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Seydel et al.

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[54] **SUBSTITUTED 2,4-DIAMINO-5-BENZYLPYRIMIDINES, THEIR PREPARATION AND THEIR USE AS MEDICAMENTS WITH AN ANTIMICROBIAL ACTIVITY**

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[30] **Foreign Application Priority Data**

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[51] **Int. Cl.**[4] **C07D 239/49**; A61K 31/505
[52] **U.S. Cl.** **514/275**; 544/325
[58] **Field of Search** 544/325; 514/275

[56] **References Cited**

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[57] **ABSTRACT**

Novel substituted 2,4-diamino-5-benzyl pyrimidines are described. The novel substances have antimicrobial activity and are particularly suitable for inhibiting the growth of mycobacteria. Combined with inhibitors such as diaminodiphenylsulphones, ring-substituted 4-aminodiphenylsulphones or ring and/or nitrogen-substituted diaminodiphenylsulphones, they have a marked synergistic activity.

21 Claims, 2 Drawing Sheets

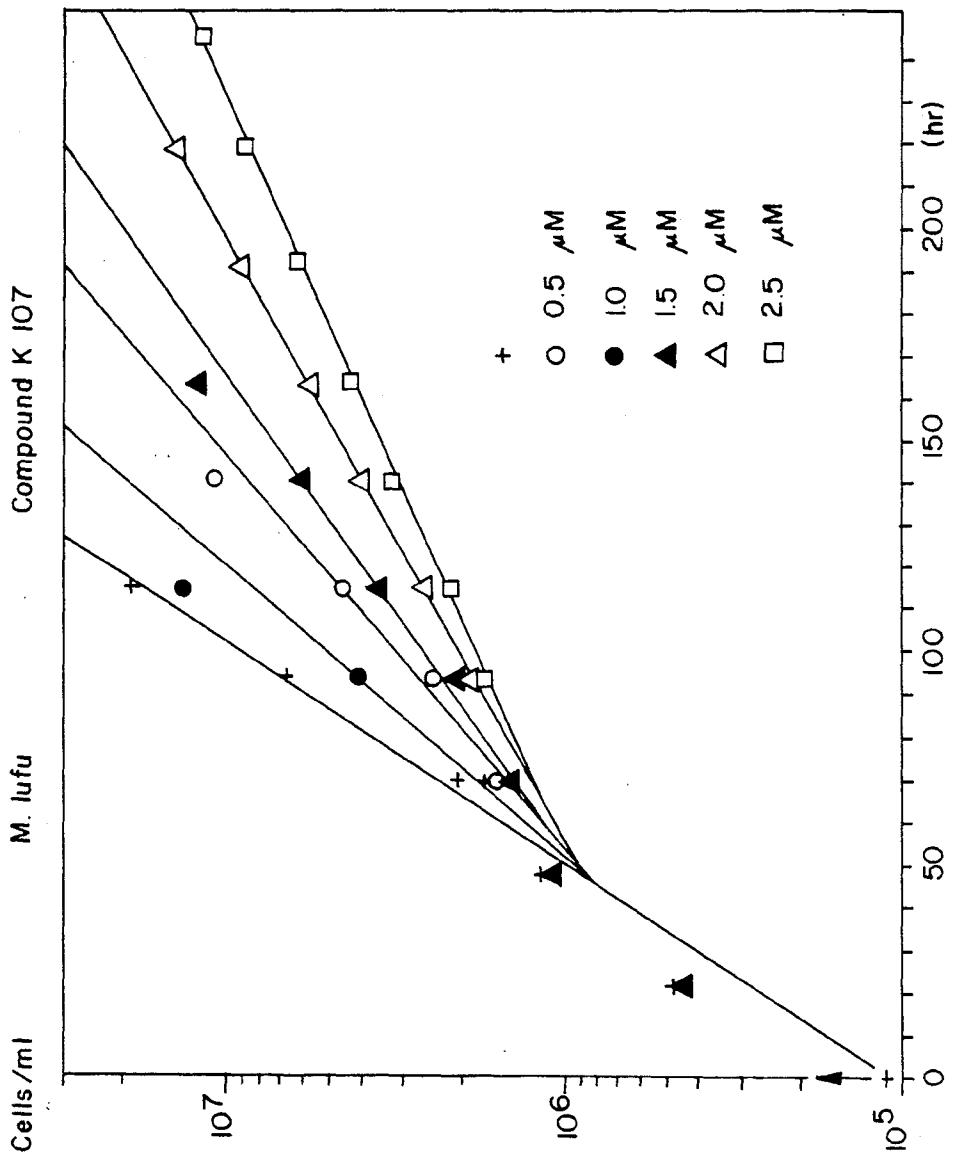


FIG. 1

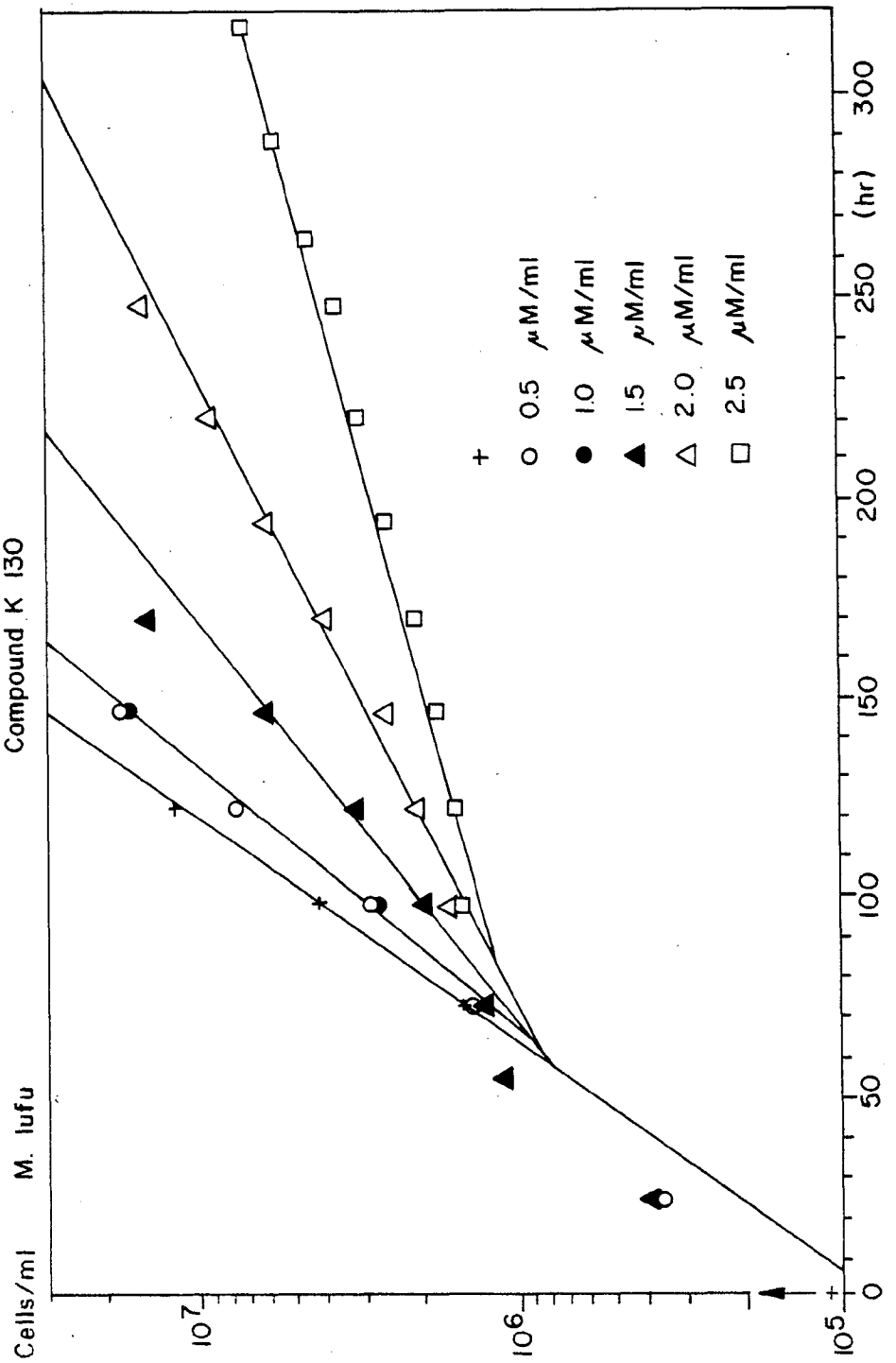


FIG. 2

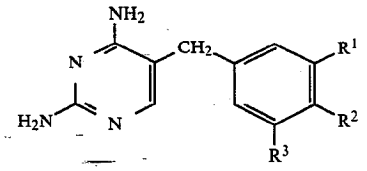
SUBSTITUTED 2,4-DIAMINO-5-BENZYLPYRIMIDINES, THEIR PREPARATION AND THEIR USE AS MEDICAMENTS WITH AN ANTIMICROBIAL ACTIVITY

The invention relates to novel substituted 2,4-diamino-5-benzylpyrimidines, their preparation and their use as medicaments for the treatment of microbial and in particular mycobacterial infections.

The antibacterial activity of compounds of the benzylpyrimidinetype is known. Such compounds, such as e.g. the known products trimethoprim, brodimoprim and tetroxoprim exert their activity by inhibiting dihydrofolic acid reductase (DHFR) in the case or Gram negative and Gram positive bacteria. However, it has been found that these compounds have only an extremely limited activity with respect to mycobacteria. With these agents the concentrations necessary for inhibiting mycobacterial growth are so high, that they cannot be attained in vivo or are not acceptable.

The problem of the present invention is therefore to provide compounds, which in low physiologically acceptable concentrations constitute effective inhibitors of microbial growth and particularly mycobacterial growth.

According to the invention this problem is solved by the novel substituted 2,4-diamino-5-benzylpyrimidines of general formula I



I

in which one of the substituents R^1 to R^3

(i) is an alkoxy or alkylthio group with more than 4 carbon atoms and advantageously 4 to 10 carbon atoms, a phenylalkoxy, phenylalkylthio, phenoxyalkoxy, phenoxyalkylthio, phenylaminoalkoxy, phenylaminoalkylthio group with 3 to 6 C atoms in the alkyl chain or a, cycloalkoxy, cycloalkylthio, cycloalkylalkylthio or cycloalkylalkoxy group wherein the cyclic radical as well as the alkyl chain have 3 to 6 carbon atoms respectively or

(ii) a 2',4'-substituted phenyl-4-sulphonylphenyl aminoalkoxy, phenyl-4-sulphonylphenyl-aminoalkylthio, phenyl-4-sulphonylphenylalkoxy or phenyl-4-sulphonylphenylakylthio group, in which the substituents in the 2',4'-position are the same or different and are hydrogen, amino, alkylamino, dialkylamino, alkoxy, alkyl, nitro, alkylthio and/or acetamino groups wherein the alkyl radical has 1 to 6 C-atoms in the chain and the two others of the substituents R^1 to R^3 are the same or different and are hydrogen, alkoxy, alkylthio and/or alkylamino groups.

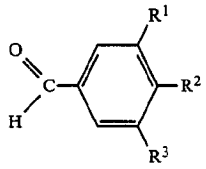
The alkyl radical of the two other substituents R^1 to R^3 preferably has 1 to 3 C-atoms and in particular 1 C-atom.

Representative examples of compounds of the invention include 2,4-diamino-5-(4-propoxyphenyl-benzyl)-pyrimidine; 2,4-diamino-5-(4-propoxyphenyl-3-methoxy-benzyl)-pyrimidine; 2,4-diamino-5-(4-pentloxy-3-methoxybenzyl)-pyrimidine; 2,4-diamino-5-(4-hexyloxy-3-methoxybenzyl)-pyrimidine; 2,4-diamino-5-(4-heptyloxy-3-methoxybenzyl)-pyrimidine; 2,4-diamino-5-(4-octyloxy-3,5-dimethoxybenzyl)-pyrimidine; 2,4-diamino-5-(4-nonyloxy-3,5-dimethoxybenzyl)-pyrimidine; 2,4-diamino-5-(4-decyloxy-3-methoxybenzyl)-pyrimidine; 2,4-diamino-5-[3,5-dimethoxy-4-(4'-nitrophenyl-4-sulphonylphenyl)-methoxybenzyl]-pyrimidine; 2,4-diamino-5-(3,5-dimethoxy-4-[3-(4'-nitrophenyl-4-sulphonylphenylamino)propoxy]benzyl)-pyrimidine; 2,4-diamino-5-(4-methoxy-3-[2-(4'-nitrophenyl-4-sulphonylphenylamino)ethoxy]benzyl)-pyrimidine; 2,4-diamino-5-(4-methoxy-3-[3-(4'-nitrophenyl-4sulphonylphenylamino)propoxy]benzyl)-pyrimidine; 2,4-diamino-5[4-(4'-aminophenyl-4-sulphonylphenylmethoxy)-3,5-dimethoxybenzyl]-pyrimidine; 2,4-diamino-5-(4-[3-(4'-aminophenyl-4-sulphonylphenylamino)-propoxy]-3,5-dimethoxybenzyl)-pyrimidine; 2,4-diamino-5-[3-(4'-aminophenyl-4-sulphonylphenylmethoxy)-4-methoxybenzyl] -pyrimidine; 2,4-diamino-5-(3-[2-(4'-aminophenyl-4-sulphonylphenylamino)-ethoxy]-4-methoxybenzyl)-pyrimidine; 2,4-diamino-5-(4-[3-(4-aminophenyl-4-sulphonylphenylamino)propoxy]-3,5-dimethoxybenzyl)-pyrimidine; 2,4-diamino-5-(4'-aminophenyl-4-sulphonylphenylmethoxy)-3-methoxybenzyl]pyrimidine; 2,4-diamino-5-(4-[3-(4'-methylphenyl-4-sulphonylphenylamino) -propoxy]-3,5-dimethoxybenzyl)-pyrimidine; 2,4-diamino-5-(4-[2-(4'-aminophenyl-4-sulphonylphenylamino)ethoxy]-3,5-dimethoxybenzyl)-pyrimidine; 2,4-diamino-5-(4-[2-(2'-methyl-4'-aminophenyl-4-sulphonylphenylamino)ethoxy)-3,5-dimethoxybenzyl)-pyrimidine.

According to the invention, it has surprisingly been found that the introduction of substituents according to formula I into compound of the benzylpyrimidine type leads to a dramatic increase in the activity of these compounds as mycobacterial growth inhibitors (cf. table 1).

The inventive substituted 2,4-diamino-5-benzylpyrimidines can be prepared in that for obtaining compounds according to formula I (i)

(aa) a compound of general formula II



II

in which one or the substituents R^1 to R^3 is a hydroxyl or a mercapto group and the two other of the substituents R^1 to R^3 are the same or different and are hydrogen, alkoxy, alkylthio and/or alkylamino groups is etherified with a halide suitable for forming an alkoxy, alkylthio, phenylalkoxy, phenylalkylthio, phenylalkoxy, phenoxyalkylthio, phenylaminoalkoxy, phenylaminoalkylthio, cycloalkoxy, cycloalkylthio, cycloalkylalkylthio or cycloalkylalkoxy group,

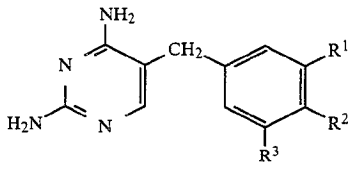
(ab) the compound obtained in stage aa) is condensed with a β-morpholinopropionitrile,

(ac) the compound obtained in stage ab) is reacted with aniline and

(ad) the compound obtained in stage ac) is cyclized with guanidine.

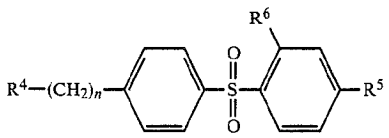
For the preparation of compounds according to formula I (ii) it is possible to either

(ba) a compound of general formula III



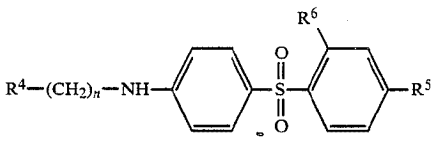
III

in which one of the substituents R^1 to R^3 is a hydroxyl or a mercapto group and the two other of the substituents R^1 to R^3 are the same or different and are hydrogen, alkoxy, alkylthio and/or alkylamino groups is etherified with a compound of general formula IV



IV

or formula V



V

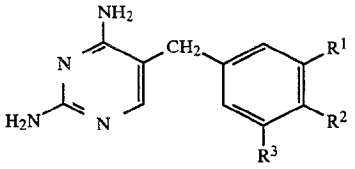
in which R^4 is a halogen radical and R^5 and R^6 are the same or different and are hydrogen, amino, alkylamino, dialkylamino, alkoxy, alkyl, nitro, alkylthio and/or acetamino groups.

Etherification appropriately takes place in per se known manner in solvents such a water, methanol, ethanol, n-propanol, isoproaanol, butanol, dimethylformamide, dimethylsulphoxide, acetone, methylethylketone and monoalkylated and dialkylated ethers of ethyleneglycol and diethyleneglycol and mixtures thereof, accompanied by the addition or a base such as sodium, sodium ethoxide, sodium or potassium hydroxide, potassium or sodium carbonate at a temperature between −20° C. and the boiling point of the solvent used, but preferably at ambient temperature.

According to a preferred embodiment of the invention, etherification is carried out in ethyleneglycol monomethylether as the solvent and the sodium alkoxide of the ethyleneglycol monomethylether.

The compounds according to formula I (ii) can also be prepared in that

(bb) a compound of general formula VI



VI

is reduced, in which one of the substituents R^1 to R^3 is a 2',4' substituted phenyl-4-sulphonylphenylaminoalkoxy, phenyl-4-sulphonylphenylaminoalkylthio, phenyl-4-sulphonylphenylalkoxy or phenyl-4-sulphonylalkylthio group with a terminal nitro group, the substituents in the 2 '4'-position being the same or different and hydrogen, amino, alkylamino, dialkylamino, alkoxy, alkyl, nitro, alkylthio and/or acetamino groups and the two other of the substituents R^1 to R^3 are the same or different and are hydrogen, alkoxy, alkylthio and/or alkylamino groups.

Reduction is appropriately carried out in per se known manner in solvents such as water, methanol, ethanol, glacialacetic acid, ethylacetate, dimethylformamide, water/ethanol, water/dioxan, water tetrahydrofuran, ethyleneglycol monomethylester and further alkyl and aryl ethers of ethylene glycol, diethyleneglycol and mixtures thereof in the presence of a hydrogenating catalyst such as Raney nickel, platinum or palladium/charcoal. Reduction can take place with metals such as iron, tin or zinc in the presence of an acid such as hydrochloric or acetic acid, with salts such as ferrous sulphate, stannous chloride/hydrochloric acid or sodium dithionide in the presence of a base such as sodium hydroxide solution, pyridine or hydrazine and Raney nickel, the temperatures being between 0° and 100° C., but preferably 50° C.

It has proved to be particularly advantageous to carry out the reduction in ethyleneglycol monomethylether, methanol or mixtures thereof at 50° C, 1 to 6 bar and in the presence of Raney nickel W2 (produced in accordance with Org. Synth. Coll. 3, 181, 1955) or palladium/charcoal.

The effectiveness of the compounds according to the invention as growth inhibitors for in particular mycobacteria was proved on bacterial cell cultures by determining the minimum inhibiting concentrations and the concentrations necessary for half maximum growth inhibition (I_{50}) when using typical representatives of the inventive compounds.

There was surprisingly found to be an up to 300 times increased activity of the inventive compounds compared with commercially available products, such as e.g. pyrimethamine. There was also found to be a synergistic effect of combinations of the claimed compounds and inhibitors of dihydropteroic acid synthetase, such as e.g. with diaminodiphenylsulphone (DDS).

The inventive compounds can therefore be used as active ingredients in medicaments for the treatment of microbial infections and in particular mycobacterioses either alone or combined with inhibitors such as diaminodiphenylsulphones, ring-substituted 4-aminodiphenylsulphones or ring and/or nitrogen-substituted diaminodiphenylsulphones and/or antibacterially acting sulphonamides. Their importance lies inter alia in the possibility of treating both partially DDS and TMP-resistant mycobacterioses and avoiding the development of resistance in the case of DDS or TMP monotherapy.

The inventive medicaments contain the active substances of the invention or active substance combinations together with a pharmaceutically acceptable carrier. The latter can be an organic or inorganic carrier material suitable for enteral, percutaneous or parenteral administration, such as e.g. water, gum Arabic, lactose, starch, magnesium stearate, tallow, vegetable oils, polyalkyleneglycols, vaseline and the like. The products can also contain other pharmaceutically active substances, such as antipyrific agents, pain relieving agents, anti-inflammatory agents and the like. The pharmaceutical products can be administered orally, e.g. in the form of tablets, capsules, pills, powders, granules, solutions, syrups, suspensions, elixirs and the like. However, administration can also by effected parenterally, e.g. in the form or sterile solutions, suspensions or emulsions or

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