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(54) PHARMACEUTICALLY ACTIVE TRICYCLIC AMINES

PHARMACEUTISCHE WIRKSAME TRIZYKLISCHE AMINE
AMINES TRICYCLIQUES PHARMACEUTIQUEMENT ACTIVES

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WO-A-96/26941

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Description

Field of the Invention

[0001] This invention relates to pharmaceutically active tricyclic amines.

Background of the Invention

[0004] WO-A-91/04254 discloses pyrrolo[2,3-d]pyrimidines having no or simple groups substituted on the pyrroline ring. In two positions, the groups are H, halogen or alkyl. In the third, it is H, alkyl or aralkyl.

Summary of the Invention

[0006] Novel compounds according to the present invention, a selection from WO-A-96/26941, are pyrimido[4,5-b]indoles of formula (IV)

![Chemical Structure](IV)

where \( n_i \) is 1 to 3; and where \( NR_3,1R_3,2 \) is

1. 1-pyrrolidinyl,
2. 1-piperidinyl,
3. 4-morpholiny,
4. 2-hydroxy-1-pyrrolidinyl,
5. 3-hydroxy-1-pyrrolidinyl, or
6. 1-prolinyl;

and pharmaceutically acceptable salts thereof.

[0007] Further novel compounds according to the invention are the pyrrolidine amide, morpholine amide, 2-amimemethylpyridine amide, proline amide, 3-hydroxypyrrolidine amide or 2-hydroxypyrrolidine amide of(2,4-di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetic acid.
Description of the Invention

[0008] The compounds of the present invention can be prepared by the processes described in WO-A-93/20078 and WO-A-96/26941, and by the processes of Charts A-C, below. In Charts A-C, NR1-1 R1-2 and NR2-1 R2-2 are each 1-pyrrolidinyl.

[0009] There are two preferred methods to produce the pyrimido[4,5-b]indoles (IV) of the present invention. The first method uses the chemistry set forth in CHARTS A and B. The second method uses the chemistry set forth in CHARTS A and C. Both processes use the two steps set forth in CHART A.

[0010] In CHART A, the starting alcohols (I) are known to those skilled in the art or can be readily prepared from known compounds by methods known to those skilled in the art. See for example, J. Med. Chem., 38, 4161-3 (1995). The alcohol (I) is converted to a leaving group derivative (II) by methods well known to those skilled in the art. Suitable leaving groups, -X1, include mesylate, tosylate and para-SO2-NO2. It is preferred that X1 is mesylate. The alcohol with a leaving group (II) is then converted to the corresponding secondary amine (III) by treatment with sodium cyanide and a trace of a hindered non-nucleophilic tertiary amine (in solvents such as DMF, DMSO or acetonitrile). The secondary amine (III) is the branching point for the two processes. In the first process, CHART B, the secondary amine (III) is alkylated with a molecular fragment which contains the alkyl side chain and the amide, -(CH2)n1-CO-N(R3-1) (R3-2) where n1 is one thru three thereby directly producing the desired pyrimido[4,5-b]indole (IV). It is preferred that n1 is one. The pyrimido[4,5-b]indole (IV) is an amine base and as such forms pyrimido[4,5-b]indole salts (V) in the usual manner, see EXAMPLES 2-6.

[0011] Alternatively, when n1 is 1, the secondary amine (III) is alkylated with t-butyl bromoacetate to form the butyl is 1 ester (VI). The butyl ester (VI) is then hydrolyzed by known means to the corresponding acid (VII). The acid (VII) is then converted by known means to the corresponding pyrimido[4,5-b]indole amides (IV) and/or pyrimido[4,5-b]indole salt (V).

[0012] It is preferred that the pyrimido[4,5-b]indoles (IV) be in the form of a pharmaceutically acceptable salt, pyrimido [4,5-b]indole salt (V), and it is preferred that the salt be selected from the group consisting of hydrochloride, hydrobromide, maleate and methanesulfonate.

[0013] The pyrimido[4,6-b]indoles (IV) are useful in treating/preventing asthma (and reduction of mucous formation/secretion in the lung); dermatitis, of the atopic, inflammatory, allergic or contact form (and the reduction of itching, weeping oozing and thickening of the skin, which accompanies the dermatitis condition); rhinitis, of the atopic, inflammatory or seasonal allergic form (and the reduction of itching, weeping, oozing and mucus secretion of the nasal mucosa, which accompanies the rhinitis condition); conjunctivitis, blepharitis, iritis or combinations thereof, of the atopic, allergic, seasonal or inflammatory form (and the reduction of itching, weeping, oozing and mucus secretion of the eye or its parts, which accompanies the conjunctivitis, blepharitis, iritis or combinations thereof condition).

[0014] The pyrimido[4,5-b]indoles (IV) are useful in treating/preventing asthma (and reduction of mucous formation/secretion in the lung). In treating excess mucous secretion and asthma, the pyrimido[4,5-b]indoles (IV) are administered orally, IV and by inhalation in the standard dose. In treating excess mucous secretions the oral dose of the pyrimido [4,5-b]indoles (IV) used is from about 0.05 to about 20 mg/kg/day. The frequency of administration is one thru 4 times daily. The oral administration of the pyrimido[4,5-b]indoles (IV) to treat excess mucous secretions may go on for months or even years. The susceptible individuals can be pre-treated a few hours before an expected problem. The IV dose is about 0.05 to about 20 mg/kg/day. The aerosol formulation contains about 0.01 to about 1.0% of the tricyclic amides (IV) and is administered or used about four times daily as needed.

[0015] The pyrimido[4,5-b]indoles (IV) are also useful in treating/preventing dermatitis, of the atopic, inflammatory, allergic or contact form (and the reduction of itching, weeping oozing and thickening of the skin, which accompanies the dermatitis condition). In treating dermatitis and the associated signs and symptoms, pyrimido[4,5-b]indoles (IV) are administered orally, IV in the standard dose, and in a topical application of varying topical formulations (solution, suspension, cream, ointment, lotion, powder, gel or other recognized admixture) of pyrimido[4,5-b]indoles (IV) used is from about 0.01% to about 20% concentration of pyrimido[4,5-b]indoles (IV) to the base materials. The frequency of administration is one thru 4 times daily. The signs and/or symptoms of dermatitis may go on for months or even years. The susceptible individuals can be pre-treated a few hours before an expected problem. The IV dose is about 0.05 to about 20 mg/kg/day.

[0016] The pyrimido[4,5-b]indoles (IV) are useful in treating/preventing rhinitis, of the atopic, inflammatory or seasonal allergic form (and the reduction of itching, weeping, oozing and mucus secretion of the nasal mucosa, which accompanies the rhinitis condition). In treating rhinitis and the associated signs and symptoms, pyrimido[4,5-b]indoles (IV) are administered orally, IV and in the standard dose, and in a topical application of varying topical formulations (solution, suspension, cream, ointment, lotion, powder, gel or other recognized admixture) of pyrimido[4,5-b]indoles (IV) used is from about 0.01% to about 20% concentration of pyrimido[4,5-b]indoles (IV) to the base materials. The frequency of administration is one thru 4 times daily. The oral and topical administration of the pyrimido[4,5-b]indoles (IV) to treat the signs and/or symptoms of rhinitis may go on for months or even years. The susceptible individuals can
be pre-treated a few hours before an expected problem. The IV dose is about 0.05 to about 20 mg/kg/day.

[0017] The pyrimido[4,5-b]indoles (IV) are useful in treating/preventing conjunctivitis, blepharitis, iritis or combinations thereof, of the atopic, allergic, seasonal or inflammatory form (and the reduction of itching, weeping, oozing and mucus secretion of the eye or its parts, which accompanies the conjunctivitis, blepharitis, iritis or combinations thereof condition). In treating conjunctivitis, blepharitis, iritis or combinations thereof and the associated signs and symptoms, pyrimido[4,5-b]indoles (IV) are administered orally, and IV in the standard dose, and in a topical application of varying topical formulations (solution, suspension, cream, ointment, lotion, powder, gels or other recognized admixture) of pyrimido[4,5-b]indoles (IV) used is from about 0.001% to about 20% concentration of pyrimido[4,5-b]indoles (IV) to the base materials. The frequency of administration is one thru 4 times daily. The oral and topical administration of the pyrimido[4,5-b]indoles (IV) to treat the signs and/or symptoms of conjunctivitis, blepharitis, iritis or combinations thereof may go on for months or even years. The susceptible individuals can be pre-treated a few hours before an expected problem. The IV dose is about 0.05 to about 20 mg/kg/day.

[0018] The term treatment or treating as used in this patent is used broadly and includes both treatment of an existing condition as well as preventing the same condition from occurring where such is possible as is well known to those skilled in the art. For example, the pyrimido[4,5-b]indoles (IV) can be used to treat existing asthma conditions and to prevent future ones from occurring; existing dermatitis conditions and to prevent future ones from occurring; existing rhinitis conditions and to prevent future ones from occurring; existing conjunctivitis, blepharitis, iritis or combinations thereof conditions and to prevent future ones from occurring.

[0019] The exact dosage and frequency of administration depends on the particular pyrimido[4,5-b]indoles (IV) used, the particular type of condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, other medication the individual may be taking as is well known to those skilled in the art and can be more accurately determined by measuring the blood level or concentration of the tricyclic amides (IV) in the patient's blood and/or the patient's response to the particular condition being treated.

DEFINITIONS

[0020] The definitions below are for the terms as used throughout this entire document including both the specification and the claims.

[0021] All temperatures are in degrees Centigrade.

[0022] THP refers to tetrahydrofuran.

[0023] DMSO refers to dimethylsulfoxide.

[0024] IR refers to infrared spectroscopy.

[0025] NMR refers to nuclear (proton) magnetic resonance spectroscopy, chemical shifts are reported in ppm (δ) downfield from tetramethylsilane.

[0026] MS refers to mass spectrometry expressed as m/z or mass/charge unit. [M + H]+ refers to the positive ion of a parent plus a hydrogen atom. EI refers to electron impact. CI refers to chemical ionization. FAB refers to fast atom bombardment.

[0027] Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

[0028] Pharmaceutically acceptable salts include the salts of the following acids: hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, citric, methanesulfonic, \( \text{CH}_3\cdot(CH_2)_n\cdot\text{COOH} \) where \( n \) is 0 thru 4, \( \text{HOOC}\cdot(\text{CH}_2)_n\cdot\text{COOH} \) where \( n \) is as defined above, \( \text{HOOC}\cdot\text{CH}=\text{CH}\cdot\text{COOH} \), and \( \text{C}_6\text{H}_5\cdot\text{COOH} \).

[0029] When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

[0030] When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

EXAMPLES

[0031] Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

EXAMPLE 1 9-[2-(Methanesulfonyloxy)ethyl]-2,4-di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indole (II)

EXAMPLE 2 1-[2,4-Di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl]acetylpyrrolidine monohydrochloride also known as (2,4-di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetic acid, pyrrolidine amide, monohydrochloride (IV/V)

[0033] A stirred mixture of 9-[(2,4-di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetyl]pyrrolidine monohydrochloride also known as (2,4-di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetic acid, pyrrolidine amide, monohydrochloride (IV/V) is heated at 100°C for 18 hr. It is important that the starting mesylate contain traces of triethylamine either left over from its preparation, or added intentionally. The mixture is cooled to 20-25°C, diluted with water (approximately 6,000 mL) and filtered. The solid is washed with water to remove excess cyanide, then triturated with acetone. Filtration and drying gives 2,4-di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indole (III), mp 209-211°C; NMR (CDCl3) 7.88, 7.22, 7.09, 3.95, 3.67 and 1.98 δ; MS (m/z, FAB, M+H) 308.

[0034] A mixture of 2,4-di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indole (III, 93.1 g) in THF (2150 mL) is cooled to -40°C and treated over 30 min with n-butyllithium/hexane (1.6 M, 246 mL). After 30 min longer at -40°C, a mixture of bromoacetylpyrrolidine [J. Med. Chem., 30, 20-24 (1987), 93.1 g] in THF (750 mL) is added over 15 min. The reaction mixture is allowed to warm to 20-25°C 2 hr and is then re-cooled to -40°C and filtered. The solids are partitioned between methylene chloride and water and the organic layer is dried and concentrated to give the free base of the title compound (IV), mp = 201-204°C; NMR (CDCl3) 7.87, 7.38, 7.21-7.08, 5.05, 3.92, 3.62, 3.48, 3.33, 1.96 and 1.85 δ.

[0035] Treatment of a mixture the above free base (IV, 94.5 g) in methanol with one equivalent of methanolic hydrochloric acid gives the title compound (V), mp = 250-255°C; MS (m/z, M+ observed) = 418.2476, calculated for C24H30N6O = 418.2481. (The salt component, hydrochloride in this case, does not show up in the MS which is normal).

EXAMPLE 3 (2,4-Di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetic acid, pyrrolidine amide, sulfate (V)

[0036] Following the general procedure of the last paragraph of EXAMPLE 2 and making non-critical variations but starting with (2,4-di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetic acid, pyrrolidine amide (IV, EXAMPLE 2) and using sulfuric acid, the title compound is obtained, mp = 175-180°C.

EXAMPLE 4 (2,4-Di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetic acid, pyrrolidine amide, methanesulfonate salt (V)

[0037] Following the general procedure of the last paragraph of EXAMPLE 2 and making non-critical variations but starting with (2,4-di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetic acid, pyrrolidine amide (IV, EXAMPLE 2) and using methanesulfonic acid, the title compound is obtained, mp = 199-200°C.

EXAMPLE 5 (2,4-Di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetic acid, pyrrolidine amide, maleate salt (V)

[0038] Following the general procedure of the last paragraph of EXAMPLE 2 and making non-critical variations but starting with (2,4-di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetic acid, pyrrolidine amide (IV, EXAMPLE 2) and using maleic acid, the title compound is obtained, mp = 150-151°C.

EXAMPLE 6 (2,4-Di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetic acid, pyrrolidine amide, phosphate salt (V)

[0039] Following the general procedure of the last paragraph of EXAMPLE 2 and making non-critical variations but starting with (2,4-di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetic acid, pyrrolidine amide (IV, EXAMPLE 2) and using phosphoric acid, the title compound is obtained, mp = 200-201°C.

EXAMPLE 7 (2,4-Di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetic acid, t-butyl ester (VI)

[0040] n-Butyllithium (4.26 mL; 1.6 M in hexane) is added to a mixture of 2,4-di-1-pyrrolidinyl-9H-pyrimido[4,5-b] indole (II, EXAMPLE 1 and WO/9626941-A1, 165 g), sodium cyanide (180 g), water (360 mL) and DMSO (3000 mL) are heated at 100°C for 18 hr. It is important that the starting mesylate contain traces of triethylamine either left over from its preparation, or added intentionally. The mixture is cooled to 20-25°C, diluted with water (approximately 6,000 mL) and filtered. The solid is washed with water to remove excess cyanide, then triturated with acetone. Filtration and drying gives 2,4-di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indole (III), mp 209-211°C; NMR (CDCl3) 7.88, 7.22, 7.09, 3.95, 3.67 and 1.98 δ; MS (m/z, FAB, M+H) 308.

EXAMPLE 8 (2,4-Di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetic acid, hydrochloride (VII)

[0041] A mixture of (2,4-Di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetic acid, t-butyl ester (VI, EXAMPLE 7, 2.5 g) in aqueous hydrochloric acid (1.0 M) is heated at reflux for 2 hr. The mixture is then cooled and concentrated to
approximately one third of the original volume. Filtration of the resulting solid gives the title compound, mp 250-253°; NMR (CDCl₃) 8.07, 7.35, 5.21, 4.10, 3.73 and 2.11 δ; IR (neat) 2925, 1736, 1627, 1608, 1568, 1445 and 1193 cm⁻¹.

EXAMPLE 9 (2,4-Di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetic acid, morpholine amide (IV) and monohydrochloride (V)

[0042] A mixture of (2,4-di-1-pyrrolidinyl-9H-pyrimido[4,6-b]indol-9-yl)acetic acid, hydrochloride (VII, EXAMPLE 8, 1.41 g) in methylene chloride (20 mL) and acetonitrile (20 mL) is treated with triethylamine (108 mL), cooled to -5°, then treated with isobutyl chloroformate (0.50 mL). The mixture is stirred for 20 min, then treated with morpholine (0.83 mL). The mixture is stirred for 2 hr, then partitioned between methylene chloride and aqueous sodium bicarbonate. The layers are separated and the organic layer is dried and concentrated, and the residue is purified by chromatography (silica gel; acetone/methylene chloride, 10/90), to give the free base of the title compound, mp 220-222°.

[0043] A mixture of the free base (IV) of the title compound (1.3 g) in methanol (50 mL) is treated with one equivalent of methanolic hydrochloric acid. Recrystallization of the resulting solid from methanol/ethyl acetate gives the title compound, mp = 238-240°; NMR (CH₃OD) 8.0, 7.42, 7.35, 7.27, 5.31, 3.98, 3.80, 3.69, 3.59 and 2.06 δ.

EXAMPLE 10 (2,4-Di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetic acid, 2-aminomethylpyridine amide (IV) and dihydrochloride (V)

[0044] Following the general procedure of EXAMPLE 9 and making non-critical variations but using 2-(aminomethyl) pyridine in place of morpholine and two equivalents of hydrochloric acid in the salt formation, the free base (IV) of the title compound is obtained which is converted to the title compound, mp = 162-165°; NMR (CH₃OD) 8.77, 8.58, 8.00, 7.47, 7.37, 7.30, 5.33, 4.81, 4.10, 3.74 and 2.12 δ.

EXAMPLE 11 (2,4-Di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetic acid, proline amide (IV) and hydrochloride (V)

[0045] Following the general procedure of EXAMPLE 9 and making non-critical variations but using proline in place of morpholine, the free base (IV) of the title compound is obtained which is converted to the title compound, mp = 118-120°; MS (m/z) calculated = 462.2379, observed = 462.2371.

EXAMPLE 12 (2,4-Di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetic acid, 3-hydroxypyrrolidine amide (IV) and salt (V)

[0046] Following the general procedure of EXAMPLE 9 and making non-critical variations but using 3-hydroxypyrrolidine in place of morpholine, the title compound is obtained, mp = 224-226°; MS (m/z) = 434.1 (M⁺) as well as the hydrochloride salt, mp = 145-150°.

EXAMPLE 13 (2,4-Di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetic acid, 2-hydroxypyrrolidine amide (IV)

[0047] Following the general procedure of EXAMPLE 9 and making non-critical variations but using 4-aminobutyraldehyde diethyl acetal in place of morpholine, the acetal intermediate is obtained, mp = 153-156°. The acetal is hydrolyzed following the general procedure of J. Org. Chem., 48, 3667 (1983). A mixture of the acetal intermediate (103 mg), sodium iodide (80 mg), and methyltrichlorosilane (0.05 mL) in acetonitrile (2 mL) is stirred at 20-25° for 30 min. The reaction mixture is then partitioned between aqueous sodium bicarbonate, sodium thiosulfate and methylene chloride, the layers separated and the organic layer is dried and concentrated. Chromatography of the residue (silica gel; acetone/methylene chloride, 10/90) gives the title compound (free base), mp = 185-190°; MS (m/e) = calculated = 434.2430; observed = 434.2421. NMR (CDCl₃) 7.87, 7.65, 7.26, 7.16, 5.47, 5.28, 4.88, 4.84, 4.79, 3.93, 3.66-3.61 and 1.99-1.91 δ.
CHART A

(I)

(II)

(III)
CHART B

(III)

(R)

(IV)

Salt of (IV)

(V)
CHART C

(III)

(VI)

(VII)

(IV)
Claims

1. Pyrimido[4,5-b]indoles of formula (IV)

where \( n_1 \) is 1 to 3; and
where \( NR_{3-1}R_{3-2} \) is

(1) 1-pyrrolidinyl,
(2) 1-piperidinyl
(3) 4-morpholinyl,
(4) 2-hydroxy-1-pyrrolidinyl,
(5) 3-hydroxy-1-pyrrolidinyl, or
(6) 1-prolinyl;

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, where \( n_1 \) is 1.

3. A compound according to claim 1 or claim 2, where \( NR_{3-1}R_{3-2} \) is 1-pyrrolidinyl.

4. A compound which is the pyrrolidine amide, morpholine amide, 2-aminomethylpyridine amide, proline amide, 3-hydroxyprrolidine amide or 2-hydroxyprrolidine amide of(2,4-di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)acetic acid.

5. A compound according to claim 4, which is the pyrrolidine amide.

6. A compound according to claim 3 or claim 5, in the form of the monohydrochloride, sulfate, methanesulfonate, maleate or phosphate salt.

Patentansprüche

1. Pyrimido[4,5-b]indole der Formel (IV)
worin \( n_1 \) 1 bis 3 ist, und
worin \( NR_{3-1}R_{3-2} \)

(1) 1-Pyrrolidinyl,
(2) 1-Piperidinyl,
(3) 4-Morpholinyl,
(4) 2-Hydroxy-1-pyrrolidinyl,
(5) 3-Hydroxy-1-pyrrolidinyl oder
(6) 1-Prolinyl ist;

und pharmazeutisch akzeptable Salze derselben.

2. Verbindung nach Anspruch 1, worin \( n_1 \) 1 ist.

3. Verbindung nach Anspruch 1 oder Anspruch 2, worin \( NR_{3-1}R_{3-2} \) 1-Pyrrolidinyl ist.

4. Verbindung, die das Pyrrolidinamid, Morpholinamid, 2-Aminomethylpyridinamid, Prolinamid, 3-Hydroxyppyrrolidinamid oder 2-Hydroxyppyrrolidinamid von (2,4-Di-1-pyrrolidinyl-9H-pyrimido[4,5-b]indol-9-yl)essigsäure ist.

5. Verbindung nach Anspruch 4, die das Pyrrolidinamid ist.

6. Verbindung nach Anspruch 3 oder Anspruch 5 in der Form des Monohydrochlorid-, Sulfat-, Methansulfonat-, Maleat- oder Phosphatsalzes.

Revendications

1. Pyrimido[4,5-b]indoles de formule (IV)
dans laquelle \( n_1 \) a une valeur de 1 à 3 ; et

dans laquelle \( NR_{3-1}R_{3-2} \) représente un groupe

(1) 1-pyrrolidinyle,
(2) 1-pipéridinyle,
(3) 4-morpholinyle,
(4) 2-hydroxy-1-pyrrolidinyle,
(5) 3-hydroxy-1-pyrrolidinyle, ou
(6) 1-prolinyle ;

et leurs sels pharmaceutiquement acceptables.

2. Composé suivant la revendication 1, dans lequel \( n_1 \) est égal à 1.

3. Composé suivant la revendication 1 ou la revendication 2, dans lequel \( NR_{3-1}R_{3-2} \) représente un groupe 1-pyrrolidinyle.


5. Composé suivant la revendication 4, qui est le pyrrolidine-amide.

6. Composé suivant la revendication 3 ou la revendication 5, sous forme de sel consistant en mono-chlorhydrate, sulfate, méthanesulfonate, maléate ou phosphate.