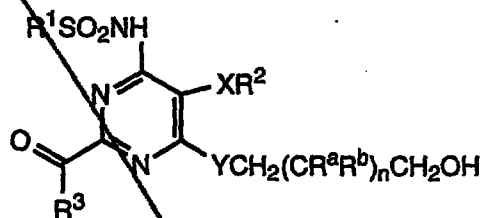


The present invention is concerned with novel sulphonamides and their use as medicaments. In particular, the invention is concerned with novel compounds of formula I



wherein

R¹ signifies phenyl, substituted phenyl or heterocyclyl;
 R² signifies phenyl or substituted phenyl;
 R³ signifies hydroxy, lower-alkoxy or a residue -NR⁴R⁵;
 R⁴ signifies hydrogen or a residue -R⁶ and
 R⁵ signifies hydrogen or a residue -(CH₂)_mR⁶ or
 R⁴ and R⁵ together with the N atom to which they are attached
 signify a N-heterocyclic residue;
 R⁶ 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 sulphur;
 Y signifies oxygen or sulphur;
 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 usable 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.



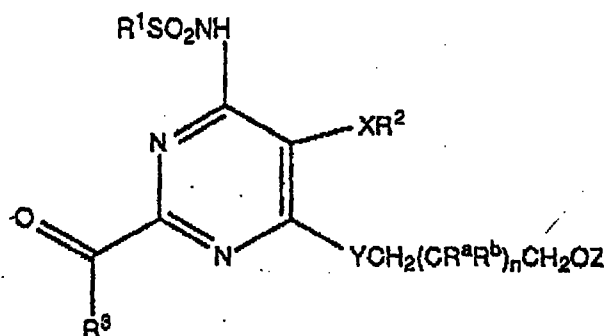
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☐ Drawing(s) : paged to paged
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 lower-alkyl or lower-alkoxycarbonyl-lower-alkyl;
 R^a signifies hydrogen, lower-alkyl or hydroxy;
 R^b signifies hydrogen or lower-alkyl;
 X signifies oxygen or sulphur;
 25 Y signifies oxygen or sulphur;
 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;
 30 and pharmaceutically usable salts thereof.

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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 sulphur 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 e.g. by lower-alkyl, lower-alkanoyl, hydroxy, lower-alkanoyloxy, lower-alkoxy, lower-alkoxycarbonyl, 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-alkylpiperazino.

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.

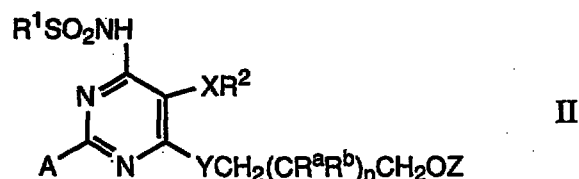
The compounds of formula I and their salts are endothelin receptor inhibitors. They can therefore be used for the treatment of disorders which are associated with endothelin activities, especially circulatory disorders such as hypertension, ischemia, vasospasms and angina pectoris.

The compounds of formula I and their salts can be manufactured in accordance with the invention by

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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 $-\text{NR}^4\text{R}^5$ or into a pharmaceutically usable 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 oxidizing agents, with groups which are present in the starting material of formula II and which are not inert towards the oxidizing agent which is employed, such as hydroxy groups, conveniently being protected. A suitable oxidizing agent for the oxidation of a formyl group to a carboxyl group is e.g. 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, e.g. as the acetonide. A furan-2-yl group can be oxidized to the carboxyl group by treatment with periodate, e.g. 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, e.g. 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 sulphur 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 sulphonamide salt of the formula R^1SO_2NHM and thereafter with a compound of the formula



wherein Y' represents oxygen or sulphur, M represents a cation, e.g. an alkali cation such as Na^+ or K^+ , and X 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 usable salt. Examples of pharmaceutically usable 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 (ETA and ETB), 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 23 I



periodate, e.g. Na periodate in the presence of ruthenium trichloride in a two-phase system containing CCl₄, acetonitrile and water.

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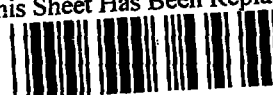
- 15 by condensation with 2-furanylamidine to give a 2-furan-2-yl-(5-XR²)pyrimidine-4,6-diol, replacement of the OH groups by Cl by treatment with POCl₃, reaction of the 4,6-dichloropyrimidine derivative with a sulphonamide salt of the formula R¹SO₂NHM and
20 thereafter with a compound of the formula



- 25 wherein Y' represents oxygen or sulphur, M represents a cation, e.g. 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.

- 30 The thus-formed carboxy group can be converted in a manner known per se into a lower-alkyl ester (R³ = lower alkoxy) or an amide (R³ = -NR⁴R⁵) or into a pharmaceutically usable salt. Examples of pharmaceutically usable salts are alkali salts such as the Na salt and the K salt and alkaline earth salts such as the
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fermentor are centrifuged off (3000 x g, 15 minutes, 4°C) 60 hours after the infection, re-suspended in Tris buffer (5 mM, pH 7.4, 1 mM MgCl₂) and again centrifuged. After a further re-suspension and centrifugation the cells are suspended in 800 ml 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 homogenized and centrifuged (25000 x g, 15 minutes, 4°C). After suspension in Tris buffer (75 mM, pH 7.4, 25 mM MgCl₂, 250 mM sucrose) 1 ml aliquots (protein content about 3.5 mg/ml) are stored at -85°C.

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 MnCl₂, 1 mM EDTA and 0.5% bovine serum albumin). 100 µl of this membrane suspension containing 5 µg of protein are incubated with 50 µl of ¹²⁵I-endothelin (specific activity 2200 Ci/mMol) in assay buffer (25000 cpm, final concentration 20 pM) and 100 µl of assay buffer containing varying concentrations of test compound. The 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.

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

Human placenta is homogenized in 5 mM Tris buffer, pH 7.4, which contains 1 mM MgCl₂ 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 at 72000 g for 30 minutes and the precipitate is washed with 75 mM Tris buffer, pH 7.4, which contains 25 mM MgCl₂. 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 MgCl₂ and 250 mM sucrose and freeze-dried at -20°C in 1 ml aliquots.

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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 MnCl₂, 1 mM EDTA and 0.5% bovine serum albumin). 100 µl of this membrane suspension containing 35 µg of protein are incubated with 50 µl of ¹²⁵I- endotheline (specific activity 2200 Ci/mMol) in assay buffer (25000 cpm, final concentration 20 pM) and 100 µl of assay buffer containing varying concentrations of test compound. The 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 on ET_A and ET_B receptors of compounds of formula I determined in these test procedures is given in Table 1 as the IC₅₀, i.e. as the concentration [µM] which is required to inhibit 50% of the specific binding of ¹²⁵I- endothelin.

Table 1

Compound of Example	ET _A IC ₅₀ [µM]	ET _B IC ₅₀ [µM]
1	73	0.08
2	1.83	0.062
5	16.4	0.29
6	38	0.63
7	18.2	0.3
8	13	0.06
9	21.4	0.086
10	13	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 ischemia, renal insufficiency, cerebral ischemia, 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, e.g. intravenously, intramuscularly, subcutaneously, intrathecally or transdermally; or sublingually or as ophthalmological 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 0.1-100 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 production of the preparations are non-toxic.

The following Examples illustrate the invention in more detail.

Example 1

- a) 25 g of resorcinol monomethyl ether and 37 g of dimethyl chloromalonate were added to a solution of 4.6 g of sodium in 150 ml of methanol. The reaction mixture was stirred at 45°C under argon for 4 hours, filtered and partitioned between toluene/water. The organic phase was dried with sodium sulphate and the solvent was distilled off. 40.7 g of methyl (RS)-(3-methoxy-phenoxy)-acetoacetate were obtained as an oil, MS: (M+H)⁺ 255.
- b) 17 g of acetamidine hydrochloride and 40 g of methyl (RS)-(3-methoxy-phenoxy)-acetoacetate were added to a sodium methylate solution prepared from 450 ml of methanol and 11.3 g of sodium. The reaction mixture was stirred at 20°C for 2 hours, concentrated and partitioned between toluene/water. The aqueous phase was adjusted to pH 4 with 2N HCl and stirred at 0°C for 16 hours. The precipitate was filtered off, washed with water and ether and dried. 25.7 g of 6-hydroxy-5-(3-methoxy-phenoxy)-2-methyl-3H-pyrimidin-4-one were obtained as a white solid, MS: (M+H)⁺ 249.
- c) 24.5 ml of Hünig base and 23.6 ml of POCl₃ were added to a solution of 11.9 g of 6-hydroxy-5-(3-methoxy-phenoxy)-2-methyl-3H-pyrimidin-4-one in 150 ml of dioxan. The reaction mixture was stirred at 120°C for 16 hours 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. 9.1 g of 4,6-dichloro-5-(3-methoxy-phenoxy)-2-methyl-pyrimidine were obtained as a yellowish oil, MS: $(\text{M}+\text{H})^+$ 286.

d) 9 g of 4,6-dichloro-5-(3-methoxy-phenoxy)-2-methyl-pyrimidine and 17 g of K p-tert.-butylsulphonamide in 35 ml of dry dimethyl sulfoxide were heated to 120°C under argon for 3 hours. 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 35 ml of methanol. 11.1 g of p-tert.butyl-N-[6-chloro-5-(m-methoxyphenoxy)-2-methyl-4-pyrimidinyl-benzenesulphonamide, m.p. 170°C , were obtained.

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

f) 0.2 g of dimethylaminopyridine and 3.9 ml of acetic anhydride were added to a solution of 1 g of p-tert.butyl-N-[6-(2-hydroxyethoxy)-2-methyl-5-(m-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide in 40 ml of dichloromethane. The reaction mixture was stirred at 20°C for 3 hours and adjusted to pH 7 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. 1.1 g of 2-[6-acetyl-(4-tert.butyl-



phenylsulphonyl)-amino]-5-(3-methoxy-phenoxy)-2-methyl-pyrimidin-4-yloxy]-ethyl acetate were obtained as a foam, MS: (M + H)⁺ 572.

g) 0.2 g of 2-[6-acetyl-(4-tert.butyl-phenylsulphonyl)-amino]-5-(3-methoxy-phenoxy)-2-methyl-pyrimidin-4-yloxy]-ethyl acetate and 0.6 g of selenium dioxide were stirred in 10 ml of dioxan at 140°C in an autoclave for 50 hours. 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. 0.27 g of 2-[6-(4-tert.butyl-phenylsulphonylamino)-2-formyl-5-(3-methoxy-phenoxy)-pyrimidin-4-yloxy]-ethyl acetate was obtained as a foam, MS: (M+H)⁺ 544.

h) 0.27 g of 2-[6-(4-tert.butyl-phenylsulphonylamino)-2-formyl-5-(3-methoxy-phenoxy)-pyrimidin-4-yloxy]-ethyl acetate and 0.19 g of dicyclohexyl-18-crown-6 in 15 ml of benzene were stirred with 0.078 g of potassium permanganate at 20°C for 16 hours. 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. 0.09 g of 4-(2-acetoxy-ethoxy)-6-(4-tert.butyl-phenylsulphonylamino)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid was obtained as a foam, MS: (M-H)⁻ 558.

i) 0.09 g of 4-(2-acetoxy-ethoxy)-6-(4-tert.butyl-phenylsulphonylamino)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid in 4 ml of methanol and 1.5 ml of water was stirred with 0.05 g of sodium carbonate at 20°C for 2 hours. 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 0.034 g of 6-(4-tert.butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid, MS: (M-H)⁻ 515.9.



Example 2

4-(4-tert. Butyl-phenylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidine-2-carboxylic acid, MS: (M-H)⁻ 550.2, was prepared from 2-chloro-5-methoxy-phenol in analogy to Example 1 via the following intermediates:

- a) Methyl (RS)-(2-chloro-5-methoxy-phenoxy)-acetoacetate,
- b) 6-hydroxy-5-(2-chloro-5-methoxy-phenoxy)-2-methyl-3H-pyrimidin-4-one,
- c) 4,6-dichloro-5-(2-chloro-5-methoxy-phenoxy)-2-methyl-pyrimidine,
- d) p-tert. butyl-N-[6-chloro-5-(2-chloro-5-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide,
- e) p-tert. butyl-N-[6-(2-hydroxyethoxy)-2-methyl-5-(2-chloro-5-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide,
- f) 2-[6-(4-tert. butyl-phenylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-2-methyl-pyrimidin-4-yloxy]-ethyl acetate,
- g) 2-[6-(4-tert. butyl-phenylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-2-formyl-pyrimidin-4-yloxy]-ethyl acetate,
- h) 4-(2-acetoxy-ethoxy)-6-(4-tert. butyl-phenylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-pyrimidine-2-carboxylic acid.

Example 3

4-(2-Hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-6-(4-methoxy-phenylsulphonylamino)-pyrimidin-2-carboxylic acid, MS: (M-H)⁻ 490.3, was prepared from 4,6-dichloro-5-(3-methoxy-

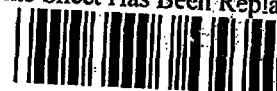


phenoxy)-2-methyl-pyrimidine in analogy to Example 1 via the following intermediates:

- a) N-[6-Chloro-5-(3-methoxy-phenoxy)-2-methyl-pyrimidin-4-yl]-4-methoxy-benzenesulphonamide,
- b) N-[6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-2-methyl-pyrimidin-4-yl]-4-methoxy-benzenesulphonamide,
- c) 2-[6-(4-methoxy-phenylsulphonylamino)-5-(m-methoxy-phenoxy)-2-methyl-pyrimidin-4-yloxy]-ethyl acetate,
- d) 2-[6-(4-methoxy-phenylsulphonylamino)-5-(m-methoxy-phenoxy)-2-formyl-pyrimidin-4-yloxy]-ethyl acetate,
- e) 4-(2-acetoxy-ethoxy)-6-(4-methoxy-phenylsulphonylamino)-5-(m-methoxy-phenoxy)-pyrimidine-2-carboxylic acid.

Example 4

- a) In analogy to Example 1b, from 34 g of ethyl (RS)-(3-methoxy-phenoxy)-acetoacetate and 23 g of 2-furanylamidine there were obtained 15.6 g of 2-(furan-2-yl)-5-(3-methoxy-phenoxy)-pyrimidine-4,6-diol as a foam, MS: (M+H)⁺ 300.
- b) In analogy to Example 1c), from 15.5 g of 2-(furan-2-yl)-5-(3-methoxy-phenoxy)-pyrimidine-4,6-diol and 43 ml of POCl₃ there were obtained 15.9 g of 4,6-dichloro-2-(furan-2-yl)-5-(3-methoxy-phenoxy)-pyrimidine, m.p. 106°C, MS: (M+H)⁺ 338.
- c) In analogy to Example 1d), from 1 g of 4,6-dichloro-2-(furan-2-yl)-5-(3-methoxy-phenoxy)-pyrimidine and 1.5 g of K p-tert.butylsulphonamide there were obtained 1.34 g of 4-tert.-butyl-N-[6-chloro-2-(furan-2-yl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide, MS: (M-H)⁻ 513.
- d) In analogy to Example 1e), from 0.3 g 4-tert.butyl-N-[6-chloro-2-(furan-2-yl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-



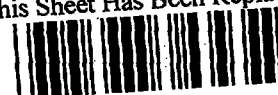
benzenesulphonamide and 12 ml of DL-isopropylidene-glycerol there was obtained 0.25 g of (RS)-4-tert.butyl-N-[6-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-2-(furan-2-yl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide, m.p. 135°C, MS: (M-H)⁻ 608.

e) A solution of 0.7 g of sodium periodate and 0.015 g of ruthenium chloride in 10 ml of water was added to a solution of 0.25 g of (RS)-4-tert.butyl-N-[6-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-2-(furan-2-yl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide in 3.6 ml of CCl₄ and 3.6 ml 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 0.04 g of (RS)-4-(4-tert.butyl-phenylsulphonylamino-6-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid, MS: (M-H)⁻ 586.

f) A solution of 0.033 g of (RS)-4-(4-tert.butyl-phenylsulphonylamino-6-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid in 2 ml of dioxan was treated with 1.3 ml 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 0.007 g of (RS)-6-(4-tert.butyl-phenylsulphonylamino)-4-(2,3-dihydroxy-propoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid as a foam, MS: (M-H)⁻ 546.

Example 5

In analogy to Example 4e), from 2-[6-(4-tert.butyl-phenylsulphonylamino)-2-(furan-2-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yloxy]-ethyl acetate there was obtained 4-(2-acetoxy-ethoxy)-6-(4-tert.butyl-phenylsulphonylamino)-5-(2-methoxy-phenoxy)-pyrimidine-2-carboxylic acid, MS: (M-H)⁻ 558, and therefrom in analogy to Example 1i) there was obtained 6-(4-tert.butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(2-



methoxy-phenoxy)-pyrimidine-2-carboxylic acid, MS: (M-H)⁻ 516.4.

Example 6

0.2 ml of Hünig base, 0.052 g of bis-(2-oxo-3-oxazolidinyl)-phosphinic acid chloride and 0.01 ml of aniline were added to a solution of 0.053 g of 6-(4-tert.butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid in 5 ml of acetonitrile. After 3 hours 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 0.032 g of 6-(4-tert.butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid phenylamide, m.p. 143°C, MS: (M-H)⁻ 591.

Example 7

4-(2-Hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-6-(4-methoxy-phenylsulphonylamino)-pyrimidine-2-carboxylic acid phenylamide, MS: (M+H)⁺ 567, was obtained in analogy to Example 6.

Example 8

6-(4-tert.Butyl-phenylsulphonylamino)-5-(2-methoxy-phenoxy)-4-(2-hydroxy-ethoxy)-pyrimidine-2-carboxylic acid phenylamide, MS: (M-H)⁻ 591, was obtained in analogy to Example 6.

Example 9

4-(4-tert.Butyl-phenylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidine-2-carboxylic acid phenylamide, MS: (M+H)⁺ 628, was obtained in analogy to Example 6.

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Example 10

4-(4-tert.Butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-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-methoxy-phenoxy)-pyrimidine there were obtained:

- a) 5-Isopropyl-pyridine-2-sulphonic acid [6-chloro-2-(furan-2-yl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-amide
- b) 5-isopropyl-pyridine-2-sulphonic acid [2-(furan-2-yl)-6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-amide
- c) 2-[6-[acetyl-(5-isopropyl-pyridin-2-ylsulphonyl)-amino]-2-(furan-2-yl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yloxy]-ethyl acetate
- d) 4-(2-acetoxy-ethoxy)-6-(5-isopropyl-pyridin-2-ylsulphonyl)-amino]-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid

and therefrom in analogy to Example 1 there was obtained 4-(2-hydroxy-ethoxy)-6-(5-isopropyl-pyridin-2-ylsulphonylamino)-5-(3-methoxy-phenoxy)-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-methoxy-phenoxy)-pyrimidine there were obtained:

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- a) 5-Methyl-pyridine-2-sulphonic acid [6-chloro-2-(furan-2-yl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-amide
- b) 5-methyl-pyridine-2-sulphonic acid [2-(furan-2-yl)-6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-amide
- c) 2-[2-(furan-2-yl)-5-(3-methoxy-phenoxy)-6-(5-methyl-pyridin-2-ylsulphonylamino)-pyrimidin-4-yloxy]-ethyl acetate
- d) 4-(2-acetoxy-ethoxy)-6-(5-methyl-pyridin-2-ylsulphonyl)-amino]-5-(3-methoxy-phenoxy)-pyrimidin-2-carboxylic acid

and therefrom in analogy to Example 1 there was obtained 4-(2-hydroxy-ethoxy)-6-(5-isopropyl-pyridin-2-ylsulphonylamino)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid, MS: (M-H)-475.

Example 13

4-(2-Hydroxyethoxy)-5-(3-methoxyphenoxy)-6-(5-methyl-pyridin-2-ylsulphonylamino)pyrimidine-2-carboxylic acid (1H-tetrazol-5-yl)amide can be obtained in analogy to Example 6.

Example 14

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

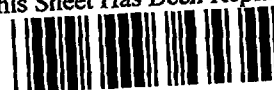
Example 15

6-(4-tert-Butylphenylsulphonylamino)-4-(2,3-dihydroxy-propoxy)-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-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-2-(morpholin-4-ylcarboxyl)-pyrimidin-4-yl]-benzene-

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sulphonamide, MS: (M-H)⁻ 585, was obtained in analogy to Example 6.

Example 17

4-(4-tert-Butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid pyridin-3-ylamide, MS: (M-H)⁻ 592, was obtained in analogy to Example 6.

Example 18

4-(4-tert-Butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid (3-hydroxy-phenyl)-amide, MS: (M-H)⁻ 607, was obtained in analogy to Example 6.

Example 19

4-(4-tert-Butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid (2-hydroxymethyl-phenyl)-amide, MS: (M+H)⁺ 623, was obtained in analogy to Example 6.

Example 20

4-(4-tert-Butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid (3-hydroxymethyl-phenyl)-amide, MS (M-H)⁻ 621, was obtained in analogy to Example 6.

Example 21

(RS)-4-(4-tert-Butyl-phenylsulphonylamino)-6-(2,3-dihydroxy-propoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid pyridin-3-ylamide, MS: (M-H)⁻ 622, was obtained in analogy to Example 6.

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Example 22

(RS)-4-(4-tert-Butyl-phenylsulphonylamino)-6-(2,3-dihydroxy-propoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid (3-hydroxy-phenyl)-amide, MS: (M-H)⁻ 637, was obtained in analogy to Example 6.

Example 23

0.2 g of 6-(4-tert-butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid in 5 ml of dimethylacetamide was stirred at 20°C for 3 hours with 0.04 g of sodium hydride and 0.07 g of 2-chloro-pyrimidine and the mixture was neutralized with saturated NH₄Cl solution. The reaction mixture was washed with ethyl acetate. The aqueous phase was adjusted to pH 2 with 1N 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 0.16 g of 4-(4-tert-butyl-phenylsulphonylamino)-5-(3-methoxy-phenoxy)-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:

<u>Ingredients</u>	<u>Per tablet</u>
Compound of formula I	10.0 - 100.0 mg
Lactose	125.0 mg
Corn starch	75.0 mg
Talc	4.0 mg
Magnesium stearate	1.0 mg

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Example B

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

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

Example C

Injection solutions can have the following composition:

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

Example D

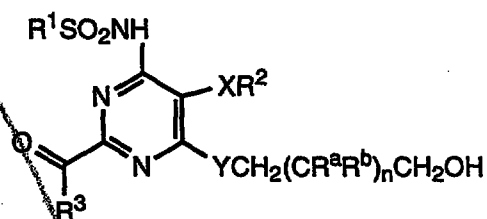
500 mg of compound of formula I are suspended in 3.5 ml of Myglyol 812 and 0.08 g of benzyl alcohol. This suspension is filled into a container having a dosage valve. 5.0 g of Freon 12 are filled into the container under pressure through the valve. The Freon is dissolved in the Myglyol-benzyl alcohol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

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1. Compounds of the formula



wherein

R¹ signifies phenyl, substituted phenyl or heterocyclyl;
 R² signifies phenyl or substituted phenyl;
 R³ signifies hydroxy, lower-alkoxy or a residue -NR⁴R⁵;
 R⁴ signifies hydrogen or a residue -R⁶ and
 R⁵ signifies hydrogen or a residue -(CH₂)_mR⁶ or
 R⁴ and R⁵ together with the N atom to which they are attached
 signify a N-heterocyclic residue;
 R⁶ 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 sulphur;
 Y signifies oxygen or sulphur;
 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 usable 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 R¹ signifies phenyl, which is substituted by lower-alkyl or lower-alkoxy.

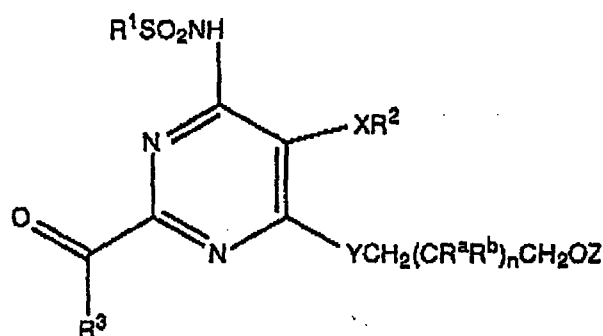




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Claims

1. Compounds of the formula



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wherein

R^1 signifies phenyl, substituted phenyl or heterocyclyl;

R^2 signifies phenyl or substituted phenyl;

10 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;

15 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;

20 X signifies oxygen or sulphur;

Y signifies oxygen or sulphur;

Z signifies hydrogen, lower-alkyl, aryl, aryl-lower-alkyl, heterocyclyl or heterocyclyl-lower-alkyl;

m signifies 0, 1 or 2; and

25 n signifies 0, 1 or 2;

and pharmaceutically usable salts thereof.

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

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

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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 R^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, C₃₋₈-cycloalkyl or heterocyclyl.

9. The compounds according to claim 4,

6-(4-tert.butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid,
4-(4-tert.butyl-phenylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidine-2-carboxylic acid,

4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-6-(4-methoxy-phenylsulphonylamino)-pyrimidine-2-carboxylic acid,
(RS)-6-(4-tert.butyl-phenylsulphonylamino)-4-(2,3-dihydroxy-propoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid,

6-(4-tert.butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidine-2-carboxylic acid,

6-(4-tert.butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid phenylamide,

4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-6-(4-methoxy-phenylsulphonylamino)-pyrimidine-2-carboxylic acid phenylamide,

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6-(4-tert.butyl-phenylsulphonylamino)-5-(2-methoxy-phenoxy)-4-(2-hydroxy-ethoxy)-pyrimidine-2-carboxylic acid phenylamide,

4-(4-tert.butyl-phenylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidine-2-carboxylic acid phenylamide,

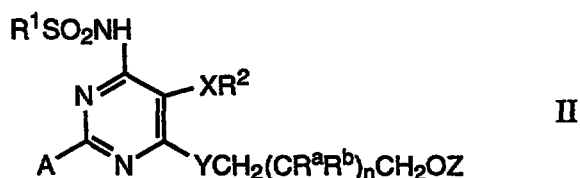
4-(4-tert.butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid (1H-tetrazol-5-yl)-amide.

10. The compounds according to claim 5,

4-(2-hydroxy-ethoxy)-6-(5-isopropyl-pyridin-2-ylsulphonylamino)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid,

4-(2-hydroxy-ethoxy)-6-(5-isopropyl-pyridin-2-ylsulphonylamino)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid.

11. 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.

12. The compounds of claims 1-10 for use as medicaments.

13. A pharmaceutical preparation, containing a compound of claims 1-10 and usual carrier materials and adjuvants.

14. The use of compounds of claims 1-10 as active ingredients for the production of medicaments for the treatment

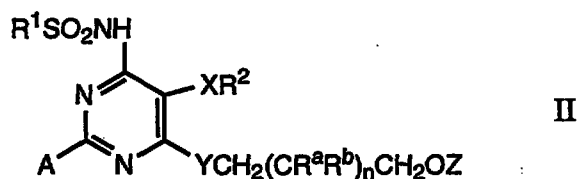




of disorders which are associated with endothelin activities, especially circulatory disorders such as hypertension, ischemia, vasospasms and angina pectoris.

15. A process for the manufacture of compounds of claims 1-10, which process comprises

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 in claim 1,

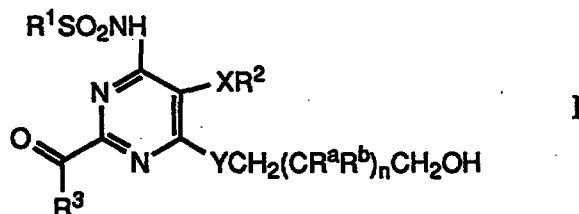
into a carboxyl group and optionally converting the hydroxy group R^3 in a thus-obtained compound of formula I in which R^3 is hydroxy the hydroxy group R^3 is converted into a lower-alkoxy group or a group $-\text{NR}^4\text{R}^5$ or into a pharmaceutically usable salt.

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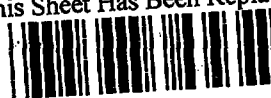
Abstract

Compounds of the general formula



wherein R^1 - R^6 , R^a , R^b , X, Y, Z, m and n have the significance given in the description, can be used as medicaments, especially for the treatment of disorders which are associated with endothelin activities.

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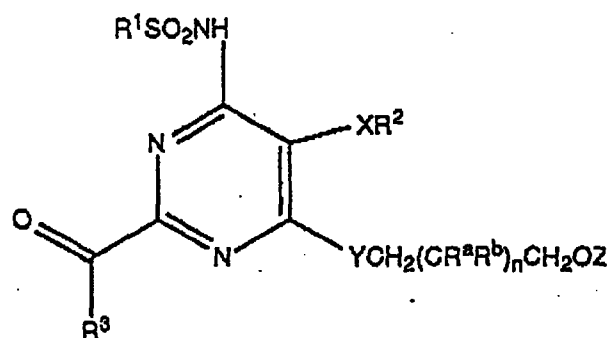
REPLACED SHEETS		SG
☒ Description	: paged 1 to paged 21	- 1 -
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☐ Drawing(s)	: paged to paged	
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NOVEL SULPHONAMIDES

REPLACEMENT SHEETS		SG
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DATE OF RECEIPT 4-3-97

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



wherein

R¹ signifies phenyl, substituted phenyl or heterocyclyl;

R² signifies phenyl or substituted phenyl;

R³ signifies hydroxy, lower-alkoxy or a residue -NR⁴R⁵;

R⁴ signifies hydrogen or a residue -R⁶ and

R⁵ signifies hydrogen or a residue -(CH₂)ₘR⁶ or

R⁴ and R⁵ together with the N atom to which they are attached signify a N-heterocyclic residue;

R⁶ signifies phenyl, substituted phenyl, cycloalkyl, heterocyclyl, lower-alkyl, hydroxy-lower-alkyl, amino-lower-alkyl, carboxy-lower-alkyl or lower-alkoxycarbonyl-lower-alkyl;

Rᵃ signifies hydrogen, lower-alkyl or hydroxy;

Rᵇ signifies hydrogen or lower-alkyl;

X signifies oxygen or sulphur;

Y signifies oxygen or sulphur;

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 usable salts thereof.

REPLACEMENT SHEET
4 MAR 1997

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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 sulphur 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 e.g. by lower-alkyl, lower-alkanoyl, hydroxy, lower-alkanoyloxy, lower-alkoxy, lower-alkoxycarbonyl, 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-alkylpiperazino.

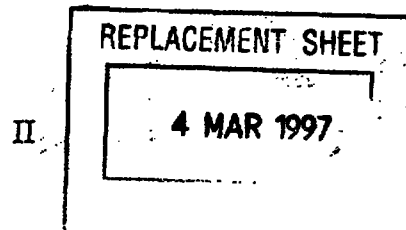
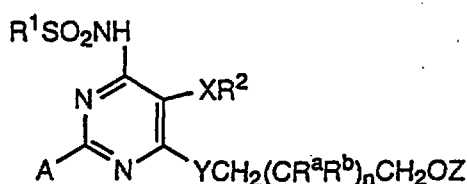
Preferred residues R^1 are phenyl, which is substituted by lower-alkyl or lower-alkoxy, and monocyclic heterocyclyl residues which contain a nitrogen atom, such as pyridyl, especially 2-pyridyl, and which can be substituted, preferably monosubstituted, by lower-alkyl. Preferred residues R^2 are phenyl, 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.

REPLACEMENT SHEET

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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, ischemia, 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 usable 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 oxidizing agents, with groups which are present in the starting material of formula II and which are not inert towards the oxidizing agent which is employed, such as hydroxy groups, conveniently being protected. A suitable oxidizing agent for the oxidation of a formyl group to a carboxyl group is e.g. 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, e.g. as the acetonide. A furan-2-yl group can be oxidized to the carboxyl group by treatment with

periodate, e.g. 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, e.g. 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 sulphur can be prepared starting from compounds of the formula



by condensation with 2-furanylamidine to give a 2-furan-2-yl-(5-XR²)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 sulphonamide salt of the formula $\text{R}^1\text{SO}_2\text{NHM}$ and thereafter with a compound of the formula



wherein Y' represents oxygen or sulphur, M represents a cation, e.g. 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 = $-\text{NR}^4\text{R}^5$) or into a pharmaceutically usable salt. Examples of pharmaceutically usable 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.

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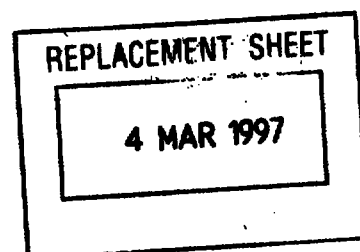
4 MAR 1997

The compounds of formula I exhibit a selective inhibitory activity on endothelin receptors A and B (ETA and ETB), 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 23 l fermentor are centrifuged off (3000 x g, 15 minutes, 4°C) 60 hours after the infection, re-suspended in Tris buffer (5 mM, pH 7.4, 1 mM MgCl₂) and again centrifuged. After a further re-suspension and centrifugation the cells are suspended in 800 ml 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 homogenized and centrifuged (25000 x g, 15 minutes, 4°C). After suspension in Tris buffer (75 mM, pH 7.4, 25 mM MgCl₂, 250 mM sucrose) 1 ml aliquots (protein content about 3.5 mg/ml) are stored at -85°C.

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 MnCl₂, 1 mM EDTA and 0.5% bovine serum albumin). 100 µl of this membrane suspension containing 5 µg of protein are incubated with 50 µl of ¹²⁵I-endothelin (specific activity 2200 Ci/mMol) in assay buffer (25000 cpm, final concentration 20 pM) and 100 µl of assay buffer containing varying concentrations of test compound. The 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.



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

Human placenta is homogenized in 5 mM Tris buffer, pH 7.4, which contains 1 mM MgCl₂ 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 at 72000 g for 30 minutes and the precipitate is washed with 75 mM Tris buffer, pH 7.4, which contains 25 mM MgCl₂. 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 MgCl₂ 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 MnCl₂, 1 mM EDTA and 0.5% bovine serum albumin). 100 µl of this membrane suspension containing 35 µg of protein are incubated with 50 µl of ¹²⁵I-endotheline (specific activity 2200 Ci/mMol) in assay buffer (25000 cpm, final concentration 20 pM) and 100 µl of assay buffer containing varying concentrations of test compound. The 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 on ET_A and ET_B receptors of compounds of formula I determined in these test procedures is given in Table 1 as the IC₅₀, i.e. as the concentration [µM] which is required to inhibit 50% of the specific binding of ¹²⁵I-endothelin.

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Table 1

Compound of Example	ET _A IC ₅₀ [μM]	ET _B IC ₅₀ [μM]
1	73	0.08
2	1.83	0.062
5	16.4	0.29
6	38	0.63
7	18.2	0.3
8	13	0.06
9	21.4	0.086
10	13	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 ischemia, renal insufficiency, cerebral ischemia, 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, e.g. intravenously, intramuscularly, subcutaneously, intrathecally or transdermally; or sublingually or as ophthalmological 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 0.1-100 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 production of the preparations are non-toxic.

The following Examples illustrate the invention in more detail.

Example 1

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

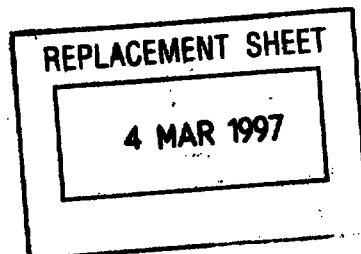
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b) 17 g of acetamidine hydrochloride and 40 g of methyl (RS)-(3-methoxy-phenoxy)-acetoacetate were added to a sodium methylate solution prepared from 450 ml of methanol and 11.3 g of sodium. The reaction mixture was stirred at 20°C for 2 hours, concentrated and partitioned between toluene/water. The aqueous phase was adjusted to pH 4 with 2N HCl and stirred at 0°C for 16 hours. The precipitate was filtered off, washed with water and ether and dried. 25.7 g of 6-hydroxy-5-(3-methoxy-phenoxy)-2-methyl-3H-pyrimidin-4-one were obtained as a white solid, MS: (M+H)⁺ 249.

c) 24.5 ml of Hünig base and 23.6 ml of POCl₃ were added to a solution of 11.9 g of 6-hydroxy-5-(3-methoxy-phenoxy)-2-methyl-3H-pyrimidin-4-one in 150 ml of dioxan. The reaction mixture was stirred at 120°C for 16 hours 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 NaHCO₃ and with water, dried and concentrated. The residue was purified over silica gel with hexane and dichloromethane. 9.1 g of 4,6-dichloro-5-(3-methoxy-phenoxy)-2-methyl-pyrimidine were obtained as a yellowish oil, MS: (M+H)⁺ 286.

d) 9 g of 4,6-dichloro-5-(3-methoxy-phenoxy)-2-methyl-pyrimidine and 17 g of K p-tert.-butylsulphonamide in 35 ml of dry dimethyl sulphoxide were heated to 120°C under argon for 3 hours. 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 35 ml of methanol. 11.1 g of p-tert.butyl-N-[6-chloro-5-(m-methoxyphenoxy)-2-methyl-4-pyrimidinyl-benzenesulphonamide, m.p. 170°C, were obtained.



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

f) 0.2 g of dimethylaminopyridine and 3.9 ml of acetic anhydride were added to a solution of 1 g of p-tert.butyl-N-[6-(2-hydroxyethoxy)-2-methyl-5-(m-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide in 40 ml of dichloromethane. The reaction mixture was stirred at 20°C for 3 hours and adjusted to pH 7 with a sat. NaHCO₃ solution. The organic phase was washed with water, dried and evaporated. The residue was purified over silica gel with chloroform. 1.1 g of 2-[6-acetyl-(4-tert.butyl-phenylsulphonyl)-amino]-5-(3-methoxy-phenoxy)-2-methyl-pyrimidin-4-yloxy]-ethyl acetate were obtained as a foam, MS: (M + H)⁺ 572.

g) 0.2 g of 2-[6-acetyl-(4-tert.butyl-phenylsulphonyl)-amino]-5-(3-methoxy-phenoxy)-2-methyl-pyrimidin-4-yloxy]-ethyl acetate and 0.6 g of selenium dioxide were stirred in 10 ml of dioxan at 140°C in an autoclave for 50 hours. 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. 0.27 g of 2-[6-(4-tert.butyl-phenylsulphonylamino)-2-formyl-5-(3-methoxy-phenoxy)-pyrimidin-4-yloxy]-ethyl acetate was obtained as a foam, MS: (M+H)⁺ 544.

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h) 0.27 g of 2-[6-(4-tert.butyl-phenylsulphonylamino)-2-formyl-5-(3-methoxy-phenoxy)-pyrimidin-4-yloxy]-ethyl acetate and 0.19 g of dicyclohexyl-18-crown-6 in 15 ml of benzene were stirred with 0.078 g of potassium permanganate at 20°C for 16 hours. 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. 0.09 g of 4-(2-acetoxy-ethoxy)-6-(4-tert.butyl-phenylsulphonylamino)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid was obtained as a foam, MS: (M-H)⁻ 558.

i) 0.09 g of 4-(2-acetoxy-ethoxy)-6-(4-tert.butyl-phenylsulphonylamino)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid in 4 ml of methanol and 1.5 ml of water was stirred with 0.05 g of sodium carbonate at 20°C for 2 hours. 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 0.034 g of 6-(4-tert.butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid, MS: (M-H)⁻ 515.9.

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Example 2

4-(4-tert. Butyl-phenylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidine-2-carboxylic acid, MS: (M-H)⁻ 550.2, was prepared from 2-chloro-5-methoxy-phenol in analogy to Example 1 via the following intermediates:

- a) Methyl (RS)-(2-chloro-5-methoxy-phenoxy)-acetoacetate,
- b) 6-hydroxy-5-(2-chloro-5-methoxy-phenoxy)-2-methyl-3H-pyrimidin-4-one,
- c) 4,6-dichloro-5-(2-chloro-5-methoxy-phenoxy)-2-methyl-pyrimidine,
- d) p-tert.butyl-N-[6-chloro-5-(2-chloro-5-methoxyphenoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide,
- e) p-tert.butyl-N-[6-(2-hydroxyethoxy)-2-methyl-5-(2-chloro-5-methoxyphenoxy)-4-pyrimidinyl]benzenesulphonamide,
- f) 2-[6-(4-tert.butyl-phenylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-2-methyl-pyrimidin-4-yloxy]-ethyl acetate,
- g) 2-[6-(4-tert.butyl-phenylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-2-formyl-pyrimidin-4-yloxy]-ethyl acetate,
- h) 4-(2-acetoxy-ethoxy)-6-(4-tert.butyl-phenylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-pyrimidine-2-carboxylic acid.

Example 3

4-(2-Hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-6-(4-methoxy-phenylsulphonylamino)-pyrimidin-2-carboxylic acid, MS: (M-H)⁻ 490.3, was prepared from 4,6-dichloro-5-(3-methoxy-

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phenoxy)-2-methyl-pyrimidine in analogy to Example 1 via the following intermediates:

- a) N-[6-Chloro-5-(3-methoxy-phenoxy)-2-methyl-pyrimidin-4-yl]-4-methoxy-benzenesulphonamide,
- b) N-[6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-2-methyl-pyrimidin-4-yl]-4-methoxy-benzenesulphonamide,
- c) 2-[6-(4-methoxy-phenylsulphonylamino)-5-(m-methoxy-phenoxy)-2-methyl-pyrimidin-4-yloxy]-ethyl acetate,
- d) 2-[6-(4-methoxy-phenylsulphonylamino)-5-(m-methoxy-phenoxy)-2-formyl-pyrimidin-4-yloxy]-ethyl acetate,
- e) 4-(2-acetoxy-ethoxy)-6-(4-methoxy-phenylsulphonylamino)-5-(m-methoxy-phenoxy)-pyrimidine-2-carboxylic acid.

Example 4

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

b) In analogy to Example 1c), from 15.5 g of 2-(furan-2-yl)-5-(3-methoxy-phenoxy)-pyrimidine-4,6-diol and 43 ml of POCl₃ there were obtained 15.9 g of 4,6-dichloro-2-(furan-2-yl)-5-(3-methoxy-phenoxy)-pyrimidine, m.p. 106°C, MS: (M+H)⁺ 338.

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

d) In analogy to Example 1e), from 0.3 g 4-tert.butyl-N-[6-chloro-2-(furan-2-yl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-

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benzenesulphonamide and 12 ml of DL-isopropylidene-glycerol there was obtained 0.25 g of (RS)-4-tert.butyl-N-[6-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-2-(furan-2-yl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide, m.p. 135°C, MS: (M-H)⁻ 608.

e) A solution of 0.7 g of sodium periodate and 0.015 g of ruthenium chloride in 10 ml of water was added to a solution of 0.25 g of (RS)-4-tert.butyl-N-[6-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-2-(furan-2-yl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide in 3.6 ml of CCl₄ and 3.6 ml 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 0.04 g of (RS)-4-(4-tert.butyl-phenylsulphonylamino-6-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid, MS: (M-H)⁻ 586.

f) A solution of 0.033 g of (RS)-4-(4-tert.butyl-phenylsulphonylamino-6-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid in 2 ml of dioxan was treated with 1.3 ml 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 0.007 g of (RS)-6-(4-tert.butyl-phenylsulphonylamino)-4-(2,3-dihydroxy-propoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid as a foam, MS: (M-H)⁻ 546.

Example 5

In analogy to Example 4e), from 2-[6-(4-tert.butyl-phenylsulphonylamino)-2-(furan-2-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yloxy]-ethyl acetate there was obtained 4-(2-acetoxy-ethoxy)-6-(4-tert.butyl-phenylsulphonylamino)-5-(2-methoxy-phenoxy)-pyrimidine-2-carboxylic acid, MS: (M-H)⁻ 558, and therefrom in analogy to Example 1i) there was obtained 6-(4-tert.butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(2-

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methoxy-phenoxy)-pyrimidine-2-carboxylic acid, MS: (M-H)⁻ 516.4.

Example 6

0.2 ml of Hünig base, 0.052 g of bis-(2-oxo-3-oxazolidinyl)-phosphinic acid chloride and 0.01 ml of aniline were added to a solution of 0.053 g of 6-(4-tert.butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid in 5 ml of acetonitrile. After 3 hours 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 0.032 g of 6-(4-tert.butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid phenylamide, m.p. 143°C, MS: (M-H)⁻ 591.

Example 7

4-(2-Hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-6-(4-methoxy-phenylsulphonylamino)-pyrimidine-2-carboxylic acid phenylamide, MS: (M+H)⁺ 567, was obtained in analogy to Example 6.

Example 8

6-(4-tert.Butyl-phenylsulphonylamino)-5-(2-methoxy-phenoxy)-4-(2-hydroxy-ethoxy)-pyrimidine-2-carboxylic acid phenylamide, MS: (M-H)⁻ 591, was obtained in analogy to Example 6.

Example 9

4-(4-tert.Butyl-phenylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidine-2-carboxylic acid phenylamide, MS: (M+H)⁺ 628, was obtained in analogy to Example 6.

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Example 10

4-(4-tert. Butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-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-methoxy-phenoxy)-pyrimidine there were obtained:

- a) 5-Isopropyl-pyridine-2-sulphonic acid [6-chloro-2-(furan-2-yl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-amide
- b) 5-isopropyl-pyridine-2-sulphonic acid [2-(furan-2-yl)-6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-amide
- c) 2-[6-[acetyl-(5-isopropyl-pyridin-2-ylsulphonyl)-amino]-2-(furan-2-yl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yloxy]-ethyl acetate
- d) 4-(2-acetoxy-ethoxy)-6-(5-isopropyl-pyridin-2-ylsulphonyl)-amino]-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid

and therefrom in analogy to Example 1 there was obtained 4-(2-hydroxy-ethoxy)-6-(5-isopropyl-pyridin-2-ylsulphonylamino)-5-(3-methoxy-phenoxy)-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-methoxy-phenoxy)-pyrimidine there were obtained:

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- a) 5-Methyl-pyridine-2-sulphonic acid [6-chloro-2-(furan-2-yl)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-amide
- b) 5-methyl-pyridine-2-sulphonic acid [2-(furan-2-yl)-6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-amide
- c) 2-[2-(furan-2-yl)-5-(3-methoxy-phenoxy)-6-(5-methyl-pyridin-2-ylsulphonylamino)-pyrimidin-4-yloxy]-ethyl acetate
- d) 4-(2-acetoxy-ethoxy)-6-(5-methyl-pyridin-2-ylsulphonyl)-amino]-5-(3-methoxy-phenoxy)-pyrimidin-2-carboxylic acid

and therefrom in analogy to Example 1 there was obtained 4-(2-hydroxy-ethoxy)-6-(5-isopropyl-pyridin-2-ylsulphonylamino)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid, MS: (M-H)-475.

Example 13

4-(2-Hydroxyethoxy)-5-(3-methoxyphenoxy)-6-(5-methyl-pyridin-2-ylsulphonylamino)pyrimidine-2-carboxylic acid (1H-tetrazol-5-yl)amide can be obtained in analogy to Example 6.

Example 14

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

Example 15

6-(4-tert-Butylphenylsulphonylamino)-4-(2,3-dihydroxy-propoxy)-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-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-2-(morpholin-4-ylcarboxyl)-pyrimidin-4-yl]-benzene-

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sulphonamide, MS: (M-H)⁻ 585, was obtained in analogy to Example 6.

Example 17

4-(4-tert-Butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid pyridin-3-ylamide, MS: (M-H)⁻ 592, was obtained in analogy to Example 6.

Example 18

4-(4-tert-Butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid (3-hydroxy-phenyl)-amide, MS: (M-H)⁻ 607, was obtained in analogy to Example 6.

Example 19

4-(4-tert-Butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid (2-hydroxymethyl-phenyl)-amide, MS: (M+H)⁺ 623, was obtained in analogy to Example 6.

Example 20

4-(4-tert-Butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid (3-hydroxymethyl-phenyl)-amide, MS (M-H)⁻ 621, was obtained in analogy to Example 6.

Example 21

(RS)-4-(4-tert-Butyl-phenylsulphonylamino)-6-(2,3-dihydroxy-propoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid pyridin-3-ylamide, MS: (M-H)⁻ 622, was obtained in analogy to Example 6.

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Example 22

(RS)-4-(4-tert-Butyl-phenylsulphonylamino)-6-(2,3-dihydroxy-propoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid (3-hydroxy-phenyl)-amide, MS: (M-H)⁻ 637, was obtained in analogy to Example 6.

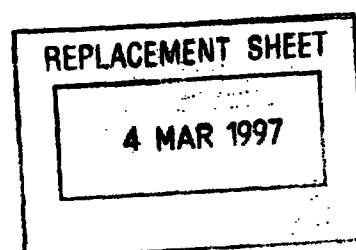
Example 23

0.2 g of 6-(4-tert-butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid in 5 ml of dimethylacetamide was stirred at 20°C for 3 hours with 0.04 g of sodium hydride and 0.07 g of 2-chloropyrimidine and the mixture was neutralized with saturated NH₄Cl solution. The reaction mixture was washed with ethyl acetate. The aqueous phase was adjusted to pH 2 with 1N 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 0.16 g of 4-(4-tert-butyl-phenylsulphonylamino)-5-(3-methoxy-phenoxy)-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:

<u>Ingredients</u>	<u>Per tablet</u>
Compound of formula I	10.0 - 100.0 mg
Lactose	125.0 mg
Corn starch	75.0 mg
Talc	4.0 mg
Magnesium stearate	1.0 mg



Example B

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

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

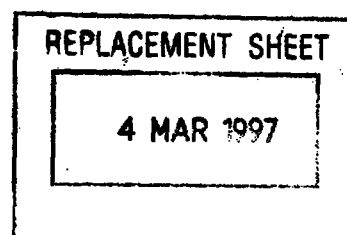
Example C

Injection solutions can have the following composition:

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

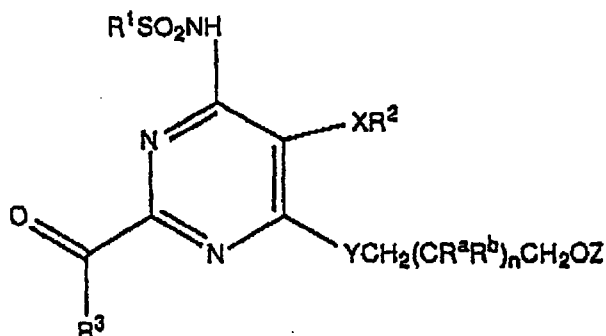
Example D

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 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.



Claims

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 sulphur;

Y signifies oxygen or sulphur;

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 usable 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.

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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 R^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, C₃-8-cycloalkyl or heterocyclyl.

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9. The compounds according to claim 4,

6-(4-tert.butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid,
4-(4-tert.butyl-phenylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidine-2-carboxylic acid,

4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-6-(4-methoxy-phenylsulphonylamino)-pyrimidine-2-carboxylic acid,
(RS)-6-(4-tert.butyl-phenylsulphonylamino)-4-(2,3-dihydroxy-propoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid,

6-(4-tert.butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidine-2-carboxylic acid,
6-(4-tert.butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid phenylamide,

4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-6-(4-methoxy-phenylsulphonylamino)-pyrimidine-2-carboxylic acid phenylamide,



6-(4-tert.butyl-phenylsulphonylamino)-5-(2-methoxy-phenoxy)-4-(2-hydroxy-ethoxy)-pyrimidine-2-carboxylic acid phenylamide,

4-(4-tert.butyl-phenylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidine-2-carboxylic acid phenylamide,

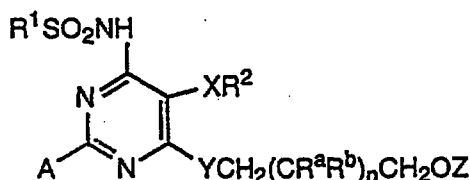
4-(4-tert.butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid (1H-tetrazol-5-yl)-amide.

10. The compounds according to claim 5,

4-(2-hydroxy-ethoxy)-6-(5-isopropyl-pyridin-2-ylsulphonylamino)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid,

4-(2-hydroxy-ethoxy)-6-(5-isopropyl-pyridin-2-ylsulphonylamino)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid.

11. Compounds of the formula



II

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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.

12. The compounds of claims 1-10 for use as medicaments.

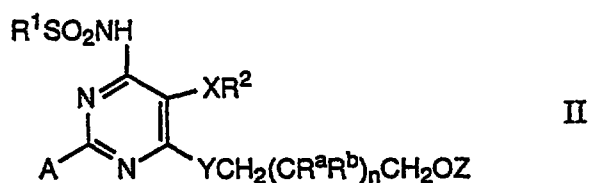
13. A pharmaceutical preparation, containing a compound of claims 1-10 and usual carrier materials and adjuvants.

14. The use of compounds of claims 1-10 as active ingredients for the production of medicaments for the treatment

of disorders which are associated with endothelin activities, especially circulatory disorders such as hypertension, ischemia, vasospasms and angina pectoris.

15. A process for the manufacture of compounds of claims 1-10, which process comprises

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 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 $-\text{NR}^4\text{R}^5$ or into a pharmaceutically usable salt.

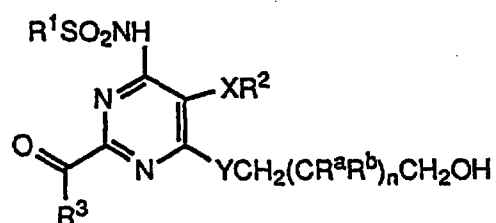
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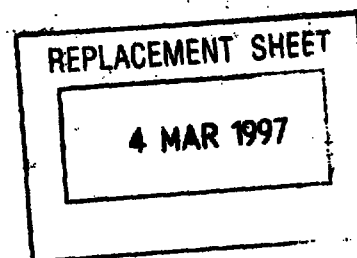
NOVEL SULPHONAMIDES

Abstract

Compounds of the general formula



wherein R^1 - R^6 , R^a , R^b , X , Y , Z , m and n have the significance given in the description, can be used as medicaments, especially for the treatment of disorders which are associated with endothelin activities.

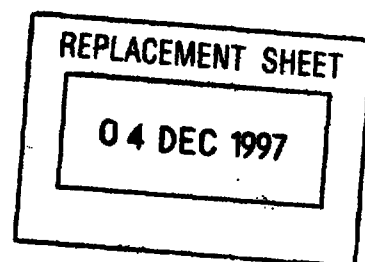
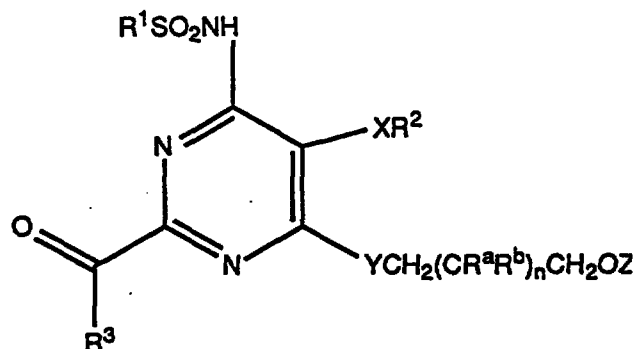


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PYRIMIDINE-SUBSTITUTED BENZENE SULFONAMIDE DERIVATIVES

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



10

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 $-NR^4R^5$;
 15 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,
 20 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 sulphur;
 25 Y signifies oxygen or sulphur;
 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;
 30 and pharmaceutically usable salts thereof.

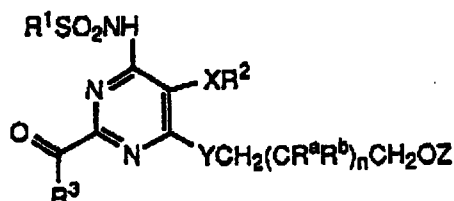


REPLACEMENT SHEET

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Claims

1. Compounds of the formula



5

wherein

 R^1 signifies phenyl, substituted phenyl or heterocyclyl; R^2 signifies phenyl or substituted phenyl;10 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;15 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;

20 X signifies oxygen or sulphur;

Y signifies oxygen or sulphur;

Z signifies hydrogen, lower-alkyl, aryl, aryl-lower-alkyl, heterocyclyl or heterocyclyl-lower-alkyl;

m signifies 0, 1 or 2; and

25 n signifies 0, 1 or 2;

and pharmaceutically usable salts thereof.

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

30

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
35 lower-alkoxy.

5. Compounds according to any one of claims 1 to 4, in which R¹ signifies a monocyclic heterocyclyl residue which contains a nitrogen atom and which can be substituted by lower-alkyl.

6. Compounds according to any one or claims 1 to 5, in which R² signifies phenyl, which is substituted by lower-alkoxy and/or halogen.

7. Compounds according to any one of claims 1 to 6, wherein R³ signifies hydroxy or -NR⁴R⁵.

8. Compounds according to any one of claims 1 to 6, wherein R³ signifies -NR⁴R⁵, R⁵ signifies -(CH₂)_mR⁶ and R⁶ signifies phenyl, substituted phenyl, C₃₋₈-cycloalkyl or heterocyclyl.

9. The compounds according to claim 4,

6-(4-tert.butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid,

4-(4-tert.butyl-phenylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidine-2-carboxylic acid,

4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-6-(4-methoxy-phenylsulphonylamino)-pyrimidine-2-carboxylic acid, (RS)-6-(4-tert.butyl-phenylsulphonylamino)-4-(2,3-dihydroxy-propoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid,

6-(4-tert.butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidine-2-carboxylic acid,

6-(4-tert.butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid phenylamide,

4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-6-(4-methoxy-phenylsulphonylamino)-pyrimidine-2-carboxylic acid phenylamide,

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6-(4-tert.butyl-phenylsulphonylamino)-5-(2-methoxy-phenoxy)-4-(2-hydroxy-ethoxy)-pyrimidine-2-carboxylic acid phenylamide,

4-(4-tert.butyl-phenylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidine-2-carboxylic acid phenylamide,

4-(4-tert.butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid (1H-tetrazol-5-yl)-amide.

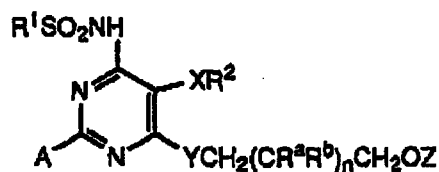
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10. The compound according to claim 5,

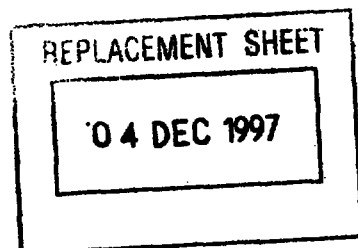
4-(2-hydroxy-ethoxy)-6-(5-isopropyl-pyridin-2-ylsulphonylamino)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid,

15

11. The use of compounds of the formula



II



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wherein A signifies formyl or furan-2-yl and R¹, R², 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 the preparation of a compound as defined in any of claims 1-10.

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12. The compounds of claims 1-10 for use as medicaments.

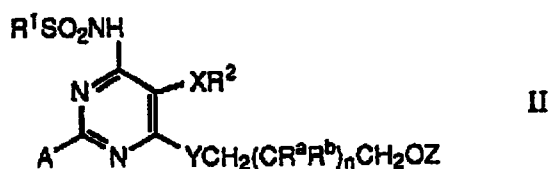
13. A pharmaceutical preparation, containing a compound of claims 1-10 and usual carrier materials and adjuvants.

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14. The use of compounds of claims 1-10 as active ingredients for the production of medicaments for the treatment of disorders which are associated with endothelin activities, especially circulatory disorders such as hypertension, ischemia, vasospasms and angina pectoris.

15. A process for the manufacture of compounds of claims 1-10, which process comprises

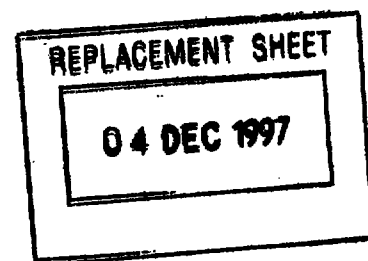
10 converting the residue A in a compound of formula II



15 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 into a lower-alkoxy group or a group $-\text{NR}^4\text{R}^5$ or into a pharmaceutically usable salt.

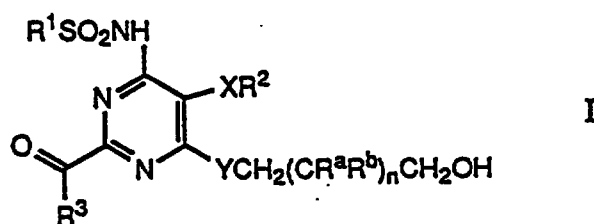
20



PYRIMIDINE-SUBSTITUTED BENZENE SULFONAMIDE DERIVATIVES

Abstract

Compounds of the general formula



wherein $\text{R}^1\text{-R}^6$, R^a , R^b , X, Y, Z, m and n have the significance given in the description, can be used as medicaments, especially for the treatment of disorders which are associated with endothelin activities.

