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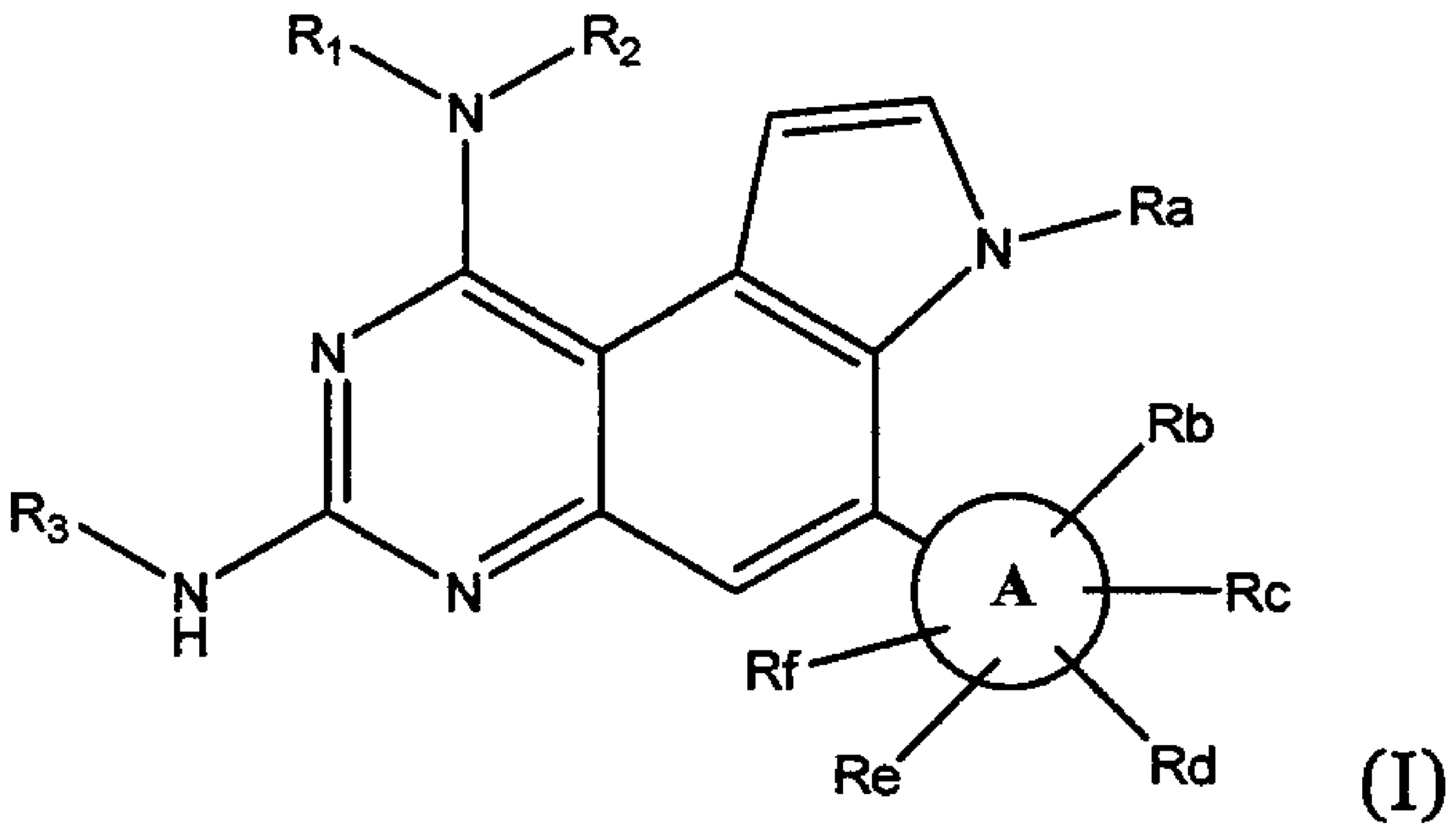
(54) Titre : COMPOSES DIAMINOPYRROLOQUINAZOLINE EN TANT QU'INHIBITEURS DE PROTEINE TYROSINE PHOSPHATASES

(54) Title: DIAMINOPYRROLOQUINAZOLINES COMPOUNDS AS PROTEIN TYROSINE PHOSPHATASE INHIBITORS



(I)

(57) Abrégé/Abstract:
This Invention relates to diaminopyrroloquinazoline compounds of formula (I) wherein R1, R2, R3, Ra, Rb, Rc, Rd, Re, Rf and A are as defined in the description and Claims, which are useful for inhibiting protein tyrosine phosphatases, particularly PTP1B, and are useful for lowering blood glucose concentrations in mammals.

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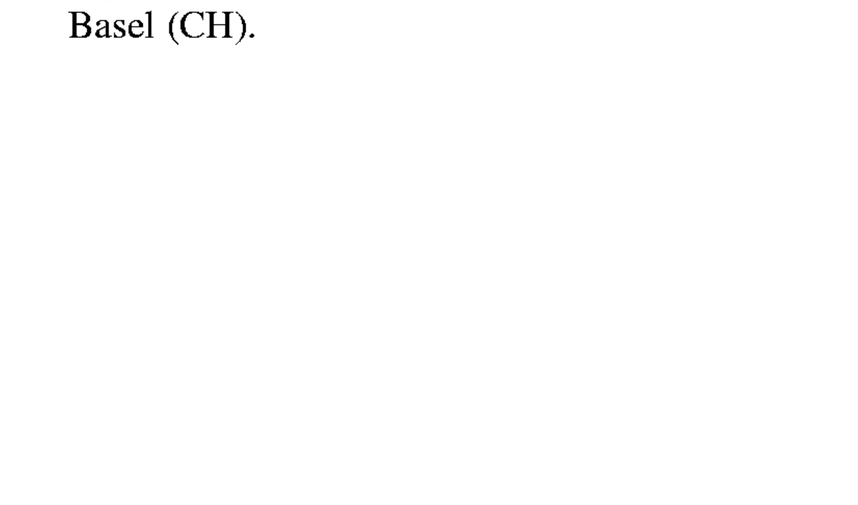
(54) Title: DIAMINOPYRROLOQUINAZOLINES COMPOUNDS AS PROTEIN TYROSINE PHOSPHATASE INHIBITORS

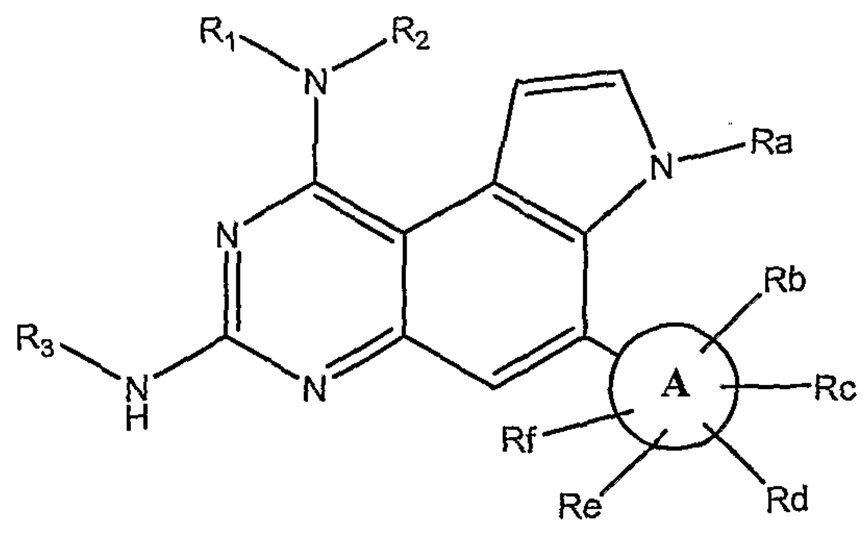


(I)

(57) Abstract: This Invention relates to diaminopyrroloquinazoline compounds of formula (I) wherein R1, R2, R3, Ra, Rb, Rc, Rd, Re, Rf and A are as defined in the description and Claims, which are useful for inhibiting protein tyrosine phosphatases, particularly PTP1B, and are useful for lowering blood glucose concentrations in mammals.

Diaminopyrroloquinazolines Compounds as Protein Tyrosine Phosphatase Inhibitors

The invention relates to diaminopyrroloquinazolines compounds, useful for inhibiting protein tyrosine phosphatases, particularly PTP1B, and for lowering blood glucose concentrations in mammals. These compounds are characterised by formula (I)



(I)

and the pharmaceutically acceptable salts thereof, wherein

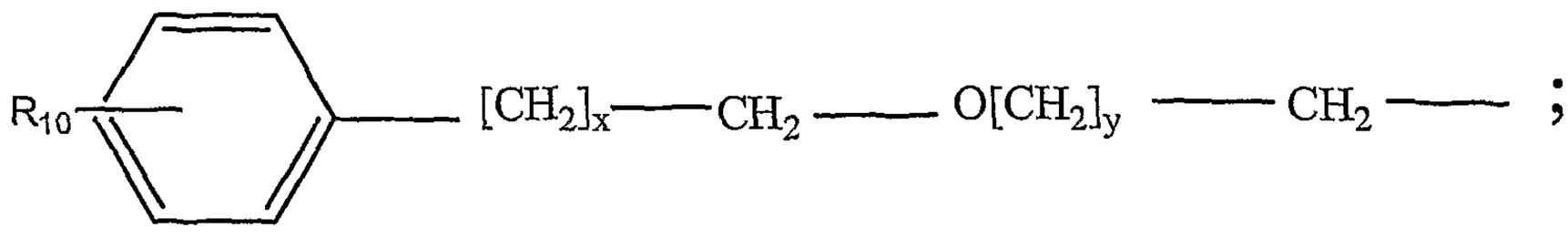
A is a 5- or 6-membered unsaturated or saturated ring, or a 5- or 6-membered unsaturated or saturated ring that contains at least one heteroatom selected from S, N and O,

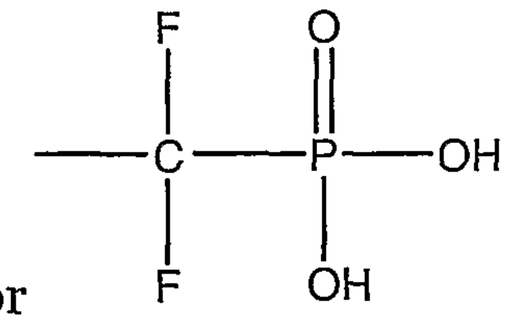
R_1 is selected from the group consisting of lower alkyl, acetyl, dimethylsulfamoyl, hydroxyalkyl, mono or di hydroxy *substituted lower alkyl, phenyl lower alkyl*, benzyloxy-alkyl, and phenyl lower alkoxy lower alkyl;

R_2 is selected *from the group consisting of* hydrogen, lower alkyl, acetyl, hydroxyalkyl, mono or di hydroxy substituted lower alkyl, phenyl lower alkyl, and phenyl lower alkoxy lower alkyl;

R_3 is hydrogen or methyl;

Ra is selected from the group consisting of hydrogen, lower alkyl, lower alkoxy hydroxyalkyl, mono or di hydroxy substituted lower alkyl, phenyl lower alkyl, benzyloxyalkyl or

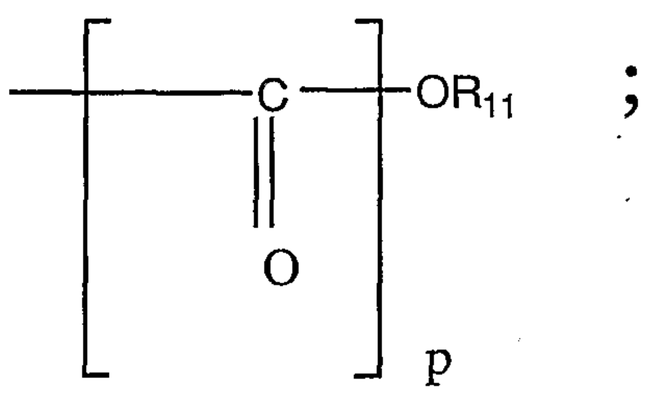




R_{10} is hydrogen or ;

x and y are individual integers from 0 to 4;

Rb and Rc are individually selected from the group consisting of hydrogen, lower alkyl, perfluro-lower alkyl, substituted alkyl, alkoxy, phenoxy, halogen, unsubstituted lower alkyl substituted phenyl lower alkyl, phenyl lower alkoxy or



;

R_{11} is hydrogen, phenyl or unsubstituted lower alkyl;

p is an integer from 0 to 1;

Rd is hydrogen, substituted alkyl or perfluro-lower alkyl;

Re is hydrogen, halogen or substituted alkyl and perfluro-lower alkyl

Rf is hydrogen or lower alkyl.

Protein tyrosine phosphatases (PTPases) are key enzymes in processes that regulate cell growth and differentiation. The inhibition of these enzymes can play a role in the modulation of multiple signaling pathways in which tyrosine phosphorylation dephosphorylation plays a role. PTP1B is a particular protein tyrosine phosphatases that is often used as a prototypical member of that class of enzymes.

PTPase inhibitors are recognized as potential therapeutic agents for the treatment of diabetes. See, e.g. Moeller et al., **3**(5):527-40, Current Opinion in Drug Discovery and Development, 2000; or Zhang, Zhong-Yin, **5**:416-23, Current Opinion in Chemical Biology, 2001. The utility of PTPase inhibitors as therapeutic agents has been a topic of discussion in several review articles, including, or example, Expert Opin Investig Drugs 12(2):223-33, Feb. 2003.

Unless otherwise indicated the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

In this specification the term "lower" is used to mean a group consisting of one to six, preferably of one to four carbon atom(s).

The term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine, with fluorine, chlorine and bromine being preferred.

The term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty carbon atoms, preferably one to sixteen carbon atoms, more preferably one to ten carbon atoms. Alkyl groups can be substituted as defined below for lower alkyl. Lower alkyl groups as defined below are preferred alkyl groups.

As used in the specification, the term "lower alkyl", alone or in combination, means a straight-chain or branched-chain alkyl group containing a maximum of six carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl and the like. Lower alkyl groups may be unsubstituted or substituted by one or more groups selected independently from cycloalkyl, nitro, aryloxy, aryl, hydroxy, halogen, cyano, lower alkoxy, lower alkanoyl, lower alkylthio, lower alkyl sulfinyl, lower alkyl sulfonyl and substituted amino. Examples of substituted lower alkyl groups include 2,3-dihydropropyl and 3-hydroxypropyl.

The term "lower alkoxy" means a straight-chain or branched-chain alkoxy group containing from one to six carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy and the like.

The term "perfluoro-lower alkyl" means any lower alkyl group wherein all the hydrogens of the lower alkyl group are substituted or replaced by fluorine. Among the prefered perfluoro-lower alkyl groups are trifluoromethyl, pentafluroethyl, heptafluoropropyl, etc.

The term "heteroaryl" means a mono- bi or tri-cyclic aromatic group containing a heteroatom such as nitrogen atom, oxygen atom and sulphur atom. Examples of "heteroaryl group" may be pyridyl group, thienyl group, benzofuranyl group, pyrimidinyl group, quinolyl group, isoquinolyl group and isoxazolyl group, indolinyl group, furyl group, oxadiazolyl group, benzothiazolyl group, pyrazinyl group, bezothiadiazolyl group, thiazolidnyl group, imidazothiazolyl group, piperidinyl group, piperazinyl group and tetrahydropyranyl group.

The term "aryl" means a mono- or bicyclic aromatic group, such as phenyl or naphthyl, which is unsubstituted or substituted by conventional substitutent groups. Preferred substituents are lower alkyl, lower alkoxy, hydroxy lower alkyl, hydroxy, hydroxyalkoxy, halogen, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, cyano, nitro, perfluoroalkyl, alkanyoyl, aroyl, aryl alkynyl, lower alkynyl and lower alkanoylamino. The especially preferred substituents are lower alkyl, lower alkoxy, hydroxy, halogen, cyano and perfluoro lower alkyl. Examples of aryl groups that may be used in accordance with this invention are phenyl, p-methoxyphenyl, p-chlorophenyl, m-hydroxy phenyl, m-methylthiophenyl, benzyloxyethyl and the like.

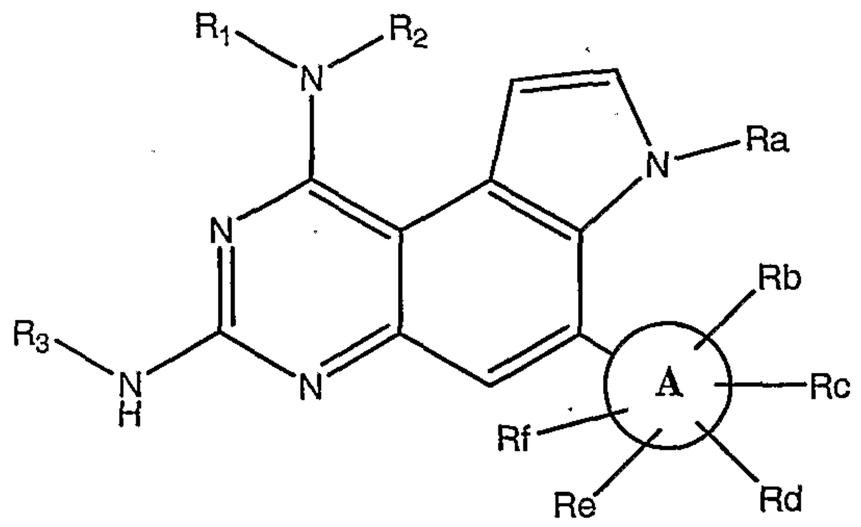
The term "lower alkyl-aryl" means a lower alkyl group in which one or more hydrogen atoms is/are replaced by an aryl group. Any conventional lower alkyl-aryl may be used in accordance with this invention, such as benzyl and the like.

The term "lower alkoxy-aryl" means a lower alkoxy group in which one or more hydrogen atoms is/are replaced by an aryl group. Any conventional lower alkoxy-aryl may be used in accordance with this invention, such as benzyloxy.

The term "pharmaceutically acceptable salts" refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of formulas I, I-A and I-B, and are formed from suitable non-toxic organic or inorganic acids, or organic or inorganic bases. Sample acid-addition salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid

and nitric acid, and those derived from organic acids such as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Sample base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethylammonium hydroxide. The chemical modification of a pharmaceutical compound (i.e., drug) into a salt is a technique well known to pharmaceutical chemists to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. See, e.g., H. Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems (6th Ed. 1995) at pp. 196 and 1456-1457

In detail, the present invention relates to compounds of formula (I)



(I)

and the pharmaceutically acceptable salts thereof, wherein

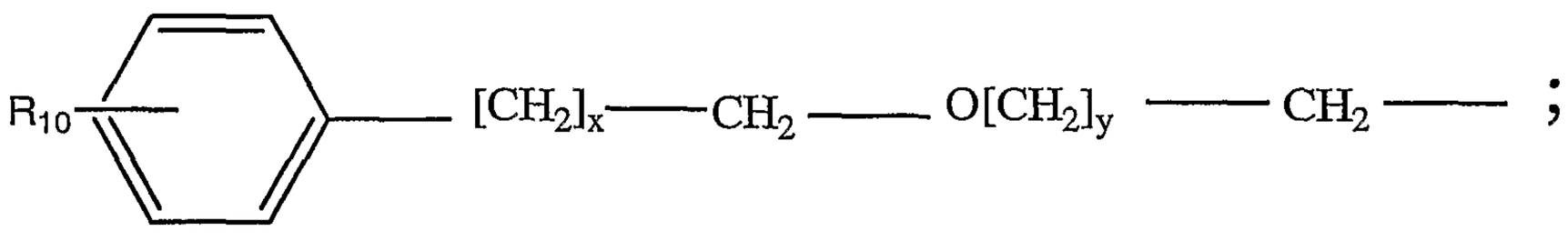
A is a 5- or 6-membered unsaturated or saturated ring, or a 5- or 6-membered unsaturated or saturated ring that contains at least one heteroatom selected from S, N and O,

R_1 is selected from the group consisting of lower alkyl, acetyl, dimethylsulfamoyl, hydroxyalkyl, mono or di hydroxy substituted lower alkyl, phenyl lower alkyl, benzyloxy-alkyl, and phenyl lower alkoxy lower alkyl;

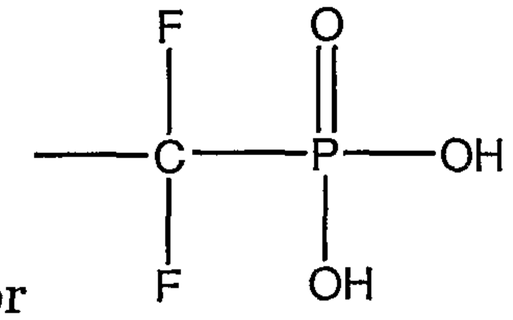
R_2 is selected from the group consisting of hydrogen, lower alkyl, acetyl, hydroxyalkyl, mono or di hydroxy substituted lower alkyl, phenyl lower alkyl, and phenyl lower alkoxy lower alkyl;

R_3 is hydrogen or methyl;

Ra is selected from the group consisting of hydrogen, lower alkyl, lower alkoxy hydroxyalkyl, mono or di hydroxy substituted lower alkyl, phenyl lower alkyl, benzyloxyalkyl or

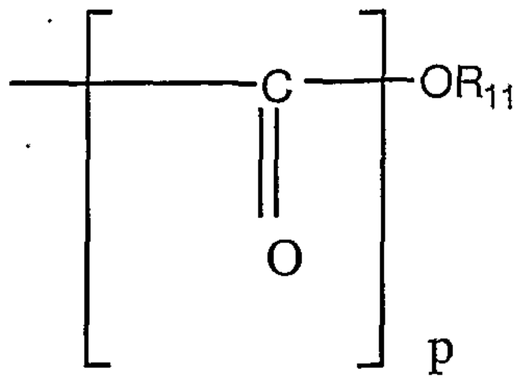


;

R_{10} is hydrogen or  ;

x and y are individual integers from 0 to 4;

Rb and Rc are individually selected from the group consisting of hydrogen, lower alkyl, perfluro-lower alkyl, substituted alkyl, alkoxy, phenoxy, halogen, unsubstituted lower alkyl substituted phenyl lower alkyl, phenyl lower alkoxy or



R_{11} is hydrogen, phenyl or unsubstituted lower alkyl;

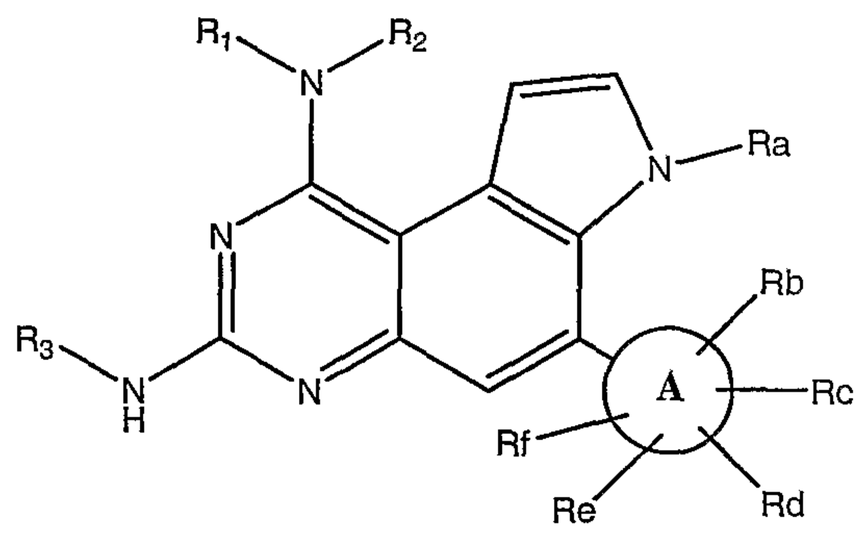
p is an integer from 0 to 1;

Rd is hydrogen, substituted alkyl or perfluro-lower alkyl;

Re is hydrogen, halogen or substituted alkyl and perfluro-lower alkyl

Rf is hydrogen or lower alkyl.

A preferred embodiment relates to compounds of formula (I) as defined above,



(I)

and the pharmaceutically acceptable salts thereof, wherein

A is a 5- or 6-membered unsaturated or saturated ring, or a 5- or 6-membered unsaturated or saturated ring that contains at least one heteroatom selected from S, N and O,

R_1 is selected from the group consisting of lower alkyl, acetyl, hydroxyalkyl, and benzyloxy-alkyl;

R_2 is selected from the group consisting of hydrogen, lower alkyl, acetyl, hydroxyalkyl

R_3 is hydrogen or methyl;

Ra is selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, hydroxyalkyl and benzyloxyalkyl;

Rb is selected from the group consisting of hydrogen, lower alkyl, perfluro-lower alkyl, substituted alkyl, alkoxy and phenoxy;

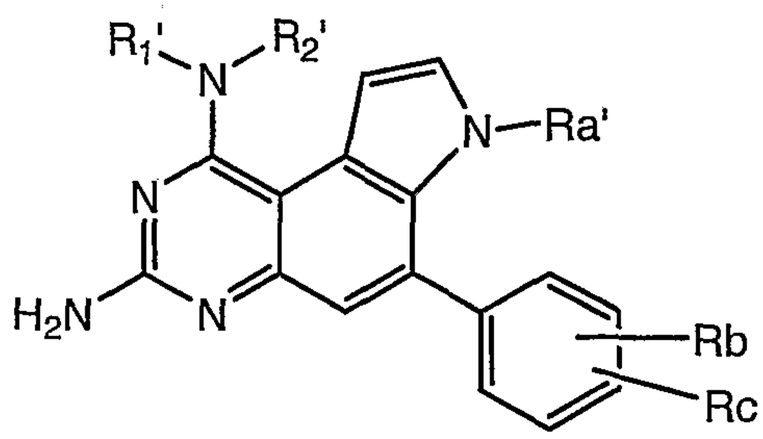
Rc and Rd independently are hydrogen or substituted alkyl, perfluro-lower alkyl;

Re is hydrogen, halogen or substituted alkyl and perfluro-lower alkyl

Rf is hydrogen or lower alkyl.

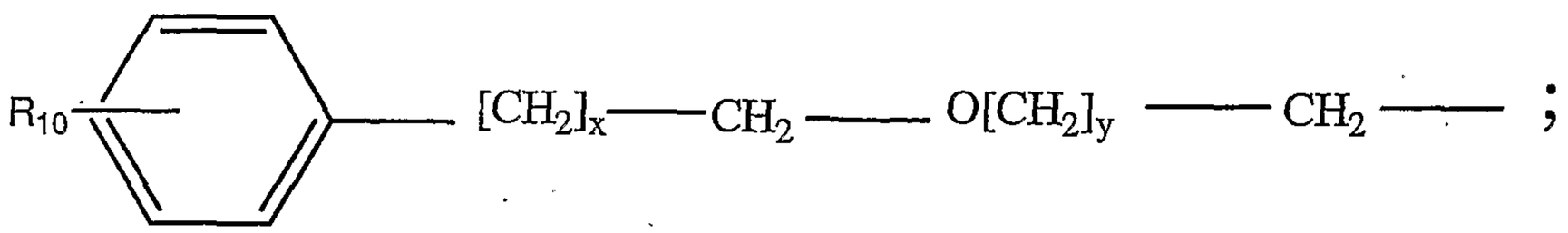
Another preferred embodiment relates to compounds as defined above, wherein
R1 is selected from the group consisting of methyl, ethyl, benzyl, acetyl, 2,3-dihydroxypropyl, 3-hydroxypropyl and 2-benzyloxyethyl;
R2 is selected from the group consisting of hydrogen, methyl, ethyl, benzyl, and acetyl;
Ra is selected from the group consisting of hydrogen, methyl, hydroxyethyl, 2-benzyloxy-ethyl and 2-[4-difluorophosphono-methyl]-benzyloxy]-ethyl;
Rb is selected from the group consisting of hydrogen, methyl, methoxy, phenoxy and trifluoromethyl;
Rc and Rd are each independently selected from hydrogen and trifluoromethyl;
Re is selected from the group consisting of hydrogen, chlorine and trifluoromethyl; and
Rf is selected from hydrogen and methyl.

Another embodiment of the present invention relates to compounds as defined above, wherein said compounds have the formula (I-B)



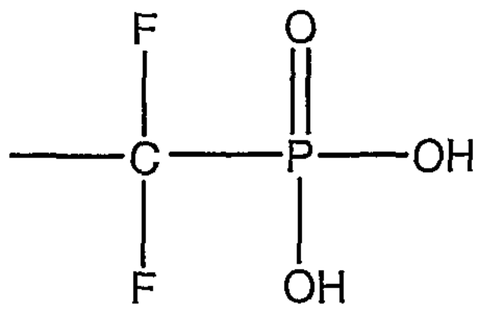
(I-B)

wherein
R_1' is lower alkyl, phenyl lower alkyl, mono or di hydroxy substituted lower alkyl, or phenyl lower alkoxy loweralkyl;
R_2' is hydrogen, lower alkyl, phenyl lower alkyl, mono or di hydroxy substituted lower alkyl, or phenyl lower alkoxy lower alkyl;
Ra' is hydrogen, lower alkyl, mono or di hydroxy substituted lower alkyl, or



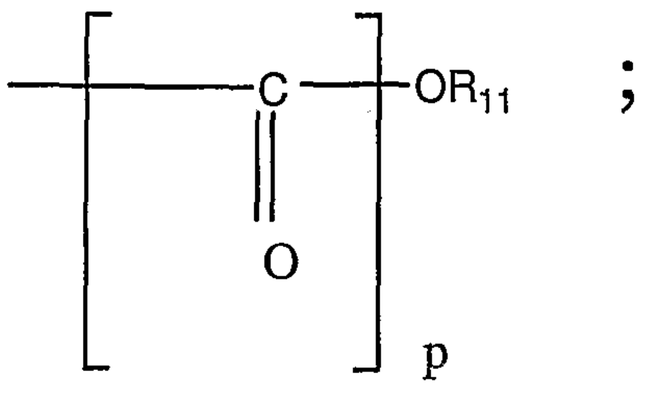
;

R_{10} is hydrogen or



;

Rb' and Rc' are individually selected from the group consisting of hydrogen, perfluoro-lower alkyl, halogen, unsubstituted lower alkyl substituted phenyl lower alkyl, lower alkyl, phenyl lower alkoxy or



;

R_{11} is hydrogen, phenyl or unsubstituted lower alkyl;

p is an integer from 0 to 1; and

x and y are individually integers from 0 to 4

or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention relates to compounds as defined above, wherein

R_1' is lower alkyl;

R_2' is hydrogen or lower alkyl; and

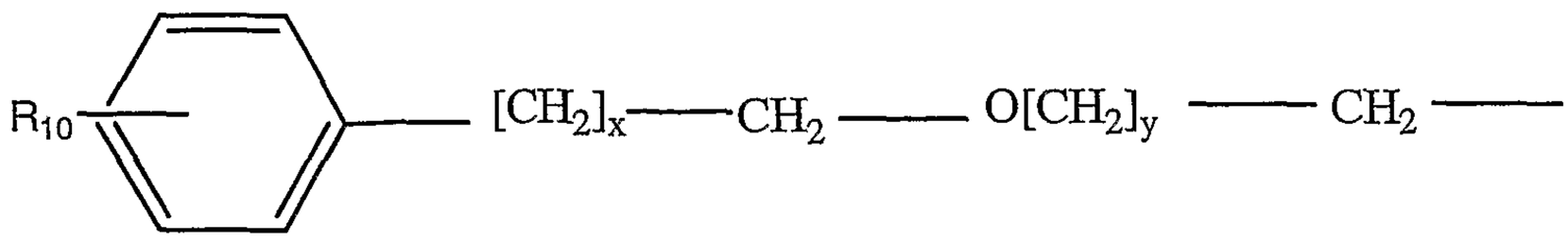
Rb' and Rc' are perfluoroloweralkyl or hydrogen

with at least one or Rb' and Rc' being perfluoroloweralkyl.

Another embodiment of the present invention relates to compounds as defined above, wherein R_1' is mono or di hydroxy substituted lower alkyl and R_2' is hydrogen or mono or di hydroxy substituted lower alkyl and Rb' and Rc' are independently perfluoroloweralkyl or hydrogen with at least one of said Rb' and Rc' being perfluoroloweralkyl.

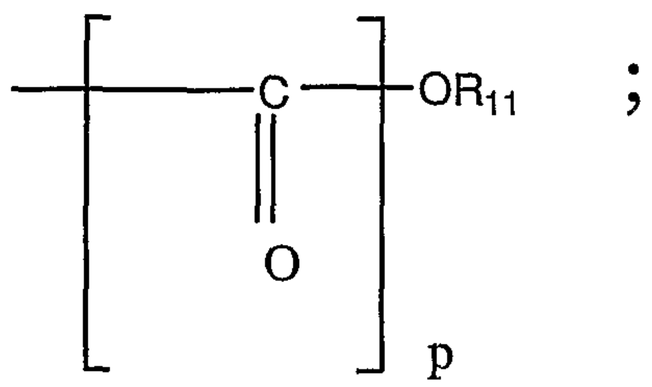
Another embodiment of the present invention relates to compounds as defined above, wherein Ra' is mono or di hydroxy substituted lower alkyl.

Another embodiment of the present invention relates to compounds as defined above, wherein Ra' is



and R_{10}, x and y are as defined above.

Another embodiment of the present invention relates to compounds as defined above, wherein one of Rb' and Rc' is



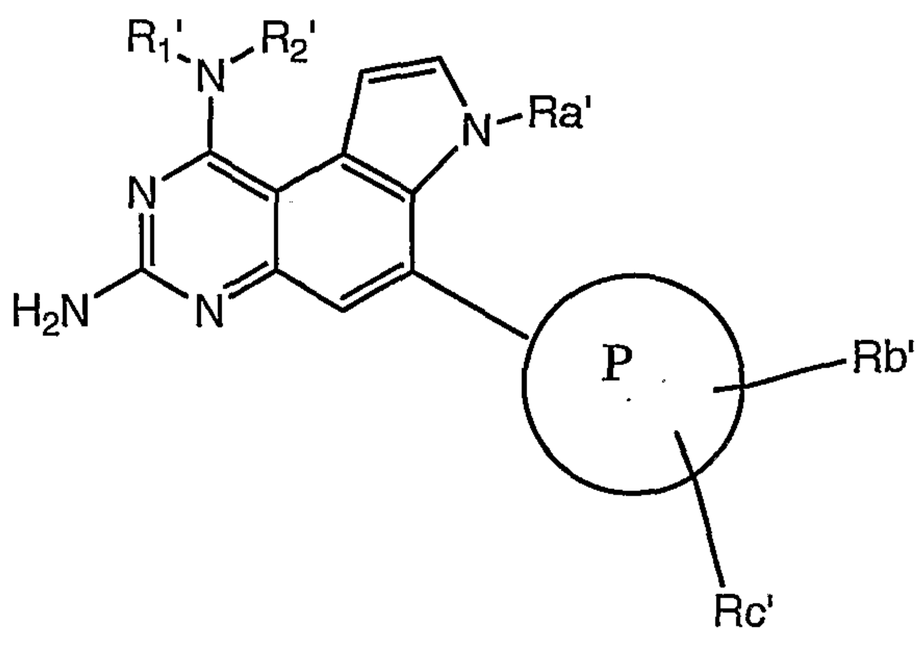
or lower alkoxy;

R_{11} is hydrogen, phenyl or unsubstituted lower alkyl; and

p is an integer from 0 to 1.

Another embodiment of the present invention relates to compounds as defined above, wherein one of Rb' and Rc' is lower alkyl.

Another embodiment of the present invention relates to compounds as defined above, wherein said compounds have the formula (I - A)



(I - A)

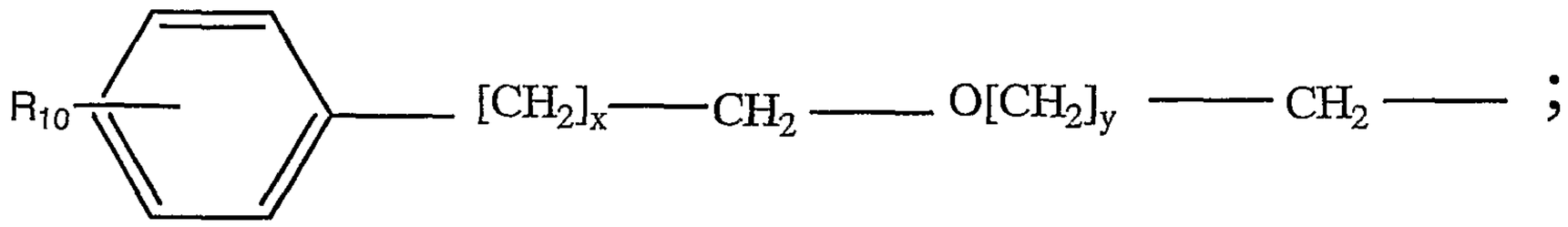
wherein

Ⓟ is a 5 or 6 membered heteroaromatic ring containing from 1 to 2 hetero atoms selected from the group consisting of oxygen, sulfur or nitrogen;

R_1' is lower alkyl, phenyl lower alkyl, mono or di hydroxy substituted lower alkyl, or phenyl lower alkoxy loweralkyl;

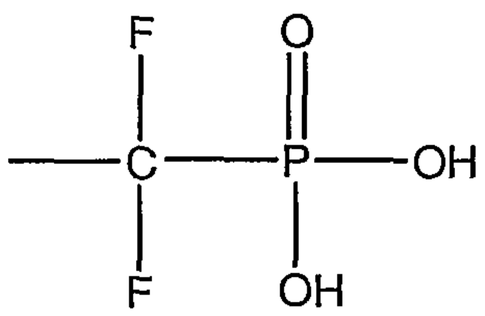
R_2' is hydrogen, lower alkyl, phenyl lower alkyl, mono or di hydroxy substituted lower alkyl, or phenyl lower alkoxy lower alkyl;

Ra' is selected from the group consisting of hydrogen, phenyl lower alkyl, lower alkyl, lower alkoxy, mono or di hydroxy substituted lower alkyl or



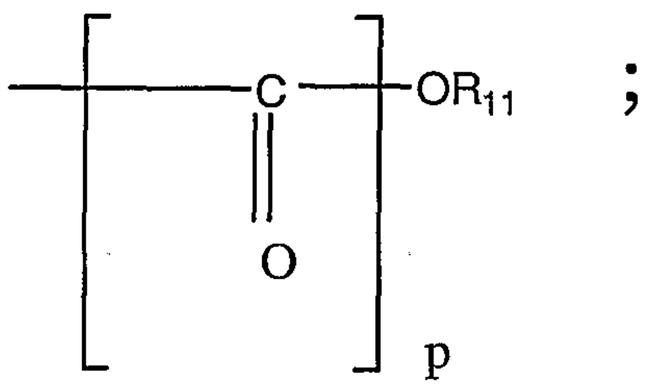
;

R_{10} is hydrogen or



;

Rb' and Rc' are individually selected from the group consisting of hydrogen, perfluoro-lower alkyl, halogen, lower alkyl substituted phenyl lower alkyl, lower alkyl, phenyl lower alkoxy or



;

R_{11} is hydrogen, lower alkyl and phenyl;

p is an integer from 0 to 1; and

x and y are individually integers from 0 to 4

or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention relates to compounds as defined above, wherein Ⓟ is a 5 or 6 membered heteroaromatic ring containing a sulfur hetero atoms as the only heteroaromatic atom in said ring.

Another embodiment of the present invention relates to compounds as defined above, wherein

Rb' and Rc' are hydrogen or lower alkyl;

R_1' is lower alkyl or mono or di hydroxy substituted lower alkyl; and

R_2' is hydrogen, lower alkyl or mono or di hydroxy substituted lower alkyl.

Another embodiment of the present invention relates to compounds as defined above, wherein

Rb' and Rc' are independently hydrogen or lower alkoxy or phenyl lower alkoxy with at least one of Rb' and Rc' being other than hydrogen;

R_1' is lower alkyl or mono or di hydroxy substituted lower alkyl; and

R_2' is hydrogen or lower alkyl or mono or di lower hydroxy substituted lower alkyl.

Another embodiment of the present invention relates to compounds as defined above, wherein

Ⓟ is a 5 or 6 membered heteroaromatic ring containing an oxygen atom as the only hetero atom.

Another embodiment of the present invention relates to compounds as defined above, wherein

R_1' is lower alkyl; and

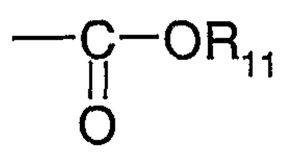
R_2' is hydrogen or lower alkyl.

Another embodiment of the present invention relates to compounds as defined above, wherein

Ⓟis a 5 or 6 membered heteroaromatic ring containing a nitrogen atom as the only hetero atom.

Another embodiment of the present invention relates to compounds as defined above, wherein

one of Rb' and Rc' is hydrogen and the other is hydrogen, lower alkyl or



wherein

R_{11} is phenyl or lower alkyl; and

R_1' and R_2' are lower alkyl.

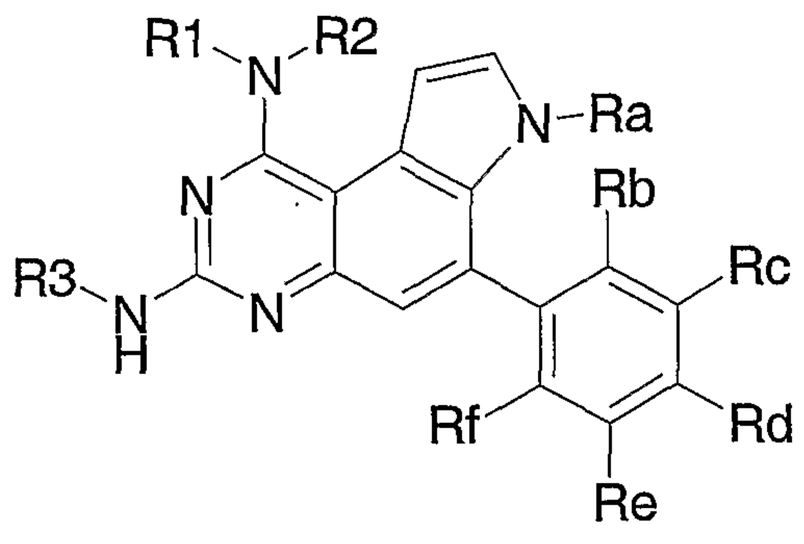
Another embodiment of the present invention relates to compounds as defined above, wherein

Ⓟ is a 5 or 6 membered heteroaromatic ring containing two heteroatoms.

Another embodiment of the present invention relates to compounds as defined above, wherein

Rb' and Rc' are lower alkyl, hydrogen or lower alkoxy.

Another embodiment of the present invention relates to compounds as defined above, having the formula (II)



(II)

and the pharmaceutically acceptable salts thereof, wherein

R_1 is selected from the group consisting of lower alkyl, acetyl, hydroxyalkyl, and benzyloxy-alkyl;

R_2 is selected from the group consisting of hydrogen, lower alkyl, acetyl, hydroxyalkyl

R_3 is hydrogen or methyl;

Ra is selected from the group consisting of hydrogen, lower alkyl, lower alkoxy hydroxyalkyl and benzyloxyalkyl;

Rb is selected from the group consisting of hydrogen, lower alkyl, perfluro-lower alkyl, substituted alkyl, alkoxy and phenoxy;

Rc and Rd independently are hydrogen or substituted alkyl, perfluro-lower alkyl;

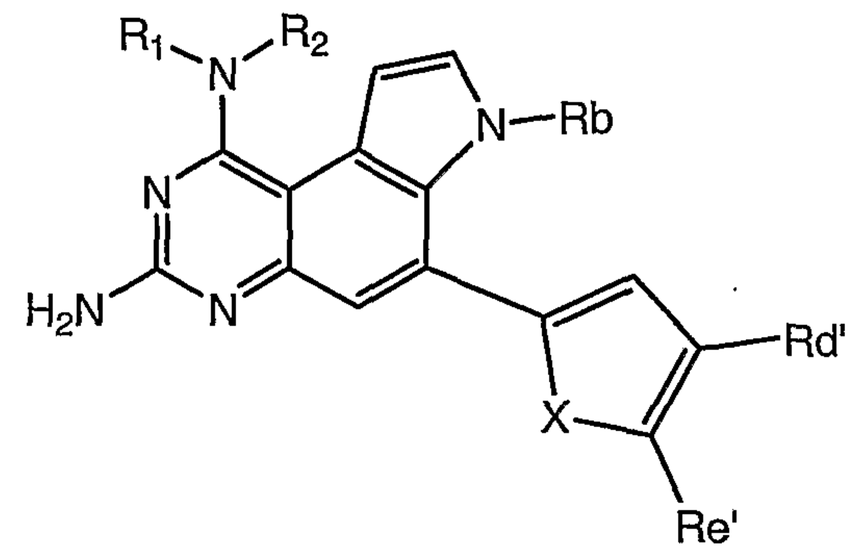
Re is hydrogen, halogen or substituted alkyl and perfluro-lower alkyl

Rf is hydrogen or lower alkyl.

Another embodiment of the present invention relates to compounds as defined above, wherein

R^1 is selected from the group consisting of methyl, ethyl, allyl, benzyl, acetyl, 2,3-dihydroxypropyl, 3-hydroxypropyl and 2-benzyloxyethyl;
R^2 is selected from the group consisting of hydrogen, methyl, ethyl, allyl, benzyl, and acetyl;
Ra is selected from the group consisting of hydrogen, methyl, hydroxyethyl, 2-benzyloxy-ethyl and 2-[4-difluorophosphono-methyl]-benzyloxy]-ethyl;
Rb is selected from the group consisting of hydrogen, methyl, methoxy, phenoxy and trifluoromethyl;
Rc and Rd independently are hydrogen or trifluoromethyl;
Re is hydrogen, chlorine halogen or trifluoromethyl; and
Rf is hydrogen or methyl.

Another embodiment of the present invention relates to compounds as defined above, having the formula (III)



(III)

and the pharmaceutically acceptable salts thereof, wherein
R^1 is selected from the group consisting of hydrogen, lower alkyl, acetyl, hydroxyalkyl
R^2 is hydrogen or methyl;
X is sulfur, oxygen, nitrogen or N-tert-butoxycarbonyl;
Rb is is selected from the group consisting of hydrogen, lower alkyl, lower alkoxy hydroxyalkyl and benzyloxyalkyl;
R_d' and R_e' independently are selected from the group consisting of hydrogen, lower alkyl and alkoxy.

Another embodiment of the present invention relates to compounds as defined above, wherein

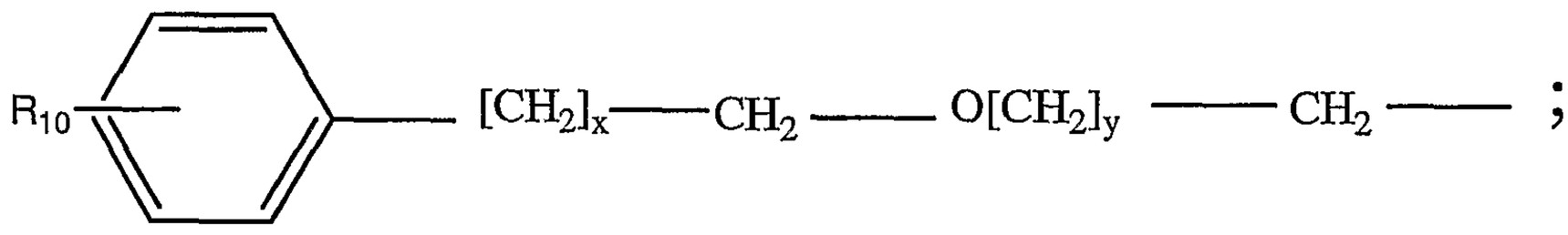
R^1 is selected from the group consisting of methyl, ethyl, acetyl, 3-hydroxypropyl and dimethylsulfamoyl;

R^2 and Rb' independently are selected from the group consisting of hydrogen, methyl and ethyl; and

Rd' and Re' independently are selected from the group consisting of hydrogen, methyl or methoxy.

In the preferred compounds of formula I-B, there are several preferred embodiments of these compounds. In accordance with a first embodiment, R_1' is hydrogen or unsubstituted lower alkyl, R_2' is unsubstituted lower alkyl and Rb' and Rc' are perfluoroloweralkyl, preferably trifluoromethyl, with at least one of Rb' and Rc' being perfluoroloweralkyl. In accordance with this first embodiment of the compound of formula I-A, Ra' can be hydrogen, unsubstituted lower alkyl or mono- or di- hydroxy substituted lower alkyl and Rb' and Rc' being perfluoroloweralkyl such as trifluoromethyl and the other being hydrogen or perfluoroloweralkyl.

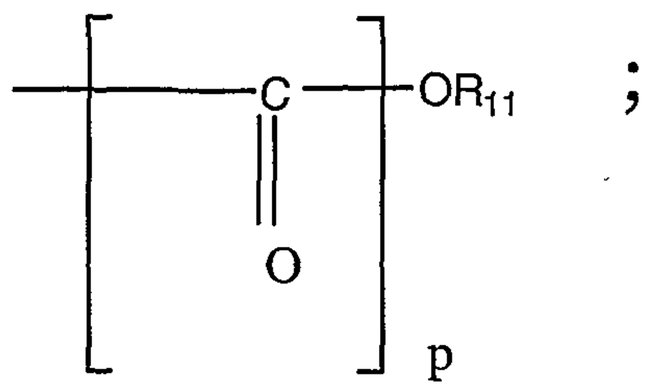
In accordance with another embodiment of the compound of formula I-B, Ra' can be



wherein R_{10}, x and y are as above. In accordance with this embodiment, R_1' can be hydrogen or lower alkyl and R_2' can be lower alkyl. In addition, in an especially preferred class of this embodiment, Rb' and Rc' can be perfluoroloweralkyl or hydrogen with at least one of Rb' and Rc' being perfluoroloweralkyl.

In accordance with still another embodiment of the compound of formula I-B, one of Rb' and Rc' is lower alkyl, with both of Rb' and Rc' being lower alkyl being especially preferred. On the other hand in this embodiment R_8, and R_9 can be both hydrogen or one of Rb' and Rc' can be hydrogen and the other lower alkyl. In yet

another embodiment of the compound of formula I-B, one of Rb' and Rc' is lower alkoxy or a substituent of the formula:

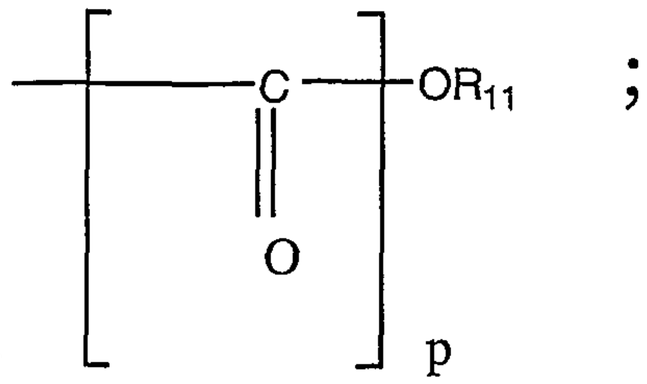


wherein R_{11} and p are as above. In this embodiment, compounds where one of Ra' and Rb' are unsubstituted lower alkyl are especially preferred. In addition, in this especially preferred embodiment, compounds where Ra' is unsubstituted lower alkyl are preferred.

With respect to the compound of formula I-A there are many embodiments in accordance with the inventions embraced within this formula. The heteroaromatic ring in accordance with this invention preferably contains 5 or six members in the ring. Among these are compounds of formula I-A where the heteroaromatic ring formed within this compound contains a sulfur hetero atom as the only heteroaromatic atom in this ring such as thiophene rings. Among the compounds containing a thiophene ring are those compounds where Rb' and Rc' are hydrogen or lower alkyl, R_1' is hydrogen, lower alkyl or mono- or di- hydroxy substituted lower alkyl and R_6 is lower alkyl or mono- or di- hydroxy substituted lower alkyl. In accordance with the embodiment of the compounds where the heteroaromatic ring is a thiophene ring, among the preferred compounds are those where Rb' and Rc' are independently hydrogen, lower alkoxy or phenyl lower alkoxy with at least one of Rb' and Rc' being other than hydrogen. In this preferred embodiment, R_1' is hydrogen or lower alkyl or mono- or di- hydroxy substituted lower alkyl and R_2' is lower alkyl or mono- or di- hydroxy substituted lower alkyl.

In accordance with another embodiment of the compounds of formula I-A, the aromatic ring is 5 or 6 membered heteroaromatic ring containing an oxygen atom as the only hetero atom such as a furanyl ring. In this embodiment, one preferred class of compounds are those where R_1' is hydrogen or lower alkyl and R_2' is lower alkyl. Another embodiment of the compounds of formula I-A are those compounds wherein the heteroaromatic ring is a 5 or 6 membered heteroaromatic

ring containing a nitrogen atom as the only heteroaromatic ring. In accordance with this embodiment, compounds where one of the Rb' and Rc' substituents are hydrogen and the other is hydrogen, lower alkyl or a substituent of the formula



where R_{11} and p are as above. In accordance with this embodiment, compounds where p is 1 is a preferred embodiment, R_{11} is phenyl or lower alkyl and R_1' and R_2' are unsubstituted lower alkyl.

In accordance with another embodiment of the compound of formula I-B, Ⓟ can be a heteroaromatic ring containing 5 or 6 members and two hetero atoms such as nitrogen or oxygen or oxygen or sulfur. In this embodiment, R_1' and R_2' can be lower alkyl, hydrogen or alkoxy.

Preferred compounds as defined above are those selected from the group consisting of

7,N1-Dimethyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

7,N1,N1-Trimethyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

7,N1-Dimethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

N1-Ethyl-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

6-(3,5-Bis-trifluoromethyl-phenyl)-7,N1,N1,N3-tetramethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

7,N1-Diethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

7-Ethyl-N1-methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

7-Ethyl-N1,N1-dimethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

N1,N1-Diethyl-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

7-Methyl-N1,N1-dipropyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

7-Methyl-1-piperidin-1-yl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-3-ylamine,

N1,N1-Dibenzyl-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

7-Methyl-1-pyrrolidin-1-yl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-3-ylamine,

6-(2-Methoxy-phenyl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

6-(2-Methoxy-phenyl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

N1,N1-Diethyl-7-methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

7,N1,N1-Trimethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

7,N1,N1,N3-Tetramethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

6-Iodo-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

7,N1,N1-Trimethyl-6-(5-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

7,N1-Dimethyl-6-(5-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

6-(5-Chloro-2-methoxy-phenyl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

6-Furan-2-yl-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

6-Furan-2-yl-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

2-[3-Amino-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-ethanol,

2-(3-Amino-7-methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazolin-1-ylamino)-ethanol,

3-[3-Amino-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-propan-1-ol,

3-(3-Amino-7-methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazolin-1-ylamino)-propan-1-ol,

2-[3-Amino-7-methyl-6-(5-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-ethanol,

6-Furan-3-yl-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

7,N1,N1-Trimethyl-6-(4-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

2-(3-Amino-1-dimethylamino-7-methyl-7H-pyrrolo[3,2-f]quinazolin-6-yl)-pyrrole-1-carboxylic acid tert-butyl ester,

6-(3,5-Dimethyl-isoxazol-4-yl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

7,N1-Dimethyl-6-(2-phenoxy-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

2-[3-Amino-7-(2-hydroxy-ethyl)-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-ethanol,

6-(4-Methoxy-thiophen-2-yl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

3-[3-Amino-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-propane-1,2-diol,

2-[3-Amino-1-dimethylamino-6-(2-trifluoromethyl-phenyl)-pyrrolo[3,2-f]quinazolin-7-yl]-ethanol,

[(4-{2-[3-Amino-1-dimethylamino-6-(2-trifluoromethyl-phenyl)-pyrrolo[3,2-f]quinazolin-7-yl]-ethoxymethyl}-phenyl)-difluoro-methyl]-phosphonic acid,

6-(5-Methoxy-thiophen-2-yl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

6-(5-Methoxy-thiophen-2-yl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

6-(4-Methoxy-thiophen-2-yl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

6-(2,6-Dimethyl-phenyl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

6-(2,6-Dimethyl-phenyl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

7,N1,N1-Trimethyl-6-(4-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

7,N1-Bis-(2-benzyloxy-ethyl)-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
2-[[3-Amino-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-1-yl]-(2-hydroxy-ethyl)-amino]-ethanol,
3-Amino-7-methyl-6-thiophen-2-yl-2,7-dihydro-pyrrolo[3,2-f]quinazolin-1-one,
7,N1,N1-Trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine, and
6-(2,4-Dimethoxy-pyrimidin-5-yl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
and pharmaceutically acceptable salts thereof.

Other preferred compounds as defined above are those selected from the group consisting of
7,N1-Dimethyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; compound with trifluoro-acetic acid,
7,N1,N1-Trimethyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7,N1-Dimethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
N1-Ethyl-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; compound with trifluoro-acetic acid,
6-(3,5-Bis-trifluoromethyl-phenyl)-7,N1,N1,N3-tetramethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7,N1-Diethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; compound with trifluoro-acetic acid,
7-Ethyl-N1-methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; compound with trifluoro-acetic acid,
7-Ethyl-N1,N1-dimethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; compound with trifluoro-acetic acid,
N1,N1-Diethyl-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; compound with trifluoro-acetic acid,
7-Methyl-N1,N1-dipropyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; compound with trifluoro-acetic acid,
7-Methyl-1-piperidin-1-yl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-3-ylamine; compound with trifluoro-acetic acid,

N1,N1-Dibenzyl-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; compound with trifluoro-acetic acid,
7-Methyl-1-pyrrolidin-1-yl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-3-ylamine; compound with trifluoro-acetic acid,
6-(2-Methoxy-phenyl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; compound with trifluoro-acetic acid,
6-(2-Methoxy-phenyl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; compound with trifluoro-acetic acid,
N1,N1-Diethyl-7-methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; compound with trifluoro-acetic acid,
7,N1,N1-Trimethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; compound with trifluoro-acetic acid,
7,N1,N1,N3-Tetramethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; compound with trifluoro-acetic acid,
6-Iodo-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7,N1,N1-Trimethyl-6-(5-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7,N1-Dimethyl-6-(5-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
6-(5-Chloro-2-methoxy-phenyl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; compound with trifluoro-acetic acid,
6-Furan-2-yl-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
6-Furan-2-yl-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; compound with trifluoro-acetic acid,
2-[3-Amino-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-ethanol; compound with trifluoro-acetic acid,
2-(3-Amino-7-methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazolin-1-ylamino)-ethanol; compound with trifluoro-acetic acid,
3-[3-Amino-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-propan-1-ol; compound with trifluoro-acetic acid,
3-(3-Amino-7-methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazolin-1-ylamino)-propan-1-ol; compound with trifluoro-acetic acid,
2-[3-Amino-7-methyl-6-(5-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-ethanol; compound with trifluoro-acetic acid,

6-Furan-3-yl-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7,N1,N1-Trimethyl-6-(4-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
2-(3-Amino-1-dimethylamino-7-methyl-7H-pyrrolo[3,2-f]quinazolin-6-yl)-pyrrole-1-carboxylic acid tert-butyl ester,
6-(3,5-Dimethyl-isoxazol-4-yl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; compound with trifluoro-acetic acid,
7,N1-Dimethyl-6-(2-phenoxy-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; compound with trifluoro-acetic acid,
2-[3-Amino-7-(2-hydroxy-ethyl)-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-ethanol; compound with trifluoro-acetic acid,
6-(4-Methoxy-thiophen-2-yl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
3-[3-Amino-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-propane-1,2-diol; compound with trifluoro-acetic acid,
2-[3-Amino-1-dimethylamino-6-(2-trifluoromethyl-phenyl)-pyrrolo[3,2-f]quinazolin-7-yl]-ethanol; compound with trifluoro-acetic acid,
[(4-{2-[3-Amino-1-dimethylamino-6-(2-trifluoromethyl-phenyl)-pyrrolo[3,2-f]quinazolin-7-yl]-ethoxymethyl}-phenyl)-difluoro-methyl]-phosphonic acid,
6-(5-Methoxy-thiophen-2-yl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
6-(5-Methoxy-thiophen-2-yl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
6-(4-Methoxy-thiophen-2-yl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
6-(2,6-Dimethyl-phenyl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; compound with trifluoro-acetic acid,
6-(2,6-Dimethyl-phenyl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; compound with trifluoro-acetic acid,
7,N1,N1-Trimethyl-6-(4-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7,N1-Bis-(2-benzyloxy-ethyl)-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; compound with trifluoro-acetic acid,

2-[[3-Amino-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-1-yl]-(2-hydroxy-ethyl)-amino]-ethanol; compound with trifluoro-acetic acid,
3-Amino-7-methyl-6-thiophen-2-yl-2,7-dihydro-pyrrolo[3,2-f]quinazolin-1-one,
7,N1,N1-Trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine, and
6-(2,4-Dimethoxy-pyrimidin-5-yl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
and pharmaceutically acceptable salts thereof.

Particularly preferred compounds as defined above are those selected from the group consisting of
7,N1-dimethyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7,N1-dimethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
6-(2,6-Dimethyl-phenyl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7-ethyl-N1-methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
6-(4-methoxy-thiophen-2-yl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
6-(5-methoxy-thiophen-2-yl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine, and
6-furan-2-yl-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
and pharmaceutically acceptable salts thereof.

Other particularly preferred compounds as defined above are those selected from the group consisting of
7,N1-dimethyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt,
7,N1-dimethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt,
6-(2,6-Dimethyl-phenyl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt,
7-ethyl-N1-methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt,

6-(4-methoxy-thiophen-2-yl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

6-(5-methoxy-thiophen-2-yl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine, and

6-furan-2-yl-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt,

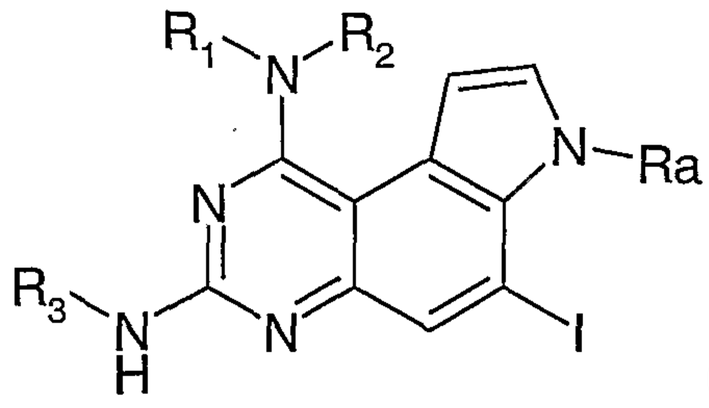
and pharmaceutically acceptable salts thereof.

Each of the compounds mentioned above individually constitutes a preferred embodiment of the present invention. Compounds as described above, which are not pharmaceutically acceptable salts and/or pharmaceutically acceptable esters are preferred.

Compounds of formula (I) have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, optically pure diastereoisomers or mixtures of diastereoisomers. The optically active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbens or eluant). The invention embraces all such forms.

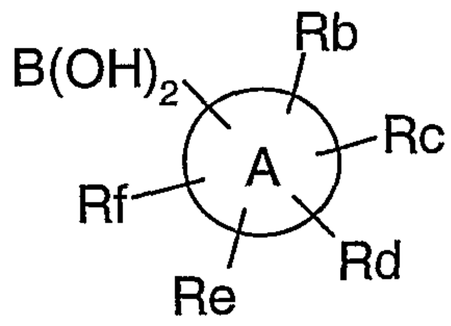
It will be appreciated, that the compounds of general formula (I) in this invention may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compound in vivo. Physiologically acceptable and metabolically labile derivatives, which are capable of producing the parent compounds of general formula (I) in vivo are also within the scope of this invention.

A further aspect of the present invention is the process for the manufacture of compounds of formula (I) as defined above, comprising reacting a compound of formula (XII)



(XII)

with a compound of formula (XIII)



(XIII)

wherein R1, R2, R3, Ra, Rb, Rc, Rd, Re, Rf and A have the significances given above.

Said reaction of a compound of formula XII with a compound of formula XIII can be carried out by methods well known to the person skilled in the art, e.g. in analogy to the examples and schemes described below. The reaction can e.g. be carried out with Pd(P(phenyl)3)4 in a solvent such as e.g. DME or ETOH and treating with Na2CO3 and H2O.

Another embodiment of the present invention relates to compounds as defined above, when prepared by a process as defined above.

As described above, the compounds of the present invention can be used as medicaments for the treatment and/or prevention of diseases which are modulated by PTP1B inhibitors. Examples of such diseases are diseases which are based on high blood glucose concentration, particularly diabetes. The compounds of the invention inhibit PTP1B *in vitro* and have been shown to lower blood glucose levels *in vivo*. Thus, the compounds of the present invention would be useful for the treatment of diabetes.

The invention therefore also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant.

Further, the invention relates to compounds as defined above for use as therapeutic active substances, particularly as therapeutic active substances for the treatment and/or prevention of diseases which are modulated by PTP1B inhibitors. Examples of such diseases are diseases which are based on high blood glucose concentration, particularly diabetes.

In another embodiment, the invention relates to a method for the treatment and/or prevention of diseases which are modulated by PTP1B inhibitors, which method comprises administering a compound as defined above to a human or animal. Preferred examples of such diseases are diseases which are based on high blood glucose concentration, particularly diabetes.

The invention further relates to the use of compounds as defined above for the treatment and/or prevention of diseases which are modulated by PTP1B inhibitors. Preferred examples of such diseases are diseases which are based on high blood glucose concentration, particularly diabetes.

In addition, the invention relates to the use of compounds as defined above for the preparation of medicaments for the treatment and/or prevention of diseases which are modulated by PTP1B inhibitors. Preferred examples of such diseases are diseases which are based on high blood glucose concentration, particularly diabetes. Such medicaments comprise a compound as defined above.

The compounds of the invention can be administered orally, rectally, or parentally, e.g., intravenously, intramuscularly, subcutaneously, intrathecally or transdermally; or sublingually, or as opthalmalogical preparations. Capsules, tablets, suspensions or solutions for oral administration, suppositories, injection solutions, eye drops, salves or spray solutions are examples of administration forms.

Intravenous, intramuscular, oral or inhalation administration are preferred forms of use. The dosages in which the compounds of the invention are administered in effective amount depend on the nature of the specific active ingredient, the age and requirements of the patient and the mode of administration. Dosages may be determined by any conventional means, e.g., by dose-limiting clinical trials. In general, dosages of about 0.1 to 100 mg/kg body weight per day are preferred, with dosages of 1-25 mg/kg per day being particularly preferred.

The invention further comprises pharmaceutical compositions that contain a pharmaceutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier. Such compositions may be formulated by any conventional means. Tablets or granulates can contain a series of binders, fillers, carriers or diluents. Liquid compositions can be, for example, in the form of a sterile water-miscible solution. Capsules can contain a filler or thickener in addition to the active ingredient. Furthermore, flavor-improving additives as well as substances usually used as preserving, stabilizing, moisture-retaining and emulsifying agents as well as salts for varying the osmotic pressure, buffers and other additives can also be present.

The previously mentioned carrier materials and diluents can comprise any conventional pharmaceutically acceptable organic or inorganic substances, e.g., water, gelatine, lactose, starch, magnesium stearate, talc, gum arabic, polyalkylene glycols and the like.

Oral unit dosage forms, such as tablets and capsules, preferably contain from 25 mg to 1000 mg of a compound of this invention. The compounds of the invention may be prepared by conventional means.

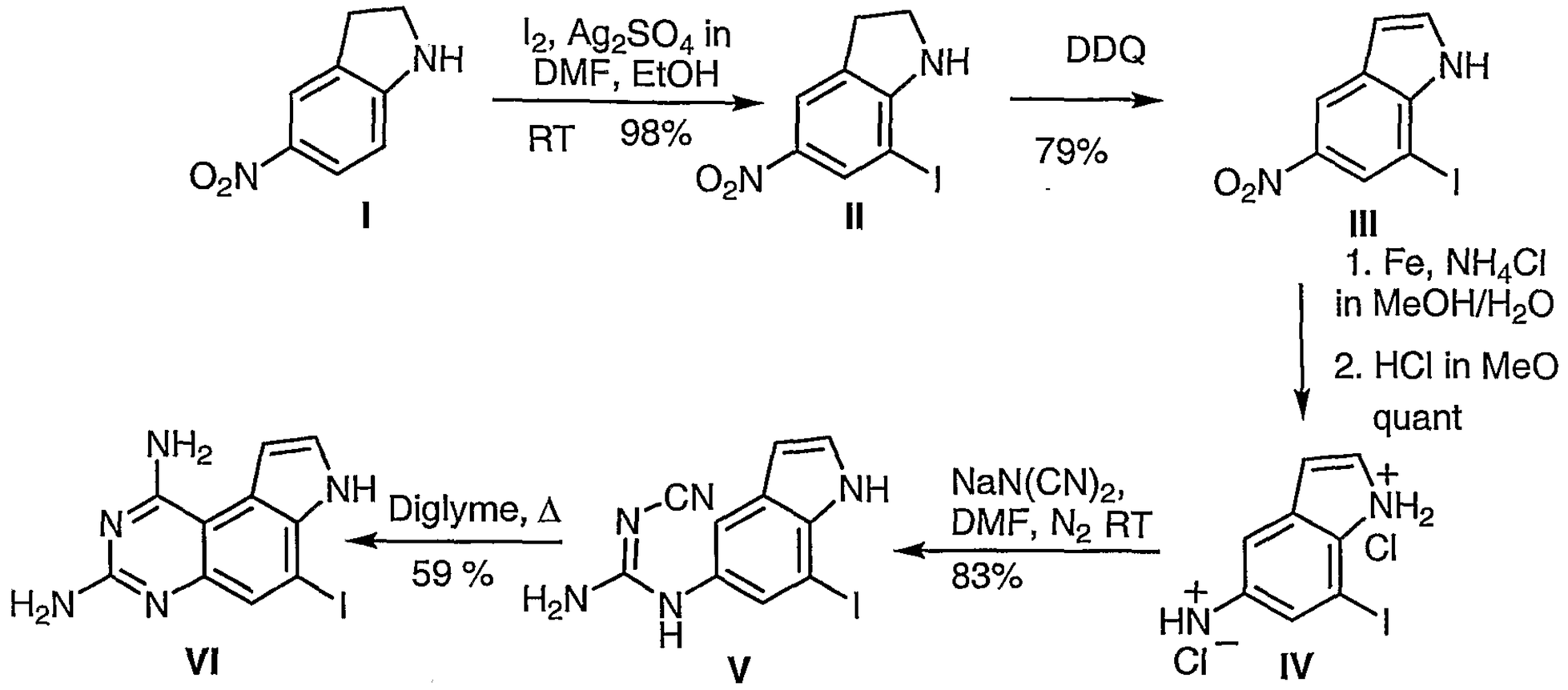
In accordance with this invention, the compounds herein as well as their pharmaceutically acceptable salts are useful in the control or prevention of illnesses associated with high blood glucose concentration. A preferred indication associated with the present invention is that associated with diabetes.

The dosage can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. In the case of oral administration, the dosage for adults may vary from about 0.01 mg to about 1000 mg per day of a compound of formulas I or II, or of the corresponding amount of a pharmaceutically acceptable salt thereof. The daily dosage may be administered as single dose or in divided doses, and in addition, the upper limit can also be exceeded when this is found to be indicated.

The compounds of formula (I) can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to a person skilled in the art. Starting materials are either commercially available or can be prepared by methods analogous to the methods given below, by methods described in references cited in the text or in the examples, or by methods known in the art.

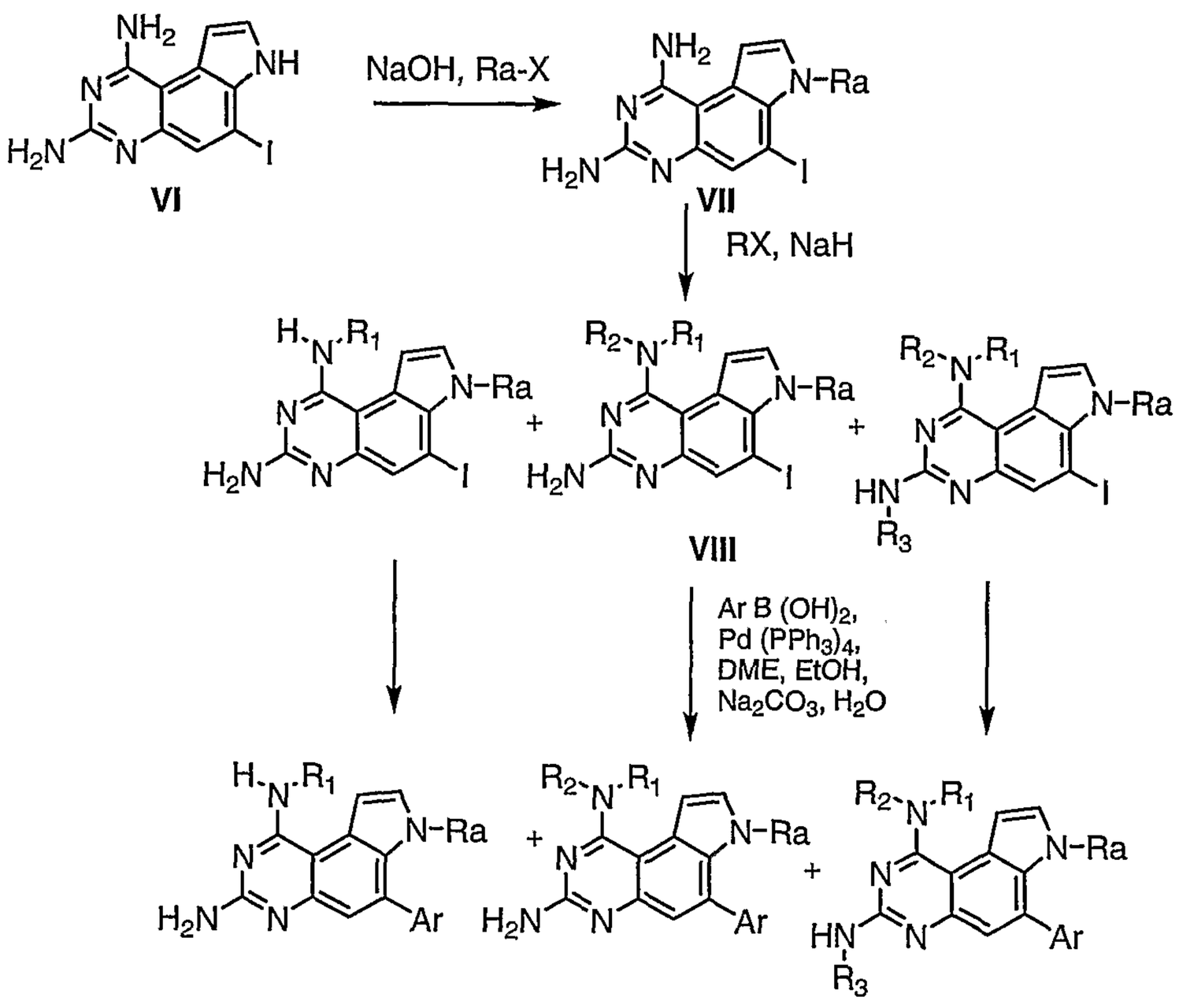
A particular method for preparing the compounds of this invention is described in the following schemes.

SCHEME 1



Scheme 2 below provides a general synthesis step, and the examples provide a detailed description of the schematic methods.

SCHEME 2



Compound **II:** A mixture of silver sulfate (100 g, 0.32 mol) and iodine (82 g, 0.32 mol) in *N*,*N*-dimethylformamide (700 mL) and ethanol (1400 mL) was treated with 5-nitro-2,3-dihydro-1H-indole **I** (48 g, 0.29 mol). The resulting mixture was stirred at 25°C for 1.5 h, filtered and the filter pad washed with ethyl acetate. The filtrate was concentrated *in vacuo* to a volume of approximately 500 mL. This solution was treated with a 1.0N aqueous sodium thiosulfate solution (100 mL) and a saturated aqueous sodium chloride solution (400 mL). The resulting precipitate was collected by filtration, washed with water and petroleum ether, and dried *in vacuo* to afford 7-iodo-5-nitro-2,3-dihydro-1H-indole **II** (83.9 g, 98.9%) as a white solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.18 (d, J = 2.20 Hz, 1H), 7.80 (d, J = 1.46 Hz, 1H), 7.03 (broad s, 1H), 3.65 (t, J = 8.97 Hz, 2H), 3.17 (t, J = 8.60 Hz, 2H).

Compound **III**: A solution of 7-iodo-5-nitro-2,3-dihydro-1H-indole **II** (15 g, 51.7 mmol) in ethanol (1200 mL) and isopropanol (20 mL) at 25°C was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (13.6 g, 59.9 mmol). The resulting solution was warmed to 65°C and air was bubbled through for 1 h. An additional 0.57 equivalents of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (6.8 g, 29.9 mmol) was added and the reaction was stirred at 65°C for another 2 h before being concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 toluene/ethyl acetate) afforded 7-iodo-5-nitro-1H-indole **III** (13.07 g, 79%) as a yellow solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.82 (broad s, 1H), 8.59 (d, J = 1.83 Hz, 1H), 8.30 (d, J = 1.83 Hz, 1H), 7.61 (t, J = 2.93 Hz, 1H), 6.90 (dd, J_1 = 1.83 Hz, J_2 = 3.30 Hz, 1H).

Compound **IV**: A solution of 7-iodo-5-nitro-1H-indole **III** (20 g, 69.4 mmol) in methanol (650 mL) at 25°C was treated with a solution of ammonium chloride (26.1 g, 485.8 mmol) in water (550 mL) and iron powder (13.6 g, 242.9 mmol). The mixture was heated to 100°C under a nitrogen atmosphere for 5 h. The resulting mixture was filtered through a pad of celite and the celite pad washed with hot methanol. The filtrate was concentrated in vacuo and the residue was partitioned between methylene chloride and water and separated. The pH of the aqueous layer was adjusted to pH=10 with ammonium hydroxide and extracted with methylene chloride. The combined organic layers were dried over sodium

sulfate, filtered, and concentrated *in vacuo* to a volume of 250 mL. This solution was treated with a 4.0M aqueous hydrochloric acid solution in dioxane and stirred at 25°C for 2 h. The precipitate was collected by filtration and washed with methylene chloride and petroleum ether to afford 7-iodo-1H-indol-5-ylamine hydrochloride **IV** (24.7 g, quant.) as a gray solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.34 (broad s, 1H), 9.93 (broad s, 2H), 7.56 (d, J = 1.46 Hz, 1H), 7.48 (t, J = 2.74 Hz, 1H), 7.44 (d, J = 1.83 Hz, 1H), 6.68 (dd, J_1 = 1.83 Hz, J_2 = 2.93 Hz, 1H).

Compound **V:** A solution of 7-iodo-1H-indol-5-ylamine hydrochloride **IV** (24.6 g, 83.7 mmol) in *N*,*N*-dimethylformamide (400 mL) at 25°C was treated with sodium dicyanamide (18.6 g, 209 mmol). The reaction mixture was warmed to 50°C for 2 h, concentrated *in vacuo*, and the residue treated with water (500 mL). The resulting mixture was allowed to stand at 25°C for 2.5 h during which time a yellow precipitate formed. The precipitate was collected by filtration and washed with water to afford N''-cyano-N-(7-iodo-1H-indol-5-yl)guanidine **V** (22.59 g, 83%) as a light yellow solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.02 (broad s, 1H), 8.89 (broad s, 1H), 7.46 (d, J = 1.83 Hz, 1H), 7.37 (d, J = 1.83 Hz, 1H), 7.35 (t, J = 2.56 Hz, 1H), 6.85 (broad s, 2H), 6.56 (dd, J_1 = 1.83 Hz, J_2 = 3.10 Hz, 1H).

Compound **VI:** A solution of N''-cyano-N-(7-iodo-1H-indol-5-yl)guanidine **V** (6.08 g, 18.7 mmol) in 2-methoxyethyl ether (50 mL) was heated to 175°C for 32.5 h. The reaction mixture was cooled to 25°C, the resulting solids removed by filtration and washed with methanol. The filtrate was concentrated *in vacuo* to give a brown oil. The residue was dissolved in methanol and then absorbed onto Merck Silica gel 60, 230-400 mesh (25 g). Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10/1 methylene chloride/methanol/ammonium hydroxide) afforded 6-iodo-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine **VI** (3.61 g, 59%) as a brown solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.36 (broad s, 1H), 7.45 (broad s, 1H), 7.43 (t, J = 2.93 Hz, 1H), 7.20 (s, 1H), 6.74 (broad s, 2H), 5.78 (broad s, 2H).

Compound **VII:** Typical condition used to carry out the alkylation of derivatives VI with a variety of halides (e.g., RaBr or RaI, where Ra is defined above) was in a suitable solvent such as ethyl ether or DME or tetrahydrofuran or DMF using suitable base such as sodium hydroxide or potassium hydroxide or lithium

hydroxide at temperatures ranging from -78°C to 25°C to provide the 6-iodo-7-alkyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine **VII**.

Compound **VIII** : The resultant 6-iodo-7-alkyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine **VII** are then further alkylated at -50°C to room temperature in a suitable solvent such as ethyl ether or DME or tetrahydrofuran or DMF using with suitable base such as sodium hydride and a variety of halides (e.g., R_1Br, R_2Br, R_3Br or R_1I, R_2I, R_3I, where R_1, R_2, R_3 are defined above) yielding mono, di-or tri substituted the 6-iodo-7-alkyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine **VIII**.

Compound **IX** : The coupling reaction can be carried out by a conventional aryl coupling method, e.g., Suzuki coupling method: (a) Suzuki *et al.*, *Synth.Commun.* **1981,** *11*, 513, (b) Suzuki, *Pure and Appl. Chem.* **1985,** *57*, 1749-1758, (c) Suzuki *et al.*, *Chem. Rev.* **1995,** *95*, 2457-2483, (d) Shieh *et al.*, *J. Org. Chem.* **1992,** *57*, 379-381, (e) Martin *et al.*, *Acta Chemica Scandinavica.* **1993,** *47*, 513.

Typical conditions used to carry out the Suzuki coupling of **VIII** include the use of either aryl or heteroaromatic boronic acid or esters (e.g., where Ar is defined as aryl) as coupling partner, in aqueous base such as sodium bicarbonate or potassium carbonate or barium hydroxide or triethylamine solution, a palladium catalyst (2-20 mole %) such as tetrakis(triphenylphosphine)-palladium (0) or [1,1'-bis(diphenylphosphino)-ferrocene]dichloro-palladium(II), in a suitable solvent such as aqueous ethanol or THF or DMF or ethyleneglycol for at temperatures ranging from 25°C to 125°C for 2-18 hr yields compound the 6-aryl substituted 7-alkyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine **IX**.

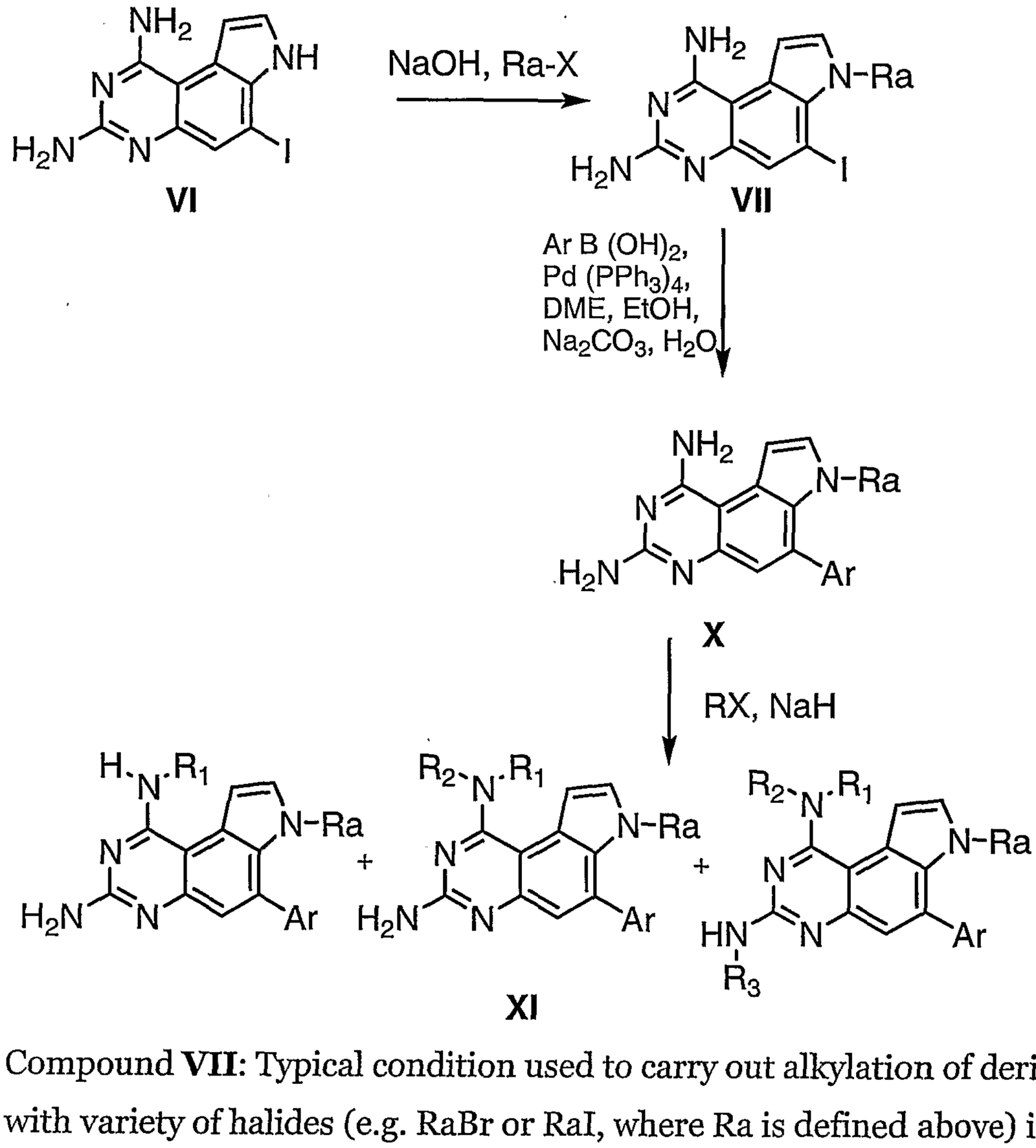
Alternatively, coupling reaction can be carried out by a conventional aryl or heteroaromatic coupling partner utilizing Stille coupling. e.g., Stille *et al.*, *Angew. Chem. Int. Ed. Engl.*, **1986,** *25*, 508.

Typical conditions used to carry out the Stille reaction include the use of an organostannane as the coupling partner, palladium catalyst (2-20 mole %) such as tetrakis(triphenylphosphine)-palladium (0) or [1,1'bis(diphenylphosphino)-ferrocene]dichloro-palladium(II), a salt such as potassium fluoride or lithium

chloride, in a suitable anhydrous solvent such as THF or DMF or ethylene glycol for at temperatures ranging from 25°C to 125°C for 2-18 hr yields 6-aryl substituted 7-alkyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine **IX.**

Scheme 3 below provides an alternatively general synthesis steps, and the examples provide a detailed description of the schematic methods

SCHEME 3



Compound **VII**: Typical condition used to carry out alkylation of derivatives VI with variety of halides (e.g. RaBr or RaI, where Ra is defined above) is carried out with suitable solvent such as tetrahydrofuran, DMF using suitable base such as sodium hydroxide at temperatures ranging from -78°C to 25°C to provide the 6-iodo-7-alkyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine **VII.**

Compound **X:** The coupling reaction can be carried out by a conventional aryl coupling method, e.g., Suzuki coupling method: (a) Suzuki et *al.*, *synth.commun.*

1981, *11*, 513, (b) Suzuki *pure and Appl. Chem.* **1985,** *57*, 1749-1758, (c) Suzuki *et al., Chem. Rev.* **1995,** *95*, 2457-2483, (d) Shieh *et al., J. Org. Chem.* **1992,** *57*, 379-381, (e) Martin *et al., Acta Chemica Scandinavica.* **1993,** *47*, 513.

Typical conditions used to carry out the Suzuki coupling of **VII** includes the use of either aryl or heteroaromatic boronic acid or esters (e.g. where Ar is defined as aryl) as coupling partner, in aqueous base such as sodium bicarbonate or potassium carbonate or barium hydroxide or triethylamine solution, a palladium catalyst (2-20 mole %) such as tetrakis(triphenylphosphine)-palladium (0) or [1,1'bis(diphenylphosphino)-ferrocene]dichloro-palladium(II), in a suitable solvent such as aqueous ethanol or THF or DMF or ethylene glycol for at temperatures ranging from 25 °C to 125 °C for 2-18 hr yields compound **X.** Alternatively, coupling reaction can be carried out by a conventional aryl or heteroaromatic coupling partner utilizing Stille coupling. e.g. Stille *et al., Angew. Chem. Int. Ed. Engl.*, **1986,** *25*, 508.

Typical conditions used to carry out the Stille reaction include the use of an organostannane as the coupling partner, palladium catalyst (2-20 mole %) such as tetrakis(triphenylphosphine)-palladium (0) or [1,1'bis(diphenylphosphino)-ferrocene]dichloro-palladium(II), a salt such as potassium fluoride or lithium chloride, in a suitable anhydrous solvent such as THF or DMF or ethylene glycol for at temperatures ranging from 25 °C to 125 °C for 2-18 hr yields compound **X.**

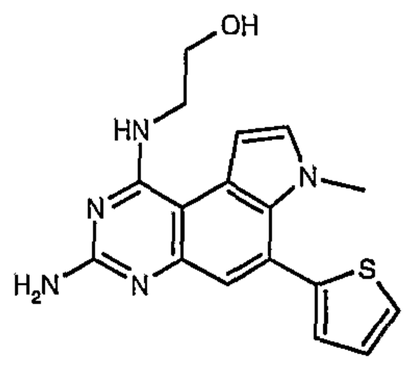
Compound **XI** : The compound **X** is then further alkylated at to -50°C to room temperature with suitable base such as sodium hydride and variety of halides (e.g., R_1Br, R_2Br, R_3 Br or R_1 I, R_2I, R_3I, where R_1, R_2, R_3 are defined above) yields mono, di- or tri substituted compounds **XI.** The control of alkylation can be controlled by selecting the appropriate equivalence of the halide used.

The invention is illustrated by the following Examples. In the Examples, Examples 2-22 was carried out by the procedure of Example 1 and Examples 24-42 was carried out by the procedure of Example 23.

EXAMPLES

Example 1

(A) 2-(3-amino-7-methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazolin-1-ylamino)-ethanol trifluoro-acetic acid salt



A solution 6-iodo-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine **VI** (2.68 g, 8.24 mmol) in tetrahydrofuran (100 mL) was treated with powdered sodium hydroxide (0.66 g, 16.5 mmol), iodomethane (0.62 mL, 9.96 mmol), and tetrabutylammonium bromide (0.8 g, 2.48 mmol) and the resulting mixture stirred at 25°C for 18 h. The resulting mixture was concentrated *in vacuo*. The residue was partitioned between methylene chloride (70 mL) and water (70 mL) and this mixture was stirred at 25°C for 30 min. The precipitate was isolated by filtration, washed with water, and dried *in vacuo* to afford 6-iodo-7-methyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine (2.67 g, 95.5%) as a yellow solid; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.58 (s, 1H), 7.47 (d, J = 2.93 Hz, 1H), 6.99 (d, J = 2.93 Hz, 1H), 6.78 (broad s, 2H), 5.83 (broad s, 2H), 4.16 (s, 3H).

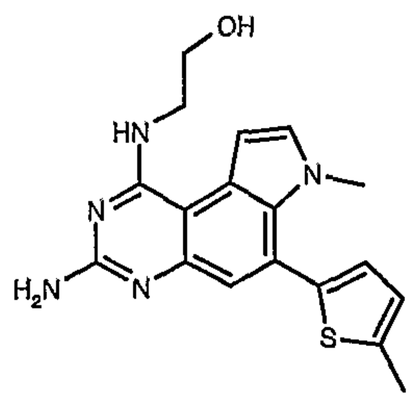
A solution of 6-iodo-7-methyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine (580 mg, 1.71 mmol) in tetrahydrofuran (20 mL) and *N*,*N*-dimethylformamide (10 mL) was cooled to -50°C and treated with 60% sodium hydride (270 mg, 6.84 mmol). The reaction mixture was warmed to -20°C and allowed to stir for 20 min. before being re-cooled to –50°C. 2-(2-bromoethoxy)tetrahydro-2-H-pyran (300 mg, 1.88 mmol) was added, the cooling bath removed, and the resulting mixture was allowed to stir at 25°C for 6 h. The reaction mixture was then recooled to -4°C and treated with another portion of 60% sodium hydride (270 mg, 6.84 mmol) followed by another portion of 2-(2-bromoethoxy)tetrahydro-2-H-pyran (300 mg, 1.88 mmol). The resulting mixture was allowed to stir at 25°C for 2 d, and then

concentrated *in vacuo*. HPLC purification (4 runs on a 21.2mm x 100mm Zorbax CombiHT column using a 5:95 to 95:5 acetonitrile:water: 0.75% TFA gradient over 15 minutes) afforded 2-(3-amino-6-iodo-7-methyl-7H-pyrrolo[3,2-f]quinazolin-1-ylamino)-ethanol trifluoroactic acid salt (270 mg, 32%) as an off-white solid; LRMS for freebase $C_{13}H_{14}IN_5O$ $(M+H)^+$ at m/z = 384.

A solution of 2-(3-amino-6-iodo-7-methyl-7H-pyrrolo[3,2-f]quinazolin-1-ylamino)-ethanol trifluoroactic acid salt (90 mg, 0.23 mmol) in ethylene glycol dimethyl ether (8.0 mL) and ethanol (4.0 mL) at 25°C was treated with thiophene-2-boronic acid (60 mg, 0.47 mmol), a 2.0M aqueous sodium bicarbonate solution (2.0 mL), and tetrakis(triphenylphosphine)-palladium (0) (5.0 mg). The resulting mixture was heated to reflux for 18 h. The resulting mixture was concentrated *in vacuo* and the residue suspended in acetonitrile and water and filtered. HPLC purification (21.2mm x 100mm Zorbax CombiHT column using a 5:95 to 95:5 acetonitrile:water: 0.75% TFA gradient over 15 minutes) afforded 2-(3-amino-7-methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazolin-1-ylamino)-ethanol trifluoro-acetic acid salt as a light yellow solid; LRMS for $C_{17}H_{17}N_5O$ $(M+H)^+$ at m/z = 340.

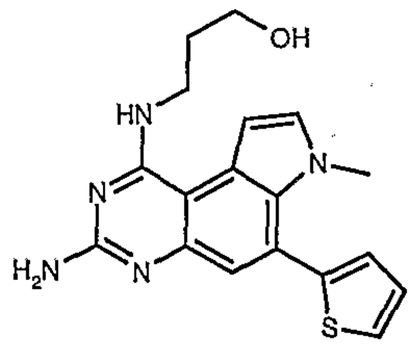
Example 2

In an analogous manner, there were obtained



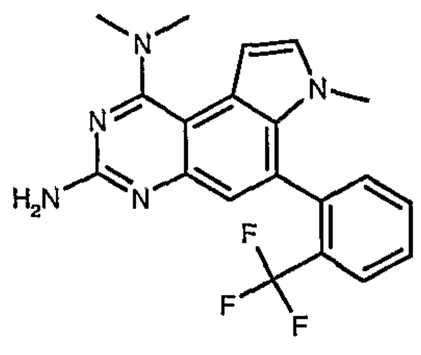
from 2-(3-amino-6-iodo-7-methyl-7H-pyrrolo[3,2-f]quinazolin-1-ylamino)-ethanol trifluoroactic acid salt and 5-methylthiophene-2-boronic acid there was produced 2-[3-Amino-7-methyl-6-(5-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-ethanol trifluoro-acetic acid salt as an off-white solid; LRMS for $C_{18}H_{19}N_5OS$ $(M+H)^+$ at m/z = 354.

Example 3



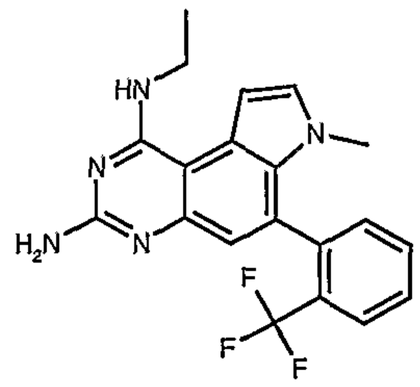
From 3-(3-Amino-6-iodo-7-methyl-7H-pyrrolo[3,2-f]quinazolin-1-ylamino)-propan-1-ol trifluoro-acetic acid salt and thiophene-2-boronic acid there was produced 3-(3-Amino-7-methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazolin-1-ylamino)-propan-1-ol trifluoro-acetic acid salt as an off-white solid; LRMS for $C_{18}H_{19}N_5OS$ $(M+H)^+$ at m/z = 354.

Example 4



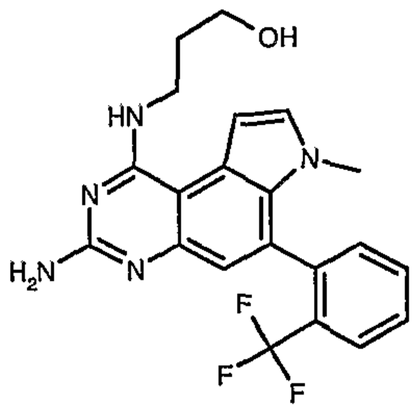
From 6-Iodo-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine and 2-(trifluoromethyl)benzeneboronic acid there was produced 7,N1,N1-Trimethyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt as a white solid; LRMS for $C_{20}H_{18}F_3N_5$ $(M+H)^+$ at m/z = 386.

Example 5



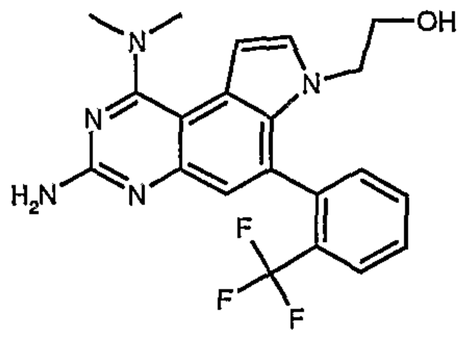
From N1-Ethyl-6-iodo-7-methyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt and 2-(trifluoromethyl)benzeneboronic acid there was produced N1-Ethyl-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt as a white solid; LRMS for $C_{20}H_{18}F_3N_5$ $(M+H)^+$ at m/z = 386.

Example 6



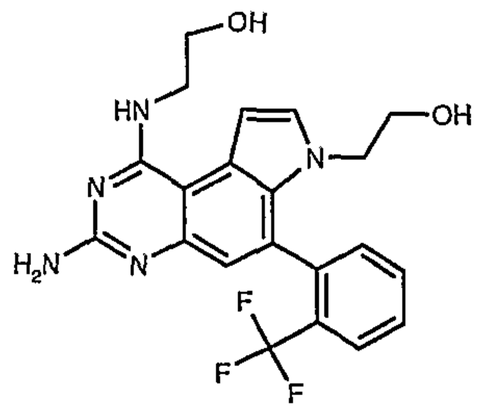
(Example 6) From 3-(3-Amino-6-iodo-7-methyl-7H-pyrrolo[3,2-f]quinazolin-1-ylamino)-propan-1-ol trifluoro-acetic acid salt and 2-(trifluoromethyl)benzeneboronic acid there was produced 3-[3-Amino-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-propan-1-ol trifluoro-acetic acid salt as an off-white solid; LRMS for $C_{21}H_{20}F_3N_5O$ $(M+H)^+$ at m/z = 416.

Example 7



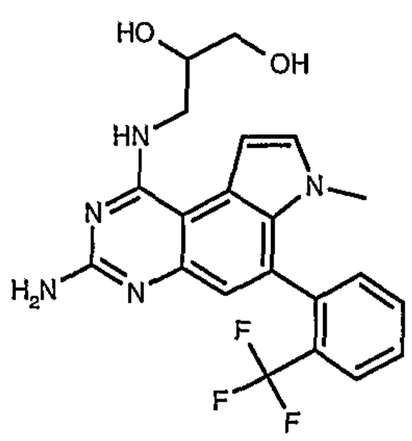
From 2-(3-Amino-1-dimethylamino-6-iodo-pyrrolo[3,2-f]quinazolin-7-yl)-ethanol trifluoro-acetic acid salt and 2-(trifluoromethyl)benzeneboronic acid there was produced 2-[3-Amino-1-dimethylamino-6-(2-trifluoromethyl-phenyl)-pyrrolo[3,2-f]quinazolin-7-yl]-ethanol trifluoro-acetic acid salt as an off-white solid; LRMS for $C_{21}H_{20}F_3N_5O$ $(M+H)^+$ at m/z = 416.

Example 8



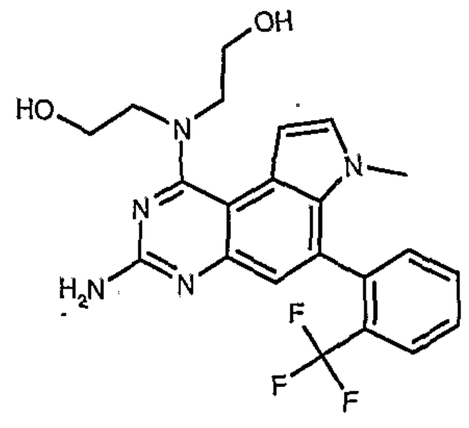
From 2-[3-Amino-7-(2-hydroxy-ethyl)-6-iodo-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-ethanol trifluoro-acetic acid salt and 2-(trifluoromethyl)benzeneboronic acid there was produced 2-[3-Amino-7-(2-hydroxy-ethyl)-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-ethanol trifluoro-acetic acid salt as an off-white solid; LRMS for $C_{21}H_{20}F_3N_5O_2$ $(M+H)^+$ at m/z = 432.

Example 9



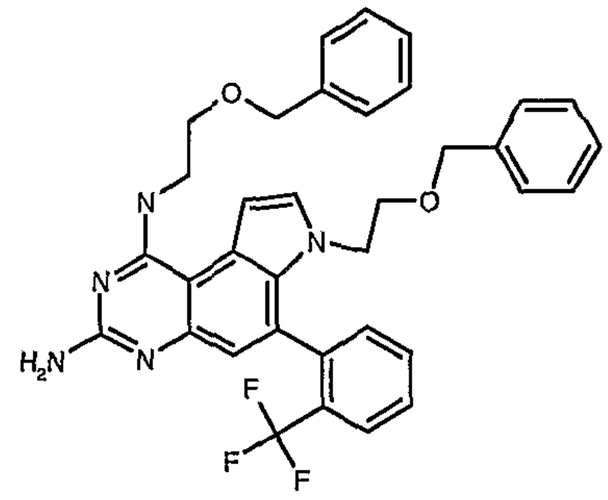
From 3-(3-Amino-6-iodo-7-methyl-7H-pyrrolo[3,2-f]quinazolin-1-ylamino)-propane-1,2-diol trifluoro-acetic acid salt and 2-(trifluoromethyl)benzeneboronic acid there was produced 3-[3-Amino-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-propane-1,2-diol trifluoro-acetic acid salt as an off-white solid; LRMS for $C_{21}H_{20}F_3N_5O_2$ $(M+H)^+$ at m/z = 432.

Example 10



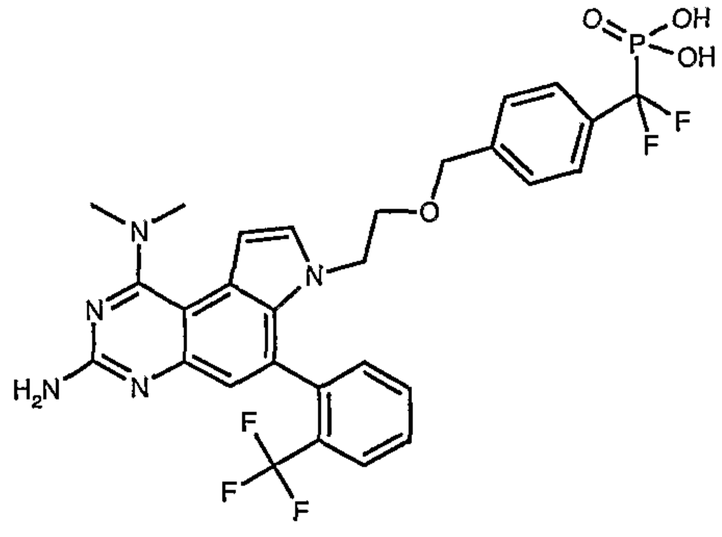
From 2-[(3-Amino-6-iodo-7-methyl-7H-pyrrolo[3,2-f]quinazolin-1-yl)-(2-hydroxy-ethyl)-amino]-ethanol trifluoro-acetic acid salt and 2-(trifluoromethyl)benzeneboronic acid there was produced 2-[[3-Amino-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-1-yl]-(2-hydroxy-ethyl)-amino]-ethanol trifluoro-acetic acid salt as a light yellow solid; LRMS for $C_{22}H_{22}F_3N_5O_2$ $(M+H)^+$ at m/z = 446.

Example 11



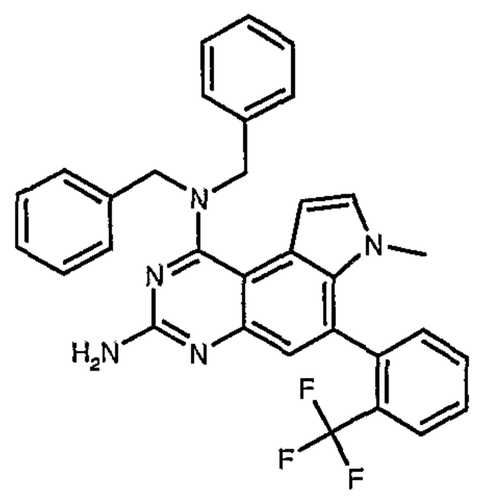
From 7,N1-Bis-(2-benzyloxy-ethyl)-6-iodo-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt and 2-(trifluoromethyl)benzeneboronic acid there was produced 7,N1-Bis-(2-benzyloxy-ethyl)-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt as a light yellow solid; LRMS for $C_{35}H_{32}F_3N_5O_2$ $(M+H)^+$ at m/z = 612.

Example 12



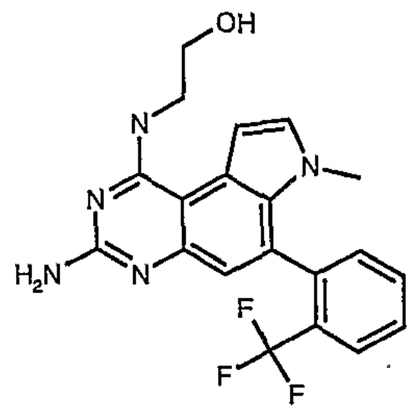
From ({4-[2-(3-Amino-1-dimethylamino-6-iodo-pyrrolo[3,2-f]quinazolin-7-yl)-ethoxymethyl]-phenyl}-difluoro-methyl)-phosphonic acid and 2-(trifluoromethyl)benzeneboronic acid there was produced [(4-{2-[3-Amino-1-dimethylamino-6-(2-trifluoromethyl-phenyl)-pyrrolo[3,2-f]quinazolin-7-yl]-ethoxymethyl}-phenyl)-difluoro-methyl]-phosphonic acid as a light yellow solid; LRMS for $C_{29}H_{27}F_5N_5O_4P$ $(M+H)^+$ at m/z = 636.

Example 13



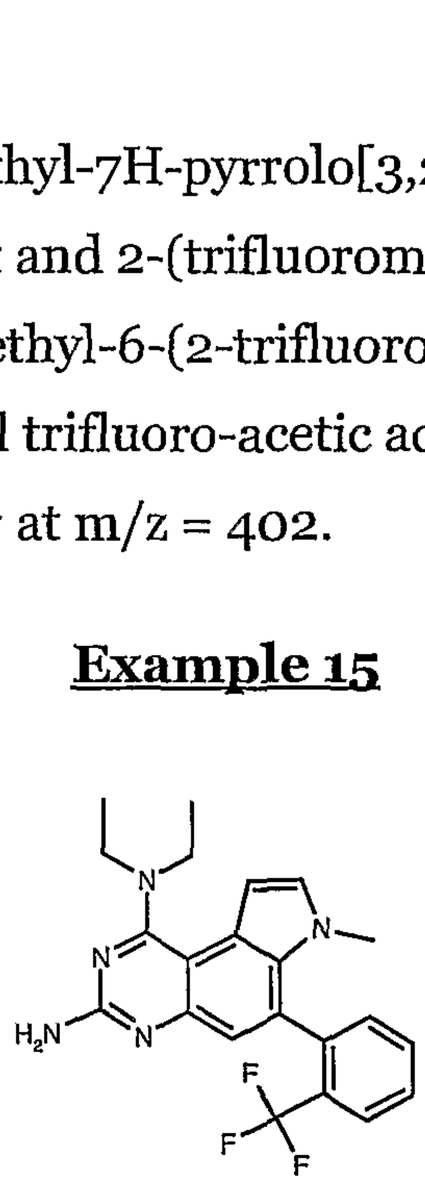
From N1,N1-Dibenzyl-6-iodo-7-methyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt and 2-(trifluoromethyl)benzeneboronic acid there was produced N1,N1-Dibenzyl-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt as a white solid; LRMS for $C_{32}H_{26}F_3N_5$ $(M+H)^+$ at m/z = 538.

Example 14



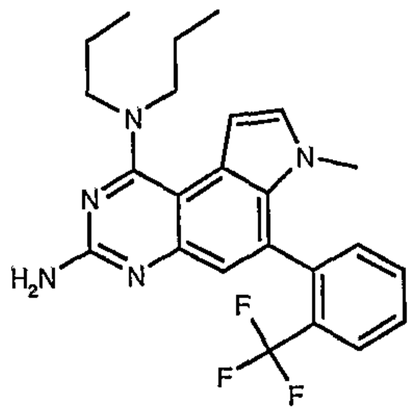
From 2-(3-Amino-6-iodo-7-methyl-7H-pyrrolo[3,2-f]quinazolin-1-ylamino)-ethanol trifluoro-acetic acid salt and 2-(trifluoromethyl)benzeneboronic acid there was produced 2-[3-Amino-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-ethanol trifluoro-acetic acid salt as an off-white solid; LRMS for $C_{20}H_{18}F_3N_5O$ $(M+H)^+$ at m/z = 402.

Example 15



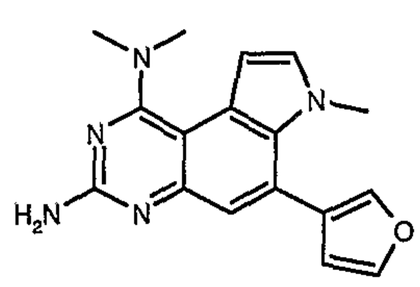
From N1,N1-Diethyl-6-iodo-7-methyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt and 2-(trifluoromethyl)benzeneboronic acid there was produced N1,N1-Diethyl-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt as an off-white solid; $(ES)^+$-HRMS m/e calcd for $C_{22}H_{19}N_5F_6$ $(M+H)^+$ 468.1617, found 468.1618.

Example 16



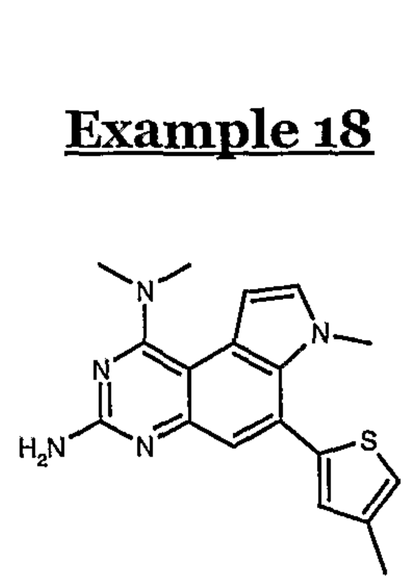
From 6-Iodo-7-methyl-N1,N1-dipropyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt and 2-(trifluoromethyl)benzeneboronic acid there was produced 7-Methyl-N1,N1-dipropyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt as a white solid; LRMS for $C_{24}H_{26}F_3N_5$ $(M+H)^+$ at m/z = 442.

Example 17



From 6-Iodo-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine and furan-3-boronic acid there was produced 6-Furan-3-yl-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; EI-HRMS m/e calcd for $C_{17}H_{17}N_5O$ (M^+) 307.1433, found 307.1427.

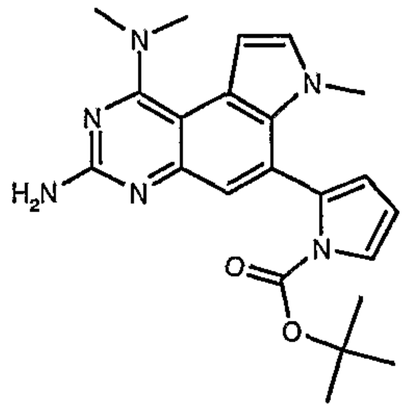
Example 18



From 6-Iodo-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine and 4-methylthiophene-2-boronic acid there was produced 7,N1,N1-Trimethyl-6-(4-

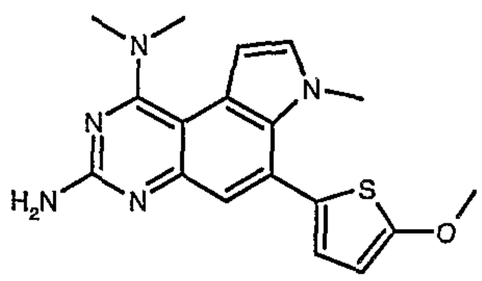
methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; (ES)+-HRMS m/e calcd for $C_{18}H_{19}N_5S$ (M^+) 337.1361, found 337.1357.

Example 19



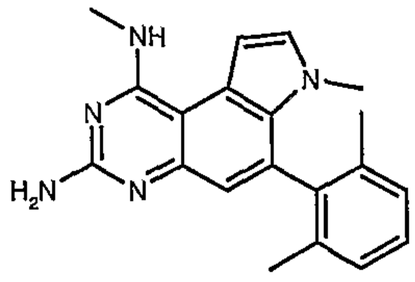
From 6-Iodo-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine and 1-(t-butoxycarbonyl)pyrrole-2-boronic acid there was produced 2-(3-Amino-1-dimethylamino-7-methyl-7H-pyrrolo[3,2-f]quinazolin-6-yl)-pyrrole-1-carboxylic acid *tert*-butyl ester; EI-HRMS m/e calcd for $C_{22}H_{26}N_6O_2$ (M^+) 406.2117, found 406.2115.

Example 20



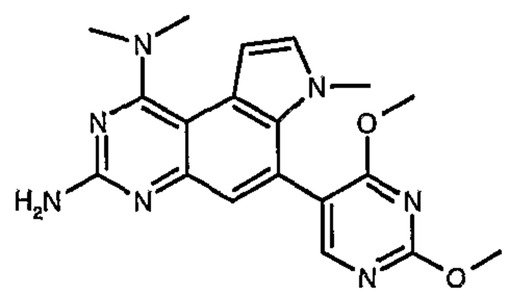
From 6-Iodo-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine and 5-methoxy-2-thiopheneboronic acid there was produced 6-(5-Methoxy-thiophen-2-yl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; EI-HRMS m/e calcd for $C_{18}H_{19}N_5OS$ (M^+) 353.1310, found 353.1306.

Example 21



From 6-Iodo-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine and 2,6-dimethylphenylboronic acid there was produced 6-(2,6-Dimethyl-phenyl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt as an off-white solid; EI-HRMS m/e calcd for $C_{20}H_{21}N_5$ (M^+) 331.1797, found 331.1786.

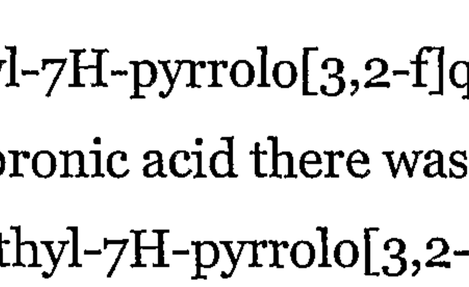
Example 22



From 6-Iodo-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine and 2,4-dimethoxypyrimidine-5-boronic acid there was produced 6-(2,4-Dimethoxy-pyrimidin-5-yl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine as a white solid; EI-HRMS m/e calcd for $C_{19}H_{21}N_7O_2$ (M^+) 379.1757, found 379.1763.

Example 23

7, N1-Dimethyl-6-(5-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine



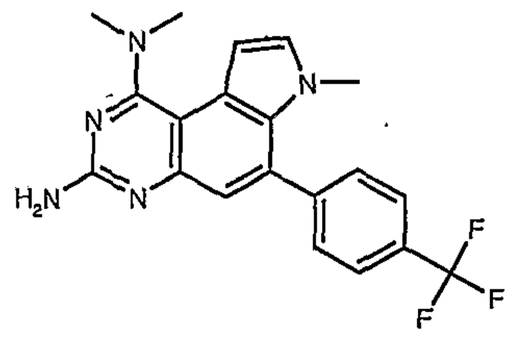
A solution of 6-iodo-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine (prepared as in Example 1, 400 mg, 1.23 mmol) in tetrahydrofuran (20 mL) at 25°C was treated with sodium hydroxide (98 mg, 2.46 mmol), methyl iodide (0.09 mL, 1.48 mmol),

and tetrabutylammonium bromide (198 mg, 0.62 mmol and stirred at 25°C for 18 h. The resulting mixture was treated with ethyl acetate, water, and a saturated aqueous sodium chloride solution, shaken and separated. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 6-iodo-7-methyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine (500 mg) as a yellow solid. The product was taken on into the next reaction without further purification.

A mixture of 6-iodo-7-methyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine (600 mg, 1.77 mmol), 2-(thiophene)benzeneboronic acid (321 mg, 2.20 mmol), tetrakis(triphenylphosphine)-palladium (0) (231 mg, 0.2 mmol) in ethanol (6.0 mL), ethylene glycol dimethyl ether (6.0 mL), and a saturated aqueous sodium carbonate solution (3.0 mL) was heated at reflux for 18 h. The resulting mixture was poured into water and extracted with a solution of 9/1 methylene chloride/methanol. The organic layers were combined and dried over magnesium sulfate, filtered, and dried *in vacuo*. Biotage chromatography (FLASH 12M, Silica, 9:1 methylene chloride/methanol) afforded 7-methyl-6-(5-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine (190 mg, 34.8%) as a solid; EI-HRMS m/e calcd for $C_{16}H_{15}N_5S$ $(M+H)^+$ 310.1121, found 310.1125.

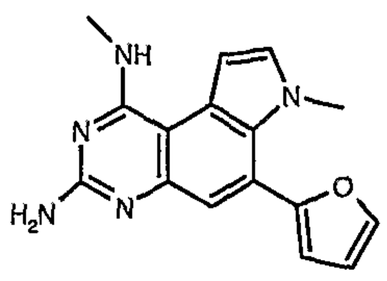
A solution of 7-methyl-6-(5-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine (100 mg, 0.32 mmol) in *N*,*N*-dimethylformamide (5.0 mL) at 25°C was treated with 60% sodium hydride (25 mg, 0.62 mmol) and iodomethane (0.62 mL, 0.35 mmol) and stirred at 25°C for 15 min. The resulting mixture was poured into water and extracted with a 9/1 methylene chloride/methanol solution. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 9:1 methylene chloride/methanol) afforded 7,N1-dimethyl-6-(5-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine (12 mg, 11.5%) as a light yellow solid; EI-HRMS m/e calcd for $C_{17}H_{17}N_5S$ $(M+H)^+$ 324.1278, found 324.1280; and 7,N1,N1-trimethyl-6-(5-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine (18 mg, 16.5%) as a dark brown solid; EI-HRMS m/e calcd for $C_{18}H_{19}N_5S$ $(M+H)^+$ 338.1434, found 338.1437.

Example 24



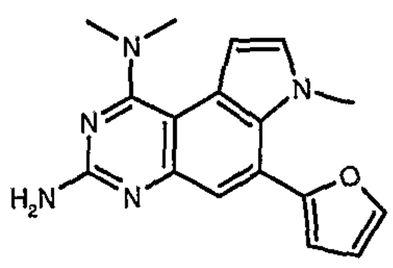
From 6-(4-Trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine there was produced 7,N1,N1-Trimethyl-6-(4-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine; EI-HRMS m/e calcd for $C_{20}H_{18}F_3N_5$ (M^+) 385.1517, found 385.1514.

Example 25



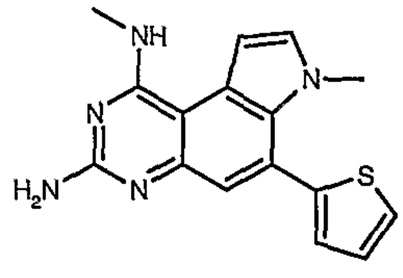
From 6-Furan-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine there was produced 6-Furan-2-yl-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt as a light yellow solid; EI-HRMS m/e calcd for $C_{16}H_{15}N_5O$ (M^+) 293.1277, found 293.1280.

Example 26



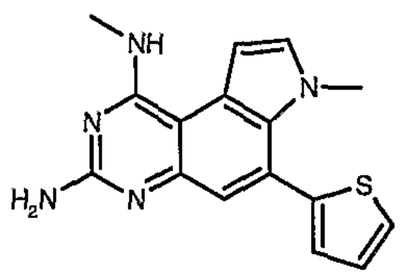
From 6-Furan-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine:6-Furan-2-yl-7,N1,N1-trimethyl-7Hpyrrolo[3,2-f]quinazoline-1,3-diamine as a yellow solid; EI-HRMS m/e calcd for $C_{17}H_{17}N_5O$ (M^+) 307.1433, found 307.1434

Example 27



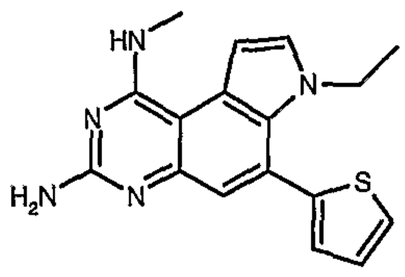
From 6-Thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt there was produced 7,N1-Dimethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt as a light yellow solid; LRMS for $C_{16}H_{15}N_5S$ $(M+H)^+$ at m/z = 310.

Example 28



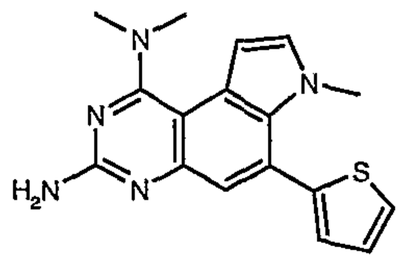
From 6-thiophene-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine there was produced 7-Ethyl-N1-methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt; $(ES)^+$-HRMS m/e calcd for $C_{17}H_{17}N_5S$ $(M+H)^+$ 324.1277, found 324.1281.

Example 29



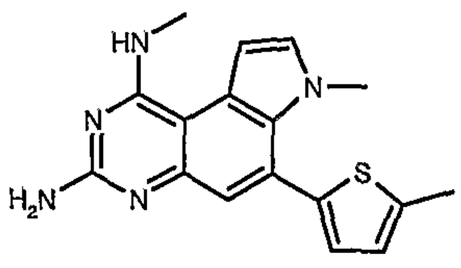
From 7-Methyl-6-(5-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine: 7,N1,N1-Trimethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine as a yellow solid; EI-HRMS m/e calcd for $C_{17}H_{17}N_5S$ (M^+) 323.1205, found 323.1209

Example 30



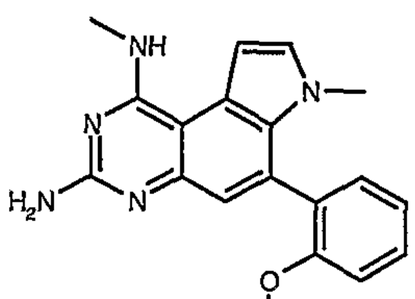
From 7-Methyl-6-(5-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine: 7,N1,N1-Trimethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine as a yellow solid; EI-HRMS m/e calcd for $C_{17}H_{17}N_5S$ (M^+) 323.1205, found 323.

Example 31



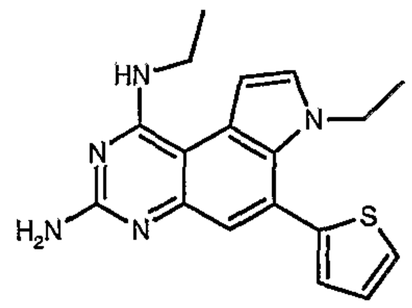
From 7-Methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine there was produced 7,N1-Dimethyl-6-(5-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine as a yellow solid; $(ES)^+$-HRMS m/e calcd for $C_{17}H_{17}N_5S$ $(M+H)^+$ 324.1278, found 324.1280.

Example 32



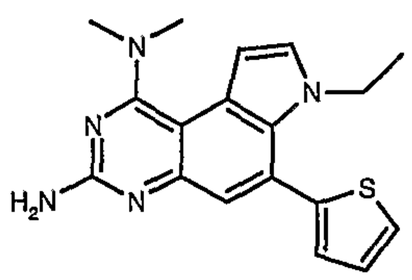
From 7-Methyl-6-(2-Methoxy-phenyl)-7H- pyrrolo [3,2-f]quinazoline-1,3-diamine there was produced 6-(2-Methoxy-phenyl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt as a white solid; LCMS for $C_{19}H_{19}N_5O$ $(M+)^+$ at m/z = 333

Example 33



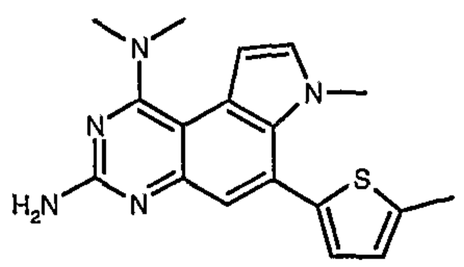
From 7-Ethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine there was produced 7,N1-Diethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt; $(ES)^+$-HRMS m/e calcd for $C_{18}H_{19}N_5S$ $(M+H)^+$ 338.1434, found 338.1437.

Example 34



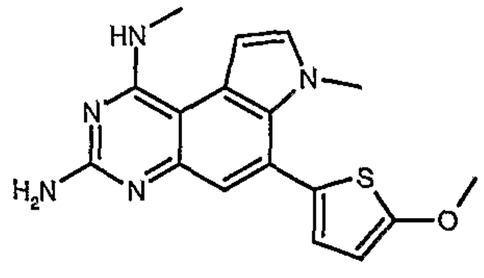
From 7-Ethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine there was produced 7-Ethyl-N1,N1-dimethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt; $(ES)^+$-HRMS m/e calcd for $C_{18}H_{19}N_5S$ $(M+H)^+$ 338.1434, found 338.1437.

Example 35



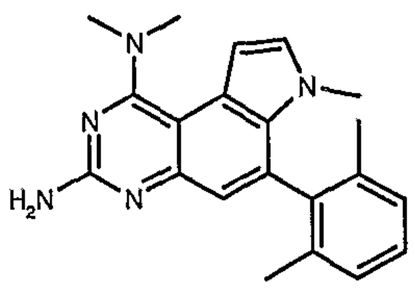
From 7-Methyl-6-(5-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine there was produced 7,N1,N1-Trimethyl-6-(5-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine as a yellow solid; $(ES)^+$-HRMS m/e calcd for $C_{18}H_{19}N_5S$ $(M+H)^+$ 338.1434, found 338.1437.

Example 36



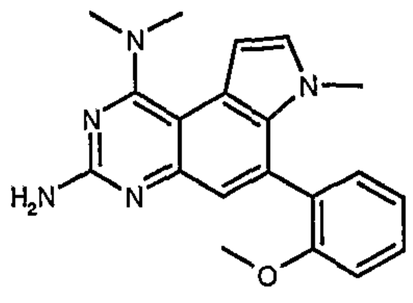
From 6-(5-Methoxy-thiophen-2-yl)-7-methyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine there was produced 6-(5-Methoxy-thiophen-2-yl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine as a white solid; EI-HRMS m/e calcd for $C_{17}H_{17}N_5OS$ (M^+) 339.1154, found 339.1159.

Example 37



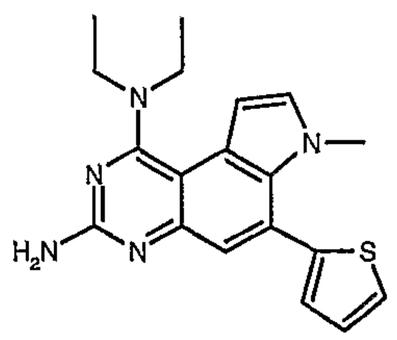
From 6-(2,6-Dimethyl-phenyl)-7-methyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine there was produced 6-(2,6-Dimethyl-phenyl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt as an off-white solid; EI-HRMS m/e calcd for $C_{21}H_{23}N_5$ (M^+) 345.1953, found 345.1958.

Example 38



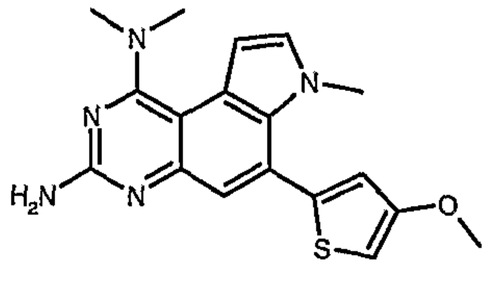
From 6-(2-Methoxy-phenyl)-7-methyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine there was produced 6-(2-Methoxy-phenyl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt as a white solid; EI-HRMS m/e calcd for $C_{20}H_{21}N_5O$ (M^+) 347.1746, found 347.1739.

Example 39



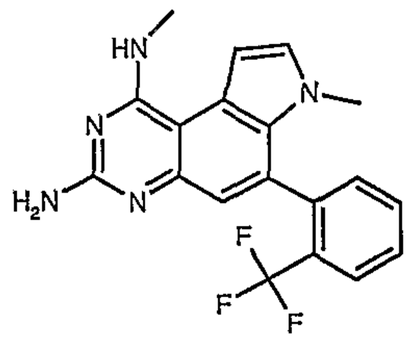
From 7-Methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine there was produced N1,N1-Diethyl-7-methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt as a light yellow solid; EI-HRMS m/e calcd for $C_{19}H_{21}N_5S$ (M^+) 351.1518, found 351.1517.

Example 40



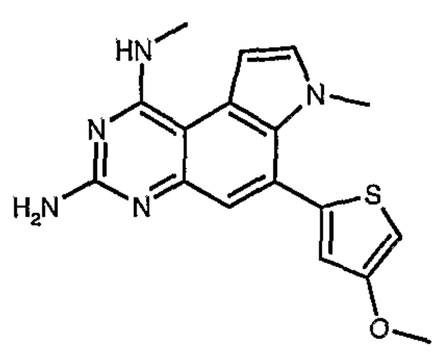
From 6-(4-Methoxy-thiophen-2-yl)-7-methyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine there was produced 6-(4-Methoxy-thiophen-2-yl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine as a yellow solid; EI-HRMS m/e calcd for $C_{18}H_{19}N_5OS$ (M^+) 353.1310, found 353.1307.

Example 41



From 7-Methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine there was produced 7,N1-Dimethyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine trifluoro-acetic acid salt; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.36 (m, 1H), 8.09 (m, 1H), 7.98 (d, J = 7.81 Hz, 1H), 7.81 (m, 3H), 7.71 (d, J = 2.93 Hz, 1H), 7.61 (d, J = 5.86 Hz, 1H), 7.41 (d, J = 3.91 Hz, 1H), 7.04 (s, 1H), 3.21 (d, J = 3.91 Hz, 3H), 3.17 (s, 3H).

Example 42



From 6-(4-Methoxy-thiophen-2-yl)-7-methyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine there was produced 6-(4-Methoxy-thiophen-2-yl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine as a light yellow solid; EI-HRMS m/e calcd for $C_{17}H_{17}N_5OS$ (M^+) 339.1154, found 339.1148.

Example 43

In vitro inhibition of PTP1B

Enzymes

Human PTP1B (1-321) was cloned from a human cDNA library using conventional molecular biology techniques. The cDNA sequence was identical to the published human PTP1B sequence (Accession number M33689). The protein was expressed

and purified from E. coli as described by Barford D. et.al J. Mol Biol (1994) 239, 726-730.

PTPase assays

The measurement of PTPase activity was carried out using one of two methods:

The first method for the measurement of PTP1B inhibitory activity a tyrosine phosphorylated peptide based on the amino acid sequence of insulin receptor tyrosine autophosphorylation site 1146 (TRDI(pY)E) was used as substrate. The reaction conditions were as follows:

PTP1B (0.5-2nM) was incubated with compound for 15 min in buffer containing 37.5 mM Bis-Tris buffer pH 6.2, 140mMNaCl, 0.05% BSA and 2mM DTT. The reaction was started by the addition of 50µM substrate. After 20 min at room temperature (22-25°C), the reaction was stopped with KOH and the amount of free phosphate measured using Malachite Green as previously described (Harder et al. 1994 Biochem J. 298; 395).

The second method was used for the measurement of general PTPase inhibitory activity across a panel of PTPases the substrate (6,8-difluoro-4-methylumbelliferyl phosphate (DiFMUP; from Molecular Probes) was used at the Km for each enzyme. The buffer conditions were identical as in the Malachite Green assay. The reaction was stopped with KOH. In this case the dephosphoryated product becomes fluorescent and the fluorescense read (Excitiation:360mM/Emmission: 460nM).

For kinetic experiments, the same buffer conditions were used except that the reaction was started using enzyme and the reaction stopped after 10 minutes.

The IC50 values (in µM) for the PTP1B inhibitory activity of the compounds in the present application are in the range of 0.1 µM to 500 µM, preferably 1 µM to 100 µM. The most preferred compounds show an IC50 of < 30.0 µM.

Examples of the some compounds with its corresponding IC50 values are

Example	IC50 (µM)
2	7.10
4	9.47
6	10.22
8	11.35

Example 44

Glucose Uptake Assay

The day before the assay the SKMC media was changed to high glucose DMEM , 25mM Hepes, pH 7.0 and 2% Charcoal/dextran treated FBS for 19 hours.

On the morning of the assay, cells were starved for max. 2 hours in low glucose (5.5mM glucose) DMEM, 25 mM Hepes, pH 7.0 and 0.5% BSA. The starvation medium was removed and replaced with test medium (150mMNaCl, 25mM Hepes, pH 7.0) containing either 1% DMSO, or test compound diluted in DMSO or Porcine Insulin to a final concentrations of 1, 0.1, 0.05, 0.01 and 0.01µM. Each assay point was performed in triplicate. The cells were incubated for 45 min at 37°C. 10µM Cytochalasin B (CB) was added to appropriate wells to stop the active glucose transport (i.e., GLUT 1 & 4). At this point 2-Deoxy-D(U-^{14}C)glucose (Amersham, Code CFB195, 200uCi/ml) was added to all wells to a final concentration of 0.8 µCi/ml. The cells were incubated for an additional 45 minutes at 37°C in an incubator. Cells were then very gently washed for three times in PBS (RT). The cells were then lysed with the addition of 0.05% NaOH solution for 20 min at RT. The lysate was transferred to a scintillation vial containing 5 ml of scintillation fluid and counted in a Beckman LS6500 Scintillation counter. Analysis of results: The counts obtained with CB (passive glucose transport values) were subtracted from every value obtained with PI (or compounds) in order to evaluate only active glucose transport. Fold increase was calculated by dividing values in the presence of PI (or compounds) by the value obtained in the presence of DMSO (control). Compounds were considered to be active when they increase glucose uptake at least 25% of the Porcine Insulin response at 0.05 µM.

In vivo inhibition of PTP1B: Effects of compounds on blood glucose levels in mouse model

To measure the anti-diabetic effect compounds were tested in well established rodent *in vivo* models of type 2 diabetes and obesity.

Example 45

Diet induced obese C57BL6/J mice (DIO mice)

Mice that have type 2 diabetes were generated by maintaining them on a high fat diet for 4-6 months (Diabetes vol. 37 Sept 1988). Male C57Bl6/J mice (age 3 - 4 weeks) were placed on high fat diet for 4-6 months. At this time they were hyperglycemic and hyperinsulinemic and weighed 40-50 g. DIO mice (n=10) were weighed and fasted for a two hour period prior to oral treatment. Immediately prior to dosing a pre-dose blood glucose reading was taken by snipping off a portion of the tail and collecting blood from the tail vein. Mice were treated either with a single dose of compound (acute) or once a day for 5 days (sub-chronic). For the acute studies, glucose was generally measured at 2h, 4h, 6h, 8h post treatment. Compounds were considered active if they showed a statistically significant ($p \leq 0.05$) glucose lowering (>15%) compared to the vehicle treated animals.

For sub-chronic (5 day) studies mice were dosed once a day by gavage as described above. On day five, glucose was measured prior to dosing (0 time) and 2 hours after dosing. Insulin and triglycerides were measured at 2 hour post dose. Compounds were considered active if they showed a statistically significant ($p \leq 0.05$) glucose, insulin and triglyceride lowering compared to the vehicle treated animals.

Example A

Tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per tablet
Compound of formula (I)	10.0 - 100.0 mg
Lactose	125.0 mg
Maize starch	75.0 mg
Talc	4.0 mg
Magnesium stearate	1.0 mg

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per capsule
Compound of formula (I)	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

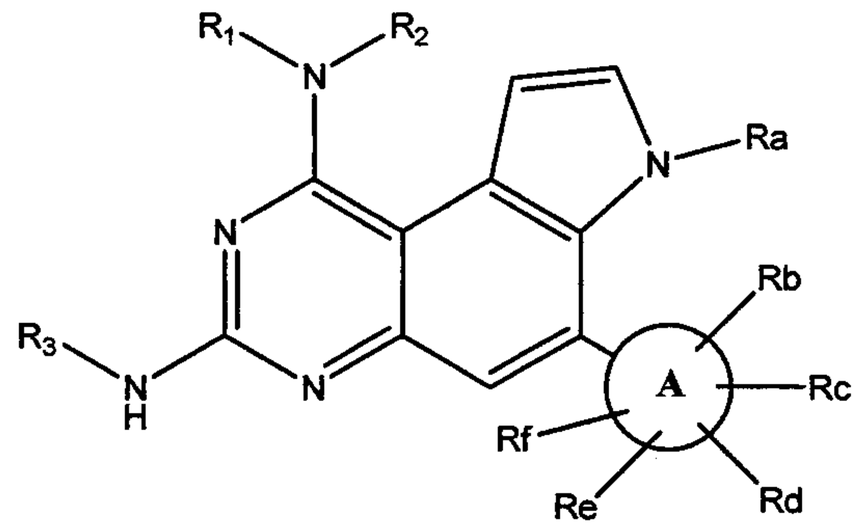
Example C

Injection solutions can have the following composition:

Compound of formula (I)	3.0 mg
Gelatine	150.0 mg
Phenol	4.7 mg
Sodium carbonate	to obtain a final pH of 7
Water for injection solutions	ad 1.0 ml

Claims

1. Compounds of the formula (I):



(I)

and the pharmaceutically acceptable salts thereof, wherein

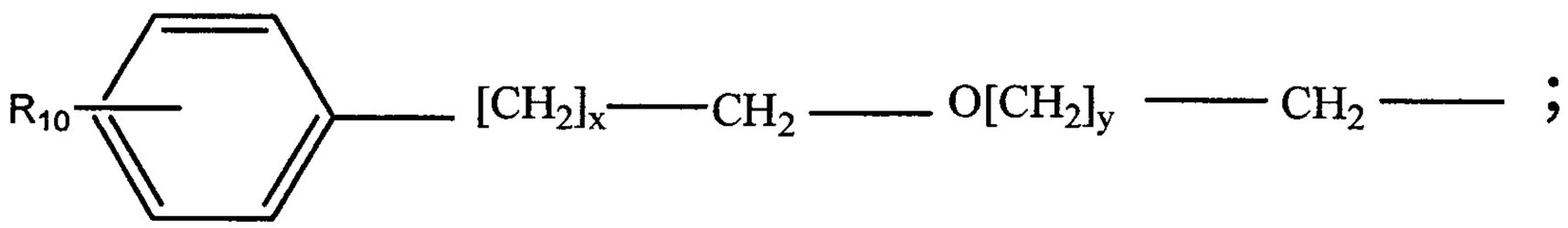
A is a 5- or 6-membered unsaturated or saturated ring, or a 5- or 6-membered unsaturated or saturated ring that contains at least one heteroatom selected from S, N and O,

R_1 is selected from the group consisting of lower alkyl, acetyl, dimethylsulfamoyl, hydroxyalkyl, mono or di hydroxy substituted lower alkyl, phenyl lower alkyl, benzyloxy-alkyl, and phenyl lower alkoxy lower alkyl;

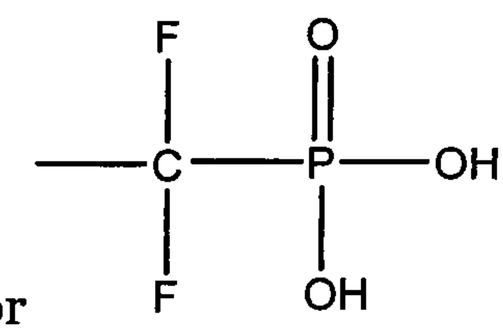
R_2 is selected from the group consisting of hydrogen, lower alkyl, acetyl, hydroxyalkyl, mono or di hydroxy substituted lower alkyl, phenyl lower alkyl, and phenyl lower alkoxy lower alkyl;

R_3 is hydrogen or methyl;

Ra is selected from the group consisting of hydrogen, lower alkyl, lower alkoxy hydroxyalkyl, mono or di hydroxy substituted lower alkyl, phenyl lower alkyl, benzyloxyalkyl, and



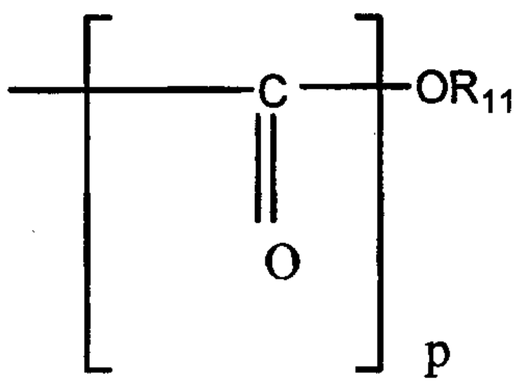
;



R_{10} is hydrogen or ;

x and y are individual integers from 0 to 4;

Rb and Rc are individually selected from the group consisting of hydrogen, lower alkyl, perfluro-lower alkyl, substituted alkyl, alkoxy, phenoxy, halogen, unsubstituted lower alkyl substituted phenyl lower alkyl, phenyl lower alkoxy, and



;

R_{11} is hydrogen, phenyl or unsubstituted lower alkyl;

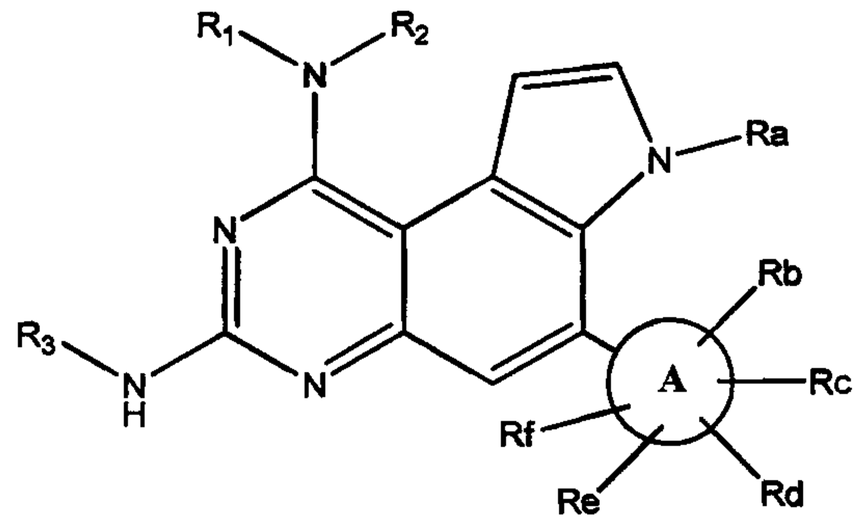
p is an integer from 0 to 1;

Rd is hydrogen, substituted alkyl or perfluro-lower alkyl;

Re is hydrogen, halogen, substituted alkyl or perfluro-lower alkyl

Rf is hydrogen or lower alkyl.

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



(I)

and the pharmaceutically acceptable salts thereof, wherein

A is a 5- or 6-membered unsaturated or saturated ring, or a 5- or 6-membered unsaturated or saturated ring that contains at least one heteroatom selected from S, N and O,

R_1 is selected from the group consisting of lower alkyl, acetyl, hydroxyalkyl, and benzyloxy-alkyl;

R_2 is selected from the group consisting of hydrogen, lower alkyl, acetyl, and hydroxyalkyl

R_3 is hydrogen or methyl;

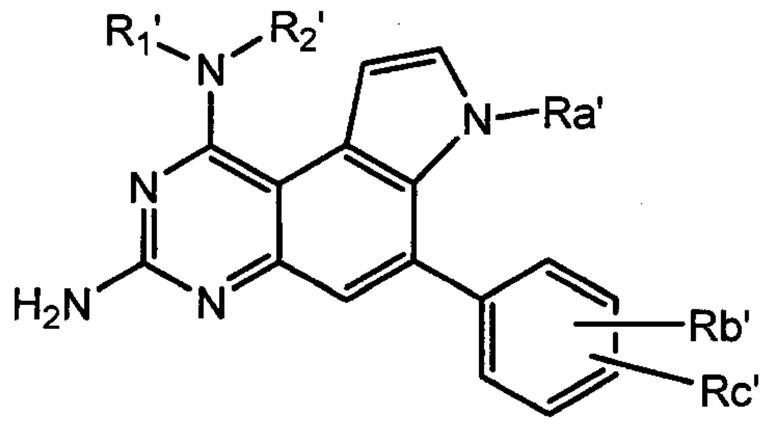
Ra is selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, hydroxyalkyl and benzyloxyalkyl;

Rb is selected from the group consisting of hydrogen, lower alkyl, perfluro-lower alkyl, substituted alkyl, alkoxy and phenoxy;

Rc and Rd independently are hydrogen or substituted alkyl, perfluro-lower alkyl;
Re is hydrogen, halogen, substituted alkyl or perfluro-lower alkyl
Rf is hydrogen or lower alkyl.

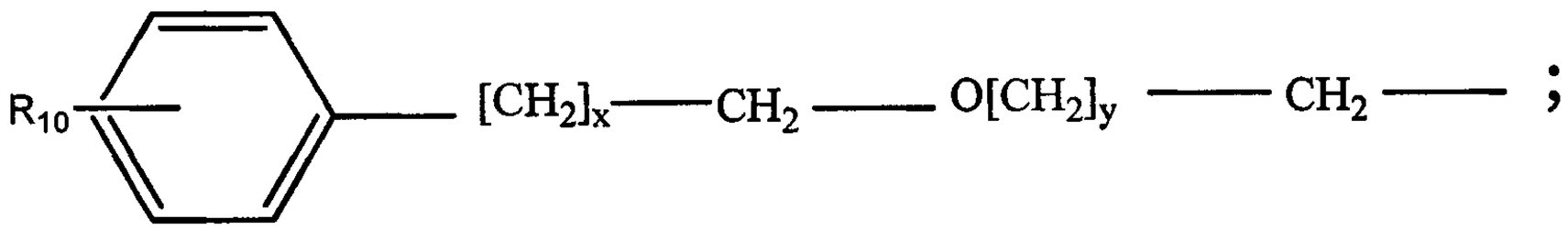
3. Compounds according to any one of claims 1 - 2, wherein
R1 is selected from the group consisting of methyl, ethyl, benzyl, acetyl, 2,3-dihydroxypropyl, 3-hydroxypropyl and 2-benzyloxyethyl;
R2 is selected from the group consisting of hydrogen, methyl, ethyl, benzyl, and acetyl;
Ra is selected from the group consisting of hydrogen, methyl, hydroxyethyl, 2-benzyloxy-ethyl and 2-[4-difluorophosphono-methyl]-benzyloxy]-ethyl;
Rb is selected from the group consisting of hydrogen, methyl, methoxy, phenoxy and trifluoromethyl;
Rc and Rd are each independently selected from hydrogen and trifluoromethyl;
Re is selected from the group consisting of hydrogen, chlorine and trifluoromethyl; and
Rf is selected from hydrogen and methyl.

4. Compounds according to claim 1, wherein said compounds have the formula (I-B)

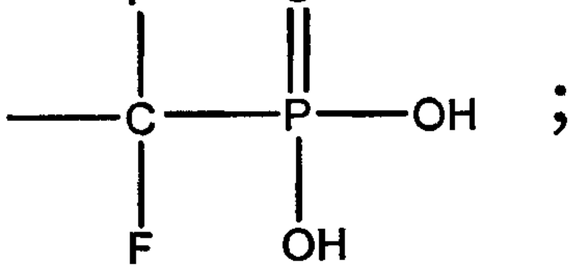


(I-B)

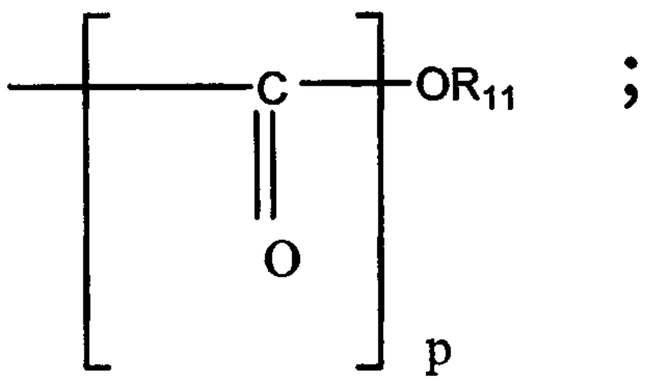
wherein
R_1' is lower alkyl, phenyl lower alkyl, mono or di hydroxy substituted lower alkyl, or phenyl lower alkoxy loweralkyl;
R_2' is hydrogen, lower alkyl, phenyl lower alkyl, mono or di hydroxy substituted lower alkyl, or phenyl lower alkoxy lower alkyl;
Ra' is hydrogen, lower alkyl, mono or di hydroxy substituted lower alkyl, or



R_{10} is hydrogen or



Rb' and Rc' are individually selected from the group consisting of hydrogen, perfluoro-lower alkyl, halogen, unsubstituted lower alkyl substituted phenyl lower alkyl, lower alkyl, phenyl lower alkoxy or



R_{11} is hydrogen, phenyl or unsubstituted lower alkyl;

p is an integer from 0 to 1; and

x and y are individually integers from 0 to 4

or a pharmaceutically acceptable salt thereof.

5. Compounds according to claim 4, wherein

R_1' is lower alkyl;

R_2' is hydrogen or lower alkyl; and

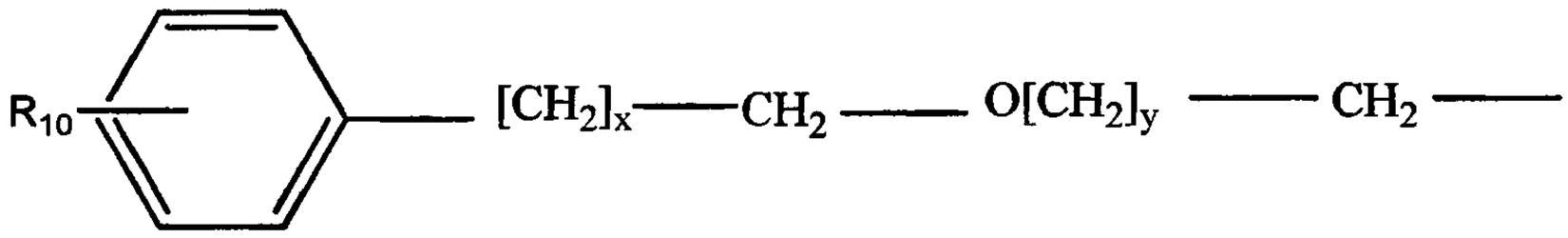
Rb' and Rc' are perfluoroloweralkyl or hydrogen

with at least one or Rb' and Rc' being perfluoroloweralkyl.

6. Compounds according to claim 4, wherein R_1' is mono or di hydroxy substituted lower alkyl and R_2' is hydrogen or mono or di hydroxy substituted lower alkyl and Rb' and Rc' are independently perfluoroloweralkyl or hydrogen with at least one of said Rb' and Rc' being perfluoroloweralkyl.

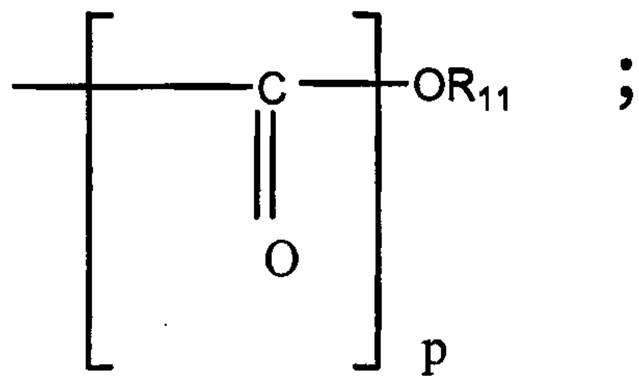
7. Compounds according to claim 5, wherein Ra' is mono or di hydroxy substituted lower alkyl.

8. Compounds according to claim 5, wherein Ra' is



and R_{10}, x and y are as defined in claim 5.

9. Compounds according to claim 4, wherein one of Rb' and Rc' is



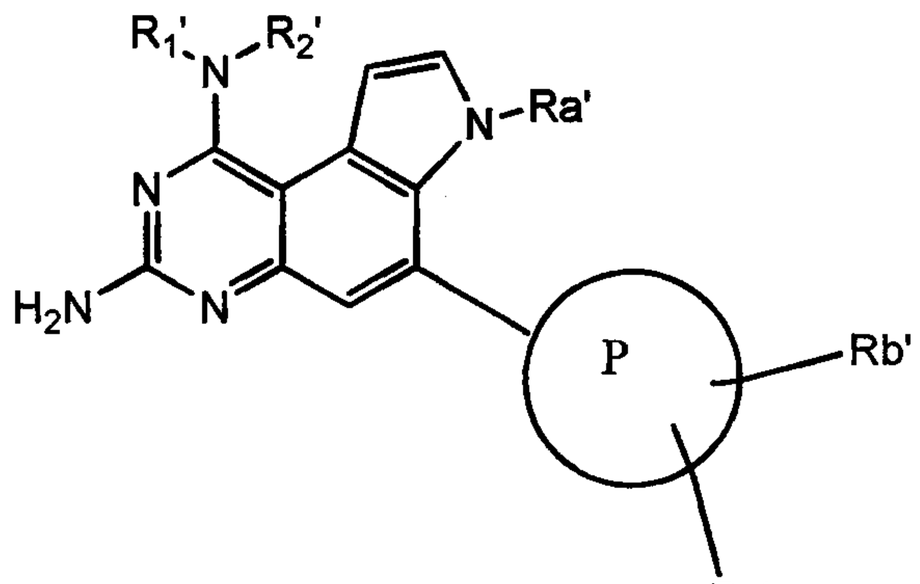
or lower alkoxy;

R_{11} is hydrogen, phenyl or unsubstituted lower alkyl; and

p is an integer from 0 to 1.

10. Compounds according to claim 4, wherein one of Rb' and Rc' is lower alkyl.

11. Compounds according to claim 1, wherein said compounds have the formula (I - A)



(I - A)

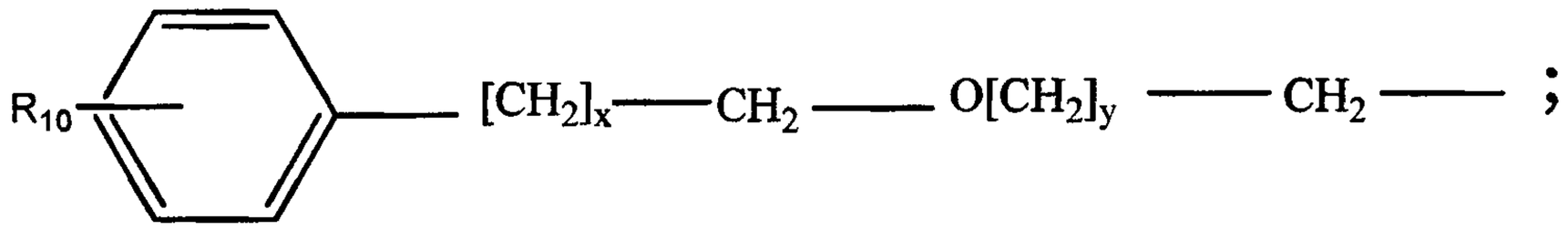
wherein

Ⓟ is a 5 or 6 membered heteroaromatic ring containing from 1 to 2 hetero atoms selected from the group consisting of oxygen, sulfur, and nitrogen;

R_1' is lower alkyl, phenyl lower alkyl, mono or di hydroxy substituted lower alkyl, or phenyl lower alkoxy lower alkyl;

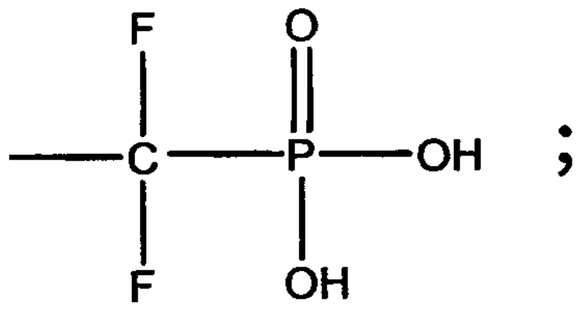
R_2' is hydrogen, lower alkyl, phenyl lower alkyl, mono or di hydroxy substituted lower alkyl, or phenyl lower alkoxy lower alkyl;

Ra' is selected from the group consisting of hydrogen, phenyl lower alkyl, lower alkyl, lower alkoxy, mono or di hydroxy substituted lower alkyl, and



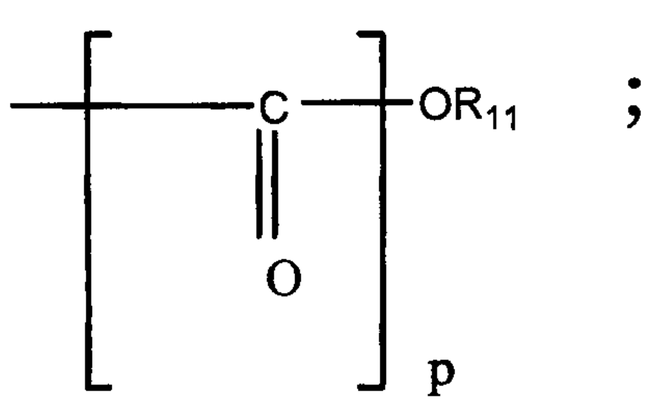
;

R_{10} is hydrogen or



;

Rb' and Rc' are individually selected from the group consisting of hydrogen, perfluoro-lower alkyl, halogen, lower alkyl substituted phenyl lower alkyl, lower alkyl, phenyl lower alkoxy, and



;

R_{11} is hydrogen, lower alkyl and phenyl;

p is an integer from 0 to 1; and

x and y are individually integers from 0 to 4

or a pharmaceutically acceptable salt thereof.

12. Compounds according to of claim 11, wherein Ⓟ is a 5 or 6 membered heteroaromatic ring containing a sulfur hetero atoms as the only heteroaromatic atom in said ring.

13. Compounds according to claim 12, wherein

Rb' and Rc' are hydrogen or lower alkyl;

R_1' is lower alkyl or mono or di hydroxy substituted lower alkyl; and

R_2' is hydrogen,lower alkyl or mono or di hydroxy substituted lower alkyl.

14. Compounds according to claim 12, wherein

Rb' and Rc' are independently hydrogen or lower alkoxy or phenyl lower alkoxy with at least one of Rb' and Rc' being other than hydrogen;

R_1' is lower alkyl or mono or di hydroxy substituted lower alkyl; and

R_2' is hydrogen or lower alkyl or mono or di lower hydroxy substituted lower alkyl.

15. Compounds according to claim 11, wherein

Ⓟ is a 5 or 6 membered heteroaromatic ring containing an oxygen atom as the only hetero atom.

16. Compounds according to claim 15, wherein

R_1' is lower alkyl; and

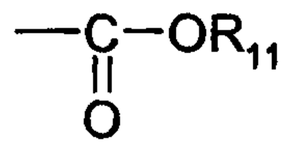
R_2' is hydrogen or lower alkyl.

17. Compounds according to claim 11, wherein

Ⓟis a 5 or 6 membered heteroaromatic ring containing a nitrogen atom as the only hetero atom.

18. Compounds according to claim 17, wherein

one of Rb' and Rc' is hydrogen and the other is hydrogen, lower alkyl or



wherein

R_{11} is phenyl or lower alkyl; and

R_1' and R_2' are lower alkyl.

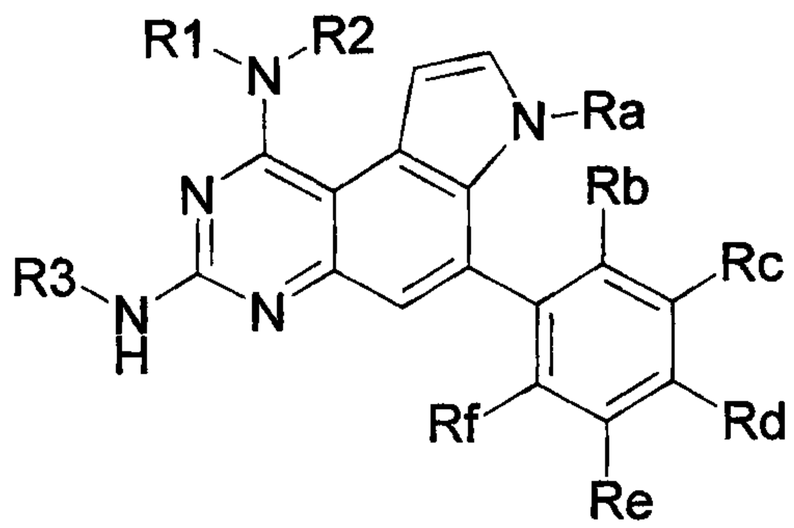
19. Compounds according to claim 11, wherein

Ⓟ is a 5 or 6 membered heteroaromatic ring containing two heteroatoms.

20. Compounds according to claim 19, wherein

Rb' and Rc' are lower alkyl, hydrogen or lower alkoxy.

21. Compounds according to any one of claims 1 - 2, having the formula (II)



(II)

and the pharmaceutically acceptable salts thereof, wherein

R_1 is selected from the group consisting of lower alkyl, acetyl, hydroxyalkyl, and benzyloxy-alkyl;

R_2 is selected from the group consisting of hydrogen, lower alkyl, acetyl, and hydroxyalkyl

R_3 is hydrogen or methyl;

Ra is selected from the group consisting of hydrogen, lower alkyl, lower alkoxy hydroxyalkyl and benzyloxyalkyl;

Rb is selected from the group consisting of hydrogen, lower alkyl, perfluro-lower alkyl, substituted alkyl, alkoxy and phenoxy;

Rc and Rd independently are hydrogen or substituted alkyl, perfluro-lower alkyl;

Re is hydrogen, halogen, substituted alkyl, or perfluro-lower alkyl

Rf is hydrogen or lower alkyl.

22. Compounds according to claim 21, wherein

R^1 is selected from the group consisting of methyl, ethyl, allyl, benzyl, acetyl, 2,3-dihydroxypropyl, 3-hydroxypropyl and 2-benzyloxyethyl;

R^2 is selected from the group consisting of hydrogen, methyl, ethyl, allyl, benzyl, and acetyl;

Ra is selected from the group consisting of hydrogen, methyl, hydroxyethyl, 2-benzyloxy-ethyl and 2-[4-difluorophosphono-methyl]-benzyloxy]-ethyl;

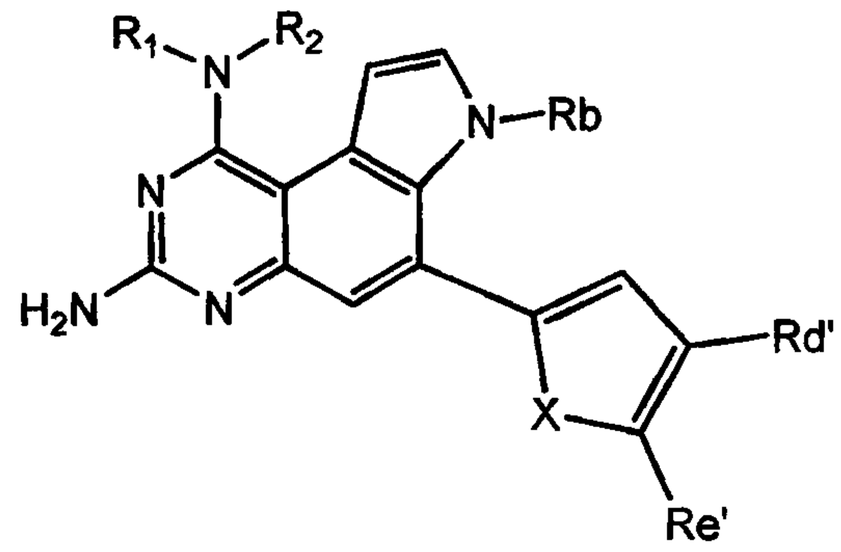
Rb is selected from the group consisting of hydrogen, methyl, methoxy, phenoxy and trifluoromethyl;

Rc and Rd independently are hydrogen or trifluoromethyl;

Re is hydrogen, chlorine halogen or trifluoromethyl; and

Rf is hydrogen or methyl.

23. Compounds according to any one of claims 1 - 2, having the formula (III)



(III)

and the pharmaceutically acceptable salts thereof, wherein

R^1 is selected from the group consisting of hydrogen, lower alkyl, acetyl, and hydroxyalkyl

R^2 is hydrogen or methyl;

X is sulfur, oxygen, nitrogen or N-tert-butoxycarbonyl;

Rb is is selected from the group consisting of hydrogen, lower alkyl, lower alkoxy hydroxyalkyl and benzyloxyalkyl;

R_d' and R_e' independently are selected from the group consisting of hydrogen, lower alkyl and alkoxy.

24. Compounds according to claim 23, wherein

R^1 is selected from the group consisting of methyl, ethyl, acetyl, 3-hydroxypropyl and dimethylsulfamoyl;

R^2 and Rb' independently are selected from the group consisting of hydrogen, methyl and ethyl; and

Rd' and Re' independently are selected from the group consisting of hydrogen, methyl, and methoxy.

25. Compounds according to any one of claims 1 - 24, selected from the group consisting of

7,N1-Dimethyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

7,N1,N1-Trimethyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7,N1-Dimethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
N1-Ethyl-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
6-(3,5-Bis-trifluoromethyl-phenyl)-7,N1,N1,N3-tetramethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7,N1-Diethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7-Ethyl-N1-methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7-Ethyl-N1,N1-dimethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
N1,N1-Diethyl-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7-Methyl-N1,N1-dipropyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7-Methyl-1-piperidin-1-yl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-3-ylamine,
N1,N1-Dibenzyl-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7-Methyl-1-pyrrolidin-1-yl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-3-ylamine,
6-(2-Methoxy-phenyl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
6-(2-Methoxy-phenyl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
N1,N1-Diethyl-7-methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7,N1,N1-Trimethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7,N1,N1,N3-Tetramethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
6-Iodo-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7,N1,N1-Trimethyl-6-(5-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7,N1-Dimethyl-6-(5-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

6-(5-Chloro-2-methoxy-phenyl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

6-Furan-2-yl-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

6-Furan-2-yl-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

2-[3-Amino-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-ethanol,

2-(3-Amino-7-methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazolin-1-ylamino)-ethanol,

3-[3-Amino-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-propan-1-ol,

3-(3-Amino-7-methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazolin-1-ylamino)-propan-1-ol,

2-[3-Amino-7-methyl-6-(5-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-ethanol,

6-Furan-3-yl-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

7,N1,N1-Trimethyl-6-(4-methyl-thiophen-2-yl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

2-(3-Amino-1-dimethylamino-7-methyl-7H-pyrrolo[3,2-f]quinazolin-6-yl)-pyrrole-1-carboxylic acid tert-butyl ester,

6-(3,5-Dimethyl-isoxazol-4-yl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

7,N1-Dimethyl-6-(2-phenoxy-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

2-[3-Amino-7-(2-hydroxy-ethyl)-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-ethanol,

6-(4-Methoxy-thiophen-2-yl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

3-[3-Amino-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-1-ylamino]-propane-1,2-diol,

2-[3-Amino-1-dimethylamino-6-(2-trifluoromethyl-phenyl)-pyrrolo[3,2-f]quinazolin-7-yl]-ethanol,

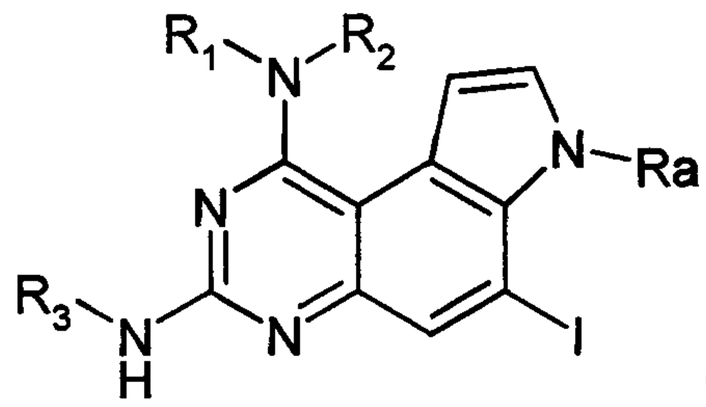
[(4-{2-[3-Amino-1-dimethylamino-6-(2-trifluoromethyl-phenyl)-pyrrolo[3,2-f]quinazolin-7-yl]-ethoxymethyl}-phenyl)-difluoro-methyl]-phosphonic acid,

6-(5-Methoxy-thiophen-2-yl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,

6-(5-Methoxy-thiophen-2-yl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
6-(4-Methoxy-thiophen-2-yl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
6-(2,6-Dimethyl-phenyl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
6-(2,6-Dimethyl-phenyl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7,N1,N1-Trimethyl-6-(4-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7,N1-Bis-(2-benzyloxy-ethyl)-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
2-[[3-Amino-7-methyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazolin-1-yl]-(2-hydroxy-ethyl)-amino]-ethanol,
3-Amino-7-methyl-6-thiophen-2-yl-2,7-dihydro-pyrrolo[3,2-f]quinazolin-1-one,
7,N1,N1-Trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine, and
6-(2,4-Dimethoxy-pyrimidin-5-yl)-7,N1,N1-trimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
and pharmaceutically acceptable salts thereof.

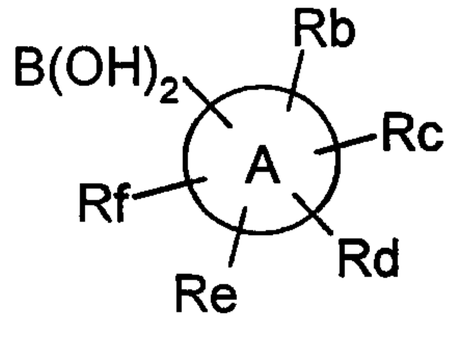
26. Compounds according to any one of claims 1 - 25, selected from the group consisting of
7,N1-dimethyl-6-(2-trifluoromethyl-phenyl)-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7,N1-dimethyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
6-(2,6-Dimethyl-phenyl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
7-ethyl-N1-methyl-6-thiophen-2-yl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
6-(4-methoxy-thiophen-2-yl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
6-(5-methoxy-thiophen-2-yl)-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine, and
6-furan-2-yl-7,N1-dimethyl-7H-pyrrolo[3,2-f]quinazoline-1,3-diamine,
and pharmaceutically acceptable salts thereof.

27. A process for the preparation of compounds according to any one of claims 1 - 26, comprising reacting a compound of formula (XII)



(XII)

with a compound of formula (XIII)



(XIII)

wherein R1, R2, R3, Ra, Rb, Rc, Rd, Re, Rf and A have the significances given in any of claims 1 to 26.

28. Compounds according to any one of claims 1 - 26, when prepared by a process according to claim 27.

29. Pharmaceutical compositions comprising a compound according to any one of claims 1 to 26 and a pharmaceutically acceptable carrier and/or adjuvant.

30. Compounds according to any one of claims 1 to 26 for use as therapeutic active substances.

31. Compounds according to any one of claims 1 to 26 for use as therapeutic active substances for the treatment and/or prevention of diseases which are modulated by PTP1B inhibitors.

32. The use of compounds according to any one of claims 1 to 26 for the treatment and/or prevention of diseases which are modulated by PTP1B inhibitors.

33. The use of compounds according to any one of claims 1 to 26 for the preparation of medicaments for the treatment and/or prevention of diseases which are modulated PTP1B inhibitors.

34. The use according to claim 32 or 33 , wherein the disease is diabetes.

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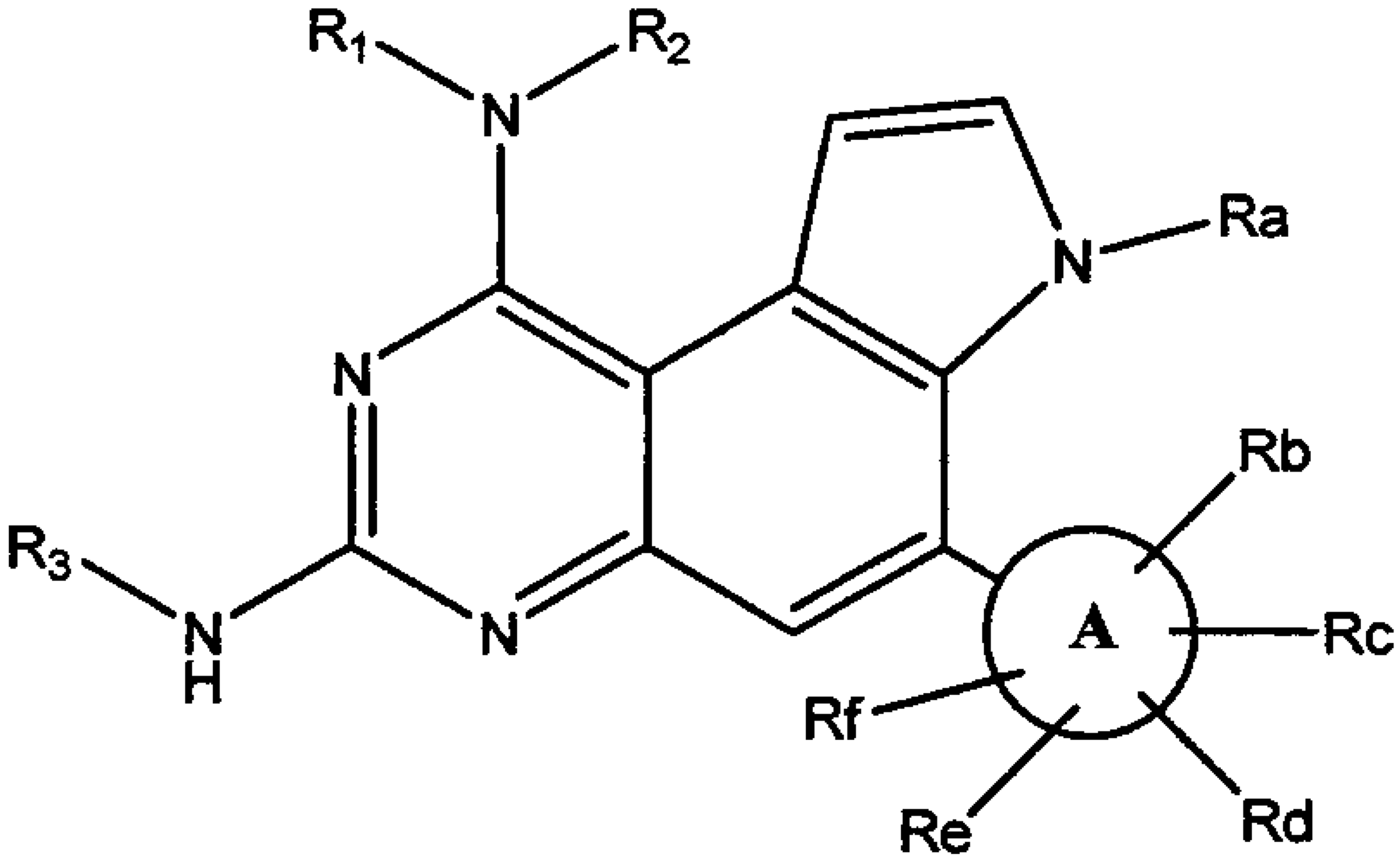

(I)