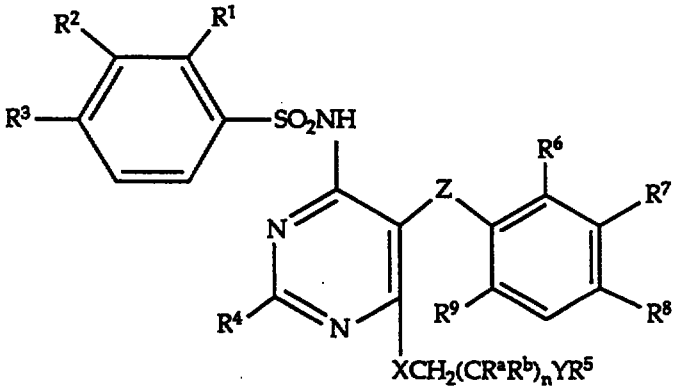
IPOS copy
9604376-5

THIS SHEET HAS BEEN REPLACED

RAN 4019/115

The present invention is concerned with novel sulphonamides and their use as medicaments. In particular, the invention is concerned with novel compounds of the formula



I

wherein

R^1 signifies hydrogen, lower-alkyl, lower-alkoxy, lower-alkylthio, halogen or trifluoromethyl;

R^2 signifies hydrogen, halogen, lower-alkoxy, trifluoromethyl or $-OCH_2COOR^a$; and

R^3 signifies hydrogen, halogen, lower-alkyl, lower-alkylthio, trifluoromethyl, cycloalkyl, lower-alkoxy or trifluoromethoxy; or

R^2 and R^3 together signify butadienyl, methylenedioxy, ethylenedioxy or isopropylidenedioxy;

R^4 signifies hydrogen, lower-alkyl, cycloalkyl, trifluoromethyl, lower-alkoxy, lower-alkylthio, lower-alkylthio-lower-alkyl, hydroxy-lower-alkyl, hydroxy-lower-alkoxy, lower-alkoxy-lower-alkyl, hydroxy-lower-alkoxy-lower-alkyl, hydroxy-lower-alkoxy-lower-alkoxy, lower-alkylsulphinyl, lower-alkylsulphonyl, 2-methoxy-3-hydroxypropoxy, 2-hydroxy-3-phenylpropyl, amino-lower-alkyl, lower-alkylamino-lower-alkyl, di-lower-alkylamino-lower-alkyl, amino, lower-alkylamino, di-lower-alkylamino, arylamino, aryl, arylthio, aryloxy, aryl-lower-alkyl or heterocyclyl;

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

R^5 signifies hydrogen, lower-alkyl, lower-alkanoyl, benzoyl, heterocyclylcarbonyl, heterocyclylmethyl or tetrahydropyran-2-yl;

R^6 to R^9 signify hydrogen, halogen, trifluoromethyl, lower-alkyl, lower-alkoxy, lower-alkylthio, hydroxy, hydroxymethyl, cyano, carboxyl, formyl, methylsulphinyl, methylsulphonyl, methylsulphonyloxy or lower-alkyloxy-carbonyloxy; or

R^7 together with R^6 or R^8 signify butadienyl, methylenedioxy, ethylenedioxy or isopropylidenedioxy;

Z signifies -O-, -S-, ethylene, vinylene, -CO-, $-OCHR^{10}-$ or $-SCHR^{10}$;

R^{10} signifies hydrogen or lower-alkyl;

X and Y each independently signify O, S or NH; or YR^5 also signifies lower-alkylsulphinyl or $-OCH_2CH(OR^c)CH_2OR^d$;

R^a, R^b, R^c and R^d each independently signify hydrogen or lower-alkyl; or R^c and R^d together signify methylene, ethylene or isopropylidene; and

n signifies 1, 2 or 3,

and salts thereof.

The term "lower" used here denotes groups with 1-7 C atoms, preferably 1-4 C atoms. Alkyl, alkoxy and alkylthio groups as well as alkyl groups as components of alkanoyl groups can be straight-chain or branched. Methyl, ethyl, propyl, isopropyl, butyl, sec. and tert.butyl are examples of such alkyl groups. Halogen denotes fluorine, chlorine, bromine and iodine, with chlorine being preferred. Cycloalkyl residues 3 to 8 C atoms, such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. Examples of aryl residues are phenyl and substituted phenyl residues, with halogen, lower-alkyl, lower-alkoxycarboxyl and trifluoromethyl especially coming into consideration as substituents. Examples of heterocyclyl residues are especially substituted, e.g. by lower alkyl, lower alkoxy, halogen, aryl, aryl-lower alkyl mono- or disubstituted, a unsubstituted mono or bicyclic 5- and 6-membered heterocyclic residues with oxygen, nitrogen or sulphur as the hetero atom, such as 2- and 3-furyl, pyrimidinyl, 2-, 3- and 4-pyridyl and pyridyl N-oxide, 1,2- and 1,4-diazinyl, morpholino, 2- and 3-thienyl, isoxazolyl, oxazolyl,

This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

imidazolyl, pyrrolyl, benzofuranyl, benzothienyl, indolyl, purinyl, quinolyl, isoquinolyl and quinazolyl.

The compounds of formula I given above are inhibitors of endothelin receptors. They can accordingly be used for the treatment of disorders which are associated with endothelin activities, especially circulatory disorders such as hypertension, ischaemia, vasospasms and angina pectoris.

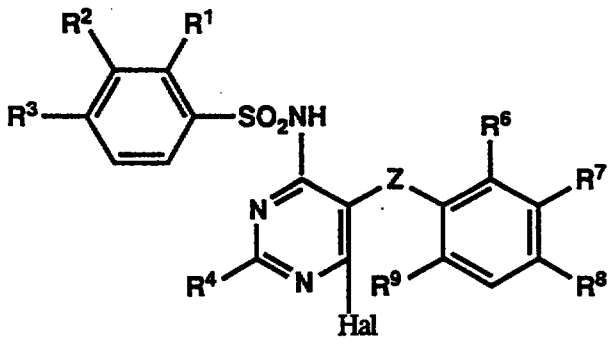
A preferred group of compounds within formula I comprises those in which Z is -O- and, furthermore, those in which R^6 is lower-alkoxy, especially methoxy, and R^7, R^8 and R^9 signify hydrogen; or R^6 and R^8 signify hydrogen, R^7 signifies lower-alkoxy, especially methoxy, and R^9 signifies halogen, especially chlorine.

Preferred substituents R^1 and R^2 are hydrogen and preferred substituents R^3 are lower-alkyl or together with R^2 methylene-dioxy. Preferred substituents R^4 are hydrogen, 2-pyrimidinyl, 2- and 3-furyl, 2- and 3-thienyl, morpholino and p-methoxyphenyl. X is preferably oxygen. Preferred residues YR^5 are hydroxy, lower-alkoxysulphinyl and furoyloxy.

The compounds of formula I can be manufactured by

a) reacting a compound of the formula

This Sheet Has Been Replaced



II

wherein R^1, R^2, R^3, R^4 and R^6 have the significance given above and Hal is halogen,

with a compound of the formula

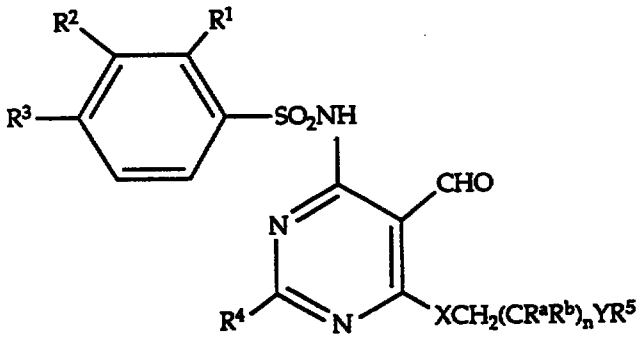
THIS SHEET HAS BEEN REPLACED

$$MX(CH_2)(CR^aR^b)_nYR^5 \qquad III$$

wherein X, Y, n, R^a, R^b and R^5 have the significance given above and M represents an alkali metal,

or

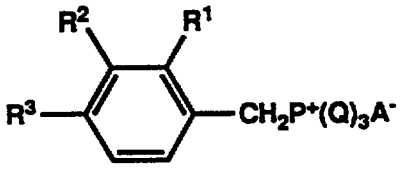
b) reacting a compound of the formula



IV

wherein R^1-R^5, R^a, R^b, X, Y and n have the significance given above,

with a compound of the formula



V

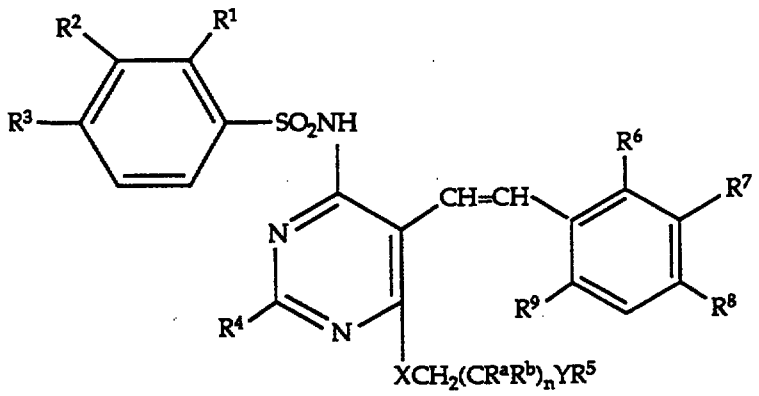
wherein R^6-R^8 have the significance given above; Q is aryl and A^- is an anion,

or

c) hydrogenating a compound of the formula

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

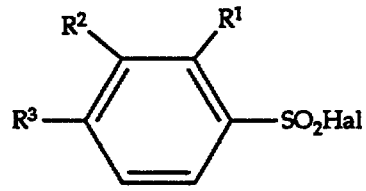


VI

wherein R^1-R^8, R^a, R^b, X, Y and n have the significance given above,

or

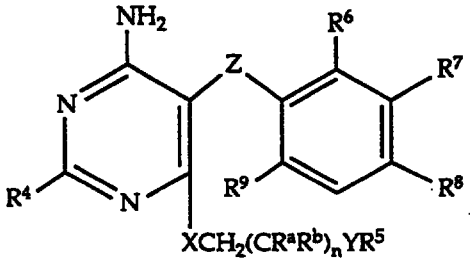
d) reacting a compound of the formula



XIV

with a compound of the formula

This Sheet Has Been Replaced



XV

wherein R^1-R^9, R^a, R^b, X, Y, Z and n have the significance given above,

and, if desired, modifying substituents present in the compound of formula I obtained and/or converting the compound of formula I obtained into a salt.

The reaction of a compound of formula II with a compound of formula III is conveniently carried out using the glycol corresponding to the compound III, e.g. in ethylene glycol when n = 2. The alkali metal M is preferably sodium. The reaction is

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

conveniently carried out while heating, e.g. to 40-120°C. In a preferred embodiment the monosodium salt of ethylene glycol, propylene glycol or butylene glycol is used as the compound of formula III.

The reaction of a compound of formula IV with a compound of formula V can be carried out in a manner known per se under the usual conditions of a Wittig reaction. The aryl residue Q is preferably phenyl; examples of anions A^- are Cl^-. Br^-, HSO_4^- and tosyloxy. The reaction partners are conveniently reacted with each other in the presence of an acid-binding agent, e.g. in the presence of a strong base such as e.g. butyllithium, sodium hydride or the sodium salt of dimethyl sulphoxide, or K tert.-butylate, but preferably in the presence of an optionally lower alkyl-substituted ethylene oxide such as 1,2-butylene oxide, optionally in a solvent, e.g. in an ether such as diethyl ether or tetrahydrofuran or in an aromatic hydrocarbon such as benzene, in a temperature range lying between room temperature and the boiling point of the reaction mixture. In the Wittig reaction interfering reactive groups in the reaction partners, such as carboxyl or amino, are conveniently intermediately protected, e.g. as a carboxylic acid ester or as the tert.butoxycarbonylamino derivative.

The hydrogenation of a compound of formula VI can be carried out in a manner known per se for the hydrogenation of olefinic double bonds, e.g. with hydrogen at normal pressure or elevated pressure in the presence of noble metal catalysts such as Pd, especially Pd on carriers such as Pd/C.

Any hydroxy groups and an amino group that may be present in the substituent R^4 to R^9 of the compound of formula XV are suitably protected when reacting this compound. Hydroxy groups may be protected, e.g., by silyl groups such as dimethyl t-butyl silyl, or acyl groups such as acetyl; and amino groups may be protected by t-butoxy carbonyl a benzyloxy carbonyl. These protecting groups can be inserted and, after the reaction of the compounds XIV and XV, be cleaved by methods known in the art.

THIS SHEET HAS BEEN REPLACED

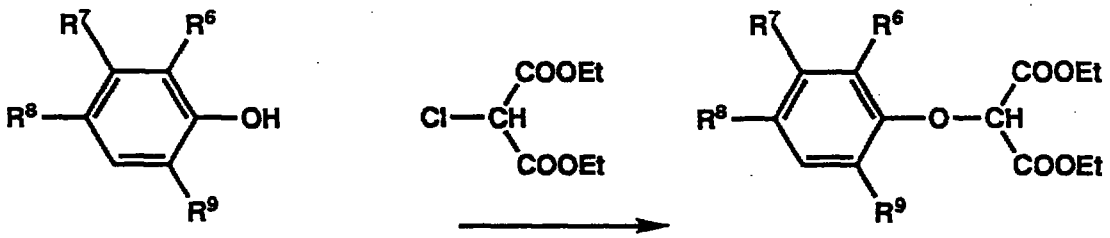
Substituents present in the thus-obtained compound of formula I can be modified. For example, a hydroxy group YR^5 can be esterified or etherified. A hydroxy group YR^5 can be converted into an ether group, e.g. the tetrahydropyranyl ether, or an ester group, e.g. the acetate, or such groups or ketals, which can be present e.g. as a substituent YR^5, contained in the initially obtained reaction product can be cleaved off in a manner known per se. Methylthio groups can be oxidized to methylsulphinyl or methyl- sulphonyl groups. Furthermore, N-heterocyclic residues such as pyridyl can be oxidized to N-oxides. All of these reactions can be carried out according to methods known per se. The compounds of formula I can be converted into salts, e.g. alkali salts such as Na and K salts, in a manner known per se.

The compounds which are used as starting materials, insofar as they are not known or their preparation is described hereinafter, can be prepared in analogy to known methods or to the methods described hereinafter.

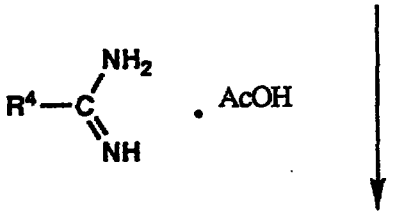
Compounds of formula II can be obtained as illustrated in the following Formula Scheme:

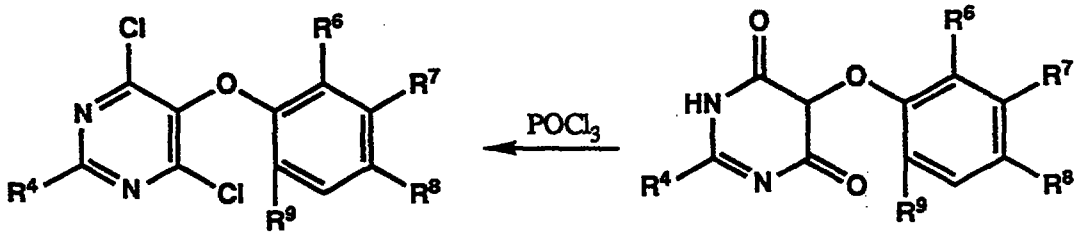
This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

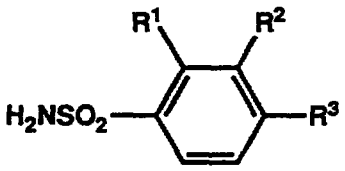


VII VIII





X IX



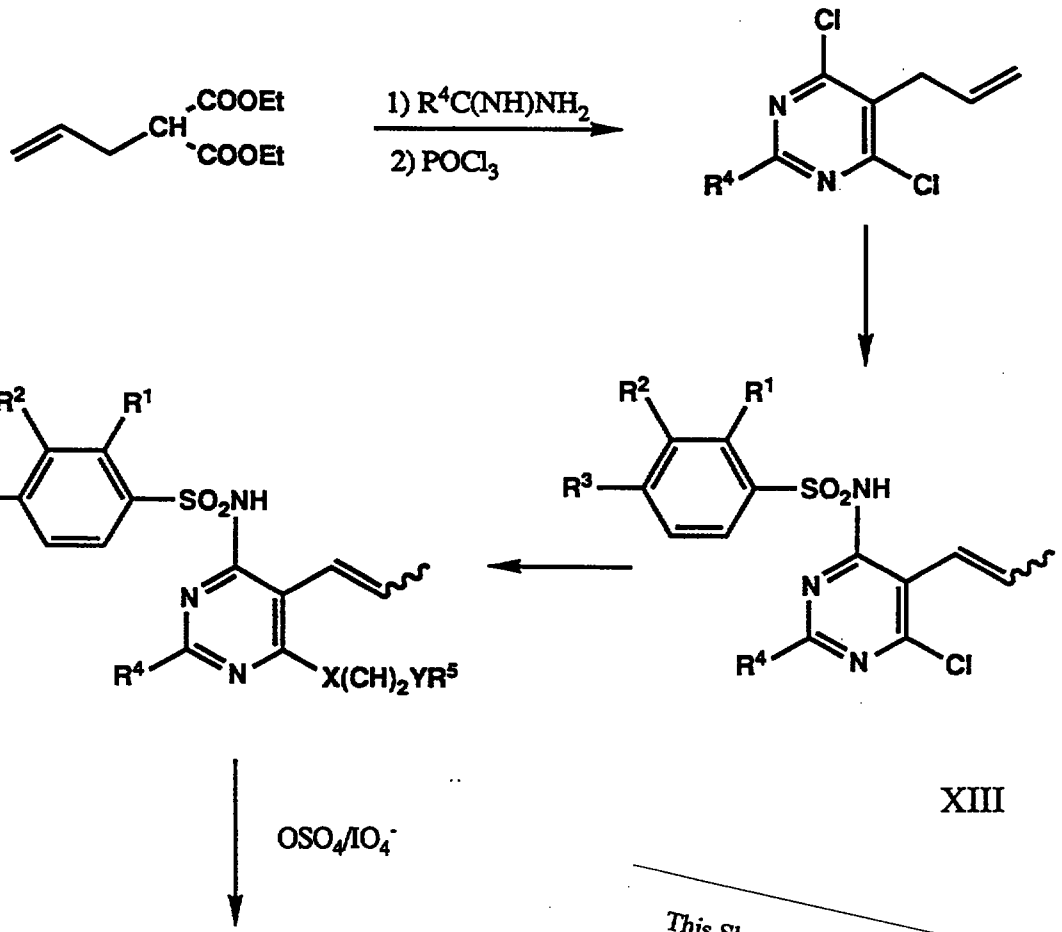
II XI

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

Alkylation of the phenol VII with diethyl chloromalonate yields compound VIII which is condensed with formamidine acetate or a homologous compound such as acetamidine acetate to the pyrimidinedione derivative IX. Using phosphorus oxychloride there is obtained therefrom the dichloro compound X which yields compound II upon reaction with a stoichiometric amount of compound XI. All of these reactions are standard operations and can be carried out under conditions which are usual for such reactions and which are familiar to a person skilled in the art.

Compounds of formula IV can be obtained according to the Reaction Scheme sketched hereinafter:



XIII

IV

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

Condensation of diethyl allyl malonate with formamidine acetate or a R^4-substituted derivative followed by replacement of the hydroxy groups by chlorine in the pyrimidinedione obtained yields the dichloropyrimidine XII which is condensed with a R^1, R^2, R^3-benzenesulphonamide alkali salt with rearrangement of the allyl double bond to the compound XIII. Reaction of compound XIII with a compound III in the manner already described leads to compound XIV. Oxidative cleavage of the double bond of the propenyl side-chain in compound XIV finally yields the aldehyde IV.

The inhibitory activity of the compounds of formula I on endothelin receptors can be demonstrated using the test procedures described hereinafter:

I: Inhibition of endothelin binding to human placenta membranes (see. Life Sci 44:1429 (1989))

Human placenta is homogenized in 5 mM Tris buffer, pH 7.4, which contains 1 mM $MgCl_2$ and 250 mM sucrose. The homogenizate is centrifuged at 4°C and 3000 g for 15 minutes, the supernatant containing the plasma membrane fraction is centrifuged with 72000 g for 30 minutes and the precipitate is washed with 75 mM Tris buffer, pH 7.4, which contains 25 mM $MgCl_2$. Thereafter, precipitate obtained from in each case 10 g of original tissue is suspended in 1 ml of 75 mM Tris buffer, pH 7.4, containing 25 mM $MgCl_2$ and 250 mM sucrose, and freeze-dried at -20°C in 1 ml aliquots.

For the binding assay, the freeze-dried membrane preparations are thawed and, after centrifugation at 20°C and 25000 g for 10 minutes, re-suspended in assay buffer (50 mM Tris buffer, pH 7.4, containing 25 mM $MnCl_2$, 1 mM EDTA and 0.5% of bovine serum albumin). 100 ml of this membrane suspension containing 70 mg of protein are incubated with 50 ml of ^{125}I-endothelin (specific activity 2200 Ci/mMol) in assay buffer (25000 cpm, final concentration 20 pM) and 100 ml of assay buffer containing varying concentrations of test compound. The

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

incubation is carried out at 20°C for 2 hours or at 4°C for 24 hours. The separation of free and membrane-bound radioligands is carried out by filtration over a glass fibre filter.

The inhibitory activity of compounds of formula I determined in this test procedure is given in Table 1 as the IC_{50}, i.e. as the concentration [mM] which is required to inhibit 50% of the specific binding of ^{125}I-endothelin.

Table 1

Compound of Example	IC_{50} [mM]
1	0.115
2	0.100
6	0.200
12	0.125
24	0.073
25	0.050
27	0.099

II. Inhibition of endothelin-induced contractions in isolated rat aorta rings

Rings with a length of 5 mm were cut out from the thorax aorta of adult Wistar-Kyoto rats. The endothelium was removed by lightly rubbing the internal surface. Each ring was immersed at 37°C in 10 ml of Krebs-Henseleit solution in an isolated bath while gassing with 95% O_2 and 5% CO_2. The isometric stretching of the rings was measured. The rings were stretched to a pretension of 3 g. After incubation for 10 minutes with the test compound or vehicle cumulative dosages of endothelin-1 were added. The activity of the test compound was determined by calculating the dosage ratios, i.e. the shift to the right (shift to higher values) of the EC_{50} of endothelin induced by 100 mM of

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

test compound, with EC_{50} denoting the endothelin concentration required for a half-maximum contraction. The greater this dosage ratio is the more potent the test compound is in inhibiting the biological activity of endothelin-1. The EC_{50} of endothelin in the absence of test compounds is 0.3 nM.

The thus-obtained values for the shift to the right of the EC_{50} of endothelin with compounds of formula I are given in Table 2.

This Sheet Has Been Replaced

Table 2

Compound of Example	Dosage ration (Shift to the right)
1	165
6	395
24	257
25	238

III. The inhibitory activity of the compounds of formula I on vasoconstriction can be observed in vivo in rats in the test procedure described hereinafter:

Rats were anaesthetized with Na thiobutabarbital (100 mg/kg i.p.). A catheter for measuring the systemic arterial blood pressure was placed through the femoral artery and a catheter was placed in the vena cava via the femoral vein for injection of the test compounds. A Doppler sonde was placed around the left renal artery and attached to a Doppler measuring apparatus. A renal ischaemia was produced by pinching off the left renal artery at its point of exit for 45 minutes. 10 minutes prior to the induction of the ischaemia he test compounds were administered intraarterially (i.a.) in dosages of 5 mg/kg or intravenously (i.v.) in dosages of 10 mg/kg. In control tests the

THIS SHEET HAS BEEN REPLACED

renal perfusion was reduced by 43 ± 4% compared to the pre-ischaemic value.

The results obtained with two compounds of formula I are given in Table 3.

Compound of Example	% Decrease in renal perfusion
1	13.4 ± 5.2
6	11.7 ± 4.7

On the basis of their capability of inhibiting endothelin binding, the compounds of formula I can be used as medicaments for the treatment of disorders which are associated with vasoconstriction of increasing occurrences. Examples of such disorders are high blood pressure, coronary disorders, cardiac insufficiency, renal and myocardial ischaemia, renal insufficiency, dialysis, cerebral ischaemia, cardiac infarct, migraine, subarachnoid haemorrhage, Raynaud syndrome and pulmonary high pressure. They can also be used in atherosclerosis, the prevention of restenosis after balloon-induced vascular dilation, inflammations, gastric and duodenal ulcers, ulcus cruris, gram-negative sepsis, shock, glomerulonephtritis, renal colic, glaucoma, asthma, in the therapy and prophylaxis of diabetic complications and complications in the administration of cyclosporin, as well as other disorders associated with endothelin activities.

The compounds of formula I can be administered orally, rectally, parentally, e.g. intravenously, intramuscularly, subcutaneously, intrathecally or transdermally, or sublingually or as opththalmological preparations, or as an areosol. Capsules, tablets, suspensions or solutions for oral administration,

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

suppositories, injection solutions, eye drops, salves or spray solutions are examples of application forms.

Intravenous, intramuscular or oral application is a preferred form of use. The dosages in which the compounds of formula I are administered in effective amounts depend on the nature of the specific active ingredient, the age and the requirements of the patient and the mode of application. In general, dosages of about 0.1-100 mg/kg body weight per day come into consideration. The preparations containing the compounds of formula I can contain inert or also pharmacodynamically active additives. Tablets or granulates e.g. can contain a series of binders, fillers, carriers or diluents. Liquid preparations can be present, 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, flavour-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 organic or inorganic substances, e.g. water, gelatine, lactose, starch, magnesium stearate, talc, gum arabic, polyalkylene glycols and the like. It is a prerequisite that all adjuvants used in the manufacture of the preparations are non-toxic.

The following Examples illustrate the invention in more detail. Of the abbreviations used therein THF signifies tetrahydrofuran; DMSO signifies dimethyl sulphoxide; MeOH signifies methanol; b.p. signifies boiling point; and m.p. signifies melting point.

This Sheet Has Been Replaced



Example 1

a) 886 mg of p-t-butyl-N-[6-chloro-5-(o-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide were added to a sodium glycolate solution from 3.0 g of ethylene glycol and 138 mg of

This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

sodium. The reaction mixture was stirred at 95°C under argon for 4 hours. Thereafter, the ethylene glycol was distilled off and the residue was partitioned between ethyl acetate and 1N hydrochloric acid. The organic phase was dried and the solvent was distilled off. The residue was crystallized from diisopropyl ether. There were obtained 870 mg of p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide. M.p. 143-148°C.

b) 775 mg of the previously obtained sulphonamide were dissolved in 20 ml of warm ethanol. The solution was treated with a stoichiometric amount of sodium ethylate, thereafter the ethanol was distilled off until a precipitate formed. 3 ml of isopropyl ether were added to complete the precipitation. There were obtained 775 mg of p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide sodium, m.p. >250°C.

The starting material was prepared as follows:

c) 25 g of guaiacol and 37 g of dimethyl chloromalonate were added dropwise in succession to a sodium methylate solution from 150 ml of methanol and 4.6 g of sodium. The suspension was stirred at 45°C for 1 hour with the exclusion of moisture, thereafter the methanol was distilled off. The residue was taken up in 200 ml of toluene and washed with water, 1% sodium hydroxide solution and water until the organic phase was colourless. After drying and evaporating the solvent the residue was distilled. There were obtained 39.5 g of dimethyl (o-methoxyphenoxy)malonate. B.p. 128°C/7 Pa.

d) 5.5 g of formamidine acetate and 12.7 g of dimethyl (o-methoxyphenoxy)malonate were added while cooling with ice to a sodium methylate solution from 150 ml of methanol and 3.5 g of sodium. The reaction mixture was stirred at 0-5°C for 1 hour with the exclusion of moisture, then at room temperature for 2 hours. Thereafter, the solvent was distilled off, the residue was taken up in 100 ml of water, the aqueous phase was

THIS SHEET HAS BEEN REPLACED

extracted with toluene and the organic phases were discarded. The aqueous phase was acidified, whereby 5-(o-methoxyphenoxy)-6-hydroxy-4(3H)-pyrimidinone separated.

e) 9.4 g of the previously obtained pyrimidinone were suspended in 20 ml of acetonitrile and treated with 12 g of collidine. Thereafter, 5 ml of $POCl_3$ in 15 ml of acetonitrile were added dropwise with the exclusion of moisture. The reaction mixture was stirred at reflux temperature for 8 hours, thereafter the solvent and excess reagent were distilled off. The residue was taken up in methylene chloride and washed with water, saturated sodium hydrogen carbonate solution and saturated sodium chloride solution. The solution was concentreated and passed over a short silica gel column with methylene chloride as the elution agent. The eluate was concentrated, the residue was recrystallized from ethanol/hexane. There were obtained 8.5 g of 4,6-dichloro-5-(o-methoxyphenoxy)pyrimidine, m.p. 79-80°C.

f) 0.8 g of 4,6-dichloro-5-(o-methoxyphenoxy)pyrimidine and 1.5 g of p-t-butylsulphonamide K in 3 ml of dry dimethyl sulphoxide were heated to 120°C under argon for 1.5 hours. Thereafter, the dimethyl sulphoxide was distilled off, the residue was partitioned between ethyl acetate and 1N hydrochloric acid and the organic phase was washed neutral. The organic phase was dried, the solvent was evaporated and the residue was treated with 3 ml of methanol. There were obtained 950 mg of p-t-butyl-N-[6-chloro-5-(o-methoxyphenoxy)-4-pyrimidinyl]benzene-sulphonamide, m.p. 152°C.

This Sheet Has Been Replaced



Example 2

In analogy to Example 1, paragraph a), from p-isopropyl-N-[6-chloro-5-(o-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide there was obtained N-[6-(hydroxyethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, m.p. 142-143°C. The compound was converted in analogy to Example 1,

THIS SHEET HAS BEEN REPLACED

paragraph b), in almost quantitative yield into the water-soluble sodium salt.

The starting material was obtained in analogy to Example 1, paragraph f), by reacting 540 mg of 4,6-dichloro-5-(o-methoxyphenoxy)pyrimidine and 360 mg of p-isopropylbenzenesulphonamide potassium.

Example 3

In analogy to Example 1, paragraph a), from N-[6-chloro-5-(o-tolyloxy)-4-pyrimidinyl]-p-t-butylsulphonamide there was obtained p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-tolyloxy)-4-pyrimidinyl]benzenesulphonamide. M.p. 190-192°C.

The starting material was prepared as follows:

Diethyl bromomalonate was converted with sodium o-cresolate into diethyl (o-tolyloxy)malonate, b.p. 120°C/7 Pa, in analogy to Example 1, paragraph c).

In analogy to Example 1, paragraph d), from the foregoing malonic ester there was obtained 5-(o-tolyloxy)-6-hydroxy-4(3H)-pyrimidinone from which there was obtained in analogy to Example 1e) 4,6-dichloro-(o-tolyloxy)pyrimidine, m.p. 78-79°C (ethanol/hexane). Reaction of the latter compound with p-t-butylsulphonamide potassium finally yielded N-[6-chloro-5-(o-tolyloxy)-4-pyrimidinyl]-p-t-butylsulphonamide.

Example 4

In analogy to Example 1, paragraph a), from p-t-butyl-N-[2-chloro-5-(o,-chlorophenoxy)-4-pyrimidinyl]benzenesulphonamide there was obtained p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-chlorophenyloxy)-4-pyrimidinyl]benzenesulphonamide, m.p. 178-179°C (from diisopropyl ether).

The starting material was prepared as follows:

This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

In analogy to Example 1, paragraph e), from diethyl bromomalonate and sodium o-chlorophenolate there was obtained diethyl (o-chlorophenoxy)malonate as a colourless liquid which was converted in analogy to Example 1, paragraph d), into 5-(o-chlorophenoxy)-6-hydroxy-4(3H)pyrimidinone. From the latter compound there was obtained in analogy to Example 1, paragraph e), 4,6-dichloro-5-(o-chlorophenoxy)pyrimidine, m.p. 76-77°C (from ethanol/hexane), and from this by reaction with p-t-butylsulphonamide potassium there was obtained p-t-butyl-N-[2-chloro-5-(o-chlorophenoxy)-4-pyrimidinyl]benzenesulphonamide, m.p. 186-187°C (from methanol).

Example 5

In an analogy to Example 1, paragraph a), from N-[6-chloro-5-(o-chlorophenoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide there was obtained N-[6-(2-hydroxyethoxy)-5-(o-chlorophenoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, m.p. 174-175°C (from ethyl acetate).

The starting material was prepared in analogy to Example 1, paragraph f), from 4,6-dichloro-5-(o-chlorophenoxy)pyrimidine and p-isopropylbenzenesulphonamide potassium. M.p. 174-176°C (from methanol).

Example 6

In analogy to Example 1, paragraph a), from p-t-butyl-N-[6-chloro-5-(m-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide there was obtained p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(m-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide, m.p. 165-167°C (from diisopropyl ether).

The potassium salt, m.p. 213-215°C, was obtained by reacting the sulphonamide with 0.5N KOH in ethanol.

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

The sodium salt was prepared in analogy to Example 1, paragraph b). M.p. 265-270°C (from diisopropyl ether).

The starting material was prepared as follows:

Diethyl bromomalonate was converted with sodium m-methoxyphenolate in analogy to Example 1, paragraph c), into diethyl (m-methoxyphenoxy)malonate, colourless liquid. B.p. 143°C/0.05 Torr. The thus-obtained malonic ester was converted in analogy to Example 1, paragraph d), into 5-(m-methoxyphenoxy)-6-hydroxy-4(3H)-pyrimidinone from which in analogy to Example 1, paragraph e), there was prepared 4,6-dichloro-5-(m-methoxyphenoxy)pyrimidine, m.p. 109-110°C. Reaction of the last-named compound with p-t-butylbenzenesulphonamide potassium yielded p-t-butyl-N-[6-chloro-5-(m-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide, m.p. 152°C (from methanol).

Example 7

In analogy to Example 1, paragraph a), from p-t-butyl-N-[6-chloro-5-phenoxy-4-pyrimidinyl]benzenesulphonamide there was obtained p-t-butyl-N-[6-(2-hydroxyethoxy)-5-phenoxy-4-pyrimidinyl]benzenesulphonamide, m.p. 165-167°C (from diisopropyl ether).

The starting material was prepared as follows:

Diethyl bromomalonate was converted with sodium phenolate in analogy to Example 1, paragraph c), into diethyl phenoxymalonate, b.p. 140°C/0.05 Torr. From the malonic ester there was obtained in analogy to Example 1, paragraph e), 5-phenoxy-6-hydroxy-4(3H)pyrimidinone and from this there was obtained in analogy to Example 1, paragraph e), 4,6-dichloro-5-phenoxypyrimidine, m.p. 89-90°C (from ethanol/hexane). Reaction of the last-named compound with p-t-butylbenzenesulphonamide potassium yielded p-t-butyl-N-[6-chloro-5-phenoxy-4-pyrimidinyl]-benzenesulphonamide, m.p. 143-144°C.

This Sheet Has Been Replaced



This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

Example 8

In analogy to Example 1, paragraph a), from 4,6-dichloro-5-(p-methoxyphenoxy)-4-pyrimidine there was obtained p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(p-methoxyphenoxy)-4-pyrimidinyl]-benzenesulphonamide, m.p. 141-142°C.

The starting material was prepared in analogy to Example 1, paragraph c), d) and e), by reacting diethyl bromomalonate with sodium p-methoxyphenolate to diethyl (p-methoxyphenoxy)malonate, b.p. 140°C/7 Pa, and reaction further to 5-(p-methoxyphenoxy)-6-hydroxy-4(3H)pyrimidinone and, respectively, 4,6-dichloro-5-(p-methoxyphenoxy)-4-pyrimidine, m.p. 107-108°C (from ethanol/hexane).

Example 9

In analogy to Example 1, paragraph a), from p-t-butyl-N-[6-chloro-5-(o-ethoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide there was obtained p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-ethoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide, m.p. 120-121°C (from diisopropyl ether).

The starting material was prepared from dimethyl chloromalonate in analogy to Example 1, paragraph c), d), e) and f), via the following intermediates:

Dimethyl (o-ethoxyphenoxy)malonate, b.pt. 150°C/7 Pa,
5-(o-ethoxyphenoxy)-6-hydroxy-4(3H)pyrimidinone,
4,6-dichloro-5-(o-ethoxyphenoxy)-4-pyrimidine,
5-p-t-butyl-N-[6-chloro-5-(o-ethoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide, m.p. 162-163°C (from methanol).

Example 10

In analogy to Example 1, paragraph a), from p-(2,2-dimethylpropyl)-N-[6-chloro-5-(o-methoxyphenoxy)-4-pyrimi-

THIS SHEET HAS BEEN REPLACED

dinyl]benzenesulphonamide there was obtained p-(2,2-dimethylpropyl)-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide, m.p. 136-137°C (from diisopropyl ether).

The starting material was prepared in analogy to Example 1, paragraph c), d) and f), via the following intermediates:

p-(2,2-Dimethylpropyl)benzenesulphonyl chloride, b.p. 105°C/0.005 Torr.,

2,2-dimethyl-p-(2,2-dimethylpropyl)benzenesulphonamide potassium,

p-(2,2-dimethylpropyl)-N-[6-chloro-5-(o-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide, m.p. 164-165°C (from methanol).

Example 11

In analogy to Example 1, paragraph a), from N-[6-chloro-2-methyl-5-(m-methoxyphenoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, m.p. 152-153°C, there was obtained p-isopropyl-N-[6-(2-hydroxyethoxy)-2-methyl-5-(m-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide, m.p. 129-130°C (from diisopropyl ether).

The starting material was prepared as follows:

In analogy to Example 1, paragraph e), using acetamidine hydrochloride in place of formamidine acetate, dimethyl (m-methoxyphenoxy)malonate was converted into 5-(m-methoxyphenoxy)-2-methyl-6-hydroxy-4(3H)pyrimidinone. Therefrom there was prepared in analogy to Example 1, paragraph e), 4,6-dichloro-2-methyl-5-(m-methoxyphenoxy)pyrimidine and therefrom with p-isopropylbenzenesulphonamide potassium there was prepared N-[6-chloro-2-methyl-5-(m-methoxyphenoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, m.p. 152-153°C (from methanol).

This Sheet Has Been Replaced

This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

Example 12

In analogy to Example 1, paragraph a), from N-[6-chloro-5(-(o-methoxy)-2-phenyl-4-pyrimidinyl]-p-isopropylbenzene-sulphonamide there was obtained N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-phenyl-4-pyrimidinyl]-p-isopropylbenzene-sulphonamide.

The starting material was prepared in analogy to Example 1, paragraph d), e) and f), from dimethyl (o-methoxyphenoxy)malonate via 5-(o-methoxy)-2-phenyl-6-hydroxy-4(3H)-pyrimidinone, 4,6-dichloro-2-phenyl-5-(o-methoxyphenoxy)pyrimidine, m.p. 135-136°C, and N-[6-chloro-5-(o-methoxy)-2-phenyl-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, m.p. 190-191°C (from methanol).

Example 13

1.3 ml of 1.6M butyllithium in hexane were added at -20°C to 780 mg of benzyltriphenylphosphonium chloride in 10 ml of abs. tetrahydrofuran. The reaction mixture was stirred at -20°C for 15 minutes and thereafter treated with 280 mg of 2-[(5-formyl-6-p-toluenesulphonamido-4-pyrimidinyl)oxy]ethyl acetate. The reaction mixture was left to warm to room temperature and was stirred at room temperature for 2 hours. The tetrahydrofuran was distilled off under reduced pressure, the residue was dissolved in ethyl acetate and the organic phase was washed with water and saturated sodium chloride solution, dried and evaporated. The residue was chromatographed over silica gel with methylene chloride/ethyl acetate (9:1 and 8:2). There were obtained 160 mg of 2-[[5-[(E/Z)-styryl]-6-p-toluenesulphonamido-4-pyrimidinyl]oxy]ethyl acetate, m.p. 146-156°C.

The starting material was prepared as follows:

From 5-allyl-4,6-dichloropyrimidine-p-toluensulphonamide potassium there was prepared N-[6-chloro-5-[(E/Z)-propenyl]-4-pyrimidinyl]-p-toluenesulphonamide and therefrom by reaction

THIS SHEET HAS BEEN REPLACED

with ethylene glycol sodium there was prepared N-[6-(2-hydroxy-ethoxy)-5-[(E/Z)-propenyl]-4-pyrimidinyl]-p-toluenesulphonamide, m.p. 130-132°C. Reaction with acetic anhydride in the presence of pyridine in tetrahydrofuran yielded 2-[[5-[(E/Z)-propenyl]-6-p-toluenesulphonamido-4-pyrimidinyl]oxy]ethyl acetate, m.p. 160-163°C.

390 mg of the previously named compound and 8 mg of osmium tetroxide were added to a mixture of 2.5 ml of water and 7 ml of dioxan and then 450 mg of sodium m-periodate were added at room temperature within 30 minutes and after stirring at room temperature for 2 hours a further 8 mg of osmium tetroxide were added. The reaction mixture was stirred for a further 5 hours and worked-up, whereby 2-[(5-formyl-6-p-toluenesulphonamido-4-pyrimidinyl)oxy]ethyl acetate, m.p. 130-144°C (after crystallization from ethyl acetate and diethyl ether), was obtained.

Example 14

120 mg of 2-[[5-[(E/Z)-styryl]-6-p-toluenesulphonamido-4-pyrimidinyl]oxy]ethyl acetate were hydrogenated in 3 ml of abs. ethanol and 3 ml of abs. tetrahydrofuran in the presence of 4 mg of 5% palladium/charcoal. After completion of the hydrogen uptake the catalyst was filtered off and the organic phases were evaporated under reduced pressure. The residue was chromatographed on silica gel with ethyl acetate and yielded 110 mg of 2-[[5-phenethyl-6-p-toluenesulphonamido-4-pyrimidinyl]oxy]ethyl acetate, m.p. 120-123°C.

This Sheet Has Been Replaced



Example 15

80 mg of 2-[(5-phenethyl-6-p-toluenesulphonamido-4-pyrimidinyl)oxy]ethyl acetate in 5 ml of methanol were stirred with 53 mg of finely powdered potassium carbonate at 20°C for 15 hours. Thereafter, the methanol was removed under reduced pressure, the residue was taken up in ethyl acetate, the organic phase was washed with water and saturated sodium chloride

THIS SHEET HAS BEEN REPLACED

solution, dried and evaporated. The residue was chromatographed over silica gel with methylene chloride/ethyl acetate(1:1) and ethyl acetate. There were obtained 40 mg of N-[6-(2-hydroxy-ethoxy)-5-phenethyl-4-pyrimidinyl]-p-toluenesulphonamide as a white resin.

Example 16

In analogy to Example 15, from 2-[[5-[(E/Z)-styryl]-6-p-toluenesulphonamido]-4-pyrimidinyl]oxy]ethyl acetate there was obtained N-[6-(2-hydroxyethoxy)-5-[(E/Z)-styryl]-4-pyrimidinyl]-p-toluenesulphonamide as a white resin.

Example 17

In analogy to Example 1, paragraph a), from N-[6-chloro-5-(2,4,6-trichlorophenoxy)-4-pyrimidinyl]-p-isopropylbenzene-sulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-(2,4,6-trichlorophenoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, m.p. 182-183°C (from methylene chloride and isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(2,4,6-trichlorophenoxy)pyrimidine and p-isopropylbenzene-sulphonamide, m.p. 217-218°C (from methylene chloride and isopropyl ether).

Example 18

In analogy to Example 1, paragraph a), from N-[6-chloro-5-(2,4,6-trichlorophenoxy)-4-pyrimidinyl]-o-toluenesulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxy-ethoxy)-6-(2,4,6-trichlorophenoxy)-4-pyrimidinyl]-o-toluene-sulphonamide, m.p. 144-145°C (from isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(2,4,6-trichlorophenoxy)-pyrimidine and o-toluenesulphonamide, m.p. 107-109°C (from isopropyl ether).

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

This Sheet Has Been Replaced

Example 19

In analogy to Example 1, paragraph a), from N-[6-chloro-5-(2,4,6-trichlorophenoxy)-4-pyrimidinyl]-2,4-xylenesulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxy-ethoxy)-5-(2,4,6-trichlorophenoxy)-4-pyrimidinyl]-2,4-xylene-sulphonamide, m.p. 157-158°C (from isopropyl ether).

The starting material was prepared as follows:

16.9 g of anhydrous K_2CO_3 were added to a solution of 18.0 g of 2,4,6-trichlorophenol and 32.0 g of diethyl bromo-malonate in 180 ml of acetone and 20 ml of toluene. The reaction mixture was heated at reflux while stirring for 24 hours, the solution was filtered off from the precipitate and evaporated under reduced pressure. The residue was taken up in toluene, the organic solution was washed with a 5% sodium carbonate solution, then with water, dried over sodium sulphate and, after filtering off the salt under suction, evaporated under reduced pressure. The residue was distilled under ≤ 1 mmHg pressure, whereby there was obtained a colourless oil (b.p. 171-174°C) from which with formamidine acetate and sodium methyl-ate there was obtained 5-(2,4,6-trichlorophenoxy)-4,6(3H,5H)-pyrimidinedione, m.p. >270°C, which, prior to the further reaction, was dried at 80°C overnight under reduced pressure.

A solution of 7.6 g of 5-(2,4,6-trichlorophenoxy)-4,6-(3H,5H)-pyrimidinedione, 6.6 g of tetraethylammonium chloride, 3.3 ml of collidine, 13.7 ml of $POCl_3$ in 70 ml of CH_3CN was heated at reflux for 4.5 hours, the solution was evaporated under reduced pressure, the residue was treated three times with ether, the combined organic solutions were filtered overnight, evapo-rated under reduced pressure and the residue was recrystallized from ether and n-hexane. There was obtained 4,6-dichloro-5-(2,4,6-trichlorophenoxy)pyrimidine, m.p. 104-105°C.

THIS SHEET HAS BEEN REPLACED

From 4,6-dichloro-5-(2,4,6-trichlorophenoxy)pyrimidine and 2,4-xylenesulphonamide there was obtained N-[6-chloro-5-(2,4,6-trichlorophenoxy)-4-pyrimidinyl]-2,4-xylenesulphonamide, m.p. 267°C (from acetonitrile and isopropyl ether).

Example 20

By reacting 4,6-dichloro-5-[(2-methoxy-4-methyl)phenoxy]pyrimidine with p-t-butylbenzenesulphonamide and thereafter with ethylene glycol Na there was obtained p-t-butyl-N-[6-(2-hydroxyethoxy)-5-[(2-methoxy-p-tolyl)oxy]-4-pyrimidinyl]benzenesulphonamide as a solid.

The starting material was prepared by the reaction of methylguaiacol with diethyl bomomalonate and thereafter with formamidine acetate to give 5-[(2-methoxy-4-methyl)phenoxy]-4,6(3H, 4H)-pyrimidinedione, m.p. 234-236°C, and further reaction of the latter compound with $POCl_3$.

Example 21

By reacting 4,6-dichloro-5-[(2-methoxy-4-methyl)phenoxy]pyrimidine with p-isopropylbenzenesulphonamide and thereafter with ethylene glycol Na there was obtained N-[5-(2-methoxy-4-methyl)phenoxy]pyrimidinyl]-p-isopropylbenzenesulphonamide, m.p. 135-136°C (from ethyl acetate).

Example 22

By reacting 4,6-dichloro-5-[(2-methoxy-4-methyl)phenoxy]pyrimidine with o-ethylbenzenesulphonamide and thereafter with ethylene glycol Na there was obtained N-[5-(2-methoxy-4-methyl)phenoxy-6-(2-hydroxyethoxy)-4-pyrimidinyl]-o-ethylbenzenesulphonamide as a solid.

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

Example 23

By reacting 4,6-dichloro-5-(2-methoxy)phenoxy-2-methyl-pyrimidine with p-tert-butylphenylsulphonamide and thereafter with ethylene glycol Na there was obtained p-tert-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-benzenesulphonamide, m.p. 123-124°C (from ethyl acetate).

Example 24

By reacting 4,6-dichloro-5-(2-methoxy)phenoxy-2-methyl-pyrimidine with p-isopropylbenzenesulphonamide and thereafter with ethylene glycol Na there was obtained N-[6-(2-hydroxy-ethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl)-p-isopropylbenzenesulphonamide, m.p. 124-126°C (from acetonitrile, isopropanol and water).

Example 25

By reacting 4,6-dichloro-5-(2-methoxyphenoxy)-2-trifluoromethylpyrimidine with p-isopropylbenzenesulphonamide and thereafter with ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-trifluoromethyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide as a solid.

Example 26

By reacting 4,6-dichloro-5-(2-methoxyphenoxy)-2-trifluoromethylpyrimidine with p-tert-butylbenzenesulphonamide and with ethylene glycol Na there was obtained p-tert-butyl-N-[6-(2-hydroxyethoxy)-5(o-methoxyphenoxy)-2-(trifluoromethyl)-4-pyrimidinyl]benzenesulphonamide, m.p. 190-192°C (from toluene). Sodium salt: M.p. 288-289°C.

This Sheet Has Been Replaced



Example 27

By reacting 5-(1,3-benzodioxol-5-yloxy)-4,6-dichloro-pyrimidine with p-tert-butylphenylsulphonamide and thereafter

THIS SHEET HAS BEEN REPLACED

with ethylene glycol Na there was obtained N-[5-(1,3-benzodioxol-5-yloxy)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-tert-butylbenzenesulphonamide as a solid.

Example 28

By reacting 5-(1,3-benzodioxol-5-yloxy)-4,6-dichloropyrimidine with p-isopropylbenzenesulphonamide and thereafter with ethylene glycol Na there was obtained N-[5-(1,3-benzodioxol-5-yloxy)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide as a solid.

Example 29

By reacting 5-(2-methoxyphenoxy)-4,6-dichloropyrimidine with o-methoxyphenylsulphonamide and thereafter with ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]-o-methoxybenzenesulphonamide, m.p. 164-165°C (from ethyl acetate).

Example 30

By reacting p-tert-butyl-N-[6-chloro-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide with the monosodium salt of 1,4-butanediol there was obtained p-tert-butyl-N-[6-(4-hydroxybutoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide as a white foam.

Example 31

By reacting 4,6-dichloro-5-(2-naphthyloxy)pyrimidine with p-isopropylphenylsulphonamide and thereafter with the sodium salt of ethylene glycol there was obtained N-[6-(2-hydroxyethoxy)-5-(2-naphthyloxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, m.p. 160-161°C (from isopropyl ether).

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

Example 32

By reacting 4,6-dichloro-5-(2-naphthyloxy)pyrimidine with p-tert-butylphenylsulphonamide and thereafter with ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-(2-naphthyloxy)-4-pyrimidinyl]-p-tert-butylbenzenesulphonamide, m.p.197-198°C (from isopropyl ether).

Example 33

By reacting 4,6-dichloro-5-(o-methoxyphenoxy)-2-propyl-pyrimidine with p-isopropylphenylsulphonamide and thereafter with ethylene glycol Na there was obtained N-[6-(2-hydroxy-ethoxy)-5-(o-methoxyphenoxy)-2-propyl-4-pyrimidinyl]-p-iso-propylbenzenesulphonamide as a solid.

Example 34

By reacting 4,6-dichloro-5-(o-methoxyphenoxy)-2-propyl-pyrimidine with p-tert-butylphenylsulphonamide and thereafter with ethylene glycol Na there was obtained p-tert-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-propyl-4-pyrimidinyl]-benzenesulphonamide.

Example 35

By reacting 4,6-dichloro-5-(o-methoxy)phenoxy-2-methyl-pyrimidine with α,α,α-trifluoro-p-toluenesulphonamide and thereafter with ethylene glycol Na there was obtained α,α,α-trifluoro-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-p-toluenesulphonamide, m.p. 144-145°C (from ethyl acetate).

This Sheet Has Been Replaced



Example 36

By reacting 4,6-dichloro-5-(o-methoxy)phenoxy-2-methyl-pyrimidine with p-chlorophenylsulphonamide and thereafter with ethylene glycol Na there was obtained p-chloro-N-[6-(2-hydroxy-

THIS SHEET HAS BEEN REPLACED

ethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzene-sulphonamide, m.p. 134-135°C (from ethyl acetate).

Example 37

By reacting 4,6-dichloro-5-(o-methoxy)phenoxy-2-methyl-pyrimidine with p-(trifluoromethoxy)benzenesulphonamide and thereafter with ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-p-(trifluoromethoxy)benzenesulphonamide, m.p. 138-140°C (from ethyl acetate).

Example 38

By reacting 4,6-dichloro-5-(o-methoxy)phenoxy-2-methyl-pyrimidine with o-ethylbenzenesulphonamide and thereafter with ethylene glycol Na there was obtained o-ethyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-benzenesulphonamide as a white foam.

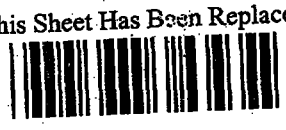
Example 39

By reacting 4,6-dichloro-5-(o-methoxy)phenoxy-2-methyl-pyrimidine with p-toluenesulphonamide thereafter with ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-p-toluene-sulphonamide as a white foam.

Example 40

By reacting 4,6-dichloro-5-(o-methoxy)phenoxy-2-methylpyrimidine with 2-naphthylsulphonamide and thereafter with ethylene glycol Na there was obtained N-[6-(2-hydroxy-ethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-2-naphthylsulphonamide as a foam.

This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

Example 41

By reacting p-tert-butyl-N-[6-chloro-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide with the monosodium salt of 1,3-propanediol there was obtained p-tert-butyl-N-[6-(3-hydroxypropoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide as a white foam.

Example 42

In analogy to Example 1, paragraph a), 300 mg of p-t-butyl-N-[6-chloro-5-[(o-methylthio)phenoxy]-4-pyrimidinyl]benzenesulphonamide were converted into N-[6-(2-hydroxyethoxy)-5-[(o-methylthio)phenoxy]-4-pyrimidinyl]benzenesulphonamide. There were obtained 250 mg of p-t-butyl-N-[6-(2-hydroxyethoxy)-5-[(o-methylthio)phenoxy]-4-pyrimidinyl]benzenesulphonamide, m.p. 149-150°C.

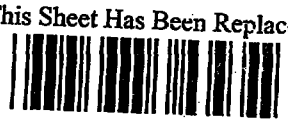
The starting material was prepared as follows:

a) Dimethyl (o-methylthio)phenoxymalonate was obtained from dimethyl chloromalonate and (o-methylthio)phenol in analogy to Example 1, paragraph c). From 17 g of (o-methylthio)phenol there were obtained 23 g of malonate from toluene-hexane.

b) 9.15 g of 5-[(o-methylthio)phenoxy]-6-hydroxy-4-(3H)-pyrimidinone, MS:250 (M), were obtained from 13.5 g of the malonate from a) and formamidine acetate in analogy to Example 1, paragraph d).

c) 2.5 g of this compound and 2.9 g of diisopropylethylamine were suspended in 15 ml of acetonitrile. 2 ml of $POCl_3$ were added dropwise to the suspension and the mixture was subsequently boiled at reflux for 5 hours. 4,6-Dichloro-5-[(o-methylthio)phenoxy]pyrimidine was obtained after working-up in analogy to Example 1, paragraph e). After crystallization from n-hexane there was obtained 1 g of pyrimidine derivative, m.p. 89-90°C.

This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

d) In analogy to Example 1, paragraph f), 580 mg of 4,6-dichloro-5-[(o-methylthio)phenoxy]pyrimidine were converted with 850 mg of p-t-butylbenzenesulphonamide K into p-t-butyl-N-[6-chloro-5-[(o-methylthio)phenoxy]-4-pyrimidinyl]benzene-sulphonamide. After crystallization from MeOH there were obtained 480 mg of white crystals, m.p. 154-155°C.

Example 43

a) In analogy to Example 1, paragraph a), 350 mg of p-t-butyl-N-[(6-chloro-5-(o-methoxyphenoxy)-2-phenyl-4-pyrimidinyl]-benzenesulphonamide were converted into p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-phenyl-4-pyrimidinyl]-benzenesulphonamide. After crystallization from diisopropyl ether there were obtained 330 mg of white crystals, m.p. 160-161°C.

b) 225 mg of this compound were dissolved in EtOH. The stoichiometric amount of KOH in MeOH was added to the solution. Then, the solvent was distilled off and diisopropyl ether was added to the residue, whereby there was obtained p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-phenyl-4-pyrimi-dinyl]benzenesulphonamide potassium, MS: 588 [(M + K)$^+$].

Example 44

In analogy to Example 1, paragraph a), from N-[2-amino-6-chloro-5-(o-methoxyphenoxy)-4-pyrimidinyl]-p-tert.-butylben-zenesulphonamide there was obtained N-[2-amino-6-(2-hydroxy-ethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]-p-tert.-butyl-benzenesulphonamide, white crystals of melting point 168°C (from diisopropyl ether).

The starting material was prepared as follows:

a) 7.65 g of dimethyl (5-o-methoxy)phenoxymalonate and 3 g of guanidine hydrochloride were added to a solution of 2.3 g of Na in 100 ml of methanol. The suspension was stirred at room

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

temperature under argon for 3 hours. Then, the methanol was distilled off and the residue was taken up in H_2O. After the usual treatment, as already described, the compound was precipitated by the dropwise addition of acetic acid until the pH of the solution had reached 4.5. There were obtained 6.4 g of crude product of which 1.35 g were suspended in 10 ml of dioxan. 1.4 g of N-ethyldiisopropylamine, 2 ml of $POCl_3$ and 1 g of triethylbenzylammonium chloride were added thereto in succession. The mixture was boiled at reflux under an argon atmosphere while stirring vigorously. After 30 minutes the solvent mixture was distilled off, the residue was taken up in ethyl acetate and extracted with H_2O and saturated $NaHCO_3$ solution. Purification was carried out by chromatography on silica gel (CH_2Cl_2-ethyl acetate, 9:1 vol., as the eluent). There was obtained 2-amino-4,6-dichloro-5-(o-methoxyphenoxy)pyrimidine as a colourless solid. M.p. 190°C.

b) 0.5 g of the foregoing dichloro compound and 0.75 g of p-tert.-butylbenzenesulphonamide Na in 2 ml of DMSO were converted at 90°C into N-[2-amino-6-chloro-5-(o-methoxyphenoxy)-4-pyrimidinyl]-p-tert-butylbenzenesulphonamide, m.p. 194-195°C

Example 45

a) In analogy to Example 1, paragraph a), 478 mg of p-tert-butyl-N-[6-chloro-2-methyl-5-[o-(methylthio)phenoxy]pyrimidinyl]benzenesulphonamide and Na glycolate in ethylene glycol were converted into p-tert-butyl-N-[6-(2-hydroxyethoxy)-2-methyl-5-[o-(methylthio)phenoxy]-4-pyrimidinyl]benzenesulphonamide, m.p. 166-167°C.

b) 225 mg of this compound were converted into the sulphonamide salt by adding the stoichiometric amount of aqueous NaOH. Then, it was diluted with methanol to give a homogeneous solution. 100 mg of $NaIO_4$ dissolved in 2 ml of H_2O were added to this solution and the mixture was stirred at room temperature for 8 hours. Then, it was evaporated to dryness. The residue was

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

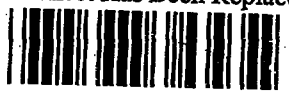
partitioned between ethyl acetate and aqueous 0.1N H_2SO_4. After evaporating the organic phase the p-tert-butyl-N-[6-(2-hydroxy-ethoxy)-2-methyl-5-[o-(R,S-methylsulphinyl)phenoxy]-4-pyrimidinyl]benzenesulphonamide was crystallized from diiso-propyl ether. 150 mg of white crystals were obtained. MS: m/e = 520 $(M+H)^+$.

g The starting material was prepared as follows:

5.4 g of dimethyl (o-methylthiophenoxy)malonate and 2.1 g of acetamidine hydrochloride were converted into 6-hydroxy-2-methyl-5-[o-(methylthio)phenoxy]-4(3H)-pyrimidine and this was converted into 4,6-dichloro-2-methyl-5-[o-(methylthiophenoxy)-pyrimidine, m.p. 132-133°C.

0.9 g of the foregoing dichloro compound and 1.3 g of p-tert-butylbenzenesulphonamide K were converted into p-tert-butyl-N-[6-chloro-2-methyl-5-[o-methylthio)phenoxy]-4-pyrimi-dinyl]benzenesulphonamide. M.p. 162-163°C.

This Sheet Has Been Replaced



Example 46

1.22 g of (S)-1,2-di-O-isopropylidene-glycerol were added dropwise under an argon atmosphere to a suspension of 170 mg of NaH in 2 ml of dry THF. Subsequently, 1.03 g of p-tert-butyl-N-[6-chloro-5-(o-methoxyphenoxy)-2-(p-methoxyphenyl)-4-pyrimidinyl]benzenesulphonamide and 2 ml of DMSO were added. The mixture was left to react at 95°C for 4 hours, whereby the THF distilled off. Then, 0.5 ml of H_2O was added and the solvent mixture and the excess reagent were distilled off under reduced pressure. The residue was taken up in 20 ml of dioxan; 1 ml of aqueous 1N HCl was added and the mixture was left to react at 65°C for 45 minutes. The mixture was then evaporated to dryness. The residue was partitioned between ethyl acetate and 1N hydrochloric acid. After the usual working-up the compound was purified on silica gel with ethyl acetate as the eluent. There was obtained 0.98 g of (S)-4-tert-butyl-N-[6-(2,3-dihydroxy-propyloxy)-5-(o-methoxy-phenoxy)-2-(p-methoxyphenyl)-

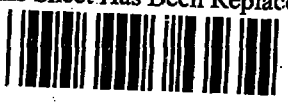
THIS SHEET HAS BEEN REPLACED

pyrimidin-4-yl]-benzenesulphonamide, m.p. 141-142°C (from diethyl ether).

The starting material was prepared as follows:

In analogy to Example 1, paragraph d), 7.63 g of dimethyl (o-methoxyphenoxy)malonate and 5,6 g of p-methoxy-benzamidine hydrochloride were condensed to give 2-(p-methoxyphenyl)-5-(o-methoxyphenoxy)-6-hydroxy-4(3H)-pyrimidinone. Reaction of this compound in analogy to Example 1, paragraph e), yielded 4,6-dichloro-2-(p-methoxyphenyl)-5-(o-methoxyphenoxy)-pyrimidine, m.p. 113-114°C, from which in analogy to Example 1, paragraph f), there was obtained p-tert-butyl-N-[6-chloro-5-(o-methoxyphenoxy)-2-(p-methoxyphenyl)-4-pyrimidinyl]benzenesulphonamide, m.p. 221-222°C.

This Sheet Has Been Replaced



Example 47

210 mg of 4-tert-butyl-N-[5-(2-chloro-5-methoxyphenoxy)-2-ethyl-6-(2-methylsulphanyl-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide were dissolved in 5 ml of MeOH and 0.2 ml of 1N NaOH. 95 mg of $NaIO_4$ dissolved in 0.5 ml of H_2O were added thereto and the mixture was stirred at room temperature for 5 hours, whereby a suspension resulted. Then, 0.2 ml of 1N HCl was added and the mixture was subsequently evaporated to dryness. The residue was partitioned between ethyl acetate and 0.1N HCl and worked-up as usual. For purification, the compound was chromatographed on silica gel using ethyl acetate-MeOH (6:1 by vol.) as the eluent. There were obtained 160 mg of (RS)-4-tert-butyl-N-[5-(2-chloro-5-methoxyphenoxy)-2-ethyl-6-(2-methylsulphinyl-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide as a white powder. MS: 581 (M).

The starting material was prepared as follows:

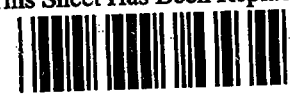
In analogy to Example 1, paragraph c), from 2-chloro-5-methoxy-phenol and dimethyl chloromalonate there was obtained dimethyl (2-chloro-5-methoxy-phenoxy)malonate, m.p. 68-69°C.

THIS SHEET HAS BEEN REPLACED

Condensation with propanidine hydrochloride yielded 2-ethyl-5-(2-chloro-5-methoxy-phenoxy)-6-hydroxy-4(3H)-pyrimidinone from which in analogy to Example 1, paragraph e), there was obtained 4,6-dichloro-2-ethyl-5-(2-chloro-5-methoxy-phenoxy)-pyrimdine, m.p. 113-113.5°C. This compound was converted analogously to Example 1, paragraph f), into 4-tert-butyl-N-[6-chloro-5-(2-chloro-5-methoxy-phenoxy)-2-ethyl-pyrimidin-4-yl]-benzenesulphonamide, m.p. 142-143°C (from ethanol).

300 mg of 2-(methylthio)ethanol were added dropwise under argon to a suspension of 63 mg of NaH in dry THF. Subsequently, 300 mg of the previously obtained sulphonamide and 1 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone were added thereto. The mixture was left to react at 80°C for 3 hours. After the usual working-up of the reaction mixture and purification on silica gel (CH_2Cl_2-diethyl ether, 95/5 vol, as the eluent) there were obtained 160 mg of 4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-2-ethyl-6-(2-methylsulphanyl-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide as a white powder.

This Sheet Has Been Replaced



Example 48

a) In analogy to Example 1, from 4-tert-butyl-N-[6-chloro-5-(2-chloro-5-methoxy-phenoxy)-2-methylpyrimidine-4-yl]-benzenesulphonamide there were manufactured 4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-2-methyl-pyrimidin-4-yl]-benzenesulphonamide. From 500 mg of the starting material there were obtained 430 mg of white crystals. M.p. 141-141.5°C (from isopropyl ether).

b) 140 mg of the compound obtained were esterified with 3-furancarboxylic acid under the following conditions: 140 mg of the previously obtained sulphonamide, 170 mg of N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride, 170 mg of Et_3N and 5 mg of dimethylamino pyridine were dissolved in 2 ml of dichloromethane and the solution was left to stand at room temperature for 24 hours. Then, 5 ml of THF and 1 ml of

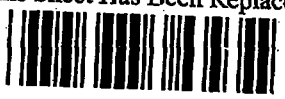
THIS SHEET HAS BEEN REPLACED

H_2O were added thereto and the solution was stirred for 30 minutes. Subsequently, it was evaporated to dryness. The residue was partitioned between dichloromethane and 1N HCl, then washed three times with H_2O and isolated as usual. The compound was purified on silica gel using dichloromethane-diethyl ether (95:5 by vol.) as the eluent. There were obtained 120 mg of 4-tert-butyl-N-[5-(2-chloro-5-(2-chloro-5-methoxy-phenoxy)-6-(2-(3-furoyloxy)ethoxy)-2-methyl-pyrimidin-4-yl]-benzenesulphonamide.

The starting material was prepared as follows:

In analogy to Example 1, paragraph d), dimethyl (2-chloro-5-methoxy-phenoxy)malonate was condensed with acetamidine hydrochloride to give (2-chloro-5-methoxy-phenoxy)-2-methyl-6-hydroxy-4(3H)-pyrimidinone. Therefrom in analogy to Example 1, paragraph e), there was obtained 4,6-dichloro-5-(2-chloro-5-methoxy-phenoxy)-2-methyl-pyrimidine, m.p. 125-130°C, and therefrom in analogy to Example 1, paragraph f), there was obtained 4-tert-butyl-N-[6-chloro-5-(2-chloro-5-methoxy-phenoxy)-2-methyl-pyrimidin-4-yl]-benzenesulphonamide, m.p. 182°C (from MeOH).

This Sheet Has Been Replaced



Example 49

In analogy to Example 47, 90 mg of N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2-methylsulphanyl-ethoxy)-pyrimidin-4-yl]-1,3-benzodioxol-5-sulphonamide were oxidized with $NaIO_4$ to give (RS)-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2-methyl-sulphinyl-ethoxy)-pyrimidin-4-yl]-1,3-benzodioxol-5-sulphonamide. There were obtained 65 mg of white powder. MS: 542.1 ($M+H^+$).

The starting material was prepared as follows:

In analogy to Example 1, paragraph d), dimethyl (2-chloro-5-methoxy-phenoxy)malonate was condensed with formamidine acetate to give (2-chloro-5-methoxy-phenoxy)-6-hydroxy-4(3H)-

THIS SHEET HAS BEEN REPLACED

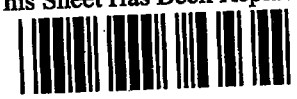
pyrimidinone. Therefrom in analogy to Example 1, paragraph e), there was obtained 4,6-dichloro-5-(2-chloro-2-methoxy-phenoxy)-pyrimidine, m.p. 88-89°C (from ethanol).

Reaction of 611 mg of 4,6-dichloro-5-(2-chloro-2-methoxy-phenoxy)-pyrimidine with 813 mg of 1,3-benzodioxol-5-sulphonamide K yielded 535 mg of N-[6-chloro-5-(2-chloro-5-methoxy-phenoxy)-pyrimidin-4-yl]-1,3-benzodioxol-5-sulphonamide. The last-named compound was converted into N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2-methylsulphanyl-ethoxy)-pyrimidin-4-yl]-1,3-benzodioxol-5-sulphonamide as described in the preparation of the starting material in Example 47.

Example 50

A solution of 0.11 g of sodium in 3.0 ml of ethylene glycol was heated to 110°C with 0.265 g of 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(thiophen)-2-yl-pyrimidin-4-yl]-benzenesulphonamide, cooled for a further 4 hours, poured on to ice and adjusted to pH 3 with 1M tartaric acid. The suspension obtained was extracted with ethyl acetate, the organic extracts were combined, washed with water, dried with sodium sulphate and concentrated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2-ethyl acetate 9:1 and yielded 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzenesulphonamide as a white foam. MS: M^+ = 555.

This Sheet Has Been Replaced



The starting material was prepared as follows:

a) A solution of 5.17 g of Na in 200 ml of abs. methanol was treated with 21.15 g of diethyl (o-methoxyphenoxy)malonate and 16.2 g of thiophene-2-carboxamidine hydrochloride and the suspension was stirred at room temperature overnight and evaporated under reduced pressure. The residue was taken up in 1N NaOH, the alkaline solution was acidified with 1N HCl, the precipitate was filtered off under suction, washed thoroughly with

THIS SHEET HAS BEEN REPLACED

water and dried in a high vacuum at 80°C. The 5-(o-methoxyphenoxy)-2-(2-thienyl)-4,6-dihydroxy-pyrimidine of m.p. >250°C (dec.) was used in the next step without further purification.

b) A suspension of 4.6 g of 5-(o-methoxyphenoxy)-2-(2-thienyl)-4,6-dihydroxy-pyrimidine, 4.7 ml of N,N-diisopropyl-N-ethylamine and 6.4 g of PCl_5 was boiled at reflux for 20 hours. The mixture was then evaporated under reduced pressure and the residue was poured on to ice and extracted with ethyl acetate. The combined extracts were washed with water, dried and evaporated in a vacuum. The residue was chromatographed on silica gel with toluene and yielded 4,6-dichloro-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidine, m.p. 118-120°C.

c) A solution of 0.353 g of 4,6-dichloro-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidine in 5 ml of DMSO was heated to 150°C with 0.376 g of p-tert-butylbenzenesulphon-amide for 30 minutes. The solution was concentrated in a high vacuum and the oily residue was poured on to ice, made acid (pH = 3) and the suspension was extracted with ethyl acetate. The organic extracts were combined, washed with water, dried over sodium sulphate and concentrated under reduced pressure. The residue was chromatographed on silica gel with toluene-ethyl acetate 9:1 and yielded 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzenesulphon-amide as a white foam.

Example 51

In an analogous manner to Example 50, from 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzenesulphonamide and ethylene glycol Na there was obtained 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzene-sulphonamide, m.p. 152-153°C (from toluene).

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

The 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzenesulphonamide (foam) was prepared starting from thiophene-3-carboxamidine hydrochloride via rac-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-3,4,5,6-tetrahydro-pyrimidine-4,6-dione (solid of m.p. >250°C) and 4,6-dichloro-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidine (m.p. 98-99°C).

Example 52

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-2-(furan-2-yl)-5-(2-methoxy-phenoxy)-pyrimidinyl-4-yl]-benzenesulphonamide and ethylene glycol Na there was obtained 4-tert-butyl-N-[2-(furan-2-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide as an amorphous solid.

The 4-tert-butyl-N-[6-chloro-2-(furan-2-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide (foam) was prepared starting from furan-2-carboxamidine hydrochloride via rac-2-(furan-2-yl)-5-(2-methoxy-phenoxy)-pyrimidine-4,6-dione (solid with a decomposition point of 255-258°C) and 4,6-dichloro-2-(furan-2-yl)-5-(2-methoxy-phenoxy)-pyrimidine.

Example 53

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-2-furan-3-yl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and ethylene glycol Na there was obtained 4-tert-butyl-N-[2-(furan-3-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide as a solid of m.p. 120-122°C (from toluene/n-hexane).

The 4-tert-butyl-N-[6-chloro-2-(furan-3-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide (foam) was prepared starting from furan-3-carboxamidine hydro- chloride via rac-2-(furan-3-yl)-5-(2-methoxy-phenoxy)-4,6-dioxo-1,4,5,6-tetrahydro-pyrimidine (solid with a m.p. of more than 300°C with

This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

decomposition) and 4,6-dichloro-2-(furan-3-yl)-5-(2-methoxy-phenoxy)-pyrimidine.

Example 54

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(pyridin-2-yl)-pyrimidin-4-yl]-benzenesulphonamide and ethylene glycol Na there was obtained 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(pyridin-2-yl)-pyrimidin-4-yl]-benzenesulphonamide as a solid with a m.p. above 250°C (from ethyl acetate).

The 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(pyridin-2-yl)-pyrimidin-4-yl]-benzenesulphonamide (m.p. 197-198°C from isopropyl ether) was prepared starting from pyridine-2-carboxamidine hydrochloride via 5-(2-methoxy-phenoxy)-2-(pyridin-2-yl)pyrimidine-4,6-diol and 4,6-dichloro-5-(2-methoxy-phenoxy)-2-(pyridin-2-yl)-pyrimidine, m.p. 122-123°C.

Example 55

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(pyridin-4-yl)-pyrimidin-4-yl]-benzenesulphonamide and ethylene glycol Na there was obtained 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(pyridin-4-yl)-pyrimidin-4-yl]-benzenesulphonamide as a solid of m.p. 166-167°C from acetone-ether.

The 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(pyridin-4-yl)-pyrimidin-4-yl]-benzenesulphonamide potassium (1:1), m.p. 193-196°C from H_2O, was prepared starting from pyridine-4-carboxamidine hydrochloride via 5-(2-methoxy-phenoxy)-2-(pyridin-4-yl)-pyrimidine-4,6-diol and 4,6-dichloro-5-(2-methoxy-phenoxy)-2-(pyridin-4-yl)-pyrimidine, m.p. 173-176°C.

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

Example 56

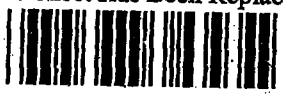
In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(pyridin-3-yl)-pyrimidin-4-yl]-benzenesulphonamide and ethylene glycol Na there was obtained 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(pyridin-3-yl)-pyrimidin-4-yl]-benzenesulphonamide K as a foam. MS: $(M+H)^+ = 551.2$.

The 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(pyridin-3-yl)-pyrimidin-4-yl]-benzenesulphonamide was prepared starting from pyridine-3-carboxamidine hydrochloride via rac-5-(2-methoxy-phenoxy)-2-(pyridin-3-yl)-tetrahydro-1H-pyrimidine-4,6-dione and 4,6-dichloro-5-(2-methoxy-phenoxy)-2-(pyridin-3-yl)-pyrimidine (m.p. 164-165°C).

Example 57

A suspension of 525 mg of 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(pyridin-2-yl)-pyrimidin-4-yl)benzene-sulphonamide in 1 ml of glacial acetic acid was treated with 2.5 ml of 40% peracetic acid and slowly heated to reflux. After 2 minutes the mixture was cooled, evaporated under reduced pressure and the residue was recrystallized from ethyl acetate. There was obtained 2-[4-(4-tert-butyl-phenylsulphonylamino)-6-chloro-5-(2-methoxy-phenoxy)-pyrimidin-2-yl]-pyridine 1-oxide of m.p. 201-202°C (with decomposition).

This Sheet Has Been Replaced



Example 58

216 mg of 2-[4-(4-tert-butyl-phenylsulphonylamino)-6-chloro-5-(2-methoxy-phenoxy)-pyrimidin-2-yl]-pyridine 1-oxide were added to a solution of 46 mg of Na in pure ethylene glycol and the solution which slowly resulted was heated at 80°C overnight. The solution was poured into aqueous acetic acid, the precipitate was extracted with ethyl acetate, triturated with ether and filtered off under suction. There was obtained 2-[4-(4-tert-butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(2-

THIS SHEET HAS BEEN REPLACED

methoxy-phenoxy)-pyrimidin-2-yl]-pyridine 1-oxide as an amorphous mass which was dried in a high vacuum at 40°C. MS: $(M+H)^+$ = 567.4.

Example 59

In analogy to Example 57, from 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(pyridin-4-yl)-pyrimidinyl-4-yl]-benzenesulphonamide and peracetic acid there was obtained 4-[4-(4-tert-butyl-phenylsulphonylamino)-6-chloro-5-(2-methoxy-phenoxy)-pyrimidin-2-yl]-pyridine 1-oxide, m.p. 247-249°C (from CH_2Cl_2 and isopropyl ether).

Example 60

In analogy to Example 58, from 4-[4-(4-tert-butyl-phenyl-sulphonylamino)-6-chloro-5-(2-methoxy-phenoxy)-pyrimidin-2-yl]-pyridine 1-oxide and Na ethylene glycolate in ethylene glycol there was obtained 4-[4-(4-tert-butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-2-yl] pyridine 1-oxide as an amorphous mass. MS: $(M+H)^+$ = 567.4, $(M+Na)^+$ = 589.4.

This Sheet Has Been Replaced



Example 61

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-2-(2-methoxy-ethyl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and ethylene glycol Na there was obtained 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-2-[2-(hydroxy-ethoxy)-ethyl]-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzene-sulphonamide. MS: M^+ = 562. The corresponding sodium salt (prepared according to usual methods) is a white solid which was dried in a high vacuum.

The 4-tert-butyl-N-[6-chloro-2-(2-methoxy-ethyl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl-benzenesulphonamide was prepared starting from methoxy-propionamidine hydrochloride via 2-(2-methoxy-ethyl)-5-(o-methoxyphenoxy)-4,6-(1H,5H)-

THIS SHEET HAS BEEN REPLACED

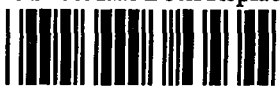
pyrimidinedione and 4,6-dichloro-2-(2-methoxy-ethyl)-5-(2-methoxy-phenoxy)-pyrimidine.

Example 62

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-2-cyclopropyl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzene-sulphonamide and ethylene glycol Na there was obtained 4-tert-butyl-N-[2-cyclopropyl-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide as a foam. MS: $M^+ = 513$.

The 4-tert-butyl-N-[6-chloro-2-cyclopropyl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide was prepared starting from cyclopropyl-formamidine hydrochloride via rac-2-cyclopropyl-5-(2-methoxy-phenoxy)-1H-pyrimidine-4,6-dione (m.p. 243-244°C) and 4,6-dichloro-2-cyclopropyl-5-(2-methoxy-phenoxy)pyrimidine (m.p. 80-82°C).

This Sheet Has Been Replaced



Example 63

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-2-ethyl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzene-sulphonamide and ethylene glycol Na there was obtained 4-tert-butyl-N-[2-ethyl-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide as a foam.

The 4-tert-butyl-N-[6-chloro-2-ethyl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide was prepared starting from propionamidine hydrochloride via rac-2-ethyl-5-(2-methoxy-phenoxy)-1H-pyrimidine-4,6-dione (m.p. 265°C with decomposition) and 4,6-dichloro-2-ethyl-5-(2-methoxy-phenoxy)-pyrimidine (m.p. 70-71°C).

Example 64

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-2-isopropyl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-

THIS SHEET HAS BEEN REPLACED

benzenesulphonamide and ethylene glycol Na there was obtained 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-2-isopropyl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide as a solid.

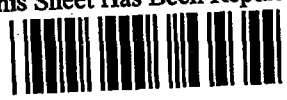
The 4-tert-butyl-N-[6-chloro-2-isopropyl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide was prepared starting from isopropionamidine hydrochloride via rac-2-isopropyl-5-(2-methoxy-phenoxy)-1,4,5,6-tetrahydro-pyrimidine-4,6-dione and 4,6-dichloro-2-isopropyl-5-(2-methoxy-phenoxy)-pyrimidine (m.p. 70-72°C).

Example 65

In analogy to Example 50, from 4-chloro-N-[6-chloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and ethylene glycol Na there was obtained 4-chloro-N-[3-(5-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide, m.p. 152-154°C (from CH_3CN and isopropyl ether).

The 4-chloro-N-[6-chloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide (m.p. 169-171°C) was prepared from 4,6-dichloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidine and 4-chlorobenzenesulphonamide K.

This Sheet Has Been Replaced



Example 66

In analogy to Example 50, from N-[6-chloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-4-trifluoromethyl-benzenesulphonamide and sodium ethylene glycolate there was obtained N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-4-trifluoromethyl-benzenesulphonamide, m.p. 154-155°C (from isopropyl ether).

The N-[6-chloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-4-trifluoromethyl-benzenesulphonamide (m.p. 185-186°C) was prepared from 4,6-dichloro-5-(5-fluoro-2-

THIS SHEET HAS BEEN REPLACED

methoxy-phenoxy)-pyrimidine and 4-trifluoromethylbenzene-sulphonamide K.

Example 67

In analogy to Example 50, but with a reaction temperature of 100°C, from 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(pyrimidin-2-yl)-pyrimidin-4-yl]-benzenesulphon- amide and sodium ethylene glycolate in ethylene glycol there was obtained 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(pyrimidin-2-yl)-pyrimidin-4-yl]-benzenesulphon- amide as a solid. Sodium salt: m.p. 195-198°C.

The 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-pyrimidin-2-yl)-pyrimidin-4-yl]-benzenesulphonamide was prepared starting from pyrimidine-2-carboxamidine hydro-chloride via rac-5-(2-methoxy-phenoxy)-2-(pyrimidin-2-yl)-tetrahydro-pyrimidine-4,6-dione and 4,6-dichloro-5-(2-methoxy-phenoxy)-2,2'-bipyrimidine.

This Sheet Has Been Replaced

Example 68

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-5-(3-methoxy-phenoxy)-2,2'-bipyrimidin-4-yl]-benzenesulphon-amide and Na ethylene glycolate in ethylene glycol there was obtained 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-2,2'-bipyrimidin-4-yl]-benzenesulphonamide as a solid.

The 4-tert-butyl-N-[6-chloro-5-(3-methoxy-phenoxy)-2,2'-bipyrimidin-4-yl]-benzenesulphonamide was prepared starting from rac-5-(3-methoxy-phenoxy)-2-(pyrimidin-2-yl)-1,4,5,6-tetrahydro-pyrimidine-4,6-dione via 4,6-dichloro-5-(3-methoxy-phenoxy)-2,2'-bipyrimidinyl.

Example 69

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-5-(4-fluoro-2-methoxy-phenoxy)-2,2'-bipyrimidin-4-yl]-

THIS SHEET HAS BEEN REPLACED

benzenesulphonamide and Na ethylene glycolate in ethylene glycol there was obtained 4-tert-butyl-N-[5-(4-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-2,2'-bipyrimidin-4-yl]-benzenesulphonamide, m.p. 161-163°C.

The 4-tert-butyl-N-[6-chloro-5-(4-fluoro-2-methoxy-phenoxy)-2,2'-bipyrimidin-4-yl]-benzenesulphonamide (m.p. 225-227°C) was prepared starting from diethyl (4-fluoro-2-methoxy-phenoxy)malonate via 5-(4-fluoro-2-methoxy-phenoxy)-2,2'-bipyrimidine-4,6-diol (decomposition point >131°C) and 4,6-dichloro-5-(4-fluoro-2-methoxy-phenoxy)-2,2'-bipyrimidine (m.p. 179-180°C).

Example 70

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-5-(4-fluoro-2-methoxy-phenoxy)-2-methyl-pyrimidin-4-yl]-benzenesulphonamide and Na ethylene glycolate in ethylene glycol there was obtained 4-tert-butyl-N-[5-(4-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-2-methyl-pyrimidin-4-yl]-benzenesulphonamide, m.p. 141-142°C (from CH_2Cl_2-isopropyl ether).

The 4-tert-butyl-N-[6-chloro-5-(4-fluoro-2-methoxy-phenoxy)-2-methyl-pyrimidin-4-yl]-benzenesulphonamide (m.p. 164-165°C) was prepared starting from diethyl (4-fluoro-2-methoxy-phenoxy)malonate via rac-5-(4-fluoro-2-methoxy-phenoxy)-2-methyl-1,4,5,6-tetrahydropyrimidine-4,6-dione and 4,6-dichloro-5-(4-fluoro-2-methoxy-phenoxy)-2-methyl-pyrimidine (m.p. 129-130°C).

This Sheet Has Been Replaced



Example 71

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-5-(4-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and Na ethylene glycolate in ethylene glycol there was obtained 4-tert-butyl-N-[5-(4-fluoro-2-methoxy-phenoxy)-6-(2-

THIS SHEET HAS BEEN REPLACED

hydroxy-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide, m.p. 143-144°C (from CH_2Cl_2-isopropyl ether).

The 4-tert-butyl-N-[6-chloro-5-(4-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide (m.p. 146-147°C) was prepared starting from diethyl (4-fluoro-2-methoxy-phenoxy)malonate via rac-5-(4-fluoro-2-methoxy-phenoxy)-1,4,5,6-tetrahydro-pyrimidine-4,6-dione and 4,6-dichloro-5-(4-fluoro-2-methoxy-phenoxy)pyrimidine (m.p. 100-101°C).

Example 72

In analogy to Example 50, from N-[6-chloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-4-isopropyl-benzenesulphonamide and Na ethylene glycolate in ethylene glycol there was obtained N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-4-isopropyl-benzenesulphonamide, m.p. 131-132°C (from isopropyl ether).

Example 73

In analogy to Example 50, from N-[6-chloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-4-tert-butyl-benzenesulphonamide and Na ethylene glycolate in ethylene glycol there was obtained N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidine-4-yl]-4-tert-butyl-benzenesulphonamide, m.p. 126-127°C (from isopropyl ether).

The N-[6-chloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-4-isopropyl-benzenesulphonamide, m.p. 138-139°C, was prepared starting from diethyl (5-fluoro-2-methoxy-phenoxy)malonate via rac-5-(5-fluoro-2-methoxy-phenoxy)-tetrahydro-pyrimidine-4,6-dione, 4,6-dichloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidine (m.p. 98-100°C) and N-[6-chloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-4-tert-butyl-benzenesulphonamide (m.p. 163-164°C).

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

Example 74

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-5-(2-fluoro-6-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and Na ethylene glycolate in ethylene glycol there was obtained 4-tert-butyl-N-[5-(2-fluoro-6-methoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide, m.p. 158-159°C (from CH_2Cl_2-isopropyl ether).

The 4-tert-butyl-N-[6-chloro-5-(2-fluoro-6-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide (m.p. 181-182°C) was prepared starting from diethyl 2-(2-fluoro-6-methoxy-phenoxy)malonate via rac-5-(2-fluoro-6-methoxy-phenoxy)-1,4,5,6-tetrahydro-pyrimidine-4,6-dione and 4,6-dichloro-5-(2-fluoro-6-methoxy-phenoxy)-pyrimidine (m.p. 78-79°C).

Example 75

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-5-(3-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzenesulphonamide and Na ethylene glycolate in ethylene glycol there was obtained 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzenesulphonamide, m.p. 159-161°C (toluene/n-hexane).

The 4-tert-butyl-N-[6-chloro-5-(3-methoxy-phenoxy)-2-(thiophene-2-yl)-pyrimidin-4-yl]-benzenesulphonamide (m.p. 206-207°C) was prepared starting from rac-5-(3-methoxy-phenoxy)-2-(thiophen-2-yl)-3,4,5,6-tetrahydropyrimidine-4,6-dione via 4,6-dichloro-5-(3-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidine (m.p. 120-121°C).

This Sheet Has Been Replaced



Example 76

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-2-(2-methoxy-ethyl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and Na ethylene glycolate in ethylene glycol there were obtained, after separation by chromatography

THIS SHEET HAS BEEN REPLACED

on silica gel, 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-2-(2-methoxy-ethyl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-2-[2-(2-hydroxy-ethoxy)-ethyl]-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide.

The 4-tert-butyl-N-[6-chloro-2-(2-methoxy-ethyl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide was prepared starting from methoxypropionamidine hydrochloride via 2-(2-methoxy-ethyl)-5-(3-methoxy-phenoxy)-1,4,5,6-tetra-hydro-pyrimidine-4,6-dione and 4,6-dichloro-2-(2-chloro-ethyl)-5-(3-methoxy-phenoxy)-pyrimidine.

Example 77

In analogy to Example 50, from p-tert-butyl-N-[6-chloro-5-(o-methoxy-phenoxy)-2-methyl-4-pyrimidinyl]-benzene-sulphonamide and (S)-2,2-dimethyl-1,3-dioxolane-4-methanol Na there was obtained (S)-4-tert-butyl-N-[6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-5-(2-methoxy-phenoxy)-2-methyl-pyrimidin-4-yl]-benzenesulphonamide, m.p. 124-125°C (from n-hexane).

Example 78

A solution of 1.85 g of (S)-4-tert-butyl-N-[6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-5-(2-methoxy-phenoxy)-2-methyl-pyrimidin-4-yl]-benzenesulphonamide in EtOH (15 ml) was treated with 3 ml of conc. HCl and heated to 50°C for 2 minutes. After evaporation the residue was extracted with ether and yielded (R)-4-tert-butyl-N-[6-(2,3-dihydroxy-propoxy)-5-(2-methoxy-phenoxy)-2-methyl-pyrimidin-4-yl]-benzenesulphonamide as a foam.

This Sheet Has Been Replaced



Example 79

From N-[6-chloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-4-tert-butyl-benzenesulphonamide and (R)-2,2-

THIS SHEET HAS BEEN REPLACED

dimethyl-1,3-dioxolane-4-methanol Na there was obtained (R)-4-tert-butyl-N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-pyrimidin-4-yl]-benzenesulphonamide (m.p. >86°C). Treatment with dilute hydrochloric acid yielded (S)-4-tert-butyl-N-5-(fluoro-2-methoxy-phenoxy)-6-(2,3-dihydroxy-propoxy)-pyrimidin-4-yl]-benzenesulphonamide as a foam.

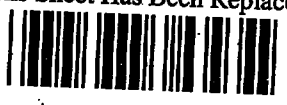
Example 80

From N-[6-chloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-4-tert-butyl-benzenesulphonamide and (S)-2,2-dimethyl-1,3-dioxolane-4-methanol sodium salt there was obtained (S)-4-tert-butyl-N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-pyrimidin-4-yl]-benzenesulphonamide (m.p. >86°C). Treatment with dilute HCl yielded (R)-4-tert-butyl-N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2,3-dihydroxy-propoxy)-pyrimidin-4-yl]-benzenesulphonamide as a foam.

Example 81

From 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzenesulphonamide and (S)-2,2-dimethyl-1,3-dioxolane-4-methanol sodium salt there was obtained 4-tert-butyl-N-[6-[(S)-1,3-dioxolan-4-ylmethoxy]-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzenesulphonamide as a foam. Treatment with dilute hydrochloric acid in dioxan yielded (R)-4-tert-butyl-N-[6-(2,3-dihydroxy-propoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzenesulphonamide as a foam.

This Sheet Has Been Replaced



Example 82

From 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzenesulphonamide and (R)-2,2-dimethyl-1,3-dioxolan-4-methanol sodium salt there was obtained 4-tert-butyl-N-[6-(R)-1,3-dioxolan-4-ylmethoxy]-5-(2-

THIS SHEET HAS BEEN REPLACED

methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzene-sulphonamide and therefrom with dilute HCl in dioxan there was obtained (S)-4-tert-butyl-N-[6-(2,3-dihydroxy-propoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzenesulphonamide.

Example 83

From 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzenesulphonamide and (R)-2,2-dimethyl-1,3-dioxolane-4-methanol sodium salt there was obtained (R)-4-tert-butyl-N-[6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzenesulphonamide and therefrom with dilute HCl in dioxan there was obtained 4-tert-butyl-N-[6-[(S)-2,3-dihydroxy-propoxy]-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzenesulphonamide.

Example 84

From 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzenesulphonamide and (S)-2,2-dimethyl-1,3-dioxolane-4-methanol sodium salt there was obtained (S)-4-tert-butyl-N-[(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzenesulphonamide and therefrom with dilute HCl in dioxan there was obtained 4-tert-butyl-N-[6-[(R)-2,3-dihydroxy-propoxy]-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzenesulphonamide.

This Sheet Has Been Replaced



Example 85

From 4-tert-butyl-N-[6-chloro-2-(furan-3-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and (S)-2,2-dimethyl-1,3-dioxolane-4-methanol sodium salt there was obtained (S)-4-tert-butyl-N-[6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-2-(furan-3-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and therefrom with dilute HCl in dioxan

THIS SHEET HAS BEEN REPLACED

there was obtained (R)-4-tert-butyl-N-[2-(furan-3-yl)-6-(2,3-dihydroxy-propoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide.

Example 86

From 4-tert-butyl-N-[6-chloro-2-(furan-3-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and (R)-2,2-dimethyl-1,3-dioxolane-4-methanol sodium salt there was obtained (R)-4-tert-butyl-N-[6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-2-(furan-3-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and therefrom with dilute HCl in dioxan there was obtained (S)-4-tert-butyl-N-[2-(furan-3-yl)-6-(2,3-dihydroxy-propoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide.

Example 87

By reaction of p-t-butyl-N-[6-(2-hydroxy-ethoxy)-5-(m-methoxy-phenoxy)-4-pyrimidinyl]benzenesulfonamide and 3-methyl-5-isoxazole carboxylic acid in the presence of dimethyl-amino pyridine and dicyclohexylcarbodiimide in methylene chloride there was obtained 3-methylisoxazole-5-carboxylic acid 2-[6-(4-t-butylbenzenesulfonamino)-5-(3-methoxy-phenoxy)-pyrimidin-4-yloxy]ethyl ester as a white solid.

Example 88

In analogy to Example 87 employing indole-2-carboxylic acid there was obtained indole-2-carboxylic acid 2-[6-(4-t-butyl-benzenesulfonamino)-5-(3-methoxyphenoxy)pyrimidin-4-yloxy]-ethyl ester.

This Sheet Has Been Replaced



Example 89

To a solution of 391.5 mg of 6-[2-(t-butyl-dimethylsilyl-oxy)ethoxy]-5-(2-methoxyphenoxy)pyrimidin-4-yl-amine in 20 ml of acetonitril there were added 200 mg of NaH (60%) and

THIS SHEET HAS BEEN REPLACED

the reaction mixture was stirred for one hour at room temperature. 400 mg of (2-methoxy-5-chlorosulfonyl)phenoxyacetic acid ethyl ester were added. The reaction mixture was stirred for 3.5 hours at room temperature, poured on ice and extracted with ethyl acetate. The organic phase was dried and evaporated. Chromatography on silica gel with methylene chloride/methanol (120:1) afforded 175 mg of 4-[6-[2-(t-butyl-dimethylsilyoxy)-ethoxy]-5-(2-methoxyphenoxy)pyrimidin-4-yl-aminosulfonyl]-2-methoxyphenoxy acetic acid ethyl ester as a white foam. That compound was dissolved in 6 ml of acetonitril and 1 ml of aqueous hydrogen fluoride (40%) were added slowly at 0°C. The reaction mixture was stirred for 30 minutes at 0°C and for 90 minutes at room temperature, poured on ice/2N $KHCO_3$ solution and extracted with methylene chloride. The organic phase was dried and evaporated and the residue chromatographed on silica gel with methylene chloride/methanol (10:1). There was obtained 5-[N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)pyrimidin-4-yl]aminosulfonyl]-2-methoxyphenoxy acetic acid ethyl ester as a white solid.

The starting material was prepared as follows:

Ca. 105 ml of ammonia were passed into a solution of 7 g of 4,6-dichloro-5-(o-methoxyphenoxy)pyrimidine in 140 ml of ethanol at -78°C. The reaction mixture was stirred for 15 hours at -78°C and for 50 hours at room temperature and then concentrated. The residue was distributed between ethyl acetate and water and the organic phase worked up. There were obtained 6.45 g of 4-amino-6-chloro-5-(o-methoxyphenoxy)pyrimidine as white crystals.

2.3 g of the above obtained compound were added to a solution of 250 mg of sodium in 40 ml of ethylene glycol at 50°C. The solution was heated to 100°C for 12 hours, distributed between half-saturated aqueous NH_4Cl solution and methylene chloride and the organic phase worked up. There were obtained 2.49 g 2-[6-amino-5-(o-methoxyphenoxy)-4-pyrimidinyl]-1-ethanol as white crystals.

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

To a solution of 2.5 g of the above obtained compound in 100 ml of methylene chloride, 2.74 g of dimethylamino pyridine and 3.39 g of t-butyl dimethylchlorosilane were added and the mixture was stirred at room temperature for 48 hours. A further 1.35 g of dimethylamino pyridine and 1.65 g of t-butyl dimethylchlorosilane were then added and the reaction mixture stirred for another 18 hours at room temperature. The reaction mixture was filtered, the filtrate concentrated and the residue distributed between half-saturated aqueous NH_4Cl solution and ethyl acetate. Work-up of the organic phase yielded 2.78 g of 6-[2-(t-butyldimethylsilyloxy]-5-(2-methoxyphenoxy)pyrimidin-4-yl amine as a white solid.

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

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

Example C

Injection solutions can have the following composition:

Compound of formula I	3.0 mg
Gelatine	150.0 mg
Phenol	4.7 mg
Water for injection solutions	ad 1.0 ml

Example D

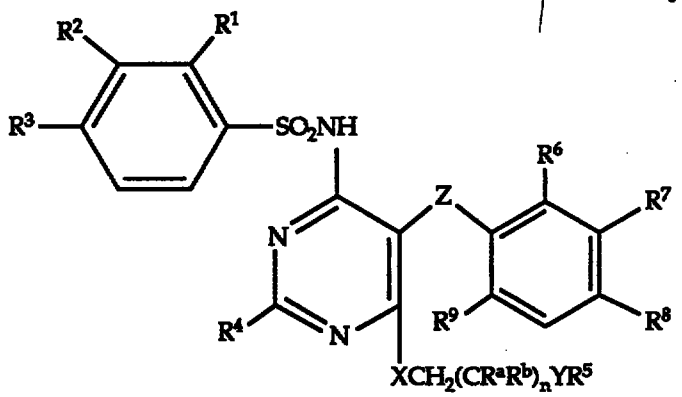
500 mg of compound of formula I are suspended in 3.5 ml of Myglyol 812 and 0.08 g of benzyl alcohol. This suspension is filled into a container having a dosage valve. 5.0 g of Freon 12 under pressure are filled into the container through the valve. The Freon is dissolved in the Myglyol-benzyl alcohol mixture by shaking. This spray container contains about 100 single dosages which can be applied individually.

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

Claims

1. Compounds of the formula



I

wherein

R^1 signifies hydrogen, lower-alkyl, lower-alkoxy, lower-alkylthio, halogen or trifluoromethyl;

R^2 signifies hydrogen, halogen, lower-alkoxy, trifluoromethyl or $-OCH_2COOR^a$; and

R^3 signifies hydrogen, halogen, lower-alkyl, lower-alkylthio, trifluoromethyl, cycloalkyl, lower-alkoxy or trifluoromethoxy; or

R^2 and R^3 together signify butadienyl, methylenedioxy, ethylenedioxy or isopropylidenedioxy;

R^4 signifies hydrogen, lower-alkyl, cycloalkyl, trifluoromethyl, lower-alkoxy, lower-alkylthio, lower-alkylthio-lower-alkyl, hydroxy-lower-alkyl, hydroxy-lower-alkoxy, lower-alkoxy-lower-alkyl, hydroxy-lower-alkoxy-lower-alkyl, hydroxy-lower-alkoxy-lower-alkoxy, lower-alkylsulphinyl, lower-alkylsulphonyl, 2-methoxy-3-hydroxypropoxy, 2-hydroxy-3-phenylpropyl, amino-lower-alkyl, lower-alkylamino-lower-alkyl, di-lower-alkylamino-lower-alkyl, amino, lower-alkylamino, di-lower-alkylamino, arylamino, aryl, arylthio, aryloxy, aryl-lower-alkyl or heterocyclyl;

R^5 signifies hydrogen, lower-alkyl, lower-alkanoyl, benzoyl, heterocyclylcarbonyl, heterocyclylmethyl or tetrahydropyran-2-yl;

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

R^6 to R^9 signify hydrogen, halogen, trifluoromethyl, lower-alkyl, lower-alkoxy, lower-alkylthio, hydroxy, hydroxymethyl, cyano, carboxyl, formyl, methylsulphinyl, methylsulphonyl, methylsulphonyloxy or lower-alkyloxy-carbonyloxy; or

R^7 together with R^6 or R^8 signify butadienyl, methylenedioxy, ethylenedioxy or isopropylidenedioxy;

Z signifies -O-, -S-, ethylene, vinylene, -CO-, $-OCHR^{10}-$ or $-SCHR^{10}$;

R^{10} signifies hydrogen or lower-alkyl;

X and Y each independently signify O, S or NH; or YR^5 also signifies lower-alkylsulphinyl or $-OCH_2CH(OR^c)CH_2OR^d$;

R^a, R^b, R^c and R^d each independently signify hydrogen or lower-alkyl; or R^c and R^d together signify methylene, ethylene or isopropylidene; and

n signifies 1, 2 or 3,

and salts thereof.

* C L M S *

2. Compounds of formula I of claim 1, wherein

R^1 signifies hydrogen, lower-alkyl, lower-alkoxy, lower-alkylthio, halogen or trifluoromethyl;

R^2 signifies hydrogen, halogen, lower-alkoxy or trifluoromethyl; and

R^3 signifies hydrogen, halogen, lower-alkyl, lower-alkylthio, trifluoromethyl, cycloalkyl, lower-alkoxy or trifluoromethoxy; or

R^2 and R^3 together signify butadienyl or methylenedioxy;

R^4 signifies hydrogen, lower-alkyl, trifluoromethyl, lower-alkoxy, lower-alkylthio, lower-alkylthio-lower-alkyl, hydroxy-lower-alkyl, amino-lower-alkyl, lower-alkylamino-lower-alkyl, di-lower-alkylamino-lower-alkyl, amino, lower-alkylamino, di-lower-alkylamino, arylamino, aryl, arylthio, aryloxy, aryl-lower-alkyl or heteroaryl;

R^5 signifies hydrogen, lower-alkanoyl, benzoyl or tetrahydropyran-2-yl;

R^6 to R^9 signify hydrogen, halogen, trifluoromethyl, lower-alkyl, lower-alkoxy, lower-alkylthio, hydroxy, hydroxymethyl,

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

cyano, carboxyl, formyl, methylsulphinyl, methylsulphonyl, methylsulphonyloxy or lower-alkyloxy-carbonyloxy; or

R^7 together with R^6 or R^8 signify butadienyl or $-OCH_2O-$;

Z signifies -O-, -S-, ethylene, vinylene, -CO-, $-OCHR^{10}-$ or $-SCHR^{10}$;

R^{10} signifies hydrogen or lower-alkyl;

X and Y each independently signify O, S or NH;

R^a and R^b signify hydrogen; and

n signifies 1, 2 or 3,

and salts thereof.

3. Compounds according to claim 1 or 2, in which Z is -O-.

4. Compounds according to claims 1-3, in which R^6 signifies lower-alkoxy and R^7, R^8 and R^9 signify hydrogen.

5. Compounds according to claims 1-3, in which R^6 and R^8 signify hydrogen, R^7 signifies lower-alkoxy and R^9 signifies halogen.

6. Compounds according to claims 1-5, in which R^4 is hydrogen, 2-pyrimidinyl, 2- or 3-furyl, 2- or 3-thienyl, morpholino or p-methoxyphenyl.

7. Compounds according to claims 1-6, in which YR^5 is hydroxy, lower-alkoxysulphinyl or furoyloxy.

8. The compounds according to claim 3,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-tolyloxy)-4-pyrimidinyl]benzenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-chlorophenyloxy)-4-pyrimidinyl]benzenesulphonamide,

This Sheet Has Been Replaced

* C L M S *

THIS SHEET HAS BEEN REPLACED

N-[6-(2-hydroxyethoxy)-5-(o-chlorophenoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(m-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-phenoxy-4-pyrimidinyl]benzenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(p-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-ethoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide,

p-(2,2-dimethylpropyl)-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide,

p-isopropyl-N-[6-(2-hydroxyethoxy)-2-methyl-5-(m-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-phenyl-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(2,4,6-trichlorophenoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-6-(2,4,6-trichlorophenoxy)-4-pyrimidinyl]-o-toluenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(2,4,6-trichlorophenoxy)-4-pyrimidinyl]-2,4-xylenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-[(2-methoxy-p-tolyl)-oxy]-4-pyrimidinyl]benzenesulphonamide,

N-[5-(2-methoxy-4-methylphenoxy)pyrimidinyl]-p-isopropylbenzenesulphonamide,

N-[5-(2-methoxy-4-methylphenoxy)6-(2-hydroxyethoxy)-4-pyrimidinyl]-o-ethylbenzenesulphonamide,

p-tert-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-(trifluoromethyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

p-tert-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-(trifluoromethyl)-4-pyrimidinyl]benzenesulphonamide,

N-[5-(1,3-benzodioxol-5-yloxy)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-tertbutylbenzenesulphonamide,

This Sheet Has Been Replaced

* C L M S *

THIS SHEET HAS BEEN REPLACED

N-[5-(1,3-benzodioxol-5-yloxy)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]-o-methoxybenzenesulphonamide,

p-tert-butyl-N-[6-(4-hydroxybutoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(2-naphthyloxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(2-naphthyloxy)-4-pyrimidinyl]-p-tert-butylbenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-propyl-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

p-tert-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-propyl-4-pyrimidinyl]benzenesulphonamide,

α,α,α-trifluoro-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-p-toluenesulphonamide,

p-chloro-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-p-(trifluoromethoxy)benzenesulphonamide,

o-ethyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-p-toluenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-2-naphthylsulphonamide,

p-tert-butyl-N-[6-(3-hydroxypropoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-[(o-methylthio)-phenoxy]-4-pyrimidinyl]benzenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-phenyl-4-pyrimidinyl]benzenesulphonamide,

N-[2-amino-6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]-p-t-butylbenzenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-2-methyl-5-[o-(methylthio)phenoxy]-4-pyrimidinyl]benzenesulphonamide and

p-t-butyl-N-[6-(2-hydroxyethoxy)-2-methyl-5-[o-(R,S-methylsulphinyl)phenoxy]-4-pyrimidinyl]benzenesulphonamide.

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

9. The compounds according to claim 3,

4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-2-methyl-pyrimidin-4-yl]-benzene-sulphonamide,

4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-[(2-(3-furoyloxy)ethoxy]-2-methyl-pyrimidin-4-yl]-benzene-sulphonamide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzene-sulphonamide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzene-sulphonamide,

4-tert-butyl-N-[2-(furan-2-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[2-(furan-3-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(pyridin-2-yl)-pyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(pyridin-4-yl)-pyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(pyridin-3-yl)-pyrimidin-4-yl]-benzenesulphonamide,

2-[4-(4-tert-butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-2-yl]-pyridine 1-oxide,

4-[4-(4-tert-butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-2-yl]-pyridine 1-oxide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-2-[2-(2-hydroxy-ethoxy)ethyl]-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide,

This Sheet Has Been Replaced

* C L M S *

THIS SHEET HAS BEEN REPLACED

4-tert-butyl-N-[2-cyclopropyl-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[2-ethyl-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-2-isopropyl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide,

4-chloro-N-[3-(5-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide,

N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-4-trifluoromethyl-benzenesulphonamide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-2,2'-bipyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[5-(4-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-2,2'-bipyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[5-(4-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-2-methyl-pyrimidin-4-yl]-benzene-sulphonamide,

4-tert-butyl-N-[5-(4-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide,

N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-4-isopropyl-benzenesulphonamide,

N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-4-tert-butyl-benzenesulphonamide,

4-tert-butyl-N-[5-(2-fluoro-6-methoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzene-sulphonamide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-2-(2-methoxy-ethyl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-benzene-sulphonamide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-2-[2-(2-hydroxy-ethoxy)ethyl]-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-benzene-sulphonamide,

(S)-4-tert-butyl-N-[6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-5-(2-methoxy-phenoxy)-2-methyl-pyrimidin-4-yl]-benzenesulphonamide,

This Sheet Has Been Replaced

* C L M S *

THIS SHEET HAS BEEN REPLACED

(R)-4-tert-butyl-N-[6-(2,3-dihydroxy-propoxy)-5-(2-methoxy-phenoxy)-2-methyl-6-(2-pyrimidin-4-yl]-benzene-sulphonamide,

(R)-4-tert-butyl-N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-pyrimidin-4-yl]-benzenesulphonamide,

(S)-4-tert-butyl-N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-pyrimidin-4-yl]-benzenesulphonamide,

(R)-4-tert-butyl-N-(5-fluoro-2-methoxy-phenoxy)-6-(2,3-dihydroxy-propoxy-pyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[6-[(S)-1,3-dioxolan-4-ylmethoxy]-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzene-sulphonamide,

(R)-4-tert-butyl-N-[6-(2,3-dihydroxy-propoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzene-sulphonamide,

4-tert-butyl-N-[6-(R)-1,3-dioxolan-4-ylmethoxy]-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzene-sulphonamide,

(S)-4-tert-butyl-N-[6-(2,3-dihydroxy-propoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzene-sulphonamide,

(R)-4-tert-butyl-N-[6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[6-[(S)-2,3-dihydroxy-propoxy]-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzene-sulphonamide,

(S)-4-tert-butyl-N-[(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[6-[(R)-2,3-dihydroxy-propoxy]-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzene-sulphonamide,

(S)-4-tert-butyl-N-[6-(2,2-dimethyl-1,3-dioxolan-4-yl-methoxy)-2-(furan-3-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide,

This Sheet Has Been Replaced

* C L M S *

THIS SHEET HAS BEEN REPLACED

(R)-4-tert-butyl-N-[2-(furan-3-yl)-6-(2,3-dihydroxy-propoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzene-sulphonamide,

(R)-4-tert-butyl-N-[6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-2-(furan-3-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide,

(S)-4-tert-butyl-N-[2-(furan-3-yl)-6-(2,3-dihydroxy-propoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzene-sulphonamide,

3-methylisoxazole-5-carboxylic acid 2-[6-(4-t-butyl-benzenesulfonamino)-5-(3-methoxyphenoxy)pyrimidin-4-yloxy]-ethyl ester,

indole-2-carboxylic acid 2-[6-(4-t-butylbenzenesulfon-amino)-5-(3-methoxyphenoxy)pyrimidin-4-yloxy]ethyl ester, and

5-[N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-pyrimidin-4-yl]aminosulfonyl]-2-methoxyphenoxy acetic acid ethyl ester.

10. (S)-4-tert-Butyl-N-[6-(2,3-dihydroxy-propyloxy)-5-(2-methoxy-phenoxy)-2-(4-methoxyphenyl)-pyrimidin-4-yl]-benzenesulphonamide.

11. (RS)-4-tert-Butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-2-ethyl-6-(2-methylsulphinyl-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide.

12. (RS)-N-[5-(2-Chloro-5-methoxy-phenoxy)-6-(2-methylsulphinyl-ethoxy)-pyrimidin-4-yl]-1,3-benzodioxol-5-sulphonamide.

13. 4-tert-Butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(pyrimidin-2-yl)-pyrimidin-4-yl]-benzenesulphonamide.

14. Compounds according to claim 1 or 2, in which Z is ethylene or vinylene.

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

15. The compounds according to claim 14,

2-[[5-[(E/Z)-styryl]-6-p-toluenesulphonamido-4-pyrimidinyl]oxy]ethyl acetate,

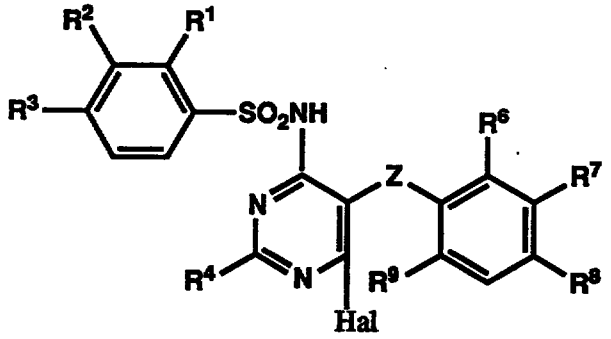
2-[[5-phenethyl-6-p-toluenesulphonamido-4-pyrimidinyl]-oxy]ethyl acetate

N-[6-(2-hydroxyethoxy)-5-phenethyl-4-pyrimidinyl]-p-toluenesulphonamide and

N-[6-(2-hydroxyethoxy)-5-([E/Z)-styryl]-4-pyrimidinyl]-p-toluenesulphonamide.

16. Compounds of the formula

* C L M S *



II

wherein R^1-R^5, R^a, R^b, Y and n have the significance given in claim 1.

17. The compounds of claims 1-15 for use as medicaments.

18. Pharmaceutical preparations, containing a compound of claims 1-15 and usual carriers and adjuvants.

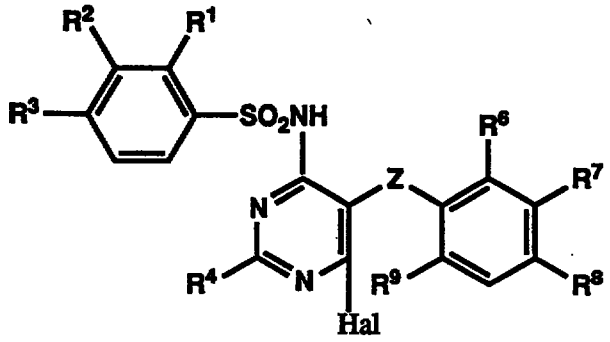
19. The use of compounds of claims 1-15 as active ingredients in the manufacture of medicaments for the treatment of disorders which are associated with endothelin activities, especially circulatory disorders such as hypertension, ischaemia, vasospasms and angina pectoris.

20. A process for the manufacture of compounds of claims 1-15, which process comprises

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

a) reacting a compound of the formula



II

wherein R^1, R^2, R^3, R^4 and R^6 have the significance given above and Hal is halogen,

with a compound of the formula

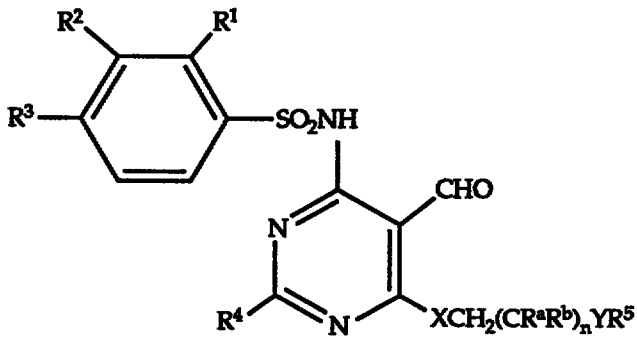


III

wherein X, Y, n, R^a, R^b and R^5 have the significance given above and M represents an alkali metal,

or

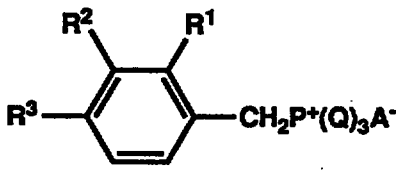
b) reacting a compound of the formula



IV

wherein R^1-R^5, R^a, R^b, X, Y and n have the significance given above,

with a compound of the formula



V

This Sheet Has Been Replaced

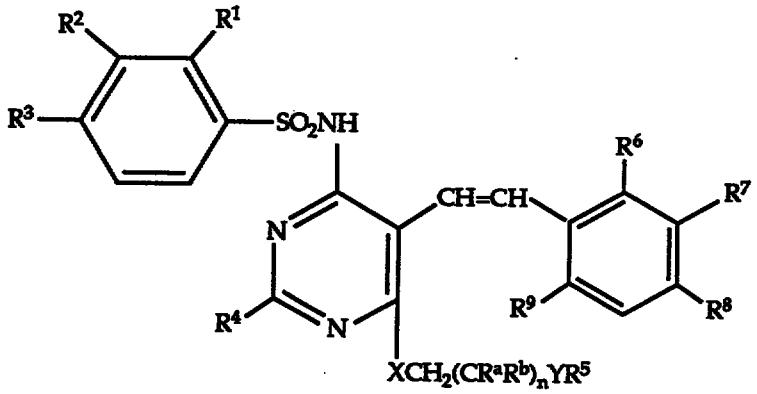
THIS SHEET HAS BEEN REPLACED

wherein R^6-R^8 have the significance given above; Q is aryl and A^- is an anion,

CLMS

or

c) hydrogenating a compound of the formula

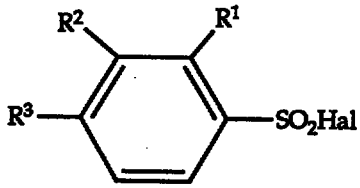


VI

wherein R^1-R^8, R^a, R^b, X, Y and n have the significance given above,

or

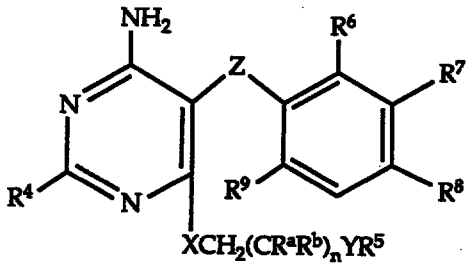
d) reacting a compound of the formula



XIV

with a compound of the formula

This Sheet Has Been Replaced



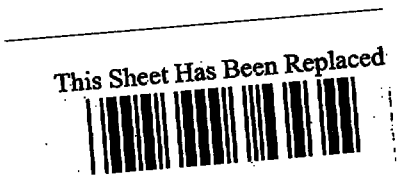
XV

wherein R^1-R^9, R^a, R^b, X, Y, Z and n have the significance given above,

THIS SHEET HAS BEEN REPLACED

and, if desired, modifying substituents present in the compound of formula I obtained and/or converting the compound of formula I obtained into a salt.





THIS SHEET HAS BEEN REPLACED

RAN 4019/115

Abstract

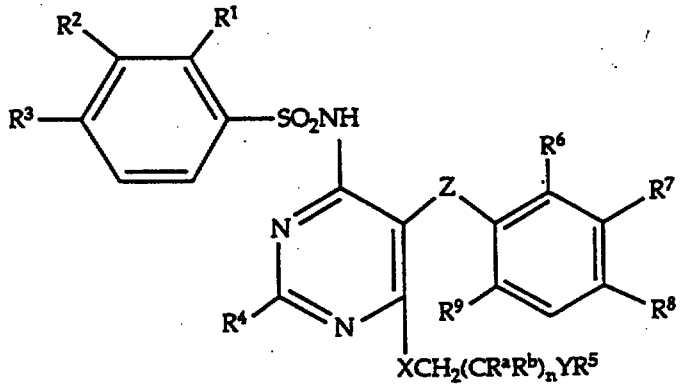
The novel sulphonamides of formula I, in which the symbols R^1-R^9, R^a, R^b, X, Y and n have the significance given in the description and salts thereof can be used as active ingredients for the manufacture of medicaments for the treatment of circulatory disorders, especially hypertension, ischemia, vasopasms and angina pectoris.

9604376-5
IPOS copy

REPLACEMENT SHEET
15 OCT 1996

NOVEL SULFONAMIDES

The present invention is concerned with novel sulphonamides and their use as medicaments. In particular, the invention is concerned with novel compounds of the formula



I

wherein

R^1 signifies hydrogen, lower-alkyl, lower-alkoxy, lower-alkylthio, halogen or trifluoromethyl;

R^2 signifies hydrogen, halogen, lower-alkoxy, trifluoromethyl or $-OCH_2COOR^a$; and

R^3 signifies hydrogen, halogen, lower-alkyl, lower-alkylthio, trifluoromethyl, cycloalkyl, lower-alkoxy or trifluoromethoxy; or

R^2 and R^3 together signify butadienyl, methylenedioxy, ethylenedioxy or isopropylidenedioxy;

R^4 signifies hydrogen, lower-alkyl, cycloalkyl, trifluoromethyl, lower-alkoxy, lower-alkylthio, lower-alkylthio-lower-alkyl, hydroxy-lower-alkyl, hydroxy-lower-alkoxy, lower-alkoxy-lower-alkyl, hydroxy-lower-alkoxy-lower-alkyl, hydroxy-lower-alkoxy-lower-alkoxy, lower-alkylsulphinyl, lower-alkylsulphonyl, 2-methoxy-3-hydroxypropoxy, 2-hydroxy-3-phenylpropyl, amino-lower-alkyl, lower-alkylamino-lower-alkyl, di-lower-alkylamino-lower-alkyl, amino, lower-alkylamino, di-lower-alkylamino, arylamino, aryl, arylthio, aryloxy, aryl-lower-alkyl or heterocyclyl;

REPLACEMENT SHEET
15 OCT 1996

R^5 signifies hydrogen, lower-alkyl, lower-alkanoyl, benzoyl, heterocyclylcarbonyl, heterocyclylmethyl or tetrahydropyran-2-yl;

R^6 to R^9 signify hydrogen, halogen, trifluoromethyl, lower-alkyl, lower-alkoxy, lower-alkylthio, hydroxy, hydroxymethyl, cyano, carboxyl, formyl, methylsulphinyl, methylsulphonyl, methylsulphonyloxy or lower-alkyloxy-carbonyloxy; or

R^7 together with R^6 or R^8 signify butadienyl, methylenedioxy, ethylenedioxy or isopropylidenedioxy;

Z signifies -O-, -S-, ethylene, vinylene, -CO-, $-OCHR^{10}-$ or $-SCHR^{10}$;

R^{10} signifies hydrogen or lower-alkyl;

X and Y each independently signify O, S or NH; or YR^5 also signifies lower-alkylsulphinyl or $-OCH_2CH(OR^c)CH_2OR^d$;

R^a, R^b, R^c and R^d each independently signify hydrogen or lower-alkyl; or R^c and R^d together signify methylene, ethylene or isopropylidene; and

n signifies 1, 2 or 3,

and salts thereof.

The term "lower" used here denotes groups with 1-7 C atoms, preferably 1-4 C atoms. Alkyl, alkoxy and alkylthio groups as well as alkyl groups as components of alkanoyl groups can be straight-chain or branched. Methyl, ethyl, propyl, isopropyl, butyl, sec. and tert.butyl are examples of such alkyl groups. Halogen denotes fluorine, chlorine, bromine and iodine, with chlorine being preferred. Cycloalkyl residues 3 to 8 C atoms, such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. Examples of aryl residues are phenyl and substituted phenyl residues, with halogen, lower-alkyl, lower-alkoxycarboxyl and trifluoromethyl especially coming into consideration as substituents. Examples of heterocyclyl residues are especially substituted, e.g. by lower alkyl, lower alkoxy, halogen, aryl, aryl-lower alkyl mono- or disubstituted, a unsubstituted mono or bicyclic 5- and 6-membered heterocyclic residues with oxygen, nitrogen or sulphur as the hetero atom, such as 2- and 3-furyl, pyrimidinyl, 2-, 3- and 4-pyridyl and pyridyl N-oxide, 1,2- and 1,4-diazinyl, morpholino, 2- and 3-thienyl, isoxazolyl, oxazolyl,

REPLACEMENT SHEET
15 OCT 1996

imidazolyl, pyrrolyl, benzofuranyl, benzothienyl, indolyl, purinyl, quinolyl, isoquinolyl and quinazolyl.

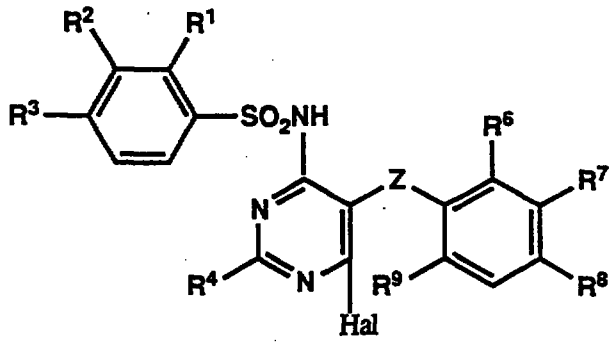
The compounds of formula I given above are inhibitors of endothelin receptors. They can accordingly be used for the treatment of disorders which are associated with endothelin activities, especially circulatory disorders such as hypertension, ischaemia, vasospasms and angina pectoris.

A preferred group of compounds within formula I comprises those in which Z is -O- and, furthermore, those in which R^6 is lower-alkoxy, especially methoxy, and R^7, R^8 and R^9 signify hydrogen; or R^6 and R^8 signify hydrogen, R^7 signifies lower-alkoxy, especially methoxy, and R^9 signifies halogen, especially chlorine.

Preferred substituents R^1 and R^2 are hydrogen and preferred substituents R^3 are lower-alkyl or together with R^2 methylene-dioxy. Preferred substituents R^4 are hydrogen, 2-pyrimidinyl, 2- and 3-furyl, 2- and 3-thienyl, morpholino and p-methoxyphenyl. X is preferably oxygen. Preferred residues YR^5 are hydroxy, lower-alkoxysulphinyl and furoyloxy.

The compounds of formula I can be manufactured by

a) reacting a compound of the formula



II

wherein R^1, R^2, R^3, R^4 and R^6 have the significance given above and Hal is halogen,

with a compound of the formula

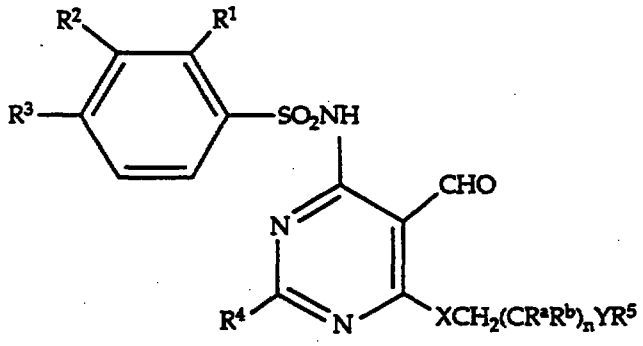
REPLACEMENT SHEET
15 OCT 1996

$$MX(CH_2)(CR^aR^b)_nYR^5 \qquad III$$

wherein X, Y, n, R^a, R^b and R^5 have the significance given above and M represents an alkali metal,

or

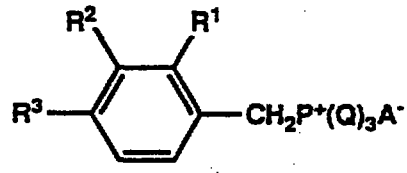
b) reacting a compound of the formula



IV

wherein R^1-R^5, R^a, R^b, X, Y and n have the significance given above,

with a compound of the formula



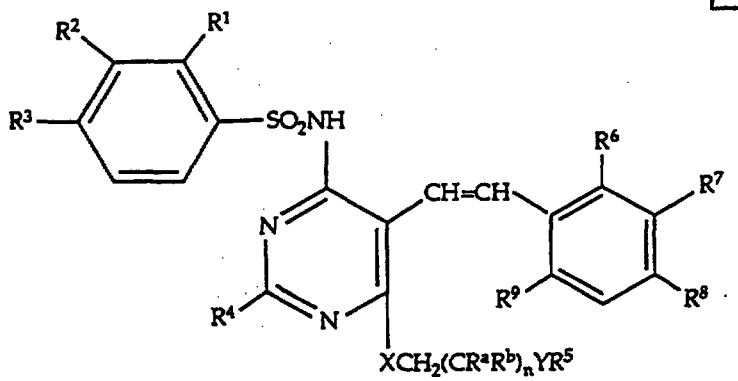
V

wherein R^6-R^8 have the significance given above; Q is aryl and A^- is an anion,

or

c) hydrogenating a compound of the formula

REPLACEMENT SHEET
15 OCT 1996

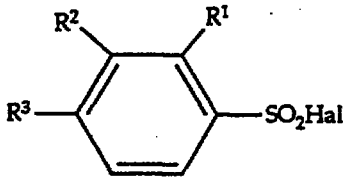


VI

wherein R^1-R^8, R^a, R^b, X, Y and n have the significance given above,

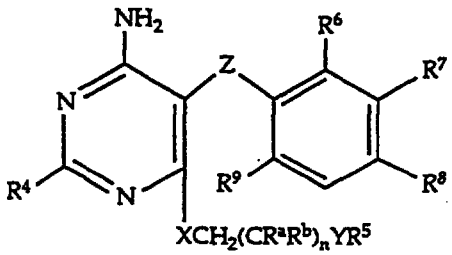
or

d) reacting a compound of the formula



XIV

with a compound of the formula



XV

wherein R^1-R^9, R^a, R^b, X, Y, Z and n have the significance given above,

and, if desired, modifying substituents present in the compound of formula I obtained and/or converting the compound of formula I obtained into a salt.

The reaction of a compound of formula II with a compound of formula III is conveniently carried out using the glycol corresponding to the compound III, e.g. in ethylene glycol when n = 2. The alkali metal M is preferably sodium. The reaction is

REPLACEMENT SHEET
15 OCT 1996

conveniently carried out while heating, e.g. to 40-120°C. In a preferred embodiment the monosodium salt of ethylene glycol, propylene glycol or butylene glycol is used as the compound of formula III.

The reaction of a compound of formula IV with a compound of formula V can be carried out in a manner known per se under the usual conditions of a Wittig reaction. The aryl residue Q is preferably phenyl; examples of anions A^- are Cl^-. Br^-, HSO_4^- and tosyloxy. The reaction partners are conveniently reacted with each other in the presence of an acid-binding agent, e.g. in the presence of a strong base such as e.g. butyllithium, sodium hydride or the sodium salt of dimethyl sulphoxide, or K tert.-butylate, but preferably in the presence of an optionally lower alkyl-substituted ethylene oxide such as 1,2-butylene oxide, optionally in a solvent, e.g. in an ether such as diethyl ether or tetrahydrofuran or in an aromatic hydrocarbon such as benzene, in a temperature range lying between room temperature and the boiling point of the reaction mixture. In the Wittig reaction interfering reactive groups in the reaction partners, such as carboxyl or amino, are conveniently intermediately protected, e.g. as a carboxylic acid ester or as the tert.butoxycarbonylamino derivative.

The hydrogenation of a compound of formula VI can be carried out in a manner known per se for the hydrogenation of olefinic double bonds, e.g. with hydrogen at normal pressure or elevated pressure in the presence of noble metal catalysts such as Pd, especially Pd on carriers such as Pd/C.

Any hydroxy groups and an amino group that may be present in the substituent R^4 to R^9 of the compound of formula XV are suitably protected when reacting this compound. Hydroxy groups may be protected, e.g., by silyl groups such as dimethyl t-butyl silyl, or acyl groups such as acetyl; and amino groups may be protected by t-butoxy carbonyl a benzyloxy carbonyl. These protecting groups can be inserted and, after the reaction of the compounds XIV and XV, be cleaved by methods known in the art.

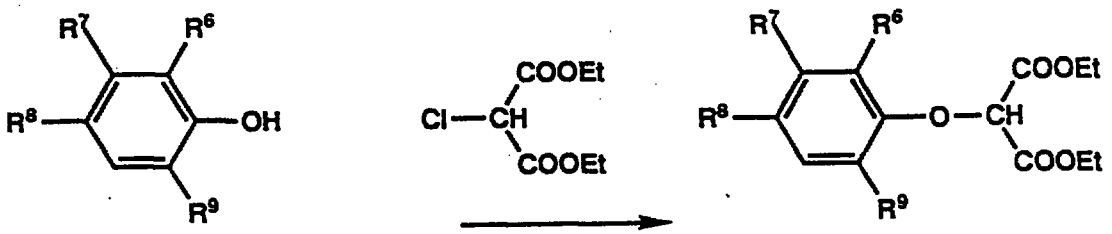
REPLACEMENT SHEET
15 OCT 1996

Substituents present in the thus-obtained compound of formula I can be modified. For example, a hydroxy group YR^5 can be esterified or etherified. A hydroxy group YR^5 can be converted into an ether group, e.g. the tetrahydropyranyl ether, or an ester group, e.g. the acetate, or such groups or ketals, which can be present e.g. as a substituent YR^5, contained in the initially obtained reaction product can be cleaved off in a manner known per se. Methylthio groups can be oxidized to methylsulphinyl or methyl- sulphonyl groups. Furthermore, N-heterocyclic residues such as pyridyl can be oxidized to N-oxides. All of these reactions can be carried out according to methods known per se. The compounds of formula I can be converted into salts, e.g. alkali salts such as Na and K salts, in a manner known per se.

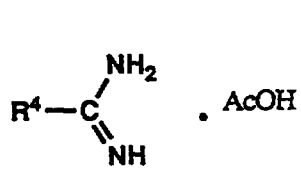
The compounds which are used as starting materials, insofar as they are not known or their preparation is described hereinafter, can be prepared in analogy to known methods or to the methods described hereinafter.

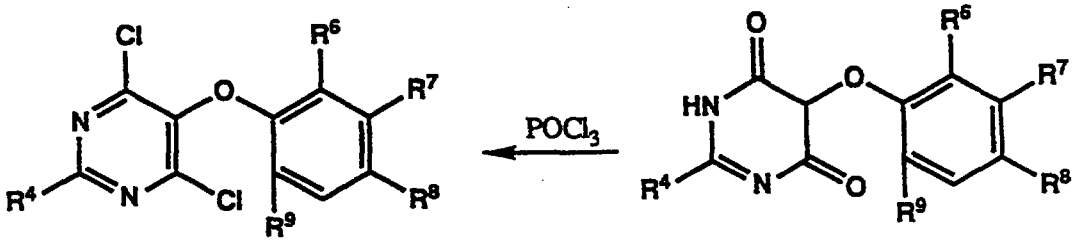
Compounds of formula II can be obtained as illustrated in the following Formula Scheme:

REPLACEMENT SHEET
15 OCT 1996

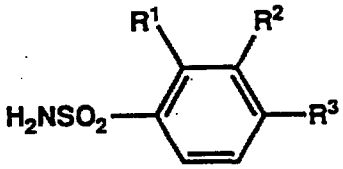


VII VIII





X IX

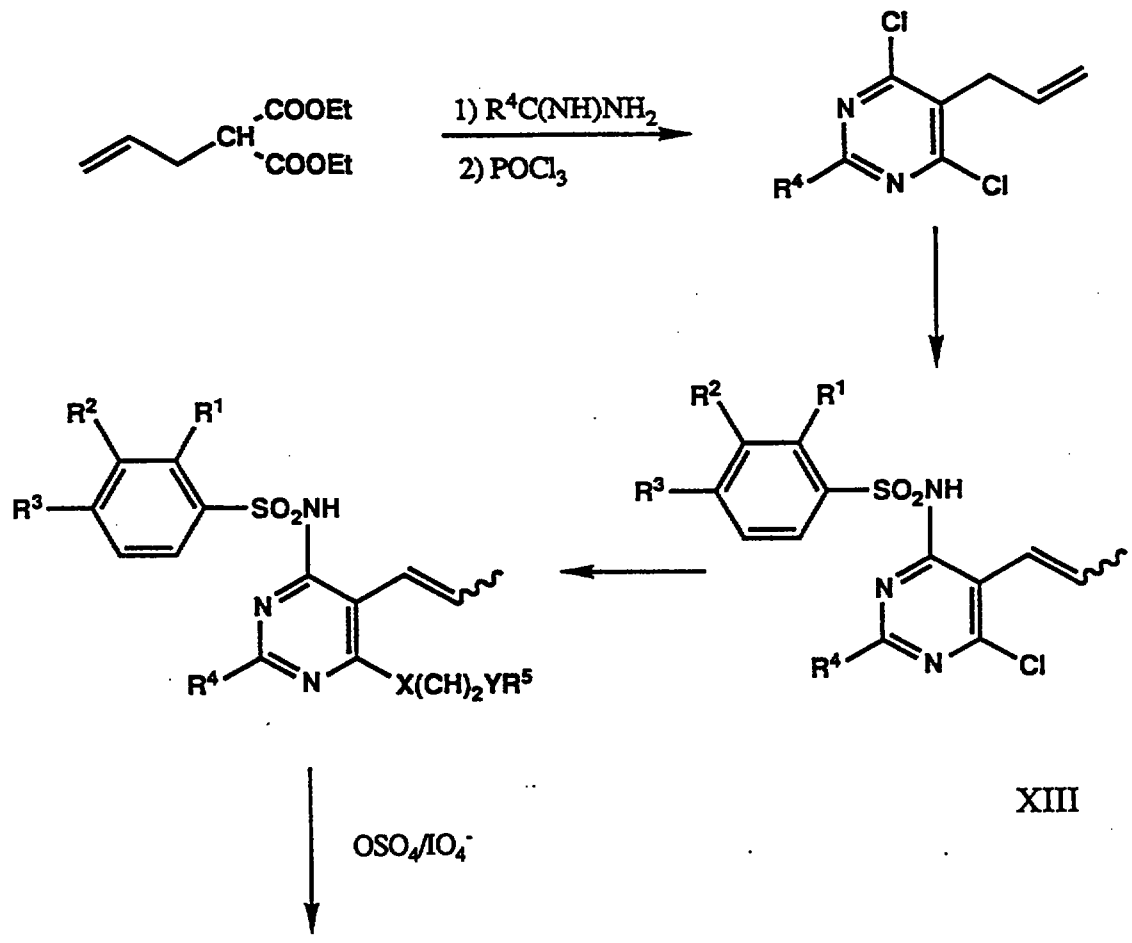


II XI

REPLACEMENT SHEET
15 OCT 1996

Alkylation of the phenol VII with diethyl chloromalonate yields compound VIII which is condensed with formamidine acetate or a homologous compound such as acetamidine acetate to the pyrimidinedione derivative IX. Using phosphorus oxychloride there is obtained therefrom the dichloro compound X which yields compound II upon reaction with a stoichiometric amount of compound XI. All of these reactions are standard operations and can be carried out under conditions which are usual for such reactions and which are familiar to a person skilled in the art.

Compounds of formula IV can be obtained according to the Reaction Scheme sketched hereinafter:



XIII

IV

REPLACEMENT SHEET
15 OCT 1996

Condensation of diethyl allyl malonate with formamidine acetate or a R^4-substituted derivative followed by replacement of the hydroxy groups by chlorine in the pyrimidinedione obtained yields the dichloropyrimidine XII which is condensed with a R^1, R^2, R^3-benzenesulphonamide alkali salt with rearrangement of the allyl double bond to the compound XIII. Reaction of compound XIII with a compound III in the manner already described leads to compound XIV. Oxidative cleavage of the double bond of the propenyl side-chain in compound XIV finally yields the aldehyde IV.

The inhibitory activity of the compounds of formula I on endothelin receptors can be demonstrated using the test procedures described hereinafter:

I: Inhibition of endothelin binding to human placenta membranes (see. Life Sci 44:1429 (1989))

Human placenta is homogenized in 5 mM Tris buffer, pH 7.4, which contains 1 mM $MgCl_2$ and 250 mM sucrose. The homogenizate is centrifuged at 4°C and 3000 g for 15 minutes, the supernatant containing the plasma membrane fraction is centrifuged with 72000 g for 30 minutes and the precipitate is washed with 75 mM Tris buffer, pH 7.4, which contains 25 mM $MgCl_2$. Thereafter, precipitate obtained from in each case 10 g of original tissue is suspended in 1 ml of 75 mM Tris buffer, pH 7.4, containing 25 mM $MgCl_2$ and 250 mM sucrose, and freeze-dried at -20°C in 1 ml aliquots.

For the binding assay, the freeze-dried membrane preparations are thawed and, after centrifugation at 20°C and 25000 g for 10 minutes, re-suspended in assay buffer (50 mM Tris buffer, pH 7.4, containing 25 mM $MnCl_2$, 1 mM EDTA and 0.5% of bovine serum albumin). 100 ml of this membrane suspension containing 70 mg of protein are incubated with 50 ml of ^{125}I-endothelin (specific activity 2200 Ci/mMol) in assay buffer (25000 cpm, final concentration 20 pM) and 100 ml of assay buffer containing varying concentrations of test compound. The

REPLACEMENT SHEET
15 OCT 1996

incubation is carried out at 20°C for 2 hours or at 4°C for 24 hours. The separation of free and membrane-bound radio-ligands is carried out by filtration over a glass fibre filter.

The inhibitory activity of compounds of formula I determined in this test procedure is given in Table 1 as the IC_{50}, i.e. as the concentration [mM] which is required to inhibit 50% of the specific binding of ^{125}I-endothelin.

Table 1

Compound of Example	IC_{50} [mM]
1	0.115
2	0.100
6	0.200
12	0.125
24	0.073
25	0.050
27	0.099

II. Inhibition of endothelin-induced contractions in isolated rat aorta rings

Rings with a length of 5 mm were cut out from the thorax aorta of adult Wistar-Kyoto rats. The endothelium was removed by lightly rubbing the internal surface. Each ring was immersed at 37°C in 10 ml of Krebs-Henseleit solution in an isolated bath while gassing with 95% O_2 and 5% CO_2. The isometric stretching of the rings was measured. The rings were stretched to a pre-tension of 3 g. After incubation for 10 minutes with the test compound or vehicle cumulative dosages of endothelin-1 were added. The activity of the test compound was determined by calculating the dosage ratios, i.e. the shift to the right (shift to higher values) of the EC_{50} of endothelin induced by 100 mM of

REPLACEMENT SHEET
15 OCT 1996

test compound, with EC_{50} denoting the endothelin concentration required for a half-maximum contraction. The greater this dosage ratio is the more potent the test compound is in inhibiting the biological activity of endothelin-1. The EC_{50} of endothelin in the absence of test compounds is 0.3 nM.

The thus-obtained values for the shift to the right of the EC_{50} of endothelin with compounds of formula I are given in Table 2.

Table 2

Compound of Example	Dosage ration (Shift to the right)
1	165
6	395
24	257
25	238

III. The inhibitory activity of the compounds of formula I on vasoconstriction can be observed in vivo in rats in the test procedure described hereinafter:

Rats were anaesthetized with Na thiobutabarbital (100 mg/kg i.p.). A catheter for measuring the systemic arterial blood pressure was placed through the femoral artery and a catheter was placed in the vena cava via the femoral vein for injection of the test compounds. A Doppler sonde was placed around the left renal artery and attached to a Doppler measuring apparatus. A renal ischaemia was produced by pinching off the left renal artery at its point of exit for 45 minutes. 10 minutes prior to the induction of the ischaemia he test compounds were administered intraarterially (i.a.) in dosages of 5 mg/kg or intravenously (i.v.) in dosages of 10 mg/kg. In control tests the

renal perfusion was reduced by 43 ± 4% compared to the pre-ischaemic value.

The results obtained with two compounds of formula I are given in Table 3.

Compound of Example	% Decrease in renal perfusion
1	13.4 ± 5.2
6	11.7 ± 4.7

On the basis of their capability of inhibiting endothelin binding, the compounds of formula I can be used as medicaments for the treatment of disorders which are associated with vasoconstriction of increasing occurrences. Examples of such disorders are high blood pressure, coronary disorders, cardiac insufficiency, renal and myocardial ischaemia, renal insufficiency, dialysis, cerebral ischaemia, cardiac infarct, migraine, subarachnoid haemorrhage, Raynaud syndrome and pulmonary high pressure. They can also be used in atherosclerosis, the prevention of restenosis after balloon-induced vascular dilation, inflammations, gastric and duodenal ulcers, ulcus cruris, gram-negative sepsis, shock, glomerulonephtritis, renal colic, glaucoma, asthma, in the therapy and prophylaxis of diabetic complications and complications in the administration of cyclosporin, as well as other disorders associated with endothelin activities.

The compounds of formula I can be administered orally, rectally, parentally, e.g. intravenously, intramuscularly, subcutaneously, intrathecally or transdermally, or sublingually or as opththalmological preparations, or as an areosol. Capsules, tablets, suspensions or solutions for oral administration,

REPLACEMENT SHEET
15 OCT 1996

suppositories, injection solutions, eye drops, salves or spray solutions are examples of application forms.

Intravenous, intramuscular or oral application is a preferred form of use. The dosages in which the compounds of formula I are administered in effective amounts depend on the nature of the specific active ingredient, the age and the requirements of the patient and the mode of application. In general, dosages of about 0.1-100 mg/kg body weight per day come into consideration. The preparations containing the compounds of formula I can contain inert or also pharmacodynamically active additives. Tablets or granulates e.g. can contain a series of binders, fillers, carriers or diluents. Liquid preparations can be present, 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, flavour-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 organic or inorganic substances, e.g. water, gelatine, lactose, starch, magnesium stearate, talc, gum arabic, polyalkylene glycols and the like. It is a prerequisite that all adjuvants used in the manufacture of the preparations are non-toxic.

The following Examples illustrate the invention in more detail. Of the abbreviations used therein THF signifies tetrahydrofuran; DMSO signifies dimethyl sulphoxide; MeOH signifies methanol; b.p. signifies boiling point; and m.p. signifies melting point.

Example 1

a) 886 mg of p-t-butyl-N-[6-chloro-5-(o-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide were added to a sodium glycolate solution from 3.0 g of ethylene glycol and 138 mg of

REPLACEMENT SHEET
15 OCT 1996

sodium. The reaction mixture was stirred at 95°C under argon for 4 hours. Thereafter, the ethylene glycol was distilled off and the residue was partitioned between ethyl acetate and 1N hydrochloric acid. The organic phase was dried and the solvent was distilled off. The residue was crystallized from diisopropyl ether. There were obtained 870 mg of p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide. M.p. 143-148°C.

b) 775 mg of the previously obtained sulphonamide were dissolved in 20 ml of warm ethanol. The solution was treated with a stoichiometric amount of sodium ethylate, thereafter the ethanol was distilled off until a precipitate formed. 3 ml of isopropyl ether were added to complete the precipitation. There were obtained 775 mg of p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide sodium, m.p. >250°C.

The starting material was prepared as follows:

c) 25 g of guaiacol and 37 g of dimethyl chloromalonate were added dropwise in succession to a sodium methylate solution from 150 ml of methanol and 4.6 g of sodium. The suspension was stirred at 45°C for 1 hour with the exclusion of moisture, thereafter the methanol was distilled off. The residue was taken up in 200 ml of toluene and washed with water, 1% sodium hydroxide solution and water until the organic phase was colourless. After drying and evaporating the solvent the residue was distilled. There were obtained 39.5 g of dimethyl (o-methoxyphenoxy)malonate. B.p. 128°C/7 Pa.

d) 5.5 g of formamidine acetate and 12.7 g of dimethyl (o-methoxyphenoxy)malonate were added while cooling with ice to a sodium methylate solution from 150 ml of methanol and 3.5 g of sodium. The reaction mixture was stirred at 0-5°C for 1 hour with the exclusion of moisture, then at room temperature for 2 hours. Thereafter, the solvent was distilled off, the residue was taken up in 100 ml of water, the aqueous phase was

REPLACEMENT SHEET
15 OCT 1996

extracted with toluene and the organic phases were discarded. The aqueous phase was acidified, whereby 5-(o-methoxyphenoxy)-6-hydroxy-4(3H)-pyrimidinone separated.

e) 9.4 g of the previously obtained pyrimidinone were suspended in 20 ml of acetonitrile and treated with 12 g of collidine. Thereafter, 5 ml of $POCl_3$ in 15 ml of acetonitrile were added dropwise with the exclusion of moisture. The reaction mixture was stirred at reflux temperature for 8 hours, thereafter the solvent and excess reagent were distilled off. The residue was taken up in methylene chloride and washed with water, saturated sodium hydrogen carbonate solution and saturated sodium chloride solution. The solution was concentreated and passed over a short silica gel column with methylene chloride as the elution agent. The eluate was concentrated, the residue was recrystallized from ethanol/hexane. There were obtained 8.5 g of 4,6-dichloro-5-(o-methoxyphenoxy)pyrimidine, m.p. 79-80°C.

f) 0.8 g of 4,6-dichloro-5-(o-methoxyphenoxy)pyrimidine and 1.5 g of p-t-butylsulphonamide K in 3 ml of dry dimethyl sulphoxide were heated to 120°C under argon for 1.5 hours. Thereafter, the dimethyl sulphoxide was distilled off, the residue was partitioned between ethyl acetate and 1N hydrochloric acid and the organic phase was washed neutral. The organic phase was dried, the solvent was evaporated and the residue was treated with 3 ml of methanol. There were obtained 950 mg of p-t-butyl-N-[6-chloro-5-(o-methoxyphenoxy)-4-pyrimidinyl]benzene-sulphonamide, m.p. 152°C.

Example 2

In analogy to Example 1, paragraph a), from p-isopropyl-N-[6-chloro-5-(o-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide there was obtained N-[6-(hydroxyethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, m.p. 142-143°C. The compound was converted in analogy to Example 1,

REPLACEMENT SHEET
15 OCT 1996

paragraph b), in almost quantitative yield into the water-soluble sodium salt.

The starting material was obtained in analogy to Example 1, paragraph f), by reacting 540 mg of 4,6-dichloro-5-(o-methoxyphenoxy)pyrimidine and 360 mg of p-isopropylbenzenesulphonamide potassium.

Example 3

In analogy to Example 1, paragraph a), from N-[6-chloro-5-(o-tolyloxy)-4-pyrimidinyl]-p-t-butylsulphonamide there was obtained p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-tolyloxy)-4-pyrimidinyl]benzenesulphonamide. M.p. 190-192°C.

The starting material was prepared as follows:

Diethyl bromomalonate was converted with sodium o-cresolate into diethyl (o-tolyloxy)malonate, b.p. 120°C/7 Pa, in analogy to Example 1, paragraph c).

In analogy to Example 1, paragraph d), from the foregoing malonic ester there was obtained 5-(o-tolyloxy)-6-hydroxy-4(3H)-pyrimidinone from which there was obtained in analogy to Example 1e) 4,6-dichloro-(o-tolyloxy)pyrimidine, m.p. 78-79°C (ethanol/hexane). Reaction of the latter compound with p-t-butylsulphonamide potassium finally yielded N-[6-chloro-5-(o-tolyloxy)-4-pyrimidinyl]-p-t-butylsulphonamide.

Example 4

In analogy to Example 1, paragraph a), from p-t-butyl-N-[2-chloro-5-(o,-chlorophenoxy)-4-pyrimidinyl]benzenesulphonamide there was obtained p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-chlorophenyloxy)-4-pyrimidinyl]benzenesulphonamide, m.p. 178-179°C (from diisopropyl ether).

The starting material was prepared as follows:

REPLACEMENT SHEET
15 OCT 1996

In analogy to Example 1, paragraph e), from diethyl bromomalonate and sodium o-chlorophenolate there was obtained diethyl (o-chlorophenoxy)malonate as a colourless liquid which was converted in analogy to Example 1, paragraph d), into 5-(o-chlorophenoxy)-6-hydroxy-4(3H)pyrimidinone. From the latter compound there was obtained in analogy to Example 1, paragraph e), 4,6-dichloro-5-(o-chlorophenoxy)pyrimidine, m.p. 76-77°C (from ethanol/hexane), and from this by reaction with p-t-butylsulphonamide potassium there was obtained p-t-butyl-N-[2-chloro-5-(o-chlorophenoxy)-4-pyrimidinyl]benzenesulphonamide, m.p. 186-187°C (from methanol).

Example 5

In an analogy to Example 1, paragraph a), from N-[6-chloro-5-(o-chlorophenoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide there was obtained N-[6-(2-hydroxyethoxy)-5-(o-chlorophenoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, m.p. 174-175°C (from ethyl acetate).

The starting material was prepared in analogy to Example 1, paragraph f), from 4,6-dichloro-5-(o-chlorophenoxy)pyrimidine and p-isopropylbenzenesulphonamide potassium. M.p. 174-176°C (from methanol).

Example 6

In analogy to Example 1, paragraph a), from p-t-butyl-N-[6-chloro-5-(m-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide there was obtained p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(m-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide, m.p. 165-167°C (from diisopropyl ether).

The potassium salt, m.p. 213-215°C, was obtained by reacting the sulphonamide with 0.5N KOH in ethanol.

REPLACEMENT SHEET
15 OCT 1996

The sodium salt was prepared in analogy to Example 1, paragraph b). M.p. 265-270°C (from diisopropyl ether).

The starting material was prepared as follows:

Diethyl bromomalonate was converted with sodium m-methoxyphenolate in analogy to Example 1, paragraph c), into diethyl (m-methoxyphenoxy)malonate, colourless liquid. B.p. 143°C/0.05 Torr. The thus-obtained malonic ester was converted in analogy to Example 1, paragraph d), into 5-(m-methoxyphenoxy)-6-hydroxy-4(3H)-pyrimidinone from which in analogy to Example 1, paragraph e), there was prepared 4,6-dichloro-5-(m-methoxyphenoxy)pyrimidine, m.p. 109-110°C. Reaction of the last-named compound with p-t-butylbenzenesulphonamide potassium yielded p-t-butyl-N-[6-chloro-5-(m-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide, m.p. 152°C (from methanol).

Example 7

In analogy to Example 1, paragraph a), from p-t-butyl-N-[6-chloro-5-phenoxy-4-pyrimidinyl]benzenesulphonamide there was obtained p-t-butyl-N-[6-(2-hydroxyethoxy)-5-phenoxy-4-pyrimidinyl]benzenesulphonamide, m.p. 165-167°C (from diisopropyl ether).

The starting material was prepared as follows:

Diethyl bromomalonate was converted with sodium phenolate in analogy to Example 1, paragraph c), into diethyl phenoxymalonate, b.p. 140°C/0.05 Torr. From the malonic ester there was obtained in analogy to Example 1, paragraph e), 5-phenoxy-6-hydroxy-4(3H)pyrimidinone and from this there was obtained in analogy to Example 1, paragraph e), 4,6-dichloro-5-phenoxypyrimidine, m.p. 89-90°C (from ethanol/hexane). Reaction of the last-named compound with p-t-butylbenzenesulphonamide potassium yielded p-t-butyl-N-[6-chloro-5-phenoxy-4-pyrimidinyl]-benzenesulphonamide, m.p. 143-144°C.

REPLACEMENT SHEET
15 OCT 1996

Example 8

In analogy to Example 1, paragraph a), from 4,6-dichloro-5-(p-methoxyphenoxy)-4-pyrimidine there was obtained p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(p-methoxyphenoxy)-4-pyrimidinyl]-benzenesulphonamide, m.p. 141-142°C.

The starting material was prepared in analogy to Example 1, paragraph c), d) and e), by reacting diethyl bromomalonate with sodium p-methoxyphenolate to diethyl (p-methoxyphenoxy)malonate, b.p. 140°C/7 Pa, and reaction further to 5-(p-methoxyphenoxy)-6-hydroxy-4(3H)pyrimidinone and, respectively, 4,6-dichloro-5-(p-methoxyphenoxy)-4-pyrimidine, m.p. 107-108°C (from ethanol/hexane).

Example 9

In analogy to Example 1, paragraph a), from p-t-butyl-N-[6-chloro-5-(o-ethoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide there was obtained p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-ethoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide, m.p. 120-121°C (from diisopropyl ether).

The starting material was prepared from dimethyl chloromalonate in analogy to Example 1, paragraph c), d), e) and f), via the following intermediates:

Dimethyl (o-ethoxyphenoxy)malonate, b.pt. 150°C/7 Pa,
5-(o-ethoxyphenoxy)-6-hydroxy-4(3H)pyrimidinone,
4,6-dichloro-5-(o-ethoxyphenoxy)-4-pyrimidine,
5-p-t-butyl-N-[6-chloro-5-(o-ethoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide, m.p. 162-163°C (from methanol).

Example 10

In analogy to Example 1, paragraph a), from p-(2,2-dimethylpropyl)-N-[6-chloro-5-(o-methoxyphenoxy)-4-pyrimi-

REPLACEMENT SHEET
15 OCT 1996

dinyl]benzenesulphonamide there was obtained p-(2,2-dimethylpropyl)-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide, m.p. 136-137°C (from diisopropyl ether).

The starting material was prepared in analogy to Example 1, paragraph c), d) and f), via the following intermediates:

p-(2,2-Dimethylpropyl)benzenesulphonyl chloride, b.p. 105°C/0.005 Torr.,

2,2-dimethyl-p-(2,2-dimethylpropyl)benzenesulphonamide potassium,

p-(2,2-dimethylpropyl)-N-[6-chloro-5-(o-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide, m.p. 164-165°C (from methanol).

Example 11

In analogy to Example 1, paragraph a), from N-[6-chloro-2-methyl-5-(m-methoxyphenoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, m.p. 152-153°C, there was obtained p-isopropyl-N-[6-(2-hydroxyethoxy)-2-methyl-5-(m-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide, m.p. 129-130°C (from diisopropyl ether).

The starting material was prepared as follows:

In analogy to Example 1, paragraph e), using acetamidine hydrochloride in place of formamidine acetate, dimethyl (m-methoxyphenoxy)malonate was converted into 5-(m-methoxyphenoxy)-2-methyl-6-hydroxy-4(3H)pyrimidinone. Therefrom there was prepared in analogy to Example 1, paragraph e), 4,6-dichloro-2-methyl-5-(m-methoxyphenoxy)pyrimidine and therefrom with p-isopropylbenzenesulphonamide potassium there was prepared N-[6-chloro-2-methyl-5-(m-methoxyphenoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, m.p. 152-153°C (from methanol).

REPLACEMENT SHEET
15 OCT 1996

Example 12

In analogy to Example 1, paragraph a), from N-[6-chloro-5(-(o-methoxy)-2-phenyl-4-pyrimidinyl]-p-isopropylbenzene-sulphonamide there was obtained N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-phenyl-4-pyrimidinyl]-p-isopropylbenzene-sulphonamide.

The starting material was prepared in analogy to Example 1, paragraph d), e) and f), from dimethyl (o-methoxyphenoxy)malonate via 5-(o-methoxy)-2-phenyl-6-hydroxy-4(3H)-pyrimidinone, 4,6-dichloro-2-phenyl-5-(o-methoxyphenoxy)pyrimidine, m.p. 135-136°C, and N-[6-chloro-5-(o-methoxy)-2-phenyl-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, m.p. 190-191°C (from methanol).

Example 13

1.3 ml of 1.6M butyllithium in hexane were added at -20°C to 780 mg of benzyltriphenylphosphonium chloride in 10 ml of abs. tetrahydrofuran. The reaction mixture was stirred at -20°C for 15 minutes and thereafter treated with 280 mg of 2-[(5-formyl-6-p-toluenesulphonamido-4-pyrimidinyl)oxy]ethyl acetate. The reaction mixture was left to warm to room temperature and was stirred at room temperature for 2 hours. The tetrahydrofuran was distilled off under reduced pressure, the residue was dissolved in ethyl acetate and the organic phase was washed with water and saturated sodium chloride solution, dried and evaporated. The residue was chromatographed over silica gel with methylene chloride/ethyl acetate (9:1 and 8:2). There were obtained 160 mg of 2-[[5-[(E/Z)-styryl]-6-p-toluenesulphonamido-4-pyrimidinyl]oxy]ethyl acetate, m.p. 146-156°C.

The starting material was prepared as follows:

From 5-allyl-4,6-dichloropyrimidine-p-toluensulphonamide potassium there was prepared N-[6-chloro-5-[(E/Z)-propenyl]-4-pyrimidinyl]-p-toluenesulphonamide and therefrom by reaction

REPLACEMENT SHEET
15 OCT 1996

with ethylene glycol sodium there was prepared N-[6-(2-hydroxy-ethoxy)-5-[(E/Z)-propenyl]-4-pyrimidinyl]-p-toluenesulphonamide, m.p. 130-132°C. Reaction with acetic anhydride in the presence of pyridine in tetrahydrofuran yielded 2-[[5-[(E/Z)-propenyl]-6-p-toluenesulphonamido-4-pyrimidinyl]oxy]ethyl acetate, m.p. 160-163°C.

390 mg of the previously named compound and 8 mg of osmium tetroxide were added to a mixture of 2.5 ml of water and 7 ml of dioxan and then 450 mg of sodium m-periodate were added at room temperature within 30 minutes and after stirring at room temperature for 2 hours a further 8 mg of osmium tetroxide were added. The reaction mixture was stirred for a further 5 hours and worked-up, whereby 2-[(5-formyl-6-p-toluenesulphonamido-4-pyrimidinyl)oxy]ethyl acetate, m.p. 130-144°C (after crystallization from ethyl acetate and diethyl ether), was obtained.

Example 14

120 mg of 2-[[5-[(E/Z)-styryl]-6-p-toluenesulphonamido-4-pyrimidinyl]oxy]ethyl acetate were hydrogenated in 3 ml of abs. ethanol and 3 ml of abs. tetrahydrofuran in the presence of 4 mg of 5% palladium/charcoal. After completion of the hydrogen uptake the catalyst was filtered off and the organic phases were evaporated under reduced pressure. The residue was chromatographed on silica gel with ethyl acetate and yielded 110 mg of 2-[[5-phenethyl-6-p-toluenesulphonamido-4-pyrimidinyl]oxy]ethyl acetate, m.p. 120-123°C.

Example 15

80 mg of 2-[(5-phenethyl-6-p-toluenesulphonamido-4-pyrimidinyl)oxy]ethyl acetate in 5 ml of methanol were stirred with 53 mg of finely powdered potassium carbonate at 20°C for 15 hours. Thereafter, the methanol was removed under reduced pressure, the residue was taken up in ethyl acetate, the organic phase was washed with water and saturated sodium chloride

REPLACEMENT SHEET
15 OCT 1996

solution, dried and evaporated. The residue was chromatographed over silica gel with methylene chloride/ethyl acetate(1:1) and ethyl acetate. There were obtained 40 mg of N-[6-(2-hydroxy-ethoxy)-5-phenethyl-4-pyrimidinyl]-p-toluenesulphonamide as a white resin.

Example 16

In analogy to Example 15, from 2-[[5-[(E/Z)-styryl]-6-p-toluenesulphonamido]-4-pyrimidinyl]oxy]ethyl acetate there was obtained N-[6-(2-hydroxyethoxy)-5-[(E/Z)-styryl]-4-pyrimi-dinyl]-p-toluenesulphonamide as a white resin.

Example 17

In analogy to Example 1, paragraph a), from N-[6-chloro-5-(2,4,6-trichlorophenoxy)-4-pyrimidinyl]-p-isopropylbenzene-sulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-(2,4,6-trichlorophenoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, m.p. 182-183°C (from methylene chloride and isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(2,4,6-trichlorophenoxy)pyrimidine and p-isopropylbenzene-sulphonamide, m.p. 217-218°C (from methylene chloride and isopropyl ether).

Example 18

In analogy to Example 1, paragraph a), from N-[6-chloro-5-(2,4,6-trichlorophenoxy)-4-pyrimidinyl]-o-toluenesulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxy-ethoxy)-6-(2,4,6-trichlorophenoxy)-4-pyrimidinyl]-o-toluene-sulphonamide, m.p. 144-145°C (from isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(2,4,6-trichlorophenoxy)-pyrimidine and o-toluenesulphonamide, m.p. 107-109°C (from isopropyl ether).

REPLACEMENT SHEET
15 OCT 1996

Example 19

In analogy to Example 1, paragraph a), from N-[6-chloro-5-(2,4,6-trichlorophenoxy)-4-pyrimidinyl]-2,4-xylenesulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxy-ethoxy)-5-(2,4,6-trichlorophenoxy)-4-pyrimidinyl]-2,4-xylene-sulphonamide, m.p. 157-158°C (from isopropyl ether).

The starting material was prepared as follows:

16.9 g of anhydrous K_2CO_3 were added to a solution of 18.0 g of 2,4,6-trichlorophenol and 32.0 g of diethyl bromo-malonate in 180 ml of acetone and 20 ml of toluene. The reaction mixture was heated at reflux while stirring for 24 hours, the solution was filtered off from the precipitate and evaporated under reduced pressure. The residue was taken up in toluene, the organic solution was washed with a 5% sodium carbonate solution, then with water, dried over sodium sulphate and, after filtering off the salt under suction, evaporated under reduced pressure. The residue was distilled under ≤ 1 mmHg pressure, whereby there was obtained a colourless oil (b.p. 171-174°C) from which with formamidine acetate and sodium methyl-ate there was obtained 5-(2,4,6-trichlorophenoxy)-4,6(3H,5H)-pyrimidinedione, m.p. >270°C, which, prior to the further reaction, was dried at 80°C overnight under reduced pressure.

A solution of 7.6 g of 5-(2,4,6-trichlorophenoxy)-4,6-(3H,5H)-pyrimidinedione, 6.6 g of tetraethylammonium chloride, 3.3 ml of collidine, 13.7 ml of $POCl_3$ in 70 ml of CH_3CN was heated at reflux for 4.5 hours, the solution was evaporated under reduced pressure, the residue was treated three times with ether, the combined organic solutions were filtered overnight, evapo-rated under reduced pressure and the residue was recrystallized from ether and n-hexane. There was obtained 4,6-dichloro-5-(2,4,6-trichlorophenoxy)pyrimidine, m.p. 104-105°C.

REPLACEMENT SHEET
15 OCT 1996

From 4,6-dichloro-5-(2,4,6-trichlorophenoxy)pyrimidine and 2,4-xylenesulphonamide there was obtained N-[6-chloro-5-(2,4,6-trichlorophenoxy)-4-pyrimidinyl]-2,4-xylenesulphonamide, m.p. 267°C (from acetonitrile and isopropyl ether).

Example 20

By reacting 4,6-dichloro-5-[(2-methoxy-4-methyl)phenoxy]pyrimidine with p-t-butylbenzenesulphonamide and thereafter with ethylene glycol Na there was obtained p-t-butyl-N-[6-(2-hydroxyethoxy)-5-[(2-methoxy-p-tolyl)oxy]-4-pyrimidinyl]benzenesulphonamide as a solid.

The starting material was prepared by the reaction of methylguaiacol with diethyl bomomalonate and thereafter with formamidine acetate to give 5-[(2-methoxy-4-methyl)phenoxy]-4,6(3H, 4H)-pyrimidinedione, m.p. 234-236°C, and further reaction of the latter compound with $POCl_3$.

Example 21

By reacting 4,6-dichloro-5-[(2-methoxy-4-methyl)phenoxy]pyrimidine with p-isopropylbenzenesulphonamide and thereafter with ethylene glycol Na there was obtained N-[5-(2-methoxy-4-methyl)phenoxy]pyrimidinyl]-p-isopropylbenzenesulphonamide, m.p. 135-136°C (from ethyl acetate).

Example 22

By reacting 4,6-dichloro-5-[(2-methoxy-4-methyl)phenoxy]pyrimidine with o-ethylbenzenesulphonamide and thereafter with ethylene glycol Na there was obtained N-[5-(2-methoxy-4-methyl)phenoxy-6-(2-hydroxyethoxy)-4-pyrimidinyl]-o-ethylbenzenesulphonamide as a solid.

REPLACEMENT SHEET
15 OCT 1996

Example 23

By reacting 4,6-dichloro-5-(2-methoxy)phenoxy-2-methylpyrimidine with p-tert-butylphenylsulphonamide and thereafter with ethylene glycol Na there was obtained p-tert-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-benzenesulphonamide, m.p. 123-124°C (from ethyl acetate).

Example 24

By reacting 4,6-dichloro-5-(2-methoxy)phenoxy-2-methylpyrimidine with p-isopropylbenzenesulphonamide and thereafter with ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl)-p-isopropylbenzenesulphonamide, m.p. 124-126°C (from acetonitrile, isopropanol and water).

Example 25

By reacting 4,6-dichloro-5-(2-methoxyphenoxy)-2-trifluoromethylpyrimidine with p-isopropylbenzenesulphonamide and thereafter with ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-trifluoromethyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide as a solid.

Example 26

By reacting 4,6-dichloro-5-(2-methoxyphenoxy)-2-trifluoromethylpyrimidine with p-tert-butylbenzenesulphonamide and with ethylene glycol Na there was obtained p-tert-butyl-N-[6-(2-hydroxyethoxy)-5(o-methoxyphenoxy)-2-(trifluoromethyl)-4-pyrimidinyl]benzenesulphonamide, m.p. 190-192°C (from toluene). Sodium salt: M.p. 288-289°C.

Example 27

By reacting 5-(1,3-benzodioxol-5-yloxy)-4,6-dichloropyrimidine with p-tert-butylphenylsulphonamide and thereafter

REPLACEMENT SHEET
15 OCT 1996

with ethylene glycol Na there was obtained N-[5-(1,3-benzodioxol-5-yloxy)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-tert-butylbenzenesulphonamide as a solid.

Example 28

By reacting 5-(1,3-benzodioxol-5-yloxy)-4,6-dichloropyrimidine with p-isopropylbenzenesulphonamide and thereafter with ethylene glycol Na there was obtained N-[5-(1,3-benzodioxol-5-yloxy)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide as a solid.

Example 29

By reacting 5-(2-methoxyphenoxy)-4,6-dichloropyrimidine with o-methoxyphenylsulphonamide and thereafter with ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]-o-methoxybenzenesulphonamide, m.p. 164-165°C (from ethyl acetate).

Example 30

By reacting p-tert-butyl-N-[6-chloro-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide with the monosodium salt of 1,4-butanediol there was obtained p-tert-butyl-N-[6-(4-hydroxybutoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide as a white foam.

Example 31

By reacting 4,6-dichloro-5-(2-naphthyloxy)pyrimidine with p-isopropylphenylsulphonamide and thereafter with the sodium salt of ethylene glycol there was obtained N-[6-(2-hydroxyethoxy)-5-(2-naphthyloxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, m.p. 160-161°C (from isopropyl ether).

REPLACEMENT SHEET
15 OCT 1996

Example 32

By reacting 4,6-dichloro-5-(2-naphthyloxy)pyrimidine with p-tert-butylphenylsulphonamide and thereafter with ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-(2-naphthyloxy)-4-pyrimidinyl]-p-tert-butylbenzenesulphonamide, m.p.197-198°C (from isopropyl ether).

Example 33

By reacting 4,6-dichloro-5-(o-methoxyphenoxy)-2-propyl-pyrimidine with p-isopropylphenylsulphonamide and thereafter with ethylene glycol Na there was obtained N-[6-(2-hydroxy-ethoxy)-5-(o-methoxyphenoxy)-2-propyl-4-pyrimidinyl]-p-iso-propylbenzenesulphonamide as a solid.

Example 34

By reacting 4,6-dichloro-5-(o-methoxyphenoxy)-2-propyl-pyrimidine with p-tert-butylphenylsulphonamide and thereafter with ethylene glycol Na there was obtained p-tert-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-propyl-4-pyrimidinyl]-benzenesulphonamide.

Example 35

By reacting 4,6-dichloro-5-(o-methoxy)phenoxy-2-methyl-pyrimidine with α,α,α-trifluoro-p-toluenesulphonamide and thereafter with ethylene glycol Na there was obtained α,α,α-trifluoro-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-p-toluenesulphonamide, m.p. 144-145°C (from ethyl acetate).

Example 36

By reacting 4,6-dichloro-5-(o-methoxy)phenoxy-2-methyl-pyrimidine with p-chlorophenylsulphonamide and thereafter with ethylene glycol Na there was obtained p-chloro-N-[6-(2-hydroxy-

REPLACEMENT SHEET
15 OCT 1996

ethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzene-sulphonamide, m.p. 134-135°C (from ethyl acetate).

Example 37

By reacting 4,6-dichloro-5-(o-methoxy)phenoxy-2-methyl-pyrimidine with p-(trifluoromethoxy)benzenesulphonamide and thereafter with ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-p-(trifluoromethoxy)benzenesulphonamide, m.p. 138-140°C (from ethyl acetate).

Example 38

By reacting 4,6-dichloro-5-(o-methoxy)phenoxy-2-methyl-pyrimidine with o-ethylbenzenesulphonamide and thereafter with ethylene glycol Na there was obtained o-ethyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-benzenesulphonamide as a white foam.

Example 39

By reacting 4,6-dichloro-5-(o-methoxy)phenoxy-2-methyl-pyrimidine with p-toluenesulphonamide thereafter with ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-p-toluene-sulphonamide as a white foam.

Example 40

By reacting 4,6-dichloro-5-(o-methoxy)phenoxy-2-methylpyrimidine with 2-naphthylsulphonamide and thereafter with ethylene glycol Na there was obtained N-[6-(2-hydroxy-ethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-2-naphthylsulphonamide as a foam.

REPLACEMENT SHEET
15 OCT 1996

Example 41

By reacting p-tert-butyl-N-[6-chloro-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide with the monosodium salt of 1,3-propanediol there was obtained p-tert-butyl-N-[6-(3-hydroxypropoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide as a white foam.

Example 42

In analogy to Example 1, paragraph a), 300 mg of p-t-butyl-N-[6-chloro-5-[(o-methylthio)phenoxy]-4-pyrimidinyl]benzenesulphonamide were converted into N-[6-(2-hydroxyethoxy)-5-[(o-methylthio)phenoxy]-4-pyrimidinyl]benzenesulphonamide. There were obtained 250 mg of p-t-butyl-N-[6-(2-hydroxyethoxy)-5-[(o-methylthio)phenoxy]-4-pyrimidinyl]benzenesulphonamide, m.p. 149-150°C.

The starting material was prepared as follows:

a) Dimethyl (o-methylthio)phenoxymalonate was obtained from dimethyl chloromalonate and (o-methylthio)phenol in analogy to Example 1, paragraph c). From 17 g of (o-methylthio)phenol there were obtained 23 g of malonate from toluene-hexane.

b) 9.15 g of 5-[(o-methylthio)phenoxy]-6-hydroxy-4-(3H)-pyrimidinone, MS:250 (M), were obtained from 13.5 g of the malonate from a) and formamidine acetate in analogy to Example 1, paragraph d).

c) 2.5 g of this compound and 2.9 g of diisopropylethylamine were suspended in 15 ml of acetonitrile. 2 ml of $POCl_3$ were added dropwise to the suspension and the mixture was subsequently boiled at reflux for 5 hours. 4,6-Dichloro-5-[(o-methylthio)phenoxy]pyrimidine was obtained after working-up in analogy to Example 1, paragraph e). After crystallization from n-hexane there was obtained 1 g of pyrimidine derivative, m.p. 89-90°C.

REPLACEMENT SHEET
15 OCT 1996

d) In analogy to Example 1, paragraph f), 580 mg of 4,6-dichloro-5-[(o-methylthio)phenoxy]pyrimidine were converted with 850 mg of p-t-butylbenzenesulphonamide K into p-t-butyl-N-[6-chloro-5-[(o-methylthio)phenoxy]-4-pyrimidinyl]benzene-sulphonamide. After crystallization from MeOH there were obtained 480 mg of white crystals, m.p. 154-155°C.

Example 43

a) In analogy to Example 1, paragraph a), 350 mg of p-t-butyl-N-[(6-chloro-5-(o-methoxyphenoxy)-2-phenyl-4-pyrimidinyl]-benzenesulphonamide were converted into p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-phenyl-4-pyrimidinyl]-benzenesulphonamide. After crystallization from diisopropyl ether there were obtained 330 mg of white crystals, m.p. 160-161°C.

b) 225 mg of this compound were dissolved in EtOH. The stoichiometric amount of KOH in MeOH was added to the solution. Then, the solvent was distilled off and diisopropyl ether was added to the residue, whereby there was obtained p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-phenyl-4-pyrimi-dinyl]benzenesulphonamide potassium, MS: 588 [(M + K)$^+$].

Example 44

In analogy to Example 1, paragraph a), from N-[2-amino-6-chloro-5-(o-methoxyphenoxy)-4-pyrimidinyl]-p-tert.-butylben-zenesulphonamide there was obtained N-[2-amino-6-(2-hydroxy-ethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]-p-tert.-butyl-benzenesulphonamide, white crystals of melting point 168°C (from diisopropyl ether).

The starting material was prepared as follows:

a) 7.65 g of dimethyl (5-o-methoxy)phenoxymalonate and 3 g of guanidine hydrochloride were added to a solution of 2.3 g of Na in 100 ml of methanol. The suspension was stirred at room

REPLACEMENT SHEET
15 OCT 1996

temperature under argon for 3 hours. Then, the methanol was distilled off and the residue was taken up in H_2O. After the usual treatment, as already described, the compound was precipitated by the dropwise addition of acetic acid until the pH of the solution had reached 4.5. There were obtained 6.4 g of crude product of which 1.35 g were suspended in 10 ml of dioxan. 1.4 g of N-ethyldiisopropylamine, 2 ml of $POCl_3$ and 1 g of triethylbenzylammonium chloride were added thereto in succession. The mixture was boiled at reflux under an argon atmosphere while stirring vigorously. After 30 minutes the solvent mixture was distilled off, the residue was taken up in ethyl acetate and extracted with H_2O and saturated $NaHCO_3$ solution. Purification was carried out by chromatography on silica gel (CH_2Cl_2-ethyl acetate, 9:1 vol., as the eluent). There was obtained 2-amino-4,6-dichloro-5-(o-methoxyphenoxy)pyrimidine as a colourless solid. M.p. 190°C.

b) 0.5 g of the foregoing dichloro compound and 0.75 g of p-tert.-butylbenzenesulphonamide Na in 2 ml of DMSO were converted at 90°C into N-[2-amino-6-chloro-5-(o-methoxyphenoxy)-4-pyrimidinyl]-p-tert-butylbenzenesulphonamide, m.p. 194-195°C

Example 45

a) In analogy to Example 1, paragraph a), 478 mg of p-tert-butyl-N-[6-chloro-2-methyl-5-[o-(methylthio)phenoxy]pyrimidinyl]benzenesulphonamide and Na glycolate in ethylene glycol were converted into p-tert-butyl-N-[6-(2-hydroxyethoxy)-2-methyl-5-[o-(methylthio)phenoxy]-4-pyrimidinyl]benzenesulphonamide, m.p. 166-167°C.

b) 225 mg of this compound were converted into the sulphonamide salt by adding the stoichiometric amount of aqueous NaOH. Then, it was diluted with methanol to give a homogeneous solution. 100 mg of $NaIO_4$ dissolved in 2 ml of H_2O were added to this solution and the mixture was stirred at room temperature for 8 hours. Then, it was evaporated to dryness. The residue was

REPLACEMENT SHEET
15 OCT 1996

partitioned between ethyl acetate and aqueous 0.1N H_2SO_4. After evaporating the organic phase the p-tert-butyl-N-[6-(2-hydroxy-ethoxy)-2-methyl-5-[o-(R,S-methylsulphinyl)phenoxy]-4-pyrimidinyl]benzenesulphonamide was crystallized from diisopropyl ether. 150 mg of white crystals were obtained. MS: m/e = 520 $(M+H)^+$.

g The starting material was prepared as follows:

5.4 g of dimethyl (o-methylthiophenoxy)malonate and 2.1 g of acetamidine hydrochloride were converted into 6-hydroxy-2-methyl-5-[o-(methylthio)phenoxy]-4(3H)-pyrimidine and this was converted into 4,6-dichloro-2-methyl-5-[o-(methylthiophenoxy)-pyrimidine, m.p. 132-133°C.

0.9 g of the foregoing dichloro compound and 1.3 g of p-tert-butylbenzenesulphonamide K were converted into p-tert-butyl-N-[6-chloro-2-methyl-5-[o-methylthio)phenoxy]-4-pyrimidinyl]benzenesulphonamide. M.p. 162-163°C.

Example 46

1.22 g of (S)-1,2-di-O-isopropylidene-glycerol were added dropwise under an argon atmosphere to a suspension of 170 mg of NaH in 2 ml of dry THF. Subsequently, 1.03 g of p-tert-butyl-N-[6-chloro-5-(o-methoxyphenoxy)-2-(p-methoxyphenyl)-4-pyrimidinyl]benzenesulphonamide and 2 ml of DMSO were added. The mixture was left to react at 95°C for 4 hours, whereby the THF distilled off. Then, 0.5 ml of H_2O was added and the solvent mixture and the excess reagent were distilled off under reduced pressure. The residue was taken up in 20 ml of dioxan; 1 ml of aqueous 1N HCl was added and the mixture was left to react at 65°C for 45 minutes. The mixture was then evaporated to dryness. The residue was partitioned between ethyl acetate and 1N hydrochloric acid. After the usual working-up the compound was purified on silica gel with ethyl acetate as the eluent. There was obtained 0.98 g of (S)-4-tert-butyl-N-[6-(2,3-dihydroxy-propyloxy)-5-(o-methoxy-phenoxy)-2-(p-methoxyphenyl)-

REPLACEMENT SHEET
15 OCT 1996

pyrimidin-4-yl]-benzenesulphonamide, m.p. 141-142°C (from diethyl ether).

The starting material was prepared as follows:

In analogy to Example 1, paragraph d), 7.63 g of dimethyl (o-methoxyphenoxy)malonate and 5,6 g of p-methoxy-benzamidine hydrochloride were condensed to give 2-(p-methoxyphenyl)-5-(o-methoxyphenoxy)-6-hydroxy-4(3H)-pyrimidinone. Reaction of this compound in analogy to Example 1, paragraph e), yielded 4,6-dichloro-2-(p-methoxyphenyl)-5-(o-methoxyphenoxy)-pyrimidine, m.p. 113-114°C, from which in analogy to Example 1, paragraph f), there was obtained p-tert-butyl-N-[6-chloro-5-(o-methoxyphenoxy)-2-(p-methoxyphenyl)-4-pyrimidinyl]benzenesulphonamide, m.p. 221-222°C.

Example 47

210 mg of 4-tert-butyl-N-[5-(2-chloro-5-methoxyphenoxy)-2-ethyl-6-(2-methylsulphanyl-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide were dissolved in 5 ml of MeOH and 0.2 ml of 1N NaOH. 95 mg of $NaIO_4$ dissolved in 0.5 ml of H_2O were added thereto and the mixture was stirred at room temperature for 5 hours, whereby a suspension resulted. Then, 0.2 ml of 1N HCl was added and the mixture was subsequently evaporated to dryness. The residue was partitioned between ethyl acetate and 0.1N HCl and worked-up as usual. For purification, the compound was chromatographed on silica gel using ethyl acetate-MeOH (6:1 by vol.) as the eluent. There were obtained 160 mg of (RS)-4-tert-butyl-N-[5-(2-chloro-5-methoxyphenoxy)-2-ethyl-6-(2-methylsulphinyl-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide as a white powder. MS: 581 (M).

The starting material was prepared as follows:

In analogy to Example 1, paragraph c), from 2-chloro-5-methoxy-phenol and dimethyl chloromalonate there was obtained dimethyl (2-chloro-5-methoxy-phenoxy)malonate, m.p. 68-69°C.

REPLACEMENT SHEET
15 OCT 1996

Condensation with propanidine hydrochloride yielded 2-ethyl-5-(2-chloro-5-methoxy-phenoxy)-6-hydroxy-4(3H)-pyrimidinone from which in analogy to Example 1, paragraph e), there was obtained 4,6-dichloro-2-ethyl-5-(2-chloro-5-methoxy-phenoxy)-pyrimdine, m.p. 113-113.5°C. This compound was converted analogously to Example 1, paragraph f), into 4-tert-butyl-N-[6-chloro-5-(2-chloro-5-methoxy-phenoxy)-2-ethyl-pyrimidin-4-yl]-benzenesulphonamide, m.p. 142-143°C (from ethanol).

300 mg of 2-(methylthio)ethanol were added dropwise under argon to a suspension of 63 mg of NaH in dry THF. Subsequently, 300 mg of the previously obtained sulphonamide and 1 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone were added thereto. The mixture was left to react at 80°C for 3 hours. After the usual working-up of the reaction mixture and purification on silica gel (CH_2Cl_2-diethyl ether, 95/5 vol, as the eluent) there were obtained 160 mg of 4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-2-ethyl-6-(2-methylsulphanyl-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide as a white powder.

Example 48

a) In analogy to Example 1, from 4-tert-butyl-N-[6-chloro-5-(2-chloro-5-methoxy-phenoxy)-2-methylpyrimidine-4-yl]-benzenesulphonamide there were manufactured 4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-2-methyl-pyrimidin-4-yl]-benzenesulphonamide. From 500 mg of the starting material there were obtained 430 mg of white crystals. M.p. 141-141.5°C (from isopropyl ether).

b) 140 mg of the compound obtained were esterified with 3-furancarboxylic acid under the following conditions: 140 mg of the previously obtained sulphonamide, 170 mg of N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride, 170 mg of Et_3N and 5 mg of dimethylamino pyridine were dissolved in 2 ml of dichloromethane and the solution was left to stand at room temperature for 24 hours. Then, 5 ml of THF and 1 ml of

REPLACEMENT SHEET
15 OCT 1996

H_2O were added thereto and the solution was stirred for 30 minutes. Subsequently, it was evaporated to dryness. The residue was partitioned between dichloromethane and 1N HCl, then washed three times with H_2O and isolated as usual. The compound was purified on silica gel using dichloromethane-diethyl ether (95:5 by vol.) as the eluent. There were obtained 120 mg of 4-tert-butyl-N-[5-(2-chloro-5-(2-chloro-5-methoxy-phenoxy)-6-(2-(3-furoyloxy)ethoxy)-2-methyl-pyrimidin-4-yl]-benzenesulphonamide.

The starting material was prepared as follows:

In analogy to Example 1, paragraph d), dimethyl (2-chloro-5-methoxy-phenoxy)malonate was condensed with acetamidine hydrochloride to give (2-chloro-5-methoxy-phenoxy)-2-methyl-6-hydroxy-4(3H)-pyrimidinone. Therefrom in analogy to Example 1, paragraph e), there was obtained 4,6-dichloro-5-(2-chloro-5-methoxy-phenoxy)-2-methyl-pyrimidine, m.p. 125-130°C, and therefrom in analogy to Example 1, paragraph f), there was obtained 4-tert-butyl-N-[6-chloro-5-(2-chloro-5-methoxy-phenoxy)-2-methyl-pyrimidin-4-yl]-benzenesulphonamide, m.p. 182°C (from MeOH).

Example 49

In analogy to Example 47, 90 mg of N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2-methylsulphanyl-ethoxy)-pyrimidin-4-yl]-1,3-benzodioxol-5-sulphonamide were oxidized with $NaIO_4$ to give (RS)-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2-methyl-sulphinyl-ethoxy)-pyrimidin-4-yl]-1,3-benzodioxol-5-sulphon-amide. There were obtained 65 mg of white powder. MS: 542.1 ($M+H^+$).

The starting material was prepared as follows:

In analogy to Example 1, paragraph d), dimethyl (2-chloro-5-methoxy-phenoxy)malonate was condensed with formamidine acetate to give (2-chloro-5-methoxy-phenoxy)-6-hydroxy-4(3H)-

REPLACEMENT SHEET
15 OCT 1996

pyrimidinone. Therefrom in analogy to Example 1, paragraph e), there was obtained 4,6-dichloro-5-(2-chloro-2-methoxy-phenoxy)-pyrimidine, m.p. 88-89°C (from ethanol).

Reaction of 611 mg of 4,6-dichloro-5-(2-chloro-2-methoxy-phenoxy)-pyrimidine with 813 mg of 1,3-benzodioxol-5-sulphonamide K yielded 535 mg of N-[6-chloro-5-(2-chloro-5-methoxy-phenoxy)-pyrimidin-4-yl]-1,3-benzodioxol-5-sulphonamide. The last-named compound was converted into N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2-methylsulphanyl-ethoxy)-pyrimidin-4-yl]-1,3-benzodioxol-5-sulphonamide as described in the preparation of the starting material in Example 47.

Example 50

A solution of 0.11 g of sodium in 3.0 ml of ethylene glycol was heated to 110°C with 0.265 g of 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(thiophen)-2-yl-pyrimidin-4-yl]-benzenesulphonamide, cooled for a further 4 hours, poured on to ice and adjusted to pH 3 with 1M tartaric acid. The suspension obtained was extracted with ethyl acetate, the organic extracts were combined, washed with water, dried with sodium sulphate and concentrated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2-ethyl acetate 9:1 and yielded 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzenesulphonamide as a white foam. MS: M^+ = 555.

The starting material was prepared as follows:

a) A solution of 5.17 g of Na in 200 ml of abs. methanol was treated with 21.15 g of diethyl (o-methoxyphenoxy)malonate and 16.2 g of thiophene-2-carboxamidine hydrochloride and the suspension was stirred at room temperature overnight and evaporated under reduced pressure. The residue was taken up in 1N NaOH, the alkaline solution was acidified with 1N HCl, the precipitate was filtered off under suction, washed thoroughly with

REPLACEMENT SHEET
15 OCT 1996

water and dried in a high vacuum at 80°C. The 5-(o-methoxyphenoxy)-2-(2-thienyl)-4,6-dihydroxy-pyrimidine of m.p. >250°C (dec.) was used in the next step without further purification.

b) A suspension of 4.6 g of 5-(o-methoxyphenoxy)-2-(2-thienyl)-4,6-dihydroxy-pyrimidine, 4.7 ml of N,N-diisopropyl-N-ethylamine and 6.4 g of PCl_5 was boiled at reflux for 20 hours. The mixture was then evaporated under reduced pressure and the residue was poured on to ice and extracted with ethyl acetate. The combined extracts were washed with water, dried and evaporated in a vacuum. The residue was chromatographed on silica gel with toluene and yielded 4,6-dichloro-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidine, m.p. 118-120°C.

c) A solution of 0.353 g of 4,6-dichloro-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidine in 5 ml of DMSO was heated to 150°C with 0.376 g of p-tert-butylbenzenesulphon-amide for 30 minutes. The solution was concentrated in a high vacuum and the oily residue was poured on to ice, made acid (pH = 3) and the suspension was extracted with ethyl acetate. The organic extracts were combined, washed with water, dried over sodium sulphate and concentrated under reduced pressure. The residue was chromatographed on silica gel with toluene-ethyl acetate 9:1 and yielded 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzenesulphon-amide as a white foam.

Example 51

In an analogous manner to Example 50, from 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzenesulphonamide and ethylene glycol Na there was obtained 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzene-sulphonamide, m.p. 152-153°C (from toluene).

REPLACEMENT SHEET
15 OCT 1996

The 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzenesulphonamide (foam) was prepared starting from thiophene-3-carboxamidine hydrochloride via rac-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-3,4,5,6-tetrahydro-pyrimidine-4,6-dione (solid of m.p. >250°C) and 4,6-dichloro-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidine (m.p. 98-99°C).

Example 52

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-2-(furan-2-yl)-5-(2-methoxy-phenoxy)-pyrimidinyl-4-yl]-benzenesulphonamide and ethylene glycol Na there was obtained 4-tert-butyl-N-[2-(furan-2-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide as an amorphous solid.

The 4-tert-butyl-N-[6-chloro-2-(furan-2-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide (foam) was prepared starting from furan-2-carboxamidine hydrochloride via rac-2-(furan-2-yl)-5-(2-methoxy-phenoxy)-pyrimidine-4,6-dione (solid with a decomposition point of 255-258°C) and 4,6-dichloro-2-(furan-2-yl)-5-(2-methoxy-phenoxy)-pyrimidine.

Example 53

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-2-furan-3-yl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and ethylene glycol Na there was obtained 4-tert-butyl-N-[2-(furan-3-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide as a solid of m.p. 120-122°C (from toluene/n-hexane).

The 4-tert-butyl-N-[6-chloro-2-(furan-3-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide (foam) was prepared starting from furan-3-carboxamidine hydro- chloride via rac-2-(furan-3-yl)-5-(2-methoxy-phenoxy)-4,6-dioxo-1,4,5,6-tetrahydro-pyrimidine (solid with a m.p. of more than 300°C with

REPLACEMENT SHEET
15 OCT 1996

decomposition) and 4,6-dichloro-2-(furan-3-yl)-5-(2-methoxy-phenoxy)-pyrimidine.

Example 54

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(pyridin-2-yl)-pyrimidin-4-yl]-benzenesulphonamide and ethylene glycol Na there was obtained 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(pyridin-2-yl)-pyrimidin-4-yl]-benzenesulphonamide as a solid with a m.p. above 250°C (from ethyl acetate).

The 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(pyridin-2-yl)-pyrimidin-4-yl]-benzenesulphonamide (m.p. 197-198°C from isopropyl ether) was prepared starting from pyridine-2-carboxamidine hydrochloride via 5-(2-methoxy-phenoxy)-2-(pyridin-2-yl)pyrimidine-4,6-diol and 4,6-dichloro-5-(2-methoxy-phenoxy)-2-(pyridin-2-yl)-pyrimidine, m.p. 122-123°C.

Example 55

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(pyridin-4-yl)-pyrimidin-4-yl]-benzenesulphonamide and ethylene glycol Na there was obtained 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(pyridin-4-yl)-pyrimidin-4-yl]-benzenesulphonamide as a solid of m.p. 166-167°C from acetone-ether.

The 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(pyridin-4-yl)-pyrimidin-4-yl]-benzenesulphonamide potassium (1:1), m.p. 193-196°C from H_2O, was prepared starting from pyridine-4-carboxamidine hydrochloride via 5-(2-methoxy-phenoxy)-2-(pyridin-4-yl)-pyrimidine-4,6-diol and 4,6-dichloro-5-(2-methoxy-phenoxy)-2-(pyridin-4-yl)-pyrimidine, m.p. 173-176°C.

REPLACEMENT SHEET
15 OCT 1996

Example 56

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(pyridin-3-yl)-pyrimidin-4-yl]-benzenesulphonamide and ethylene glycol Na there was obtained 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(pyridin-3-yl)-pyrimidin-4-yl]-benzenesulphonamide K as a foam. MS: $(M+H)^+ = 551.2$.

The 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(pyridin-3-yl)-pyrimidin-4-yl]-benzenesulphonamide was prepared starting from pyridine-3-carboxamidine hydrochloride via rac-5-(2-methoxy-phenoxy)-2-(pyridin-3-yl)-tetrahydro-1H-pyrimidine-4,6-dione and 4,6-dichloro-5-(2-methoxy-phenoxy)-2-(pyridin-3-yl)-pyrimidine (m.p. 164-165°C).

Example 57

A suspension of 525 mg of 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(pyridin-2-yl)-pyrimidin-4-yl)benzene-sulphonamide in 1 ml of glacial acetic acid was treated with 2.5 ml of 40% peracetic acid and slowly heated to reflux. After 2 minutes the mixture was cooled, evaporated under reduced pressure and the residue was recrystallized from ethyl acetate. There was obtained 2-[4-(4-tert-butyl-phenylsulphonylamino)-6-chloro-5-(2-methoxy-phenoxy)-pyrimidin-2-yl]-pyridine 1-oxide of m.p. 201-202°C (with decomposition).

Example 58

216 mg of 2-[4-(4-tert-butyl-phenylsulphonylamino)-6-chloro-5-(2-methoxy-phenoxy)-pyrimidin-2-yl]-pyridine 1-oxide were added to a solution of 46 mg of Na in pure ethylene glycol and the solution which slowly resulted was heated at 80°C overnight. The solution was poured into aqueous acetic acid, the precipitate was extracted with ethyl acetate, triturated with ether and filtered off under suction. There was obtained 2-[4-(4-tert-butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(2-

REPLACEMENT SHEET
15 OCT 1996

methoxy-phenoxy)-pyrimidin-2-yl]-pyridine 1-oxide as an amorphous mass which was dried in a high vacuum at 40°C. MS: $(M+H)^+$ = 567.4.

Example 59

In analogy to Example 57, from 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(pyridin-4-yl)-pyrimidinyl-4-yl]-benzenesulphonamide and peracetic acid there was obtained 4-[4-(4-tert-butyl-phenylsulphonylamino)-6-chloro-5-(2-methoxy-phenoxy)-pyrimidin-2-yl]-pyridine 1-oxide, m.p. 247-249°C (from CH_2Cl_2 and isopropyl ether).

Example 60

In analogy to Example 58, from 4-[4-(4-tert-butyl-phenyl-sulphonylamino)-6-chloro-5-(2-methoxy-phenoxy)-pyrimidin-2-yl]-pyridine 1-oxide and Na ethylene glycolate in ethylene glycol there was obtained 4-[4-(4-tert-butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-2-yl] pyridine 1-oxide as an amorphous mass. MS: $(M+H)^+$ = 567.4, $(M+Na)^+$ = 589.4.

Example 61

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-2-(2-methoxy-ethyl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and ethylene glycol Na there was obtained 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-2-[2-(hydroxy-ethoxy)-ethyl]-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzene-sulphonamide. MS: M^+ = 562. The corresponding sodium salt (prepared according to usual methods) is a white solid which was dried in a high vacuum.

The 4-tert-butyl-N-[6-chloro-2-(2-methoxy-ethyl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl-benzenesulphonamide was prepared starting from methoxy-propionamidine hydrochloride via 2-(2-methoxy-ethyl)-5-(o-methoxyphenoxy)-4,6-(1H,5H)-

REPLACEMENT SHEET
15 OCT 1996

pyrimidinedione and 4,6-dichloro-2-(2-methoxy-ethyl)-5-(2-methoxy-phenoxy)-pyrimidine.

Example 62

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-2-cyclopropyl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzene-sulphonamide and ethylene glycol Na there was obtained 4-tert-butyl-N-[2-cyclopropyl-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide as a foam. MS: $M^+ = 513$.

The 4-tert-butyl-N-[6-chloro-2-cyclopropyl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide was prepared starting from cyclopropyl-formamidine hydrochloride via rac-2-cyclopropyl-5-(2-methoxy-phenoxy)-1H-pyrimidine-4,6-dione (m.p. 243-244°C) and 4,6-dichloro-2-cyclopropyl-5-(2-methoxy-phenoxy)pyrimidine (m.p. 80-82°C).

Example 63

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-2-ethyl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzene-sulphonamide and ethylene glycol Na there was obtained 4-tert-butyl-N-[2-ethyl-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide as a foam.

The 4-tert-butyl-N-[6-chloro-2-ethyl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide was prepared starting from propionamidine hydrochloride via rac-2-ethyl-5-(2-methoxy-phenoxy)-1H-pyrimidine-4,6-dione (m.p. 265°C with decomposition) and 4,6-dichloro-2-ethyl-5-(2-methoxy-phenoxy)-pyrimidine (m.p. 70-71°C).

Example 64

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-2-isopropyl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-

REPLACEMENT SHEET
15 OCT 1996

benzenesulphonamide and ethylene glycol Na there was obtained 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-2-isopropyl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide as a solid.

The 4-tert-butyl-N-[6-chloro-2-isopropyl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide was prepared starting from isopropionamidine hydrochloride via rac-2-isopropyl-5-(2-methoxy-phenoxy)-1,4,5,6-tetrahydro-pyrimidine-4,6-dione and 4,6-dichloro-2-isopropyl-5-(2-methoxy-phenoxy)-pyrimidine (m.p. 70-72°C).

Example 65

In analogy to Example 50, from 4-chloro-N-[6-chloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and ethylene glycol Na there was obtained 4-chloro-N-[3-(5-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide, m.p. 152-154°C (from CH_3CN and isopropyl ether).

The 4-chloro-N-[6-chloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide (m.p. 169-171°C) was prepared from 4,6-dichloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidine and 4-chlorobenzenesulphonamide K.

Example 66

In analogy to Example 50, from N-[6-chloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-4-trifluoromethyl-benzenesulphonamide and sodium ethylene glycolate there was obtained N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-4-trifluoromethyl-benzenesulphonamide, m.p. 154-155°C (from isopropyl ether).

The N-[6-chloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-4-trifluoromethyl-benzenesulphonamide (m.p. 185-186°C) was prepared from 4,6-dichloro-5-(5-fluoro-2-

REPLACEMENT SHEET
15 OCT 1996

methoxy-phenoxy)-pyrimidine and 4-trifluoromethylbenzene-sulphonamide K.

Example 67

In analogy to Example 50, but with a reaction temperature of 100°C, from 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(pyrimidin-2-yl)-pyrimidin-4-yl]-benzenesulphon- amide and sodium ethylene glycolate in ethylene glycol there was obtained 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(pyrimidin-2-yl)-pyrimidin-4-yl]-benzenesulphon- amide as a solid. Sodium salt: m.p. 195-198°C.

The 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-pyrimidin-2-yl)-pyrimidin-4-yl]-benzenesulphonamide was prepared starting from pyrimidine-2-carboxamidine hydro-chloride via rac-5-(2-methoxy-phenoxy)-2-(pyrimidin-2-yl)-tetrahydro-pyrimidine-4,6-dione and 4,6-dichloro-5-(2-methoxy-phenoxy)-2,2'-bipyrimidine.

Example 68

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-5-(3-methoxy-phenoxy)-2,2'-bipyrimidin-4-yl]-benzenesulphon-amide and Na ethylene glycolate in ethylene glycol there was obtained 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-2,2'-bipyrimidin-4-yl]-benzenesulphonamide as a solid.

The 4-tert-butyl-N-[6-chloro-5-(3-methoxy-phenoxy)-2,2'-bipyrimidin-4-yl]-benzenesulphonamide was prepared starting from rac-5-(3-methoxy-phenoxy)-2-(pyrimidin-2-yl)-1,4,5,6-tetrahydro-pyrimidine-4,6-dione via 4,6-dichloro-5-(3-methoxy-phenoxy)-2,2'-bipyrimidinyl.

Example 69

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-5-(4-fluoro-2-methoxy-phenoxy)-2,2'-bipyrimidin-4-yl]-

REPLACEMENT SHEET
15 OCT 1996

benzenesulphonamide and Na ethylene glycolate in ethylene glycol there was obtained 4-tert-butyl-N-[5-(4-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-2,2'-bipyrimidin-4-yl]-benzenesulphonamide, m.p. 161-163°C.

The 4-tert-butyl-N-[6-chloro-5-(4-fluoro-2-methoxy-phenoxy)-2,2'-bipyrimidin-4-yl]-benzenesulphonamide (m.p. 225-227°C) was prepared starting from diethyl (4-fluoro-2-methoxy-phenoxy)malonate via 5-(4-fluoro-2-methoxy-phenoxy)-2,2'-bipyrimidine-4,6-diol (decomposition point >131°C) and 4,6-dichloro-5-(4-fluoro-2-methoxy-phenoxy)-2,2'-bipyrimidine (m.p. 179-180°C).

Example 70

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-5-(4-fluoro-2-methoxy-phenoxy)-2-methyl-pyrimidin-4-yl]-benzenesulphonamide and Na ethylene glycolate in ethylene glycol there was obtained 4-tert-butyl-N-[5-(4-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-2-methyl-pyrimidin-4-yl]-benzenesulphonamide, m.p. 141-142°C (from CH_2Cl_2-isopropyl ether).

The 4-tert-butyl-N-[6-chloro-5-(4-fluoro-2-methoxy-phenoxy)-2-methyl-pyrimidin-4-yl]-benzenesulphonamide (m.p. 164-165°C) was prepared starting from diethyl (4-fluoro-2-methoxy-phenoxy)malonate via rac-5-(4-fluoro-2-methoxy-phenoxy)-2-methyl-1,4,5,6-tetrahydropyrimidine-4,6-dione and 4,6-dichloro-5-(4-fluoro-2-methoxy-phenoxy)-2-methyl-pyrimidine (m.p. 129-130°C).

Example 71

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-5-(4-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and Na ethylene glycolate in ethylene glycol there was obtained 4-tert-butyl-N-[5-(4-fluoro-2-methoxy-phenoxy)-6-(2-

REPLACEMENT SHEET
15 OCT 1996

hydroxy-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide, m.p. 143-144°C (from CH_2Cl_2-isopropyl ether).

The 4-tert-butyl-N-[6-chloro-5-(4-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide (m.p. 146-147°C) was prepared starting from diethyl (4-fluoro-2-methoxy-phenoxy)malonate via rac-5-(4-fluoro-2-methoxy-phenoxy)-1,4,5,6-tetrahydro-pyrimidine-4,6-dione and 4,6-dichloro-5-(4-fluoro-2-methoxy-phenoxy)pyrimidine (m.p. 100-101°C).

Example 72

In analogy to Example 50, from N-[6-chloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-4-isopropyl-benzenesulphonamide and Na ethylene glycolate in ethylene glycol there was obtained N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-4-isopropyl-benzenesulphonamide, m.p. 131-132°C (from isopropyl ether).

Example 73

In analogy to Example 50, from N-[6-chloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-4-tert-butyl-benzene-sulphonamide and Na ethylene glycolate in ethylene glycol there was obtained N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidine-4-yl]-4-tert-butyl-benzenesulphonamide, m.p. 126-127°C (from isopropyl ether).

The N-[6-chloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-4-isopropyl-benzenesulphonamide, m.p. 138-139°C, was prepared starting from diethyl (5-fluoro-2-methoxy-phenoxy)malonate via rac-5-(5-fluoro-2-methoxy-phenoxy)-tetrahydro-pyrimidine-4,6-dione, 4,6-dichloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidine (m.p. 98-100°C) and N-[6-chloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-4-tert-butyl-benzenesulphonamide (m.p. 163-164°C).

REPLACEMENT SHEET
15 OCT 1996

Example 74

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-5-(2-fluoro-6-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and Na ethylene glycolate in ethylene glycol there was obtained .4-tert-butyl-N-[5-(2-fluoro-6-methoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide, m.p. 158-159°C (from CH_2Cl_2-isopropyl ether).

The 4-tert-butyl-N-[6-chloro-5-(2-fluoro-6-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide (m.p. 181-182°C) was prepared starting from diethyl 2-(2-fluoro-6-methoxy-phenoxy)malonate via rac-5-(2-fluoro-6-methoxy-phenoxy)-1,4,5,6-tetrahydro-pyrimidine-4,6-dione and 4,6-dichloro-5-(2-fluoro-6-methoxy-phenoxy)-pyrimidine (m.p. 78-79°C).

Example 75

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-5-(3-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzenesulphonamide and Na ethylene glycolate in ethylene glycol there was obtained 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzenesulphonamide, m.p. 159-161°C (toluene/n-hexane).

The 4-tert-butyl-N-[6-chloro-5-(3-methoxy-phenoxy)-2-(thiophene-2-yl)-pyrimidin-4-yl]-benzenesulphonamide (m.p. 206-207°C) was prepared starting from rac-5-(3-methoxy-phenoxy)-2-(thiophen-2-yl)-3,4,5,6-tetrahydropyrimidine-4,6-dione via 4,6-dichloro-5-(3-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidine (m.p. 120-121°C).

Example 76

In analogy to Example 50, from 4-tert-butyl-N-[6-chloro-2-(2-methoxy-ethyl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and Na ethylene glycolate in ethylene glycol there were obtained, after separation by chromatography

REPLACEMENT SHEET
15 OCT 1996

on silica gel, 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-2-(2-methoxy-ethyl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-2-[2-(2-hydroxy-ethoxy)-ethyl]-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide.

The 4-tert-butyl-N-[6-chloro-2-(2-methoxy-ethyl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide was prepared starting from methoxypropionamidine hydrochloride via 2-(2-methoxy-ethyl)-5-(3-methoxy-phenoxy)-1,4,5,6-tetra-hydro-pyrimidine-4,6-dione and 4,6-dichloro-2-(2-chloro-ethyl)-5-(3-methoxy-phenoxy)-pyrimidine.

Example 77

In analogy to Example 50, from p-tert-butyl-N-[6-chloro-5-(o-methoxy-phenoxy)-2-methyl-4-pyrimidinyl]-benzene-sulphonamide and (S)-2,2-dimethyl-1,3-dioxolane-4-methanol Na there was obtained (S)-4-tert-butyl-N-[6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-5-(2-methoxy-phenoxy)-2-methyl-pyrimidin-4-yl]-benzenesulphonamide, m.p. 124-125°C (from n-hexane).

Example 78

A solution of 1.85 g of (S)-4-tert-butyl-N-[6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-5-(2-methoxy-phenoxy)-2-methyl-pyrimidin-4-yl]-benzenesulphonamide in EtOH (15 ml) was treated with 3 ml of conc. HCl and heated to 50°C for 2 minutes. After evaporation the residue was extracted with ether and yielded (R)-4-tert-butyl-N-[6-(2,3-dihydroxy-propoxy)-5-(2-methoxy-phenoxy)-2-methyl-pyrimidin-4-yl]-benzenesulphonamide as a foam.

Example 79

From N-[6-chloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-4-tert-butyl-benzenesulphonamide and (R)-2,2-

REPLACEMENT SHEET
15 OCT 1996

dimethyl-1,3-dioxolane-4-methanol Na there was obtained (R)-4-tert-butyl-N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-pyrimidin-4-yl]-benzenesulphonamide (m.p. >86°C). Treatment with dilute hydrochloric acid yielded (S)-4-tert-butyl-N-5-(fluoro-2-methoxy-phenoxy)-6-(2,3-dihydroxy-propoxy)-pyrimidin-4-yl]-benzenesulphonamide as a foam.

Example 80

From N-[6-chloro-5-(5-fluoro-2-methoxy-phenoxy)-pyrimidin-4-yl]-4-tert-butyl-benzenesulphonamide and (S)-2,2-dimethyl-1,3-dioxolane-4-methanol sodium salt there was obtained (S)-4-tert-butyl-N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-pyrimidin-4-yl]-benzenesulphonamide (m.p. >86°C). Treatment with dilute HCl yielded (R)-4-tert-butyl-N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2,3-dihydroxy-propoxy)-pyrimidin-4-yl]-benzenesulphonamide as a foam.

Example 81

From 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzenesulphonamide and (S)-2,2-dimethyl-1,3-dioxolane-4-methanol sodium salt there was obtained 4-tert-butyl-N-[6-[(S)-1,3-dioxolan-4-ylmethoxy]-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzenesulphonamide as a foam. Treatment with dilute hydrochloric acid in dioxan yielded (R)-4-tert-butyl-N-[6-(2,3-dihydroxy-propoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzenesulphonamide as a foam.

Example 82

From 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzenesulphonamide and (R)-2,2-dimethyl-1,3-dioxolan-4-methanol sodium salt there was obtained 4-tert-butyl-N-[6-(R)-1,3-dioxolan-4-ylmethoxy]-5-(2-

REPLACEMENT SHEET
15 OCT 1996

methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzene-sulphonamide and therefrom with dilute HCl in dioxan there was obtained (S)-4-tert-butyl-N-[6-(2,3-dihydroxy-propoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzenesulphonamide.

Example 83

From 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzenesulphonamide and (R)-2,2-dimethyl-1,3-dioxolane-4-methanol sodium salt there was obtained (R)-4-tert-butyl-N-[6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzenesulphonamide and therefrom with dilute HCl in dioxan there was obtained 4-tert-butyl-N-[6-[(S)-2,3-dihydroxy-propoxy]-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzenesulphonamide.

Example 84

From 4-tert-butyl-N-[6-chloro-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzenesulphonamide and (S)-2,2-dimethyl-1,3-dioxolane-4-methanol sodium salt there was obtained (S)-4-tert-butyl-N-[(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzenesulphonamide and therefrom with dilute HCl in dioxan there was obtained 4-tert-butyl-N-[6-[(R)-2,3-dihydroxy-propoxy]-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzenesulphonamide.

Example 85

From 4-tert-butyl-N-[6-chloro-2-(furan-3-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and (S)-2,2-dimethyl-1,3-dioxolane-4-methanol sodium salt there was obtained (S)-4-tert-butyl-N-[6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-2-(furan-3-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and therefrom with dilute HCl in dioxan

REPLACEMENT SHEET
15 OCT 1996

there was obtained (R)-4-tert-butyl-N-[2-(furan-3-yl)-6-(2,3-dihydroxy-propoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide.

Example 86

From 4-tert-butyl-N-[6-chloro-2-(furan-3-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and (R)-2,2-dimethyl-1,3-dioxolane-4-methanol sodium salt there was obtained (R)-4-tert-butyl-N-[6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-2-(furan-3-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide and therefrom with dilute HCl in dioxan there was obtained (S)-4-tert-butyl-N-[2-(furan-3-yl)-6-(2,3-dihydroxy-propoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide.

Example 87

By reaction of p-t-butyl-N-[6-(2-hydroxy-ethoxy)-5-(m-methoxy-phenoxy)-4-pyrimidinyl]benzenesulfonamide and 3-methyl-5-isoxazole carboxylic acid in the presence of dimethyl-amino pyridine and dicyclohexylcarbodiimide in methylene chloride there was obtained 3-methylisoxazole-5-carboxylic acid 2-[6-(4-t-butylbenzenesulfonamino)-5-(3-methoxy-phenoxy)-pyrimidin-4-yloxy]ethyl ester as a white solid.

Example 88

In analogy to Example 87 employing indole-2-carboxylic acid there was obtained indole-2-carboxylic acid 2-[6-(4-t-butyl-benzenesulfonamino)-5-(3-methoxyphenoxy)pyrimidin-4-yloxy]-ethyl ester.

Example 89

To a solution of 391.5 mg of 6-[2-(t-butyl-dimethylsilyl-oxy)ethoxy]-5-(2-methoxyphenoxy)pyrimidin-4-yl-amine in 20 ml of acetonitril there were added 200 mg of NaH (60%) and

REPLACEMENT SHEET
15 OCT 1996

the reaction mixture was stirred for one hour at room temperature. 400 mg of (2-methoxy-5-chlorosulfonyl)phenoxyacetic acid ethyl ester were added. The reaction mixture was stirred for 3.5 hours at room temperature, poured on ice and extracted with ethyl acetate. The organic phase was dried and evaporated. Chromatography on silica gel with methylene chloride/methanol (120:1) afforded 175 mg of 4-[6-[2-(t-butyl-dimethylsilyoxy)-ethoxy]-5-(2-methoxyphenoxy)pyrimidin-4-yl-aminosulfonyl]-2-methoxyphenoxy acetic acid ethyl ester as a white foam. That compound was dissolved in 6 ml of acetonitril and 1 ml of aqueous hydrogen fluoride (40%) were added slowly at 0°C. The reaction mixture was stirred for 30 minutes at 0°C and for 90 minutes at room temperature, poured on ice/2N $KHCO_3$ solution and extracted with methylene chloride. The organic phase was dried and evaporated and the residue chromatographed on silica gel with methylene chloride/methanol (10:1). There was obtained 5-[N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)pyrimidin-4-yl]aminosulfonyl]-2-methoxyphenoxy acetic acid ethyl ester as a white solid.

The starting material was prepared as follows:

Ca. 105 ml of ammonia were passed into a solution of 7 g of 4,6-dichloro-5-(o-methoxyphenoxy)pyrimidine in 140 ml of ethanol at -78°C. The reaction mixture was stirred for 15 hours at -78°C and for 50 hours at room temperature and then concentrated. The residue was distributed between ethyl acetate and water and the organic phase worked up. There were obtained 6.45 g of 4-amino-6-chloro-5-(o-methoxyphenoxy)pyrimidine as white crystals.

2.3 g of the above obtained compound were added to a solution of 250 mg of sodium in 40 ml of ethylene glycol at 50°C. The solution was heated to 100°C for 12 hours, distributed between half-saturated aqueous NH_4Cl solution and methylene chloride and the organic phase worked up. There were obtained 2.49 g 2-[6-amino-5-(o-methoxyphenoxy)-4-pyrimidinyl]-1-ethanol as white crystals.

REPLACEMENT SHEET
15 OCT 1996

To a solution of 2.5 g of the above obtained compound in 100 ml of methylene chloride, 2.74 g of dimethylamino pyridine and 3.39 g of t-butyl dimethylchlorosilane were added and the mixture was stirred at room temperature for 48 hours. A further 1.35 g of dimethylamino pyridine and 1.65 g of t-butyl dimethyl-chlorosilane were then added and the reaction mixture stirred for another 18 hours at room temperature. The reaction mixture was filtered, the filtrate concentrated and the residue distributed between half-saturated aqueous NH_4Cl solution and ethyl acetate. Work-up of the organic phase yielded 2.78 g of 6-[2-(t-butyl-dimethylsilyloxy]-5-(2-methoxyphenoxy)pyrimidin-4-yl amine as a white solid.

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

REPLACEMENT SHEET
15 OCT 1996

Example C

Injection solutions can have the following composition:

Compound of formula I	3.0 mg
Gelatine	150.0 mg
Phenol	4.7 mg
Water for injection solutions	ad 1.0 ml

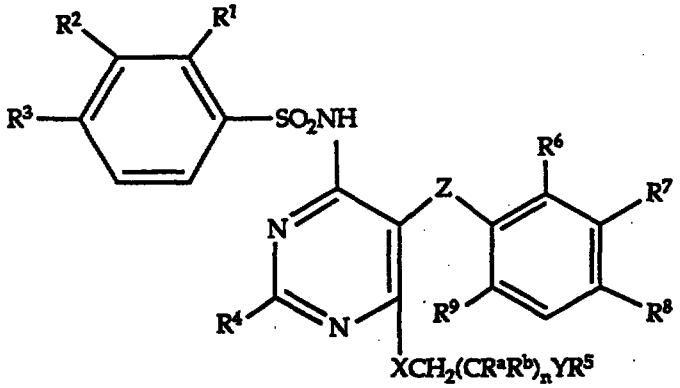
Example D

500 mg of compound of formula I are suspended in 3.5 ml of Myglyol 812 and 0.08 g of benzyl alcohol. This suspension is filled into a container having a dosage valve. 5.0 g of Freon 12 under pressure are filled into the container through the valve. The Freon is dissolved in the Myglyol-benzyl alcohol mixture by shaking. This spray container contains about 100 single dosages which can be applied individually.

REPLACEMENT SHEET
15 OCT 1996

Claims

1. Compounds of the formula



I

wherein

R^1 signifies hydrogen, lower-alkyl, lower-alkoxy, lower-alkylthio, halogen or trifluoromethyl;

R^2 signifies hydrogen, halogen, lower-alkoxy, trifluoromethyl or $-OCH_2COOR^a$; and

R^3 signifies hydrogen, halogen, lower-alkyl, lower-alkylthio, trifluoromethyl, cycloalkyl, lower-alkoxy or trifluoromethoxy; or

R^2 and R^3 together signify butadienyl, methylenedioxy, ethylenedioxy or isopropylidenedioxy;

R^4 signifies hydrogen, lower-alkyl, cycloalkyl, trifluoromethyl, lower-alkoxy, lower-alkylthio, lower-alkylthio-lower-alkyl, hydroxy-lower-alkyl, hydroxy-lower-alkoxy, lower-alkoxy-lower-alkyl, hydroxy-lower-alkoxy-lower-alkyl, hydroxy-lower-alkoxy-lower-alkoxy, lower-alkylsulphinyl, lower-alkylsulphonyl, 2-methoxy-3-hydroxypropoxy, 2-hydroxy-3-phenylpropyl, amino-lower-alkyl, lower-alkylamino-lower-alkyl, di-lower-alkylamino-lower-alkyl, amino, lower-alkylamino, di-lower-alkylamino, arylamino, aryl, arylthio, aryloxy, aryl-lower-alkyl or heterocyclyl;

R^5 signifies hydrogen, lower-alkyl, lower-alkanoyl, benzoyl, heterocyclylcarbonyl, heterocyclylmethyl or tetrahydropyran-2-yl;

* C L M S *

REPLACEMENT SHEET
15 OCT 1996

R^6 to R^9 signify hydrogen, halogen, trifluoromethyl, lower-alkyl, lower-alkoxy, lower-alkylthio, hydroxy, hydroxymethyl, cyano, carboxyl, formyl, methylsulphinyl, methylsulphonyl, methylsulphonyloxy or lower-alkyloxy-carbonyloxy; or

R^7 together with R^6 or R^8 signify butadienyl, methylenedioxy, ethylenedioxy or isopropylidenedioxy;

Z signifies -O-, -S-, ethylene, vinylene, -CO-, $-OCHR^{10}-$ or $-SCHR^{10}$;

R^{10} signifies hydrogen or lower-alkyl;

X and Y each independently signify O, S or NH; or YR^5 also signifies lower-alkylsulphinyl or $-OCH_2CH(OR^c)CH_2OR^d$;

R^a, R^b, R^c and R^d each independently signify hydrogen or lower-alkyl; or R^c and R^d together signify methylene, ethylene or isopropylidene; and

n signifies 1, 2 or 3,

and salts thereof.

2. Compounds of formula I of claim 1, wherein

R^1 signifies hydrogen, lower-alkyl, lower-alkoxy, lower-alkylthio, halogen or trifluoromethyl;

R^2 signifies hydrogen, halogen, lower-alkoxy or trifluoromethyl; and

R^3 signifies hydrogen, halogen, lower-alkyl, lower-alkylthio, trifluoromethyl, cycloalkyl, lower-alkoxy or trifluoromethoxy; or

R^2 and R^3 together signify butadienyl or methylenedioxy;

R^4 signifies hydrogen, lower-alkyl, trifluoromethyl, lower-alkoxy, lower-alkylthio, lower-alkylthio-lower-alkyl, hydroxy-lower-alkyl, amino-lower-alkyl, lower-alkylamino-lower-alkyl, di-lower-alkylamino-lower-alkyl, amino, lower-alkylamino, di-lower-alkylamino, arylamino, aryl, arylthio, aryloxy, aryl-lower-alkyl or heteroaryl;

R^5 signifies hydrogen, lower-alkanoyl, benzoyl or tetrahydropyran-2-yl;

R^6 to R^9 signify hydrogen, halogen, trifluoromethyl, lower-alkyl, lower-alkoxy, lower-alkylthio, hydroxy, hydroxymethyl,

REPLACEMENT SHEET
15 OCT 1996

cyano, carboxyl, formyl, methylsulphinyl, methylsulphonyl, methylsulphonyloxy or lower-alkyloxy-carbonyloxy; or

R^7 together with R^6 or R^8 signify butadienyl or $-OCH_2O-$;

Z signifies -O-, -S-, ethylene, vinylene, -CO-, $-OCHR^{10}-$ or $-SCHR^{10}$;

R^{10} signifies hydrogen or lower-alkyl;

X and Y each independently signify O, S or NH;

R^a and R^b signify hydrogen; and

n signifies 1, 2 or 3,

and salts thereof.

3. Compounds according to claim 1 or 2, in which Z is -O-.

4. Compounds according to claims 1-3, in which R^6 signifies lower-alkoxy and R^7, R^8 and R^9 signify hydrogen.

5. Compounds according to claims 1-3, in which R^6 and R^8 signify hydrogen, R^7 signifies lower-alkoxy and R^9 signifies halogen.

6. Compounds according to claims 1-5, in which R^4 is hydrogen, 2-pyrimidinyl, 2- or 3-furyl, 2- or 3-thienyl, morpholino or p-methoxyphenyl.

7. Compounds according to claims 1-6, in which YR^5 is hydroxy, lower-alkoxysulphinyl or furoyloxy.

8. The compounds according to claim 3,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-tolyloxy)-4-pyrimidinyl]benzenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-chlorophenyloxy)-4-pyrimidinyl]benzenesulphonamide,

REPLACEMENT SHEET
15 OCT 1996

N-[6-(2-hydroxyethoxy)-5-(o-chlorophenoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(m-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-phenoxy-4-pyrimidinyl]benzenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(p-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-ethoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide,

p-(2,2-dimethylpropyl)-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide,

p-isopropyl-N-[6-(2-hydroxyethoxy)-2-methyl-5-(m-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-phenyl-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(2,4,6-trichlorophenoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-6-(2,4,6-trichlorophenoxy)-4-pyrimidinyl]-o-toluenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(2,4,6-trichlorophenoxy)-4-pyrimidinyl]-2,4-xylenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-[(2-methoxy-p-tolyl)-oxy]-4-pyrimidinyl]benzenesulphonamide,

N-[5-(2-methoxy-4-methylphenoxy)pyrimidinyl]-p-isopropylbenzenesulphonamide,

N-[5-(2-methoxy-4-methylphenoxy)6-(2-hydroxyethoxy)-4-pyrimidinyl]-o-ethylbenzenesulphonamide,

p-tert-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-(trifluoromethyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

p-tert-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-(trifluoromethyl)-4-pyrimidinyl]benzenesulphonamide,

N-[5-(1,3-benzodioxol-5-yloxy)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-tertbutylbenzenesulphonamide,

REPLACEMENT SHEET
15 OCT 1996

N-[5-(1,3-benzodioxol-5-yloxy)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]-o-methoxybenzenesulphonamide,

p-tert-butyl-N-[6-(4-hydroxybutoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(2-naphthyloxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(2-naphthyloxy)-4-pyrimidinyl]-p-tert-butylbenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-propyl-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

p-tert-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-propyl-4-pyrimidinyl]benzenesulphonamide,

α,α,α-trifluoro-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-p-toluenesulphonamide,

p-chloro-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-p-(trifluoromethoxy)benzenesulphonamide,

o-ethyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-p-toluenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]-2-naphthylsulphonamide,

p-tert-butyl-N-[6-(3-hydroxypropoxy)-5-(o-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-[(o-methylthio)-phenoxy]-4-pyrimidinyl]benzenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-phenyl-4-pyrimidinyl]benzenesulphonamide,

N-[2-amino-6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-4-pyrimidinyl]-p-t-butylbenzenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-2-methyl-5-[o-(methylthio)phenoxy]-4-pyrimidinyl]benzenesulphonamide and

p-t-butyl-N-[6-(2-hydroxyethoxy)-2-methyl-5-[o-(R,S-methylsulphinyl)phenoxy]-4-pyrimidinyl]benzenesulphonamide.

REPLACEMENT SHEET
15 OCT 1996

9. The compounds according to claim 3,

4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-2-methyl-pyrimidin-4-yl]-benzene-sulphonamide,

4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-[(2-(3-furoyloxy)ethoxy]-2-methyl-pyrimidin-4-yl]-benzene-sulphonamide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzene-sulphonamide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzene-sulphonamide,

4-tert-butyl-N-[2-(furan-2-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[2-(furan-3-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(pyridin-2-yl)-pyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(pyridin-4-yl)-pyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(pyridin-3-yl)-pyrimidin-4-yl]-benzenesulphonamide,

2-[4-(4-tert-butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-2-yl]-pyridine 1-oxide,

4-[4-(4-tert-butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-2-yl]-pyridine 1-oxide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-2-[2-(2-hydroxy-ethoxy)ethyl]-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide,

REPLACEMENT SHEET
15 OCT 1996

4-tert-butyl-N-[2-cyclopropyl-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[2-ethyl-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-2-isopropyl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide,

4-chloro-N-[3-(5-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide,

N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-4-trifluoromethyl-benzenesulphonamide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-2,2'-bipyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[5-(4-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-2,2'-bipyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[5-(4-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-2-methyl-pyrimidin-4-yl]-benzene-sulphonamide,

4-tert-butyl-N-[5-(4-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide,

N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-4-isopropyl-benzenesulphonamide,

N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-4-tert-butyl-benzenesulphonamide,

4-tert-butyl-N-[5-(2-fluoro-6-methoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzene-sulphonamide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-2-(2-methoxy-ethyl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-benzene-sulphonamide,

4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-2-[2-(2-hydroxy-ethoxy)ethyl]-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-benzene-sulphonamide,

(S)-4-tert-butyl-N-[6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-5-(2-methoxy-phenoxy)-2-methyl-pyrimidin-4-yl]-benzenesulphonamide,

REPLACEMENT SHEET
15 OCT 1996

(R)-4-tert-butyl-N-[6-(2,3-dihydroxy-propoxy)-5-(2-methoxy-phenoxy)-2-methyl-6-(2-pyrimidin-4-yl]-benzene-sulphonamide,

(R)-4-tert-butyl-N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-pyrimidin-4-yl]-benzenesulphonamide,

(S)-4-tert-butyl-N-[5-(5-fluoro-2-methoxy-phenoxy)-6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-pyrimidin-4-yl]-benzenesulphonamide,

(R)-4-tert-butyl-N-(5-fluoro-2-methoxy-phenoxy)-6-(2,3-dihydroxy-propoxy-pyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[6-[(S)-1,3-dioxolan-4-ylmethoxy]-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzene-sulphonamide,

(R)-4-tert-butyl-N-[6-(2,3-dihydroxy-propoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzene-sulphonamide,

4-tert-butyl-N-[6-(R)-1,3-dioxolan-4-ylmethoxy]-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzene-sulphonamide,

(S)-4-tert-butyl-N-[6-(2,3-dihydroxy-propoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-2-yl)-pyrimidin-4-yl]-benzene-sulphonamide,

(R)-4-tert-butyl-N-[6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[6-[(S)-2,3-dihydroxy-propoxy]-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzene-sulphonamide,

(S)-4-tert-butyl-N-[(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzenesulphonamide,

4-tert-butyl-N-[6-[(R)-2,3-dihydroxy-propoxy]-5-(2-methoxy-phenoxy)-2-(thiophen-3-yl)-pyrimidin-4-yl]-benzene-sulphonamide,

(S)-4-tert-butyl-N-[6-(2,2-dimethyl-1,3-dioxolan-4-yl-methoxy)-2-(furan-3-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide,

REPLACEMENT SHEET
15 OCT 1996

(R)-4-tert-butyl-N-[2-(furan-3-yl)-6-(2,3-dihydroxy-propoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzene-sulphonamide,

(R)-4-tert-butyl-N-[6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-2-(furan-3-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide,

(S)-4-tert-butyl-N-[2-(furan-3-yl)-6-(2,3-dihydroxy-propoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzene-sulphonamide,

3-methylisoxazole-5-carboxylic acid 2-[6-(4-t-butyl-benzenesulfonamino)-5-(3-methoxyphenoxy)pyrimidin-4-yloxy]-ethyl ester,

indole-2-carboxylic acid 2-[6-(4-t-butylbenzenesulfon-amino)-5-(3-methoxyphenoxy)pyrimidin-4-yloxy]ethyl ester, and

5-[N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-pyrimidin-4-yl]aminosulfonyl]-2-methoxyphenoxy acetic acid ethyl ester.

10. (S)-4-tert-Butyl-N-[6-(2,3-dihydroxy-propyloxy)-5-(2-methoxy-phenoxy)-2-(4-methoxyphenyl)-pyrimidin-4-yl]-benzenesulphonamide.

11. (RS)-4-tert-Butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-2-ethyl-6-(2-methylsulphinyl-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide.

12. (RS)-N-[5-(2-Chloro-5-methoxy-phenoxy)-6-(2-methylsulphinyl-ethoxy)-pyrimidin-4-yl]-1,3-benzodioxol-5-sulphonamide.

13. 4-tert-Butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(pyrimidin-2-yl)-pyrimidin-4-yl]-benzenesulphonamide.

14. Compounds according to claim 1 or 2, in which Z is ethylene or vinylene.

REPLACEMENT SHEET
15 OCT 1996

15. The compounds according to claim 14,

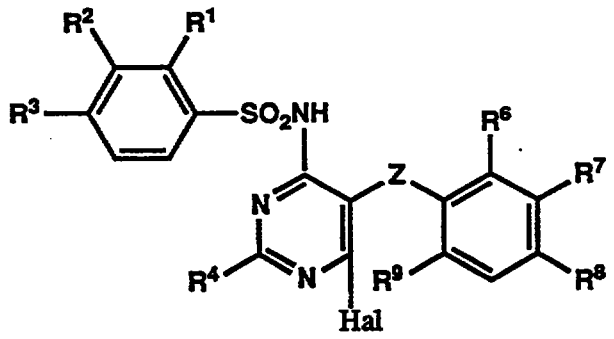
2-[[5-[(E/Z)-styryl]-6-p-toluenesulphonamido-4-pyrimidinyl]oxy]ethyl acetate,

2-[[5-phenethyl-6-p-toluenesulphonamido-4-pyrimidinyl]-oxy]ethyl acetate

N-[6-(2-hydroxyethoxy)-5-phenethyl-4-pyrimidinyl]-p-toluenesulphonamide and

N-[6-(2-hydroxyethoxy)-5-([E/Z)-styryl]-4-pyrimidinyl]-p-toluenesulphonamide.

16. Compounds of the formula



II

wherein R^1-R^5, R^a, R^b, Y and n have the significance given in claim 1.

17. The compounds of claims 1-15 for use as medicaments.

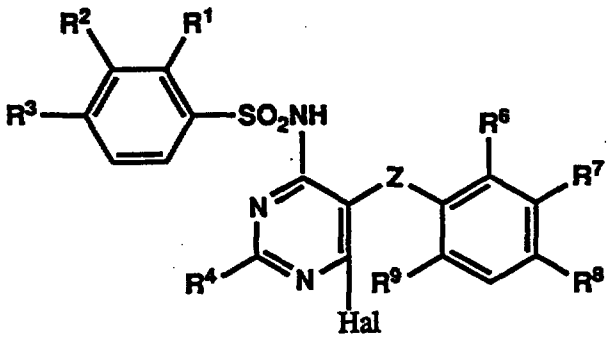
18. Pharmaceutical preparations, containing a compound of claims 1-15 and usual carriers and adjuvants.

19. The use of compounds of claims 1-15 as active ingredients in the manufacture of medicaments for the treatment of disorders which are associated with endothelin activities, especially circulatory disorders such as hypertension, ischaemia, vasospasms and angina pectoris.

20. A process for the manufacture of compounds of claims 1-15, which process comprises

REPLACEMENT SHEET
15 OCT 1996

a) reacting a compound of the formula



II

wherein R^1, R^2, R^3, R^4 and R^6 have the significance given above and Hal is halogen,

with a compound of the formula

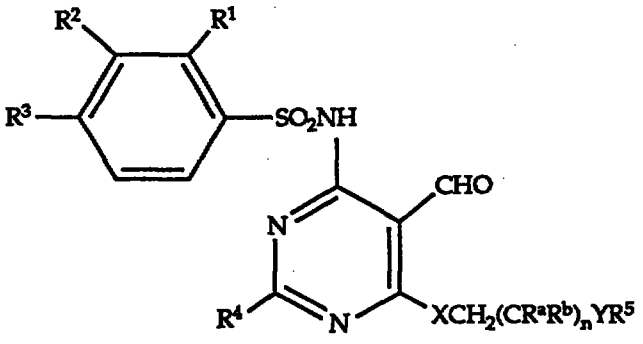


III

wherein X, Y, n, R^a, R^b and R^5 have the significance given above and M represents an alkali metal,

or

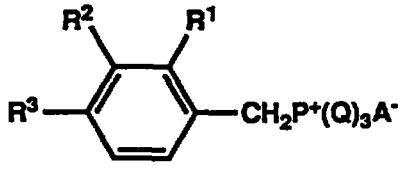
b) reacting a compound of the formula



IV

wherein R^1-R^5, R^a, R^b, X, Y and n have the significance given above,

with a compound of the formula



V

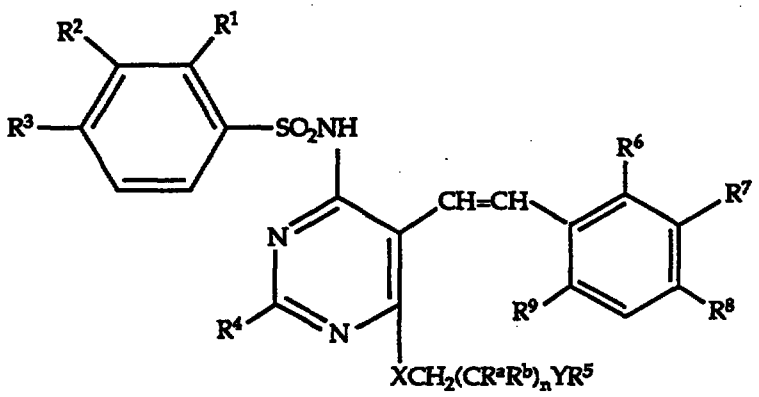
* C L M S *

REPLACEMENT SHEET
15 OCT 1996

wherein R^6-R^8 have the significance given above; Q is aryl and A^- is an anion,

or

c) hydrogenating a compound of the formula

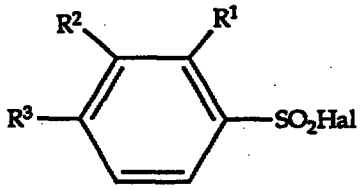


VI

wherein R^1-R^8, R^a, R^b, X, Y and n have the significance given above,

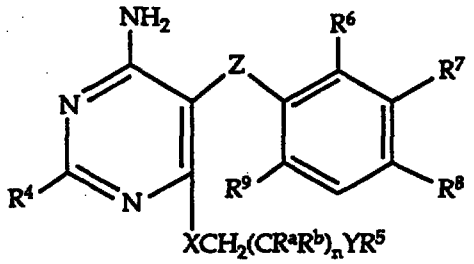
or

d) reacting a compound of the formula



XIV

with a compound of the formula



XV

wherein R^1-R^9, R^a, R^b, X, Y, Z and n have the significance given above,

REPLACEMENT SHEET
15 OCT 1996

and, if desired, modifying substituents present in the compound of formula I obtained and/or converting the compound of formula I obtained into a salt.

REPLACEMENT SHEET
15 OCT 1996

NOVEL SULFONAMIDES

Abstract

The novel sulphonamides of formula I, in which the symbols R^1-R^9, R^a, R^b, X, Y and n have the significance given in the description and salts thereof can be used as active ingredients for the manufacture of medicaments for the treatment of circulatory disorders, especially hypertension, ischemia, vasopasms and angina pectoris.