

AUSTRALIA

Patents Act 1990

NOTICE OF ENTITLEMENT
(To be filed before acceptance)

We, **SYNTEX (U.S.A.) INC.** of 3401 Hillview Avenue, Palo Alto, California 94304, United States of America, being the applicant in respect of Application No. **27815/92** state the following:-

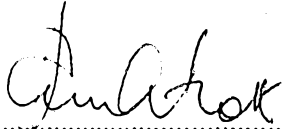
The person nominated for the grant of the patent has entitlement from the actual inventors by virtue of employment of the inventors.

The person nominated for the grant of the patent has entitlement from the applicant of the application listed in the declaration under Article 8 of the PCT.

The basic application listed on the request form is the first application made in a Convention country in respect of the invention.

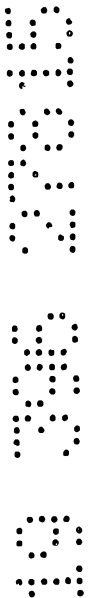
SYNTEX (U.S.A.) INC.

By our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS



14 March, 1996.

.....
Ian A. Scott
Registered Patent Attorney





AU9227815

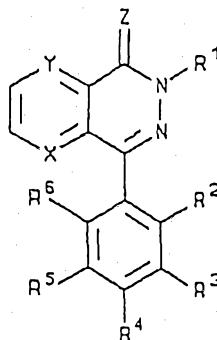
(12) PATENT ABRIDGMENT (11) Document No. AU-B-27815/92
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 670544

- (54) Title
BENZO AND PYRIDO PYRIDAZINONE AND PYRIDAZINTHIONE COMPOUNDS WITH PDE IV INHIBITING ACTIVITY
- International Patent Classification(s)
(51)⁵ C07D 471/04 A61K 031/50 C07C 069/76 C07D 213/80
A61K 031/495
- (21) Application No. : 27815/92 (22) Application Date : 08.10.92
- (87) PCT Publication Number : WO93/07146
- (30) Priority Data
- (31) Number (32) Date (33) Country
775679 09.10.91 US UNITED STATES OF AMERICA
- (43) Publication Date : 03.05.93
- (44) Publication Date of Accepted Application : 25.07.96
- (71) Applicant(s)
SYNTEX (U.S.A.) INC.
- (72) Inventor(s)
ROBERT STEPHEN WILHELM; BRADLEY EARL LOE; BRUCE HENRY DEVENS; ROBERT ALVAREZ;
MICHAEL GRANT MARTIN
- (74) Attorney or Agent
WATERMARK PATENT & TRADEMARK ATTORNEYS , Locked Bag 5, HAWTHORN VIC 3122
- (56) Prior Art Documents
WO 91/12251
- (57)

This invention relates to pyridopyridazinones and pyridazinthiones useful as anti-inflammatory agents, antasthmatic agents, immunosuppressive agents, anti-allograft rejection agents, anti-graft-vs-host disease agents, anti-autoimmune agents or analgetic agents, to their intermediates, to their preparation and to pharmaceutical compositions using the compounds of the invention.

CLAIM

1. A compound of the formula:



wherein:

- X and Y are carbon or nitrogen, provided both are not the same;
Z is oxygen or sulfur;

(11) AU-B-27815/92

-2-

(10) 670544

R¹ is hydrogen, lower alkyl, aryl, heteroaryl, or heterocycle lower alkyl;

R², R³, R⁴, R⁵ and R⁶ are independently selected from hydrogen, lower alkyl, halo, carboxy, alkoxy-carbonyl, carbamoyl, acyl, methylthio, trifluoromethyl, cyano or nitro;

with the proviso that when R¹ is lower alkyl, cycloalkyl, cycloalkylmethyl, benzyl or imidazolyl lower alkyl,

R², R³, R⁴, R⁵ and R⁶ are independently carbamoyl, acyl, cyano or nitro;

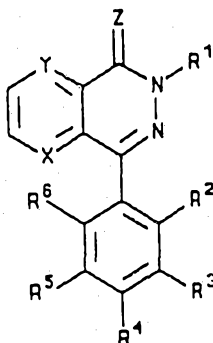
or a pharmaceutically acceptable ester, ether or salt thereof.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁵ : C07D 471/04, 237/32 A61K 31/50, C07D 213/79 C07C 69/76 // (C07D 471/04 C07D 237:00, 221:00)</p>	<p>A1</p>	<p>(11) International Publication Number: WO 93/07146 (43) International Publication Date: 15 April 1993 (15.04.93)</p>
<p>(21) International Application Number: PCT/US92/08398 (22) International Filing Date: 8 October 1992 (08.10.92) (30) Priority data: 07/775,679 9 October 1991 (09.10.91) US (71) Applicant: SYNTEX (U.S.A.) INC. [US/US]; 3401 Hillview Avenue, Palo Alto, CA 94304 (US). (72) Inventors: WILHELM, Robert, Stephen ; 1438 Todd Street, Mountain View, CA 94040 (US). LOE, Bradley, Earl ; 154 Stockton Avenue, Santa Cruz, CA 95050 (US). DEVENS, Bruce, Henry ; 627 Channing Avenue, Palo Alto, CA 94301 (US). ALVAREZ, Robert ; 2111 Mills Avenue, Menlo Park, CA 94024 (US). MARTIN, Michael, Grant ; 11 Harper Street, San Francisco, CA 94131 (US).</p>	<p>(74) Agents: CLARKE, Pauline, Ann et al.; Syntex (U.S.A.) Inc., 3401 Hillview Avenue, A2-200, Palo Alto, CA 94304 (US). (81) Designated States: AU, CA, FI, HU, JP, KR, NO, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> <p style="text-align: center; font-size: 2em; font-weight: bold;">670544</p>	

(54) Title: BENZO AND PYRIDO PYRIDAZINONE AND PYRIDAZINTHIONE COMPOUNDS WITH PDE IV INHIBITING ACTIVITY



(I)

(57) Abstract

Benzo or pyridopyridazinones and pyridazinthiones of formula (I) wherein: X and Y are nitrogen or carbon, provided that at least one is carbon, and Z is oxygen or sulfur; R¹ is hydrogen, lower alkyl, aryl, heteroaryl, or heterocycle lower alkylene; R², R³, R⁴, R⁵ and R⁶ are independently selected from hydrogen, lower alkyl, halo, carboxy, alkoxycarbonyl, carbamoyl, acyl, acyl halide, thiomethyl, trifluoromethyl, cyano or nitro; or a pharmaceutically acceptable ester, ether or salt thereof, have been found to be useful as an anti-inflammatory, antiasthmatic, immunosuppressive, anti-allograft rejection, anti-graft-vs-host rejection, autoimmune disease or analgetic agent(s).

PYRIDO PYRIDAZINONE
AND PYRIDAZINTHIONE COMPOUNDS

5

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

10

This invention relates to pyridopyridazinones and pyridazin-
thiones useful as anti-inflammatory agents, antasthmatic agents,
immunosuppressive agents, anti-allograft rejection agents, anti-
graft-vs-host disease agents, anti-autoimmune agents or analgetic
agents, to their intermediates, to their preparation and to
pharmaceutical compositions using the compounds of the invention.

15

BACKGROUND INFORMATION

20

Cyclic 3', 5'-adenosine monophosphate (cAMP) modulates a variety
of cellular and physiologic functions in mammals, such as, cell
division, endocrine function, and the immune response. The level of
cAMP is controlled, in part, by a class of enzymes called phospho-
diesterases, which enzymatically degrade cAMP. There are five families
of phosphodiesterase that are categorized according to their function.
For instance, phosphodiesterase III (PDE III) is isolated from human
platelet cells and modulates platelet aggregation. Another type of
phosphodiesterase, (PDE IV), is found in various cells but it is the
predominant form in human leukocytes. This enzyme modulates leukocyte
activation and function associated with the immune response and
inflammation. Both of these phospho-diesterases implement their control
by modulating the cellular level of cAMP in their respective cells.
Thus, inhibition of phosphodiesterases provides a method of modulating
any cellular and bodily function that is controlled by cAMP.

25

30

Compounds that are nonspecific phosphodiesterase inhibitors are
known, i.e., these compounds inhibit all or multiple types of
phosphodiesterases. [See, Beavo, J.A. and D.H. Reifsyder, *Trends in
Pharm. Science*, 11:150-155 (1990); and Nicholson, C.D., R.A.J. Challiss
and M. Shahid, *Trends in Pharm. Science*, 12:19-27 (1991).]

35

Nonspecific phosphodiesterase inhibitors are of limited value
because of numerous side-effects. Since cAMP is involved in so many
functions throughout the body, a nonspecific phosphodiesterase inhibitor
has the potential to alter all of the functions modulated by cAMP.

40

WO-A-91/12251 discloses a series of fused heterocyclic compounds
which have both bronchodilating and thromboxane A₂ synthetase inhibiting
action and are useful as bronchodilators and antiasthmatic agents.

45

It has been surprisingly discovered that certain
pyridopyridazinones are potent selective inhibitors of phosphodiesterase
IV (PDE IV). These compounds are well suited for use as a treatment
for any disorder in which PDE IV function plays a role, such as where
leukocyte activation or function is involved.

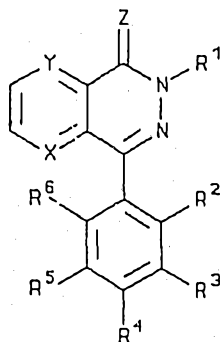
50

pyridopyridazinones are potent selective inhibitors of phosphodiesterase IV (PDE IV). These compounds are well suited for use as a treatment for any disorder in which PDE IV function plays a role, such as where leukocyte activation or function is involved.

In particular, these compounds are especially well suited for use as anti-inflammatory agents, antasthmatic agents, immunosuppressive agents, anti-allograft rejection agents, anti-graft-vs-host disease agents or anti-autoimmune disease agents.

SUMMARY OF THE INVENTION

One aspect of the present invention relates to pyridopyridazinones and pyridazinthiones, i.e., the compounds of Formula I:



Formula I

wherein:

X and Y are nitrogen or carbon, provided both are not the same, and Z is oxygen or sulfur;

R¹ is hydrogen, lower alkyl, aryl, heteroaryl, or heterocycle lower alkyl;

R², R³, R⁴, R⁵ and R⁶ are independently selected from hydrogen, lower alkyl, halo, carboxy, alkoxycarbonyl, carbamoyl, acyl, methylthio, trifluoromethyl, cyano or nitro;

with the proviso that when R¹ is lower alkyl, cycloalkyl, cycloalkylmethyl, benzyl or imidazolyl lower alkyl,

R², R³, R⁴, R⁵ and R⁶ are independently carbamoyl, acyl, cyano or nitro;

a pharmaceutically acceptable ester, ether or salt thereof.

In another aspect, the invention relates to a pharmaceutical composition containing a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable ester or salt thereof admixed with at least one pharmaceutically acceptable excipient.

In still another aspect, the invention relates to a method of use as an anti-inflammatory, antasthmatic, immunosuppressive, anti-allograft

rejection, anti-graft-vs-host rejection, autoimmune disease, or analgetic agent, by administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable ester or salt thereof.

5 Yet another aspect of the invention relates to the treatment of the above conditions or diseases by the selective inhibition of phosphodiesterase (PDE) IV.

Another aspect of the invention relates to processes for making the compounds of Formula I and the pharmaceutically acceptable salts and esters thereof.

10 For example, a compound of Formula I (where Z is oxygen) is made by reacting a compound of Formula II with a suitably substituted hydrazine. Or, a compound of Formula I (where Z is oxygen) is treated with a thiation reagent for ketones, e.g., Lawesson's Reagent, to give the corresponding compound of Formula I where Z is sulfur.

15 Another aspect of the invention relates to processes for making the compounds of Formula I (where R¹ is lower alkyl, aryl or heterocycle lower alkyl) by reacting a compound of Formula I (where R¹ is hydrogen) with a suitably substituted alcohol.

20 In another aspect, this invention provides compositions useful in the treatment of inflammatory, asthmatic, allograft rejection, graft-vs-host or autoimmune conditions or diseases, or pain in mammals through its use as an anti-inflammatory, antasthmatic, immunosuppressive, anti-allograft rejection, anti-graft-vs-host rejection, autoimmune disease, 25 or analgetic agent, wherein the composition comprises a therapeutically effective amount of a compound of Formula I as described above and a pharmaceutically acceptable excipient.

30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
150
155
160
165
170
175
180
185
190
195
200
205
210
215
220
225
230
235
240
245
250
255
260
265
270
275
280
285
290
295
300
305
310
315
320
325
330
335
340
345
350
355
360
365
370
375
380
385
390
395
400
405
410
415
420
425
430
435
440
445
450
455
460
465
470
475
480
485
490
495
500
505
510
515
520
525
530
535
540
545
550
555
560
565
570
575
580
585
590
595
600
605
610
615
620
625
630
635
640
645
650
655
660
665
670
675
680
685
690
695
700
705
710
715
720
725
730
735
740
745
750
755
760
765
770
775
780
785
790
795
800
805
810
815
820
825
830
835
840
845
850
855
860
865
870
875
880
885
890
895
900
905
910
915
920
925
930
935
940
945
950
955
960
965
970
975
980
985
990
995

DETAILED DESCRIPTION

DEFINITIONS AND GENERAL PARAMETERS

The following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The term "alkyl" refers to a cyclic, branched or straight chain monovalent alkyl radical of one to twenty-four carbon atoms.

The term "lower alkyl" refers to a cyclic, substituted cyclic, branched or straight chain monovalent alkyl radical of one to nine carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, isopropyl, cyclopropylmethyl, i-butyl, n-butyl, t-butyl, pentyl, cyclopentyl, cyclopentylmethyl, n-hexyl, cyclohexyl, cyclohexylmethyl, cyclohexylethyl, n-heptyl, cycloheptyl, cycl.cneptylmethyl or cycloheptylethyl.

The term "lower alkoxy" refers to the group $-O-R'$ where R' is lower alkyl.

The term "carboxy" refers to the group $-C(O)OH$.

The term "alkoxycarbonyl" refers to the group $-C(O)OR$ where R is alkyl.

The term "carbamoyl" refers to the group $-C(O)NR'R''$ where R' and R'' are independently hydrogen or lower alkyl.

The term "aryl" refers to a monovalent unsaturated aromatic carbocyclic radical having a single ring (e.g., phenyl) or two condensed rings (e.g., naphthyl), which can optionally be mono-, di-, tri-, tetra- or penta-substituted, independently, with hydroxy (phenol), lower alkyl (toluenyl or benzyl), lower alkoxy, chloro, fluoro, trifluoromethyl, carbamoyl, nitro and/or cyano.

The term "heteroaryl" refers to a 5- or 6-membered ring which contains 1 to 4, preferably 1 to 3, identical or different hetero atoms such as nitrogen, oxygen or sulfur.

Typical examples are: pyridyl, pyridyl-N-oxide, thienyl, furyl, pyrrolyl, pyrrolidinyl, imidazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyridonyl, and the like.

The term "halo" refers to fluoro, bromo, chloro, iodo.

The term "heterocycle" refers to saturated, unsaturated or aromatic monovalent mono- or poly- carbocyclic radicals having at least one hetero atom (such as nitrogen, oxygen or sulfur) or a combination thereof, which can optionally be substituted, independently, with, e.g., hydroxy, amino, imino, lower alkyl, lower alkoxy, carboxy, carbamoyl, acyl, aryl, halo, and/or cyano. Further, the term also includes instances where an atom of a heterocycle has been oxidized, e.g., N-oxides, sulfoxides, sulfones, or oxo. For example, typical heterocycles with one or more nitrogen or sulfur atoms are pyrrole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazine, pyrrolidine, pyrrolidinone, pyrazolidine, piperidine, piperazine, morpholine, pyridine, pyridone, triazole, oxazole, oxadiazole, thiazole, and the like.

The term "heterocycle lower alkyl" refers to the group heterocycle-R-, wherein heterocycle is as defined above, and R represents lower alkyl as defined above. Typical heterocycle lower alkyl groups are, e.g. 4-pyridylmethyl, 3-pyridylethyl, 2-pyridylmethyl, 2-pyridylpropyl, 3-thienylmethyl, or 2-thienylethyl.

The term "N-oxide" refers to nitrogen heterocycles where a nitrogen atom in the ring has been oxidized, e.g., 4-pyridyl-N-oxide, 3-pyridyl-N-oxide, or 2-pyridyl-N-oxide.

The term "esterification reagent" refers to a reagent (e.g., diazomethane, methanol, methyl iodide, ethyl iodide or ethanol) that when contacted with a carboxy group results in the formation of the corresponding alkoxy carbonyl group.

5 The term "alkylating agent" refers to a halo-substituted alkyl, aryl or heterocycle compound (e.g., iodoethane, 2-iodopropane, iodobutane, iodopentane, 4-picoly l chloride, 3-picoly l chloride or benzyl bromide) that, when in the presence of a base, can join the alkyl, aryl or heterocycle moiety to a nitrogen atom.

10 The term "compound", as used in the detailed description in reference to the compound of Formula I, is intended to refer to the pharmaceutically acceptable salts, esters and ethers of the compound, unless expressly stated otherwise, such as "the compound of Formula I as a free base".

15 The term "pharmaceutically acceptable salt" refers to any salt derived from an inorganic or organic acid or base. The term "pharmaceutically acceptable anion" refers to the anion of such acid addition salts. The term "pharmaceutic- ally acceptable cation" refers to the cation of such base addition salts. The salt, anion and/or the cation are chosen not to be biologically or otherwise undesirable.

20 The anions are derived from inorganic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid (giving the sulfate and bisulfate salts), nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, 25 cyclopentanepropionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxy-benzoyl)benzoic acid, benzenesulfonic acid, p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, cinnamic acid, mandelic acid, 30 methanesulfonic acid, ethanesulfonic acid, 1,2-ethane disulfonic acid, 2-hydroxyethanesulfonic acid, salicylic acid, p-toluenesulfonic acid and the like.

35 The cations are derived from bases, such as alkaline earth hydroxides, including calcium hydroxide, potassium hydroxide, potassium carbonate, sodium hydroxide, sodium hydride, lithium hydroxide and the like, preferably sodium hydroxide.

40 The term "pharmaceutically acceptable esters" and "pharmaceutically acceptable ethers" refer to those compounds of Formula I where an oxygen or a nitrogen has been modified, e.g., acylated by the addition of the group $-C(=O)-W$, wherein W is an alkyl group containing 1 to 20 carbon atoms including adamantyl, aryl, amino, alkylamino, dialkylamino, an alkoxy group containing 1 to 20 carbon atoms, $-CH_2-O-CH_3$, or $-CH_2-NH_2$. This invention contemplates those compounds of Formula I which are esters as described herein and at the same time are

the pharmaceutically acceptable acid addition salts thereof.

The terms "inert organic solvent" or "inert solvent" refer to a solvent inert under the conditions of the reaction being described in conjunction therewith [including, for example, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), dimethylformamide ("DMF"), chloroform, methylene chloride (or dichloromethane), diethyl ether, pyridine and the like]. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert organic solvents.

As used herein, the term "autoimmune disease" refers to disorders wherein the immune system of a mammal mounts a humoral or cellular immune response to the mammal's own tissue or to antigenic agents that are not intrinsically harmful to the mammal, thereby producing tissue injury in such a mammal. Examples of such disorders include, but are not limited to, systemic lupus erythematosus, rheumatoid arthritis and type I diabetes.

As used herein, the term "allograft rejection" refers to the humoral or cellular immune response mounted by the immune system of a mammal after it has received a histo-incompatible tissue graft from another mammal of the same species, thereby producing tissue injury in such a mammal.

As used herein, the term "graft-vs-host disease" refers to the immune response that originates from transplanted graft tissue, in particular, transplanted bone-marrow tissue, and that is directed towards the host tissue, thereby producing tissue injury in the host.

As used herein, the term "treatment" or "treating" means any treatment of a disease in a mammal, including:

- (i) preventing the condition or disease, that is, avoiding any clinical symptoms of the disease;
- (ii) inhibiting the condition or disease, that is, arresting the development or progression of clinical symptoms; and/or
- (iii) relieving the condition or disease, that is, causing the regression of clinical symptoms.

As used herein, the term "therapeutically effective amount" refers to that amount of a compound of Formula I which, when administered to a mammal in need thereof, is sufficient to effect treatment (as defined above) as an anti-inflammatory, antasthmatic, immunosuppressive, anti-allograft rejection, anti-graft-vs-host disease, autoimmune disease or analgetic agent(s). What amount constitutes a "therapeutically effective amount" will vary depending on the compound, the condition and its severity, and the mammal to be treated, but may be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

As used herein, the term "q.s." means adding a quantity sufficient

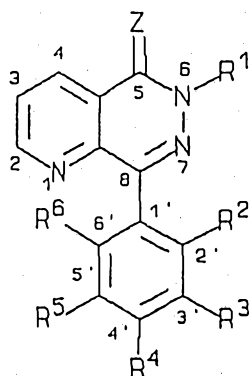
to achieve a stated function, e.g., to bring a solution to a desired volume (e.g., 100 mL).

Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about -100°C to about 200°C, more preferably from about 10°C to about 50°C, and most preferably at about room (or "ambient") temperature, e.g., about 20°C.

Isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, preparative high pressure liquid chromatography (preparative HPLC), thin-layer chromatography or thick-layer chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the examples hereinbelow. However, other equivalent separation or isolation procedures can, of course, also be used.

Naming of Compounds

For the compounds of the instant invention containing a pyridopyridazinone ring moiety, where X is nitrogen, Y is carbon, and Z is oxygen (i.e., pyrido[2,3-d]pyridazin-5-one compounds), the following numbering system will be used:



Formula I

Representative compounds are named in the following examples.

The compound of Formula I where X is nitrogen, Y is carbon, Z is oxygen, R¹ is 4-pyridyl-N-oxide-methyl, R³ is chloro, R², R⁴, R⁵ and R⁶ are hydrogen, can be named 6-(4-pyridyl-N-oxide-methyl)-8-(3-chlorophenyl)-

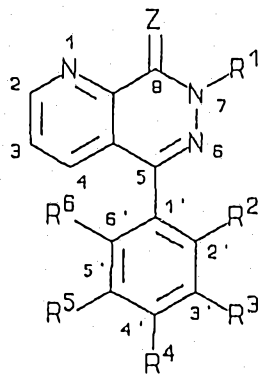
pyrido[2,3-d]pyridazin-5-one.

The compound of Formula I where X is nitrogen, Y is carbon, Z is sulfur, R¹ is benzyl, R³ is chloro, R², R⁴, R⁵ and R⁶ are hydrogen, can be named 6-benzyl-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-thione.

5

For the compounds of the instant invention containing a pyridopyridazinone ring moiety, where X is carbon, Y is nitrogen, and Z is oxygen (i.e., pyrido[2,3-d]pyridazin-8-one compounds), the following numbering system will be used:

10



15

20

Formula I

25

The compound of Formula I where X is carbon, Y is nitrogen, Z is oxygen, R¹ is benzyl, R³ is nitro, R², R⁴, R⁵ and R⁶ are hydrogen, can be named 7-benzyl-5-(3-nitrophenyl)pyrido[2,3-d]pyridazin-8-one.

30

SYNTHESIS OF THE COMPOUNDS OF FORMULAE I AND II

The compounds of Formulae I and II are synthesized as described with reference to Reaction Scheme A. As used in Reaction Scheme A, X and Y are nitrogen or carbon atoms, provided both are not the same, and Z is oxygen, R¹ is hydrogen, lower alkyl, aryl, heteroaryl or heterocycle lower alkyl; and R², R³, R⁴, R⁵ and R⁶ are independently selected from hydrogen, lower alkyl, halo, carboxy, alkoxycarbonyl, carbamoyl, acyl, methylthio, trifluoromethyl, cyano or nitro.

35

Reaction Scheme A illustrates the preparation of novel pyridopyridazinones (Formula I where X is nitrogen, Y is carbon, and Z is oxygen) and the corresponding intermediate pyridoarylketoesters (Formula II).

40

Reaction Scheme B illustrates a preparation for the intermediate pyridoarylketoesters (Formula II where X and Y are carbon or nitrogen,

provided both are not the same, using an organolithium, organocadmium or Grignard reagent.

Reaction Scheme C illustrates an alternative preparation of novel pyridopyridazinones (Formula I where Z is oxygen) from
 5 pyridopyridazinones, where R¹ is hydrogen.

Reaction Scheme D illustrates a preparation for the intermediate pyridoaryl ketoesters (Formula II where X and Y are carbon or nitrogen, provided both are not the same, and R³ is nitro).

Reaction Scheme E illustrates a preparation of novel pyridyl-N-oxide-methyl substituted pyridopyridazinones (Formula I) from
 10 pyridopyridazinones (Formula I), where R¹ is hydrogen.

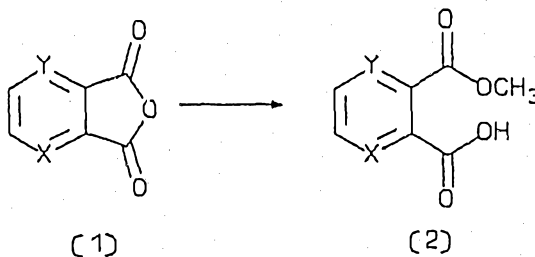
Reaction Schemes F and G illustrate an alternative preparation of novel optionally substituted compounds of Formula I, where X is nitrogen, Y is carbon, and Z is oxygen.

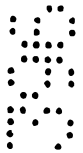
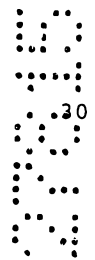
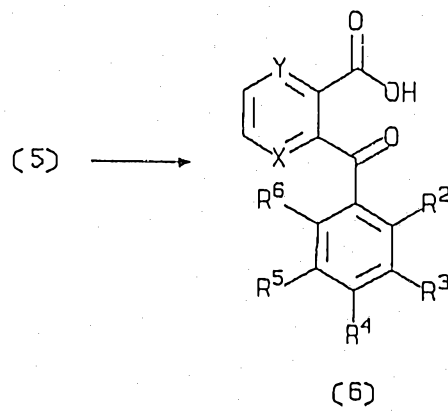
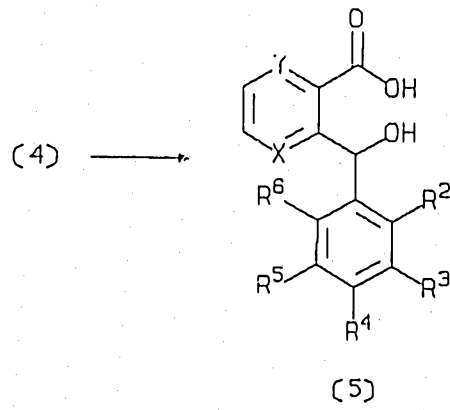
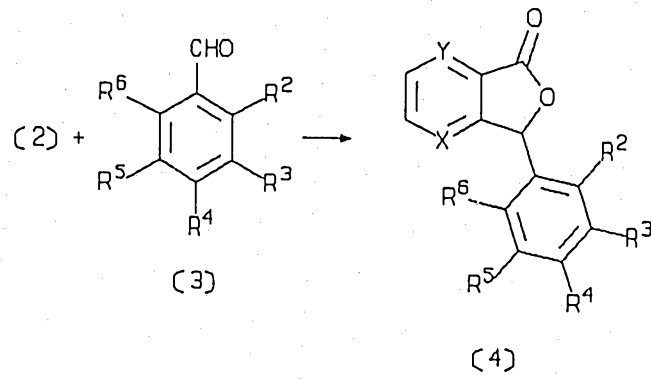
Shown in Reaction Scheme F is the preparation of optionally substituted nitrophenyl heteroaryl hetero-oxide pyridopyridazinones (compounds of
 15 Formula I, where X is nitrogen, Y is carbon, Z is oxygen, R¹ is heteroaryl hetero-oxide, and R³ is nitro).

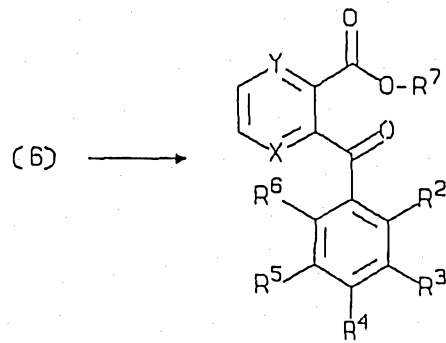
Shown in Reaction Scheme G is the preparation of optionally substituted chlorophenyl heteroaryl hetero-oxide pyridopyridazinones (Formula I,
 20 where X is nitrogen, Y is carbon, Z is oxygen, R¹ is heteroaryl hetero-oxide, and R³ is chloro).

25

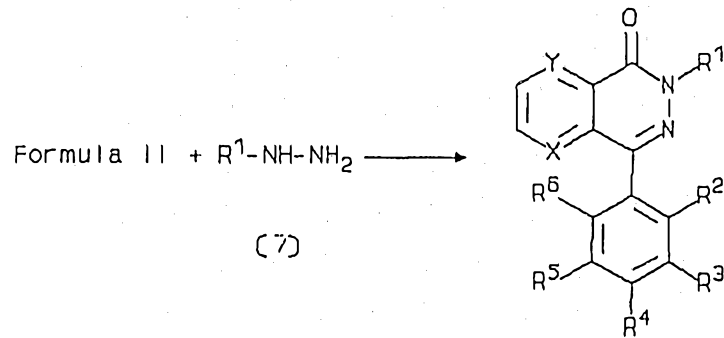
REACTION SCHEME A



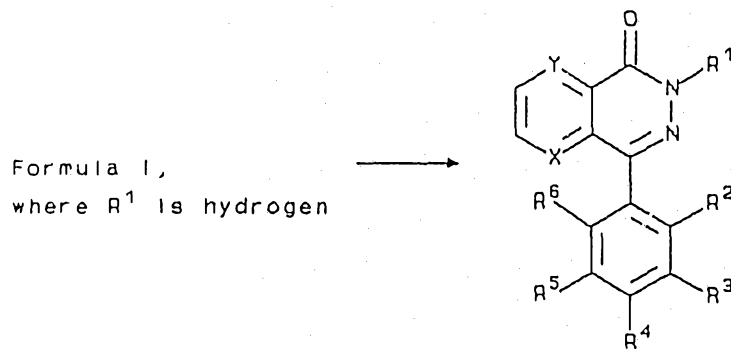




Formula II



Formula I



Formula I

where R^1 is lower alkyl, aryl, hetero-
aryl or heterocycle lower alkylene

STARTING MATERIALS

Referring to Reaction Scheme A, most of the compounds of Formula I

are commercially available from Aldrich Chemicals and ICN Chemicals. Similarly, many of the substituted hydrazines (Formula 7) are commercially available from Aldrich Chemicals, those that are not can be prepared by following the disclosures of S.R. Sandler and W. Karo, "Organic Functional Group Preparations" 2nd Ed. 1983, Vol 12-I, Academic Press, New York.

PREPARATION OF FORMULA 2

A pyridodicarboxylic anhydride (Formula 1) is dissolved in a solvent [e.g., an alcohol (methanol or ethanol), preferably methanol] and heated for a period of about 2 to 20 minutes, preferably about 10 minutes at a temperature of about 80 to 120°C, preferably about 100°C.

The desired product is taken directly to the next step without purification.

PREPARATION OF FORMULA 4

An optionally substituted pyridoacidester (Formula 2) is added to about 5.0 molar equivalents of an optionally substituted benzaldehyde (Formula 3) and about 5.0 molar equivalents of a solvent, such as *p*-cymene, dibromobenzene, nitrotoluene, bromoanisole or xylene, preferably *p*-cymene. The mixture is heated to a temperature of about 150°C to 210°C, preferably about 180°C for a period of about 2 to 6 hours, preferably about 4 hours. The solution is cooled and the excess benzaldehyde and solvent are removed yielding the desired optionally substituted pyridolactone (the compound of Formula 4). The desired compound can be purified by silica gel chromatography or the like, however, preferably the desired compound is taken without purification directly to the next step.

PREPARATION OF FORMULA 5

An optionally substituted pyridolactone (Formula 4) is suspended in a basic solution (e.g., potassium hydroxide, sodium hydroxide or ammonium hydroxide in a solvent such as, methanol or ethanol, preferably potassium hydroxide in methanol at a ratio of about 4.5 grams/100ml) and refluxed for a period of about 3 to 9 hours, preferably about 6 hours. The mixture is cooled and the solvent removed yielding a pyridobenzylhydroxy acid (Formula 5).

PREPARATION OF FORMULA 6

A pyridobenzylhydroxy acid (Formula 5) is suspended in a solvent that is inert to oxidation agents (e.g., methylene chloride, chloroform or carbon tetrachloride, preferably methylene chloride). To this solution is added about 1.0 molar equivalent of an oxidation agent, such

as pyridinium dichromate, pyridinium chlorochromate or manganese dioxide, preferably pyridinium dichromate. The solution is stirred at a temperature in the range of about 0°C to 50°C, preferably about 21°C (room temperature) for a period of about 9 to 27 hours, preferably about 18 hours, yielding the desired optionally substituted pyridobenzoylacid (Formula 6). The desired product can be isolated and purified, however, the product is preferably taken directly to the next step without purification.

PREPARATION OF FORMULA II

A pyridobenzoylacid (Formula 6) is dissolved in a solvent (e.g., methylene chloride, chloroform or carbon tetrachloride, preferably methylene chloride) and cooled to a temperature in the range of about -20°C to 20°C, preferably about 0°C. About 1.2 molar equivalent of an esterification reagent such as, diazomethane, is added to the solution and stirred for a period of about 1 to 5 hours, preferably the reaction is monitored by TLC to completion (about 2 hours). The desired optionally substituted pyridobenzoylester (Formula II) is isolated and purified by the removal of the solvent followed by chromatography.

Alternatively, an optionally substituted pyridobenzoylester (Formula II) is prepared by dissolving a suitably substituted pyridobenzoylacid (Formula 6) in a solvent (e.g., methanol, ethanol or the like, preferably methanol) to which is added about 1 molar equivalent of a strong acid (e.g., concentrated H₂SO₄, HCl (gas), BF₃·Et₂O, preferably concentrated H₂SO₄).

The solution is stirred for a period of about 6 to 30 hrs, preferably about 18 hrs at the reflux temperature of the solvent used. The solution is cooled and made basic. The desired optionally substituted pyridobenzoylester (Formula II) is isolated and purified by chromatography.

As indicated the desired compound may be purified by silica gel chromatography or the like, however, preferably the desired compound is taken without further purification to the next step.

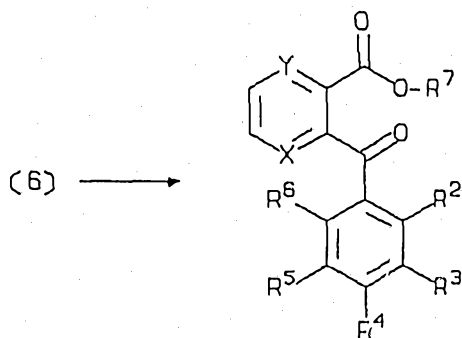
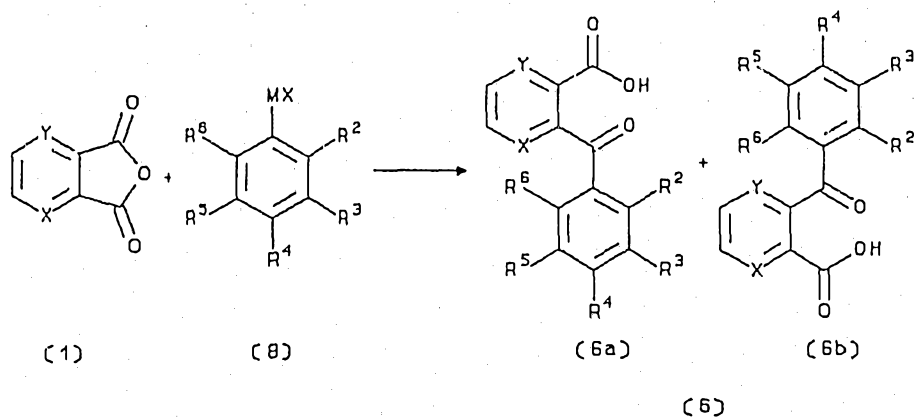
PREPARATION OF FORMULA I

An optionally substituted pyridobenzoylester (Formula II) is suspended in a solvent (about 15 ml/mmol) (e.g., ethanol, methanol or the like, preferably ethanol). To this suspension is added about 2 molar equivalents of an unsubstituted or substituted hydrazine (Formula 7, where R¹ is hydrogen, lower alkyl, aryl, heteroaryl, or heterocycle lower alkyl). The mixture is refluxed for a period of about 4 hours to 240 hours. The specific time is dependent on the substituent (i.e., R¹) of the hydrazine. Preferably, the reaction mixture is monitored by TLC for completion. The mixture is allowed to cool and

filtered to give a crude product. The desired pyridobenzoylpyridazinones (Formula I) are purified and isolated following extraction and chromatography.

Other optionally substituted compounds of Formula I are prepared by suspending a suitably substituted compound of Formula I, where R¹ is hydrogen, in a solvent (about 10 to 100ml/mole). To this suspension is added about 1 to 20 molar equivalents of a suitable base (e.g., sodium hydride, potassium carbonate, potassium iodide) and about 1 to 20 molar equivalents of a suitable alkylating agent (e.g., iodoethane, 4-picoly chloride, 2-iodopropane). The mixture is refluxed under an inert atmosphere for about 6 to 48 hours, preferably about 18 hours, most preferably the reaction is monitored by TLC for completion. The mixture is allowed to cool and purified following standard chromatographic techniques yielding the desired pyridobenzoylpyridazinones (Formula I).

REACTION SCHEME B



Formula II

ALTERNATE PREPARATION OF FORMULA II

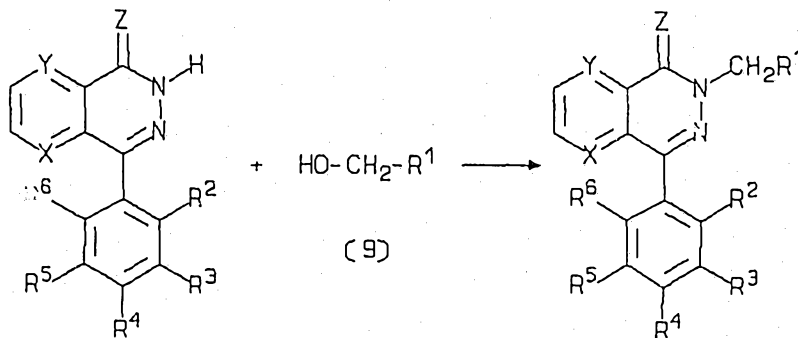
Alternatively, the compounds of Formula II can be prepared using an organolithium or organocadmium reagent as illustrated in "Preparation of Arylbenzoic Acid. Reaction of Aryllithium Reagents with Phthalic Anhydride", *J. Organic Chem.*, 41(7), 1268 (1976), or by Grignard reagent.

The Grignard preparation is illustrated in Reaction Scheme B (where M is Mg). A Grignard reagent is prepared by adding to a solution of an optionally substituted halogenated aryl compound (Formula 8) in a solvent (e.g., tetrahydrofuran or ethyl ether, preferably tetrahydrofuran) about 1 molar equivalent of magnesium followed by stirring for a period of 12 to 24 hours, preferably 18 hours, at a temperature in the range of about 0°C to 50°C, preferably room temperature under an inert atmosphere. The Grignard reagent (Formula 8) is added to a pyridodicarboxylic anhydride (Formula 1) in a solvent (e.g., tetrahydrofuran, methylene chloride, chloroform or ethyl ether, preferably tetrahydrofuran) at a temperature in the range of about 0°C to -150°C, preferably about -78°C in a gradual manner over a period of about 2 hours. After the addition, the solution is stirred for a period of about 15 minutes to 75 minutes, preferably about 45 minutes. An acid (e.g., 1N HCl) is added to the solution at a slight molar excess and stirred for a period of about 1 hour. In the case where Formula 1 is pyridodicarboxylic anhydride (i.e., where either X or Y are nitrogen), the preparation results in two positional isomers of the Formula 6, i.e. Formulae 6a and 6b. Depending on the desired product, i.e., Formula I where X is nitrogen and Y is carbon, or Formula I where X is carbon and Y is nitrogen, the suitable isomer of Formula 6 (Formulae 6a or 6b) is isolated and purified and used in the following preparations as the compound of Formula 6.

PREPARATION OF FORMULA II

An optionally substituted pyridobenzoylester (Formula II) can be prepared from a pyridobenzoylester (Formula 6) by following the procedures set forth in Reaction Scheme A

REACTION SCHEME C

PREPARATION OF FORMULA I WHERE R¹ IS LOWER ALKYL, ARYL OR HETEROCYCLE.

20 Alternatively, optionally substituted pyridopyridazinone compounds (Formula I, where R¹ is lower alkyl, aryl, heteroaryl, or heterocycle lower alkyl) can be prepared from a pyridopyridazinone compound (Formula I) where R¹ is hydrogen by following Mitsunobu reaction conditions, as illustrated in O. Mitsunobu, *Synthesis*, 1, 1981, and incorporated herein by reference.

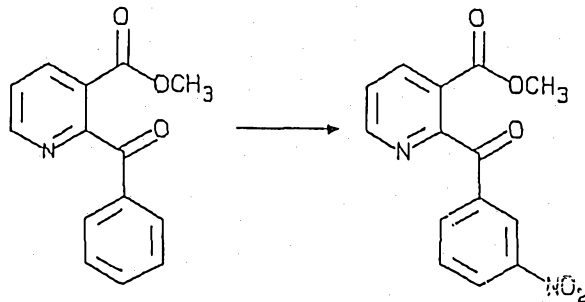
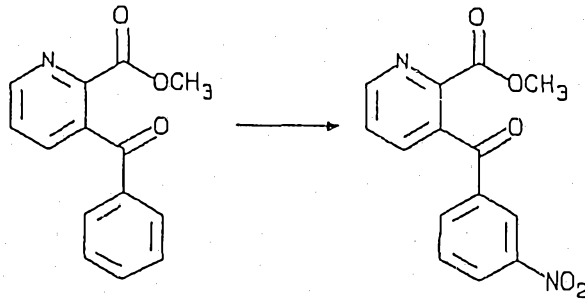
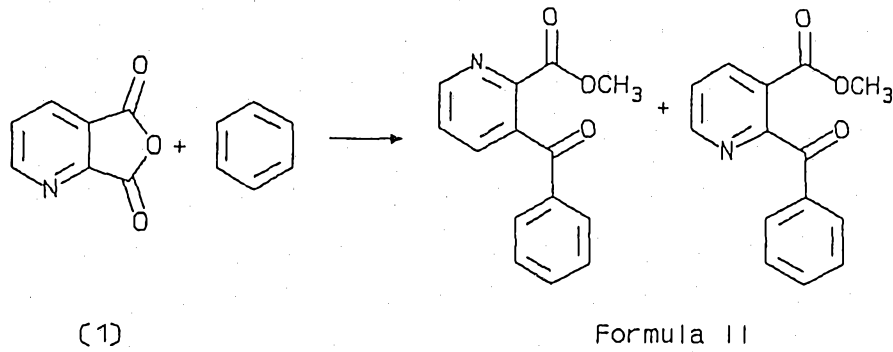
25 To a suspension of a pyridopyridazinone (Formula I) where R¹ is hydrogen in a solvent (e.g., tetrahydrofuran, diethyl ether, dioxane, preferably tetrahydrofuran) is added about 1 molar equivalent of an optionally substituted alcohol (Formula 9, where R¹ is lower alkyl, aryl, heteroaryl, or heterocycle lower alkyl) and about 1.5 molar equivalent of a trisubstituted phosphine, preferably triphenylphosphine. To the solution is added about 1.5 molar equivalent of a disubstituted azodicarboxylate, such as diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD), preferably diisopropyl azodicarboxylate in a gradual manner. The solution is stirred for a period of about 12 to 24 hours, preferably, about 18 hours at a temperature in the range of about 0°C to 50°C, preferably about 21°C (room temperature). The solvent is removed and the desired optionally substituted pyridopyridazinone (Formula I, where R¹ is lower alkyl, aryl, heteroaryl, or heterocycle lower alkyl) is isolated and purified by chromatography.

30

35

40

REACTION SCHEME D



PREPARATION OF FORMULA II WHERE X IS CARBON AND Y IS NITROGEN.

35

A pyridophenylketoester (i.e., Formula II where X and Y are carbon or nitrogen, provided both are not the same, and R², R³, R⁴, R⁵ and R⁶ are hydrogen) can be prepared following the procedures in U.S. Patent 4,806,535.

PREPARATION OF FORMULA II WHERE X IS CARBON, Y IS NITROGEN AND R³ IS NITRO

40

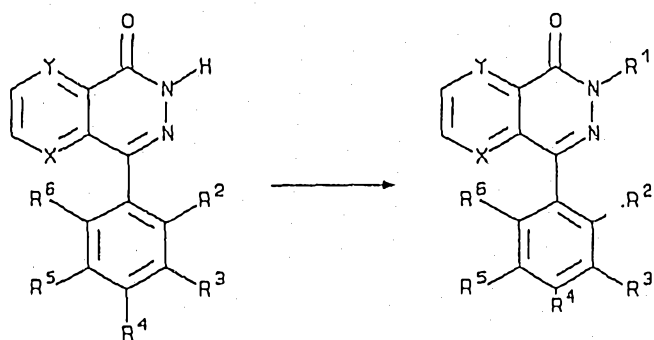
A pyrido(3-nitrobenzoyl)ketoester (Formula II where X is carbon, Y is nitrogen and R³ is nitro) is prepared by dissolving a pyridophenylketoester in an acid (such as hydrochloric acid, nitric acid,

sulfuric acid, preferably, sulfuric acid) and adding in a dropwise manner a solution of nitric acid and sulfuric acid (about 1 to 3 molar equivalent of nitric acid with about 2 ml of sulfuric acid per molar equivalent of nitric acid). The solution is stirred for about 10 to 60 minutes, preferably about 30 minutes, cooled and adjusted to a pH of about 7 to 8. The solvent is removed and the desired optionally substituted pyridopyridazinone (Formula I, where X is carbon, Y is nitrogen and R¹ is nitro) is isolated and purified by chromatography.

PREPARATION OF THE SALT OF FORMULA I

The pharmaceutically acceptable salts of Formula I are prepared by dissolving a compound of Formula I in a suitable solvent (such as methanol) adding 1 to 3 molar equivalents (preferably about two molar equivalent) of an appropriate acid (such as hydrochloric acid) or base (such as an alkaline earth hydroxide, e.g., lithium hydroxide, calcium hydroxide, potassium hydroxide, sodium hydroxide, preferably sodium hydroxide) with stirring. The salt is isolated by lyophilization or by precipitation, using techniques that will be apparent to those skilled in the art.

REACTION SCHEME E



Formula I, where
R¹ is hydrogen

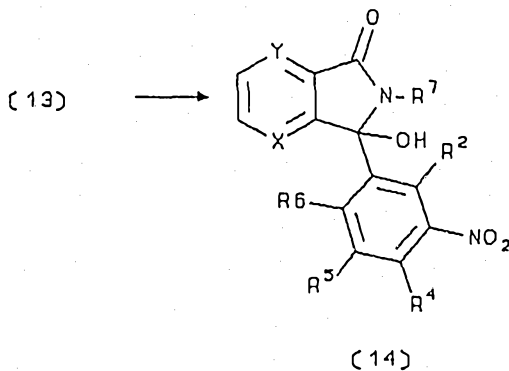
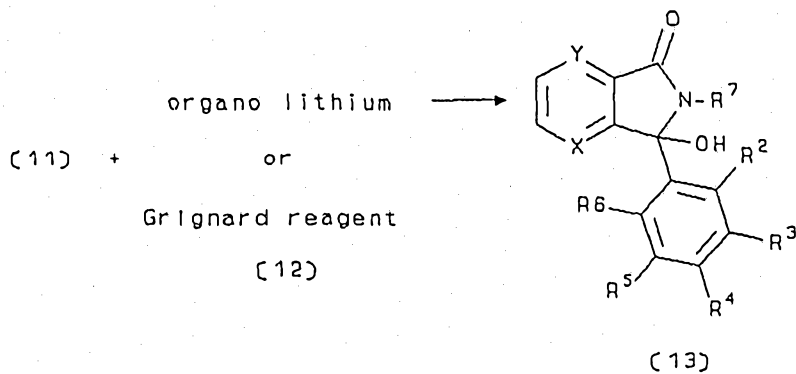
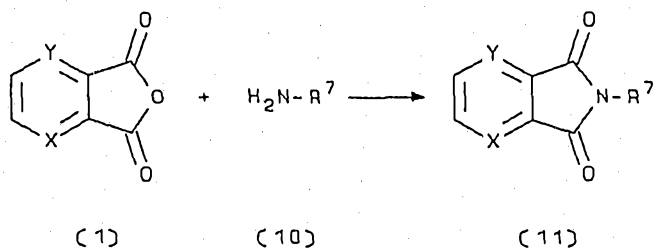
Formula I
where R¹ is N-oxide
heterocycle lower alkylene

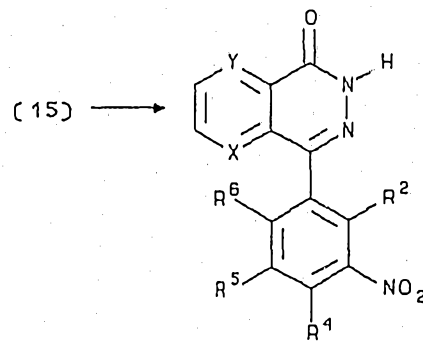
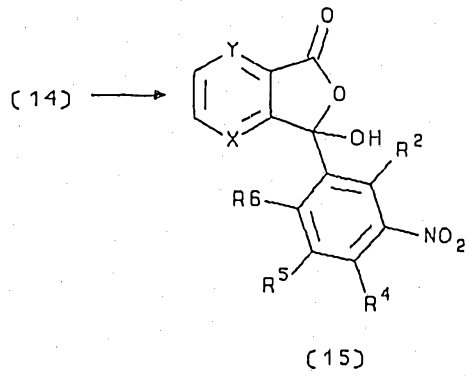
PREPARATION OF FORMULA I WHERE R¹ IS PYRIDYL-N-OXIDE-ALKYL.

Optionally substituted pyridyl-N-oxide-alkyl pyridopyridazinones are prepared by following Mitsunobu reaction conditions, as illustrated in O. Mitsunobu, *Synthesis*, 1, 1981, and incorporated herein by reference. An optionally substituted pyridopyridazinone (Formula I) where R¹ is hydrogen is combined into a suspension with about 1.1 molar equivalents of an optionally substituted pyridylcarbinol N-oxide, about

1.5 molar equivalents of triphenylphosphine in a solvent (e.g., tetrahydrofuran, diethyl ether, dioxane, preferably tetrahydrofuran). The suspension is stirred for a period of about 12 to 24 hours, preferably about 18 hours, at a temperature in the range of 12 to 36°C, preferably about 24°C. The solvent is removed and the desired optionally substituted pyridyl-N-oxide-alkyl pyridopyridazinone is isolated by chromatography, e.g., elution by 100% ethylacetate, followed by 10% methanol/ethylacetate or like solvent systems.

REACTION SCHEME F

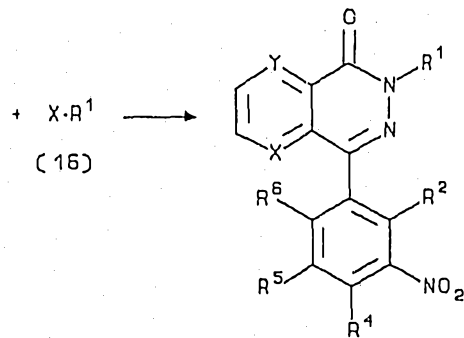




Formula I, where

R¹ is hydrogen and
R³ is nitro

Formula I, where
R¹ is hydrogen and
R³ is nitro



Formula I, where
R¹ is heteroaryl
R³ is nitro

Formula I, where
 R^1 is heteroaryl and
 R^3 is nitro

→

Formula I, where
 R^1 is heteroaryl
hetero-oxide and
 R^3 is nitro

5

PREPARATION OF A COMPOUND OF FORMULA 11

A pyridodicarboxylic anhydride (Formula 1, where X is nitrogen and Y is carbon) is suspended in a solvent (such as toluene, ethyl acetate, tetrahydrofuran, preferably ethyl acetate) and a primary amine (Formula 10, where R^7 is lower alkyl, such as, ethyl, propyl, butyl, hexyl, or n-butyl, preferably n-butyl) is added. The temperature is kept in a range of about -10°C to about 80°C , preferably room temperature. After a period of about 10 minutes to about 24 hours, preferably about 1 hour, a dehydrating reagent (such as, acetic anhydride, trifluoroacetic anhydride, phosphorous pentoxide, or thionyl chloride, preferably thionyl chloride) is added. The temperature of the mixture is kept in a range of about 0°C to about 80°C (depending on the dehydrating reagent) for a period of about 30 minutes to about 4 hours, preferably about 1 hour. The resulting pyridoimide (Formula 11, where X is nitrogen, Y is carbon and R^7 is lower alkyl) is isolated by chromatography or crystallization, preferably crystallization.

10

15

20

PREPARATION OF A COMPOUND OF FORMULA 13

The pyridoimide (Formula 11) is dissolved in a solvent that is inert to Grignard reagents and organolithium reagents (e.g., tetrahydrofuran, diethyl ether, toluene, preferably toluene) and cooled to a temperature in the range of about -100°C to room temperature, preferably about -65°C . About 0.5 to 3.0 molar equivalent, preferably about 1.0 molar equivalent of an optionally substituted phenyl Grignard reagent or optionally substituted phenyl organolithium reagent, preferably an optionally substituted phenyl Grignard reagent (Formula 8) in either tetrahydrofuran or diethyl ether, preferably tetrahydrofuran is added at such a rate that the internal temperature of the solution is maintained in a range of about -78°C to about room temperature, preferably about -45°C . After a period of about 10 minutes to about 5 hours, preferably about 30 minutes, the reaction is quenched with dilute hydrochloric acid, dilute acetic acid, aqueous ammonium chloride solution, dilute sulfuric acid, or the like, preferably aqueous ammonium chloride solution. The resulting phenyl pyridolactam compound (Formula 13 where X is nitrogen, Y is carbon, R^7 is lower alkyl, and R^3 is hydrogen) can be isolated by chromatography, crystallization or used as a crude mixture in the next reaction, preferably the product is isolated by crystallization.

25

30

35

40

PREPARATION OF A COMPOUND OF FORMULA 14 WHERE R³ IS NITRO

The phenyl pyridolactam compound (Formula 13) is suspended in sulfuric acid and cooled to a temperature in the range of about -10°C to about 40°C, preferably room temperature. Nitric acid is added at such a rate that the temperature is maintained below about 60°C, preferably below about 45°C. Following the addition of the nitric acid the mixture is stirred for a period of about 10 minutes to about 6 hours, preferably about 30 minutes. The mixture is then added to water and extracted with a water immiscible solvent (e.g., diethyl ether, ethyl acetate, toluene, methylene chloride, preferably ethyl acetate). The resulting optionally substituted nitrophenyl pyridolactam compound (Formula 14 where X is nitrogen, Y is carbon, and R³ is nitro) can be isolated by chromatography, crystallization or preferably used directly in the next step.

PREPARATION OF A COMPOUND OF FORMULA 15 WHERE R³ IS NITRO

An optionally substituted nitrophenyl pyridolactam compound (Formula 14) as prepared in the previous step is dissolved or suspended in about 2 to 6 molar equivalent, preferably about 3 molar equivalent, dilute acid (such as, hydrochloric acid, hydrobromic acid, sulfuric acid, preferably hydrochloric acid) and heated to reflux for about 4 hours to about 48 hours, preferably about 24 hours. The optionally substituted nitrophenyl pyridolactone compound (Formula 15 where X is nitrogen, Y is carbon, and R³ is nitro) is isolated by filtration or neutralization and extraction, followed by crystallization or chromatography, preferably filtration.

PREPARATION OF A COMPOUND OF FORMULA I, WHERE R¹ IS HYDROGEN AND R³ IS NITRO

An optionally substituted nitrophenyl pyridolactone compound (Formula 15) is mixed with a solvent inert and miscible with hydrazine (e.g., methanol, ethanol, dimethylformamide, preferably methanol) and heated to a temperature in the range of about room temperature to about 80°C, preferably about 65°C. After stirring the reaction for a period of about 1 hour to about 24 hours, preferably about 18 hours, an optionally substituted nitrophenyl pyridopyridazinone (Formula I where X is nitrogen, Y is carbon, Z is oxygen, R¹ is hydrogen, and R³ is nitro) is isolated by filtration.

PREPARATION OF A COMPOUND OF FORMULA I WHERE R¹ IS HETEROARYL AND R³ IS NITRO

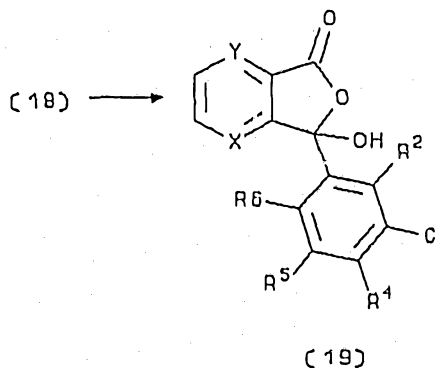
An optionally substituted nitrophenyl pyridopyridazinone (Formula I where X is nitrogen, Y is carbon, R¹ is hydrogen and R³ is nitro) is dissolved in an aprotic solvent (e.g., tetrahydrofuran,

dimethylformamide, dimethylacetamide, preferably dimethylformamide) and treated with a base (e.g., sodium hydride, potassium hydride, preferably sodium hydride). The resulting solution is heated to a temperature in the range of about room temperature to about 95°C, preferably about 65°C. About 1.2 molar equivalent of an optionally substituted heteroaryl alkylating reagent (Formula 16, where R¹ is heteroaryl) is added. The resulting optionally substituted nitrophenyl heteroaryl pyridopyridazinone (Formula I where X is nitrogen, Y is carbon, Z is oxygen, R¹ is heteroaryl, and R³ is nitro) is isolated by crystallization or chromatography, preferably crystallization.

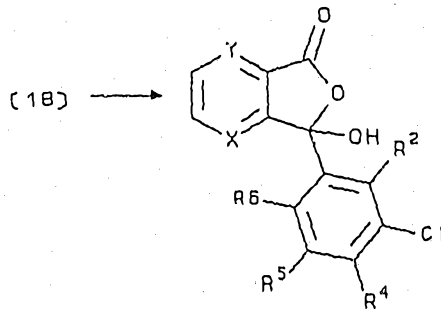
PREPARATION OF A COMPOUND OF FORMULA I WHERE R¹ IS HETEROARYL HETERO-OXIDE AND R³ IS NITRO

An optionally substituted nitrophenyl heteroaryl pyridopyridazinone (Formula I where X is nitrogen, Y is carbon, R¹ is heteroaryl and R³ is nitro) is dissolved in a solvent compatible with peroxyacid (e.g., ethyl acetate, toluene, methylene chloride, acetic acid, preferably methylene chloride) and a peroxyacid (such as, *m*-chloroperoxybenzoic acid, peroxyacetic acid, trifluoroperoxyacetic acid, magnesium monoperoxyphthalate, preferably *m*-chloroperoxybenzoic acid) is added. The resulting mixture is stirred for a period of about 1 hour to about 48 hours, preferably about 18 hours at a temperature in the range of about 0°C to about 50°C, preferably room temperature. The resulting optionally substituted nitrophenyl heteroaryl hetero-oxide pyridopyridazinone (Formula I, where X is nitrogen, Y is carbon, Z is oxygen, R¹ is heteroaryl hetero-oxide and R³ is nitro) is isolated by crystallization or chromatography, preferably crystallization.

REACTION SCHEME G



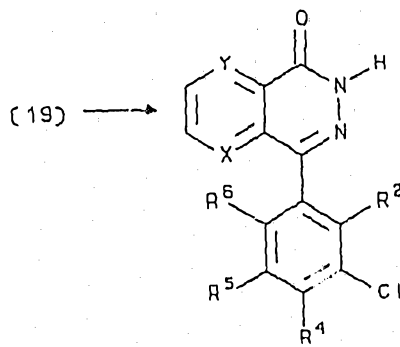
5



10

(19)

15



20

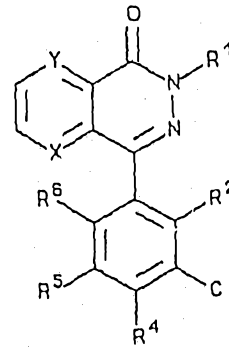
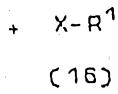
Formula I, where

R¹ is hydrogen and

R³ is chloro

25

Formula I, where
R¹ is hydrogen and
R³ is chloro



Formula I, where

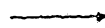
R¹ is heteroaryl

R³ is chloro

30

35

Formula I, where
R¹ is heteroaryl and
R³ is chloro



Formula I, where
R¹ is heteroaryl
hetero-oxide and
R³ is chloro

40

PREPARATION OF A COMPOUND OF FORMULA 18 WHERE R³ IS CHLORO

An optionally substituted *m*-chlorophenyl pyridolactam is made by following the procedure for preparing Formula 13 set forth in Reaction Scheme F. An optionally substituted *m*-chloro Grignard reagent or organolithium reagent (Formula 17) is used in lieu of Formula 12, resulting in the desired optionally substituted *m*-chlorophenyl pyridolactam (Formula 18, where X is nitrogen, Y is carbon and R³ is chloro).

PREPARATION OF A COMPOUND OF FORMULA 19 WHERE R³ IS CHLORO

An optionally substituted *m*-chlorophenyl pyridolactone (Formula 19 where R³ is chloro) is prepared by following the procedure for preparing Formula 15 set forth in Reaction Scheme F.

PREPARATION OF COMPOUND C. FORMULA I WHERE R¹ IS HYDROGEN AND R³ IS CHLORO

An optionally substituted *m*-chlorophenyl pyridopyridazinone (Formula I where R¹ is hydrogen and R³ is chloro) is prepared by following the procedure for preparing Formula I where R¹ is hydrogen and R³ is nitro set forth in Reaction Scheme F.

PREPARATION OF A COMPOUND OF FORMULA I WHERE R¹ IS HETEROARYL AND R³ IS CHLORO

An optionally substituted *m*-chlorophenyl heteroaryl pyridopyridazinone (Formula I where R¹ is heteroaryl and R³ is chloro) is prepared by following the procedure for preparing Formula I where R¹ is heteroaryl and R³ is nitro set forth in Reaction Scheme F.

PREPARATION OF A COMPOUND OF FORMULA I WHERE R¹ IS HETEROARYL HETERO-OXIDE AND R³ IS CHLORO

An optionally substituted *m*-chlorophenyl heteroaryl hetero-oxide pyridopyridazinone (Formula I where R¹ is heteroaryl and R³ is chloro) is prepared by following the procedure for preparing Formula I where R¹ is heteroaryl hetero-oxide and R³ is nitro set forth in Reaction Scheme F.

PREFERRED COMPOUNDS

Presently preferred are the compound of Formula I where X is nitrogen, Y is carbon, Z is oxygen, R³ is chloro or nitro and R¹ is ethyl, 2-propyl, 4-pyridylmethyl, 4-pyridyl-N-oxide-methyl, 3-pyridylmethyl, 3-pyridyl-N-oxide-methyl, benzyl, 3-thienylmethyl or cyclopentylmethyl.

Preferred are the compounds of Formula I where R³ is chloro and R¹

is ethyl, 4-pyridylmethyl, 4-pyridyl-N-oxide-methyl, 3-pyridylmethyl, 3-pyridyl-N-oxide-methyl, benzyl or 3-thienylmethyl;

particularly the compounds where R², R⁴, R⁵ and R⁶ are hydrogen.

Similarly preferred are the compounds of Formula I where
 5 R³ is nitro and R¹ is 4-pyridylmethyl, 4-pyridyl-N-oxide-methyl, 3-pyridylmethyl, 3-pyridyl-N-oxide-methyl, benzyl, 3-thienylmethyl, 2-propyl or cyclopentyl;

particularly the compounds where R², R⁴, R⁵ and R⁶ are hydrogen.

Most preferred are the compounds 6-(4-pyridylmethyl)-8-
 10 (3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one, 6-(4-pyridyl-N-oxide-methyl)-8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one, 6-(3-pyridylmethyl)-9-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one, 6-(3-pyridyl-N-oxide-methyl)-8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one,
 15 6-benzyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one, 6-ethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one and 6-(3-thienylmethyl)-8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one.

Also most preferred are the compounds 6-(4-pyridylmethyl)-8-
 (3-chlorophenyl)-pyrido[2,3-d]pyridazin-5-one, 6-(4-pyridyl-N-oxide-methyl)-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one, 6-(3-pyridylmethyl)-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one, 6-(3-pyridylmethyl)-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one, 6-benzyl-8-
 20 (3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one, 6-(2-propyl)-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one, 6-cyclopentyl-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one, and 6-(3-thienylmethyl)-
 25 8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one.

PREFERRED PROCESSES AND LAST STEPS

30 A preferred process for making optionally substituted pyrido[2,3-d]pyridazin-5-one or pyrido[2,3-d]pyridazin-8-one compounds entails contacting a suitably substituted 2-benzoyl-3-methoxycarbonylpyridine with a suitably substituted hydrazine.

A preferred process for making optionally substituted 2-benzoyl-3-methoxycarbonylpyridine entails contacting a suitably substituted 2-benzoyl-3-carboxypyridine with an esterification reagent.

35 A preferred process for making optionally substituted 2-benzoyl-3-carboxypyridine entails contacting a suitably substituted pyridodicarboxylic anhydride with a suitably substituted Grignard reagent.

40 A preferred process for making 6-substituted pyrido[2,3-d]pyridazin-5-one entails contacting of the 6-unsubstituted pyrido[2,3-d]pyridazin-5-one with a suitable base, followed by the addition of an alkylating agent.

A preferred process for making 7-substituted pyrido[2,3-d]-

pyridazin-8-one entails contacting of the 7-unsubstituted pyrido[2,3-d]-pyridazin-8-one with a suitable base, followed by the addition of an alkylating agent.

5 A preferred process for making 6-substituted pyrido[2,3-d]-pyridazin-5-one entails contacting the 6-unsubstituted pyrido[2,3-d]-pyridazin-5-one compound with a suitably substituted alcohol and triphenylphosphine, followed by diisopropyl azodicarboxylate (i.e., Mitsunobu reaction conditions).

10 A preferred process for making 7-substituted pyrido[2,3-d]-pyridazin-8-one entails contacting the 7-unsubstituted pyrido[2,3-d]-pyridazin-8-one compound with a suitably substituted alcohol and triphenylphosphine, followed by diisopropyl azodicarboxylate (i.e., Mitsunobu reaction conditions).

15 A preferred process for making 6-substituted pyrido-N-oxide-alkyl[2,3-d]pyridazin-5-one entails suspending the 6-unsubstituted pyrido[2,3-d]pyridazin-5-one compound with a suitably substituted pyridylcarbinol N-oxide and triphenylphosphine, followed by diisopropyl azodicarboxylate (i.e., Mitsunobu reaction conditions).

20 A preferred process for making 7-substituted pyrido-N-oxide-alkyl[2,3-d]pyridazin-8-one entails suspending the 7-unsubstituted pyrido[2,3-d]pyridazin-8-one compound with a suitably substituted pyridylcarbinol N-oxide and triphenylphosphine, followed by diisopropyl azodicarboxylate (i.e., Mitsunobu reaction conditions).

25 A preferred process for converting a 6,8-disubstituted pyrido[2,3-d]pyridazin-5-one into the corresponding 6,8-disubstituted pyrido[2,3-d]pyridazin-5-thione entails treating the 6,8-disubstituted pyrido[2,3-d]pyridazin-5-one with a reagent for the thiation of ketones (such as Lawesson's Reagent or phosphorus pentasulfide) in an appropriate solvent, preferably at reflux.

UTILITY, TESTING AND ADMINISTRATION

GENERAL UTILITY

25 The compounds of this invention, including the pharmaceutically acceptable salts and esters thereof, and the compositions containing them are particularly useful as anti-inflammatory, antasthmatic, immunosuppressive, anti-allograft rejection, anti-graft-vs-host disease, autoimmune disease or analgetic agents. The compounds of this invention act as PDE IV selective inhibitors, thereby modulating CAMP levels. Thus, these compounds are of use for the treatment of conditions or diseases that are modulated by leukocyte cAMP.

40 For example, inflammation, immunosuppression, auto-immune diseases, graft-vs-host disease and allograft rejection are conditions

that are manifested by the proliferation of lymphocytes. The proliferation is triggered by the presence of cAMP at specific levels. Inhibition of lymphocyte proliferation is accomplished by increasing levels of cAMP resulting from the inhibition of lymphocyte phosphodiesterase.

TESTING

Potency and selectivity of compounds as inhibitors of PDE IV is determined by following, for example, the procedures described in Example 46, or modifications thereof.

The immunomodulatory and anti-inflammatory activity of the compounds of the invention can be determined by a variety of assays utilizing both *in vitro* and *in vivo* procedures.

Inhibition of the proliferation of lymphocytes in response to mitogenic stimulation is determined by the procedures described by Greaves, et al. ["Activation of human T and B lymphocytes by polyclonal mitogens," *Nature*, 248, 698-701 (1974)]., or modifications thereof (see Example 48).

Inhibition of lymphocyte activation in response to antigenic challenge is determined *in vitro* by inhibition of a cytolytic T-cell assay (CTL) as described by Wunderlich, et al., *Nature* (1970), Vol. 228, p. 62, or a modification thereof.

Immune modulation is determined by *in vivo* procedures utilizing the Jerne Hemolytic Plaque Assay, [Jerne, et al., "The agar plaque technique for recognizing antibody producing cells," *Cell-bound Antibodies*, Amos, B. and Kaprowski, H. editors (Wistar Institute Press, Philadelphia) 1963, p. 109] or a modification thereof (see Example 47).

Anti-inflammatory activity is determined by the Arachidonic Acid-Induced Mouse Ear Edema Assay [Young, et al., *J. Invest. Derm.*, 82: 367-371 (1984)] (see Example 49).

Analgetic activity is determined by the Phenylquinone-induced Mouse Writhing Assay [Hendershot, et al., *J. Pharmacol. Exp. Ther.*, 125: 237-240 (1959)].

ADMINISTRATION

The compounds of this invention are administered at a therapeutically effective dosage, i.e., that amount which, when administered to a mammal in need thereof, is sufficient to effect treatment, as described above (for example, to reduce or otherwise treat inflammation, pain and/or pyrexia in the mammal). Administration of the active compounds and salts described herein can be via any of the accepted modes of administration for agents that serve similar utilities.

The level of the drug in a formulation can vary within the full

range employed by those skilled in the art, e.g., from about 0.01 percent weight (%w) to about 99.99%w of the drug based on the total formulation and about .01%w to 99.99%w excipient. Preferably the drug is present at a level of about 10%w to about 70%w.

5 Generally, an acceptable daily dose is of about 0.0001 to 150 mg per kilogram body weight of the recipient per day, preferably about 0.01 to 75 mg per kilogram body weight per day, and most preferably about 0.1 to 30 mg per kilogram body weight per day. Thus, for administration to a 70 kg person, the dosage range would be about 0.007 mg to 10.5 g per day, preferably about 0.7 to 5.25 g per day, and most preferably about 7.0 mg to 2.1 g per day.

10 Administration can be via any accepted systemic or local route, for example, via parenteral, oral (particularly for infant formulations), intravenous, nasal, transdermal or topical routes, in the form of solid, semi-solid or liquid dosage forms, such as for example, 15 tablets, suppositories, pills, capsules, powders, solutions, suspensions, aerosols, emulsions or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The compositions will include a conventional pharmaceutical carrier or 20 excipient and an active compound of Formula I and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc. Carriers can be selected from the various oils, including those of petroleum, animal, vegetable or synthetic origin, for example, peanut oil, soybean oil, mineral oil, sesame oil, and the like. 25 Water, saline, aqueous dextrose, and glycols are preferred liquid carriers, particularly for injectable solutions. Suitable pharmaceutical carriers include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium 30 chloride, dried skim milk, glycerol, propylene glycol, water, ethanol, and the like. Other suitable pharmaceutical carriers and their formulations are described in "*Remington's Pharmaceutical Sciences*" by E. W. Martin.

35 If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc.

40 The compounds of this invention are generally administered as a pharmaceutical composition which comprises a pharmaceutical excipient in combination with a compound of Formula I. The level of the drug in a formulation can vary within the full range employed by those skilled in the art, e.g., from about .01 percent weight (%w) to about 99.99%w of the drug based on the total formulation and about .01%w to 99.99%w

excipient. Preferably, the formulation will be about 3.5 to 60% by weight of the pharmaceutically active compound, with the rest being suitable pharmaceutical excipients.

5 INTRAVENOUS ADMINISTRATION

Intravenous injection has proven to be an important route of administration for antiviral agents. The compounds of the present invention can be administered via this route, for example, by dissolving the compound, salt, ester or ether in a suitable solvent (such as water
10 or saline) or incorporation in a liposomal formulation followed, by dispersal into an acceptable infusion fluid. A typical daily dose of a compound of the invention can be administered by one infusion, or by a series of infusions spaced over periodic intervals.

15 ORAL ADMINISTRATION

Oral administration can be used to deliver the compound of Formula I using a convenient daily dosage regimen which can be adjusted according to the degree of affliction or for renal impairment, or to compensate for the toxic effects of other medications administered
20 contemporaneously. For such oral administration, a pharmaceutically acceptable, non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, gelatin, sucrose,
25 magnesium carbonate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like. Such compositions may contain between .01 wt/wt% and 99.99 wt/wt% of the compound of Formula I, but preferably such compositions will contain between 25 wt/wt% and about
30 80 wt/wt%.

Preferably the compositions will take the form of a capsule, pill or tablet and thus the composition will contain, along with the active ingredient, a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as starch or derivatives thereof; a
35 lubricant such as magnesium stearate and the like; and a binder such as a starch, polyvinylpyrrolidone, gum acacia, gelatin, cellulose and derivatives thereof, and the like. For oral administration to infants, a liquid formulation (such as a syrup or suspension) is preferred.

40 LIPOSOMAL FORMULATIONS

Pharmaceutical formulations based on liposomes have recently reached human clinical trials. Their benefits are believed related to favorable changes in tissue distribution and pharmacokinetic parameters that result from liposome entrapment of drugs, and may be applied to the

compounds of the present invention by those skilled in the art.

The formulations can be designed to either target drug to disease sites [see: Lopez-Berestein et al., *J. Infect. Dis.*, 151: 704-710 (1985); Gotfredsen et al., *Biochemical Pharmacology*, 32: 3389-3396 (1983)]; or to the reticuloendothelial system [see Eppstein et al., *Int. J. Immunotherapy*, 2: 115-126 (1986)], to increase duration of drug action [see: Gabizon et al., *Cancer Res.*, 42: 4734 (1982); Eppstein et al., *Delivery Systems for Peptide Drugs*, Eds. S.S. Davis, L. Illum and E. Tomlinson, Plenum Pub. Corp., New York, pp. 277-283; C.A. Hunt, *Biochemica et Biophysica Acta.*, 719: 450-463 (1982); and Senior et al., *Biochemica et Biophysica Acta.*, 839: 1-8 (1985)], or to divert a drug away from organs that are particularly sensitive to its toxic effects [see: Weinstein et al., *Pharmac. Ther.*, 24: 207-233 (1983); Olson et al., *Eur. J. Cancer Clin. Oncol.*, 18: 167-176 (1982); and Gabzion et al., *supra.*].

Controlled release liposomal liquid pharmaceutical formulations for injection or oral administration are described in U.S. Patent No. 4,016,100. Liposomal applications for oral drug delivery of a lyophilized liposome/peptide drug mixture filled into intestine capsules have also been suggested, see U.S. Patent No. 4,348,384. The foregoing is incorporated herein by reference.

SUPPOSITORIES

For systemic administration via suppository, traditional binders and carriers include, for example, polyalkaline glycol or triglycerides [e.g., PEG 1000 (96%) and PEG 4000 (4%)]. Such suppositories may be formed from mixtures containing active ingredients in the range of from about 0.5 wt/wt% to about 10 wt/wt%; preferably from about 1 wt/wt% to about 2 wt/wt%.

LIQUIDS

Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc. an active compound (about 0.5% to about 20%), as described above, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension.

Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easton, Pennsylvania, 16th Ed., 1980. The composition to be administered will, in any event, contain a quantity of the active compound(s) in a pharmaceutically effective amount for relief of the particular condition being treated in accordance with the teachings of this invention.

EXAMPLES

5 The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

EXAMPLE 1

Preparation of 7-(3-nitrophenyl)-furo-
[3,4-b]pyridin-5-one

10 1. Formula 4, Where X is nitrogen, Y is carbon, R³ is nitro, and R², R⁴, R⁵ and R⁶ are hydrogen.

15 A solution of 2,3-pyridinyldicarboxylic anhydride (20g, 134mmoles) in 25ml of anhydrous methanol was refluxed for 30 minutes. The methanol was removed and the two positional isomers (2-carboxy-3-methoxycarbonylpyridine and 2-methoxycarbonyl-3-carboxypyridine) are isolated and separated. The 2-carboxy-3-methoxycarbonylpyridine was added to a
20 solution of 3-nitrobenzaldehyde (101.35g, 670mmoles) in p-cymene (105ml, 670mmoles) and heated at 180°C for 13.5 hours. The solution was cooled, filtered and the excess 3-nitrobenzaldehyde and p-cymene removed by bulb to bulb distillation using a Kugelrohr apparatus. The residue was
25 triturated with methylene chloride and the solid residue was discarded. The product was isolated from the filtrate yielding 12.7g of 7-(3-nitrophenyl)furo[3,4-b]pyridin-5-one (37.2%).

EXAMPLE 2

Preparation of 2-(α -hydroxymethyl-3-nitrophenyl)-3-carboxypyridine

30 2. Formula 5, Where X is nitrogen, Y is carbon, R³ is nitro and R², R⁴, R⁵ and R⁶ are hydrogen.

35 7-(3-nitrophenyl)-furo[3,4-b]pyridin-5-one was suspended in methanol (100ml), solid potassium hydroxide (4.5g, 80mmoles) was added and the mixture refluxed for 6 hours under an inert atmosphere yielding 2-(α -hydroxymethyl-3-nitrophenyl)-3-carboxypyridine.

Example 3

Preparation of 2-(3-nitrobenzoyl)-3-carboxypyridine

3. Formula 6, Where X is nitrogen, Y is carbon, R³ is nitro and R², R⁴, R⁵ and R⁶ are hydrogen.

To a solution of 2-(α -hydroxymethyl-3-nitrophenyl)-3-carboxypyridine (2.25g, 8.2mmoles) in methylene chloride (20ml), pyridinium dichromate (4.63g, 12.3mmoles) was added and stirred at room temperature (22°C) for 18 hours. The solution was filtered and the solvent removed yielding 3.43g of crude 2-(3-nitrobenzoyl)-3-carboxypyridine.

Example 4

Preparation of 2-(3-nitrobenzoyl)-3-methoxycarbonylpyridine

4. Formula II, Where X is nitrogen, Y is carbon, R³ is nitro and R², R⁴, R⁵ and R⁶ are hydrogen.

2-(3-Nitrobenzoyl)-3-carboxypyridine was dissolved in 20ml of methylene chloride and the solution was cooled in an ice/water bath. Diazomethane (25ml, 0.33M) was added to the solution and stirred for 2 hours. The solvent was removed and the residue chromatographed (methylene chloride) yielding 0.26g of 2-(3-nitrobenzoyl)-3-methoxycarbonylpyridine.

EXAMPLE 5

Preparation of 8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one

5. Formula I, Where X is nitrogen, Y is carbon, Z is oxygen, R³ is nitro and R¹, R², R⁴, R⁵ and R⁶ are hydrogen.

To a solution of 2-(3-nitrobenzoyl)-3-methoxycarbonylpyridine (0.58g, 2mmoles) dissolved in ethanol (50ml), was added hydrazine monohydrate (0.25ml, 5.1mmoles). The mixture was refluxed for 4 hours, cooled and ethyl acetate (50ml) was added. The solid material was collected and dried, yielding 0.58g of 8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one, mp. 302°C.

EXAMPLE 6

Preparation of 6-phenyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one

6. Formula I, Where X is nitrogen, Y is carbon, Z is oxygen, R¹ is phenyl, R³ is nitro and R², R⁴, R⁵ and R⁶ are hydrogen.

To a solution of 2-(3-nitrobenzoyl)-3-methoxycarbonylpyridine (0.26g, 0.97mmoles) dissolved in ethanol (50ml), was added phenylhydrazine (0.25ml, 2.4mmoles). The mixture was refluxed for 168 hours. The solvent was removed and the solid was precipitated from

ethanol and dried, yielding 0.07g of 6-phenyl-8-(3-nitrophenyl)pyrido-[2,3-d]pyridazin-5-one (21%), mp 167°C.

EXAMPLE 7

Preparation of

6-benzyl-8-(3-nitrophenyl)pyrido-[2,3-d]pyridazin-5-one

7. Formula I, Where X is nitrogen, Y is carbon, Z is oxygen, R¹ is benzyl, R³ is nitro and R², R⁴, R⁵ and R⁶ are hydrogen.

To a solution of 2-(3-nitrobenzoyl)-3-methoxycarbonylpyridine (0.20g, 0.75mmoles) dissolved in ethanol (50ml), was added benzylhydrazine hydrochloride (0.36g, 1.86mmoles). The mixture was heated to 85°C for 144 hours. The mixture was purified by chromatography yielding 0.11g of 6-benzyl-8-(3-nitrophenyl)-pyrido[2,3-d]pyridazin-5-one (41%), mp 132°C.

EXAMPLE 8

Preparation of 6-ethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one

8. Formula I, Where X is nitrogen, Y is carbon, Z is oxygen, R¹ is ethyl, R³ is nitro and R², R⁴, R⁵ and R⁶ are hydrogen.

8-(3-Nitrophenyl)-pyrido[2,3-d]pyridazin-5-one (0.20g, 0.75mmoles), sodium hydride (0.04g, 0.9mmoles) and iodoethane (0.3ml, 3.75mmoles) was dissolved in 25ml of tetrahydrofuran and refluxed under a nitrogen atmosphere for 18 hours. The solvent was removed and the product chromatographed and eluted with 100% methylene chloride yielding 0.05g of 6-ethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one (22.6%), mp. 138°C.

EXAMPLE 9

Preparation of

6-(4-pyridylmethyl)-8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one

9. Formula I, Where X is nitrogen, Y is carbon, Z is oxygen, R¹ is 4-pyridylmethyl, R³ is nitro and R², R⁴, R⁵ and R⁶ are hydrogen.

To a solution of 8-(3-nitrophenyl)-pyrido[2,3-d]pyridazin-5-one (0.16 g, 0.6 mmoles) in tetrahydrofuran (50ml) was added potassium carbonate (0.19 g, 7.1 mmoles), potassium iodide (1.0 g, 6.0 mmoles) and 4-picoyl chloride (0.98 g, 6.0 mmoles). The mixture was stirred and refluxed under an inert atmosphere for 18 hours. The solvent was removed under vacuum. The residue was partitioned in methanol/ethyl acetate (1:1), chromatographed in 100% hexane followed by 100% ethyl acetate. The remaining solvent was removed yielding 0.58g of crude 6-(4-pyridylmethyl)-8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one, which was

recrystallized from methanol yielding 0.08 g of the pure compound (37.1%), mp. 167-168°C.

EXAMPLE 10

5 Preparation of 7-(3-chlorophenyl)-furo[3,4-b]pyridin-5-one

10. Formula 4, Where X is nitrogen, Y is carbon, R³ is chloro and R², R⁴, R⁵ and R⁶ are hydrogen.

10 A solution of 2,3-pyridinyldicarboxylic anhydride (20.0g, 134mmoles) in methanol (25g, 617mmoles) was refluxed for 10 minutes and the solvent removed. The solution was filtered and the remaining solvent was removed. The residue was added to 3-chlorobenzaldehyde (76 ml, 671 mmoles) and *p*-cymene (105 ml, 671 mmoles) and the mixture was stirred at 180°C for 18 hours under an inert atmosphere. The solvent was removed and the residue was chromatographed yielding 7-(3-chlorophenyl)furo-
15 [3,4-b]pyridin-5-one.

EXAMPLE 11

20 Preparation of 2-(α -hydroxymethyl-3-chlorophenyl)-3-carboxypyridine

11. Formula 5, Where X is nitrogen, Y is carbon, R³ is chloro and R², R⁴, R⁵ and R⁶ are hydrogen.

25 7-(3-Chlorobenzoyl)furo[3,4-b]pyridin-5-one (4.77g, 19.4mmoles) and 0.2N sodium hydroxide (21.4mmoles) was dissolved in methanol and tetrahydrofuran (100ml, 1:1). The mixture was heated to 75°C and stirred for 3 hours and cooled. 1N Hydrochloric acid (20ml) and water (200ml) was added to the mixture. The resulting solution was extracted with ethyl acetate and dried over Na₂SO₄. The solution was filtered and the solvent removed yielding 4.94g (96.8%) of 2-(α -hydroxymethyl-3-chlorophenyl)-3-carboxypyridine.
30

EXAMPLE 12

Preparation of 2-(3-chlorobenzoyl)-3-carboxypyridine

35 12. Formula 6, Where X is nitrogen, Y is carbon, R³ is chloro and R², R⁴, R⁵ and R⁶ are hydrogen.

2-(α -hydroxymethyl-3-chlorophenyl)-3-carboxypyridine was dissolved in a solution of methylene chloride/glacial acetic acid (5:1). Pyridinium dichromate (10.95g, 29mmoles) was added and the solution was stirred at room temperature under an inert atmosphere. The solvent was removed yielding 2-(3-chlorobenzoyl)-3-carboxypyridine.
40

EXAMPLE 13

Preparation of 2-(3-chlorobenzoyl)-3-methoxycarbonylpyridine

13. Formula II, Where X is nitrogen, Y is carbon, R³ is chloro and R¹, R⁴, R⁵ and R⁶ are hydrogen.

2-(3-Chlorobenzoyl)-3-carboxypyridine was dissolved in a solution of 10% methanol and methylene chloride. Diazomethane was added and the solution was stirred for 1 hour at room temperature. The solution was extracted with 100% methylene chloride followed by methylene chloride +1% methanol. The desired product was combined from recrystallization (ethyl ether/hexane) and from the filtrate to yield 1.23g of 2-(3-chlorobenzoyl)-3-methoxycarbonylpyridine.

EXAMPLE 14

Preparation of 8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one

14. Formula I, Where X is nitrogen, Y is carbon, Z is oxygen, R¹ is hydrogen, R³ is chloro and R², R⁴, R⁵ and R⁶ are hydrogen.

A solution of 2-(3-chlorobenzoyl)-3-methoxycarbonylpyridine (0.55g, 2.0mmoles), hydrazine hydrate (0.15ml, 3.0mmoles) in ethanol (50ml) was stirred at 100°C for 8 hours under an inert atmosphere. The solution was cooled and solid. The solution was collected, washed with ethyl ether and dried to give 0.26g of 8-(3-chlorophenyl)pyrido[2,3-d]-pyridazin-5-one (50.5%), mp 268-269°C.

EXAMPLE 15

Preparation of 6-phenyl-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one

15. Formula I, Where X is nitrogen, Y is carbon, Z is oxygen, R¹ is phenyl, R³ is chloro and R², R⁴, R⁵ and R⁶ are hydrogen.

A solution of 2-(3-chlorobenzoyl)-3-methoxycarbonylpyridine (0.30g, 1.09mmoles), phenylhydrazine (0.27ml, 2.72mmoles) in ethanol (18ml) was stirred at 100°C for 72 hours. The solution was cooled and the solvent was removed. The residue was triturated with methanol to give a white solid, which was collected and air dried, yielding 0.26g of 6-phenyl-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one (71.5%), mp 144-145°C.

EXAMPLE 16

Preparation of 6-benzyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one

16. Formula I, Where X is nitrogen, Y is carbon, Z is oxygen, R¹ is benzyl, R³ is chloro and R², R⁴, R⁵ and R⁶ are hydrogen.

A solution of 2-(3-chlorobenzoyl)-3-methoxycarbonylpyridine (0.30g, 1.09mmoles), benzylhydrazine hydrochloride (0.53ml, 2.72mmoles) in ethanol (18ml) was refluxed for 132 hours (5 days). The solution was cooled and the solvent was removed. The residue was dissolved in ethanol (minimal amount used) and stored in a freezer to induce crystallization. The solid material was collected from the solution, chromatographed, eluted with 100% methylene chloride, and crystallized from methanol to yield 0.21g of 6-benzyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one (55.4%), mp 141°C.

EXAMPLE 17

Preparation of 6-ethyl-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one

17. Formula I, Where X is nitrogen, Y is carbon, Z is oxygen, R¹ is ethyl, R³ is chloro and R², R⁴, R⁵ and R⁶ are hydrogen.

To a suspension of 8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one (0.32g, 1.24mmoles) in tetrahydrofuran (50ml) was added sodium hydride (0.06g, 1.4mmoles). The mixture was stirred for 1 hour at room temperature. Iodoethane (0.48g, 3.1mmoles) was added and the solution was refluxed for 18 hours under an inert atmosphere. The mixture was cooled and acidified by the addition of 50ml of 1N HCl. The desired compound was isolated by extraction with ethyl acetate (extracted until no product detected in aqueous layer), washed with sodium bicarbonate, brine and dried over magnesium sulfate. The solution was filtered and the solvent removed yielding 0.85g of the crude desired product. The product was purified by recrystallization from methanol to yield 0.24g of 6-ethyl-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one (67.8%), mp. 117-118°C.

EXAMPLE 18

Preparation of

6-(2-propyl)-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one

18. Formula I, Where X is nitrogen, Y is carbon, Z is oxygen, R¹ is 2-propyl, R³ is chloro and R², R⁴, R⁵ and R⁶ are hydrogen.

To a suspension of 8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one (0.33g, 1.28mmoles) in tetrahydrofuran (50ml) was added sodium hydride (0.07g, 1.53mmoles). The mixture was stirred at room temperature for 30 minutes under an inert atmosphere. 2-Iodopropane (0.64ml, 6.4mmoles) was added and the mixture refluxed for 48 hours. The mixture was cooled and

acidified by the addition of 50ml of 1N HCl. The mixture was extracted with ethyl acetate (3x50ml) and dried over magnesium sulfate. The solution was filtered and the solvent removed to yield the crude product. The product was purified by crystallization (ethyl ether/hexane) yielding 0.15g of 6-(2-propyl)-8-(3-chlorophenyl)pyrido[2,3-d]-pyridazin-5-one (39%), mp 80-81°C

EXAMPLE 19

Preparation of

6-(4-pyridylmethyl)-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one

19. Formula I, Where X is nitrogen, Y is carbon, Z is oxygen, R¹ is 4-pyridylmethyl, R³ is chloro and R², R⁴, R⁵ and R⁶ are hydrogen.

To a suspension of 8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one (0.50g, 1.90mmoles) in dimethylformamide (50ml) was added potassium carbonate (3.22g, 23.3mmoles). The mixture was stirred at room temperature for 1 hour under an inert atmosphere.

4-Picolyl chloride (1.59g, 9.7mmoles) and potassium iodide (1.61g, 9.7mmoles) was added, the mixture was stirred at 80°C for 168 hours (7 days). The mixture was cooled, the insoluble material was filtered out and the solvent removed yielding 2.13g of the crude product. The product was purified by chromatography, eluted with 100% ethylacetate and crystallized from methanol yielding 0.091g of 6-(4-pyridylmethyl)-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one (13.7%), mp 152°C.

EXAMPLE 20

Preparation of 2-(3-chlorobenzoyl)-3-carboxypyridine
and 2-carboxy-3-(3-chlorobenzoyl)pyridine
Using A Grignard Reagent

20. Formula 6, Where X is nitrogen, Y is carbon, R³ is chloro and R¹, R⁴, R⁵ and R⁶ are hydrogen.

A Grignard reagent was prepared by adding 1-bromo-3-chlorobenzene (11.75ml, 100mmoles) to a suspension of magnesium (2.43g, 100mmoles) in tetrahydrofuran (100ml) and stirred at room temperature for 18 hours under an inert atmosphere. The Grignard reagent was added in a dropwise manner to a solution of 2,3-pyridyldicarboxylic anhydride (14.91ml, 100mmoles) in tetrahydrofuran (200ml) at a temperature of -78°C over a 2 hour period. After the addition the solution was stirred for an additional 45 minutes. 1N HCl (110ml) was added and the solution was stirred for 1 hour. The desired product was extracted with ethyl acetate, washed in brine and dried over Na₂SO₄, yielding 2-(3-chlorobenzoyl)-3-carboxypyridine and 2-carboxy-3-(3-chlorobenzoyl)pyridine.

2-(3-Chlorobenzoyl)-3-carboxypyridine (Formula 6, where X is

nitrogen, Y is carbon, R³ is chloro and R², R⁴, R⁵ and R⁶ are hydrogen) can be converted to the corresponding compounds of Formulae II and I by following the procedures of Examples 13-19, respectively.

5

EXAMPLE 21

Preparation of 2-methoxycarbonyl 3-(3-chlorobenzoyl)pyridine

21. Formula II, Where X is carbon and Y is nitrogen, R³ is chloro, and R², R⁴, R⁵ and R⁶ are hydrogen.

10

Following the procedures of Example 13 and substituting 2-(3-chlorobenzoyl)-3-carboxypyridine with 2-carboxy-3-(3-chlorobenzoyl)-pyridine there is obtained 2-methoxycarbonyl-3-(3-chlorobenzoyl)-pyridine.

15

EXAMPLE 22

Preparation of 5-(3-chlorophenyl)pyrido[2,3-d]pyridazin-8-one

22. Formula I, Where X is carbon, Y is nitrogen, Z is oxygen, R³ is chloro and R¹, R², R⁴, R⁵ and R⁶ are hydrogen.

20

Following the procedures of Example 14 and substituting 2-(3-chlorobenzoyl)-3-methoxycarbonylpyridine with 2-methoxycarbonyl-3-(3-chlorobenzoyl)pyridine there is obtained 5-(3-chlorophenyl)pyrido[2,3-d]pyridazin-8-one.

25

EXAMPLE 23

Preparation of 5-(3-chlorophenyl)-7-phenylpyrido[2,3-d]pyridazin-8-one

23. Formula I, Where X is carbon, Y is nitrogen, Z is oxygen, R¹ is phenyl, R³ is chloro and R², R⁴, R⁵ and R⁶ are hydrogen.

30

Following the procedures of Example 15 and substituting 2-(3-chlorobenzoyl)-3-methoxycarbonylpyridine with 2-methoxycarbonyl-3-(3-chlorobenzoyl)pyridine there is obtained 5-(3-chlorophenyl)-7-phenylpyrido[2,3-d]pyridazin-8-one.

35

EXAMPLE 24

Preparation of 5-(3-chlorophenyl)-7-benzylpyrido[2,3-d]pyridazin-8-one

24. Formula I, Where X is carbon, Y is nitrogen, Z is oxygen, R¹ is benzyl, R³ is chloro and R², R⁴, R⁵ and R⁶ are hydrogen.

40

Following the procedures of Example 16 and substituting 2-(3-chlorobenzoyl)-3-methoxycarbonylpyridine with 2-methoxy carbonyl-3-(3-chlorobenzoyl)pyridine there is obtained 5-(3-chlorophenyl)-7-benzylpyrido[2,3-d]pyridazin-8-one.

EXAMPLE 25

Preparation of 5-(3-chlorophenyl)-7-ethylpyrido[2,3-d]pyridazin-8-one

25. Formula I, Where X is carbon, Y is nitrogen, Z is oxygen, R¹ is ethyl, R³ is chloro and R², R⁴, R⁵ and R⁶ are hydrogen.

Following the procedures of Example 17 and substituting 8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one with 5-(3-chlorophenyl)pyrido[2,3-d]pyridazin-8-one there is obtained 5-(3-chlorophenyl)-7-ethylpyrido[2,3-d]pyridazin-8-one.

EXAMPLE 26

Preparation of

5-(3-chlorophenyl)-7-(2-propyl)pyrido[2,3-d]pyridazin-8-one

26. Formula I, Where X is carbon, Y is nitrogen, Z is oxygen, R¹ is 2-propyl, R³ is chloro and R², R⁴, R⁵ and R⁶ are hydrogen.

Following the procedures of Example 18 and substituting 8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one with 5-(3-chlorophenyl)pyrido[2,3-d]pyridazin-8-one there is obtained 5-(3-chlorophenyl)-7-(2-propyl)pyrido[2,3-d]pyridazin-8-one.

EXAMPLE 27

Preparation of

5-(3-chlorophenyl)-7-(4-pyridylmethyl)pyrido[2,3-d]pyridazin-8-one

27. Formula I, Where X is carbon, Y is nitrogen, Z is oxygen, R¹ is 4-pyridylmethyl, R³ is chloro and R², R⁴, R⁵ and R⁶ are hydrogen.

Following the procedures of Example 19 and substituting 8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one with 5-(3-chlorophenyl)pyrido[2,3-d]pyridazin-8-one there is obtained 5-(3-chlorophenyl)-7-(4-pyridomethyl)pyrido[2,3-d]pyridazin-8-one.

EXAMPLE 28

Preparation of 2-Methoxycarbonyl-3-benzoylpyridine

28. Formula II, Where X is carbon, Y is nitrogen and R², R³, R⁴, R⁵ and R⁶ are hydrogen.

A solution of 2,3-pyridyldicarboxylic anhydride (10 g, 67.1 mmoles) in dry benzene (80 ml, 888 mmoles) was stirred at 50-55°C while aluminum chloride (AlCl₃, 20 g, 148 mmoles) was gradually added. The mixture was refluxed for 18 hours. The reaction mixture was cooled and poured into 250 ml of 5% aqueous HCl and extracted with ethyl acetate. The ethyl acetate was removed and the residue was dried under vacuum. The residue was dissolved in 500 ml methanol and 4 ml

concentrated H₂SO₄ (67.1 mmoles) was added. The solution was refluxed at 80°C for 24 hours. The mixture was cooled, neutralized with saturated sodium bicarbonate solution and extracted with ethyl acetate. The ethyl acetate extract was washed with saturated brine and dried over sodium sulfate. The solution was filtered and the ethyl acetate removed under vacuum to yield 2-methoxycarbonyl-3-benzoylpyridine (7.92 g, 32.8 mmoles, 49% crude yield). The product was purified by column chromatography eluting with 5% ethyl acetate in methylene chloride to give after crystallization from ether the purified product (5.61 g, 23 mmoles, 35% yield), mp 85-86°C.

EXAMPLE 29

Preparation of 2-(3-nitrobenzoyl)-3-methoxycarbonylpyridine

29. Formula II, Where X is nitrogen, Y is carbon, R³ is nitro, and R², R⁴, R⁵ and R⁶ are hydrogen.

2-Benzoyl-3-methoxycarbonylpyridine (3.86 g, 16.0 mmoles) was dissolved in H₂SO₄ (10 ml) to which a mixture of HNO₃ (0.88 ml) and H₂SO₄ (2.0 ml) was added dropwise. The reaction mixture was stirred for 30 minutes and poured onto ice. The solution was stirred for 60 minutes, basified to pH 7.8 with saturated sodium bicarbonate and extracted with ethyl acetate. The organic ethyl acetate solution was washed with brine and dried over magnesium sulfate. The solution was filtered and the solvent removed yielding 4.49 g of the crude product, 2-(3-nitrobenzoyl)-3-methoxycarbonylpyridine.

EXAMPLE 30

Preparation of 5-(3-nitrophenyl)pyrido[2,3-d]pyridazin-8-one

30. Formula I, Where X is carbon, Y is nitrogen, Z is oxygen, R³ is nitro and R¹, R², R⁴, R⁵ and R⁶ are hydrogen.

Following the procedures of Example 5 and substituting 2-(3-nitrobenzoyl)-3-methoxycarbonylpyridine with 2-methoxycarbonyl-3-(3-nitrobenzoyl)pyridine, as prepared according to the procedure of Example 29B, there is obtained 5-(3-nitrophenyl)pyrido[2,3-d]pyridazin-8-one.

EXAMPLE 31

Preparation of 5-(3-nitrophenyl)-7-phenylpyrido[2,3-d]pyridazin-8-one

31. Formula I, Where X is carbon, Y is nitrogen, Z is oxygen, R¹ is phenyl, R³ is nitro and R², R⁴, R⁵ and R⁶ are hydrogen.

Following the procedures of Example 6 and substituting 2-(3-nitrobenzoyl)-3-methoxycarbonylpyridine with 2-methoxycarbonyl-3-(3-nitrobenzoyl)pyridine there is obtained 5-(3-nitrophenyl)-7-phenylpyrido-

[2,3-d]pyridazin-8-one.

EXAMPLE 32

Preparation of 5-(3-nitrophenyl)-7-benzylpyrido[2,3-d]pyridazin-8-one

5

32. Formula I, Where X is carbon, Y is nitrogen, Z is oxygen, R¹ is benzyl, R³ is nitro and R², R⁴, R⁵ and R⁶ are hydrogen.

10

Following the procedures of Example 7 and substituting 2-(3-nitrobenzoyl)-3-methoxycarbonylpyridine with 2-oxocarbonyl-3-(3-nitrobenzoyl)pyridine there is obtained 5-(3-nitrophenyl)-7-benzylpyrido[2,3-d]pyridazin-8-one.

EXAMPLE 33

Preparation of 5-(3-nitrophenyl)-7-ethylpyrido[2,3-d]pyridazin-8-one

15

33. Formula I, Where X is carbon, Y is nitrogen, Z is oxygen, R¹ is ethyl, R³ is nitro and R², R⁴, R⁵ and R⁶ are hydrogen.

20

Following the procedures of Example 8 and substituting 8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one with 5-(3-nitrophenyl)pyrido[2,3-d]pyridazin-8-one there is obtained 5-(3-nitrophenyl)-7-ethylpyrido[2,3-d]pyridazin-8-one.

EXAMPLE 34

Preparation of

25

5-(3-nitrophenyl)-7-(4-pyridylmethyl)pyrido[2,3-d]pyridazin-8-one

34. Formula I, Where X is carbon, Y is nitrogen, Z is oxygen, R¹ is 4-pyridylmethyl, R³ is nitro and R², R⁴, R⁵ and R⁶ are hydrogen.

30

Following the procedures of Example 9 and substituting 8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one with 5-(3-nitrophenyl)pyrido[2,3-d]pyridazin-8-one there is obtained 5-(3-nitrophenyl)-7-(4-pyridomethyl)pyrido[2,3-d]pyridazin-8-one.

EXAMPLE 35

Preparation of

35

6-(3-thienylmethyl)-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one

35A. Formula I, Where X is nitrogen, Y is carbon, Z is oxygen, R¹ is 3-thiophenemethyl, R³ is chloro and R², R⁴, R⁵ and R⁶ are hydrogen.

40

To a suspension of 8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one (0.21g, 0.82mmoles) in tetrahydrofuran (25ml) was added 3-thiophenemethanol (0.085ml, 0.9 mmoles) and triphenylphosphine (0.32g, 1.22 mmoles). To this mixture was added a solution of diisopropyl azodicarboxylate (0.24ml, 1.22 mmoles) in tetrahydrofuran (5ml) in a

dropwise manner. The solution was stirred for 3 hours at room temperature. The solvent was removed and the residue chromatographed from hot methanol, yielding 0.15 g of 6-(3-thienylmethyl)-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one, mp 165-166°C.

5

35B. Preparation of Other Compounds of Formula I Where X is nitrogen, Y is carbon, and Z is oxygen.

Following the procedures of Example 35A and substituting 3-thiophenemethanol with the following:

10

4-(2-hydroxyethyl)morpholine;
3-pyridinepropanol;
2-(hydroxyethyl)pyridine;
1-(2-hydroxyethyl)pyrrolidine; and
1-(2-hydroxyethyl)-2-pyrrolidinone,

15

their were obtained the following compounds:

6-[4-(2-hydroxyethyl)morpholinyl]-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one, mp 135°C;

6-(3-pyridopropyl)-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one, mp 91°C;

20

6-[2-(hydroxyethyl)pyridyl]-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one, mp 98°C;

6-[1-(2-hydroxyethyl)pyrrolidyl]-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one, mp 149°C; and

25

6-[1-(2-hydroxyethyl)-2-pyrrolidinonyl]-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one, mp 78°C.

EXAMPLE 36

Preparation of

6-(4-pyridylmethyl)-8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one hydrochloride

35

To a suspension of 6-(4-pyridylmethyl)-8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one in methanol is added 5% HCl/MeOH in a dropwise manner with stirring until a clear solution is obtained. The solvent is stripped off. The resulting solid is triturated with ethyl ether. The product is filtered off and dried under vacuum yielding 6-(4-pyridylmethyl)-8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one hydrochloride.

40

In a similar manner, all compounds of Formula I may be converted to the acid addition salts by treatment with the appropriate acid, for example, hydrobromic acid, sulfuric acid (giving the sulfate and bisulfate salts), nitric acid, phosphoric acid and the like.

EXAMPLE 37

By following the procedures in Examples 1-36 the following compounds were made:

Formula I, where X is nitrogen, Y is carbon, and Z is oxygen.

5 R³ is chloro, R¹ is 2-propyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 80°C;

R³ is chloro, R¹ is 4-pyridylmethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 152°C;

10 R³ is chloro, R¹ is N-ethylmorpholinyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 135 °C;

R³ is chloro, R¹ is N-ethylpyrrolidonyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 78 °C;

R³ is chloro, R¹ is 3-thienylmethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 165°C;

15 R³ is chloro, R¹ is (4-methoxy-3-pyridyl)methyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 145°C;

R³ is chloro, R¹ is 3-pyridylmethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 165°C;

20 R³ is chloro, R¹ is n-butyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 119°C;

R³ is chloro, R¹ is methyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 180°C;

R³ is chloro, R¹ is benzyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 111-112°C;

25 R³ is chloro, R¹ is ethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 117°C;

R³ is chloro, R¹, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 268-269°C;

30 R³ is chloro, R¹ is phenyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 144-145°C;

R³ is chloro, R¹ is N-methylpiperidinyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 142°C;

R³ is chloro, R¹ is 2-pyridylethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 98°C;

35 R³ is chloro, R¹ is 3-pyridylpropyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 91°C;

R³ is chloro, R¹ is phenylethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 108°C;

R³ is chloro, R¹ is cyclopentyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 93°C;

40 R³ is chloro, R¹ is cyclohexyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 98°C;

R³ is chloro, R¹ is N-ethylpyrrolidinyl, R², R⁴, R⁵ and R⁶ are

hydrogen, melting point 149°C;

R³ is chloro, R¹ is *n*-propyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 93°C;

5 R³ is chloro, R¹ is *t*-butyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 105°C;

R³ is chloro, R¹ is *N*-methylmorpholinyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 161°C;

R³ is chloro, R¹ is 2-methylaminoethyl and R², R⁴, R⁵ and R⁶ are hydrogen, melting point 90°C.

10 R³ is chloro, R¹ is cyclopentylmethyl and R², R⁴, R⁵ and R⁶ are hydrogen, melting point 125°C.

R³ is chloro, R¹ is α -methyl-cyclopropylmethyl and R², R⁴, R⁵ and R⁶ are hydrogen, melting point 76°C.

15 R³ is chloro, R¹ is 2-thienyl and R², R⁴, R⁵ and R⁶ are hydrogen, melting point 175°C.

R³ is chloro, R¹ is furfuryl and R², R⁴, R⁵ and R⁶ are hydrogen, melting point 164°C.

R³ is chloro, R¹ is 4-pyridyl-*N*-oxide-methyl and R², R⁴, R⁵ and R⁶ are hydrogen, melting point 175-176°C (recryst. from MeOH).

20 R³ is chloro, R¹ is dimethylaminoethyl and R², R⁴, R⁵ and R⁶ are hydrogen, melting point 90°C.

R³ and R⁴ are chloro, R¹ is hydrogen and R², R⁵ and R⁶ are hydrogen, melting point 270-272°C.

25 R³ and R⁴ are chloro, R¹ is ethyl and R², R⁵ and R⁶ are hydrogen, melting point 114°C.

R³ and R⁴ are chloro, R¹ is isopropyl and R², R⁵ and R⁶ are hydrogen, melting point 133°C.

R³ and R⁴ are chloro, R¹ is benzyl and R², R⁵ and R⁶ are hydrogen, melting point 145°C.

30 R³ and R⁴ are chloro, R¹ is 4-pyridylmethyl and R², R⁵ and R⁶ are hydrogen, melting point 162°C.

R³ is fluoro, R¹ is 4-pyridylmethyl and R², R⁴, R⁵ and R⁶ are hydrogen, melting point 158°C.

35 R³ is fluoro, R¹ is 3-pyridylmethyl and R², R⁴, R⁵ and R⁶ are hydrogen, melting point 151°C.

R³ is fluoro, R¹ is ethyl and R², R⁴, R⁵ and R⁶ are hydrogen, melting point 117-118°C.

R³ is fluoro, R¹ is benzyl and R², R⁴, R⁵ and R⁶ are hydrogen, melting point 130-131°C.

40 R³ is nitro, R¹ is 4-pyridylmethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 172°C;

R³ is nitro, R¹ is 4-pyridylmethyl, R², R⁴, R⁵ and R⁶ are hydrogen, as hydrochloride; melting point 195.9-203.9°C;

R³ is nitro, R¹ is 3-pyridylmethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 190°C;

R³ is nitro, R¹ is 3-thienylmethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 175°C;

5 R³ is nitro, R¹ is phenyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 167-168°C;

R³ is nitro, R¹ is ethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 138-139°C;

10 R³ is nitro, R¹ is allyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 99°C;

R³ is nitro, R¹, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 302-304°C;

R³ is nitro, R¹ is benzyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 141°C;

15 R³ is nitro, R¹ is 2-methoxybenzyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 189°C;

R³ is nitro, R¹ is 3-fluorobenzyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 139°C;

20 R³ is nitro, R¹ is 3-methoxybenzyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 162°C;

R³ is nitro, R¹ is 3,5-dichlorobenzyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 189°C;

R³ is nitro, R¹ is 4-nitrobenzyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 205°C;

25 R³ is nitro, R¹ is 4-fluorobenzyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 155°C;

R³ is nitro, R¹ is 4-chlorobenzyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 177°C;

30 R³ is nitro, R¹ is 4-methoxybenzyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 155°C;

R³ is nitro, R¹ is cyclopentylmethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 88°C;

R³ is nitro, R¹ is dimethylaminoethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 108°C;

35 R³ is nitro, R¹ is 2-tetrahydrofuranlylmethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 109°C;

R³ is nitro, R¹ is 3-tetrahydrofuranlylmethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 76°C;

R³ is nitro, R¹ is cyclopropylmethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 129-130°C;

40 R³ is nitro, R¹ is α -methyl-cyclopropylmethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 99°C;

R³ is nitro, R¹ is 4-pyridyl-N-oxide-methyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 208°C;

R³ is nitro, R¹ is 2-propyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 126°C;

5 R³ is nitro, R¹ is 1,2-(methylenedioxy)phenyl-5-methyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 199°C;

R³ is nitro, R¹ is 2-bromoethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 163°C;

10 R³ is nitro, R¹ is 2-fluoroethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 167°C;

R³ is nitro, R¹ is 2-chloroethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 166°C;

R³ is nitro, R¹ is (3-methyl-3-oxetanyl)methyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 159°C;

15 R³ is nitro, R¹ is 2-cyanoethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 145°C;

R³ is nitro, R¹ is 3-methyl-3-butenyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 97°C;

20 R³ is nitro, R¹ is methylthioethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 96°C;

R³ is nitro, R¹ is 3-methyl-2-butenyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 119°C;

R³ is nitro, R¹ is methoxyethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 135°C;

25 R³ is nitro, R¹ is methylthiopropyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 71°C;

R³ is nitro, R¹ is 3,4-dichlorophenyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 168°C;

30 R³ is nitro, R¹ is 2-hydroxyethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 155°C;

R³ is nitro, R¹ is 2-thienyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 173°C;

R³ is nitro, R¹ is benzyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 141°C;

35 R³ is nitro, R¹ is 1-pyrrolidinyethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 149°C;

R³ is nitro, R¹ is furfuryl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 159°C;

40 R³ is nitro, R¹ is 2-acetoxyethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 116°C;

R³ is nitro, R¹ is 2-(4-chlorophenyl)-4-thiazolylmethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 206°C;

R³ is nitro, R¹ is 2-phenyl-4-oxazolylmethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 170°C;

R³ is nitro, R¹ is 5-norbornen-2-yl-methyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 152°C;

5 R³ is nitro, R¹ is norbornylmethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 153°C;

R³ is nitro, R¹ is 3-[5-(3,5-dimethylisoxazol-4-yl)-1,2,4-oxadiazolyl]methyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 190°C;

10 R³ is trifluoromethyl, R¹ is cyanoethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 133°C;

R³ is trifluoromethyl, R¹ is ethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 116°C;

R³ is trifluoromethyl, R¹ is 3-pyridylmethyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 142°C;

15 R³ is trifluoromethyl, R¹ is benzyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 137°C;

R³ is trifluoromethyl, R¹ is *n*-butyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 103°C;

20 R³ is cyano, R¹ is benzyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 158°C;

R³ is methyl, R¹ is benzyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 88°C;

R³ is methoxycarbonyl, R¹ is benzyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 128-130°C;

25 R¹ is benzyl, R², R³, R⁴, R⁵ and R⁶ are hydrogen, melting point 169-170°C;

R¹ is 4-pyridylmethyl, R², R³, R⁴, R⁵ and R⁶ are hydrogen, melting point 175-176°C;

R¹, R², R³, R⁴, R⁵ and R⁶ are hydrogen, melting point 230-231°C;

30 R¹ is ethyl, R², R³, R⁴, R⁵ and R⁶ are hydrogen, melting point 114-115°C;

Formula I, Where X is carbon, Y is nitrogen, and Z is oxygen.

R¹ is phenyl, R², R³, R⁴, R⁵ and R⁶ are hydrogen, having a melting point of 221-222°C;

R¹, R², R³, R⁴, R⁵ and R⁶ are hydrogen, having a melting point of 232-233°C;

R¹ is ethyl, R², R³, R⁴, R⁵ and R⁶ are hydrogen, having a melting point of 164-165°C;

R¹ is benzyl, R², R³, R⁴, R⁵ and R⁶ are hydrogen, having a melting point of 210-211°C; and

40 R¹ is 4-pyridylmethyl, R², R³, R⁴, R⁵ and R⁶ are hydrogen, having a melting point of 230-231°C.

Formula I, where X is nitrogen, Y is carbon, and Z is sulfur.

R³ is chloro, R¹ is benzyl, R², R⁴, R⁵ and R⁶ are hydrogen, melting point 132°C;

5

EXAMPLE 38

Preparation of 6-(4-pyridyl-N-oxide-methyl)-
8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one

10

38. Formula I, where X is nitrogen, Y is carbon, Z is oxygen, R¹ is 4-pyridyl-N-oxide-methyl, R³ is chloro and R², R⁴, R⁵ and R⁶ are hydrogen.

15

To a suspension of 8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one (0.50 g, 1.94 mmoles), 4-pyridylcarbinol N-oxide (0.27 g, 2.13 mmoles), triphenylphosphine (0.76 g, 2.9 mmoles) in tetrahydrofuran (50 ml) was added diisopropylazodicarboxylate (0.57 ml, 2.9 mmoles) in a dropwise fashion. The suspension was stirred under nitrogen for 18 hours at room temperature. The solvent was removed and the product purified by chromatography, eluted with 100% ethylacetate and 10% methanol/ethylacetate to yield 0.382 g of 6-(4-pyridyl-N-oxide-methyl)-8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one (54%), mp 99°C.

20

EXAMPLE 39

Preparation of 6-(4-pyridyl-N-oxide-methyl)-
8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one

25

39. Formula I, where X is nitrogen, Y is carbon, Z is oxygen, R¹ is 4-pyridyl-N-oxide-methyl, R³ is nitro and R², R⁴, R⁵ and R⁶ are hydrogen.

30

To a solution of 8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one (0.40 g, 1.5 mmoles), 4-pyridylcarbinol N-oxide (0.205 g, 1.64 mmoles), triphenylphosphine (0.587 g, 2.24 mmoles) in tetrahydrofuran (50 ml) was added diisopropylazodicarboxylate (0.44 ml, 2.24 mmoles) in a dropwise fashion. The suspension was stirred under nitrogen for 18 hours at room temperature. The solvent was removed and the product purified by chromatography, i.e., eluted with 100% ethylacetate and 10% methanol/ethylacetate. The fractions were combined, the solvent removed yielding 0.390 g of product which was recrystallized from methanol to give 0.237 g of 6-(4-pyridyl-N-oxide-methyl)-8-(3-nitrophenyl)pyrido[2,3-d]pyridazin-5-one (42.1%),

35

EXAMPLE 40

(Reaction Scheme F)

40

Alternate Preparation of Formula II, where X is nitrogen, Y is carbon and R⁷ is n-butyl.

40

A suspension of 2,3-pyridinyldicarboxylic anhydride (Formula I) (90g, 603mmoles) was prepared with 400mL of ethyl acetate. The mixture was

cooled to 3°C and n-butylamine (61mL, 610mmoles) was added at such a rate that the temperature remained below 25°C. Following the addition, the cooling bath was removed and thionyl chloride (51mL; 700mmoles) was added at such a rate that the temperature remained below 50°C. The mixture was stirred for 1 hour. The resulting suspension was then cooled to 5°C and dilute sodium hydroxide (240mL of a 6M solution, 1.4moles) was added at such a rate that the temperature remained below 35°C. The resulting layers were separated. The bulk of the ethyl acetate was removed by atmospheric distillation. Methanol (500mL) was then added and the distillation continued until 250mL of solution remained. The solution was allowed to cool during which time crystallization occurred. Water (250mL) was then added and the mixture aged for 18 hours. The product was isolated by filtration and washed twice with 200mL of a 1:1 (v:v) mixture of water and methanol. After drying 115g of product (Formula 11) was obtained.

Preparation of Formula 13, where X is nitrogen, Y is carbon, R⁷ is n-butyl, and R², R³, R⁴, R⁵, R⁶ are hydrogen.

The imide (formula 11) (40.4g, 198mmoles) was dissolved in toluene (1L) and cooled to -65°C. Phenylmagnesium chloride (100mL, 2M in THF, 200mmoles) was added over 15 minutes. The cooling bath was then removed and the mixture allowed to warm to -10°C. The reaction was quenched by addition of 25mL of saturated ammonium chloride solution. The room temperature solution was diluted with 500mL of ethyl acetate and 500mL of water. The layers were separated. Removal of most of the organic solvent was accomplished by atmospheric distillation. When the remaining volume reached 150mL the mixture was cooled to below 80°C and 1L of hexanes was added. The resulting crystalline mass was filtered and dried to give 50.6g of product (Formula 13).

Preparation of Formula 14, where X is nitrogen, Y is carbon, R⁷ is n-butyl, R³ is nitro, and R², R⁴, R⁵, R⁶ are hydrogen.

The product from the Grignard addition (47.15g, 167mmoles) was mixed with 250mL of concentrated sulfuric acid (96%). The resulting mixture was placed in a cooling bath. Nitric acid (70%, 12mL, 189mmoles) was added at such a rate that the temperature remains below 45°C. The mixture was stirred for 30 minutes poured onto ice (500g) and diluted with 1L of water. The mixture was extracted twice with 700mL of ethyl acetate. The organic solvent was removed and the reaction product used directly in the next reaction.

Preparation of Formula 15, where X is nitrogen, Y is carbon, R³ is nitro, and R², R⁴, R⁵, R⁶ are hydrogen.

The crude material from the preceding reaction was mixed with

500mL of water and 250mL of concentrated hydrochloric acid was added. The mixture was heated under reflux for 20 hours. After cooling the mixture was diluted with 500mL of water and the solid was removed by filtration. After washing the solid with water (500mL) and methanol (200mL) the material was dried to give 39.85g of product.

Preparation of Formula I, where X is nitrogen, Y is carbon, R³ is nitro, and R¹, R², R⁴, R⁵, R⁶ are hydrogen.

The material from the preceding reaction (38.65g, 142mmoles) was mixed with 800mL of methanol. To this heterogenous mixture was added 35mL of anhydrous hydrazine. The resulting solution was then heated under reflux for 5 hours. After a 17 hour aging at room temperature the product was isolated by filtration. Washing the crystalline mass twice with methanol (250mL) and drying yielded 25.6g of product.

Preparation of Formula I, where X is nitrogen, Y is carbon, R¹ is 4-pyridylmethyl, R³ is nitro, and R², R⁴, R⁵, R⁶ are hydrogen.

The material from the preceding reaction (5.12g, 19.1mmoles), sodium hydride (50% in oil, 1g, 20.1mmoles) were mixed in 100mL of 1-methyl-2-pyrrolidone and the mixture heated to 65°C. In a separatory funnel, 4-picoyl chloride hydrochloride [(4-chloromethyl)pyridine hydrochloride] (4.5g, 27.4mmoles), 20mL of saturated potassium carbonate and 75mL of toluene are mixed. After separation, the toluene solution was added to the reaction mixture dropwise over the period of 1 hour. The reaction mixture was diluted with water (250mL) and extracted twice with ethyl acetate (200mL). After concentrating the organic fractions, methanol and hexanes (75mL each) were added and the mixture allowed to stir at room temperature for 17 hours. The material was filtered and dried to yield 5.2g of product.

Preparation of Formula I, where X is nitrogen, Y is carbon, R¹ is 4-pyridyl-N-oxide-methyl, R³ is nitro, and R², R⁴, R⁵, R⁶ are hydrogen.

The material from the preceding reaction (4.2g, 11.5mmoles) was dissolved in 100mL of methylene chloride. To this solution was added m-chloroperoxybenzoic acid (85%, 4.2g, 20.7mmoles). The solution was stirred for 17 hours. After partitioning between methylene chloride and potassium carbonate the organic layer was directly chromatographed using silica gel. The product was eluted with 20% methanol in ethyl acetate. Recrystallization of the solid material obtained after solvent removal from methanol (200mL) gave after filtering 3.2g of product.

EXAMPLE 41
(Reaction Scheme G)

Preparation of Formula 18, where X is nitrogen, Y is carbon,
5 R¹ is n-butyl, R³ is chlorine and R², R⁴, R⁵, R⁶ are hydrogen.

The imide (Formula 11) (20g, 98mmoles) was dissolved in
toluene(500mL) and cooled to -65°C. To this mixture was added
3-chlorophenylmagnesium bromide (prepared by heating under reflux
2.5g magnesium metal, 20g of 3-chlorobromobenzene and 100mL of
10 tetrahydrofuran for 1 hour) at such a rate that the temperature of the
reaction remained below -40°C. After the addition was complete, the
cooling bath was removed and the mixture allowed to warm to 0°C.
The reaction mixture was quenched with aqueous ammonium chloride (25mL)
diluted with ethyl acetate (250mL) and water (250mL). After separating
15 the resulting 2 layers, the organic fraction was dried with sodium
sulfate (50g). Filtration, followed by solvent removal gave an oil
which was used directly in the next reaction.

Preparation of Formula 19, where X is nitrogen, Y is carbon, R³ is
20 chlorine, and R², R⁴, R⁵, R⁶ are hydrogen.

To the crude material from the preceding reaction was added 500mL
of water, 250mL of concentrated hydrochloric acid and the mixture was
heated under reflux for 24 hours. The solution was then filtered,
cooled and made basic with sodium hydroxide. An ethyl acetate
25 extraction removed unhydrolyzed starting material and the pH of the
resulting aqueous fraction was adjusted to pH2 with hydrochloric acid.
Extraction of the resulting aqueous fraction twice with ethyl acetate
(250mL) and solvent removal gave 16g of product, which was used directly
in the next reaction.

Preparation of Formula I, where X is nitrogen, Y is carbon,
30 R³ is chlorine, and R¹, R², R⁴, R⁵, R⁶ are hydrogen.

The material from the preceding reaction was mixed with 100mL of
methanol. To this mixture was added 20mL of anhydrous hydrazine. The
mixture was heated under reflux for 2 hours at which time an additional
35 100mL of methanol and 200mL of xylenes are added. The mixture was
heated under reflux for an additional 17 hours. Additional xylenes
(200mL) were added and 200mL of solvent was distilled. Isolation of the
product was accomplished by cooling the reaction mixture and filtration.
40 Washing of the resulting crystalline mass with toluene (200mL) and
drying gave 14.2g of product.

Preparation of Formula I, where X is nitrogen, Y is carbon, R¹ is 4-pyridylmethyl, R³ is chlorine, and R², R⁴, R⁵, R⁶ are hydrogen.

The material from the proceeding reaction (14.2g, 55mmoles) and sodium hydride (50% in oil, 2.7g, 55mmoles) were mixed in 150mL of 1-methyl-2-pyrrolidone and the mixture was heated to 55°C. In a separatory funnel, 4-picoyl chloride hydrochloride [(4-chloromethyl)-pyridine hydrochloride] (11g, 67mmoles), 50mL of saturated potassium carbonate and 150mL of toluene were mixed. After separation the toluene solution was added to the reaction mixture dropwise over the period of 30 minutes. The mixture was heated to 60°C for an additional 30 minutes, cooled to room temperature and poured into 300mL of water. The mixture was extracted twice with ethyl acetate (500mL). After drying the organic fraction with sodium sulfate (50g), filtering and solvent removal the crude product was crystallized from isopropyl acetate (300mL). The material was filtered and dried to yield 10.5 grams of product. An additional 4.6 grams of product was obtained as a second crop by concentration of the filtrates and filtering the resulting crystalline mass.

Preparation of Formula I, where X is nitrogen, Y is carbon, R¹ is 4-pyridyl-N-oxide-methyl, R³ is chlorine, and R², R⁴, R⁵, R⁶ are hydrogen.

The product from the preceding reaction (6g, 17.2mmoles) was mixed with m-chloroperoxybenzoic acid (85%, 4.5g, 22.1mmoles) in methylene chloride (50mL). The mixture was stirred for 2 hours at room temperature. Saturated sodium carbonate (25mL) was added the resulting layers separated and the methylene chloride fraction dried with sodium sulfate (25g). After filtration, the solvent was removed and the resulting solid crystallized from methanol (20mL). Filtration and drying yielded 3.8g of product.

EXAMPLE 42

Preparation of

8-(3-chlorophenyl)-6-benzylpyrido-[2,3-d]pyridazin-5-thione.

Conversion of a Pyrido[2,3-d]pyridazin-5-one of Formula I, where X is nitrogen, Y is carbon, Z is oxygen, R¹ is benzyl, R³ is chloro, and R², R⁴, R⁵, R⁶ are hydrogen, into the corresponding Pyrido[2,3-d]pyridazin-5-thione of Formula I, where X is nitrogen, Y is carbon and Z is sulfur.

To a solution of 8-(3-chlorophenyl)-6-benzylpyrido[2,3-d]pyridazin-5-one (0.96g, 2.76mmoles) in toluene (100mL) at room temperature under a nitrogen atmosphere was added solid 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide

(Lawesson's Reagent) (0.67g, 1.66mmoles). The reaction mixture was heated under reflux for 18 hours, and then cooled and concentrated. Chromatography on silica gel using ethyl acetate/hexane (1:4) gave 0.233g of product (23.2%), mp 132°C.

5

EXAMPLE 43

Preparation of 8-(3-chlorophenyl)-6-(6-methoxy-3-pyridylmethyl)pyrido-[2,3-d]pyridazin-5-one.

10 Formula I, where X is nitrogen, Y is carbon, Z is oxygen, R¹ is 6-methoxy-3-pyridylmethyl, R³ is chloro, and R², R⁴, R⁵, R⁶ are hydrogen.

To a suspension of 8-(3-chlorophenyl)pyrido[2,3-d]pyridazin-5-one (0.515g, 2.0 mmoles), 6-methoxy-3-hydroxymethyl pyridine (0.306g, 2.2 mmoles) and triphenylphosphine (0.792g, 3.0 mmoles) in THF (50mL) was added diisopropylazodicarboxylate (0.6mL, 3.0 mmoles). The reaction mixture was stirred for 18 hours at room temperature. The solvent was removed and the product was purified by chromatography (ethyl acetate/hexane 2:3) and crystallized from methanol to yield 0.588g of 8-(3-chlorophenyl)-6-(6-methoxy-3-pyridylmethyl)pyrido-[2,3-d]pyridazin-5-one, mp 145°C.

20

EXAMPLE 44

Preparation of 8-(3-chlorophenyl)-6-(3-pyridon-6-ylmethyl)pyrido[2,3-d]pyridazin-5-one.

25

Formula I, where X is nitrogen, Y is carbon, Z is oxygen, R¹ is 3-pyridon-6-ylmethyl, R³ is chloro, and R², R⁴, R⁵, R⁶ are hydrogen.

To a solution of 8-(3-chlorophenyl)-6-(6-methoxy-3-pyridylmethyl)pyrido[2,3-d]pyridazin-5-one (0.566g, 1.5 mmoles) in acetonitrile was added solid sodium iodide (0.224g). The suspension was stirred for 30 min at room temperature, and then trimethylsilyl chloride (0.19mL, 1.5 mmoles) was added. The reaction mixture was heated under reflux for 18 hours, then allowed to cool. Water (50mL) was added. The solution was extracted with ethyl acetate, washed with 10% sodium thiosulfate and brine, dried over magnesium sulfate, filtered and concentrated. Chromatography with 10% methanol/ethyl acetate yielded 0.317g of 8-(3-chlorophenyl)-6-(3-pyridon-6-ylmethyl)pyrido-[2,3-d]pyridazin-5-one, mp 233°C.

30

35

40

EXAMPLE 45

Preparation of 8-(3-chlorophenyl)-6-(1-methyl-3-pyridon-6-ylmethyl)pyrido-[2,3-d]pyridazin-5-one.

Formula I, where X is nitrogen, Y is carbon, Z is oxygen, R¹ is 1

methyl-3-pyridon-6-ylmethyl, R³ is chloro, and R², R⁴, R⁵, R⁶ are hydrogen.

To a suspension of 8-(3-chlorophenyl)-6-(3-pyridon-6-ylmethyl)pyrido-[2,3-d]pyridazin-5-one (0.35g, 0.96 mmoles) in DMF (15mL) was added potassium carbonate (0.16g, 1.15 mmoles). The suspension was stirred at room temperature for 1 hour under nitrogen, then methyl iodide (0.12mL) was slowly added via syringe. The reaction mixture was heated under reflux for 18 hours, then allowed to cool. 1N HCl (35mL) was added, the solid material collected, dried and chromatographed with ethyl acetate and then 5% methanol/ethyl acetate to give 0.055g of 8-(3-chlorophenyl)-6-(1-methyl-3-pyridon-6-ylmethyl)-pyrido[2,3-d]pyridazin-5-one, mp 171°C.

EXAMPLE 46

Determination of Potency and Selectivity of Inhibitors for PDE IV

Preparation of Human Platelet Phosphodiesterase (PDE III)

Platelet high-affinity cAMP PDE (PDE III) was obtained from human blood in accordance with previously described procedures described in *Mol. Pharmacol.* 20:302-309, Alvarez, R., Taylor, A., Fazarri, J.J., and Jacobs, J.R. (1981).

Blood was collected into evacuated tubes containing EDTA (7.7 mM, final concentration). PRP was obtained by centrifuging the blood in polycarbonate tubes at 200 x g for 15 min at 4°C. A platelet pellet was resuspended in a volume of buffer A (0.137 M NaCl, 12.3 mM Tris-HCl buffer, pH 7.7, containing 1 mM MgCl₂). The hypotonically-lysed platelet suspension was centrifuged at 48,000 x g for 15 min and the supernatant was saved. The pellets were frozen on dry ice and briefly thawed at 22°C. The supernatant was combined with the pellet fraction and the resulting suspension was centrifuged at 48,000 x g for 30 min. The supernatant fraction was stored in 0.5 ml aliquots at -20°C and used as the soluble PDE. Enzyme activity was adjusted to 10-20% hydrolysis after 10 minutes of incubation by dilution with 10mM cold Tris-HCl buffer, pH 7.7.

Preparation of Human Lymphocyte Phosphodiesterase (PDE IV)

Human B cell line (43D) was cultured at 37°C in 7% CO₂ in RPMI 1640 with L-glutamine and 10% Nu-Serum. Prior to the assay $\sim 1.5 \times 10^8$ cells were centrifuged at 1000 rpm for 10 minutes in a table top clinical centrifuge. The pellet was resuspended in 2-3 ml of 45 mM Tris-HCl buffer, pH 7.4. The suspension was homogenized and centrifuged at 12,000 x g 4°C for 10 minutes. The supernatant was diluted to 28 ml with Tris-HCl buffer and used directly in the assay or stored at -20°C. The final concentration of DMSO in the PDE incubation medium was 1%.

Nitraquazone was included in each assay (10 and 100 μ M) as a reference standard.

Human Platelet cAMP Phosphodiesterase Assay

5 The phosphodiesterase incubation medium contained 10 mM Tris-HCl
buffer, pH 7.7, 10 mM MgSO₄, 0.1-1 μ M [³H]-AMP (0.2 μ Ci) in a total volume
of 1.0 ml. Following addition of the enzyme, the contents were mixed
and incubated for 10 min at 30°C. The reaction was terminated by
immersing the tubes in a boiling-water bath for 90 sec. After the tubes
10 were cooled in an ice-water bath, 0.1 ml (100 μ g) of 5'-nucleotidase from
snake venom (*Crotalus atrox*, Sigma V-7000) was added to each tube. The
contents were mixed and incubated for 30 min at 30°C. The nucleotidase
reaction was terminated by immersing the tubes in a boiling water bath
for 60 sec. Labeled adenosine was isolated from alumina columns
15 according to the method described in *Anal. Biochem.*, 52:505-516 (1973),
Filburn, C.R., and Karn, J.. Assays were performed in triplicate.
Hydrolysis of cAMP ranged from 10-20%. Test compounds were dissolved in
DMSO. The final concentration of DMSO in the phosphodiesterase assay
was 1% when tested with compounds up to 0.1 mM. When tested at 1 mM the
20 DMSO concentration was 10% and this activity was compared to control PDE
activity in the presence of 10% DMSO.

Human Lymphocyte cAMP Phosphodiesterase Assay

25 The phosphodiesterase incubation medium contained 40 mM Tris-HCl
buffer, pH 7.7, 0.1 mM MgSO₄, 3.75 mM mercaptoethanol, and 0.1-1.0 μ M
[³H] cAMP (0.2 μ Ci) in a total volume of 1.0 ml. The reaction was
performed and processed according to the procedure used (above) for
human platelet PDE. The final concentration of DMSO was 1%.

The compounds of the present invention exhibit potency and
selectivity as inhibitors of PDE IV when tested by this method.

Inhibition of Human Lymphocyte PDE IV

Compound I	IC ₅₀ :	0.00022 μ M
Compound II	IC ₅₀ :	0.001 μ M

35 Compound I is the compound of Formula I where X is nitrogen and Y
is carbon, R¹ is 4-pyridylmethyl, R³ is nitro, R², R⁴, R⁵ and R⁶ are
hydrogen, namely 6-(4-pyridylmethyl)-8-(3-nitrophenyl)pyrido[2,3-d]-
pyridazin-5-one.

40 Compound II is the compound of Formula I where X is nitrogen and Y
is carbon, R¹ is 4-pyridylmethyl, R³ is chloro, R², R⁴, R⁵ and R⁶ are
hydrogen, namely 6-(4-pyridylmethyl)-8-(3-chlorophenyl)pyrido[2,3-d]-
pyridazin-5-one.

EXAMPLE 47

Determination of Immunosuppressive Activity

Utilizing The Hemolytic Plaque Forming Cell (PFC) Assay

This procedure is a modification of "The agar plaque technique for recognizing antibody producing cells," a procedure initially described by Jerne, et al. [*Cell-bound Antibodies*, Amos and Kaprowski editors (Wistar Institute Press, Philadelphia, 1963) p. 109].

Groups of 5-6 adult C3H female mice were sensitized with 1.25×10^8 sheep red blood cells (SRBC) and simultaneously treated with an oral dosage form of the test material in an aqueous vehicle. Animals in a control group receive the same volume of vehicle. Four days after SRBC inoculation, spleens are dispersed in glass homogenizers. The number of nucleated cells (WBC) is determined and the spleen cell suspension is mixed with SRBC, guinea pig complement and agar solution at 0.5% concentration. Aliquots of the above mixture (0.1 ml) are dropped on four separate quadrants of a Petri dish and are covered with cover slips. After two hours incubation at 37°C, areas of hemolysis around plaque-forming cells (PFC) are counted with a dissecting microscope. Total WBC/spleen, PFC/spleen and PFC/ 10^6 WBC (PPM) are calculated for each mouse spleen. Geometric means of each treatment group are then compared with the vehicle-treated control group.

The compounds of the present invention show immunosuppressive activity when tested by this method.

Immunosuppressive Activity of Compounds I and II

	Immune PFC	
Compound I	ED ₅₀	1 mg/kg
Compound II	ED ₅₀	3 mg/kg

EXAMPLE 48

Determination of Immunosuppressive Activity Utilizing Responses of Human Peripheral Blood Lymphocytes to Mitogen

This procedure is a modification of a procedure initially described by Greaves, et al. ["Activation of human T and B lymphocytes by polyclonal mitogens," *Nature*, 248, 698-701 (1974)].

Human mononuclear cells (PBL) are separated from heparinized whole blood by density gradient centrifugation in Ficoll-Paque (Pharmacia). After washing, 5×10^4 cells/well are cultured in microtiter plates with minimal essential media supplemented with 1% human serum, gentamicin, sodium bicarbonate, 2-mercaptoethanol, glutamine, non-essential amino acids, and sodium pyruvate. The mitogen concanavalin A (Sigma) is used at a concentration of 2 μ g/ml. Test materials are tested at concentrations between 10^{-4} and 10^{-10} M, by addition to the culture at time

0. Cultures are set up in quadruplicate and incubated at 37°C in a humidified atmosphere with 5% CO₂ for 48 hours. A pulse of 1.0 µCi/well of ³H-thymidine is added for the last 4 hours. Cells are collected on glass fiber filters with an automatic harvester and radioactivity is measured by standard scintillation procedures. The 50% inhibitory concentration ("IC₅₀") for mitogenic stimulation is determined graphically. The compounds of the present invention show immunosuppressive activity when tested by this method.

Effect of Compounds on Mitogenic Response of Human PBL
to Concanavalin in a Stimulation

Concentration	% Suppression	
	Compound I	Compound II
100 µM	100	100
10 µM	85	87
1 µM	80	83
0.1 µM	83	74

The % suppression represents test well counts minus background (wells with no concanavalin A) divided by control well counts (wells with no compound) minus background times 100.

EXAMPLE 49

Determination of Anti-Inflammatory Activity Utilizing
Arachidonic Acid-Induced Ear Edema (AAEE) in the Mouse

This procedure is a modification of a procedure described by Young et al., J. Invest. Derm., 82:367-371 (1984).

Female Charles River ICR mice 23-27 grams are administered 0.2 ml of test material. The mice are later challenged with 20 µl of arachidonic acid applied topically to the ear. One hour after challenge, the weight of an 8 mm disc is determined. The mean increase in ear plug weight is calculated. Materials with anti-inflammatory activity inhibit the increase in ear plug weight.

The compounds of the present invention exhibit anti-inflammatory activity when tested by this method.

Antiinflammatory Activity of Compounds I and II

	AAEE	
Compound I	ED ₅₀	0.003mg/kg
Compound II	ED ₅₀	0.009mg/kg

EXAMPLE 50

Capsule Formulation

This example illustrates the preparation of a representative pharmaceutical formulation for oral administration containing an active compound of Formula I.

Ingredients	Quantity (mg/capsule)
Active compound	200 mg
lactose, spray-dried	148 mg
magnesium stearate	2 mg

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

EXAMPLE 51

Oral Formulation

This example illustrates the preparation of a representative pharmaceutical formulation containing an active compound of Formula I.

An suspension for oral administration is prepared having the following composition:

Ingredients	Quantity
Active compound	1.0 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.1 g
granulated sugar	25.5 g
sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
flavoring	0.035 mL
colorings	0.5 mg
distilled water	q.s. to 100 mL

Other compounds of Formula I, such as those prepared in accordance with Examples 1-45 can be used as the active compound in the preparation of the orally administrable formulations of this example.

EXAMPLE 52

Tablet Formulation

This example illustrates the preparation of a representative pharmaceutical formulation containing an active compound of Formula I.

A tablet for oral administration is prepared having the following composition:

	Ingredients	Quantity (mg/tablet)
	Active compound	400 mg
	corn starch	50 mg
	lactose	145 mg
5	magnesium stearate	5 mg

The above ingredients are mixed intimately and pressed into single scored tablets.

10 Other compounds of Formula I, such as those prepared in accordance with Examples 1-45 can be used as the active compound in the preparation of the tablet formulations of this example.

EXAMPLE 53

Injectable Formulation

15 This example illustrates the preparation of a representative pharmaceutical formulation containing an active compound of Formula I.

An injectable preparation is prepared having the following composition:

	Ingredients	Quantity
20	Active compound	200 mg
	water (distilled, sterile)	q.s. to 20.0 mL

25 Other compounds of Formula I, such as those prepared in accordance with Examples 1-45 can be used as the active compound in the preparation of the injection administrable formulations of this example.

EXAMPLE 54

Suppository Formulation

30 This example illustrates the preparation of a representative pharmaceutical formulation containing an active compound of Formula I.

A suppository totalling 2.5 grams is prepared having the following composition:

	Ingredients	Quantity
35	Active compound	0.5 g
	Witepsol H-15 [*]	q.s. to 2.5 g

(*triglycerides of saturated vegetable fatty acid; a product of Riches-Nelson, Inc., New York, N.Y.).

40 Other compounds of Formula I, such as those prepared in accordance with Examples 1-45 can be used as the active compound in the preparation of the suppository formulations of this example.

Other compounds of Formula I, such as those prepared in accordance with Examples 1-45 can be used as the active compound in the preparation of the injection administrable formulations of this example.

TOXICOLOGY

SPECIES: mice
COMPOUND: compounds I, II
5 DOSAGE; 3 to 25 mg/kg/day
DURATION OF DOSING: 2 weeks
CONCLUSION: no mortality occurred at any
of the dose levels tested.

10 The Ames test (in vitro Salmonella mutagenicity assay) was negative.

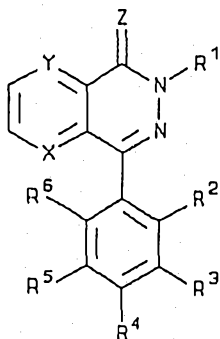
0
0
0
0

0
0
0

0
0

WHAT IS CLAIMED IS:

1. A compound of the formula:



5

10

15

wherein:

X and Y are carbon or nitrogen, provided both are not the same;
Z is oxygen or sulfur;

R¹ is hydrogen, lower alkyl, aryl, heteroaryl, or heterocycle lower alkyl;

20

R², R³, R⁴, R⁵ and R⁶ are independently selected from hydrogen, lower alkyl, halo, carboxy, alkoxycarbonyl, carbamoyl, acyl, methylthio, trifluoromethyl, cyano or nitro;

with the proviso that when R¹ is lower alkyl, cycloalkyl, cycloalkylmethyl, benzyl or imidazolyl lower alkyl,

25

R², R³, R⁴, R⁵ and R⁶ are independently carbamoyl, acyl, cyano or nitro;

or a pharmaceutically acceptable ester, ether or salt thereof.

2. The compound of Claim 1 wherein X is nitrogen, Y is carbon and Z is oxygen.

30

3. The compound of Claim 2 wherein R³ is hydrogen, halo or nitro and R², R⁴, R⁵ and R⁶ are hydrogen.

35

4. The compound of Claim 3 wherein R¹ is hydrogen, lower alkyl, aryl, or heterocycle lower alkyl.

5. The compound of Claim 4 wherein R¹ is ethyl, 2-propyl, cyclopropylmethyl, cyclopentylmethyl, benzyl, 4-pyridylmethyl, 4-pyridyl-N-oxide-methyl, 3-pyridylmethyl, 3-pyridyl-N-oxide-methyl, or 3-thienylmethyl.

40

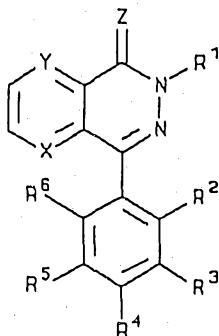
6. The compound of Claim 1 wherein X is carbon, Y is nitrogen and Z is oxygen.

7. The compound of Claim 6 wherein R¹ is hydrogen, lower alkyl, aryl, or heterocycle lower alkyl and R³ is hydrogen, halo or nitro and R², R⁴, R⁵ and R⁶ are hydrogen.

5 8. The compound of Claim 1 wherein X is nitrogen, Y is carbon and Z is sulfur.

9. The compound of Claim 8 wherein R³ is hydrogen, halo or nitro and R², R⁴, R⁵ and R⁶ are hydrogen.

10 10. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a therapeutically effective amount of a compound of the formula



25 wherein:

X and Y are carbon or nitrogen, provided both are not the same;
Z is oxygen or sulfur;

R¹ is hydrogen, lower alkyl, aryl, heteroaryl, or heterocycle lower alkyl;

30 R², R³, R⁴, R⁵ and R⁶ are independently selected from hydrogen, lower alkyl, halo, carboxy, alkoxy, carbonyl, carbamoyl, acyl, methylthio, trifluoromethyl, cyano or nitro;

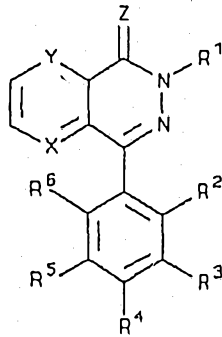
with the proviso that when R¹ is lower alkyl, cycloalkyl, cycloalkylmethyl, benzyl or imidazolyl lower alkyl,

35 R², R³, R⁴, R⁵ and R⁶ are independently carbamoyl, acyl, cyano or nitro;

or a pharmaceutically acceptable ester, ether or salt thereof.

40

11. A method of treating asthma, pain, inflammatory disease, allograft rejection, graft-vs-host-rejection, and autoimmune disease in mammals, which comprises administering to a mammal suffering therewith a therapeutically effective amount of a compound represented by the formula



wherein:

X and Y are carbon or nitrogen, provided both are not the same;
Z is oxygen or sulfur;

R¹ is hydrogen, lower alkyl, aryl, heteroaryl, or heterocycle lower alkyl;

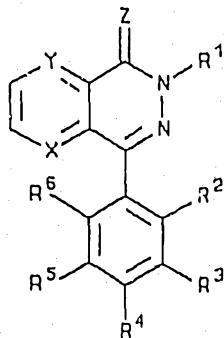
R², R³, R⁴, R⁵ and R⁶ are independently selected from hydrogen, lower alkyl, halo, carboxy, alkoxy, carbonyl, carbamoyl, acyl, methylthio, trifluoromethyl, cyano or nitro;

with the proviso that when R¹ is lower alkyl, cycloalkyl, cycloalkylmethyl, benzyl or imidazolyl lower alkyl,

R², R³, R⁴, R⁵ and R⁶ are independently carbamoyl, acyl, cyano or nitro;

or a pharmaceutically acceptable ester, ether or salt thereof.

12. A process for making a compound of the formula (I)



wherein:

X and Y are carbon or nitrogen, provided both are not the

same; Z is oxygen or sulfur;

R¹ is hydrogen, lower alkyl, aryl, heteroaryl, or heterocycle lower alkyl;

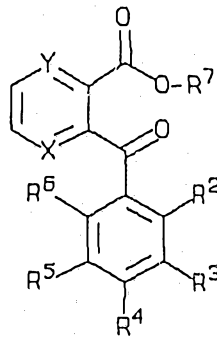
R², R³, R⁴, R⁵ and R⁶ are independently selected from hydrogen, lower alkyl, halo, carboxy, alkoxy carbonyl, carbamoyl, acyl, methylthio, trifluoromethyl, cyano or nitro;

with the proviso that when R¹ is lower alkyl, cycloalkyl, cycloalkylmethyl, benzyl or imidazolyl lower alkyl,

R², R³, R⁴, R⁵ and R⁶ are independently carbamoyl, acyl, cyano or nitro;

or a pharmaceutically acceptable salt thereof, which comprises

a) reacting a compound of the formula (II)



wherein:

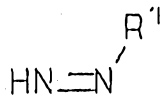
X is nitrogen and Y is carbon, or X is carbon and Y is nitrogen;

R², R³, R⁵ and R⁶ are independently selected from hydrogen, lower alkyl, halo, carboxy, alkoxy carbonyl, carbamoyl, acyl, methylthio, trifluoromethyl, cyano or nitro;

R⁴ is hydrogen, lower alkyl, iodo, bromo, chloro, carboxy, esters, carbamoyl, acyl, methylthio, trifluoromethyl, cyano or nitro; and

R⁷ is lower alkyl,

with a compound of the formula



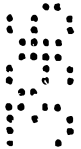
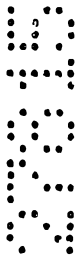
wherein:

R¹ is hydrogen, lower alkyl, aryl, heteroaryl, or heterocycle lower alkyl; or

b) converting a compound of the formula (I) to a pharmaceutically acceptable salt of the formula (I); or

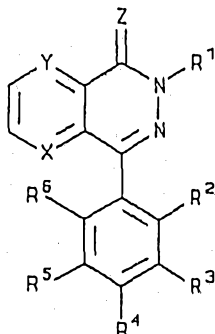
5 c) converting a salt of a compound of the formula (I) to the corresponding free base or to another pharmaceutically acceptable salt of the formula (I).

10 13. The process of claim ~~12~~¹² further comprising the step of treating a compound of formula I wherein Z is oxygen with a thiation reagent to produce a compound of formula I wherein Z is sulfur.



ABSTRACT OF THE DISCLOSURE

Pyridopyridazinones and pyridazinthiones of the formula



wherein:

X and Y are nitrogen or carbon, provided both are not the same,
and Z is oxygen or sulfur;

R¹ is hydrogen, lower alkyl, aryl, heteroaryl, or heterocycle lower
alkyl;

R², R³, R⁴, R⁵ and R⁶ are independently selected from hydrogen, lower
alkyl, halo, carboxy, alkoxy carbonyl, carbamoyl, acyl,
methylthio, trifluoromethyl, cyano or nitro;

with the proviso that when R¹ is lower alkyl, cycloalkyl,
cycloalkylmethyl, benzyl or imidazolyl lower alkyl,

R², R³, R⁴, R⁵ and R⁶ are independently carbamoyl, acyl, cyano
or nitro; or a pharmaceutically acceptable ester, ether or salt
thereof, have been found to be useful as an anti-inflammatory,
antasthmatic, immunosuppressive, anti-allograft rejection,
anti-graft-vs-host rejection, autoimmune disease or analgetic
agent(s).

INTERNATIONAL SEARCH REPORT

PCT/US 92/08398

International Application No

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 Int.Cl. 5 C07D471/04; C07D237/32; A61K31/50; C07D213/79 C07C69/76; //(C07D471/04, 237:00, 221:00)		
II. FIELDS SEARCHED Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07D ; A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	NAUNYN-SCHMIEDEBERG'S ARCHIVES OF PHARMACOLOGY vol. 342, no. 2, 1990, BERLIN, DE pages 221 - 227 GALVAN, M., ET AL. 'Actions of the phosphodiesterase inhibitor zardaverine on guinea-pig ventricular muscle' see page 221, summary and page 223, figure 1	1, 29
X	--- WO,A,9 112 251 (CHUGAI SEIYAKU) 22 August 1991 see abstract --- ---/---	1, 29
¹⁰ Special categories of cited documents : "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. "A" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 25 JANUARY 1993		Date of Mailing of this International Search Report - 8. 02. 93
International Searching Authority EUROPEAN PATENT OFFICE		Signature of Authorized Officer ALFARO FAUS I.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category ^o	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	TETRAHEDRON, vol. 45, no. 17, 1989, OXFORD GB pages 5539 - 5548 CSAMPAI, A., ET AL. 'Bromoalkylphthalazinones and isomeric oxazolinium salts as intermediates and synthons' see pages 5540 and 5544, 4c ---	1
X	TETRAHEDRON, vol. 40, no. 15, 1984, OXFORD GB pages 2983 - 2984 FEKRY ISMAIL, M., ET AL. 'New convenient one-step synthesis of 4-arylphthalaz-1-ones' see compounds 2a, 2b, 2c, 2d, 2e, 2g ---	1
X	JOURNAL OF ORGANIC CHEMISTRY vol. 56, no. 17, 16 August 1991, EASTON US pages 5218 - 5221 JOHNSON, R.E. ET AL. 'Synthesis of alpha-substituted 1,2-benzenedimethanamines' see table I, compounds 4a, 4b, 4e, 4f, 4h, 4i ---	1
X	CHIMICA TERAPEUTICA vol. VI, no. 2, 1971, FR pages 109 - 115 WERMUTH, C.G., ET AL. 'Dérives pyridaziques présentant un intérêt thérapeutique.' see compound 25 ---	1
X	CHEMICAL ABSTRACTS, vol. 108, 1988, Columbus, Ohio, US; abstract no. 131719n, BANSAL, R.K. 'Synthesis of substituted phthalazinones' page 747 ; see abstract & Proc. Natl. Acad. Sci., India, Sect A 1986, 56(4), 384-7 ---	1
X	CHEMICAL ABSTRACTS, vol. 106, 1987, Columbus, Ohio, US; abstract no. 156382u, AFIFY, A.A. 'Synthesis and reactions of phthalazine derivatives' page 682 ; see abstract & J. Chem. Soc. Pak. 1986, 8(1), 53-7 ---	1

-/--

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	CHEMICAL ABSTRACTS, vol. 105, 1986, Columbus, Ohio, US; abstract no. 42152t, BANSAL, R.J. 'Mass spectral analysis of phthalazinones' page 678 ; see abstract & Chim. Acta Turc. 1984, 12(2), 365-8 ---	1
X	CHEMICAL ABSTRACTS, vol. 100, 1984, Columbus, Ohio, US; abstract no. 51532r, OISHI, E. 'Condensed pyridazines. II. Chemical properties of 5-phenylpyrido(2,3-d)pyridazine 7-oxide' page 576 ; see abstract and 11th Chemical Substance Index, page 59254, column 2 , lines 18-20 & Yakugaku Zasshi 1983, 103(6), 631-43 ---	1
X	CHEMICAL ABSTRACTS, vol. 111, 1989, Columbus, Ohio, US; abstract no. 39286h, YAKOLEV, S.V. ET AL. 'Reaction of 2-arylbenzoic acids with 4-nitro and 2,4-dinitrohydrazine' page 593 ; see abstract & Zh. Org. Khim. 1988, 24(11), 2433-6 ---	1
X	CHEMICAL ABSTRACTS, vol. 83, 1975, Columbus, Ohio, US; abstract no. 178862j, FAHMY, A.F.M., ET AL 'Acid azides. III. New syntheses of benzimidazolones, phthalaz-4-ones, and benzoxazolones involving base-catalyzed Curtius rearrangement and displacement of acid azides' page 558 ; see abstract & Indian J. Chem. 1975, 13(7), 652-4 ---	1
X	MONATSHFTE FUR CHEMIE vol. 121, 1990, WIEN AT pages 909 - 921 EPSZTAJN, J. ET AL. 'Application of organolithium and related reagents in synthesis.' see page 911, formulas 12 and 13 ---	26

-/--

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	CHEMICAL ABSTRACTS, vol. 80, 1974, Columbus, Ohio, US; abstract no. 59626p, MAREK, V., ET AL. 'Polarographic reduction' page 332 ; see abstract & Chem. Zvesti 1973, 27(6), 787-91 ----	26
X	JOURNAL OF ORGANIC CHEMISTRY vol. 44, no. 6, 1979, EASTON US pages 984 - 989 VIVEKANANDA BHATT M., ET AL. 'Aspects of tautomerism. 7. Study of keto participation in alkaline hydrolysis of normal esters of gamma-keto acids' see page 985, table I, lines 1 - 6 ----	26
X	JOURNAL OF THE CHEMICAL SOCIETY, SECTION B: PHYSICAL ORGANIC CHEMISTRY 1971, LETCHWORTH GB pages 145 - 148 BOWDEN, K. ET AL 'Reactions of carbonyl compounds in basic solutions. Part II. The mechanism of the alkaline hydrolysis of methyl 2-benzoylbenzoates' see page 146, table I, lines 1 - 9 and 11 ----	26
X	EP,A,0 407 808 (SHOWA DENKO KABUSHIKI) 16 January 1991 see examples 1,11-16 -----	26