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(54) **Thienopyridine derivatives and pharmaceutical compositions containing them**

Thienopyridinderivate und diese enthaltende pharmazeutische Zubereitungen

Dérivés de la thiénopyridine et compositions pharmaceutiques les contenant

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(56) References cited:
EP-A- 0 059 698 **EP-A- 0 094 271**
EP-A- 0 452 873

- **JOURNAL OF CHEMICAL RESEARCH (S), no. 6, 1982, LONDON, GB; page 158; J. M. BARKER et al.: "Thienopyridines . Part 4. Preparation of some dithieno(3,2-b:2,3- d)pyridine derivatives."**
- **JOURNAL OF CHEMICAL RESEARCH (S), no. 7, 1985, LONDON, GB; pages 214 - 215; J. M. BARKER et al.: "Thienopyridines, part 6. Synthesis and nucleophilic substitution of some chlorothieno(2,3-b)pyridine derivatives, and comparisons with the analogous quinoline compounds"**
- **CHEMICAL SOCIETY REVIEWS, vol. 18, 1979, pages 563-580.**

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

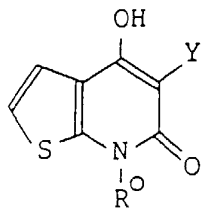
EP 0 505 058 B1

Description

This invention relates to thienopyridine derivatives which are useful as immunoregulators and for the prevention and treatment of osteoporosis and pharmaceutical preparations containing them.

EP-A-0 059 698 discloses carboxamide compounds that apparently enhance cell-mediated immunity. These compounds are cyclic and include a benzene ring.

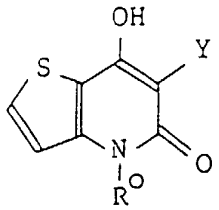
Thienopyridine derivatives represented by Formula (A), possess the 4-hydroxythieno[2,3-b]pyridin-6-one skeleton and are described in J. Chem. Res. (S), 214 (1985) and J. Chem. Res. (S),122 (1986):



(A)

wherein R^o represents hydrogen or methyl and Y represents hydrogen or ethoxycarbonyl.

Furthermore, thienopyridine derivatives represented by Formula (B), possess the 7-hydroxythieno[3,2-b]-pyridin-5-one skeleton, and are described in J. Chem. Res. (S), 6 (1980) and J. Chem. Res. (S), 84 (1984):

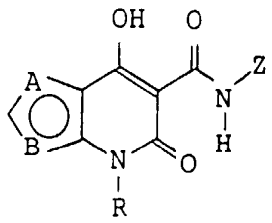


(B)

wherein R^o represents hydrogen or methyl and Y represents hydrogen, ethoxycarbonyl, nitrile, acetyl or the like.

In compounds (A) and (B), their pharmacological activities are unknown.

The present invention relates to thienopyridine derivatives [hereinafter referred to as Compound (I)] represented by formula (I):



(I)

wherein one of A and B represents -S-, and the other represents -CH=; R represents hydrogen or lower alkyl, and Z represents pyridyl; or a pharmaceutically acceptable salt thereof.

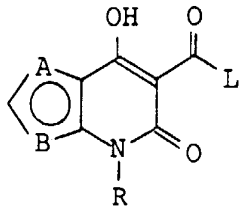
In the definition of each group in formula (I), the lower alkyl means a straight or branched alkyl having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, hexyl, etc.

The pharmaceutically acceptable salt of Compound (I) includes acid addition salts, metal salts, etc. The acid addition salt includes, for example, an inorganic acid salt such as hydrochloride, sulfate, phosphate, etc.; an organic acid salt such as acetate, maleate, fumarate, tartarate, citrate, etc. The metal salt includes for example, salts of alkali metal such as sodium, potassium, etc., salts of alkaline earth metal such as magnesium, calcium, etc.; aluminum salts, zinc salts and the like.

Next, a process for preparing Compound (I) is described.

In the process shown below, in cases where the defined group(s) change under the conditions or are inappropriate for the practice of the process, the process can be easily operated by applying thereto means conventionally used in organic synthetic chemistry, for example, protection of functional groups, removal of protective groups, etc.

Compound (I) may be obtained by reacting Compound (II) represented by formula (II):



(II)

wherein L represents a leaving group; and A, B and R have the same significance as described above, with Compound (III) represented by formula (III):

$$H_2N - Z \qquad \text{(III)}$$

wherein Z has the same significance as described above, preferably in the presence of a base.

Herein as the leaving group denoted by L, halogen such as chlorine, bromine, iodine, etc.; alkoxy such as methoxy, ethoxy, etc.; aryloxy such as phenoxy, etc.; alkanoyloxy such as propionyloxy, etc.; aroyloxy such as benzoyloxy, etc. are used.

As the base, alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate, etc.; alkali metal carbonates such as sodium carbonate, potassium carbonate, etc.; alkali metal hydrides such as sodium hydride, etc.; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, etc.; alkali metal salts such as butyl lithium, etc. are used.

As the solvent used in the reaction, any solvent may be usable, as long as it is inert to the reaction. For example, ethers such as tetrahydrofuran, dioxane, etc.; amides such as dimethylformamide, dimethylacetamide, etc.; ketones such as acetone, methyl ethyl ketone, etc.; alcohols such as methanol, ethanol, isopropyl alcohol, etc.; halogenated hydrocarbons such as methylene chloride, chloroform, dichloroethane, etc.; esters such as ethyl acetate, etc.; aromatic hydrocarbons such as benzene, toluene, xylene, etc.; dimethylsulfoxide and the like may be used singly or in combination.

The reaction is carried out at -30 to 200°C, preferably -10 to 100°C and generally completed in 30 minutes to 20 hours.

The starting compound (II) can be synthesized by known methods [J. Chem. Res. (S), 6 (1980); ibid., 84 (1984); ibid., 214 (1985); J. Chem. Res. (M), 113 (1980); ibid., 771 (1984); ibid., 2501 (1985)] or by a modified method of these methods.

The desired product in the process described above can be isolated and purified by means of purification conventionally used in organic synthetic chemistry, for example, by filtration, extraction, washing, drying, concentration, recrystallization, various chromatographies, etc.

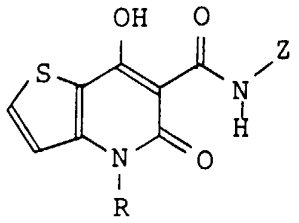
Where it is desired to obtain the salts of Compound (I), Compound (I) may be purified as it is in case that Compound (I) is obtained in the form of its salt. In case that Compound (I) is obtained in its free form, Compound (I) is dissolved or suspended in an appropriate solvent and an appropriate acid or base is added to the solution or suspension to form its salts.

Compound (I) and a pharmaceutically acceptable salt thereof may also be present in the form of addition products with water or various solvents. These addition products are also included in the present invention.

Furthermore Compound (I) includes all possible steric isomers and mixtures thereof.

Specific examples of Compound (I) obtained by the process described above are shown in Tables 1 and 2.

Table 1



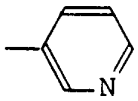
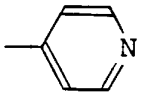
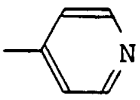
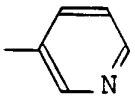
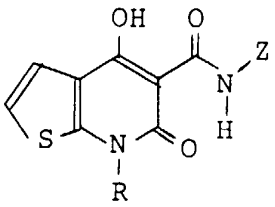
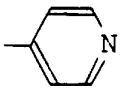
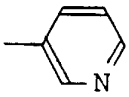
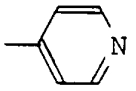
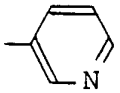
Compound No.	R	Z
1	H	
2	H	
3	$(CH_2)_3CH_3$	
4	$(CH_2)_3CH_3$	

Table 2



Compound No.	R	Z
5	$(CH_2)_3CH_3$	
6	$(CH_2)_3CH_3$	
7	H	
8	H	

Next, the immunoregulating activity, activity of inhibiting bone absorption and acute toxicity of Compound (I) are described by referring to test examples.

Test Example 1 Plaque Forming Cell Assay

The methods developed by Jerne [Science, 140, 405 (1963)] and Yamamoto, et al[Drugs. Exptl. Clin. Res., 8, 5 (1982)] were modified for plaque forming cell assay.

That is, Balb/c strain male mice (age of 7 weeks, Charles River Japan Inc.) were sensitized with 1 x 10^8 sheep red blood cells (Bio Test Research Institute) and the spleen was extirpated on the sixth or seventh day. The cells obtained from the spleen were treated with ACT solution (Tris-ammonium chloride isotonic buffer) to remove red blood cells. The cells were washed three times with RPMI1640 medium (Nissui Pharmaceutical Co.). The cells (1 x10^7) were incubated in RPMI-1640 medium containing 10% calf fetal serum (Gibco Co.), 50 μg/ml streptomycin, 50 IU/ml of penicillin, 2-mercaptoethanol (5 x 10^{-5} M), sheep red blood cells (5 x 10^6 cells) and a test compound dissolved in dimethyl sulfoxide supplied on a microculture plate (NUNC Co., 24 wells) in a carbon dioxide gas incubator (TABAI ESPEC CORP) at 37°C for 5 days.

After completion of the incubation, the cells were transferred to a plastic test tube and centrifuged at 2000 rpm. After the supernatant was removed, the cells were resuspended in 1 ml of RPMI-1640 medium. The cell suspension was sealed in a Cunnigham chamber (Takahashi Giken Co.) together with sheep red blood cells and guinea pig complement (Cedarlane Research Institute) according to the method of Cunnigham [Immunology, 14, 599 (1968)] and incubated at 37°C for 1 to 2 hours. Direct plaque forming cell (PFC) count was counted.

A rate of inhibiting antibody production by the test compound was determined by the following equation.

$$\text{Inhibition rate (\%)} = \frac{A - B}{A} \times 100$$

A : PFC count in the absence of test compound (dimethylsulfoxide alone)
B : PFC count in the presence of test compound

The results are shown in Table 3.

Table 3

Compound No.	Concentration (M)	Direct PFC Count (mean ± S.E.M.)	Inhibition Rate (%)
Control		5023 ± 38	
3	10^{-4}	101 ± 76	98.0
	10^{-5}	59 ± 38	98.8
4	10^{-4}	336 ± 124	93.3
	10^{-5}	395 ± 52	92.1
5	10^{-4}	109 ± 77	97.8
	10^{-5}	227 ± 131	95.5
6	10^{-4}	42 ± 29	99.2
	10^{-5}	59 ± 29	98.8

Autoimmune diseases such as chronic articular rheumatism or the like are considered to result from tissue injury due to accentuation of B cells as the result of hypofunction of T cells. It is thus expected that Compound (I) would be effective against autoimmune disease by inhibiting antibody production.

Test Example 2 Activity of inhibiting bone absorption

A calvaria of a 5 to 6 day-old dd mouse was aseptically cut off, washed with Dulbecco's modified phosphate buffered saline not containing calcium and magnesium (manufactured by Gibco Oriental Co.) and separated along the sutura of its center. One half of the calvaria so separated was cultured in 1.5 ml of Dulbecco's modified Eagle medium (manufactured by Gibco Oriental Co.) containing 15% of thermally inactivated (at 56°C for 20 minutes) horse serum and 2.5% of fetal calf serum. The test compound was dissolved in dimethyl sulfoxide, and 10 µl (final concentration: 1 x 10^{-4} M or 1 x 10^{-5} M) of the solution so prepared was added to the culture. Parathyroid hormone (human PTH 1-34, manufactured by Sigma Co.) was dissolved in 0.15 M sodium chloride solution (pH 3), and 3 µl (final concentration: 1 x 10^{-8} M) of the solution so prepared was added to the culture. The cultivation was carried out for 96 hours at 37°C in an atmosphere consisting of 95% of air and 5% of carbon dioxide. The culture medium was once replaced with a fresh one after 48 hours from the beginning of the cultivation. The concentration of dissolved calcium (i.e., absorption of bone) from the PTH-intensified bone was determined by measuring the quantity of calcium accumulated in the culture collected in 96 hours of cultivation, whereby the concentration of total calcium contained in the culture was measured with Calcium C-Test Wako (manufactured by Wako Pure Chemicals Co., Ltd.), and the inhibition rate was calculated therefrom in accordance with the equation set forth below. The results are shown in Table 4.

$$\text{Inhibition rate (\%)} = \frac{Cp - Cd}{Cp - Co} \times 100$$

Cd : Total calcium concentration in the culture treated with both test compound and PTH
Cp : Total calcium concentration in the culture treated with PTH alone
Co : Total calcium concentration in the culture treated with neither test compound nor PTH

Table 4

Compound No.	Concentration (µM)	Inhibition Rate (%)
1	100	-1
2	100	51
3	10	141
4	10	58
5	10	53
6	10	38

Table 4 (continued)

Compound No.	Concentration (μM)	Inhibition Rate (%)
7	10	32
8	10	18

Test Example 3 Acute toxicity test

A test compound was orally administered to three dd-strain male mice weighing 20 ± 1 g. The minimum lethal dose (MLD) was determined by observing the mortality for 7 days after the administration.

The results are shown in Table 5.

Table 5

Compound No.	MLD (mg/kg)
4	> 300
7	> 300

Compound (I) or a pharmaceutically acceptable salt thereof may be used as it is, or in various pharmaceutical forms. The pharmaceutical composition of the present invention can be prepared by uniformly mixing an effective amount of Compound (I) or a pharmaceutically acceptable salt thereof as the active ingredient with pharmaceutically acceptable carriers. The pharmaceutical compositions are desirably in a single dose unit suited for oral or parenteral administration.

In preparing the composition suited for oral administration, any pharmaceutically acceptable carrier may be used. Liquid preparations suited for oral administration, for example, a suspension and a syrup can be prepared using water; sugars such as sucrose, sorbitol, fructose, etc.; glycols such as polyethylene glycol, propylene glycol, etc.; oils such as sesame oil, olive oil, soybean oil, etc.; antiseptics such as p-hydroxybenzoic acid ester, etc.; flavors such as strawberry flavor, pepper mint, etc. Further a capsule, a tablet, a powder and a granule can be prepared using an excipient such as lactose, glucose, sucrose, mannitol, etc.; a disintegrator such as starch, sodium alginate, etc.; a lubricant such as magnesium stearate, talc, etc.; a binder such as polyvinyl alcohol, hydroxypropyl cellulose, gelatin, etc.; a surfactant such as a fatty acid ester, etc.; a plasticizer such as glycerine, etc. A tablet and a capsule are most useful single dose unit for oral administration because their administration is easy.

Effective dose and number of administration of Compound (I) or a pharmaceutically acceptable salt thereof may vary depending upon modes of administration, age and body weight, conditions, etc. of a patient but it is generally preferred to administer Compound (I) in a dose of 1 to 1,000 mg/60 kg by dividing into one to four times.

The present invention is described by referring to Examples and Reference Examples below.

Example 1

4,5-Dihydro-7-hydroxy-5-oxo-N-(3-pyridyl)thieno[3,2-b]pyridine-6-carboxamide (Compound 1)

A mixture of 2.43 g (10.2 mmols) of ethyl 4,5-dihydro-7-hydroxy-5-oxothieno[3,2-b]pyridine-6-carboxylate [J. Chem. Res. (S), 6 (1980); J. Chem. Res. (M), 113 (1980)], 1.00 g (10.6 mmols) of 3-aminopyridine, 50 ml of xylene and 10 ml of dimethylformamide was heated at 140°C for an hour. After completion of the reaction, insoluble matters were filtered and recrystallized from dimethylformamide to give 1.56 g (yield: 54%) of Compound 1.

Elemental analysis: $C_{13}H_9N_3O_3S$			
Calcd. (%) :	C 54.35,	H 3.16,	N 14.63
Found (%) :	C 54.11,	H 2.85,	N 14.48

IR (KBr) cm^{-1}: 3450(br), 1638, 1594, 1547, 1480, 1408, 1364, 1264, 1228, 799, 761

NMR (CF_3 CO_2 D) δ (ppm): 9.79(1H, s), 8.81(1H, d, J= 8.8Hz), 8.63(1H, d, J=5.1Hz), 8.15(1H, m), 8.10 (1H, d, J=5.4Hz), 7.28(1H, d, J=5.4Hz)

Example 2

4,5-Dihydro-7-hydroxy-5-oxo-N-(4-pyridyl)thieno[3,2-b]pyridine-6-carboxamide (Compound 2)

A mixture of 2.48 g (10.4 mmols) of ethyl 4,5-dihydro-7-hydroxy-5-oxothieno[3,2-b]pyridine-6-carboxylate [J. Chem. Res. (S), 6 (1980); J. Chem. Res. (M), 113 (1980)], 1.01 g (10.7 mmols) of 4-aminopyridine, 50 ml of xylene and 10 ml of dimethylformamide was heated at 140°C for an hour. After completion of the reaction, insoluble matters were filtered and tritylated with dimethylformamide with heating to give 1.99 g (yield: 67%) of Compound 2.

Elemental analysis: $C_{13}H_9N_3O_3S$			
Calcd. (%):	C 54.35,	H 3.16,	N 14.63
Found (%):	C 54.31,	H 2.96,	N 14.45

IR (KBr) cm^{-1}: 3440(br), 1662, 1632, 1575, 1536, 1498, 1411, 1370, 1212, 1006, 826, 751

NMR (CF_3 CO_2 D) δ (ppm): 8.64(2H, d, J=7.0Hz), 8.46 (2H, d, J=7.0Hz), 8.11(1H, d, J=5.4Hz), 7.27(1H, d, J=5.4Hz)

Example 3

4-(n-butyl)-4,5-dihydro-7-hydroxy-5-oxo-N-(4-pyridyl)thieno[3,2-b]pyridine-6-carboxamide (Compound 3)

A solution of 1.18 g (4.00 mmols) of the Compound a obtained in Reference Example 1, 0.39 g (4.13 mmols) of 4-aminopyridine and 20 ml of toluene was heated to reflux for 2 hours. After cooling, the reaction mixture was poured into 1 N sodium hydroxide aqueous solution, and washed twice with chloroform. 2 N Hydrochloric acid aqueous solution was added to the aqueous layer and the precipitated white crystals were filtered and dried to give 0.73 g (yield: 53%) of Compound 3.

Melting point: 211.9 -216.5°C

MS (EI) m/e: 343 (M^+)

IR (KBr) cm^{-1}: 3420(br), 1661, 1617, 1591, 1546, 1509, 1393, 1196, 796, 758

NMR (DMSO-d_6) δ (ppm): 13.59(1H, s), 8.79(2H, d, J= 6.6Hz), 8.38(1H, d, J=5.1Hz), 8.21(2H, d, J= 6.6Hz), 7.57 (1H, d, J=5.1Hz), 4.24(2H, t, J= 7.6Hz), 1.66(2H, m), 1.40(2H, m), 0.93(3H, t, J= 7.1Hz)

Example 4

4-(n-butyl)-4,5-dihydro-7-hydroxy-5-oxo-N-(3-pyridyl)thieno[3,2-b]pyridine-6-carboxamide (Compound 4)

Compound 4 was obtained (yield: 72%) in a manner similar to Example 3 except for using 3-aminopyridine in place of 4-aminopyridine.

Melting point: 179.7 -182.6°C

MS (EI) m/e: 343 (M^+)

IR (KBr) cm^{-1}: 3388, 1627, 1540, 1390, 798, 770, 668

NMR (DMSO-d_6) δ (ppm): 13.03(1H, s), 9.20(,1H, d, J= 2.2Hz), 8.62(1H, d, J=4.4Hz), 8.57(1H, dd, J= 2.2Hz, 8.5Hz), 8.34(1H, d, J=5.4Hz), 7.90(,1H, dd, J=4.4Hz, 8.5Hz), 7.55(1H, d, J=5.4Hz), 4.24 (2H, t, J=7.5Hz), 1.65(2H, m), 1.40(2H, m), 0.93(3H, t, J=7.3Hz)

Example 5

7-(n-butyl)-6,7-dihydro-4-hydroxy-6-oxo-N-(4-pyridyl)thieno[2,3-b]pyridine-5-carboxamide (Compound 5)

Compound 5 was obtained (yield: 78%) in a manner similar to Example 3 except for using Compound b obtained in Reference Example 2 in place of Compound a.

Melting point: 131.6 -139.4°C

MS (EI) m/e: 343 (M^+)

IR (KBr) cm^{-1} : 2952, 1614, 1507, 1380, 1289, 1229, 1197, 834, 663

NMR (DMSO-d_6) δ(ppm): 13.34(1H, s), 8.78(2H, d, J= 6.4Hz), 8.20(2H, d, J=6.4Hz), 7.48(1H, d, J= 5.6Hz), 7.39 (1H, d, J=5.6Hz), 4.13(2H, t, J= 7.4Hz), 1.75(2H, m), 1.41(2H, m), 0.95(3H, t, J=7.3Hz)

Example 6

7-(n-butyl)-6,7-dihydro-4-hydroxy-6-oxo-N-(3-pyridyl)thieno[2,3-b]pyridine-5-carboxamide (Compound 6)

Compound 6 was obtained (yield: 76%) in a manner similar to Example 3 except for using Compound b obtained in Reference Example 2 in place of Compound a and using 3-aminopyridine in place of 4-aminoyyridine.

Melting point: 158.0 -158.4°C
MS (EI) m/e: 343 (M^+)
IR (KBr) cm^{-1}: 1616, 1585, 1561, 1542, 1535, 1482, 752
NMR (DMSO-d_6) δ (ppm): 15.87(1H, s), 12.49(1H, s), 8.80(1H, d, J=2.1Hz), 8.37(1H, d, J=3.7Hz), 8.11 (1H, d, J=8.2Hz), 7.39-7.44(1H, m), 7.42(1H, d, J=5.5Hz), 7.35(1H, d, J=5.5Hz), 4.10(2H, t, J= 7.5Hz), 1.74(2H, m), 1.40(2H, m), 0.95(3H, t, J= 7.3Hz)

Example 7

6,7-Dihydro-4-hydroxy-6-oxo-N-(4-pyridyl)thieno[2,3-b]pyridine-5-carboxamide (Compound 7)

Compound 7 was obtained (yield: 58%) in a manner similar to Example 3 except for using ethyl 6,7-dihydro-4-hydroxy-6-oxothieno[2,3-b]pyridine-5-carboxylate [J. Chem. Res. (S), 214 (1985)] in place of Compound a.

Melting point: >300°C
MS (EI) m/e: 287 (M^+)
IR (KBr) cm^{-1}: 1660, 1633, 1573, 1544, 1487, 1426, 1356, 1009, 799, 560, 465
NMR (DMSO-d_6) δ (ppm): 15. 58 (1H, bs), 12. 80-12. 98 (2H, m), 8.51(2H, d, J=6.4Hz), 7.64(2H, d, J=6.4Hz), 7.29 (2H, s)

Example 8

6,7-Dihydro-4-hydroxy-6-oxo-N-(3-pyridyl)thieno[2,3-b]pyridine-5-carboxamide (Compound 8)

Compound 8 was obtained (yield: 75%) in a manner similar to Example 3 except for using ethyl 6,7-dihydro-4-hydroxy-6-oxothieno[2,3-b]pyridine-5-carboxylate [J. Chem. Res. (S), 214 (1985)] in place of Compound a, and using 3-aminopyridine in place of 4-aminopyridine.

Melting point: 294.8 8 - 295.9°C
MS (EI) m/e: 287 (M^+)
IR (KBr) cm^{-1}: 1648, 1601, 1562, 1482, 1427, 1356, 1263, 801, 554, 472
NMR (DMSO-d_6) δ (ppm): 15.85(1H, s), 12.97(1H, s), 12.61(1H, s), 8.80(1H, d, J=2.5Hz), 8.37(1H, dd, J=1.1Hz, 4.7Hz), 8.04-8.13(1H, m), 7.42(1H, dd, J=8.2Hz, 4.5Hz), 7.29(1H, d, J=4.5Hz), 7.29(1H, dd, J=9.9Hz, 5.4Hz)

Example 9 Tablet

A tablet having the following ingredients is prepared in a conventional manner.

Compound 1	50 mg
Lactose	60 mg
Potato starch	30 mg
Polyvinyl alcohol	2 mg
Magnesium stearate	1 mg
Tar pigment	trace

Example 10 Syrup

A syrup preparation having the following ingredients is prepared in a conventional manner.

Compound 2	50 mg
Refined sugar	30 mg
Ethyl p-hydroxybenzoate	40 mg
Propyl p-hydroxybenzoate	10 mg
Strawberry flavor	0.1 cc
Water is added until the total volume is 100 cc.	

Reference Example 1

Ethyl 4-(n-butyl)-4,5-dihydro-7-hydroxy-5-oxothieno[3,2-b]pyridine-6-carboxylate (Compound a)

A) To a solution of 15.7 g (0.100 mol) of methyl 3-aminothiophene-2-carboxylate and 15.2 g (0.110 mol) of potassium carbonate in 200 ml of dimethylformamide was added 34.1 ml (0.300 mol) of n-butyl iodide at 25°C. The mixture was stirred at 120°C for 10 hours. After cooling, the solvent was evaporated under reduced pressure and 200 ml of ethyl acetate was added to the residue. An inorganic salt was removed by filtration. The filtrate was again concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent: ethyl acetate/n-hexane = 1/9 v/v) to give 10.2 g (yield: 48%) of methyl 3-(n-butylaminothiophene-2-carboxylate (Compound a-1).

NMR ($CDCl_3$) δ (ppm): 7.35(1H, d, J=5.3Hz), 7.01-7.30 (1H, br), 6.98(1H, d, J=5.3Hz), 3.83(3H, s), 3.28 (2H, m), 1.21-1.88(4H, m), 0.95(3H, t, J=7.5Hz)

B) 10.0 g (46.9 mmols) of Compound a-1 was dissolved in a solvent mixture of 90 ml of 1,2-dichloroethane and 9 ml of 1,4-dioxane. 16.9 ml (0.141 mol) of trichloromethyl chloroformate was dropwise added to the solution at 25°C. The mixture was stirred at 75°C for 7 hours. After cooling, 0.50 g of activated carbon was added to the reaction mixture followed by reflux for an hour in a nitrogen flow. After cooling, activated carbon was removed by filtration. The filtrate was concentrated under reduced pressure and 15 ml of ethyl acetate and 50 ml of n-hexane were added to the residue. The mixture was then stirred. The precipitated white crystals were filtered and dried to give 6.96 g (yield: 66%) of 4-(n-butyl)-5H-thieno[3,2-d]oxazine-5,7(4H)-dione (Compound a-2).

NMR ($CDCl_3$) δ (ppm): 7.95(1H, d, J=5.0Hz), 6.97(1H, d, J=5.0Hz), 4.01(2H, t, J=7.2Hz), 1.17-1.98(4H, m), 0.98(3H, t, J=7.4Hz)

C) Under ice cooling, 552 mg (24.0 mmols) of sodium hydride was added to 67.4 ml (0.444 mol) of ethyl malonate. The mixture was stirred at 25°C for 30 minutes. To the solution mixture was added 5.00 g (22.2 mmols) of Compound a-2 and the mixture was stirred at 150°C for an hour. After cooling, 300 ml of water was added to the reaction mixture. The mixture was washed twice with chloroform and 6 N hydrochloric acid aqueous solution was added to the aqueous layer. The precipitated crystals were filtered and dried to give 3.33 g (yield: 51%) of Compound a.

NMR ($CDCl_3$) δ (ppm): 7.69(1H, d, J=5.0Hz), 7.02(1H, d, J=5.0Hz), 4.18(2H, q, J=7.0Hz), 3.64(2H, t, J=7.5Hz), 1.08-1.76(4H, m), 1.22(3H, t, J=7.0Hz), 0.91(3H, t, J=6.1Hz)

Reference Example 2

Ethyl 7-butyl(n-)-6,7-dihydro-4-hydroxy-6-oxothieno[2,3-b]pyridine-5-carboxylate (Compound b)

A) Methyl 2-butyl(n-)aminothiophene-3-carboxylate (Compound b-1) was obtained (yield: 23%) in a manner similar to Reference Example 1,A) step except for using methyl 2-amino-3-thiopenecarboxylate [Chem. Ber., 98, 3571 (1965)] in place of methyl 3-aminothiophene-2-carboxylate.

NMR ($CDCl_3$) δ (ppm): 7.08-7,38(1H, br), 7.03(1H, d, J=5.5Hz), 6.14(1H, d, J=5.5Hz), 3.83(3H, s), 3.23 (2H, q, J=6.2Hz), 1.22-1.90(4H, m), 0.96(3H, t, J=7.4Hz)

B) 7-(N-butyl)-6H-thieno[2,3-d]oxazine-4,6(7H)-dione (Compound b-2) was obtained (yield: 80%) in a manner similar to Reference Example 1,B) step except for using Compound b-1 in place of Compound a-1.

NMR ($CDCl_3$) δ(ppm): 7.59(1H, d, J=5.2Hz), 6.30(1H, d, J=5.2Hz), 3.97(2H, t, J=7.0Hz), 1.15-1.93(4H, m), 0.96(3H, t, J=7.4Hz)

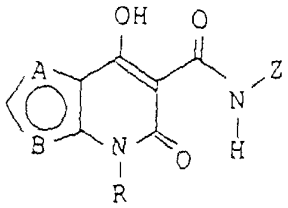
C) Compound b was obtained (yield: 92%) in a manner similar to Reference Example 1,C) step except for using Compound b-2 in place of Compound a-2.

NMR (DMSO-d_6) δ (ppm): 7.34(1H, d, J=5.7Hz), 7.29(1H, d, J=5.7Hz), 4.32(2H, q, J=7.0Hz), 3.97(2H, t, J=7.3Hz), 1.60-1.71L2H, m), 1.30(3H, t, J=7.1Hz), 1.26-1.40(2H, m), 0.92(3H, t, J=7.3Hz)

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, MC, NL, PT, SE

1. A thienopyridine derivative of the formula (I):



(I)

wherein:

one of A and B represents -S- and the other represents -CH=;
R represents hydrogen or C_1 - C_6 alkyl; and
Z represents pyridyl; or

a pharmaceutically acceptable acid addition or metal salt thereof.

2. A Compound according to claim 1, wherein, in said formula, A is - S-, and B is -CH=.

3. 4-(n-Butyl)-4,5-dihydro-7-hydroxy-5-oxo-N-(4-pyridyl)thieno[3,2-b]pyridine-6-carboxamide, and its pharmaceutically acceptable acid addition and metal salts.

4. A pharmaceutical composition comprising a compound or salt as defined by any one of claims 1-3 in a admixture with a pharmaceutically acceptable carrier or diluent.

5. An immunoregulatory pharmaceutical preparation comprising as the immunoregulator a compound or salt according to any one of claims 1-3.

6. An antiosteoporosis pharmaceutical preparation comprising as the antiosteoporosis agent a compound or salt according to any one of claims 1-3.

7. For use as an immunoregulator: a compound or salt as claimed in any one of claims 1-3.

8. For use as an antiosteoporosis agent: a compound or salt as claimed in any one of claims 1-3.

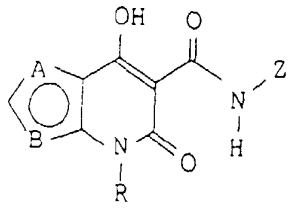
9. A compound or salt according to any one of claims 1 to 3 for use as a pharmaceutical.

10. Use of a compound or salt according to any one of claims 1 to 3 in the manufacture of an immunoregulator or an antiosteoporosis agent.

11. Use of a compound or salt according to any one of claims 1 to 3 in the manufacture of a medicament to suppress the immune system by inhibiting antibody production.

Claims for the following Contracting States : ES, GR

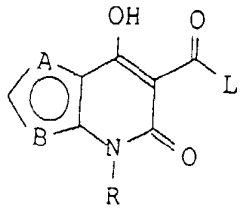
1. A method for the preparation of a thiefiopyridine derivative of the formula (I):



(I)

wherein:

one of A and B represents -S- and the other represents -CH=;
R represents hydrogen or C_1 - C_6 alkyl; and
Z represents pyridyl, which comprises reacting a compound of the formula II:



(II)

with an amine of the formula [I]

$$H_2N - Z \qquad III$$

where in said formula II and III A, B, R and Z are as defined above, and L is halogen, alkoxy, aryloxy, alkanoyloxy or aroyloxy.

2. A method according to claim 1, wherein the reaction is carried out in the presence of a base.

3. A method according to claim 1 or 2, wherein the reaction is performed at a temperature in the range -30 to 200°C, preferably -10 to 100°C.

4. A method according to any one of claims 1-3, wherein the compound of formula I is recovered as or is subsequently converted into a pharmaceutically acceptable acid addition or metal salt.

5. A method according to any one of claims 1-4, wherein in said formulae A is -S-, and B is -CH=.

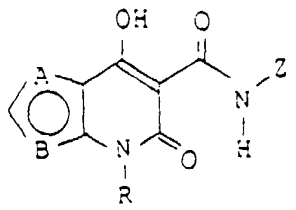
6. A method according to any one of claims 1-4 as applied to the preparation of the compound 4-(n-butyl)-4,5-dihydro-7-hydroxy-5-oxo-N-(4-pyridyl)thieno[3,2-b]pyridine-6-carboxamide,or its pharmaceutically acceptable acid addition or metal salts.

7. A method according to any one of claims 1-6, which comprises the further step of mixing the compound of formula I, optionally after conversion thereof into a pharmaceutically acceptable acid addition or metal salt, with a pharmaceutically acceptable carrier or diluent.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, MC, NL, PT, SE

1. Thienopyridinderivat der Formel (I):



(I)

in der:

einer der Reste A und B eine Gruppe der Formel -S- darstellt, und der andere eine Gruppe der Formel -CH= bedeutet;
R ein Wasserstoffatom oder einen C_1-C_6-Alkylrest darstellt, und
Z eine Pyridylgruppe bedeutet; oder

ein pharmazeutisch verträgliches Säureadditions- oder Metallsalz davon.

2. Verbindung nach Anspruch 1, wobei in der Formel A eine Gruppe der Formel -S- ist, und B eine Gruppe der Formel -CH= ist.

3. 4-(n-Butyl)-4,5-dihydro-7-hydroxy-5-oxo-N-(4-pyridyl)thieno-[3,2-b]-pyridin-6-carbonsäureamid und seine pharmazeutisch verträglichen Säureadditions- und Metallsalze.

4. Arzneimittel, umfassend eine Verbindung oder ein Salz nach einem der Ansprüche 1-3 im Gemisch mit einem pharmazeutisch verträglichen Träger oder Verdünnungsmittel.

5. Immunregulierende pharmazeutische Zubereitung, umfassend eine Verbindung oder ein Salz nach einem der Ansprüche 1-3 als Immunregulator.

6. Pharmazeutische Zubereitung gegen Osteoporose, umfassend eine Verbindung oder ein Salz nach einem der Ansprüche 1-3 als Mittel gegen Osteoporose.

7. Zur Verwendung als Immunregulator: Verbindung oder Salz nach einem der Ansprüche 1-3 .

8. Zur Verwendung als Mittel gegen Osteoporose: Verbindung oder Salz nach einem der Ansprüche 1-3 .

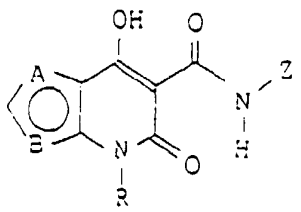
9. Verbindung oder Salz nach einem der Ansprüche 1 bis 3 zur Verwendung als Arzneimittel.

10. Verwendung einer Verbindung oder eines Salzes nach einem der Ansprüche 1 bis 3 zur Herstellung eines Immunregulators oder eines Mittels gegen Osteoporose.

11. Verwendung einer Verbindung oder eines Salzes nach einem der Ansprüche 1 bis 3 zur Herstellung eines Arzneimittels zur Unterdrückung des Immunsystems durch Inhibierung der Antikörperbildung.

Patentansprüche für folgende Vertragsstaaten : ES, GR

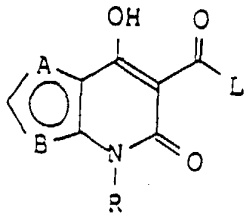
1. Verfahren zur Herstellung eines Thienopyridinderivats der Formel (I):



(I)

in der:

einer der Reste A und B eine Gruppe der Formel -S- darstellt, und der andere eine Gruppe der Formel -CH= bedeutet;
R ein Wasserstoffatom oder einen C_1-C_6-Alkylrest darstellt, und
Z eine Pyridylgruppe bedeutet; das die Umsetzung einer Verbindung der Formel (II):



(II)

mit einem Amin der Formel (III)

$$H_2N\text{-}Z \qquad \text{(III)}$$

umfaßt, wobei in den Formeln (II) und (III) A, B, R und Z wie vorstehend definiert sind, und L ein Halogenatom, ein Alkoxy-, Aryloxy-, Alkanoyloxy- oder ein Aroyloxyrest ist.

2. Verfahren nach Anspruch 1, wobei die Umsetzung in Gegenwart einer Base durchgeführt wird.

3. Verfahren nach Anspruch 1 oder 2, wobei die Umsetzung bei einer Temperatur im Bereich von -30 bis 200°C, bevorzugt -10 bis 100°C, durchgeführt wird.

4. Verfahren nach einem der Ansprüche 1-3, wobei die Verbindung der Formel (I) als pharmazeutisch verträgliches Säureadditions- oder Metallsalz gewonnen wird oder anschließend darin umgewandelt wird.

5. Verfahren nach einem der Ansprüche 1-4, wobei in den Formeln A eine Gruppe der Formel -S- ist, und B eine Gruppe der Formel -CH= ist.

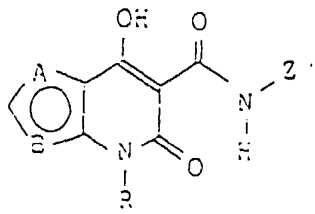
6. Verfahren nach einem der Ansprüche 1-4, wie es auf die Herstellung der Verbindung 4-(n-Butyl)-4,5-dihydro-7-hydroxy-5-oxo-N-(4-pyridyl)thieno-[3,2-b]-pyridin-6-carbonsäureamid oder seiner pharmazeutisch verträglichen Säureadditions- oder Metallsalze angewendet wird.

7. Verfahren nach einem der Ansprüche 1-6, das den weiteren Schritt des Mischens der Verbindung der Formel (I), gegebenenfalls nach deren Umwandlung in ein pharmazeutisch verträgliches Säureadditions- oder Metallsalz, mit einem pharmazeutisch verträglichen Träger oder Verdünnungsmittel umfaßt.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, MC, NL, PT, SE

1. Dérivé de thiénopyridine, de formule (I) :



(I)

dans laquelle l'un des symboles A et B représente un chaînon -S- et l'autre représente un chaînon -CH=, R représente un atome d'hydrogène ou un groupe alkyle en C_1-C_6, et Z représente un groupe pyridyle,
ou sel de métal ou d'addition d'acide d'un tel dérivé, admissible en pharmacie.

2. Composé conforme à la revendication 1, dans lequel, dans ladite formule, A représente un chaînon -S- et B représente un chaînon -CH=.

3. 4-(n-butyl)-4,5-dihydro-7-hydroxy-5-oxo-N-(4-pyridyl)thiéno[3,2-b]pyridine-6-carboxamide, et ses sels de métal ou d'addition d'acide, admissibles en pharmacie.

4. Composition pharmaceutique comprenant un composé ou un sel conforme à l'une des revendications 1 à 3, mélangé avec un véhicule ou un diluant admissible en pharmacie.

5. Préparation pharmaceutique immunorégulatrice, qui contient, comme agent immunorégulateur, un composé ou un sel conforme à l'une des revendications 1 à 3.

6. Préparation pharmaceutiques anti-ostéoporose, qui contient, comme agent anti-ostéoporose, un composé ou un sel conforme à l'une des revendications 1 à 3.

7. Composé ou sel conforme à l'une des revendications 1 à 3, destiné à être utilisé comme agent immunorégulateur.

8. Composé ou sel conforme à l'une des revendications 1 à 3, destiné à être utilisé comme agent anti-ostéoporose.

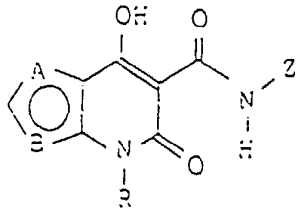
9. Composé ou sel conforme à l'une des revendications 1 à 3, destiné à être utilisé comme agent pharmaceutique.

10. Utilisation d'un composé ou d'un sel conforme à l'une des revendications 1 à 3, pour la fabrication d'un agent anti-ostéoporose ou d'un agent immunorégulateur.

11. Utilisation d'un composé ou d'un sel conforme à l'une des revendications 1 à 3, pour la fabrication d'un médicament immunodépresseur qui agit en inhibant la production d'anticorps.

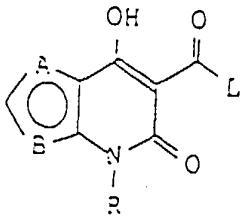
Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de préparation d'un dérivé de thiénopyridine, de formule (I) :



(I)

dans laquelle l'un des symboles A et B représente un chaînon -S- et l'autre représente un chaînon -CH=, R représente un atome d'hydrogène ou un groupe alkyle en C_1-C_6, et Z représente un groupe pyridyle,
qui comporte le fait de faire réagir un composé de formule (II) :



(II)

avec une amine de formule (III) :

$$H_2N - Z \qquad \text{(III)}$$

dans lesquelles formules (II) et (III) A, B, R et Z ont les définitions indiquées ci-dessus et L représente un atome d'halogène ou un groupe alcoxy, aryloxy, alcanoyloxy ou aroyloxy.

2. Procédé conforme à la revendication 1, dans lequel on effectue la réaction en présence d'une base.

3. Procédé conforme à la revendication 1 ou 2, dans lequel on effectue la réaction à une température située dans l'intervalle allant de -30°C à 200°C, de préférence de -10°C à 100°C.

4. Procédé conforme à l'une des revendications 1 à 3, dans lequel on récupère le composé de formule (I) sous la forme d'un sel de métal ou d'addition d'acide, admissible en pharmacie, ou l'on transforme ultérieurement ce composé en un tel sel.

5. Procédé conforme à l'une des revendications 1 à 4, dans lequel, dans lesdites formules, A représente un chaînon -S- et B représente un chaînon -CH=.

6. Procédé conforme à l'une des revendications 1 à 4, mis en oeuvre pour préparer du 4-(n-butyl)-4,5-dihydro-7-hydroxy-5-oxo-N-(4-pyridyl)thiéno[3,2-b]pyridine6-carboxamide, ou un sel de métal ou d'addition d'acide, admissible en pharmacie, de ce composé.

7. Procédé conforme à l'une des revendications 1 à 6, qui comporte l'étape supplémentaire consistant à mélanger le composé de formule (I), après l'avoir éventuellement converti en un sel de métal ou d'addition d'acide, admissible en pharmacie, avec un véhicule ou un diluant admissible en pharmacie.