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(71) Applicant(s)
F. Hoffmann-La Roche AG

(72) Inventor(s)
Volker Breu; Jean-Marie Cassal; Georges Hirth; Marcel Muller; Henri Ramuz; Kaspar Burri; Martine Clozel; Bernd-Michael Loffler; Werner Neidhart

(74) Agent/Attorney
SPRUSON and FERGUSON,GPO Box 3898,SYDNEY NSW 2001

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(54) Title
NOVEL SULFONYLAMINOPYRIMIDINES

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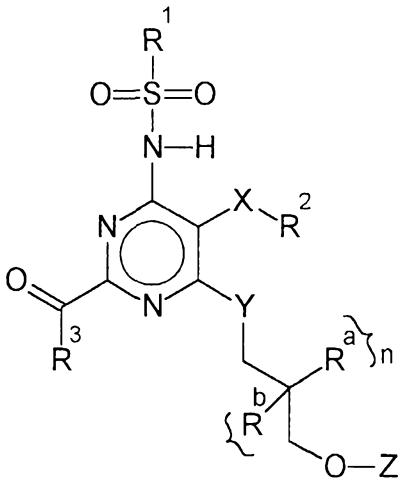
(71) Applicant(s)
F.HOFFMANN-LA ROCHE AG

(72) Inventor(s)
VOLKER BREU; JEAN-MARIE CASSAL; GEORGES HIRTH; MARCEL MULLER; HENRI RAMUZ; KASPAR BURRI; MARTINE CLOZEL; BERND-MICHAEL LOFFLER; WERNER NEIDHART

(74) Attorney or Agent
SPRUSON & FERGUSON , GPO Box 3898, SYDNEY NSW 2001

(57) Claim

1. Compounds of the formula

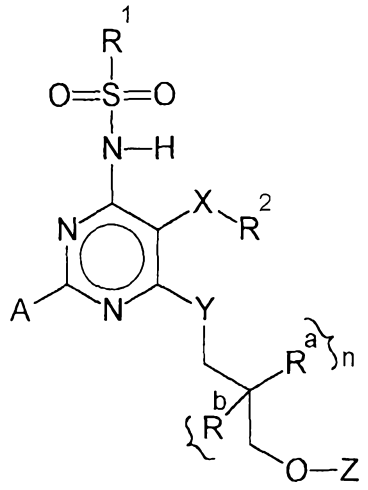


wherein R^1 signifies phenyl, substituted phenyl or heterocyclyl; R^2 signifies phenyl or substituted phenyl; R^3 signifies hydroxy, lower-alkoxy or a residue $-NR^4R^5$; R^4 signifies hydrogen or a residue $-R^6$ and R^5 signifies hydrogen or a residue $-(CH_2)_mR^6$ or R^4 and R^5 together with the N atom to which they are attached signify a N-heterocyclic residue; R^6 signifies phenyl, substituted phenyl, cycloalkyl, heterocyclyl, lower-alkyl, hydroxy-lower-alkyl, amino-lower-alkyl, carboxy-lower-alkyl or lower-alkoxycarbonyl-lower-alkyl; R^a signifies hydrogen, lower-alkyl or hydroxy; R^b signifies hydrogen or lower-alkyl; X signifies oxygen or sulfur; Y signifies oxygen or sulfur; Z signifies hydrogen, lower-alkyl, aryl, aryl-lower-alkyl, heterocyclyl or heterocyclyl-lower-alkyl; m signifies 0, 1 or 2; and n signifies 0, 1 or 2; and pharmaceutically useable salts thereof.

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29. A method for the treatment or prophylaxis of a disorder associated with endothelin activities in a mammal requiring said treatment or prophylaxis, which method comprises administering to said mammal an effective amount of at least one compound according to any one of claims 1 to 21 or 24, or of a composition according to claim 26 or claim 27.

32. Compounds of the formula



wherein A signifies formyl or furan-2-yl and R^1, R^2, X, Z, R^a, R^b, Y and n have the significance given in claim 1 and wherein a hydroxy group represented in formula II by OZ and a hydroxy group which may be present as R^a can be present in protected form.

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FOR A STANDARD PATENT

ORIGINAL

Name and Address of Applicant: F.Hoffmann-La Roche AG
124 Grenzacherstrasse
CH-4070 Basle
SWITZERLAND

Actual Inventor(s): Volker Breu, Jean-Marie Cassal, Georges Hirth, Marcel Muller, Henri Ramuz, Kaspar Burri, Martine Clozel, Bernd-Michael Loffler and Werner Neidhart

Address for Service: Spruson & Ferguson, Patent Attorneys
Level 33 St Martins Tower, 31 Market Street
Sydney, New South Wales, 2000, Australia

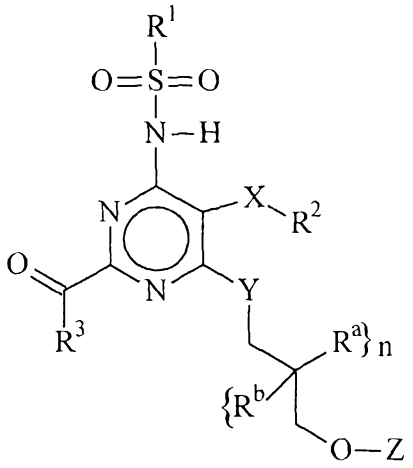
Invention Title: ~~Novel Sulfonylaminopyrimidines~~
Novel pyrimidinesubstituted benzene (or heterocyclyl) sulfonamide derivatives

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

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Novel pyrimidinesubstituted benzene (or heterocyclyl) sulfonamide derivatives

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



wherein R^1 signifies phenyl, substituted phenyl or heterocyclyl; R^2 signifies phenyl or substituted phenyl; R^3 signifies hydroxy, lower-alkoxy or a residue $-NR^4R^5$; R^4 signifies hydrogen or a residue R^6 and R^5 signifies hydrogen or a residue $(CH_2)_mR^6$ or R^4 and R^5 together with the N atom to which they are attached signify a N-heterocyclic residue; R^6 signifies phenyl, substituted phenyl, cycloalkyl, heterocyclyl, lower-alkyl, hydroxy-lower-alkyl, amino-lower-alkyl, carboxy-lower-alkyl or lower-alkoxycarbonyl-lower-alkyl; R^a signifies hydrogen, lower-alkyl or hydroxy; R^b signifies hydrogen or lower-alkyl; X signifies oxygen or sulfur; Y signifies oxygen or sulfur; Z signifies hydrogen, lower-alkyl, aryl; aryl-lower-alkyl, heterocyclyl or heterocyclyl-lower-alkyl; m signifies 0, 1 or 2; and n signifies 0, 1 or 2; and pharmaceutically useable salts thereof.

Phenyl residues can be substituted by lower-alkyl, lower-alkoxy, methylenedioxy, ethylenedioxy, lower-alkanoyl, hydroxy, amino, mono- or di-lower-alkylamino and/or halogen. The term "lower" used herein denotes groups with 1-7 C atoms, preferably 1-4 C atoms. Alkyl and alkoxy groups as well as alkyl groups as components of alkanoyl groups can be straight-chain or branched.

Methyl, ethyl, propyl, isopropyl, butyl, sec.butyl and tert.butyl are examples of such alkyl groups. Halogen denotes fluorine, chlorine, bromine and iodine, with chlorine being preferred.

Examples of heterocyclyl residues are mono- or bicyclic 5- and 6-membered heterocyclic residues containing oxygen, nitrogen or sulfur as the hetero atom(s), such as 2- and 3-furyl, pyrimidinyl, 2-, 3- and 4-pyridyl, 2-tetrazolyl-4-pyridyl, 1,2- and 1,4-diazinyl, morpholino, 2- and 3-thienyl, isoxazolyl, oxazolyl, thiazolyl, imidazolyl, pyrrolyl and tetrazolyl, which can be substituted eg. by lower-alkyl, lower-alkanoyl, hydroxy, lower-alkanoyloxy, lower-alkoxy, lower-alkoxycarbonyl,

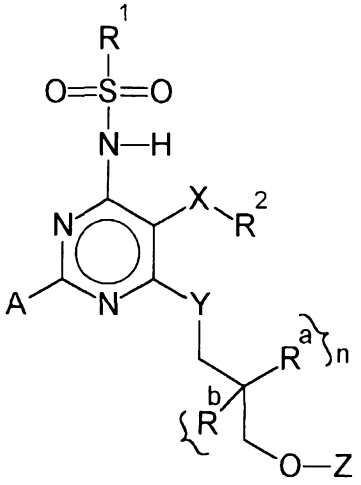
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formyl, amino, mono- or di-lower-alkylamino or halogen. N-Heterocyclic residues formed with R^4 and R^5 are preferably monocyclic 6-membered heterocyclyl residues which can contain a further oxygen or nitrogen atom, such as morpholino, piperidino, piperazino and N^4-lower-alkyl piperazino.

Preferred residues R^1 are phenyl, which is substituted by lower-alkyl or lower-alkoxy, and monocyclic heterocyclyl residues which contain a nitrogen atom, such as pyridyl, especially 2-pyridyl, and which can be substituted, preferably monosubstituted, by lower-alkyl. Preferred residues R^2 are phenyl, which is substituted by lower-alkoxy and/or halogen. Preferred residues R^3 are hydroxy and $-NR^4R^5$, with R^4 being hydrogen and R^5 being phenyl or tetrazolyl. R^a is preferably hydrogen or hydroxy. R^b is preferably hydrogen. X and Y are preferably oxygen. Z is preferably hydrogen. n is preferably 0 or 1.

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

The compounds of formula I and their salts can be manufactured in accordance with the invention by converting the residue A in a compound of formula II

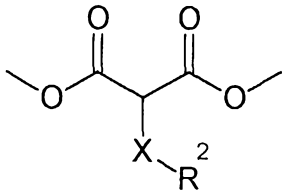


wherein A represents a residue convertible into a carboxyl group and R^1, R^2, X, Y, Z, R^a, R^b and n have the significance given above, into a carboxyl group and optionally converting the hydroxy group R^3 in a thus-obtained compound of formula I in which R^3 is hydroxy into a lower-alkoxy group or a group $-NR^4R^5$ or into a pharmaceutically useable salt.

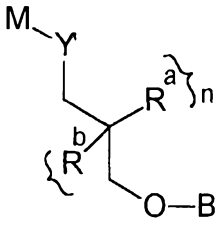
Examples of residues A are especially the formyl group and the furan-2-yl residue. These residues can be converted into a carboxy group in a manner known per se by treatment with oxidising agents, with groups which are present in the starting material of formula II and which are not inert towards the oxidising agent which is employed, such as hydroxy groups, conveniently being protected. A

suitable oxidising agent for the oxidation of a formyl group to a carboxyl group is eg. potassium permanganate. The oxidation can be carried out in a suitable inert solvent such as benzene in the presence of a crown ether at room temperature. The hydroxy group explicitly indicated in formula I as well as hydroxy groups present as R^a and/or in R^1 can be protected in a manner known per se in the form of an ester such as the acetate or as a ketal, eg. as the acetonide. A furan-2-yl group can be oxidised to the carboxyl group by treatment with periodate, eg. Na periodate in the presence of ruthenium trichloride in a two-phase system containing CCl_4, acetonitrile and water.

The compounds of formula II are novel and are likewise an object of the invention. Compounds of formula II in which A is a formyl residue can be prepared from corresponding methyl compounds (see European Patent Publication EP-A 0526708) by oxidation, eg. with selenium dioxide (see European Patent Publication EP-A 0601386). Compounds of formula II in which A is the furan-2-yl residue and Y is oxygen or sulfur can be prepared starting from compounds of the formula



by condensation with 2-furanylamidine to give a 2-furan-2-yl-(5-XR^2)pyrimidine-4,6-diol, replacement of the OH groups by Cl by treatment with $POCl_3$, reaction of the 4,6-dichloropyrimidine derivative with a sulfonamide salt of the formula R^1SO_2NHM and thereafter with a compound of the formula



wherein Y' represents oxygen or sulfur, M represents a cation, eg. an alkali cation such as Na^+ or K^+, and B represents a protecting group and wherein a hydroxy group which may be represented by R^a is present in protected form.

The thus-formed carboxy group can be converted in a manner known *per se* into a lower-alkyl ester (R^3 = lower alkoxy) or an amide (R^3 =-NR^4R^5) or into a pharmaceutically useable salt.

Examples of pharmaceutically useable salts are alkali salts such as the Na salt and the K salt and alkaline earth salts such as the Ca salt and the Mg salt.

The compounds of formula I exhibit a selective inhibitory activity on endothelin receptors A and B (ET_A and ET_B), which can be demonstrated using the test procedures described hereinafter:

I, Inhibition of endothelin binding to recombinant ETA receptors

A cDNA coding for human ETA receptors of human placenta was cloned (M. Adachi, Y.-Y. Yang, Y. Furuichi and C Miyamoto, BBRC 180, 1265-1272) and expressed in the baculovirus-insect cell system. Baculovirus-infected insect cells from a 23L fermentor are centrifuged off (3000 x g, 15 minutes, 4°C) 60h after the infection, re-suspended in Tris buffer (5mM, pH7.4, 1mM $MgCl_2$) and again centrifuged. After a further re-suspension and centrifugation the cells are suspended in 800mL of the same buffer and freeze-dried at -120°C. The cells disintegrate when the suspension in this hypotonic buffer mixture is thawed. After a repeated freeze-drying/thawing cycle the suspension is homogenised and centrifuged (25000 x g, 15 minutes, 4°C). After suspension in Tris buffer (75mM, pH7.4, 25mM $MgCl_2$, 250mM sucrose) 1mL aliquots (protein content about 3.5mg/mL) are stored at -85°C.

For the binding assay, the freeze-dried membrane preparations are thawed and, after centrifugation at 20°C and 25000g for 10 minutes, re-suspended in assay buffer (50mM Tris buffer pH7.4, containing 25mM $MnCl_2$, 1mM EDTA and 0.5% bovine serum albumin). 100µL of this membrane suspension containing 5µg of protein are incubated with 50µL of ^{125}I-endothelin (specific activity 2200Ci/mMol) in assay buffer (25000cpm, final concentration 20pM) and 100µL of assay buffer containing varying concentrations of test compound. The incubation is carried out at 20°C for 2h or at 4°C for 24h. The separation of free and membrane-bound radioligands is carried out by filtration over a glass fibre filter.

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

Human placenta is homogenised in 5mM Tris buffer, pH7.4, which contains 1mM $MgCl_2$ and 250mM sucrose. The homogenisate is centrifuged at 4°C and 3000g for 15 minutes the supernatant containing the plasma membrane fraction is centrifuged at 72000g for 30 minutes and the precipitate is washed with 75 mM Tris buffer, pH7.4, which contains 25mM $MgCl_2$. Thereafter, precipitate obtained from in each case 10g of original tissue is suspended in 1mL of 75mM Tris buffer, pH7.4, containing 25mM $MgCl_2$ and 250mM sucrose and freeze-dried at -20°C in 1mL aliquots.

For the binding assay, the freeze-dried membrane preparations are thawed and, after centrifugation at 20°C and 25000g for 10 minutes, re-suspended in assay buffer (50mM Tris buffer, pH7.4, containing 25mM $MnCl_2$, 1mM EDTA and 0.5% bovine serum albumin). 100µL of this membrane suspension containing 35µg of protein are incubated with 50µL of ^{125}I-endothelin (specific activity 2200Ci/mMol)

in assay buffer (25000cpm, final concentration 20pM) and 100µL of assay buffer containing varying concentrations of test compound. The incubation is carried out at 20°C for 2h or at 4°C for 24h. The separation of free and membrane-bound radioligands is carried out by filtration over a glass fibre filter.

The inhibitory activity on ET_A and ET_B receptors of compounds of formula I determined in these test procedures is given in Table 1 as the IC_{50}, ie. as the concentration [µM] which is required to inhibit 50% of the specific binding of ^{125}I-endothelin.

Table 1

Compound of Example	ET_A IC_{50} [µM]	ET_B IC_{50} [µM]
1	73	0.08
2	1.83	0062
5	1 6.4	0.29
6	38	063
7	18.2	0.3
8	1 3	0.06
9	21.4	0.086
10	1 3	0.14

On the basis of their capability of inhibiting endothelin binding, the compounds of formula I can be used as medicament for the treatment of disorders which are associated with vasoconstriction of increasing occurrences. Examples of such disorders are high blood pressure, especially pulmonary high pressure, as well as sub-arachnoid haemorrhage. Further indications for which the compounds in accordance with the invention can be used are coronary disorders, cardiac insufficiency, renal and myocardial ischaemia, renal insufficiency, cerebral ischaemia, cerebral infarct, migraine and Raynaud's syndrome. The compounds in accordance with the invention can also be used in atherosclerosis, the prevention of restenosis after balloon-induced vascular dilation, inflammations, gastric and duodenal ulcers, ulcers cruris, gram-negative sepsis, shock, glomerulonephritis, renal colic, glaucoma, asthma, in dialysis and 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, eg. intravenously, intramuscularly, subcutaneously, intrathecally or transdermally; or sublingually or as opthalmalogical preparations, or as an aerosol. Capsules, tablets, suspensions or solutions for oral administration, suppositories, injection solutions, eye drops, salves or spray solutions are examples of administration forms.

Intravenous, intramuscular or oral administration 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 administration. In general, dosages of about 0.1-100mg/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 eg. 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, stabilising, 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, eg. water, gelatine, lactose, starch, magnesium stearate, talc, gum arabic, polyalkylene glycols and the like. It is a prerequisite that all adjuvants used in the production of the preparations are non-toxic.

The following Examples illustrate the invention in more detail.

Example 1

a) 25g of resorcinol monomethyl ether and 37g of dimethyl chloromalonate were added to a solution of 4.6g of sodium in 150mL of methanol. The reaction mixture was stirred at 45°C under argon for 4h, filtered and partitioned between toluene/ water. The organic phase was dried with sodium sulfate and the solvent was distilled off. 40.7g of methyl (RS)-(3-methoxyphenoxy)-acetoacetate were obtained as an oil, MS: $(M^+H)^+$ 255.

b) 17g of acetamidine hydrochloride and 40g of methyl (RS)-(3-methoxyphenoxy)-acetoacetate were added to a sodium methylate solution prepared from 450mL of methanol and 11.3g of sodium. The reaction mixture was stirred at 20°C for 2h, concentrated and partitioned between toluene/water. The aqueous phase was adjusted to pH4 with 2N HCl and stirred at 0°C for 1 6h. The precipitate was filtered off, washed with water and ether and dried. 25.7g of 6-hydroxy-5-(3-methoxyphenoxy)-2-methyl-3H-pyrimidin-4-one were obtained as a white solid, MS: $(M^+H)^+$ 249.

c) 24.5mL of Hünig base and 23.6mL of $POCl_3$ were added to a solution of 11.9g of 6-hydroxy-5-(3-methoxyphenoxy)-2-methyl-3H-pyrimidin-4-one in 1 50mL of dioxan. The reaction mixture was stirred at 120°C for 16h and thereafter the excess reagent and the dioxan were distilled off. The residue was concentrated twice with toluene and partitioned between chloroform-water. The organic phase was washed with $NaHCO_3$ and with water, dried and concentrated. The residue was purified over silica gel with hexane and dichloromethane. 9.1g of 4,6-dichloro-

5-(3-methoxyphenoxy)-2-methyl-pyrimidine were obtained as a yellowish oil, MS: $(M^+H)^+$ 286.

d) 9g of 4,6-dichloro-5-(3-methoxyphenoxy)-2-methylpyrimidine and 17g of K p-tert.-butylsulfonamide in 35mL of dry dimethylsulfoxide were heated to 120°C under argon for 3h. Thereafter, DMSO 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 35mL of methanol. 11.1g of p-tert.butyl-N-[6-chloro-5-(m-methoxyphenoxy)-2-methyl-4-pyrimidinyl-benzenesulfonamide, m.p. 170°C, were obtained.

e) 11g of p-tert.butyl-N-[6-chloro-5-(m-methoxyphenoxy)-2-methyl-4-pyrimidinyl-benzenesulfonamide were added to a sodium glycolate solution prepared from 35g of ethylene glycol and 1.66g of sodium. The reaction mixture was stirred at 95°C under argon for 16h, thereafter treated with 100mL of 1 N hydrochloric acid and 50mL of water and extracted twice with 100mL of ethyl acetate. The organic phase was washed with water, dried and evaporated. The residue was crystallised from dichloromethane-isopropyl ether. There were obtained 8.8g of p-tert.butyl-N-[6-(2-hydroxyethoxy)-2-methyl-5-(m-methoxyphenoxy)-4-pyrimidinyl]benzenesulfonamide, m.p. 139°C, MS: $(M^+H)^+$ 488.

f) 0.2g of dimethylaminopyridine and 3.9mL of acetic anhydride were added to a solution of 1g of p-tert.butyl-N-[6-(2-hydroxyethoxy)-2-methyl-5-(m-methoxyphenoxy)-4-pyrimidinyl]benzenesulfonamide in 40mL of dichloromethane. The reaction mixture was stirred at 20°C for 3h and adjusted to pH7 with a sat. $NaHCO_3$ solution. The organic phase was washed with water, dried and evaporated. The residue was purified over silica gel with chloroform. 1.1g of 2-[6-acetyl-(4-tert.butyl-phenylsulfonyl)-amino]-5-(3-methoxyphenoxy)-2-methylpyrimidin-4-yloxy]-ethyl acetate were obtained as a foam, MS: $(M^+H)^+$ 572.

g) 0.2g of 2-[6-acetyl-(4-tert.butyl-phenylsulfonyl)-amino]-5-(3-methoxyphenoxy)-2-methylpyrimidin-4-yloxy]-ethyl acetate and 0.6g of selenium dioxide were stirred in 10mL of dioxan at 140°C in an autoclave for 50h. The reaction mixture was filtered and the filtrate was concentrated. The residue was partitioned between ethyl acetate and water. The organic phase was dried, the solvent was evaporated and the residue was purified over silica gel with chloroform-methanol 95:5. 0.27g of 2-[6-(4-tert.butyl-phenylsulfonylamino)-2-formyl-5-(3-methoxyphenoxy)-pyrimidin-4-yloxy]-ethyl acetate was obtained as a foam, MS: $(M^+H)^+$ 544.

h) 0.27g of 2-[6-(4-tert.butyl-phenylsulfonylamino)-2-formyl-5-(3-methoxyphenoxy)-pyrimidin-4-yloxy]-ethyl acetate and 0.19g of dicyclohexyl-18-crown-6 in 15mL of benzene were stirred with 0.078g of potassium permanganate at 20°C for 16h. The reaction mixture was partitioned between toluene and water.

The organic phase was dried and evaporated, and the residue was purified over silica gel with chloroform-methanol. 0.09g of 4-(2-acetoxy-ethoxy)-6-(4-tert.butyl-phenylsulfonylamino)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid was obtained as a foam, MS: $(M^-H)^-$ 558.

j) 0.09g of 4-(2-acetoxy-ethoxy)-6-(4-tert.butyl-phenylsulfonylamino)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid in 4mL of methanol and 1.5mL of water was stirred with 0.05g of sodium carbonate at 20°C for 2h. The methanol was evaporated and the residue was partitioned between chloroform and aqueous 1N hydrochloric acid. The organic phase was dried and evaporated. The residue was purified over silica gel with chloroform-methanol-water, 60:35:5. There was obtained 0.034g of 6-(4-tert.butyl-phenylsulfonylamino)-4-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid, MS: $(M^-H)^-$ 5 15.9.

Example 2

4-(4-tert.butyl-phenylsulfonylamino)-5-(2-chloro-5-methoxyphenoxy)-6-(2-hydroxyethoxy)-pyrimidine-2-carboxylic acid, MS: $(M^-H)^-$ 550.2, was prepared from 2-chloro-5-methoxyphenol in analogy to Example 1 *via* the following intermediates:

a) methyl (RS)-(2-chloro-5-methoxyphenoxy)-acetoacetate,

b) 6-hydroxy-5-(2-chloro-5-methoxyphenoxy)-2-methyl-3H-pyrimidin-4-one,

c) 4,6-dichloro-5-(2-chloro-5-methoxyphenoxy)-2-methylpyrimidine,

d) p-tert.butyl-N-[6-chloro-5-(2-chloro-5-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulfonamide,

e) p-tert.butyl-N-[6-(2-hydroxyethoxy)-2-methyl-5-(2-chloro-5-methoxyphenoxy)-4-pyrimidinyl]benzenesulfonamide,

f) 2-[6-(4-tert.butyl-phenylsulfonylamino)-5-(2-chloro-5-methoxyphenoxy)-2-methylpyrimidin-4-yloxy]-ethyl acetate,

g) 2-[6-(4-tert.butyl-phenylsulfonylamino)-5-(2-chloro-5-methoxyphenoxy)-2-formyl-pyrimidin-4-yloxy]-ethyl acetate,

h) 4-(2-acetoxy-ethoxy)-6-(4-tert.butyl-phenylsulfonylamino)-5-(2-chloro-5-methoxyphenoxy)-pyrimidine-2-carboxylic acid.

Example 3

4-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-6-(4-methoxyphenylsulfonylamino)-pyrimidin-2-carboxylic acid, MS: $(M^-H)^-$ 490.3, was prepared from 4,6-dichloro-5-(3-methoxyphenoxy)-2-methyl-pyrimidine in analogy to Example 1 *via* the following intermediates:

a) N-[6-chloro-5-(3-methoxyphenoxy)-2-methylpyrimidin-4-yl]-4-methoxybenzenesulfonamide,

b) N-[6-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-2-methylpyrimidin-4-yl]-4-methoxybenzenesulfonamide,

c) 2-[6-(4-methoxyphenylsulfonylamino)-5-(m-methoxyphenoxy)-2-methylpyrimidin-4-yloxy]-ethyl acetate,

d) 2-[6-(4-methoxyphenylsulfonylamino)-5-(m-methoxyphenoxy)-2-formylpyrimidin-4-yloxy]-ethyl acetate,

e) 4-(2-acetoxyethoxy)-6-(4-methoxyphenylsulfonylamino)-5-(m-methoxyphenoxy)-pyrimidine-2-carboxylic acid.

Example 4

a) In analogy to Example 1b, from 34g of ethyl (RS)-(3-methoxyphenoxy)-acetoacetate and 23g of 2-furanylamidine there were obtained 15.6g of 2-(furan-2-yl)-5-(3-methoxyphenoxy)-pyrimidine-4,6-diol as a foam, MS: $(M^+H)^+$ 300.

b) In analogy to Example 1c), from 15.5g of 2-(furan-2-yl)-5-(3-methoxyphenoxy)-pyrimidine-4,6-diol and 43mL of $POCl_3$ there were obtained 15.9g of 4,6-dichloro-2-(furan-2-yl)-5-(3-methoxyphenoxy)-pyrimidine, m.p. 1 06°C, MS: $(M^+H)^+$ 338.

c) In analogy to Example 1d), from 1g of 4,6-dichloro-2-(furan-2-yl)-5-(3-methoxyphenoxy)-pyrimidine and 1.5g of K p-tert.butylsulfonamide there were obtained 1.34g of 4-tert.butyl-N-[6-chloro-2-(furan-2-yl)-5-(3-methoxyphenoxy)-pyrimidin-4-yl]-benzenesulfonamide, MS: $(M^-H)^-$ 513.

d) In analogy to Example 1e), from 0.3g 4-tert.butyl-N-[6-chloro-2-(furan-2-yl)-5-(3-methoxyphenoxy)-pyrimidin-4-yl]-benzenesulfonamide and 12mL of DL-isopropylidene-glycerol there was obtained 0.25g of (RS)-4-tert.butyl-N-[6-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-2-(furan-2-yl)-5-(3-methoxyphenoxy)-pyrimidin-4-yl]-benzenesulfonamide, m.p. 135°C, MS: $(M^-H)^-$ 608.

e) A solution of 0.7g of sodium periodate and 0.015g of ruthenium chloride in 10mL of water was added to a solution of 0.25g of (RS)-4-tert.butyl-N-[6-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-2-(furan-2-yl)-5-(3-methoxyphenoxy)-pyrimidin-4-yl]-benzenesulfonamide in 3.6mL of CCl_4 and 3.6mL of acetonitrile. The reaction mixture was stirred at 20°C for 1 hour and extracted with methylene chloride. The organic phase was dried and evaporated. The residue was purified over silica gel with chloroform. There was obtained 0.04g of (RS)-4-(4-tert.butyl-phenylsulfonylamino-6-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid, MS: $(M^-H)^-$ 586.

f) A solution of 0.033g of (RS)-4-(4-tert.butyl-phenylsulfonylamino-6-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid in 2mL of dioxan was treated with 1.3mL of 1N HCl and heated to 90°C for 30 minutes. After evaporation the residue was chromatographed over silica gel with chloroform-methanol-water 60:35:5 as the eluent and yielded 0.007g of (RS)-6-(4-tert.butyl-phenylsulfonylamino)-4-(2,3-dihydroxypropoxy)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid as a foam, MS: $(M^-H)^-$ 546.

Example 5

In analogy to Example 4e), from 2-[6-(4-tert.butyl-phenylsulfonylamino)-2-(furan-2-yl)-5-(2-methoxyphenoxy)-pyrimidin-4-yloxy]-ethyl acetate there was obtained 4-(2-acetoxy-ethoxy)-6-(4-tert.butyl-phenylsulfonylamino)-5-(2-methoxyphenoxy)-pyrimidine-2-carboxylic acid, MS: $(M^-H)^-$ 558, and therefrom in analogy to Example 1i) there was obtained 6-(4-tert.butyl-phenylsulfonylamino)-4-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-pyrimidine-2-carboxylic acid, MS: $(M^-H)^-$ 516.4.

Example 6

0.2mL of Hünig base, 0.052g of bis-(2-oxo-3-oxazolidinyl)-phosphinic acid chloride and 0.01mL of aniline were added to a solution of 0.053g of 6-(4-tert.butyl-phenylsulfonylamino)-4-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid in 5mL of acetonitrile. After 3h the reaction mixture was evaporated and partitioned between ethyl acetate and water. The organic phase was dried and evaporated, and the residue purified over silica gel with chloroform. There was obtained 0.032g of 6-(4-tert.butyl-phenylsulfonylamino)-4-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid phenylamide, m.p. 143°C, MS: $(M^-H)^-$ 591.

Example 7

4-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-6-(4-methoxyphenylsulfonylamino)-pyrimidine-2-carboxylic acid phenylamide, MS: $(M^+H)^+$ 567, was obtained in analogy to Example 6.

Example 8

6-(4-tert.butyl-phenylsulfonylamino)-5-(2-methoxyphenoxy)-4-(2-hydroxyethoxy)-pyrimidine-2-carboxylic acid phenylamide, MS: $(M^-H)^-$ 591, was obtained in analogy to Example 6.

Example 9

4-(4-tert.butyl-phenylsulfonylamino)-5-(2-chloro-5-methoxyphenoxy)-6-(2-hydroxyethoxy)-pyrimidine-2-carboxylic acid phenylamide, MS: $(M^+H)^+$ 628, was obtained in analogy to Example 6.

Example 10

4-(4-tert.butyl-phenylsulfonylamino)-6-(2-hydroxyethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid (1H-tetrazol-5-yl)-amide, MS: $(M^-H)^-$ 583, was obtained in analogy to Example 6.

Example 11

In analogy to Example 4, paragraph c), d), e), from 4,6-dichloro-2-(furan-2-yl)-5-(3-methoxyphenoxy)-pyrimidine there were obtained:

a) 5-isopropylpyridine-2-sulfonic acid [6-chloro-2-(furan-2-yl)-5-(3-methoxyphenoxy)-pyrimidin-4-yl]-amide

b) 5-isopropyl-pyridine-2-sulfonic acid [2-(furan-2-yl)-6(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-pyrimidin-4-yl]-amide

c) 2-[6-[acetyl-(5-isopropylpyridin-2-ylsulfonyl)-amino]-2-(furan-2-yl)-5-(3-methoxyphenoxy)-pyrimidin-4-yloxy]-ethyl acetate

d) 4-(2-acetoxyethoxy)-6-(5-isopropylpyridin-2-ylsulfonyl)-amino]-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid and therefrom in analogy to Example 1 there was obtained 4-(2-hydroxyethoxy)-6-(5-isopropylpyridin-2-ylsulfonylamino)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid, MS: $(M^-H)^-$ 503.

Example 12

In analogy to Example 4, paragraph c), d), e) from 4,6-dichloro-2-(furan-2-yl)-5-(3-methoxyphenoxy)-pyrimidine there were obtained:

a) 5-methylpyridine-2-sulfonic acid [6-chloro-2-(furan-2-yl)-5-(3-methoxyphenoxy)-pyrimidin-4-yl]-amide

b) 5-methyl-pyridine-2-sulfonic acid [2-(furan-2-yl)-6-(2-hydroxyethoxy)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-amide

c) 2-[2-(furan-2-yl)-5-(3-methoxyphenoxy)-6-(5-methylpyridin-2-ylsulfonylamino)-pyrimidin-4-yloxy]-ethyl acetate

d) 4-(2-acetoxyethoxy)-6-(5-methylpyridin-2-ylsulfonyl)-amino]-5-(3-methoxyphenoxy)-pyrimidin-2-carboxylic acid and therefrom in analogy to Example 1 there was obtained 4-(2-hydroxyethoxy)-6-(5-isopropylpyridin-2-ylsulfonylamino)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid, MS: $(M^-H)^-$475.

Example 13

4-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-6-(5-methylpyridin-2-ylsulfonylamino)-pyrimidine-2-carboxylic acid (1H-tetrazol-5-yl)amide can be obtained in analogy to Example 6.

Example 14

(R,S)-6-(2,3-dihydroxypropoxy)-5-(3-methoxyphenoxy)-4-(5-methylpyridin-2-yl-sulfonylamino)-pyrimidine-2-carboxylic acid can be obtained in analogy to Example 4.

Example 15

6-(4-tert.butylphenylsulfonylamino)-4-(2,3-dihydroxypropoxy)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid (1H-tetrazol-5-yl)amide can be obtained in analogy to Example 6.

Example 16

4-tert-butyl-N-[6-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-2-(morpholin-4-ylcarboxy)-pyrimidin-4-yl]-benzene-sulfonamide, MS: $(M^-H)^-$ 585, was obtained in analogy to Example 6.

Example 17

4-(4-tert-butyl-phenylsulfonylamino)-6-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid pyridin-3-ylamide, MS: $(M^-H)^-$ 592, was obtained in analogy to Example 6.

Example 18

4-(4-tert-butyl-phenylsulfonylamino)-6-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid (3-hydroxyphenyl)-amide, MS: $(M^-H)^-$ 607, was obtained in analogy to Example 6.

Example 19

4-(4-tert-butyl-phenylsulfonylamino)-6-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid (2-hydroxymethylphenyl)-amide, MS: $(M^+H)^+$ 623, was obtained in analogy to Example 6.

Example 20

4-(4-tert-butyl-phenylsulfonylamino)-6-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid (3-hydroxymethylphenyl)-amide, MS $(M^-H)^-$ 621, was obtained in analogy to Example 6.

Example 21

(RS)-4-(4-tert-butyl-phenylsulfonylamino)-6-(2,3-dihydroxypropoxy)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid pyridin-3-ylamide, MS: $(M^-H)^-$ 622, was obtained in analogy to Example 6.

Example 22

(RS)-4-(4-tert-butyl-phenylsulfonylamino)-6-(2,3-dihydroxypropoxy)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid (3-hydroxyphenyl)-amide, MS: $(M^-H)^-$ 637, was obtained in analogy to Example 6.

Example 23

0.2g of 6-(4-tert-butyl-phenylsulfonylamino)-4-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid in 5mL of dimethylacetamide was stirred at 20°C for 3h with 0.04g of sodium hydride and 0.07g of 2-chloropyrimidine and the mixture was neutralised with saturated NH_4Cl solution. The reaction mixture was washed with ethyl acetate. The aqueous phase was adjusted to pH2 with 1 N HCl and extracted with chloroform. The organic phase was dried, the solvent was evaporated and the residue was purified over silica gel-with chloroform-methanol-water 60:35:5. There was obtained 0.16g of 4-(4-tert-butyl-

phenylsulfonylamino)-5-(3-methoxyphenoxy)-6-(2-pyrimidin-2-yloxy-ethoxy)-pyrimidine-2-carboxylic acid, MS: $(M^+H)^+$ 596.

Example A

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

Ingredients	Per tablet
Compound of formula 1	10.0 - 100.0mg
Lactose	125.0mg
Corn starch	75.0mg
Talc	4.0mg
Magnesium stearate	1.0mg

Example B

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

Ingredients	Per capsule
Compound of formula I	25.0mg
Lactose	150.0mg
Corn starch	20.0mg
Talc	5.0mg

Example C

Injection solutions can have the following composition:

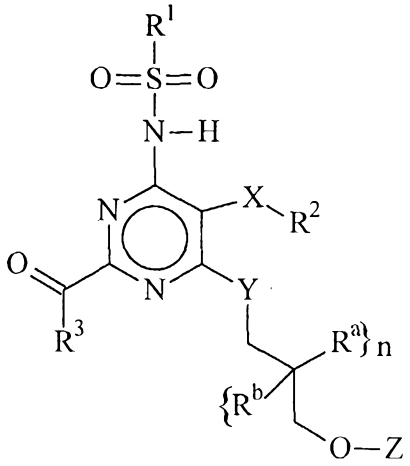
Compound of formula I	3.0mg
Gelatine	150.0mg
Phenol	4.7mg
Water for injection solutions	ad 1.0mL

Example D

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

The claims defining the invention are as follows:

1. Compounds of the formula



wherein R^1 signifies phenyl, substituted phenyl or heterocyclyl; R^2 signifies phenyl or substituted phenyl; R^3 signifies hydroxy, lower-alkoxy or a residue $-NR^4R^5$; R^4 signifies hydrogen or a residue $-R^6$ and R^5 signifies hydrogen or a residue $-(CH_2)_mR^6$ or R^4 and R^5 together with the N atom to which they are attached signify a N-heterocyclic residue; R^6 signifies phenyl, substituted phenyl, cycloalkyl, heterocyclyl, lower-alkyl, hydroxy-lower-alkyl, amino-lower-alkyl, carboxy-lower-alkyl or lower-alkoxycarbonyl-lower-alkyl; R^a signifies hydrogen, lower-alkyl or hydroxy; R^b signifies hydrogen or lower-alkyl; X signifies oxygen or sulfur; Y signifies oxygen or sulfur; Z signifies hydrogen, lower-alkyl, aryl, aryl-lower-alkyl, heterocyclyl or heterocyclyl-lower-alkyl; m signifies 0, 1 or 2; and n signifies 0, 1 or 2; and pharmaceutically useable salts thereof.

2. Compounds according to claim 1, in which X and Y are oxygen.

3. Compounds according to claim 1 or 2, in which n is 0 or 1.

4. Compounds according to any one of claims 1 to 3, in which R^1 signifies phenyl, which is substituted by lower-alkyl or lower-alkoxy.

5. Compounds according to any one of claims 1 to 4, in which R^1 signifies a monocyclic heterocyclyl residue which contains a nitrogen atom and which can be substituted by lower alkyl.

6. Compounds according to any one of claims 1 to 5, in which R^2 signifies phenyl, which is substituted by lower-alkoxy and/or halogen.

7. Compounds according to any one of claims 1 to 6, wherein R^3 signifies hydroxy or $-NR^4R^5$.

8. Compounds according to any one of claims 1 to 6, wherein R^3 signifies $-NR^4R^5$, R^5 signifies $-(CH_2)_mR^6$ and R^6 signifies phenyl, substituted phenyl, C_{3-8}-cycloalkyl or heterocyclyl.

9. 6-(4-tert.butyl-phenylsulfonylamino)-4-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid.

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10. 4-(4-tert.butyl-phenylsulfonylamino)-5-(2-chloro-5-methoxyphenoxy)-6-(2-hydroxyethoxy)-pyrimidine-2-carboxylic acid,

11. 4-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-6-(4-methoxyphenylsulfonylamino)-pyrimidine-2-carboxylic acid,

12. (RS)-6-(4-tert.butyl-phenylsulfonylamino)-4-(2,3-dihydroxypropoxy)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid,

13. 6-(4-tert.butyl-phenylsulfonylamino)-4-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-pyrimidine-2-carboxylic acid,

14. 6-(4-tert.butyl-phenylsulfonylamino)-4-2-hydroxyethoxy)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid phenylamide,

15. 4-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-6-(4-methoxyphenylsulfonylamino)-pyrimidine-2-carboxylic acid phenylamide,

16. 6-(4-tert.butyl-phenylsulfonylamino)-5-(2-methoxyphenoxy)-4-(2-hydroxyethoxy)-pyrimidine-2-carboxylic acid phenylamide,

17. 4-(4-tert.butyl-phenylsulfonylamino)-5-(2-chloro-5-methoxyphenoxy)-6-(2-hydroxyethoxy)-pyrimidine-2-carboxylic acid phenylamide,

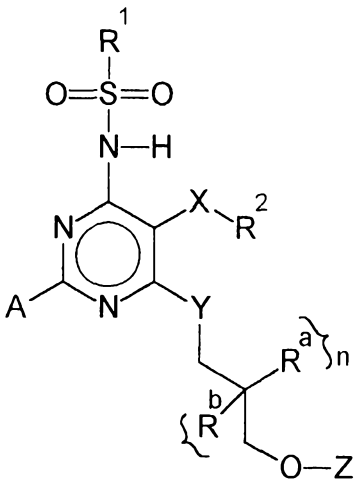
18. 4-(4-tert.butyl-phenylsulfonylamino)-6-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid (1H-tetrazol-5-yl)-amide.

19. 4-(2-hydroxyethoxy)-6-(5-isopropylpyridin-2-ylsulfonylamino)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid,

20. 4-(2-hydroxyethoxy)-6-(5-isopropylpyridin-2-ylsulfonylamino)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid.

21. A 6-(sulfonylamino)-4-(hydroxyalkoxy or hydroxyalkylthio)-pyrimidine-2-carboxylic acid derivative, substantially as hereinbefore described with reference to any one of the examples.

22. A process for the manufacture of compounds of any one of claims 1 to 21, which process comprises converting the residue A in a compound of formula II



II

wherein A represents a residue convertible into a carboxyl group and R^1, R^2, X, Y, Z, R^a, R^b and n have the significance given in claim 1, into a carboxyl group and

optionally converting the hydroxy group R^3 in a thus-obtained compound of formula I in which R^3 is hydroxy the hydroxy group R^3 is converted into a lower-alkoxy group or a group $-NR^4R^5$ or into a pharmaceutically useable salt.

23. A process for the manufacture of a 6-(sulfonylamino)-4-(hydroxyalkoxy or hydroxyalkylthio)-pyrimidine-2-carboxylic acid derivative, substantially as hereinbefore described with reference to any one of the examples.

24. A 6-(sulfonylamino)-4-(hydroxyalkoxy or hydroxyalkylthio)-pyrimidine-2-carboxylic acid derivative, produced by the process of claim 22 or claim 23.

25. A pharmaceutical preparation, containing a compound of any one of claims 1 to 21 or 24 and pharmaceutically acceptable carrier materials and adjuvants.

26. A pharmaceutical preparation, substantially as hereinbefore described with reference to any one of examples A to D.

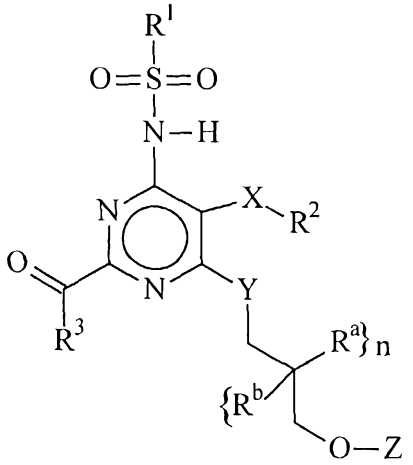
27. The use of compounds of any one of claims 1 to 21 or 24, as active ingredients for the production of medicaments for the treatment of disorders which are associated with endothelin activities, including circulatory disorders such as hypertension, ischaemia, vasospasms and angina pectoris.

28. A method for the treatment or prophylaxis of a disorder associated with endothelin activities in a mammal requiring said treatment or prophylaxis, which method comprises administering to said mammal an effective amount of at least one compound according to any one of claims 1 to 21 or 24, or of a composition according to claim 25 or claim 26.

29. The method according to claim 28, wherein the disorder is a circulatory disorder.

30. The method according to claim 28, wherein the disorder is hypertension, ischaemia, vasospasm or angina pectoris.

31. Compounds of the formula



wherein A signifies formyl or furan-2-yl and R^1, R^2, X, Z, R^a, R^b, Y and n have the significance given in claim 1 and wherein a hydroxy group represented in formula II by OZ and a hydroxy group which may be present as R^a can be present in protected form.

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32. A compound according to any one of claims 1 to 21 or 24, when used in the treatment of a disorder associated with endothelin activities.

33. A compound as claimed in claim 32, wherein said disorder is a circulatory disorder.

34. A compound as claimed in claim 32, wherein said disorder is hypertension, ischaemia, vasospasm or angina pectoris.

35. A composition according to claim 25 or claim 26, when used in the treatment of a disorder associated with endothelin activities.

36. A composition as claimed in claim 35, wherein said disorder is a circulatory disorder.

37. A composition as claimed in claim 35, wherein said disorder is hypertension, ischaemia, vasospasm or angina pectoris.

Dated 23 April, 1999
F Hoffmann-La Roche AG

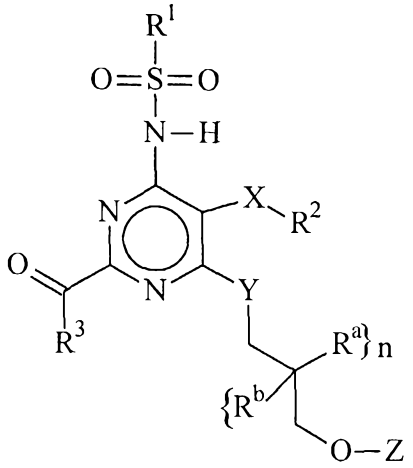
Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON

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Novel pyrimidinesubstituted benzene (or heterocyclyl) sulfonamide derivatives

Abstract

Compounds of the general formula



wherein R^1 signifies phenyl, substituted phenyl or heterocylyl; R^2 signifies phenyl or substituted phenyl; R^3 signifies hydroxy, alkoxy or a residue NR^4R^5; R^4 signifies hydrogen or a residue R^6, and R^5 signifies hydrogen or a residue $(CH_2)_mR^6$ or R^4 and R^5 together with the N atom to which they are attached signify a N-heterocyclic residue; R^6 signifies phenyl, substituted phenyl, cycloalkyl, heterocyclyl, alkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl or alkoxycarbonylalkyl; R^a signifies hydrogen, alkyl or hydroxy; R^b signifies hydrogen or loweralkyl; X signifies oxygen or sulfur; Y signifies oxygen or sulfur; Z signifies hydrogen, alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl; m signifies 0, 1 or 2; and n signifies 0, 1 or 2; can be used as medicaments, especially for the treatment of disorders which are associated with endothelin activities.

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