CRF RECEPTOR ANTAGONISTS

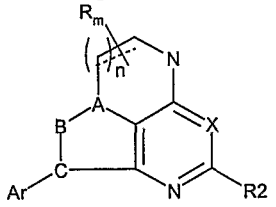
The present invention relates to tricyclic derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in therapy.

The first corticotropin-releasing factor (CRF) was isolated from ovine hypothalami and identified as a 41-amino acid peptide (Vale et al., Science 213: 1394-1397,1981).
CRF has been found to produce profound alterations in endocrine, nervous and immune system function. CRF is believed to be the major physiological regulator of the basal and stress-release of adrenocorticotropic hormone ("ACTH"), Bendorphin, and other propiomelanocortin ("POMC")-derived peptides from the anterior pituitary (Vale et al., Science 213: 1394-1397,1981).

In addition to its role in stimulating the production of ACTH and POMC, CRF appears to be one of the pivotal central nervous system neurotransmitters and plays a crucial role in integrating the body's overall response to stress.
Administration of CRF directly to the brain elicits behavioral, physiological, and endocrine responses identical to those observed for an animal exposed to a stressful environment.
Accordingly, clinical data suggests that CRF receptor antagonists may be useful in the treatment of the neuropsychiatric disorders manifesting hypersecretion of CRF, and, in particular, may represent novel antidepressant and/or anxiolytic drugs.

The first CRF receptor antagonists were peptides (see, e. g., Rivier et al., U. S. Patent No. 4,605,642; Rivier et al., Science 224: 889,1984). While these peptides established that CRF receptor antagonists can attenuate the pharmacological responses to CRF, peptide CRF receptor antagonists suffer from the usual drawbacks of peptide therapeutics including lack of stability and limited oral activity. More recently, small molecule CRF receptor antagonists have been reported.

WO 00/27846 discloses CRF receptor antagonists with the following general formula (A)



(A)

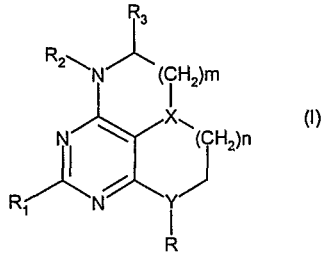
with the proviso that at least one of A, B and C is nitrogen, A, B and C are not all nitrogen and either A-B or B-C is a double bond. A, B and C may be nitrogen or carbon.

Due to the physiological significance of CRF, the development of biologically-active small molecules having significant CRF receptor binding activity and which are capable of antagonizing the CRF receptor remains a desirable goal. Such CRF receptor antagonists would be useful in the treatment of endocrine, psychiatric and neurologic conditions or illnesses, including stress-related disorders in general.

While significant strides have been made toward achieving CRF regulation through administration of CRF receptor antagonists, there remains a need in the art for effective small molecule CRF receptor antagonists. There is also a need for pharmaceutical compositions containing such CRF receptor antagonists, as well as methods relating to the use thereof to treat, for example, stress-related disorders. The present invention fulfills these needs, and provides other related advantages.

In particular the invention relates to novel compounds which are potent and specific antagonists of corticotropin-releasing factor (CRF) receptors.

The present invention provides compounds of formula (I) including stereoisomers, prodrugs and pharmaceutically acceptable salts or solvates thereof



(I)

wherein

R	is aryl or heteroaryl, wherein each of the above groups R may be substituted by 1 to 4 substituents indendently selected from the group consisting of: halogen, C1-C6 alkyl, C1-C6 alkoxy, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, C1-C6 mono or dialkylamino, nitro, cyano and a group R_4;
R_1	is hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkyl, halo C1-C6 alkoxy, NH_2, halogen or cyano;
R_2	is hydrogen or $C(H)_n(R_5)_q(CH_2)_pZR_6$;
R_3	is hydrogen, C2-C6 alkenyl, C2-C6 alkynyl or $[CH(R_5)(CH_2)_p]_mZR_6$;
R_4	is C3-C7 cycloalkyl, which may contain one or more double bonds; aryl; or a 5-6 membered heterocycle; wherein each of the above groups R_4 may be substituted by one or more groups selected from: halogen, C1-C6 alkyl, C1-C6 alkoxy, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, C1-C6 mon a or dialkylamino, nitro, and cyano;
R_5	is hydrogen, C2-C6 alkenyl, C2-C6 alkynyl or $(CH_2)_pZR_6$;
R_6	is C1-C6 alkyl, which may be substituted by one or more groups selected from halogen, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, C1-C6 alkoxy, C1-C6 mono or dialkylamino, nitro, cyano and a group R4;
Y and X	are independently carbon or nitrogen;
m and n	are independently 0 or 1;
p	is 0 or an integer from 1 to 4;
q	is 1 or 2;

Z is a bond, O, NH or S.

Acid addition salts of the free base amino compounds of the present invention may be prepared by methods well known in the art, and may be formed from organic and inorganic acids. Suitable organic acids include maleic, malic, fumaric, benzoic, ascorbic, succinic, methanesulfonic, p-toluensulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, mandelic, cinnamic, aspartic, stearic, palmitic, glycolic, glutamic, and benzenesulfonic acids. Suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids. Thus, the term "pharmaceutically acceptable salt" of structure (I) is intended to encompass any and all acceptable salt forms.

The solvates may, for example, be hydrates.

References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable acid addition salts together with pharmaceutically acceptable solvates.

In addition, prodrugs are also included within the context of this invention. Prodrugs are any covalently bonded carriers that release a compound of structure (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, sulfhydryl and amine functional groups of the compounds of structure (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 structure (I) may have chiral centers and may occur as recemates, 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 structure (I) may exist as polymorphs, which are included in the present invention.

The term C1-C6 alkyl as used herein as a group or a part of the group refers to a straight or branched alkyl group containing from 1 to 6 carbon atoms; examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert butyl, pentyl or hexyl.

The term C3-C7 cycloalkyl group means a non aromatic monocyclic hydrocarbon ring of 3 to 7 carbon atom such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl; while unsaturated cycloalkyls include cyclopentenyl and cyclohexenyl, and the like.

The term halogen refers to a fluorine, chlorine, bromine or iodine atom.

The term halo C1-C6 alkyl means an alkyl group having one or two carbon atoms and wherein at least one hydrogen atom is replaced with halogen such as for example a trifluoromethyl group and the like.

The term C2-C6 alkenyl defines straight or branched chain hydrocarbon radicals containing one or more double bond and having from 2 to 6 carbon atoms such as, for example, ethenyl, 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl or 3-hexenyl and the like.

The term C1-C6 alkoxy group may be a straight or a branched chain alkoxy group, for example methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy or methylprop-2-oxy and the like.

The term halo C1-C6 alkoxy group may be a C1-C6 alkoxy group as defined before substituted with at least one halogen, preferably fluorine, such as $OCHF_2$, or OCF_3.

The term C2-C6 alkynyl defines straight or branched chain hydrocarbon radicals containing one or more triple bond and having from 2 to 6 carbon atoms including acetylenyl, propynyl, 1-butynyl, 1-pentynyl, 3-methyl-1-butynyl and the like.

The term C1-C6 mono or dialkylamino represents an amino group independently substituted with one or two C1-C6 alkyl groups, as defined before.

The term aryl means an aromatic carbocyclic moiety such as phenyl, biphenyl or naphthyl.

The term heteroaryl means an aromatic heterocycle ring of 5-to 10 members and having at least one heteroatom selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono-and bicyclic ring systems.

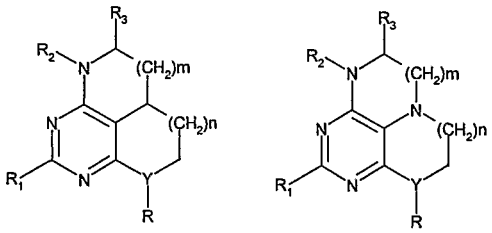
Representative heteroaryls include (but are not limited to) furyl, benzofuranyl, thiophenyl, benzothiophenyl, pyrrolyl, indolyl, isoindolyl, azaindolyl, pyridyl, quinolinyl, isoquinolinyl, oxazolyl, isooxazolyl, benzoxazolyl, pyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, and quinazolinyl.

The term heterocycle means a 5 to 7-membered monocyclic, or 7-to 14-membered polycyclic, heterocycle ring which is either saturated, unsaturated or aromatic, and which contains from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized, including bicyclic rings in which any of the above heterocycles are fused to a benzene ring as well as tricyclic (and higher) heterocyclic rings. The heterocycle may be attached via any heteroatom or carbon atom. Heterocycles include

heteroaryls as defined above. Thus, in addition to the aromatic heteroaryls listed above, heterocycles also include (but are not limited to) morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

The term 5-6 membered heterocycle means, according to the above definition, a monocyclic heterocyclic ring which is either saturated, unsaturated or aromatic, and which contains from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized. The heterocycle may be attached via any heteroatom or carbon atom. Thus, the term includes (but is not limited to) morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

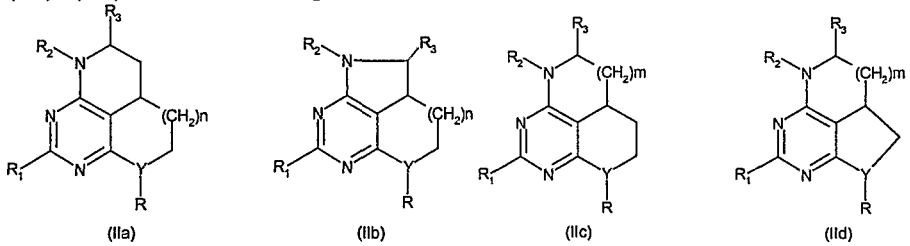
Representative compounds of this invention include the following structure (II) and (III)



(II) (III)

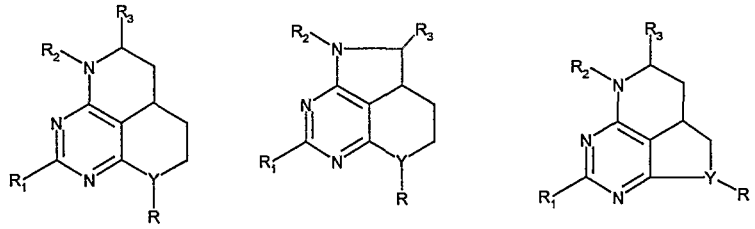
wherein, respectively, X corresponds to a carbon and a nitrogen atom.

Thus, representative compounds of this invention include the following structures (IIa), (IIb), (IIc), (IId), when X corresponds to a carbon atom



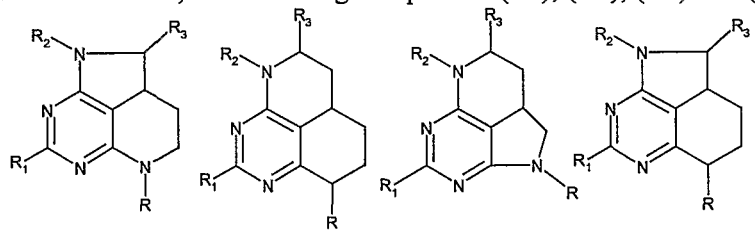
(IIa) (IIb) (IIc) (IId)

Depending upon the choice of X, the representative compounds of this invention include, but are not limited to, the following compounds (Ia-1), (Ib-1), (Ic-1).



(Ia-1) (Ib-1) (Ic-1)

Depending upon the choice of X and Y the representative compounds of this invention include, but are not limited to, the following compounds (I-1), (I-2), (I-3) and (I-4).



(I-1) (I-2) (I-3) (I-4)

More specific embodiments of the invention include, but are not limited to, compounds of the formula (I); (II), (III), (IIa), (IIb), (IIc), (IId); (Ia-1), (Ib-1), (Ic-1); (I-1), (I-2), (I-3), (I-4): wherein:

- R_2 and R_3 are not simultaneously hydrogen.

Furtehr specific embodiments of the invention include, but are not limited to, compounds of the formula (I); (II), (III), (IIa), (IIb), (IIc), (IId); (Ia-1), (Ib-1), (Ic-1); (I-1), (I-2), (I-3), (I-4): wherein:

- R_1 is C1-C3 alkyl group or halo C1-C3 alkyl group, preferably methyl or trifluoromethyl.

Preferred embodiments of the invention include, but are not limited to, compounds of the formula (I); (II), (III), (IIa), (IIb), (IIc), (IId); (Ia-1), (Ib-1), (Ic-1); (I-1), (I-2), (I-3), (I-4): wherein:

- R_2 and R_3 are not simultaneously hydrogen; and
- R_1 is C1-C3 alkyl group or halo C1-C3 alkyl group, preferably methyl or trifluoromethyl;

More preferred embodiments of the invention include, but are not limited to, compounds of the formula (I); (II), (III), (IIa), (IIb), (IIc), (IId); (Ia-1), (Ib-1), (Ic-1); (I-1), (I-2), (I-3), (I-4): wherein:

- R_2 and R_3 are not simultaneously hydrogen;
- R_1 is C1-C3 alkyl group or halo C1-C3 alkyl group, preferably methyl or trifluoromethyl;
- R is an aryl group selected from: 2,4-dichlorophenyl, 2-chloro-4-methylphenyl, 2-chloro-4-trifluoromethyl, 2-chloro-4-methoxyphenyl, 2,4,5-trimethylphenyl, 2,4-dimethyl-phenyl, 2-methyl-4-methoxyphenyl, 2-methyl-4-chlorophenyl, 2-methyl-4-trifluoromethyl, 2,4-dimethoxyphenyl, 2-methoxy-4-trifluoromethylphenyl, 2-methoxy-4-chlorophenyl, 3-methoxy-4-chlorophenyl, 2,5-dimethoxy-4-chlorophenyl,

2-methoxy-4-isopropylphenyl, 2-methoxy-4-trifluoromethylphenyl, 2-methoxy-4-isopropylphenyl 2-methoxy-4-methylphenyl, 2-trifluoromethyl-4-chlorophenyl, 2,4-trifluoromethylphenyl, 2-trifluoromethyl-4-methylphenyl, 2-trifluoromethyl-4-methoxyphenyl, 2-bromo-4-isopropylphenyl, 4-methyl-6-dimethylaminopyridin-3-yl, 4-dimethylamino-6-methyl-pyridin-3-yl, 6-dimethylamino-pyridin-3-yl and 4-dimethylamino-pyridin-3-yl.

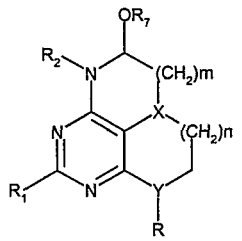
Preferred compounds according to the invention are:

5-(2,4-dichlorophenyl)-1-(1-ethylpropyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene (I-1-1);
5-(2,4-dichlorophenyl)-1-(2-ethylbutyl)-7-methyl-1,2,2a,3,4,5,5a,8b-octahydro-1,5,6,8-tetraazaacenaphthylene (I-1-2);
5-(2,4-dichlorophenyl)-1-(2-methoxy-1-methoxymethylethyl)-7-methyl-1,2,2a,3,4,5,5a,8b-octahydro-1,5,6,8-tetraazaacenaphthylene (I-1-3);
7-methyl-1-(1-propylbutyl)-5-[4-(1,1,2-trifluoroethyl)-2-trifluoromethylphenyl]-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraazaacenaphthylene (I-1-4);
7-methyl-1-(1-propylbutyl)-5-[4-(1,1,2-trifluoroethyl)-2-trifluoromethylphenyl]-1,2,2a(*S*),-3,4,5-hexahydro-1,5,6,8-tetraazaacenaphthylene;
7-methyl-1-(1-propylbutyl)-5-[4-(1,1,2-trifluoroethyl)-2-trifluoromethylphenyl]-1,2,2a-(*R*),3,4,5-hexahydro-1,5,6,8-tetraazaacenaphthylene;
5-(2,4-dichlorophenyl)-7-methyl-1-(1-propylbutyl)-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene (I-1-5);
5-(2,4-dichlorophenyl)-7-methyl-1-(1-propylbutyl)-1,2,2a-(S),3,4,5,5a,8b-octahydro-1,5,6,8-tetraazaacenaphthylene;
5-(2,4-dichlorophenyl)-7-methyl-1-(1-propylbutyl)-1,2,2a-(R),3,4,5,5a,8b-octahydro-1,5,6,8-tetraazaacenaphthylene;
9-(2,4-dichlorophenyl)-4-(1-ethylpropyl)-2-methyl-5,6,6a,7,8,9-hexahydro-4*H*-1,3,4-triazaphenalene (isomer 1) and 9-(2,4-dichlorophenyl)-4-(1-ethylpropyl)-2-methyl-5,6,6a,7,8,9-hexahydro-4*H*-1,3,4-triazaphenalene (isomer 2) (2-1-1);
5-cyclopropylmethyl-1-(2,4-dichlorophenyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraazaacenaphthylene (3-1-1);
1-(2,4-dichlorophenyl)-5-(2-methoxyethyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene (3-1-2);
1-(2,4-dichlorophenyl)-5-(1-ethylpropyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene (3-1-3);
1-(2,4-dichlorophenyl)-5-(2-ethylbutyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene (3-1-4);
1-(2,4-dichlorophenyl)-7-methyl-5-(1-propylbutyl)-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene (3-1-5);
7-methyl-5-(1-propylbutyl)-1-[4-(1,1,2-trifluoro-ethyl)-2-trifluoromethylphenyl]-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraazaacenaphthylene (3-1-6);
5-cyclopropylmethyl-1-(2,4-dichlorophenyl)-7-methyl-4-propyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraazaacenaphthylene (3-1-7);

4-butyl-5-cyclopropylmethyl-1-(2,4-dichlorophenyl)-7-methyl-1,2,2a,3,4,5-hexahydro1,5,6,8-tetraazaacenaphthylene (3-1-8);
5-cyclopropylmethyl-1-(2,4-dichlorophenyl)-7-methyl-4-propoxy-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraazaacenaphthylene (3-1-9);
4,5-dibutyl-1-(2,4-dichlorophenyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene (3-1-10);
5-(2,4-dichlorophenyl)-1-(1-ethylpropyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,6,8-triaza-acenaphthylene (4-1-1).

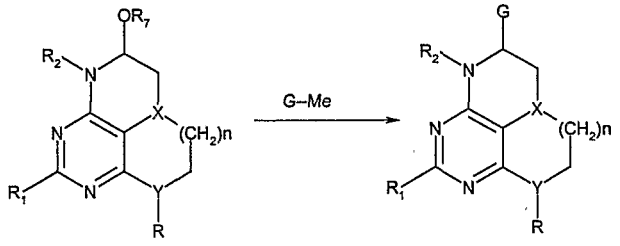
Compounds of formula (I), and salts and solvates thereof, may be prepared by the general methods outlined hereinafter. In the following description, the groups R, R_1, R_2, R_3, R_4, R_5, R_6, X, Y, Z, m, n, p and q have the meaning as previously defined for compounds of formula (I) unless otherwise stated.

Compounds of formula (I) when R_3 is different from hydrogen and m is 1 are equivalent to compounds of formula (IV), in which G corresponds to the previous meanings of R_3 other than hydrogen, may be prepared by reaction of a compound of formula (V),



(V)

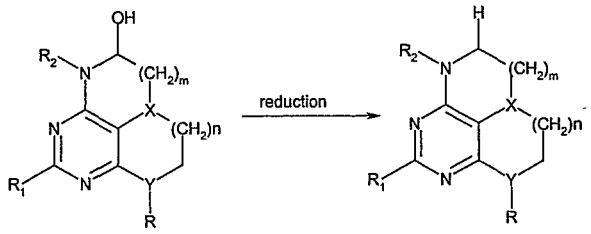
wherein R_7 is a C1-C4 linear or branched alkyl group and m is 1, equivalent to compounds of formula (VI). Then compounds of formula (VI) may react with the organo-metallic compound GM,



(VI) (IV)

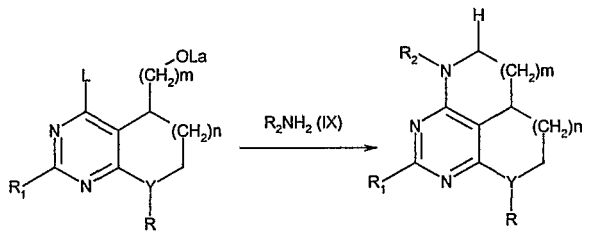
wherein M is a metal to give compounds of formula (IV), optionally in the presence of a Lewis acid such as borontrifluoride etherate. Suitable metals for this reaction include lithium, copper or magnesium.

Compounds of formula (I) when R_3 is hydrogen are equivalent to compounds of formula (Ia), may be prepared by reduction of a compound of formula (V) wherein R_7 is hydrogen and equivalent to compounds of formula (Va), in the presence of an organic acid (e.g. trifluoroacetic). Convenient reducing agents for this reaction are trialkylsilanes (e.g. triethylsilane). The reaction is preferably carried out in an aprotic solvent such as dichloromethane.



(Va) (Ia)

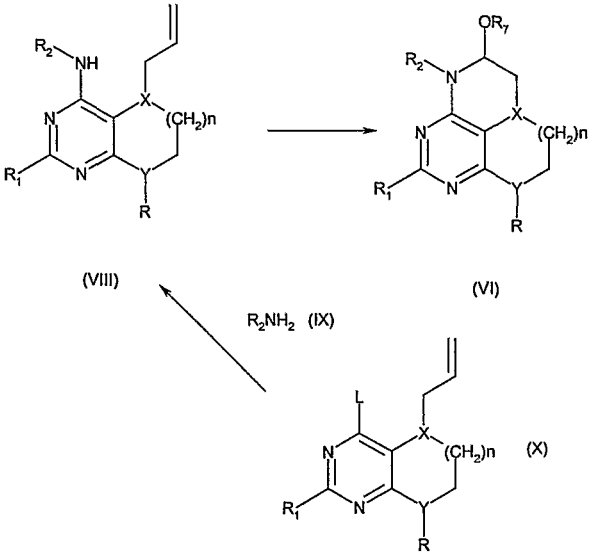
Compounds of formula (IIb), corresponding to compounds of formula (II) in which R_3 is hydrogen, may be prepared from compounds of formula (VII) according to the following general Scheme:



(VII) (IIb)

wherein L is a leaving group selected in a group consisted from halogens, preferably chlorine and reactive residue of sulphonic acid (such as mesylate, triflate) and La represents a suitable reactive group able to render OLa a good leaving group (such as mesylate, triflate).
The reaction takes place by heating using the amine R_2NH_2 (IX) in excess, preferably as solvent.

Compounds of formula (VI), may be prepared by oxidation of the allyl group of compounds of formula (VIII) to the corresponding aldehyde followed by in situ cyclisation and conversion of the hydroxy group into the alkoxy group which will be described in details later on.



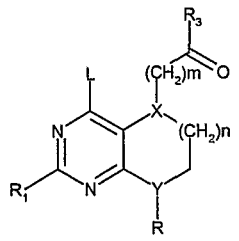
(VIII) (VI) (X)

The oxidation is carried out with osmium tetroxide in the presence of N-methylmorpholine oxide (NMO), followed by treatment with sodium periodate. The reaction is conveniently carried out in a water miscible organic solvent such acetone, tetrahydrofuran optionally in the presence of water.

The conversion of the hydroxy group into C1-C4 alkoxy may be carried out by treatment of the hydroxy group with C1-C4 alcohol in the presence of a suitable inorganic acid, e.g. hydrochloric acid.

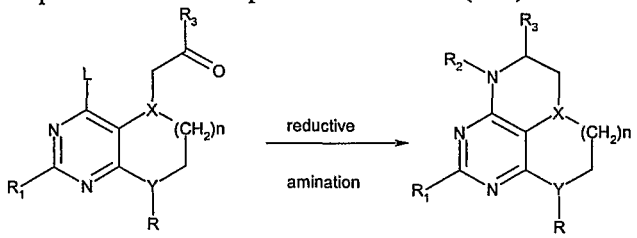
Compounds of formula (VIII) may be prepared by treatment of a compound of formula (X), with the amine R_2NH_2 (IX).

In an alternative process, compounds of formula (IIa), may be prepared by reaction of a compound of formula (XI),



(XI)

and when m is 1 it is equivalent to a compound of formula (XIa)



(XIa) (IIa)

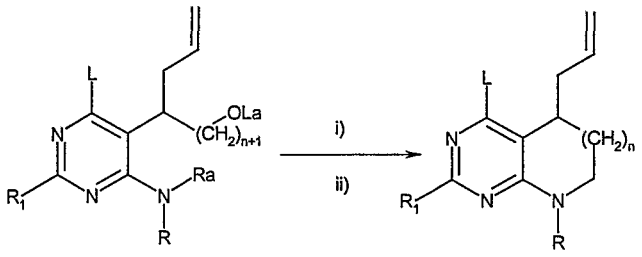
with the amine (IX) in the presence of a suitable reducing agent, followed by in situ cyclisation.

Suitable reducing agents for this reaction include hydride, for example a borane hydride, or a metal hydride complex like lithium aluminum hydride, borohydride, or an organo-metallic complex such as borane methyl sulphide, 9-borabicyclononane (9-BBN), triethylsilane, sodium triacetoxyborohydride, sodium cyanoborohydride.

Alternatively, boranes may be produced in situ by reacting Sodium Borohydride in the presence of Iodine, an inorganic acid (e.g. sulphoric acid) or an organic acid such as formic acid, trifluoroacetic, acetic acid or methansulphonic acid.

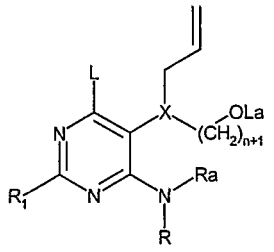
Suitable solvents for this reaction are alcohol (e.g. methanol), ether (e.g. tetrahydrofuran), or halohydrocarbon (e.g. dichloromethane) or an amide (e.g. N,N-dimethylformamide) at a temperature within the range of room temperature to the reflux temperature of the reaction mixture.

Compounds of formula (X) wherein Y is nitrogen and X is carbon are equivalent to compounds of fomula (Xa), may be obtained from a compound of formula (XIIa),



(XIIa) (Xa)

equivalent to compounds of formula (XII)



(XII)

in which X is carbon, La is a suitable reactive group able to render OLa a good leaving group, (such as mesylate) and Ra corresponds to hydrogen or a suitable nitrogen protecting group, if necessary.

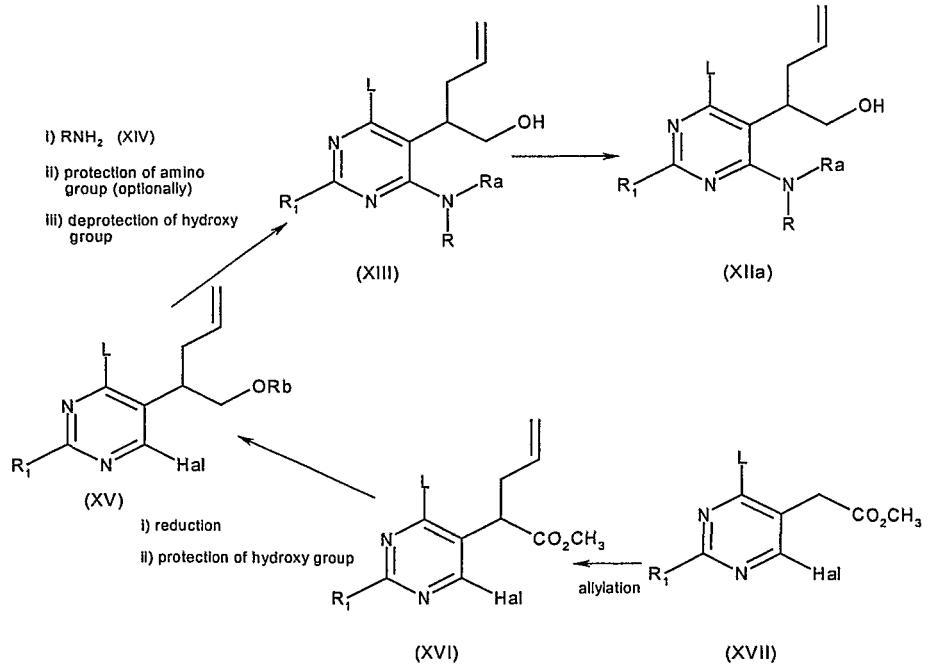
Compounds of formula (XIIa) may be subjected to the following reactions:

i) optionally removal of the nitrogen protecting group Ra; and

ii) cyclisation in the presence of organic base such as a tertiary amine e.g. triethylamine.

These reactions are preferably carried out in an aprotic solvent such as ether (e.g. tetrahydrofuran), halohydrocarbon such as dichloromethane or amide such as N,N-dimethylformamide.

Compounds of formula (XII) in which X is carbon and n is 0 are equivalent to compounds of formula (XIIa), may be prepared by introduction of the suitable reactive group La on a compound of formula (XIII) in which Hal, Ra, n, are defined as above.



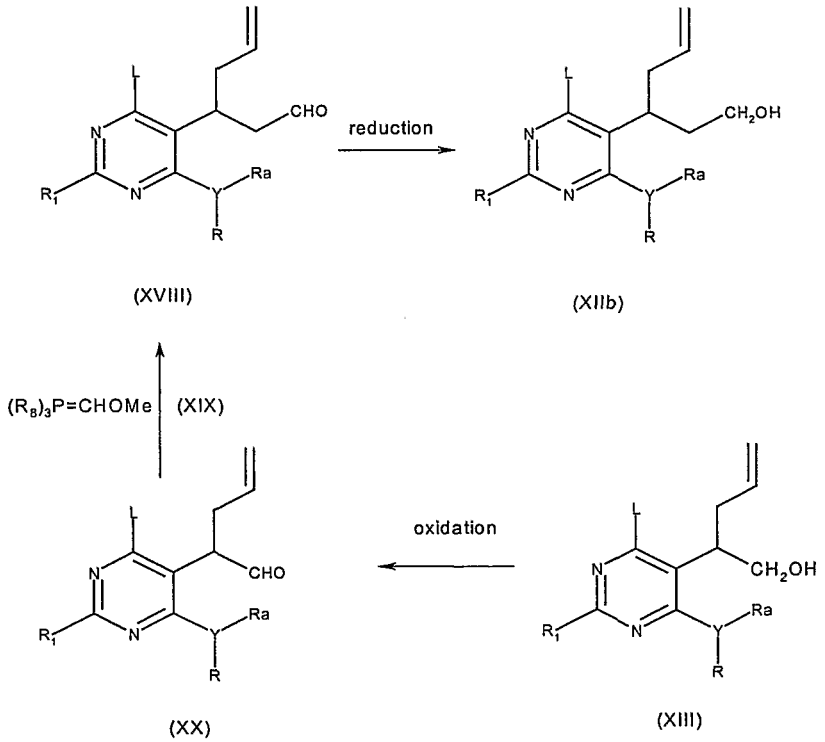
Compounds of formula (XIII) may be obtained by reaction of a compound of formula (XV), wherein Rb is a suitable hydroxy protecting group, with amine (XIV), followed by protection of the nitrogen group (if necessary) and removal of hydroxy protecting group.

The reaction with the amine is suitably carried out in an aprotic solvent such as DMF (dimethylformamide) in the presence of a strong base (e.g. sodium hydride).

Compounds of formula (XV) may be prepared by reduction of an ester of formula (XVI) to the corresponding hydroxy with a suitable reducing agent, such as diisobutylaluminumhydride followed by protection of the hydoxy group with a hydroxy suitable protecting group.

Compounds of formula (XVI) may be prepared by reaction of a compound of formula (XVII) with allyl halide (e.g. allyl iodide). The reaction is carried out in the presence of an organic base such as lithiumhexamethyldisilazane at low temperature and in an aprotic solvent (e.g. tetrahydrofuran).

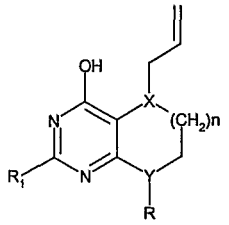
Compounds of formula (XII) wherein n is 1 and X is carbon are equivalent to compounds of formula (XIIb), may be prepared by reduction of a compound of formula (XVIII), with a suitable reducing agent, e.g. sodium borohydride in a solvent such as for example an alcohol (e.g. methanol).



Compounds of formula (XVIII) may be prepared by Wittig reaction of a compound of formula (XX) with a phosphorus ylide (XIX), in which R_8 is a phenyl derivative, followed by hydrolysis with an acid (e.g hydrochloric acid). The reaction is carried out in an aprotic solvent such as acetonitrile or an ether such as tetrahydrofuran.

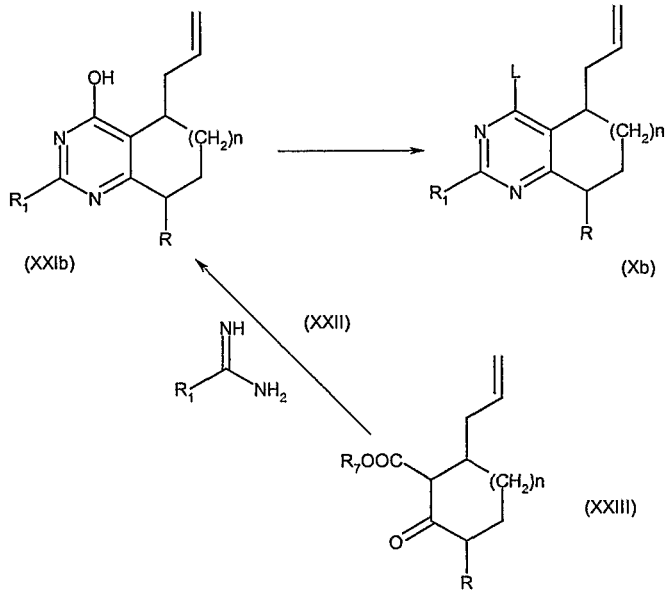
Compounds of formula (XX) may also be prepared by oxidation of a compound of formula (XIII). The oxidation may be carried out using the conventional methods known for converting a hydroxy group into an aldehyde group. Thus, for example, the reaction may be carried out using Swern conditions.

Compounds of formula (X) when Y is carbon and X is carbon are equivalent to compounds of formula (Xb), may be prepared by halogenation of a compound of formula (XXI),



(XXI)

in which, when X and Y are both carbon, is equivalent to a compound of formula (XXIb).



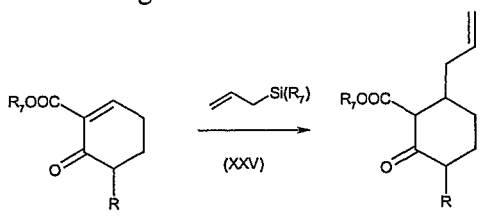
(XXIb) (XXII) (Xb) (XXIII)

The halogenation reaction may be carried out using conventional methods known in the art. Thus for example the reaction may be carried out by treatment with $PO(Hal)_3$, wherein within the halogens, chlorine is preferred.

Compounds of formula (XXIb) may be obtained by reaction of a cyclohexanone of formula (XXIII), in which R_7 is defined as before, with a salt (e.g hydrochloride) of acetamidine (XXII).

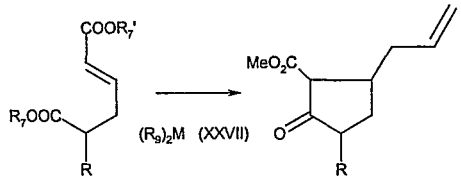
The reaction is carried out in the presence of a C1-C4 alkaline alkoxylate (e.g. sodium methoxylate), in a solvent such as methyl alcohol.

Compounds of formula (XXIII) when n is 1 are equivalent to compounds of formula (XXIIIa), may be prepared by reaction of a compound of formula (XXIV) with a silane derivative (XXV), wherein R_7 is as defined before. The reaction is carried out in the presence of Lewis acid and in an organic solvent.



(XXIV) (XXV) (XXIIIa)

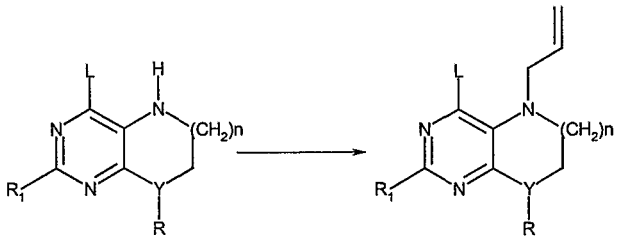
Compounds of formula (XXIII) when n is 0 are equivalent to compounds of formula (XXIIIb), may be prepared by reaction of a compound of formula (XXVI), in which R7 is defined as before and R7' has the same meanings as R7 but not at the same time,



(XXVI) (XXIIIb)

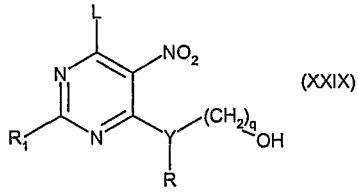
with an organo metallic compound $(R_9)_2M$ (XXVII), in which R_9 is an allyl group and M is a metal, optionally in the presence of a Lewis acid such as boron trifluoride etherate. Suitable metals for this reaction include lithium, copper and magnesium.

Compounds of formula (X) when X is nitrogen are equivalent to compound of formula (Xc), may be prepared by reaction of a compound of formula (XXVIII) with allyl halide (e.g. allyl bromide). The reaction is carried out in the presence of an inorganic base such as sodium hydride at low temperature and in aprotic solvent (e.g. tetrahydrofuran or NN-dimethylformamide).



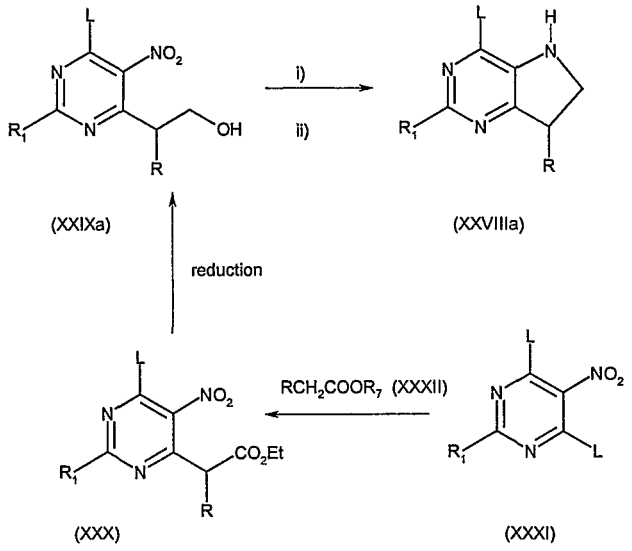
(XXVIII) (Xc)

Compounds of formula (XXVIII) when n is 0 and Y is carbon are equivalent to compounds of formula (XXVIIIa), may be prepared by subjecting a compound of formula (XXIX), in which q is as previously defined,



(XXIX)

Compounds of formula (XXIXa), corresponding to compounds (XXIX) in which q is1 and Y is carbon, may be subjected to the following reactions:



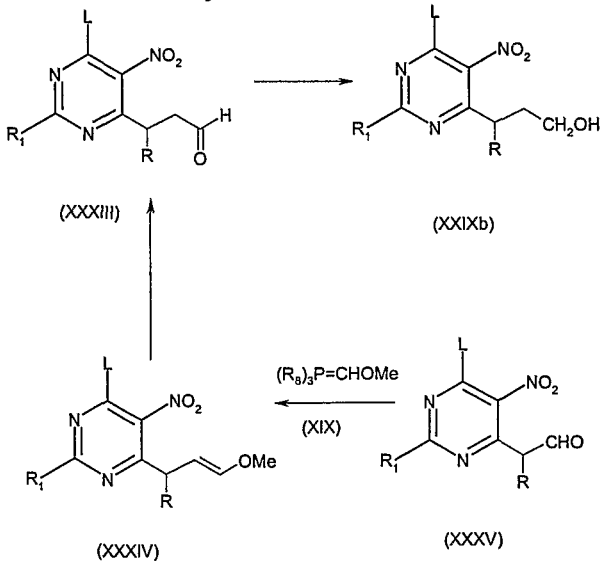
i) conversion of the hydroxy group into a suitable leaving group such as mesylate,

ii) conversion of the nitro group into the amine by reduction in the presence of $Na_2S_2O_4$ and an inorganic base such as potassium carbonate and in situ cyclisation.

Compounds of formula (XXIXa), may be prepared by reduction of an ester compound of formula (XXX). The reduction can be conveniently carried out with sodium borohydride in a protic solvent such alcohol (e.g. methanol or ethanol) and preferably heating e.g. 40-100°C. Compounds of formula (XXX) may be prepared by reaction of a compound of formula (XXXI), with an ester compound (XXXII).

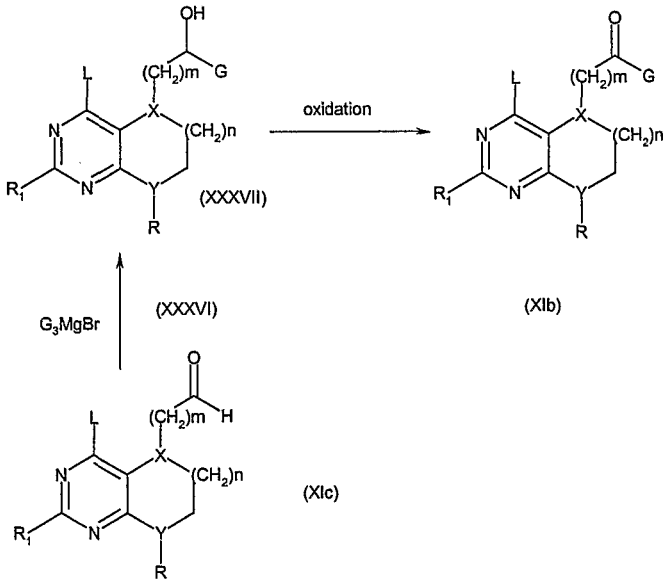
The reaction takes place in an aprotic solvent such as DMF and in the presence of an inorganic base (i.e. sodium hydride).

Compounds of formula (XXIX) when n is 2 and Y is carbon are equivalent to compounds of formula (XXIXb), may be prepared by reduction of compounds of formula (XXXIII) using conventional reducing reagent to convert aldehyde into alcohol. Thus a suitable reducing agent for this reaction is sodium borohydride.

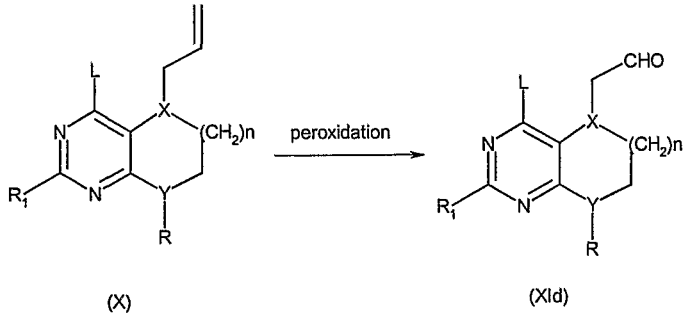


Compounds of formula (XXXIII) may be obtained by hydrolysis of enolether of formula (XXXIV). The reaction is preferably carried out in the presence of an inorganic acid such as for example hydrogen chloride. Compounds of formula (XXXIV) may be obtained from (XXXV) by Wittig reaction with the ylide (XIX), in the presence of a suitable organic base like n-BuLi. The reaction is carried out in an aprotic solvent such as acetonitrile or an ether such as tetrahydrofuran. Compounds of formula (XXXV) may be prepared by oxidation of compounds (XXIXa) when Y corresponds to carbon, by using conventional methods known to convert alcohol to aldehyde.

Compounds of formula (XI) when R_3 is different from hydrogen are equivalent to compounds of formula (XIb), may be prepared by reaction of a compound of formula (XI) when R_3 is hydrogen (equivalent to a compound of formula (XIc)), with the organo metallic compound GMgBr (XXXVI), to give the alcohol compound (XXXVII), which may be oxidised to the keto compound (XIb) according to the following scheme



Compounds of formula (XIc) when m is 1 are equivalent to compounds of formula (XId), may be prepared by oxidation of a compound of formula (X).



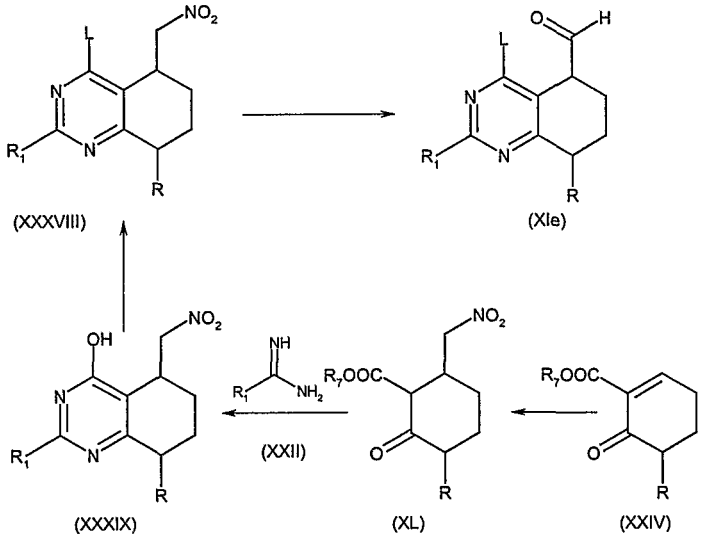
(X) (XId)

The oxidation reaction is conveniently carried out in the presence of ozone at low temperature e.g. –78°C in a solvent such as dicholoromethane.

Alternatively, the oxidation takes place by reaction with with osmium tetraoxide in the presence of N-methyl morpholine oxide (NMO) followed by treatment with sodium

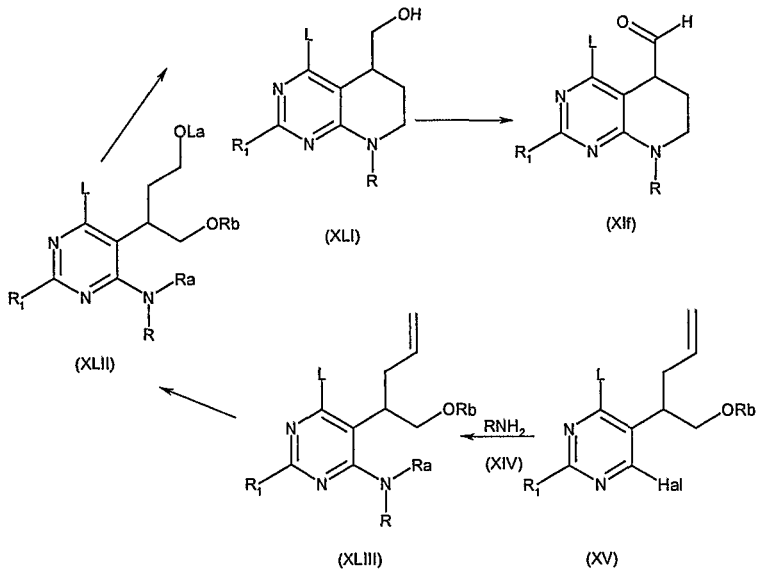
periodate. The reaction is conveniently carried out in a water miscible organic solvent such as acetone or tetrahydrofuran optionally in the presence of water.

Compounds of formula (XIc) when X and Y are carbon, m is 0 and n is 1 are equivalent to compounds of formula (XIe), may be prepared by treating compounds of formula (XXXVIII) with an inorganic base such as potassium hydroxide in a solvent such as alcohol, followed by reaction with potassium permanganate. The reaction is suitably carried out in water.



Compounds of formula (XXXVIII), may be prepared by halogenation of a compound of formula (XXXIX). The halogenation reaction may be carried as described above.
Compounds of formula (XXXIX) may be prepared by reaction of a compound of formula (XL) with a salt (e.g hydrochloric acid) of acetamidine (XXII) using condition as described above. Compounds of formula (XL) may be prepared by reacting compounds of formula (XXIV), in which R7 is as defined before, with nitromethane.

Compounds of formula (XIc) when X is carbon, m is 0, n is 1 and Y is nitrogen are equivalent to compounds of formula (XIf), may be prepared by oxidation of a compound of formula (XLI), using conventional oxidation methods known to convert a hydroxy group into an aldehyde.



Compounds of formula (XLI) may be prepared by subjecting a compound of formula (XLII), wherein La is a suitable leaving group, such as mesylate, Ra and Rb are as defined above, to the following reactions:

i) optionally, removal of the nitrogen protecting group,

ii) cyclisation and

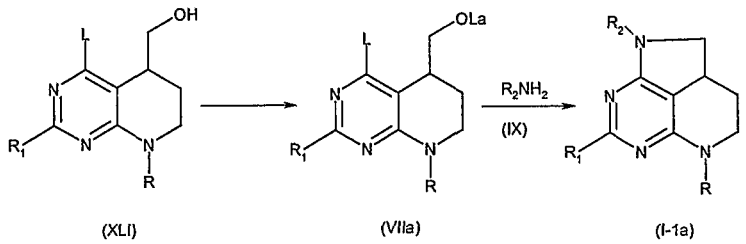
iii) removal of the hydroxy protecting group Rb.

Compounds of formula (XLII) may be prepared as discussed before by oxidation of a compound of formula (XLIII), followed by reduction to hydroxy group and conversion in a leaving group.

The oxidation reaction is conveniently carried out in the presence of ozone at low temperature e.g. –78°C in a solvent such as dichloromethane. The reduction is carried out using sodium borohydride as reducing agent.

Compounds of formula (XLIII) may be obtained from a compound of formula (XV) with amine (XIV), followed by protection of the nitrogen group.

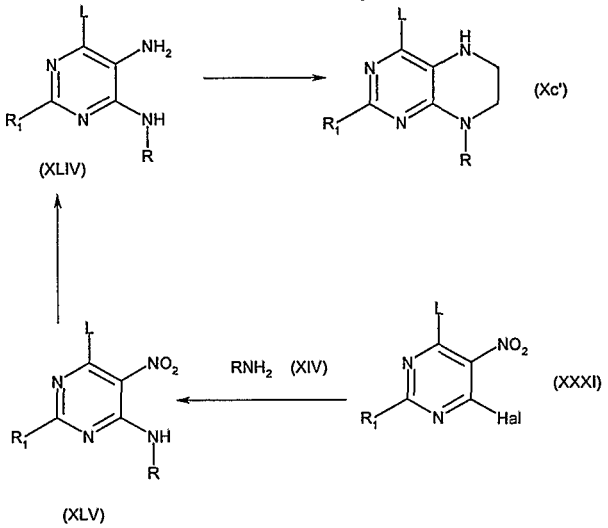
Compounds of formula (XLI) may be converted to compounds of formula (VIIa), corresponding to compounds of formula (VII) in which X is carbon, Y is nitrogen m and n are1, according to known methods.



According to a previous Scheme, compounds of formula (VIIa) may be converted to compound of formula (I-1a), corresponding to compound of formula (I-1) in which R_3 is hydrogen.

Compounds of formula (Xc) in which X and Y are nitrogen and n is 1 are equivalent to compounds of formula (Xc'), may be prepared by reaction of a compound of formula (XLIV)

with dibromoethane, in the presence of an organic or inorganic base. The reaction is suitably carried out in an aprotic solvent such as NN-dimethylformamide or acetonitrile.

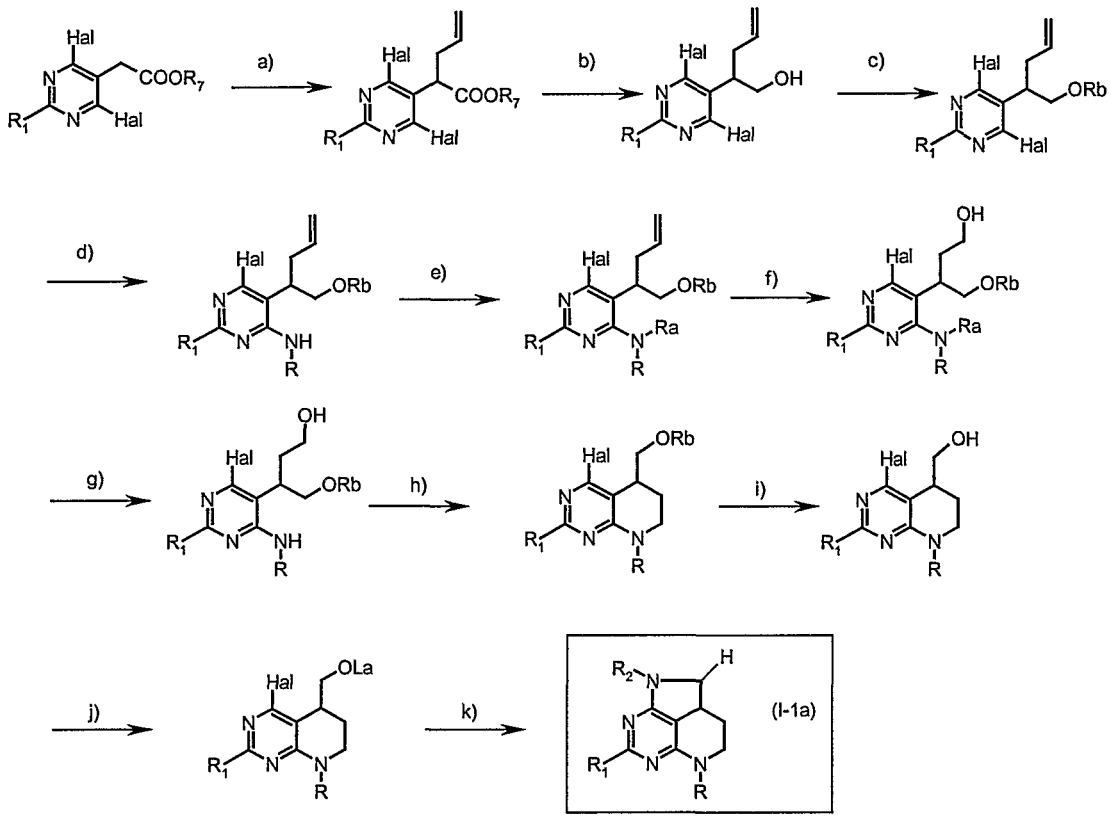


Compounds of formula (XLIV) may be prepared by compounds of formula (XLV) by treatment with iron and an inorganic acid e.g. hydrochloric acid. Compounds of formula (XLV) may be prepared by reaction of compound (XXXI) and the amine (XIV).

Compounds of formula (XVII), (XXIV), (XXVI) and (XXXI) are either known compounds or may be prepared by analogous method to those described for known compounds.

In summary, compounds of formula (I-1a), may be prepared according to the following Scheme 1:

Scheme 1



in which Hal, R, R_1, R_7, R_2, La, Ra and Rb are defined as above and preferably R_7 is a methyl group, Hal is chlorine, Ra is *t*-butylcarbonyl, Rb is t-BuPh_2 Si derivative, OLa is a mesyl group and

step a stands for allylation with allyl iodide at 0°C in basic conditions (e.g. LiHMDS); the starting material may be prepared in similar way to what described in Wayne G. C. et al., J. Prakt. Chem., (2000), 342(5), 504-7;

step b stands for reduction of the ester group with a suitable reducing agent, e.g. DIBAl-H, in usual conditions (CH_2Cl_2, 0°C to r.t.);

step c stands for protection of the hydroxy group, preferably with t-BuPh_2SiCl, in DMF with DMAP as catalyst (0°C to r.t);

step d stands for reaction with the amine RNH_2 (XIV) as described above;

step e stands for protection of the amino group with a suitale protecting group, for example by treatment with $(BOC)_2O$ in presence of DMAP;

step f stands for, i) oxidation with OsO_4 in acetone/water, then ii) treatment with $NaIO_4$ in THF/water, and finally iii) reduction with $NaBH_4$ in a suitable solvent (e.g. EtOH);

step g stands for deprotection of the amino protecting group (e.g. CF_3CO_2H in CH_2Cl_2);

step h stands for intramolecular cyclisation, for example by mesylation of the hydroxy group in basic conditions (i.e. Et_3N);

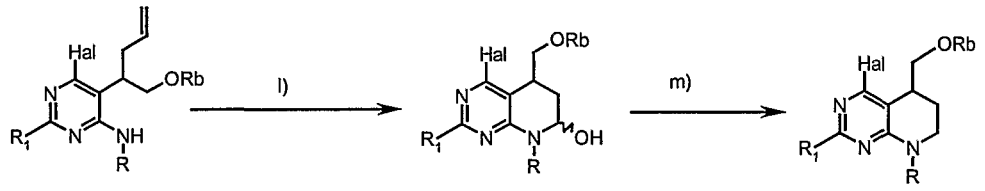
step i stands for deprotection of the hydroxy protecting group (e.g. Et_3N - 3HF in DMF at 40°C);

step j stands for transformation of the hydroxy group in a suitable leaving group (e.g. mesylation);

step k stands for reaction with the amine (IX) as described above.

Alternatively, the synthesis can be modified following the steps below (starting from an already described intermediate) according to Scheme 2

Scheme 2



in which

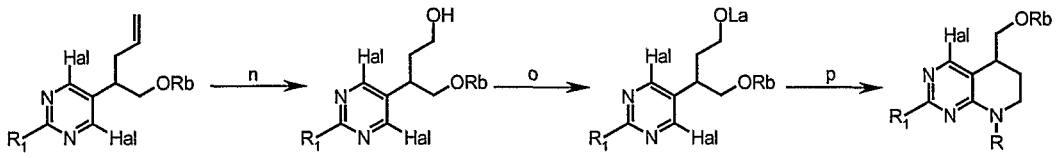
step l stands for the first two reactions of previous step f, and

step m stands for treatment with Et_3SiH in the presence of BF_3-Et_2O.

The synthesis is then completed as described in Scheme 1.

In another alternative, the protection of the amino group can be avoided through the following sequence of steps (starting from an already described intermediate) according to scheme 2a

Scheme 2a



in wich

step n corresponds to previous step f);

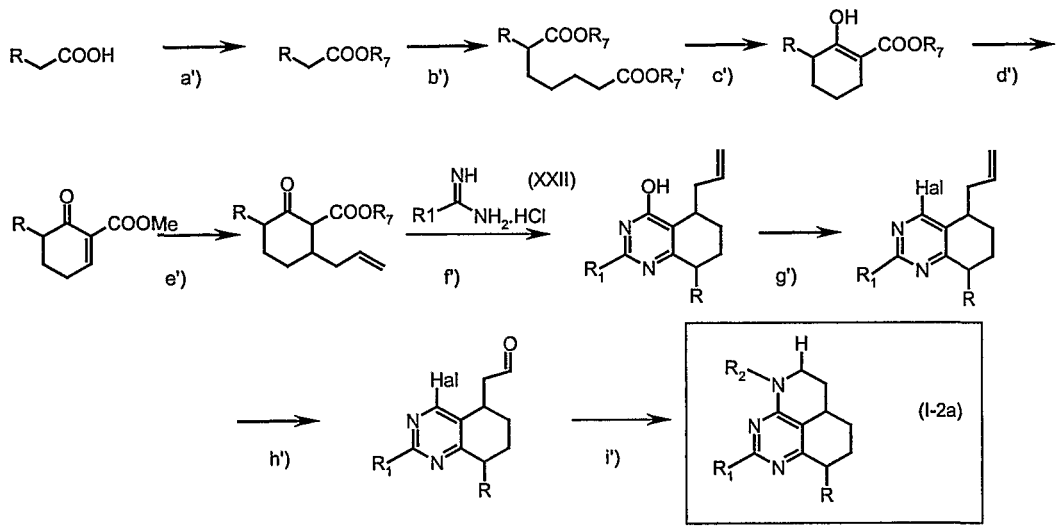
step o corresponds to previous step j);

step p stands for reaction with the amine RNH_2 (XIV) as described above;

The synthesis is then completed as described in Scheme 1.

In another embodiment of the invention, compounds of formula (I-2), in which R3 is hydrogen are equivalent to compounds of formula (I-2a), may be prepared according to the following Scheme 3

Scheme 3



in which Hal, R, R_1, R_2, R_7, Rb are defined as above and preferably R_7 is a methyl group, Hal is chlorine, Rb is t-BuPh_2 Si derivative, OLa is a mesyl group and

step a' stands for esterification in usual conditions (R_7OH, acid catalyst, reflux);

step b' stands for alkylation with the suitable alkylating agent (e.g. methyl 5-iodovalerate in the presence of LiHMDS);

step c' stands for intramolecular cyclisation in basic conditions (i.e. MeONa, refluxing toluene);

step d' stands for phenylselenylation followed by oxidation with H_2O_2 and subsequent elimination;

step e' stands for 1,4-carbonyl addition with a suitable silane such as allyltrimethylsilane catalysed by $TiCl_4$;

step f' stands for reaction with the amidine (XXII) as described above;

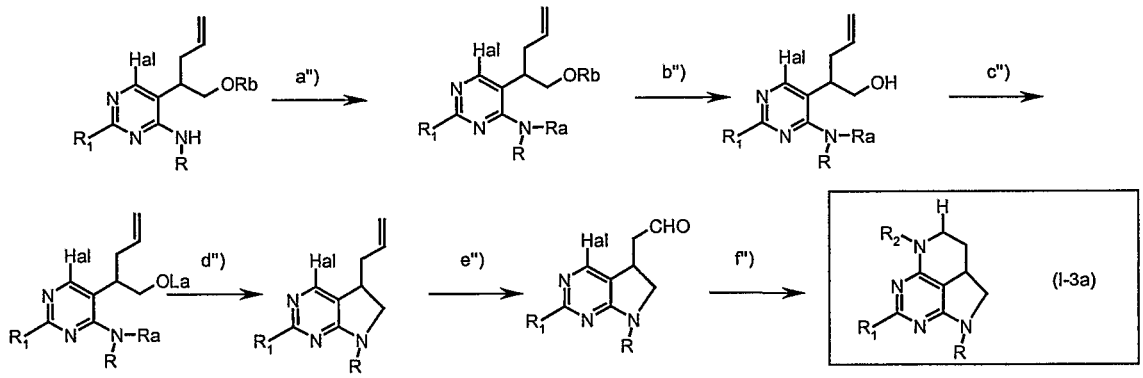
step g' stands for halogenation of the hydroxy group (e.g. by treatment with $POCl_3$ at reflux);

step h' stands for oxidative cleavage of the double bond by, for example, ozonization;

step i' stands for reductive amination in the presence of $NaBH_3CN$ with the amine (IX) and subsequent intramolecular cyclisation.

In a further embodiment of the invention, compounds of formula (I-3) in which R3 is hydrogen are equivalent to compounds of formula (I-3a) may be prepared according to Scheme 4

Scheme 4



in which

step a'' stands for protection of the amino group with a suitale protecting group, for example by treatment with $(BOC)_2O$ in presence of DMAP;

step b'' corresponds to previous step i);

step c'' stands for mesylation of the hydroxy group in basic conditions (i.e. Et_3N);

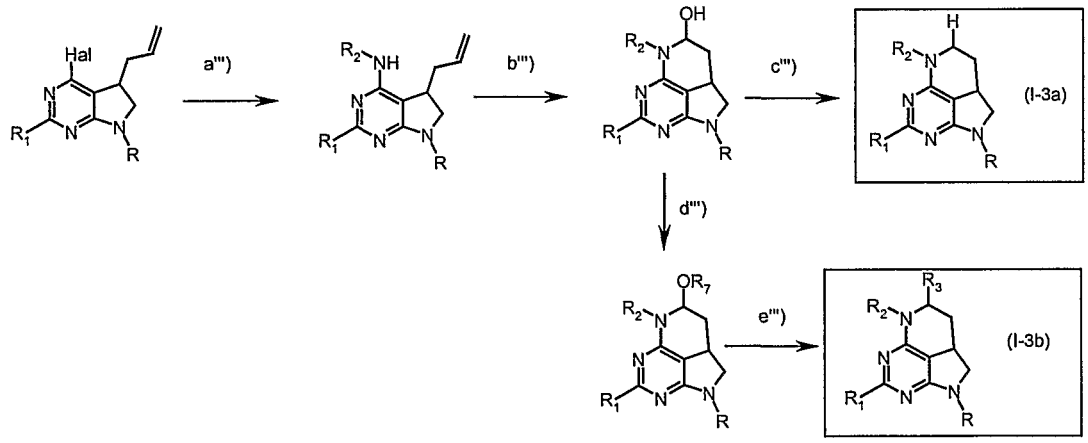
step d'' stands for deprotection of the protective group of the amino, e.g. by treatment with TFA and then subsequent cyclisation in basic conditions, e.g. Et_3N;

step e'' corresponds to previous step h') or corresponds to previous step l);

step f'' corresponds to previous step i');

In another alternative, the last stages of the synthesis could be done as follow and compounds of formula (I-3) in which R_3 is different from hydrogen corresponding to compounds of formula (I-3b) according to Scheme 5

Scheme 5



in which

step a''' corresponds to previous step k);

step b''' corresponds to previous step l);

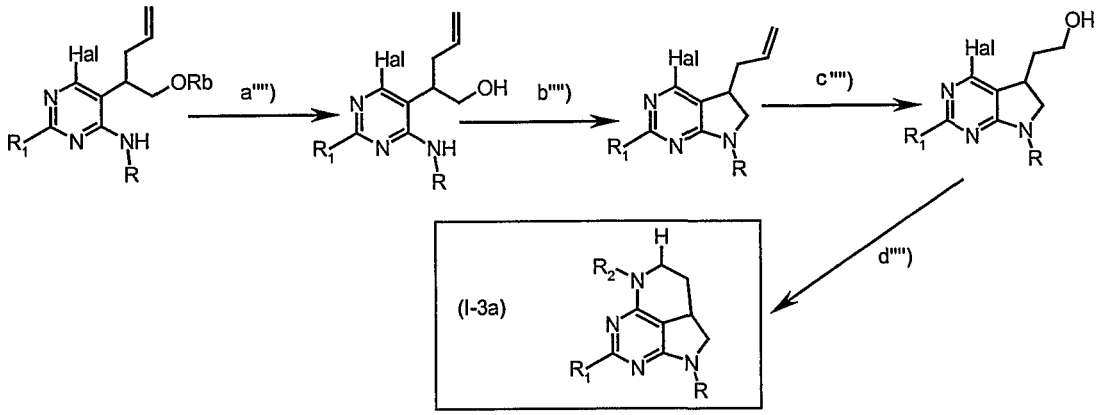
step c''' stands for reduction, e.g. by treatment with Et_3SiH, TFA;

step d''' stands for formation of the ether group, e.g. by treatment with methanol in presence of PTSA;

step e''' stands for reaction with an organo-metallic compound, such as R_3Cu in presence of $BF_3.Et_2O$.

Alternatively compounds of formula (I-3a), when it is not necessary to protect the amino group, may be prepared as examplified below in Scheme 6, starting from an already known intermediate:

Scheme 6



wherein

step a'''' corresponds to previous step i);

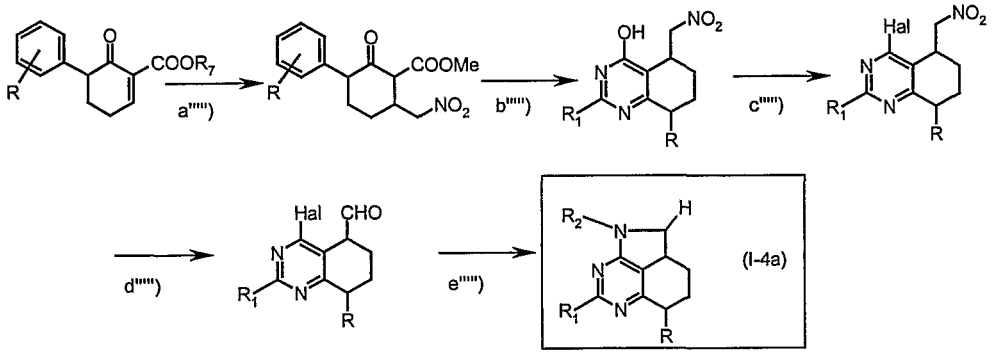
step b'''' corresponds to previous step j), followed by in situ intramolecular cyclisation;

step c'''' corresponds to previous step f);

step d'''' corresponds to previous steps j) and k).

In another embodiment of the invention, compounds of formula (1-4) when R_3 is hydrogen corresponding to compounds of formula (I-4a) may be prepared according to Scheme 7

Scheme 7



in which

step a''''' stands for reaction with nitromethane in usual conditions;

step b''''' stands for reaction with the amidine (XXII) as described above;

step c''''' corresponds to previous step g');

step d''''' stands for formation of the aldehyde group, e.g. by treatment with KOH in methanol and subsequent oxidation by $KMnO_4$;

step e''''' corresponds to previous step i').

Examples of suitable nitrogen protecting group include alkoxycarbonyl, e.g. t-butoxycarbonyl and arylsulphonyl, e.g phenylsulphonyl.

In any of the above reaction the nitrogen protecting group may be removed by conventional procedures known for removing such groups (such as those described in Protective Groups in Organic Chemistry, pages 46-119, Edited by J F W McOmie (Plenum Press, 1973)). Thus, when Ra is alkoxycarbonyl, the group may be removed by acid hydrolisis using for example trifluoro acetic acid.

Examples of suitable hydroxy protecting group include trihydrocarbyl silyl ethers such as the trimethylsilyl or t-butyldimethylsilyl ether.
The hydroxyl protectin groups may be removed by well-known standard procedures (such as those described in Protective Groups in Organic Chemistry, pages 46-119, Edited by J F W McOmie (Plenum Press, 1973)). For example when Rb is a t-butyldimethylsilyl group, this may be removed by treatment with triethylamine trihydrofluoride.

Pharmaceutical acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts, of the compound of formula (I) using conventional methods.

The compounds of formula (I) may readily be isolated in association with solvent molecules by crystallisation or evaporation of an appropriate solvent to give the corresponding solvates.

When a specific enantiomer of a compound of general formula (I) is required, this may be obtained for example by resolution of a corresponding enantiomeric mixture of a compound of formula (I) using conventional methods. Thus the required enantiomer may be obtained from the racemic compound of formula (I) by use of chiral HPLC procedure.

The subject invention also includes isotopically-labeled compounds, which are identical to those recited in formulas I and following, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, iodine, and chlorine, such as ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{123}I and ^{125}I.
Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically - labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H, ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^{8}F isotopes are particularly useful in PET (positron emission tomography), and ^{125}I are particularly useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for

example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of formula I and following of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagen.

The CRF receptor antagonists of the present invention demonstrate activity at the CRF receptor site including CRF 1 and CRF 2 receptors and may be used in the treatment of conditions mediated by CRF or CRF receptors.

The effectiveness of a compound as a CRF receptor antagonist may be determined by various assay methods. Suitable CRF antagonists of this invention are capable of inhibiting the specific binding of CRF to its receptor and antagonizing activities associated with CRF. A compound of structure (I) may be assessed for activity as a CRF antagonist by one or more generally accepted assays for this purpose, including (but not limited to) the assays disclosed by DeSouza et al. (J. Neuroscience 7: 88,1987) and Battaglia et al. (Synapse 1: 572,1987).

The CRF receptors-binding assay was performed by using the homogeneous technique of scintillation proximity (SPA). The ligand binds to recombinant membrane preparation expressing the CRF receptors which in turn bind to wheatgerm agglutinin coated SPA beads. In the Experimental Part will be disclosed the details of the experiments.

With reference to CRF receptor binding affinities, CRF receptor antagonists of this invention have a Ki less than 10 μm. In a preferred embodiment of this invention, a CRF receptor antagonist has a Ki of less than 10 μm.
In a more preferred embodiment the value of Ki is less than 1 μm and more preferably less than 0.1 μm. As set forth in greater detail below, the Ki values of representative compounds of this invention were assayed by the methods set forth in Example 5.
Preferred compounds having a Ki of less than 1 μm are compound numbers 3-1-3 and 3-1-10. More preferred compounds having a Ki less than 0.1 μm are compound numbers 1-1-1, 1-1-4, 1-1-5, 1-2-1, 3-1-5, and 3-1-6.

Compounds of the invention may be useful in the treatment of central nervous system disorders where CRF receptors are involved. In particular in the treatment or prevention of major depressive disorders including bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, the treatment of anxiety and the treatment of panic disorders. Other mood disorders encompassed within the term major depressive disorders include dysthymic disorder with early or late onset and with or without atypical features, neurotic depression, post traumatic stress disorders and social phobia; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type; and adjustment disorder with

depressed mood. Major depressive disorders may also result from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc.

Compounds of the invention are useful as analgesics. In particular they are useful in the treatment of traumatic pain such as postoperative pain; traumatic avulsion pain such as brachial plexus; chronic pain such as arthritic pain such as occurring in osteo-, rheumatoid or psoriatic arthritis; neuropathic pain such as post-herpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia, fibromyalgia, causalgia, peripheral neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy, AIDS related neuropathy, occipital neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, reflex sympathetic dystrophy, phantom limb pain; various forms of headache such as migraine, acute or chronic tension headache, temporomandibular pain, maxillary sinus pain, cluster headache; odontalgia; cancer pain; pain of visceral origin; gastrointestinal pain; nerve entrapment pain; sport's injury pain; dysmennorrhoea; menstrual pain; meningitis; arachnoiditis; musculoskeletal pain; low back pain e.g. spinal stenosis; prolapsed disc; sciatica; angina; ankylosing spondyolitis; gout; burns; scar pain; itch; and thalamic pain such as post stroke thalamic pain.

Compounds of the invention are also useful for the treatment of dysfunction of appetite and food intake and in circumstances such as anorexia, anorexia nervosa and bulimia.

Compounds of the invention are also useful in the treatment of sleep disorders including dysomnia, insomnia, sleep apnea, narcolepsy, and circadian ritmic disorders.

Compounds of the invention are also useful in the treatment or prevention of cognitive disorders. Cognitive disorders include dementia, amnestic disorders and cognitive disorders not otherwise specified.

Furthermore compounds of the invention are also useful as memory and/or cognition enhancers in healthy humans with no cognitive and/or memory deficit.

Compounds of the invention are also useful in the treatment of tolerance to and dependence on a number of substances. For example, they are useful in the treatment of dependence on nicotine, alcohol, caffeine, phencyclidine (phencyclidine like compounds), or in the treatment of tolerance to and dependence on opiates (e.g. cannabis, heroin, morphine) or benzodiazepines; in the treatment of cocaine, sedative ipnotic, amphetamine or amphetamine-related drugs (e.g. dextroamphetamine, methylamphetamine) addiction or a combination thereof.

Compounds of the invention are also useful as anti-inflammatory agents. In particular they are useful in the treatment of inflammation in asthma, influenza, chronic bronchitis and rheumatoid arthritis; in the treatment of inflammatory diseases of the gastrointestinal tract such as Crohn's disease, ulcerative colitis, inflammatory bowel disease (IBD) and non-steroidal anti-inflammatory drug induced damage; inflammatory diseases of the skin such as

herpes and eczema; inflammatory diseases of the bladder such as cystitis and urge incontinence; and eye and dental inflammation.

Compounds of the invention are also useful in the treatment of allergic disorders, in particular allergic disorders of the skin such as urticaria, and allergic disorders of the airways such as rhinitis.

Compounds of the invention are also useful in the treatment of emesis, i.e. nausea, retching and vomiting. Emesis includes acute emesis, delayed emesis and anticipatory emesis. The compounds of the invention are useful in the treatment of emesis however induced. For example, emesis may be induced by drugs such as cancer chemotherapeutic agents such as alkylating agents, e.g. cyclophosphamide, carmustine, lomustine and chlorambucil; cytotoxic antibiotics, e.g. dactinomycin, doxorubicin, mitomycin-C and bleomycin; anti-metabolites, e.g. cytarabine, methotrexate and 5- fluorouracil; vinca alkaloids, e.g. etoposide, vinblastine and vincristine; and others such as cisplatin, dacarbazine, procarbazine and hydroxyurea; and combinations thereof; radiation sickness; radiation therapy, e.g. irradiation of the thorax or abdomen, such as in the treatment of cancer; poisons; toxins such as toxins caused by metabolic disorders or by infection, e.g. gastritis, or released during bacterial or viral gastrointestinal infection; pregnancy; vestibular disorders, such as motion sickness, vertigo, dizziness and Meniere's disease; post-operative sickness; gastrointestinal obstruction; reduced gastrointestinal motility; visceral pain, e.g. myocardial infarction or peritonitis; migraine; increased intercranial pressure; decreased intercranial pressure (e.g. altitude sickness); opioid analgesics, such as morphine; and gastro-oesophageal reflux disease, acid indigestion, over-indulgence of food or drink, acid stomach, sour stomach, waterbrash/regurgitation, heartburn, such as episodic heartburn, nocturnal heartburn, and meal-induced heartburn and dyspepsia.

Compounds of the invention are of particular use in the treatment of gastrointestinal disorders such as irritable bowel syndrome (IBS); skin disorders such as psoriasis, pruritis and sunburn; vasospastic diseases such as angina, vascular headache and Reynaud's disease; cerebral ischeamia such as cerebral vasospasm following subarachnoid haemorrhage; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders related to immune enhancement or suppression such as systemic lupus erythematosus and rheumatic diseases such as fibrositis; and cough.

Compounds of the invention are useful for the treatment of neurotoxic injury which follows cerebral stroke, thromboembolic stroke, hemorrhagic stroke, cerebral ischemia, cerebral vasospam, hypoglycemia, hypoxia, anoxia, perinatal asphyxia cardiac arrest.

The invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in therapy, in particular in human medicine.

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the preparation of a medicament for use in the treatment of conditions mediated by CRF.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, in particular in the treatment of condition mediated by CRF, comprising administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or a solvate thereof.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.
Compounds of formula (I) may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical formulation.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound of formula (I) or a pharmaceutically acceptable salt thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the composition may take the form of tablets or formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

A proposed dose of the compounds of the invention is 1 to about 1000mg per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected.

Thus for parenteral administration a daily dose will typically be in the range of 1 to about 100 mg, preferably 1 to 80 mg per day. For oral administration a daily dose will typically be within the range 1 to 300 mg e.g. 1 to 100 mg.

EXAMPLES

In the Intermediates and Examples unless otherwise stated:

Melting points (m.p.) were determined on a Gallenkamp m.p. apparatus and are uncorrected. All temperatures refers to °C. Infrared spectra were measured on a FT-IR instrument. Proton Magnetic Resonance (^{1}H-NMR) spectra were recorded at 400 MHz, chemical shifts are reported in ppm downfield (d) from Me_4Si, used as internal standard, and are assigned as singlets (s), doublets (d), doublets of doublets (dd), triplets (t), quartets (q) or multiplets (m). Column chromathography was carried out over silica gel (Merck AG Darmstaadt, Germany). The following abbreviations are used in text: EtOAc = ethyl acetate, cHex = cyclohexane, CH_2Cl_2 = dichloromethane, Et_2O = dietyl ether, DMF = N,N-dimethylformamide, DIPEA=N,N-diisopropylethylamine, MeOH = methanol, Et_3N = triethylamine, TFA = trifluoroacetic acid, THF = tetrahydrofuran, DIBAL-H=diisobutylaluminium hydride, DMAP = dimethylaminopyridine, LHMDS = lithium hexamethyldisilazane; Tlc refers to thin layer chromatography on silica plates, and dried refers to a solution dried over anhydrous sodium sulphate; r.t. (RT) refers to room temperature.

Intermediate 1

(4,6-Dichloro-2-methyl-pyrimidin-5-yl)-acetic acid methyl ester

Sodium (1.74g) was added portionwise to anh. MeOH (60mL), at 0°C, under N_2. After consumption of metallic sodium, acetamidine hydrochloride (7.06g) was added. After 20 min of stirring, the precipitated NaCl was filtered off. A solution of 2-ethoxycarbonyl-succinic acid diethyl ester (6.04g) in anh. MeOH (20mL) was added to the solution of free acetamidine and the mixture was stirred at r.t. for 2 days. The reaction mixture was concentrated to dryness *in vacuo* and the yellow foam (8.69g) obtained was then mixed with $POCl_3$ (70mL) and heated at reflux for 3.5 hr. The resulting solution was cooled to r.t. and poured slowly into ice/water (600mL) and NH_4OH (50mL) with vigorous stirring. The product was extracted with EtOAc (3x50mL) and with Et_2O (3x20mL). The combined organic extracts were washed with H_2O (60mL) and brine (40mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by flash chromatography (silica gel, cHex/EtOAc 9:1) to give the title compound as a yellow solid (4.27g).

NMR (^{1}H, $CDCl_3$): δ 5.85 (m, 1H), 5.15 (dq, 1H), 5.11 (dq, 1H), 3.61 (dt, 2H), 2.67 (s, 3H).

MS (*m/z*): 202 $[M]^+$.2Cl; 167 $[MH\text{-}Cl]^+$,1Cl.

Intermediate 2

2-(4,6-Dichloro-2-methyl-pyrimidin-5-yl)-pent-4-enoic acid methyl ester

A solution of intermediate 1 (1.33g, 5.68mmol) in anh. THF (8mL), under N_2, was treated with lithium bis(trimethylsilyl) amide (1M solution in hexane, 11.5mL, 2eq,) at 0°C for 15 min before allylbromide (0.99mL, 2eq) was added. The mixture was stirred for 4 hr at r.t. and quenched with water (20mL). The product was extracted with EtOAc (2x15mL) and the organic phase was washed with H_2O (2x15mL) and with brine (1x15mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, EtOAc/cHex 1:9) to give the title compound (673.8mg) as a white solid.

NMR (^{1}H, $CDCl_3$): δ 5.77 (m, 1H), 5.03 (m, 2H), 4.43 (dd, 1H), 3.76 (s, 3H), 3.12 (m, 1H), 2.78 (m, 1H), 2.73 (s, 3H).
MS (*m/z*): 374[M] +2Cl.

Intermediate 3
2-(4,6-Dichloro-2-methyl-pyrimidin-5-yl)-pent-4-en-1-ol
To a solution of intermediate 2 (257mg) in anh. CH_2Cl_2 (9.3mL), at –78°C, under N_2, was added DIBAl-H (1M solution in hexane, 5.6mL, 6eq). After the addition was complete the reaction mixture was stirred at –78°C for 1 hr and at 0°C for 2 hr. The reaction mixture was poured into a solution of HCl 0.5N in ice (20mL) and extracted with CH_2Cl_2 (3x10mL). The combined organic extracts were dried over anh. Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (200mg) as a colourless oil.
NMR (^{1}H, $CDCl_3$): δ 5.76 (m, 1H), 5.12 (m, 1H), 5.01 (m, 1H), 4.16 (m, 1H), 4.06 (m, 1H), 3.91 (m, 1H), 2.8-2.6 (m, 2H), 2.70 (s, 3H), 1.50 (t, 1H).
MS (*m/z*): 247 $[M]^+$, 2Cl

Intermediate 4
5-[1-(*tert*-Butyl-dimethyl-silanyloxymethyl)-but-3-enyl]-4,6-dichloro-2-methylpyrimidine
To a solution of intermediate 3 (200mg) in anh. DMF (12mL), at 0°C, under N_2, was added *tert*-butyl-dimethylsilylchloride (245mg, 2eq) and imidazole (553mg, 10eq). The reaction was stirred at r.t. for 2 hr and more *tert*-butyl-dimethylsilylchloride (61mg, 0.5eq) was added. After 1 hr, sat.aq. NH_4Cl (15mL) and EtOAc (15mL) were added and the aqueos phase was extracted with additional EtOAc (2x15mL). The combined extracts were washed with H_2O (10mL), dried over anh. Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 19:1) to give the title compound (237mg) as a colorless oil.
NMR (^{1}H, $CDCl_3$): δ 5.72 (m, 1H), 5.10 (d, 1H), 4.98 (d, 1H), 4.11 (m, 1H), 3.94 (m, 2H), 2.69 (s, 3H), 2.6-2.7 (m, 2H), 0.82 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H).
MS (*m/z*): 361 $[M]^+$, 2Cl

Intermediate 5
{5-[1-(*tert*-Butyl-dimethyl-silanyloxymethyl)-but-3-enyl]-6-chloro-2-methyl-pyrimidin-4-yl}-(2,4-dichlorophenyl)amine
A solution of 2,4-dichloro-aniline (192mg) in anh. THF (12mL), under N_2, was treated with sodium hydride (80% in mineral oil, 393mg) at 0°C for 15 min and then intermediate 4 (434mg, 1.19mmol) in anh. THF (4mL) was added. The mixture was heated to reflux for 3 hr and quenched with water (20mL). The product was extracted with EtOAc (2x20mL), dried over anh. Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, EtOAc/cHex 9:1) to give the title compound (419mg) as a yellow oil.
NMR (^{1}H, $CDCl_3$), T=55°C: δ 8.35 (bs, 1H), 8.13 (bd, 2H), 7.42 (d, 1H), 7.25 (dd, 1H), 5.73 (m, 1H), 5.03 (m, 2H), 4.10 (dd, 1H), 3.99 (dd, 1H), 3.65 (bm, 1H), 2.75 (m, 2H), 2.47 (s, 3H), 0.82 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H).
MS (*m/z*): 486 $[MH]^+$, 3Cl.

Intermediate 6

{5-[1-(*tert*-Butyl-dimethyl-silanyloxymethyl)-but-3-enyl]-6-chloro-2-methyl-pyrimidin-4-yl}-(2,4-dichlorophenyl)-carbamic acid *tert*-butyl ester

To a solution of intermediate 5 (419mg) in anh. CH_2Cl_2 (17mL), under N_2, was added $(Boc)_2O$ (376mg, 2eq) and DMAP (cat). The reaction mixture was stirred at r.t. for 18 hr. The solution was diluted with water (10mL) and extracted with EtOAc (3x15mL). The combined organic extracts were dried over anh. Na_2SO_4, filtered and concentrated to dryness *in vacuo*. Flash chromatography of the crude product (silica gel, cHex/EtOAc 9:1) gave the title compound (420mg) as a yellow solid.

NMR (^1H, $CDCl_3$, 40°C): δ 7.47 (d, 1H), 7.30 (d, 1H), 7.14 (dd, 1H), 5.66 (m, 1H), 5.03-4.89 (m, 2H), 3.98-3.8 (m, 2H), 3.43 (b, 1H), 2.8-2.6 (m, 2H), 2.56 (bs, 3H), 1.41 (s, 9H), 0.77 (s, 9H), -0.02 (s, 3H), -0.10 (s, 3H).

IR (nujol, cm^{-1}): 1716.

MS (*m/z*): 588 $[MH]^+$, 3Cl

Intermediate 7

[6-Chloro-5-(1-hydroxymethyl-but-3-enyl)-2-methyl-pyrimidin-4-yl]-(2,4-dichlorophenyl)-carbamic acid *tert*-butyl ester

To a solution of intermediate 6 (50mg) in anh. DMF (1mL), under N_2, was added TEA·3HF (21µl, 1.5eq). The reaction was stirred at r.t. for 18 hr. The solution was diluted with water (10mL) and extracted with EtOAc (3x15mL). The combined organic extracts were dried over anh. Na_2SO_4, filtered and concentrated to dryness *in vacuo*. Flash chromatography of the crude product (silica gel, cHex/EtOAc 8:2) gave the title compound (30mg) as colourless oil.

NMR (^1H, DMSO, T=70°C): δ 7.69 (d, 1H), 7.43-7.33 (m, 2H), 5.64 (m, 1H), 5.00-4.88 (m, 2H), 4.54 (1H, m), 3.71 (m, 2H), 3.29 (m, 1H), 2.66 (m, 2H), 2.5 (s, 3H), 1.31 (s, 9H).

MS (*m/z*): 472 $[MH]^+$, 3Cl

Intermediate 8

Methanesulfonic acid 2-{4-[*tert*-butoxycarbonyl-(2,4-dichlorophenyl)-amino]-6-chloro-2-methyl-pyrimidin-5-yl}-pent-4-enyl ester

To a solution of intermediate 7 (130mg) in anh. CH_2Cl_2 (5.52mL), at r.t, under N_2, was added Et_3N (192µl, 5eq) and CH_3SO_2Cl (43µl, 2eq). The reaction was stirred at r.t. for 18 hr. The reaction mixture was diluted with water (20mL) and extracted with EtOAc (3x25mL). The combined organic extracts were dried over anh. Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 8:2) to give the title compound (148mg) as a colourless oil.

NMR (^1H, DMSO, T=70°C): δ 7.72 (d, 1H), 7.36 (dd, 1H), 7.28 (d, 1H), 5.56 (m, 1H), 5.00 (d, 1H), 4.92 (d, 1H), 4.46 (m, 2H), 3.51 (m, 1H), 3.02 (s, 3H), 2.65 (m, 1H), 2.54 (s, 3H), 2.50 (m, 1H), 1.38 (s, 9H).

IR (cm^{-1}): 1725, 1641, 1362

MS (*m/z*): 550 $[MH]^+$, 3Cl

Intermediate 9

5-Allyl-4-chloro-7-(2,4-dichlorophenyl)-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*] pyrimidine

A solution of intermediate 8 (120mg) in TFA 20%/CH_2Cl_2 (7mL) was stirred at r.t. for 2 hr. To remove TFA, the solvent of the reaction mixture was evaporated *in vacuo* and repeated additions of CH_2Cl_2 and evaporation were made. The crude intermediate was then dissolved in anh. THF (5mL) and Et_3N (284µl, 5eq) was added. After 1 hr of stirring at r.t., H_2O was added and the aqueous layer was extracted with EtOAc (3x10mL). The combined organic extracts were dried over anh. Na_2SO_4, filtered and concentrated to dryness *in vacuo* to give the title compound (124mg) as a colourless oil.

NMR (^1H, $CDCl_3$): δ 7.49 (dd, 1H), 7.30 (d+s, 2H), 5.77 (m, 1H), 5.16-5.12 (m, 2H), 4.00 (t, 1H), 3.77 (m, 1H), 3.57 (m, 1H), 2.7 (m, 1H), 2.47 (m, 1H), 2.45 (s, 3H).

MS (*m/z*): 354 $[MH]^+$, 3Cl

Intermediate 10

[4-Chloro-7-(2,4-dichlorophenyl)-2-methyl-6,7-dihydro-5H-pyrrolo[2,3d]pyrimidin-5-yl]-acetaldehyde

A solution of intermediate 9 (30mg) in CH_2Cl_2 (4mL) was ozonized (5g.h^{-1}) at -78°C for 5 min. When all the starting material had disappeared (according to TLC in cHex/EtOAc 75/25), the reaction mixture was first flushed with oxygen and then with nitrogen for 20 min. To the cooled reaction mixture was added $(CH_3)_2S$ (25µl, 4eq) and the temperature was allowed to warm up to r.t.. The solution was stirred for 18 hr at that temperature. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography (silica gel, cHex/EtOAc 3:1) to give the title compound (8mg) as a colourless oil.

NMR (^1H, $CDCl_3$): δ 9.87 (s, 1H), 7.48 (t, 1H), 7.30 (m, 2H), 4.23 (t, 1H), 3.90 (m, 1H), 3.60 (dd, 1H), 3.29 (dd, 1H), 2.90 (dd, 1H), 2.42 (s, 3H).

MS (*m/z*): 356 $[MH]^+$, 3Cl.

Intermediate 11

5-[1-(*tert*-Butyl-diphenyl-silanyloxymethyl)-but-3-enyl]-4,6-dichloro-2-methyl-pyrimidine

To a solution of intermediate 3 (152mg) in anh. DMF (4mL), at 0°C, under N_2, was added DMAP (3.8mg), imidazole (420mg) and $Ph_2tBuSiCl$ (0.32mL). The reaction mixture was stirred at r.t. for 2 hr. To this solution were added 5mL of sat.aq. NH_4Cl and the mixture was extracted with Et_2O (2x15mL). The combined organic extracts were washed once with water, once with brine and dried over Na_2SO_4. The solids were filtered, the solvent was evaporated and the crude yellow oil was purified by flash chromatography (silica gel, cHex/EtOAc 95:5) to give the title compound as a colourless oil (270mg).

NMR (^1H, $CDCl_3$): δ 7.65 (dd, 2H), 7.56 (dd, 2H), 7.49-7.36 (m, 6H), 5.67 (m, 1H), 5.03 (dd, 1H), 4.94 (dd, 1H), 4.17 (m, 1H), 4.00 (m, 2H), 2.70 (s, 3H), 2.69 (m, 1H), 2.55 (m, 1H), 0.98 (s, 9H).

MS (*m/z*): 485 $[MH]^+$, 2Cl.

Intermediate 12

{5-[1-(*tert*-Butyl-diphenyl-silanyloxymethyl)-but-3-enyl]-6-chloro-2-methyl-pyrimidin-4-yl}-(2,4-dichlorophenyl)-amine

To a solution of 2,4-dichloroaniline (80mg) in anh. THF (1mL), at 0°C, under N_2, was added NaH (80 % in mineral oil, 31mg) and left to react at r.t. for 30 min. To this mixture cooled back at 0°C was added a solution of intermediate 11 (227mg, 0.467mmol) in anh. THF (2mL). The reaction mixture was stirred at reflux for 5 hr. It was then quenched with water (20mL), and extracted with Et_2O (4x20mL). The combined organic extracts were washed once with water, once with brine and dried over anh. Na_2SO_4. The solids were filtered, the solvent evaporated and the crude orange oil was purified by flash chromatography (silica gel, cHex/EtOAc 95:5) to give the title compound as yellow oil (131.6mg).

NMR (^{1}H, $CDCl_3$): δ 8.2-7.7 (broad d, 1H), 7.55 (d, 2H), 7.50 (d, 2H), 7.40-7.20 (m, 9H), 5.70 (m, 1H), 5.07 (dd, 1H), 4.94 (dd, 1H), 4.06 (m, 2H), 3.70 (m, 1H), 2.71 (m, 2H), 2.50 (m, 3H), 0.95 (s, 9H).

MS (*m/z*): 610 $[MH]^+$, 3 Cl.

Intermediate 13

{5-[1-(*tert*-Butyl-diphenyl-silanyloxymethyl)-but-3-enyl]-6-chloro-2-methyl-pyrimidin-4-yl}-(2,4-dichlorophenyl)-carbamic acid *tert*-butyl ester

To a solution of intermediate 12 (128mg) in anh. CH_2Cl_2 (2mL), at r.t., under N_2, were added Boc_2O (61mg) and DMAP (3mg). The reaction mixture was stirred at r.t. for 16 hr. The complete conversion of the starting material was obtained after 2 days by addition of fresh Boc_2O (58mg + 46mg) and catalytic amounts of DMAP. The reaction mixture was then diluted with water and extracted with CH_2Cl_2 (2x5mL). The combined organic extracts were washed once with water and dried over anh. Na_2SO_4. The solids were filtered, the solvent evaporated and the crude yellow oil was purified by flash chromatography (silica gel, cHex/EtOAc 9:1) to give the title compound as pale yellow oil (138mg).

NMR (^{1}H, DMSO, 70 °C): δ 7.67 (d, 1H), 7.54-7.30 (m, 5H+5H), 7.19 (m, 2H), 5.51 (m, 1H), 4.87 (d, 1H), 4.82 (d, 1H), 3.94 (m, 1H), 3.84 (bm, 1H), 3.53 (m, 1H), 2.57 (s, 3H), 2.62 (m, 1H), 2.35 (m, 1H), 1.35 (s, 9H), 0.90 (s, 9H).

IR (nujol, cm^{-1}): 1732.

MS (*m/z*): 710 $[MH]^+$, 3 Cl, 722 $[M+Na]^+$, 610 $[MH-Boc+H]^+$.

Intermediate 14

{5-[1-(*tert*-Butyl-diphenyl-silanyloxymethyl)-3-hydroxy-propyl]-6-chloro-2-methyl-pyrimidin-4-yl}-(2,4-dichlorophenyl)-carbamic acid *tert*-butyl ester

A solution of intermediate 13 (108mg) in 3mL of CH_2Cl_2/CH_3OH (9:1) was cooled at –78°C. O_3 was bubbled in the solution for 30 min under magnetic stirring. $NaBH_4$ (23.1mg) was then added under N_2 atmosphere at low temperature. The reaction mixture was stirred for 3 hr at r.t.. It was then quenched with water and extracted with CH_2Cl_2 (2x5mL). The combined organic extracts were washed once with sat.aq. NH_4Cl and dried over anh. Na_2SO_4. The solids were filtered, the solvent was evaporated and the crude yellow oil was purified by flash chromatography (silica gel, cHex/EtOAc 9:1) to give the title compound as a colourless oil (59mg).

NMR (^{1}H, DMSO, 70 °C): δ 7.65 (d, 1H), 7.48-7.34 (m, 5H+5H), 7.28 (d, 1H), 7.12 (bd, 1H), 5.51 (m, 1H), 4.18 (t, 1H), 4.02 (bt, 1H), 3.82 (bm, 1H), 3.51 (m, 1H), 3.29 (bm, 2H), 2.55 (s, 3H), 2.05 (m, 1H), 1.84 (bm, 1H), 1.35 (s, 9H), 0.89 (s, 9H).

IR (film, cm^{-1}): 1733.
MS (*m/z*): 714 $[MH]^+$, 3 Cl, 736 $[M+Na]^+$, 3 Cl, 678 $[MH-HCl]^+$, 2 Cl, 614 $[MH-Boc+H]^+$.

Intermediate 15

Methanesulfonic acid 3-{4-[*tert*-butoxycarbonyl-(2,4-dichlorophenyl)-amino]-6-chloro-2-methyl-pyrimidin-5-yl}-4-(*tert*-butyl-diphenyl-silanyloxy)-butyl ester

To a solution of intermediate 14 (57mg) in anh. CH_2Cl_2 (1mL), were added Et_3N (55µl) and MsCl (13µl) at r.t., under N_2. The reaction mixture was stirred for 5 hr, diluted with water and extracted with CH_2Cl_2 (2x5mL). The combined organic extracts were washed once with water, once with brine, and dried over anh. Na_2SO_4. The solids were filtered, the solvent evaporated to obtain the crude colourless title compound (60mg).
NMR (^1H, DMSO, 70 °C): δ 7.65 (d, 1H), 7.50-7.34 (m, 5H+5H), 7.24 (bd, 1H), 7.15 (bd, 1H), 4.20-4.00 (m, 3H), 3.80-3.60 (m, 2H), 3.02 (s, 3H), 2.56 (s, 3H), 2.30-2.10 (m, 2H), 1.35 (s, 9H), 0.89 (s, 9H).
IR (nujol, cm^{-1}): 1725.
MS (*m/z*): 794 $[MH]^+$, 3 Cl, 694 $[MH-Boc+H]^+$.

Intermediate 16

Methanesulfonic acid 4-(*tert*-butyl-diphenyl-silanyloxy)-3-[4-chloro-6-(2,4-dichlorophenyl-amino)-2-methyl-pyrimidin-5-yl]-butyl ester

To a solution of intermediate 15 (58mg) in anh. CH_2Cl_2 (1mL), at r.t., under N_2, was added TFA (200µl, 35eq). The reaction mixture was stirred for 16 hr, then evaporated under reduced pressure, diluted several times with CH_2Cl_2 and evaporated again to obtain the crude title compound (64mg) as a yellow oil.
MS (*m/z*): 694 $[MH]^+$, 3 Cl.

Intermediate 17

5-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4-chloro-8-(2,4-dichlorophenyl)-2-methyl-5,6,7,8-tetrahydro-pyrido[2,3-*d*]pyrimidine

To a solution of intermediate 16 (64mg) in anh. THF (1mL), at 0°C, under N_2, was added Et_3N (100µl). The reaction mixture was stirred for 16 hr at r.t., then diluted with water and extracted with Et_2O (2x20mL). The combined organic extracts were washed once with water, once with brine and dried over anh. Na_2SO_4. The solids were filtered, the solvent was evaporated and the crude oil was purified by flash chromatography (silica gel, cHex/EtOAc 95:5). to obtain the title compound as a colourless oil (26.4mg).
NMR (^1H, $CDCl_3$): δ 7.74-6.98 (m, 5H+5H+1H+2H), 4.10-3.90, 3.76-3.55, 3.48-3.28 (m, 5H), 2.58-2.38 (m, 1H), 2.24, 2.22 (s, 3H), 2.1-1.9 (m 1H), 1.07 (s, 9H).
MS (*m/z*): 598 $[MH]^+$, 3 Cl.

Intermediate 18

[4-Chloro-8-(2,4-dichlorophenyl)-2-methyl-5,6,7,8-tetrahydro-pyrido[2,3-*d*]pyrimidin-5-yl]-methanol

To a solution of intermediate 17 (22mg) in anh. DMF (2mL), at r.t., under N_2, was added $Et_3N{\cdot}3HF$ (20µl). The reaction mixture was stirred for 4 hr at 40°C, then diluted with water

and extracted with Et_2O (3x20mL). The combined organic extracts were washed once with water, once with brine and dried over anh. Na_2SO_4. The solids were filtered, the solvent evaporated and the crude oil was purified by flash chromatography (silica gel, cHex/EtOAc 2:1) to give the title compound as colourless oil (13mg).

NMR (^{1}H, DMSO, 90 °C): δ 7.66 (bs, 1H), 7.50-7.42 (m, 2H), 4.66 (m, 1H), 3.82 (bt, 1H), 3.68 (m, 1H), 3.66-3.36 (m, 2H), 3.20 (m, 1H), 2.33 (m, 1H), 2.14 (s, 3H), 1.94 (m, 1H).
MS (*m/z*): 358 $[MH]^+$, 3 Cl, 360.

Intermediate 19

Methanesulfonic acid 4-chloro-8-(2,4-dichlorophenyl)-2-methyl-5,6,7,8-tetrahydro-pyrido[2,3-*d*]pyrimidin-5-ylmethyl ester

To a solution of intermediate 18 (13mg) in anh. CH_2Cl_2 (1mL), at 0 °C, under N_2, were added Et_3N (20.0µl) and MsCl (6.0µl). The reaction mixture was stirred for 16 hr at r.t., then diluted with water and extracted with CH_2Cl_2 (3x10mL). The combined organic extracts were washed once with water, once with brine and dried over anh. Na_2SO_4. The solids were filtered and the solvent was evaporated to give the crude title compound (14.7mg) as a colourless oil.

NMR (^{1}H, $CDCl_3$): δ 7.50 (dd, 1H), 7.40-7.15 (m, 2H), 4.50-4.15 (m, 2H), 3.90-3.70 (m, 1H), 3.65-3.30 (m, 2H), 3.05 (s, 3H), 2.45-2.2 (m, 1H), 2.25 (s, 3H), 2.2- 2.0 (m, 1H).
MS (*m/z*): 438 $[MH]^+$, 3 Cl.

Intermediate 20

5-Iodo-pentanoic acid methyl ester

To a solution of methyl 4-bromovalerate (14g) in acetone (63mL), NaI (11.5g) was added and the mixture was refluxed for 2 hr. It was then cooled to r.t. and the precipitate was filtered. The filtrate was evaporated and ether was added to the residue. The resulting suspension was filtered and the ethereal phase washed with 5% aq $NaHSO_3$ (3x100mL) and with brine (1x100mL) and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated to give the crude title compound as a yellow oil (15.85g).

NMR (^{1}H, $CDCl_3$): δ 3.68 (s, 3H), 3.19 (t, 2H), 2.34 (t, 2H), 1.86 (m, 2H), 1.74 (m, 2H).
MS (*m/z*): 242 $[M]^+$, 211 $[M\text{-}OMe]^+$,115 $[M\text{-}I]^+$.

Intermediate 21

2-(2,4-dichlorophenyl)-heptanedioic acid dimethyl ester

To a solution of methyl 2,4-dichlorophenylacetate (2g) in anh. THF (27mL), at -78°C, under N_2, a 1M solution of LHMDS in THF (10.04mL) was added dropwise and the mixture was stirred at -78°C for 30 min. Neat intermediate 20 (2.87g, 1.3eq) was then added dropwise at -78°C and the dropping funnel was washed with anh. THF (2mL). The cooling bath was then removed and the mixture was stirred at r.t. for 3.5 hr. The solvents were evaporated under reduced pressure. The residue was dissolved in ether, washed with water (3x30mL) and brine (1x30mL) and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 9:1) to give the title compound as a pale yellow oil (2.7g).

NMR (^{1}H, $CDCl_3$): δ 7.39 (d, 1H), 7.30 (d, 1H), 7.22 (dd, 1H), 4.10 (t, 1H), 3.67 (s, 3H), 3.65 (s, 3H), 2.29 (t, 2H), 2.05 (m, 1H), 1.74 (m, 1H), 1.64 (m, 2H), 1.40-1.20 (m, 2H).
IR (film, cm^{-1}): 1738.
MS (*m/z*): 332 $[M]^+$, 300 $[M-CH_3OH]^+$, 159.

Intermediate 22
3-(2,4-Dichlorophenyl)-2-hydroxy-cyclohex-1-enecarboxylic acid methyl ester
Sodium (0.7g) was added portionwise under vigorous stirring, at 0°C, under N_2, to anh. MeOH (26mL). After consumption of metallic sodium, anh. toluene (100mL) was added and a MeOH/toluene mixture (36mL) was distilled off by means of a Dean-Stark apparatus. The mixture was allowed to cool to r.t. before adding a solution of intermediate 21 (2.52g) in anh. toluene (15mL). The mixture was refluxed for 3.5 hr and then cooled to r.t. before acidifying with AcOH. The organic phase was washed with water. The aqueous phase was extracted with EtOAc (2x20mL) and the combined organic extracts were washed with water (2x20mL), brine (2x20mL) and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 95:5) to obtain the title compound (colourless oil: 1.8g)
NMR (^{1}H, $CDCl_3$): δ 12.19 (s, 1H), 7.40 (d, 1H), 7.19 (dd, 1H), 7.08 (d, 1H), 4.07 (t, 1H), 3.81 (s, 3H), 2.35 (m, 2H), 2.01 (m, 1H), 1.73 (m, 1H), 1.60 (m, 2H).
MS (*m/z*): 300 $[M]^+$, 265, 233.

Intermediate 23
5-(2,4-Dichlorophenyl)-6-oxo-cyclohex-1-enecarboxylic acid methyl ester
Phenylselenenylchloride (2.44g) was placed in a two-necked flask under nitrogen and dissolved in anh. CH_2Cl_2 (21mL). The brown solution was cooled to 0°C and anh. pyridine (0.9mL) was added resulting in a yellow solution which was stirred at 0°C for 30 min. A solution of intermediate 22 (1.5g) in anh. CH_2Cl_2 (12mL) was added dropwise at 0°C and the reaction mixture was stirred at r.t. for 4.5 hr. The reaction mixture was then transfered to a separatory funnel and washed with 1M HCl (2x10mL) and with water (3x10mL). The CH_2Cl_2 layer was then transfered to a flask and cooled to 0°C. Aqueous H_2O_2 (30% w/w, 3mL) was added and the mixture was stirred for 10 min at 0°C followed by addition of a second aliquot of H_2O_2 (3mL). The reaction mixture turned colourless and a white solid formed. After 20 min at 0°C the mixture was washed with sat.aq. $NaHCO_3$ (2x10mL) and brine (1x10mL) and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated to give the title compound (1.45g) as a pale yellow oil, which becomes solid by cooling.
NMR (^{1}H, $CDCl_3$): δ 7.77 (m, 1H), 7.43 (d, 1H), 7.24 (dd, 1H), 7.11 (d, 1H), 4.12 (dd, 1H), 3.83 (s, 3H), 2.70 (m, 2H), 2.40-2.20 (m, 2H).
IR (film, cm^{-1}): 1737, 1673.
MS (*m/z*): 298 $[M]^+$, 263 $[M-Cl]^+$, 126.

Intermediate 24
5-Allyl-8-(2,4-dichlorophenyl)-2-methyl-5,6,7,8-tetrahydroquinazolin-4-ol

To a solution of intermediate 23 (690mg) in anh. CH_2Cl_2 (6.5mL), at -78°C, $TiCl_4$ (0.255mL) was added. The resulting brown solution was stirred at -78°C for 5 min, after which a solution of allyltrimethylsilane (0.440mL) in anh. CH_2Cl_2 (6.5mL) was added. After stirring for 1.5 hr at -78°C, the reaction was quenched with water, diluted with CH_2Cl_2 and the mixture was allowed to warm to r.t.. The aqueous layer was extracted with CH_2Cl_2 and the organic phase was washed with brine (1x10mL) and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated to obtain the allylated compound (676mg) as pale yellow oil and as a mixture of diastereoisomeric enolesters and ketoesters.

Sodium (140mg, 3eq) was added portionwise to anh. MeOH (6mL) under N_2. After consumption of metallic sodium, acetamidine hydrochloride (600mg) was added. After 10 min of stirring, the precipitated NaCl was filtered off and washed with anh. MeOH (2mL). The solution of free acetamidine was added to the crude allylated product (676g) and the mixture was stirred at r.t. for 18 hr. The solvent was evaporated and the crude product was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH 98:2 → 97:3) to give the title compound as a 3:1 mixture of two diastereoisomers (538mg).

NMR (^{1}H, $CDCl_3$)(*anti* isomer): δ 11.82 (bs, 1H), 7.42 (d, 1H), 7.10 (dd, 1H), 6.58 (d, 1H), 5.87 (m, 1H), 5.06 (m, 2H), 4.34 (d, 1H), 3.01 (m, 1H), 2.68 (m, 1H), 2.37 (s, 3H), 2.20 (m, 1H), 2.07 (m, 1H), 1.80 (m, 1H), 1.70 (m, 1H), 1.49 (m, 1H).

NMR (^{1}H, $CDCl_3$)(*syn* isomer): δ 11.70 (bs, 1H), 7.36 (d, 1H), 7.12 (dd, 1H), 6.81 (d, 1H), 5.83 (m, 1H), 5.02 (m, 2H), 4.23 (bt, 1H), 2.98 (m, 1H), 2.66 (m, 1H), 2.28 (s, 3H), 2.20 (m, 1H), 2.02-1.80 (m, 2H), 1.62-1.47 (m, 2H).

MS (*m/z*): 348 $[M]^+$, 307 $[M - allyl]^+$.

Intermediate 25

Anti-5-Allyl-4-chloro-8-(2,4-dichlorophenyl)-2-methyl-5,6,7,8-tetrahydroquinazoline (isomer 1) and *Syn*-5-Allyl-4-chloro-8-(2,4-dichlorophenyl)-2-methyl-5,6,7,8-tetrahydroquinazoline (isomer 2)

Intermediate 24 (538mg) was dissolved in $POCl_3$ (5mL) and the mixture was refluxed for 2 hr. The $POCl_3$ was evaporated, the residue was dissolved in CH_2Cl_2 and treated with conc. NH_4OH. The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x10mL). The combined organic extracts were washed with brine (2x10mL) and dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 95:5)to give the title compound isomer 1 (262mg) and the title compound isomer 2 (94mg) as colourless oils.

isomer 1 :NMR (^{1}H, $CDCl_3$): δ 7.44 (d, 1H), 7.06 (dd, 1H), 6.20 (d, 1H), 5.86 (m, 1H), 5.14 (m, 2H), 4.63 (d, 1H), 3.16 (m, 1H), 2.60 (m, 1H), 2.59 (s, 3H), 2.30 (m, 1H), 2.16 (m, 1H), 1.89 (m, 1H), 1.80 (m, 1H), 1.64 (m, 1H).

MS (*m/z*): 367 $[M+H]^+$.

isomer 2 :NMR (^{1}H, $CDCl_3$): δ 7.36 (d, 1H), 7.15 (dd, 1H), 6.83 (bd, 1H), 5.82 (m, 1H), 5.10-5.06 (m, 2H), 4.35 (m, 1H), 3.12 (m, 1H), 2.62 (m, 1H), 2.48 (s, 3H), 2.25 (m, 1H), 2.22-2.00 (m, 2H), 1.90-1.78 (m, 2H).

MS (*m/z*): 367 $[M+H]^+$.

Intermediate 26

[5-Allyl-7-(2,4-dichlorophenyl)-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]-cyclopropylmethyl-amine

A solution of intermediate 9 (160mg, 0.451mmol) in cyclopropylmethylamine (0.5mL) was heated at 130°C (screw cap vial) for 4 hr. The amine was then evaporated and the residue was purified by flash chromatography (silica gel, gradient: CH_2Cl_2/EtOAc 9:1 to 7:3) to give the title compound (162mg, 0.416mmol, 92%) as a colourless oil.

NMR (^{1}H, $CDCl_3$): δ 7.43 (d, 1H), 7.36 (d, 1H), 7.24 (dd, 1H), 5.86 (m, 1H), 5.20-5.13 (m, 2H), 4.39 (bt, 1H), 3.88 (dd, 1H), 3.71 (dd, 1H), 3.40-3.30 (m, 3H), 2.46 (m, 1H), 2.35 (m, 1H), 2.36 (s, 3H), 1.08 (m, 1H), 0.60-0.27 (m, 4H).

MS (*m/z*): 389 $[M+H]^+$ (2 Cl).

Intermediate 27

5-Cyclopropylmethyl -1-(2,4-dichlorophenyl)- 7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylen-4-ol

To a solution of intermediate 26 (160mg, 0.411mmol) in a 8:1 mixture of acetone and water (8mL) was added N-methylmorpholine-N-oxide (100mg, 2eq), followed by a 4% aqueous solution of OsO_4 (0.260mL, 0.1eq) and the reaction mixture was stirred at r.t. for 3.5 hr. The solution was then concentrated under reduced pressure, and sat.aq. Na_2SO_3 (50mL) was added. The aqueous phase was extracted with EtOAc (3x10mL) and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated. The crude diol was dissolved in a 1:1 mixture of THF and water (8mL) and $NaIO_4$ (132mg, 1.5eq) was added. The reaction mixture was stirred at r.t. for 45 min. It was then diluted with water and extracted with EtOAc (3x10mL). The combined organic extracts were washed once with brine and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 1:1). The title compound was obtained as a colourless oil (111mg, 0.284mmol, 69%).

NMR (^{1}H, DMSO-d_6): δ 7.68 (d, 1H), 7.44 (m, 2H), 5.92 (d, 1H), 5.17 (m, 1H), 4.13 (t, 1H), 3.79 (m, 1H), 3.76 (dd, 1H), 3.50 (m, 1H), 3.15 (dd, 1H), 2.24 (m, 1H), 2.21 (s, 3H), 1.43 (dt, 1H), 1.06 (m, 1H), 0.50-0.20 (m, 4H).

MS (*m/z*): 391 $[M+H]^+$ (2 Cl).

Intermediate 28

5-Cyclopropylmethyl-1-(2,4-dichlorophenyl)-4-methoxy-7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene

A solution of PTSA (1.5mg, 0.042eq) in anh. MeOH (1.5mL) was added to the neat intermediate 27 (73mg, 0.187mmol) and the resulting solution was stirred at r.t. for 18 hr. The solvent was then evaporated and the residue was dissolved in CH_2Cl_2 (10mL). A solution prepared by diluting sat.aq. $NaHCO_3$ with water (1:1, 10mL) was then added and the aqueous phase was extracted with CH_2Cl_2 (2x10mL). The combined organic extracts were washed with water (1x10mL), sat.aq. NaCl (1x10mL) and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated. The title compound was obtained as a yellow oil and was used in the subsequent step without further purification (68mg, 0.168mmol, 90%).

NMR (^{1}H, acetone-d_6): δ 7.53 (d, 1H), 7.47 (d, 1H), 7.35 (dd, 1H), 4.93 (t, 1H), 4.23 (t, 1H), 4.05 (dd, 1H), 3.78 (dd, 1H), 3.51 (m, 1H), 3.39 (s, 3H), 3.13 (dd, 1H), 2.53 (dddd, 1H), 2.25 (s, 3H), 1.40 (dt, 1H), 1.09 (m, 1H), 0.50-0.20 (m, 4H).
MS (*m/z*): 405 $[MH]^+$ 2 Cl).

Intermediate 29

Alternative preparation of intermediate 2: 2-[4-Chloro-7-(2,4-dichlorophenyl)-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-ethanol

To a solution of intermediate 10 (93mg, 0.261mmol) in a 2:1 mixture of anh. CH_2Cl_2/MeOH (3mL), at 0°C, under N_2, was added $NaBH_4$ (20mg, 2eq). The reaction mixture was stirred at r.t. for 1 hr. The reaction was then quenched with water (10mL) and concentrated under reduced pressure. The aqueous phase was extracted with EtOAc (3x10mL) and the combined organic extracts were dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated. The title compound was obtained as a white solid (80mg, 0.223mmol, 85%) and was used without further purification in the subsequent step.
NMR (^{1}H, $CDCl_3$): δ 7.54 (d, 1H), 7.40-7.30 (m, 2H), 4.20 (t, 1H), 3.93 (dd, 1H), 3.87 (m, 2H), 3.75 (m, 1H), 2.57 (s, 3H), 2.27 (m, 1H), 1.99 (m, 1H).
MS (*m/z*): 358 $[MH]^+$ (3Cl).

Intermediate 30

Methanesulfonic acid 2-[4-chloro-7-(2,4-dichlorophenyl)-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-ethyl ester

To a solution of intermediate 29 (80mg, 0.223mmol) in anh. CH_2Cl_2 (2mL), at r.t., under N_2, was added triethylamine (155μL, 5eq) followed by mesyl chloride (35μL, 2eq). The reaction mixture was stirred at r.t. for 1 hr. It was then quenched with water (10mL) and extracted with CH_2Cl_2 (3x10mL). The combined organic extracts were washed once with brine and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated. The crude compound was purified by flash chromatography (silica gel, cHex/EtOAc 1:1). The title compound was obtained as a pale yellow oil (71mg, 0.163mmol, 73%).
NMR (^{1}H, $CDCl_3$): δ 7.48 (m, 1H), 7.32 (m, 2H), 4.38 (m, 2H), 4.09 (t, 1H), 3.82 (dd, 1H), 3.66 (m, 1H), 3.00 (s, 3H), 2.46 (m, 1H), 2.42 (s, 3H), 2.14 (m, 1H).
MS (*m/z*): 436 $[MH]^+$ (3Cl).

Intermediate 31

{5-[1-(*tert*- Butyl-diphenyl-silanyloxxymethyl)-but-3-enyl]-6-chloro-2-methyl-pyrimidin-4-yl}-(2,4-bis-trifluoromethyl-phenyl)-amine

To a solution of 2,4-bis(trifluoromethyl)aniline (2.11g, 9.21mmol) in anh. DMF (45mL), at 0°C, under N_2, was added NaH 80%/oil (608mg, 2.2eq). After 30 min the reaction mixture was warmed to r.t. After 30 min a solution of intermediate 11 (4.46g, 9.21mmol.) in anh. DMF (30mL) was added. The reaction mixture was left at r.t. for 15 min, then cooled down at 0°C and diluted with water. The aqueous phase was extracted with EtOAc (3x50mL) and the combined organic extracts were washed with water (50mL), brine (50mL) and then dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated. The crude product

was purified by flash chromatography (silica gel, cHex/EtOAc 97:3) to give the title compound (4.546g, 6.71mmol, 73%) as a clear oil.
NMR (^{1}H, DMSO): δ 8.34 (s, 1H), 7.97 (s, 1H), 7.53 (d, 1H), 7.48 (d, 1H), 7.54-7.31 (m, 10H), 5.7 (m, 1H), 4.97 (d, 1H), 4.90 (d, 1H), 4.11 (m, 1H), 3.99 (m, 1H), 3.72 (m, 1H), 2.56 (m, 2H), 2.18 (s, 3H), 0.91 (s, 9H).
MS (*m/z*): 678 $[MH]^+$.

Intermediate 32
5-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4-chloro-2-methyl-8-(2,4-bis-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-*d*]pyrimidin-7-ol
To a solution of intermediate 31 (2g, 2.95mmol) in an 8:1 mixture of acetone/H_2O (36mL), at r.t., were added *N*-methyl-morpholine-*N*-oxide (716mg, 2eq) and OsO_4 4%/H_2O (1.8mL, 0.1eq). After 3.5 h the solvent was evaporated and a saturated solution of Na_2SO_3 was added. The product was extracted with EtOAc (2x20mL) and the combined organic extracts were dried over anh. Na_2SO_4. The solids were filtered and the solvent was evaporated. The oil obtained was dissolved in a 9:1 mixture of THF/H_2O (45mL) and $NaIO_4$ (947mg, 1.5eq) was added. The reaction mixture was stirred at r.t. for 18 hr. It was then diluted with water and the product was extracted with EtOAc (3x20mL). The combined organic extracts were washed with brine and dried over anh. Na_2SO_4. The solids were filtered and the solvent was evaporated to give the title compound (1.932g, 2.85mmol, 96%), as a mixture of two diastereoisomers.
NMR (^{1}H, Acetone):
Isomer 1: δ 8.15 (m, 2H), 7.72 (m, 5H), 7.44 (m, 6H), 6.19 (d, 1H), 5.27 (m, 1H), 4.41 (t, 1H), 4.08 (dd, 1H), 3.52 (m, 1H), 2.81 (m, 1H), 2.35 (m, 1H), 2.15 (s, 3H), 1.07 (s, 9 H).
Isomer 2: δ 8.15 (m, 2H), 7.72 (m, 5H), 7.44 (m, 6H), 5.8-5.4 (m, 2H), 4-3.8 (m, 2H), 3.6-3.4 (m, 1H), 3-2.8 (m, 1H), 2.35 (m, 1H), 2.15 (s, 3H), 1.07 (s, 9H).
MS (*m/z*): 680 $[MH]^+$.

Intermediate 33
5-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4-chloro-2-methyl-8-(2,4-bis-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-*d*]pyrimidine
To a solution of intermediate 32 (1.93g, 2.84mmol) in anh. CH_2Cl_2 (50mL), at -78°C, were added Et_3SiH (1.82mL, 4eq) and $BF_3{\cdot}Et_2O$ (1.58mL, 4.4eq). The reaction mixture was stirred 1 hr at -78°C and then was allowed to warm to r.t. and stirred for 18 hr. A saturated solution of $NaHCO_3$ was then added and the product was extracted with CH_2Cl_2 (3x50mL). The combined organic extracts were dried over anh. Na_2SO_4, the solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 95:5) to give the title compound (0.607g, 9.16mmol, 32%) as a white solid.
NMR (^{1}H,$CDCl_3$): δ 7.98-7.94 (d, 1H), 7.88-7.80 (dd, 1H), 7.7-7.58 7.44-7.32 (m, 10H), 7.35-7.14 (d, 1H), 3.98-3.94 (dd, 1H), 3.73-3.55 (m, 1H), 3.63-3.59 (m, 1H), 3.44-3.36 3.38-3.3 (2m, 2H), 2.55-2.4 (m, 1H), 2.17-2.15 (s, 3H), 2.04-1.9 (m, 1H), 0.98 (s, 9H).
MS (*m/z*): 664$[MH]^+$.

Intermediate 34

{4-Chloro-2-methyl-8-(2,4-bis-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-*d*]pyrimidin-5-yl}-methanol

To a solution of intermediate 33 (600mg, 0.91mmol) in anh. DMF (15mL), at r.t., under N_2, was added $Et_3N{\cdot}3HF$ (1.25mL, 8.4eq) and the reaction mixture was heated at 40°C for 6.5 h. It was then cooled down to r.t. and diluted with water. The product was extracted with Et_2O (3x20mL). The combined organic extracts were washed with brine and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 6:4) to give the title compound (337mg, 0.8mmol, 88%) as a clear oil.

NMR (^{1}H, DMSO): δ 8.26-8.12 (m, 2H), 7.9-7.8 (d, 1H), 5.08-4.98 (t, 1H), 3.9-3.6 (2H), 3.7-3.3 (2H), 3.24-3.10 (1H), 2.3 (m, 1H), 2.09 (s, 3H), 2.0-1.8 (m, 1H).

MS (*m/z*): 426$[MH]^+$.

Intermediate 35

Methanesulfonic acid 4-chloro-2-methyl-8-(2,4-bis-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-*d*]pyrimidin-5-ylmethyl ester

To a solution of intermediate 34 (200mg, 0.47mmol), in anh. CH_2Cl_2 (10mL), under N_2, at 0°C, were added Et_3N (0.26mL, 4eq) and MsCl (73µl, 2eq). The reaction mixture was warmed to r.t. and stirred for 18 hr. It was then diluted with water and the product was extracted with CH_2Cl_2 (3x20mL). The combined organic extracts were washed with brine and dried over anh. Na_2SO_4. The solids were filtered, the solvent evaporated and the crude product was purified by flash chromatography (silica gel, cHex/EtOAc 6:4) to give the title compound (203mg, 0.4mmol, 86%) as a clear oil.

NMR (^{1}H,DMSO): δ 8.3 8.14 (m, 2H), 7.95-7.8 (d+d, 1H), 4.56-4.20 (2H), 3.9-3.4 (m, 3H), 3.25 (s, 3H), 2.11 (s, 3H), 2.2-1.9 (m, 2H).

MS (*m/z*): 504$[MH]^+$.

Intermediate 36

{4-Chloro-2-methyl-7-(2,4-bis-trifluoromethyl-phenyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-acetaldehyde

To a solution of intermediate 31 (0.6g, 0.886mmol) in anh. DMF (15mL), at r.t., under N_2 was added $Et_3N{\cdot}3HF$ (1.22mL, 8.4eq). The reaction mixture was stirred at r.t. for 18 hr. The reaction mixture was diluted with water and the product was extracted with Et_2O (3x20mL). The combined organic extracts were washed with brine and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 8:2) to give an alcohol intermediate (346mg, 89%) which was dissolved into anh. CH_2Cl_2 (15mL) and cooled down to 0°C. Et_3N (0.44mL, 4eq) and MsCl (0.122mL, 2eq) were added, and the reaction mixture was warmed to r.t. and stirred for 18 hr. The reaction mixture was diluted with water and the product was extracted with CH_2Cl_2 (3x20mL). The combined organic extracts were dried over anh. Na_2SO_4, the solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 8:2) to give a cyclic pyrrolidine intermediate (276mg, 83%). This intermediate was dissolved in an 8:1 mixture of acetone/H_2O (18mL)

and *N*-methyl-morpholine-*N*-oxide (230mg, 2eq) and OsO_4 (403 µl, 0.1eq) were added. The reaction mixture was stirred at r.t. for 6 h. The solvent was evaporated and a saturated solution of Na_2SO_3 was added. The product was extracted with EtOAc (3x20mL) and the combined organic extracts were dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated. The crude product was dissolved into a 9:1 mixture of THF/H_2O (15mL) and $NaIO_4$ (210mg, 1.5eq) was added. The reaction mixture was stirred at r.t. for 18 hr, then it was diluted with water and the product was extracted with EtOAc (3x20mL). The combined organic extracts were washed with brine and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated to give the title compound (250mg, 0.59mmol, 90%) as a clear oil.

NMR (^{1}H, $CDCl_3$): δ 9.86 (s, 1H), 8.05 (s, 1H), 7.93 (d, 1H), 7.5 (d, 1H), 4.24 (m, 1H), 3.93 (m, 1H), 3.65 (dd, 1H), 3.25 (dd, 1H), 2.93 (dd, 1H), 2.4 (s, 3H).

MS (*m/z*): 424$[MH]^+$.

Intermediate 37

Methanesulfonic acid 2-{4-chloro-2-methyl-7-(2,4-bis-trifluoromethyl-phenyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-ethyl ester

To a solution of intermediate 36 (250mg, 0.59mmol) in a 9:1 mixture of CH_2Cl_2/MeOH (15mL), at 0°C, under N_2, was added $NaBH_4$ (44mg, 2eq). The reaction mixture was stirred for 30 min at 0°C. Conc. HCl was added until pH = 7 was reached. The reaction mixture was then diluted with water and the product was extracted with CH_2Cl_2 (3x20mL). The combined organic extracts were washed with brine and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated to give a white solid (alcohol intermediate, 231mg, 0.54mmol, 93%) which was dissolved in anh. CH_2Cl_2 (15mL). The reaction mixture was cooled at 0°C, then Et_3N (302 µl, 4eq) and MsCl (85 µl, 2eq) were added. The reaction mixture was stirred at r.t. for 18 hr, then it was diluted with water and the product was extracted with CH_2Cl_2 (3x20mL). The combined organic extracts were dried over anh. Na_2SO_4, the solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 6:4) to give the title compound (252mg, 0.50mmol, 93%) as a clear oil.

NMR (^{1}H, $CDCl_3$): δ 8.05 (bs, 1H), 7.94 (bd, 1H), 7.53 (bd, 1H), 4.42 (m, 2H), 4.07 (t, 1H), 3.83 (dd, 1H), 3.71 (m, 1H), 3.04 (s, 3H), 2.46 (m, 1H), 2.43 (s, 3H), 2.13 (m, 1H).

MS (*m/z*): 504$[MH]^+$.

Intermediates 38 and 39

(*S*)-2-Acetoxy-propionic acid 4-chloro-2-methyl-8-(2,4-bis-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-*d*]pyrimidin-5(*S*)-ylmethyl ester and (*S*)-2-Acetoxy-propionic acid 4-chloro-2-methyl-8-(2,4-bis-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-*d*]pyrimidin-5(*R*)-ylmethyl ester

To a solution of intermediate 34 (320mg, 0.753mmol) in CH_2Cl_2 (7mL) at 0°C, under N_2, were added DMAP (230mg, 2.5eq), Et_3N (0.73mL, 7eq) and (*S*)-2-acetoxypropionyl chloride (0.61mL, 6.4eq). The reaction mixture was stirred at 0°C for 30 min, warmed to r.t and diluted with a saturated solution of $NaHCO_3$. The product was extracted with CH_2Cl_2 (3x30mL) and the combined organic extracts were dried over anh. Na_2SO_4. The solids were

filtered and the solvent was evaporated. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 8:2). The two diastereoisomers were separated by preparative chiral hplc: intermediate 38 (97mg, 0.18mmol, d.e. = 97%) and intermediate 39 (89.7mg, 0.17mmol, d.e.>99%) were obtained as white solids.

NMR (^{1}H, Acetone):

Intermediate 38: δ 8.22-8.13 (m, 2H), 7.96-7.8 (d+d, 1H), 5.06 (m, 1H), 4.56-4.34 (m, 2H), 4.07-3.54 (m, 3H), 2.34-2.05 (m, 2H), 2.7 (s, 3H), 2.06 (s, 3H), 1.48 (d+d, 3H).

Intermediate 39: δ 8.22-8.14 (m, 2H), 7.96-7.81 (d+d, 1H), 5.06 (m, 1H), 4.5-4.3 (m, 2H), 4.1-3.54 (m, 3H), 2.7 (s, 3H), 2.3-2.0 (m, 2H), 2.13 (s, 3H), 1.47 (d,3H).

MS (*m/z*): 540[MH]$^+$.

HPLC:

Preparative:

Pre-column/Guard column:	Filter Rhodyne
Column type:	Daicel CHIRALPAK AD
Column length [cm]:	25
Internal diameter [mm]:	2
Injection volume [µl]:	500
Mobile phase:	n-hexane-IPA 90/10 v/v
Flow rate [mL/min]:	6.5
Detector type:	DAD
Wavelength [nm]:	225, 292
Intermediate 38:	21.8, r.t. (min)
Intermediate 39:	26.5, r.t. (min)

Analytical:

Pre-column/Guard column:	Filter Rhodyne
Column type:	CHIRALPAK AD
Column length [cm]:	25
Internal diameter [mm]:	4.6
Particle size [µm]:	5
Column temperature [^C]:	r.t.
Autosampler temperature [^C]	r.t.
Injection volume [µl]:	20
Mobile phase:	n-hexane/isopropylalcohol 90/10 v/v
Flow rate [mL/min]:	1.0
Detector type:	DAD
Wavelength [nm]:	225
Intermediate 38:	6.88, r.t. (min)
Pre-column/Guard column:	Filter Rhodyne
Column type:	CHIRALPAK AD
Column length [cm]:	25
Internal diameter [mm]:	4.6
Column temperature [°C]:	r.t.
Autosampler temperature [°C]	r.t.
Mobile phase:	n-hexane/2- Propanol 90/10 v/v

Flow rate [mL/min]:	1.0
Detector type:	DAD
Wavelength [nm]:	220-350
Intermediate 39:	8.29, r.t. (min)

Intermediate 40

{4-Chloro-2-methyl-8-(2,4-bis-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-*d*]pyrimidin-5(*S*)-yl}-methanol

To a solution of intermediate 38 (90mg, 0.167mmol) in a 4:1 mixture of THF/H_2O (5mL), at 0°C, was added LiOH (14mg, 2eq) and the reaction mixture was stirred for 50 min. It was then diluted with water and the product was extracted with Et_2O (2x10mL) and with EtOAc (1x10mL). The combined organic extracts were dried over anh. Na_2SO_4. The solids were filtered, the solvent was evaporated and the crude product was purified by flash chromatography (silica gel, cHex/AcOEt 6:4) to give the title compound (65mg, 0.15mmol, 92%, e.e. = 97%) as a clear oil.

NMR (^{1}H, DMSO): δ 8.3-8.1 (m, 2H), 7.88-7.81 (d+d, 1H), 5.00 (broad, 1H), 3.9-3.6 (m, 2H), 3.7-3.3 (m, 2H), 3.2-3.1 (m, 1H), 2.3 (m, 1H), 2.09 (s, 3H), 2.00-1.8 (m, 1H).

MS (*m/z*): 426[MH]$^+$.

HPLC:

Analytical

Pre-column/Guard column:	Filter Rhodyne
Column type:	Daicel CHIRALPAK AD
Column length [cm]:	25
Internal diameter [mm]:	0.46
Column temperature [^C]:	r.t.
Autosampler temperature [^C]	r.t.
Injection volume [µl]:	20
Mobile phase:	n-hexane/IPA/EtOH
Step 1:	Time-Reserv.A-ReservB: 95/3.5/1.5
Flow rate [mL/min]:	1.0
Detector type:	DAD
Wavelength [nm]:	225
Intermediate 40:	10.28, r.t. (min)

Intermediate 41

Methanesulfonic acid 4-chloro-2-methyl-8-(2,4-bis-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-*d*]pyrimidin-5(*S*)-ylmethyl ester

To a solution of intermediate 40 (62mg, 0.145mmol) in anh. CH_2Cl_2 (5mL), at 0°C, under N_2, were added Et_3N (80µl, 4eq) and MsCl (23µl, 2eq). The reaction mixture was brought to r.t., stirred for 1 h. and then diluted with water. The product was extracted with CH_2Cl_2 (3x20mL) and the combined organic extracts were washed with brine and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 6:4) to give the title compound (67mg, 0.13mmol, 92%, e.e. = 95%) as a clear oil.

NMR (^{1}H, DMSO): δ 8.3-8.14 (m, 2H), 7.94-7.83 (d, 1H), 4.55-4.20 (2H), 3.94-3.4 (m, 3H), 3.25 (s, 3H), 2.11 (s, 3H), 2.25-1.94 (m, 2H).
MS (*m/z*): 504[MH]$^+$.
HPLC:
Analytical

Pre-column/Guard column:	Filter Rhodyne
Column type:	CHIRALPAK AD
Column length [cm]:	25
Internal diameter [mm]:	4.6
Particle size [μm]:	5
Column temperature [^C]:	r.t.
Autosampler temperature [^C]	r.t.
Injection volume [μl]:	20
Mobile phase:	n-hexane/EtOH/IPA 73.5/1.5/25 v/v
Flow rate [mL/min]:	1.0
Detector type:	DAD
Wavelength [nm]:	225
Intermediate 41:	6.52, r.t. (min)

Intermediate 42
{4-Chloro-2-methyl-8-(2,4-bis-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-*d*]pyrimidin-5(*R*)-yl}-methanol
To a solution of intermediate 39 (83mg, 0.154mmol) in a 4:1 mixture of THF/H_2O (5mL), at 0°C, was added LiOH (14mg, 2eq) and the reaction mixture was stirred for 20 min. It was then diluted with water and the product was extracted with Et_2O (2x10mL) and with EtOAc (1x10mL), and the combined organic extracts were dried over anh. Na_2SO_4. The solids were filtered, the solvent was evaporated and the crude product was purified by flash chromatography (silica gel, cHex/EtOAc 7:3) to give the title compound (61mg, 0.14mmol, 93%, e.e.>99%) as a clear oil.
NMR (^{1}H, DMSO): δ 8.26-8.12 (m, 2H), 7.9-7.8 (d, 1H), 5.08-4.98 (t, 1H), 3.9-3.6 (m, 2H), 3.7-3.3 (m, 2H), 3.24-3.1 (m, 1H), 2.3 (m, 1H), 2.09 (s, 3H), 2.00-1.8 (m, 1H).
MS (*m/z*): 426[MH]$^+$.
HPLC:
Analytical

Pre-column/Guard column:	Filter Rhodyne
Column type:	CHIRALPAK AD
Column length [cm]:	15
Internal diameter [mm]:	4.6
Injection volume [μl]	10
Mobile phase:	n-hexane/Ethanol/IPA
Step 1:	Time-Reserv.A-Reserv.B:95/1.5/3.5 v/v
Flow rate [mL/min]:	1.0
Detector type:	DAD
Wavelength [nm]:	225

Intermediate 42: 9.417, r.t. (min)

Intermediate 43

Methanesulfonic acid 4-chloro-2-methyl-8-(2,4-bis-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-*d*]pyrimidin-5(*R*)-ylmethyl ester

To a solution of intermediate 42 (58mg, 0.136mmol) in anh CH_2Cl_2 (5mL), at 0°C, under N_2, were added Et_3N (76µl, 4eq) and MsCl (21µl, 2eq). The reaction mixture was brought to r.t., stirred for 1 h. and then diluted with water. The product was extracted with CH_2Cl_2 (3x20mL) and the combined organic extracts were washed with brine and dried over anh. Na_2SO_4. The solids were filtered, the solvent evaporated and the crude product was purified by flash chromatography (silica gel, cHex/EtOAc 7:3) to give the title compound (57.6mg, 0.11mmol, 85%, e.e.>99%) as a clear oil.

NMR (^1H, DMSO): δ 8.3-8.14 (m, 2H), 7.95-7.8 (d, 1H), 4.56-4.20 (2H), 3.9-3.4 (m, 3H), 3.25 (s, 3H), 2.11 (s, 3H), 2.2-1.9 (m, 2H).

MS (*m/z*): 504$[MH]^+$.

HPLC:

Analytical

Pre-column/Guard column:	Filter Rhodyne
Column type:	CHIRALPAK AD
Column length [cm]:	25
Internal diameter [mm]:	4.6
Particle size [µm]:	3
Injection volume [µl]:	10
Mobile phase:	n-hexane/Ethanol/IPA
Step 1:	Time-Reserv.A-Reserv.B: 75/1.5/23.5 v/v
Flow rate [mL/min]:	1.0
Detector type	DAD
Wavelength [nm]:	225
Intermediate 43:	4.703, r.t. (min)

Intermediate 44

3-(2,4-Dichloro-phenyl)-2-hydroxy-6-nitromethyl-cyclohex-1-enecarboxylic acid methyl ester

To a solution of intermediate 23 (26mg, 0.087mmol) in an anh. mixture of Et_2O/THF (0.5mL/0.1mL) was added nitromethane (0.005mL, 1.1eq) and Amberlyst A21 (weekly basic resin: 260mg). The solvent was slowly evaporated at r.t. without agitation. After 2.5 hr, the dry resin was diluted with Et_2O and decanted. It was rinsed further with Et_2O (7x) and the combined organic fractions were evaporated. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc, 9:1) to give the title compound (25mg, 80%) as a clear oil.

NMR (^1H, $CDCl_3$): δ 12.72 (s, 1H), 7.41 (d, 1H), 7.24 (dd, 1H), 7.03 (d, 1H), 4.64 (dd, 1H), 4.50 (t, 1H), 4.07 (bm, 1H), 3.87 (s, 3H), 3.58 (m, 1H), 2.08 (bm, 1H), 1.85 (bm, 3H).

MS (*m/z*): 359 $[MH]^+$ (2 Cl).

Intermediate 45

8-(2,4-Dichloro-phenyl)-2-methyl-5-nitromethyl-5,6,7,8-tetrahydro-quinazolin-4-ol

Sodium (21mg, 3.1eq) was added portionwise to anh. MeOH (1.5mL) under N_2. After consumption of metallic sodium, acetamidine hydrochloride (96mg, 3.3eq) was added. After 10 min of stirring, the precipitated NaCl was filtered off and washed with anh. MeOH (2mL). The solution of free acetamidine was added to intermediate 44 (106mg, 0.294mmol) and the mixture was stirred at r.t. for 18 hr. The solvent was evaporated and the crude product was purified by flash chromatography (silica gel, EtOAc/cHex 8:2) to give the title compound as a clear oil (81mg, 75%).

MS (*m/z*): 368 $[MH]^+$ (2 Cl).

Intermediate 46

4-Chloro-8-(2,4-dichloro-phenyl)-2-methyl-5-nitromethyl-5,6,7,8-tetrahydro-quinazoline

A solution of intermediate 45 (73mg, 0.198mg) in $POCl_3$ (2mL) was heated at reflux for 2.5 hr. $POCl_3$ was evaporated and the residue was taken up in CH_2Cl_2. The organic phase was washed with conc. NH_4OH, the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x10mL). The combined organic extracts were washed with sat.aq. NaCl and dried over anh. Na_2SO_4. The solids were filtered and the solvent was evaporated. The crude title compound (68mg, 89%) was used as such in the next step.

MS (*m/z*): 386 $[MH]^+$ (3 Cl).

Intermediate 47

4-Chloro-8-(2,4-dichloro-phenyl)-2-methyl-5,6,7,8-tetrahydro-quinazoline-5-carbaldehyde

To a stirred solution of intermediate 46 (64mg, 0.166mmol) in anh. MeOH (1mL), at -10°C, under N_2, was added methanolic KOH (0.1M, 2.3mL) dropwise. After stirring at –10°C for 15 min, a solution of $KMnO_4$ (18mg, 0.7eq) and $MgSO_4$ (20mg, 1eq) in H_2O (2.5mL) was added dropwise (reaction temperature kept below 0°C). The reaction mixture was stirred at 0°C for 24 hr. It was then filtered on Celite, and the Celite cake washed with CH_2Cl_2. The solvent was evaporated and the aqueous phase extracted with CH_2Cl_2 (3x10mL). The combined organic extracts were dried over anh. Na_2SO_4, the solids were filtered and the solvent evaporated. The crude oil obtained was purified by flash chromatography (silica gel, cHex/EtOAC 9:1 → 8:2). The title compound was obtained as a 65:35 mixture of diastereomers (27mg, 46%, clear oil).

MS (*m/z*): 355 $[MH]^+$ (3 Cl).

EXAMPLE 1

Synthesis of representative compounds of structure (I-1)

5-(2,4-Dichlorophenyl)-1-(1-ethyl-propyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene (I-1-1)

A solution of intermediate 19 (14mg) in pure 3-pentylamine (60µl) was stirred at 120°C for 8 hr. The reaction mixture was then diluted with water and extracted with Et_2O (3x10mL). The combined organic extracts were washed once with water, once with brine and dried over anh.

Na_2SO_4. The solids were filtered, the solvent evaporated and the crude pale yellow oil was purified by flash chromatography (silica gel, cHex/EtOAc 8:2) to give the title compound as a pale yellow oil (5.9mg).

5-(2,4-Dichlorophenyl)-1-(2-ethyl-butyl)-7-methyl-1,2,2a,3,4,5,5a,8b-octahydro-1,5,6,8-tetraaza-acenaphthylene (I-1-2)

A solution of intermediate 19 (10.0mg) in pure 2-ethyl-*n*-butylamine (100µl) was stirred in a sealed vial at 120°C for 7 hr. The reaction mixture was then cooled down to r.t. and directly purified by flash chromatography (silica gel, Toluene/EtOAc 95:5) to give the title compound as pale yellow oil (1.9mg).

5-(2,4-Dichlorophenyl)-1-(2-methoxy-1-methoxymethyl-ethyl)-7-methyl-1,2,2a,3,4,5,5a,8b-octahydro-1,5,6,8-tetraaza-acenaphthylene (I-1-3)

A solution of intermediate 19 (16.5mg) in pure 2-methoxy-1-(methoxymethyl)ethylamine (52.6mg) was stirred at 150°C (screw cap vial) for 4 hr. The reaction mixture was then cooled down to r.t. and directly purified by flash chromatography (silica gel, Toluene/EtOAc 6:4) to obtain the title compound as a pale yellow oil (4.2mg).

7-Methyl-1-(1-propylbutyl)-5-(2,4-bis-trifluoromethyl-phenyl)-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene (I-1-4)

Intermediate 35 (135mg, 0.27mmol) and 4-aminoheptane (0.5mL, 12eq) were heated at 130°C (screw cap vial) for 3 hr. The reaction mixture was then cooled down to r.t. and diluted with CH_2Cl_2. The solvent was evaporated and the crude product was purified by flash chromatography (sililca gel, cHex/EtOAc 9:1) to give the title compound (29.4mg, 0.06mmol, 23%) as a yellow solid.

Enantiomeric Resolution

First enantiomer

7-Methyl-1-(1-propylbutyl)-5-(2,4-bis-trifluoromethyl-phenyl)-1,2,2a(*S*),3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene

Intermediate 41 (60mg, 0.119mmol) and 4-aminoheptane (178µl, 10eq) were heated at 130°C (screw cap vial) for 3 h. The reaction mixture was diluted with CH_2Cl_2 and the solvent was evaporated. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 95:5) to give the title compound (19.4mg, 0.04mmol, 33%, e.e. = 95%) as a clear oil.

HPLC:

Analytical

Column type:	CHIRALPAK OD
Column length [cm]:	25
Internal diameter [mm]:	4.6
Column temperature [^C]:	35
Injection volume [µl]:	10
Mobile phase:	CO_2/EtOH (0.15% Ipa) 85/15
Flow rate [mL/min]:	2.5
Detector type:	UV

Wavelength [nm]: 225
Column pressure [bar]: 150
Title compound: 2.55, r.t. (min)
^{1}H-NMR and MS data are the same as reported in the following Table 1 for compound I-1-4

Second enantiomer
7-Methyl-1-(1-propylbutyl)-5-(2,4-bis-trifluoromethyl-phenyl)-1,2,2a(*R*),3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene
Intermediate 43 (55mg, 0.109mmol) and 4-aminoheptane (163µl, 10eq) were heated at 130°C (screw cap vial) for 3 h. The reaction mixture was diluted with CH_2Cl_2 and the solvent was evaporated. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 95:5) to give the title compound (25.7mg, 0.053mmol, 49%, e.e.>99%) as a clear oil.
HPLC:
Analitical
Column type: CHIRALPAK OD
Column length [cm]: 25
Internal diameter [mm]: 4.6
Column temperature [^C]: 35
Injection volume [µl]: 10
Mobile phase: CO_2/EtOH (0.15% Ipa) 85/15
Flow rate [mL/min]: 2.5
Detector type: UV
Wavelength [nm]: 225
Column pressure [bar]: 150
Title compound: 2.12, r.t. (min)
^{1}H-NMR and MS data are the same as reported in the following Table 1 for compound I-1-4

5-(2,4-Dichlorophenyl)-7-methyl-1-(1-propylbutyl)-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene (I-1-5)
A solution intermediate 19 (20mg, 0.046mmol) in 4-aminoheptane (100µL) was heated at 130°C (screw cap vial) for 18 hr. The amine was evaporated and the residue was directly purified by flash chromatography (silica gel, toluene/EtOAc, 9:1 → 8:2) to give the title compound as a clear oil (7mg, 0.017mmol, 36%).

Enantiomeric resolution
First enantiomer
5-(2,4-Dichlorophenyl)-7-methyl-1-(1-propylbutyl)-1,2,2a-(S),3,4,5,5a,8b-octahydro-1,5,6,8-tetraaza-acenaphthylene
Intermediate 47 (120mg, 0.276mmol) and 4-aminoheptane (0.412mL, 10eq) was stirred at 130°C (screw cap vial) for 18 hr. Then it was diluted with CH_2Cl_2 (5mL) and the solvent was evaporated. The resulting crude product was purified by flash chromatography (silica gel, cHex/EtOAc 9.5:0.5) to afford the title compound (62mg, 53%, ee%>99%) as a clear oil.

HPLC:
Analytical:

Pre-column/Guard column:	Rheodyne filter
Column type:	CHIRALPAK AD
Column lenght (cm):	25
Internal diameter (mm):	4.6
Particle size (μm):	5
Column temperature (°C):	r.t.
Autosampler temperature: (°C):	r.t.
Injection volume (μL):	20
Mobile phase:	n-Hexane/tert-butanol 90/10 a/a
Flow rate (mL/min):	1
Detector type:	DAD
Wavelenght (nm):	220-350
Title compound:	10.2 rt (min)

^{1}H-NMR and MS data are the same as reported in the following Table 1 for compound I-1-5.

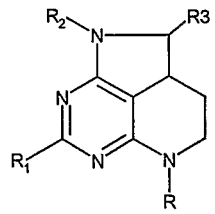
Second enantiomer
5-(2,4-Dichlorophenyl)-7-methyl-1-(1-propylbutyl)-1,2,2a-(R),3,4,5,5a,8b-octahydro-1,5,6,8-tetraaza-acenaphthylene
Intermediate 49 (130mg, 0.298mmol) and 4-aminoheptane (0.342mL, 10eq) were stirred at 130°C (screw cap vial) for 18 hr. Then it was diluted with CH_2Cl_2 (5mL) and the solvent was evaporated. The resulting crude product was purified by flash chromatography (silica gel, cHex/EtOAc 9.5:0.5) to afford the title compound (74mg, 59%, ee%=90%) as a clear oil.
HPLC:
Analytical:

Pre-column/Guard column:	Rheodyne filter
Column type:	CHIRALPAK AD
Column lenght (cm):	25
Internal diameter (mm):	4.6
Particle size (μm):	5
Column temperature (°C):	r.t.
Autosampler temperature: (°C):	r.t.
Injection volume (μL):	20
Mobile phase:	n-Hexane/tert-butanol 90/10 a/a
Flow rate (mL/min):	1
Detector type:	DAD
Wavelenght (nm):	220-350
Title compound:	7.5, rt (min), 90%.

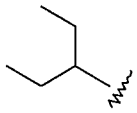
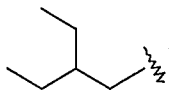
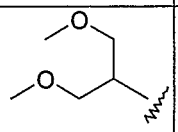
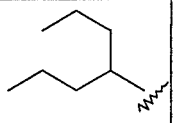
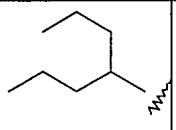
^{1}H-NMR and MS data are the same as reported in the following Table 1 for compound I-1-5.

All the analytical data are set forth in the following Table 1.

Table 1



(I-1)

Cpd. No.	R	R_1	R_2-	R_3-	Analytical Data
1-1-1	2,4-dichloro-phenyl	CH_3		H	NMR (^{1}H, $CDCl_3$, 55 °C): δ 7.46 (d, 1H), 7.35-7.25 (m, 2H), 3.86 (m, 1H), 3.69 (m, 1H), 3.63 (bm, 2H), 3.42 (m, 1H), 3.23 (m, 1H), 2.27 (s, 3H), 2.24 (m, 1H), 1.77 (m, 1H), 1.70-1.40 (m, 4H), 1.00 (t, 3H), 0.82 (t, 3H). MS (*m/z*): 391 $[MH]^+$, 2 Cl.
1-1-2	2,4-dichloro-phenyl	CH_3		H	NMR (^{1}H, $CDCl_3$): δ 7.46 (s, 1H), 7.26 (m, 2H), 3.86 (m, 1H), 3.60 (m, 2H+1H), 3.40 (m, 1H), 3.06 (m, 1H), 2.70 (dd, 1H), 2.35-2.20 (m, 2H), 2.29 (s, 3H), 1.60 (m, 1H), 1.40-1.20 (m, 4H), 0.94 (t, 6H). MS (*m/z*): 405 $[MH]^+$.
1-1-3	2,4-dichloro-phenyl	CH_3		H	NMR (^{1}H, $CDCl_3$, 55 °C): δ 7.43 (bs, 1H), 7.23 (bs, 2H), 4.30 (bm, 1H), 3.80 (bm, 1H), 3.59 (m, 5H), 3.40 (bm, 3H), 3.35 (s, 3H), 3.29 (s, 3H), 2.26 (bs, 3H), 2.24 (bm, 1H), 1.75 (bm, 1H). MS (*m/z*): 423 $[MH]^+$.
1-1-4	2,4-trifluoro-methylphenyl	CH_3		H	NMR (^{1}H, $CDCl_3$): δ 7.99 (s, 1H), 7.83 (d, 1H), 7.48 (d, 1H), 4.06-3.24 (bm, 5H), 2.23-2.2 (bm, 4H), 1.74-1.1 (bm, 10H), 0.97 (t, 3H), 0.91 (t, 3H). MS (*m/z*): 487$[MH]^+$.
1-1-5	2,4-dichloro-phenyl	CH_3		H	NMR (^{1}H, $CDCl_3$): δ 7.46 (d, 1H), 7.29 (d, 1H), 7.26 (dd, 1H), 4.04 (m, 1H), 3.67 (t, 1H), 3.64 (bm, 2H), 3.41 (m, 1H), 3.20 (t, 1H), 2.27 (m, 4H), 1.55–1.10 (m, 8H), 0.95 (t, 3H), 0.88 (t, 3H). MS (*m/z*): 419 $[MH]^+$ 2Cl.

EXAMPLE 2

Synthesis of representative compounds of structure (1-2)

9-(2,4-Dichlorophenyl)-4-(1-ethylpropyl)-2-methyl-5,6,6a,7,8,9-hexahydro-4*H*-1,3,4-triazaphenalene (isomer 1) and 9-(2,4-Dichlorophenyl)-4-(1-ethylpropyl)-2-methyl-5,6,6a,7,8,9-hexahydro-4*H*-1,3,4-triazaphenalene (isomer 2) (2-1-1)

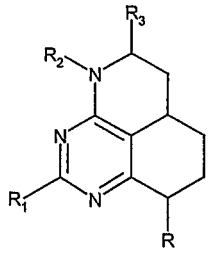
Intermediate 25 (isomer 1) was dissolved in anh. CH_2Cl_2 (6mL) and treated with O_3 (5g/hr) at -78°C for 20 min. Dimethylsulfide (1mL) was added and the mixture was allowed to warm to r.t. and stirred overnight. Then the reaction mixture was dried over Na_2SO_4, the solids were filtered and the solvent evaporated. The crude aldehyde (106mg) was obtained as a 1:1 mixture of two diastereoisomers and used without further purification.

To a solution of the aldehyde prepared above (30mg) in anh. MeOH (1mL), 1-ethyl-propylamine (0.010mL) was added and the reaction mixture was stirred at r.t. for 3 hr. A 1M solution of $NaBH_3CN$ in THF (0.162mL) was then added and the mixture was stirred at r.t. for 65 hr. Another aliquot of 1M $NaBH_3CN$ in THF (0.080mL) was added and the reaction was stirred at r.t. for 3 hr. The solvent was evaporated and the residue was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (4x10mL) and the combined organic extracts were washed with brine (2x10mL), dried over anh. Na_2SO_4.The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, CH_2Cl_2/EtOAc 7:3) to give the title compound (16mg) as a mixture of two diastereoisomers.

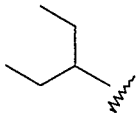
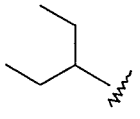
The two diastereoisomers were separated by preparative TLC (1% NH_4OH in toluene/EtOAc 95:5) to give isomer 1 (5.4mg) and isomer 2 (5.6mg) as yellow oils.

All the analytical data are set forth in the following Table 2.

Table 2



(I-2)

Cpd. No.	R	R_1	R_2-	R_3-	Analytical Data
2-1-1	2,4-dichloro-phenyl	CH_3		H	Isomer 1 :NMR (^{1}H, $CDCl_3$): δ 7.31 (d, 1H), 7.14 (dd, 1H), 7.01 (bs, 1H), 5.01 (bs, 1H), 4.41 (bs, 1H), 3.34 (bd, 1H), 3.17 (dt, 1H), 2.68 (m, 1H), 2.40-2.30 (m, 1H), 2.37 (bs, 3H), 2.04 (m, 2H), 1.67 (bd, 1H), 1.55 (m, 4H), 1.50-1.35 (m, 2H), 0.87 (t, 3H), 0.79 (t, 3H). MS (*m/z*): 404 [M+H].
	2,4-dichloro-phenyl	CH_3		H	Isomer 2:NMR (^{1}H, $CDCl_3$): δ 7.40 (bs, 1H), 7.05 (dd, 1H), 6.36 (d, 1H), 5.03 (bs, 1H), 5.00-4.50 (broad, 1H), 3.40 (bd, 1H), 3.22 (dt, 1H), 2.60 (m, 1H), 2.45 (bs, 3H), 2.16-2.06 (m, 2H), 2.03 (m, 1H), 1.75 (bd, 1H), 1.70-1.50 (m, 4H), 1.45 (dq, 1H), 1.24 (m, 1H), 0.86 (t, 6H). MS (*m/z*): 404 $[M+H]^+$.

EXAMPLE 3

Synthesis of representative compounds of structure (1-3)

5-Cyclopropylmethyl-1-(2,4-dichlorophenyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene (3-1-1)

To a solution of intermediate 10 (20mg) in anh. CH_3OH (1mL) was added (aminomethyl)cyclopropane (5µl, 1eq).The reaction was stirred at r.t. for 90 min and then $NaBH_3CN$ 1.0M/THF (113µl) was added. The mixture was stirred for an additional 18 hr at r.t. and quenched with H_2O (10mL). The product was extracted with EtOAc (2x15mL), the combined extracts were dried over anh. Na_2SO_4, filtered and concentrated to dryness *in vacuo*. Flash chromatography of the crude product (silica gel, cHex/EtOAc 9:1) gave the title compound (5mg) as a colourless oil.

1-(2,4-Dichlorophenyl)-5-(2-methoxyethyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene (3-1-2)

To a solution of intermediate 10 (16mg) in anh. THF (1mL) was added 2-methoxy-ethylamine (4µl). The reaction was stirred at r.t. for 90 min and then $NaBH_3CN$ 1.0M/THF (90µl) was added. The mixture was stirred for an additional 18 hr at r.t. and quenched with H_2O (10mL). The product was extracted with EtOAc (2x15mL). The combined extracts were dried over anh. Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude product was dissolved in anh. THF (2mL) and TEA (30µl) was added. The reaction mixture was heated to reflux for 10 hr and quenched with H_2O. The product was extracted with EtOAc (2x10mL). The combined extracts were dried over anh. Na_2SO_4, filtered and concentrated to dryness *in vacuo*. 2mg (12%) of the title compound were obtained as a light beige oil after prep-TLC purification (eluted 3 times: 1: cHex 100%, 2: cHex/EtOAc 75:25, 3: cHex/EtOAc 50:50).

1-(2,4-Dichlorophenyl)-5-(1-ethylpropyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene (3-1-3)

To a solution of intermediate 10 (20mg) in anh. THF (1mL) was added 1-ethyl-propylamine (6.5µl). The reaction mixture was stirred at r.t. for 90 min and then $NaBH_3CN$ 1.0M/THF (112µl) was added. The mixture was stirred for an additional 18 hr at r.t. and quenched with water (10mL). The product was extracted with EtOAc (2x10mL). The combined extracts were dried over anh. Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude product was dissolved in anh. toluene (2mL) and heated to reflux for 18 hr. The reaction mixture was diluted with H_2O (10mL) and extracted with EtOAc (3x10mL). The combined organic extracts were dried over anh. Na_2SO_4, filtered and concentrated to dryness *in vacuo* to give the title compound (1.6mg, 7%).) as a colourless oil after prep-TLC purification (cHex/EtOAc 75:25).

1-(2,4-Dichlorophenyl)-5-(2-ethylbutyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene (3-1-4)

To a solution of intermediate 10 (35.5mg) in anh. MeOH (2mL) was added 2-ethylbutylamine (0.014mL) at r.t., under N_2. The reaction mixture was stirred at r.t. for 90 min. $NaBH_3CN$ (1 N solution in THF, 0.2mL) was then added at r.t. and the reaction mixture was heated to 70°C for 3 hr. It was then allowed to cool to r.t. and H_2O (5mL) was added. The organic solvent was evaporated under reduced pressure and the aqueous suspension was extracted with EtOAc (3x5mL). The combined organic layers were washed with sat. aq. NaCl (5mL) and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, cHex 100% → cHex/EtOAc 95:5) to yield the title compound as a yellow solid (0.018g).

1-(2,4-Dichlorophenyl)-7-methyl-5-(1-propylbutyl)-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene (3-1-5)

A solution intermediate 30 (20mg, 0.046mmol) in 4-aminoheptane (100µL) was heated at 130°C (screw cap vial) for 6.5 hr, and then at r.t. for 18 hr. The amine was evaporated and the residue was directly purified by flash chromatography (silica gel, cHex/EtOAc, 9:1) to give the title compound as a clear oil (9mg, 0.021mmol, 47%).

7-Methyl-5-(1-propylbutyl)-1-(2,4-bis-trifluoromethyl-phenyl)-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraazaacenaphthylene (3-1-6)

Intermediate 37 (230mg, 0.457mmol) and 4-aminoheptane (0.68mL, 10eq) were heated at 130°C (screw cap vial) for 14 hr. The reaction mixture was diluted with CH_2Cl_2 and the solvent were evaporated. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 95:5) to give the title compound (54mg, 0.11mmol, 24%) as a white solid.

5-Cyclopropylmethyl-1-(2,4-dichlorophenyl)-7-methyl-4-propyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraazaacenaphthylene (3-1-7)

To a suspension of $CuBr{\cdot}Me_2S$ (48mg, 5eq) in anh. Et_2O (0.8mL) at -50°C, under N_2, was added PrMgBr 1M/THF (0.188mL, 4eq) dropwise under vigorous stirring. The dark yellow mixture was stirred for 45 min at -50°C and was then cooled to -78°C. $BF_3{\cdot}Et_2O$ (0.024mL, 4eq) was added and the reaction mixture was stirred for 20 min at -78°C. A solution of intermediate 28 (19mg, 0.047mmol) in anh. THF (0.5mL) was added and the reaction temperature was allowed to rise to r.t. over 3 hr. After a total reaction time of 4 hr, a 1:1 mixture of conc. NH_4OH and sat.aq. NH_4Cl (2mL) was added and the mixture was stirred for 15 min. Water and EtOAc were added, the phases were separated and the aqueous layer was extracted with EtOAc (3x10mL). The combined organic extracts were washed with water and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 9:1). The title compound was obtained as a light yellow oil (3mg, 0.007mmol, 15%).

4-Butyl-5-cyclopropylmethyl-1-(2,4-dichlorophenyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraazaacenaphthylene (3-1-8)

To a suspension of $CuBr{\cdot}Me_2S$ (72mg, 4.3eq) in anh. Et_2O (1mL) at –50°C, under N_2, was added dropwise n-BuLi 1.6M/hexanes (0.21mL, 4.15eq) under vigorous stirring. The dark brown mixture was stirred for 40 min at –50°C, was then cooled at –78°C and $BF_3{\cdot}Et_2O$

(0.043mL, 4.15eq) was added. After stirring for 15 minutes at –78°C, a solution of intermediate 28 (33mg, 0.081mmol) in anh. THF (0.5mL) was added and the reaction temperature was allowed to rise to r.t. over 3 hr. After a total reaction time of 3.5 hr, a 1:1 mixture of conc. NH_4OH and a sat.aq. NH_4Cl (1mL) was added and the mixture was stirred for 15 min. Water and EtOAc were then added, the phases were separated and the aqueous layer was extracted with EtOAc (3x10mL). The combined organic extracts were washed with water and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 9:1). The title compound (isomer 1: *syn*) was obtained as a pale yellow oil (16mg, 0.037mmol, 46%). A small percentage of the *anti* isomer 2 was also isolated.

5-Cyclopropylmethyl-1-(2,4-dichlorophenyl)-7-methyl-4-propoxy-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraazaacenaphthylene (3-1-9)

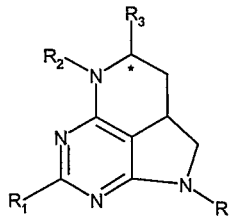
To a suspension of $CuBr{\cdot}SMe_2$ (27mg, 2eq) in anh. Et_2O (0.2mL), at –60°C, under N_2, was added a solution of propyl magnesium bromide (0.2mL, 2eq: prepared by the addition of Mg (27mg, 1.1mmol) and propyl bromide in anh. Et_2O (1.5mL), at r.t., under N_2, for 1 hr). The yellow heterogeneous reaction mixture was diluted with an additional 0.2mL of anh. Et_2O and stirred at -60°C for 30 min. It was then cooled down to -78°C and $BF_3{\cdot}Et_2O$ (17 µL, 2eq) was added. After 10 min at -78°C, a solution of intermediate 28 (27mg, 0.067mmol) in anh. THF (0.4mL) was added and the reaction mixture was slowly warmed to r.t. (4 hr). It was then diluted with a 1:1 mixture of conc. NH_4OH/sat.aq. NH_4Cl and stirred at r.t. for 10 min. The aqueous phase was then extracted with CH_2Cl_2 (4x20mL) and the combined organic extracts were washed with H_2O (2x20mL) and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated. The crude compound was purified by flash chromatography (silica gel, 9:1 → 7:3 cHex/EtOAc). The title compound was obtained as a clear oil (4mg, 0.009mmol, 14%)

4,5-Dibutyl-1-(2,4-dichlorophenyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraazaacenaphthylene (3-1-10)

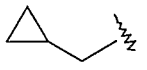
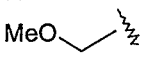
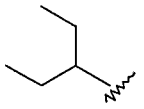
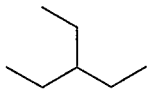
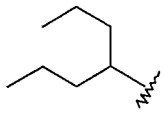
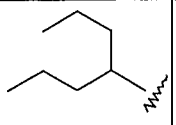
To a suspension of $CuBr{\cdot}Me_2S$ (65mg, 4.3eq) in anh. Et_2O (1mL) cooled to –50°C, under N_2, a 1.6 M solution of BuLi (0.184mL, 0.295mmol, 4eq) was added dropwise under vigorous stirring. The dark brown mixture was stirred for 40 min between –50°C and –40°C, then it was cooled to –78°C and $BF_3{\cdot}Et_2O$ (0.037mL, 4eq) was added. After stirring for 15 min at -78°C, intermediate 28 was added (30mg, 0.074mmol) dissolved in anh. THF (0.5mL) and the reaction temperature was allowed to rise to r.t. over 3 hr. After a total reaction time of 3.5 hr, a 1:1 mixture of NH_4OH and a saturated solution of NH_4Cl (1mL) was added and the mixture was stirred for 15 min. Then water and EtOAc were added, the phases were separated and the aqueous layer was extracted with EtOAc (3x10mL). The combined organic extracts were washed with water and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated. The crude product (28mg) was purified by flash chromatography (cHex/EtOAc 9:1). The title compound (12mg, 0.028mmol, 37%) was obtained as a colourless oil.

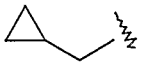
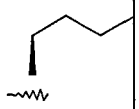
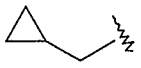
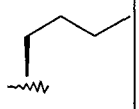
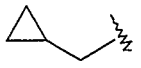
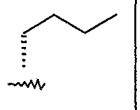
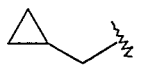
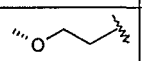
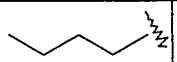
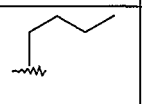
All the analytical data are set forth in the following Table 3.

Table 3



(I-3)

Cpd. No.	R	R_1	R_2-	R_3-	Analytical Data
3-1-1	2,4-dichloro-phenyl	CH_3		H	NMR (^{1}H, $CDCl_3$): δ 7.41 (d, 1H), 7.36 (d, 1H), 7.22 (dd, 1H), 4.23 (t, 1H), 3.7 (dd, 1H), 3.55 (t, 1H), 3.54-3.44 (m, 3H), 3.25 (dd, 1H), 2.37 (s, 3H), 2.24 (m, 1H), 1.66 (m, 1H), 1.00 (m, 1H), 0.52 (m, 2H), 0.29 (m, 1H). MS (*m/z*): 375 $[MH]^+$, 2Cl.
3-1-2	2,4-dichloro-phenyl	CH_3		H	NMR (^{1}H, $CDCl_3$): δ 7.41 (d, 1H), 7.35 (d, 1H), 7.22 (dd, 1H), 4.23 (t, 1H), 3.94 (m, 1H), 3.62-3.47 (m, 5H), 3.37 (s, 3H), 2.38 (s, 3H), 2.21 (m, 1H), 1.64 (m, 1H). MS (*m/z*): 379 $[MH]^+$, 2Cl.
3-1-3	2,4-dicloro-phenyl	CH_3		H	NMR (^{1}H, $CDCl_3$): δ 7.41 (d, 1H), 7.35 (d, 1H), 7.22 (dd, 1H), 4.23 (t, 1H), 3.94 (m, 1H), 3.62-3.47 (m, 5H), 3.37 (s, 3H), 2.38 (s, 3H), 2.21 (m, 1H), 1.64 (m, 1H). MS (*m/z*): 379 $[MH]^+$, 2Cl.
3-1-4	2,4-dichloro-phenyl	CH_3		H	NMR (^{1}H, $CDCl_3$): δ 7.56- 7.30 (m, 3H), 4.25 (t, 1H), 3.68-3.40 (m, 3H), 2.56 (s, 3H), 2.45-2.27 (m, 2H), 1.67 (m, 6H), 0.95 (m, 8H). MS (*m/z*): 405 $[MH]^+$.
3-1-5	2,4-dichloro-phenyl	CH_3		H	NMR (^{1}H, $CDCl_3$): δ 7.35 (m, 2H), 7.20 (d, 1H), 4.80 (m, 1H), 4.20 (t, 1H), 3.55 (m, 1H), 3.45 (m, 1H), 3.35 (m, 1H), 3.10 (m, 1H), 2.30 (s, 3H), 2.20 (m, 1H), 1.60-1.15 (m, 9H), 0.90 (m, 6H). MS (*m/z*): 419 $[MH]^+$.
3-1-6	2,4-trifluoro-methylphenyl	CH_3		H	NMR (^{1}H, $CDCl_3$): δ 7.93 (s, 1H), 7.73 (d, 1H), 7.59 (d, 1H), 4.84 (m, 1H), 4.14 (t, 1H), 3.52 (m, 1H), 3.47 (m, 1H), 3.37 (m, 1H), 3.12 (m, 1H), 2.34 (s, 3H), 2.27 (m, 1H),

					1.6-1.2 (m, 9H), 0.92 (m, 6H). MS (*m/z*): 487[MH]$^+$.
3-1-7	2,4-dichloro-phenyl	CH_3			NMR (^{1}H, $CDCl_3$): δ 7.40 (d, 1H), 7.35 (d, 1H), 7.20 (dd, 1H), 4.27-4.10 (m, 2H), 3.68 (m, 1H), 3.55-3.42 (m, 2H), 3.03 (dd, 1H), 2.35 (s, 3H), 2.40-2.25 (m, 1H), 1.85-1.75 (m, 1H), 1.75-1.50 (m, 2H), 1.45-1.25 (m, 2H), 0.95 (t, 3H), 0.85 (m, 1H), 0.55-0.25 (m, 4H). MS (*m/z*): 417 [MH]$^+$ 2Cl.
3-1-8	2,4-dichloro-phenyl	CH_3			Isomer 1 (*syn*): NMR (^{1}H, $CDCl_3$): δ 7.42 (d, 1H), 7.37(d, 1H), 7.24 (dd, 1H), 4.24 (m, 1H), 4.18 (dd, 1H), 3.72 (m, 1H), 3.53 (m, 1H), 3.49 (m, 1H), 3.06 (dd, 1H), 2.38 (s, 3H), 2.32 (m, 1H), 1.84 (m, 1H), 1.74 (m, 1H), 1.62(q, 1h), 1.45-1.25 (m, 4H), 1.02 (m, 1H), 0.94 (t, 3H), 0.52 (m, 1H), 0.44 (m, 1H), 0.38 (m, 1H), 0.30 (m, 1H). MS (*m/z*): 431 [M+H]$^+$ (2 Cl).
	2,4-dichloro-phenyl	CH_3			Isomer 2 (*anti*): NMR (^{1}H, $CDCl_3$): δ 7.43 (d 1H), 7.39 (d, 1H), 7.23 (dd, 1H), 4.27 (m, 1H), 4.08 (dd, 1H), 3.69 (m, 1H), 3.57(m, 1H), 3.49 (m, 1H), 2.99 (dd, 1H), 2.39 (s, 3H), 2.24 (m, 1H), 1.80-1.20 (m, 7H), 1.02 (m, 1H), 0.94 (t, 3H), 0.55 (m, 1H), 0.46 (m, 1H), 0.29 (m, 2H). MS (*m/z*): 431 [M+H]$^+$ 2Cl.
3-1-9	2,4-dichloro-phenyl	CH_3			NMR (^{1}H, Acetone-d_6): δ 7.55 (d, 1H), 7.48 (d, 1H), 7.37 (d, 1H), 5.03 (t, 1H), 4.25 (t, 1H), 4.03 (dd, 1H), 3.78 (dd, 1H), 3.56 (m, 3H), 3.15 (dd, 1H), 2.54 (m, 1H), 2.25 (s, 3H), 1.59 (m, 2H), 1.43 (td, 1H), 1.11 (m, 1H), 0.92 (t, 3H), 0.50-0.24 (m, 4H). MS (*m/z*): 433 [MH]$^+$.
3-1-10	2,4-dichloro-phenyl	CH_3			NMR (^{1}H, $CDCl_3$): δ 7.54 (d, 1H), 7.47 (d, 1H), 7.36 (dd, 1H), 4.39 (m, 1H), 4.19 (m, 1H), 3.68 (m, 1H), 3.59 (m, 1H), 3.50 (m, 1H), 3.07 (m, 1H), 2.40 (m, 1H), 2.20 (s, 3H), 1.90-1.70 (m, 3H), 1.60-1.50 (m, 3H), 1.40-1.20 (m, 5H), 0.95 (2t, 6H). MS (*m/z*): 433 [M+H]$^+$ (2 Cl).

EXAMPLE 4

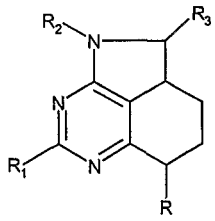
Synthesis of representative compounds of structure (1-4)

5-(2,4-Dichlorophenyl)-1-(1-ethylpropyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,6,8-triaza-acenaphthylene (4-1-1)

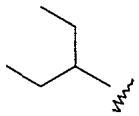
To a solution of intermediate 47 (22mg, 0.062mmol) in anh. MeOH (1mL), under N_2, at r.t., was added 1-ethyl propylamine (9μL, 1.25eq) and the reaction mixture was stirred at r.t. for 1.25 hr. $NaBH_3CN$ 1.0M/THF (0.15mL, 2.4eq) was then added and the reaction mixture was stirred at r.t. for 2 hr, then at –18°C for 4 days. The solvent was evaporated and the residue partitioned between EtOAc/H_2O. The phases were separated and the aqueous layer was extracted with EtOAc (3x5mL). The combined organic extracts were washed with sat.aq. NaCl (1x5mL) and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 9:1 → 8:2). The title compound was obtained as a clear oil (3mg, 0.008mmol, 12%).

All the analytical data are set forth in the following Table 4.

Table 4



(I-4)

Cpd. No.	R	R_1	R_2-	R_3-	Analytical Data
4-1-1	2,4-dichloro-phenyl	CH_3		H	MS (*m/z*): 390 $[MH]^+$ (2 Cl).

EXAMPLE 5

CRF Binding Activity

CRF binding affinity has been determined in vitro by the compounds' ability to displace ^{125}I-oCRF and ^{125}I-Sauvagine for CRF1 and CRF2 SPA, respectively, from recombinant human CRF receptors expressed in Chinese Hamster Ovary (CHO) cell membranes. For membrane preparation, CHO cells from confluent T-flasks were collected in SPA buffer (HEPES/KOH 50mM, EDTA 2mM; $MgCl_2$ 10mM, pH 7.4.) in 50mL centrifuge tubes, homogenized with a Polytron and centrifuged (50'000g for 5min at 4°C: Beckman centrifuge with JA20 rotor). The pellet was resuspended, homogenized and centrifuged as before.

The SPA experiment has been carried out in Optiplate by the addition of 100 µL the reagent mixture to 1µL of compound dilution (100% DMSO solution) per well. The assay mixture was prepared by mixing SPA buffer, WGA SPA beads (2.5mg/mL), BSA (1mg/mL) and membranes (50 and 5 µg of protein/mL for CRF1 and CRF2 respectively) and 50 pM of radioligand.
The plate was incubated overnight (>18 hr) at room temperature and read with the Packard Topcount with a WGA-SPA ^{125}I counting protocol.

EXAMPLE 6

CRF functional assay

Compounds of the invention were characterised in a functional assay for the determination of their inhibitory effect. Human CRF-CHO cells were stimulated with CRF and the receptor activation was evaluated by measuring the accumulation of cAMP.
CHO cells from a confluent T-flask were resuspended with culture medium without G418 and dispensed in a 96-well plate, 25'000c/well, 100 µL/well and incubated overnight. After the incubation the medium was replaced with 100 µL of cAMP IBMX buffer warmed at 37°C (5mM KCl, 5mM $NaHCO_3$, 154mM NaCl, 5mM HEPES, 2.3mM $CaCl_2$, 1mM $MgCl_2$; 1g/L glucose, pH 7.4 additioned by 1mg/mL BSA and 1mM IBMX) and 1µL of antagonist dilution in neat DMSO. After 10 additional minutes of incubation at 37°C in a plate incubator without CO2, 1µL of agonist dilution in neat DMSO was added. As before, the plate was incubated for 10 minutes and then cAMP cellular content was measured by using the Amersham RPA 538 kit.

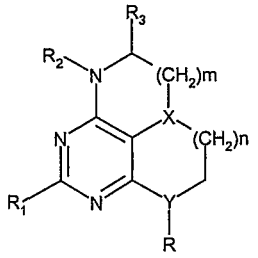
All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

It is to be understood that the present invention covers all combinations of particular and preferred groups described herein above.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

Claims

1. Compounds of general formula (I), including stereoisomers, prodrugs and pharmaceutically acceptable salts or solvates thereof

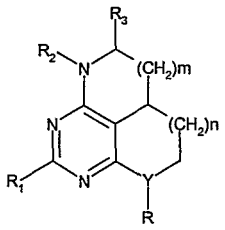


(I)

wherein

R	is aryl or heteroaryl, wherein each of the above groups R may be substituted by 1 to 4 substituents indendently selected from the group consisting of:
	halogen, C1-C6 alkyl, C1-C6 alkoxy, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, C1-C6 mono or dialkylamino, nitro, cyano and a group R_4;
R_1	is hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkyl, halo C1-C6 alkoxy, NH_2, halogen or cyano;
R_2	is hydrogen or $C(H)_n(R_5)_q(CH_2)_pZR_6$;
R_3	is hydrogen, C2-C6 alkenyl, C2-C6 alkynyl or $[CH(R_5)(CH_2)_p]_mZR_6$;
R_4	is C3-C7 cycloalkyl, which may contain one or more double bonds; aryl; or a 5-6 membered heterocycle;
	wherein each of the above groups R_4 may be substituted by one or more groups selected from: halogen, C1-C6 alkyl, C1-C6 alkoxy, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, C1-C6 mono or dialkylamino, nitro, and cyano;
R_5	is hydrogen, C2-C6 alkenyl, C2-C6 alkynyl or $(CH_2)_pZR_6$;
R_6	is C1-C6 alkyl, which may be substituted by one or more groups selected from halogen, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, C1-C6 alkoxy, C1-C6 mono or dialkylamino, nitro, cyano and a group R4;
Y and X	are independently carbon or nitrogen;
m and n	are independently 0 or 1;
p	is 0 or an integer from 1 to 4;
q	is 1 or 2;
Z	is a bond, O, NH or S.

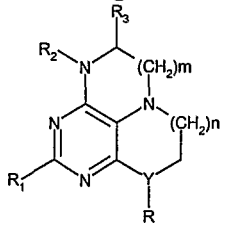
2. Compounds, according to claim 1, of general formula (II)



(II)

in which R, R_1, R_2, R_3, m, n and Y are defined as in claim 1.

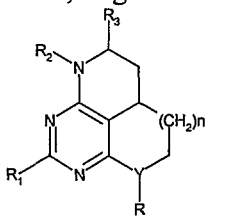
3. Compounds, according to claim 1, of general formula (III)



(III)

in which R, R_1, R_2, R_3, m, n and Y are defined as in claim 1.

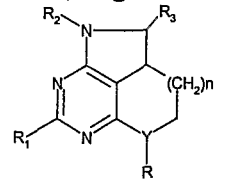
4. Compounds, according to claim 2, of general formula (IIa)



(IIa)

in which R, R_1, R_2, R_3, n and Y are defined as in claim 1.

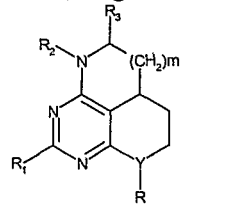
5. Compounds, according to claim 2, of general formula (IIb)



(IIb)

in which R, R_1, R_2, R_3, n and Y are defined as in claim 1.

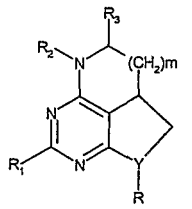
6. Compounds, according to claim 2, of general formula (IIc)



(IIc)

in which R, R_1, R_2, R_3, m and Y are defined as in claim 1.

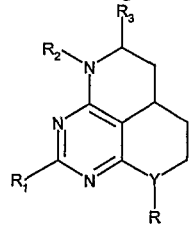
7. Compounds, according to claim 2, of general formula (IId)



(IId)

in which R, R_1, R_2, R_3, m and Y are defined as in claim 1.

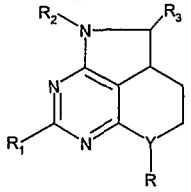
8. Compounds, according to claim 6, of general formula (Ia-1)



(Ia-1)

in which R, R_1, R_2, R_3 and Y are defined as in claim 1.

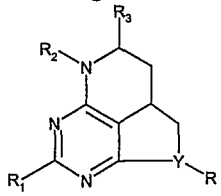
9. Compounds, according to claim 6, of general formula (Ib-1)



(Ib-1)

in which R, R_1, R_2, R_3 and Y are defined as in claim 1.

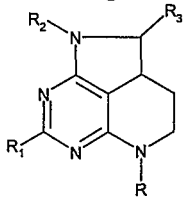
10. Compounds, according to claim 6, of general formula (Ic-1)



(Ic-1)

in which R, R_1, R_2, R_3 and Y are defined as in claim 1.

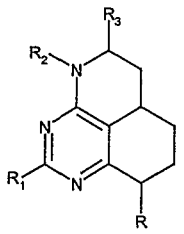
11. Compounds, according to claim 9, of general formula (I-1),



(I-1)

in which R, R_1, R_2, R_3 are defined as in claim 1.

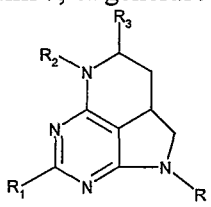
12. Compounds, according to claim 8, of general formula (I-2),



(I-2)

in which R, R_1, R_2, R_3 are defined as in claim 1.

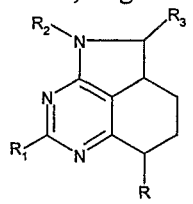
13. Compounds, according to claim 7, of general formula (I-3),



(I-3)

in which R, R_1, R_2, R_3 are defined as in claim 1.

14. Compounds, according to claim 9, of general formula (I-4),



(I-4)

in which R, R_1, R_2, R_3 are defined as in claim 1.

15. Compounds, according to any of claims from 1 to 14, wherein R_2 and R_3 are not simultaneously hydrogen.

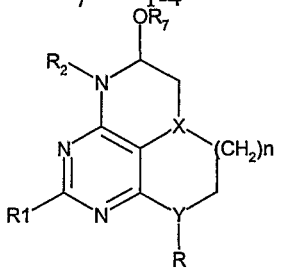
16. Compounds, according to any of claims from 1 to 15, wherein R_1 is C1-C3 alkyl group or halo C1-C3 alkyl group.

17. Compounds, according to any of claims from 1 to 16, wherein
R is an aryl group selected from: 2,4-dichlorophenyl, 2-chloro-4-methylphenyl, 2-chloro-4-trifluoromethyl, 2-chloro-4-methoxyphenyl, 2,4,5-trimethylphenyl, 2,4-dimethyl-phenyl, 2-methyl-4-methoxyphenyl, 2-methyl-4-chlorophenyl, 2-methyl-4-trifluoromethyl, 2,4-dimethoxyphenyl, 2-methoxy-4-trifluoromethylphenyl, 2-methoxy-4-chlorophenyl, 3-methoxy-4-chlorophenyl, 2,5-dimethoxy-4-chlorophenyl, 2-methoxy-4-isopropylphenyl, 2-methoxy-4-trifluoromethylphenyl, 2-methoxy-4-isopropylphenyl 2-methoxy-4-methylphenyl, 2-trifluoromethyl-4-chlorophenyl, 2,4-trifluoromethylphenyl, 2-trifluoromethyl-4-methyl-phenyl, 2-trifluoromethyl-4-methoxyphenyl, 2-bromo-4-isopropylphenyl, 4-methyl-6-dimethylaminopyridin-3-yl, 4-dimethylamino-6-methyl-pyridin-3-yl, 6-dimethylamino-pyridin-3-yl and 4-dimethylamino-pyridin-3-yl.

18. A compound, according to any of claims from 1 to 17, selected in a group consisting from:

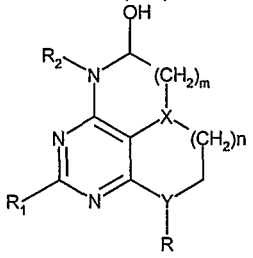
5-(2,4-dichlorophenyl)-1-(1-ethylpropyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene;
5-(2,4-dichlorophenyl)-1-(2-ethylbutyl)-7-methyl-1,2,2a,3,4,5,5a,8b-octahydro-1,5,6,8-tetraazaacenaphthylene;
5-(2,4-dichlorophenyl)-1-(2-methoxy-1-methoxymethylethyl)-7-methyl-1,2,2a,3,4,5,5a,8b-octahydro-1,5,6,8-tetraazaacenaphthylene;
7-methyl-1-(1-propylbutyl)-5-[4-(1,1,2-trifluoroethyl)-2-trifluoromethylphenyl]-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraazaacenaphthylene;
7-methyl-1-(1-propylbutyl)-5-[4-(1,1,2-trifluoroethyl)-2-trifluoromethylphenyl]-1,2,2a(*S*),-3,4,5-hexahydro-1,5,6,8-tetraazaacenaphthylene;
7-methyl-1-(1-propylbutyl)-5-[4-(1,1,2-trifluoroethyl)-2-trifluoromethylphenyl]-1,2,2a-(*R*),3,4,5-hexahydro-1,5,6,8-tetraazaacenaphthylene;
5-(2,4-dichlorophenyl)-7-methyl-1-(1-propylbutyl)-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene;
5-(2,4-dichlorophenyl)-7-methyl-1-(1-propylbutyl)-1,2,2a-(S),3,4,5,5a,8b-octahydro-1,5,6,8-tetraazaacenaphthylene;
5-(2,4-dichlorophenyl)-7-methyl-1-(1-propylbutyl)-1,2,2a-(R),3,4,5,5a,8b-octahydro-1,5,6,8-tetraazaacenaphthylene;
9-(2,4-dichlorophenyl)-4-(1-ethylpropyl)-2-methyl-5,6,6a,7,8,9-hexahydro-4*H*-1,3,4-triazaphenalene (isomer 1) and 9-(2,4-dichlorophenyl)-4-(1-ethylpropyl)-2-methyl-5,6,6a,7,8,9-hexahydro-4*H*-1,3,4-triazaphenalene (isomer 2);
5-cyclopropylmethyl-1-(2,4-dichlorophenyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraazaacenaphthylene;
1-(2,4-dichlorophenyl)-5-(2-methoxyethyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene;
1-(2,4-dichlorophenyl)-5-(1-ethylpropyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene;
1-(2,4-dichlorophenyl)-5-(2-ethylbutyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene;
1-(2,4-dichlorophenyl)-7-methyl-5-(1-propylbutyl)-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene;
7-methyl-5-(1-propylbutyl)-1-[4-(1,1,2-trifluoro-ethyl)-2-trifluoromethylphenyl]-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraazaacenaphthylene;
5-cyclopropylmethyl-1-(2,4-dichlorophenyl)-7-methyl-4-propyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraazaacenaphthylene;
4-butyl-5-cyclopropylmethyl-1-(2,4-dichlorophenyl)-7-methyl-1,2,2a,3,4,5-hexahydro1,5,6,8-tetraazaacenaphthylene;
5-cyclopropylmethyl-1-(2,4-dichlorophenyl)-7-methyl-4-propoxy-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraazaacenaphthylene;
4,5-dibutyl-1-(2,4-dichlorophenyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,5,6,8-tetraaza-acenaphthylene;
5-(2,4-dichlorophenyl)-1-(1-ethylpropyl)-7-methyl-1,2,2a,3,4,5-hexahydro-1,6,8-triaza-acenaphthylene.

19. A process for the preparation of a compound of formula (I) as claimed in claim 1, wherein R_3 is different from hydrogen and m is 1, which comprises the reaction of a compound of formula (VI), wherein R_7 is C_{1-4} linear or branched alkyl group,



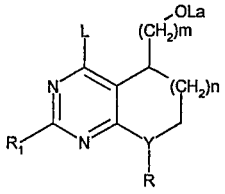
(VI)

with the organo metallic compound GM, wherein G is C2-C6 alkenyl, C2-C6 alkynyl or $[CH(R_5)(CH_2)_p]_mZR_6$ as defined in claim 1, and M is a metal;
a process for the preparation of a compound of formula (I) wherein R_3 is hydrogen which comprises a reduction of a compound of formula (Va)



(Va)

or a process for the preparation of a compound of formula (I), wherein X is carbon, which comprises the reaction by heating of a compound of formula (VII),



(VII)

wherein

L is a leaving group selected in a group consisted from halogens, and reactive residue of sulphonic acid and

La represents a suitable reactive group able to render OLa a good leaving group with the amine R_2NH_2 (IX).

20. The use of a compound according to any of claims 1 to 18, in the preparation of a medicament for use in the treatment of conditions mediated by CRF (corticotropin-releasing factor).

21. The use of a compound according to claim 20, in the preparation of a medicament for use in the treatment of depression and anxiety.

22. The use of a compound according to claim 20, in the preparation of a medicament for use in the treatment of IBS (irritable bowel disease) and IBD (inflammatory bowel disease).

23. A compound according to any of claims 1 to 18, for use in the treatment of conditions mediated by CRF (corticotropin-releasing factor).

24. A compound according to any of claims 1 to 18, for use in the treatment of depression and anxiety.

25. A compound according to any of claims 1 to 18, for use in the treatment of IBS (irritable bowel disease) and IBD (inflammatory bowel disease).

26. A pharmaceutical composition comprising a compound according to any of claims 1 to 18 in admixture with one or more physiologically acceptable carriers or excipients.

27. A method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated by CRF, comprising administration of an effective amount of a compound according to any of claims 1 to 18.

28. A method, according to claim 27, in the treatment of depression and anxiety, comprising administration of an effective amount of a compound according to any of claims 1 to 18.

29. A method, according to claim 27, in the treatment of IBS (irritable bowel disease) and IBD (inflammatory bowel disease), comprising administration of an effective amount of a compound according to any of claims 1 to 18.

30. A compound according to any of claims 1 to 18, for use in therapy.