P/00/008
Section 29(1)
Regulation 3.1(2)

AUSTRALIA
Patents Act 1990

NOTICE OF ENTITLEMENT

We SCHERING CORPORATION

of 2000 Galloping Hill Road, Kenilworth, NJ 07033, U.S.A.

being the Applicant and Nominated Person, in respect of Application No. 32773/93

state the following:

Neng-Yang Shih; Robert Aslanian; Andrew Lupo, Jr.; John J Piwinski; Michael J Green and Ashit K Ganguly are the actual inventors of the invention the subject of the Application.

The applicant and nominated person is the assignee of the invention from the actual inventors.

The applicant and nominated person is entitled to rely on the application listed in the declaration under Article 8 of the PCT.

Convention priority is claimed from the following basic application referred to in the declaration under Article 8 of the PCT:

Basic Applicant	Application Number	Application Date	Country	Country Code
Neng-Yang Shih; Robert Aslanian; Andrew Lupo, Jr.; John J Piwinski; Michael J Green and Ashit K Ganguly	07/809,781	18 December 1991	U.S.A.	US

The basic application referred to in the declaration under Article 8 of the PCT was the first application made in a Convention country in respect of the invention the subject of the Application.

DATED this 14th day of May 19 96

SCHERING CORPORATION
By their Patent Attorney

GRIFFITH HACK & CO

P/00/008
Section 29(1)
Regulation 3.1(2)

AUSTRALIA
Patents Act 1990

NOTICE OF ENTITLEMENT 671092

We SCHERING CORPORATION

of 2000 Galloping Hill Road, Kenilworth, NJ 07033, U.S.A.

being the Applicant and Nominated Person, in respect of Application No. 32773/93

state the following:

Neng-Yang Shih; Robert Aslanian; Andrew Lupo, Jr.; John J Piwinski; Michael J Green and Ashit K Ganguly are the actual inventors of the invention the subject of the Application.

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DATED this 14th day of May 19 96

SCHERING CORPORATION
By their Patent Attorney

A. Perera

GRIFFITH HACK & CO

AU9332773

(12) PATENT ABRIDGMENT (11) Document No. AU-B-32773/93
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 671092

(54) Title
IMIDAZOLYL OR IMIDAZOYLALKYL SUBSTITUTED WITH A FOUR OR FIVE MEMBERED NITROGEN CONTAINING HETEROCYCLIC RING

(51)[5] International Patent Classification(s)
C07D 403/04 C07D 403/06 A61K 031/415

(21) Application No. : 32773/93 (22) Application Date 17.12.92

(87) PCT Publication Number : WO93/12108

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(71) Applicant(s)
SCHERING CORPORATION

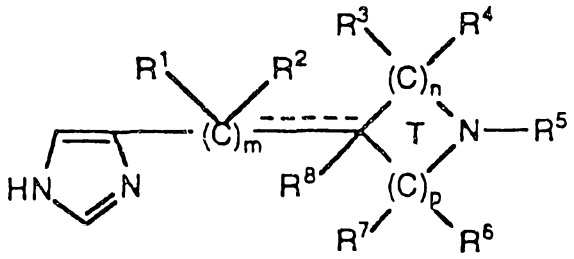
(72) Inventor(s)
NENG-YANG SHIH; ROBERT ASLANIAN; ANDREW LUPO JR.; JOHN J. PIWINSKI; MICHAEL J. GREEN; ASHIT K. GANGULY

(74) Attorney or Agent
GRIFFITH HACK & CO. , GPO Box 4164, SYDNEY NSW 2001

(56) Prior Art Documents
AU 39445/93 C07D 401/04 403/04 A61K 31/415 31/445

(57) Claim

1. A compound of the formula:



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

(A) m is an integer selected from the group consisting of: 0, 1, and 2;

(B) n and p are integers and are each independently selected from the group consisting of : 0, 1, 2, and 3 such that the sum of n and p is 2 or 3 such that when the sum of n and p is 2, T is a 4-membered ring and when the sum of n and p is 3, T is a 5-membered ring;

.../2

(C) each R^1, R^2, R^3, R^4, R^6, R^7, and R^8 is independently selected from the group consisting of:

(1) H;

(2) C_1 to C_6 alkyl;

(3) C_3 to C_6 cycloalkyl; and

(4) $-(CH_2)_q-R^9$ wherein q is an integer of: 1 to 7, and R^9 is selected from the group consisting of: phenyl, substituted phenyl, $-OR^{10}$, $-C(O)OR^{10}$, $-C(O)R^{10}$, $-OC(O)R^{10}$, $-C(O)NR^{10}R^{11}$, CN and $-SR^{10}$ wherein R^{10} and R^{11} are as defined below, and wherein the substituents on said substituted phenyl are each independently selected from the group consisting of: -OH, -O-(C_1 to C_6)alkyl, halogen, C_1 to C_6 alkyl, $-CF_3$, -CN, and $-NO_2$, and wherein said substituted phenyl contains from 1 to 3 substituents;

(D) R^5 is selected from the group consisting of:

(1) H;

(2) C_1 to C_{20} alkyl;

(3) C_3 to C_6 cycloalkyl;

(4) $-C(O)OR^{10'}$; wherein $R^{10'}$ is the same as R^{10} defined below except that $R^{10'}$ is not H;

(5) $-C(O)R^{10}$;

(6) $-C(O)NR^{10}R^{11}$;

(7) allyl;

(8) propargyl; and

(9) $-(CH_2)_q-R^9$, wherein q and R^9 are as defined above with the proviso that when q is 1 then R^9 is not -OH or -SH;

(E) R^{10} and R^{11} are each independently selected from the group consisting of: H, C_1 to C_6 alkyl, and C_3 to C_6 cycloalkyl; and, for the substituent $-C(O)NR^{10}R^{11}$, R^{10} and R^{11}, together with the nitrogen to which they are bound, can form a ring having 5, 6, or 7 atoms;

(F) the dotted line (-----) represents a double bond that is optionally present when m is 1, and T is a 5-membered ring, and n is not 0, and p is not 0, and when said double bond is present then R^2 and R^8 are absent;

(G) when m is 2, each R^1 is the same or different substituent for each m, and each R^2 is the same or different substituent for each m;

(H) when n is 2 or 3, each R^3 is the same or different substituent for each n, and each R^4 is the same or different substituent for each n; and

(I) when p is 2 or 3, each R^6 is the same or different substituent for each p, and each R^7 is the same or different substituent for each p.

OPI DATE 19/07/93 APPLN. ID 32773/93
AOJP DATE 16/09/93 PCT NUMBER PCT/US92/10743
AU9332773

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(51) International Patent Classification 5 :
C07D 401/06, A61K 31/415
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A1

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(63) Related by Continuation
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(71) Applicant *(for all designated States except US)*: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : SHIH, Neng-Yang [US/US]; 1 Maple Drive, North Caldwell, NJ 07006 (US). ASLANIAN, Robert [US/US]; 44 Hibernia Road, Rockaway, NJ 07866 (US). LUPO, Andrew, Jr. [US/US]; 8 Powell Road, Emerson, NJ 07630 (US). PIWINSKI, John, J. [US/US]; 19 Pitman Road, Parsippany, NJ 07054 (US). GREEN, Michael, J. [US/US]; 43 Meadow Run Drive, Skillman, NJ 08558 (US). GANGULY, Ashit, K. [IN/US]; 96 Cooper Avenue, Upper Montclair, NJ 07043 (US).

(74) Agents: JEANETTE, Henry, C. et al.; Schering-Plough Corporation, Patent Department, M3W, One Giralda Farms, Madison, NJ 07940-1000 (US).

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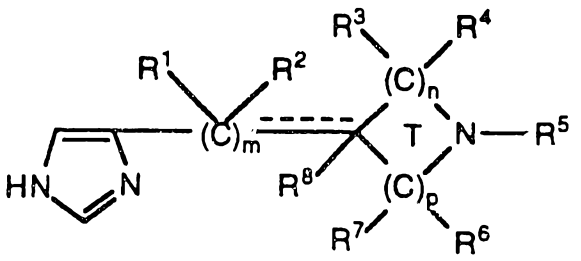
67 1092

(54) Title: IMIDAZOLYL OR IMIDAZOYLALKYL SUBSTITUTED WITH A FOUR OR FIVE MEMBERED NITROGEN CONTAINING HETEROCYCLIC RING



(I)

(57) Abstract

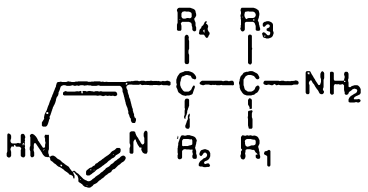
Disclosed is a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof. Also disclosed are pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an effective amount of a compound of formula (I). Further disclosed is a method of treating allergy (for example asthma), inflammation, hypertension, raised intraocular pressure (such as glaucoma)--i.e., a method of lowering intraocular pressure, sleeping disorders, states of hyper and hypo motility and acidic secretion of the gastrointestinal tract, hypo and hyperpactivity of the central nervous system (for example, agitation and depression) and other CNS disorders (such as Alzheimers, schizophrenia, and migraine) comprising administering an effective amount of a compound of formula (I) to a patient in need of such treatment.

IMIDAZOLYL OR IMIDAZOYLALKYL SUBSTITUTED WITH A FOUR OR FIVE MEMBERED NITROGEN CONTAINING HETEROCYCLIC RING

BACKGROUND

H_3 receptor sites are known and are of current interest to those skilled in the art--for example, see: West, Jr. et al., "Biexponential Kinetics of (R)-α-[^{3}H]Methylhistamine Binding to the Rat Brain H_3 Histamine Receptor", Journal of Neurochemistry, Vol. 55, No. 5, pp. 1612-1616, 1990; West, Jr. et al., "Identification of Two H_3-Histamine Receptor Subtypes", Molecular Pharmacology, 38:610-613; and Korte et al., "Characterization and Tissue Distribution of H_3 Histamine Receptors in Guinea Pigs by N^{α}-Methylhistamine", Biochemical and Biophysical Research Communications, Vol. 168, No. 3, pp. 979-986..

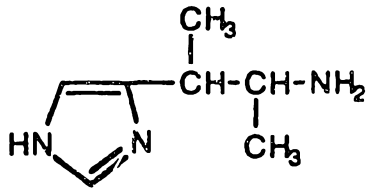
Arrang et al. in U.S. 4,767, 778 (Issued August 30, 1988) disclose a pharmaceutical composition containing a histamine derivative of the formula:



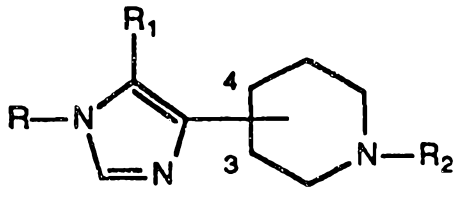
wherein each of R_1, R_2, and R_4, represents a hydrogen or a methyl, or R_1 and R_2 taken together represent a methylene, and R_3 is a hydrogen, a methyl or a carboxy, with the proviso that R_1, R_2, R_3, and R_4 are not

simultaneously methyl groups. It is disclosed that the derivatives behave as complete agonists of the H_3 receptors in rat brain and produce a maximal inhibition of release identical to that induced by histamine (approximately 60%). It is also disclosed that the histamine derivatives powerfully inhibit the release and synthesis of histamine by very selectively stimulating the H_3 receptors. Consequently, according to Arrang et al., the derivatives are likely to decrease histaminergic transmission in the digestive tract and in the nervous, cardiovascular and immune systems. Arrang et al. disclose that the derivatives can be used in therapy as a drug having sedative effects, as a sleep regulator, anticonvulsant, regulator of hypothalamo-hypophyseal secretion, antidepressant, and modulator of cerebral circulation. According to Arrang et al., inhibition of the release of inflammation messengers in various allergic conditions (e.g., asthma) is expected to result from stimulation of the H_3 receptors of the lung. It is further disclosed that the inhibition of release of gastric histamine is likely to exert antisecretory and antiulcerative effects. According to Arrang et al., modification of release of the messengers of immune responses is likely to modulate the latter responses.

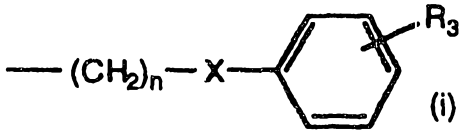
EP 0 338 939 discloses compounds of the formula:



Derwent abstract 86-273706/42 for EP 0 197 840 discloses imidazole derivatives of the formula:

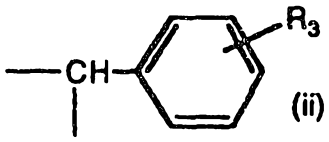


wherein R_1 is H, methyl or ethyl; R is H or R_2; and R_2 is 1-6C alkyl, piperonyl, 3-(benzimidazolon-1-yl)propyl, -CZ-NHR$_5$ or a group (i):



(i)

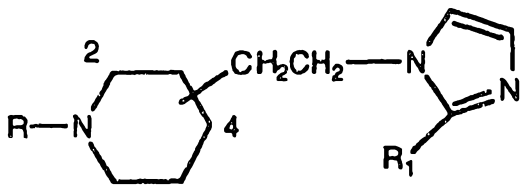
wherein n is 0-3; X is a bond, O, S, NH, CO, CH=CH or a group (ii):



(ii)

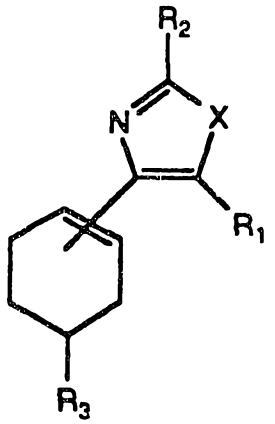
R_3 is H, methyl, halo, CN, CF_3 or COR_4; R_4 is 1-6C alkyl, 3-6C cycloalkyl or phenyl (optionally substituted by methyl or F); Z is O, S, NH, N-methyl or N-CN; and R_5 is 1-8C alkyl, 3-6C cycloalkyl (optionally substituted by phenyl), 3-6C cycloalkyl(1-3C)alkyl, phenyl (optionally substituted by methyl, halo or CF_3), phenyl(1-3C)alkyl, naphthyl, adamantyl or p-toluenesulphonyl. It is disclosed that these compounds are psychotropic agents. It is also disclosed that these compounds antagonise the histamine H3 receptors and increase the speed of cerebral histamine renewal.

Derwent abstract 90-184730/24 for U.S. 4,925,851 discloses 2- or 4-(2-(1H-imidazol-1-yl)ethyl) piperidine compounds useful as antitumour agents for inhibiting lymphoma, sarcoma, myeloma and leukaemia. The compounds have the formula:



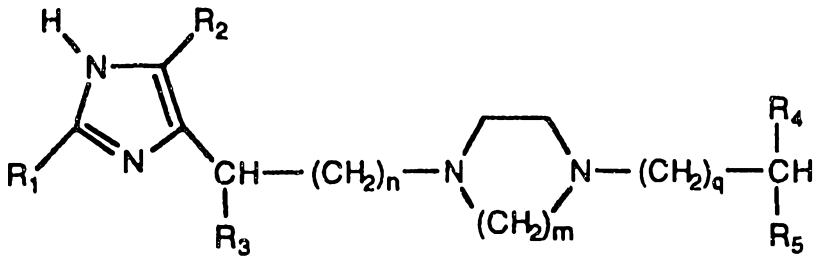
wherein R is $-CH_2(CH_2)_m-Me$, $-CO-(CH_2)_m-Me$ or $-CO-CMe_2-R_2$; m is 2-18; R_2 is H or Me; R_1 is $-(CH_2)_n-R_3$; n is 0-13; R_3 is H, i-Pr or t-Bu; and the floating group is at the 2- or 4- position; with the proviso that (1) the sum of C atoms in R_1 does not exceed 13; and (2) the sum of C atoms in R and R_1 does not exceed 25.

Derwent abstract 90-180087/24 for EP 372125A discloses compounds of the formula:



wherein X is O or S; R_1 is halo, CF_3, CN, NO_2, OH, or 1-6C alkoxy; R_2 is H, 1-6C alkyl, aryl, 7-13C aralkyl, optionally substituted amino or 5- or 6-membered N-containing ring; and R_3 is 1-6C hydrocarbyl, 7-13C aralkyl or 1-13C acyl. It is disclosed that these compounds have alpha2-antagonist activity with no dopamine activity and that they are useful for treating depression and other related illnesses (e.g., anxiety or cognitive disorders).

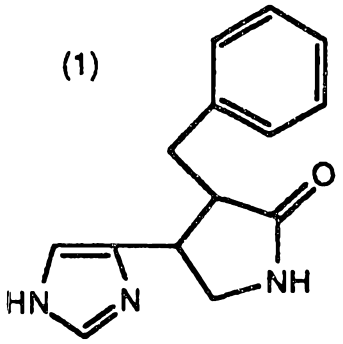
Derwent abstract 88-309195/44 for U.S. 4935417 discloses compounds of the formula:



wherein (according to U.S. 4935417) R^1 is aryl, lower alkyl, cycloalkyl or hydrogen; R^2 is aryl, lower alkyl.or hydrogen; R^3 is lower alkyl, hydroxy or hydrogen; R^4 is aryl or hydrogen; R^5 is aryl or hydrogen; m is two or three; n is zero, one or two, provided that when R^3 is hydroxy, n is one or two; and q is zero, one, two or three. U.S. 4935417 discloses that these compounds are calcium channel antagonists useful for treating mammals having a variety of disease states, such as stroke, epilipsy, hypertension, angina, migraine, arrhythmia, thrombosis, embolism and also for treatment of spinal injuries.

Compounds known in the art include:

(1)



RN 85651-90-7
CA98(23):194919y

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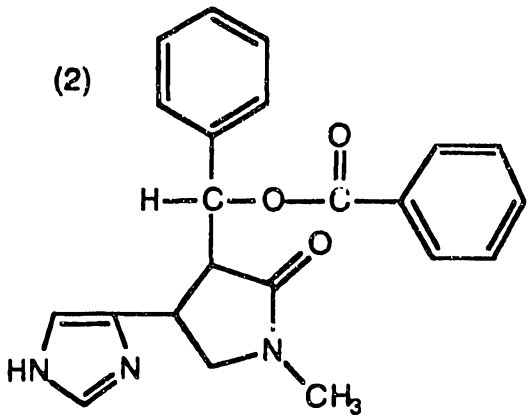
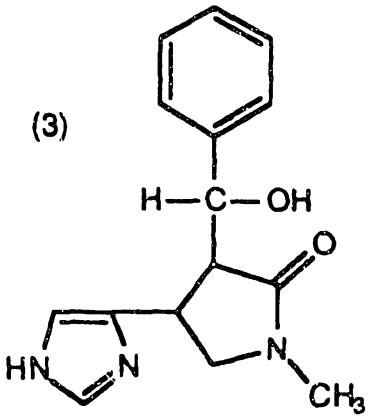


RN 81345-39-3
CA96(17):139642m

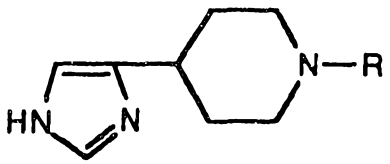
(3)



RN 81345-38-2
CA96(17):139642m

and .

Known compounds in the art also include compounds of the formula:



wherein R (Table 1) is:

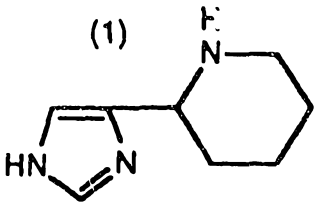
TABLE 1

NO.	B	RN	CA
1	$-CH_3$	106243-44-1	106(11):84602r
2	$-CH(CH_3)_2$	106243-45-2	106(11):84602r
3	H	106243-23-6	106(11):84602r
4	$-C(S)NHC(CH_3)_2CH_2C(CH_3)$	106243-93-0	106(11):84602r
5	-C(O)NHCH(CH_3)(phenyl)	106243-90-7	---
6	-C(S)NH(p-chlorophenyl)	106243-85-0	---
7	-C(O)NH(phenyl)	106243-77-0	---

8	-C(NH)N(CH_3)(cyclopropyl)	106243-73-6	—
9	-C(S)NHCH_3	106243-61-2	—
10	-CH_2CH_2-phenyl	106243-49-6	—
11	-CH_2CH_2-p-flurophenyl	106243-67-8	—
12	benzyl	106243-25-8	—

Additionally known compounds include:

(1)



RN 51746-84-0
CA80(15):82801a

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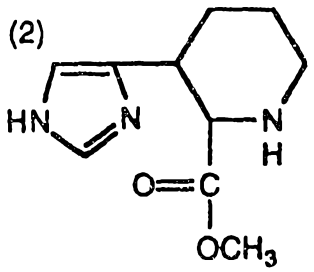
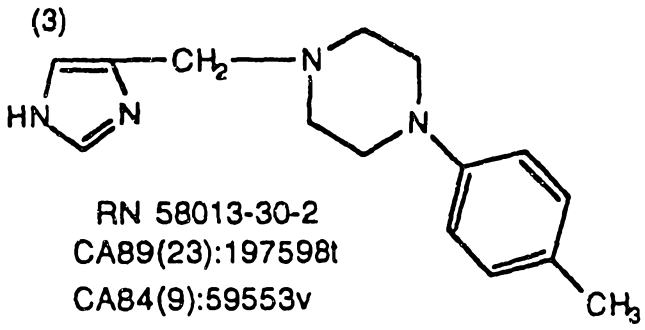


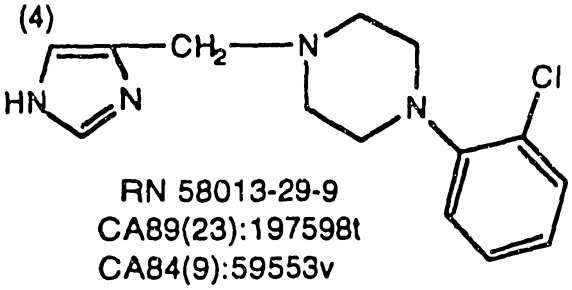
RN 67319-35-1
CA89(13):109229v

(3)



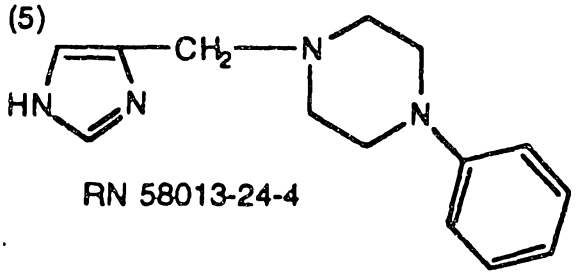
RN 58013-30-2
CA89(23):197598t
CA84(9):59553v

(4)



RN 58013-29-9
CA89(23):197598t
CA84(9):59553v

(5)



RN 58013-24-4

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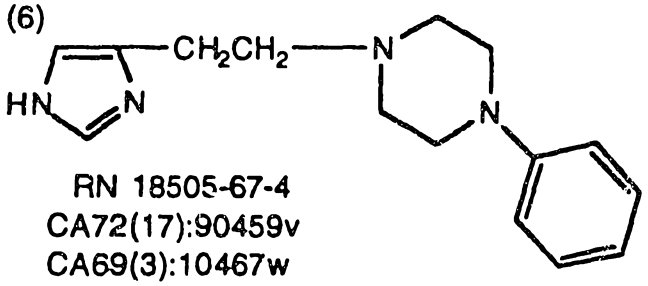
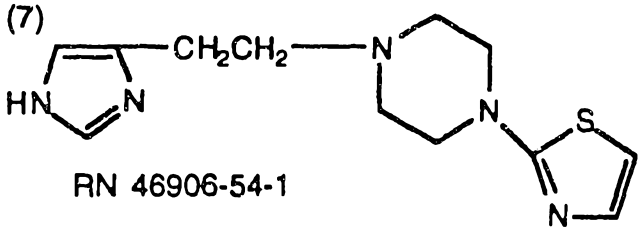


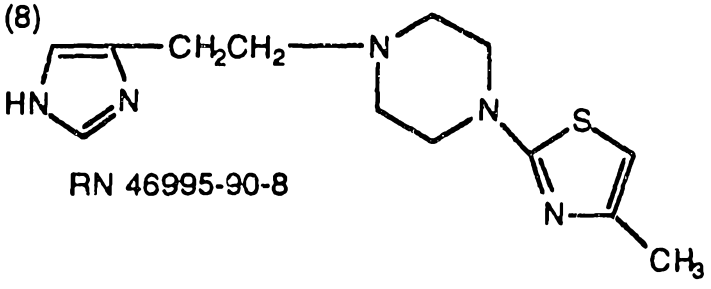
RN 18505-67-4
CA72(17):90459v
CA69(3):10467w

(7)



RN 46906-54-1

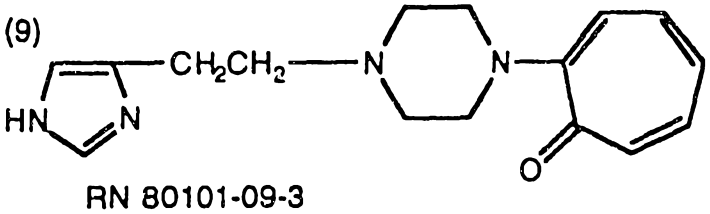
(8)



RN 46995-90-8

and

(9)

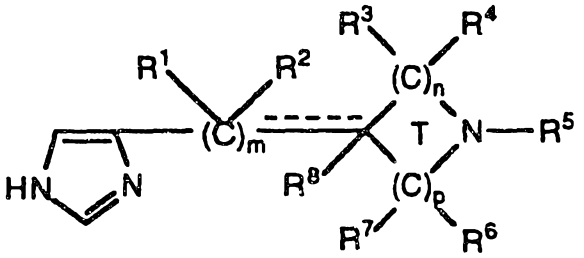


RN 80101-09-3
CA96(1):6760b

In view of the art's interest in compounds which effect the H_3 receptors, novel compounds having agonist or antagonist activity on H_3 receptors would be a welcome contribution to the art. This invention provides just such a contribution by providing novel compounds having H_3 agonist or antagonist activity.

SUMMARY OF THE INVENTION

This invention provides compounds of the formula:



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

(A) m is an integer selected from the group consisting of: 0, 1, and 2;

(B) n and p are integers and are each independently selected from the group consisting of : 0, 1, 2, and 3 such that the sum of n and p is 2 or 3 such that when the sum of n and p is 2, T is a 4-membered ring and when the sum of n and p is 3, T is a 5-membered ring;

(C) each R^1, R^2, R^3, R^4, R^6, R^7, and R^8 is independently selected from the group consisting of:

(1) H;

(2) C_1 to C_6 alkyl;

(3) C_3 to C_6 cycloalkyl; and

(4) $-(CH_2)_q-R^9$ wherein q is an integer of: 1 to 7, and R^9 is selected from the group consisting of: phenyl, substituted phenyl, $-OR^{10}$, $-C(O)R^{10}$, $-C(O)R^{10}$,

-OC(O)R^{10}, -C(O)$NR^{10}R^{11}$, CN and -SR^{10} wherein R^{10} and R^{11} are as defined below, and wherein the substituents on said substituted phenyl are each independently selected from the group consisting of: -OH, -O-(C_1 to C_6)alkyl, halogen, C_1 to C_6 alkyl, -CF_3, -CN, and -NO_2, and wherein said substituted phenyl contains from 1 to 3 substituents; examples of -$(CH_2)_q$-R^9 include benzyl substituted benzyl and the like, wherein the substituents on the substituted benzyl are as defined above for said substituted phenyl;

(D) R^5 is selected from the group consisting of:

(1) H;

(2) C_1 to C_{20} alkyl;

(3) C_3 to C_6 cycloalkyl;

(4) -C(O)$OR^{10'}$; wherein $R^{10'}$ is the same as R^{10} defined below except that $R^{10'}$ is not H;

(5) -C(O)R^{10};

(6) -C(O)$NR^{10}R^{11}$;

(7) allyl;

(8) propargyl; and

(9) -$(CH_2)_q$-R^9, wherein q and R^9 are as defined above with the proviso that when q is 1 then R^9 is not -OH or -SH;

(E) R^{10} and R^{11} are each independently selected from the group consisting of: H, C_1 to C_6 alkyl, and C_3 to C_6 cycloalkyl; and, for the substituent -C(O)$NR^{10}R^{11}$, R^{10} and R^{11}, together with the nitrogen to which they are bound, can form a ring having 5, 6, or 7 atoms;

(F) the dotted line (----) represents a double bond that is optionally present when m is 1, and T is a 5-membered ring, and n is not 0, and p is not 0 (i.e., the nitrogen in the ring is not bound directly to the carbon atom bearing the

double bond), and when said double bond is present then R^2 and R^8 are absent;

(G) when m is 2, each R^1 is the same or different substituent for each m, and each R^2 is the same or different substituent for each m;

(H) when n is 2 or 3, each R^3 is the same or different substituent for each n, and each R^4 is the same or different substituent for each n; and

(I) when p is 2 or 3, each R^6 is the same or different substituent for each p, and each R^7 is the same or different substituent for each p.

This invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an effective amount of a Compound of Formula I.

This invention further provides a method of treating allergy, (for example asthma), inflammation, hypertension, raised intraocular pressure (such as glaucoma)--i.e., a method of lowering intraocular pressure, sleeping disorders (e.g., hypersomnia, somnolence, narcolepsy and sleeplessness, such as insomnia), states of hyper and hypo motility and acidic secretion of the gastrointestinal tract, hypo and hyperactivity of the central nervous system (for example, agitation and depression) and other CNS disorders (such as Alzheimers, Schizophrenia, and migraine) comprising administering an effective amount of a compound of Formula I to a patient in need of such treatment.

DETAILED DESCRIPTION OF THE INVENTION

As used herein the following terms have the following meanings unless indicated otherwise:

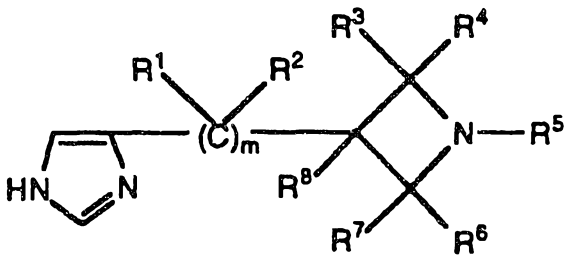
alkyl - represents a straight or branched, saturated hydrocarbon chain having from 1 to 20 carbon atoms;

cycloalkyl - represents a saturated carbocyclic ring having from 3 to 6 carbon atoms; and

halogen (halo) - represents fluoro, chloro, bromo or iodo.

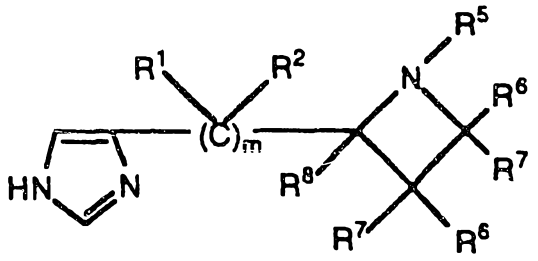
Preferably, for compounds of Formula I, m is 0 or 1; R^5 is selected from the group consisting of H and C_1 to C_{20} alkyl; and R^1 to R^4 and R^6 to R^8 are each independently selected from the group consisting of: H, C_1 to C_6 alkyl, and $-(CH_2)_q-R^9$ wherein R^9 is phenyl. Most preferably, R^5 is selected from the group consisting of H and methyl; and R^1, R^2, R^3, R^4, R^6, R^7, and R^8 are each independently selected from the group consisting of: H, methyl, ethyl, pentyl, benzyl, and 2-phenylethyl.

Representative compounds of this invention include compounds of the formula:



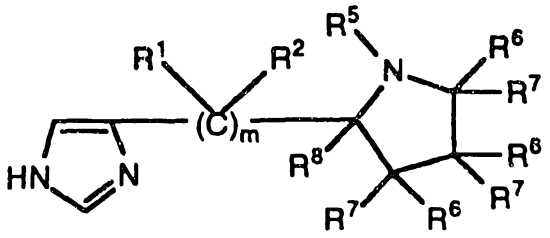
(II)

;



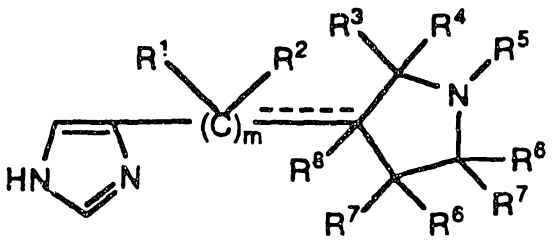
(IIA)

;



(III)

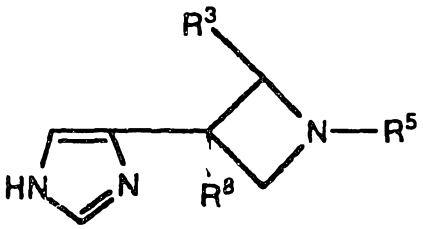
; and



(IV)

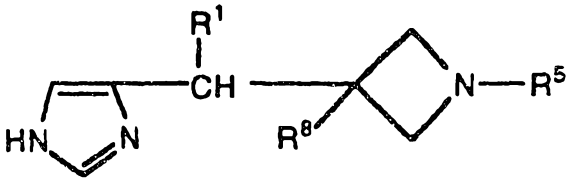
wherein m and R^1 to R^8 are as defined for Formula I.

Representative compounds of Formula II include compounds of Formulas II-1, II-2 and II-3:



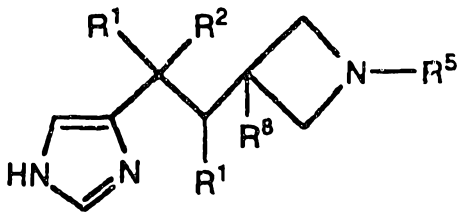
(II-1)

;



(II-2)

; and

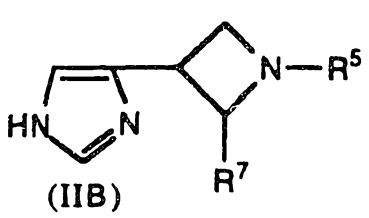


(II-3)

;

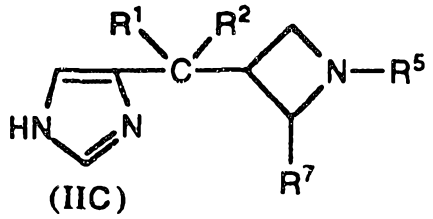
wherein R^1, R^2, R^3, R^5, and R^8 are as defined for Formula I.

Preferably, for compounds of Formula II, R^3, R^4, R^6, and R^8 are H. Preferred compounds of Formula II are represented by compounds of Formulas IIB and IIC:



(IIB)

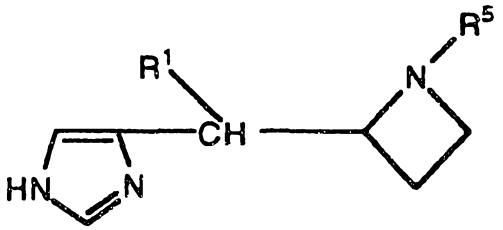
and



(IIC)

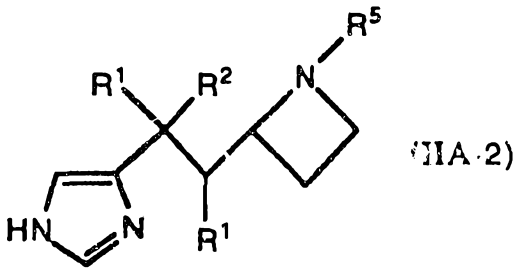
wherein R^1 and R^2 are as defined for Formula I with H being preferred, R^5 is as defined for Formula I with H and methyl being preferred and R^7 is selected from the group consisting of H, C_1 to C_6 alkyl, and $-(CH_2)_q-R^9$ wherein R^9 is phenyl. Preferably, R^7 is C_1 to C_6 alkyl, and most preferably methyl.

Representative compounds of Formula IIA include compounds of Formulas IIA-1 and IIA-2:



(IIA-1)

; and

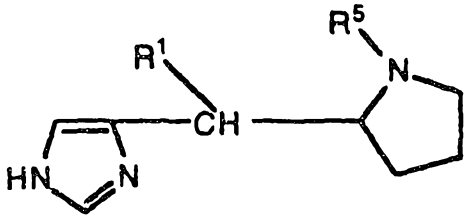


(IIA-2)

;

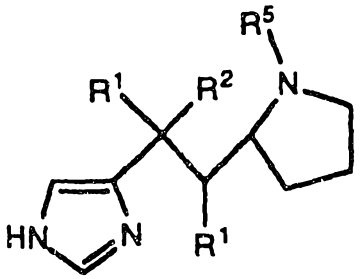
wherein R^1, R^2, and R^5 are as defined for Formula I.

Representative compounds of Formula III include compounds of Formulas III-1 and III-2:



(III-1)

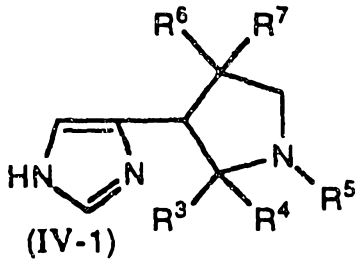
; and



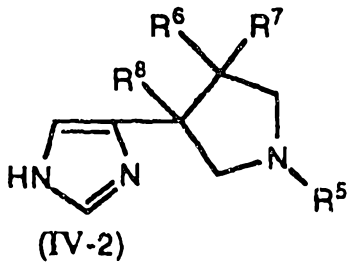
(III-2)

wherein R^1, R^2, and R^5 are as defined for Formula I.

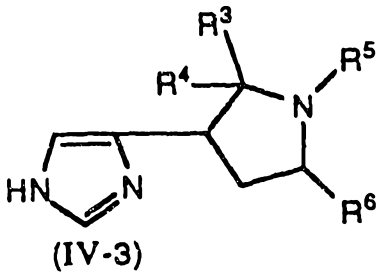
Representative compounds of Formula IV include compounds of Formulas IV-1, IV-2, IV-3, IV-4, IV-5, IV-6 and IV-7:



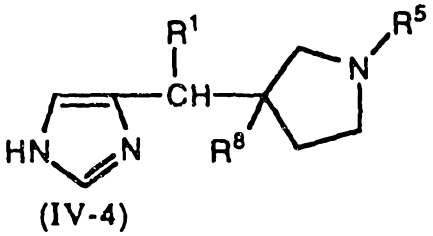
(IV-1) ;



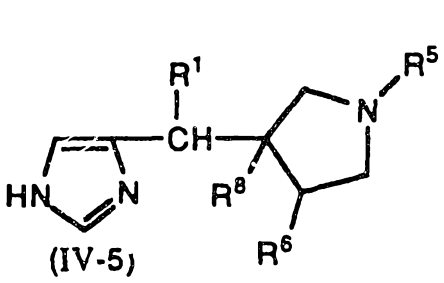
(IV-2) ;



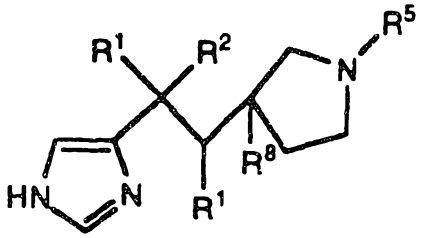
(IV-3) ;



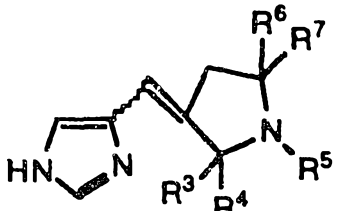
(IV-4) ;



(IV-5) ;



(IV-6) ;

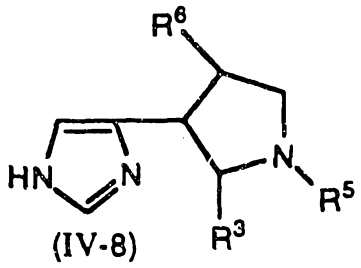


(IV-7)

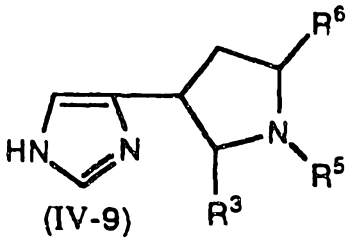
and

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 are as defined for Formula I.

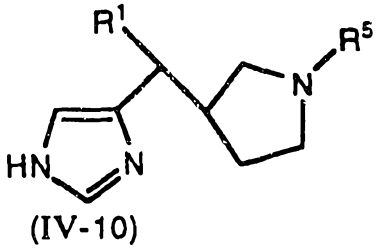
Representative compounds of Formula IV also include compounds of Formulas IV-8, IV-9, and IV-10:



(IV-8) ;



(IV-9) and

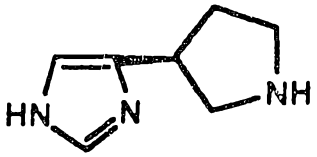


(IV-10)

wherein R^1, R^3, R^5, and R^6 are as defined for Formula I .

Representative compounds of Formula I include:

(A1)



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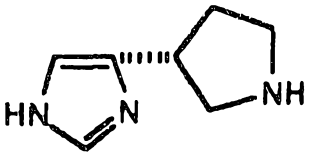
(A2)



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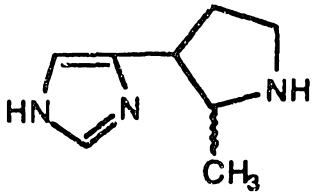
(B)



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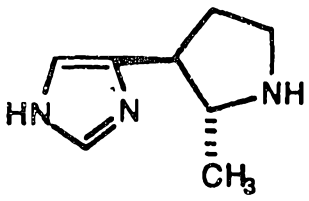
(B1)



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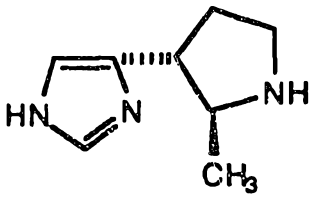
(B2)



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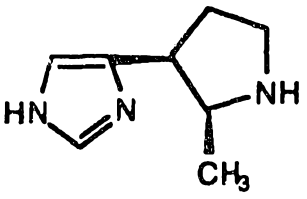
(B3)



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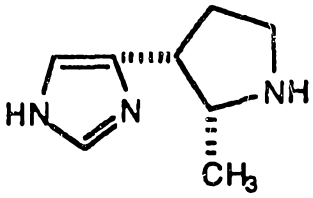
(B4)



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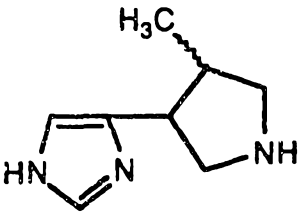
(C)



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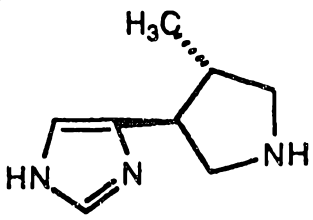
(C1)



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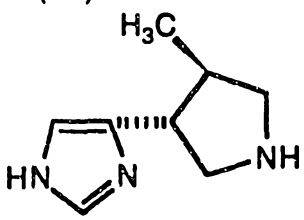
(C2)



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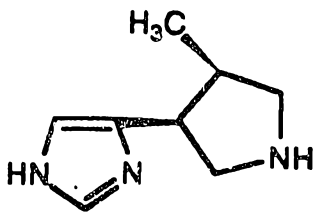
(C3)



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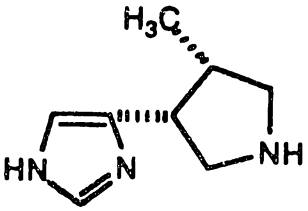
(C4)



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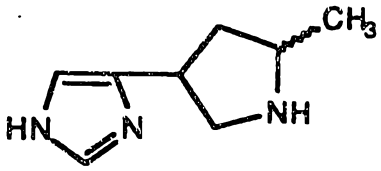
(D)



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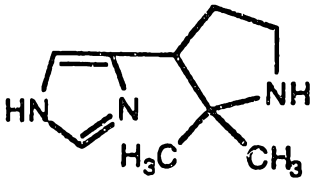
(E)



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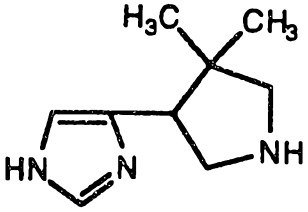
(F)



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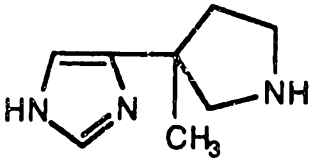
(G)



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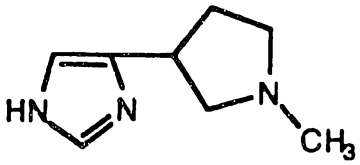
(H)



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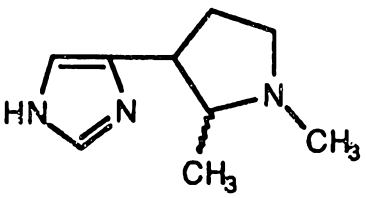
(I)



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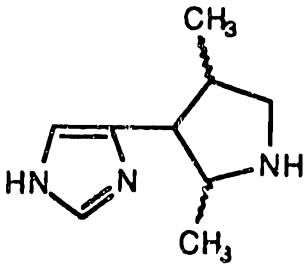
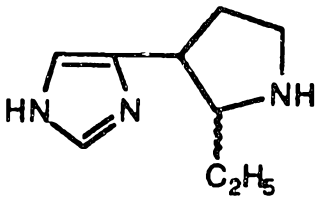
(J)



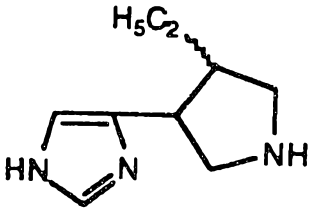
;

(K)



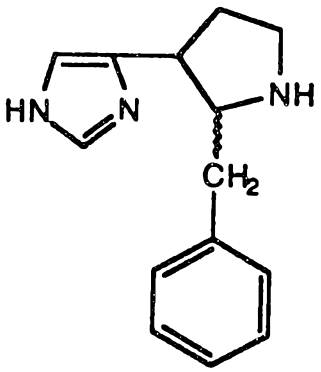
;

(L)



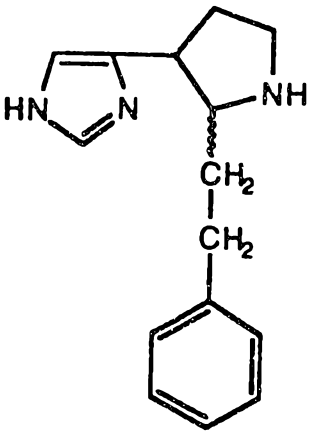
;

(M)



;

(N)



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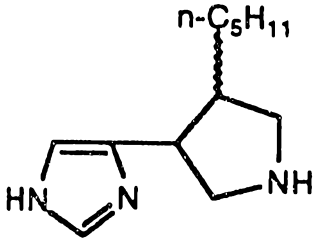

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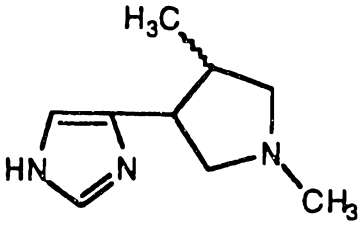

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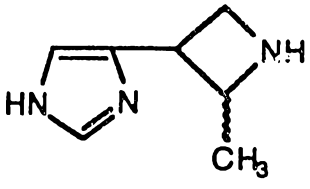

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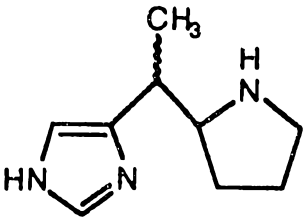

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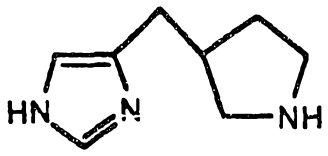
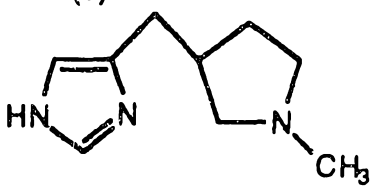
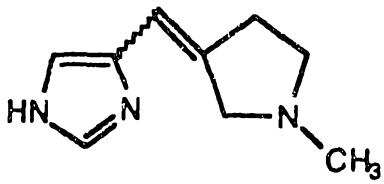
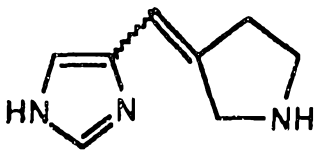
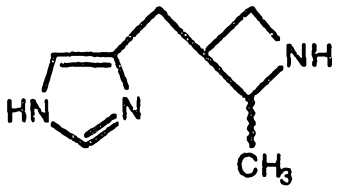
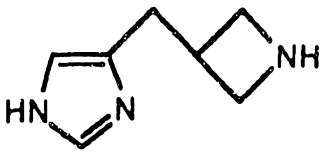
(S)  ;

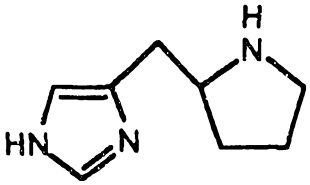
(T)  ;

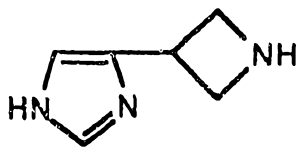
(U)  ;

(V)  ;

(W)  ;

(X)  ;

(Y)  ; and

(Z)  .

Certain compounds of the invention may exist in different isomeric (e.g., enantiomers and diastereoisomers) forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

The compounds of Formula I can exist in unsolvated as well as solvated forms, including hydrated forms, e.g., hemi-hydrate. In general, the solvated forms, with pharmaceutically acceptable solvents

such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of the invention.

Certain compounds of the invention will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Certain basic compounds of the invention also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the nitrogen atoms may form salts with acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

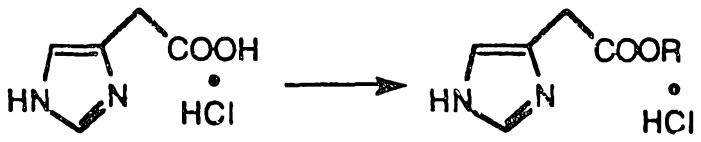
All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

The following processes may be employed to produce compounds of Formula I. Unless stated otherwise, reactions are conducted at an appropriate temperature which allows the reaction to proceed at a reasonable rate to completion. Also, unless indicated

otherwise, the substituent groups referred to in the following processes are as defined above for Formula I.

A. PREPARATION OF COMPOUNDS WHEREIN m is 0, n is 1 and p is 1 PRODUCING COMPOUNDS OF FORMULA II

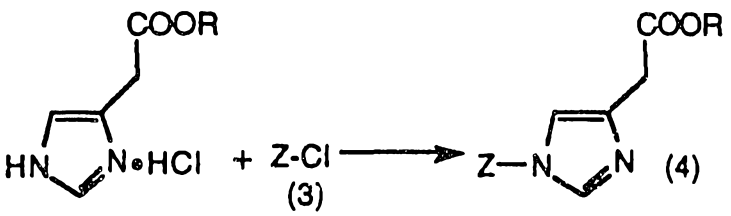
STEP 1-Preparation A:



(1) (2)

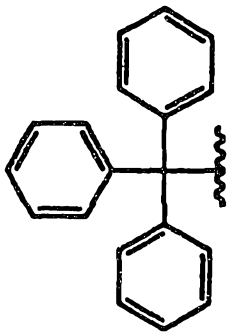
In Step 1, commercially available compound (1) is dissolved in a suitable alcohol, ROH wherein R is a lower alkyl such as a C_1 to C_6 alkyl (e.g., methyl, ethyl, isopropyl and the like), preferably methanol, containing a catalytic amount of concentrated hydrochloric acid or similar acid. The reaction mixture is heated at a temperature of about 50 to about 70°C to produce compound (2). There are many other esterification methods known in the art that may also be employed.

STEP 2-Preparation A:



(2)

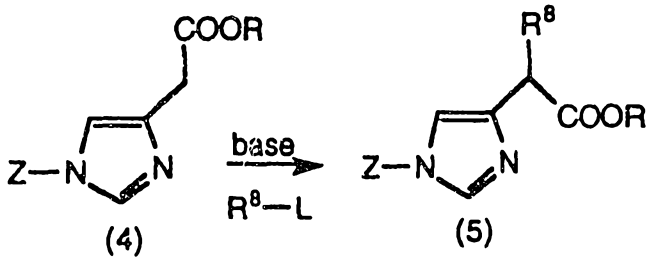
In Step 2, compound (2) is reacted with compound (3) in a polar organic solvent at a temperature of about 0 to about 50°C in the presence of an organic base to produce compound (4). In compounds (3) and (4), Z represents the protecting group:



(trityl group). Z can be other protecting groups, such as 2-(trimethylsilyl)ethoxymethyl, benzyloxycarbonyl, and the like; however, unless stated otherwise, Z preferably represents the trityl group in the processes described below for making the compounds of this invention. Suitable organic solvents include: DMF (N, N-dimethylformamide), CH_2Cl_2 and the like. DMF is preferred. Preferably, triethylamine is used as the base. Other suitable bases include N,N-diisopropylethylamine and the like.

Those skilled in the art will appreciate that other protecting groups known in the art may be used--such as, for example, base sensitive groups wherein the protected compounds would be deprotected using basic conditions (e.g., NaOH). The processes described herein wherein the protected compound is deprotected under acidic conditions may also be carried out under basic conditions when a base sensitive protecting group is used.

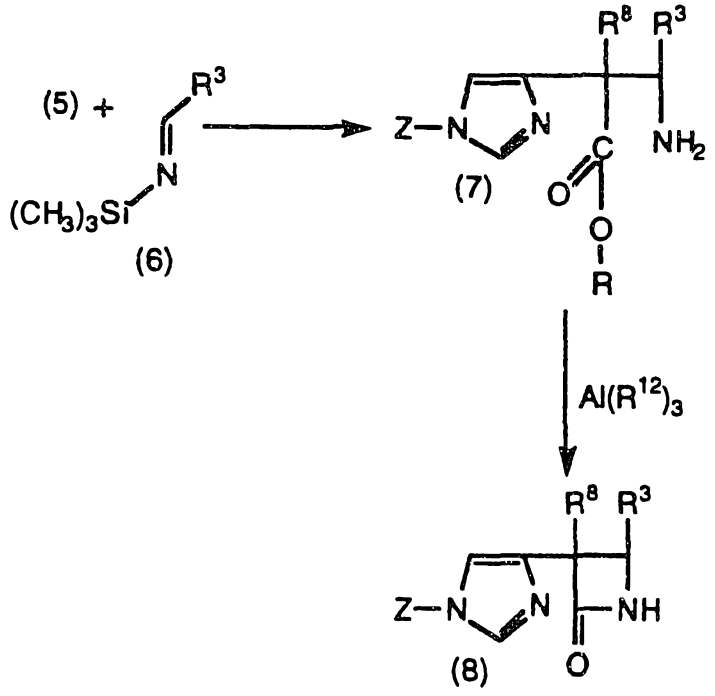
STEP 3-Preparation A:



In Step 3, the enolate of compound (4) reacts with R^8-L in an organic solvent to produce compound (5). The reaction is conducted

at a temperature in the range of about 0 to about 50°C. L is a suitable leaving group such as Cl, Br, I and the like. Preferably, LDA (lithium diisopropylamide) is used as the organic base to form the enolate, but other suitable bases include sodium hydride and the like. Suitable organic solvents include tetrahydrofuran, 1,4-dioxane and the like. Preferably, THF (tetrahydrofuran) is used.

STEP 4-Preparation A:



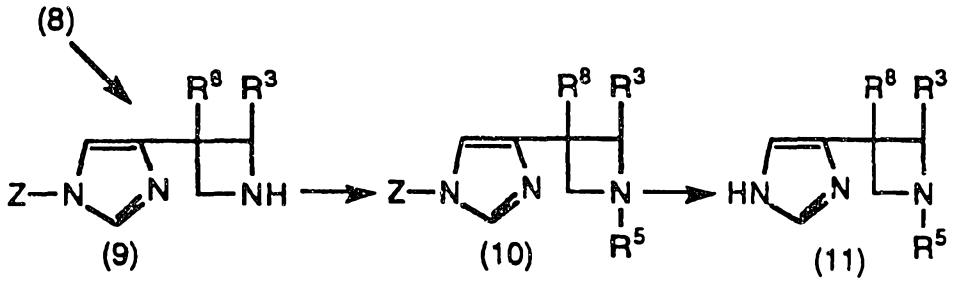
In Step 4, the enolate of compound (5) is reacted with compound (6) in an organic solvent in the presence of a Lewis acid to produce compound (7). Suitable organic solvents include tetrahydrofuran, diethyl ether, 1,4-dioxane and the like. Preferably, tetrahydrofuran or diethyl ether is used. Suitable organic bases used to generate the anion of (5) include lithium diisopropylamide, $LiN(Si(CH_3)_3)_2$, and NaH. Preferably, $LiN(Si(CH_3)_3)_2$ is used. Representative Lewis acids include $BF_3{\bullet}(C_2H_5)_2O$, $(CH_3)_3SiCl$ and the

like, with $BF_3 \cdot (C_2H_5)_2O$ being preferred. The reaction is conducted at a temperature within the range of about -78 to about 0°C.

Compound (7) is converted to compound (8) by reacting compound (7) with $Al(R^{12})_3$ in an organic solvent at a temperature of about 50°C. R^{12} is a suitable alkyl group such as methyl, ethyl, isopropyl, butyl, and the like. Methylene chloride is a preferred solvent for this reaction, but others, such as 1,2-dichloroethane, can be employed.

Compound (6) in Step 4 is prepared according to known in the art procedures--for example: Cainelli et al., Tetrahedron Letters, Vol. 28, No. 44, p. 5369 (1987); and Uyehara et al., Tetrahedron Letters, Vol. 30, No.32, p. 4275 (1989). In compound (6), R^3 is as defined above.

STEPS 5, 6 AND 7-Preparation A:



In Step 5, compound (8) is reduced to compound (9). The reaction is conducted in an organic solvent at a temperature within the range of about 20 to about 70°C using a known reducing agent. Examples of suitable reducing agents include DIBALH (diisobutyl aluminum hydride) and AlH_3. Preferably tetrahydrofuran is used as the organic solvent, but other suitable solvents include 1,4-dioxane and the like.

In Step 6, compound (9) is reacted with (i) R^5-X (when R^5 is $-C(O)R^{10}$, $-C(O)OR^{10'}$, $-C(O)NR^{10}R^{11}$ or alkyl) in an organic solvent optionally in the presence of a siutable base (e.g., triethylamine); or (ii) R^{5A}-CHO (when R^5 is alkyl, cycloalkyl, allyl, propargyl, benzyl or substituted benzyl) in the presence of $NaBH_3(CN)$ (sodium

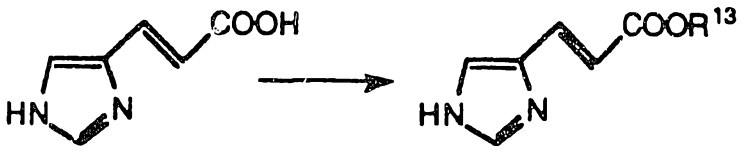
cyanoborohydride) or other hydrogenating conditions (e.g. H_2/Pd/ROH) in an organic solvent; to produce compound (10). R^{5A} represents an R^5 group that has one less -CH_2- group. Preferably, CH_2Cl_2 is used as the solvent when R^5-X is used, and tetrahydrofuran or an alcohol is used as the solvent when R^{5A}-CHO is used. X represents a suitable leaving group such as Cl, Br, I, or -OCH_3. The reaction ((i) or (ii)) can be performed at a temperature within the range of about -30 to about 80°C. Compound (10), when R^5 is -C(O)NR^{10}H, is prepared by reacting compound (9) with O=C=N-R^{10} in an organic solvent, such as CH_3CN or toluene. The reaction is performed at a temperature in the range of about 20 to about 110°C. Alternatively, compounds wherein R^5 is -C(O)N$R^{10}R^{11}$ may be made from compounds wherein R^5 is -C(O)O$R^{10'}$ by reacting such compounds with N$HR^{10}R^{11}$ in an organic solvent (e.g., THF) at a temperature of about 25 to about 100°C. Compound (9), or compound (10) wherein R^5 is -C(O)O(t-butyl), can be reacted with aqueous acid (e.g., HCl, HBr, and the like), at a temperature of about 25 to about 100°C, to produce compound (11) wherein R^5 is H.

In Step 7, compound (10) is deprotected by treatment with dilute aqueous acid, such as HCl or HBr, at a temperature of about 25 to about 90°C to produce compound (11). Other protecting groups are removed by methods well known in the art.

In all the preparations that follow, intermediate compounds wherein the imidazole nitrogen is protected by Z and the nitrogen of the cyclic four or five membered amine is substituted with -C(O)O(t-butyl) or unsubstituted, i.e., hydrogen is bound to the amine nitrogen, such as in compounds (10) or (9), respectively, such intermediate compounds can be reacted with aqueous acid (e.g., HCl, HBr, and the like), at a temperature of about 25 to about 100°C, to produce deprotected final products wherein R^5 is H, e.g., compound (11).

B. PREPARATION OF COMPOUNDS WHEREIN m IS 0, n is 1 and p is 2 PRODUCING COMPOUNDS OF FORMULA IV

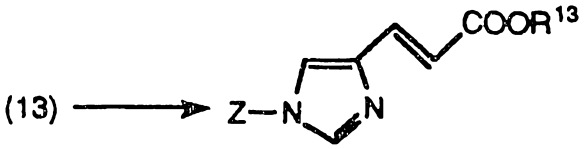
STEP 1-Preparation B:



(12) (13)

In Step 1, urocanic acid (12) is heated with a catalytic amount of concentrated sulfuric acid in a solvent $R^{13}OH$ to produce a compound (13). R^{13} is an alkyl group such as methyl, ethyl, and the like. The reaction is conducted at a temperature equivalent to the boiling point of the solvent ($R^{13}OH$), for example 65°C for methanol.

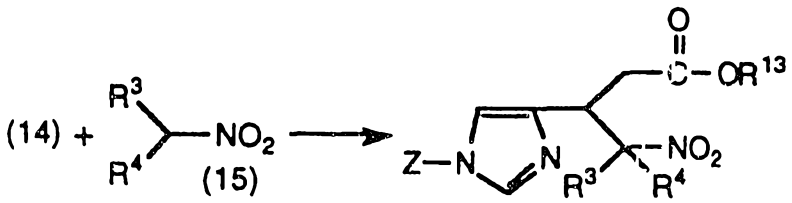
STEP 2-Preparation B:



(14)

In Step 2, compound (13) is reacted with trityl chloride (see compound (3) in Preparation A above) to produce compound (14), wherein Z represents the trityl group. Other suitable compounds which provide protecting groups (Z) which can be used instead of trityl chloride include SEM (2-(trimethylsilyl)ethoxymethyl) chloride.

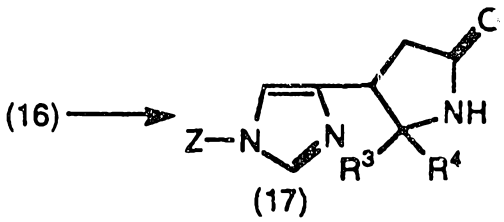
STEP 3-Preparation B:



(16)

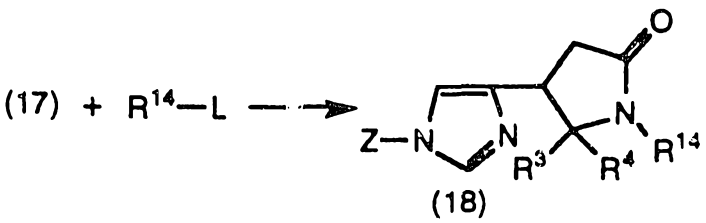
In Step 3, compound (14) (from Step 2) is reacted with compound (15) to produce compound (16). The reaction takes place at a temperature within the range of about 20 to about 100°C in an organic solvent containing an organic base. Suitable organic bases include DBU (1, 8-diazabicyclo[5.4.0]undec-7-ene), and TMG (1, 1, 3, 3-tetramethylguanidine). Suitable solvents include acetonitrile, tetrahydrofuran, N, N-dimethylformamide and the like.

STEP 4-Preparation B:



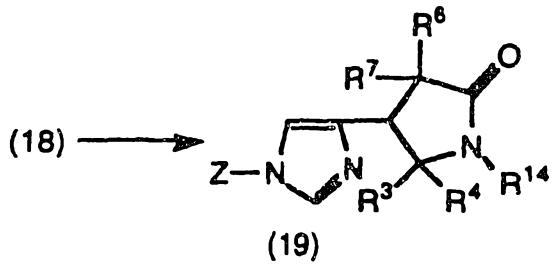
In Step 4, compound (16) (from Step 3) is hydrogenated to produce compound (17). The hydrogenation takes place in an organic solvent, using Raney-Nickel, at a temperature of about 20 to about 60°C. Preferably ethanol is used as the organic solvent. Under these conditions cyclization occurs in situ to provide the desired lactam (17).

STEP 5-Preparation B:



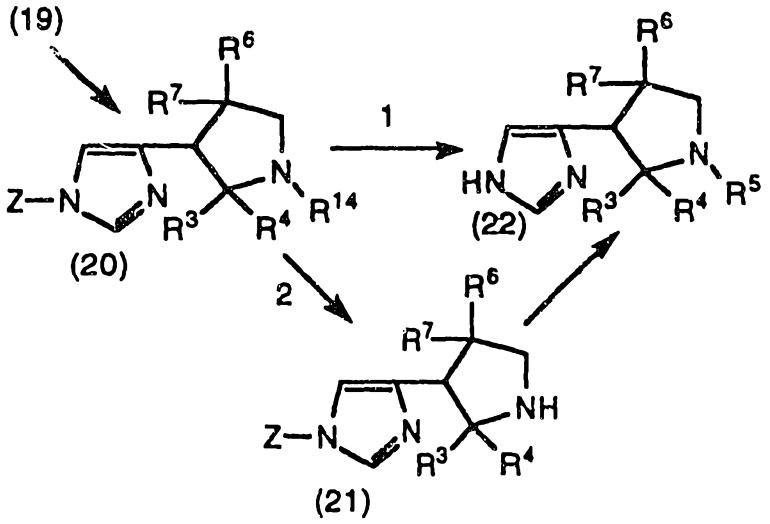
In Step 5, the anion of compound (17) is reacted with R^{14}-L to place the R^{14} on the indicated nitrogen atom in compound (18). R^{14} can be a suitable protecting group such as $Si(CH_3)_2C(CH_3)_3$ or -C(O)O(t-butyl), or R^{14} can be an alkyl, cycloalkyl, benzyl, substitued benzyl, allyl, or propargyl group. L is a leaving group, such as Cl, Br, I or $-OSO_2CF_3$. The reaction is conducted in an organic solvent such as THF, diethyl ether, 1,4-dioxane or DMSO in the presence of a suitable base, such as lithium diisopropylamide or NaH. The reaction takes place at a temperature within the range of about -78 to about 80°C.

STEP 6-Preparation B:



In Step 6, the enolate of compound (18) reacts with R^6-X and then with R^7-X to produce compound (19). X represents a suitable leaving group, such as Cl, Br, I or $-OSO_2CF_3$. Each reaction to place each substituent group on the ring takes place in an organic solvent using an organic base. Tetrahydrofuran is the solvent usually used; however, other suitable solvents include 1,4-dioxane, diethyl ether and the like. Examples of organic bases include lithium diisopropylamide, $M^+N[Si(CH_3)_3]_2$, KH and the like. M^+ represents a suitable metal cation such as Na, Li, K, and the like. The reaction is usually conducted at a temperature of about -78 to about 80 °C.

STEPS 7, 8 AND 9-Preparation B:



In Step 7, compound (19) is reduced to compound (20) with a reducing agent in an organic solvent at a suitable temperature. Preferably, $LiAlH_4$ (lithium aluminium hydride) is used with tetrahydrofuran at a temperature of about 0 to about 70°C. Other suitable reducing agents include BH_3 (borane) and the like. Other organic solvents which may be used include 1,4-dioxane and the like.

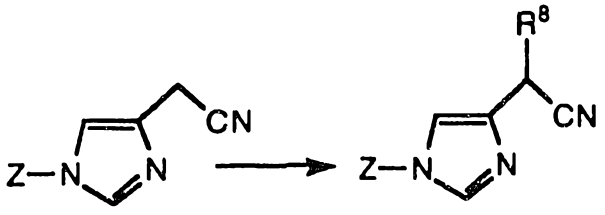
In reaction path 1 (compound (20) to (22)), R^{14} is alkyl, cycloalkyl, benzyl, substituted benzyl, allyl, or propargyl. In reaction path 2 (compound (20) to (21)), R^{14} is $-Si(CH_3)_2C(CH_3)_3$ or -C(O)O(t-butyl).

In Step 8, following reaction path 1, compound (20) is deprotected by following the procedure in Step 7 of Preparation A to produce compound (22). Alternatively, following reaction path 2, when R^{14} is $-Si(CH_3)_2C(CH_3)_3$, compound (20) is treated with tetrabutylammonium fluoride in tetrahydrofuran at a temperature of about 0 to about 50°C to produce compound (21), or compound (20), when R^{14} is -C(O)O(t-butyl), is treated with dilute aqueous acid (e.g., HCl, HBr and the like).

In Step 9, the procedures in Steps 6 and 7 of Preparation A are followed so that compound (21) may be converted to compound (22).

C. PREPARATION OF COMPOUNDS WHEREIN m IS 0, n is 1 and p is 2 PRODUCING COMPOUNDS OF FORMULA IV

STEP 1-Preparation C:

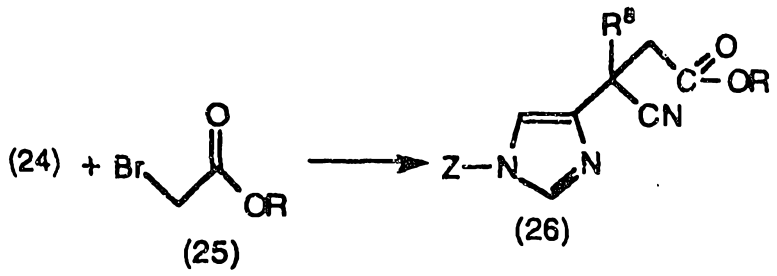


(23) (24)

In Step 1, compound (23), synthesized according to Degraw et al. J. Med. Chem., 1977, 20, 1671, wherein Z is the trityl group, is reacted with R^8-L in an organic solvent, in the presence of an organic base, at a temperature of about 0 to about 50°C to produce

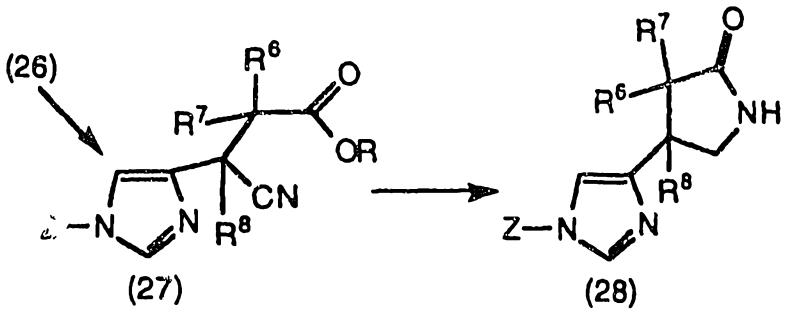
compound (24). L is a suitable leaving group such as, for example, halogen (halides) selected from the group consisting of: Cl, Br, and I; $-OSO_2-C_6H_4-CH_3$ (wherein C_6H_4 is phenyl); $-OSO_2-CH_3$; and the like. Suitable organic bases include lithium diisopropylamide, $LiN[Si(CH_3)_3]_2$, and the like. Preferably, the organic solvent is tetrahydrofuran. Other suitable solvents which may be used include 1,4-dioxane and the like.

STEP 2-PREPARATION C:

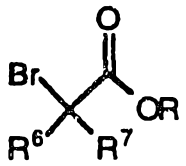


In Step 2, the anion of compound (24) is reacted with compound (25) (wherein R is alkyl) to produce compound (26). The reaction is conducted at a temperature of about -78 to about 50°C in an organic solvent containing an organic base. Suitable organic bases include lithium diisopropylamide, $LiN(Si(CH_3)_3)_2$, and the like. Preferably, the organic solvent is tetrahydrofuran. Other suitable solvents which may be used include DMF and the like.

STEPS 3 AND 4-PREPARATION C:



In Step 3, following the procedure set forth in Step 6 of Preparation B, compound (26) is substituted with substituent groups R^6 and R^7 to produce compound (27). Alternatively, compound (27) is prepared by the reaction of compound (24) with compound (26A)

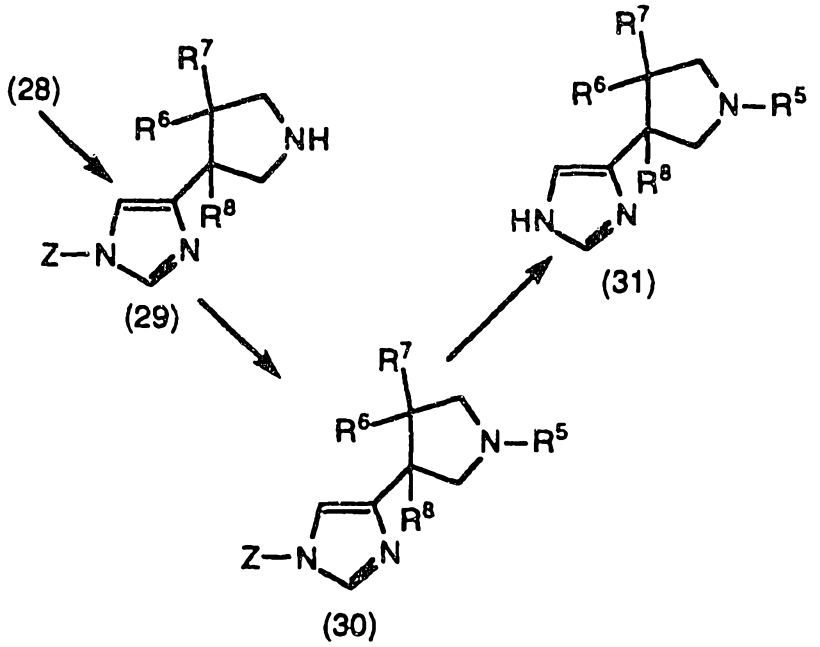


(26A)

under similar conditions for the reaction of compound (24) with compound (25).

In Step 4, compound (27) is reduced using H_2 and Raney-Nickel. The reduction takes place in ethanol at a temperature of about 25 (room temperature) to about 80°C. Other reducing agents can be used such as $NaBH_4/CoCl_2$ wherein the reduction takes place in ethanol at about room temperature. Subsequent cyclization in situ provides compound (28).

STEPS 5, 6 AND 7-PREPARATION C:



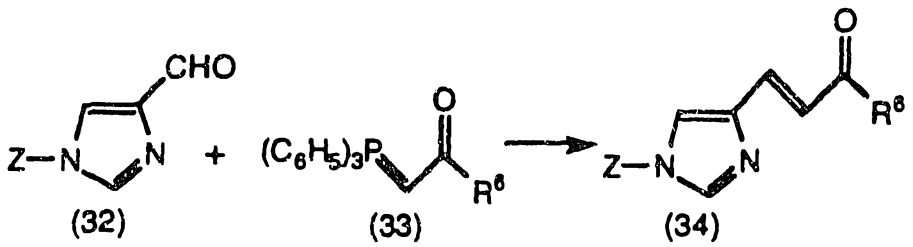
In Step 5, compound (28) is reduced to compound (29) in tetrahydrofuran using $LiAlH_4$ and a reaction temperature of about 0 to about 70°C. Another suitable reducing agent is BH_3.

In Step 6, compound (29) is converted to compound (30) according to the procedure described in Step 6 of Preparation A.

In Step 7, compound (30) is deprotected to produce compound (31) by following the procedure described in Step 7 of Preparation A.

D. PREPARATION OF COMPOUNDS WHEREIN m is 0, n is 1 and p is 2 PRODUCING COMPOUNDS OF FORMULA IV

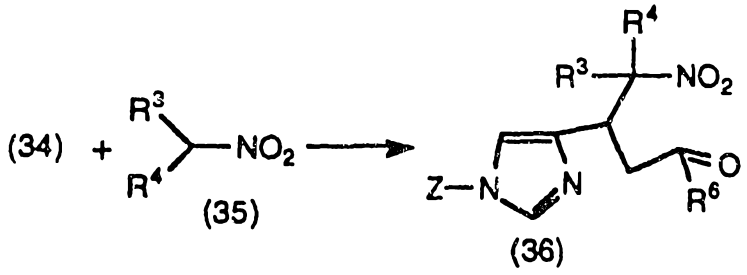
STEP 1-PREPARATION D



(32) (33) (34)

In Step 1, compound (32) is reacted with compound (33) to produce compound (34). The reaction is conducted in tetrahydrofuran at a temperature of about 25 to about 70°C. Other usable organic solvents besides tetrahydrofuran include DMF and the like. Compound (32) is prepared following the literature procedure set forth in J. L. Kelley et al., J. Med. Chem., 20, 721(1977). The Wittig reagent, compound (33), is either commercially available or may be prepared from the corresponding α-halo ketone and triphenylphosphine using standard reaction conditions known in the art.

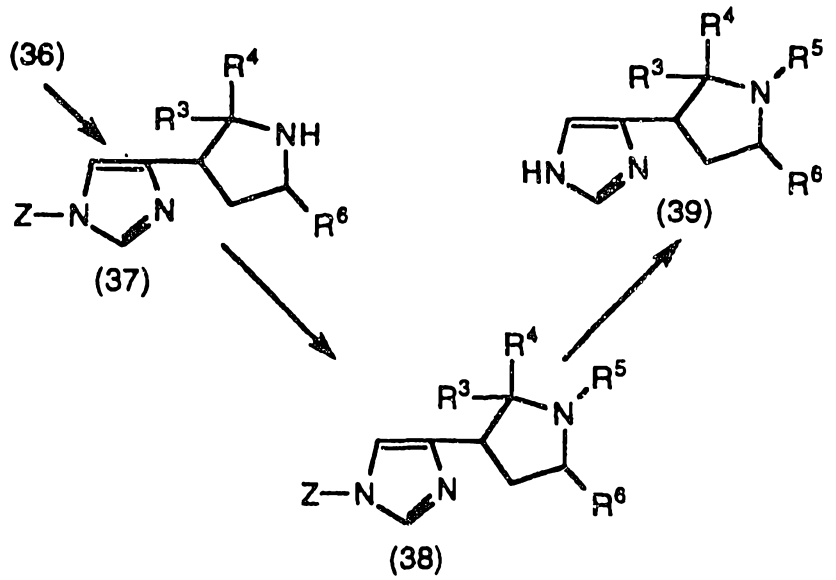
STEP 2-PREPARATION D:



(36)

In Step 2, compound (34) is reacted with compound (35) to produce compound (36). The reaction is carried out according to the procedure set forth in Step 3 of Preparation B.

STEPS 3, 4 AND 5-PREPARATION D:



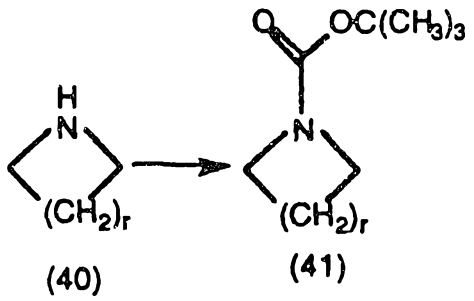
In Step 3, compound (36) is hydrogenated at a temperature of about 25 to about 70°C using H_2 and Raney-Nickel. The reaction is conducted in ethanol in similar fashion to the reaction described in Step 4 of Preparation C.

In Step 4, following the procedure in Step 6 of Preparation A, compound (37) is reacted with R^5-X or R^{5A}-CHO to produce compound (38).

In Step 5, compound (38) is deprotected at a temperature of about 50 to about 100°C using aqueous acid such as 10 % aqueous hydrochloric acid to produce compound (39).

E. PREPARATION OF COMPOUNDS WHEREIN m IS 1, n is 0 and p is 2 or 3 PRODUCING COMPOUNDS OF FORMULAS IIA AND III

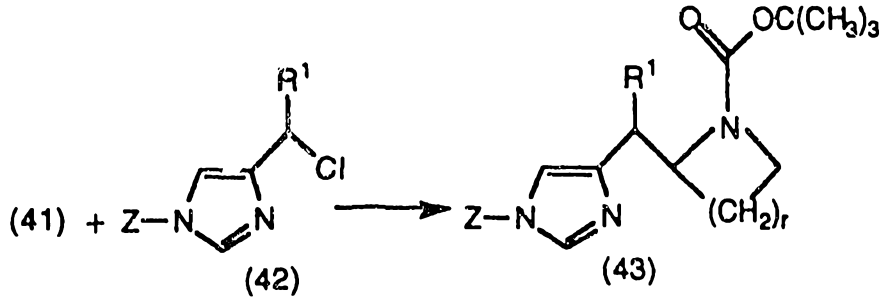
STEP 1-PREPARATION E:



(40) (41)

In Step 1, compound (40) is reacted with di-tert-butyl dicarbonate ($(tBOC)_2O$) in an organic solvent in the presence of an organic base. The reaction is conducted at a temperature of about 0 to about 30°C. Preferably, methylene chloride is used as the organic solvent, but other suitable organic solvents include DMF and the like. Triethylamine is used as the organic base. Other bases which can be used include 4-dimethylaminopyridine and the like. In compounds (40) and (41) r represents 1 or 2. The desired starting reactant (40) can be obtained commercially. In compound (41), the BOC group is chosen as an activating group on nitrogen which increases the kinetic acidity of the α-proton such that a lithio salt would result (for example, Step 2). Other activating groups on nitrogen, known in the art that can also be employed include nitroso, phosphoryl, hindered acyl, and formamidyl. (see Aldrichimica Acta, Vol. 8, No. 3, 1985).

STEP 2-PREPARATION E

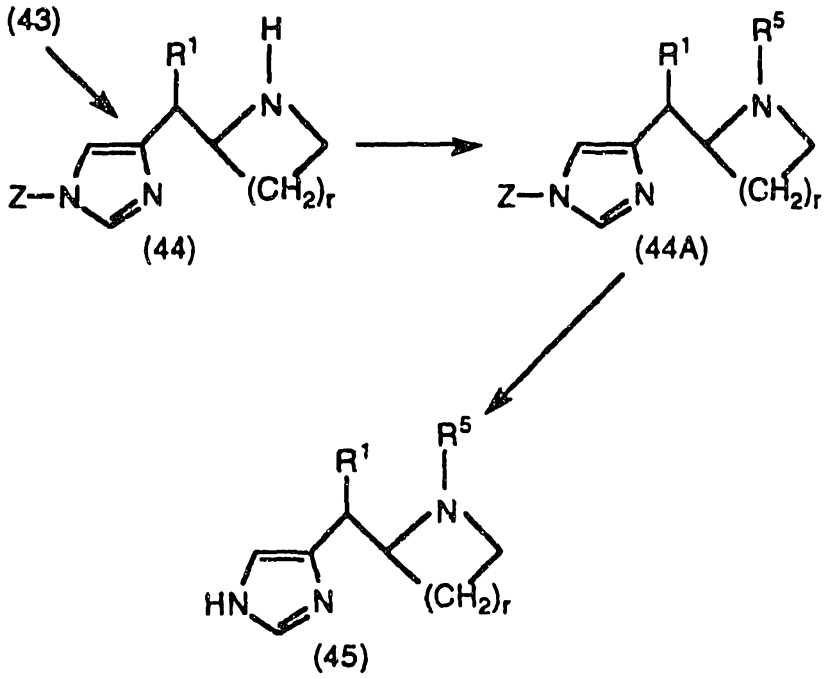


(42) (43)

In Step 2, the anion of compound (41) is reacted with compound (42), to produce compound (43). The reaction is conducted

in an organic solvent containing an organic base and TMEDA (tetramethylethylenediamine). The reaction is conducted at a temperature of about -78 to about 25°C (room temperature). Tetrahydrofuran is preferably used as the solvent, other suitable solvents include diethyl ether and the like. The anion of (41) is prepared by metalation of (41) with sec-butyllithium in THF at -78°C. Compound (42) is obtained by reacting compound (32) with an organometallic reagent R^1M, wherein M is Li or MgBr, and then with thionyl chloride ($SOCl_2$).

STEPS 3 TO 5-PREPARATION E:



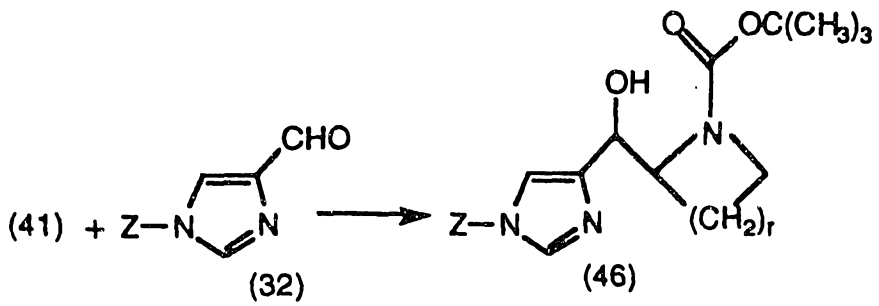
In Step 3, compound (43) is treated with HCl or similar acid in an inert organic solvent such as ethyl acetate or dioxane, at a temperature of about 0°C to selectively deprotect (43) thus producing compound (44).

In Step 4, compound (44) is reacted with R^5-X or R^{5A}-CHO in accordance with the procedure set forth in Step 6 of Preparation A to produce compound (44A).

In Step 5, compound (44A) is [illegible] deprotected to produce compound (45) by following the procedure set forth in Step 7 of Preparation A.

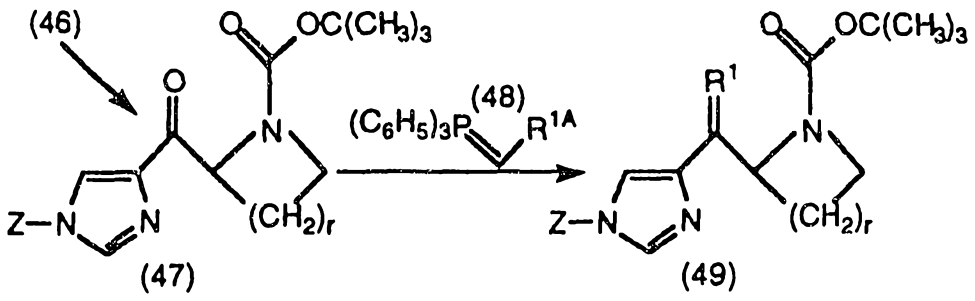
F. PREPARATION OF COMPOUNDS WHEREIN m IS 1, n is 0 and p is 2 or 3 PRODUCING COMPOUNDS OF FORMULAS IIA AND III

STEP 1-PREPARATION F:



In Step 1, compound (41)--see Step 1 of Preparation E--is reacted with compound (32) in accordance with the procedure set forth in Step 2 of Preparation E. r is 1 or 2.

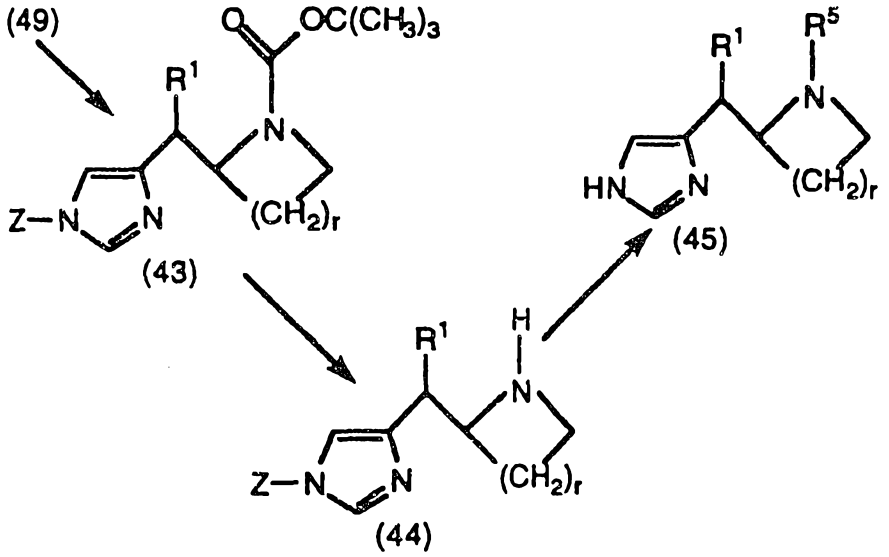
STEPS 2 AND 3-PREPARATION F:



In Step 2, compound (46) is oxidized to produce compound (47). The oxidation is accomplished by treating compound (46) with an oxidizing agent, such as MnO_2 or PDC (pyridinium dichromate), in an inert organic solvent, such as tetrahydrofuran or methylene chloride, at a temperature of about 20 to about 70°C.

In Step 3, compound (47) reacts, under usual Wittig reaction conditions, with compound (48) in an organic solvent at a temperature of about 25 to about 70°C to produce compound (49). In compound (48), R^{1A} represents an R^1 group which has one less $-CH_2-$ group. Preferably, the organic solvent is tetrahydrofuran; however, other suitable solvents, such as 1,4-dioxane and the like, can be used.

STEPS 4 AND 5-PREPARATION F:

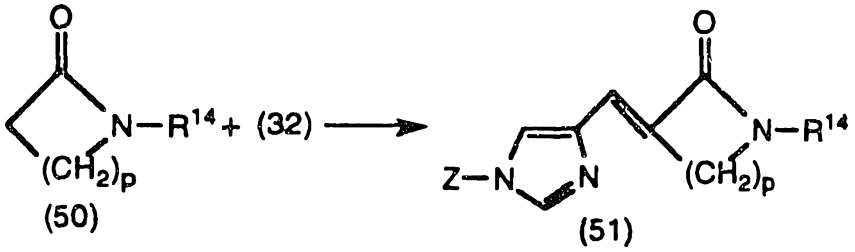


In Step 4, compound (43) is produced when compound (49) is hydrogenated in tetrahydrofuran with H_2 using a Pd-C (palladium/carbon) catalyst. Other organic solvents which can be used include ethyl acetate, methanol and the like. Other suitable metal catalysts such as Pt, $Pd-Al_2O_3$, Ra-Ni, NiB, and $Pd-CaCO_3$ can also be employed as the hydrogenation catalyst.

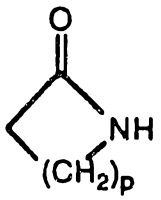
In Step 5, conversion of compound (43) to compound (44) and then to compound (45) is accomplished by following the same process described in Steps 3, 4, and 5 of Preparation E.

G. PREPARATION OF COMPOUNDS WHEREIN m IS 1, n is 1 and p is 1 or 2 PRODUCING COMPOUNDS OF FORMULAS II AND IV

STEP 1-PREPARATION G:

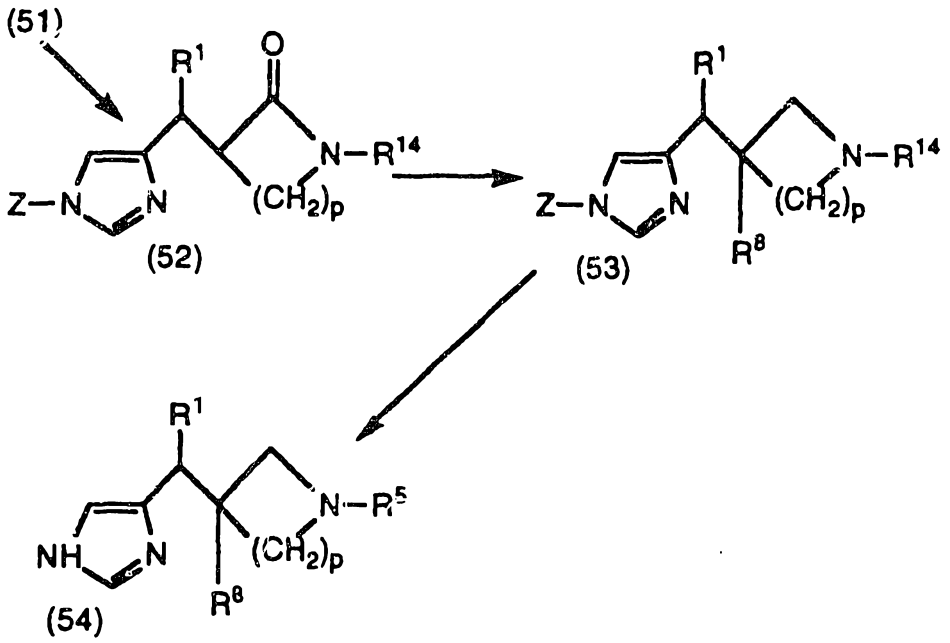


In Step 1, the anion of compound (50) reacts with compound (32) in an organic solvent at a temperature of about -78 to about 25°C to produce compound (51) wherein p is 1 or 2. Suitable organic solvents include tetrahydrofuran and the like. Preferably, the organic base used to generate the anion of (50) is lithium diisopropylamide or $M^+N[Si(CH_3)_3]_2$ wherein M^+ is a metal cation such as Li, Na, or K. Z is trityl. Compound (50) is obtained from the commercially available unprotected precursor



according to known methods--see, for example, Step 5 of Preparation B.

STEPS 2-4-PREPARATION G:



In Step 2, compound (51) is reacted with R^1-Q, wherein Q is Li or MgBr, in tetrahydrofuran containing CuCN and a Lewis acid, such as BF_3, $(CH_3)_3SiCl$ and the like, to produce compound (52). The reaction is conducted at a temperature of about -78 to about 20°C. Tetrahydrofuran is the preferred organic solvent; however, other suitable solvents include diethyl ether and the like.

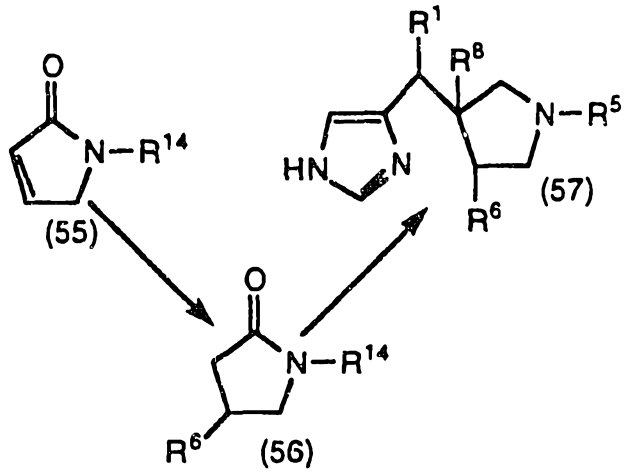
In Step (3), compound (52) is reacted with R^8-L according to the procedure set forth in Step 3 of Preparation A. Then the resulting R^8 substituted compound is reduced with either AlH_3 or DIBALH (when p = 1); or with $LiAlH_4$ (when p = 2) at a temperature of about 25 to about 65°C to produce compound (53). The reduction is conducted in tetrahydrofuran; however, other organic solvents, such as 1,4-dioxane and the like, can be used.

In Step 4, compound (53) is converted to compound (54) according to the processes described in Steps 8 and 9 of Preparation B for the conversion of compound (20) to compound (22).

H. PREPARATION OF COMPOUNDS WHEREIN m IS 1, n is 1 and p is 1 or 2 PRODUCING COMPOUNDS OF FORMULAS II AND IV

The anion of compound (50), which is prepared by reacting compound (50) with lithium diisopropylamide at a temperature of about -20°C to about 20°C in THF (see Step 1 of Preparation G) reacts with compound (42)--see Step 2 of Preparation E-- in tetrahydrofuran at a temperature of about -78 to about 25°C to produce compound (52)--see Step 2 Preparation G. Other suitable solvents besides tetrahydrofuran can also be used, such as DMF and the like. Other suitable bases which can be used to generate the anion of (50) include $NaN[Si(CH_3)_3]_2$, $KN[Si(CH_3)_3]_2$, KH and the like. Compound (52) is converted to compound (54) following the procedures in Steps 3 and 4 of Preparation G.

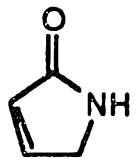
I. PREPARATION OF COMPOUNDS WHEREIN m IS 1, n is 1 and p is 2



Compound (55) reacts with R^6-M (wherein M is Li, ZnBr or MgBr) in tetrahydrofuran containing $BF_3 \cdot (C_2H_5)_2O$ and CuCN at a temperature of about -78 to about 20°C to produce compound (56). Other suitable solvents such as diethyl ether can be used. Compound

(56) is converted to compound (57) in accordance with the reaction steps set forth in Preparation G or Preparation H.

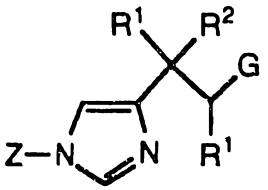
Compound (55) is obtained by reacting the commercially available unprotected precursor



with R^{14}-L according to known methods--see, for example, Step 5 of Preparation B.

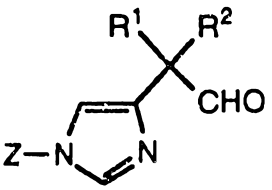
J. PREPARATION OF COMPOUNDS WHEREIN m IS 2, n IS 0 AND p is 2 or 3; OR m IS 2, n IS 1 AND p IS 1 OR 2

By following the steps in Preparations E, F, G or H with the exception that compound (58)



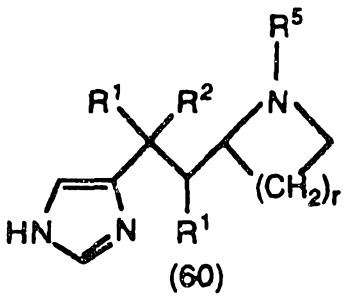
(58)

is used instead of compound (42) and compound (59)

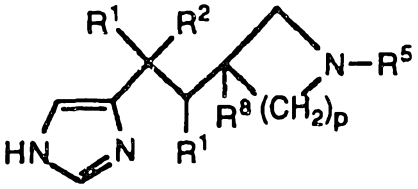


(59)

is used in place of compound (32), compounds (60) and/or (61)



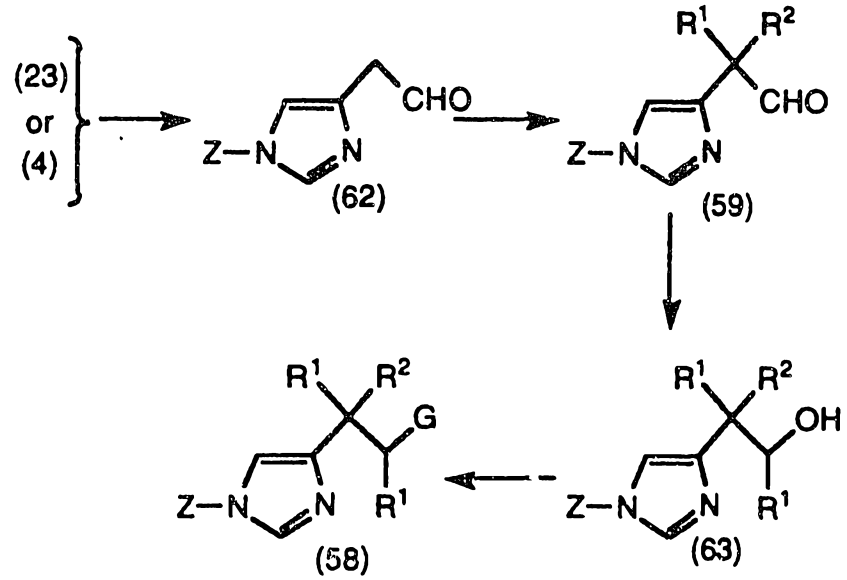
(60)



(61)

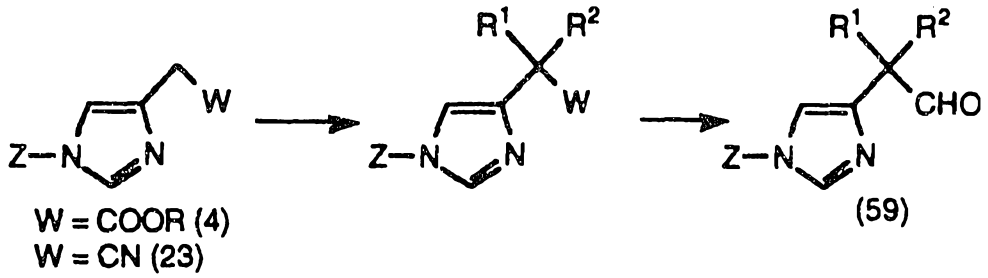
are produced. Compound (60) is produced following Preparation E or Preparation F, and compound (61) is produced following Preparation G or Preparation H. In compound (60), r is 1 or 2 and therefore p is 2 or 3, and in compound (61), p is 1 or 2. In compound (58), G represents a suitable leaving group such as Br, I, $-OSO_2-C_6H_4-CH_3$, $-OSO_2-CH_3$, $-OSO_2-CF_3$ and the like. The preparation of compound (58) is described below.

K. PREPARATION OF COMPOUND (58):



Compound (62) is produced by the reduction of compound (23) in tetrahydrofuran at a temperature of about 0 to about 70°C using diisobutylaluminum hydride as the reducing agent followed by an aqueous work up. Alternatively, reduction of compound (4) by bis(2-methoxyethoxy)aluminum hydride also can produce compound (62), see for example R. Kanazawa & T. Tokoroyama, Synthesis, 526(1976). Compound (59) is produced by reacting compound (62) in an organic solvent containing an organic base with R^1-L and then with R^2-L in accordance with the method set forth in Step 3 of Preparation A. Preferably, the organic solvent is tetrahydrofuran and the organic base is lithium diisopropylamide. L is a suitable leaving group such as Cl, Br, I, $-OSO_2-CF_3$ and the like.

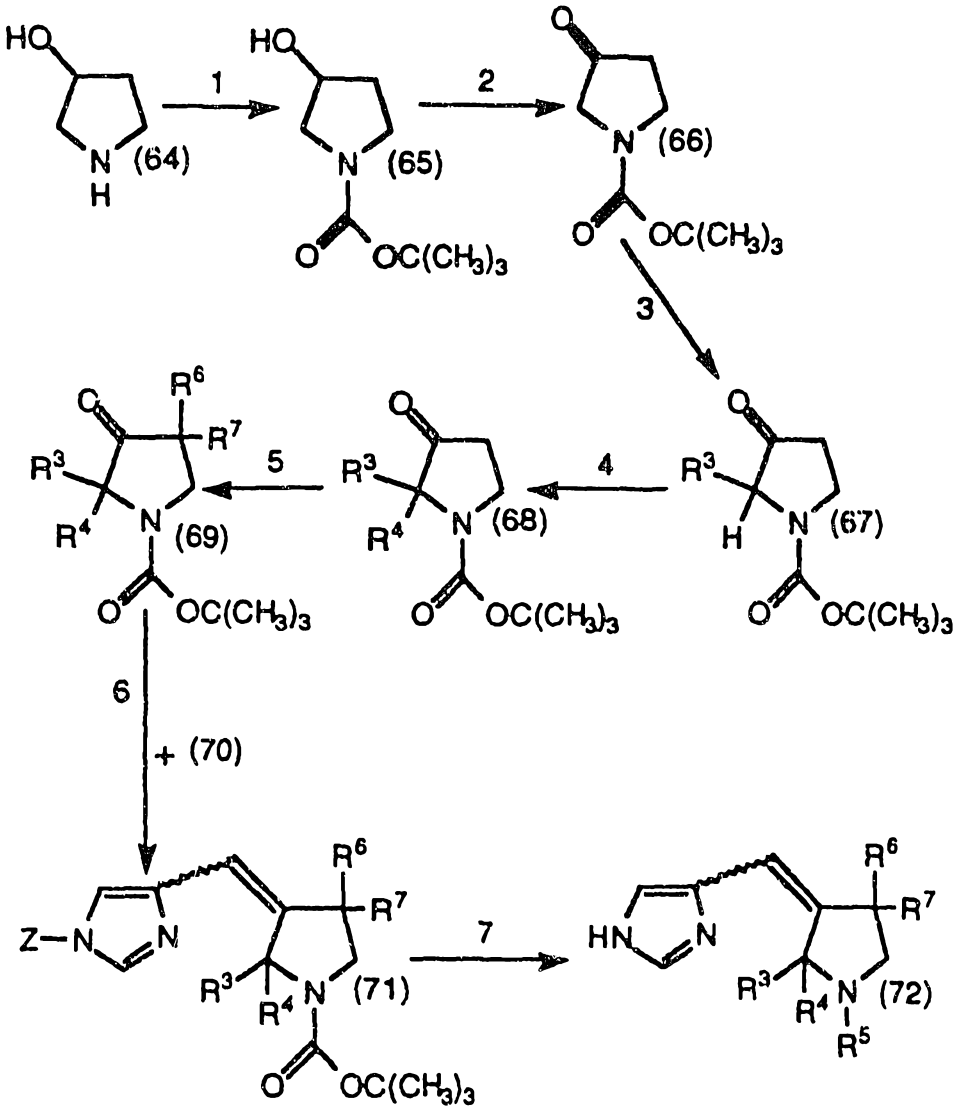
Alternatively, the sequence of the preparation of compound (59), from compound (4) or (23), can be switched, i.e., alkylation first to introduce R^1 and R^2 and then reduction.



W = COOR (4)
W = CN (23)

Compound (59) then reacts with either lithium aluminum hydride (when R^1 = H) or R^1-Q (R^1 is not H) in tetrahydrofuran at a temperature of about -78 to about 0°C to produce compound (63). Q represents Li or MgBr. When G represents a halide (i.e., Cl, Br, or I), then compound (58) is produced by either reacting compound (63) with $(H_5C_6)_3P/CG_4$ or $(H_5C_6)_3PG_2$ (see Fiser & Fiser, Reagents for Organic Synthesis, Vol. 1, p1247(1967)). When G represents $-OSO_2-C_6H_4-CH_3$, $-OSO_2-CH_3$ or $-OSO_2-CF_3$, then compound (58) is produced by reacting compound (63) with $Cl-SO_2-C_6H_4-CH_3$, $Cl-SO_2-CH_3$ or $Cl-SO_2-CF_3$, respectively, in methylene chloride containing triethylamine (as base) at a temperature of about -78 to about 0°C.

L. PREPARATION OF COMPOUNDS WHEREIN m is 1, n is 1 AND p is 2 AND WHEREIN THE DOUBLE BOND INDICATED IN FORMULA I IS PRESENT



In Step 1, compound (65) is produced when compound (64) is reacted with (t-BOC)$_2$O and triethylamine. The reaction is conducted in an organic solvent, such as methylene chloride or DMF, using a temperature within the range of about 0 to about 25°C (room temperature).

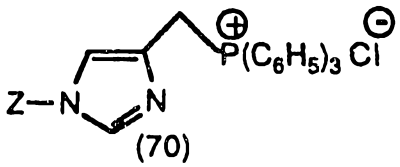
In Step 2, compound (66) is produced by treating compound (65) with an oxidizing agent such as pyridinium dichromate. The oxidation reaction is conducted in an organic solvent, such as methylene chloride, using a temperature of about 25 to about 50°C.

In Step 3, compound (67) is produced when the enolate of compound (66) is reacted with R^3-L wherein L is a suitable leaving group, such as halogen (e.g., Cl, Br, or I), $-OSO_2CF_3$ and the like. The reaction takes place in an organic solvent, such as tetrahydrofuran or benzene, containing a suitable base, such as NaH, LDA, or $LiN(Si(CH_3)_3)_2$. Preferably, tetrahydrofuran is used as the solvent and LDA is used as the base. The reaction is conducted at a temperature of about 0 to about 80°C.

In Step 4, compound (67) is reacted with R^4-L using the same procedure set forth in Step 3 in order to produce compound (68).

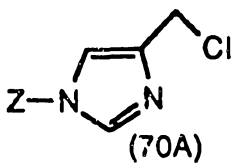
In Step 5, compound (69) is produced when compound (68) is first reacted with R^6-L and then reacted with R^7-L. Each reaction is conducted using the same procedure set forth in Step 3.

In Step 6, compound (71) is obtained when compound (69) is reacted with compound (70)



(70)

The reaction takes place in an organic solvent, such as tetrahydrofuran, DMF or benzene, containing a suitable base, such as NaH, LDA, or $LiN(Si(CH_3)_3)_2$. Preferably, tetrahydrofuran is used as the solvent and LDA is used as the base. The reaction is conducted at a temperature of about 0 to about 80°C. Compound (70) is obtained by reacting



(70A)

with $P(C_6H_5)_3$ in an organic solvent, such as methylene chloride, CH_3CN, tetrahydrofuran and the like, using a temperature of about 25 to about 50°C. In compounds (70) and (70A), Z represents trityl or SEM.

In Step 7, compound (72) is produced by using compound (71) and following the same procedures set forth in Steps 3, 4 and 5 of Preparation E.

In the steps of Preparation L, alkylations (i.e., Steps 3, 4 and 5) are only if desired and R^3, R^4, R^5, R^6, and R^7 are as defined for Formula I.

In the above processes, certain functional groups may be incompatable with some transformations described herein and consequently it is sometimes desirable and/or necessary to protect certain groups during the reactions. Certain protecting groups are employed in the above processes but, as those skilled in the art will recognize, other protecting groups may be used in their place. Conventional protecting groups are operable as described in Greene, T.W., and Wuts, P.G.M., "Protective Groups In Organic Synthesis," John Wiley & Sons, New York, 1991; the disclosure of which is incorporated herein by reference thereto. After the reaction or reactions, the protecting groups may be removed by standard procedures.

The compounds of this invention are either agonists or antagonists of the histamine H_3 receptor. The binding affinity of the compounds of the invention to the H_3 receptor may be demonstrated by the procedure described below:

<u>H_3 Receptor Binding Assay</u>

The source of the H_3 receptors in this experiment was guinea pig brain. The animals used weighed 400-600 g. The tissue was homogenized using a Polytron in a solution of 50 mM Tris, pH 7.5. The final concentration of tissue in the homogenization buffer was 10% w/v. The homogenates were centrifuged at 1000 x g for 10 min. in order

to remove clumps of tissue and debris. The resulting supernatants were then centrifuged at 50,000 x g for 20 min. in order to sediment the membranes, which were next washed 3 times in homogenization buffer (50,000 x g for 20 min. each). The membranes were frozen and stored at -70°C until needed.

All compounds to be tested were dissolved in DMSO and then diluted into the binding buffer (50 mM Tris, pH 7.5) such that the final concentration was 2 µg/mL with 0.1% DMSO. Membranes were then added (400 µg of protein) to the reaction tubes. The reaction was started by the addition of 3 nM [^{3}H]R-α-methylhistamine (8.8 Ci/mmol) or [^{3}H]-N-methylhistamine (80 Ci/mmol) and incubated at 30° for 30 min. Bound ligand was separated from unbound ligand by filtration, and the amount of radioactive ligand bound to the membranes was quantitiated by liquid scintillation spectrometry. All incubations were performed in duplicate and the standard error was less than 10% in all instances. Compounds that inhibited greater than 70% of the specific binding of radioactive ligand to the receptor were serially diluted to determine a K_i (µM). The results are given in Table 2.

In Table 2, the compound represented by (a*) is known in the art.

TABLE 2

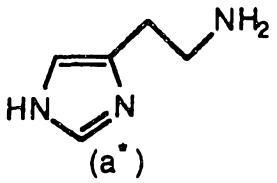
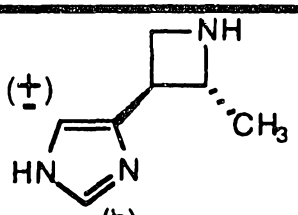
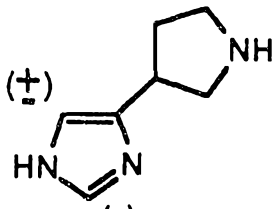
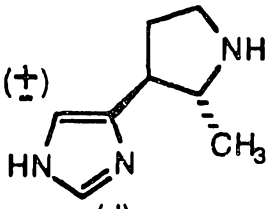
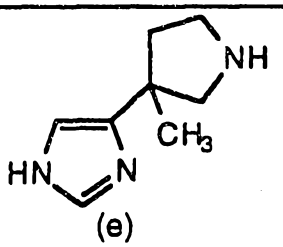
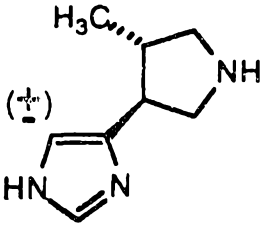
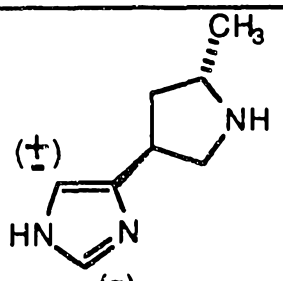
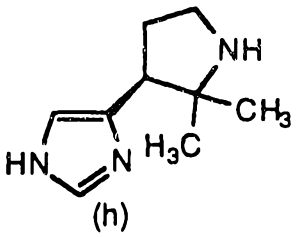
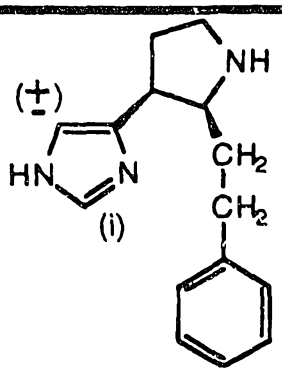
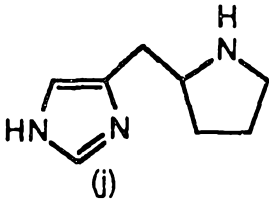
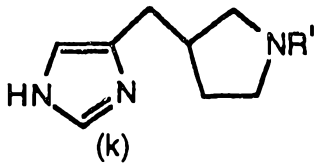
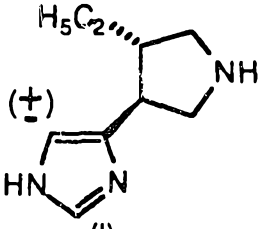
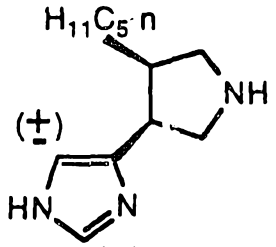
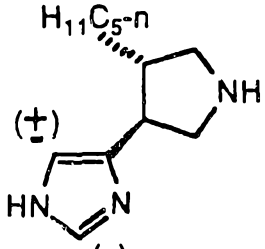
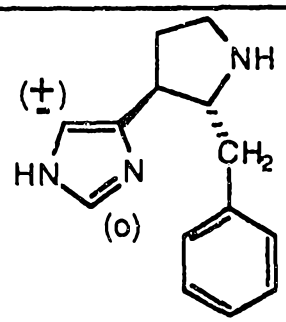
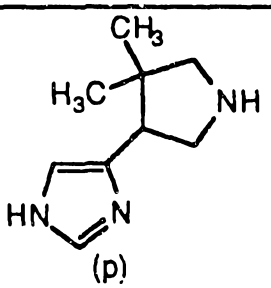
COMPOUND	H_3 Binding $K_i(\mu M)$	COMPOUND	H_3 Binding $K_i(\mu M)$
 (a*)	0.014	 (b)	0.007
 (c)	0.003	 (d)	0.006
 (e)	0.17	 (f)	0.008
 (g)	0.076	 (h)	0.066

TABLE 2-CONTINUED

COMPOUND	H_3 Binding $K_i(\mu M)$	COMPOUND	H_3 Binding $K_i(\mu M)$
 (i)	0.60	 (j)	0.11
 (k) R' is methyl	0.003	 (l)	0.15
 (m)	0.077	 (n)	0.45
 (o)	7%**	 (p)	68%**

In Table 2, the "**" values for compounds (o) and (p) represent the % inhibition at a concentration of 2 µg/mL. It is expected that at higher concentrations higher activities will be obtained.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg to 500 mg, according to the particular application.

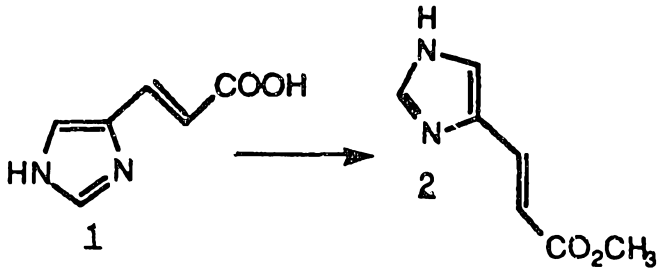
The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen is oral administration of from 1 mg to 2000 mg/day preferably 10 to 1000 mg/day, in one to four divided doses to achieve relief of the symptoms. The compounds are non-toxic when administered within this dosage range.

The invention disclosed herein is exemplified by the following preparative examples, which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

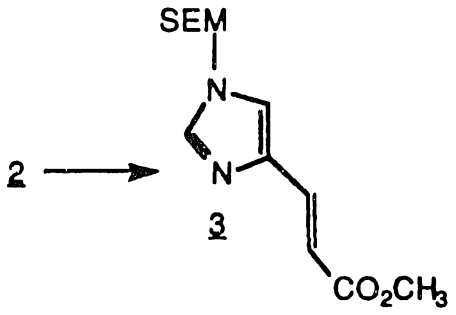
EXAMPLE 1

A. Preparation of Methyl Ester (2).



To a suspension of urocanic acid 1 (13.8 g, 100 mmol) in methanol (250 mL) was added concentrated sulfuric acid (10 mL) and the mixture was heated to reflux for 24 h. The mixture was cooled to 5°C and concentrated ammonium hydroxide (25 mL) was added slowly. The solvents were removed by rotary evaporation and to the residue was added water (50 mL) and ethyl acetate (750 mL). The mixture was shaken, the layers separated, and the aqueous layer was extracted with ethyl acetate (500 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated to give 2 as a white solid (14.9 g, 98%).

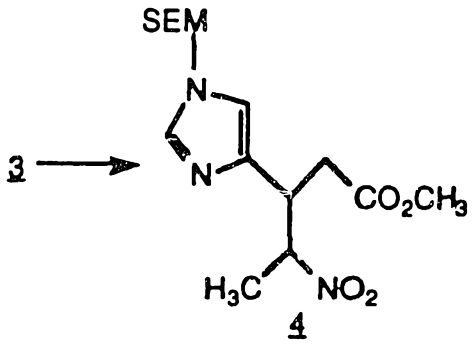
B. Preparation of (2-Trimethylsilyl)ethoxymethyl-imidazole (3).



To a suspension of the methyl ester 2 (12.2 g, 80.0 mmol) in tetrahydrofuran (80 mL) was added triethylamine (28 mL, 200 mmol)

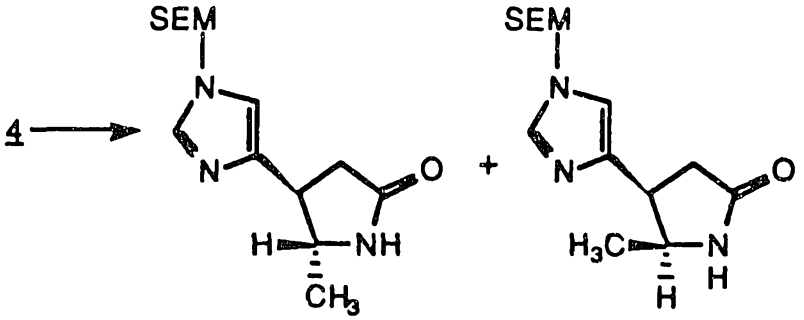
and then (2-trimethylsilyl)ethoxymethyl chloride (30 mL, 170 mmol). The mixture was stirred at room temperature for 1 h and then to this mixture was added 5% aqueous sodium hydroxide (200 mL) and methylene chloride (1200 mL). The mixture was shaken vigorously, the layers separated, and the aqueous layer was extracted with methylene chloride (1200 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated to give an orange, oily residue which was purified by flash chromatography (ethyl acetate) to give 3 as a slightly yellow solid (10.8 g, 48%).

C. Preparation of Nitro-Ester (4).



To a solution of unsaturated ester 3 (10.8 g, 38 mmol) in acetonitrile (25 mL) was added nitroethane (15 mL, 209 mmol) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (6 mL, 40 mmol). The mixture was stirred at room temperature for 72 h, the solvents were removed by rotary evaporation and the dark, oily residue was purified by flash chromatography (ethyl acetate) to give the nitro-ester 4 as a mixture of diastereomers (13.3 g, 97%).

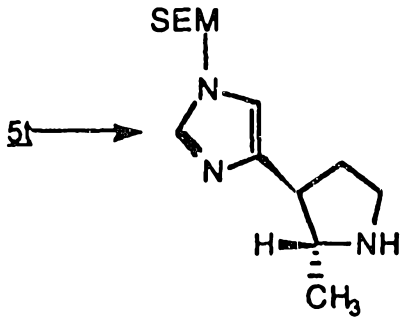
D. Preparation of Lactams (5t) and (5c).



5t 5c

A mixture of the nitro-ester 4 (8.3 g, 23 mmol) and Raney nickel (8 g) in absolute ethanol (60 mL) was shaken under 60 psi of hydrogen at 55°C in a Parr apparatus for 6 h. The mixture was filtered and the filtrate was evaporated to give an oily residue which was purified by flash chromatography (a: 5% MeOH/NH_3 in CH_2Cl_2, b: 7% MeOH/NH_3 in THF:Hexane, 2:1) to give two compounds; the first compound to elute was the *trans*-diastereomer 5t (2.64 g, 39%). The second compound to elute was the *cis*-diastereomer 5c (1.67 g, 26%).

E. Preparation of pyrrolidine (6t).

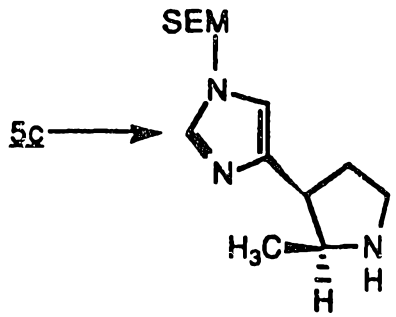


6t

To a solution of the *trans*-lactam 5t (2.60 g, 8.8 mmol) in tetrahydrofuran (175 mL) was added a solution of lithium aluminum hydride in diethyl ether (1.0 M, 44.0 mL, 44 mmol). The mixture was

stirred at room temperature for 4 h and to the reaction mixture was added diethyl ether (440 mL) and saturated aqueous sodium sulfate (7 mL) dropwise. The mixture was dried over anhydrous sodium sulfate, filtered, and evaporated to give an oily residue which was purified by flash chromatography (gradient elution; CH_2Cl_2: MeOH/NH_3, 7:1 to 5:1) to give 6t as a colorless oil (1.15 g, 46%).

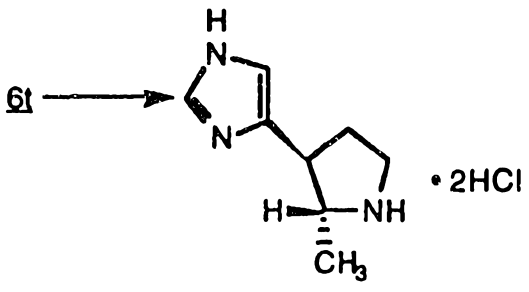
F. Preparation of pyrrolidine (6c).



6c

The *cis*-lactam 5c (0.60 g, 2.0 mmol) was treated in the same manner as described for the preparation of pyrrolidine 6t. The crude reaction product was purified by flash chromatography (gradient elution; CH_2Cl_2: MeOH/NH_3, 6:1 to 4:1) to give 6c as a colorless oil (0.36 g, 63%).

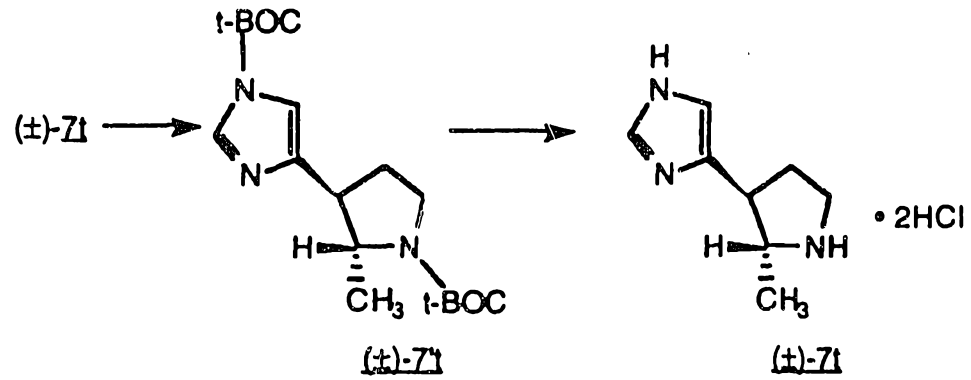
G. Preparation of ((±)-7t).



(±)-7t

To a solution of the pyrrolidine 6t (563 mg, 2.0 mmol) in 95% ethanol (3 mL) was added concentrated hydrochloric acid (1 mL) and the mixture was heated to reflux for 16 h. The solvents were removed by rotary evaporation and to the residue was added 1 N aqueous hydrochloric acid (8 mL). This solution was extracted with ethyl acetate (3 x 4 mL) and the aqueous layer was concentrated by rotary evaporation. To the residue was added distilled water (15 mL) and the resulting solution was filtered through a glass wool plug. The filtrate was concentrated by rotrary evaporation to give (±)-7t as a cream-colored solid (395 mg, 88%).

H. Purification of ((±)-7t).



To a solution of (±)-7t (336 mg, 1.5 mmol) in dimethylformamide (5.0 mL) was added triethylamine (1.05 mL, 7.53 mmol) and then a solution of di-*tert*-butyl dicarbonate $(t\text{-BOC})_2O$ (720 mg, 3.3 mmol) in dimethylformamide (1 mL). The mixture was stirred at room temperature for 2 h, the solvents were removed by vacuum distillation (1.0 mm Hg) and the resulting residue was purified by flash chromatography (gradient elution; EtOAc: hexane, 1:1 to 2:1) to give the corresponding di-*t*-BOC derivative (±)-7t (488 mg) as a white solid. This material was dissolved in ethyl acetate (3 mL), cooled to 5°C, and to this solution was added a saturated solution of hydrogen chloride in ethyl acetate (14 mL). The mixture was gradually warmed to room temperature (30 min) and stirred at this temperature for 16 h. The ethyl

acetate was removed from the precipitated product by pipet and the precipitate was dried under high vacuum (0.1 mm Hg) to give (±)-7t as a white solid (286 mg, 85% recovery); MS (CI) 152 (M + 1).

I. Resolution of ((±)-7t.

The racemic (±)-7't was resolved by High Performance Liquid Chromatography using a Daicel Chiralcel OJ chiral chromatography column (2.0 cm x 50.0 cm, 4 % isopropanol in hexane). Multiple injections (13 injections of about 150 mg each) provided the levorotatory enantiomer (-)-7't :

950 mg; $[\alpha]_D^{26}$ = -12.8°, c = 0.50, $CHCl_3$, and

the dextrorotatory enantiomer (+)-7't:

904 mg; $[\alpha]_D^{26}$ = +12.0°, c = 0.50, $CHCl_3$.

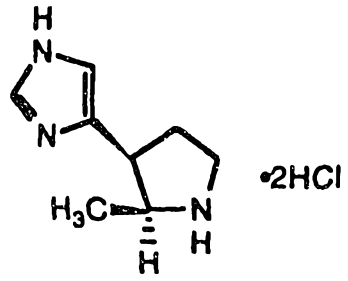
Treatment of (-)-7't with a saturated solution of hydrogen chloride in ethyl acetate as described above for the purification of (±)-7t provided (-)-7t:

$[\alpha]_D^{26}$ = -34.6°, c = 1.00, H_2O.

Similar treatment of (+)-7't gave (+)-7t:

$[\alpha]_D^{26}$ =+39.4°, c = 1.00, H_2O.

I. Preparation of ((±)-7c).



(±)-7c

The *cis*-pyrrolidine 6c (394 mg, 1.4 mmol) was treated as described for the preparation of (±)-7t to give (±)-7c as a cream-colored solid (288 mg, 95%). Compound (±)-7c (224 mg, 1.0 mmol) was purified as described for the purification of (±)-7t to give (±)-7c as a white solid (177 mg, 79% recovery); MS (CI) 152 (M + 1).

Compounds 8, 9, 10t, 10c, 11t, 11c, 12t and 12c were prepared using the procedure described above for (±)-7t and 7c. The procedure is summarized below, A and B, and hence the compounds produced, are defined in Table 3.

K. Resolution of (±)-(7c).

In a manner similar to that described in Example 1, Steps H and I, racemic (±)-7c was resolved by High Performance Liquid Chromatography using a Daicel Chiralcel OD chiral chromatography column (5.0 cm x 50.0 cm, 1% isopropanol in hexane) followed by deprotection with a saturated solution of hydrogen chloride in ethyl acetate to give the levorotatory enantiomer (-)-7c:

$$[\alpha]_D^{26} = -35.7°, c = 1.00, H_2O$$

and the dextrorotatory enantiomer (+)-7c:

$$[\alpha]_D^{26} = +33.2°, c = 1.00, H_2O.$$

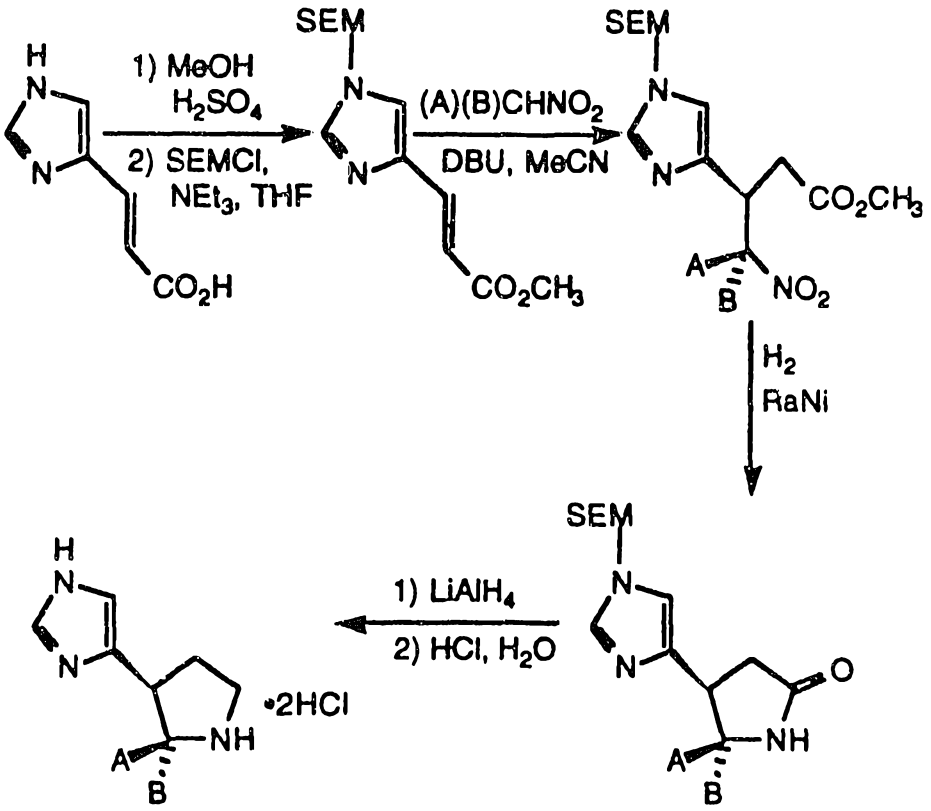
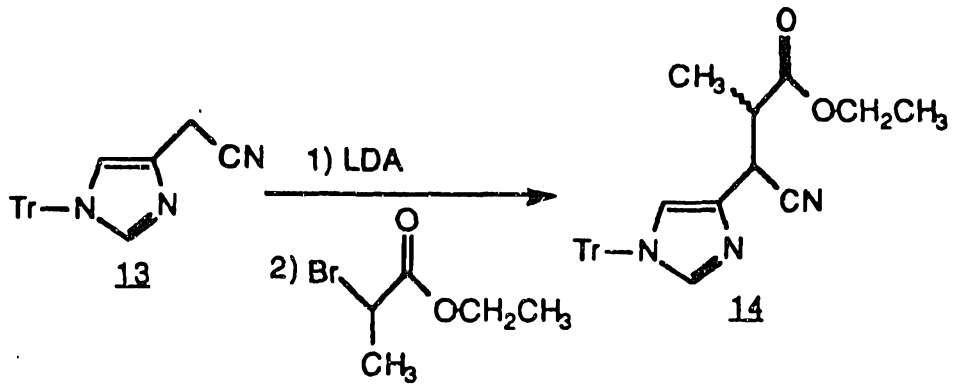


TABLE 3

COMPOUND	A	B	MS(CI)(M + 1)
8	H	H	138
9	$-CH_3$	$-CH_3$	166
10t	H	$-CH_2CH_3$	166
10c	$-CH_2CH_3$	H	166
11t	H	$-CH_2C_6H_5$	228
11c	$-CH_2C_6H_5$	H	228
12t	H	$-CH_2CH_2C_6H_5$	242
12c	$-CH_2CH_2C_6H_5$	H	242

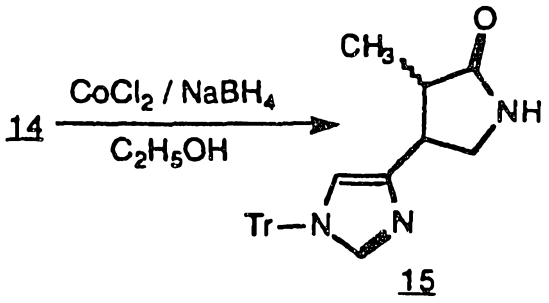
EXAMPLE 2

A.



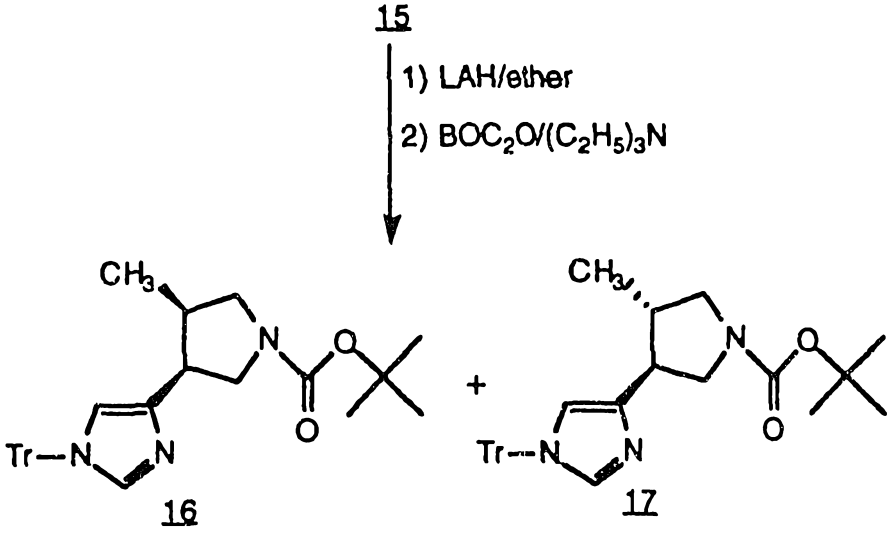
To a cooled (0°C) solution of diisopropylamine (4 mmol, 561 µL) in dry THF (7 mL) was added n-BuLi (n-butyllithium) (2.5 mL of a 1.6 M solution in hexane) dropwise. After 10 minutes at this temperature, the solution of LDA was cooled to -30°C and a solution of 1 trityl-4-cyanomethyl imidazole 13 (4 mmol, 1.4 g, Tr = trityl)) in THF (6 mL) was added dropwise. After an additional 30 minutes at this temperature, a solution of ethyl-2-bromopropionate (4 mmol; 520 µL) in THF (5 mL) was added dropwise. The reaction was slowly warmed to RT (room temperature) (45 minutes) and quenched with 15 mL H_2O. The reaction was extracted with diethyl ether (3 x 25 mL) and the combined organic fractions were washed with brine, dried with $MgSO_4$, and filtered. Concentration on the rotovap yielded 1.65 g of an oil which was purified via column chromatography (75:25 hexane:ethyl acetate). 0.75 g (42%) of 14 was obtained as a mixture of diastereomers. MS (CI) 450 (M+1).

B.



To a solution of 14 (6.23 mmol; 2.8g) and $CoCl_2$•6 H_2O (6.23 mmol; 1.48 g) in absolute ethanol (150 mL) was added $NaBH_4$ (31.2 mmol; 1.18g) portionwise over 30 minutes. After 4 hours, the black reaction mixture was concentrated to 1/3 the volume, shaken with ice-cold 3N HCl (50 mL) to dissolve the solids and rapidly basified to pH=9 with concentrated NH_4OH. The crude reaction was extracted with ethyl acetate (3 x 150 mL), and the combined organic layers were washed with brine, and dried ($MgSO_4$). Purification on a flash column (250 g SiO_2; 93:7 CH_2Cl_2: MeOH/NH_3) yielded 1.53 g (60%) of 15 as a white solid.

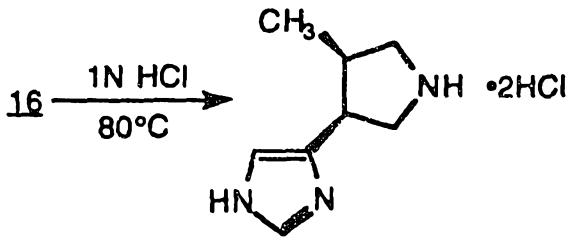
C.



To a solution of lactam 15 (2.46 mmol; 1 g) in THF (30 mL) was added lithium aluminum hydride in diethyl ether (1M; 12.3 mL). The reaction was heated to 50°C for 5.5h, cooled to room temperature, diluted with diethyl ether, and quenched by careful dropwise addition of saturated aqueous Na_2SO_4. When H_2 evolution ceased, an additional 50 mL diethyl ether and solid Na_2SO_4 was added. The organic layer was filtered and concentrated to obtain 870 mg of a solid.

To a solution of the solid from the previous step in THF (20 mL) was added triethylamine (4.4 mmol; 614 µL) followed by di-t-butyl dicarbonate (2.75 mmol; 600 mg). After 2.5h, brine was added and the reaction was extracted into EtOAc (100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. 600 mg (48%) of 16 and 660 mg (52%) of 17 were obtained after chromatography on a flash column (150 g SiO_2; 65:35 EtOAc:Hexane).

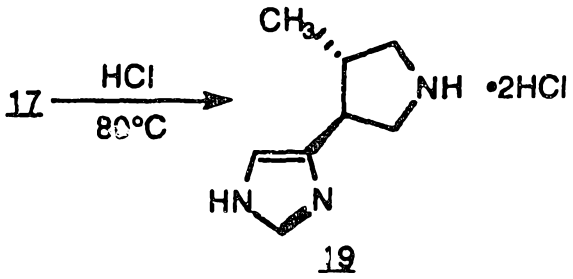
D.



(±)-18

A suspension of 16 (1.2 mmol; 600 mg) in 1NHCl (30 mL) was heated to 80°C for 1 hour. Compound 16 slowly dissolved and was replaced by a new solid. The reaction was cooled, filtered and the aqueous layer was concentrated. Compound (±)-18, 170 mg, was obtained as a clear glass (64%) MS (EI) 151 (M^+).

In a similar manner, 17 yielded (±)-19 (175 mg, 60%) MS (EI) 151 (M^+).



E. Resolution of (±)18 and (±)19.

In a manner similar to that described in Example1, Steps H and I, racemic (±)18 and (±)19 were resolved by High Performance Liquid Chromatography on a Chiralcel OD preparative column (2 x 50 cm) and gave after deprotection:

(+)-18 $[\alpha]_D^{21.5}$ = +37.6°, c = 0.43, MeOH

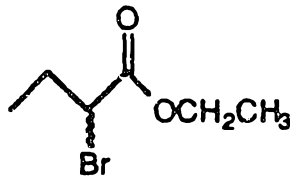
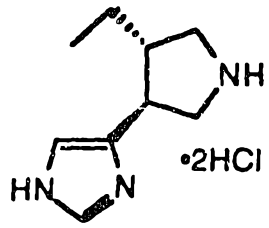
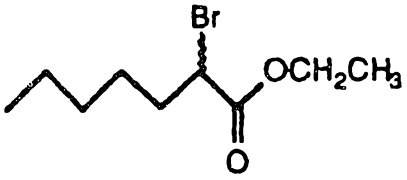
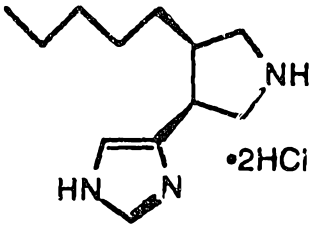
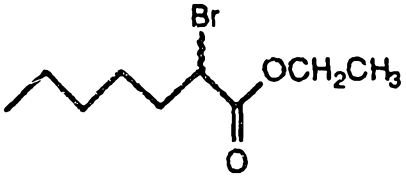
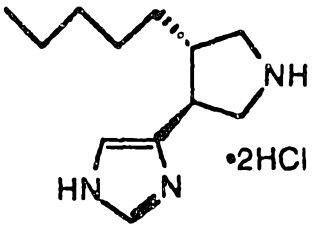
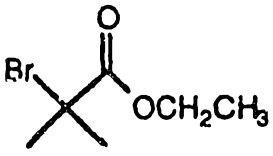
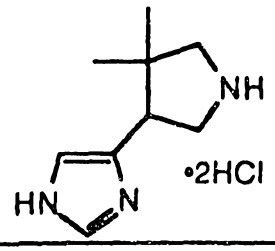
(-)-18 $[\alpha]_D^{22}$ = -32.2°, c = 0.43, MeOH

(+)-19 $[\alpha]_D^{22}$ = +39.0°, c = 0.18, MeOH and

(-)-19 $[\alpha]_D^{22}$ = -36.0°, c = 0.20, MeOH.

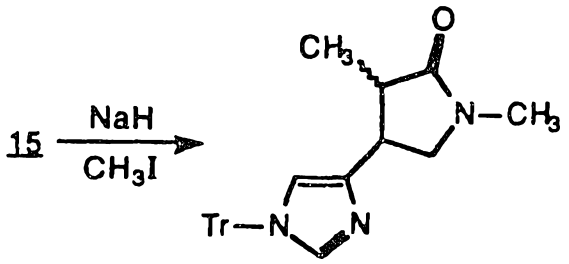
By using the route described above for preparing (±)-18, the compounds listed in Table 4 were prepared:

TABLE 4

STARTING MATERIAL	PRODUCT	MS
		166 (M+1) (CI)
		207 (M+) (EI)
		207 (M+) (EI)
		166 (M+1) (CI)

EXAMPLE 3

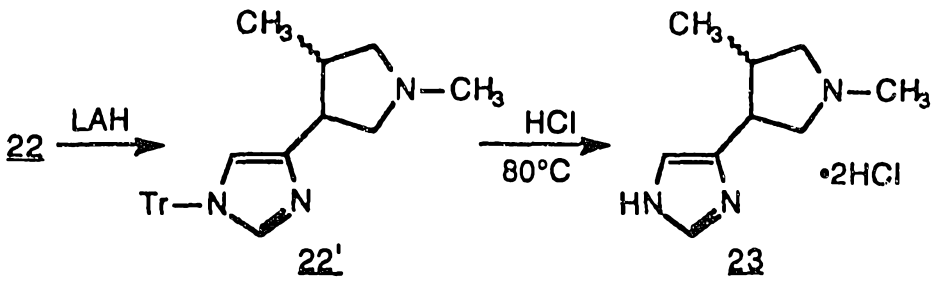
A.



22

To a solution of 15 (1.4 mmol; 570 mg; see Step B of Example 2) in DMSO (10 mL) at room temperature was added NaH (1.4 mmol; 56 mg of a 60% dispersion in mineral oil). After 1.5 hours, CH_3I (1.4 mmol 87 µL) was added, and the reaction was stirred overnight. The reaction was diluted with H_2O and extracted into diethyl ether (3 x 25 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified on a flash column (100 g SiO_2; 95:5 CH_2Cl_2: CH_3OH/NH_3). Compound 22, 290 mg (49%), was obtained.

B.

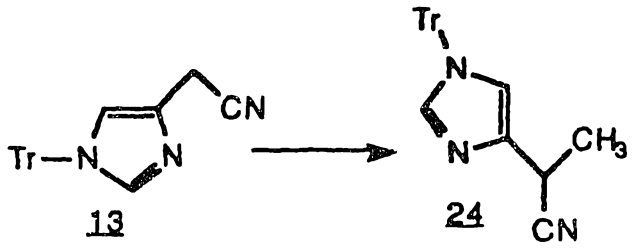


22' 23

By using the route described in Example 2, Steps C and D, compound 22 was converted to 23 (62 mg, 67%); MS (CI) 166 (M + 1).

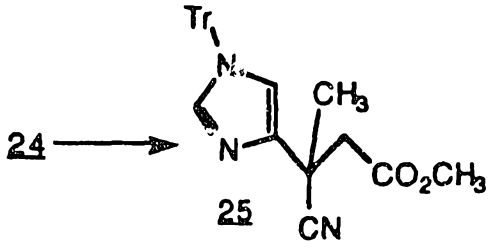
EXAMPLE 4

A. Preparation of α-methyl-nitrile (24).



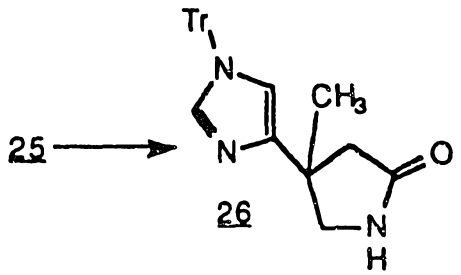
To a solution of diisopropylamine (0.775 mL, 5.5 mmol) in tetrahydrofuran (15 mL) at -78°C was added a solution of n-butyllithium in hexane (2.5 M, 2.1 mL, 5.25 mmol) and the mixture was stirred at -78°C for 1 h. To this was added a solution of the nitrile 13 (1.75 g, 5.0 mmol, see Step A of Example 2) in tetrahydrofuran (10 mL) and the mixture was stirred at -78°C for 1 h. To this solution was added a solution of methyl iodide (325 µL, 5.2 mmol) in tetrahydrofuran (2.5 mL), the mixture was stirred at -78°C for 30 min and then warmed to 0°C (1 h). To the mixture was added saturated aqueous ammonium chloride (2 mL), the solvents were removed by rotary evaporation and to the residue was added methylene chloride (200 mL), water (25 mL) and saturated aqueous sodium bicarbonate (25 mL). The mixture was shaken vigorously, the layers separated and the organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to give a yellow solid residue. This crude product was purified by flash chromatography (hexane:isopropanol, 4:1) to give the α-methyl-nitrile 24 as an off-white solid (1.33 g, 73%).

B. Preparation of nitrile-ester (25).



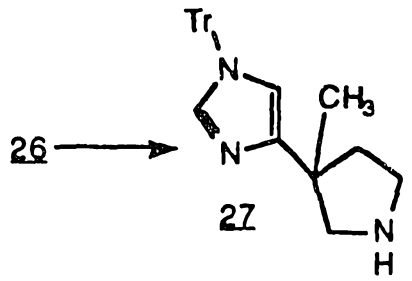
To a solution of diisopropylamine (0.550 mL, 3.9 mmol) in tetrahydrofuran (12 mL) at -78°C was added a solution of n-butyllithium in hexane (2.5 M, 1.50 mL, 3.75 mmol) and the mixture was stirred at -78°C for 1 h. To this was added a solution of the α-methyl-nitrile 24 (1.27 g, 3.5 mmol) in tetrahydrofuran (10 mL) and the mixture was stirred at -78°C for 1 h. To this solution was added a solution of ethyl bromoacetate (420 µL, 3.79 mmol) in tetrahydrofuran (2.0 mL), the mixture was stirred at -78°C for 1 h and then warmed to 0°C (1 h). To the mixture was added saturated aqueous ammonium chloride (1.5 mL), the solvents were removed by rotary evaporation and to the residue was added methylene chloride (200 mL) and saturated aqueous sodium chloride (40 mL). The mixture was shaken vigorously, the layers separated and the organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to give a yellow oily residue. This crude product was purified by flash chromatography (hexane:acetone, 3:1 to 2:1) to give the nitrile-ester 25 as a colorless glass (1.44 g, 90%).

C. Preparation of Lactam (26).



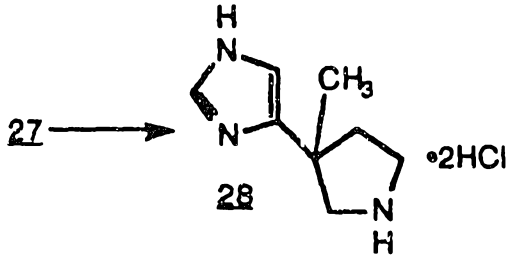
To a solution of the nitrile-ester 25 (1.39 g, 3.1 mmol) in absolute ethanol (70 mL) was added a solution of cobalt dichloride hexahydrate (736 mg, 3.1 mmol) in absolute ethanol (10 mL) and then portionwise (5 min) sodium borohydride (700 mg, 18.5 mmol). The mixture was stirred at room temperature for 2 h, the solvents were removed by rotary evaporation and to the black residue was added cold (5°C) 3 M aqueous hydrochloric acid (34 mL). The mixture was shaken until the black precipitate dissolved (5 min) and then to this mixture was added concentrated ammonium hydroxide (10 mL). This solution was extracted with ethyl acetate (2 x 250 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated to give an off-white solid residue which was purified by flash chromatography (gradient elution: 8% to 10% CH_3OH/NH_3 in CH_2Cl_2) to give the lactam 26 as a white solid (1.05 g, 83%).

D. Preparation of the Pyrrolidine (27).



The lactam 26 (1.05 g, 2.58 mmol) was treated with a solution of lithium aluminum hydride in diethyl ether (1.0 M, 13.0 mL, 13.0 mmol) as described for the preparation of the pyrrolidine 61 (see Example 1, Step E). The crude product was purified by flash chromatography (gradient elution: CH_2Cl_2: CH_3OH/NH_3, 8:1 to 7:1 to 6:1) to give the pyrrolidine 27 as a colorless glass (720 mg, 71%).

E. Preparation of Compound (28).



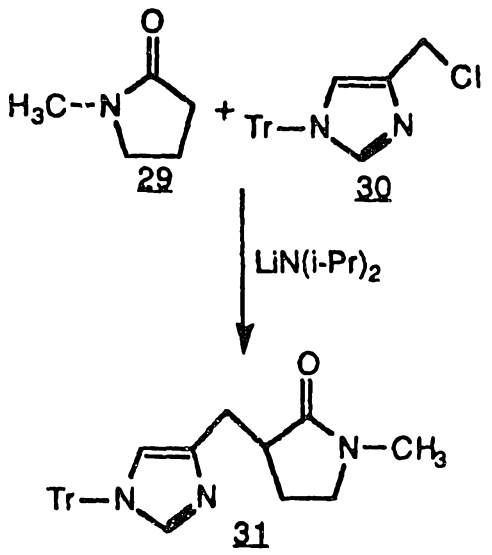
A suspension of the pyrrolidine 27 (750 mg, 1.91 mmol) in 1 N aqueous hydrochloric acid (15 mL) was heated to reflux for 1 h. The white precipitate that formed during the course of the reaction was removed by filtration and the aqueous filtrate was extracted with ethyl acetate (2 x 5 mL). The aqueous layer was concentrated by rotary evaporation to give compound 28 as an off-white solid (390 mg, 91%).

F. Purification of Compound (28).

Compound 28 (75 mg, 0.33 mmol) was purified as described for the purification of Compound (±)-71 (see Example 1, Step H) to give Compound 28 as a white solid (57 mg, 76% recovery); MS (CI) 152 (M + 1).

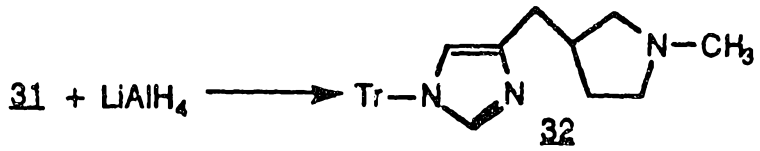
EXAMPLE 5

A.



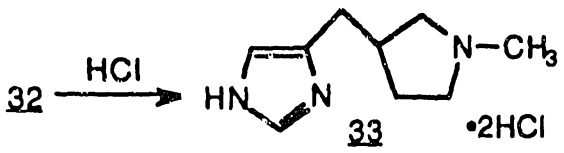
To a solution of 1.08 mL of freshly distilled N,N-diisopropylamine in 1 mL of anhydrous THF was added 3.1 mL of 2.5 M n-butyllithium at 0°C under nitrogen. The resulting solution was stirred at 0°C for 40 minutes (resulting in the production of lithium diisopropylamide ($LiN(i\text{-}Pr)_2$)), cooled to -23°C and then 0.672 mL of N-methyl-2-pyrrolidinone 29 was added slowly. The solution was stirred for 0.5 hours at -23°C and an additional 1 hour at -78°C. A solution of 2.69 g of 4-chloromethyl-(N-trityl)imidazole 30 in 14 mL of anhydrous THF was then added dropwise. The resulting solution was stirred for 4 hours at -78°C and slowly warmed to room temperature. After a couple of hours of stirring at room temperature, the reaction mixture was quenched by water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated to give crude product. The crude product was purified by flash chromatography on SiO_2 (1% to about 5% of ammonia saturated methanol in CH_2Cl_2) to give 1.77 (60% yield) of compound 31.

B.



To a solution of 1.54 g of 31 in 8 mL of anhydrous THF was added 11.34 mL of lithium aluminum hydride solution (1.0 M in diethyl ether) slowly. The resulting solution was stirred at room temperature for 2 hours, and 110 mL of diethyl ether was added. Saturated aqueous Na_2SO_4 solution was carefully added to the above mixture till hydrogen evolution ceased. The organic fraction was separated, and the aqueous solution was basified with K_2CO_3 and extracted with ethyl acetate many times. The combined organic solutions were washed with brine, dried over anhydrous K_2CO_3, and then concentrated to give a crude product. The crude product was purified by flash chromatography on SiO_2 (5% CH_3OH (NH_3) in CH_2Cl_2) to give 1.273 g (85% yield) of compound 32.

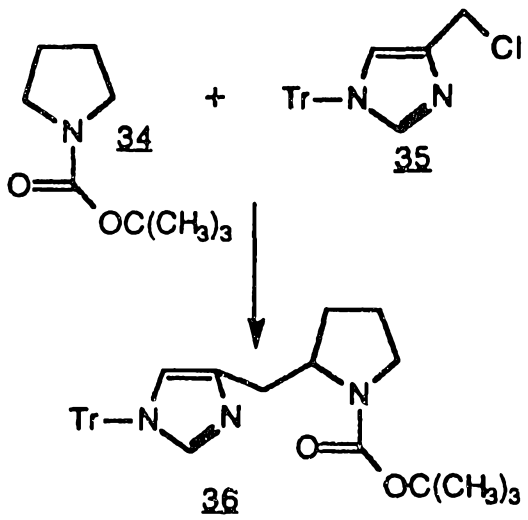
C.



A solution of 1.2 g of 32 in 100 mL of 0.5N aqueous hydrochloric acid was heated in a 90°C oil bath for 30 minutes. After the solution was cooled to room temperature, the mixture was extracted with diethyl ether (4 x 50 mL). The aqueous solution was concentrated under vacuum to yield crude product which was then recrystallized from 2-propanol/diethyl ether to give 0.5 g (85%) of compound 33; MS (FAB) 166 (M + 1).

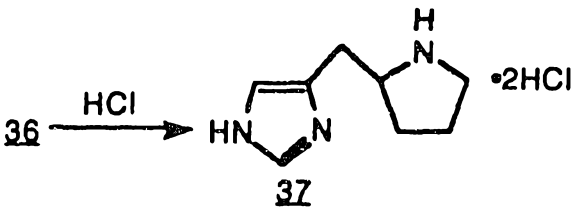
EXAMPLE 6

A.



To a solution of 1.194 g of compound of formula 34 and 2.49 mL of tetramethylethylenediamine in 7.5 ml of anhydrous diethyl ether was added 6.06 ml of 1.3 N sec-butyllithium at -78°C. The resulting solution was stirred for 3 hours 45 minutes at -78°C, and a solution of 1.074 g of chloromethyl (N-trityl)imidazole 35 in 4 ml of tetrahydrofuran was added dropwise over 15 minutes. After 15 minutes of stirring at -78°C, the reaction mixture was slowly warmed to room temperature for over 1 hour. Saturated aqueous NH_4Cl solution was added. The mixture was extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by flash chromatography on SiO_2 to give 0.23 g (17%) of product 36.

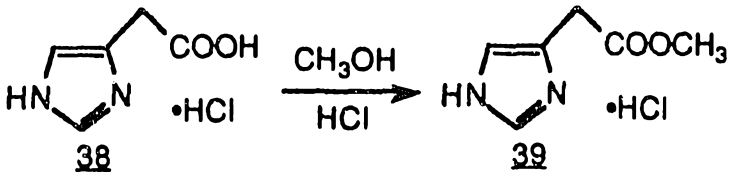
B.



A solution of 0.23 g of 36 in 20 mL of 0.5 N HCl was heated to reflux for 45 minutes. After cooling to room temperature, the mixture was extracted with diethyl ether three times. The aqueous solution was then concentrated and the crude product was crystallized with CH_3OH/diethyl ether to give 0.075 g (70% yield) of the product 37; MS (CI)152 (M+ 1).

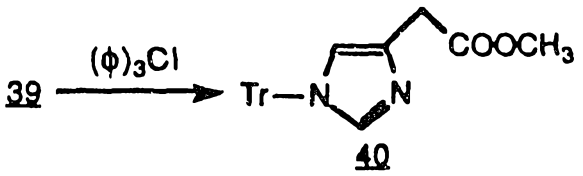
EXAMPLE 7

A.



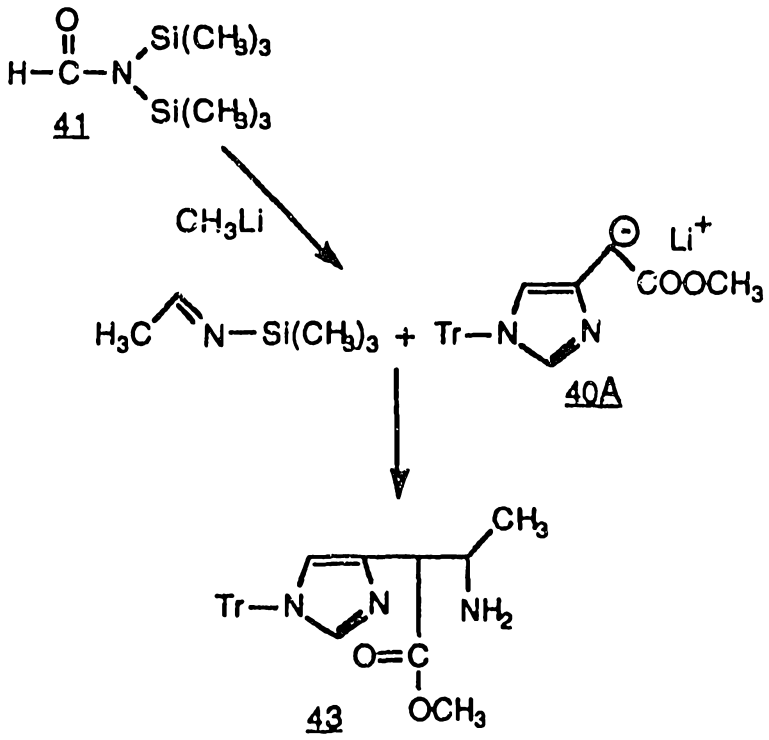
To a solution of 11.59 g of imidazole acetic acid hydrochloride 38 in 100 mL of anhydrous methanol was added 1 mL of concentrated HCl. The resulting mixture was refluxed for 5.5 hours, and then cooled to room temperature. After concentration of the solvent, 11.9 g (95%) of the product 39 was isolated.

B.



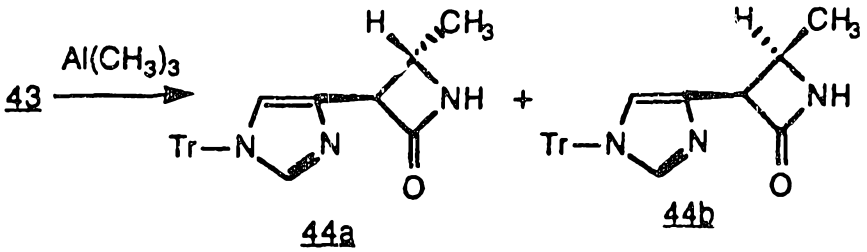
To a solution of 7.8 g of 39 in 70 mL of anhydrous DMF at 0°C was added 12.94 g of trityl chloride ($(\phi)_3Cl$) and 18.4 mL of triethyl amine. The resulting solution was stirred at room temperature for 24 hours, and the solvent was removed under vacuum. The residue was purified by flash chromatography on SiO_2 (eluting solvent: CH_2Cl_2 and increase polarity slowly by addition of ethyl acetate) to give 16.1 g of product 40 (95% yield).

C.



To a solution of 8.15 mL of compound 41 in 50 mL of anhydrous THF was added 26.25 mL of 1.4M methyllithium at -78°C. The above solution was stirred for 1 hour at -78°C, and a solution of 40A (prepared by the addition of 25 mL of 1M $LiN(Si(CH_3)_3)_2$ to a solution of 9.55 g of 40 in 100 mL of anhydrous THF at -78°C and stirring the solution for 2 hours at -78°C before transferring) was added by cannula over 30 minutes. Ten minutes later, 4.6 mL of $BF_3 \cdot (C_2H_5)_2O$ was added to the above mixture, and the resulting solution was stirred at -78°C for 2 hours. The reaction mixture was slowly warmed up to room temperature (over 2 hours 45 minutes), and then saturated aqueous $NaHCO_3$ solution was added. The organic layer was separated and the aqueous layer was extracted with EtOAc. The organic layer and EtOAc extracts were combined and the combined organic solution was washed with brine, dried over $MgSO_4$ and then concentrated. The residue was purified by flash chromatography (silica gel was deactivated with triethylamine, eluting solvent: 1 to 10 % of CH_3OH in EtOAc) to give compound 43 (6.4 g; 60% yield).

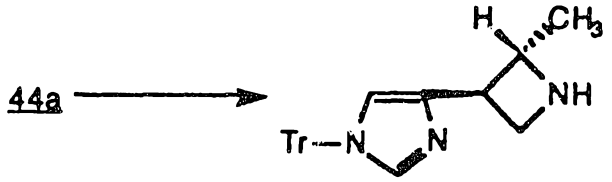
D.



To a solution of 6.4 g of 43 in 250 mL of anhydrous methylene chloride was added 11.3 mL of 2.0M trimethyl aluminum. The resulting mixture was stirred at room temperature for 45 minutes, heated to reflux (5 hours), cooled to 0°C, and to this mixture was added saturated aqueous $NaHCO_3$ solution. The organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel deactivated with

triethylamine; eluting solvent EtOAc to 1 to about 2% CH_3CH in EtOAc) to give 0.91 g of 44a (trans isomer) and 0.39 g of 44b (cis isomer).

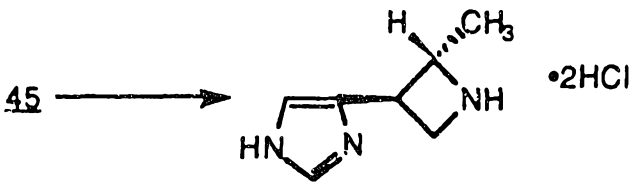
E.



45

To a solution of 0.3225 g of 44a in 8 mL of anhydrous THF was added 3.28 mL of 1M solution of diisobutylaluminum hydride in toluene dropwise at room temperature. After the addition was complete, the solution was refluxed for 2 hours and cooled to room temperature. Water (2 mL) was added slowly to the above solution and 20 ml of methylene chloride was added to the resulting mixture. The mixture was vigorously stirred until a white solid precipitated out. Filtration and concentration gave crude product, which was purified by preparative TLC (deactivated with triethylamine; eluting solvent 7.5% CH_3OH in CH_2Cl_2) to give 0.187 g (60% yield) of 45.

F.



46

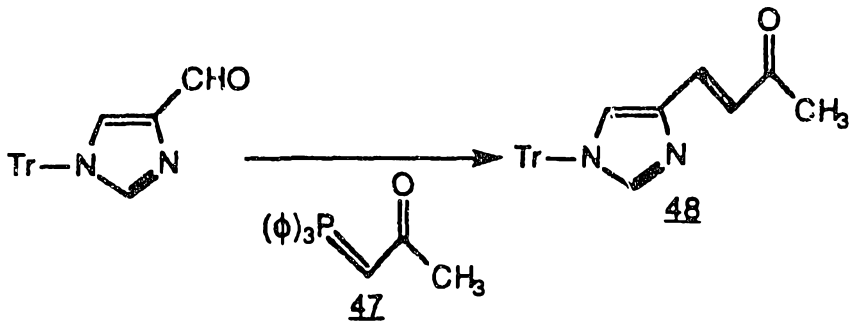
A solution of 0.148 g of 45 in 12 mL of 0.5N HCl was heated in an oil bath at 90°C for 0.5 hours. The solution was then cooled to room temperature. The mixture was extracted with diethyl

ether three times, and the aqueous solution was concentrated to give a crude product. The crude product was recrystallized in CH_3OH/diethyl ether to give 70 mg (85%) of 46; MS (CI) 138 (M + 1).

By following the procedures set forth in Example 7, Steps E and F, compound 44b can be converted to the cis isomer of 46.

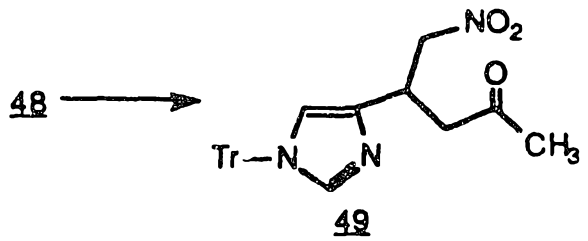
EXAMPLE 8

A



A mixture of 9.78 g of 4-(N-tritylimidazoyl) carboxaldehyde and 9.55 g of Wittig reagent 47 in 30 mL of anhydrous THF was refluxed for 21 hours. An additional 4.8 g of Wittig reagent 47 and 10 mL of THF were added to the above mixture; the resulting mixture was continually refluxed for 30 hours. The solvent was concentrated. The residue was dissolved in CH_2Cl_2 and washed with water. The organic layer was separated and concentrated. The residue was purified by flash chromatography on SiO_2(CH_2Cl_2/EtOAc) to give 6.14 g (81% yield) of 48.

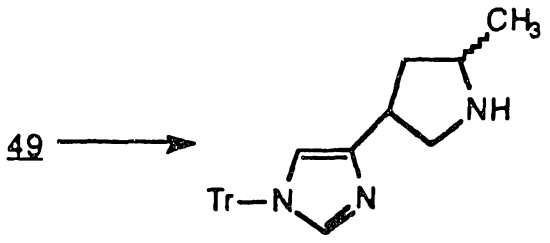
B.



49

To a mixture of 4.5 g of ketone 48 in 18 mL of CH_3CN was added 6.62 mL of nitromethane and 75 mL of THF. To the above homogenous solution was added 1.835 mL of DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene) and the resulting solution was stirred at room temperature overnight (18 hours). The reaction mixture was poured into ice cold 0.1N HCl solution and the mixture was extracted with EtOAc. The combined EtOAc extracts were washed with brine, dried over $MgSO_4$ and concentrated to give 4.54 g (87%) of product 49.

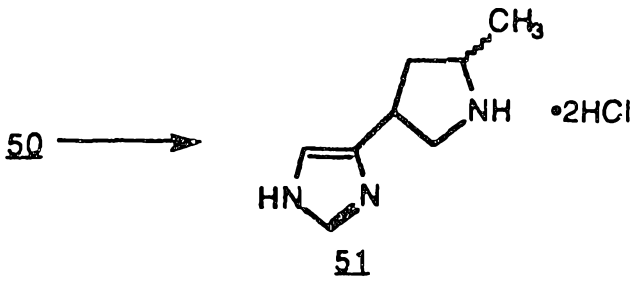
C.



50

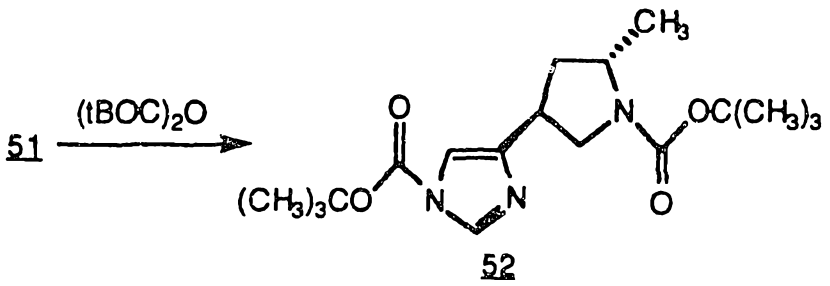
Compound 49 was reduced by mixing 1.5 g of 49, 1.5 g of Raney-Ni and 1.5 g of anhydrous Na_2SO_4 in 50 mL of absolute ethanol and subjecting the resulting mixture to 60 psi. of H_2 for 26 hours. The reaction mixture was filtered through a pad of celite and the pad was washed with ethanol and CH_2Cl_2. The filtrate was concentrated to yield 0.83 g of 50 (62%).

D.



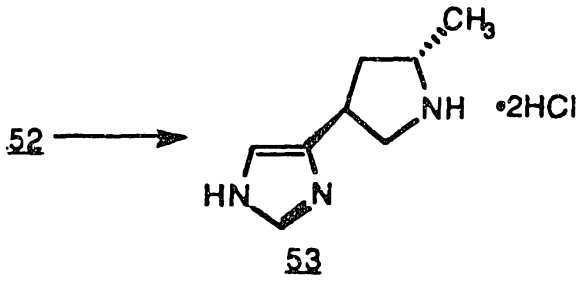
A solution of 0.83 g of 50 in 30 mL of 0.5N HCl was heated to reflux for 45 minutes. After the mixture was cooled to room temperature, it was extracted with diethyl ether. The aqueous layer was evaporated to dryness to give 0.43 g of crude product 51.

E.



To a mixture of 0.34 g of 51 in 5 mL of anhydrous DMF was added 1.69 mL of triethylamine; the mixture was stirred for 5 minutes and 0.77 mL of di-tert-butyldicarbonate ($(tBOC)_2O$)was added. The reaction mixture was stirred for 18 hours at room temperature, filtered and concentrated. The residue was dissolved in water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by preparative TLC (1:1 EtOAc/hexane) to give 0.13 g (24% yield) of 52; MS (m/e) 352 (M+1).

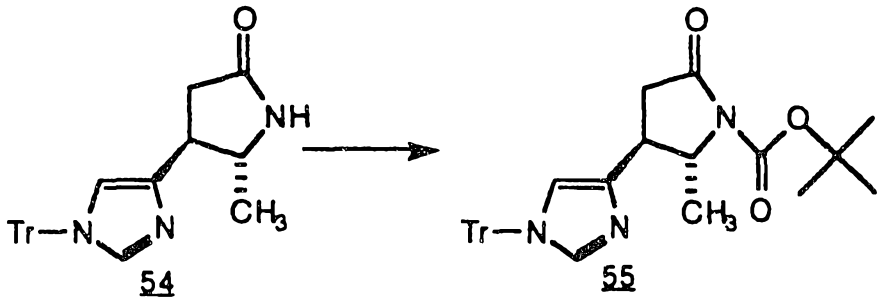
F.



A solution of 0.13 g of 52 in 6 mL of EtOAc (saturated with HCl) was stirred for 45 minutes at 0°C, then the solvent was evaporated under vacuum. The residue was recrystallized in 2-propanol/diethyl ether to give 0.067 (81% yield) of 53; MS (CI) 152 (M+1).

EXAMPLE 9

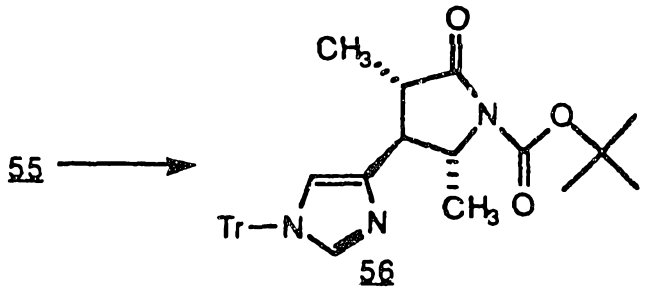
A.



To a solution of lactam 54 (10 mmole; 4.07g) (synthesized in a manner similar to 51) in dry THF (55mL) at -78°C was added a solution of LDA (11 mmol, 1.18g) in THF (15 mL). After 45 minutes at this temperature, the reaction was warmed to room temperature for 20 minutes and then recooled to -78°C. A solution of $(tBOC)_2O$ (11 mmol, 2.41g) in THF (15mL) was added and the reaction was slowly warmed to room temperature. The reaction was then quenched with water and extracted into diethyl ether. The combined ether extracts were washed

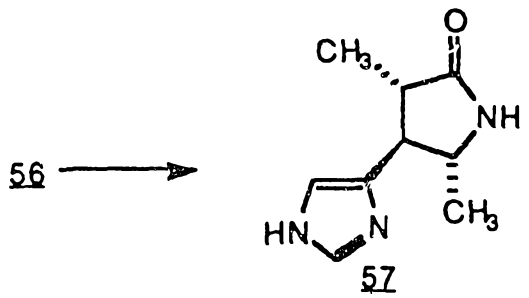
with brine and dried ($MgSO_4$). Concentration yielded a solid that was recrystallized from hexane: 2-propanol. Compound 55, 3.5 g (69%), was obtained as an off-white solid.

B.



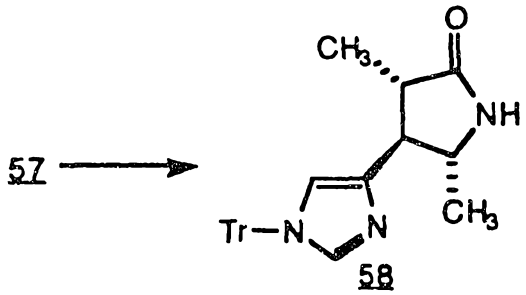
To a solution of 55 (6.9 mmol, 3.5g) in dry THF (50 mL) at -78°C was added a solution of $KN(Si(CH_3)_3)_2$ (8.63 mmol, 1.72g) in THF (20 mL) over 10 minutes. An additional 10 mL THF was used to rinse the flask and syringe. After one hour at -78°C, neat CH_3I (8.63 mmol, 1.22g, filtered through basic alumina) was added, and the reaction was warmed to room temperature. After 2.5 hours, the reaction was recooled to -78°C, quenched with saturated NH_4Cl (pH = 7.3) and extracted into diethyl ether. The combined ether extracts were washed with brine and dried ($MgSO_4$). Concentration and purification via flash column chromatography (400 g SiO_2; 90:10 hexane: 2-propanol) yielded 56 (2.35 g; 65%).

C.



To a solution of 56 (4.2 mmol, 2.19g) in dry $CHCl_3$ (40 mL) at room temperature was added iodotrimethylsilane (10.51 mmol, 2.1g). After one hour at 40°C, the reaction was diluted with methanol and concentrated on the rotary evaporator. Purification via flash chromatography (150 g, SiO_2, 80:10:10 CH_2Cl_2:2-propanol: methanol-/ammonia) gave 600 mg (80%) of 57.

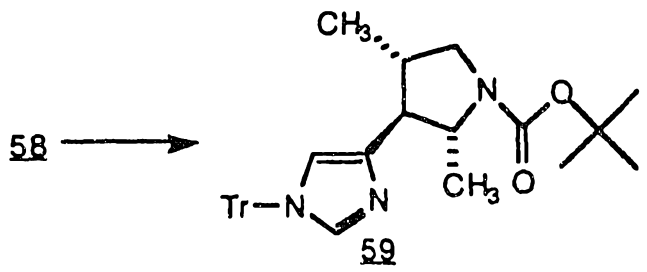
D.



58

Compound 57 (3.6 mmol, 640 mg) was combined with trityl chloride (3.9 mmol, 1.48 g) and triethylamine (3.9 mmol, 0.39 g) in dry CH_2Cl_2 (25 mL) at room temperature under nitrogen. After 6 hours, the reaction was quenched with water and extracted with EtOAc/CH_2Cl_2 (4:1) (EtOAc represents ethyl acetate). The combined organic layers were washed with saturated aqueous sodium metabisulfite and dried ($MgSO_4$). The crude material was purified on a flash column (175g SiO_2, 95:5 CH_2Cl_2 : methanol/ammonia) and yielded 900 mg (59%) of 58.

E.

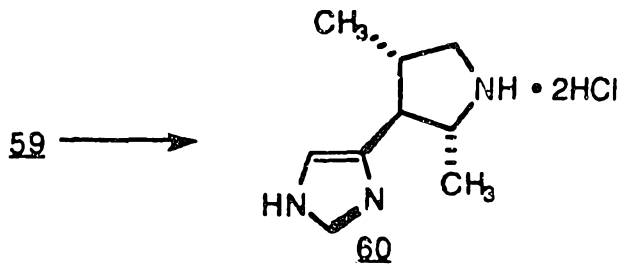


59

To a solution of 58 (2.14 mmol, 900mg) in dry THF (30 mL) was added a solution of LAH in diethyl ether (5.34 mL of a 1M solution). The reaction was heated to reflux for 2 hours, cooled to room temperature, diluted with diethyl ether, and quenched with saturated aqueous Na_2SO_4. Solid Na_2SO_4 was added and the mixture was filtered. The filter cake was washed with 150 mL of boiling THF. Removal of the solvent on the rotary evaporator yielded 920 mg of a crude solid.

To a solution of the crude solid (920 mg) from the previous reaction in THF (15 mL) was added $(t\text{-BOC})_2O$ (2.7 mmol, 0.59g). After 30 minutes, the reaction was diluted with CH_2Cl_2, washed with water, and dried ($MgSO_4$). Concentration yielded a crude solid which was purified on a flash column (200 g SiO_2, 80:20 hexane : acetone). This material was further purified via HPLC (SiO_2, 97:3 hexane : 2-propanol) to give 230 mg (21%) of 59.

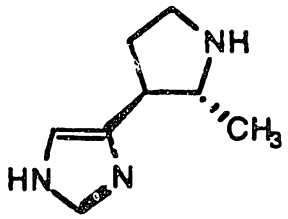
F.



60

Compound 59 (0.47 mmol, 230 mg) was combined with 15 mL 1N HCl and heated to 90°C for one hour. The reaction was cooled, filtered, and extracted with diethyl ether. The aqueous layer was concentrated in vacuo to give 60 (110 mg, 100%). MS (CI) 166 (M + 1).

The following are examples of pharmaceutical dosage forms which contain a compound of the invention. As used therein, the term "active compound" is used to designate the compound



The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided, since any other compound of structural formula I can be substituted into the pharmaceutical composition examples.

Pharmaceutical Dosage Form Examples

EXAMPLE A

Tablets

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp

granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE B

Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	4	7
	Total	250	700

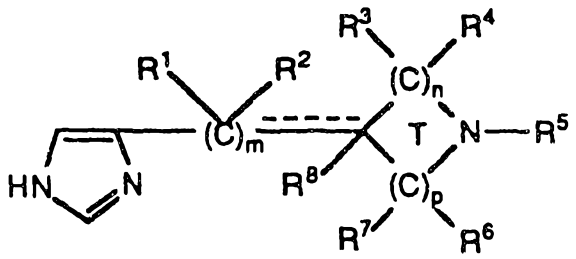
Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A compound of the formula:



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

(A) m is an integer selected from the group consisting of: 0, 1, and 2;

(B) n and p are integers and are each independently selected from the group consisting of : 0, 1, 2, and 3 such that the sum of n and p is 2 or 3 such that when the sum of n and p is 2, T is a 4-membered ring and when the sum of n and p is 3, T is a 5-membered ring;

(C) each R^1, R^2, R^3, R^4, R^6, R^7, and R^8 is independently selected from the group consisting of:

(1) H;

(2) C_1 to C_6 alkyl;

(3) C_3 to C_6 cycloalkyl; and

(4) $-(CH_2)_q-R^9$ wherein q is an integer of: 1 to 7, and R^9 is selected from the group consisting of: phenyl, substituted phenyl, $-OR^{10}$, $-C(O)OR^{10}$, $-C(O)R^{10}$, $-OC(O)R^{10}$, $-C(O)NR^{10}R^{11}$, CN and $-SR^{10}$ wherein R^{10} and R^{11} are as defined below, and wherein the substituents on said substituted phenyl are each independently selected from the group consisting of: -OH, -O-(C_1 to C_6)alkyl, halogen, C_1 to C_6 alkyl,

$-CF_3$, -CN, and $-NO_2$, and wherein said substituted phenyl contains from 1 to 3 substituents;

(D) R^5 is selected from the group consisting of:

(1) H;

(2) C_1 to C_{20} alkyl;

(3) C_3 to C_6 cycloalkyl;

(4) $-C(O)OR^{10'}$; wherein $R^{10'}$ is the same as R^{10} defined below except that $R^{10'}$ is not H;

(5) $-C(O)R^{10}$;

(6) $-C(O)NR^{10}R^{11}$;

(7) allyl;

(8) propargyl; and

(9) $-(CH_2)_q-R^9$, wherein q and R^9 are as defined above with the proviso that when q is 1 then R^9 is not -OH or -SH;

(E) R^{10} and R^{11} are each independently selected from the group consisting of: H, C_1 to C_6 alkyl, and C_3 to C_6 cycloalkyl; and, for the substituent $-C(O)NR^{10}R^{11}$, R^{10} and R^{11}, together with the nitrogen to which they are bound, can form a ring having 5, 6, or 7 atoms;

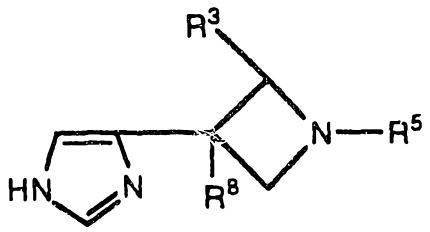
(F) the dotted line (------) represents a double bond that is optionally present when m is 1, and T is a 5-membered ring, and n is not 0, and p is not 0, and when said double bond is present then R^2 and R^8 are absent;

(G) when m is 2, each R^1 is the same or different substituent for each m, and each R^2 is the same or different substituent for each m;

(H) when n is 2 or 3, each R^3 is the same or different substituent for each n, and each R^4 is the same or different substituent for each n; and

(I) when p is 2 or 3, each R^6 is the same or different substituent for each p, and each R^7 is the same or different substituent for each p.

2. The compound of Claim 1 wherein said compound is selected from the group consisting of compounds having the formula:



(II-1)

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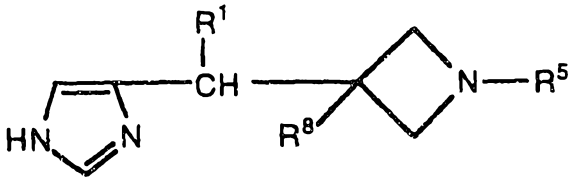
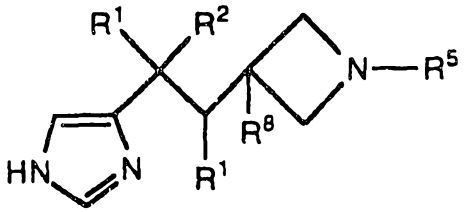


(II-2)

;



(II-3)

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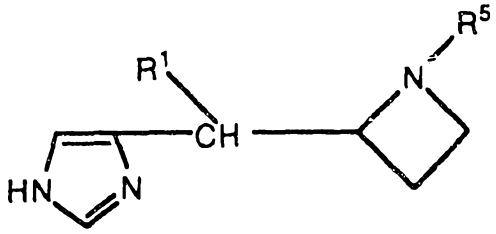
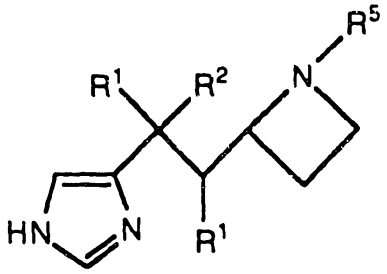


(IIA-1)

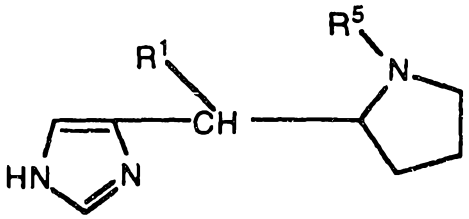
; and



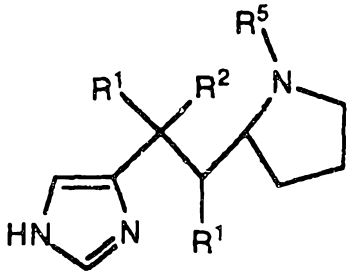
(IIA-2)

wherein R^1, R^2, R^3, R^5, and R^8 are as defined for Formula I.

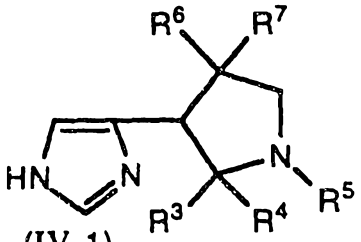
3. The compound of Claim 1 wherein said compound is selected from the group consisting of compounds having the formula:



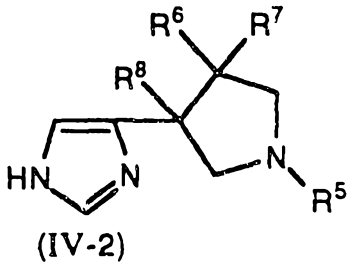
(III-1) ;



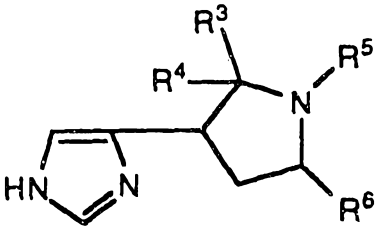
(III-2) ;



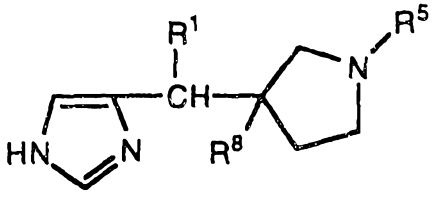
(IV-1) ;



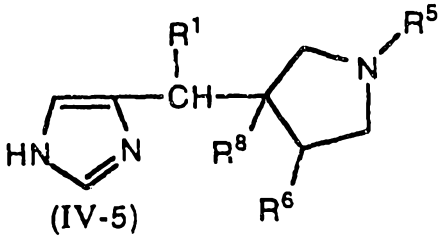
(IV-2) ;



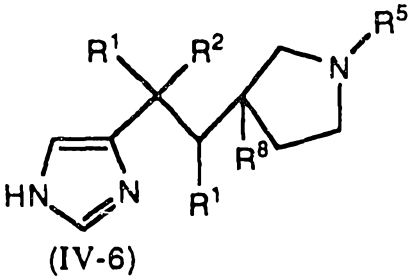
(IV-3) ;



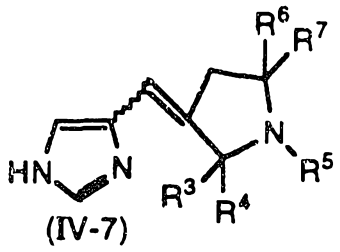
(IV-4) ;



(IV-5) ;



(IV-6) ;



and (IV-7)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 are as defined for Formula I.

4 The compound of Claim 1 wherein m is 0 or 1.

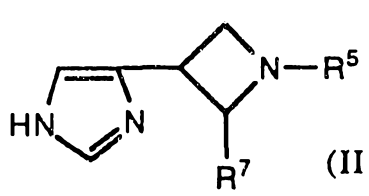
5. The compound of Claim 4 wherein R^5 is selected from the group consisting of H, C_1 to C_{20} alkyl and $(CH_2)_q$-R^9 wherein R^9 is phenyl.

6. The compound of Claim 5 wherein R^1 to R^4 and R^6 to R^8 are each independently selected from the group consisting of H, C_1 to C_6 alkyl, and -$(CH_2)_q$-R^9 wherein R^9 is phenyl.

7. The compound of Claim 6 wherein each R^1 to R^4 and R^6 to R^8 are independently selected from the group consisting of H, methyl, ethyl, pentyl, benzyl, and 2-phenylethyl.

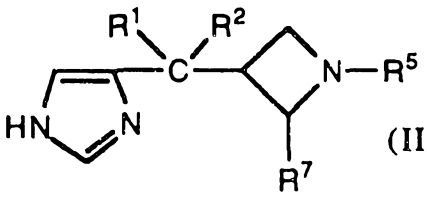
8. The compound of Claim 7 wherein R^5 is H or methyl.

9. The compound of Claim 1 having the formula selected from the group consisting of:



(IIB)

and

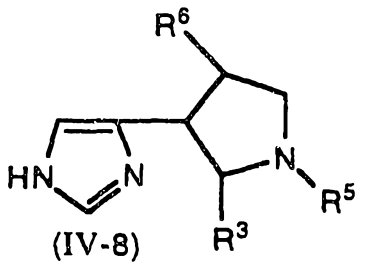


(IIC)

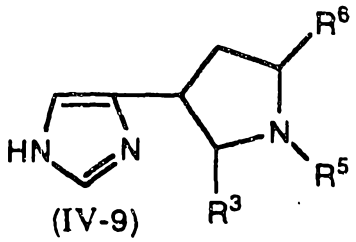
wherein R^7 is selected from the group consisting of H, C_1 to C_6 alkyl, and $-(CH_2)_q-R^9$ wherein R^9 is phenyl.

10. The compound of Claim 9 wherein R^7 is C_1 to C_6 alkyl, R^1 is H, and R^2 is H.

11. The compound of Claim 1 having the formula selected from the group consisting of:

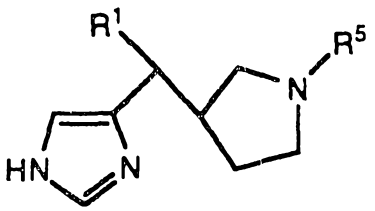


(IV-8)



(IV-9)

and



(IV-10)

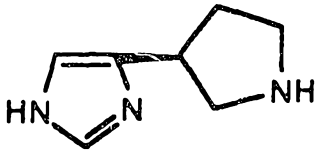
wherein R^1, R^3 and R^6 are each independently selected from the group consisting of H, C_1 to C_6 alkyl and $-(CH_2)_q-R^9$ wherein R^9 is phenyl.

12. The compound of Claim 11 wherein R^5 is selected from the group consisting of H and methyl.

13. The compound of Claim 12 wherein R^1 is H.

14. The compound of Claim 1 wherein said compound is selected from the group consisting of:

(A1)



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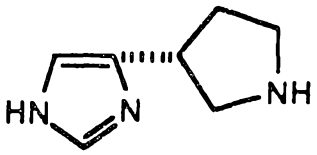
(A2)



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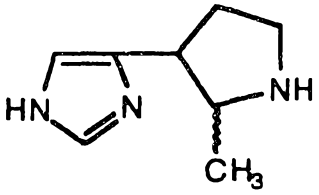
(B)



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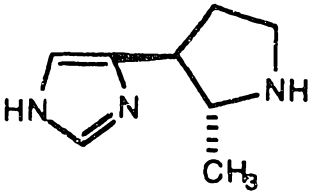
(B1)



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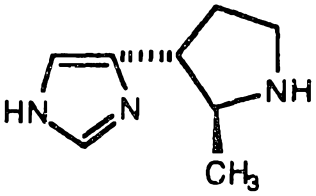
(B2)



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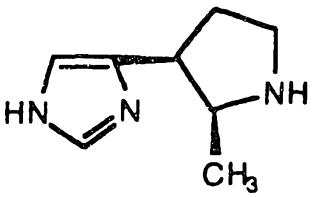
(B3)



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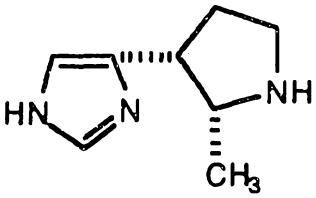
(B4)



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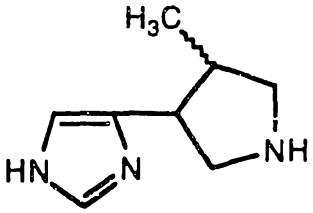
(C)



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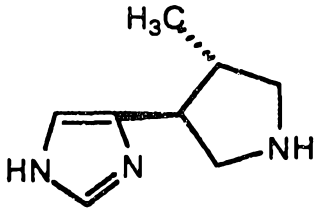
(C1)



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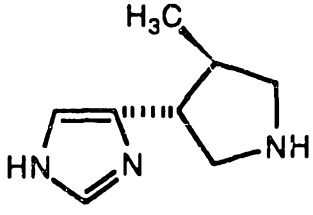
(C2)



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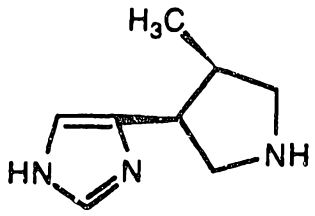
(C3)



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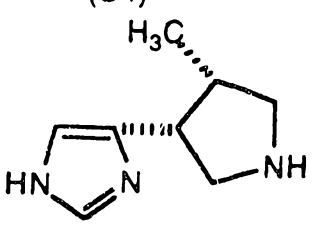
(C4)



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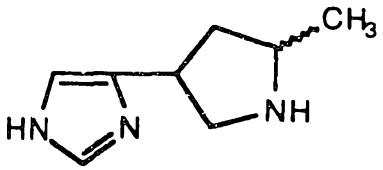
(D)



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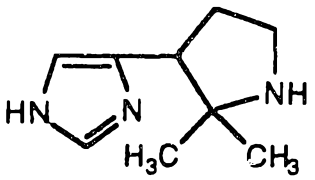
(E)



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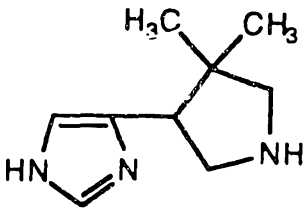
(F)



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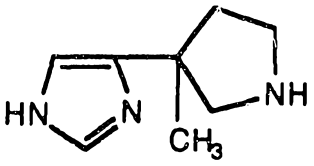
(G)



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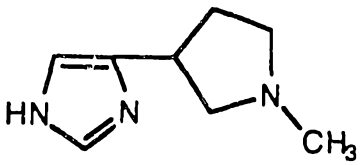
(H)



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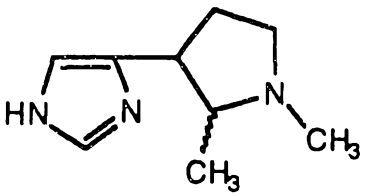
(I)



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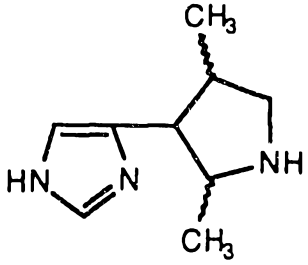
(J)



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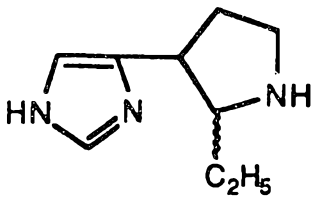
(K)



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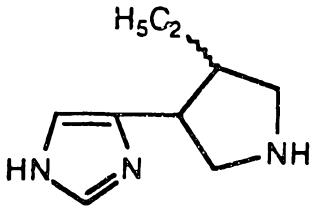
(L)



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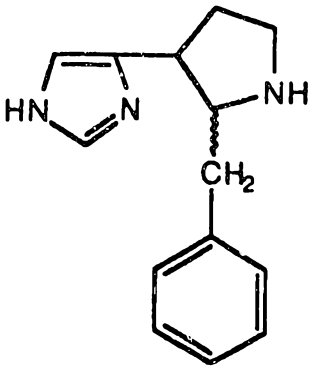
(M)



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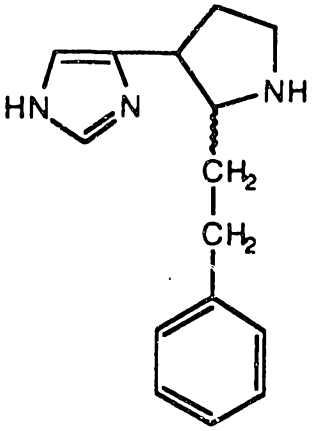
(N)



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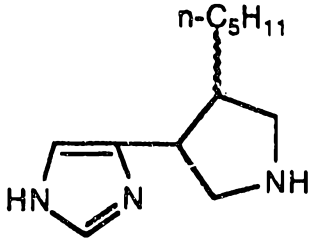
(O)



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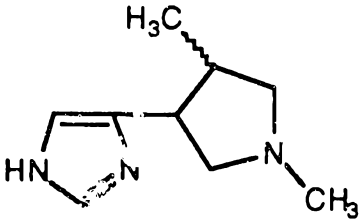

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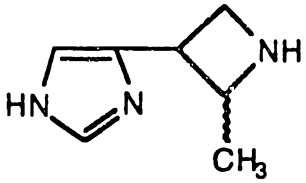
(Q)



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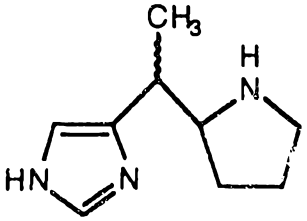
(R)



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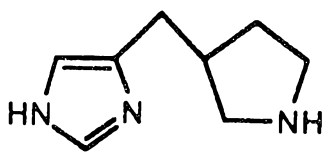
(S)



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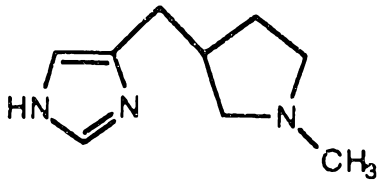
(T)



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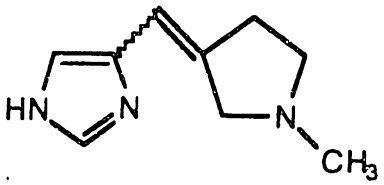
(U)



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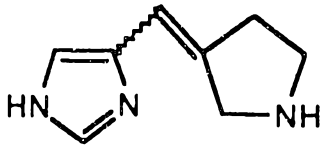
(V)



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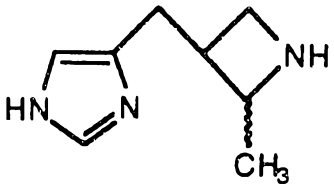
(W)



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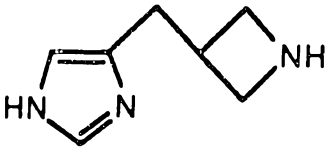
(X)



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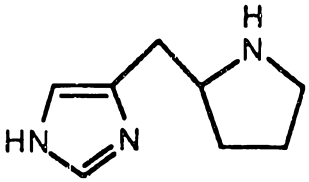
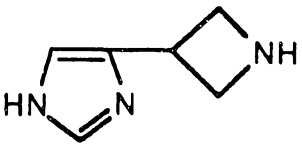
(Y)



; and

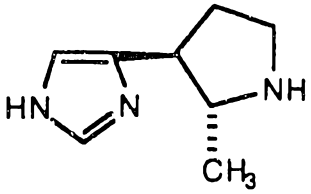
(Z)



.

15. The compound of Claim 14 having the formula:

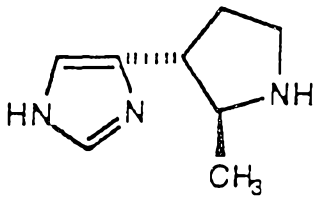
(B1)



.

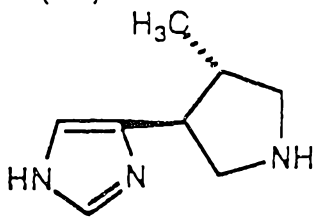
16. The compound of Claim 14 having the formula:

(B2)



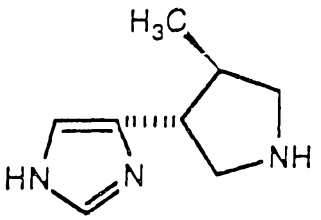
17. The compound of Claim 14 having the formula:

(C1)

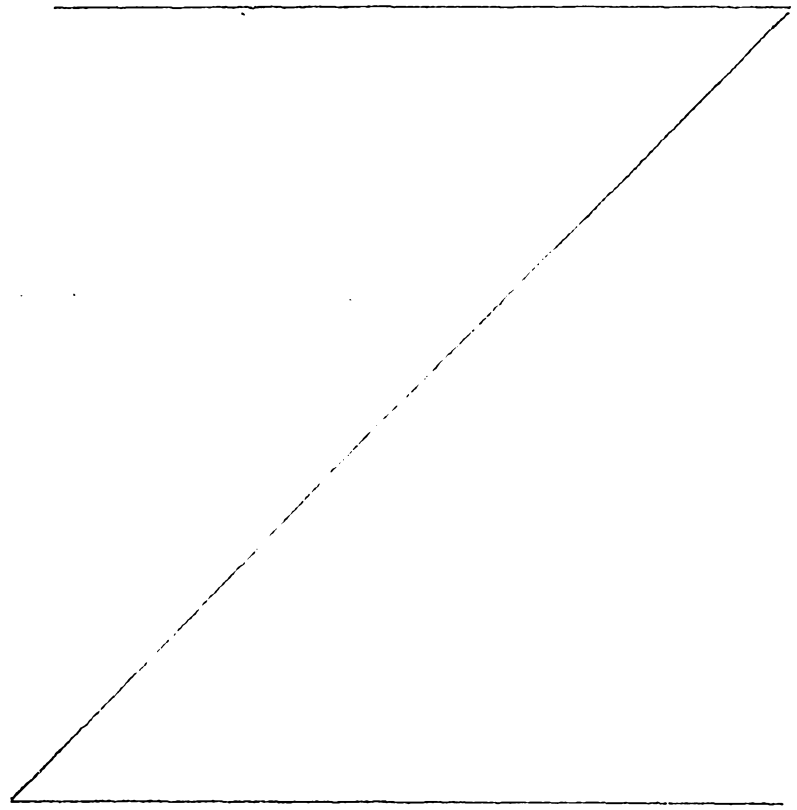


18. The compound of Claim 14 having the formula:

(C2)

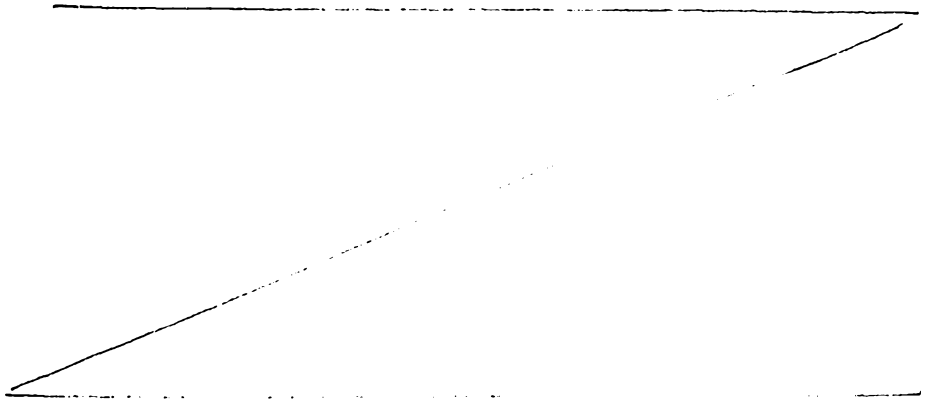


19. A pharmaceutical composition for use as an H_3 receptor agonist or antagonist, comprising a pharmaceutically acceptable carrier and an effective amount of a Compound of Claim 1.

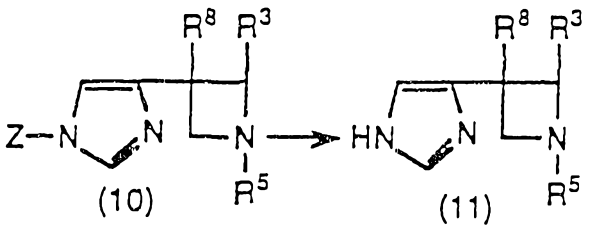


20. A method of preparing a pharmaceutical composition comprising admixing a compound of Claim 1 with a pharmaceutically acceptable carrier.

21. A process for preparing a compound of Claim 1 comprising:

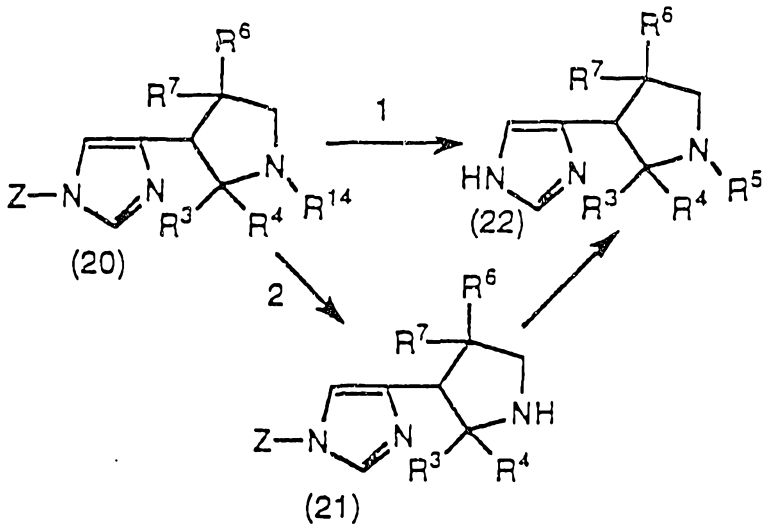


(I) When m is 0, n is 1 and p is 1



1) deprotecting compound (10) by treatment with dilute aqueous acid, at a temperature of about 25 to about 90°C, to produce compound (11);

(II) When m is 0, n is 1 and p is 2



1) deprotecting compound (20) by treatment with dilute aqueous acid, at a temperature of about 25 to about 90°C, to produce compound (22), said reaction following reaction path 1 when R^{14} is alkyl, cycloalkyl, benzyl, substituted benzyl, allyl or propargyl; or

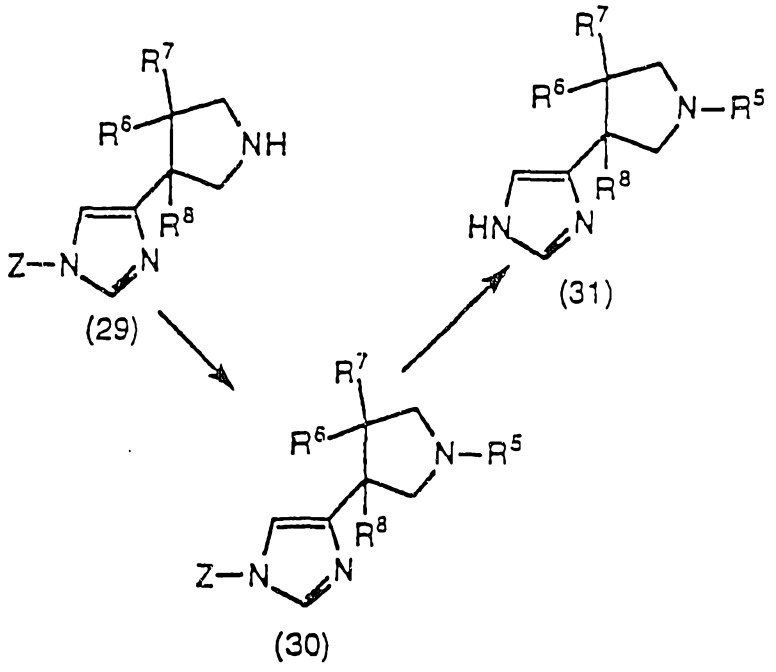
2) (a) treating compound (20), when R^{14} is $-Si(CH_3)_2C(CH_3)_3$, with tetrabutylammonium fluoride in tetrahydrofuran at a temperature of about 0 to about 50°C to produce compound (21); or treating compound (20), when R^{14} is -C(O)O(t-butyl), with dilute aqueous acid to produce compound (21);

(b) reacting compound (21) with (i) R^5-X , when R^5 is $-C(O)R^{10}$, $-C(O)OR^{10'}$, $-C(O)NR^{10}R^{11}$ or alkyl in an organic solvent

optionally in the presence of a suitable base; or (ii) with R^{5A}-CHO, when R^5 is alkyl, cycloalkyl, allyl, propargyl, benzyl or substituted benzyl, under hydrogenating conditions, or in the presence of $NaBH_3(CN)$, in an organic solvent; wherein R^{5A} represents an R^5 group that has one less $-CH_2-$ group and X represents a suitable leaving group; said reaction (i) or (ii) being performed at a temperature within the range of about -30 to about 80°C; and

(c) *deprotecting the compound produced in 2)(b)* by treatment with dilute aqueous acid at a temperature of about 25 to about 90°C to produce compound (22);

(III) When m is 0, n is 1 and p is 2

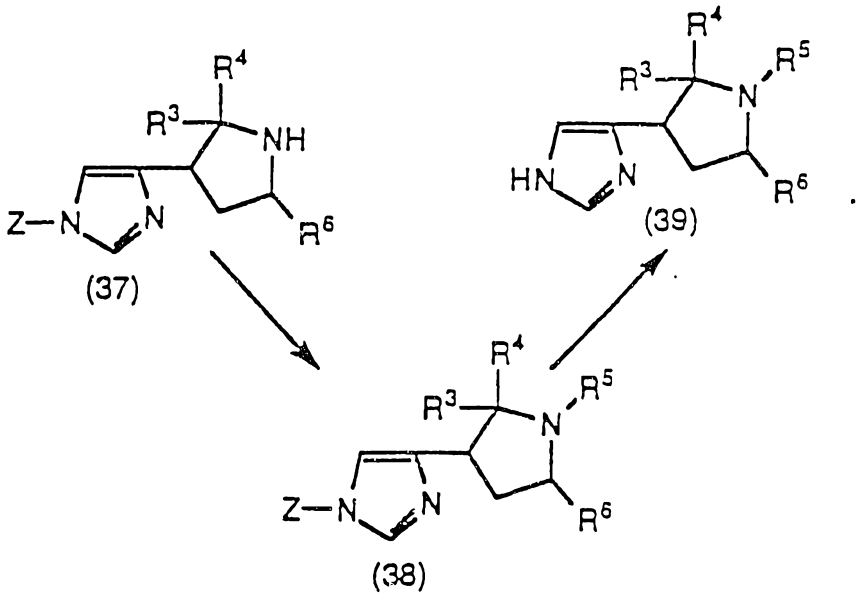


1) reacting compound (29) with (i) R^5-X ,when R^5 is $-C(O)R^{10}$, $-C(O)OR^{10'}$, $-C(O)NR^{10}R^{11}$ or alkyl in an organic solvent optionally in the presence of a suitable base; or (ii) with R^{5A}-CHO, when R^5 is alkyl, cycloalkyl, allyl, propargyl, benzyl or substituted benzyl, under hydrogenating conditions, or in the presence of $NaBH_3(CN)$, in an organic solvent; wherein R^{5A} represents an R^5 group that has one less

$-CH_2-$ group and X represents a suitable leaving group; said reaction (i) or (ii) being performed at a temperature within the range of about -30 to about 80°C, to produce compound (30); and

2) deprotecting compound (30) by treatment with dilute aqueous acid at a temperature of about 25 to about 90°C to produce compound (31);

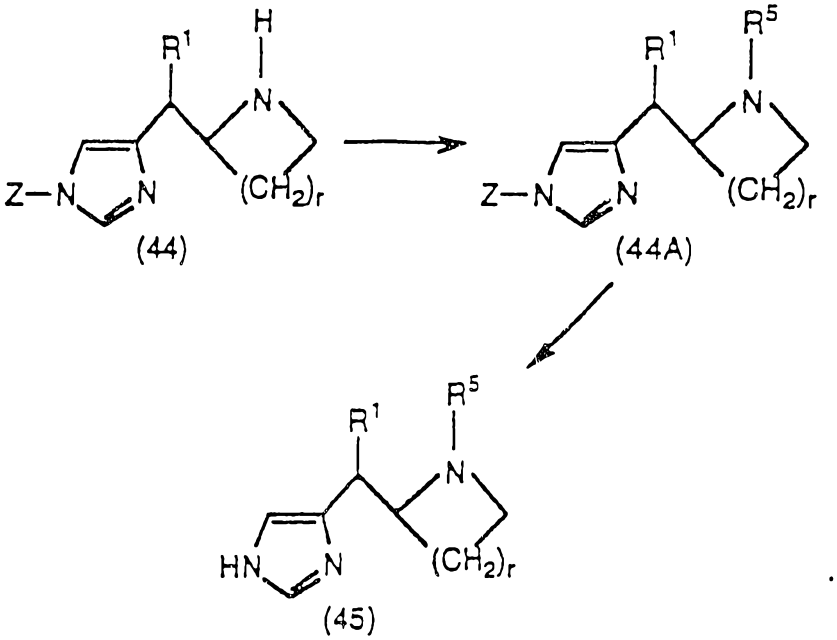
(IV) When m is 0, n is 1 and p is 2



1) reacting compound (37) with (i) R^5-X ,when R^5 is $-C(O)R^{10}$, $-C(O)OR^{10'}$, $-C(O)NR^{10}R^{11}$ or alkyl in an organic solvent optionally in the presence of a suitable base; or (ii) with R^{5A}-CHO, when R^5 is alkyl, cycloalkyl, allyl, propargyl, benzyl or substituted benzyl, under hydrogenating conditions, or in the presence of $NaBH_3(CN)$, in an organic solvent; wherein R^{5A} represents an R^5 group that has one less $-CH_2-$ group and X represents a suitable leaving group; said reaction (i) or (ii) being performed at a temperature within the range of about -30 to about 80°C, to produce compound (38); and

2) deprotecting compound (38) by treatment with dilute aqueous acid at a temperature of about 25 to about 100°C to produce compound (39);

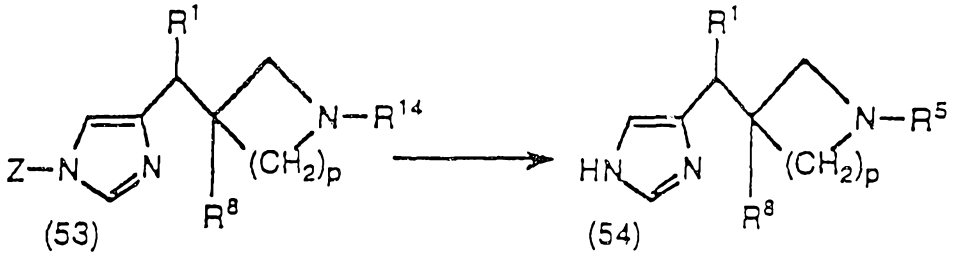
(V) When m is 1, n is 0 and p is 2 or 3



1) reacting compound (44), wherein r is 1 or 2, with (i) R^5-X ,when R^5 is -C(O)R^{10}, -C(O)O$R^{10'}$, -C(O)N$R^{10}R^{11}$ or alkyl in an organic solvent optionally in the presence of a suitable base; or (ii) with R^{5A}-CHO, when R^5 is alkyl, cycloalkyl, allyl, propargyl, benzyl or substituted benzyl, under hydrogenating conditions, or in the presence of $NaBH_3(CN)$, in an organic solvent; wherein R^{5A} represents an R^5 group that has one less -CH_2- group and X represents a suitable leaving group; said reaction (i) or (ii) being performed at a temperature within the range of about -30 to about 80°C, to produce compound (44A); and

2) deprotecting compound (44A) by treatment with dilute aqueous acid at a temperature of about 25 to about 90°C to produce compound (45);

(VI) When m is 1, n is 1 and p is 1 or 2



(53) (54)

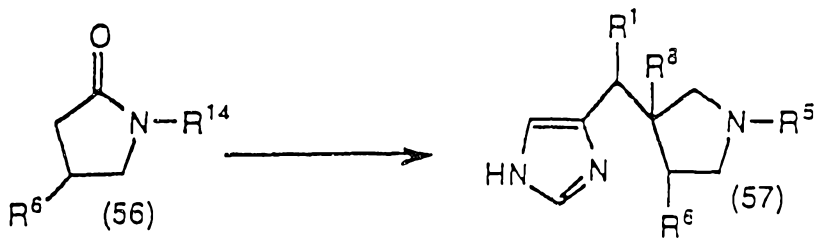
1) deprotecting compound (53), wherein p is 1 or 2, by treatment with dilute aqueous acid, at a temperature of about 25 to about 90°C, to produce compound (54), said reaction being used when R^{14} is alkyl, cycloalkyl, benzyl, substituted benzyl, allyl or propargyl; or

2) (a) treating compound (53), when R^{14} is $-Si(CH_3)_2C(CH_3)_3$, with tetrabutylammonium fluoride in tetrahydrofuran at a temperature of about 0 to about 50°C; or treating compound (53), when R^{14} is -C(O)O(t-butyl), with dilute aqueous acid;

(b) reacting the compound produced in 2)(a) with (i) R^5-X ,when R^5 is $-C(O)R^{10}$, $-C(O)OR^{10'}$, $-C(O)NR^{10}R^{11}$ or alkyl in an organic solvent optionally in the presence of a sutable base; or (ii) with R^{5A}-CHO, when R^5 is alkyl, cycloalkyl, allyl, propargyl, benzyl or substituted benzyl, under hydrogenating conditions, or in the presence of $NaBH_3(CN)$, in an organic solvent; wherein R^{5A} represents an R^5 group that has one less $-CH_2-$ group and X represents a suitable leaving group; said reaction (i) or (ii) being performed at a temperature within the range of about -30 to about 80°C; and

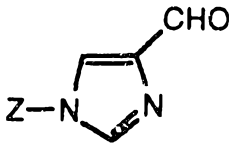
(c) deprotecting the compound produced in 2)(b) by treatment with dilute aqueous acid at a temperature of about 25 to about 90°C to produce compound (54);

(VII) When m is 1, n is 1 and p is 2



(56) (57)

1) preparing the anion of compound (56) by reacting compound (56) with a suitable base at a temperature of about -20 to about 20°C, and reacting said anion with compound (32)



(32)

in an organic solvent at a temperature of about -78 to about 25°C;

2) reacting the product of 1) with R^1-Q, wherein Q is Li or MgBr, in a suitable solvent containing CuCN and a Lewis acid, said reaction is conducted at a temperature of about -78 to about 20°C;

3) reacting the enolate of the product of 2) with R^8-L, wherein L represents a suitable leaving group, in an organic solvent, said reaction is conducted at a temperature of about 0 to about 50°C;

4) reducing the resulting R^8 substituted compound from 3) with $LiAlH_4$ at a temperature of about 25 to about 65°C in an organic solvent;

5) deprotecting the reaction product of 4) by treatment with dilute aqueous acid, at a temperature of about 25 to about 90°C, to produce compound (57), said reaction being used when R^{14} is alkyl, cycloalkyl, benzyl, substituted benzyl, allyl or propargyl; or

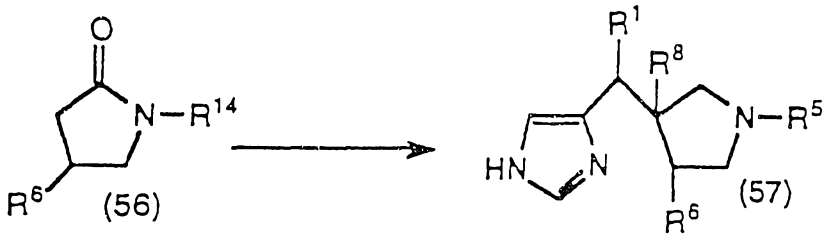
6) (a) treating the reaction product of 4), when R^{14} is $-Si(CH_3)_2C(CH_3)_3$, with tetrabutylammonium fluoride in tetrahydrofuran at a temperature of about 0 to about 50°C; or treating the reaction product of 4), when R^{14} is -C(O)O(t-butyl), with dilute aqueous acid;

(b) reacting the compound produced in 6)(a) with (i) R^5-X ,when R^5 is $-C(O)R^{10}$, $-C(O)OR^{10'}$, $-C(O)NR^{10}R^{11}$ or alkyl in an organic solvent optionally in the presence of a suitable base; or (ii) with R^{5A}-CHO, when R^5 is alkyl, cycloalkyl, allyl, propargyl, benzyl or substituted benzyl, under hydrogenating conditions, or in the presence of $NaBH_3(CN)$, in an organic solvent; wherein R^{5A} represents an R^5 group that has one less $-CH_2-$ group and X represents a suitable leaving

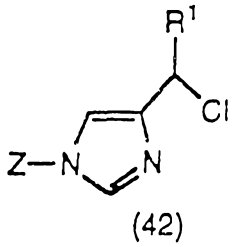
group; said reaction (i) or (ii) being performed at a temperature within the range of about -30 to about 80°C; and

(c) deprotecting the compound produced in 6)(b) by treatment with dilute aqueous acid at a temperature of about 25 to about 90°C to produce compound (57);

(VIII) When m is 1, n is 1 and p is 2



1) preparing the anion of compound (56) by reacting compound (56) with a suitable base at a temperature of about -20 to about 20°C, and reacting said anion with compound 42



(42)

in a suitable solvent at a temperature of about -78 to about 25°C

2) reacting the enolate of the product of 1) with R^8-L, wherein L represents a suitable leaving group, in an organic solvent, said reaction is conducted at a temperature of about 0 to about 50°C;

3) reducing the resulting R^8 substituted compound from 2) with $LiAlH_4$ at a temperature of about 25 to about 65°C in an organic solvent;

4) deprotecting the reaction product of 3) by treatment with dilute aqueous acid, at a temperature of about 25 to about 90°C, to

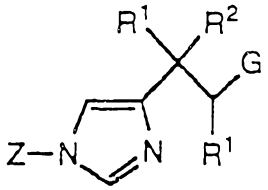
produce compound (57), said reaction being used when R^{14} is alkyl, cycloalkyl, benzyl, substituted benzyl, allyl or propargyl; or

5) (a) treating the reaction product of 3), when R^{14} is $-Si(CH_3)_2C(CH_3)_3$, with tetrabutylammonium fluoride in tetrahydrofuran at a temperature of about 0 to about 50°C; or treating the reaction product of 3), when R^{14} is -C(O)O(t-butyl), with dilute aqueous acid;

(b) reacting the compound produced in 5)(a) with (i) R^5-X ,when R^5 is $-C(O)R^{10}$, $-C(O)OR^{10'}$, $-C(O)NR^{10}R^{11}$ or alkyl in an organic solvent optionally in the presence of a suitable base; or (ii) with R^{5A}-CHO, when R^5 is alkyl, cycloalkyl, allyl, propargyl, benzyl or substituted benzyl, under hydrogenating conditions, or in the presence of $NaBH_3(CN)$, in an organic solvent; wherein R^{5A} represents an R^5 group that has one less $-CH_2-$ group and X represents a suitable leaving group; said reaction (i) or (ii) being performed at a temperature within the range of about -30 to about 80°C; and

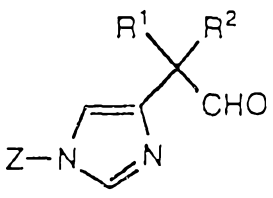
(c) deprotecting the compound produced in 5)(b) by treatment with dilute aqueous acid at a temperature of about 25 to about 90°C to produce compound (57);

(IX) When m is 2, n is 0 and p is 2 or 3 or m is 2, n is 1 and p is 1 or 2 using compound (58):



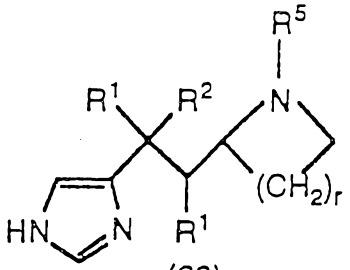
(58)

in place of compound (42) and compound (59):



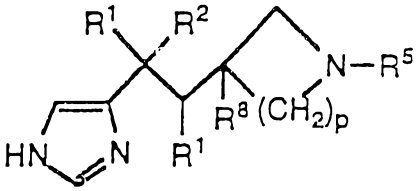
(59)

in place of compound (32) to produce compound (60):



(60)

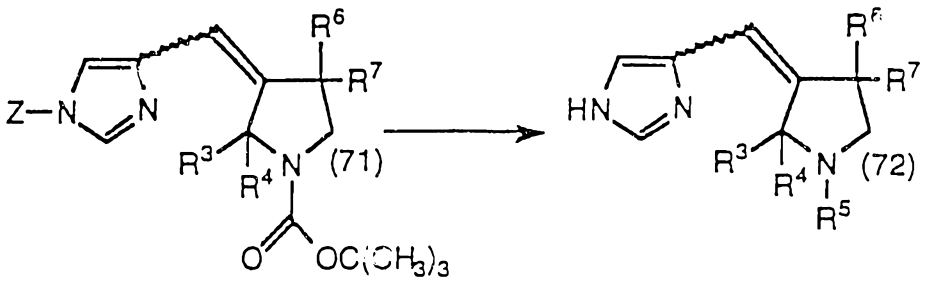
by following the steps in (V) above, or to produce compound (61)



(61)

by following the steps in (VI) above, wherein for compound (60) r is 1 or 2 and for compound (61) p is 1 or 2, and wherein G in compound (58) represents a suitable leaving group;

(X) When m is 1, n is 1 and p is 2 and where the double bond indicated in formula I is present

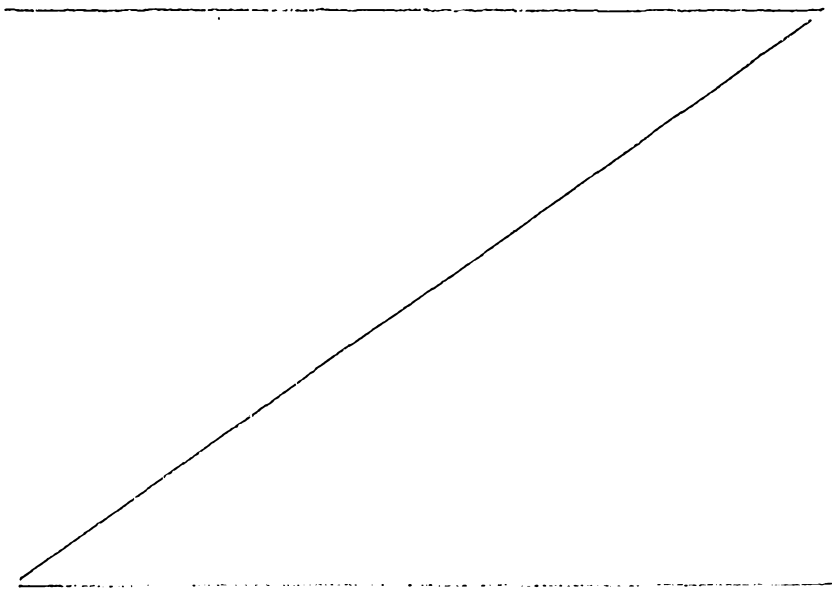


1) treating compound (71) with acid in an inert organic solvent at a temperature of about 0°C to cause selective deprotection of the pyrrolidine ring;

2) reacting the reaction product of 1) with (i) R^5-X, when R^5 is -C(O)R^{10}, -C(O)O$R^{10'}$, -C(O)N$R^{10}R^{11}$ or alkyl in an organic solvent optionally in the presence of a suitable base; or (ii) with R^{5A}-CHO, when R^5 is alkyl, cycloalkyl, allyl, propargyl, benzyl or substituted benzyl, under hydrogenating conditions, or in the presence of $NaBH_3(CN)$, in an organic solvent; wherein R^{5A} represents an R^5 group that has one less -CH_2- group and X represents a suitable leaving group; said reaction (i) or (ii) being performed at a temperature within the range of about -30 to about 80°C; and

2) deprotecting the reaction product of 2) by treatment with dilute aqueous acid at a temperature of about 25 to about 90°C to produce compound (72); or

(XI) Preparing compounds of Claim 1, wherein R^5 is H, by reacting an intermediate compound of one of the above process steps (I), (II), (III), (IV), (V), (VI), (VII), (VII), (VIII), (IX), or (X), with aqueous acid, at a temperature of about 25 to about 100°C, said intermediate compound having the imidazole nitrogen protected by Z and having the nitrogen of the cyclic four or five membered amine substituted with -C(O)O(t-butyl) or unsubstituted.



22. A compound of formula I or a pharmaceutically acceptably salt or solvate thereof substantially as herein described with reference to any one of Examples 1 to 9.

23. A process for preparing a compound of formula I or a pharmaceutically acceptably salt or solvate thereof substantially as herein described with reference to any one of Examples 1 to 9.

24. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of formula I substantially as herein described with reference to Example A or B.

25. A method of preparing a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of formula I substantially as herein described with reference to Example A or B.

Dated this 9th day of May 1996

SCHERING CORPORATION

By their Patent Attorneys

GRIFFITH HACK & CO

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/10743

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 C07D401/06; A61K31/415; C07D403/06

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 RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0 197 840 (INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM)) 15 October 1986 cited in the application page 18, first paragraph see claim 1	1-19,21, 23,24
A	US,A,4 925 851 (HOULIHAN) 15 May 1990 cited in the application formula I	1-19,21, 23,24
A	US,A,4 767 778 (ARRANG) 30 August 1988 cited in the application formula I	1-19,21, 23,24

° Special categories of cited documents : [10]

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

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

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

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

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

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

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

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

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
15 MARCH 1993	23.03.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	GETTINS M.P.

3

INTERNATIONAL SEARCH REPORT

....ernational application No.
PCT/US92/10743

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. [X] Claims Nos.: 20,21
because they relate to subject matter not required to be searched by this Authority, namely:
Please see Rule 39.1(iv) - PCT:

Methods for the treatment of the human or animal body by surgery or therapy, as well as diagnostic methods

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

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

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

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

Remark on Protest

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

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

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9210743
SA 68311

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 15/03/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0197840	15-10-86	FR-A- 2579596	03-10-86
		JP-A- 61267574	27-11-86
		US-A- 4707487	17-11-87
US-A-4925851	15-05-90	None	
US-A-4767778	30-08-88	FR-A- 2586562	06-03-87
		DE-A- 3685170	11-06-92
		EP-A,B 0214058	11-03-87
		JP-A- 62123174	04-06-87

EPO FORM P079

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82