PD-3561-01-JT

CONVENTION APPLICATION BY A COMPANY

FORM 8 - REGULATION 12 (2)

AUSTRALIA
PATENTS ACT 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

In support of the Convention Application made by

(a) Here Insert (in full) Name of Company.

(a) WARNER-LAMBERT COMPANY

(hereinafter referred to as "Applicant") for a patent for an invention entitled:

(b) Here Insert Title of Invention.

(b) 7-DEAZAGUANINES AS IMMUNOMODULATORS

(c) and (d) Here Insert Full Name and Address of Company Official authorised to make declaration.

I, (c) Christine A. Trautwein, Assistant Secretary

of (d) 2800 Plymouth Road, Ann Arbor, Michigan 48105 U.S.A.

do solemnly and sincerely declare as follows:

1. I am authorised by Applicant to make this declaration on its behalf.

2. The basic Application(s) as defined by section 141 of the Act ~~was~~ / were made

(e) Here Insert Basic Country followed by date of Basic Application.

(f) Here Insert Full Name(s) of Applicant(s) in Basic Country.

in (e) U.S.A. on the 24th day of October 19 86

by (f) Thomas Charles Malone and Jagadish Chandra Sircar

in U.S.A. on the 20th day of August 19 87

by Thomas Charles Malone and Jagadish Chandra Sircar

in ..... on the ..... day of 19

by .....

in ..... on the ..... day of 19

by .....

(g) Here Insert (in full) Name and Address of actual Inventor or Inventors.

3. (g) Thomas Charles Malone, 42337 Carriage Cove Circle, Canton, Michigan 48187, U.S.A.
Jagadish Chandra Sircar, 3615 Charter Place, Ann Arbor, Michigan 48105, U.S.A.

~~is~~/are the actual Inventor(s) of the invention and the facts upon which Applicant is entitled to make the Application are as follows:

See reverse side of this form for guidance in completing this part.

APPLICANT IS THE ASSIGNEE OF THE SAID INVENTORS

4. The basic Application(s) referred to in paragraph 2 of this Declaration was/were the first Application(s) made in a Convention country in respect of the invention, the subject of the Application.

DECLARED at Ann Arbor, Michigan, U.S.A.

this 3rd day of April 19 89

(h) Personal Signature

(12) PATENT ABRIDGMENT (11) Document No. AU-B-83281/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 614947

(54) Title
7-DEAZAGUANINES AS IMMUNOMODULATORS

International Patent Classification(s)
(51)[4] C07D 487/04 C07D 209/00 C07D 239/42 A61K 031/505

(21) Application No. : 83281/87 (22) Application Date : 19.10.87

(87) PCT Publication Number : WO88/03142

(30) Priority Data

(31) Number	(32) Date	(33) Country
923521	24.10.86	US UNITED STATES OF AMERICA
086231	20.08.87	US UNITED STATES OF AMERICA

(43) Publication Date : 25.05.88

(44) Publication Date of Accepted Application : 19.09.91

(71) Applicant(s)
WARNER-LAMBERT COMPANY

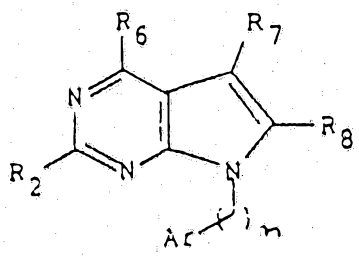
(72) Inventor(s)
THOMAS C. MALONE; JAGADISH C. SIRCAR

(74) Attorney or Agent
SHELSTON WATERS , 55 Clarence Street, SYDNEY NSW 2000

(56) Prior Art Documents
AU 14398/88 C07H 019/04 019/24 C07D 487/04
AU 77416/87 C07D 487/04 239/48 409/06

(57) Claim

1. A compound of formula (I)



I

wherein R_6 is OH or SH, R_2 is hydrogen or NH_2, R_7 and R_8 are independently hydrogen or NH_2 with the proviso that both cannot be NH_2 at once, n is an integer of from one through four, Ar is (i) phenyl unsubstituted or substituted by halogen, trifluoromethyl, alkyl of one to four carbon atoms, hydroxy or alkoxy of from one to four carbon atoms, (ii) 2- or 3-thienyl, or (iii) 2- or 3-furanyl, with the proviso that when R_6 is OH, R_2 is H_2N, and R_7 and R_8 are both hydrogen then Ar cannot be phenyl when n is 1; or a pharmaceutically acceptable base or acid addition salt thereof.

.../2

8. A method for treating autoimmune disease or rejection of transplantation which comprises administering a composition of Claim 7 in unit dosage form.

9. A method for treating psoriasis which comprises administering a composition of Claim 7 in unit dosage form.

AU-AI-83281/87

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

614947

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 :
C07D 487/04, A61K 31/505
C07D 239/42 // (C07D 487/04
C07D 239:00, 209:00)

A2

(11) International Publication Number: WO 88/ 03142

(43) International Publication Date: 5 May 1988 (05.05.88)

(21) International Application Number: PCT/US87/02727

(22) International Filing Date: 19 October 1987 (19.10.87)

(31) Priority Application Numbers: 923,521
086,231

(32) Priority Dates: 24 October 1986 (24.10.86)
20 August 1987 (20.08.87)

(33) Priority Country: US

(60) Parent Applications or Grants
(63) Related by Continuation
US 923,521 (CON)
Filed on 24 October 1986 (24.10.86)
US 086,231 (CON)
Filed on 20 August 1987 (20.08.87)

(71) Applicant *(for all designated States except US)*: WARNER-LAMBERT COMPANY [US/US]; 2800 Plymouth Road, Ann Arbor, MI 48105 (US).

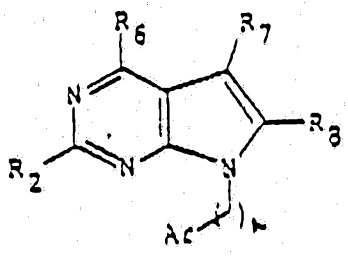
(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : MALONE, Thomas, C. [US/US]; 42337 Carriage Cove Circle, Canton, MI 48187 (US). SIRCAR, Jagadish, C. [US/US]; 3615 Charter Place, Ann Arbor, MI 48105 (US).

(74) Agents: THIERSTEIN, Joan; Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105 (US) et al.

(81) Designated States: AT (European patent), AU, BB, BE (European patent), BG, BJ (OAPI patent), BR, CF (OAPI patent), CG (OAPI patent), CH (European patent), CM (OAPI patent), DE (European patent), DK, FI, FR (European patent), GA (OAPI patent), GB (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL (European patent), NO, RO, SD, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US, US.

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: 7-DEAZAGUANINES AS IMMUNOMODULATORS



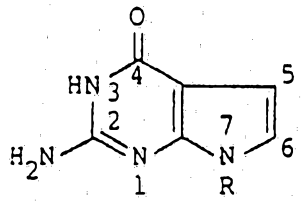
(I)

(57) Abstract

Various 7-deazaguanines of formula (I), wherein R_6 is OH or SH, R_2 is hydrogen or NH_2, R_7 and R_8 are hydrogen or NH_2, n is an integer of from one through four, Ar is (i) phenyl unsubstituted or substituted by halogen, trifluoromethyl, alkyl, hydroxy or alkoxy, (ii) 2- or 3-thienyl, or (iii) 2- or 3-furanyl; having activity as immunomodulators. Also included are pharmaceutical compositions and methods of use thereof.

BACKGROUND OF THE INVENTION

The pyrrolo[2,3-d]pyrimidin-4-ones of the following formula 2, 3 and 4



2, R is n-C_3H_7
3, R is $CH_2C_6H_5$
4, R is cyclopentyl

are known. R.K. Robins, et al, synthesized the compounds of formula 2 and 3 as reported in J. Het. Chem., 1964, 34, but gave no biological activity for either compound. M. Legraverend, et al, reported the synthesis of the compounds of formula 3 and 4 in Tetrahedron Letters, 1985, 2001, but again gave no biological activity for either compound.

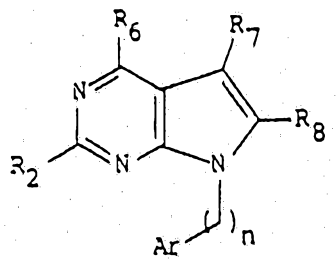
Of lesser interest the following references provide a background in which a 7-(substituted phenyl)pyrrolo[2,3-d] pyrimidin-4-one having a methyl at each of the five (5) and six (6) positions for treating CNS illnesses or inflammations is disclosed generically in US Patent No. 4,229,453. Similarly, 4-mercapto-7-(phenyl substituted or unsubstituted)pyrrollo [2,3-d]pyrimidine derivatives requiring an alkyl or phenyl at the five (5) and six (6) positions are disclosed in German 3145287 (Derwent Abstract No. 49344 K/21). Other pyrrolo [2,3-d]pyrimidin-4-one or thione, distinguished by having

various substituents at the five (5) position, are found in US Patent No. 4,435,570 and 4,140,851; European publications 160,910 (Derwent Abstract No. 85-284574/46); 89,055 (corresponding to US Patent No. 4,571,423); 119,591 (Derwent Abstract No. 84-238735/39); 79,447 (corresponding to US Patent No. 4,435,569); German 3,306-390 (Derwent Abstract No. 39438 E/20); German 3145287 (Derwent Abstract No. 49344 K/21); British Patent No. 981,458 (Derwent Abstract No. 15,454); Japanese J6 0204,788 (Derwent Abstract No. 85/298810/48); and Japanese J5 9036615 (Derwent Abstract No. 84-086061/84).

Finally, hydroxy and mercapto analogs of the antibiotic sparsomycin A are pyrrolo[2,3-d]pyrimidin-4-one or thione having a sugar moiety in the seven (7) position are disclosed by Upjohn in Netherlands 6,407,785 (Derwent Abstract No. 15,466) and similarly by Warner Lambert in European publication 57,548 (Derwent Abstract No. 68572 E/33).

Copending Applications Serial Number PD-3557 and Serial Number 767,202 filed August 22, 1985, now pending, which is a continuation-in-part of US Serial No. 660,152 filed October 12, 1984, now abandoned, disclose similar activity as now found in the present invention for different ring systems.

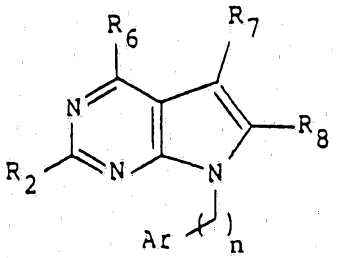
The present invention relates to a compound of the formula (I)



I

wherein R_6 is OH or SH, R_2 is hydrogen or NH_2, R_7 and R_8 are independently hydrogen or NH_2 with the proviso that both cannot be NH_2 at once, n is an integer of from one through four, Ar is (i) phenyl unsubstituted or substituted by halogen, trifluoromethyl, alkyl of one to four carbon atoms, hydroxy, or alkoxy of from one to four carbon atoms, (ii) 2- or 3-thienyl, or (iii) 2- or 3-furanyl with the proviso that when R_6 is OH, and R_2 is H_2N, and R_7 and R_8 are both hydrogen then Ar cannot be phenyl when n is 1; or a pharmaceutically acceptable base or acid addition salt thereof.

The present invention also includes methods of manufacturing and novel intermediates therein, and a pharmaceutical composition for treating autoimmune diseases such as arthritis, systemic lupus erythematosus, inflammatory bowel diseases, juvenile diabetes, myasthenia gravis, multiple sclerosis, gout and gouty arthritis, as well as psoriasis, viral infections and cancer, or rejection of transplantation, comprising an anti-psoriatic, immunomodulator or antirejection effective amount such as an advantageously cytotoxic to T-cell amount, of a compound of the formula (I)

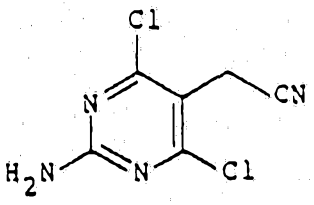


I

or a pharmaceutically acceptble base or acid addition salt thereof wherein R_6 is OH or SH, R_2 is hydrogen or NH_2, R_7 and R_8 are independently hydrogen and NH_2 with the proviso that both cannot be NH_2 at once, n is an integer of from one to four, Ar is (i) phenyl unsubstituted or substituted by halogen, trifluoromethyl, alkyl of one to four carbon atoms, hydroxy, alkoxy of from one to four carbon atoms, (ii) 2- or 3-thienyl,

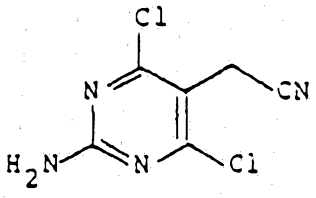
or (iii) 2- or 3-furanyl with a pharmaceutically acceptable carrier. Thus, the invention is also a method of treating psoriasis, an autoimmune disease, such as is listed above, or rejection of transplantation comprising administering to a host, such as a mammal including a human, suffering from psoriasis, the autoimmune disease or rejection of transplantation comprising administering an effective amount; i.e. an amount advantageously affecting T-cells by toxicity thereto, of a pharmaceutical composition of the formula I as defined above in unit dosage form. It is understood, an ordinarily skilled physician would begin treatment with a less than effective amount and increase the dose until the desired effect is obtained exercising care to administer an amount less than the amount toxic to the host of the disease.

The novel intermediates of the present invention are compounds of formula (X)



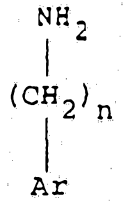
X

The method of manufacture of the present invention is a novel process for the preparation of a compound of the formula I as defined above; which comprises treating a compound of the formula (X)



X

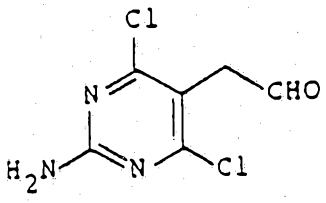
with a compound of the formula (V)



V

wherein Ar and n are as defined above and then treating with an acid to obtain the compound of formula I wherein R_6 is oxygen and R_8 is NH_2 and alternatively, if desired, further deaminating by known methods or treating also by known methods, to obtain a compound of formula I wherein R_6 is sulfur and then, if desired, deaminating.

The compound of formula X is prepared by treating a compound of the formula (IX)



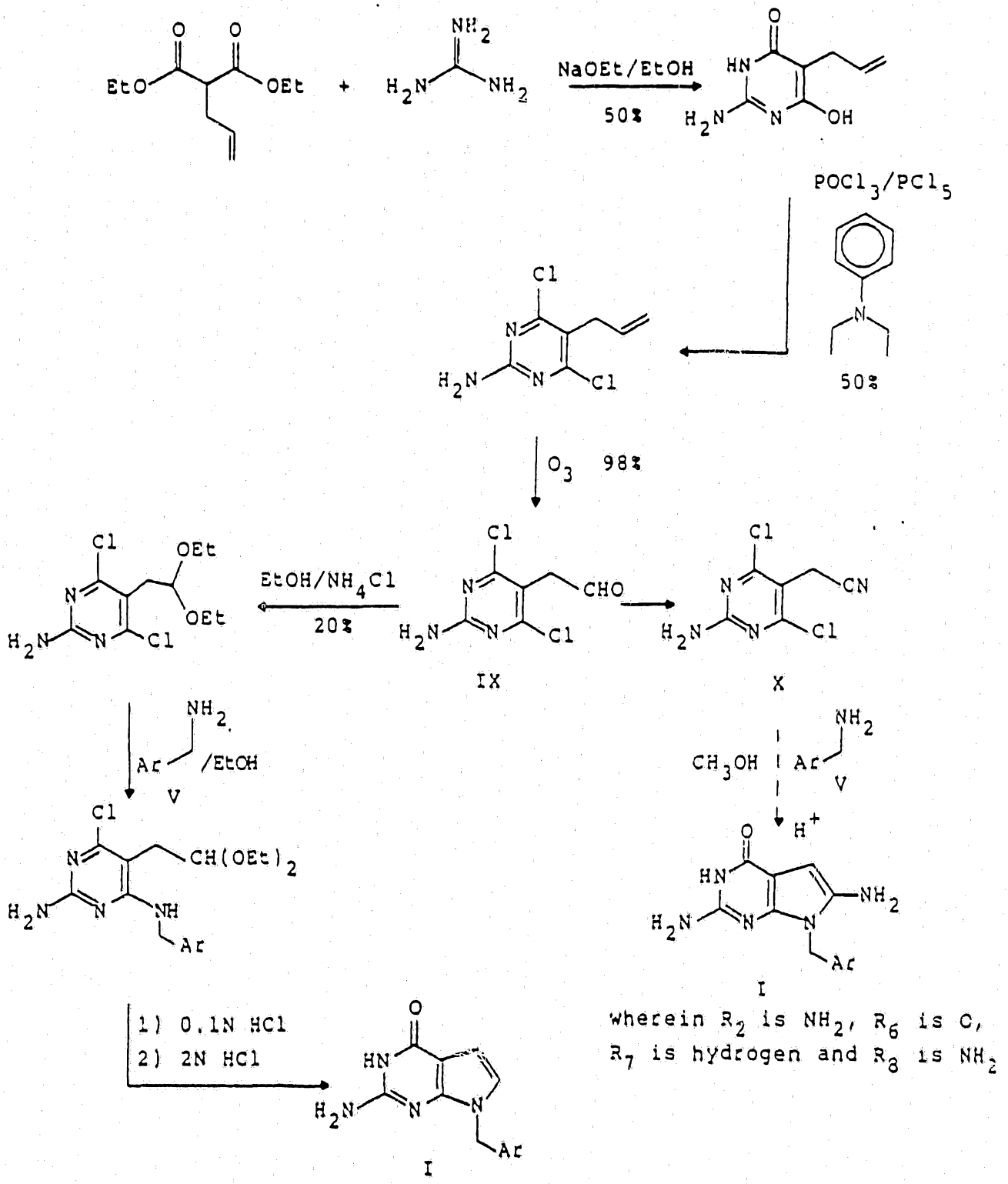
IX

with a cyanation agent, such as O,N-bistrifluoroacetyl-hydroxylamine, in the presence of a base, such as pyridine to obtain the compound of formula X.

The above preparations use standard synthetic techniques or techniques as shown or similar to those as shown in the examples hereinafter. The starting materials for the preparation are readily available, known or can be prepared by known methods.

The methods of manufacture for the compounds of the present invention are summarized in the following Schemes I and II.

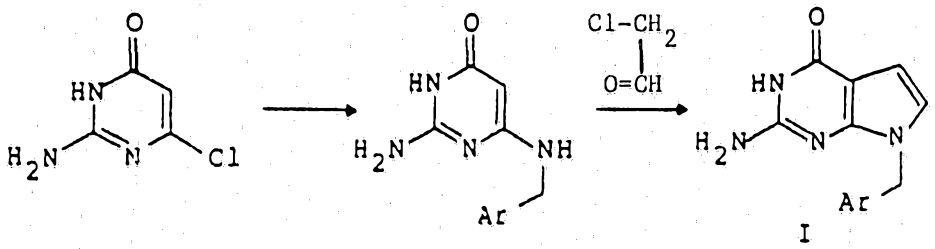
Scheme I



wherein R_2 is NH_2, R_6 is C, R_7 is hydrogen and R_8 is NH_2

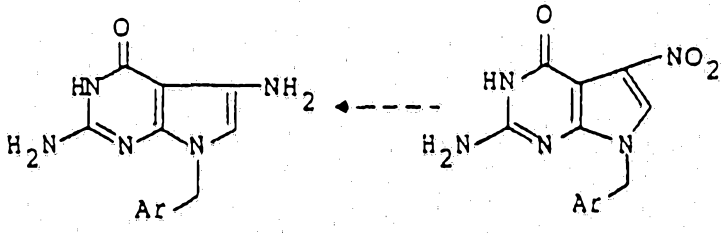
wherein R_2 is NH_2, R_6 is O, and R_7 and R_8 are both hydrogen

Scheme II



VI VII I

wherein R_2 is NH_2 and R_8 and R_7 both are hydrogen and R_6 is O



I

wherein R_2 is NH_2, R_6 is O, R_7 is NH_2 and R_8 is hydrogen

Under certain circumstances it may be necessary to protect either the N or O of intermediates in the above noted process with suitable protecting groups which are known. Introduction and removal of such suitable oxygen and nitrogen protecting groups are well-known in the art of organic chemistry; see for example, (1) "Protective Groups in Organic Chemistry," J. F. W. McOmie, ed., (New York, 1973), pp 43ff, 95ff; (2) J. F. W. McOmie, Advances in Organic Chemistry, Vol. 3, 191-281 (1963); (3) R. A. Borssonas, Advances in Organic Chemistry, Vol. 3, 159-190 (1963); and (4) J. F. W. McOmie, Chem. & Ind., 603 (1979).

Examples of suitable oxygen protecting groups are benzyl, t-butyldimethylsilyl, methyl, isopropyl, ethyl, tertiary butyl, ethoxyethyl, and the like. Protection of an N-H containing moiety is necessary for some of the processes described herein for the preparation of compounds of this invention. Suitable nitrogen protecting groups are benzyl, triphenylmethyl, trialkylsilyl, trichloroethylcarbamate, trichloroethoxycarbonyl, vinyloxycarbamate, and the like.

Under certain circumstances it is necessary to protect two different oxygens with dissimilar protecting groups such that one can be selectively removed while leaving the other in place. The benzyl and t-butyldimethylsilyl groups are used in this way; either is removable in the presence of the other, benzyl being removed by catalytic hydrogenolysis, and t-butyldimethylsilyl being removed by reaction with, for example, tetra-n-butylammonium fluoride.

In the process described herein for the preparation of compounds of this invention the requirements for protective groups are generally well recognized by one skilled in the art of organic chemistry, and accordingly the use of appropriate protecting groups is necessarily implied by the processes of the charts herein, although not expressly illustrated.

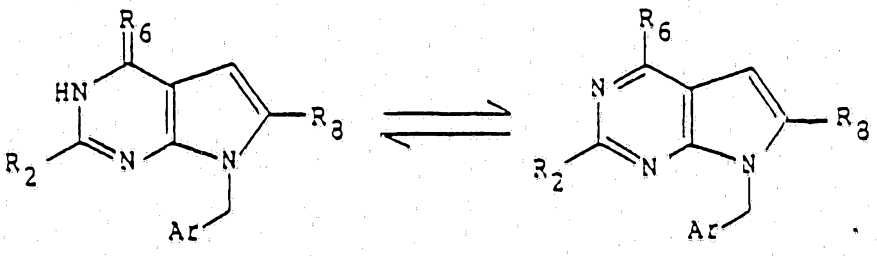
The products of the reactions described herein are isolated by conventional means such as extraction, distillation, chromatography, and the like.

The salts of compounds of formula I described above are prepared by reacting the appropriate base with stoichometric equivalent of the acid compounds of formula I to obtain pharmacologically acceptable salts thereof.

The compounds of this invention may also exist in hydrated or solvated forms.

DETAILED DESCRIPTION

The compounds of formula I of the present invention exist in tautomeric forms as purines or guanines as illustrated below. Both forms are included as part of the invention and are indiscriminately described in the specification.



Guanine I

Purine I

The term "alkyl of one to four carbon atoms" means a straight or branched hydrocarbon chain up to four carbon atoms such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secondary butyl or tertiary butyl. Alkoxy of one to four carbon atoms includes methoxy, ethoxy, propoxy, butoxy and isomers thereof. Halogen is fluorine, chlorine, bromine, or iodine.

The compounds of formula I are useful both in the free base form, in the form of base salts where possible, and in the form of acid addition salts. The three forms are within the scope of the invention. In practice, use of the salt form amounts to use of the base form. Appropriate pharmaceutically acceptable salts within the scope of the invention are those derived from mineral acids such as hydrochloric acid and

sulfuric acid, and organic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonate, and the like, respectively, or those derived from bases such as suitable organic and inorganic bases. Examples of suitable inorganic bases for the formation of salts of compounds of this invention include the hydroxides of ammonia, sodium, lithium, potassium, calcium, magnesium, aluminum, zinc, and the like.

Salts may also be formed with suitable organic bases. Bases suitable for the formation of pharmaceutically acceptable base addition salts with compounds of the present invention include organic bases which are nontoxic and strong enough to form such salts. These organic bases form a class whose limits are readily understood by those skilled in the art. Merely for purposes of illustration, the class may be said to include mono-, di-, and trialkylamines, such as methylamine, dimethylamine, and triethylamine; mono-, di-, or trihydroxyalkylamines such as mono-, di-, and triethanolamine; amino acids such as arginine, and lysine; guanidine; N-methylglucamine; L-glutamine; N-methylpiperazine; morpholine; ethylenediamine; N-benzylphenethylamine; tri(hydroxymethyl)aminomethane; and the like. (See for example, "Pharmaceutical Salts," J. Pharm. Sci. (1977) 66(1):1-19.)

The acid addition salts of said basic compounds are prepared either by dissolving the free base of compound I in aqueous or aqueous alcohol solution or other suitable solvent containing the appropriate acid or base and isolating the salt by evaporating the solution, or by reacting the free base of compound I with an acid as well as reacting compound I having an acid group thereon with a base such that the reactions are in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

A preferred embodiment of the present invention is a compound of formula I wherein R_6 is OH or SH; R_2 and R_8 are NH_2, n is one, and Ar is 2- or 3-thienyl. A more preferred embodiment is 2-amino-7-(2-thienylmethyl)-4-pyrrolo[2,3-d)] pyrimidone.

The compositions having compounds of the formula I of the present invention are shown to exhibit significant enzyme inhibition activity and cytotoxicity activity. In the purine nucleoside phosphorylase (PNP-4) enzyme assay, an IC_{50} is achieved at a dose of 1.0 micromoles on a selected compound of the present invention. PNP-4 activity for the compound of formula I is measured radiochemically by measuring the formation of [^{14}-C]hypoxanthine from [^{14}-C]inosine [Biomedicine, 33, 39 (1980)] using human erythrocyte as the enzyme source.

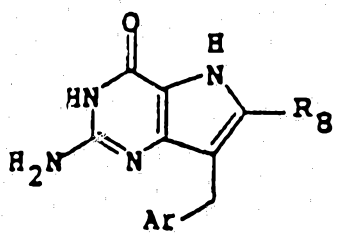
It is known that an in vivo inhibition of purine nucleoside phosphorylase (HPLC-1) enzyme assay may also be used essentially as disclosed in the Annals of New York Academy of Sciences, Volume 451, Page 313 (1985) to further show the activity for compositions of the compounds of formula I of the present invention. The present invention compositions also are generally shown by a standard test (HTBA-1) [Science, 214, 1137, (1981)] to be selectively cytotoxic for T-cells in the presence of 2'-deoxyguanosine at a similar concentration range and nontoxic to B-cell in the presence of the same amount of 2'-deoxyguanosine by the compound of Example 2, thus demonstrating utility for the compounds of formula I in pharmaceutical compositions as described herein. Since PNP inhibition and removal of T-cells or modulation of T-cells are known to be characteristics of compounds beneficial in the treatment of psoriasis, rejection phenomenon in transplantation, and autoimmune diseases, the present invention compositions of compounds being selectively cytotoxic to T-cells and being PNP inhibitors will, therefore, also be useful in such treatment. For example, 8-Aminoguanosine, a known PNP-inhibitor, has been shown to be efficacious for inhibiting rejection of skin graft in dogs [J. B. Benear, et al, Transplantation, 1986, 41:274]. Clinically it has been shown that modulation and/or removal of T-cells by thoracic duct drainage, lymphapheresis or total lymphoid irradiation gave partial to complete relief from rheumatoid arthritis in patients who were totally refractory to other forms of therapy

patients who were totally refractory to other forms of therapy

(A. Tanay, et al, Arthritis and Rheumatism, Vol. 30, No. 1, p. 1 (1987). S. Strober, et al, Annual of Internal Medicine, V-102, No. 4, 441-449 (1985); H. G. Nusslein, et al, Arthritis and Rheumatism, V-28, No. 11, 1205-1210 (1985); E. Brahn, et al, ibid, V-27, No. 5, 481-487 (1984), and J. Karsh, et al, ibid, V-24, No. 7, 867-873 (1981)). Cyclosporin A, a T-cell modulator, showed beneficial effects in the treatment of juvenile diabetes. (A. Assan, et al, The Lancet, January 12, p. 67 (1985).) Additionally, cyclosporin A is presently the drug of choice for the prevention of transplant rejection, (R. M. Merion, et al, New Eng. J. Med., (1984) 148). More recently, cyclosporin A is shown to be useful to treat psoriasis. Further, it is suggested the cyclosporin therapy is shown to markedly reduce activated T-cells in psoriatic lesions. Therefore, it is reasonable to believe the basis of the successful treatment of psoriasis is modulation of T-cell activity as shown by compounds in the present invention composition. (See C. N. Ellis, et al, JAMA, V-256, No. 22, Dec. 12, 1986, pp. 3110-3116.) Finally, cyclosporin A is shown to be efficacious in rheumatoid arthritis. (M. E. Weinblatt, et al, Arthritis and Rheumatism, V-30, No. 1, pp. 11-17 (January, 1987); O. Forre, et al, Arthritis and Rheumatism, V-30, No. 1, pp. 88-92 (January, 1987); M. Dougados, et al, Arthritis and Rheumatism, Vol. 30, No. 1, pp. 83-87 (January, 1987).

Representative examples from the present invention are shown in the following activity table to provide the activity discussed above.

ACTIVITY TABLE



Number	R_7	R_8	Ar	PNP-4 IC_{50} (μM)	HTBA-1 T-Cell + 10 μM 2'-d Gua; IC_{50} μM
2	H	H	2-Th	1.0	2.3

Th = Thiophene

In vivo studies based on the above noted disclosures may be used to determine activity in the particular disease states noted.

Since T-cells play a central role in immune response, use of the compounds of the invention is contemplated for the immunoregulation to prevent rejection in transplantation or in the treatment of psoriasis and in the treatment of autoimmune disease such as rheumatoid arthritis, systemic lupus erythrematosus, inflammatory bowel disease, multiple sclerosis, myasthemia gravis, gout or gouty arthritis, juvenile diabetes, cancer, and viral diseases. The present invention thus includes compositions containing a compound of formula I in treating rejection of transplantation or disease such as psoriasis in humans or autoimmune disease characterized by abnormal immune response in primates or humans. According to this aspect of the invention, the properties of the compounds of the invention are utilized by administering to a warmblooded animal an effective amount of a pharmaceutical composition

containing as the active ingredient at least about 0.1 percent by weight, based on the total weight of the composition of at least one such compound of the invention.

Pharmaceutical compositions of the invention can be formulated in any suitable way, preferably with an inert carrier for administration orally, parenterally, ophthalmically, topically, or by suppository.

For example, the compounds of the present invention are formulated into dosage forms such as tablets or syrups by blending with an inert pharmaceutical carrier such as lactose or simple syrup by methods well-known in the art. For injectable dosage forms, they are formulated with vehicles such as water, propylene glycol, peanut oil, sesame oil, and the like. In these dosage forms, the active ingredient is from about 0.05 grams to 0.5 grams per dosage unit.

The present invention is further illustrated by way of the following examples.

Example 1

2-Amino-6-[(2-thienylmethyl)amino]-4-pyrimidinol

2-Amino-6-chloro-4-pyrimidinol, monohydrate (85%, 100 g, 0.5197 mol) was suspended in methoxyethanol (700 ml) and 2-thienylmethylamine (96%, 61.3 g, 0.5197 mol) was added to the suspension. The mixture was heated under reflux for two hours and then 73 ml (d = 0.726; 0.52 mol) of triethylamine was added and the refluxing continued for an additional 18 hours. The reaction mixture was poured into ice water (1000 ml), acidified with acetic acid (ph 4.0) and the precipitated solid was filtered, washed, and dried. Yield: 110 g (72.6%). This was used in the next step without further purification.

Example 2

2-Amino-7-(2-thienylmethyl)-4-pyrrolo[2,3-d]pyrimidones

Chloroacetaldehyde dimethyl acetal (14 ml) was added to water (50 ml) and concentrated HCl (2.0 ml). The mixture was heated at reflux temperature for 30 minutes and then

neutralized with sodium acetate (10 g). The resulting solution was added in one portion to a mixture of 2-amino-4-(2-thienylmethylamino)-6-pyrimidone (10 g; 45 mmol), sodium acetate (5.0 g) and hot water (50 ml). The mixture was allowed to stir on a steam bath (80°C) for 30 minutes, and the precipitated solid was filtered, washed with water, and dried in vacuo. The crude product was dissolved in methanol and concentrated HCl and treated with charcoal to remove coloring matter. The product (3.2 g) thus obtained was recrystallized from methanol and 1N HCl (100 ml) to give 1.68 g (13.5%) of the desired product as light brown solid, mp 243-245°C (dec).

2-Amino-4-chloro-6-[2-thienylmethyl)amino]-5-(2,2-diethoxy-ethyl)pyrimidine

A solution of 2-amino-4,6-dichloro-5-(2,2-diethoxyethyl) pyrimidine (M. Legraverend, et al, J. Med. Chem., 1985, 28:1477) (906 mg, 3.20 mmol) in 40 ml of n-butanol containing Et_3N (1ml) and 2-thienylmethylamine (425 mg, 3.75 mmol) was heated at 100°C for 48 hours. The reaction mixture was cooled to 25°C and concentrated. The residue was cooled to 25°C and concentrated. The residue was purified by column chromatography over silica gel and eluted with chloroform to give the desired product (1.045 g) (91.5%) as a yellow oil.

2-Amino-4-chloro-7-(2-thienylmethyl)pyrrolo[2,3-d]pyrimidine

A suspension of 2-amino-4-chloro-6-[(2-thienylmethyl) amino]-5-(2,2-diethoxyethyl)pyrimidine (1.0 g, 2.80 mmol) in 65 ml of 0.3N HCl and ethanol (2.25:1) was stirred at 25°C for 24 hours. The reaction mixture was neutralized with ammonium hydroxide solution and the product collected

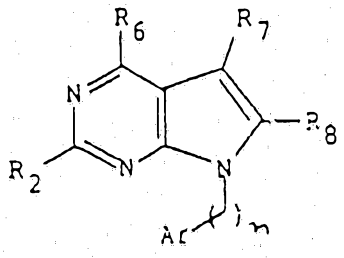
by filtration. TLC analysis showed that the reaction was not complete, so, the product was resuspended in 50 ml of 0.2N HCl and stirred for 48 hours. The reaction mixture was neutralized with NH_4OH solution and concentrated. The residue was taken up in water and then evaporated to dryness to give yellow solid (573 mg) (77.3%). This was used in the next step without further purification.

2-Amino-7-(2-thienylmethyl)-4-pyrrolo[2,3-d]pyrimidone

2-Amino-4-chloro-7-(2-thienylmethyl)pyrrolo[2,3-d] pyrimidine (563 mg, 2.10 mmol) was suspended in 30 ml of 1N HCl and ethanol (1:1) and the mixture was heated at reflux for 8 hours. Removal of solvent gave a residue which was chromatographed over silica gel and eluted with a mixture of hexane-ethyl-acetate (10:1) to give 139 mg of a mixture of 4-chloro and 4-ethoxy derivatives. So, it was dissolved in 30 ml of 3N HCl and the solution was heated to reflux for 2 hours and then allowed to cool. The precipitated solid was filtered and then recrystallized from methanol - 1N HCl (1:1) mixture to give 55 mg of the desired product as hydrochloride salt, mp 235-237°C (dec).

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A compound of formula (I)



I

wherein R_6 is OH or SH, R_2 is hydrogen or NH_2, R_7 and R_8 are independently hydrogen or NH_2 with the proviso that both cannot be NH_2 at once, n is an integer of from one through four, Ar is (i) phenyl unsubstituted or substituted by halogen, trifluoromethyl, alkyl of one to four carbon atoms, hydroxy or alkoxy of from one to four carbon atoms, (ii) 2- or 3-thienyl, or (iii) 2- or 3-furanyl, with the proviso that when R_6 is OH, R_2 is H_2N, and R_7 and R_8 are both hydrogen then Ar cannot be phenyl when n is 1; or a pharmaceutically acceptable base or acid addition salt thereof.

2. A compound of Claim 1 wherein R_7 is hydrogen.

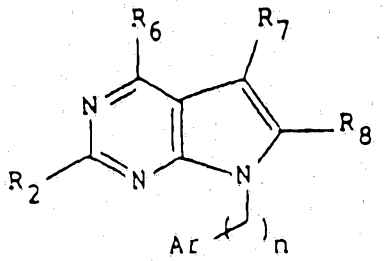
3. A compound of Claim 2 wherein R_8 is hydrogen.

4. A compound of Claim 2 wherein R_8 is amino.

5. A compound of Claim 3 and being 2-amino-7-(2-thienylmethyl)-4-pyrrolo[2,3-d]pyrimidone.

6. A compound of Claim 5 and being the hydrochloride salt thereof.

7. A pharmaceutical composition for treating psoriasis, autoimmune diseases or rejection of transplantation comprising an antipsoriatic, antiautoimmune disease or antirejection of transplantation effective amount of a compound of formula (I)or a pharmaceutically acceptable



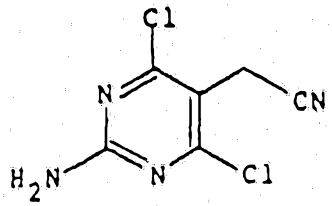
I

base or acid addition salt thereof; wherein R_6 is OH or SH, R_2 is hydrogen or NH_2, R_7 and R_8 are independently hydrogen and NH_2 with the proviso that both can not be NH_2 at once, n is an integer of from one to four, Ar is (i) phenyl unsubstituted or substituted by halogen, trifluoromethyl, alkyl of one to four carbon atoms, hydroxy, alkoxy of from one to four carbon atoms, (ii) 2- or 3-thienyl, or (iii) 2- or 3-furanyl and a pharmaceutically acceptable carrier.

8. A method for treating autoimmune disease or rejection of transplantation which comprises administering a composition of Claim 7 in unit dosage form.

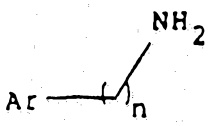
9. A method for treating psoriasis which comprises administering a composition of Claim 7 in unit dosage form.

10. A process for preparing a compound of formula I as defined in claim 7 which comprises treating a compound of the formula (X)



X

with a compound of the formula (V)



V

wherein Ar and n are as defined above and then treating with an acid to obtain the compound of formula I wherein R_6 is oxygen and R_8 is NH_2 and, alternatively, if desired, further deaminating by known methods, or treating by also known methods to obtain a compound of formula I wherein R_6 is sulfer and then, further deaminating.

DATED THIS 9TH DAY OF JULY 1991
WARNER-LAMBERT COMPANY

Attorney: WILLIAM S. LLOYD
Fellow Institute of Patent Attorneys of Australia
of SHELSTON WATERS

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 87/02727

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 D 487/04; A 61 K 31/505; C 07 D 239/42;//(C 07 D 487/04, 239:00,209:00)

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	C 07 D 487/00; A 61 K 31/00; C 07 D 239/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	Tetrahedron Letters, volume 26, no. 16, 1985, Pergamon Press Ltd (GB) M. Legraverend et al.: "A new route to 7-deazaguanine derivatives", pages 2001-2002, see compound 10a cited in the application	1
A	EP, A, 0156559 (WARNER-LAMBERT) 2 October 1985, see claim 1; page 7, lines 11,12; page 8	1,7
A	FR, A, 2574407 (RHONE-POULENC) 13 June 1986, see claim 1; page 5, lines 26-31	1,7

---

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16th February 1988	26 APR 1988
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	P.C.G. VAN DER PUTTEN

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 8,9, because they relate to subject matter not required to be searched by this Authority, namely:

See PCT-Rule 39.1 (iv): methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers ....., because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers ....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 8702727 SA 19649

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 18/04/88
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0156559	02-10-85	AU-A- 4021985	03-10-85
		JP-A- 60248690	09-12-85
FR-A- 2574407	13-06-86	None	