased (formula **13**, scheme 4, i.e. 5-acetyl-2,2-dimethyl-1,3-dioxane-4,6-dione, CAS-No. 72324-39-1) or synthesized as depicted in scheme 5 starting from commercially available Meldrum´s acid **17** (2,2-dimethyl-1,3-dioxan-4,6-dion, CAS-No. 2033-24-1) and an appropriate acylating reagent, such as, for example, 1-(acetyl)-imidazole in an aprotic polar solvent, such as, for example, chloroform, at temperatures between -20°C and the boiling point of the solvent, preferably at room temperature, according to *Yamamoto et al.* (*Chem. Commun.* **1997**, 359 - 360) or via an activated acetic acid derivative, which is obtainable, for example, from carbonyldiimidazole according to *Duval et al.* (*Bioorganic and Medicinal Chemistry* **1997**, *5*, 749 – 764).

Scheme 5



18 19 20 10

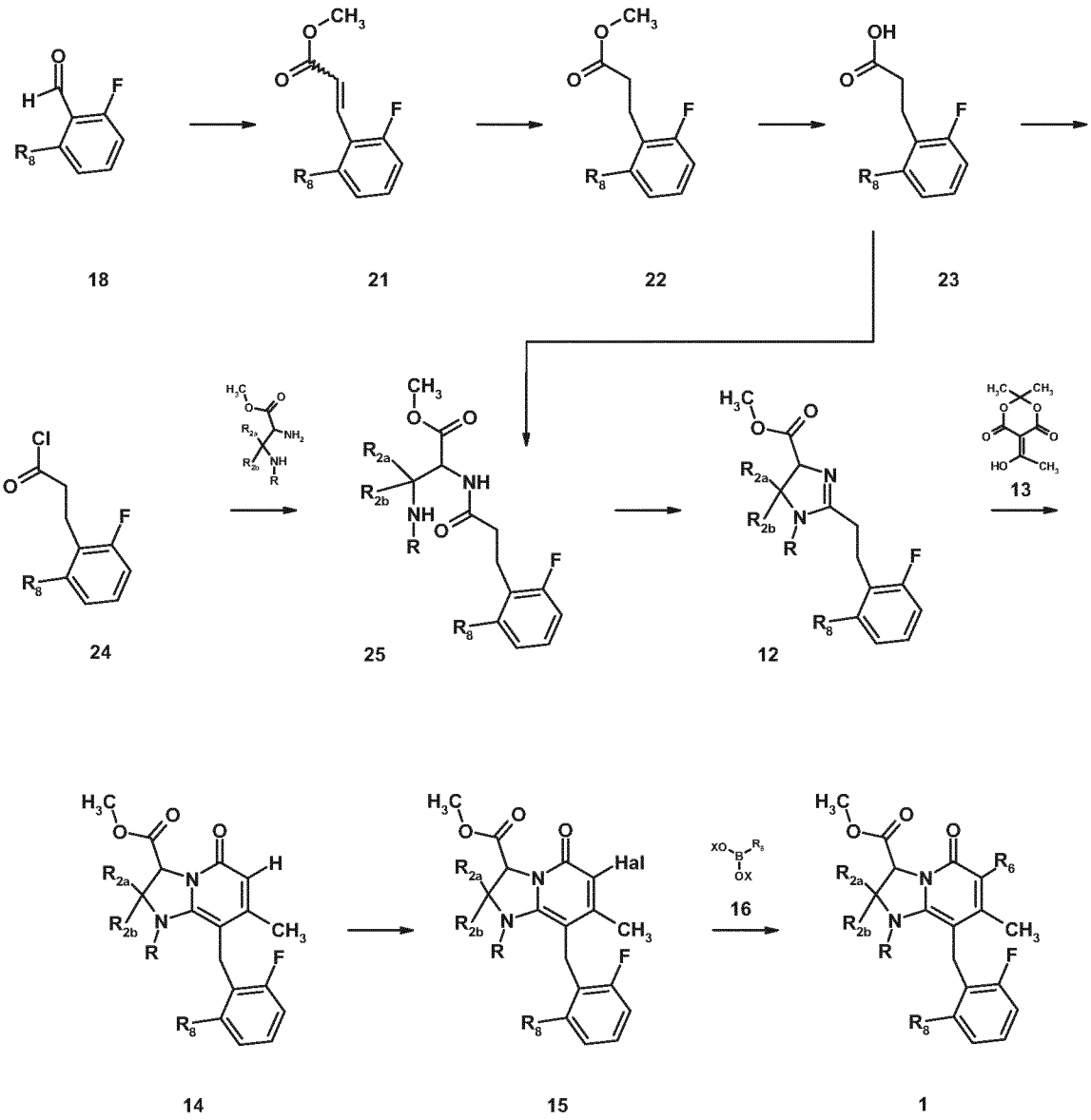
Scheme 5 General procedures for the preparation of an propionitrile of general formula **10** from benzaldehyde of general formula **18**, and R_8 is as defined in the description and claims of this invention.

A propionitrile of general formula **10** can either be purchased [e.g. 3-phenylpropionitrile (CAS-No. 645-59-0); or 3-(2-chloro-6-fluorophenyl)propionitrile from PARAGOS] or be synthesized as depicted in scheme 5 starting from a suitably functionalized benzaldehyde of general formula **18**.

A suitable precursor of propionitrile **10** is a suitable functionalized cinnamon nitrile **20** which can be reduced by, however, all processes that are known for reduction of cinnamon nitriles to the person skilled in the art, such as, for example, reduction by magnesium in methanol or catalytic hydrogenation by employing palladium and hydrogen. For the synthesis of lower 2-fluoroalkyl-6-fluoro derivatives, in practice 6-difluoromethyl-2-fluoro and 2-fluoro-6-fluoromethyl, respectively, 2-fluoro-6-trifluoromethyl cinnamon nitrile acts as starting material. The reduction by magnesium in methanol has to be done under more harsh conditions, such as, for example extended reaction time.

A cinnamon nitrile of general formula **20** can by synthesized either direct from suitably functionalized benzaldehyde **18** by Wittig-Horner-reaction according to the literature (*Robert M. Garbaccio et al., Bioorganic & Medicinal Chemistry Letters* **2007**, *17*, 6280–6285) or by a two step procedure employing a Knoevenagel condensation / decarboxylation sequence as outlined in scheme 5. To do so, suitably functionalized benzaldehyde **18** is condensed with 50% aq. solution of sodium cyanoacetate (CAS-No. 1071-36-9) and the acid **19** is subjected to copper-catalyzed decarboxylation (*Fairhurst et al., Tetrahedron Lett.* **1975**, *44*, 3843 – 3844).

Scheme 6



Scheme 6 General procedures for the preparation of an ester of general formula **1** from an benzaldehyde of general formula **18**, and R, R_{2a}, R_{2b}, R_6, and R_8 are as defined in the description and claims of this invention.

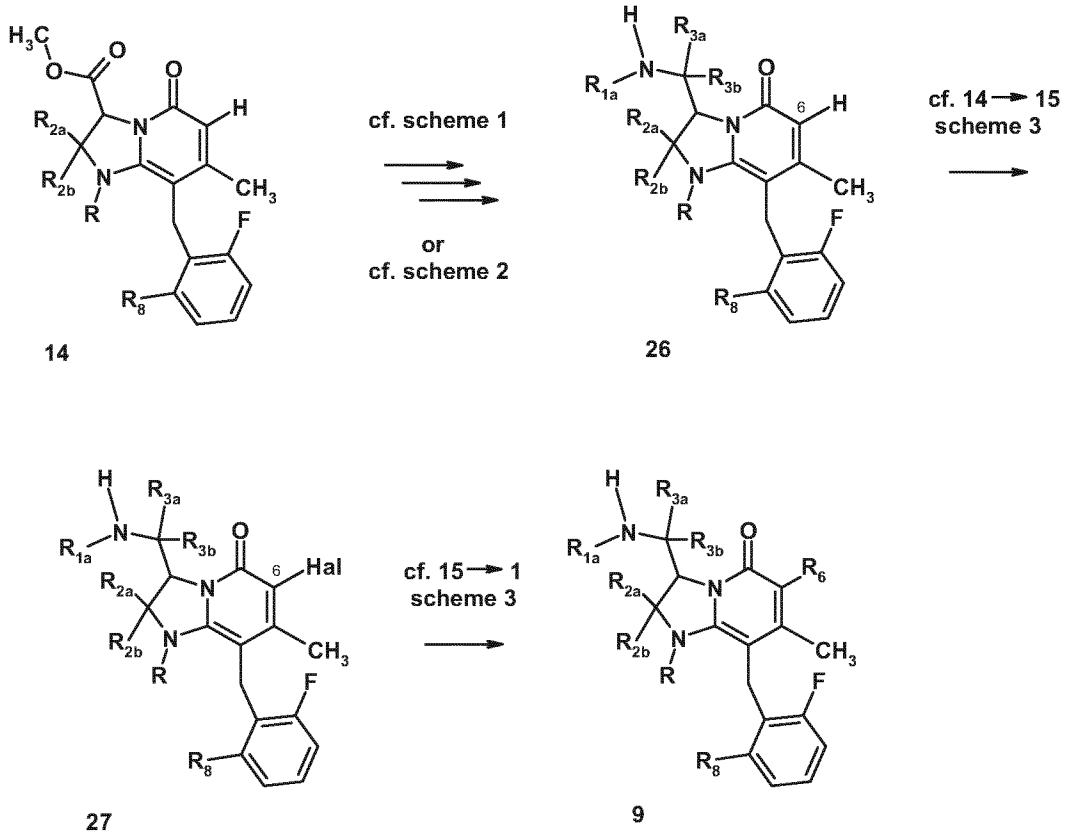
An esters of general formula **1** can be synthesized according to the alternate procedure depicted in Scheme 6, in analogy to *Almqvist et al.* (*Tetrahedron* **2008**, *64*, 9368 – 9376). Synthetic steps for the introduction of the halogen (**14** → **15**) and the R_6 moiety (**15** → **1**) are the same outlined in scheme 3. The 6-H-pyridinone **14** can be synthesized via two methods in analogy to *Almqvist et al.* (*Tetrahedron* **2008**, *64*, 9368 – 9376), or else by dehydrative cyclisation in toluene and trifluoro acetic acid from a suitable functionalized amide **25**. For amide formation, however, all processes that are known from peptide chemistry to the

person skilled in the art are available. The appropriate propionic acid of general formula **23**, which can be obtained from the corresponding ester of general formula **22** by saponification, can be reacted with 2,3-diaminopropanoic acid and derivatives thereof in an aprotic polar solvent, such as, for example, DMF, via an activated acid derivative, which is obtainable, for example, with hydroxybenzotriazole and a carbodiimide, such as, for example, diisopropylcarbodiimide, at temperatures between 0°C and the boiling point of the solvent, preferably at room temperature, or else with preformed reagents, such as, for example, O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (see for example *Chem. Comm.* **1994**, 201 - 203), at temperatures between 0°C and the boiling point of the solvent, preferably at room temperature, or else with activating agents such as dicyclohexylcarbodiimide / *N,N*-dimethylaminopyridine or *N*-ethyl-*N',N'*-dimethylaminopropyl-carbodiimide / *N,N*-dimethylaminopyridine. The addition of a suitable base such as, for example, *N*-methylmorpholine, TEA, DIPEA may be necessary.

Amide formation may also be accomplished via the acid halide **24** (which can be formed from a carboxylic acid by reaction with e.g. oxalyl chloride, thionyl chloride or sulfuryl chloride), mixed acid anhydride (which can be formed from a carboxylic acid **23** by reaction with e.g. isobutylchloroformate), imidazolide (which can be formed from a carboxylic acid by reaction with e.g. carbonyldiimidazole) or azide (which can be formed from a carboxylic acid by reaction with e.g. diphenylphosphorylazid. A suitable precursor of ester **22** is the suitable functionalized cinnamic acid ester **21** which can be reduced by, however, all processes that are known for reduction of cinnamic acids to the person skilled in the art. Such as, for example, reduction by magnesium in methanol or catalytic hydrogenation by employing palladium and hydrogen (see *Hamilton et al. Journal of Medicinal Chemistry*. **2002**, *45,* 3549 – 3557). Cinnamic acid ester of general formula **21** can by synthesized from a suitably functionalized benzaldehyde **18** by Wittig-Horner-reaction according to the literature employing *N,N,N',N'*-tetramethylguanidine (see *Barrett et al. Organic Letters* **1999**, *4*, 579 – 582), sodium hydride (see WO2007/93963) or butyl lithium (see *Etemad-Moghadam et al. Tetrahedron* **1984**, *40*, 5153 – 5166) as base and a suitable methyl phosphonoacetate, e.g. methyl diethylphosphonoacetate (CAS 1067-74-9).

As above-mentioned the order of transformations as exemplified in Schemes 1 to 3 can be modified in various ways. The order of transformations exemplified in Schemes 1 to 3 is therefore not intended to be limiting.

Scheme 7



Scheme 7 General procedures for the preparation of a compound of the general formula **9** starting from an ester of general formula **14**, R, R_{1a}, R_{2a}, R_{2b}, R_{3a}, R_{3b}, R_6, and R_8 are as defined in the description and claims of this invention.

A compound of general formula **9** can be synthesized by introducing benzo[1,3]dioxolyl- or (hetero)aryl moieties (R_6 at C-6) in late stage of the synthesis starting from suitably functionalized 6-halopyridinones **27** as depicted in scheme 7 employing synthetic methods outlined for the transformation **15** → **1** in scheme 3.

As precursors of **27** act the corresponding suitably functionalized 6-H-pyridinones **26** which are halogenated in the same manner as outlined for the transformation **14** → **15** in scheme 3.

Suitably functionalized 6-H-pyridinones **26** are easily obtained from ester **14** by employing synthetic steps and methods outlined in schemes 1 and 2.

GENERAL PROCEDURES

In the subsequent paragraphs detailed general procedures for the synthesis of key intermediates and compounds of the present invention are described.

General Procedure 1 (GP 1): Wittig-Horner reaction (**18** → **21**, scheme 6)

In analogy to *Garbaccio et al., Bioorganic & Medicinal Chemistry Letters* **2007**, *17*, 6280 – 6285.

At 0°C 1,8-diazabicyclo[5,4,0]undec-7en (1 - 2 eq.) is added dropwise to a stirred solution of the respective carbaldehyde **18**, lithium chloride (1 - 2 eq.) and diethylcyanomethyl-phosphonate (1 - 2 eq.) in acetonitrile (app. 1 - 5 mL per mmol carbaldehyde) at such a rate that the temperature remained at about 0°C. The mixture is allowed to warm to room temperature under continued stirring. The mixture is concentrated and poured into ice-cooled water. After collection and washing of the crystals the crude product is used in the subsequent reaction without further purification steps.

General Procedure 2 (GP 2): Knoevenagel reaction (**18** → **19**, scheme 5)

In analogy to *Lapworth & Baker, α-Cyano-β-phenylacrylic acid. Organic Synthesis*; Wiley: New York, **1941**; *Collect. Vol. 1*, 181 – 183.

At 40°C the respective carbaldehyde **18** is added to a vigorously stirred solution of sodium cyanoacetate (50% aq. sol., 1 – 1.5 eq.) and sodium hydroxide (0.5 - 1% aq. sol., 0.1 - 0.2 eq.). After 30 - 60 minutes the heating bath is removed and the reaction is allowed to cool to room temperature. After TLC and/or LCMS indicate complete consumption of the starting material, pH is adjusted to 1 - 4 (conc. aq. hydrochloric acid), the precipitated acid **19** is filtered off, washed with cold water and dried in vacuum. The target compound is typically used in the subsequent reaction without further purification steps.

General Procedure 3 (GP 3): Decarboxylation reaction, (**19** → **20**, scheme 5)

In analogy to *Fairhurst et al., Tetrahedron Lett.* **1975**, *44*, 3843 – 3844.

Respective acid **19** and copper(II)oxide (0.01 – 0.2 eq.) are mixed and stirred vigorously while heated to 120°C [some acids may require higher reaction temperatures (up to 200°C bath temperature)]. At app. 120°C the decarboxylation starts heavily with fuming. After the carbon dioxide evolution stops and TLC and/or LCMS indicate complete consumption of the starting material the oily suspension is filtered over silica gel. The target compound **20** is

isolated by distillation and/or flash column chromatography and/or preparative HPLC purification.

General Procedure 4a (GP 4a): Reduction of cinnamon nitrile, (**20** → **10**, scheme 5) (conditions A)

In analogy to *Montgomery et al., J. Med. Chem.* **1993**, *36*, 55 – 69.
At room temperature magnesium turnings (3.0 – 50.0 eq.) are added to a stirred solution of respective cinnamon nitrile **20** in methanol (app. 2 – 10 mL per mmol cinnamon nitrile). After the reaction started (2-3 minutes) it is cooled immediately to 0°C and stirred at this temperature until TLC and/or LCMS indicate complete consumption of the starting material (usually 2 hours). The reaction is quenched by the addition of 6 N aqueous hydrochloric acid, solids are filtered off and a quantum of methanol is evaporated. The reaction mixture is partitioned between ethyl acetate and water, the aqueous layer is extracted with ethyl acetate and the combined organic layers are dried and concentrated in vacuum. The target compound **10** is isolated by distillation and/or flash column chromatography and/or preparative HPLC purification or is used in the subsequent reaction without further purification steps.

General Procedure 4b (GP 4b): Reduction of cinnamon nitrile, (**20** → **10**, scheme 5) (conditions B) and Reduction of cinnamon ester, (**21** → **22**, scheme 6)

In analogy to *Bellamy et al., Journal of the Chemical Society, Perkin Transactions 2,* **1982** 161 – 168.
At room temperature the solution of respective cinnamon nitrile **20** in ethyl acetate (app. 2 – 10 mL per mmol cinnamon nitrile) and glacial acetic acid (5.0 – 10.0 eq.) is hydrogenated using palladium on charcoal (5 – 10% palladium, app. 2 – 50 weight-%) and hydrogen at normal or elevated pressure. After TLC and/or LCMS indicate completion of the reaction, filtration of the reaction mixture over celite®, washing with toluene, co-stripping of glacial acetic acid with toluene and chromatography and/or destillation of the crude product, delivers the target propionitrile **10**.

General Procedure 5a (GP 5a): Preparation of iminoether (**10** → **11**, scheme 3) (conditions A)

In analogy to *Almqvist et al., J. Org. Chem.* **2001**, *66*, 6756 – 6761.

At 0°C dry hydrochloric acid $_{(g)}$ is passed through a solution of respective propionitrile **10** in dry ethanol (app. 0.2 – 10 mL per mmol nitrile) over 0.5 - 4 hours. The mixture is concentrated to give ethyl iminoether hydrochloride **11** as crystals or oil. The target compound is typically used in the subsequent reaction without further purification steps.

General Procedure 5b (GP 5b): Preparation of iminoether (**10** → **11**, scheme 3) (conditions B)

At 0°C dry hydrochloric acid $_{(g)}$ is passed through a solution of respective propionitril **10** in dry ethanol (app. 0.2 – 10 mL per mmol nitrile) over 0.5 - 4 hours. After LCMS indicates completion of the reaction dry N_2 is passed through the solution. The obtained ethanolic solution of iminoether hydrochloride **11** is directly used in the subsequent reaction.

General Procedure 6a (GP 6a): Preparation of 4,5-dihydro-imidazoles (**11** → **12**, scheme 3) (conditions A)

In analogy to *Almqvist et al., J. Org. Chem.* **2001**, *66*, 6756 – 6761.
At 0°C triethylamine (1.0 – 10.0 eq.) is added to a suspension of methyl 3-aminoalaninate or a derivative thereof (1.0 – 5 eq.) in dry DCM (app. 0.5 – 10 mL per mmol amino acid derivative). Then the respective iminoether **11** hydrochloride in DCM (0.5 – 10 mL per mmol iminoether) is added, and the mixture is allowed to warm up to room temperature while stirring until TLC and/or LCMS indicate complete consumption of the starting material. The reaction mixture is partitioned between DCM and water, the aqueous layer is extracted with DCM and the combined organic layers are washed, dried and concentrated in vacuum. The target compound **12** is isolated by crystallization and/or flash column chromatography and/or preparative HPLC purification.

General Procedure 6b (GP 6b): Preparation of 4,5-dihydro-imidazoles (**11** → **12**, scheme 3) (conditions B)

At 0°C an ethanolic solution (see GP 5b) of iminoether hydrochloride **11** (app. 0.2 – 10 mL per mmol iminoether) is added to a solution of methyl 3-aminoalaninate or a derivative thereof (1.0 – 5 eq.) in dry ethanol (app. 0.5 – 10 mL per mmol amino acid derivative). Triethylamine (1.0 – 12 eq.) is added until the pH of the mixture turns basic. The mixture is allowed to warm up to room temperature while stirring until TLC and/or LCMS indicate complete consumption of the starting material. The reaction mixture is concentrated in vacuum and the obtained residue partitioned between DCM and aqueous saturated sodium

bicarbonate, the aqueous layer is extracted with DCM and the combined organic layers are washed, dried and concentrated in vacuum. The target compound **12** is isolated by crystallization and/or flash column chromatography and/or preparative HPLC purification.

General Procedure 7a (GP 7a): Preparation of pyridinones (**12** → **14**, scheme 3) (conditions A)

In analogy to *Almqvist et al., Molecular Diversity* **2003**, *7*, 165 – 169.
At room temperature 1,2-dichloroethane (app. 0.05 – 2.0 mL per mmol 4,5-dihydro-imidazole), pre-saturated with hydrochloric acid $_{(g)}$, is added to the solution of the respective 4,5-dihydro-imidazoles **12** and Meldrum's acid derivative **13** (1.0 – 5.0 eq.) in 1,2-dichloroethane (app. 0.5 – 10 mL per mmol 4,5-dihydro-imidazole). The reaction mixture is heated to 140°C for 120 seconds in a Biotage Initiator microwave oven upon which TLC and/or LCMS analysis usually shows complete turnover (otherwise Meldrum's acid derivative **13** is added again and heating to 140°C is continued until TLC and/or LCMS analysis shows completion of turnover). After removal of the solvent the target compound **14** is isolated by crystallization and/or flash column chromatography and/or preparative HPLC purification. Alternatively the reaction mixture is concentrated in vacuum and the obtained residue taken up with DCM. The organic layer is washed with aqueous sodium bicarbonate and brine, dried and concentrated in vacuum. The target compound **14** is isolated by crystallization and/or flash column chromatography and/or preparative HPLC purification.

General Procedure 7b (GP 7b): Preparation of pyridinones (**12** → **14**, scheme 3) (conditions B)

At room temperature trifluoroacetic acid (1 eq.) is added to the solution of the respective 4,5-dihydro-imidazole **12** and Meldrum's acid derivative **13** (1.0 – 5.0 eq.) in toluene or 1,2-dichloroethane (app. 0.5 – 10 mL per mmol 4,5-dihydro-imidazole). The reaction mixture is refluxed for 2 hours upon which TLC and/or LCMS analysis usually shows complete turnover (otherwise Meldrum's acid derivative **13** is added again and refluxing is continued until TLC and/or LCMS analysis shows completion of turnover, the removal of 10% of the solvent may be necessary). After removal of the solvent the target compound **14** is isolated by crystallization and/or flash column chromatography and/or preparative HPLC purification. Alternatively the reaction mixture is concentrated in vacuum and the obtained residue taken up with DCM. The organic layer is washed with aqueous sodium bicarbonate and brine, dried and concentrated in vacuum. The target compound **14** is isolated by crystallization and/or flash column chromatography and/or preparative HPLC purification.

General Procedure 7c (GP 7c): Preparation of pyridinones (**12** → **14**, scheme 3) (conditions C)

At room temperature 1,2-dichloroethane (app. 0.05 – 2.0 mL per mmol 4,5-dihydro-imidazole), pre-saturated with hydrochloric acid $_{(g)}$, is added to the solution of the respective 4,5-dihydro-imidazole **12** and Meldrum's acid derivative **13** (1.0 – 5.0 eq.) in 1,2-dichloroethane (app. 0.5 – 10 mL per mmol 4,5-dihydro-imidazole). The reaction mixture is refluxed for 2 hours upon which TLC and/or LCMS analysis usually shows complete turnover (otherwise Meldrum's acid derivative **13** is added again and refluxing is continued until TLC and/or LCMS analysis shows completion of turnover). After removal of the solvent the target compound **14** is isolated by crystallization and/or flash column chromatography and/or preparative HPLC purification. Alternatively the reaction mixture is concentrated in vacuum and the obtained residue taken up with DCM. The organic layer is washed with aqueous sodium bicarbonate and brine, dried and concentrated in vacuum. The target compound **14** is isolated by crystallization and/or flash column chromatography and/or preparative HPLC purification.

General Procedure 8 (GP 8): Preparation of 6-iod-pyridinones (**14** → **15**, Hal is I, scheme 3)

In analogy to *Almqvist et al., J. Org. Chem.* **2004**, *69*, 7830 – 7835.
At room temperature N-iodosuccinimide (1.5 – 5.0 eq.) is added to a stirred solution of respective pyridinone **14** in acetic acid (app. 2 – 6 mL per mmol pyridinone) and TFA (app. 0.1 – 0.25 mL per mmol pyridinone). After TLC and/or LCMS indicate complete consumption of the starting material the reaction mixture is poured on ice-water and the precipitate is washed with aqueous saturated sodium bicarbonate. Alternatively the reaction mixture is partitioned between DCM and aqueous sodium thiosulfate, the aqueous layer is extracted with DCM and the combined organic layers are washed, dried and concentrated in vacuum. The target compound **15** (Hal is I) is isolated by crystallization and/or flash column chromatography and/or preparative HPLC purification.

General Procedure 9 (GP 9): Preparation of 6-brom-pyridinones (**14** → **15**, Hal is Br, scheme 3)

In analogy to *Almqvist et al., J. Org. Chem.* **2004**, *69*, 7830 – 7835.
At 10°C bromine (0.85 – 2.0 eq.) is added dropwise to a stirred solution of respective pyridinone **14** in acetic acid (app. 2 – 10 mL per mmol pyridinone). After the mixture is

allowed to warm to room temperature and TLC and/or LCMS indicate complete consumption of the starting material the reaction mixture is poured on ice-water and the precipitate is washed with aqueous saturated sodium bicarbonate. Alternatively the reaction mixture is partitioned between DCM and aqueous sodium thiosulfate, the aqueous layer is extracted with DCM and the combined organic layers are washed, dried and concentrated in vacuum. The target compound **15** (Hal is Br) is isolated by crystallization and/or flash column chromatography and/or preparative HPLC purification.

General Procedure 10a (GP 10a): Suzuki Coupling (**15** → **1**, scheme 3) (conditions A)

At room temperature the respective boronic acid (ester) (1.0 – 5.0 eq.) and aqueous potassium carbonate (0.8 – 5.0 eq., 1,5 M) are added to a solution of 6-halo-pyridinone **15** in dioxane (app. 2 – 50 mL per mmol pyridinone). Then Argon is bubbled through the reaction mixture for several minutes followed by the addition of dichloro(1,1'-bis(diphenylphosphin)ferrocene) palladium dichloromethane complex (0.1 – 0.5 eq.). The reaction mixture is heated to 130°C for 60 minutes in a Biotage Initiator microwave oven upon which TLC and/or LCMS analysis usually shows complete turnover (otherwise respective boronic acid and/or catalyst is added again and heating to 130°C is continued until TLC and/or LCMS analysis shows completion of turnover). After completion of the reaction the mixture is filtered through a pad of celite®, the filtrate is diluted with ethyl acetate and washed with water and brine. Drying of the organic layer, evaporation of the solvent and flash column chromatography and/or preparative HPLC yields the target compound **1**.

General Procedure 10b (GP 10b): Suzuki Coupling (**15** → **1**, scheme 3) (conditions B)

At room temperature the respective boronic acid (ester) (1.0 – 5.0 eq.) is added to a solution of 6-halo-pyridinone **15** in dioxane (app. 2 – 50 mL per mmol pyridinone). Then Argon is bubbled through the reaction mixture for several minutes followed by the addition of aqueous potassium carbonate (0.8 – 5.0 eq., 1.5 M) and dichloro(1,1'-bis(diphenylphosphin)ferrocene) palladium (0.1 – 0.5 eq.). The reaction mixture is put in a preheated oilbath (80°C) and then heated under reflux until TLC and/or LCMS indicate complete consumption of the starting material. Further additions of respective boronic acid, aqueous potassium carbonate and dichloro(1,1'-bis(diphenylphosphin)ferrocene)palladium may be necessary for complete conversion. After completion of the reaction the mixture is filtered through a pad of celite®, the filtrate is diluted with ethyl acetate and washed with water and brine. Drying of the organic layer, evaporation of the solvent and flash column chromatography and/or preparative HPLC yields the target compound **1**.

General Procedure 10c (GP 10c): Suzuki Coupling (**15** → **1**, scheme 3) (conditions C)

In analogy to Guram A. S. et al. *Org. Lett.* **2006**, *8*, 1787.

Potassium carbonate (1.0 - 5.0 eq.) is added to a suspension of respective boronic acid (1.0 - 3.0 eq.), 6-halo-pyridinone **15** in toluene (app. 2 – 50 mL per mmol pyridinone) / water (5-15 vol.-%). The mixture is stirred at 90°C for 1 hour. Then bis(di-tert-butyl(4-dimethylaminophenyl)phosphin dichloro palladium (II) (0.01 – 0.10 eq.) is added and stirring is continued until TLC and/or LCMS analysis shows completion of turnover. After completion of the reaction the mixture is filtered through a pad of celite®, the filtrate is diluted with ethyl acetate and washed with water and brine. Drying of the organic layer, evaporation of the solvent and flash column chromatography and/or preparative HPLC yields the target compound **1**.

General Procedure 11a (GP 11a): Saponification (**1** → **5**, scheme 2) (conditions A)

At room temperature aqueous lithium hydroxide (1 - 10 eq.) is added to a stirred solution of respective ester **1** in THF (app. 1 – 10 mL per mmol ester) and/or methanol and /or alcohol (app. 1 – 10 mL per mmol ester) and stirred until TLC and/or LCMS indicate complete consumption of the starting material (usually 2 hours). Then pH is adjusted to 3-4 (aqueous citric acid or 2 N aqueous hydrochloric acid). The aqueous layer is extracted with ethyl acetate and the organic layer is dried and concentrated in vacuum. Prior to the extraction evaporation of some THF and/or methanol might be necessary. The target compound **5** is isolated by flash column chromatography and/or preparative HPLC purification or is used in the subsequent reaction without further purification steps.

General Procedure 11b (GP 11b): Saponification (**1** → **5**, scheme 2) (conditions B)

At room temperature aqueous sodium hydroxide (1 - 10 eq.) is added to a stirred solution of respective ester **1** in THF (app. 1 – 10 mL per mmol ester) and/or methanol and /or alcohol (app. 1 – 10 mL per mmol ester) and stirred until TLC and/or LCMS indicate complete consumption of the starting material (usually 2 hours). Then pH is adjusted to 3-4 (aqueous citric acid or 2 N aqueous hydrochloric acid). The aqueous layer is extracted with ethyl acetate and the organic layer is dried and concentrated in vacuum. Prior to the extraction evaporation of some THF and/or methanol might be necessary. The target compound **5** is isolated by flash column chromatography and/or preparative HPLC purification or is used in the subsequent reaction without further purification steps.

General Procedure 12a (GP 12a): Amide formation (**23** → **25**, scheme 6) (conditions A)

At room temperature 1H-hydroxybenzotriazole (1.0 – 1.5 eq.) and N-ethyl-N',N'-dimethylamino-propylcarbodiimide (1.0 – 1.5 eq.) are added to a stirred solution of respective acid **23** in DMF (app. 1 – 10 mL per mmol acid). After 1 hour at room tempemperature a solution of the respective amino acid ester in DMF (app. 1 – 10 mL per mmol acid) is added and stirring is continued upon TLC and/or LCMS indicate complete consumption of the starting material. The reaction mixture is partitioned between ethyl acetate and water, the aqueous layer is extracted with ethyl acetate and the combined organic layers are dried and concentrated in vacuum. The target compound **25** is isolated by flash column chromatography and/or preparative HPLC purification or crystallization. Alternatively the product can by isolated by pouring the reaction mixture into ice-water and filtration of the target compound **25**.

General Procedure 12b (GP 12b): Amide formation (**23** → **25**, scheme 6) (conditions B)

In analogy to *Almqvist et al.* (*Tetrahedron* **2008**, *64*, 9368 – 9376),
At room temperature chloro-1,1,3,3-tetramethyluronium hexachloroantimonate (ACTU) or 2-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (0.5 – 4.0 eq) is added to a stirred solution of 1H-hydroxybenzotriazole (1.0 – 2.0 eq.), the respective propionic acid **23** (2.0 – 4.0 eq.) and 2,6-lutidin (2.0 – 6.0 eq.) in DMF (app. 1 – 50 mL per mmol amino acid). Then a solution of amino acid methyl ester or the respective amino acid or a amino acid hydrochloride/triethylamine (1:1) mixture in DMF or DCM (app. 1 – 10 mL per mmol amino acid) is added and stirring is continued upon TLC and/or LCMS indicate complete consumption of the starting material. Further addition of triethylamine may be required. The reaction mixture is partitioned between ethyl acetate and water, the aqueous layer is extracted with ethyl acetate and the combined organic layers are dried and concentrated in vacuum. The target compound **25** is isolated by flash column chromatography and/or preparative HPLC purification or crystallization. Alternatively the product can by isolated by pouring the reaction mixture into ice-water and filtration of the target compound **25**.

General Procedure 13 (GP 13): Reduction (**1** → **2**, scheme 1)

At -20°C lithium borohydride (1.0 – 4.0 eq.; 2 M solution in THF) is added to a stirred solution of respective ester **1** in THF (app. 1 – 10 mL per mmol ester). After stirring at that

temperature for 30 minutes, the reaction mixture is allowed to warm to room temperature. After TLC and/or LCMS indicate complete consumption of the starting material the reaction mixture is quenched by the addition of water. The reaction mixture is partitioned between ethyl acetate and water, the aqueous layer is extracted with ethyl acetate and the combined organic layers are dried and concentrated in vacuum. The target compound **2** is isolated by flash column chromatography and/or preparative HPLC purification or is used in the subsequent reaction without further purification steps.

General Procedure 14 (GP 14): Formation of tosylate (**2** → **3**, LG is OTs, scheme 1)

At 0°C N,N-dimethylaminopyridine (2.0 – 5.0 eq.) and p-toluenesulfonic anhydride (1.0 – 2.5 eq.) are added to a stirred solution of respective alcohol **2** in DCM (app. 1 – 20 mL per mmol alcohol). The reaction mixture is kept between 0 and 10°C upon TLC and/or LCMS indicate complete consumption of the starting material. The reaction mixture is partitioned between DCM and water, the aqueous layer is extracted with DCM and the combined organic layers are washed, dried and concentrated in vacuum. The target compound **3** (LG is OTs) is isolated by flash column chromatography and/or preparative HPLC purification or is used in the subsequent reaction without further purification steps.

General Procedure 15 (GP 15): Formation of chloride (**2** → **3**, LG is Cl, scheme 1)

At 0°C N,N-dimethylaminopyridine (0.1 – 1.0 eq.) and p-toluenesulfonic chloride (1.0 – 2.5 eq.) are added to a stirred solution of respective alcohol **2** in DCM (app. 1 – 10 mL per mmol alcohol). The reaction mixture is allowed to warm to room temperature and monitored until TLC and/or LCMS indicate complete consumption of the starting material. The reaction mixture is partitioned between DCM and water, the aqueous layer is extracted with DCM and the combined organic layers are dried and concentrated in vacuum. The target compound **3** (LG is Cl) is isolated by flash column chromatography and/or preparative HPLC purification or is used in the subsequent reaction without further purification steps.

General Procedure 16a (GP 16a): Amine formation (**3** → **4**, LG is OTs, scheme 1) (conditions A)

At room temperature the respective amine (1.0 – 10.0 eq.) is added to a stirred solution of respective tosylate **3** (LG is OTs, scheme 1) in THF (app. 1 – 50 mL per mmol tosylate) and warmed up to 50°C until TLC and/or LCMS indicate complete consumption of the starting material. The reaction mixture is partitioned between ethyl acetate and water, the aqueous

layer is extracted with ethyl acetate, and the combined organic layers are washed, dried and concentrated in vacuum. The target compound **4** is isolated by flash column chromatography and/or preparative HPLC purification or crystallization.

General Procedure 16b (GP 16b): Amine formation (**3** → **4**, LG is OTs, scheme 1) (conditions B; for parallel synthesis)

At room temperature the respective amine (1.0 – 10.0 eq.) in DMF (app. 0.5 – 25 mL per mmol tosylate) is added to a stirred solution of respective tosylate **3** (LG is OTs, scheme 1) in DMF (app. 0.5 – 25 mL per mmol tosylate) and warmed up to 50°C for 15 hours. The reaction mixture is diluted with methanol (app. 1 – 50 mL per mmol tosylate) and concentrated in vacuum. The target compound **4** is isolated by preparative HPLC purification and lyophilization.

General Procedure 17 (GP 17): Amine formation (**3** → **4**, LG is Cl, scheme 1)

At room temperature the respective amine (1.0 – 30.0 eq.) is added in portions to a stirred solution of respective chloride **3** (LG is Cl, scheme 1), sodium carbonate (1.0 – 10.0 eq.) and sodium iodide (1.0 – 10.0 eq) in DMF (app. 1.0 – 75 mL per mmol chloride) and warmed up to 80-150°C until TLC and/or LCMS indicate complete consumption of the starting material. The reaction mixture is partitioned between ethyl acetate and water, the aqueous layer is extracted with ethyl acetate, and the combined organic layers are washed, dried and concentrated in vacuum. The target compound **4** is isolated by flash column chromatography and/or preparative HPLC purification or crystallization.

General Procedure 18 (GP 18): Reductive amination [**3** → **4**, LG is O, scheme 1]

At room temperature sodium trisacetoxyborohydride (1.0 – 10.0 eq.) is added in portions to a stirred solution of respective aldehyde **3** (LG is O, scheme 1) and respective amine (1.0 – 5.0 eq.) in toluene (app. 1 – 50 mL per mmol aldehyde) and stirred at this temperature upon TLC and/or LCMS indicate complete consumption of the starting material. The reaction mixture is partitioned between ethyl acetate and water, the aqueous layer is extracted with ethyl acetate, and the combined organic layers are washed, dried and concentrated in vacuum. The target compound **4** is isolated by flash column chromatography and/or preparative HPLC purification or crystallization.

General Procedure 19 (GP 19): Thioester formation (**5** → **6**, scheme 2)

At room temperature 1H-hydroxybenzotriazole (1.0 – 1.5 eq.) and *N*-ethyl-*N'N'*-dimethylamino-propylcarbodiimide (1.0 – 1.5 eq.) are added to a stirred solution of respective acid **5** in DMF (app. 1 – 15 mL per mmol acid). After 1 hour at room temperature the solution of thiophenol in DMF (app. 1 – 35 mL per mmol acid) is added and stirring is continued upon TLC and/or LCMS indicate complete consumption of the starting material. The reaction mixture is partitioned between ethyl acetate and water, the aqueous layer is extracted with ethyl acetate and the combined organic layers are dried and concentrated in vacuum. Alternatively the reaction mixture is poured into a mixture of ice-water and aqueous saturated sodium bicarbonate. The formed precipitate is filtered off and washed excessively with toluene and water. The filtrate is separated and the aqueous layer extracted with toluene. The combined organic layers are washed, dried and concentrated in vacuum. The target compound **6** is isolated by flash column chromatography and/or preparative HPLC purification and/or crystallization or is used in the subsequent reaction without further purification steps.

General Procedure 20a (GP 20a): Liebeskind coupling (**6** → **7**, scheme 2) (conditions A)

In analogy to *Liebeskind et al., J. Am. Chem. Soc.* **2000**, *122*, 11260 – 11261.
At room temperature the respective thioester **6** in THF (app. 1 – 50 mL per mmol thioester, degassed with argon) is added to the respective boronic acid (1.0 – 1.5 eq.), 2-thiophenecarboxylic acid, copper(1+) salt (1.0 – 1.5 eq.) and tris-(dibenzylidenaceton)-dipalladium (0) (0.05 – 0.5 eq.). Then phosphorous acid triethyl ester (0.1 – 1.0 eq.) is added and the reaction mixture is heated under reflux until TLC and/or LCMS indicate complete consumption of the starting material. Further additions of respective boronic acid, 2-thiophenecarboxylic acid, copper(1+) salt, tris-(dibenzylidenaceton)-dipalladium (0) and phosphorous acid triethyl ester may be necessary for complete conversion. The reaction mixture is partitioned between ethyl acetate and aqueous sodium bicarbonate, the aqueous layer is extracted with ethyl acetate and the combined organic layers are dried and concentrated in vacuum. The target compound **7** is isolated by flash column chromatography and/or preparative HPLC purification and/or crystallization.

General Procedure 20b (GP 20b): Liebeskind coupling (**6** → **7**, scheme 2) (conditions B)

In analogy to *Liebeskind et al., Org. Lett.* **2003**, *5*, 3033 – 3035.
At room temperature and under Argon atmosphere the respective stannane (1.0 – 2 eq.) is added to a stirred solution of the respective thioester **6** in THF (app. 1 – 25 mL per mmol

thioester). Then copper(I)diphenylphosphinate (1 – 2.5 eq.), tri-(2-furyl)phosphin (0.04 – 0.8 eq.) and finally tris-(dibenzylidenaceton)-dipalladium (0) (0.005 – 0.1 eq.) are added and the reaction mixture is heated to 50°C until TLC and/or LCMS indicate complete consumption of the starting material. Further additions of respective stannane, copper(I)diphenylphosphinate, tri-(2-furyl)phosphin and tris-(dibenzylidenaceton)-dipalladium (0) may be necessary for complete conversion. The reaction mixture is filtered through a pad of celite® and the filtrate concentrated in vacuum. The target compound **7** is isolated by flash column chromatography and/or preparative HPLC purification and/or crystallization.

General Procedure 21a (GP 21a): Oxime formation (**7** → **8**, R_{1c} is hydroxy or hydroxymethyl; scheme 2) (conditions A)

At room temperature the respective hydroxylamine hydrochloride salt (1.0 – 10.0 eq.) is added to a stirred solution of the respective ketone **7** in tert-butyl alcohol (app. 1 – 25 mL per mmol ketone) and ethanol (app. 1 – 25 mL per mmol ketone). Then titanium(IV) tert-butylat (2.0 – 8.0 eq.) is added and the reaction mixture is heated to 80°C until TLC and/or LCMS indicate complete consumption of the starting material. The reaction mixture is partitioned between ethyl acetate and water, the aqueous layer is extracted with ethyl acetate and the combined organic layers are dried and concentrated in vacuum. The target compound **8** is isolated by flash column chromatography and/or preparative HPLC purification and/or crystallization or is used in the subsequent reaction without further purification steps.

General Procedure 21b (GP 21b): Oxime formation (**7** → **8**, R_{1c} is hydroxy or hydroxymethyl; scheme 2) (conditions B)

At room temperature the respective hydroxylamine hydrochloride salt (1.0 – 10.0 eq.) is added to a stirred solution of the respective ketone **7** in tert-butyl alcohol (app. 1 – 25 mL per mmol ketone) and toluene (app. 1 – 25 mL per mmol ketone). Then pyridine (app. 1 – 10 mL per mmol ketone) is added and the reaction mixture is heated to 100°C until TLC and/or LCMS indicate complete consumption of the starting material. The reaction mixture is partitioned between ethyl acetate and water, the aqueous layer is extracted with ethyl acetate and the combined organic layers are dried and concentrated in vacuum. The target compound **8** is isolated by flash column chromatography and/or preparative HPLC purification and/or crystallization or is used in the subsequent reaction without further purification steps.

General Procedure 22 (GP 22): Imine formation (**7** → **8**, scheme 2)

In analogy to *Capretta et al., Tetrahedron Lett.* **2002**, *43*, 7687 – 7690
At room temperature the appropriate titanium(IV) Lewis acid (1.0 – 8.0 eq.) is added to a stirred solution of the respective amine (1.0 – 10.0 eq.) and the respective ketone **7** in toluene (app. 1 – 50 mL per mmol ketone). Depending on the nature of the amine the reaction mixture is stirred at ambient temperature or is heated to elevated temperature or 100°C until TLC and/or LCMS indicate complete consumption of the starting material. The reaction mixture is partitioned between ethyl acetate and water, solids are filtered off, the aqueous layer is extracted with ethyl acetate and the combined organic layers are dried and concentrated in vacuum. The target compound **8** is isolated by flash column chromatography and/or preparative HPLC purification and/or crystallization or is used in the subsequent reaction without further purification steps. Alternatively, the reaction mixture is concentrated in vacuum and the obtained crude target compound **8** is used in the subsequent reaction without further purification steps.

General Procedure 23a (GP 23a): Reduction of oxime (**8** → **9**, R_{1c} is hydroxy or hydroxymethyl; scheme 2) (conditions A)

At 0°C lithium borohydride (1.0 – 8.0 eq., 2 M solution in THF) is added slowly to a stirred solution of titanium(IV)chloride (1.0 – 4.0 eq.) in 1,2-dimethoxyethane (app. 1 – 50 mL per mmol oxime). After 10 minutes the respective oxime **8** in 1,2-dimethoxyethane (app. 1 – 20 mL per mmol oxime) is added and stirring is continued at 0°C for one hour. Then the reaction mixture is allowed to warm up to room temperature and stirred until TLC and/or LCMS indicate complete consumption of the starting material. After cooling to 0°C the reaction is quenched by the addition of water and aqueous ammonia (33 weight-%) or an excess solid caesium carbonate. The mixture is partitioned between DCM and water, solids are filtered off, the aqueous layer is extracted with DCM and the combined organic layers are dried and concentrated in vacuum. The target compound **9** is isolated by flash column chromatography and/or preparative HPLC purification and/or crystallization.

General Procedure 23b (GP 23b): Reduction of oxime (**8** → **9**, R_{1c} is hydroxy or hydroxymethyl; scheme 2) (conditions B)

In analogy to *Ohhara et al., Acta Cryst.* **2000**, *B56*, 245 – 253.
At 0°C sodium borodeuteride (1.0 – 25.0 eq.) is added slowly to a stirred solution of titanium(IV)chloride (1.0 – 15.0 eq.) in 1,2-dimethoxyethane (app. 1 – 50 mL per mmol oxime). After 10 minutes the respective oxime **9** in 1,2-dimethoxyethane (app. 1 – 20 mL per

mmol oxime) is added and stirring is continued at 0°C for one hour. Then the reaction mixture is allowed to warm up to room temperature and stirred until TLC and/or LCMS indicate complete consumption of the starting material. After cooling to 0°C the reaction is quenched by the addition of water and aqueous ammonia (33 weight-%) or an excess solid caesium carbonate. The mixture is partitioned between DCM and water, solids are filtered off, the aqueous layer is extracted with DCM and the combined organic layers are dried and concentrated in vacuum. The target compound **9** is isolated by flash column chromatography and/or preparative HPLC purification and/or crystallization.

General Procedure 23c (GP 23c): Reduction of oxime (**8** → **9**, R_{1c} is hydroxy or hydroxymethyl; scheme 2) (conditions C)

In analogy to *Kano et al., Synthesis* **1980**, 695 – 697.
At 0°C sodium borohydride (1.0 – 8.0 eq.) is added slowly to a stirred solution of titanium(IV)chloride (1.0 – 4.0 eq.) in 1,2-dimethoxyethane (app. 1 – 50 mL per mmol oxime). After 10 minutes the respective oxime **8** in 1,2-dimethoxyethane (app. 1 – 20 mL per mmol oxime) is added and stirring is continued at 0°C for one hour. Then the reaction mixture is allowed to warm up to room temperature and stirred until TLC and/or LCMS indicate complete consumption of the starting material. After cooling to 0°C the reaction is quenched by the addition of water and aqueous ammonia (33 weight-%) or an excess solid caesium carbonate. The mixture is partitioned between DCM and water, solids are filtered off, the aqueous layer is extracted with DCM and the combined organic layers are dried and concentrated in vacuum. The target compound **9** is isolated by flash column chromatography and/or preparative HPLC purification and/or crystallization.

General Procedure 24a (GP 24a): Addition of C-nucleophiles to oxime (**8** → **9**, scheme 2) (conditions A)

In analogy to *Kano et al., Synthesis* **1980**, 695 – 697.
At -78°C titanium(IV)chloride (1.0 – 10.0 eq., 1 M solution in CH_2Cl_2) is added slowly to a stirred solution of the respective oxime **8** in 1,2-dimethoxyethane (app. 1 – 50 mL per mmol oxime). The respective Grignard reagent (1.0 – 10.0 eq.) is subsequently added and stirring is continued while gradually warming the reaction mixture to 60°C until TLC and/or LCMS indicate complete consumption of the starting material. Subsequent additions of Lewis acid and/or Grignard reagent may be necessary to drive the reaction to completion. The reaction is quenched by the addition of water and aqueous sodium hydroxide (2 M). The mixture is partitioned between ethyl acetate and water, the aqueous layer is extracted with ethyl

acetate and the combined organic layers are dried and concentrated in vacuum. The target compound **9** is isolated by flash column chromatography and/or preparative HPLC purification and/or crystallization.

General Procedure 24b (GP 24b): Addition of C-nucleophiles to imine (**8** → **9**, scheme 2) (conditions B);

In analogy to *Jenkins et al., J. Org. Chem.* **2009**, *74*, 1304 – 1313.
At 0°C a solution of the respective Grignard reagent (1.0 – 10.0 eq.) is added slowly to a stirred solution of the respective imine **8** in toluene (app. 1 – 25 mL per mmol imine) and stirring is continued at 0°C or room temperature until TLC and/or LCMS indicate complete consumption of the starting material. The reaction is quenched by the addition of water, the aqueous layer is extracted with ethyl acetate and the combined organic layers are dried and concentrated in vacuum. The target compound **9** is isolated by flash column chromatography and/or preparative HPLC purification and/or crystallization.

General Procedure 25a (GP 25a): N-alkylation or N-acylation of primary amines [**9** wherein R_{1a} is Hydrogen → **9** wherein R_{1a} is different from hydrogen, scheme 2]. (conditions A)

At room temperature the solution of appropriate alkylation or acylation reagent (1.0 – 10.0 eq.) is added to a stirred solution of the respective primary amine **9** and N-ethyl diisopropyl amine (1.0 – 10.0 eq.) in a acetonitrile or DMF (app. 1 – 25 mL per mmol primary amine). The reaction mixture is stirred at ambient or elevated temperature as required until TLC and/or LCMS indicate complete consumption of the starting material. Subsequent additions of alkylation or acylation reagent and/or base may be necessary to drive the reaction to completion. The reaction mixture is partitioned between ethyl acetate and water, the aqueous layer is extracted with ethyl acetate and the combined organic layers are dried and concentrated in vacuum. The alkylated/acylated compound **9** is isolated by flash column chromatography and/or preparative HPLC purification and/or crystallization or is used in the subsequent reaction without further purification steps. Alternatively, the reaction mixture is concentrated in vacuum and the obtained crude alkylated/acylated compound **9** is used in the subsequent reaction without further purification steps or directly subjected to flash column chromatography and/or preparative HPLC purification.

General Procedure 25b (GP 25b): N-alkylation of primary amines via reductive amination [**9** wherein R_{1a} comprises hydrogen → **9** wherein R_{1a} is different from hydrogen, scheme 2]. (conditions B)

At room temperature sodium trisacetoxyborohydride (1.0 – 10.0 eq.) is added in portions to a stirred solution of respective aldehyde (1.0 – 5.0 eq.) and respective primary amine **9** in an appropriate solvent, such as, for example toluene, THF or methanol (app. 1 – 50 mL per mmol amine) and stirred at this temperature until TLC and/or LCMS indicate complete consumption of the starting material. The reaction mixture is partitioned between ethyl acetate and water, the aqueous layer is extracted with ethyl acetate, and the combined organic layers are washed, dried and concentrated in vacuum. The alkylated compound **9** is isolated by flash column chromatography and/or preparative HPLC purification or crystallization.

General Procedure 25c (GP 25c): N-alkylation of primary amines via reductive amination [**9** wherein R_{1a} comprises hydrogen → **9** wherein R_{1a} is different from hydrogen, scheme 2]. (conditions C)

At -78 to 0°C, preferrable at -20°C, lithium boron hydride (1.0 – 10.0 eq., 2M in THF) is added to a stirred solution of the imine in THF (app. 1 – 50 mL per mmol amine), obtained from the condensation of the respective aldehyde (1.0 – 5.0 eq.) and respective primary amine **9** in an appropriate solvent, such as, for example toluene (app. 1 – 50 mL per mmol amine) under Dean-Starck conditions, and stirred at this temperature until TLC and/or LCMS indicate complete consumption of the starting material. The reaction mixture is partitioned between ethyl acetate and water, the aqueous layer is extracted with ethyl acetate, and the combined organic layers are washed, dried and concentrated in vacuum. The alkylated compound **9** is isolated by flash column chromatography and/or preparative HPLC purification or crystallization.

General Procedure 25d (GP 25d): N-acylation of primary amines [**9** wherein R_{1a} is hydrogen → **9** wherein R_{1a} is different from hydrogen, scheme 2]. (conditions D, for parallel synthesis)

The amine **9** (0.1 - 0.3 mmol in 0.2 - 0.6 mL DCM, THF or DMF) is cooled to 0°C under inert gas, and triethylamine (0.1 - 0.6 mmol in 0.1 - 0.4 mL DCM, THF or DMF) and the acylating agent (carbonyl chloride, sulfonyl chloride, isocyanate or isothiocyanate; 0.1 - 0.6 mmol in 0.2 - 0.6 mL DCM, THF or DMF) are successively added. After additional 10 minutes at 0°C the mixture is warmed to 20 - 80°C, stirred at this temperature for 2 to 24 h, and concentrated. The target compound **9** is isolated by preparative HPLC purification and lyophilization.

General Procedure 26 (GP 26): Amide formation (**24** → **25**, scheme 6)

Under nitrogen at -0°C the appropriate 2-amino acid ester (10 mmol) is added to a stirred solution of the appropriate acid chloride (1.0 – 1.6 eq.) and *N*-ethyldiisopropylamine (1.0 - 1.6 eq.; in case of using the amino acid ester hydrochloride the amount of base has to be adjusted accordingly) in acetonitrile or DCM (150 mL). After stirring until TLC and/or LCMS indicate complete consumption of the starting material the mixture is quenched with saturated ammoniumchloride solution (150 mL). The mixture is partitioned between ethyl acetate and water, the aqueous layer is extracted with ethyl acetate and the combined organic layers are dried and concentrated in vacuum to yield the desired amide.

General Procedure 27a (GP 27a): Cleavage of N-Boc protection group (conditions A)

At 0°C trifluoro acetic acid (TFA) (1.0 – 20 eq.) is added to a stirred solution of the carbamate in DCM (app. 1 – 50 mL per mmol carbamate). After stirring until TLC and/or LCMS indicate complete consumption of the starting material the mixture is quenched with saturated sodium bicarbonate solution. The mixture is partitioned between DCM and water, the aqueous layer is extracted with DCM and the combined organic layers are dried and concentrated in vacuum to yield the deprotected amine, which can by purified by flash column chromatography and/or preparative HPLC purification or crystallization.

General Procedure 27b (GP 27b): Cleavage of N-Boc protection group (conditions B)

At 0°C hydrochloric acid (1.0 – 20 eq., 4N in dioxane) is added to a stirred solution of the carbamate in dioxane (app. 1 – 50 mL per mmol carbamate). After stirring until TLC and/or LCMS indicate complete consumption of the starting material the mixture is quenched with saturated sodium bicarbonate solution. The mixture is partitioned between DCM and water, the aqueous layer is extracted with DCM and the combined organic layers are dried and concentrated in vacuum to yield the deprotected amine, which can by purified by flash column chromatography and/or preparative HPLC purification or crystallization.

General Procedure 28a (GP 28a): Cleavage of N-Cbz (N-Z) protection group (conditions A)

At room temp. the respective carbamate in THF or alcohole (app. 1 – 50 mL per mmol carbamate) is hydrogenated at normal pressure with palladium on charcoal (0.01 – 0.2 eq., 10% Pd) until TLC and/or LCMS indicate complete consumption of the starting material.

Filtration of the catalyst, evaporation of the solvent and by flash column chromatography and/or preparative HPLC purification or crystallization yield the target compound.

General Procedure 28b (GP 28b): Cleavage of N-Cbz (N-Z) protection group (conditions B)

At 90°C hydroxylamine hydrochloride salt (1.0 – 10.0 eq.) is added to a stirred solution of the respective carbamate in pyridine (app. 1 – 50 mL per mmol carbamate). The reaction mixture is until TLC and/or LCMS indicate complete consumption of the starting material. The mixture is concentrated and partitioned between ethyl acetate and saturated sodium bicarbonate, the aqueous layer is extracted with ethyl acetate and the combined organic layers are dried and concentrated in vacuum to yield the deprotected amine, which can by purified by flash column chromatography and/or preparative HPLC purification or crystallization.

General Procedure 29a (GP 29a): Pyridone formation (**25** → **14**, scheme 6)

In analogy to *Ishihara et al.* (*Tetrahedron* **2009**, *65*, 2102 – 2109) and *Almqvist et al.* (*Tetrahedron* **2008**, *64*, 9368 – 9376),
At room temperature ammonium molybdate [$(NH_4)_2MoO_4$] (0.005 – 0.50 eq.) is added to a stirred solution of amide **25** in toluene (10 – 100 mL per mmol amide). The solution is heated to reflux with removal of water using a Soxhlet apparatus containing activated 3 Å molecular sieves. After TLC and/or LCMS indicate complete consumption of the starting material the reaction mixture is cooled to room temperature. Meldrum's acid derivative **13** (1.0 – 3.0 eq.) followed by TFA (1.0 – 10.0 eq.) is added. The solution is heated to reflux until TLC and/or LCMS indicate complete consumption of the starting material. Further additions of Meldrum's acid derivative **13** may be required. The solution is allowed to cool to room temperature, filtered through Celite and concentrated. The target compound **14** is isolated by flash column chromatography and/or preparative HPLC purification and/or crystallization. Alternatively the reaction mixture is partitioned between ethyl acetate and aqueous sodium bicarbonate, the aqueous layer is extracted with ethyl acetate and the combined organic layers are dried and concentrated in vacuum. The target compound **14** is isolated by flash column chromatography and/or preparative HPLC purification and/or crystallization.

General Procedure 30 (GP 30): Dihydroimidazole formation (**25** → **12**, scheme 6)

At 0°C trifluoromethanesulfonic anhydride (Tf_2O) (1.0 – 5.0 eq.) is added to a stirred solution of triphenylphosphine oxide (2.0 - 7.0 eq.) in DCM (10 – 100 mL per mmol amide). After complete addition the mixture is stirred for 10 minutes, then the solution of amide **25** in DCM

(10 – 100 mL per mmol amide) is added and stirring is continued until TLC and/or LCMS indicate complete consumption of the starting material. The reaction mixture ist partitionated between saturated sodium bicarbonate solution and DCM, the phases are separated and the organic layer is washed with saturated sodium chloride solution, dried over sodium sulphate and evaporated. The target compound **12** is isolated by flash column chromatography and/or preparative HPLC purification and/or crystallization.

General Procedure 31 (GP 31): Pyridone formation (**12** → **14**, scheme 6)

Meldrum's acid derivative **13** (1.0 – 3.0 eq.) followed by TFA or pyridinium toluenesulfonate (1.0 – 10.0 eq.) is added to a stirred solution of appropriate dihydroimidazole **12** in toluene. The solution is heated to reflux until TLC and/or LCMS indicate complete consumption of the starting material. Further additions of Meldrum's acid derivative **13** may be required. The solution is allowed to cool to room temperature, filtered through Celite and concentrated. The target compound **14** is isolated by flash column chromatography and/or preparative HPLC purification and/or crystallization. Alternatively the reaction mixture is partitioned between ethyl acetate and aqueous sodium bicarbonate, the aqueous layer is extracted with ethyl acetate and the combined organic layers are dried and concentrated in vacuum. The target compound **14** is isolated by flash column chromatography and/or preparative HPLC purification and/or crystallization.

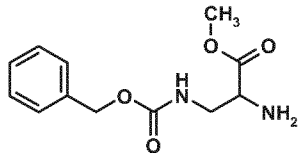
General Procedure 32 (GP 32): Synthesis of boronic acids **16** (scheme 3) (in the case of not being commercially available)

At -78°C tert-butyllithiium (1.90 – 2.50 eq.) is added to a stirred solution of the respective aryl-, heteroaryl-, benzo[1,3]dioxolyl- or 2,3-dihydro-1,4-benzodioxinyl-halide (preferentially bromide) in diethyl ether (10 – 100 mL per mmol halide). Stirring is continued for 30 minutes at -78°C. Then triisopropyl borate (2.00 – 4.00 eq.) is added and the mixture is allowed to warm to room temperature slowly. After the addition of hydrochloric acid (2N) the precipitated boronic acid **16** is filtered off. Alternatively the mixture is partitioned between ethyl acetate and water, the aqueous layer is extracted with ethyl acetate and the combined organic layers are dried and concentrated in vacuum. The boronic acid **16** is isolated by flash column chromatography and/or preparative HPLC purification and/or crystallization.

SYNTHESIS OF KEY INTERMEDIATES

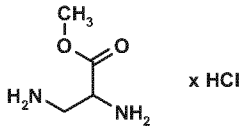
Intermediate A.1

Preparation of methyl 3-{[(benzyloxy)carbonyl]amino}alaninate



Intermediate A.1a (methode 1)

Preparation of methyl 3-aminoalaninate hydrochloride

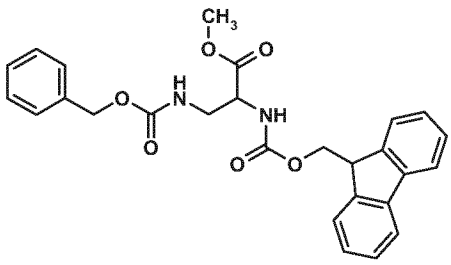


At 0°C thionyl chloride (5.7 mL, 9.3 g, 78.3 mmol, 5.5 eq.) was added drop wise to methanol (55 mL) and stirred for 10 minutes. Then commercially available 3-aminoalanine hydrochloride (2.0 g, 14.2 mmol) was added in portions and the mixture was allowed to warm to room temperature. After heating to reflux for 2 hours, the mixture was allowed to stand over night, concentrated to dryness and used in the subsequent reaction without further purification (2.7 g).

^{1}H-NMR (D_2O, 400 MHz): AB signal (δ_A = 3.51, δ_B = 3.60, 2H); 3.87 (s, 3H); 4.50 (dd, 1H).

Intermediate A.1aa (methode 2, in analogy to *Almqvist et al., Tetrahedron* **2008**, *64*, 9367 - 9376)

Preparation of methyl 3-{[(benzyloxy)carbonyl]amino}-N-[(9H-fluoren-9-ylmethoxy)carbonyl] alaninate

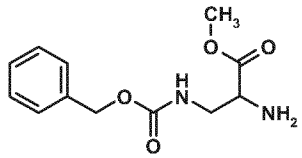


At room temp. N,N-carbonyldiimidazolide (CDI) (53 g, 325 mmol, 3.0 eq.) was added to a stirred solution of commercially available 3-{[(benzyloxy)carbonyl]amino}-N-[(9H-fluoren-9-

ylmethoxy)carbonyl]alanine (50 g, 108 mmol) in DCM (840 mL). The resulting suspension was stirred for 1.5 hours and methanol (13.2 mL, 325 mmol, 3.0 eq.) was added. After stirring for 1 hour the reaction mixture was deluted with DCM and washed with citric acid, water and saturated sodium chloride solution. Drying over sodium sulphate and evaporation of the solvent yielde the title compound which was used directly in the next step (83.3 g).
UPLC-MS (ESI+): R_T = 1.37, $[M+H]^+$ = 475.

Intermediate A.1 (methode 1, in analogy to *Egbertson et al, Synth. Commun.* **1993**, *23*, 703 - 709)

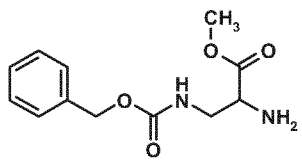
Preparation of methyl 3-{[(benzyloxy)carbonyl]amino}alaninate



At room temp. freshly powdered 3-aminoalaninate hydrochloride (intermediate A.1a) (0.5 g, 3.23 mmol) was suspended in DCM (80 mL) and then cooled to -78°C. Triethylamine (1.8 mL, 1.3 g, 12.9 mmol, 4.0 eq.) was added followed by the solution of benzyl carbonochloridate (Cbz-Cl) (0.4 mL, 0.5 g, 2.9 mmol, 0.9 eq.) in DCM (20 mL). After 10 minutes the mixture was allowed to warm to 0°C and stirring was continued for 1.5 hours. The reaction was quenched by the addition of saturated sodium bicarbonate solution (10 mL). Extraction with DCM, washing of the organic layer with saturated sodium chloride solution, drying over sodium sulphate, evaporation of the solvent and flash chromatography yielde the title compound (415 mg).
^{1}H-NMR (methanol-d4, 300 MHz): 3.38 (m, 2H); 3.55 (m, 1H); 3.67 (s, 3H); 5.06 (s, 2H); 7.22 – 7.41 (m, 5H).
UPLC-MS (ESI+): $[M+H]^+$ = 253.

Intermediate A.1 (methode 2)

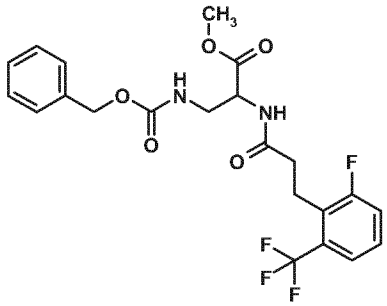
Preparation of methyl 3-{[(benzyloxy)carbonyl]amino}alaninate



At 0°C diethylamine (181 mL, 128 g, 0.79 mol, 7.3 eq.) was added to a stirred solution of crude 3-{[(benzyloxy)carbonyl]amino}-N-[(9H-fluoren-9-ylmethoxy)carbonyl] alaninate (intermediate A1.aa) (83 g, 108 mmol) in acetonitrile (360 mL). After stirring for 2 hours the reaction mixture was diluted with ethyl acetate. Washing with saturated sodium bicarbonate solution, drying over sodium sulphate, evaporation of the solvent and chromatography yielded the title compound (15 g). The material was identical with the one described above.

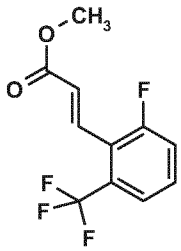
Intermediate B.1

Preparation of methyl 3-{[(benzyloxy)carbonyl]amino}-N-{3-[2-fluoro-6-(trifluoromethyl)phenyl] propanoyl}alaninate



Intermediate B.1a

Preparation of methyl (*2E*)-3-[2-fluoro-6-(trifluoromethyl)phenyl]acrylate



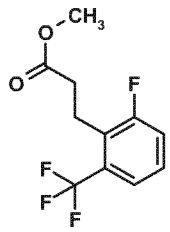
Under nitrogen at room temperature trimethylphosphonoacetate (355 g, 1.95 mol) was added to a stirred solution of 2-fluoro-6-trifluoromethyl-benzaldehyde (250 g, 1.3 mol) and lithiumhydroxide monohydrate (82 g, 1.95 mol) in tetrahydrofurane (3 L). After stirring for 24 hours the mixture was partitioned between ethyl acetate and water, the aqueous layer is extracted with ethyl acetate and the combined organic layers are dried and concentrated in vacuum to yield (*2E*)-3-[2-fluoro-6-(trifluoromethyl)phenyl]acrylate (329 g).

^{1}H-NMR ($CDCl_3$, 400 MHz): 3.82 (s , 3H); 6.57 – 6.66 (m , 1H) 7.24 – 7.58 (m, 3H); 7.72 – 7.83 (m, 1H).

UPLC-MS (ESI+): $[M + H]^+$ = 249.

Intermediate B.1b

Preparation of methyl 3-[2-fluoro-6-(trifluoromethyl)phenyl]propanoate

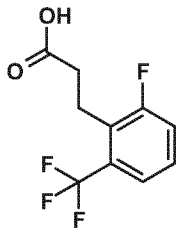


Methyl (*2E*)-3-[2-fluoro-6-(trifluoromethyl)phenyl]acrylate (intermediate B.1a) (248 g, 1 mol) was hydrogenated in ethanol (2,5 L) with a Pd/C catalyst (50 g , 10 % Pd , 50% water) until the hydrogen uptake stops (appr. 24 L hydrogen consumed). The catalyst was filtered off and filtrate was evaporated to yield methyl 3-[2-fluoro-6-(trifluoromethyl)phenyl]propanoate (240 g).

^{1}H-NMR ($CDCl_3$, 400 MHz): 2.58 (m, 2H); 3.14 (m, 2H); 3.72 (s , 3H); 7.24 (m, 1H); 7.32 (m, 1H); 7.45 (m, 1H).

Intermediate B.1c

Preparation of 3-[2-fluoro-6-(trifluoromethyl)phenyl]propanoic acid

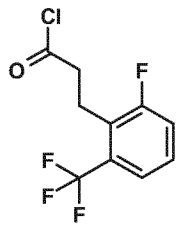


Lithiumhydroxid monohydrate (83 g, 1.98 mol) was added to a solution of methyl 3-[2-fluoro-6-(trifluoromethyl)phenyl]propanoate (intermediate B.1b) (240 g, 0.96 mol) in a mixture of water (2 L) and tetrahydrofurane (2 L) and stirred at room temperature overnight. The tetrahydrofurane was evaporated and the residue was acidified with concentrated hydrochloric acid to pH 2 while the product precipitates. The precipitate was filtered, washed with water and dried to give 3-[2-fluoro-6-(trifluoromethyl)phenyl]propanoic acid (223 g).

^{1}H-NMR ($CDCl_3$, 400 MHz): 2.65 (m, 2H); 3.15 (m, 2H); 7.26 (m, 1H); 7.34 (m, 1H); 7.46 (m, 1H).

Intermediate B.1d

Preparation of 3-[2-fluoro-6-(trifluoromethyl)phenyl]propanoyl chloride

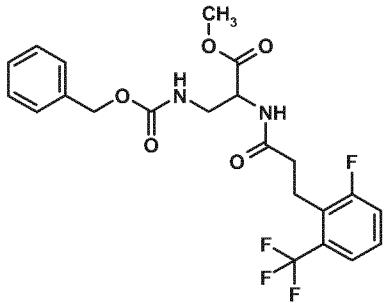


Oxalylchloride (239 g, 1.88 mol) was added to a solution of 3-[2-fluoro-6-(trifluoromethyl)phenyl]propanoic acid (intermediate B.1c) (222 g, 0.94 mol) in dichloromethane (2.2 L) at room temperature and stirred overnight. Then the mixture was evaporated to give 3-[2-fluoro-6-(trifluoromethyl)phenyl]propanoyl chloride (231 g).

^{1}H-NMR ($CDCl_3$, 400 MHz): 3.18 (m, 4H); 7.28 (m, 1H); 7.37 (m, 1H); 7.47 (m, 1H).

Intermediate B.1 (in analogy to *Almqvist et al., Tetrahedron* **2008**, *64*, 9367 - 9376)

Preparation of methyl 3-{[(benzyloxy)carbonyl]amino}-N-{3-[2-fluoro-6-(trifluoromethyl)phenyl] propanoyl}alaninate



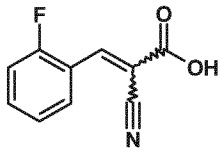
Under nitrogen at -10 to -5°C triethylamine (13.7 mL, 9.93 g, 98.1 mmol, 1.5 eq.) was added to a stirred solution of methyl 3-{[(benzyloxy)carbonyl]amino}alaninate (16.5 g, 65.4 mmol) in DCM (300 mL). The mixture was stirred at this temperature for 20 minutes. Then the solution of 3-[2-fluoro-6-(trifluoromethyl)phenyl]propanoyl chloride (intermediate B.1d) (20.0 g, 78.5 mmol) in DCM (50 mL) was added keepting the temperature between -10 and -5°C. The mixture was allowed to warm to room temp. and stirring was continued for 3.5 hours. Then saturated sodium bicarbonate solution was added. After extraction with DCM washing of the organic layer with saturated sodium chloride solution, drying over sodium sulphate and evaporation of the solvent the crude product was recrystallized from tert-butyl-methyl ether and hexane (yield: 25,04 g).

^{1}H-NMR (methanol-d4, 300 MHz): 2.46 (m, 2H); 3.06 (m, 2H); 3.40 – 3.58 (m, 2H); 3.68 (s, 3H); 4.48 – 4.57 (m, 1H); 5.05 (s, 2H); 7.17 – 7.57 (m, 8H).

UPLC-MS (ESI+): $[M + H]^+ = 471$.

Intermediate C.1

Preparation of 2-cyano-3-(2-fluoro-phenyl)-acrylic acid

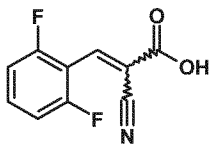


In an adaptation of GP 2: At 40°C commercially available 2-fluoro benzaldehyde (21.2 mL, 25.0 g, 201 mmol) was added to a vigorously stirred solution of sodium cyanoacetate (50% aq. sol., 18.5 mL, 48.7 g, 227 mmol, 1.13 eq.) and sodium hydroxide [1% aq. sol., 1.11 g, 28 mmol, 0.14 eq.]. After 60 minutes the heating bath was removed and the reaction was allowed to cool to room temperature. After TLC indicated complete consumption of the starting material, pH was adjusted to 3 - 4 (conc. aq. hydrochloric acid), the precipitated acid was filtered off, washed with cold water and dried in vacuum. Further adjustment of the pH to 1 yielded a second crop, which was washed with cold water and dried in vacuum. The target compound was used in the subsequent reaction without further purification steps (yield: 21.8 g).

^{1}H-NMR (d6-DMSO, 400 MHz): 7.36 – 7.44 (m, 2H); 7.63 – 7.70 (m, 1H); 8.11 – 8.17 (m, 1H); 8.33 (s, 1H).

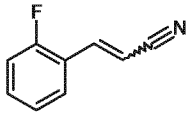
UPLC-MS (ESI+): $[M + H]^+ = 191$.

Table 1: The following intermediate C.2 was prepared in analogy to intermediate C.1 and GP 2 starting from commercially available 2,6-difluoro benzaldehyde.

No	Structure	Name	Analytical data
C.2		2-cyano-3-(2,6-difluoro-phenyl)-acrylic acid	^{1}H-NMR (d6-DMSO, 400 MHz): 7.25 – 7.33 (m, 2H); 7.59 – 7.71 (m, 1H); 8.19 (m, 1H). UPLC-MS (ESI+): $[M + H]^+ = 210$.

Intermediate D.1

Preparation of 3-(2-fluoro-phenyl)-acrylonitrile



In an adaptation of GP 3: 2-cyano-3-(2-fluoro-phenyl)-acrylic acid (intermediate C.1) (1 g, 5 mmol) and copper(II)oxide (40 mg, 0.5 mmol; 0.1 eq.) were mixed and stirred vigorously while heated with the aid of a heating gun. After the carbon dioxide evolution stopped and TLC indicated complete consumption of the starting material the oily suspension was filtered over a pad of celite®. The target compound was isolated by flash column chromatography (yield: 638 mg).

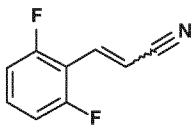
^{1}H-NMR ($CDCl_3$, 300 MHz): 5.56 (d, 1H); 7.08 – 7.19 (m, 1H); 7.20 – 7.30 (m, 1H); 7.38 – 7.50 (m, 2H); 8.16 – 8.26 (m, 1H). (*Z*-isomer)

MS (EI+): M^+ = 147.

^{1}H-NMR ($CDCl_3$, 300 MHz): 6.04 (d, 1H); 7.08 – 7.23 (m, 2H); 7.37 – 7.46 (m, 2H); 7.49 (d, 1H). (*E*-isomer)

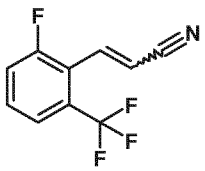
MS (EI+): M^+ = 147.

Table 2: The following intermediate D.2 was prepared in analogy to intermediate D.1 and GP 3 starting from intermediate C.2.

No	Structure	Name	Analytical data
D.2		3-(2,6-difluoro-phenyl)-acrylonitrile	^{1}H-NMR ($CDCl_3$, 400 MHz): 5.79 (d, 0.55H); 6.26 (d, 0.45H); 6.91 – 7.05 (m, 2H); 7.10 – 7.51 (m, 2H). (*E* and *Z*-isomer) UPLC-MS (ESI+): $[M + H]^+$ = 166.

Intermediate D.3

Preparation of 3-(2-fluoro-6-trifluoromethyl-phenyl)-acrylonitrile



In an adaptation of GP 1: At room temperature 1,8-diazabicyclo[5,4,0]undec-7en (79.78 g, 524 mmol, 2.0 eq.) was added dropwise to a stirred solution of commercially available 2-fluoro-6-(trifluoromethyl)benzaldehyde (50.34 g, 262 mmol), lithium chloride (21.75 g, 513 mmol, 1.95 eq.) and diethylcyanomethylphosphonate (90.51 g, 511 mmol, 1.95eq.) in acetonitrile (500 mL) at such a rate that the temperature remained at about room temperature. After TLC showed complete consumption of the starting material the mixture

was concentrated, poured into ice-cooled water (3 L) and stirred for 30 minutes. The precipitate was filtered off and washed with n-hexane. (yield: 32 g).

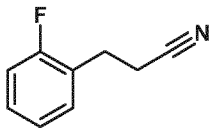
^{1}H-NMR ($CDCl_3$, 400 MHz): 5.89 (d, 1H); 7.27 – 7.30 (m, 1H); 7.36 – 7.64 (m, 3H). (Z-isomer).

^{1}H-NMR ($CDCl_3$, 400 MHz): 6.21 (d, 1H); 7.36 – 7.64 (m, 4H). (E-isomer).

UPLC-MS (ESI+): $[M + H]^+$ = 216.

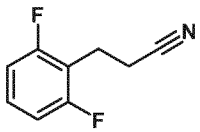
Intermediate E.1

Preparation of 3-(2-fluoro-phenyl)-propionitrile



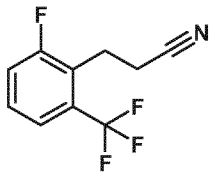
In an adaptation of GP 4a: At room temperature magnesium turnings (1.64 g, 67 mmol, 40 eq.) were added to a stirred solution of 3-(2-fluoro-phenyl)-acrylonitrile (intermediate D.1) (248 mg, 1.69 mmol) in methanol (10 mL). After the reaction had started (2-3 minutes) it was cooled immediately to 0°C and stirred at this temperature until TLC indicated complete consumption of the starting material. The reaction was quenched by the addition of 6 N aqueous hydrochloric acid. The mixture was partitioned between ethyl acetate and water, the aqueous layer was extracted with ethyl acetate and the combined organic layers were dried with sodium sulfate, filtered and concentrated in vacuum. The target compound was used in the subsequent reaction without further purification steps (yield: 169 mg).

Table 3: The following intermediate E.2 was prepared in analogy to intermediate E.1 and GP 4a starting from intermediate D.2.

No	Structure	Name	Analytical data
E.2		3-(2,6-difluoro-phenyl)-propionitrile	^{1}H-NMR ($CDCl_3$, 400 MHz): 2.64 (t, 2H); 3.07 (t, 2H); 6.86 - 6.96 (m, 2H); 7.19 – 7.30 (m, 1H). UPLC-MS (ESI+): $[M + H]^+$ = 168.

Intermediate E.3

Preparation of 3-(2-fluoro-6-trifluoromethyl-phenyl)-propionitrile



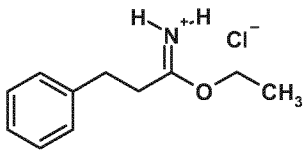
In an adaptation of GP 4b: At room temperature a solution of 3-(2-fluoro-6-trifluoromethyl-phenyl)-acrylonitrile (intermediate D.3) (27.1 g, 126 mmol) in ethyl acetate (541 mL) and glacial acetic acid (54 mL, 939 mmol, 7.5 eq.) was hydrogenated using palladium on charcoal (10% palladium, 5.4 g, 20 weight-%) and hydrogen at normal pressure for 4.5 hours. After filtration of the reaction mixture over celite®, washing with ethyl acetate, co-stripping of glacial acetic acid with toluene and flash column chromatography the target compound was obtained (yield: 20.9 g).

^{1}H NMR ($CDCl_3$, 400 MHz): 2.65 (t, 1H); 3.21 (t, 1H); 7.28 – 7.34 (m, 1H); 7.38 – 7.44 (m, 1H); 7.49 – 7.51 (m, 1H).

UPLC-MS (ESI+): $[M + H]^+$ = 218.

Intermediate F.1

Preparation of 3-phenyl-propionimidic acid ethyl ester hydrochloride

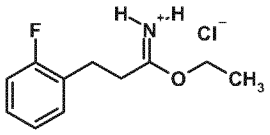
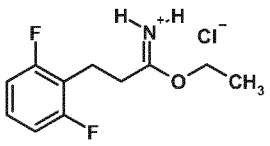
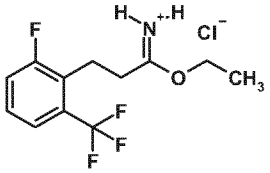


In an adaptation of GP 5a: At 0°C dry hydrochloric acid $_{(g)}$ was passed through a solution of commercially available 3-phenyl-propionitrile (25.0 g, 191 mmol) in dry ethanol (15 mL) over 2 hours. The mixture was concentrated to give target compound as crystals upon standing over night. The target compound was used in the subsequent reaction without further purification steps (yield: 43.4 g).

^{1}H-NMR (DMSO-d6, 300 MHz): 1.32 (t, 3H); 2.95 (s, 4H), 4.37 (q, 2H); 7.21 – 7.37 (m, 5H); 10.80 – 12.06 (m, 2H).

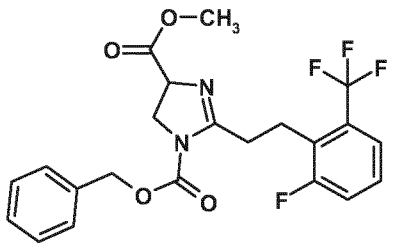
MS (EI+): M^+ = 177. (free base)

Table 4: The following intermediates F.2 to F.4 were prepared in analogy to intermediate F.1 and GP 5a or 5b starting from intermediates E.1, E.2 and E.3.

No	Structure	Name	Analytical data
F.2		3-(2-fluoro-phenyl)-propionimidic acid ethyl ester hydrochloride	The crude product was used in the subsequent reaction without further characterization.
F.3		3-(2,6-difluoro-phenyl)-propionimidic acid ethyl ester hydrochloride	The crude product was used in the subsequent reaction without further characterization.
F.4		3-(2-fluoro-6-trifluoromethyl-phenyl)- propionimidic acid ethyl ester hydrochloride	The crude product was used in the subsequent reaction without further characterization. UPLC-MS (ESI+): $[M + H]^+$ = 256. (M = free base)

Intermediate G.1

Preparation of 1-benzyl 4-methyl 2-{2-[2-fluoro-6-(trifluoromethyl)phenyl]ethyl}-4,5-dihydro-1H-imidazole-1,4-dicarboxylate

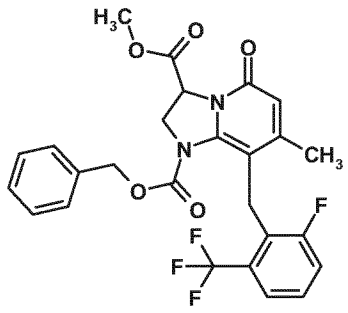


In analogy to *Almqvist et al., Tetrahedron* **2008**, *64*, 9367 - 9376): At 0°C trifluoromethanesulfonic anhydride (Tf_2O) (10.2 mL, 17.1 g, 60.6 mmol, 1.5 eq.) was added to a stirred solution of triphenylphosphine oxide (33.7 g, 121 mmol, 3.0 eq.) in DCM (800 mL). After complete addition the mixture was stirred for 10 minutes, then the solution of methyl 3-{[(benzyloxy)carbonyl]amino}-N-{3-[2-fluoro-6-(trifluoromethyl)phenyl] propanoyl} alaninate (intermediate B.1) (19.0 g, 40.4 mmol) in DCM (150 mL) was added and stirring was continued for 60 minutes. Saturated sodium bicarbonate solution was added, the phases were separated and the organic layer was washed with saturated sodium chloride solution, dried over sodium sulphate and evaporated. Filtration over silica gel yielded the title compound (10.4 g).

^{1}H-NMR (methanol-d4, 400 MHz): 2.95 – 3.08 (m, 2H); 3.09 – 3.21 (m, 2H); 3.71 (s, 3H); 3.98 – 4.08 (m, 2H); 4.56 – 4.65 (m, 1H); 5.18 (s, 2H); 7.26 – 7.52 (m, 8H).
MS (ESI+): $[M + H]^+$ = 453.

Intermediate H.1

Preparation of 1-benzyl 3-methyl 8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1,3(5H)-dicarboxylate

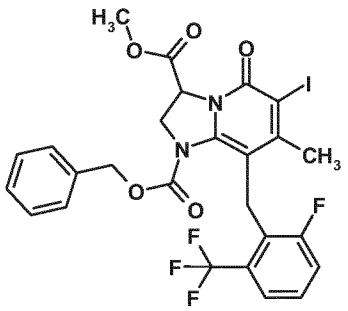


In an adaptation of GP 7b: At room temperature trifluoroacetic acid (1.85 mL, 2.74 g, 24.0 mmol, 2.0 eq.) was added to the solution of 1-benzyl 4-methyl 2-{2-[2-fluoro-6-(trifluoromethyl)phenyl]ethyl}-4,5-dihydro-1H-imidazole-1,4-dicarboxylate (intermediate G.1) (5.43 g, 12.0 mmol) and Acetyl-Meldrum's acid (6.7 g, 36 mmol, 3.0 eq.) in toluene (190 mL). The flask was placed in a pre-heated oil bath (120°C) and the mixture was refluxed for 45 minutes. At the end of the time 10% of the solvent was distilled of. Then the reaction mixture was cooled and diluted with ethyl acetate. After washing with saturated sodium bicarbonate solution and saturated sodium chloride solution, the organic layer was dried over sodium sulphate and evaporated. The target compound was isolated by flash column chromatography (yield: 3.21 g)

^{1}H-NMR (methanol-d4, 300 MHz): 1.94 (s, 3H); 3.64 (s, 3H); 4.04 (s, 2H); 4.18 (dd, 1H); 4.47 (dd, 1H); 5.04 (dd, 1H); AB-Signal (δ_A = 5.13, δ_B = 5.23, 2 x 1H); 6.18 (s, 1H); 7.22 – 7.56 (m, 8H).
MS (ESI+): $[M+H]^+$ = 519.

Intermediate I.1

Preparation of 1-benzyl 3-methyl 8-[2-fluoro-6-(trifluoromethyl)benzyl]-6-iodo-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1,3(5H)-dicarboxylate



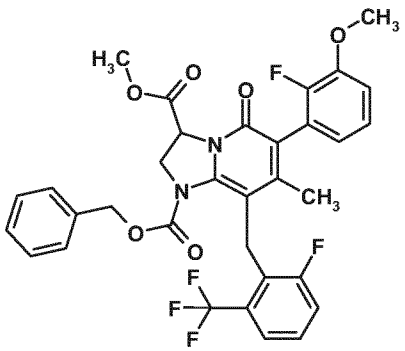
In an adaptation of GP 8: At 10°C N-iodosuccinimide (NIS) (5.31 g, 23.6 mmol, 2.4 eq.) was added to a stirred solution of 1-benzyl 3-methyl 8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1,3(5H)-dicarboxylate (intermediate H.1) (5.10 g, 9.84 mmol) in acetic acid (37.8 mL) and TFA (1.82 mL, 2.69 g, 23.6 mmol, 2.4 eq.). The reaction was allowed to warm to room temp. over 2 hours. The reaction mixture was partitioned between saturated aqueous sodium sulfite and ethyl acetate. After phase separation the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with sodium bicarbonate, dried and concentrated in vacuum. The target compound was isolated by crystallization from ethyl acetate / hexane (yield: 5.16 g).

^{1}H-NMR ($CDCl_3$, 400 MHz): 2.17 (s, 3H); 3.66 (s, 3H); 4.01 – 4.16 (m, 2H); 4.52 (dd, 1H); 5.01 (dd, 1H); AB-Signal (δ_A = 5.14, δ_B = 5.24, 2 x 1H); 7.12 – 7.20 (m, 1H); 7.29 – 7.41 (m, 6H); 7.44 – 7.49 (m, 1H).

MS (ESI+): $[M+H]^+$ = 654.

Intermediate K.1

Preparation of 1-benzyl 3-methyl 6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl) benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1,3(5H)-dicarboxylate



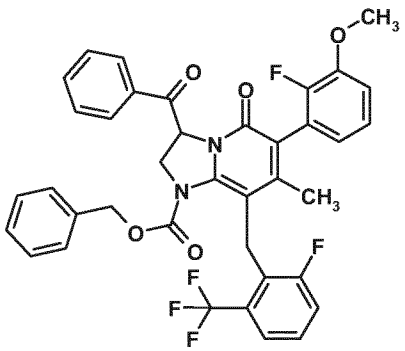
In analogy to Guram A. S. et al. *Org. Lett.* **2006**, *8*, 1787: Potassium carbonate (3.3 g, 23 mmol, 3.0 eq.) was added to a suspension of commercial available 2-fluoro-3-methoxyphenyl boronic acid (2.69 g. 15.8 mmol, 2.0 eq.), 1-benzyl 3-methyl 8-[2-fluoro-6-(trifluoromethyl) benzyl]-6-iodo-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1,3(5H)-dicarboxylate (intermediate I.1) (5.1 g, 7.9 mmol) in toluene (150 mL) / water (7.5 mL). The mixture was stirred at 90°C for 1 hour. Then bis(di-tert-butyl(4-dimethylaminophenyl)phosphin dichloro palladium (II) (112 mg, 0.16 mmol, 0.02 eq.) was added and stirring was continued for 4 hours. Then the mixture was filtered over celite® and partitioned between water and ethyl acetate. The organic layer was washed with sodium bicarbonate, dried with sodium sulphate and concentrated in vacuum. The target compound was isolated by flash chromatography (yield: 4.67 g).

^{1}H-NMR (methanol-d4, 400 MHz): 1.73 (d, 3H); 3.64 (d, 3H); 3.83 (d, 3H); 4.05 – 4.16 (m, 2H); 4.19 – 4.27 (m, 1H); 4.44 – 4.53 (m, 1H); 5.03 – 5.10 (m, 1H); 5.12 – 5.17 (m, 1H); 5.21 – 5.26 (m, 1H); 6.54 – 6.61 (m, 0.4H*); 6.67 – 6.73 (m 0.6H*); 7.01 – 7.22 (m, 2H); 7.24 – 7.37 (m, 6H); 7.38 – 7.45 (m, 1H); 7.49 – 7.54 (m, 1H).

MS (ESI+): $[M + H]^+$ = 643.

Intermediate L.1

Preparation of benzyl 3-benzoyl-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl) benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5H)-carboxylate



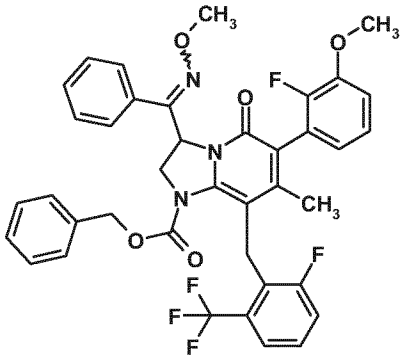
At -78°C phenylmagnesium bromide (3M in diethylether, 4.6 mL, 2.4 g, 13.7 mmol, 2.0 eq.) was added to a stirred solution of 1-benzyl 3-methyl 6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1,3(5H)-dicarboxylate (intermediate K.1) (4.4 g, 6.8 mmol) in toluene (120 mL). After complete addition the reaction mixture was stirred for 5 hours maintaining the temperature below -70°C. Then the reaction was quenched by the addition of the pre-cooled (-70°C) mixture of methanol and water (20 mL, methanol / water = 9 / 1). Then saturated aqueous ammonium chloride solution was added and the mixture was allowed to warm to room temperature. Then ethyl acetate was added and the aqueous layer was extracted 3 times with ethyl acetate. The combined organic layers were washed with brine, dried with sodium sulphate and concentrated in vacuum. The target compound was isolated by flash column chromatopgraphy (yield: 2.07 g).

^{1}H-NMR (methanol-d4, 300 MHz): 1.75 & 1.76 (2 x s, 3H); 3.82 & 3.84 (2 x s, 3H); 4.09 – 4.21 (m, 2H); 4.29 – 4.39 (m, 1H); 4.41 – 4.50 (m, 1H); 5.03 – 5.11 (m, 1H); 5.19 – 5.27 (m, 1H); 6.13 – 6.21 (m, 1H); 6.54 – 6.62 (m, 0.4H*); 6.70 – 6.78 (m, 0.6H*); 6.99 – 7.13 (m, 2H); 7.20 – 7.35 (m, 6H); 7.38 – 7.48 (m, 1H); 7.49 – 7.60 (m, 3H); 7.65 – 7.73 (m, 1H); 8.00 – 8.08 (m, 2H).

MS (ESI+): $[M + H]^+$ = 689.

Intermediate M.1

Preparation of benzyl 6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-[(methoxyimino)(phenyl)methyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5H)-carboxylate



In an adaptation of GP 21b: At room temperature O-methyl hydroxylamine hydrochloride (134 mg, 1.61 mmol, 1.2 eq.) was added to a stirred solution of benzyl 3-benzoyl-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo [1,2-a]pyridine-1(5H)-carboxylate (intermediate L.1) (922 mg, 1.34 mmol) in pyridine (9 mL). The reaction mixture was heated to 40°C for 16 hours. The an other portion O-methyl hydroxylamine hydrochloride (111 mg, 1.34 mmol, 1.0 eq.) was added and stirring was continued at 40°C for 24 hours. After two more additions of one equivalent O-methyl hydroxylamine hydrochloride and subsequent stirring periods TLC indicated complete consumption of the starting material. The pyridine was evaporated and the crude product was purified by flash chromatography (yield: 675 mg).

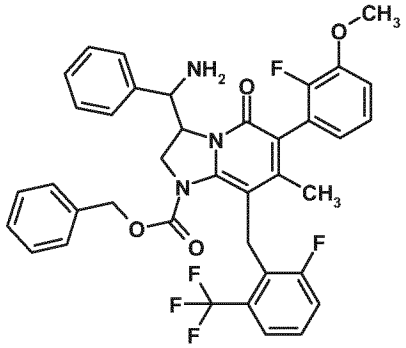
^{1}H-NMR (methanol-d4, 300 MHz), E/Z isomers as well as rotamers present: 1.63 (d, 1.8H*); 1.73 (d, 1.2H*); 3.63 (d, 1.2H*); 3.78 – 3.89 (m, 4.8H*); 3.93 – 4.03 (m, 1.2H*); 4.25 – 4.58 (m, 2H*); 4.97 – 5.34 (m, 2H*); 5.41 – 5.47 (m, 0.4H*); 5.71 – 5.83 (m, 0.6H*); 6.34 – 6.45 (m, 0.4H*); 6.49 – 6.63 (m, 0.4H*); 6.68 – 6.77 (m, 0.2H*); 6.96 – 7.15 (m, 2H); 7.19 – 7.45 (m, 12H); 7.46 – 7.56 (m, 1H).

UPLC-MS (ESI+): $[M + H]^+$ = 718.

SYNTHESIS OF EXAMPLE COMPOUNDS

Example 1.1a & b

Preparation of benzyl 3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5H)-carboxylate (diastereomer 1 & 2)



In an adaptation of GP 23a: At 0°C lithium borohydride (1.92 mL, 2 M solution in THF, 3.85 mmol, 4.0 eq.) was added slowly to a stirred solution of titanium(IV)chloride (421 µL, 3.85 mmol, 4.0 eq.) in 1,2-dimethoxyethane (40 mL). After 10 minutes benzyl 6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-[(methoxyimino)(phenyl)methyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5H)-carboxylate (intermediate M.1) (690 mg, 0.96 mmol) in 1,2-dimethoxyethane (10 mL) was added and stirring was continued at 5°C until TLC indicated complete consumption of the starting material. The reaction was quenched by the addition of caesium carbonate (7.5 g) and water (50 µL) at room temperature. After stirring for 30 minutes water (0.3 mL in portions) was added and stirring is continued for additional 90 minutes. Then the mixture was filtered and the filtrate was evaporated. The residue was partitioned between ethyl acetate and water, the aqueous layer was 3 times extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate and concentrated in vacuum. Repeated flash chromatograpy yielded the two diastereomers of the target compound (yield: 89,4 mg and 377,9 mg, respectively).

Diastereomer 1 (example 1.1a):

^{1}H-NMR (methanol-d4, 400 MHz): 1.60 – 1.73 (m, 3H); 3.61 – 3.78 (m, 1H); 3.80 – 3.92 (m, 4H); 3.92 – 4.12 (m, 1H); 4.39 – 4.47 (m, 0.5H*); 4.57 - 4.72 (m, 1.5H*); 4.99 – 5.11 (m, 0.5H*); 5.21 – 5.34 (m, 0.5H*); 6.53 – 6.61 (m, 0.5H*); 6.76 – 6.87 (m, 0.5H*); 7.02 – 7.51 (m, 15H).

UPLC-MS (ESI+): $[M + H]^+$ = 690.

Diastereomer 2 (example 1.1b):

^{1}H-NMR (methanol-d4, 400 MHz): 1.64 (d, 3H); 3.60 – 3.75 (m, 1H); 3.77 – 3.94 (m, 5H); 4.53 – 4.67 (m, 1H); 4.70 – 4.81 (m, 2H); 6.53 – 6.61 (m, 0.5H*); 6.80 – 6.88 (m, 0.5H*); 7.03 – 7.27 (m, 8H); 7.27 – 7.40 (m, 6H); 7.40 – 7.48 (m, 1H).

UPLC-MS (ESI+): $[M + H]^+$ = 690.

Chiral HPLC (Chiralpak IC 5µ 150 x 4,6 mm; ethanol + 0.1% diethyl amine; 1.0 mL/min):

enantiomer 1: R_T = 3.24 min & 3.83 min (two peaks due to dynamic atropisomerism)

enantiomer 2: R_T = 4.58 min & 6.13 min (two peaks due to dynamic atropisomerism)

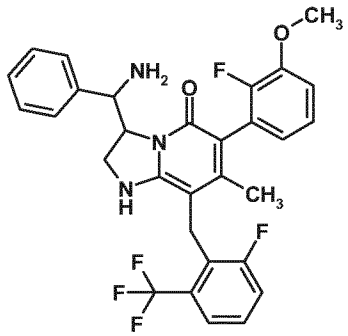
Preparative HPLC (Chiralpak IC 5µm 250 x 30 mm; ethanol + 0.1% diethyl amine; 20.0 mL/min):

Enantiomer 1: R_T = 11.1 – 12.7 min & 12.7 – 13.9 min (two peaks due to dynamic atropisomerism).

Enantiomer 2: R_T = 15.1 – 16.9 min & 20.9 – 22.9 min (two peaks due to dynamic atropisomerism).

Example 2.1a & b

Preparation of 3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one (diastereomer 1 & 2)



In an adaptation of GP 28a: At room temp. benzyl 3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5H)-carboxylate (diastereomer 1) (example 1.1a) (64.3 mg, 0.09 mmol) in THF (10 mL) was hydrogenated at normal pressure with palladium charcole (10% palladium, 9.9 mg) for 16 hours. Filtration of the catalyst and flash chromatography yielded the title compound (yield: 13 mg).

Diastereomer 1 (example 2.1a):

^{1}H-NMR (methanol-d4, 400 MHz): 1.66 (br. s, 3H); 3.53 – 3.77 (m, 2H); 3.81 – 3.97 (m, 5H); 5.03 – 5.12 (m, 1H); 6.65 – 6.71 (m, 0.5H*); 6.72 – 6.78 (m, 0.5H*); 6.98 – 7.12 (m, 2H); 7.18 – 7.57 (m, 9H).

UPLC-MS (ESI+): $[M + H]^+$ = 556.

In an adaptation of GP 28a: At room temp. benzyl 3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5H)-carboxylate (diastereomer 2) (example 1.1b) (50.0 mg, 0.09 mmol) in THF (10 mL) was hydrogenated at normal pressure with palladium charcole (10% palladium, 8.0 mg) for 16 hours. Filtration of the catalyst and flash chromatography yielded the title compound (yield: 33.3 mg).

Diastereomer 2 (example 2.1b):

^{1}H-NMR (methanol-d4, 400 MHz): 1.64 (d, 3H); 3.53 – 3.93 (m, 7H); 4.76 – 4.84 (m, 1H); 4.99 – 5.09 (m, 1H); 6.64 – 6.72 (m, 0.5H*); 6.76 – 6.84 (m, 0.5H*); 6.99 – 7.16 (m, 2H); 7.17 – 7.31 (m, 6H); 7.32 – 7.43 (m, 1H); 7.44 – 7.52 (m, 1H).

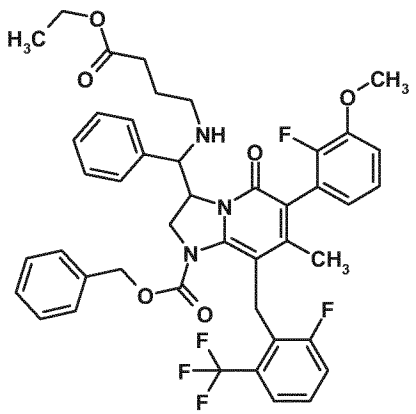
UPLC-MS (ESI+): $[M + H]^+$ = 556.

Enantiomer 1: optical rotation: $[\alpha]_D^{20}$ + 125.6° (C = 1, methanol);

Enantiomer 2: optical rotation: $[\alpha]_D^{20}$ – 163.5° (C = 1, methanol);

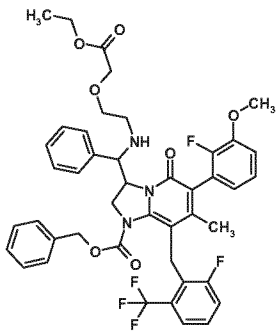
Example 3.1b

Preparation of benzyl 3-{[(4-ethoxy-4-oxobutyl)amino](phenyl)methyl}-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5H)-carboxylate (diastereomer 2)



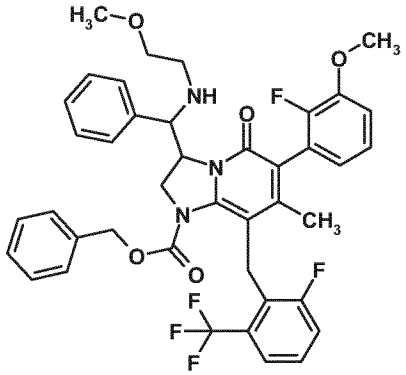
In an adaptation of GP 25a: At room temperature N-ethyl N,N-diisopropyl amine (116 µL, 90.8 mg, 700 µmol, 3.0 eq.) was added to a stirred solution of ethyl 4-bromobutanoate (34 µL, 45 mg, 230 µmol, 3.0 eq.) and 3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one (diastereomer 2) (example 1.1b) (162 mg, 230 µmol) in acetonitrile (1 mL). The reaction mixture was heated to 80°C for 17 hours. Then a second portion of N-ethyl N,N-diisopropyl amine (116 µL, 90.8 mg, 700 µmol, 3.0 eq.) and ethyl 4-bromobutanoate (34 µL, 45 mg, 230 µmol, 3.0 eq.) were added and stirring was continued for 24 hours. Two more additions with subsequent stirring periods followed (total reaction time 88 hours). Evaporation of the solvent and flash chromatography yielded the target compound (yield: 81.1 mg).
^{1}H-NMR (methanol-d4, 300 MHz): 1.19 (t, 3H); 1.62 & 1.63 (2 x s, 3H); 1.72 – 1.85 (m, 2H); 2.32 – 2.40 (m, 2H); 2.48 – 2.60 (m, 2H); 3.56 – 3.73 (m, 1H); 3.77 – 3.92 (m, 5H); 4.06 (q, 2H); 4.42 (d, 0.5H*); 4.49 (d, 0.5H*); 4.57 – 4.68 (m, 1H); 4.89 – 4.98 (m, 1H); 6.51 – 6.60 (m, 0.5H*); 6.79 – 6.86 (m, 0.5H*); 7.03 – 7.27 (m, 8H); 7.28 – 7.41 (m, 6H); 7.41 – 7.47 (m, 1H).
UPLC-MS (ESI+): $[M + H]^+$ = 804.

Table 5: The following example 3.2b was prepared in analogy to example 3.1b and GP 25a starting from example 1.1b and ethyl (2-bromoethoxy)acetate.

No	Structure	Name	Analytical data
3.2b		benzyl 3-[{[2-(2-ethoxy-2-oxoethoxy)ethyl] amino}(phenyl)methyl]-6-(2-fluoro-3-methoxy phenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a] pyridine-1(5H)-carboxylate	^{1}H-NMR (methanol-d4, 400 MHz): 1.24 (t, 3H); 1.62 & 1.64 (2 x s, 3H); 2.72 – 2.79 (m, 2H); 3.60 – 3.72 (m, 3H); 3.79 – 3.93 (m, 5H); 4.09 & 4.10 (2 x s, 2H*); 4.17 (q, 2H); 4.51 (d, 0.5H*); 4.56 (d, 0.5H*); 4.61 – 4.69 (m, 1H); 4.88 – 4.97 (m, 2H); 6.53 – 6.60 (m, 0.5H*); 6.80 – 6.87 (m, 0.5H*); 7.04 – 7.12 (m, 2H); 7.12 – 7.26 (m, 6H); 7.29 – 7.40 (m, 6H); 7.41 – 7.46 (m, 1H). UPLC-MS (ESI+): $[M + H]^+$ = 820.

Example 3.3b

Preparation of benzyl 6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-{[(2-methoxyethyl)amino](phenyl)methyl}-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5H)-carboxylate (diastereomer 2)



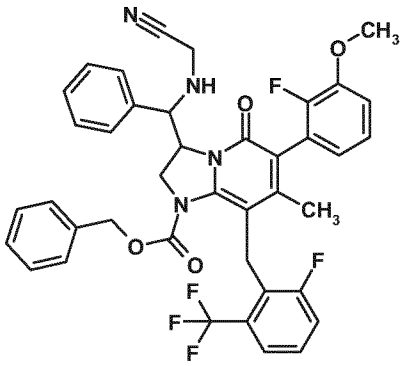
In an adaptation of GP 25a: At room temperature 1-bromo-2-methoxyethane (102 µL, 150 mg, 1.08 mmol, 10.0 eq.) was added to a stirred solution of 3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one (diastereomer 2) (example 1.1b) (74.7 mg, 0.11 mmol) in N-ethyl N,N-diisopropyl amine (Hünig´s base) (179 µL, 140 mg, 1.08 mmol, 10.0 eq.). The reaction mixture was heated to 90°C for 3 hours. Evaporation of the solvent and flash chromatography yielded the target compound (yield: 57.1 mg).

^{1}H-NMR (methanol-d4, 400 MHz): 1.62 & 1.64 (2 x s, 3H*); 2.67 – 2.75 (m, 2H); 3.31 & 3.32 (2 x s, 3H*); 3.47 (q, 2H); 3.61 – 3.72 (m, 1H); 3.78 – 3.92 (m, 5H); 4.47 (d, 0.5H*); 4.54 (d, 0.5H*); 4.58 – 4.67 (m, 1H); 4.87 – 4.95 (m, 2H); 6.54 – 6.59 (m, 0.5H*); 6.81 – 6.86 (m, 0.5H*); 7.05 – 7.26 (m, 8H); 7.28 – 7.40 (m, 6H); 7.41 – 7.46 (m, 1H).

UPLC-MS (ESI+): $[M + H]^+$ = 748.

Example 3.4b

Preparation of benzyl 3-{[(cyanomethyl)amino](phenyl)methyl}-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5H)-carboxylate (diastereomer 2)



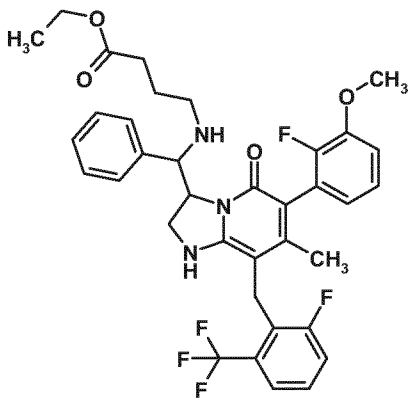
In an adaptation of GP 25a: At room temperature 2-bromo acetonitrile (10.4 mg, 87 µmol) was added to a stirred solution of 3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-2,3-dihydroimidazo [1,2-a]pyridin-5(1H)-one (diastereomer 2) (example 1.1b) (60.0 mg, 87 µmol) in N-ethyl N,N-diisopropyl amine (Hünig´s base) (43 µL, 34 mg, 0.268 mmol, 3.0 eq.) and acetinitrile (0.5 mL). The reaction mixture was heated to 90°C for 16 hours. Evaporation of the solvent and flash chromatography yielded the target compound (yield: 38.4 mg).

^{1}H-NMR (methanol-d4, 300 MHz): 1.61 & 1.63 (2 x s, 3H*); 3.37 - 3.50 (m, 1H); 3.57 – 3.74 (m, 2H); 3.76 – 3.94 (m, 5H); 4.55 – 4.73 (m, 2H); 4.92 – 4.99 (m, 1H); 6.51 – 6.59 (m, 0.5H*); 6.80 – 6.88 (m, 0.5H*); 7.05 – 7.41 (m, 14H); 7.41 – 7.47 (m, 1H).

UPLC-MS (ESI-): $[M + HCOOH]^-$ = 773.

Example 4.1b

Preparation of ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate (diastereomer 2)



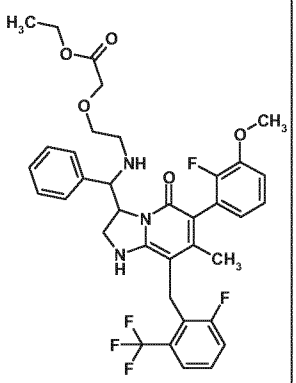
In an adaptation of GP 28a: At room temp. benzyl 3-{[(4-ethoxy-4-oxobutyl) amino](phenyl)methyl}-6-(2-fluoro-3-methoxy phenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5H)-carboxylate (diastereomer 2) (example

3.1b) (35 mg, 44 µmol) in THF (5 mL) was hydrogenated at normal pressure with palladium charcole (10% palladium, 10.0 mg) for 16 hours. Filtration of the catalyst and flash chromatography yielded the title compound (yield: 17.2 mg).

^{1}H-NMR (methanol-d4, 400 MHz): 1.18 (dt, 3H*); 1.61 & 1.62 (2 x s, 3H*); 1.72 – 1.82 (m, 2H); 2.30 – 2.37 (m, 2H); 2.48 – 2.59 (m, 2H); 3.53 – 3.90 (m, 6H); 4.05 (dq, 2H*); 4.48 (d, 0.5H*); 4.53 (d, 0.5H*); 5.05 – 5.13 (m, 1H); 6.63 – 6.69 (m, 0.5H*); 6.76 – 6.82 (m, 0.5H*); 6.99 – 7.14 (m, 2H); 7.17 - 7.28 (m, 6H); 7.32 – 7.40 (m, 1H); 7.44 – 7.49 (m, 1H).

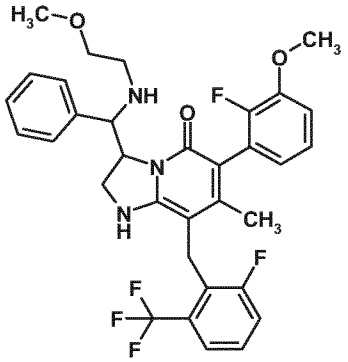
UPLC-MS (ESI+): $[M + H]^+$ = 670.

Table 6: The following example 4.2b was prepared in analogy to example 4.1b and GP 28a starting from example 3.2b.

No	Structure	Name	Analytical data
4.2b		ethyl (2-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo [1,2-a]pyridin-3-yl} (phenyl)methyl]amino} ethoxy)acetate	^{1}H-NMR (methanol-d4, 400 MHz): 1.23 & 1.24 (2 x t, 3H*); 1.61 (s, 3H); 2.69 – 2.79 (m, 2H); 3.32 (s, 2H); 3.50 – 3.72 (m, 5H); 3.83 – 3.94 (m, 4H); 4.07 & 4.08 (2 x s, 2H*); 4.17 (q, 2H); 4.57 (d, 0.5H*); 4.61 (d, 0.5H*); 5.08 – 5.16 (m, 1H); 6.63 – 6.70 (m, 0.5H*); 6.75 – 6.83 (m, 0.5H*); 6.98 – 7.15 (m, 2H); 7.15 – 7.26 (m, 6H); 7.31 – 7.42 (m, 1H); 7.43 – 7.49 (m, 1H). UPLC-MS (ESI+): $[M + H]^+$ = 686.

Example 4.3b

Preparation of 6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-{[(2-methoxyethyl)amino](phenyl)methyl}-7-methyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one (diastereomer 2)



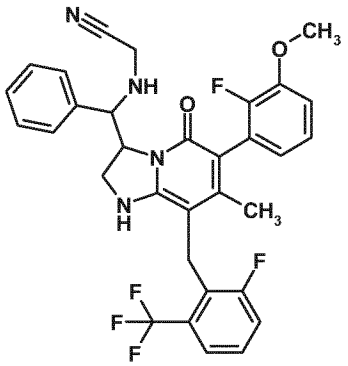
In an adaptation of GP 28a: At room temp. benzyl 6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-{[(2-methoxyethyl)amino](phenyl)methyl}-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5H)-carboxylate (diastereomer 2) (example 3.3b) (49.4 mg, 66.0 µmol) in THF (5 mL) was hydrogenated at normal pressure with palladium charcole (10% palladium, 10.0 mg) for 45 minutes. Filtration of the catalyst and flash chromatography yielded the title compound (yield: 36.7 mg).

^{1}H-NMR (methanol-d4, 300 MHz): 1.62 (br. s, 3H); 2.67 – 2.76 (m, 2H); 3.42 – 3.55 (m, 2H); 3.56 – 3.76 (m, 3H); 3.80 – 3.92 (m, 4H); 4.55 (d, 0.5H*); 4.60 (d, 0.5H*); 5.06 – 5.16 (m, 1H); 6.64 – 6.71 (m, 0.5H*); 6.76 – 6.84 (m, 0.5H*); 6.98 – 7.17 (m, 2H); 7.17 – 7.29 (m, 6H);7.31 – 7.42 (m, 1H); 7.43 – 7.50 (m, 1H).

UPLC-MS (ESI+): $[M + H]^+$ = 614.

Example 4.4b

Preparation of {[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}acetonitrile (diastereomer 2)



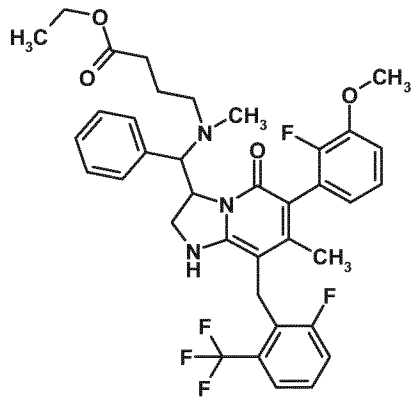
In an adaptation of GP 28a: At room temp. benzyl 3-{[(cyanomethyl)amino](phenyl)methyl}-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5H)-carboxylate (diastereomer 2) (example 3.4b) (60 mg, 82 µmol) in THF (2 mL) was hydrogenated at normal pressure with palladium charcole (10% palladium, 10.0 mg) for 50 minutes. Filtration of the catalyst and flash chromatography yielded the title compound (yield: 21.6 mg).

^{1}H-NMR (methanol-d4, 300 MHz): 1.61 & 1.62 (2 x s, 3H*); 3.32 – 3.46 (m, 1H); 3.57 – 3.81 (m, 4H); 3.84 & 3.88 (2 x s, 3H*); 4.62 (d, 0.5H*); 4.69 (d, 0.5H*); 5.04 – 5.12 (m, 1H); 6.62 – 6.69 (m, 0.5H*); 6.76 – 6.83 (m, 0.5H*); 6.98 – 7.15 (m, 2H); 7.16 – 7.42 (m, 7H); 7.44 – 7.50 (m, 1H).

UPLC-MS (ESI+): $[M + H]^+$ = 596.

Example 5.1b

Preparation of ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl](methyl)amino} butanoate (diastereomer 2)



At room temp. palladium on charcole (10% palladium, 6.0 mg) was added to a stirred solution of ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate (example 4.1b) (40.0 mg, 0.06 mmol) and formaldehyde (37% in water, 450 µL 484 mg, 5.97 mmol, 100 eq.) in methanol (1 mL). The mixture was hydrogenated at normal pressure for 16 hours. Filtration of the catalyst and flash chromatography yielded the title compound (yield: 37.4 mg).

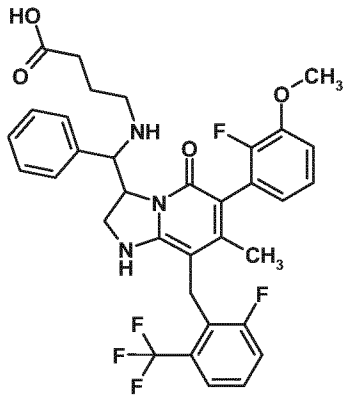
^{1}H-NMR (methanol-d4, 300 MHz): 1.15 – 1.24 (m, 3H); 1.55 (s, 3H); 1.69 – 1.93 (m, 2H); 2.22 - 3.32 (m, 5H); 3.32 – 2.40 (m, 1H); 2.40 – 2.56 (m, 1H); 3.42 – 3.54 (m, 1H); 3.54 – 3.65 (m, 1H); 3.65 – 3.80 (m, 1H); 3.85 & 3.89 (2 x s, 3H*); 4.00 – 4.20 (m, 4H); 5.32 – 5.43

(m, 1H); 6.59 – 6.67 (m, 0.5H*); 6.72 – 6.80 (m, 0.5H*); 6.97 – 7.32 (m, 8H); 7.32 – 7.43 (m, 1H); 7.43 – 7.51 (m, 1H).

UPLC-MS (ESI+): $[M + H]^+$ = 684.

Example 6.1b

Preparation of 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoic acid (diastereomer 2)



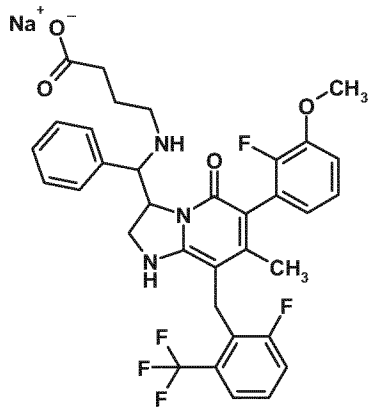
In an adaptation of GP 11b: At room temperature a solution of sodium hydroxide (27 µL of an 32% aq. sol, 37 mg, 290 µmol, 2.1 eq.) in water (0.5 mL) was added to a stirred solution of ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimi-dazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate (diastereomer 2) (example 4.1b) (92.9 mg, 140 µmol) in ethanol (2 mL) and stirred at room temp. for 2 hours and at -20°C over night. The mixture was partitioned between methyl tert-butyl ether and water. The aqueous layer was extracted 3 times with methyl isobutyl ketone and the combined organic layers were treated with hexanes to precipitate the target compound (yield: 13 mg). HPLC chromatography of the mother liquid yielded another portion of the target compound (yield: 15 mg).

^{1}H-NMR (methanol-d4, 400 MHz): 1.64 & 1.65 (2 x s, 3H*); 1.74 – 1.86 (m, 2H); 2.19 – 2.44 (m, 2H); 2.67 – 2.80 (m, 1H); 2.87 – 3.00 (m, 1H); 3.58 – 3.81 (m, 4H); 3.85 & 3.87 (2 x s, 3H*); 4.71 (d, 0.5H*); 4.76 (d, 0.5H*); 5.31 – 5.41 (m, 1H); 6.63 – 6.69 (m, 0.5H*); 6.75 – 6.80 (m, 0.5H*); 7.00 – 7.14 (m, 2H); 7.21 - 7.29 (m, 1H); 7.34 – 7.43 (m, 6H); 7.48 – 7.52 (m, 1H).

UPLC-MS (ESI+): $[M + H]^+$ = 642.

Example 7.1b

Preparation sodium 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate (diastereomer 2)

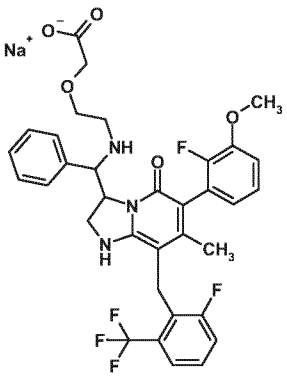


In an adaptation of GP 11b: At room temperature a solution of sodium hydroxide (6 µL of an 32% aq. sol, 8 mg, 60 µmol, 1.05 eq.) in water (0.25 mL) was added to a stirred solution of ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimi-dazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate (diastereomer 2) (example 4.1b) (40.6 mg, 60 µmol) in ethanol (1 mL) and stirred at room temp. for 48 hours and at 40°C for 8 hours. After evaporation of the ethanol the product was isolated by lyophilization from in tert butyl alcohol and water (9 : 1) (yield: 36.7 mg).

^{1}H-NMR (methanol-d4, 400 MHz): 1.59 (br. s, 3H); 1.72 – 1.86 (m, 2H); 2.11 – 2.22 (m, 2H); 2.48 – 2.67 (m, 2H); 3.46 – 3.72 (m, 3H); 3.82 – 3.99 (m, 4H); 4.54 (d, 0.5H*); 4.58 (d, 0.5H*); 5.07 – 5.15 (m, 1H); 6.62 – 6.69 (m, 0.5H*); 6.75 – 6.83 (m, 0.5H*); 6.97 – 7.15 (m, 2H); 7.15 - 7.29 (m, 6H); 7.29 – 7.41 (m, 1H); 7.42 – 7.49 (m, 1H).

UPLC-MS (ESI+): $[M + H]^+$ = 642 (free acid).

Table 7: The following example 7.2b was prepared in analogy to example 7.1b and GP 11b starting from example 4.2b.

No	Structure	Name	Analytical data
7.2b		sodium (2-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}ethoxy)acetate	^{1}H-NMR (methanol-d4, 300 MHz): 1.59 (s, 3H); 2.69 – 2.80 (m, 2H); 3.46 – 3.57 (m, 5H); 3.80 – 3.92 (m, 5H); 3.95 – 4.05 (m, 1H); 4.56 – 4.64 (m, 1H); 5.10 – 5.21 (m, 1H); 6.62 – 6.70 (m, 0.5H*); 6.75 – 6.83 (m, 0.5H*); 6.97 – 7.13 (m, 2H); 7.13 – 7.29 (m, 6H); 7.29 – 7.40 (m, 1H); 7.42 – 7.48 (m, 1H). UPLC-MS (ESI+): $[M + H]^+$ = 658 (free acid).

BIOLOGICAL ASSAYS

1. MATERIALS

Buserelin was purchased from Welding (Frankfurt/Main, Germany) or USbiological (#B8995, Swampscott, USA) for IP-One HTRF® assays and LHRH from Sigma-Aldrich® (Munich, Germany). Labelled cells, Tag-Lite buffer, labelled and unlabelled GnRHR binding peptide for Tag-lite® binding assay was purchased by Cisbio Bioassays (Bagnols-sur-Cèze Cedex, France). The radio labelling was performed in the Department of Isotope Chemistry of Bayer Schering Pharma AG (Berlin, Germany) by the iodogen method using [^{125}I]sodium iodide (2000 Ci/mmol; PerkinElmer Life and Analytical Sciences, USA) yielding [^{125}I]monoiodo-buserelin. The radio-tracer was purified by reversed phase HPLC on a Spherisorb ODS II column (250 x 4 mm, particle size 3 µm) by elution with acetonitrile / water (34 : 66) containing 39 mM trifluoracetic acid at a flow rate of 1 mL / min.
The retention time of [^{125}I]monoiodo-buserelin was approximately 17 min. All other chemicals were obtained from commercial sources at the highest purity grade available.

2. METHODS

2.1. RECEPTOR BINDING ASSAY USING RADIOLABELLED BUSERELIN

Binding studies for competition curves were run in triplicate samples in 96 well polypropylene microtiter plates (Nunc, New Jersey, USA). One assay sample contained 70µl of 300,000 cells for CHO cells stably transfected with the human GnRH receptor, 20 µl of ^{125}I-labelled buserelin (100,000 cpm per sample for competition curves) and 10 µl of assay buffer or test compound solution. Test compounds were dissolved in DMSO. Cetrorelix was dissolved in 0.1 M hydrochloric acid. Serial dilutions (5 x 10^{-6} M to 5 x 10^{-12} M) were prepared in assay buffer (DMEM or DMEM/Ham's F12 medium, 10 mM Hepes buffer pH 7.5, 0.5 % BSA). Nonspecific binding was determined in presence of excess unlabelled buserelin (10^{-5} M). Test samples were incubated for 60 min at room temperature. Bound and free ligand were separated by filtration over Unifilter GF/C filter microtiter plates (PerkinElmer, CT, USA) by applying negative pressure and washing twice with 200 mL of 0.02 M Tris/hydrochloric acid, pH 7.4. The filter plates were soaked with 0.3% polyethylenimine (Serva; Heidelberg, Germany) for 30 min prior to use in order to reduce nonspecific binding. The radioactivity retained by the filters was determined in a TopCount NXT HTS (PerkinElmer, CT, USA) using 20µl/well MicroScint40 scintillator cocktail (PerkinElmer, CT, USA). Competition curves

were obtained by plotting the measured radioactivity against the respective test compound concentration by using an in-house software.

2.2. TAG-LITE® RECEPTOR BINDING ASSAY

This binding assay is based on the fluorescence resonance energy transfer between fluorescence donor labelled human GnRHR and a green-labelled GnRHR binding peptide. Compounds interfering with the ligand binding side of the human GnRHR will replace the labelled peptide resulting in a signal decrease. The assay principle was established by Cisbio Bioassays (Bagnols-sur-Cèze Cedex, France) and further details are available on their homepage.

The assay procedure was further optimized for use in-house with reduced assay volumes. Frozen Hek293 cells, transiently transfected with human GnRHR and Terbium-labelling of the receptor, were supplied by Cisbio Bioassays as well as Tag-Lite buffer and green-labelled GnRHR binding peptide. Cells were thawed and transferred to cold Tag-Lite buffer. A volume of 8 µl of this cell suspension were added to 100 nl of a 160-fold concentrated solution of the test compound in DMSO pre-dispensed in a well of a white low-volume 384-well microtiter plate (Greiner Bio-One, Frickenhausen, Germany). The mixture was incubated for 5 min at room temperature. In the next step either 4 µl Tag-Lite buffer or as control 4 µl of an exceeding amount unlabelled binding peptide in Tag-Lite buffer were transferred to the mixture. The green-labelled GnRHR binding peptide was added in a final step at EC_{50} in a volume of 4 µl Tag-Lite buffer. After an incubation of 1 h at room temperature plates were measured in a microplate reader, e.g. a PHERAstar (BMG Labtechnologies, Offenburg, Germany) by using a specific optic module.

A ratio from the fluorescence emissions at 520 nm (green fluorescence) and at 490 nm (background signal of Terbium-labelled GnRHR) was calculated and the data were normalized (reaction without test compound = 0% inhibition of binding of green-labelled peptide; reaction without test compound with exceeding amount unlabelled binding peptide = 100% inhibition of binding of green-labelled peptide). On the same microtiter plate, compounds were tested at 10 different concentrations in the range of 12.5 µM to 0.64 nM (12.5 µM, 4.2 µM, 1.4 µM, 0.46 µM, 0.15 µM, 51 nM, 17 nM, 5.7 nM, 1.9 nM and 0.64 nM; dilution series prepared before the assay at the level of the 160-fold conc. stock solutions by serial 1:3 dilutions in 100% DMSO) in duplicate values for each concentration. By using an in-house software, the IC_{50} values were calculated by a 4 parameter fit.

2.3. IP-ONE HTRF® ASSAY

By using homogenous time-resolved fluorescence resonance energy transfer (HTRF), the generation of one component of the GnRH-R signalling cascade can be measured. After stimulation of CHO cells stably expressing human GnRH receptor (established by Prof. Thomas Gudermann, currently University of Marburg, Germany; supplied as frozen cell aliquots by Cell Culture Services, Hamburg, Germany) with the EC_{80} of the GnRH agonist buserelin, Gq protein-coupled receptor signalling cascade is activated resulting in PLC-dependent cleavage of PIP2 to Inositol-1,4,5-triphosphate (IP3) and Diacylglycerol. The second messenger IP3 is degraded intracellularly to myo-inositol. Inhibition of the final degradation step from Inositol-1-phosphate (IP1) to myo-inositol by addition of lithium chloride leads to accumulation of IP1 in the cells. In cell lysates, IP1 can be detected via an antibody-based HTRF detection technology, where IP1 can displace the FRET acceptor IP1-d2 from binding by Terbium-labelled anti-IP1 antibody as donor resulting in a signal decrease. Compounds were tested for their capability of inhibiting GnRH-R activation by buserelin. For all IP-One HTRF® assays reagents of Cisbio Bioassays (IP-One Tb Jumbo kit, #62IPAPEJ; Cisbio Bioassays, Bagnols sur Cèze Cedex, France) were used.

For the assay, frozen cell aliquots were thawed and a cell suspension ($3.33x10^6$ cells/mL) containing IP1-d2 (dilution 1:40) was prepared and incubated at 37°C. After 1 h 3 µl of the cell suspension were added to 50 nl of a 100-fold concentrated solution of the test compound in DMSO pre-dispensed in a well of a white low-volume 384-well microtiter plate (Greiner Bio-One, Frickenhausen, Germany). The mixture was incubated for 20 min at 22°C to allow for pre-binding of the test compound to the GnRH-R. The receptor signalling cascade was stimulated by addition of 2 µl buserelin or LHRH (at EC_{50} or EC_{80}) in stimulation buffer (10 mM Hepes pH 7.4, 1 mM CaCl2, 0.5 mM MgCl2, 4.2 mM KCl, 146 mM NaCl, 5.5 mM alpha-D-Glucose, 0.05% BSA, 125 mM LiCl (final assay concentration 50 mM) in aqua dest.). Plates were incubated for 1 h at 37°C and 5% CO2 before the cells were lysed by adding 3 µl Terbium-labelled anti-IP1 antibody (1:40) diluted in Conjugate & Lysis buffer as supplied with the kit. After an incubation for 1 h at 22°C to enable complete cell lysis and antibody binding to free IP1 or IP1-d2, plates were measured in an HTRF reader, e.g. a RUBYstar, PHERAstar (both BMG Labtechnologies, Offenburg, Germany) or a Viewlux (PerkinElmer LAS, Rodgau-Jügesheim, Germany).
From the fluorescence emissions at 665 nm (FRET) and at 620 nm (background signal of Terbium-antibody), the ratio (emission at 665 nm divided by emission at 620 nm) was calculated and the data were normalized (reaction without test compound = 0% inhibition; all other assay components except agonist = 100% inhibition). On the same microtiter plate,

compounds were tested at 10 different concentrations in the range of 20 µM to 1 nM (20 µM, 6.7 µM, 2.2 µM, 0.74 µM, 0.25 µM, 82 nM, 27 nM, 9.2 nM, 3.1 nM and 1 nM; dilution series prepared before the assay at the level of the 100-fold conc. stock solutions by serial 1:3 dilutions in 100% DMSO) in duplicate values for each concentration. By using an in-house software, the IC_{50} values were calculated by a 4 parameter fit.

2.4. IN VIVO ASSAY IN OVARIECTOMIZED CYNOMOLGUS MONKEYS

Studies of castrate animals provide a sensitive *in vivo* assay for the effects of GnRH antagonist (*Andrology* **1993**, *25*, 141 - 147). GnRH receptors in the pituitary gland mediate GnRH-stimulated LH release into the circulation. Castration results in elevated levels of circulating LH due to reduction of the negative feedback of gonadal steroids, leading to an enhancement of GnRH-stimulated LH release. Consequently, measurement of suppression of circulating LH levels in castrated macaques can be used as a sensitive *in vivo* measure of GnRH antagonism. Female macaques are surgically castrated and allowed to recover for four weeks at which point elevated levels of LH are established. Animals are then administered the test compound as an oral, s.c., i.p or i.v. dose, and serial blood samples are taken for measurement of LH.

Ovariectomized cynomolgus monkeys (3.5 - 6 kg b.w.) are treated i.p. and/or p.o. with a single dose of the respective compound dissolved in an appropriate vehicle, e.g. aqueous physiological sodium chloride solution. The administered doses are 10 and/or 30 and/or 100 mg/kg. Blood samples of are drawn 0; 0.5 hr; 1hr; 2hrs; 4hrs; 7hrs; 24hrs post application. Serum LH levels are monitored by RIA. The biological reagents were provided by National Hormone & Pituitary Program, HUMC, CA., U.S.A , Prof. Dr. A.F. Parlow (Parlow@humc.edu). Cynomolgus monkey LH is radioiodinated using the Chloramine-T method as described in the RIA immunoreactant manual.

RESULTS

The data reveal that the compounds of the present invention have antagonist activities on the human GnRH receptor.

Within the meaning of the present invention the antagonist activity is reflected by the ability of a compound of the invention to antagonize human GnRH receptor stimulation in IP-One HTRF® assay at least three times the standard deviation over the background level.

Table 8: Potency in receptor binding assay using TAG-LITE® technology; the potency is given as IC_{50} [µM]. Values marked with an asterisk refer to the potency of the enantiomer derived from the most active enantiomer of the parent amine (examples 1.1b and 2.1b, respectively).

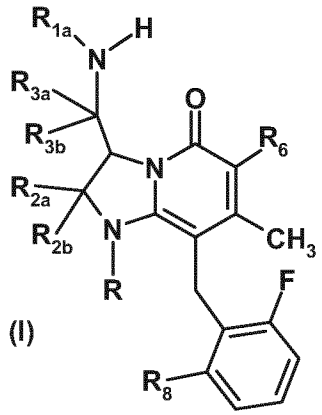
Example	Potency [µM]
2.1b	0.044*
4.4b	0.076*
7.1b	0.049

Table 9: Potency in IP-One HTRF® assay with buserelin (at EC_{80}) stimulation; the potency is given as IC_{50} [µM]. Values in *italic* and round brakets refer to the potency of single enantiomers, the values are given to enantiomer 1 and 2 subsequently (i.e. 2.1b: racemic mixture =0.008, enantiomer 1=0.008, enantiomer 2=0.636). Values marked with an asterisk refer to the potency of the enantiomer derived from the most active enantiomer of the parent amine (examples 1.1b and 2.1b, respectively).

Example	Potency [µM]	Potency [µM] enantiomer(s)
1.1a	1.67	
1.1b	2.60	*(5.5, > 20)*
2.1a	0.017	
2.1b	0.008	*(0.008, 0.636)*
3.1b		*(8.5, > 20)*
3.2b		*(3.080)**
3.3b		*(6.7, 18.8)*
3.4b		*(> 20)**
4.1b	0.186	*(0.245)**
4.3b		*(0.129, 4.2)*
4.4b		*(0.071, 5.2)*
6.1b		*(0.008)**
7.1b	0.016	*(0.010)**

CLAIMS

1. A compound of the formula **(I)**



(I)

in which

R_{1a} represent a hydrogen atom, a
C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_3-C_8-cycloalkyl-,
aryl-, heteroaryl-, -C_1-C_6-alkylene-aryl, -C_1-C_6-alkylene-heteroaryl,
-C_1-C_6-alkylene-C_3-C_{10}-cycloalkyl,
-C_1-C_6-alkylene-(3- to 10-membered heterocycloalkyl),
-C(=O)-C_1-C_6-alkyl, -C(=O)-C_1-C_6-alkylene-aryl,
-C(=O)-C_1-C_6-alkylene-heteroaryl, -$S(=O)_2R^9$ group;
wherein said groups are optionally substituted one to three times, in the same way or differently, with a substituent selected from :
halo-, hydroxy-, oxo, cyano-, C_1-C_6-alkyl-,
halo-C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-,
C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-,
aryl-, -C_1-C_6-alkylene-aryl, heteroaryl-, -C(=O)OH,
-C(=O)O-C_1-C_6-alkyl, -OC(=O)-C_1-C_6-alkyl,
$-N(H)C(=O)R^9$, $-C(=O)NR^9R^{10}$, $-N(C_1\text{-}C_6\text{-alkyl})C(=O)OR^9$,
$-N(C_1\text{-}C_6\text{-alkyl})C(=O)NR^9R^{10}$,
$-SR^9$, $-S(=O)R^9$, $-S(=O)_2OH$, $-S(=O)_2R^9$, $-NR^9R^{10}$, and wherein
R^9 and R^{10} represent, independently of one another, a hydrogen atom, a
C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-,
halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_{10}-cycloalkyl-, aryl-, heteroaryl-,
or

R^9 and R^{10} joined, and taken together with the atom to which they are attached, form a 3- to 10-membered heterocycloalkyl-, optionally substituted one or two times, in the same way or differently, with a substituent selected from the group consisting of halo-, hydroxyl-, cyano-, oxo, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, -C(=O)OH,

R_{2a} and R_{2b} are both a hydrogen atom or a methyl group;

R_{3a} is a phenyl group optionally substituted one to three times with a halogen atom, cyano, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy or halo-C_1-C_6-alkoxy;

R_{3b} is hydrogen or C_1-C_6-alkyl;

R represent a hydrogen atom, a
C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, -C(=O)R^9, -C(=O)OR^9, -C(=O)NR^9R^{10}, or -S(=O)$_2R^9$ group,
R^9 and R^{10} represent, independently of one another, a hydrogen atom, a C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_{10}-cycloalkyl-, aryl-, -C_1-C_6-alkylene-aryl, heteroaryl-,
or
R^9 and R^{10} joined, and taken together with the atom to which they are attached, form a 3- to 10-membered heterocycloalkyl-, optionally substituted one or two times, in the same way or differently, with a substituent selected from the group consisting of halo-, hydroxyl-, cyano-, oxo, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, -C(=O)OH,

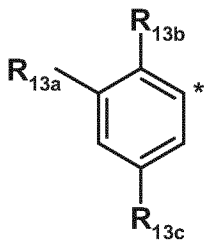
R_6 represents an aryl-, a heteroaryl-, a benzo[1,3]dioxolyl- or 2,3-dihydro-1,4-benzodioxinyl group wherein said group is optionally substituted one to three times, in the same way or differently, with a substituent R_{11} selected from : hydrogen, halogen, hydroxy, cyano, nitro, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-hydroxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkyl-C(=O)OH, -C(=O)OH, -C(=O)C_1-C_6-alkyl;

R_8 is selected from the group consisting of a hydrogen atom, a fluorine atom or a fluorinated C_1-C_6-alkyl group, in particular a $-CF_3$;

2. A compound according to claim 1, in which
R_{1a} is selected from the group consisting of a hydrogen atom, a C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, -C_1-C_6-alkenyl-, aryl-, heteroaryl-, -C_1-C_6-alkylene-aryl, -C_1-C_6-alkylene-heteroaryl, -C(=O)-C_1-C_6-alkyl, optionally substituted one to three times times, in the same way or differently, with a substituent selected from :
halo-, hydroxy-, cyano-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $-C(=O)OH$, $-C(=O)NH_2$, $-S(=O)_2OH$, $-N(H)C(=O)NH_2$, $-N(H)C(=NH)NH_2$, -C(=O)O-C_1-C_6-alkyl, $-NH_2$

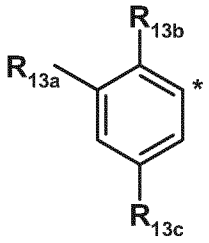
3. A compound according to claim 1 or 2 in which
R_{1a} is a $-CH_2-CH_2-CH_2-C(=O)O-CH_2-CH_3$, $-CH_2-CH_2-O-CH_2-C(=O)O-CH_3$, $-CH_2-CH_2-O-CH_2-C(=O)O-CH_2-CH_3$, $-CH_2-CH_2-CH_2-C(=O)OH$, $-CH_2-CH_2-O-CH_2-C(=O)OH$.

4. A compound according to any one of the claims 1 to 3 in which
R_{3a} is



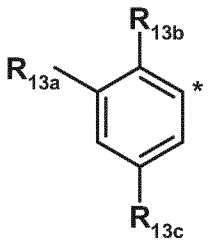
wherein R_{13a} and R_{13c} is an hydrogen or an halogen, particularly a fluorine atom, and R_{13b} is an hydrogen or an halogen, particularly a fluorine atom.

5. A compound according to any one of the claims 1 to 3 in which
R_{3a} is



wherein R_{13a}, R_{13b} and R_{13c} is an hydrogen.

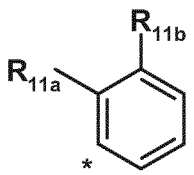
6. A compound according to any one of the claims 1 to 3 in which R_{3a} is



wherein R_{13a} and R_{13c} is an hydrogen and R_{13b} is a fluorine atom or R_{13b} is an hydrogen and R_{13a} and R_{13c} is a fluorine atom.

7. A compound according to any one of the claims 1 to 6 in which R_6 is phenyl, pyridyl or pyridazyl group wherein said group is optionally substituted one to three times, in the same way or differently, with a substituent R_{11} selected from an hydrogen or an halogen, particularly a fluorine atom, and a -O-C_1-C_6-alkyl or -O-C_1-C_6-haloalkyl group, particularly $-OCH_3$, $-OCF_2H$ or $-OCF_3$.

8. A compound according to any one of the claims 1 to 6 in which R_6 is



wherein R_{11a} is an hydrogen or an halogen, particularly a fluorine atom, and R_{11b} is a -O-C_1-C_6-alkyl or -O-C_1-C_6-haloalkylgroup, particularly $-OCH_3$, $-OCF_2H$ or $-OCF_3$.

9. {3*R*-[3*R**(*R**)]}-benzyl 3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*S*-[3*R**(*R**)]}-benzyl 3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*R*-[3*R**(*S**)]}-benzyl 3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*S*-[3*R**(*S**)]}-benzyl 3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*R*-[3*R**(*R**)]}-3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1*H*)-one

{3*S*-[3*R**(*R**)]}-3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1*H*)-one

{3*R*-[3*R**(*S**)]}-3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1*H*)-one

{3*S*-[3*R**(*S**)]}-3-[amino(phenyl)methyl]-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1*H*)-one

{3*R*-[3*R**(*R**)]}-benzyl 3-{[(4-ethoxy-4-oxobutyl)amino](phenyl)methyl}-6-(2-fluoro-3-methoxy phenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyri-dine-1(5*H*)-carboxylate

{3*S*-[3*R**(*R**)]}-benzyl 3-{[(4-ethoxy-4-oxobutyl)amino](phenyl)methyl}-6-(2-fluoro-3-methoxy phenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyri-dine-1(5*H*)-carboxylate

{3*R*-[3*R**(*S**)]}-benzyl 3-{[(4-ethoxy-4-oxobutyl)amino](phenyl)methyl}-6-(2-fluoro-3-methoxy phenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyri-dine-1(5*H*)-carboxylate

{3*S*-[3*R**(*S**)]}-benzyl 3-{[(4-ethoxy-4-oxobutyl)amino](phenyl)methyl}-6-(2-fluoro-3-methoxy phenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyri-dine-1(5*H*)-carboxylate

{3*R*-[3*R**(*R**)]}-benzyl 3-[{[2-(2-ethoxy-2-oxoethoxy)ethyl] amino}(phenyl)methyl]-6-(2-fluoro-3-methoxy phenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a] pyridine-1(5*H*)-carboxylate

{3*S*-[3*R*(R*)*]}-benzyl 3-[{[2-(2-ethoxy-2-oxoethoxy)ethyl] amino}(phenyl)methyl]-6-(2-fluoro-3-methoxy phenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a] pyridine-1(5*H*)-carboxylate

{3*R*-[3*R*(S*)*]}-benzyl 3-[{[2-(2-ethoxy-2-oxoethoxy)ethyl] amino}(phenyl)methyl]-6-(2-fluoro-3-methoxy phenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a] pyridine-1(5*H*)-carboxylate

{3*S*-[3*R*(S*)*]}-benzyl 3-[{[2-(2-ethoxy-2-oxoethoxy)ethyl] amino}(phenyl)methyl]-6-(2-fluoro-3-methoxy phenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a] pyridine-1(5*H*)-carboxylate

{3*R*-[3*R*(R*)*]}-benzyl 6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-{[(2-methoxyethyl)amino](phenyl)methyl}-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*S*-[3*R*(R*)*]}-benzyl 6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-{[(2-methoxyethyl)amino](phenyl)methyl}-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*S*-[3*R*(R*)*]}-benzyl 6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-{[(2-methoxyethyl)amino](phenyl)methyl}-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*R*-[3*R*(S*)*]}-benzyl 6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-{[(2-methoxyethyl)amino](phenyl)methyl}-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*R*-[3*R*(R*)*]}-benzyl 3-{[(cyanomethyl)amino](phenyl)methyl}-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*S*-[3*R*(R*)*]}-benzyl 3-{[(cyanomethyl)amino](phenyl)methyl}-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*R*-[3*R*(S*)*]}-benzyl 3-{[(cyanomethyl)amino](phenyl)methyl}-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*S*-[3*R*(S*)*]}-benzyl 3-{[(cyanomethyl)amino](phenyl)methyl}-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-2,3-dihydroimidazo[1,2-a]pyridine-1(5*H*)-carboxylate

{3*R*-[3*R*(R*)*]}-ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate

{3*S*-[3*R**(*R**)]}-ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate

{3*R*-[3*R**(*S**)]}-ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate

{3*S*-[3*R**(*S**)]}-ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate

{3*R*-[3*R**(*R**)]}-ethyl (2-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl} (phenyl)methyl]amino} ethoxy)acetate

{3*S*-[3*R**(*R**)]}-ethyl (2-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl} (phenyl)methyl]amino} ethoxy)acetate

{3*R*-[3*R**(*S**)]}-ethyl (2-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl} (phenyl)methyl]amino} ethoxy)acetate

{3*S*-[3*R**(*S**)]}-ethyl (2-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl} (phenyl)methyl]amino} ethoxy)acetate

{3*R*-[3*R**(*R**)]}-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-{[(2-methoxyethyl)amino](phenyl)methyl}-7-methyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one

{3*S*-[3*R**(*R**)]}-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-{[(2-methoxyethyl)amino](phenyl)methyl}-7-methyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one

{3*R*-[3*R**(*S**)]}-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-{[(2-methoxyethyl)amino](phenyl)methyl}-7-methyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one

{3*S*-[3*R**(*S**)]}-6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-3-{[(2-methoxyethyl)amino](phenyl)methyl}-7-methyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one

{3*R*-[3*R**(*R**)]}-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}acetonitrile

{3*S*-[3*R**(*R**)]}-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}acetonitrile

{3*R*-[3*R**(*S**)]}-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}acetonitrile

{3*S*-[3*R**(*S**)]}-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}acetonitrile

{3*R*-[3*R**(*R**)]}-ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl](methyl)amino} butanoate

{3*S*-[3*R**(*R**)]}-ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl](methyl)amino} butanoate

{3*R*-[3*R**(*S**)]}-ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl](methyl)amino} butanoate

{3*S*-[3*R**(*S**)]}-ethyl 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl](methyl)amino} butanoate

{3*R*-[3*R**(*R**)]}-4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoic acid

{3*S*-[3*R**(*R**)]}-4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoic acid

{3*R*-[3*R**(*S**)]}-4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoic acid

{3*S*-[3*R**(*S**)]}-4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoic acid

{3*R*-[3*R**(*R**)]}-sodium 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate

{3*S*-[3*R*(R*)*]}-sodium 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate

{3*R*-[3*R*(S*)*]}-sodium 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate

{3*S*-[3*R*(S*)*]}-sodium 4-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}butanoate

{3*R*-[3*R*(R*)*]}-sodium (2-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}ethoxy)acetate

{3*S*-[3*R*(R*)*]}-sodium (2-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}ethoxy)acetate

{3*R*-[3*R*(S*)*]}-sodium (2-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}ethoxy)acetate

{3*S*-[3*R*(S*)*]}-sodium (2-{[{6-(2-fluoro-3-methoxyphenyl)-8-[2-fluoro-6-(trifluoromethyl)benzyl]-7-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-3-yl}(phenyl)methyl]amino}ethoxy)acetate

10. A compound according to any one of the claims 1 to 9 for use as a medicament.

11. A compound according to any one of the claims 1 to 9 for use in the treatment of endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, gonadal steroid-dependent neoplasia such as cancers of the prostate, breast and ovary, gonadotrope pituitary adenomas, sleep apnea, irritable bowel syndrome, premenstrual syndrome, benign prostatic hypertrophy, contraception, infertility, assisted reproductive therapy such as in vitro fertilization, in the treatment of growth hormone deficiency and short stature, and in the treatment of systemic lupus erythematosus.

12. A pharmaceutical composition comprising a compound according to any one of the claims 1 to 9.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/061742

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P5/04
ADD.

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)
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 practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/33831 A1 (TAKEDA CHEMICAL INDUSTRIES LTD [JP]; FURUYA SHUICHI [JP]; IMAEDA TOSHI) 8 July 1999 (1999-07-08) claims	1-12
A	WO 01/29044 A1 (NEUROCRINE BIOSCIENCES INC [US]; ZHU YUN FEI [US]; GROSS TIMOTHY D [US) 26 April 2001 (2001-04-26) cited in the application claims; examples	1-12
A,P	WO 2011/076687 A1 (BAYER SCHERING PHARMA AG [DE]; HUEBNER JAN [DE]; WEGSCHEID-GERLACH CHR) 30 June 2011 (2011-06-30) the whole document	1-12

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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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INTERNATIONAL SEARCH REPORT

Information on patent family members

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