EUROPEAN PATENT SPECIFICATION

Pyrimido (4,5-c) pyridazines, their use in pharmaceutical preparations, and process for their preparation.

Priority: 08.07.77 GB 2876577

Date of publication of application: 24.01.79 Bulletin 79/2

Publication of the grant of the patent: 13.10.82 Bulletin 82/41

Designated Contracting States: CH DE FR GB

References cited:
CHEMICAL ABSTRACTS 84, 59531m (1976), Abstract

Proprietor: THE WELLCOME FOUNDATION LIMITED
183-193 Euston Road
London NW1 2BP (GB)

Inventor: Morrison Jr., Robert William
5009 Larchmont Drive
Raleigh North Carolina 27612 (US)

Inventor: Mallory, William Revill
5904 Tafton Court
Raleigh North Carolina 27609 (US)

Inventor: Styles, Virgil Lee
2704 Smokey Ridge
Raleigh North Carolina 27612 (US)

Representative: Berg, Wilhelm, Dr. et al,
Dr. Berg, Dipl.-Ing. Stapf, Dipl.-Ing. Schwabe, Dr.
Dr. Sandmair Patentanwälte Postfach 860245
D-8000 München 86 (DE)

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European patent convention).
This invention relates to pyrimido(4,5-c)pyridazines, their methods of synthesis, formulations containing them and their use as inhibitors of dihydropteroic acid biosynthesis (DHPB).

The first pyrimido(4,5-c)pyridazines were disclosed by Pfleiderer and Ferch in 1958, *Am. Chem.*, 615, 48 (1958) but no pharmacological activity was disclosed for these compounds which have the formula (I):

![Formula I](image)

wherein R is a hydrogen atom or —CO₂C₅H₄ group. We have now discovered a group of pyrimido(4,5-c)pyridazines which are useful as inhibitors of dihydropteroic acid biosynthesis (DHPB).

The present invention provides novel pyrimido(4,5-c)pyridazines of formula (II), or their tautomers, or salts thereof,

![Formula II](image)

wherein R¹ is a lower alkyl group, a hydroxymethyl group, a phenyl group, a carboxy group, a benzyl group optionally substituted in the phenyl ring with one or more nitro or lower alkoxy groups, a phenacyl group optionally substituted in the phenyl ring with one or more hydroxy or lower alkoxy groups, a lower acyloxymethyl group, an indolyl or indolylmethyl group, a group CH(CN)CH₂C₆H₅ optionally substituted in the phenyl ring with one or more lower alkoxy groups, a group CH(Y)CO₂Z or a group CH₂CH₂CO₂Z in which Y is a hydrogen atom or a lower alkyl or alkoxy group and Z is a hydrogen atom or a lower alkyl group.

The term “lower” as used herein in conjunction with an alkyl, alkoxy or acyl group is indicative of the fact that such groups have from 1 to 6 carbon atoms arranged in a straight or branched chain. The expression “phenacyl group” however is used to denote solely a C₆H₅COCH₂ — group.

It is to be understood that compounds where tautomerism is possible between, on the one hand, a hydroxy group and an oxo group, and on the other hand, an amino group and an imino group, at a particular position in either of the rings of the pyrimido(4,5-c)pyridazines of formula (II), the more stable forms are respectively: the oxo group and the amino group. However, the general formulae used in the present specification do not necessarily represent the more stable forms of such pyrimido pyridazines.

The above compounds of formula (II) inhibit the enzyme dihydropteridine synthetase which enables microorganisms to synthesize an essential intermediate in the production of tetrahydrofolate co-factors. Most of these co-factors are one-carbon adducts of tetrahydrofolic acid and they are essential metabolites in cells for the biosynthesis of purines, thymidyl acid, serine, and several other biologically important compounds. Man and other higher animals are unable to synthesise folic acid and therefore they have to obtain them from food which contains the required preformed folates.

On the other hand, microorganisms synthesize the co-factors themselves from simpler chemicals. Generally the biosynthetic process first provides “dihydropteridine” (*Pt*), i.e. 2 - amino - 4 - hydroxy - 6 - hydroxymethyl - 7,8 - dihydropteridine (HMPt) pyrophosphate ester, from its immediate precursor HMP in the presence of the enzyme dihydropteridine pyrophosphokinase (HMPPS). Pt then condenses with p-aminobenzoic acid (pAB) in the presence of the enzyme dihydropterate synthetase to form dihydropteroic acid (DPGA). This intermediate further condenses with a glutamate to form dihydrofolic acid (DFA or “folate”) which is then enzymatically reduced to produce the essential tetrahydrofolate. It is in the formation of DFA from pAB and Pt that the present compounds have inhibitory activity.
On the basis of such inhibitory activity the pyrimido(4,5-c)pyridazines of formula (II) have anti-
microbial, in particular anti-bacterial, activity.

Within the class of pyrimido(4,5-c)pyridazines of formula (III) there is a group of compounds which are particularly active and these have R1 as a methyl group, a phenyl group, a benzyl group optionally substituted in the phenyl ring with a nitro or 2 or 3 methoxy groups, a hydroxymethyl group, a phenacyl group optionally substituted in the phenyl ring with a hydroxy group, or 2 or 3 methoxy groups, a group CH3 CH2 CO2H, an acetyl group, an indolylmethyl group or a group CH(CY)CO2Z in which Y is a methyl group, methoxy group or a hydrogen atom and Z is a hydrogen atom, or a C2 alkyl group.

As examples of compounds which are particularly active and which fall within this class are 7 - amino - 1,3 - dimethyl - 4 - oxo - 5 - hydroxy - 1,4 - dihydropyrimido(4,5-c) - pyridazine; 7 - amino - 1 - methyl - 3 - phenyl - 4 - oxo - 5 - hydroxy - 1,4 - dihydropyrimido(4,5-c) - pyridazine; 7 - amino - 1 - methylene - 3 - hydroxymethyl - 4 - oxo - 5 - hydroxy - 1,4 - dihydropyrimido(4,5-c) - pyridazine; 7 - amino - 1 - methyl - 3 - benzyl - 4 - oxo - 5 - hydroxy - 1,4 - dihydropyrimido(4,5-c) - pyridazine; 7 - amino - 1 - methyl - 3 - (2 - nitrobenzyl) - 4 - oxo - 5 - hydroxy - 1,4 - dihydropyrimido(4,5-c) - pyridazine; 7 - amino - 1 - methyl - 3 - (2 - carboxymethyl) - 4 - oxo - 5 - hydroxy - 1,4 - dihydropyrimido(4,5-c) - pyridazine; 7 - amino - 1 - methyl - 3 - (1 - ethoxycarbonylethyl) - 4 - oxo - 5 - hydroxy - 1,4 - dihydropyrimido(4,5-c) - pyridazine. However, a more preferred class of even higher activity compounds, are those of formula (III) wherein R1 is a benzyl group or especially wherein R1 is a phenacyl group optionally substituted in the phenyl ring with a hydroxy group or 2 or 3 methoxy groups. Examples of compounds falling within this most preferred class are 7 - amino - 1,3 - dimethyl - 4 - oxo - 5 - hydroxy - 1,4 - dihydropyrimido(4,5-c) - pyridazine; 7 - amino - 1 - methyl - 3 - phenyl - 4 - oxo - 5 - hydroxy - 1,4 - dihydropyrimido(4,5-c) - pyridazine; 7 - amino - 1 - methyl - 3 - (2 - carboxymethyl) - 4 - oxo - 5 - hydroxy - 1,4 - dihydropyrimido(4,5-c) - pyridazine; 7 - amino - 1 - methyl - 3 - (1 - ethoxycarbonylethyl) - 4 - oxo - 5 - hydroxy - 1,4 - dihydropyrimido(4,5-c) - pyridazine.

It has previously been stated that in 1958 Pfleiderer W. and Ferch H. (Justus Liebig’s Ann. Chem., 1958, 615, 48) reported the preparation of 4 - hydroxy - 6,8 - dimethylpyrimido(4,5-c) - pyridazine - 5,7 - (6H, 8H) - dione by the cyclisation of glyoxylic acid ethyl ester - 1,3 - dimethyluracil - (4) - dione. It has now been found that this cyclisation reaction can surprisingly be extended to a novel class of intermediates which have a number of different substituents. Thus the present invention further provides a method of preparing a compound of formula (III), except those wherein R1 is a carboxy group, or a tautomeric or a salt thereof, as hereinbefore defined which process comprises the cyclisation of a compound of the formula (III):

wherein R3 is a lower alkyl group and R2 is a lower alkyl group, a lower acyloxyethyl group, a phenyl group, a benzyl group optionally substituted in the phenyl ring with one or more nitro or lower alkoxyl groups, a phenacyl group optionally substituted in the phenyl ring with one or more hydroxy or lower alkoxyl groups, an indolyl or indolylmethyl group, a group CH(CY)CO2Z or a group CH3 CH2 CO2Z in which Y is a hydrogen atom or a lower alkyl or alkoxyl group and Z is a hydrogen atom or a lower alkyl group.

[Diagram of compound (III)]
and thereafter and optionally hydrolysing the lower acyloxymethyl group to a hydroxymethyl group.

Such is the nature of the substituents on the pyrimidine ring of the compounds of formula (III) that, unlike the above prior art teaching, ring closure can apparently only be achieved when the hydrazino nitrogen atom attached at the pyrimidine 6-position is substituted as hereinabove. In other words, when this particular nitrogen atom is unsubstituted, corresponding compounds of formula (III) do not appear to cyclise. Moreover, this cyclisation reaction is particularly surprising since the report of Pfleiderer and Ferch teaches that such reactions only work for those hydrazone intermediates which have a glyoxylic acid alkyl ester substitution, yet a corresponding substitution in the present intermediates results in little, if any, pyrimido(4,5-c)pyridazine.

The reaction itself may be carried out in any suitable solvent but most desirably a hydroxylic solvent, for example glacial acetic acid, water or C1-4 alkanol, at reflux temperature for up to several days. Optimally, the reaction is carried out in refluxing methanol, or in ethanol at the reflux temperature of methanol.

The hydrolysis of the lower acyloxymethyl group will preferably take place under alkaline conditions, for example, by using aqueous sodium hydroxide. The hydrolysis will be carried out at a non extreme temperature, i.e. between 10° and 100°C, and preferably at room temperature.

The compounds of formula (III) can be prepared, preferably in situ, by condensing a 2-amino-4-oxo-6-hydrazinopyrimidine of formula (IV) (or a tautomer thereof).

\[
\begin{align*}
\text{(IV)} \\
\end{align*}
\]

with an \(\alpha\)-keto ester of formula (V):

\[
R^2\text{CO.CO.OR}^3 
\]

wherein \(R^2\) and \(R^3\) are as hereinbefore defined.

The preparation is suitably achieved using the conditions as specified for the cyclisation reaction above, for example by refluxing the reactants in methanol.

In the preparation of those compounds of formula (III), in which \(R^1\) is a group \(\text{CH}(Y)\text{CO}_2Z\), a group \(\text{CH}_2\text{CH}_2\text{CO}_2Z\), or an optionally substituted phenacyl group, some other bi-cyclic compound may be formed as a by-product. In such instances it may be necessary to isolate the required compound by the usual procedures known in the art.

The compounds of formula II wherein \(R^1\) is a group \(\text{CH}(Y)\text{CO}_2Z\) or a group \(\text{CH}_2\text{CH}_2\text{CO}_2Z\) in which \(Y\) is as hereinbefore defined and \(Z\) is a lower alkyl group may be hydrolysed to give further compounds of formula II wherein \(R^1\) is a group \(\text{CH}(Y)\text{CO}_2Z\) or a group \(\text{CH}_2\text{CH}_2\text{CO}_2Z\) in which \(Y\) is as hereinbefore defined and \(Z\) is a hydrogen atom. The starting compounds of formula II may be prepared from the corresponding compound of formula (III) as described previously.

The conditions for this reaction are preferably alkaline which may be achieved by using, for instance, aqueous sodium hydroxide, and the reaction may be conveniently performed at room temperature for 15 to 150 minutes, for example 90 minutes.

Compounds of formula (II) wherein \(R^1\) is other than an acyloxymethyl group or any group containing an ester function may be prepared by the hydrolysis of a compound of formula (VI):

\[
\begin{align*}
\text{(VI)} \\
\end{align*}
\]

wherein \(R^2\) is as hereinbefore defined or a group \(\text{CO}_2R^4\) wherein \(R^4\) is a lower alkyl group.

The conditions for this reaction are preferably alkaline which may be achieved by using, for instance, aqueous sodium hydroxide, and the reaction may be conveniently performed under reflux for 10 to 40 hours, for example 24 hours. However, it should be noted that during the course of this
reaction some decarboxylation may take place, possible giving rise to small amounts of by-products which may necessitate subsequent separation by known methods.

This hydrolysis reaction is not preferred for those compounds of the formula (VI) wherein R² is a group which may undergo hydrolytic cleavage, for example when R² is an optionally substituted phenacyl group if it is desired to prepare a compound of the formula (II) having identical substituent R¹ corresponding to R².

The compounds of formula (VI), may be prepared by the cyclisation of a compound of formula (VII):

\[
\text{NH} \quad \text{C(R²)CO₂R³} \quad \text{CH₃}
\]

wherein R² and R³ are as hereinbefore defined.

The reaction may be carried out in any suitable solvent but most desirably a hydroxylic solvent, for example glacial acetic acid, water, or C₃₋₄ alkanol, at reflux temperature for up to several days. Optimally, the reaction is carried out in refluxing methanol, or in ethanol at the reflux temperature of methanol.

The compounds of formula (VII) can be prepared preferably in situ, by condensing a 2-amino-4-imino-6-hydrazinopyrimidine of formula (VIII), or a tautomer thereof,

\[
\text{NH} \quad \text{H}_{2}\text{N} \quad \text{N} \quad \text{NH}_2 \quad \text{CH₃}
\]

with an α-keto ester of formula (V).

The preparation is suitably achieved using the conditions as specified for the cyclisation reaction immediately above, for example by refluxing the reactants in methanol.

In the preparation of those compounds of formula (VI) in which R² is a group CH(Y)CO₂Z, a group CH₂CH₂CO₂Z, or an optionally substituted phenacyl group, some other bicyclic compound may be formed as a by-product. In such instances it may be necessary to isolate the required compound by the usual procedures known in the art.

It should be noted that although, in general, hydrolysis of a compound of formula (VI) results in a correspondingly substituted compound of formula (II) except that the 5-position is oxo rather than imino substituted; in the case wherein R² in the starting material is a group CH(Y)CO₂Z or a group CH₂CH₂CO₂Z in which Z is a lower alkyl group, Z in the end-product of formula (II) is a hydrogen atom.

All the starting materials specified above for the various syntheses may be prepared by standard methods taught in the art.

In another aspect of the present invention, therefore, there is provided a pharmaceutical formulation comprising a compound of formula (II) in combination with a pharmaceutically acceptable carrier. In yet another aspect the present invention provides a method of making a pharmaceutical formulation by admixing the compound of formula (II) with a carrier by known techniques.
The compounds of formula (II), for use alone, may be presented in the form of their pharmaceutically acceptable salts. Examples of pharmaceutically acceptable salts are those derived from mineral or organic acids, for example hydrochloric acid, hydrobromic acid, sulphuric acid, acetic acid, citric acid, tartaric acid, lactic acid, maleic acid, or salicylic acid. Acid addition salts which are not pharmaceutically acceptable may be rendered so by a conventional metathetical reaction. Further examples of pharmaceutically acceptable salts are, in the case when $R_1$ in formula (II) is a carboxy group, a group $CH(Y)CO_2Z$, or a group $CH_2CH_2CO_2Z$ in which $Z$ is a hydrogen atom, are alkali metal, for example sodium, salts.

Humans an other animals suffering from microbial infections may be treated by administering a non-toxic effective antimicrobial treatment amount of a compound of formula (II), or preferably administering a pharmaceutical formulation comprising the said amount of a compound of formula (II) and a pharmaceutically acceptable carrier, to the infected human or other animal.

The compounds of formula (II) may be administered at a dose range of 1 to 60 mg/kg bodyweight daily in one or several doses.

Further advantages of the present invention can be ascertained from the following examples which should not be construed as limiting the scope of the invention in any way.

**Example 1**

6-(1-Methylhydrazino)isocytosine

**Example 2**

7-Amino-1,3-dimethylpyrimido(4,5-c)pyridazine-4,5-(1H, 6H)-dione

**Example 3**

7-Amino-3-acetoxymethyl-1-methylpyrimido(4,5-c)pyridazine-4,5-(1H, 6H)-dione
Example 4

7-Amino-3-hydroxymethyl-1-methylpyrimido(4,5-c)pyridazine-4,5-(1H, 6H)-dione Sodium Salt

(R¹ = CH₂OH)

To 7-amino-3-acetoxymethyl-1-methylpyrimido(4,5-c)pyridazine-4,5-(1H, 6H)-dione (0.100 g) in water (1 ml) was added dropwise with shaking 10% (w/w) aqueous sodium hydroxide (0.25 ml), the orange solution becoming quickly cloudy. The mixture was allowed to stand at room temperature for 30 minutes after which time the off-white granular solid which had formed was collected by filtration, rinsed well with methanol and dried under vacuum at room temperature to yield 7-amino-3-hydroxymethyl-1-methylpyrimido(4,5-c)pyridazine-4,5-(1H, 6H)-dione as its sodium salt (0.082 g; 81% of theoretical yield; m.p. >300°C).

Elemental analysis: Calcd. for C₈H₈N₅NaO₃.H₂O: C, 36.50%; H, 3.83%; N, 26.61%; Na, 8.73; Found: C, 36.55%; H, 3.91%; N, 26.50%; Na, 8.70. nmr (TFA) δ 4.29 (s, 3H), 5.19 (s, 2H), 7.20 (br s, 2H).

Example 5

7-Amino-3-(1-ethoxycarbonylethyl)-1-methylpyrimido(4,5-c)pyridazine-4,5-(1H, 6H)-dione

R¹ = CH(Y)CO₂Z; Z = C₂H₅; Y = CH₃

To a stirred, refluxing solution of 6-(1-methylhydrazino)isocytosine hemihydrate (1.86 g) in water (120 ml) was added diethyl 3-methyl-2-oxo-succinate (4.59 g). After refluxing for a further 3 hours, the solid formed during the course of the reaction was collected by filtration of the hot reaction mixture, washed with two portions of water (20 ml each) and dried under vacuum at 70°C to yield 7-amino-3-(1-ethoxycarbonylethyl)-1-methylpyrimido(4,5-c)pyridazine-4,5-(1H, 6H)-dione (1.93 g; 58% theoretical yield; m.p. >280°C).

Elemental analysis: Calcd. for C₁₂H₁₅NsO₄: C, 49.14%; H, 5.16%; N, 23.88%. Found: C, 49.10%; H, 5.18%; N, 23.62%. nmr (CF₃COOH) δ 1.38 (t, 3H), 1.77 (d, 3H), 4.28 (s, 3H), 4.41 (q, 3H), 7.17 (br s, 2H).

Example 6

7-Amino-3-(1-carboxyethyl)-1-methylpyrimido(4,5-c)pyridazine-4,5-(1H, 6H)-dione Disodium Salt

A. A mixture of 7-amino-3-(1-ethoxycarbonylethyl)-1-methylpyrimido(4,5-c)pyridazine-4,5-(1H, 6H)-dione (2.97 g) in 10% (w/w) aqueous sodium hydroxide (67 ml) was swirled vigorously for 25 minutes. Although a complete solution was not obtained during the agitation, a solid began to precipitate after 20 minutes. The mixture was then allowed to stand at room temperature for 1 hour before being chilled at 0°C for 1½ hours to allow complete precipitation of the product. The precipitate was collected by filtration, washed with three portions of 95% ethanol (25 ml each) and dried overnight at room temperature in a vacuum desiccator to yield 7-amino-3-(1-carboxyethyl)-1-methylpyrimido(4,5-c)pyridazine-4,5-(1H, 6H)-dione disodium salt (2.42 g; 70% of theoretical yield; m.p. > 300°C; hygroscopic crystals).

Elemental analysis: Calcd. for C₁₀H₉N₅Na₂O₄.O.₅H₂O: C, 37.74%; H, 3.17%; N, 22.01%; Na, 14.45%. Found: C, 37.69%; H, 3.21%; N, 22.05%; Na, 16.44%. nmr (CF₃COOH) δ 1.81 (d, 3H), 4.30 (s, 3H), 4.45 (q, 1H), 7.17 (br s, 2H). uv λ max (0.1 N HCl) 255 nm (ε 41,500), 301 (7,800).

B. The 3-CH₂CH₂CO₂H compound (disodium salt) was prepared in a manner similar to that of 6A from the 3-CH₂CH₂CO₂H starting material except that collected precipitated solid was washed with CH₃OH, yield 82%. Calcd. for C₁₀H₁₀N₅Na₂O₄.₄CH₃OH.₀.₄H₂O: C, 37.94%; H, 3.49%; N, 21.27%; Na, 13.97%. Found: C, 37.91%; H, 3.21%; N, 21.36%; Na, 13.99.

C. The 3-CH(OCH₃)CO₂C₂H₅ compound (disodium salt) was prepared in a manner similar to that of 6A from the 3-CH(OCH₃)CO₂CH₃ starting material, yield 69%. Calcd. for C₁₀H₁₃N₅Na₂O₄: C, 36.93%; H, 2.79%; N, 21.54%; Na, 14.14%. Found: C, 36.70%; H, 2.92%; N, 21.38%; Na, 14.01.

Example 7

3-Carbomethoxy-5,7-diamino-1-methylpyrimido(4,5-c)pyridazin-4(1H)-one

(R² = CH₃)

To a stirred mixture of 2,4-diamino-6-(1-methylhydrazino)pyrimidine (0.77 g) in a hydrous methanol (50 ml) was added diethyl ketomalonate (1.16 g) at room temperature. An orange solution
resulted as the mixture was heated to reflux over a five minute period. After a further 72 hours of refluxing, the crude product which had separated out was collected by suction filtration of the hot mixture, washed with methanol and dried under reduced pressure at 70°C to give a pale yellow solid (0.80 g; m.p. 272—274°C). Recrystallisation of 0.70 g of this solid from methanol yielded pure pale yellow 3-carboxymethoxy-5,7-diamino-1-methylpyrimido(4,5-c)pyridazin-4(1H)-one (0.55 g; m.p. 274—276°C).

Elemental analysis: Calcd. for C9H10N6O3: C, 43.20%; H, 4.03%; N, 33.59%; Found: C, 43.12%; H, 4.05%; N, 33.54%. nmr (DMSO-d6) δ 3.80 (s, 3H), 3.82 (s, 3H), 7.07 (br s, 2H) 7.90(br d, 1H, J = 4Hz), 8.80(br d, 1H, J = 4Hz). uv (CH3OH) λ max 288 nm (ε 15,200), 255.5 (30,300) 261 sh (29,000), 313(8,700).

Example 8
7-Amino-3-carboxy-1-methylpyrimido(4,5-c)pyridazine-4,5-(1H, 6H)-dione Disodium Salt

A mixture of 3-carboxymethoxy-5,7-diamino-1-methylpyrimido(4,5-c)pyridazin-4-one (0.250 g) in 4N aqueous sodium hydroxide (12.5 ml) was stirred at reflux for 2½ hours and then allowed to stand at room temperature for 1 hour before being filtered. The collected white solid was recrystallised twice from water/methanol, dried under vacuum at 70°C, and allowed to air-equilibrate to give 7-amino-3-carboxy-1-methylpyrimido(4,5-c)pyridazine-4,5-(1H, 6H)-dione as its disodium salt (0.146 g; 45% of theoretical yield; m.p. > 300°C).

Elemental analysis: Calcd. for C8H5N5O4Na2.2.25H2O: C, 29.87%; H, 2.98%; N, 21.77%; Na 14.29%; nmr (CF3COOH) 8 4.30(s, 3H) 7.12(br s, 2H). uv λ max (pH 2), 266.6 nm (E 45,700), 314.5(6,300).

Example 9
5,7-Diamino-1,3-dimethylpyrimido(4,5-c)pyridazine-4(1H)-one

To a refluxing solution of 2,4-diamino-6-(1-methylhydrazino)pyrimidine (500 mg) in anhydrous methanol (15 ml) was added methyl pyruvate (496 mg) over a five minute period. Reflux was continued for 5 hours after which time the solid which had separated was collected by suction filtration of the hot mixture, washed with methanol, and dried under vacuum at 70°C to yield tan crystals of 5,7-diamino-1,3-dimethylpyrimido(4,5-c)pyridazine-4(1H)-one (508 mg; 76% of theoretical yield; m.p. > 275°C).

Elemental analysis: Calcd. for C8H10N6O: C, 46.59%; H, 4.89%; N, 40.76%. Found: C, 46.66%, H, 4.98%; N, 40.89. nmr (DMSO-d6) δ 2.14(s, 3H), 3.74(s, 3H), 6.84(br s, 2H)*, 7.72(br d, 1H, J = 4Hz)*, 8.86(br d, 1H, J = 4Hz)*. uv λ max (CH3OH) 222 nm (ε 12,800), 247(31,100), 306 (11,600).

Example 10
7-Amino-1,3-dimethylpyrimido(4,5-c)pyridazine-4,5-(1H, 6H)-dione

A mixture of 5,7-diamino-1,3-dimethylpyrimido(4,5-c)pyridazine-4(1H)-one (0.50 g) and 1.5N aqueous sodium hydroxide (35 ml) was stirred at reflux for 24 hours after which time a small amount of solid was removed by filtration of the hot mixture. On cooling, the yellow filtrate deposited white needles which were collected by filtration and dissolved in warm water (20 ml). Adjustment of this aqueous solution to pH 5 by dropwise addition of 6N hydrochloric acid and subsequent cooling to room temperature provided a very finely divided white precipitate which was collected, washed with water and dried under vacuum at 70°C to give 7-amino-1,3-dimethylpyrimido(4,5-c)pyridazine-4,5-(1H, 6H)-dione (0.38 g; 76% of theoretical yield). The u.v., i.r., and n.m.r. spectra of this compound were identical to those of the sample made according to the procedure of Example 2.

Example 11
Adopting the general procedure of Example 2, that is to say, addition of the appropriate α-ketoester of formula (V) to a refluxing mixture or solution prepared from a very pure, appropriately substituted alkylhydrazino isocytosine of formula (IV) and filtered solvent in the proportion of 1 g in 100 ml, collected by filtration of the precipitated compound of formula (II) from the hot reaction mixture washing with a small portion of fresh reaction solvent and drying under vacuum at 70°C, the following compounds of formula (II) were prepared:

* = exchangeable with D2O.
<table>
<thead>
<tr>
<th>Molar Ratio (V:IV)</th>
<th>Reflux Solvent and Reflux time</th>
<th>Yield (%)</th>
<th>Elemental Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>F = Found; Ca = Calculated</td>
</tr>
<tr>
<td>P1</td>
<td></td>
<td></td>
<td>Ca: C47.31% H: 4.69% N: 25.06%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C5: C47.0% H: 4.78% N: 25.02%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ca: C59.35% H: 4.83% N: 24.72%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C5: C59.33% H: 4.85% N: 24.65%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ca: C61.22% H: 6.56% N: 25.38%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C5: C61.26% H: 6.71% N: 25.40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ca: C65.97% H: 6.90% N: 24.50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C5: C65.07% H: 6.90% N: 24.40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ca: C49.99% H: 6.12% N: 25.98%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C5: C49.96% H: 6.17% N: 25.98%</td>
</tr>
<tr>
<td></td>
<td>CH₃OH (under N₂)</td>
<td>37</td>
<td>Ca: C47.99% H: 6.12% N: 25.98%</td>
</tr>
<tr>
<td></td>
<td>CH₃OH (under N₂)</td>
<td>53</td>
<td>C5: C49.96% H: 6.17% N: 25.98%</td>
</tr>
<tr>
<td></td>
<td>CH₃OH (under N₂)</td>
<td>40</td>
<td>Ca: C61.18% H: 6.69% N: 25.38%</td>
</tr>
<tr>
<td></td>
<td>CH₃OH (under N₂)</td>
<td>58</td>
<td>C5: C61.26% H: 6.71% N: 25.40%</td>
</tr>
<tr>
<td></td>
<td>CH₃OH (under N₂)</td>
<td>38</td>
<td>Ca: C65.97% H: 6.90% N: 24.50%</td>
</tr>
<tr>
<td></td>
<td>CH₃OH (under N₂)</td>
<td>56</td>
<td>C5: C65.07% H: 6.90% N: 24.40%</td>
</tr>
<tr>
<td></td>
<td>CH₃OH (under N₂)</td>
<td>60</td>
<td>Ca: C49.99% H: 6.12% N: 25.98%</td>
</tr>
<tr>
<td></td>
<td>CH₃OH (under N₂)</td>
<td>82</td>
<td>C5: C49.96% H: 6.17% N: 25.98%</td>
</tr>
<tr>
<td></td>
<td>CH₃OH (under N₂)</td>
<td>51</td>
<td>Ca: C49.99% H: 6.12% N: 25.98%</td>
</tr>
<tr>
<td></td>
<td>CH₃OH (under N₂)</td>
<td>62</td>
<td>C5: C49.96% H: 6.17% N: 25.98%</td>
</tr>
<tr>
<td>R¹</td>
<td>Molar Ratio (V:IV)</td>
<td>Reflux Solvent &amp; Reflux time</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>----</td>
<td>--------------------</td>
<td>------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 3-Indolylmethyl | 1.2:1 | 6:1 CH₃OH/H₂O 21 hours | 11 | Ca: C59.62% H4.38% N26.08%  
|                |       |                             |           | F: C59.53% H4.41% N26.12% |
| 3-Indoly | 1.5:1 | CH₃OH 5 days | 36 | Ca: C58.43% H3.92% N27.26%  
|           |       |                             |           | F: C58.47% H3.96% N27.14% |
| CH(OCH₃)CO₂C₆H₄ | 1.5:1 | CH₃OH 9 days | 39 | Ca: C46.60% H4.89% N22.65%  
|             |       |                             |           | F: C46.62% H4.93% N22.63% |
| CH₂ [OCH₃ | 1.2:1 | CH₃OH (under N₂) 50 hours | 25 | Ca: C54.68% H5.13% N18.76%  
| OCH₃     |       |                             |           | F: C54.71% H5.14% N18.81% |
| CH(CH)₂OCH₃ | 1.2:1 | CH₃OH 166 hours | 34 (after recrystallisation from CH₃OH) | Ca: C55.33% H4.89% N20.38%  
| OCH₃     |       |                             |           | F: C55.11% H4.87% N20.30% |
Example 12
7-Amino-3-phenacyl-1-methylpyrimido[4,5-c]pyridazine-4,5-(1H, 6H)-dione

(R\(^1\) = CH\(_2\)CO.C\(_6\)H\(_5\)\)

To a stirred, refluxing mixture of 6-(1-methylhydrazino)isocytosine hemihydrate (1.00 g) in methanol (100 ml) was added ethyl benzoylpyruvate (2.01 g). After 67 hours yellowish-brown solid was collected from the hot reaction mixture, washed with three portions of methanol totalling 20 ml, and dried under vacuum at 75°C, yield 0.130 g (7%): m.p. > 300°; nmr (CF\(_3\)COOH) \(\delta\) 4.28 (s, 3H), 4.87 (s, 2H), 7.17 (br s, 2H), 7.4-8.3 (m, 5H); uv \(\lambda\) max (CH\(_3\)OH) 259 nm (\(\epsilon\) 44,900), 301 (8,300), 310 sh (6,900), 375 sh (900). Mass spectrum (240°): M, m/e 311, 17%; m/e 166, 1%; m/e 105, 100%. The following accurate mass was determined 166.0487 (C\(_{15}\)H\(_{13}\)N\(_5\)O\(_3\)).

Anal. Calcd. for C\(_{15}\)H\(_{13}\)N\(_5\)O\(_3\): C, 57.87%; H, 4.21%; N, 22.50%. Found: C, 57.80%; H, 4.26%; N, 22.46%.

Example 13
7-Amino-3-(3-hydroxyphenacyl)-1-methylpyrimido[4,5-c]pyridazine-4,5-(1H, 6H)-dione

(R\(^1\) = CH\(_2\)CO.C\(_6\)H\(_5\)OH)

Adopting the general procedure of Example 12, the above compound was synthesized and isolated.

Reaction time of 22 hours. Yield 7%: m.p. 290—295° dec; nmr (CF\(_3\)COOH) \(\delta\) 4.28 (s, 3H), 4.83 (s, 2H), 7.16 (br s, 2H), 7.4-8.0 (m, 4H); uv \(\lambda\) max (CH\(_3\)OH) 213.5 nm (\(\epsilon\) 26,300), 259(47,400), 303(10,600), 309 sh (9,700).

Anal. Calcd. for C\(_{15}\)H\(_{13}\)N\(_5\)O\(_4\).0.5H\(_2\)O: C, 43.16%; H, 5.55%; N, 16.78%. Found: C, 43.15%; H, 5.59%; N, 16.83%.

Example 14
7-Amino-3-(2,4,6-trimethoxyphenacyl)-1-methylpyrimido[4,5-c]pyridazine-4,5-(1H, 6H)-dione

(R\(^1\) = CH\(_2\)CO.C\(_6\)H\(_5\)(OCH\(_3\))\(_3\))

Adopting the general procedures of Example 12, the above compound was synthesized and isolated.

Reaction time of 19½ hours. Yield 5%: m.p. 280° dec; nmr (CF\(_3\)COOH) \(\delta\) 4.18, 4.24 and 4.25 (overlapping s's, 12H), 4.96 (s, 2H), 6.52 (s, 2H), 7.22 (br s, 2H); uv \(\lambda\) max (CH\(_3\)OH) 258 nm (\(\epsilon\) 37,500), 296.5 sh (12,700), 311.5 sh (9,800).

Anal. Calcd. for C\(_{17}\)H\(_{17}\)N\(_5\)O\(_6\): C, 53.86%; H, 4.77%; N, 17.45%. Found: C, 53.68%; H, 4.81%; N, 17.46%.

Example 15
7-Amino-3-(2,5-dimethoxyphenacyl)-1-methylpyrimido[4,5-c]pyridazine-4,5-(1H, 6H)-dione

(R\(^1\) = CH\(_2\)CO.C\(_6\)H\(_5\)(OCH\(_3\))\(_2\))

To a stirred, refluxing mixture of 6-(1-methylhydrazino)isocytosine hemihydrate (4.00 g) in methanol (400 ml) was added methyl 2,5-dimethoxybenzoylpyruvate (7.14 g). After 19 hours reddish-orange solid was collected from the hot mixture, washed with two portions of methanol totalling 50 ml, and dried under vacuum at 75°C to yield 0.628 g. This solid was an inseparable 1:1 mixture of the desired 4,5-dione and its 3,5-dione isomer.

The filtrate was refluxed an additional 22.5 hours, and pale yellow solid was collected from the hot mixture, washed with several portions of methanol totalling 30 ml, and dried under vacuum at 75°, yield 0.09 g of the 4,5-dione isomer (1%): m.p. > 300°; nmr (CF\(_3\)COOH) \(\delta\) 4.02 (s, 3H), 4.07 (s, 3H), 4.28 (s, 3H), 4.90 (s, 2H), 6.8—7.7 (m, 5H); uv \(\lambda\) max (CH\(_3\)OH) 223 nm weak sh (\(\epsilon\) 22,800), 258.5 (48,500), 302.5 (10,000), 311.5 sh (9,000), 332.5 sh (5,500).

Anal. Calcd. for C\(_{17}\)H\(_{17}\)N\(_5\)O\(_5\): C, 54.98%; H, 4.61%; N, 18.86%. Found: C, 54.68%; H, 4.64%; N, 19.03%.

Example 16
7-Amino-3-(2,4-dimethoxyphenacyl)-1-methylpyrimido[4,5-c]pyridazine-4,5-(1H, 6H)-dione

(R\(^1\) = CH\(_2\)CO.C\(_6\)H\(_5\)(OCH\(_3\))\(_2\))

Following the general procedure of Example 15, the above compound was synthesized and isolated.
A 2:1 mixture of 4,5-dione and 3,5-dione isomers, respectively, was collected after 18 hours. The filtrate was refluxed an additional 47 hours for a 9% yield of 4,5-dione isomer: m.p. 290-300° dec; nmr (CF₃COOH) δ 4.02 and 4.06 overlapping s’s, (6H), 4.27(s, 3H), 4.84(s, 2H), 6.6—8.2(m, 5H); uv λ max (CH₃OH) 227.5 nm (ε 20,200), 259.5 (40,700), 304(17,400), 413(2,800), 435(2,700), 460(2,900).

Anal. Cald. for C₁₇H₁₇N₅O₅: C, 54.98%; H, 4.61%; N, 18.86%. Found C, 54.97%; H, 4.69%; N, 18.98%.

Example 17

7-Amino-3-(3,4-dimethoxyphenacyl)-1-methylpyrimido(4,5-c)pyridazine-4,5-(1H, 6H)-dione

Following the general procedure of Example 15, the above compound was synthesized and isolated.

An insoluble mixture was collected after 17 hours. The filtrate was refluxed an additional 47 hours for a 2% yield of 4,5-dione isomer: m.p. > 300°; nmr (CF₃COOH) δ 4.04 and 4.08 (overlapping s’s, 6H), 4.28(s, 3H), 4.30(s, 2H), 7.0-7.4(m, 3H), 7.7-8.2(m, 2H); uv λ max (CH₃OH) 229 nm (ε 23,300), 259 (42,000), 274 sh (22,200), 304(18,700).

Anal. Calcd. for C₁₇H₁₇N₅O₅·H₂O: C, 54.72%; H, 4.65%; N, 18.77%. Found: C, 54.71%; H, 4.68%; N, 18.71%.

Example 18

7-Amino-3-(3,4,5-trimethoxyphenacyl)-1-methylpyrimido(4,5-c)pyridazine-4,5-(1H, 6H)-dione

Following the general procedure of Example 15, the above compound was synthesized and isolated.

A 1:1 mixture of 4,5-dione and 3,5-dione isomers, respectively, was collected after 18½ hours. The filtrate was refluxed an additional 23 hours for a 2% yield of 4,5-dione isomer: m.p. > 300°; nmr (CF₃COOH) δ 4.07 and 4.13 (overlapping s’s, 9H), 4.30(s, 3H), 4.86(s, 2H), 7.18(br s, 2H), 7.54(s, 2H); uv λ max (CH₃OH) 213 nm (ε 32,500), 258.5(43,700), 297 sh (17,200) 310 sh (13,700). Mass spectrum (250°): M, m/e 401, 7%; m/e 195, 100%; m/e 166, 2%. The following accurate mass was determined: 166.0488 (C₆H₆N₄O₂).

Anal. Calcd. for C₁₈H₁₉N₅O₆: C, 53.86%; H, 4.77% N, 17.45%. Found: C, 53.82%; H, 4.85%; N, 17.55%.

Example 19

Potential inhibitors of DHPB synthesis may be tested by investigating the inhibitory effect they impose in the enzymes responsible for the biosynthesis of dihydropterolic acid (DPTA), namely hydroxymethyldihydropteridine pyrophosphokinase (HMPPS), and dihydropteroate synthetase, hereinafter referred to as “synthetase.” In the following reaction equations the compounds are referred to by their abbreviated forms defined hereinbefore in the specification.

1. HMPPS:–

\[
\text{HMPt} + \text{ATP} \xrightarrow{Mg} \text{Pt} + \text{AMP}
\]

2. 'Synthetase':–

\[
\text{Pt} + \text{pAB} \xrightarrow{Mg} \text{DPTA} + \text{pyrophosphate}
\]

This reaction requires two enzymes since the starting substrates are H₃PtCH₂OH, ATP, and pAB, and the products are H₂PtE₀ and AMP. In crude extracts of E. coli (and the 0—50% ammonium sulfate fraction used by us) the first enzyme, 2 - amino - 4 - hydroxy - 6 - hydroxymethyl - 7,8 - dihydropteridine pyrophosphokinase ("kinase"), has a threefold lower specific activity that the second enzyme, dihydropteroate synthetase ("synthetase").

The reactions are followed by determining the amount of ¹⁴C in H₂PtE₀ after separation from the substrate, p-aminobenzoate-7-¹⁴C, by paper chromatography.

The following results were obtained by the coupled assay method.
<table>
<thead>
<tr>
<th>Compound of formula (II)</th>
<th>Concentration in µM required to give 50% inhibition of DHPB</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>16.0</td>
</tr>
<tr>
<td>C₂H₅</td>
<td>15.0</td>
</tr>
<tr>
<td>CH₃OH</td>
<td>12.0</td>
</tr>
<tr>
<td>CH₂OOCOCH₃</td>
<td>15.0</td>
</tr>
<tr>
<td>CO₂H (disodium salt)</td>
<td>21.0</td>
</tr>
<tr>
<td>CH(CH₃)CO₂C₂H₅</td>
<td>1.6</td>
</tr>
<tr>
<td>CH(CH₃)CO₂H</td>
<td>3.7</td>
</tr>
<tr>
<td>CH₂CH₂CO₂H</td>
<td>5.5</td>
</tr>
<tr>
<td>CH₂CH₂CO₂C₂H₅</td>
<td>16.0</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>33.0</td>
</tr>
<tr>
<td>CH₃C₆H₅</td>
<td>11.0</td>
</tr>
<tr>
<td>n-C₆H₇</td>
<td>45.0</td>
</tr>
<tr>
<td>n-C₆H₁₃</td>
<td>50.0</td>
</tr>
<tr>
<td>Iso-C₆H₅</td>
<td>20.0</td>
</tr>
<tr>
<td>NO₂</td>
<td>12.0</td>
</tr>
<tr>
<td>3-Indolylmethyl</td>
<td>3.0</td>
</tr>
<tr>
<td>3-Indolyl</td>
<td>30.0</td>
</tr>
<tr>
<td>CH₃CO₂C₂H₅</td>
<td>6.2</td>
</tr>
<tr>
<td>CH(OCH₃)CO₂C₂H₅</td>
<td>17.0</td>
</tr>
<tr>
<td>CH(OCH₃)CO₂H</td>
<td>2.8</td>
</tr>
<tr>
<td>CH₂COC₆H₅</td>
<td>0.76</td>
</tr>
<tr>
<td>CH₂CO-</td>
<td></td>
</tr>
<tr>
<td>OCH₃</td>
<td>0.15</td>
</tr>
<tr>
<td>CH₂CO-</td>
<td></td>
</tr>
<tr>
<td>OCH₃</td>
<td>0.03</td>
</tr>
<tr>
<td>CH₂CO-</td>
<td></td>
</tr>
<tr>
<td>Compound of formula (II)</td>
<td>Concentration in μM required to give 50% inhibition of DHPB</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td>CH₂COOCH₃OCH₃OCH₃</td>
<td>0.14</td>
</tr>
<tr>
<td>CH₂OCH₃OCH₃</td>
<td>0.77</td>
</tr>
<tr>
<td>CH₂COOCH₃OCH₃OCH₃</td>
<td>0.06</td>
</tr>
<tr>
<td>CH₂COOCH₃OCH₃OCH₃</td>
<td>2.7</td>
</tr>
<tr>
<td>CH₂COOCH₃OH</td>
<td>0.22</td>
</tr>
<tr>
<td>CH₂COOCH₃OCH₃OCH₃</td>
<td>0.86</td>
</tr>
<tr>
<td>CH(CH)₂OCH₃OCH₃OCH₃</td>
<td>11.0</td>
</tr>
</tbody>
</table>
Claims

1. A compound of the formula (II):

![Chemical Structure](image)

or a tautomer, or salt thereof, wherein R¹ is a lower (C₁₋₆) alkyl group, a hydroxymethyl group, a phenyl group, a benzyl group optionally substituted in the phenyl ring with one or more nitro or lower (C₁₋₆) alkoxy groups, a phenacetyl group optionally substituted in the phenyl ring with one or more hydroxy or lower (C₁₋₆) alkoxy groups, a lower (C₁₋₆) acyloxymethyl group, an indolyl or indolyl methyl group, a group CH(CN)CH₂C₆H₅ optionally substituted in the phenyl ring with one or more lower (C₁₋₆) alkoxy groups, a group CH(Y)CO₂Z or a group CH₂CH₂CO₂Z in which Y is a hydrogen atom or a lower (C₁₋₆) alkyl or alkoxy group and Z is a hydrogen atom or a lower (C₁₋₆) alkyl group.

2. A compound according to claim 1 wherein R¹ is a methyl group, a phenyl group, a benzyl group optionally substituted in the phenyl ring with a nitro or 2 or 3 methoxy groups, a hydroxymethyl group, a phenacetyl group optionally substituted in the phenyl ring with a hydroxy group or 2 or 3 methoxy groups, a group CH₂CH₂CO₂H, an acetyloxymethyl group, an indolylmethyl group, a group CH(CN)CH₂C₆H₅ substituted in the phenyl ring with 3 methoxy groups, or a group CH(Y)CO₂Z in which Y is a methyl group, methoxy group or a hydrogen atom and Z is a hydrogen atom or a C₁₋₄ alkyl group.

3. A compound according to either claim 1 or 2 wherein R¹ is a benzyl group or a phenacetyl group optionally substituted in the phenyl ring with a hydroxy or 2 or 3 methoxy groups.

4. Pharmaceutical composition which comprises a compound of the formula (II), as defined in any one of claims 1 to 3, in conjunction with a pharmaceutically acceptable carrier.

5. A method of making a pharmaceutical composition, as defined in claim 4, which comprises admixing the compound of formula (II) with a carrier.

6. A pharmaceutical composition according to claim 4 in unit dose form.

7. A process for the preparation of a compound of the formula (II) except that wherein R¹ is a carboxy group, or a tautomer or salt thereof, as defined in claim 1, which comprises the cyclisation of a compound of the formula (III):

![Chemical Structure](image)

or a tautomer or salt thereof, wherein R² is a lower alkyl group, and R³ is a lower (C₁₋₆) alkyl group, a lower (C₁₋₆) acyloxymethyl group, a phenyl group, a benzyl group optionally substituted in the phenyl ring with one or more nitro or lower (C₁₋₆) alkoxy groups, a phenacetyl group optionally substituted in the phenyl ring with one or more hydroxy or lower (C₁₋₆) alkoxy groups, an indolyl or indolyl methyl group, a group CH(CN)CH₂C₆H₅ optionally substituted in the phenyl ring with one or more lower (C₁₋₆) alkoxy groups, a group CH(Y)CO₂Z or a group CH₂CH₂CO₂Z in which Y is a hydrogen atom or a lower (C₁₋₆) alkyl group and Z is a hydrogen or a lower (C₁₋₆) alkyl and thereafter optionally hydrolysing the lower (C₁₋₆) acyloxymethyl group to a hydroxymethyl group.

8. A process for the preparation of compounds of the formula (II) wherein R¹ is a group CH(Y)CO₂H or a group CH₂CH₂CO₂H wherein Y is as defined in Claim 1 which comprises the hydrolysis of the corresponding compound of the formula (II) wherein R¹ is a group CH(Y)CO₂Z or a group CH₂CH₂CO₂Z respectively, Y being as defined in Claim 1, and Z being a lower (C₁₋₆) alkyl group.

9. A process for the preparation of compounds of the formula (II) as defined in claim 1 except that R¹ is not a lower (C₁₋₆) acyloxymethyl group, which process comprises the hydrolysis of a compound of the formula (VI):
wherein R² is as defined in claim 7 or a group CO₂R⁴ wherein R⁴ is a lower (C₁₋₆) alkyl group.

10. A process for the preparation of a compound of the formula (VI) as defined in claim 9 which comprises the cyclisation of a compound of the formula (VII):

11. A compound of the formula (VI) as defined in claim 9.

12. A compound as defined in claim 1 for use in human therapy.

Patentansprüche

1. Verbindung der Formel (II)

2. Verbindung nach Anspruch 1, durch gekennzeichnet, daß R¹ eine Methylgruppe, eine Phenylgruppe, eine Benzylgruppe, die gegebenenfalls am Phenylring mit einer Hydroxylgruppe oder zwei oder drei Methoxygruppen substituiert ist, eine Hydroxymethylgruppe, eine Phenacylgruppe, die gegebenenfalls am Phenylring mit einer oder mehreren Hydroxylgruppen substituiert ist, eine niedrigmolekulare (C₁₋₆)-Alkylgruppe, eine Indolyl- oder Indolylmethyl-Gruppe, eine Gruppe der Formel CH(CN)CH₂C₆H₅, die am Phenylring mit drei Methoxygruppen substituiert ist, oder eine Gruppe der Formel CH₂CH₂CO₂H, oder eine Acetyloxymethylgruppe, eine Indolylmethylgruppe, eine Gruppe der Formel CH(CN)CH₂C₆H₅, die am Phenylring mit einer oder mehreren Hydroxylgruppen substituiert ist, eine niedrigmolekulare (C₁₋₆)-Alkylgruppe, eine Phenacylgruppe, die gegebenenfalls am Phenylring mit einer oder mehreren Hydroxylgruppen substituiert ist, eine Phenacetylgroup, oder eine Phenacylgruppe, die gegebenenfalls am Phenylring mit einer oder mehreren Hydroxylgruppen substituiert ist, bedeuten.

3. Verbindung nach den Ansprüchen 1 oder 2, durch gekennzeichnet, daß R¹ eine Benzylgruppe oder eine Phenacylgruppe, die gegebenenfalls am Phenylring mit einer oder mehreren Hydroxylgruppen substituiert ist, bedeuten.

4. Pharmazeutische Zubereitung enthaltend eine Verbindung der Formel (II), wie sie in den Ansprüchen 1 bis 3 definiert ist, neben einem pharmazeutisch annehmbaren Träger.

5. Verfahren zur Herstellung einer pharmazeutischen Zubereitung, wie sie in Anspruch 4 definiert ist, dadurch gekennzeichnet, daß man die Verbindung der Formel (II) mit einem Träger vermischt.
6. Pharmazeutische Zubereitung nach Anspruch 1 in Einheitsdosisform.

7. Verfahren zur Herstellung einer Verbindung der Formel (II), mit Ausnahme jener Verbindungen, worin R¹ eine Carboxygruppe bedeutet, oder eines Tautomeren oder eines Salzes davon, wie sie in Anspruch 1 definiert ist, dadurch gekennzeichnet, daß man eine Verbindung der Formel (III):

$$\text{or ein Tautomeres oder ein Salz davon, worin } R³ \text{ eine niedrigmolekulare Alkylgruppe und } R² \text{ eine niedrigmolekulare } (C_{1-6})\text{-Alkylgruppe, eine niedrigmolekulare } (C_{1-6})\text{-Acyloxymethylgruppe, eine Phenylgruppe, eine Benzygruppe, die gegebenenfalls am Phenylring mit einer oder mehreren Nitrogruppen oder niedrigmolekularen } (C_{1-6})\text{-Alkoxygruppen substituiert ist, eine Phenacylgruppe, die gegebenenfalls am Phenylring einer oder mehreren Hydroxygruppen oder niedrigmolekularen } (C_{1-6})\text{-Alkoxygruppen substituiert ist, eine Phenylgruppe, eine Benzylgruppe, die gegebenenfalls am Phenylring mit einer oder mehreren Hydroxygruppen oder niedrigmolekularen } (C_{1-6})\text{-Alkoxygruppen substituiert ist, eine Indolyl- oder Indolylmethylgruppe, eine Gruppe der Formel } \text{CH(CN)CH}_2\text{C}_6\text{H}_5, \text{die gegebenenfalls am Phenylring einer oder mehreren niedrigmolekularen } (C_{1-6})\text{-Alkoxygruppen substituiert ist, eine Gruppe der Formel } \text{CH(Y)CO}_2\text{Z} \text{ oder eine Gruppe der Formel } \text{CH}_2\text{CH}_2\text{CO}_2\text{Z}, \text{worin } Y \text{ ein Wasserstoffatom oder eine niedrigmolekulare } (C_{1-6})\text{-Alkylgruppe und } Z \text{ ein Wasserstoffatom oder eine } (C_{1-6})\text{-Alkylgruppe darstellen, bedeuten, cyclisiert und anschließend gegebenenfalls die niedrigmolekulare } (C_{1-6})\text{-Acyloxymethylgruppe zu einer Hydroxymethylgruppe hydrolysiert.}

8. Verfahren zur Herstellung der Verbindungen der Formel (II), in der R¹ eine Gruppe der Formel CH(Y)CO₂H oder eine Gruppe der Formel CH₂CH₃CO₂H, worin Y die in Anspruch 1 angegebenen Bedeutungen besitzt, bedeutet, dadurch gekennzeichnet, daß man die entsprechende Verbindung der Formel (II), worin R¹ eine Gruppe der Formel CH(Y)CO₂Z bzw. eine Gruppe der Formel CH₂CH₃CO₂Z, worin Y die in Anspruch 2 angegebenen Bedeutungen besitzt und Z für eine niedrigmolekulare (C₁₋₆)-Alkygruppe steht, hydrolysiert.

9. Verfahren zur Herstellung der Verbindungen der Formel (II), wie sie in Anspruch 1 definiert sind, ausgenommen der Verbindungen, worin R¹ eine niedrigmolekulare (C₁₋₆)-Acyloxymethylgruppe darstellt, dadurch gekennzeichnet, daß man eine Verbindung der Formel (VI):

$$\text{worin } R² \text{ die in Anspruch 7 angegebenen Bedeutungen besitzt oder eine Gruppe der Formel CO₂R⁴, worin } R⁴ \text{ eine niedrigmolekulare } (C_{1-6})\text{-Alkylgruppe darstellt, bedeutet, hydrolysiert.}

10. Verfahren zur Herstellung eine Verbindung der Formel (VI), wie sie in Anspruch 9 definiert ist, dadurch gekennzeichnet, daß man eine Verbindung der Formel (VII):

$$\text{worin } R² \text{ und } R³ \text{ die in Anspruch 7 angegebenen Bedeutungen besitzen, cyclisiert.}

11. Verbindung der Formel (VI), wie sie in Anspruch 9 definiert ist.

12. Verbindung nach Anspruch 1 für die Verwendung in der Humantherapie.
Reprises

1. Les composés de formule générale II

\[ \text{(II)} \]

ainsi que leurs tautomères et leurs sels, formule dans laquelle \( R^1 \) représente un groupe alkyle inférieur, hydroxyméthyle, phényle ou carboxy, un groupe benzyle éventuellement substitué sur le cycle phénylique par un ou plusieurs groupes nitro ou alcoxy inférieurs, un groupe phénacyle éventuellement substitué sur le cycle phénylique par un ou plusieurs groupes hydroxy ou alcoxy inférieurs, un alcoxyphényle inférieur, un groupe indolylique ou indolylméthyle, un groupe CH(CN)CH₂CH₅

2. Composé selon la revendication 1 dans laquelle \( R^1 \) est un méthyle ou un phényle, un benzyle éventuellement substitué sur le cycle phénylique par un groupe nitro ou deux ou trois groupes méthoxy, un hydroxyméthyle, un phénacyle éventuellement substitué dans le cycle phénylique par un hydroxyle ou deux ou trois groupes méthoxy, un groupe CH₂CH₂CO₂H, un groupe acétyloxyméthyle, un groupe indolylméthyle ou un groupe CH(CN)CH₂CH₅ substitué sur le cycle phénylique par trois méthoxy, ou encore un groupe CH(Y)CO₂Z dans lequel \( Y \) est un méthyle, un méthoxy ou un atome d'hydrogène et \( Z \) un atome d'hydrogène ou un atome d'acétylène.

3. Composé selon la revendication 1 ou 2 dans lequel \( R^1 \) est un groupe benzyle ou un groupe phénacyle éventuellement substitué sur le cycle phénylique par un hydroxyle ou deux ou trois groupes méthoxy.

4. Composition pharmaceutique comprenant un composé de formule II selon l'une quelconque des revendications 1 à 3, associé à un véhicule pour usages pharmaceutiques.

5. Procédé de préparation d'une composition pharmaceutique selon la revendication 4, consistant à mélanger le composé de formule II avec le véhicule.

6. Composition pharmaceutique selon la revendication 4, sous forme de doses unitaires.

7. Procédé de préparation des composés de formule II selon la revendication 1 (à l'exception de ceux dans lesquels \( R^1 \) est un groupe carboxy), ainsi que de leurs tautomères et sels, procédé selon lequel on cyclise un composé de formule III

\[ \text{(III)} \]

ou un tautomère ou un sel de celui-ci (formule dans laquelle \( R^3 \) est un alkyle inférieur et \( R^2 \) un alkyle en C₁₋₆, un acétoxyphényle en C₁₋₆, un phényle, un benzyle éventuellement substitué sur le cycle phénylique par un ou plusieurs groupes nitro ou alcoxy en C₁₋₆, un phénacyle éventuellement substitué sur le cycle phénylique par un ou plusieurs groupes hydroxy ou alcoxy en C₁₋₆, un groupe indolylique ou indolylméthyle, un groupe CH(CN)CH₂CH₅ éventuellement substitué sur le cycle phénylique par un ou plusieurs alcoxy [en C₁₋₆], ou encore un groupe CH(Y)CO₂Z ou CH₂CH₂CO₂Z, Y étant un atome d'hydrogène ou bien un alkyle ou un alcoxy inférieur et Z un atome d'hydrogène ou un alkyle inférieur [en C₁₋₆]), puis le cas échéant on hydrolyse le groupe acétyloxyméthyle inférieur [en C₁₋₆] en un groupe hydroxyméthyle.

8. Procédé de préparation des composés de formule II dans lesquels \( R^1 \) est un groupe CH(Y)CO₂H ou CH₂CH₂CO₂H, Y ayant la signification donnée à la revendication 1, procédé selon lequel on hydrolyse le composé correspondant de formule II dans lesquels \( R^1 \) est un groupe CH(Y)CO₂Z ou CH₂CH₂CO₂Z respectivement, Y ayant la signification donnée à la revendication 2 et Z étant un alkyle inférieur en C₁₋₆.
9. Procédé de préparation des composés de formule II selon la revendication 1 (à l'exception de ceux dans lesquels R¹ n'est pas un groupe acyloxyméthyle inférieur en C₁₋₆), procédé selon lequel on hydrolyse un composé de formule VI

\[
\begin{align*}
\text{(VI)}
\end{align*}
\]

10. Procédé de préparation d'un composé de formule VI selon la revendication 9, suivant lequel on cyclise un composé de formule VII

\[
\begin{align*}
\text{(VII)}
\end{align*}
\]

R² et R³ ayant les significations données à la revendication 7.

11. Les composés de formule VI selon la revendication IX.

12. L'utilisation en thérapeutique humaine des composés selon la revendication 1.