COMMONWEALTH of AUSTRALIA
Patents Act 1952

APPLICATION FOR A STANDARD PATENT

I/We

Sandoz Ltd.

of

Lichtstrasse 35, CH-4002 Basle, Switzerland

626295

hereby apply for the grant of a Standard Patent for an invention entitled:

"Imidazo [1,2-a] furo- and thieno pyridine derivatives."

which is described in the accompanying complete specification.

Details of basic application(s):-

Number	Convention Country	Date
190566	United States of America	5 May 1988

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

DATED this THIRD day of MAY 1989

To: THE COMMISSIONER OF PATENTS

....
a member of the firm of
DAVIES & COLLISON for
and on behalf of the
applicant(s)

Davies & Collison, Melbourne

[illegible] 03/05/89

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

DECLARATION IN SUPPORT OF CONVENTION OR NON-CONVENTION APPLICATION FOR A PATENT

Insert title of invention.

In support of the Application made for a patent for an invention entitled: 5-ARYL-SUBSTITUTED-2,3-DIHYDRO-IMIDAZO[1,2-a] FURO[3,2-c]- or THIENO[2,3-c]PYRIDINES

Insert full name(s) and address(es) of declarant(s) being the applicant(s) or person(s) authorized to sign on behalf of an applicant company.

~~I~~ We JEAN KRAMER and HANS RUDOLF HAUS, both of
SANDOZ LTD., 35 Lichtstrasse, CH-4002 Basle,
Switzerland,

Cross out whichever of paragraphs 1(a) or 1(b) does not apply
1(a) relates to application made by individual(s)
1(b) relates to application made by company; insert name of applicant company.

do solemnly and sincerely declare as follows :–

1. (a) ~~I am~~ We are ~~the applicant for the patent~~

or (b) ~~I am~~ authorized by SANDOZ LTD.

the applicant............. for the patent to make this declaration on its ~~their~~ behalf.

Cross out whichever of paragraphs 2(a) or 2(b) does not apply
2(a) relates to application made by inventor(s)
2(b) relates to application made by company(s) or person(s) who are not inventor(s); insert full name(s) and address(es) of inventors.

2. (a) ~~I am~~ ~~We are~~ ~~the actual inventor of the invention~~

or (b)

Seung Hoon Cheon, 120 Carteret Street, Glen Ridge, N.J. 07028, U.S.A.; a citizen of South Korea and

William Joseph Houlihan, 15 Raynold Road, Mountain Lakes, N.J., U.S.A.; a U.S. citizen

~~is~~ are the actual inventor.s........ of the invention and the facts upon which the applicant........... is ~~are~~ entitled to make the application are as follows :–

State manner in which applicant(s) derive title from inventor(s)

the inventors have assigned the invention to the applicant

Cross out paragraphs 3 and 4 for non-convention applications. For convention applications, insert basic country(s) followed by date(s) and basic applicant(s).

3. The basic application........... as defined by Section 141 of the Act was ~~were~~ made

in the United States of America on the 5th May 1988
by the said Seung Hoon Cheon and William Joseph Houlihan
in .... on the ....
by ....
in .... on the ....
by ....

4. The basic application......... referred to in paragraph 3 of this Declaration was ~~were~~ the first application......... made in a Convention country in respect of the invention the subject of the application.

Insert place and date of signature.

Declared at Basle, this 7th day of April 1989

Signature of declarant(s) (no attestation required)

SANDOZ Ltd.

duly authorized officers

Note: Initial all alterations.

DAVIES & COLLISON, MELBOURNE and CANBERRA.

(12) **PATENT ABRIDGMENT** (11) Document No. **AU-B-33977/89**
(19) **AUSTRALIAN PATENT OFFICE** (10) Acceptance No. **626295**

(54) Title
IMIDAZO(1,2-A)FURO-AND THIENO PYRIDINE DERIVATIVES

International Patent Classification(s)
(51)^4 **C07D 491/147** **A61K 031/44** **C07D 495/14** **A61K 031/695**

(21) Application No. : **33977/89** (22) Application Date : **03.05.89**

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190566	**05.05.88**	**US UNITED STATES OF AMERICA**

(43) Publication Date : **09.11.89**

(44) Publication Date of Accepted Application : **30.07.92**

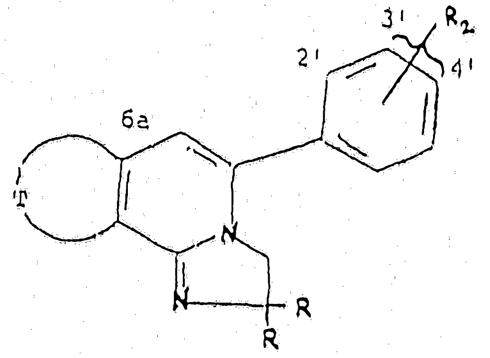
(71) Applicant(s)
SANDOZ LTD.

(72) Inventor(s)
SEUNG HOON CHEON; WILLIAM JOSEPH HOULIHAN

(74) Attorney or Agent
DAVIES COLLISON CAVE , 1 Little Collins Street, MELBOURNE VIC 3000

(57) Claim

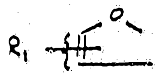
1. A compound of formula I:

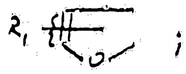


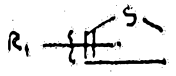
I

wherein
each R is, independently, hydrogen or methyl;

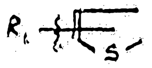
T is


(a)


(b)


(c)

or


(d)

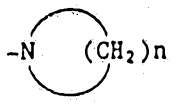
where R_1 is hydrogen or methyl; and

R_2 is straight or branched chain C_{1-6}alkyl; tri-C_{1-3}alkylsilyl; a group of the formula

.../2

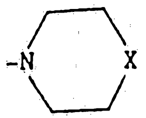
$-CH_2-N(R_3)_2$

where each R_3, independently, is straight or branched chain C_{1-4}alkyl, or the two R_3's together with the nitrogen atom to which they are attached form a group of the formula



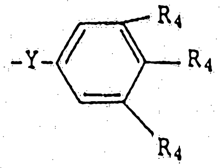
,

where n is an integer 4,5 or 6, of a group of the formula



, where X is -O-, -S- or $-NCH_3$;

or a group of the formula



, where

Y is $-(CH_2)_{1-3}$, $-OCH_2-$ or $-OCH_2CH_2$; and each R_4, independenly, is hydrogen or C_{1-3}alkoxy;

in free base form or in acid addition salt form.

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

626295

NAME & ADDRESS
OF APPLICANT:

Sandoz Ltd.
Lichtstrasse 35
CH-4002 Basle
Switzerland

NAME(S) OF INVENTOR(S):

Seung Hoon CHEON
William Joseph HOULIHAN

ADDRESS FOR SERVICE:

DAVIES & COLLISON
Patent Attorneys
1 Little Collins Street, Melbourne, 3000.

COMPLETE SPECIFICATION FOR THE INVENTION ENTITLED:

"Imidazo [1,2-a] furo- and thieno pyridine derivatives."

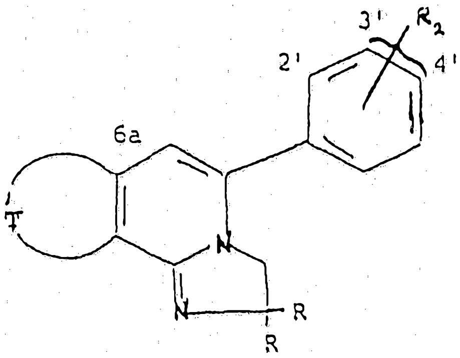
The following statement is a full description of this invention, including the best method of performing it known to me/us:-

The present invention relates to 5-aryl-sustituted-2,3-dihydro-imidazo[1,2-a]furo- and thieno pyridines and to their use as platelet activating factor (PAF) receptor antagonists and anti-tumor agents. The invention also relates to pharmaceutical compositions containing the afore-mentioned compounds as an active ingredient thereof and to the method of using such compositions for inhibiting PAF-mediated bronchoconstriction and extravasation, for controlling hyperreactive airways induced by PAF or allergen, for protection against endotoxin-induced hypotension and death and in treating tumors.

USP 3,887,566 discloses ---- 2,3-dihydroimidazoisoquinolines exhibiting analgesic, anti-inflammatory, anti-bacterial, anti-viral and cardiovascular properties. USP 4,100,165 discloses ---- 5-hydroxy-2,3,5,6-tetrahydrofuran imidazo[2,1-a]isoquinolines containing a pyridyl-, thienyl- or furyl ring in the 5-position, which compounds are useful as anorexics and anti-depressants. USP 4,101,553 discloses ---- 5-hydroxy-2,3,5,6-tetrahydrofuran imidazo[2,1-a]isoquinolines containing an optionally substituted aryl group in the 5-position, which compounds are useful as anorexics and anti-depressants.

WO 88/587 discloses 5-aryl- or 5-heteroaryl-substituted imidazo-[2,1-a]isoquinolines exhibiting PAF-receptor antagonistic and anti-tumor activity.

The present invention concerns compounds of formula I



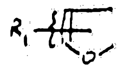
I

wherein
each R is, independently, hydrogen or methyl;

T is

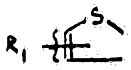
(a)

;



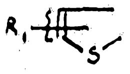
(b)

;



(c)

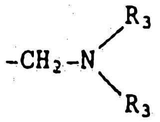
; or



(d)

where R_1 is hydrogen or methyl; and

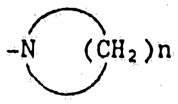
R_2 is straight or branched chain C_{1-6}alkyl; tri-C_{1-3}alkylsilyl; a group of the formula



$$-CH_2-N\begin{matrix}R_3\\R_3\end{matrix}$$

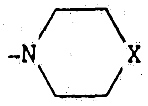
,

where each R_3, independently, is straight or branched chain C_{1-4}alkyl, or the two R_3's together with the nitrogen atom to which they are attached form a group of the formula



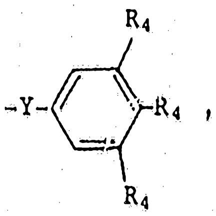
,

where n is an integer 4, 5 or 6, or a group of the formula



, where X is -O-, -S- or $-NCH_3$;

or a group of the formula

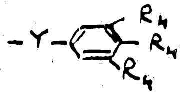


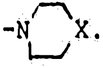
, where

Y is $-(CH_2)_{1-3}$, $-OCH_2-$ or $-OCH_2CH_2-$, and each R_4, independently, is hydrogen or C_{1-3} alkoxy;

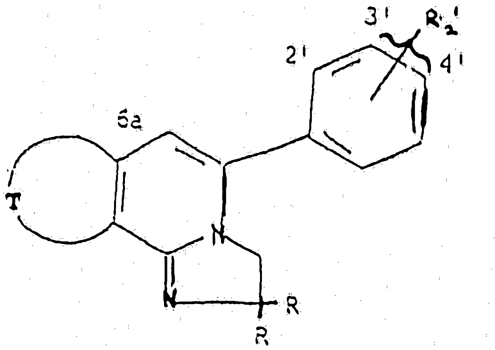
in free base form or in acid addition salt form.

It will be appreciated that R_2 in formula I is attached to the phenyl ring in the 3′ or 4′ position. It preferably is attached in the 4′ position.

Each R preferably is hydrogen. T preferably is a group (a), (c) or (d) as defined above, especially a group (d). R_2 preferably is C_{1-6}alkyl, tri-C_{1-3}alkylsilyl or a group of formula  .

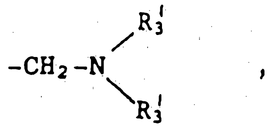
R_1 preferably is hydrogen. When it is methyl, it preferably is attached to the carbon atom at the position adjacent to the sulfur or oxygen atom. C_{1-6}alkyl preferably is of 1 to 4 carbon atoms, it especially is tert-butyl. Tri-C_{1-3}alkylsilyl preferably is trimethylsilyl. C_{1-4}alkyl preferably is of 1 or 2 carbon atoms, it especially is methyl. n preferably is 4 or 5. X preferably is -O-. R_3 preferably is a group of the formula .

A group of compounds of formula I is the compounds of formula I′:



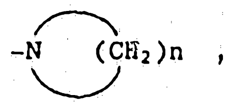
I′

where R_2' is straight or branched chain C_{1-4}alkyl; tri-C_{1-3}alkylsilyl; a group of the formula

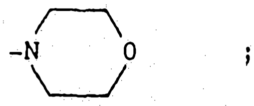


$$-CH_2-N\begin{matrix}R_3'\\R_3'\end{matrix}\ ,$$

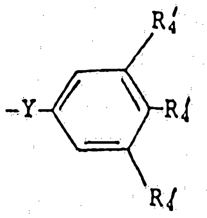
where the R_3' 's are the same and are straight chain C_{1-4}alkyl, or the two R_3' 's together with the nitrogen atom to which they are attached form a group of the formula



where n is as defined above, or a group of the formula



or a group of the formula

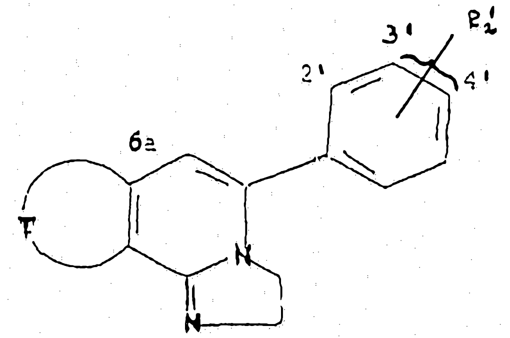


, where

Y is as defined above and the R_4' 's are the same and are C_{1-3}alkoxy; and the R 's and T are as defined above,

in free base form or in acid addition salt form.

A further group of compounds of formula I is the compounds of formula I":

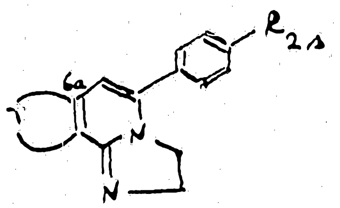


I"

wherein T and R_2' are as defined above,

in free base form or in acid addition salt form.

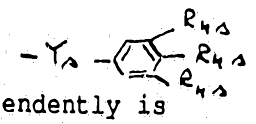
A further group of compound of formula I is the compounds of formula Is:



Is

wherein

T is as defined above and

R_{2s} is straight or branched chain C_{1-4}alkyl;
tri-C_{1-3}alkylsilyl;or a group of formula 

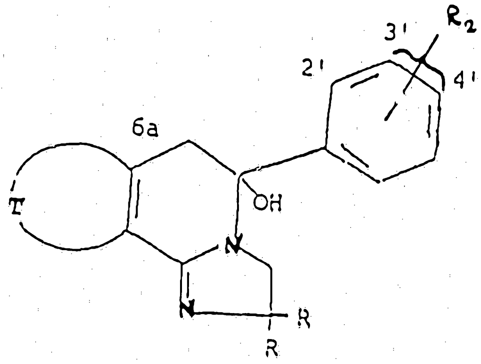
wherein Y_s is $-(CH_2)_{1-3}-$ and each R_{4s} independently is C_{1-3}alkoxy,

in free base form or in acid addition salt form.

In a subgroup of compounds of formula Is T is (a), (c) or (d) as defined above.

A further group of compounds of formula I is the compounds of formula I as defined above with the proviso that T is other than a group (b) or (c) as defined above, in free base form or in acid addition salt form.

A compound of formula I may be prepared by a process comprising dehydrating a corresponding compound of formula V:



V

where the R's, T and R_2 are as defined above,

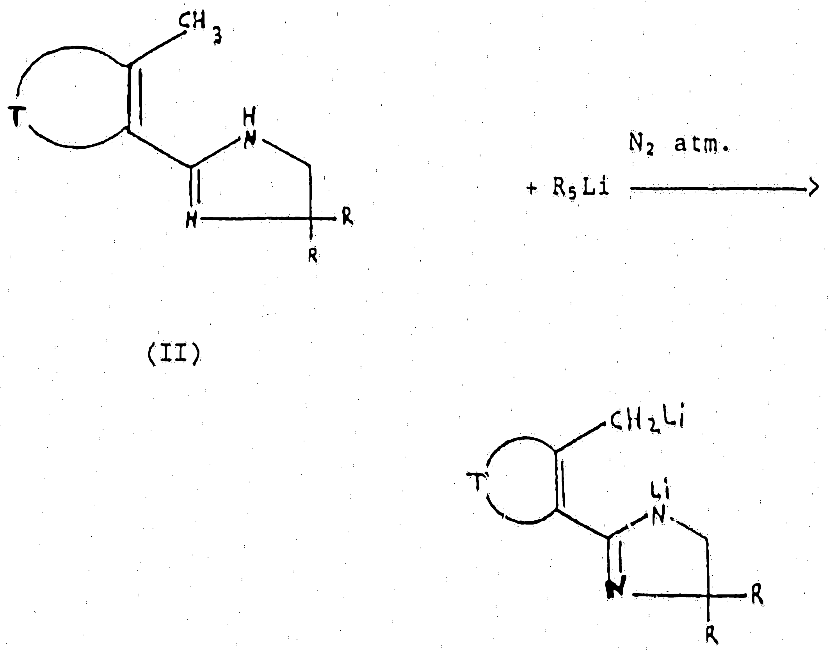
and recovering the resultant compound of formula I in free base form or in acid addition salt form.

The above process may be effected in accordance with known methods. The dehydration preferably is effected in an inert, organic solvent in the presence of an acid catalyst, which ---- can be any mineral acid such as hydrochloric acid, sulfuric acid, phosphoric acid ---- or an organic acid, e.g., an alkylcarboxylic acid such as acetic acid, an arylcarboxylic acid such as benzoic acid, an alkylsulfonic acid such as methanesulfonic acidor an arylsulfonic acid such as p-toluenesulfonic acid. The preferred acid catalysts are alkylcarboxylic acids, more preferably, acetic acid, and arylsulfonic acids, more preferably, p-toluenesulfonic acid. The inert solvent is usually an aliphatic hydrocarbon such as hexane, heptane, an aromatic hydrocarbon such as benzene, toluene, ---- a chlorinated hydrocarbon such as chloroform, methylene chloride, ---- an aliphatic ether such as diethyl ether, a cyclic ether such as tetrahydrofuran, or an excess of a liquid acid catalyst, preferably acetic acid, or p-toluenesulfonic acid may serve as the solvent.

The temperature preferably is in the range of between 35° and 200°C, especially between about 75° and about 120°C.

The starting materials can be prepared in accordance with known procedures, e.g. according to the following reaction scheme:

REACTION A

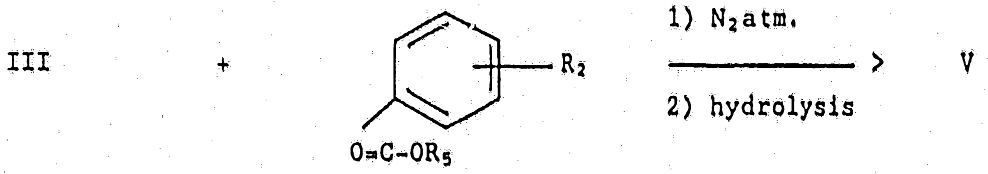


(II)

(III)

where R_5 is straight or branched chain C_{1-4}alkyl, T is (a), (b), (c) or (d) as defined above and the R 's are as defined above.

REACTION B



(IV)

where R_5, T, R_2 and the R 's are as defined above.

Reaction A is generally carried out in an inert, organic solvent. An inert atmosphere of nitrogen is preferred. A complexing or activating agent for the lithium compound, e.g. tetramethylethylenediamine is optionally added. The temperature is in the range of between about 0° and about -78°C, preferably between about -50° and about -78°C.

Reaction B is also usually effected under a nitrogen atmosphere in the first step. Preferably an aliphatic hydrocarbon is used as the solvent, or an aliphatic or cyclic ether. The temperature is in the range of from about -78° to 25°C, preferably about -78° to about 20°C. The adduct formed is then hydrolyzed in a second step, e.g. employing water, dilute mineral acid ammonium chloride solution

The starting materials of formula II and IV are either known and/or may be obtained analogously to known methods in conventional manner.

Final products and intermediates may be isolated and purified in conventional manner. Intermediates, where appropriate, may be employed directly in the following reaction step without purification.

As is evident to those skilled in the art, the compounds of formula I may exist in racemic or enantiomeric form and the invention is intended to cover all forms. Enantiomeric forms may be recovered in conventional manner, e.g. by resolution of end or intermediate products or by employing optically active starting materials.

Examples of pharmaceutically acceptable acid addition salts include those with mineral acids, e.g. hydrochloric, hydrobromic, phosphoric and sulfuric acids, and organic acids, e.g. tartaric, acetic, citric, malic, maleic, methanesulfonic and gluconic acids, which may be prepared in conventional manner.

The compounds of formula I in free base form or in pharmaceutically acceptable acid addition salt form, hereinafter referred to as "the compounds", are indicated for use as platelet activating factor (PAF) receptor antagonists, as indicated by their ability to inhibit specific binding of [^{3}H]-PAF to platelets according to the Human Platelet PAF Receptor Assay test (test A) as described in WO 88/587.

Moreover, in view of their activity as PAF receptor antagonists, the compounds are indicated for use as inhibitors of PAF-mediated bronchoconstriction, which property is evaluated by the PAF-induced Pulmonary Inflation Pressure (PIP) Increase test (test B) as described in WO 88/587, to generate an ED_{50} (dose needed to effect a 50 % response).

Furthermore, the compounds are indicated for use as inhibitors of PAF-mediated extravasation (the extrusion of plasma from the lumen of the blood vessels into the vessel wall and surrounding tissues) measured as a function of hemoconcentration according to the PAF-induced Extravasation test (test C) as described in WO 88/587. From the values obtained an ED_{50} is generated.

Still further, the compounds are indicated for use in controlling hyperreactive airways induced by PAF or allergen, which property can be measured in accordance with the following procedure (test D):

Male Hartley guinea pigs weighing 250gm are sensitized to ovalbumin by aerosol inhalation exposure. The test animals are then subsequently rechallenged with ovalbumin aerosol repeatedly (3 to 6 times) over a period of two to three weeks. Airway reactivity is assessed by an acetylcholine dose response curve at times (1 to 3 days) after the last ovalbumin exposure. The test compound is assessed for its ability to control hyperreactivity airways by administering it orally with a gavage tube in an acceptable vehicle prior to each ovalbumin antigen exposure.

Yet still further, the compounds are indicated for use in protecting against endotoxin-induced hypotension, which property can be measured according to the following procedure (test E):

Male Sprague-Dawley rats weighing between 250 and 270gm are anesthetized with sodium pentobarbital (50mg/kg i.p.) and the left common carotid artery is cannulated (PE-50 tubing) and connected to a P50 pressure transducer. Mean arterial pressures and diastolic and systolic measurements are recorded using a Gould 2400S physiograph. Blood flow of the mesenteric artery is measured on a calibrated electromagnetic flowmeter probe. Blood is collected via the femoral artery into heparinized capillary tubes and centrifuged to determine hematocrit values.

Endotoxin from E.coli serotype 0111:B_4 is prepared fresh daily and administered by i.v. injection to the test animals in tris-Tyrode's buffer over a 1 to 50 mg/kg dosage range to establish a dose-response profile. The administration of endotoxin at 15mg/kg i.v. produced a $54 \pm 8\%$ decrease in mean arterial pressure and a corresponding 80% decrease in mesenteric artery blood flow. The test compound is assessed for its ability to protect against endotoxin-induced hypotension by administering it intravenously after endotoxin administration and measuring the recovery of blood pressure and mesenteric artery blood flow. The ED_{50} value of the test compound is determined using linear regression fitting of inhibition profiles from 5 to 6 doses (3 animals per dose).

Yet even still further, the compounds are indicated for use in protecting against endotoxin-induced death, which property can be measured according to the following procedure (test F):

Healthy male BALB/c mice weighing between 24 and 27g. are allowed to acclimate for 1 week with access to food and water. The test animals are then placed in a ventilated plexiglass restrainer that allows access to the tails. After the tails are allowed to immerse in warm water (38°C) for 30 seconds, endotoxin from E. coli serotype 0111:B_4 is administered in a single injection at 2ml/kg body weight to produce lethality at the desired effect of LD 70-90. The test compound is assessed for its ability to protect against endotoxin-induced death by administering it orally in a single bolus at a volume of 1ml/kg body weight. Each treatment group consists of 7 to 10 test animals, every dosage is considered as a separate group and control groups are dosed with vehicles (water, tris-Tyrodes's buffer, 1% CMC, etc) only. The percent mortality (or survival) is expressed by the number of deaths (or survivors) within the observation period. Values obtained are mean and standard error of mean of a single treatment which represents multiple days results for reproducibility. The ED_{50} value of the test compound is determined using a Students t test (2 tail) for significance.

The compounds are thus indicated for use in treating PAF-mediated bronchoconstriction and extravasation, for controlling hyperreactive airways induced by PAF or allergen and protecting against endotoxin-induced hypotension and death. An indicated daily dosage is from about 100 mg to about 2000 mg, preferably from about 10 mg to about 350 mg. A typical oral dosage is 50 mg or 100 mg, two or three times a day.

Further, the compounds are indicated for use as anti-tumor agents and, particularly, in inhibiting the growth of lymphomas, sarcomas, myelomas and leukemia cell lines. The ability of the compounds in treating tumors can be measured by the Tumor Cell Cytotoxicity test (TCC test) as described in WO 88/587.

The anti-tumor activity may also be demonstrated employing the Influence on Cytotoxicity of ET-18-OCH_3 test (IC-ET test) as described in WO 88/587 or the test described as test F in WO 88/587.

The compounds are thus further indicated for use in inhibiting tumors. An indicated daily dosage is from about 500 mg to about 2000 mg, preferably from about 1000 mg to about 1500 mg. A typical oral dosage is about 400 mg, two to three times a day, or about 20 mg/kg intravenously over a 24 hour period.

The compounds may be combined with one or more pharmaceutically acceptable carriers and, optionally, one or more other conventional pharmaceutical adjuvants and administered orally in the form of tablets, dispersible powders, granules, capsules, elixirs, suspensions, etc., or parenterally in the form of sterile injectable solutions or suspensions. The compositions may be prepared by conventional means.

Pharmaceutical compositions comprising a compound of formula I in free base form or in pharmaceutically acceptable acid additin salt form are also part of the invention.

Examples of pharmaceutical compositions are:

Ingredients	Weight (mg) tablet	capsule
compound of formula I, e.g., the compound of Example I in hydrochloride acid addition salt form	50	50
tragacanth	10	-
lactose (spray-dried)	212.5	100
corn starch	15	-
talcum	10	-
magnesium stearate	2.5	-
Total	300.0	100

Ingredients	Weight (mg) tablet	capsule
compound of formula I, e.g., the compound of Example I in hydrochloride acid addition salt form	400	400
tragacanth	10	-
lactose (spray-dried)	197.5	250
corn starch	25	-
talcum	15	-
magnesium stearate	2.5	-
Total	650.0	650

Ingredients	Weight (mg) sterile injectable suspension	oral liquid suspension
compound of formula I, e.g., the compound of Example I in hydrochloride acid addition salt form	5	3
sodium carboxymethlcellulose U.S.P.	1	8
methyl cellulose	0.3	-
polyvinylpyrrolidone	2.7	-
lecithin	1.5	-
benzyl alcohol	0.01	-
magnesium aluminium silicate	-	25
flavor	-	q.s
color	-	q.s
methyl paraben, U.S.P.	-	3
propyl paraben, U.S.P.	-	0.7
polysorbate 80 (e.g.Tween 80),U.S.P.	-	5
sorbitol solution, 70%, U.S.P.	-	1450
buffer agent to adjust pH for desired stability	q.s. for injection	q.s
water	q.s. to 1 ml	q.s. to 5 ml

The preferred pharmaceutical compositions from the standpoint of preparation and ease of administration are solid compositions, particularly liquid or hard-filled capsules and tablets containing from about 10 mg to about 100 mg of the active ingredient concerning the PAF inhibition use and from about 350 mg to about 450 mg of the active ingredient with respect to tumor inhibition.

The compound of Example 1, especially the compound of Example 1 in hydrochloride acid addition salt form, is preferred.

The following results were obtained in the above tests:

Compound of Example 1 (hydrochloride):
Test A: $IC_{50} = 0.01$ µM
Test B: $ED_{50} = 1.0$ mg/kg p.o.
Test C: $ED_{50} = 1.0$ mg/kg p.o.
Compound of Example 2 (hydrochloride):
Test A: $IC_{50} = 0.07$ µM
Test B: 38 % inhibition at 10 mg/kg p.o.
Test C: 59 % inhibition at 10 mg/kg p.o.

The invention also includes a method for the preparation of a pharmaceutical composition comprising mixing a compound of formula I in free base form or in pharmaceutically acceptable acid addition salt form with a pharmaceutically acceptable carrier or diluent.

It also includes the use of such a compound for the preparation of a pharmaceutical composition comprising a compound of formula I in free base form or in pharmaceutically acceptable acid addition salt form.

It also includes the use of such a compound in the above indications and a method of treatment which comprises administering to a subject in need of such treatment a therapeutically effective amount of a compound of formula I in free base form or in pharmaceutically acceptable acid addition salt form.

It also includes the compounds of formula I in free base form or in pharmaceutically acceptable acid addition salt form for use in the above indications.

The following Examples, in which all temperatures are in °C, illustrate the invention:

EXAMPLE 1

2,3-Dihydro-5-[4-[2-(3,4,5-trimethoxyphenyl)ethyl] phenyl]imidazo[1,2-a]thieno[2,3-c]pyridine.

[R_5' = H; R_2 = 2-(3,4,5-trimethoxyphenyl)ethyl in the 4′ position; T = a group (d) wherein R_1 is H]

To a solution of 2.8 g (6.1 mmol) of the compound prepared as described below in 100 ml of dry benzene was added 0.3 g of p-toluenesulfonic acid monohydrate and the resultant mixture was heated at reflux for 16 hours using a Dean-Stark trap to remove water. The reaction mixture was then cooled to room temperature, diluted with methylene chloride, washed successively with water, a saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and filtered. The filtrate was then evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel employing a mixture of methylene chloride and methanol in a 9:1 ratio as the eluent to yield the title compound in free base form as a yellow foam.

Dry hydrochloride gas was bubbled into a solution of 0.4 g (0.9 mmol) of the above free base in a mixture of 20 ml of dry ethanol and 5 ml of methylene chloride for 5 minutes. The excess gas and the solvents were evaporated under reduced pressure and the crude residue was purified by crystallization from a mixture of methylene chloride and ether to yield the title compound in hydrochloride acid addition salt form (hemihydrate) as a - - - tan solid (M.P. 240-242°C).

The starting material is obtained as follows:

To a solution of 1.0 g (6.1 mmol) of 4,5-dihydro-2-(3-methythien-2-yl)-1H-imidazole in a mixture of 40 ml of dry tetrahydrofuran and 1.69g (15mmol) of N,N,N′,N′-tetramethylethylenediamine was added, at -78°C under a nitrogen atmosphere, 8.4ml of a 1.6M solution of N-butyl-lithium in hexane, and the resultant mixture was stirred at -78°C for 15 minutes. To this mixture was added a solution of 2.0 g (6.1 mmol) of methyl-4-[2-(3,4,5-trimethoxyphenyl)ethyl]benzoate in 10ml of dry tetrahydrofuran and the reaction mixture was allowed to warm to ambient temperature and then stirred at ambient temperature for 2 hours. The mixture was then quenched with saturated ammonium chloride solution and extracted with methylene chloride. The combined organic extracts were then washed successively with water and brine, dried over magnesium sulfate and filtered. The filtrate was then evaporated under reduced pressure to yield an orange foam.

The following compounds are obtained in analogous manner:

EXAMPLE 2

2,3-Dihydro-8-methyl-5-[4-[2-(3,4,5-trimethoxyphenyl)ethyl]phenyl]imidazo[1,2-a]furo[3,2-c]pyridine

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[R'3 = H; R_2 = 2-(3,4,5-trimethoxyphenyl)ethyl in 4' position; T = a group (a) wherein R_1 is methyl adjacent to the oxygen atom];

free base form: tan solid foam;
hydrochloride acid addition salt form (hemihydrate): light tan solid (M.P. 220-222°C)

from:
2,3,5,6-tetrahydro-8-methyl-5-[4-[2-(3,4,5-trimethoxyphenyl)ethyl]phenyl]imidazo[1,2-a]furo[3,2-c]pyridin-5-ol

(yellow foam);

EXAMPLE 3

2,3-Dihydro-8-methyl-5-[4-[2-(3,4,5-trimethoxyphenyl)ethyl]phenyl]imidazo[1,2-a]thieno[3,2-c]pyridine

[R_5= H; R_2 = 2-(3,4,5-trimethoxyphenyl)ethyl in the 4' position; T = a group (c) wherein R_1 is methyl adjacent to the sulfur atom]:

free base form: orange foam;
hydrochloride acid addition salt form: tan solid (M.P. 245-247°C)
from : 2,3,5,6-tetrahydro-8-methyl-5-[4-[2-(3,4,5-trimethoxyphenyl)ethyl]phenyl]imidazo[1,2-a]thieno[3,2-c]pyridin-5-ol

(red foam).

EXAMPLE 4

2,3-Dihydro-8-methyl-5-[4'-*t*-butylphenyl]imidazo[1,2-a]thieno[3,2-c]pyridine

[R_5= H; R_2 = *t*-butyl in the 4' position; T = a group (c) wherein R_1 is methyl adjacent to the sulfur atom]:

free base form: light yellow solid;
hydrochloride acid addition salt form: light yellow solid (M.P. > 280°C);
from : 2,3,5,6-tetrahydro-8-methyl-5-[4'-*t*-butylphenyl]imidazo[1,2-a]thieno[3,2-c] pyridin-5-ol

(off-white solid);

EXAMPLE 5

2,3-Dihydro-8-methyl-5-[4'-trimethylsilylphenyl]-imidazo[1,2-a]thieno[3,2-c]pyridine

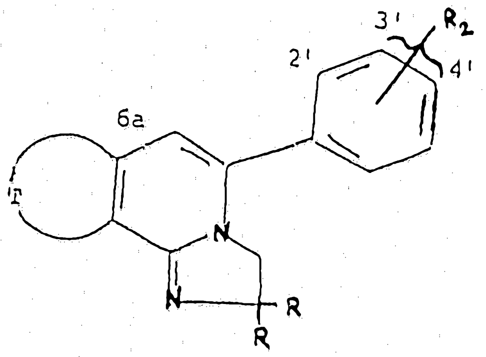
[R_5= H; R_2 = trimethylsilyl in the 4′ position; T = a group (c) wherein R_1 is methyl adjacent to the sulfur atom]:

free base form: light yellow foam;
hydrochloride acid addition salt form: light yellow solid (M.P. > 280°C);
from : 2,3,5,6-tetrahydro-8-methyl-5-[4'-trimethylsilylphenyl]imidazo[1,2-a]thieno[3,2-c]pyridin-5-ol

(off-white solid).

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of formula I:

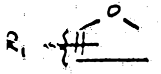


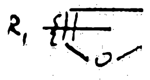
I

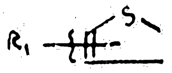
wherein

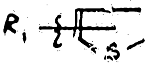
each R is, independently, hydrogen or methyl;

T is


(a) ;


(b) ;


(c) ; or

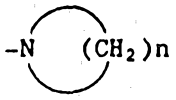

(d)

where R_1 is hydrogen or methyl; and

R_2 is straight or branched chain C_{1-6}alkyl; tri-C_{1-3}alkylsilyl; a group of the formula

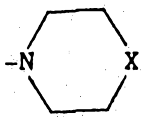
$-CH_2-N(R_3)_2$

where each R_3, independently, is straight or branched chain C_{1-4}alkyl, or the two R_3's together with the nitrogen atom to which they are attached form a group of the formula



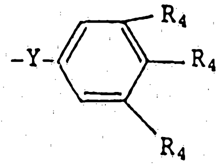
,

where n is an integer 4,5 or 6, of a group of the formula



, where X is -O-, -S- or -NCH$_3$;

or a group of the formula

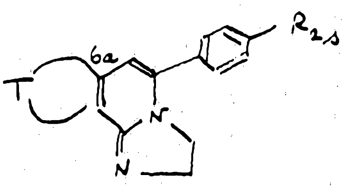


, where

Y is -(CH$_2$)$_{1-3}$, -OCH$_2$- or -OCH$_2$CH$_2$; and each R$_4$, independenly, is hydrogen or C$_{1-3}$alkoxy;

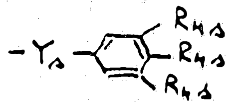
in free base form or in acid addition salt form.

2. A compound according to claim 1 of formula Is:



Is

wherein
T is as defined in claim 1 and
R_{2s} is straight or branched chain C_{1-4}alkyl; tri-C_{1-3}alkylsilyl; or a group of the formula



wherein Y_s is $-(CH_2)_{1-3}-$ and each R_{4S} independently, is C_{1-3}alkoxy;

in free base form or in acid addition salt form.

3. A compound according to claim 2 of formula Is wherein T is a group of formula (a), (c) or (d), ----------------------------- in free base form or in acid addition salt form.

4. A compound according to claim 1 of formula I wherein the substituents are as defined in claim 1 with the proviso that T is other than a group of formula (b) or (c), ---------------------- in free base form or in acid addition salt form.

5. The compound according to claim 1 where the R's are hydrogen, R_2 is 2-(3,4,5-trimethoxyphenyl)ethyl in the 4' position, and

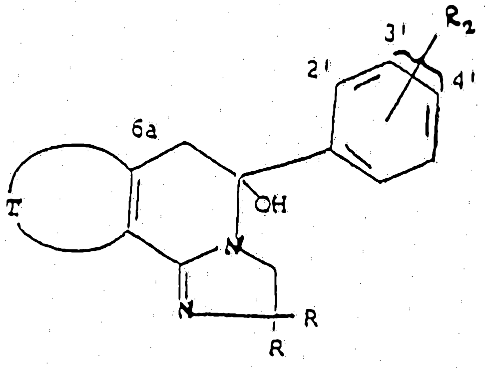
T is a group (d) wherein R_1 is hydrogen, in free base form or in acid addition salt form.

6. The compounds according to claim 1 wherein
either
the R's are hydrogen,
R_2 is 2-(3,4,5-trimethoxyphenyl)ethyl in the 4' position and T is either a group (a) wherein R_1 is methyl in the position adjacent to the oxygen atom, or is a group (c) wherein R_1 is methyl in the position adjacent to the sulfur atom,
or
the R's are hydrogen, T is a group (c) wherein R_1 is methyl in the position adjacent to the sulfur atom and R_2 is either <u>t</u>-butyl in 4' position or trimethylsilyl in 4' position,
in free base form or in acid addition salt form.

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 in free base form or in pharmaceutically acceptable acid addition salt form.

8. A process for the preparation of a compound according to claim 1 in free base form or in acid addition salt form which comprises

dehydrating a corresponding compound of formula V



V

where the R's, T and R_2 are as defined in claim 1,

and recovering the resultant compound of formula I in free base form or in acid addition salt form.

9. A process for the preparation of a pharmaceutical composition which comprises mixing a compound of formula I as defined in claim 1 in free base form or in pharmaceutically acceptable acid addition salt form, with a pharmaceutically acceptable carrier or diluent.

10. Use of a compound of formula I as defined in claim 1 in free base form or in pharmaceutically acceptable acid addition salt form for the preparation of a pharmaceutical composition according to the process of claim 9.

11. Compounds of formula I or processes for their preparation, substantially as hereinbefore described with reference to the Examples.

DATED this 6th day of May, 1992
Sandoz Ltd.
By Its Patent Attorneys
DAVIES COLLISON CAVE