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CA 2279796 C 2003/09/30

(11)(21) 2 279 796

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(22) Date de dépôt/Filing Date: 1999/08/06
(41) Mise à la disp. pub./Open to Public Insp.: 2000/02/10
(45) Date de délivrance/Issue Date: 2003/09/30
(30) Priorité/Priority: 1998/08/10 (98114978.4) EP

(51) Cl.Int.[6]/Int.Cl.[6] C07D 401/04, C07D 417/14, C07D 413/14, C07D 409/14, C07D 405/14, C07D 401/14, C07D 473/00

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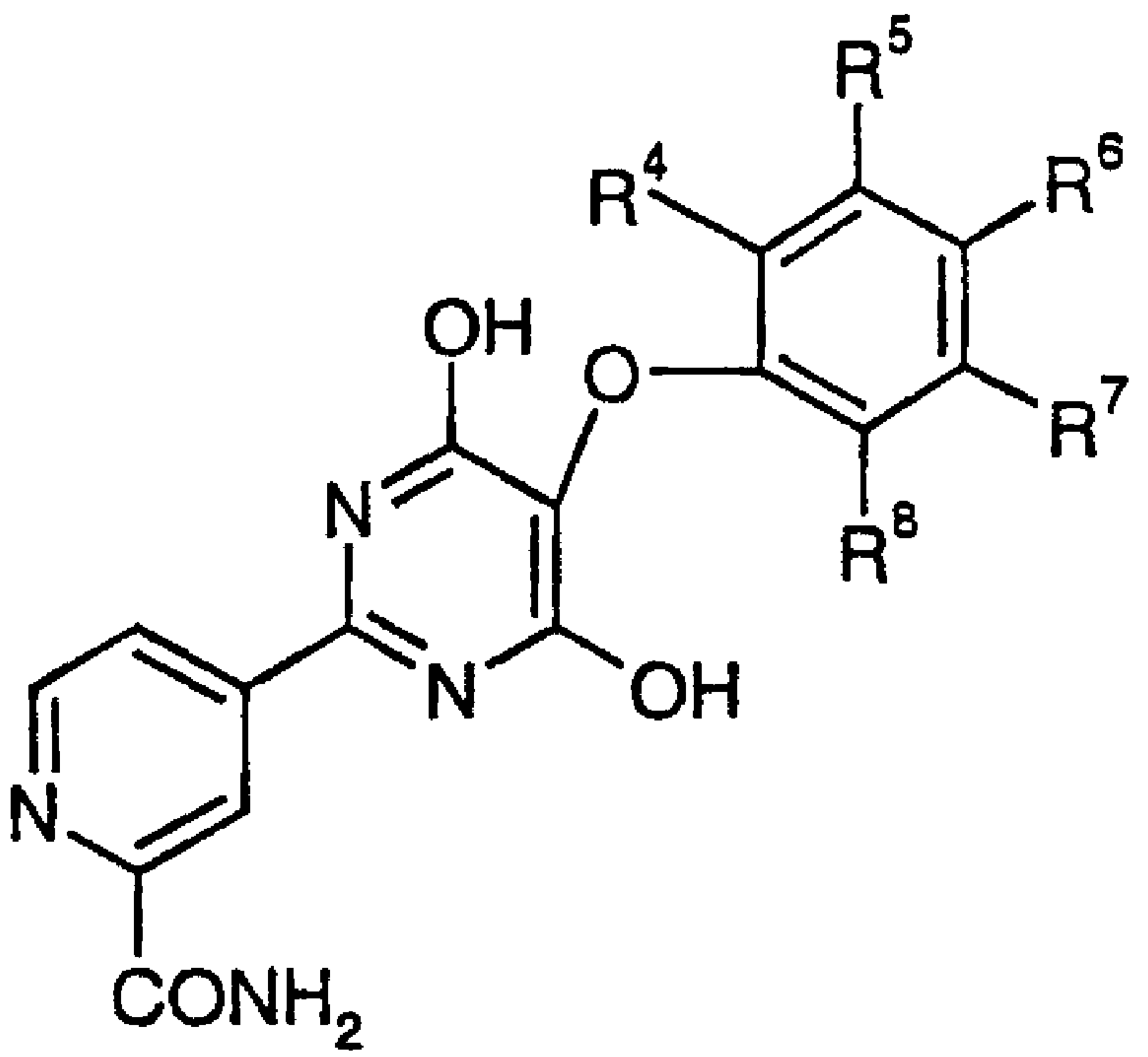
(54) Titre : PROCEDE DE PREPARATION DE PYRIDINES SUBSTITUEES
(54) Title: PROCESS FOR THE PREPARATION OF SUBSTITUTED PYRIDINES

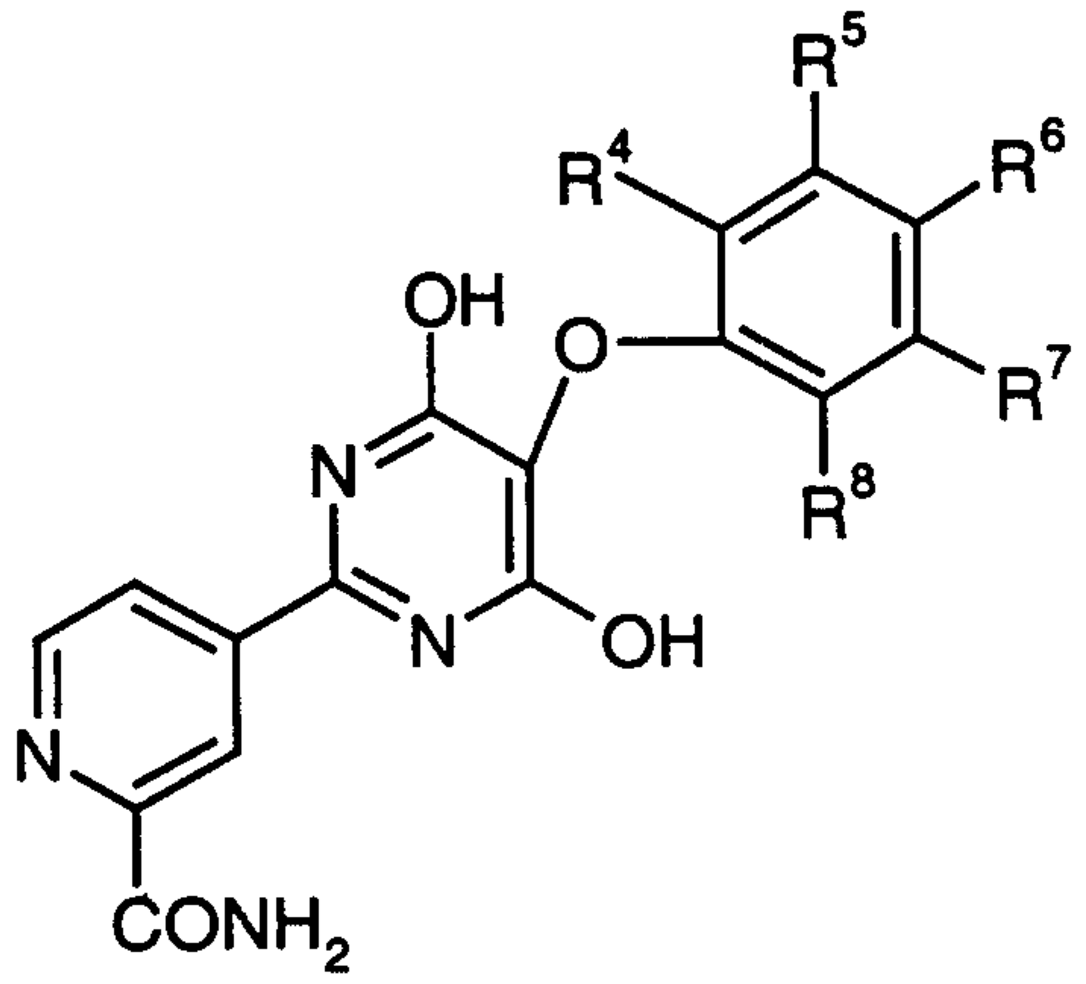


I

(57) Abrégé/Abstract:
The present invention is concerned with a novel process for the carbamoylation of substituted pyridines, especially with a process for the preparation of compounds of formula I (see formula I) wherein R^4 to R^8 represent hydrogen, lower-alkoxy or halogen; or optionally salts thereof.

Abstract

The present invention is concerned with a novel process for the carbamoylation of substituted pyridines, especially with a process for the preparation of compounds of formula I



I

wherein R^4 to R^8 represent hydrogen, lower-alkoxy or halogen;

or optionally salts thereof.

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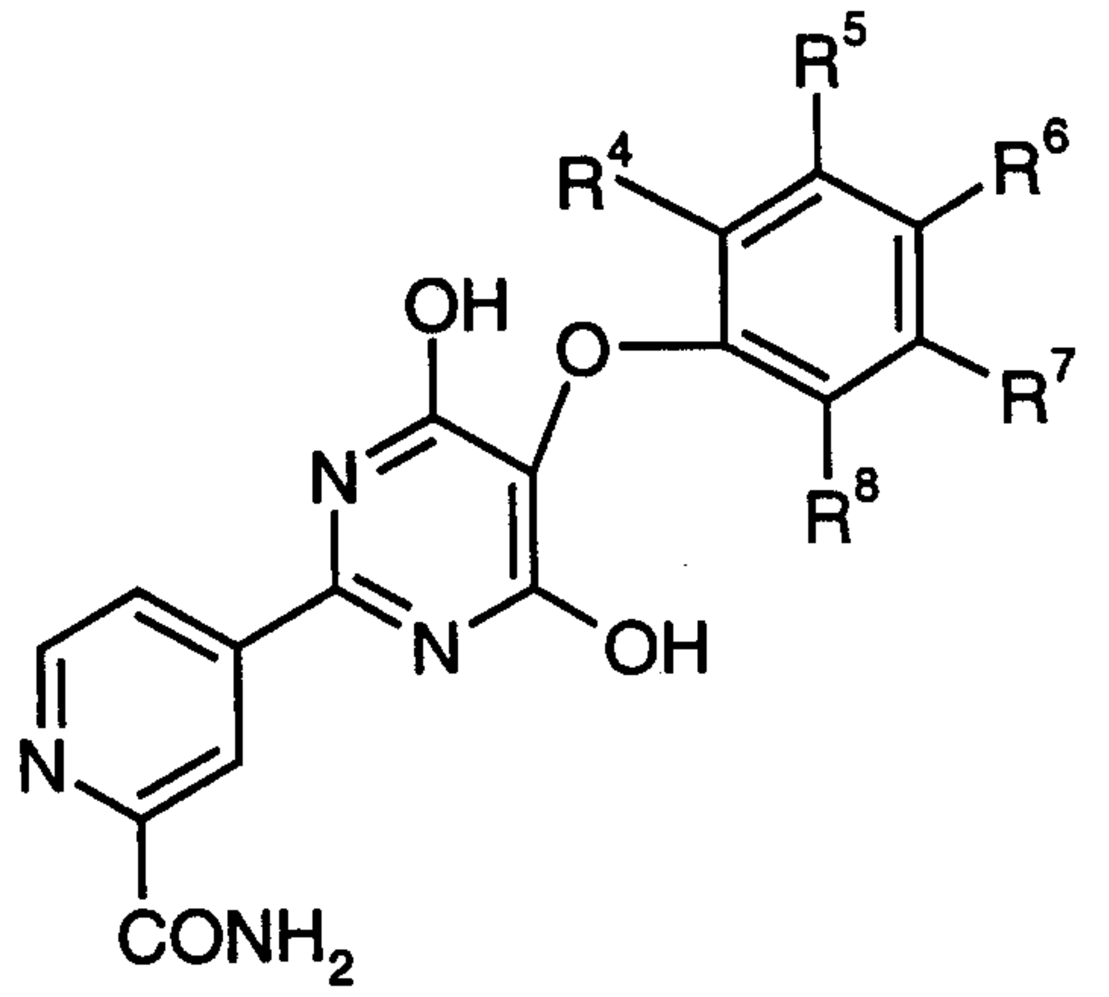
The present invention is concerned with a novel process for the carbamoylation of substituted pyridines, especially with a process for the preparation of compounds of formula I



I

wherein R^4 to R^8 represent hydrogen, lower-alkoxy or halogen;

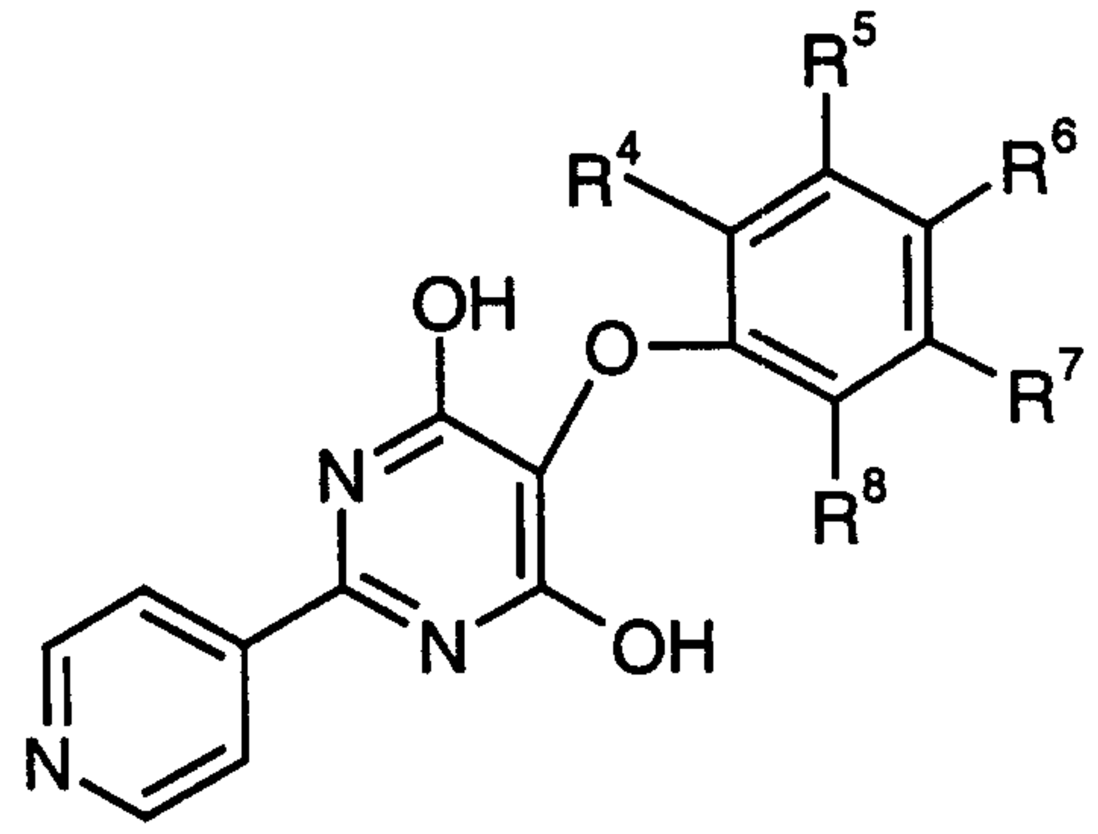
or optionally salts thereof.

The process according to the present invention is useful for the preparation of endothelin receptor inhibitors which can be used for the treatment of disorders associated with endothelin receptor activities, especially circulatory disorders such as hypertension, ischaemia, vasospasms and angina pectoris.

Radical carbamoylation of basic heteroaromates has been described by F. Minisci et al. in Tetrahedron (1985), 41, 4157. The reaction disclosed therein is performed in the presence of a catalytic amount of iron(II)sulfate.

Surprisingly it has been found that using the reaction according to the present invention, namely performing the reaction in the presence of a much higher amount of iron(II)salt, an outstanding yield for the specific compounds of formula I can be obtained.

The process according to the present invention is characterized in that a substituted pyridine, preferably a compound of formula II



II

wherein R^4 to R^8 represent hydrogen, lower-alkoxy or halogen;

or optionally salts thereof is reacted with formamide and an oxidizing agent in the presence of a high amount of iron(II)salt in an acidic aqueous medium.

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

The term „lower“ refers to a group consisting of one to seven, preferably one to four carbon atom(s), unless otherwise indicated.

The term „lower-alkyl“ refers to a branched or straight chain monovalent alkyl radical of one to seven carbon atoms, preferably one to four carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, isopropyl, i-butyl, n-butyl, t-butyl and the like.

The term „ lower-alkoxy“ refers to the group -O-R', where R' is a lower-alkyl.

The term „halogen“ refers to fluoro, chloro, bromo and iodo, with chloro being preferred.

The term „aryl“ refers to a monovalent carbocyclic aromatic radical (e.g. phenyl), optionally substituted, independently, with halogen, lower-alkyl, lower-alkoxy, lower-alkylenedioxy, carboxy, trifluoromethyl and the like.

The term „lower-aralkyl“ refers to a lower-alkyl group substituted by aryl, e.g. phenyl or substituted phenyl, preferably benzyl.

The term „heterocyclyl“ refers to mono- or bicyclic, 5- and 6-membered heterocycles having oxygen, nitrogen or sulphur as the hetero atom, such as 2- and 3-furyl, 2-, 4- and 5-pyrimidinyl, 2-, 3- and 4-pyridyl, 1,2- and 1,4-diazinyl, 2- and 3-thienyl, oxazolyl, thiazolyl, imidazolyl, benzofuranyl, benzothienyl, purinyl, quinolyl, isoquinolyl and quinazolyl, which residues can be substituted, e.g. by 1 or 2 lower-alkyl groups. Preferably, heterocyclyl is a pyridyl residue or a substituted pyridyl residue.

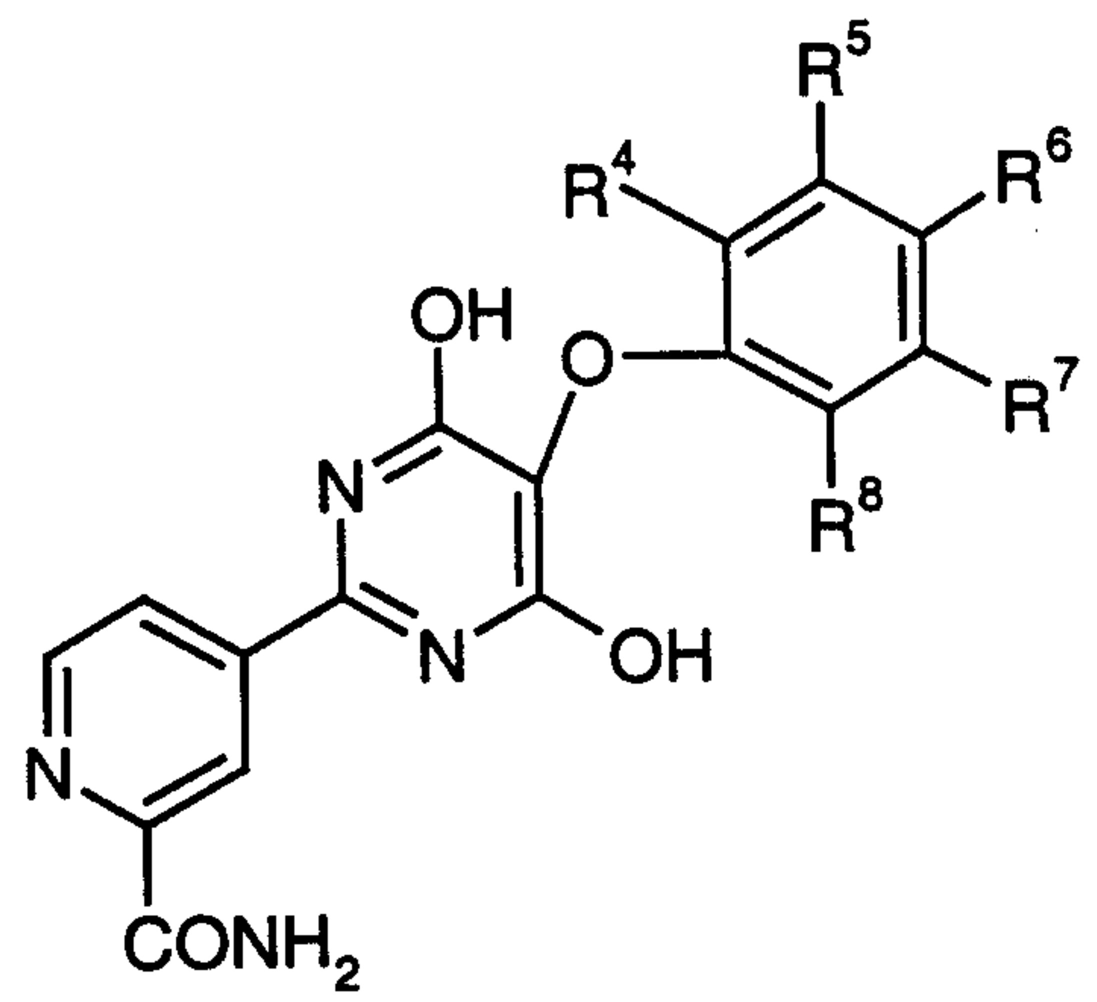
The term „substituted phenyl" refers to a phenyl group which is mono-, di- or tri-substituted, independently, with halogen, lower-alkyl, lower-alkoxy, lower-alkylenedioxy, carboxy, trifluoromethyl and the like.

The term „substituted pyridyl" refers to a pyridyl group which is mono-, di- or tri-substituted, independently, with halogen, lower-alkyl, lower-alkoxy, lower-alkylenedioxy, carboxy, trifluoromethyl and the like.

The term „lower-alkylenedioxy" refers to the group $-O-(CH_2)_n-O-$, wherein n is an integer of two to seven, preferably an integer of two to four.

The term „pharmaceutically acceptable salts" embraces alkali salts such as Na or K salts or alkaline earth metal salts such as Ca or Mg salts or salts with amines such as monoethanolamine as well as salts with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like, which are non-toxic to living organisms.

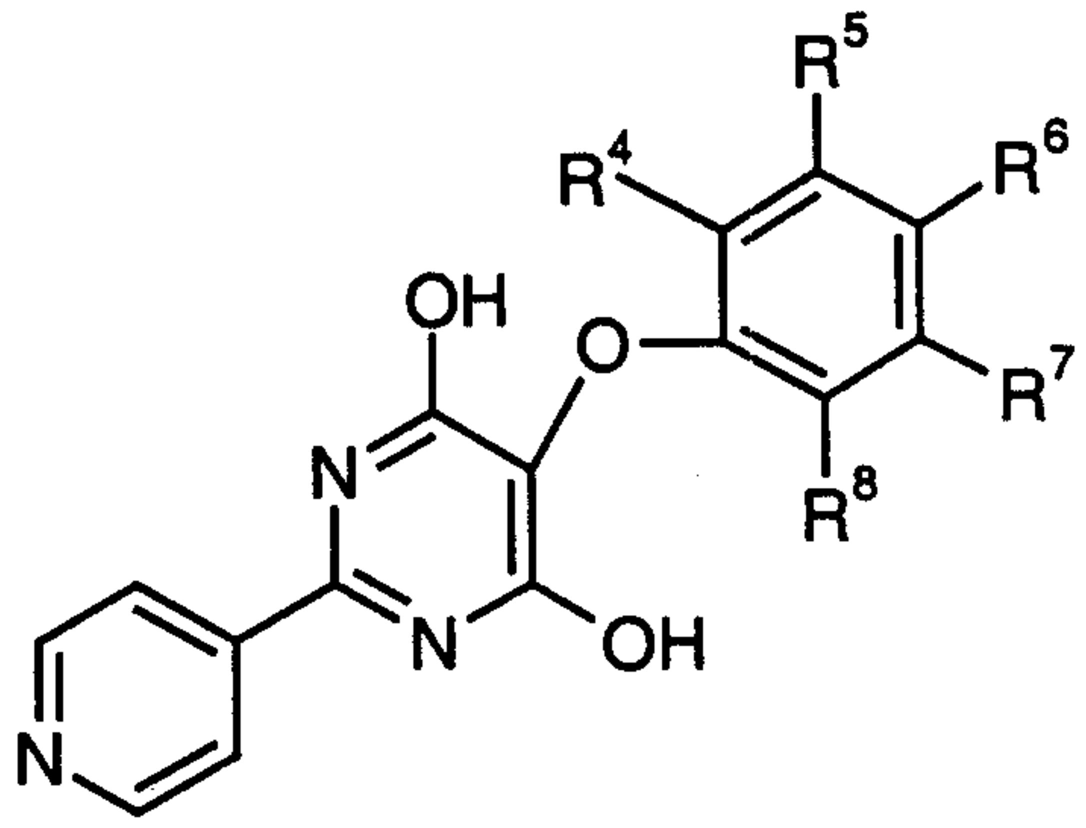
In a preferred aspect the present invention is concerned with the preparation of compounds of the formula I



I

wherein R^4 to R^8 represent hydrogen, lower-alkoxy or halogen;

characterized in that the process comprises the reaction of a compound of formula II



II

wherein R^4 to R^8 represent hydrogen, lower-alkoxy or halogen;

or optionally salts thereof with formamide and an oxidizing agent in an aqueous acid solution in the presence of 15 to 40 mol% iron(II)salts concerning compounds of formula II. If desired, the compounds of formula I may be obtained as salts.

In another preferred aspect, the reaction is performed with an iron(II)salt comprising an anion selected from chloride, bromide, sulfate, phosphate, tetrafluoroborate, or hexafluoroborate.

Yet another preferred aspect is the reaction in the presence of 20 to 30 mol% iron(II)salts concerning compounds of formula II.

The reaction is performed at a temperature of 0°C to 35°C, preferably at a temperature of 0°C to 20°C, more preferably at a temperature of 0°C to 10 °C.

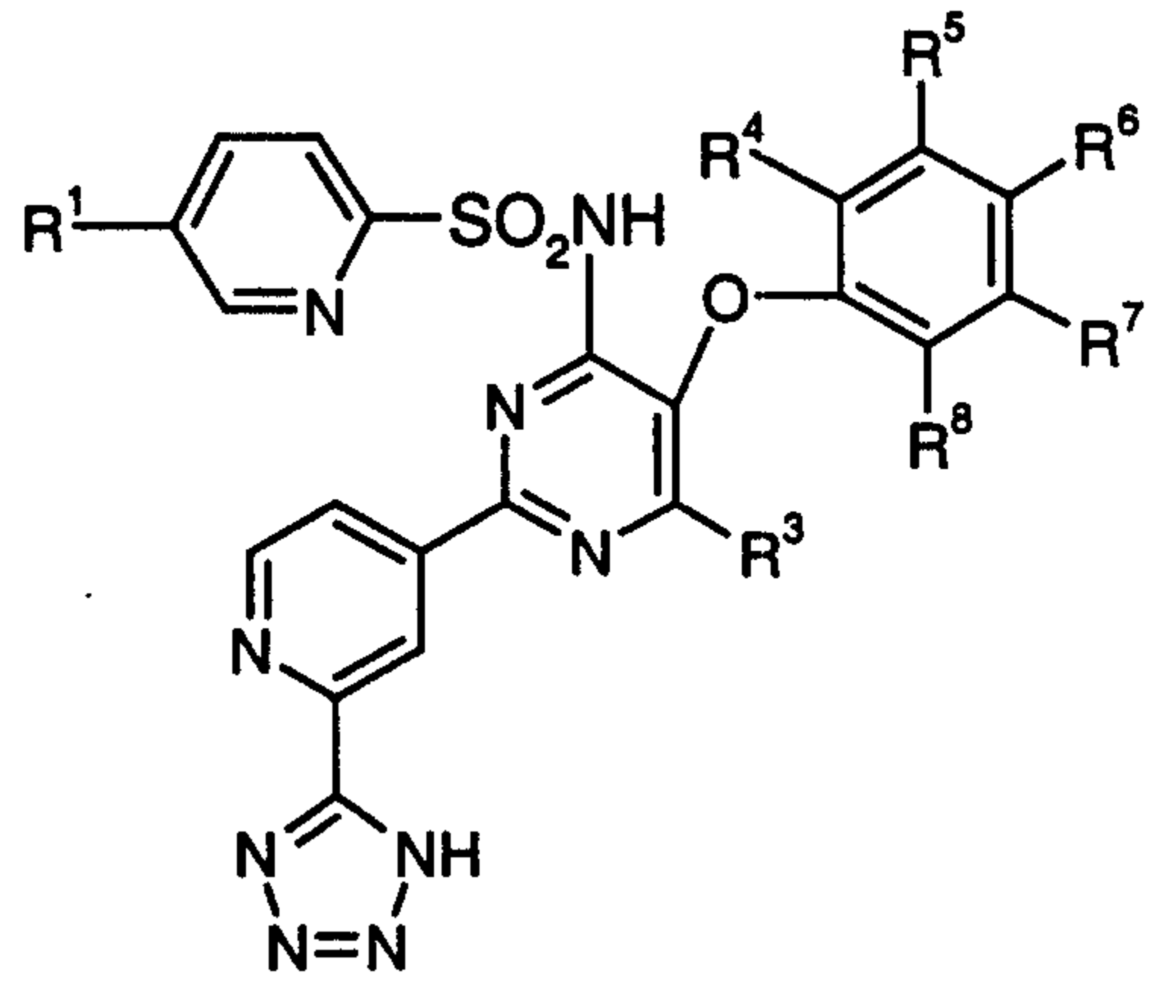
In a preferred aspect the oxidizing agent is hydrogen peroxide.

In another preferred embodiment the reaction is performed in the presence of about 1.5 to 2.5 mol, preferably about 2 mol of the oxidizing agent (with respect to the compound of formula II).

The aqueous acid solution may be an inorganic or organic acid solution, e.g. a sulfonic acid solution.

More particularly the reaction refers to the conversion of 5-(2-methoxy-phenoxy)-2-pyridine-4-yl-pyrimidine-4,6-diole to 4-[4,6-dihydroxy-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carboxylic acid amide using the reaction conditions as described above.

The compounds of formula I as defined above can be converted to endothelin receptor inhibitors of formula VI



VI

wherein

R^1 represents lower-alkyl;

R^3 represents $-O-(CR_aR_b)_n-OR^9$;

R^4 to R^8 represent hydrogen, lower-alkoxy or halogen;

R^9 represents hydrogen, aryl, lower-aralkyl, heterocyclyl or a residue $-C(O)NHR^{10}$;

R^{10} represents lower-alkyl, phenyl, substituted phenyl, pyridyl or substituted pyridyl;

R_a and R_b represent hydrogen or lower-alkyl; and

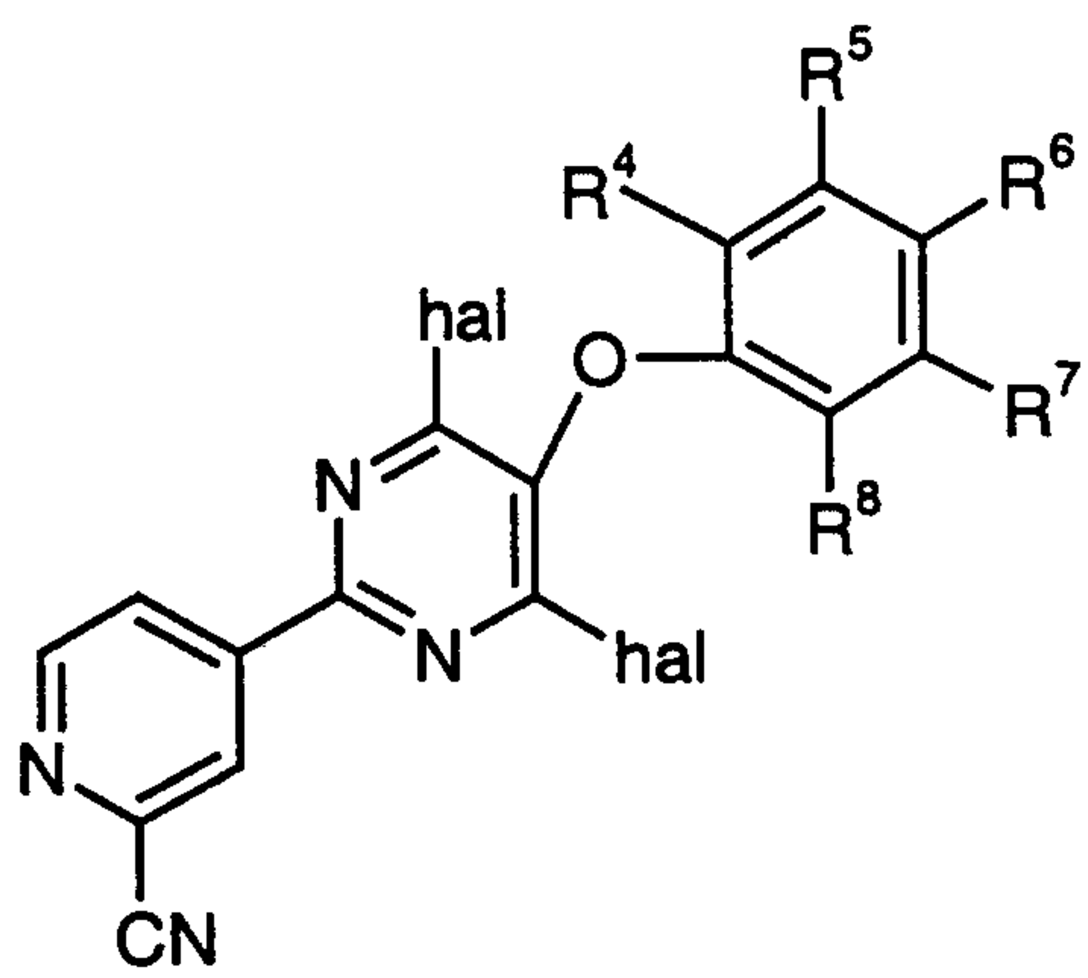
n represents 2, 3 or 4;

or salts thereof.

These compounds of formula VI are known and have been described for example in International Patent Application WO 9619459.

The process for the preparation of compounds of formula VI may comprise the following steps:

A compound of formula I as defined above may be converted into a compound of formula III



III

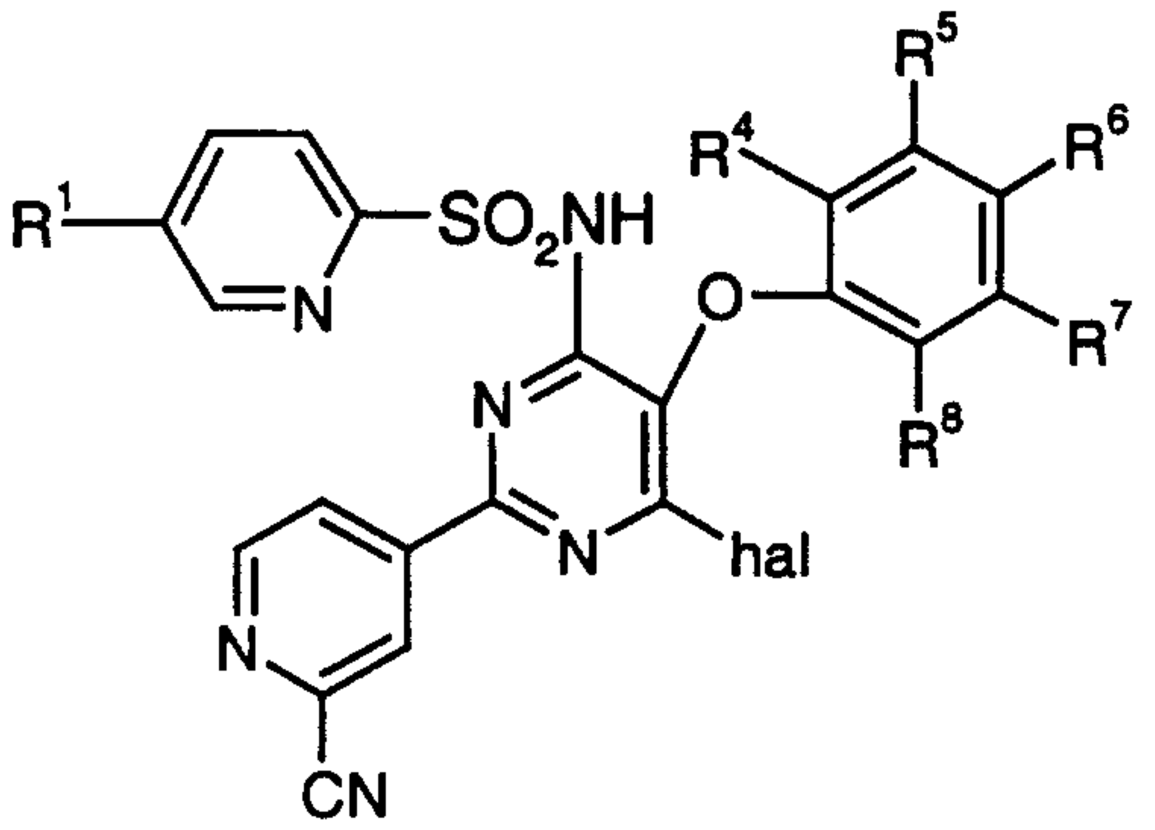
wherein

R^4 to R^8 represent hydrogen, lower-alkoxy or halogen; and

hal represents halogen;

or optionally salts thereof characterized in that the compound of formula I as defined above is reacted with a water removing and halogenating agent. Examples of water removing and halogenating agents are $POCl_3$, PCl_5 or $SOCl_2$, preferably $POCl_3$. The reaction is preferably carried out in a solvent like diisopropyl ethylamine.

The compounds of formula III as defined above may be converted into compounds of formula IV



IV

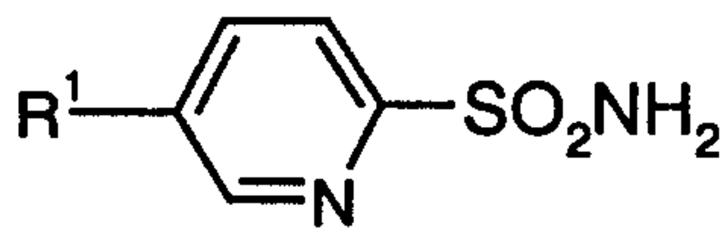
wherein

R^1 represents lower-alkyl;

R^4 to R^8 represent hydrogen, lower-alkoxy or halogen; and

hal represents halogen;

or optionally salts thereof characterized in that the compound of formula III is reacted with a compound of formula V

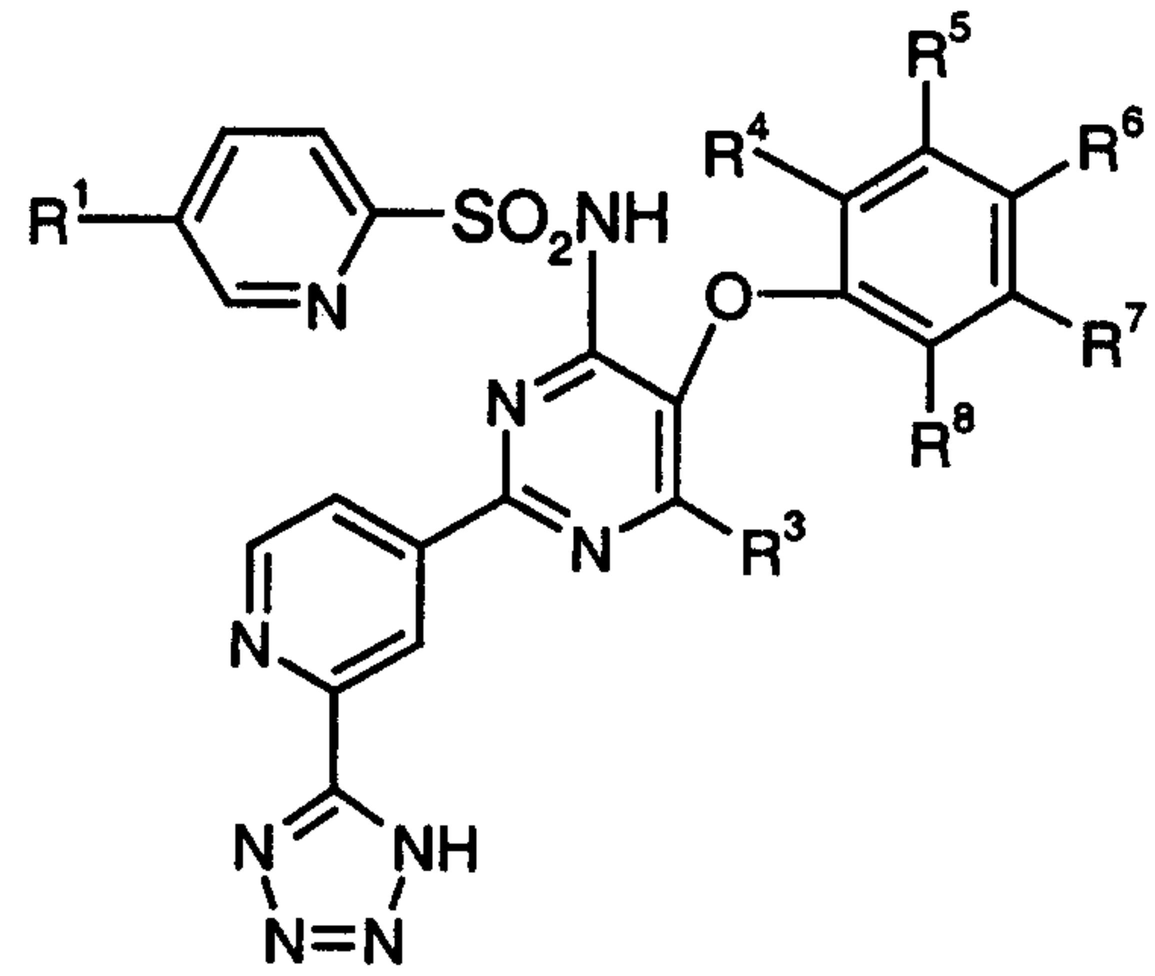


V

wherein R^1 represents lower-alkyl, preferably methyl or isopropyl.

The reaction type is known in the art and may be performed under basic conditions for example in the presence of a coupling agent, e.g. 1,4-diazobicyclo[2.2.2]octane, together with potassium carbonate in acetone.

The compounds of formula IV as defined above may then be converted into compounds of formula VI



VI

wherein

R^1 represents lower-alkyl

R^3 represents $-O-(CR_aR_b)_n-OR^9$;

R^4 to R^8 represent hydrogen, lower-alkoxy or halogen;

R^9 represents hydrogen, aryl, lower-aralkyl, heterocyclyl or a residue $-C(O)NHR^{10}$;

R^{10} represents lower-alkyl, phenyl, substituted phenyl, pyridyl or substituted pyridyl;

R_a and R_b represent hydrogen or lower-alkyl; and

n represents 2, 3 or 4;

or salts thereof characterized in that the compound of formula IV as defined above is reacted with hydrazine hydrate and a nitrite salt, e.g. an alkali nitrite salt such as sodium nitrite, followed by a reaction under basic conditions with a compound of the formula $H-O-C(R_aR_b)_n-OR^9$, wherein R^9, R^{10}, R_a, R_b, and n have the significance as defined above.

Alternatively, the compound of formula IV as defined above may be reacted under basic conditions with a compound of the formula $H-O-C(R_aR_b)_n-OR^9$, wherein R^9, R^{10}, R_a, R_b, and n have the significance as defined above, followed by a reaction with hydrazine hydrate and a nitrite salt as defined above. In the above, the term „basic conditions“ means in the presence of a base, preferably in the presence of a metal hydroxide, more preferably in the presence of sodium hydroxide.

The reaction is conveniently carried out by heating, e.g. to 40°C-100°C, in a glycol corresponding to the compound of the formula $H-O-C(R_aR_b)_n-OR^9$ as a solvent, e.g. in ethylene glycol when n = 2 and R_a and R_b are hydrogen. R^3 is preferably $-O(CH_2)_nOH$ and n is preferably 2.

Particularly preferred are the above processes wherein R^1 is lower alkyl; R^2 is tetrazolyl; R^3 is 2-hydroxy-ethoxy; R^4 to R^7 are hydrogen and R^8 is lower alkoxy. More particularly preferred is the process wherein R^1 is methyl or isopropyl; R^2 is tetrazolyl; R^3 is 2-hydroxy-ethoxy; R^4 to R^7 are hydrogen and R^8 is methoxy.

A particularly preferred embodiment of the present invention is the process for the preparation of 5-methyl-pyridine-2-sulfonic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide or salts thereof using the reaction conditions as described above characterized in that the process comprises

a) the reaction of 5-(2-methoxy-phenoxy)-2-pyridine-4-yl-pyrimidine-4,6-diole to 4-[4,6-dihydroxy-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carboxylic acid amide as described above;

b) the reaction of 4-[4,6-dihydroxy-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carboxylic acid amide to 4-[4,6-dichloro-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carbonitrile as described above;

c) the reaction of 4-[4,6-dichloro-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carbonitrile to 5-methyl-pyridine-2-sulfonic acid [6-chloro-2-(2-cyano-pyridine-4-yl)-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide as described above;

d) the reaction of 5-methyl-pyridine-2-sulfonic acid [6-chloro-2-(2-cyano-pyridine-4-yl)-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide to 5-methyl-pyridine-2-sulfonic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide or salts thereof as described above.

Step d) comprises

aa) the reaction of 5-methyl-pyridine-2-sulfonic acid [6-chloro-2-(2-cyano-pyridine-4-yl)-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide to 5-methyl-pyridine-2-sulfonic acid [6-chloro-2-[2-(hydrazino-imino-methyl)-pyridine-4-yl]-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide by reaction with hydrazine, followed by conversion of the reaction product to 5-methyl-pyridine-2-sulfonic acid [6-chloro-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide or salts thereof by reaction with an alkali nitrite, e.g. sodium nitrite; and

bb) the reaction of 5-methyl-pyridine-2-sulfonic acid [6-chloro-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide to 5-methyl-pyridine-2-sulfonic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide or salts thereof by reaction with ethylene glycol;

The sequence of the corresponding reactions of steps aa) and bb) may optionally be exchanged.

Another particularly preferred embodiment of the present invention is the process for the preparation of 5-isopropyl-pyridine-2-sulfonic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide or salts thereof using the reaction conditions as described above characterized in that the process comprises the steps a) and b) as described above followed by

c) the reaction of 4-[4,6-dichloro-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carbonitrile to 5-isopropyl-pyridine-2-sulfonic acid [6-chloro-2-(2-cyano-pyridine-4-yl)-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide as described above;

d) the reaction of 5-isopropyl-pyridine-2-sulfonic acid [6-chloro-2-(2-cyano-pyridine-4-yl)-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide to 5-isopropyl-pyridine-2-sulfonic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide or salts thereof as described above.

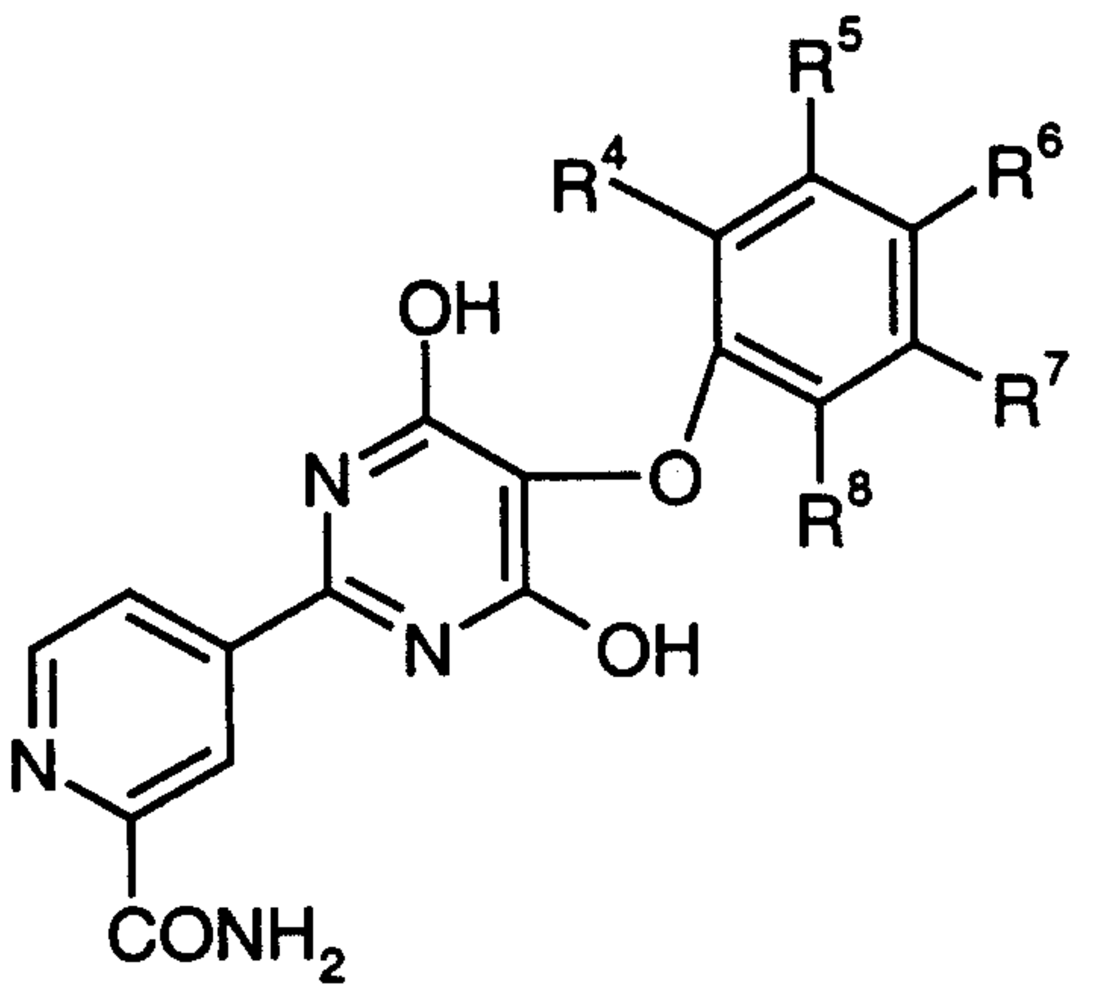
Step d) comprises

aa) the reaction of 5-isopropyl-pyridine-2-sulfonic acid [6-chloro-2-(2-cyano-pyridine-4-yl)-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide to 5-isopropyl-pyridine-2-sulfonic acid [6-chloro-2-[2-(hydrazino-imino-methyl)-pyridine-4-yl]-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide by reaction with hydrazine, followed by conversion of the reaction product to 5-isopropyl-pyridine-2-sulfonic acid [6-chloro-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide or salts thereof by reaction with an alkali nitrite, e.g. sodium nitrite; and

bb) the reaction of 5-isopropyl-pyridine-2-sulfonic acid [6-chloro-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide to 5-isopropyl-pyridine-2-sulfonic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide or salts thereof by reaction with ethylene glycol;

The sequence of the corresponding reactions of steps aa) and bb) may optionally be exchanged.

Compounds of the formula I and their salts are new and are also part of the present invention:

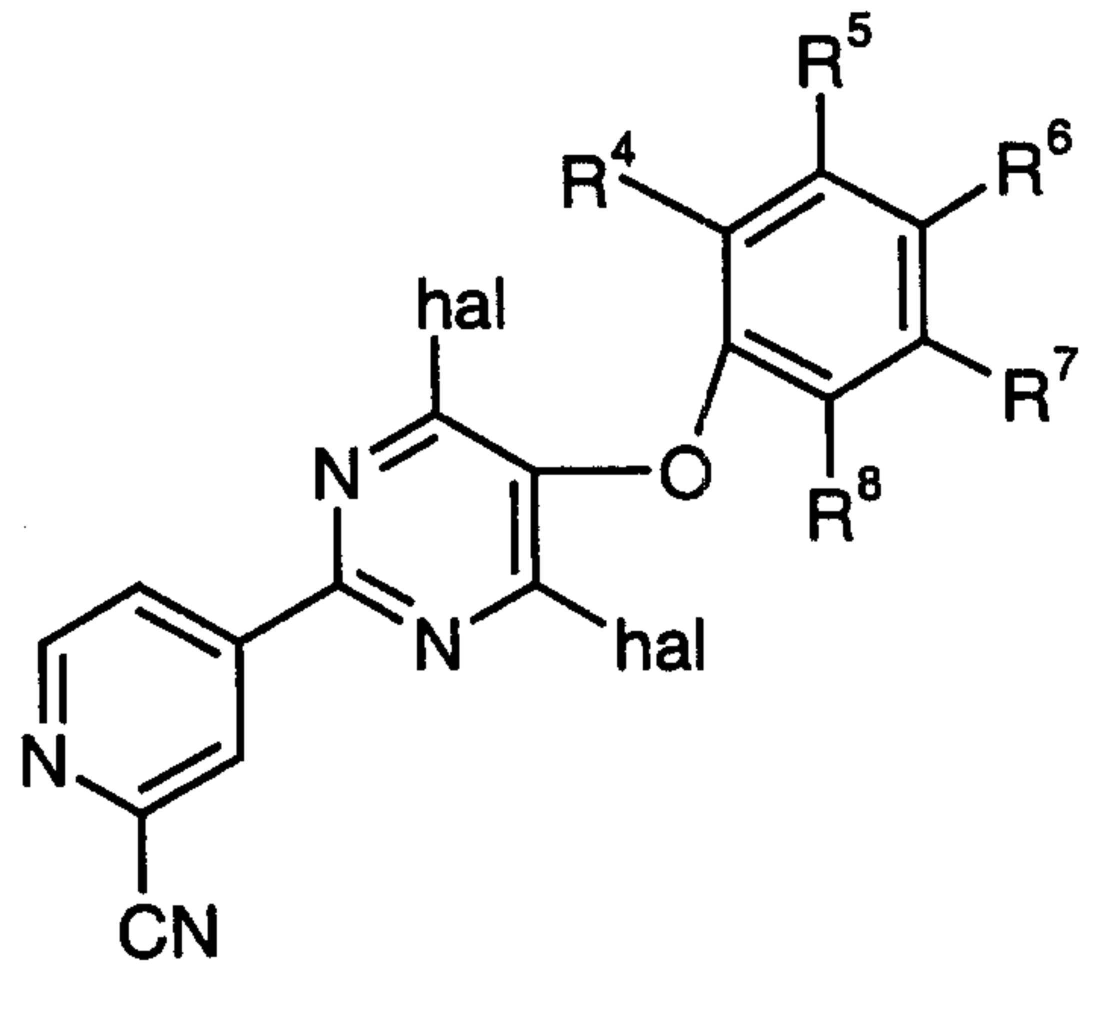


I

wherein R^4 to R^8 represent hydrogen, lower-alkoxy or halogen;

Particularly preferred are the compounds of formula I and salts thereof as defined above wherein R^4 to R^7 represent hydrogen and R^8 represents lower alkoxy. More particularly preferred is 4-[4,6-dihydroxy-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carboxylic acid amide and salts thereof.

Another embodiment of the present invention are compounds of the formula III and their salts:



III

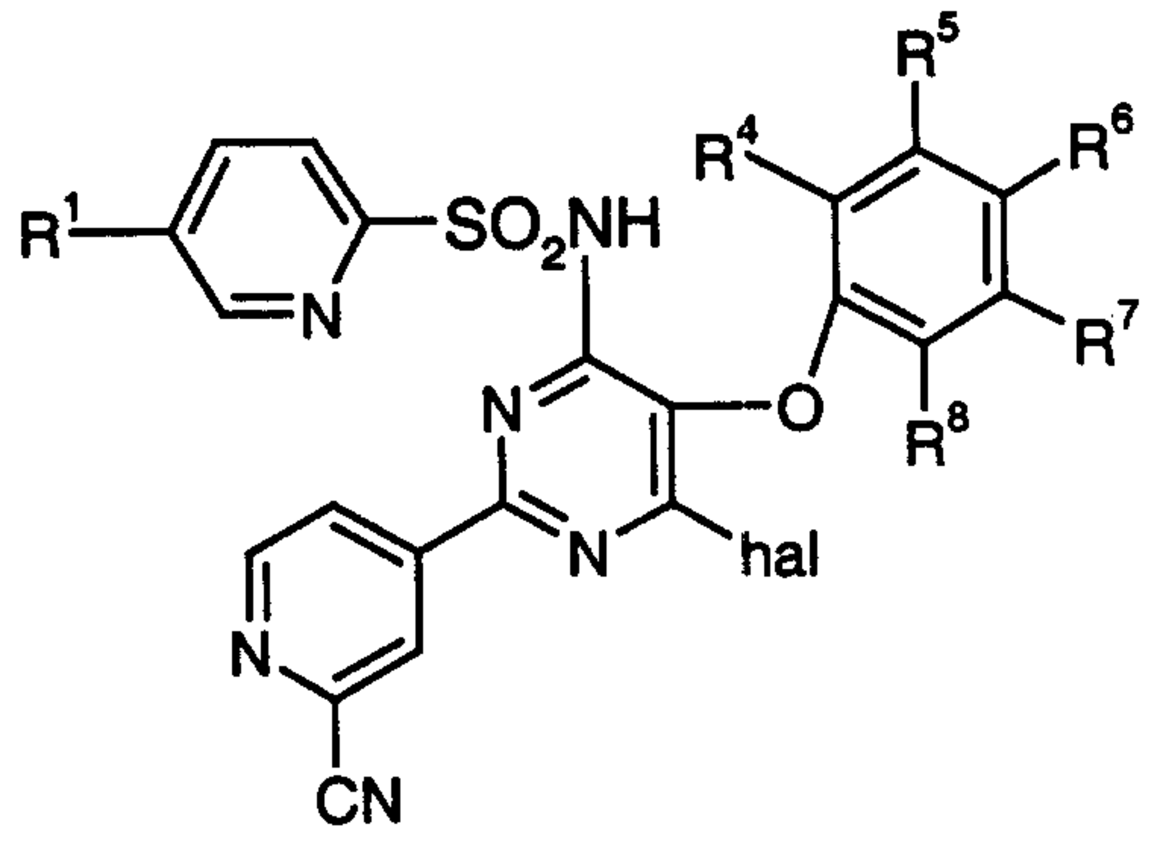
wherein

R^4 to R^8 represent hydrogen, lower-alkoxy or halogen; and

hal represents halogen;

Particularly preferred are the compounds of formula III and salts thereof as defined above wherein R^4 to R^7 represent hydrogen, R^8 represents lower alkoxy and hal represents chloro. More particularly preferred is 4-[4,6-dichloro-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carbonitrile and salts thereof.

Furthermore, compounds of the formula IV and their salts are new and are also part of the present invention:



IV

wherein

R^1 represents lower-alkyl;

R^4 to R^8 represent hydrogen, lower-alkoxy or halogen; and

hal represents halogen;

Particularly preferred are the compounds of formula IV and salts thereof as defined above wherein R^1 represents methyl or isopropyl, R^4 to R^7 represent hydrogen, R^8 represents lower alkoxy and hal represents chloro. More particularly preferred are 5-methyl-pyridine-2-sulfonic acid [6-chloro-2-(2-cyano-pyridine-4-yl)-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide and salts thereof as well as 5-isopropyl-pyridine-2-sulfonic acid [6-chloro-2-(2-cyano-pyridine-4-yl)-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide and salts thereof.

The compounds of formula VI as defined above can be converted in a manner known per se into pharmaceutically acceptable salts. The compounds of formulas I to IV as defined above can be optionally obtained as salts, for example as pharmaceutically acceptable salts, or of course as other salts, which do not necessarily have to be pharmaceutically acceptable.

The compounds which are used as starting materials in the present invention are known from WO 9619459 or can be prepared in analogy to the methods described therein. In principle, the preparation of the starting compounds comprises the reaction of 4-amidino-pyridine hydrochloride with a corresponding dimethyl- or diethyl(2-methoxyphenoxy)malonate.

The following examples shall illustrate preferred embodiments of the present invention but are not intended to limit the scope of the invention.

Examples

Example 1

1360 ml of formamide were added to 136 g (437 mmol) of 5-(2-methoxy-phenoxy)-2-pyridine-4-yl-pyrimidine-4,6-diole. Then, at a temperature of 0°C, 11.7 ml (219 mmol) of concentrated sulfuric acid and thereafter 36.5 g (130 mmol) of iron(II)sulfate heptahydrate were added to the suspension. After that, 89 ml (874 mmol) of 30% hydrogen peroxide were added dropwise within 1 hr at a temperature of 0°C to 5°C. The viscous yellow-brownish suspension was stirred at 0°C for 1.5 hr. Subsequently, a solution of 83 g (437 mmol) of sodium pyrosulfite in 680 ml of de-ionized water was added dropwise to the reaction mixture within 30 min. at 0°C to 5°C and the reaction mixture was stirred at 0°C to 5°C for 30 min. The suspension was then filtered under reduced pressure. The filtrate was first washed with 1750 ml of de-ionized water and thereafter with 700 ml of ethanol. Then the solid was dried at 80°C, 2000 Pa for 16 hr. There were obtained 132.4 g (91% of theory) of 4-[4,6-dihydroxy-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carboxylic acid amide with a HPLC purity of 91.4% (w/w).

Preparation of starting material:

a) 53.1 g of 4-cyano-pyridine (98%) are added all at once to a solution of 1.15 g of sodium in 200 ml of abs. MeOH. After 6 hr 29.5 g of NH_4Cl are added while stirring vigorously. The mixture is stirred at room temperature overnight. 600 ml of ether are added thereto, whereupon the precipitate is filtered off under suction and thereafter dried at 50°C under reduced pressure. There is thus obtained 4-amidino-pyridine hydrochloride (decomposition point 245-247°C).

b) 112.9 g of diethyl (2-methoxyphenoxy)malonate are added dropwise within 30 min. to a solution of 27.60 g of sodium in 400 ml of MeOH. Thereafter, 74.86 g of the amidine hydrochloride obtained in a) are added all at once. The mixture is stirred at room temperature overnight and evaporated at 50°C under reduced pressure. The residue is treated with 500 ml of ether and filtered off under suction. The filter cake is dissolved in 1000 ml of H_2O and treated little by little with 50 ml of CH_3COOH. The precipitate is filtered off under suction, washed with 400 ml of H_2O and dried at 80°C under reduced pressure. There is thus obtained 5-(2-methoxy-phenoxy)-2-(pyridine-4-yl)-pyrimidine-4,6-diole (or tautomer), melting point above 250°C.

Example 2

Within 20 min. 61 ml (633 mmol) of $POCl_3$ were added dropwise to 34 ml (200 mmol) of diisopropyl ethylamine at 5°C to 10°C followed by stirring at 5°C to 10°C for 15 min. Then 23.5 g (66 mmol) of 4-[4,6-dihydroxy-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carboxylic acid amide were added in four portions under cooling followed by stirring at 90°C for 25 hr. The reaction mixture was cooled down to 20°C and transferred to a new flask together with 50 ml of dichloromethane. Volatile components (i.e. excess of $POCl_3$) was removed by evaporation from 20°C to 70°C followed by re-distillation with 100 ml of toluene. After adding 250 ml of dichloromethane to the residue (88 g of a black oil) the solution was heated to 35°C to 40°C and 80 ml of de-ionized water were added dropwise within 30 min. whereby the pH was kept constant by the subsequent addition of 28% NaOH solution (60 ml) within 5 to 6 hr. The mixture was stirred at 35°C to 40°C for 30 min. followed by removal of dichloromethane by distillation. The resulting suspension was allowed to cool down to 20°C and was stirred for additional 2 hr. The solid was filtered off under suction, washed with 500 ml of water and dried at 70°C, 2000 Pa for 16 hr. There were obtained 21.3 g (86% of theory) of 4-[4,6-dichloro-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carbonitrile with a HPLC purity of 94.3% (w/w).

Example 3

12.5 g (33.5 mmol) of 4-[4,6-dichloro-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carbonitrile and 6.06 g (35 mmol) of 5-methyl-pyridine-2-sulfonamide were added to 130 ml of acetone. 15 g of potassium carbonate and 190 mg (1.6 mmol) of 1,4-diazobicyclo[2.2.2]octane were added and the suspension was stirred at 40°C for 5 hr and at 20°C for 15 hr. Then 50 ml of de-ionized water were added followed by dropwise addition of 50 ml of 3 N hydrochloric acid (pH of the solution = 1). Acetone was removed by evaporation and the suspension was stirred for 1 hr. The solid was filtered and washed with 100 ml of water. The residue was heated (reflux) in 100 ml of methanol for 1 hr followed by cooling to 20°C. The solid was filtered and dried at 80°C, 2000 Pa for 16 hr. There were obtained 16.0 g (93% of theory) of 5-methyl-pyridine-2-sulfonic acid [6-chloro-2-(2-cyano-pyridine-4-yl)-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide with a HPLC purity of 90.3% (w/w).

Example 4

8.95 g (24 mmol) of 4-[4,6-dichloro-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carbonitrile were suspended in 100 ml of acetone. At a temperature of 20°C, 5.04 g (25 mmol) of 5-isopropyl-pyridine-2-sulfonamide, 1 ml of de-ionized water, 10.6 g (77 mmol) of potassium carbonate and 135 mg (1.2 mmol) 1,4-diazobicyclo[2.2.2]octane were added. The mixture was stirred at 40°C for 20 hr. Thereafter, another 240 mg (1.2 mmol) of 5-isopropyl-pyridine-2-sulfonamide and 80 mg (0.7 mmol) of 1,4-diazobicyclo[2.2.2]octane were added. The reaction mixture was stirred for 24 hr at 40°C followed by cooling to 20°C. Then 50 ml of de-ionized water and 45 ml of 3 N aqueous hydrochloric acid were added slowly until pH = 1. The acetone was removed by distillation and the resulting suspension was stirred at 20°C for 1.5 hr. The solid was filtered off under suction, washed first with 100 ml of de-ionized water and thereafter with 50 ml of t-butylmethylether. Then the solid was dried at 70°C, 2000 Pa for 20 hr. There were obtained 13.2 g (102% of theory) of 5-isopropyl-pyridine-2-sulfonic acid [6-chloro-2-(2-cyano-pyridine-4-yl)-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide with a HPLC purity of 87.8% (w/w).

Example 5

20 g (39 mmol) of 5-methyl-pyridine-2-sulfonic acid [6-chloro-2-(2-cyano-pyridine-4-yl)-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide were suspended in 100 ml of N,N-dimethyl formamide and 7.6 ml (156 mmol) of hydrazine hydrate were added within 15 min. The reaction mixture was allowed to warm up slowly to 20°C. After 17.5 hr, at a temperature of 15°C, 250 ml of de-ionized water were added followed by slow addition of 10.5 ml acetic acid (until pH = 5.4). The resulting suspension was stirred for 2 hr at 20°C and then for additional 2 hr 0°C. The solid was filtered off under suction, firstly washed with 200 ml of de-ionized water and thereafter with 100 ml of t-butylmethylether. The residue was dried at 40°C, 2000 Pa for 18 hr. There were obtained 21.7 g (102% of theory) of 5-methyl-pyridine-2-sulfonic acid [6-chloro-2-[2-(hydrazino-imino-methyl)-pyridine-4-yl]-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide with a HPLC purity of 81.4% (w/w).

Example 6

122 g (233 mmol) of 5-isopropyl-pyridine-2-sulfonic acid [6-chloro-2-(2-cyano-pyridine-4-yl)-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide was suspended in 450 ml of N,N-dimethyl formamide and the mixture was cooled down to 15°C. At this temperature, 35 ml of hydrazine hydrate were added dropwise within 1 hr. The resulting solution was stirred at 15°C to 20°C for 16 hr and thereafter diluted with 600 ml of de-ionized water. Then 50 ml of glacial acetic acid were added dropwise at 0°C to 5°C until pH = 5.5. 600 g of ice were added and the suspension was stirred for 1 hr. The solid was filtered off under suction, washed with 3000 ml of water and dried at 40°C, 2000 Pa for 24 hr. There were obtained 126 g (97% of theory) of 5-isopropyl-pyridine-2-sulfonic acid [6-chloro-2-[2-(hydrazino-imino-methyl)-pyridine-4-yl]-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide with a HPLC purity of 91.8% (w/w).

Example 7

20 g (37 mmol) of 5-methyl-pyridine-2-sulfonic acid [6-chloro-2-[2-(hydrazino-imino-methyl)-pyridine-4-yl]-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide were added to 160 ml of N,N-dimethyl formamide. To this solution was added dropwise 23 ml of 6 N aqueous hydrochloric acid at a temperature of 15°C. Then a solution containing 5.1 g (74 mmol) of sodium nitrite in 20 ml de-ionized water was added slowly. The reaction mixture was allowed to warm up to 20°C and was stirred for 1.5 hr. Then 160 ml of de-ionized water were added and the suspension was stirred for 1 hr. The solid was filtered off under suction, washed with 100 ml of de-ionized water and dried at 50°C, 2000 Pa for 17 hr. There were obtained 18.9 g (92% of theory) of 5-methyl-pyridine-2-sulfonic acid [6-chloro-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide with a HPLC purity of 89.6% (w/w).

Example 8

20 g (35 mmol) of 5-isopropyl-pyridine-2-sulfonic acid [6-chloro-2-[2-(hydrazino-imino-methyl)-pyridine-4-yl]-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide were added to 160 ml of N,N-dimethyl formamide. The solution was kept at 15°C to 20°C and 23 ml of 6 N aqueous hydrochloric acid were added, followed by addition of a solution containing 4.8 g (7 mmol) of sodium nitrite in 20 ml de-ionized water within 10 min. The mixture was stirred at 20°C for 1 hr, then 140 ml of de-ionized water were added and the suspension was stirred at 0°C for 1 hr. The solid was filtered, firstly washed with 80 ml of

de-ionized water and thereafter with 80 ml of t-butylmethylether. Then the solid was dried at 70°C and 2000 Pa for 16 hr. The crude product (23.4 g) was taken up with 117 ml of tetrahydrofuran for 1 hr. After filtration at 0°C the crystallized product was washed with 25 ml of t-butylmethylether and was then dried at 70°C, 2000 Pa for 16 hr. There were obtained 17.3 g (84% of theory) of 5-isopropyl-pyridine-2-sulfonic acid [6-chloro-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide with a HPLC purity of 91.1% (w/w).

Example 9

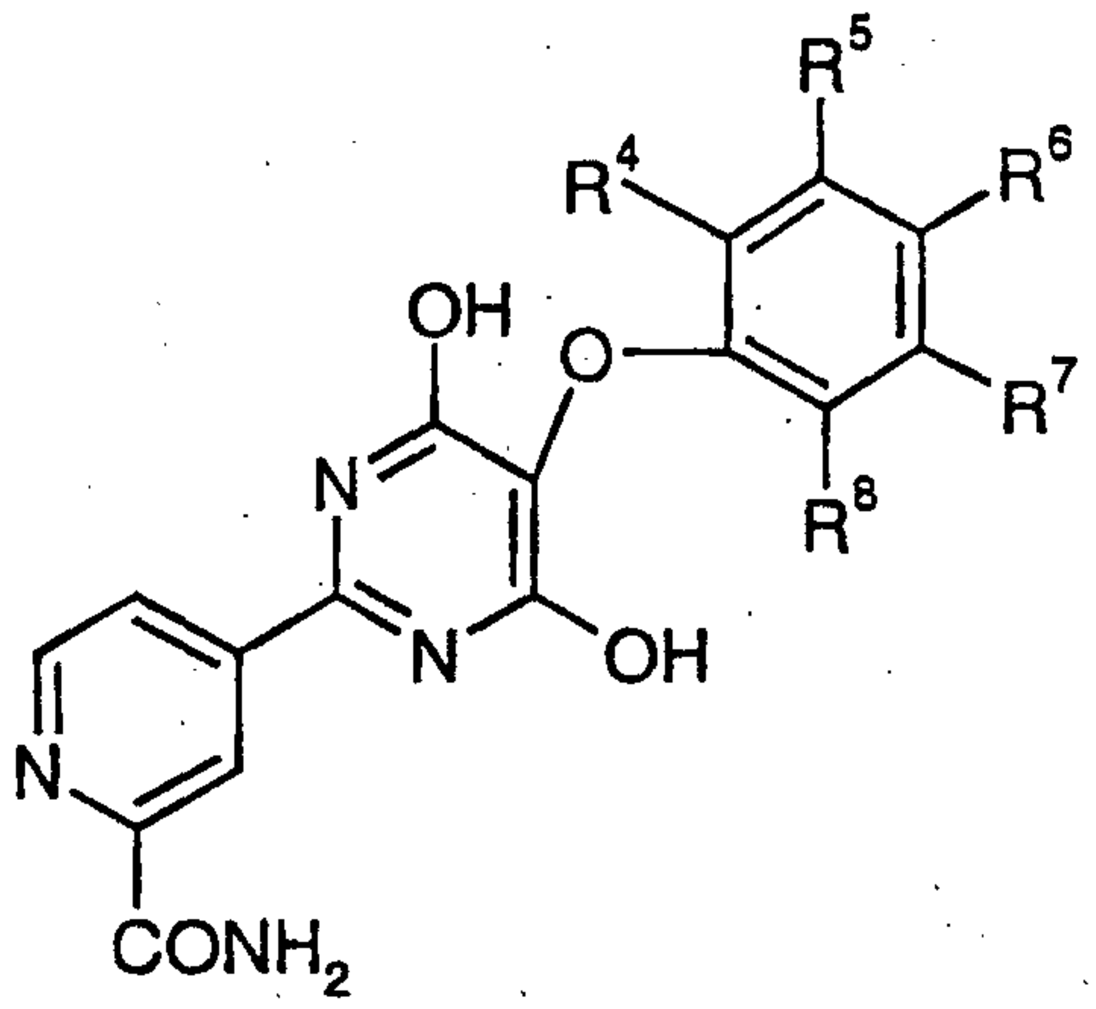
15 g (27 mmol) of 5-methyl-pyridine-2-sulfonic acid [6-chloro-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide were suspended in 75 ml of ethylene glycol and 6.5 g (163 mmol) of sodium hydroxide were added. The reaction mixture was heated to 85°C and stirred for 5 hr. Then 55 ml of de-ionized water and thereafter 55 ml of 3 N aqueous hydrochloric acid were added dropwise. The suspension was stirred at 20°C for 1 hr. The solid was filtered off under suction, washed with 150 ml of de-ionized water and dried at 70°C, 2000 Pa for 17 hr. The crude product (16.4 g) was dissolved in 50 ml of N,N-dimethyl formamide and 40 ml of dioxane at 70°C. Gaseous ammonia was introduced into this solution until pH = 9. The resulting suspension was allowed to cool down slowly. The suspension was stirred at 0°C. The solid was filtered off under suction, firstly washed with 25 ml of dioxane and thereafter with 25 ml of ethanol. Then the solid was dried at 50°C, 2000 Pa for 23 hr. The resulting ammonium salt (10.4 g, 17.5 mmol) was suspended in 50 ml of methanol and thereafter 6.5 ml (35 mmol) of a 5.4 N sodium methylate solution were added. The solution was heated (reflux) for 3 hr, cooled down slowly to 20°C and then to 0°C. The solid was separated by filtering, washed with 10 ml of ice-cold methanol and dried at 70°C, 2000 Pa for 17 hr. There were obtained 6.9 g (41% of theory) of 5-methyl-pyridine-2-sulfonic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide sodium salt (1:2) with a HPLC purity of 98.2% (w/w).

Example 10

6.2 g of sodium hydroxide were added to 15 g (26 mmol) of 5-isopropyl-pyridine-2-sulfonic acid [6-chloro-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amid and 75 ml of ethylene glycol. The mixture was heated to 85°C for 5 hr. Then 55 ml of de-ionized water were added and thereafter 55 ml of 3 N hydrochloric acid were added dropwise. The mixture was allowed to cool down to 20°C and was stirred for 1 hr. The solid was filtered off and dried at 70°C, 2000 Pa for 18 hr. There were obtained 16.2 g (103%) of 5-isopropyl-pyridine-2-sulfonic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide with a HPLC purity of 92% (w/w). 80 ml of dioxane and 80 ml of ethanol were added to this solid. At a temperature of 60°C, gaseous ammonia was introduced into the liquid until pH = 9 to 10. The resulting suspension was allowed to cool down to 20°C and was stirred at 20°C for 20 hr and thereafter at 0°C for 2.5 hr. Then the solid was filtered off and dried at 70°C, 2000 Pa for 18 hr. There were obtained 14.2 g of mono ammonium salt with a HPLC purity of 96.2% (w/w). The solid was heated (reflux) in 70 ml of methanol, cooled down slowly to 20°C and stirred at 20°C for 19 hr and thereafter at 0°C for 2 hr. Then the solid was filtered off and dried at 70°C, 2000 Pa for 19 hr. There were obtained 11.5 g (66% of theory) of 5-isopropyl-pyridine-2-sulfonic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide sodium salt (1:2) with a HPLC purity of 98.6% (w/w).

CLAIMS

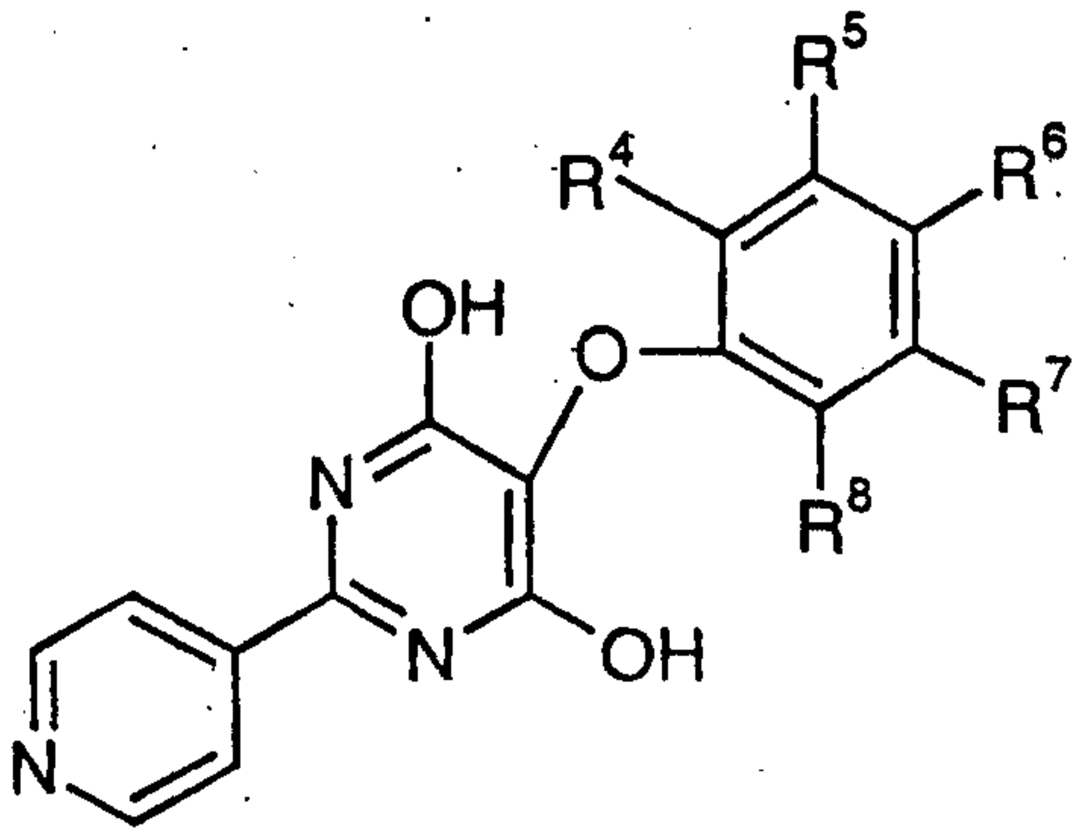
1. A process for the preparation of compounds of formula I



I

wherein R^4 to R^8 represent hydrogen, lower-alkoxy or halogen;

or optionally salts thereof characterized in that the process comprises the reaction of a compound of formula II



II

wherein R^4 to R^8 represent hydrogen, lower-alkoxy or halogen;

or optionally salts thereof with formamide in an aqueous acidic solution in the presence of 15 to 40 mol% iron (II) salts, said mol% being based upon the moles of said compound of formula II, and an oxidizing agent.

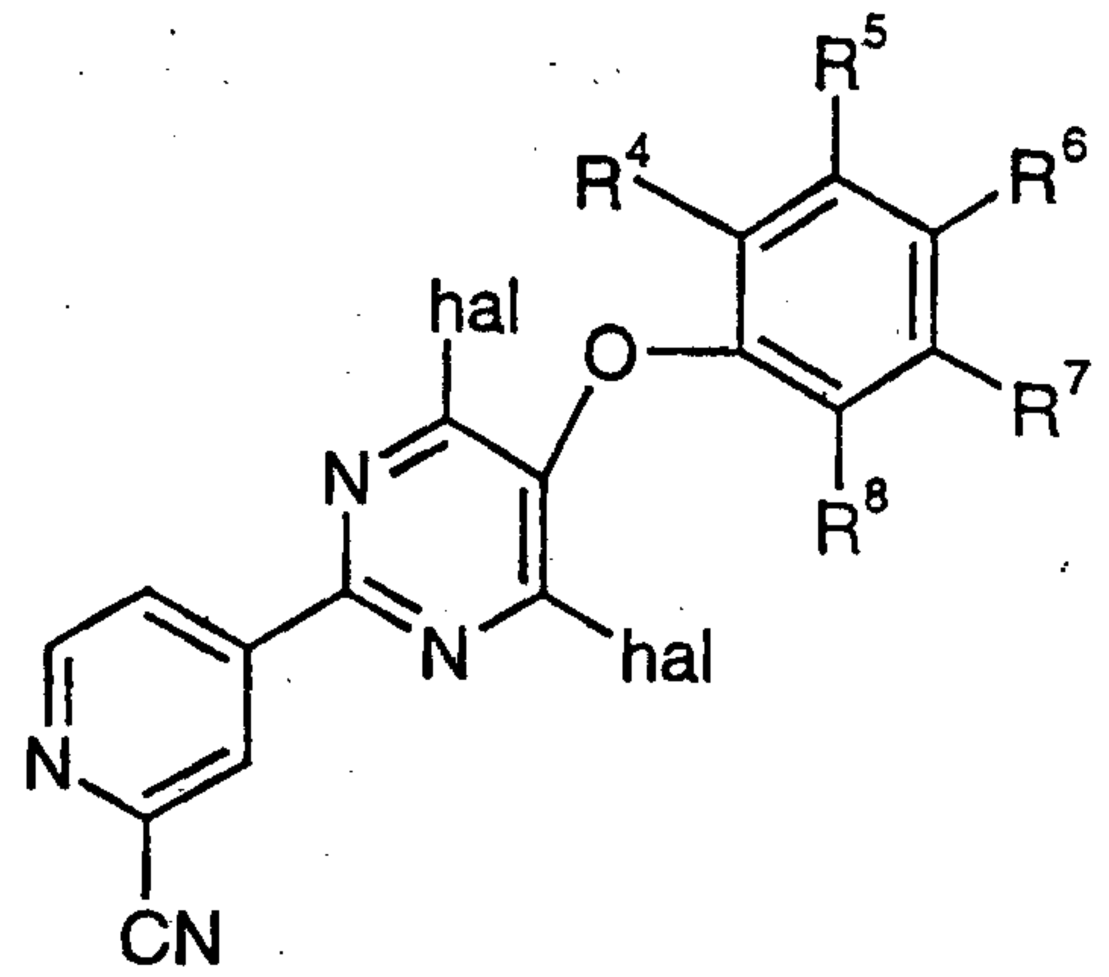
2. The process according to claim 1, characterized in that the reaction is performed with an iron(II)salt comprising an anion selected from the group consisting of chloride, bromide, sulfate, phosphate, tetrafluoroborate and hexafluoroborate.

3. The process according to any of claims 1 to 2, characterized in that the reaction is performed in a temperature range of 0°C to 35°C.

4. A process according to any of claims 1 to 3, characterized in that the reaction is performed in the present of 20 to 30 mol% iron (II) salts, said mol% being based upon the moles of said compound of formula II.

5. The process according to any of claims 1 to 4, characterized in that the oxidizing agent is hydrogen peroxide.

6. A process for the preparation of a compound of formula III



III

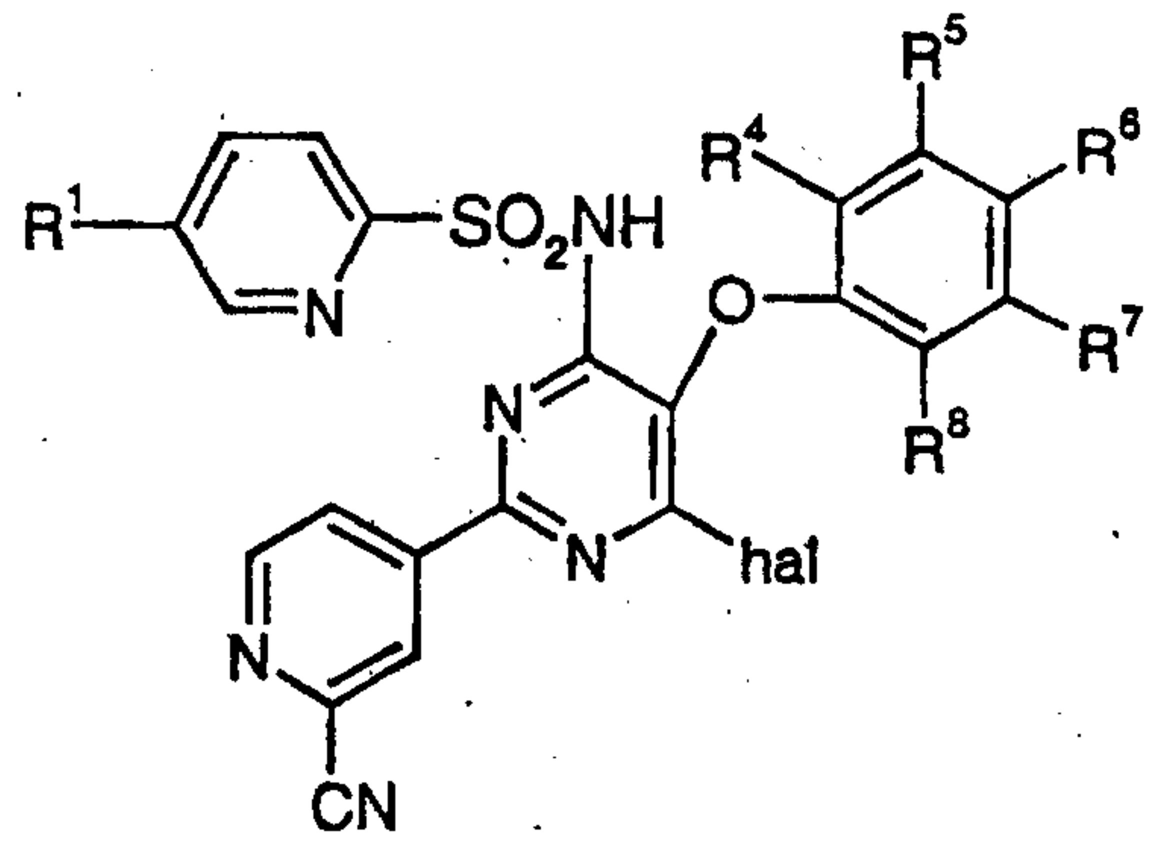
wherein

R^4 to R^8 represent hydrogen, lower-alkoxy or halogen; and
hal represents halogen;

or optionally salts thereof comprising reacting a compound of formula I, as prepared by the process of any one of claims 1 to 5, with a water removing and halogenating agent.

7. The process according to claim 6, characterized in that the water removing and halogenating agent is $POCl_3$.

8. A process for the preparation of a compound of formula IV

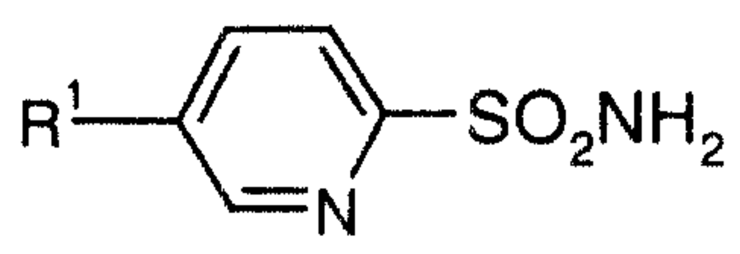


IV

wherein

R^1 represents lower-alkyl;
R^4 to R^8 represent hydrogen, lower-alkoxy or halogen; and
hal represents halogen;

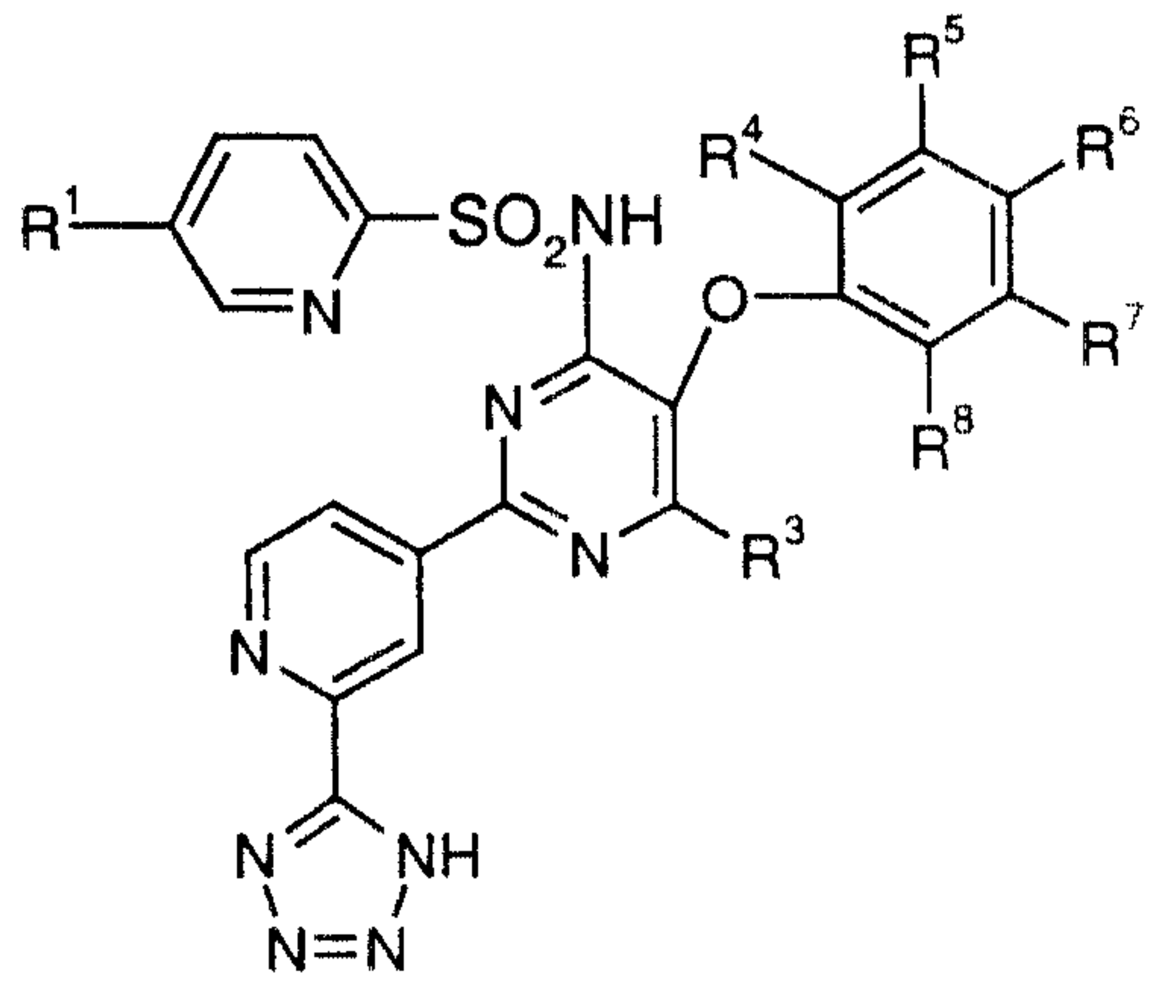
or optionally salts thereof comprising reacting a compound of formula III, as prepared by any one of claims 6 to 7, with a compound of formula V



V

wherein R^1 represents lower-alkyl.

9. A process for the preparation of a compound of formula VI



VI

wherein

R^1 represents lower-alkyl;

R^3 represents $-O-(CR_aR_b)_n-OR^9$;

R^4 to R^8 represent hydrogen, lower-alkoxy or halogen;

R^9 represents hydrogen, aryl, lower-aralkyl, heterocyclyl or a residue $-C(O)NHR^{10}$;

R^{10} represents lower-alkyl, phenyl, substituted phenyl, pyridyl or substituted pyridyl;

R_a and R_b represent hydrogen or lower-alkyl; and

n represents 2, 3 or 4;

or salts thereof comprising reacting a compound of formula IV, as prepared by claim 8, with hydrazine hydrate and a nitrite salt followed by a reaction under basic conditions with a compound of the formula $H-O-C(R_aR_b)_n-OR^9$, wherein R^9, R^{10}, R_a, R_b, and n have the significance as defined above.

10. The process according to claim 9, characterized in that the compound of formula IV is reacted with a compound of the formula $H-O-C(R_aR_b)_n-OR^9$, wherein R^9, R^{10}, R_a, R_b, and n have the significance as defined in claim 9, followed by a reaction with hydrazine hydrate and a nitrite salt.

11. The process according to any of claims 9 or 10, characterized in that R^1 is methyl; R^3 is 2-hydroxy-ethoxy; R^4 to R^7 are hydrogen and R^8 is methoxy.

12. The process according to any of claims 9 or 10, characterized in that R^1 is isopropyl; R^3 is 2-hydroxy-ethoxy; R^4 to R^7 are hydrogen and R^8 is methoxy.

13. A process for the preparation of 4-[4,6-dihydroxy-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carboxylic acid amide characterized in that the process comprises the reaction of 5-(2-methoxy-phenoxy)-2-pyridine-4-yl-pyrimidine-4,6-diole according to any of claims 1-5.

14. A process for the preparation of 5-methyl-pyridine-2-sulfonic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide or salts thereof characterized in that the process comprises the steps of:

a) the reaction of 5-(2-methoxy-phenoxy)-2-pyridine-4-yl-pyrimidine-4,6-diole to 4-[4,6-dihydroxy-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carboxylic acid amide according to any of claims 1 to 5;

b) the reaction of 4-[4,6-dihydroxy-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carboxylic acid amide to 4-[4,6-dichloro-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carbonitrile according to any of claims 6 to 7;

c) the reaction of 4-[4,6-dichloro-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carbonitrile to 5-methyl-pyridine-2-sulfonic acid [6-chloro-2-(2-cyano-pyridine-4-yl)-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide according to claim 8;

d) the reaction of 5-methyl-pyridine-2-sulfonic acid [6-chloro-2-(2-cyano-pyridine-4-yl)-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide to 5-methyl-pyridine-2-sulfonic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide or salts thereof according to any of claims 9 to 10.

15. A process according to claim 14 characterized in that step d) of claim 14 comprises

aa) the reaction of 5-methyl-pyridine-2-sulfonic acid [6-chloro-2-(2-cyano-pyridine-4-yl)-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide to 5-methyl-pyridine-2-sulfonic acid [6-chloro-2-[2-(hydrazino-imino-methyl)-pyridine-4-yl]-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide by reaction with hydrazine, followed by conversion of the reaction product to 5-methyl-pyridine-2-sulfonic acid [6-chloro-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide or salts thereof by reaction with an alkali nitrite; and bb) the reaction of 5-methyl-pyridine-2-sulfonic acid [6-chloro-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide to 5-methyl-pyridine-2-sulfonic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide or salts thereof by reaction with ethylene glycol;

whereas the sequence of the corresponding reactions of steps aa) and bb) may optionally be exchanged.

16. A process for the preparation of 5-isopropyl-pyridine-2-sulfonic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide or salts thereof characterized in that the process comprises the steps of:

a) the reaction of 5-(2-methoxy-phenoxy)-2-pyridine-4-yl-pyrimidine-4,6-diole to 4-[4,6-dihydroxy-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carboxylic acid amide according to any of claims 1 to 5;

b) the reaction of 4-[4,6-dihydroxy-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carboxylic acid amide to 4-[4,6-dichloro-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carbonitrile according to any of claims 6 to 7;

c) the reaction of 4-[4,6-dichloro-5-(2-methoxy-phenoxy)-pyrimidine-2-yl]-pyridine-2-carbonitrile to 5-isopropyl-pyridine-2-sulfonic acid [6-chloro-2-(2-cyano-pyridine-4-yl)-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide according to claim 8;

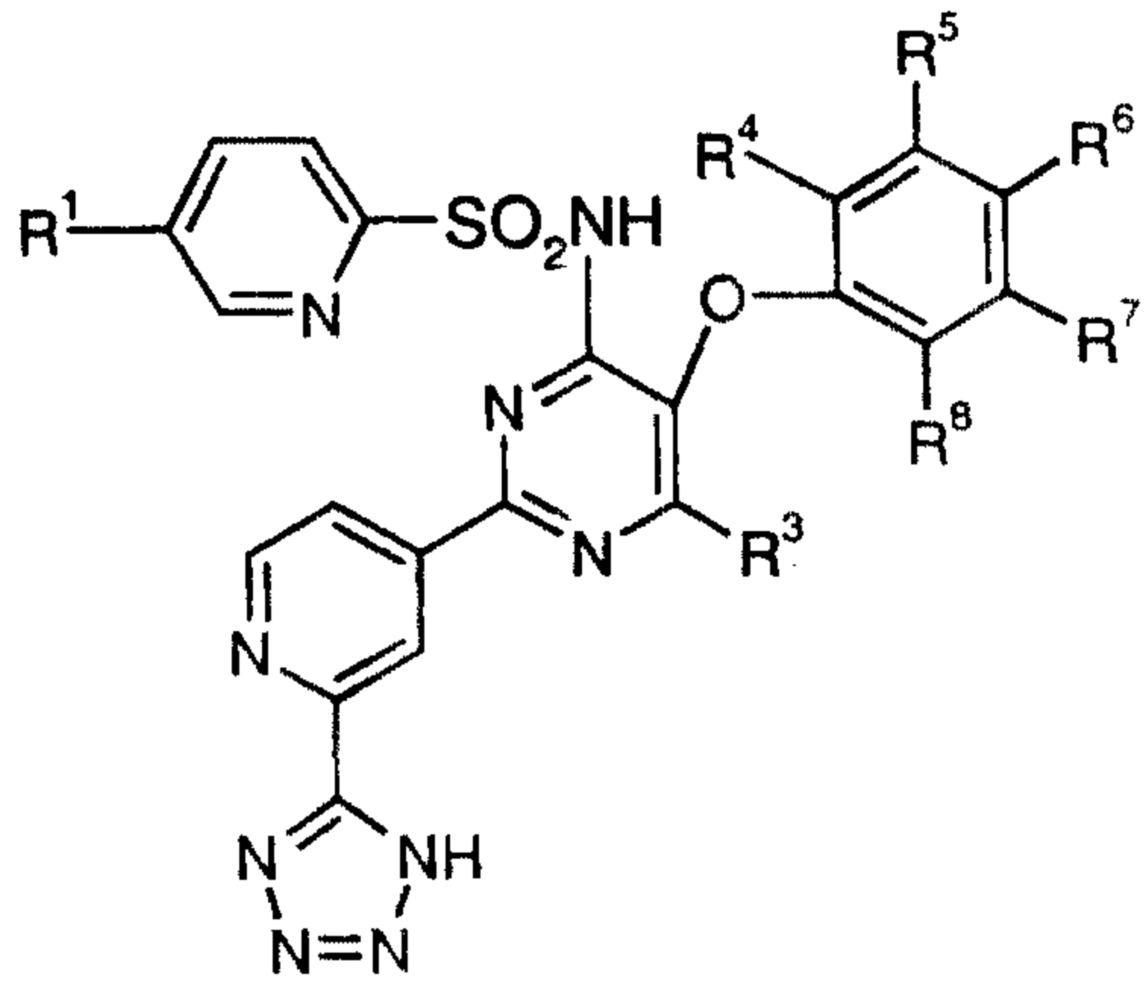
d) the reaction of 5-isopropyl-pyridine-2-sulfonic acid [6-chloro-2-(2-cyano-pyridine-4-yl)-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide to 5-isopropyl-pyridine-2-sulfonic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide or salts thereof according to any of claims 9 to 10.

17. A process according to claim 16 characterized in that step d) of claim 16 comprises

aa) the reaction of 5-isopropyl-pyridine-2-sulfonic acid [6-chloro-2-(2-cyano-pyridine-4-yl)-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide to 5--isopropyl-pyridine-2-sulfonic acid [6-chloro-2-[2-(hydrazino-imino-methyl)-pyridine-4-yl]-5-(2-methoxy-phenoxy)-pyrimidine-4-yl]-amide by reaction with hydrazine, followed by conversion of the reaction product to 5-isopropyl-pyridine-2-sulfonic acid [6-chloro-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide or salts thereof by reaction with an alkali nitrite and bb) the reaction of 5-isopropyl-pyridine-2-sulfonic acid [6-chloro-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide to 5-isopropyl-pyridine-2-sulfonic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide or salts thereof by reaction with ethylene glycol;

whereas the sequence of the corresponding reactions of steps aa) and bb) may optionally be exchanged.

18. Use of the process according to any of claims 1 to 17 for the production of compounds of the formula VI



VI

wherein

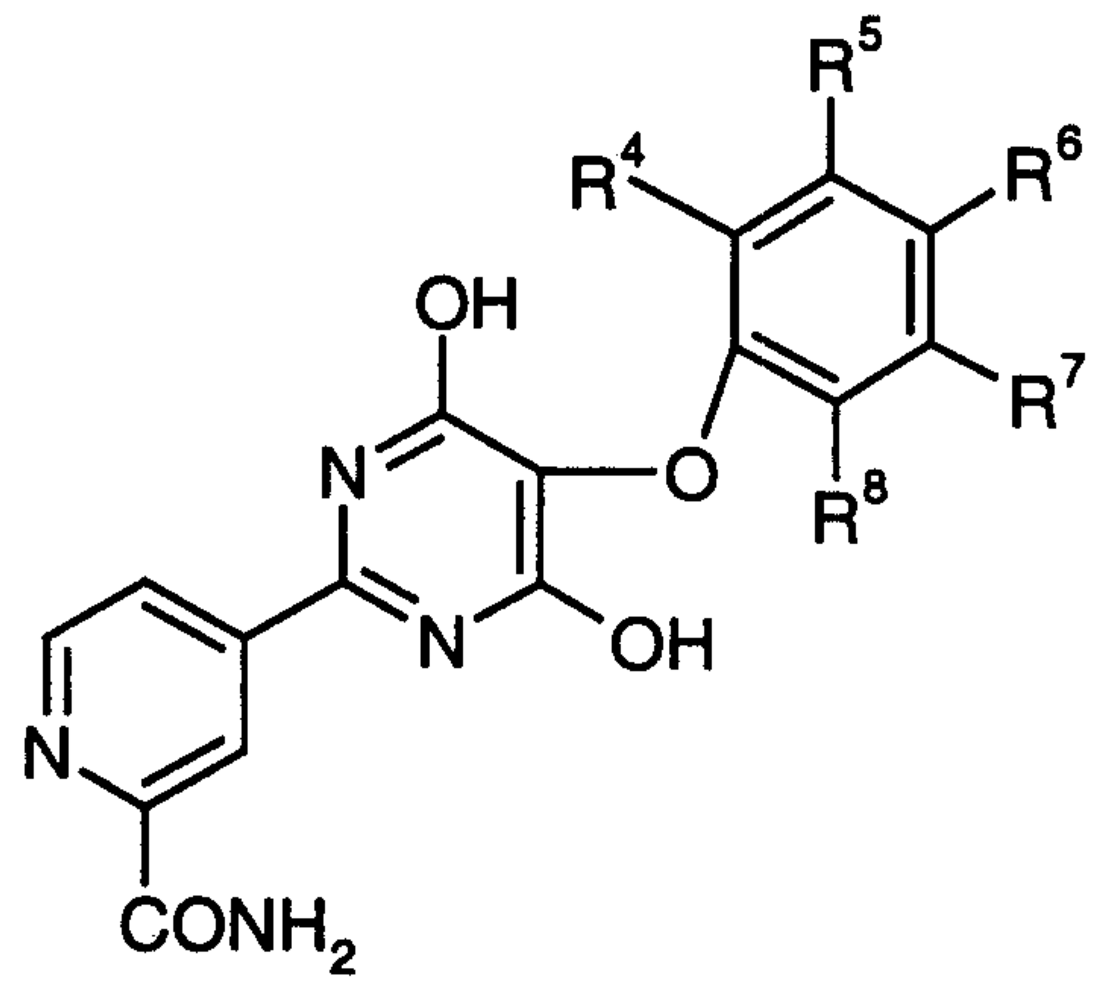
R^1 represents lower-alkyl
R^3 represents $-O-(CR_aR_b)_n-OR^9$;
R^4 to R^8 represent hydrogen, lower-alkoxy or halogen;
R^9 represents hydrogen, aryl, lower-aralkyl, heterocyclyl or a residue $-C(O)NHR^{10}$;
R^{10} represents lower-alkyl, phenyl, substituted phenyl, pyridyl or substituted pyridyl;
R_a and R_b represent hydrogen or lower-alkyl;

and pharmaceutically acceptable salts thereof.

19. The use according to claim 18 for the production of 5-methyl-pyridine-2-sulfonic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide and pharmaceutically acceptable salts thereof.

20. The use according to claim 18 for the production of 5-isopropyl-pyridine-2-sulfonic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazole-5-yl)-pyridine-4-yl]-pyrimidine-4-yl]-amide and pharmaceutically acceptable salts thereof.

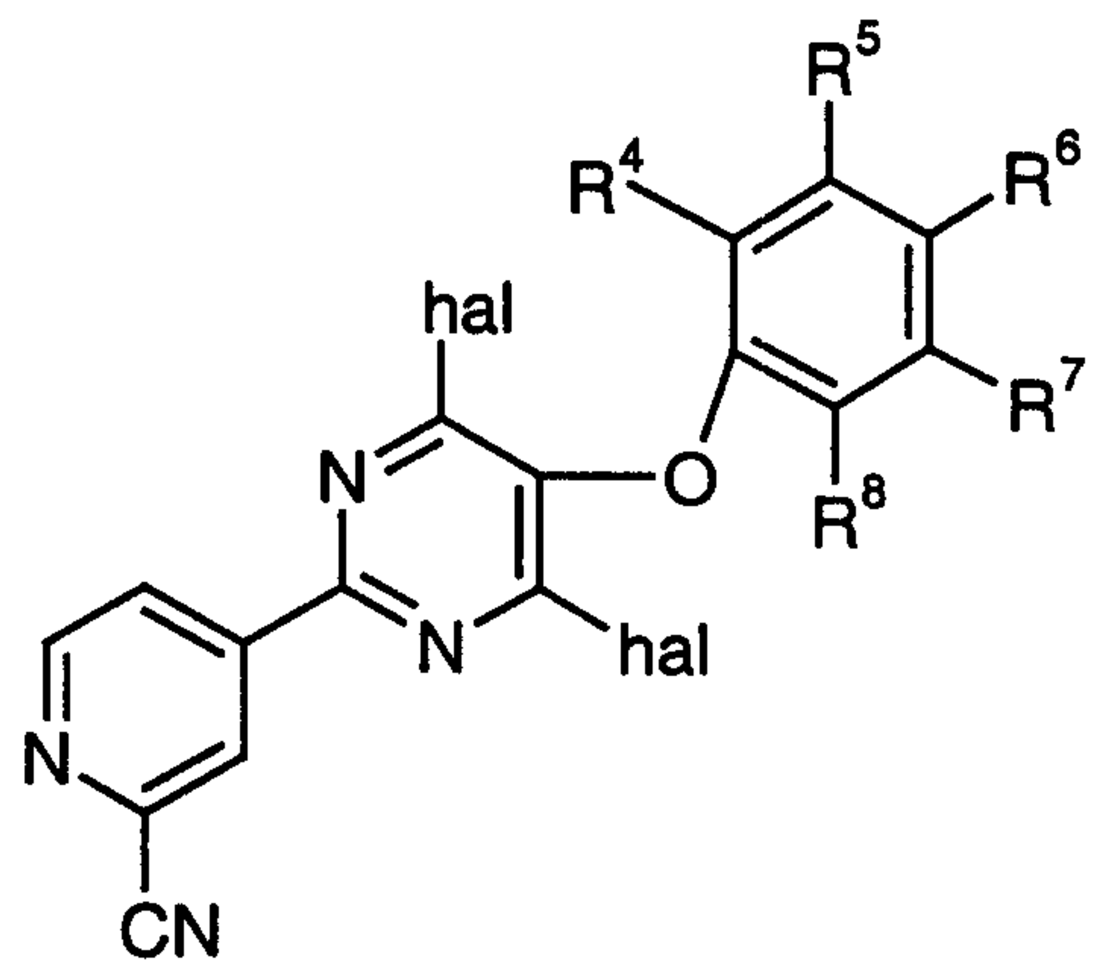
21. A compound of formula I



I

wherein R^4 to R^8 represent hydrogen, lower-alkoxy or halogen.

22. A compound of formula III



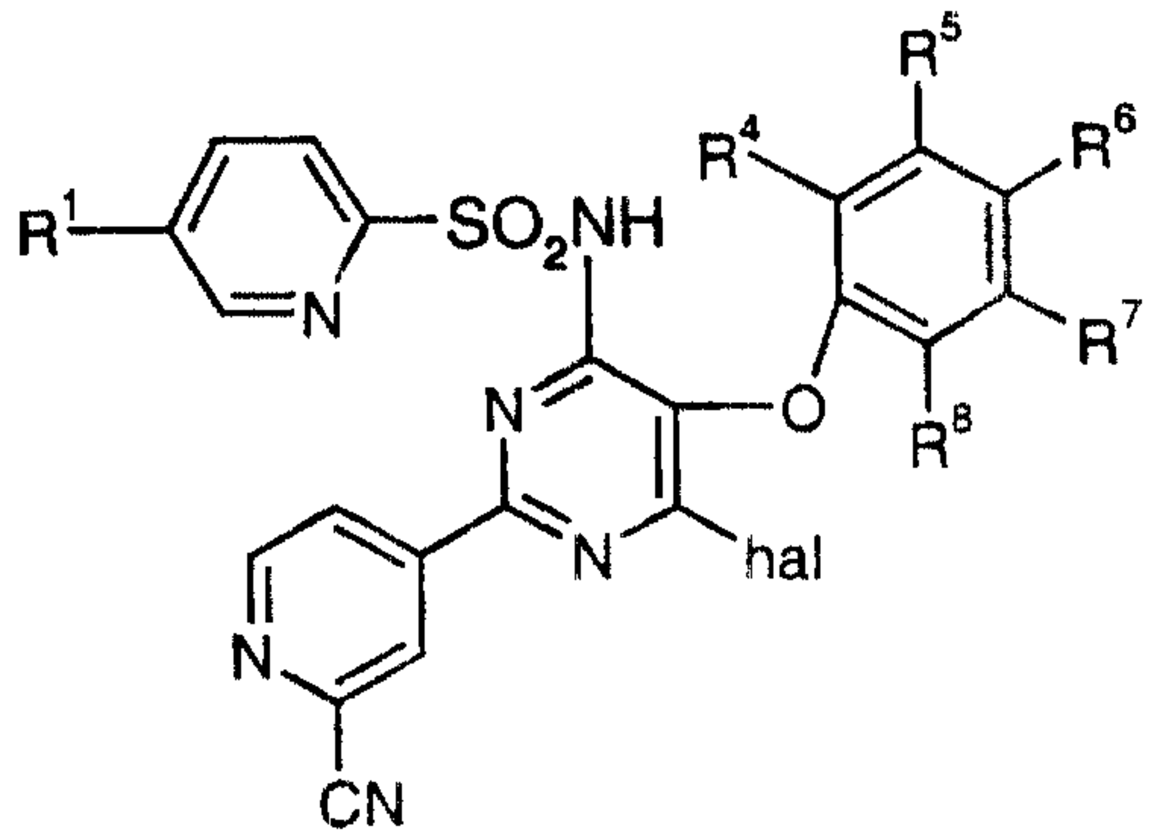
III

wherein

R^4 to R^8 represent hydrogen, lower-alkoxy or halogen; and

hal represents halogen.

23. A compound of formula IV



IV

wherein

R^1 represents lower-alkyl;

R^4 to R^8 represent hydrogen, lower-alkoxy or halogen; and

hal represents halogen.

24. A process according to claim 15 or 17, wherein said alkalinitrite is sodium nitrite.

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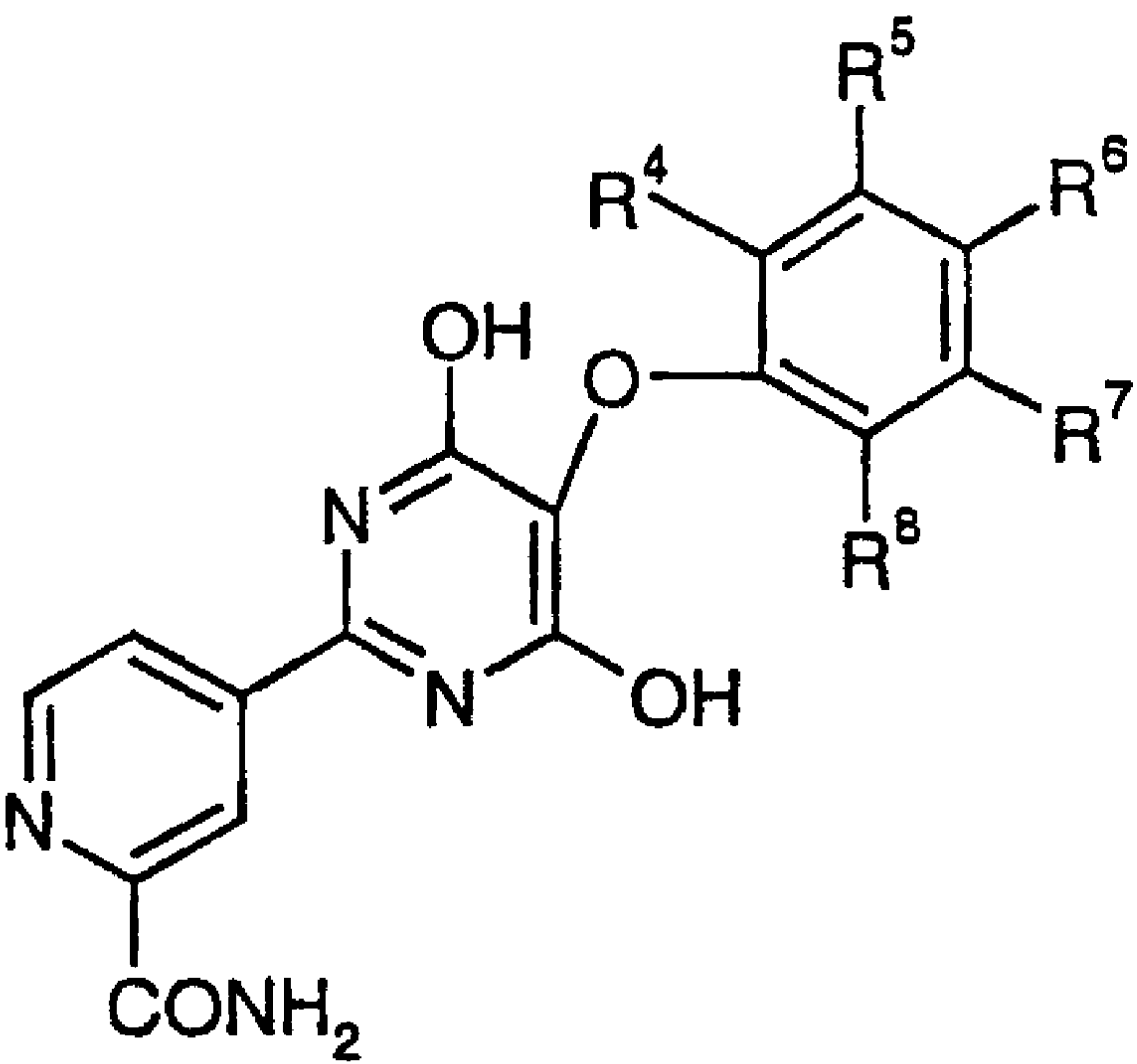

I