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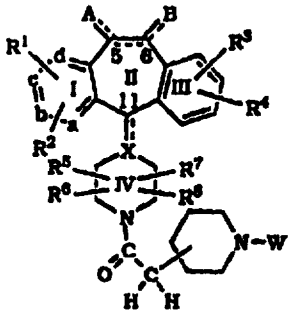

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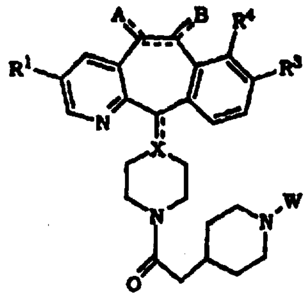

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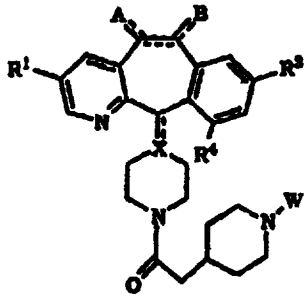

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(57) Abstract

Novel compounds of formula (1.0) are disclosed. Compounds of formula (1.0) are represented by the compounds of formulas (1.4) or (1.5) wherein R^1, R^3 and R^4 are each independently selected from halo. W represents a group selected from: $-SO_2R^{12}$ or $-P(O)R^{13}R^{14}$. Also disclosed are methods of inhibiting farnesyl protein transferase and the growth of abnormal cells, such as tumor cells.

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SUBSTITUTED BENZOCYCLOHEPTAPYRIDINE DERIVATIVES USEFUL FOR INHIBITION OF FARNESYL PROTEIN TRANSFERASE

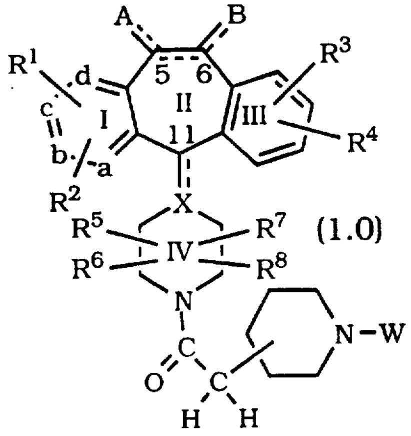
BACKGROUND

WO 95/10516, published April 20, 1995 discloses tricyclic compounds useful for inhibiting farnesyl protein transferase.

In view of the current interest in inhibitors of farnesyl protein transferase, a welcome contribution to the art would be compounds useful for the inhibition of farnesyl protein transferase. Such a contribution is provided by this invention.

SUMMARY OF THE INVENTION

This invention provides compounds useful for the inhibition of farnesyl protein transferase (FPT). The compounds of this invention are represented by the formula:



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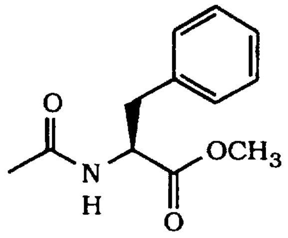
or a pharmaceutically acceptable salt or solvate thereof, wherein: one of a, b, c and d represents N or NR^9 wherein R^9 is O$^-$, -CH$_3$ or -(CH$_2$)$_n$CO$_2$H wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR^1 or CR^2; or

each of a, b, c, and d are independently selected from CR^1 or CR^2;

each R^1 and each R^2 is independently selected from H, halo, -CF$_3$, -OR^{10} (e.g., -OCH$_3$), -COR^{10}, -SR^{10} (e.g., -SCH$_3$ and -SCH$_2$C$_6$H$_5$), -S(O)$_t$R^{11} (wherein t is 0, 1 or 2, e.g., -SOCH$_3$ and -SO$_2$CH$_3$), -SCN, -N(R^{10})$_2$, -NR^{10}R^{11}, -NO$_2$, -OC(O)R^{10}, -CO$_2$R^{10}, -OCO$_2$R^{11}, -CN, -NHC(O)R^{10}, -NHSO$_2$R^{10}, -CONHR^{10}, -CONHCH$_2$CH$_2$OH, -NR^{10}COOR^{11},



,

$-SR^{11}C(O)OR^{11}$ (e.g., $-SCH_2CO_2CH_3$), $-SR^{11}N(R^{75})_2$ wherein each R^{75} is independently selected from H and $-C(O)OR^{11}$ (e.g., $-S(CH_2)_2NHC(O)O$-t-butyl and $-S(CH_2)_2NH_2$), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio (e.g., alkyl substituted tetrazol-5-ylthio such as 1-methyl-tetrazol-5-ylthio), alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, $-OR^{10}$ or $-CO_2R^{10}$;

R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2, or R^3 and R^4 taken together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring (Ring III);

R^5, R^6, R^7 and R^8 each independently represents H, $-CF_3$, $-COR^{10}$, alkyl or aryl, said alkyl or aryl optionally being substituted with $-OR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$, $-NR^{10}COOR^{11}$, $-N(R^{10})_2$, $-NO_2$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{11}$, $-CO_2R^{10}$, OPO_3R^{10} or R^5 is combined with R^6 to represent =O or =S and/or R^7 is combined with R^8 to represent =O or =S;

R^{10} represents H, alkyl, aryl, or aralkyl (e.g., benzyl);

R^{11} represents alkyl or aryl;

X represents N, CH or C, which C may contain an optional double bond (represented by the dotted line) to carbon atom 11;

the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent $-R^{10}$, halo, $-OR^{11}$, $-OCO_2R^{11}$ or $-OC(O)R^{10}$, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2, $-(OR^{11})_2$; H and halo, dihalo, alkyl and H, $(alkyl)_2$, -H and $-OC(O)R^{10}$, H and $-OR^{10}$, =O, aryl and H, $=NOR^{10}$ or $-O-(CH_2)_p-O-$ wherein p is 2, 3 or 4; and

W represents a group selected from: $-SO_2R^{12}$ or $-P(O)R^{13}R^{14}$;

R^{12} is selected from the group consisting of:

(1) alkyl, e.g., methyl, ethyl and propyl (such as n-propyl and iso-propyl);

(2) aralkyl, e.g., benzyl;

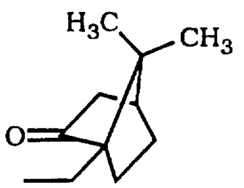
(3) cycloalkyl;

(4) aryl, e.g., phenyl;

(5) heteroaryl, e.g., pyridyl, thienyl and imidazolyl (e.g., 4- or 5-imidazolyl);

(6) substituted heteroaryl wherein said heteroaryl is as defined above and said substituents are selected from: (a) heteroaryl (e.g., pyridyl, and imidazolyl), (b) alkyl (e.g., methyl), (c) aryl (e.g., phenyl), (d) aralkyl (e.g., benzyl), (e) $-OR^{10}$, and (f) $N(R^{10})_2$;

(7) camphor, e.g.,



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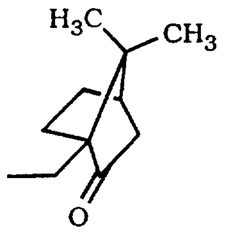


; and

(8) $-NR^{15}R^{16}$ wherein R^{15} and R^{16} are independently selected from the group consisting of: (a) H, (b) alkyl (e.g., methyl), (c) aryl (e.g., phenyl), (d) aralkyl (e.g., benzyl), (e) heteroaryl (e.g., pyridyl), and (f) heterocycloalkyl (e.g., piperidinyl), and preferably, R^{15} and R^{16} are the same; and

R^{13} and R^{14} are independently selected from the group consisting of:

(1) H;

(2) alkyl, e.g., methyl;

(3) aryl, e.g., phenyl;

(4) aralkyl, e.g., benzyl; and

(5) $-OR^{13}$ wherein R^{13} is as defined above;

preferably R^{13} and R^{14} are the same.

The compounds of this invention: (i) potently inhibit farnesyl protein transferase, but not geranylgeranyl protein transferase I, in vitro; (ii) block the phenotypic change induced by a form of transforming Ras which is a farnesyl acceptor but not by a form of transforming Ras engineered to be a geranylgeranyl acceptor; (iii) block intracellular processing of Ras which is a farnesyl acceptor but not of Ras engineered to be a geranylgeranyl acceptor; and (iv) block abnormal cell growth in culture induced by transforming Ras.

The compounds of this invention inhibit farnesyl protein transferase and the farnesylation of the oncogene protein Ras. Thus, this invention further provides a method of inhibiting ~~ras~~ farnesyl protein transferase, (e.g., ras farnesyl protein transferase) in mammals, especially humans, by the administration of an effective amount of the tricyclic compounds described above. The administration of the compounds of this invention to patients, to inhibit farnesyl protein transferase, is useful in the treatment of the cancers described below.

This invention provides a method for inhibiting or treating the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of this invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; and (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs.

This invention also provides a method for inhibiting or treating tumor growth by administering an effective amount of the tricyclic compounds, described herein, to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a method for inhibiting or treating the growth of tumors expressing an activated Ras oncogene by the administration of an effective amount of the above described compounds. Examples of tumors which may be inhibited or treated include, but are not limited to, lung cancer (e.g., lung adenocarcinoma), pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), bladder carcinoma, epidermal carcinoma, breast cancer and prostate cancer.

It is believed that this invention also provides a method for inhibiting or treating proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes--i.e., the Ras gene itself is not activated by mutation to an oncogenic form--with said inhibition or treatment being accomplished by the administration of an effective amount of the tricyclic compounds described herein, to a mammal (e.g., a human) in need of such treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which Ras is activated due to mutation or overexpression of tyrosine kinase oncogenes (e.g., neu, src, abl, lck, and fyn), may be inhibited or treated by the tricyclic compounds described herein.

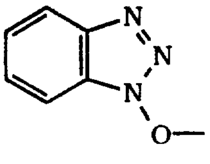
The tricyclic compounds useful in the methods of this invention inhibit or treat the abnormal growth of cells. Without wishing to be bound by theory, it is believed that these compounds may function through the inhibition of G-protein function, such as ras p21, by blocking G-protein isoprenylation, thus making them useful in the treatment of proliferative diseases such as tumor growth and cancer. Without wishing to be bound by theory, it is believed that these compounds inhibit ras farnesyl protein transferase, and thus show antiproliferative activity against ras transformed cells.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the following terms are used as defined below unless otherwise indicated:

MH$^+$-represents the molecular ion plus hydrogen of the molecule in the mass spectrum;

benzotriazol-1-yloxy represents



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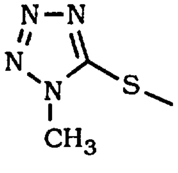
1-methyl-tetrazol-5-ylthio represents



;

alkenyl-represents straight and branched carbon chains having at least one carbon to carbon double bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms and most preferably from 3 to 6 carbon atoms;

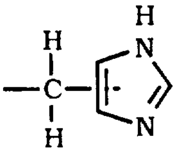
alkynyl-represents straight and branched carbon chains having at least one carbon to carbon triple bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms;

alkyl-(including the alkyl portions of alkoxy, aralkyl and heteroarylalkyl)-represents straight and branched carbon chains and contains from one to twenty carbon atoms, preferably one to six carbon atoms;

aralkyl-represents an aryl group, as defined below, bound to an alkyl group, as defined above, preferably the alkyl group is $-CH_2-$, (e.g., benzyl);

aryl (including the aryl portion of aralkyl)-represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is a phenyl ring), with all available substitutable carbon atoms of the carbocyclic group being intended as possible points of attachment, said carbocyclic group being optionally substituted (e.g., 1 to 3) with one or more of halo, alkyl, hydroxy, alkoxy, phenoxy, CF_3, amino, alkylamino, dialkylamino, $-COOR^{10}$ or $-NO_2$;

$-CH_2$-imidazolyl represents an imidazolyl group bound by any substitutable carbon of the imidazole ring to a $-CH_2-$, that is:



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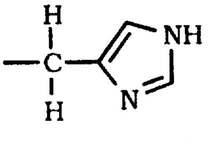
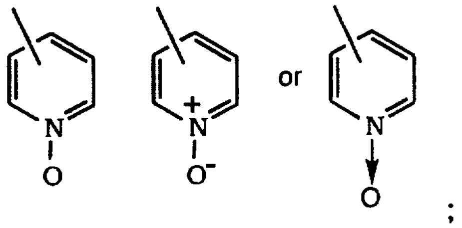
such as $-CH_2$-(2-, 4- or 5-)imidazolyl, for example



cycloalkyl-represents saturated carbocyclic rings branched or unbranched of from 3 to 20 carbon atoms, preferably 3 to 7 carbon atoms;

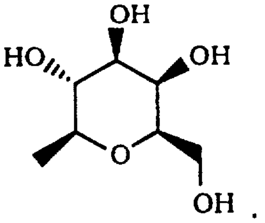
halo-represents fluoro, chloro, bromo and iodo;

heteroaryl-represents cyclic groups, optionally substituted with R^3 and R^4, having at least one heteroatom selected from O, S or N, said heteroatom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups preferably containing from 2 to 14 carbon atoms, e.g., thienyl, (2-, 4- or 5-)imidazolyl, triazolyl, 2-, 3- or 4-pyridyl or pyridyl N-oxide (optionally substituted with R^3 and R^4), wherein pyridyl N-oxide can be represented as:



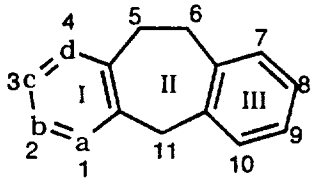
heteroarylalkyl-represents a heteroaryl group, as defined above, bound to an alkyl group, as defined above, preferably the alkyl group is $-CH_2-$ (e.g., $-CH_2-$(4- or 5-)imidazolyl);

heterocycloalkyl-represents a saturated, branched or unbranched carbocylic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 hetero groups selected from -O-, -S- or - NR^{10}-; suitable heterocycloalkyl groups include: (1) 2- or 3-tetrahydrofuranyl, (2) 2- or 3- tetrahydrothienyl, (3) 2-, 3- or 4-piperidinyl, (4) 2- or 3-pyrrolidinyl, (5) 2- or 3-piperizinyl, (6) 2- or 4-dioxanyl, (7) tetrahydopyranyl, and (8) substituted tetrahydropyranyl wherein said substituents are selected from hydroxy and hydroxyalkyl (e.g., hydroxymethyl), for example D-galactosyl, i.e.,



The following solvents and reagents are referred to herein by the abbreviations indicated: ethanol (EtOH); methanol (MeOH); acetic acid (HOAc or AcOH); ethyl acetate (EtOAc); N,N-dimethylformamide (DMF); trifluoroacetic acid (TFA); trifluoroacetic anhydride (TFAA); 1-hydroxybenzo-triazole (HOBT); 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (DEC); diisobutylaluminum hydride (DIBAL); and 4-methylmorpholine (NMM).

Reference to the position of the substituents R^1, R^2, R^3, and R^4 is based on the numbered ring structure:



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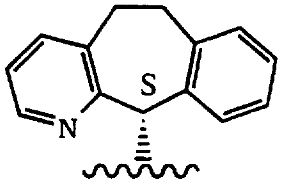
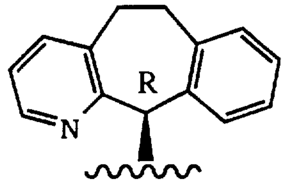
Those skilled in the art will also appreciate that the S and R stereochemistry at the C-11 bond are:





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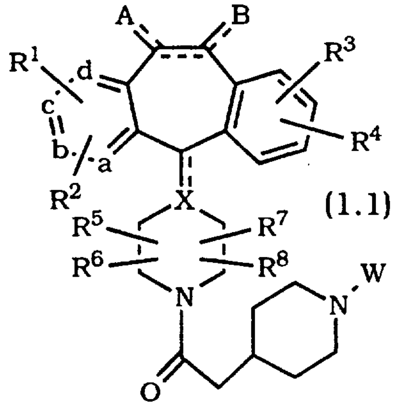
Compounds of Formula 1.0 include compounds wherein the bottom piperidinyl group is a 4- or 3-piperidinyl group, i.e.,



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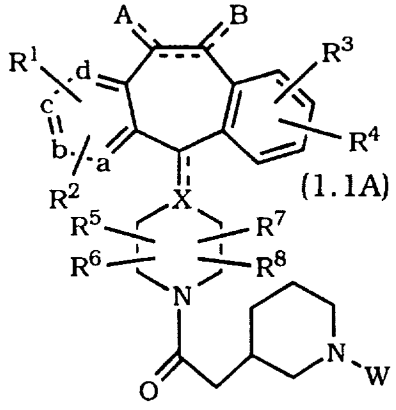

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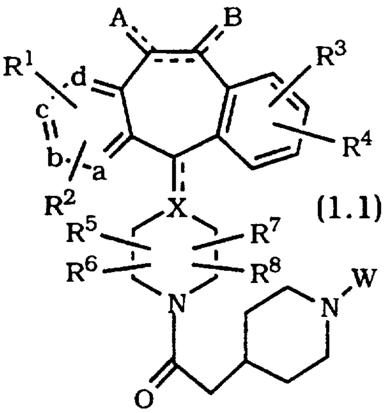
Compounds of Formula 1.0 include compounds wherein R^2 and R^4 are H, and R^1 and R^3 are halo (preferably independently selected from Br or Cl). For example, R^1 is Br and R^3 is Cl. These compounds include compounds wherein R^1 is in the 3-position and R^3 is in the 8-position, e.g., 3-Br and 8-Cl. Compounds of Formula 1.0 also include compounds wherein R^2 is H, and R^1, R^3 and R^4 are halo (preferably independently selected from Br or Cl).

Preferably, compounds of Formula 1.0 are represented by compounds of Formula 1.1:

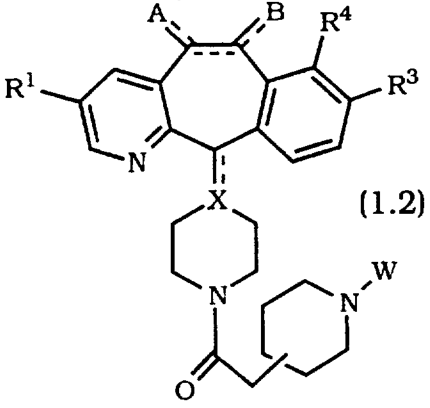


(1.1)

wherein all substituents are as defined for Formula 1.0.

Preferably, R^2 is H and R^1, R^3 and R^4 are halo; a is N and b, c and d are carbon; A and B are each H_2; the optional bond between C5 and C6 is absent; X is CH; and R^5, R^6, R^7 and R^8 are H. More preferably, R^1, R^3 and R^4 are independently selected from Br or Cl. Most preferably, R^1 is Br, and R^3 and R^4 are independently selected from Cl and Br.

More preferably, compounds of Formula 1.0 are represented by compounds of Formula 1.2 and Formula 1.3:



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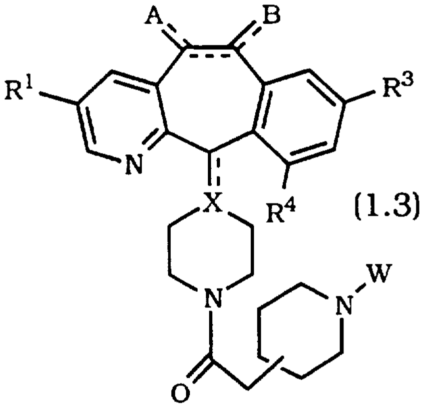

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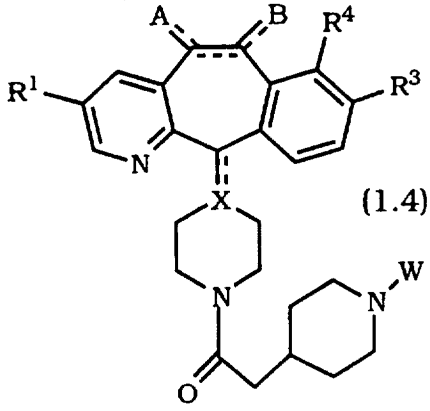
and most preferably, compounds of Formulas 1.4 and 1.5



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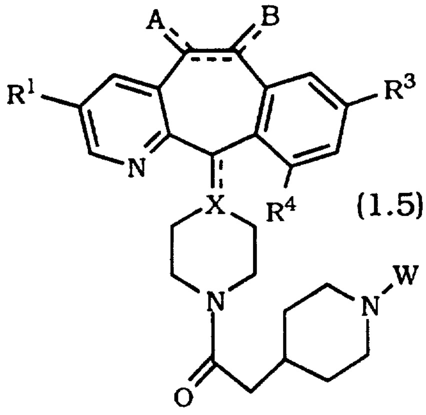
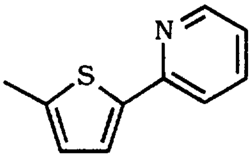


(1.5)

wherein R^1, R^3 and R^4 are each independently selected from halo, preferably, Br or Cl; and A, B, X and W are as defined for

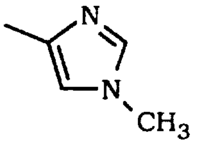
Formula 1.0. More preferably, A and B are each H_2; the optional bond between C5 and C6 is absent; and X is CH. Most preferably, R^1 is Br; R^3 and R^4 are independently Br or Cl, and still more preferably R^3 is Cl and R^4 is Br; A and B are each H_2; the optional bond between C5 and C6 is absent; X is CH; and R^5, R^6, R^7 and R^8 are H.

When W represents $-SO_2R^{12}$, R^{12} is preferably selected from the group consisting of: (1) alkyl (e.g., methyl, ethyl, n-propyl or iso-propyl), (2) aryl (e.g., phenyl), (3) heteroaryl (e.g., thienyl), (4) substituted heteroaryl (e.g.,



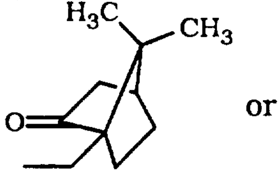
,

i.e., 2-(pyrid-2-yl)thien-5-yl, or N-methylimidazol-4-yl, i.e.,

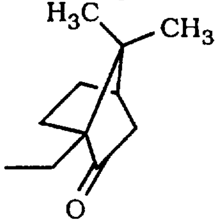


);

(5) aralkyl (e.g., benzyl), (6) camphor (e.g.,



or



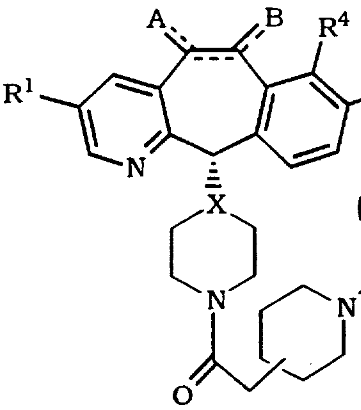
), and

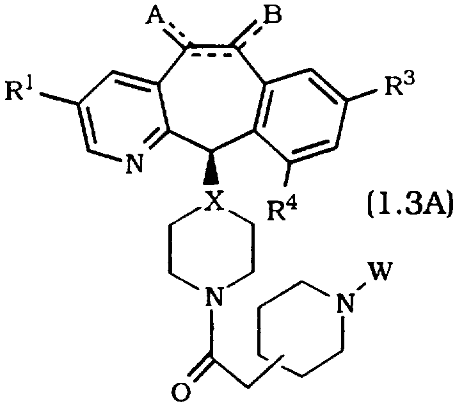
(7) $-NR^{15}R^{16}$ wherein R^{15} and R^{16} are independently selected from the group consisting of: H or alkyl (e.g., methyl).

More preferably, R^{12} is selected from methyl, ethyl, propyl, isopropyl, N-methylimidazol-4-yl, $-NH_2$ or $-N(CH_3)_2$.

Preferably, when W represents $-P(O)R^{13}R^{14}$, R^{13} and R^{14} are independently alkyl (e.g., each are the same and each is methyl).

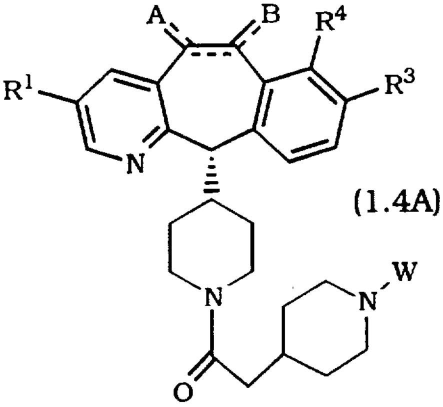
Compounds of Formulas 1.2A and 1.3A:


(1.2A)

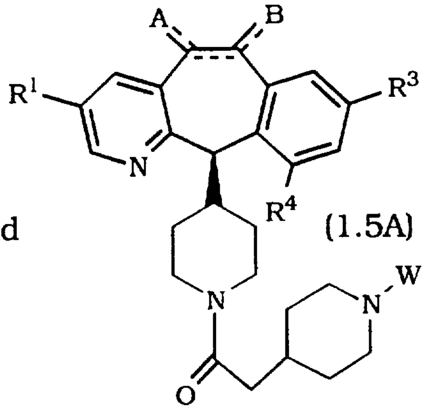

(1.3A)

are preferred when X is CH or N, and R^1, R^3 and R^4 are halo.

The preferred compounds of this invention are represented by the compounds of Formulas:

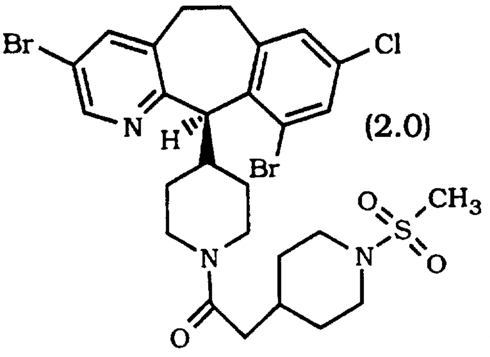

(1.4A)

and

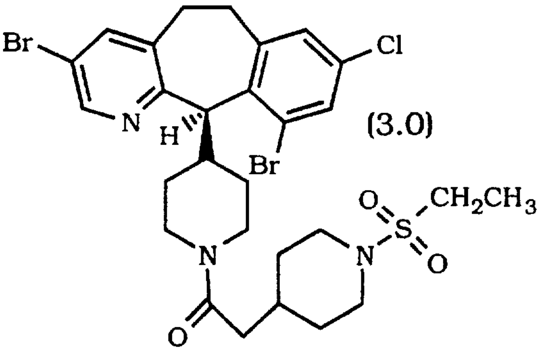

(1.5A)

wherein R^1, R^3 and R^4 are halo and the remaining substituents are as defined above, with the compounds of Formula 1.5A being more preferred.

Representative compounds of Formula 1.0 wherein W is $-SO_2R^{12}$ include:

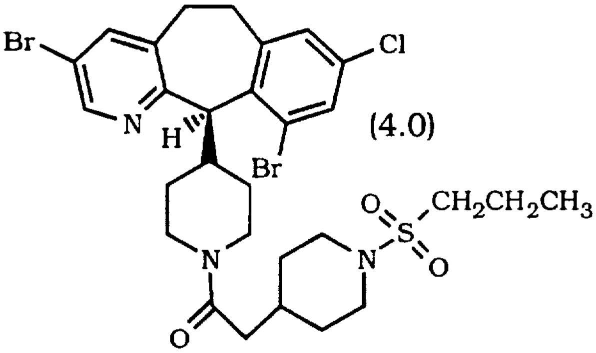

(2.0)

;


Br
Cl
N
H
Br
N
O
CH_2CH_3
O
S
N
O

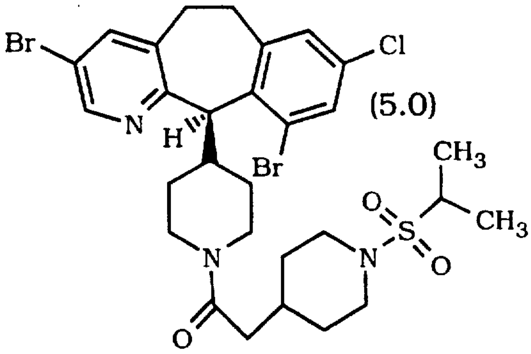
(3.0)

;


Br
Cl
N
H
Br
N
O
$CH_2CH_2CH_3$
O
S
N
O

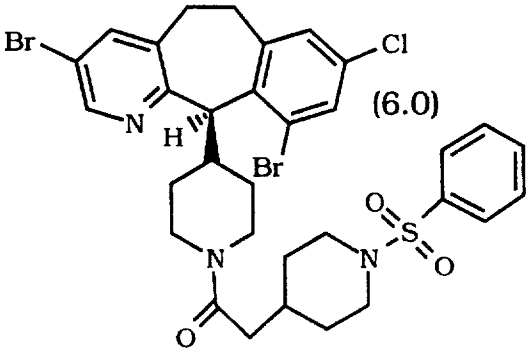
(4.0)

;


Br
Cl
N
H
Br
CH_3
O
CH_3
S
N
O
N
O

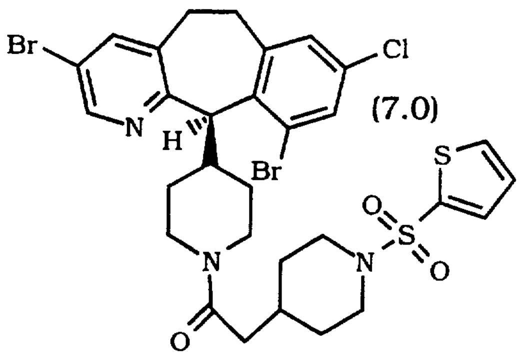
(5.0)

;


Br
Cl
N
H
Br
O
S
N
O
N
O

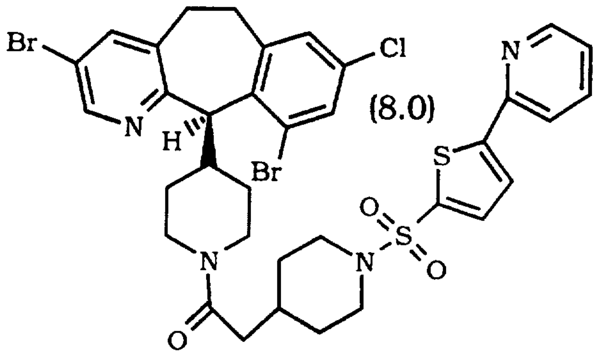
(6.0)

;



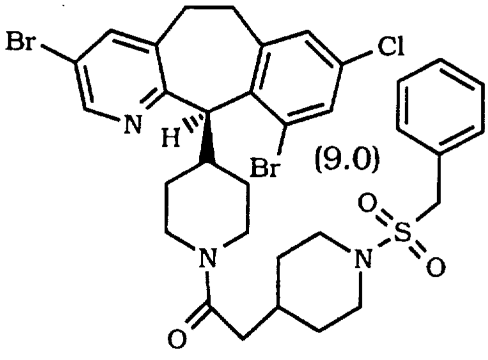
(7.0)

;



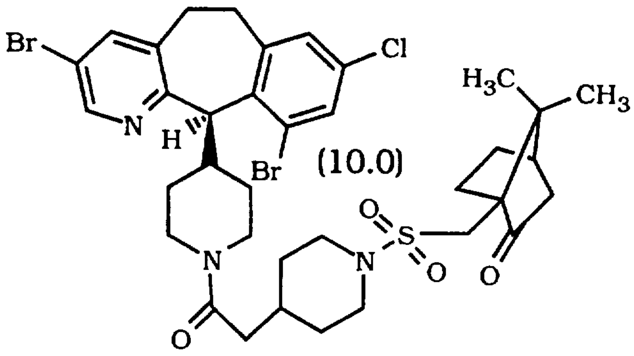
(8.0)

;



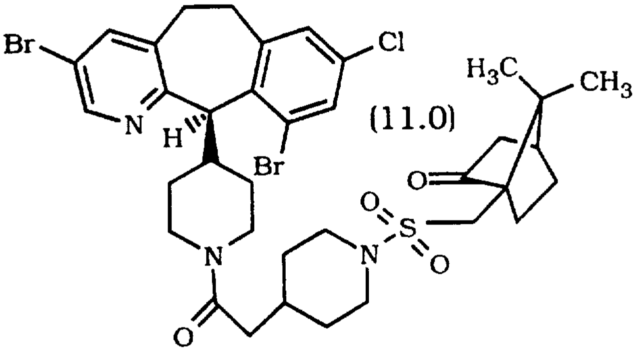
(9.0)

;

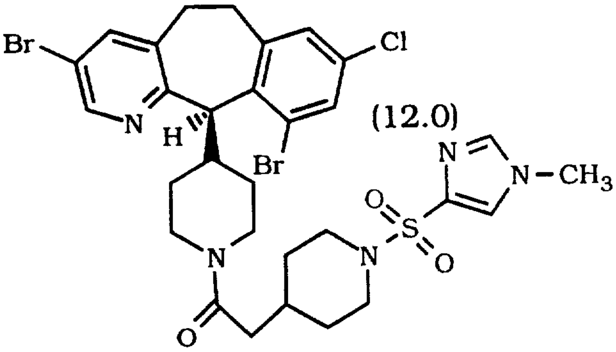


(10.0)

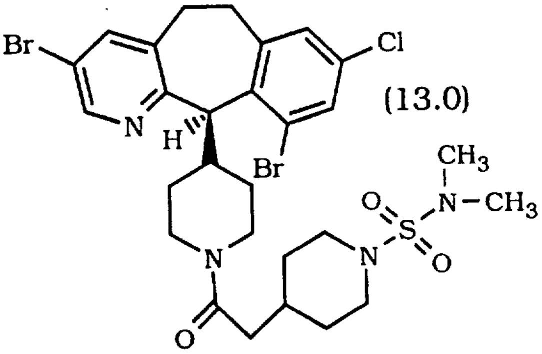
;



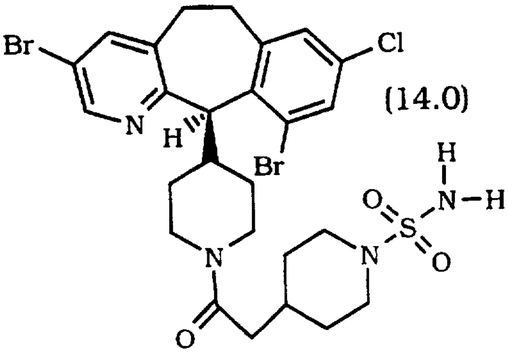
(11.0) ;



(12.0) ;

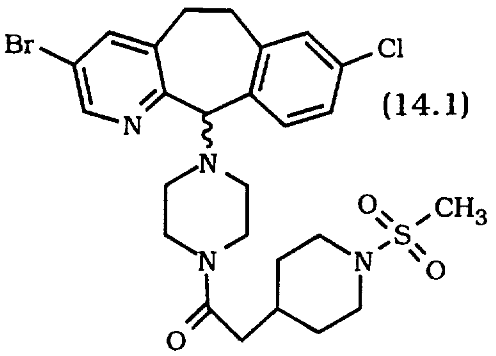


(13.0) and



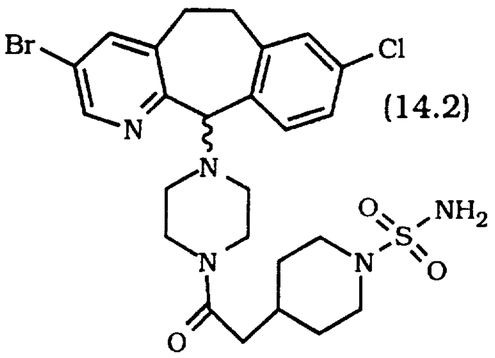
(14.0) .

Representative compounds of Formula 1.0 wherein W is $-SO_2R^{12}$ also include:



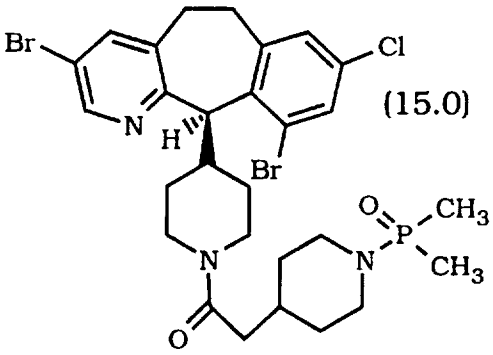
(14.1)

and



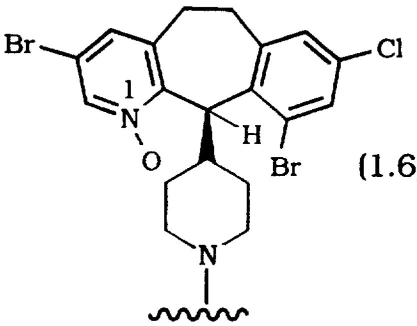
(14.2)

Representative compounds of Formula 1.0 wherein W is $-P(O)R^{13}R^{14}$ include:



(15.0)

The compounds of this invention also include the 1-N-oxides--i.e, for example, compounds of the the formula:



(1.6)

wherein ∿∿∿ represents the remainder of the compound, or pharmaceutically acceptable salts or solvates thereof.

Optical rotation of the compounds ((+)- or (-)-) are measured in methanol or ethanol at 25°C.

This invention includes the above compounds in the amorphous state or in the cyrstalline state.

Lines drawn into the ring systems indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

Certain compounds of the present invention may exist in different isomeric forms (e.g., enantiomers or diastereoisomers) including atropisomers (i.e., compounds wherein the 7-membered ring is in a fixed conformation such that the 11-carbon atom is positioned above or below the plane of the fused beznene rings due to the presence of a 10-bromo substituent). The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

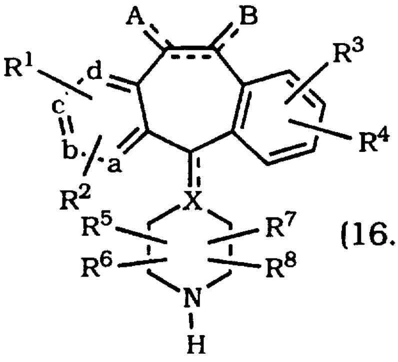
Certain tricyclic compounds will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated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

Certain basic tricyclic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker 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 NaOH, 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.

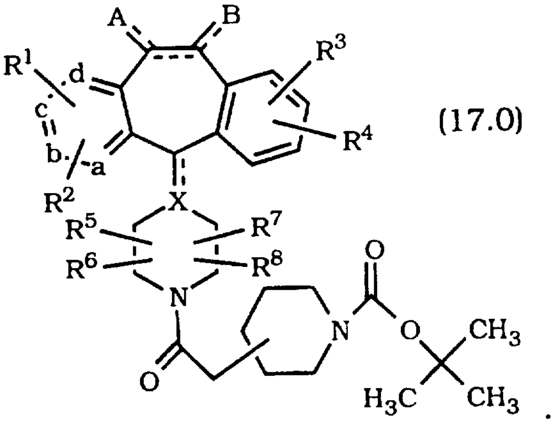
Compounds of the invention may be prepared according to the procedures described in WO 95/10516 published April 20, 1995, Application Serial No. 08/410,187 filed March 24, 1995, Application Serial No. 08/577,951 filed December 22, 1995 (now abandoned), Application Serial No. 08/615,760 filed March 13, 1996 (now abandoned), WO 97/23478 published July 3, 1997 which discloses the subject matter of Serial No. 08/577,951 and 08/615,760, and Application Serial No. 08/712,924 filed September 13, 1996; the disclosures of each being incorporated herein by reference thereto; and according to the procedures described below.

Compounds of the invention can be prepared by reacting a compound of the formula:



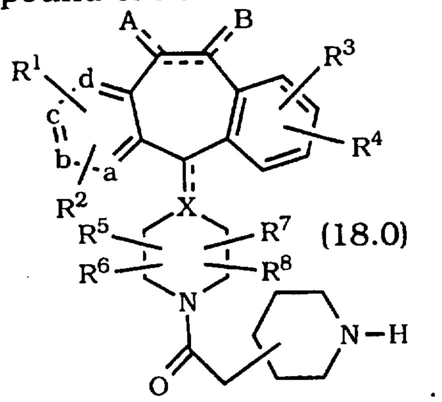
(16.0)

wherein all substituents are as defined for Formula 1.0, with the appropriate protected piperidinyl acetic acid (e.g., 1-N-t-butoxycarbonylpiperidinyl acetic acid together with DEC/HOBT/NMM in DMF at about 25°C for about 18 hours to produce a compound of the formula:



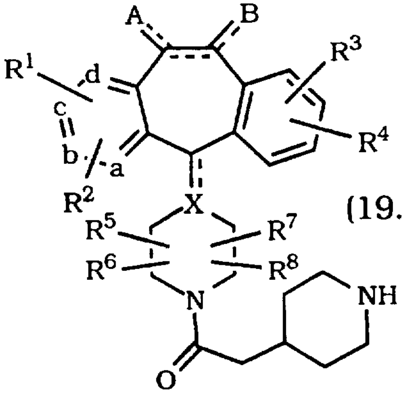
(17.0)

The compound of Formula 17.0 is then reacted either with TFA or 10% sulfuric acid in dioxane and methanol followed by NaOH to produce the compound of Formula 18.0



(18.0)

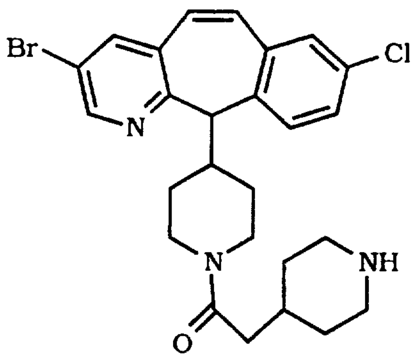
For example, the compound of formula



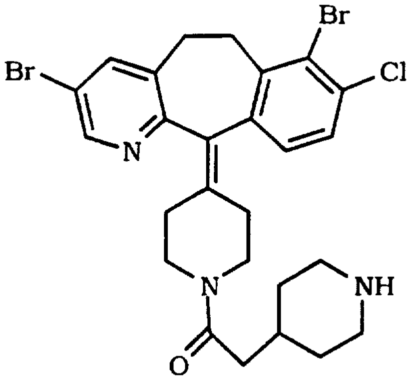
(19.0)

can be prepared by reaction of a compound of Formula 16.0 with 1-N-t-butoxy-carbonylpiperidinyl-4-acetic acid as described above.

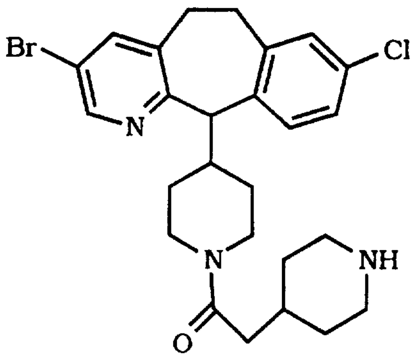
For Example, compounds of Formula 19.0 include the compounds:


Br
Cl
N
N
NH
O

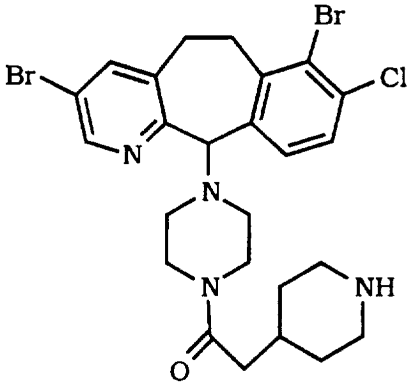
;


Br
Br
Cl
N
N
NH
O

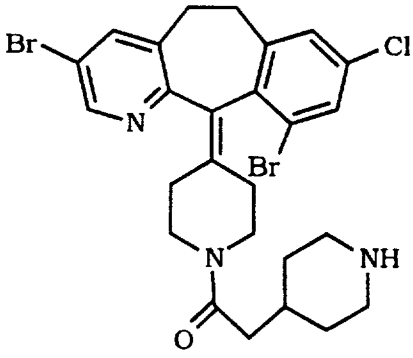
;


Br
Cl
N
N
NH
O

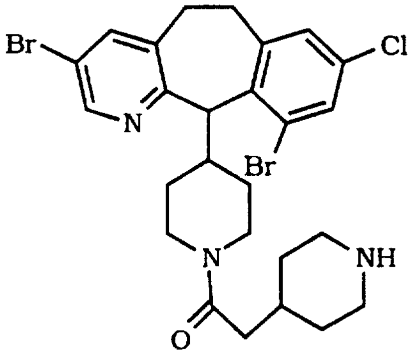
;


Br
Br
Cl
N
N
N
NH
O

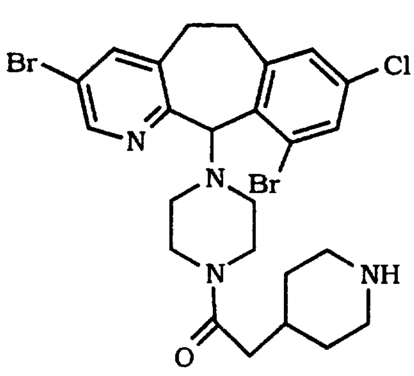
;


Br
Cl
N
Br
N
NH
O

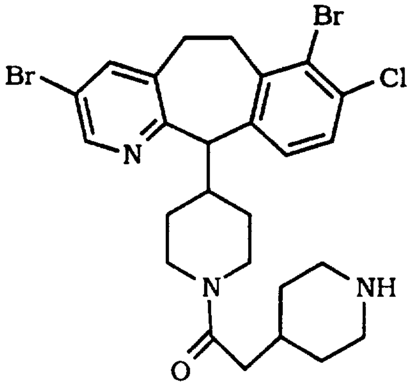
;


Br
Cl
N
Br
N
NH
O

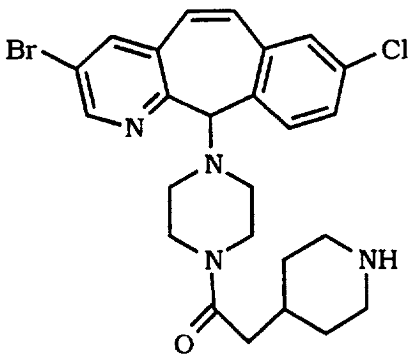
;


Br
Cl
N
N
Br
N
NH
O

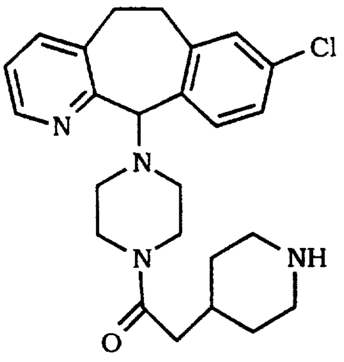
;


Br
Br
Cl
N
N
NH
O

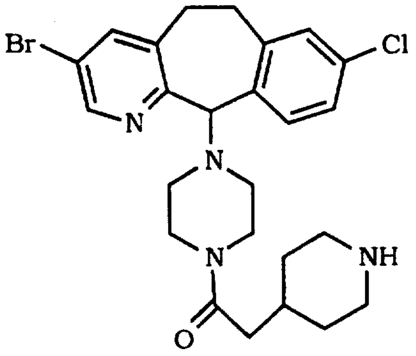
;



;



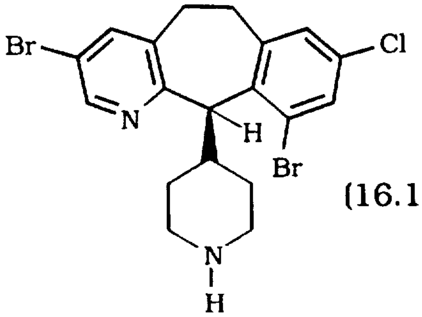
; and



.

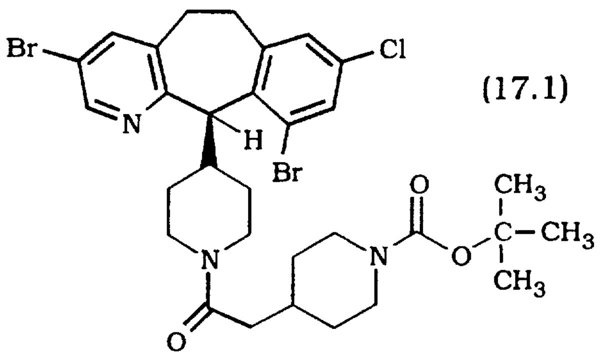
The preparation of these compounds are described in Preparative Examples 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13, respectively, below.

The compounds of the invention can be prepared by reacting a compound of the formula:



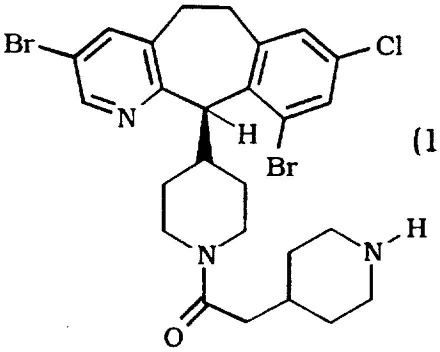
(16.1)

with the appropriate protected piperidinyl acetic acid (e.g., 1-N-t-butoxycarbonylpiperidinyl acetic acid together with DEC/HOBT/NMM in DMF at about 25°C for about 18 hours to produce a compound of the formula:



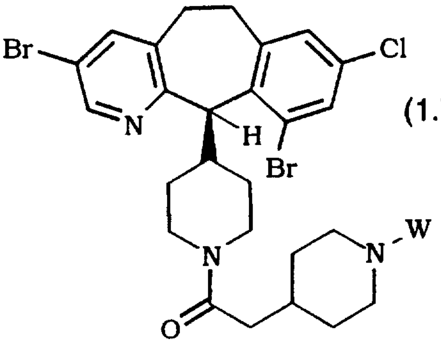
(17.1)

The compound of Formula 17.1 is then reacted either with TFA or 10% sulfuric acid in dioxane and methanol followed by NaOH to produce the compound of Formula 19.1



(19.1)

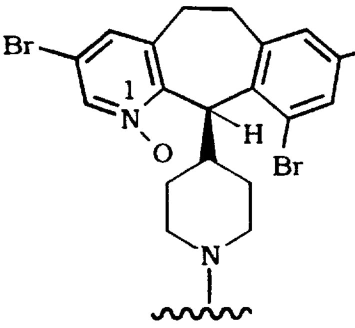
The amide compounds of this invention, represented by Formula 1.7



(1.7)

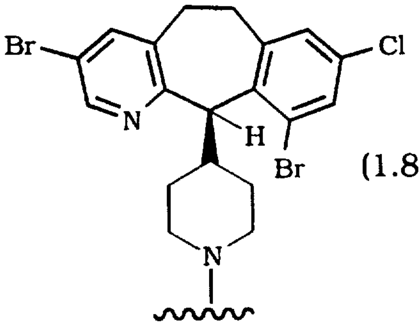
can be prepared by reacting the compound of Formula 19.1 with the appropriate carboxylic acid in the presence of a coupling agent such as DEC and HOBT in dimethylformamide. Alternatively, the compound of Formula 19.1 can be reacted with an acid chloride or anhydride in a solvent such as pyridine.

Compounds having an 1-N-O group:



(1.6)

can be prepared from the corresponding pyridyl compounds:

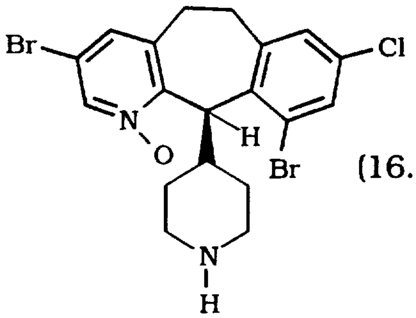


(1.8)

by oxidation with meta-chloroperoxybenzoic acid. This reaction is conducted in a suitable organic solvent, e.g., dichloromethane (usually anhydrous) or methylene chloride, at a suitable temperature, to produce the compounds of the invention having the N-O substituent at position 1 of Ring I of the tricyclic ring system.

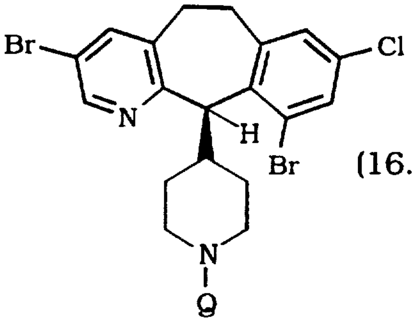
Generally, the organic solvent solution of the starting tricyclic reactant is cooled to about 0°C before the m-chloroperoxybenzoic acid is added. The reaction is then allowed to warm to room temperature during the reaction period. The desired product can be recovered by standard separation means. For example, the reaction mixture can be washed with an aqueous solution of a suitable base, e.g., saturated sodium bicarbonate or NaOH (e.g., 1N NaOH), and then dried over anhydrous magnesium sulfate. The solution containing the product can be concentrated in vacuo. The product can be purified by standard means, e.g., by chromatography using silica gel (e.g., flash column chromatography).

Alternatively, N-O compounds can be made from intermediate:



(16.1A)

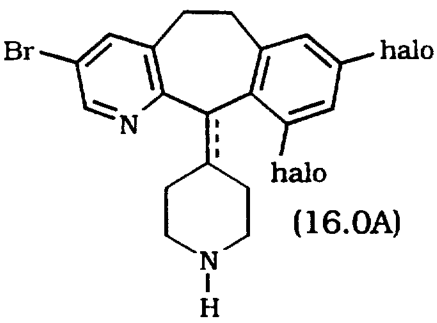
by the above oxidation procedure with m-chloroperoxybenzoic acid and



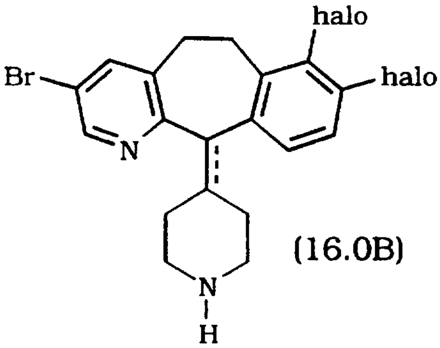
(16.1B)

wherein Q is a protecting group, e.g., BOC. After oxidation the protecting group is removed by techniques well known in the art. The N-O intermediate are then reacted further to produce the compounds of the invention.

Compounds of Formula 16.0 include the compounds of formulas:



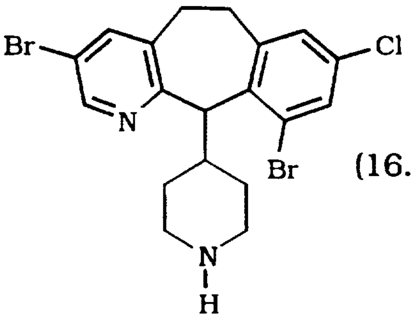
(16.0A)



(16.0B)

,

for example, the compound of formula

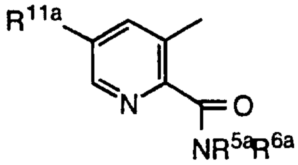


(16.2)

.

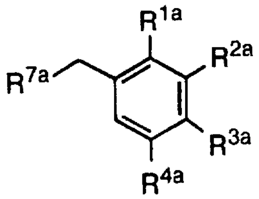
The compound of Formula 16.0A or 16.0B is prepared by methods known in the art, for example by methods disclosed in WO 95/10516, in U.S. 5,151,423 and those described below. The above intermediate compound can also be prepared by a procedure comprising the following steps:

(a) reacting an amide of the formula

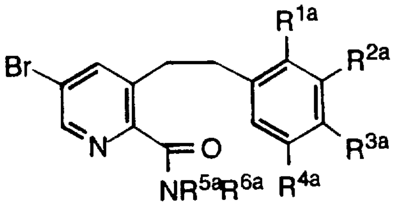


wherein R^{11a} is Br, R^{5a} is hydrogen and R^{6a} is C_1-C_6 alkyl, aryl or heteroaryl; R^{5a} is C_1-C_6 alkyl, aryl or heteroaryl and R^{6a} is hydrogen; R^{5a} and R^{6a} are independently selected from the group consisting of C_1-C_6 alkyl and aryl; or R^{5a} and R^{6a}, together with the nitrogen to which they are attached, form a ring comprising 4 to 6 carbon atoms or comprising 3 to 5 carbon atoms and one hetero moiety selected from the group consisting of -O- and $-NR^{9a}-$, wherein R^{9a} is H, C_1-C_6 alkyl or phenyl;

with a compound of the formula

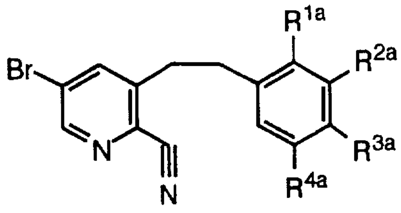


wherein R^{1a}, R^{2a}, R^{3a} and R^{4a} are are independently selected from the group consisting of hydrogen and halo and R^{7a} is Cl or Br, in the presence of a strong base to obtain a compound of the formula



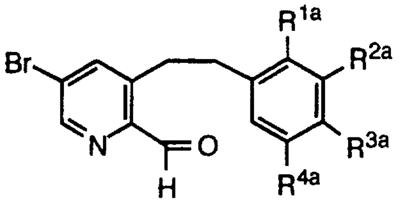
(b) reacting a compound of step (a) with

(i) $POCl_3$ to obtain a cyano compound of the formula



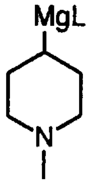
; or

(ii) DIBALH to obtain an aldehyde of the formula

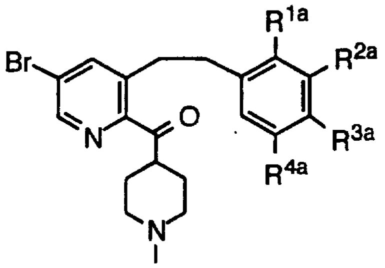


;

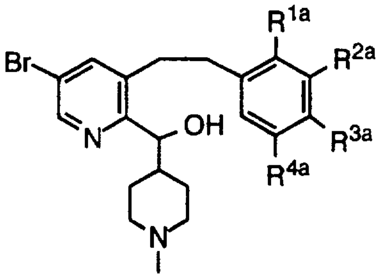
(c) reacting the cyano compound or the aldehyde with a piperidine derivative of the formula



wherein L is a leaving group selected from the group consisting of Cl and Br, to obtain a ketone or an alcohol of the formula below, respectively:



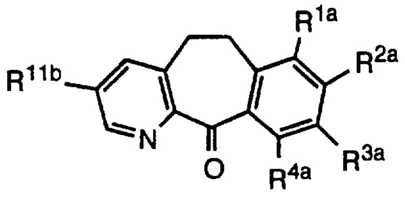
or



(d)(i) cyclizing the ketone with CF_3SO_3H to obtain a compound of Formula 16.0A or 16.0B wherein the dotted line represents a double bond; or

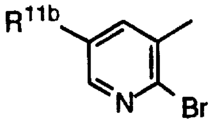
(d)(ii) cyclizing the alcohol with polyphosphoric acid to obtain an Intermediate compound wherein the dotted line represents a single bond.

Methods for preparing the Intermediate compounds disclosed in WO 95/10516, U.S. 5,151,423 and described below employ a tricyclic ketone intermediate. Such intermediates of the formula

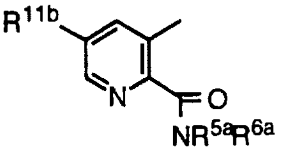


wherein R^{11b}, R^{1a}, R^{2a}, R^{3a} and R^{4a} are independently selected from the group consisting of hydrogen and halo, can be prepared by the following process comprising :

(a) reacting a compound of the formula

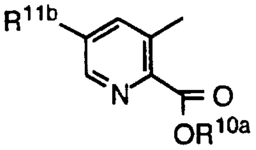


(i) with an amine of the formula $NHR^{5a}R^{6a}$, wherein R^{5a} and R^{6a} are as defined in the process above; in the presence of a palladium catalyst and carbon monoxide to obtain an amide of the formula:



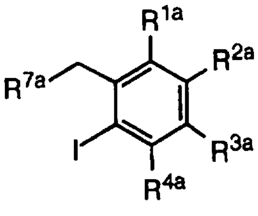
or

(ii) with an alcohol of the formula $R^{10a}OH$, wherein R^{10a} is C_1-C_6 lower alkyl or C_3-C_6 cycloalkyl, in the presence of a palladium catalyst and carbon monoxide to obtain the ester of the formula

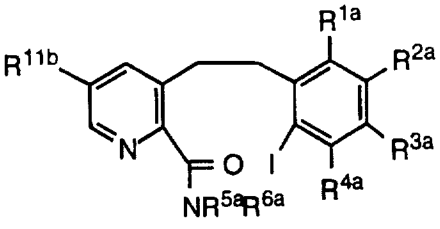


followed by reacting the ester with an amine of formula $NHR^{5a}R^{6a}$ to obtain the amide;

(b) reacting the amide with an iodo-substituted benzyl compound of the formula



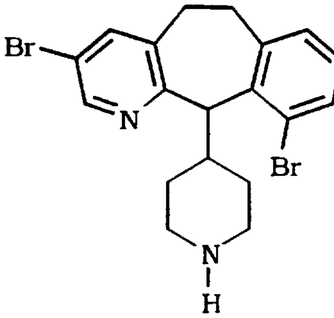
wherein R^{1a}, R^{2a}, R^{3a}, R^{4a} and R^{7a} are as defined above, in the presence of a strong base to obtain a compound of the formula



; and

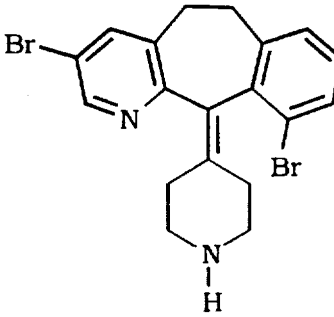
(c) cyclizing a compound of step (b) with a reagent of the formula $R^{8a}MgL$, wherein R^{8a} is C_1-C_8 alkyl, aryl or heteroaryl and L is Br or Cl, provided that prior to cyclization, compounds wherein R^{5a} or R^{6a} is hydrogen are reacted with a suitable N-protecting group.

(+)-Isomers of compounds of Formula 16.2



(16.2)

can be prepared with high enantioselectivity by using a process comprising enzyme catalyzed transesterification. Preferably, a racemic compound of Formula 16.3



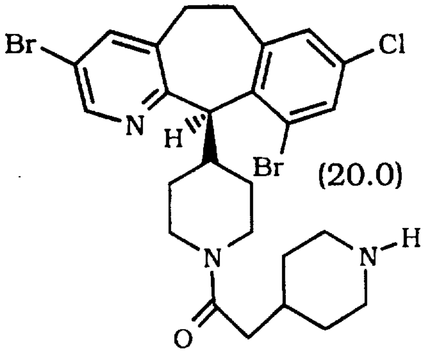
(16.3)

is reacted with an enzyme such as Toyobo LIP-300 and an acylating agent such as trifluoroethly isobutyrate; the resultant (+)-amide is then isolated from the (-)-enantiomeric amine by techniques well known in the art, and then the (+)-amide is hydrolyzed, for example by refluxing with an acid such as H_2SO_4, and the resulting compound is then reduced with DIBAL by techniques well known in the art to obtain the corresponding optically enriched (+)-isomer of Formula 16.2. Alternatively, a racemic compound of Formula 16.3, is first reduced to the corresponding racemic compound of Formula 16.2 and then treated with the enzyme (Toyobo LIP-300) and acylating agent as described above to obtain the (+)-amide, which is hydrolyzed to obtain the optically enriched (+)-isomer.

Those skilled in the art will appreciate that compounds of Formula 1.0 having other R^1, R^2, R^3 and R^4 substituents may be made by the above enzyme process.

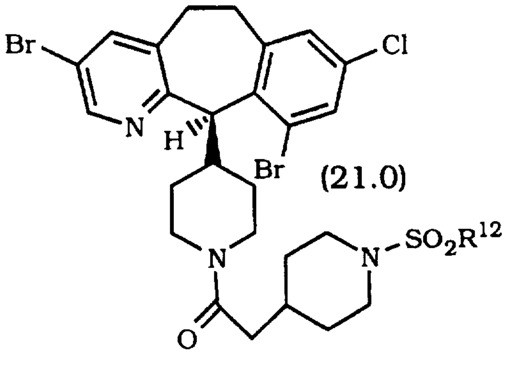
To produce the compounds of Formula 1.0, the compounds of Formulas 18.0 or 19.0 are reacted with the appropriate sulfonyl chloride ($R^{12}SO_2Cl$) or sulfamoyl chloride ($R^{15}R^{16}NSO_2Cl$) when W is $-SO_2R^{12}$, or the appropriate phosphinyl chloride ($R^{13}R^{14}P(O)Cl$) when W is $-P(O)R^{13}R^{14}$. This reaction is conducted according to procedures well known in the art. For example, the compounds of Formulas 18.0 or 19.0 are reacted with the appropriate sulfonyl chloride or sulfamoyl chloride in a suitable organic solvent (e.g., dichloromethane) with a suitable base (e.g., triethylamine).

For example, reaction of the compound of the formula



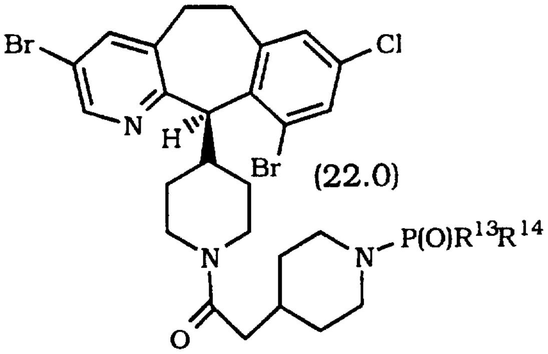
(20.0)

with ($R^{12}SO_2Cl$) or $R^{13}R^{14}P(O)Cl$ in dichloromethane and triethylamine, or $R^{15}R^{16}NSO_2Cl$ in acetonitrile and triethylamine yields compounds of the formulas:



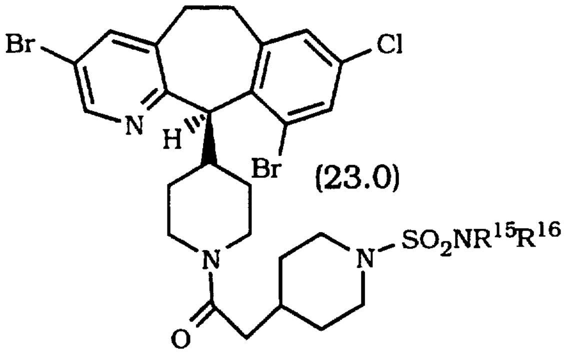
(21.0)

,



(22.0)

, or

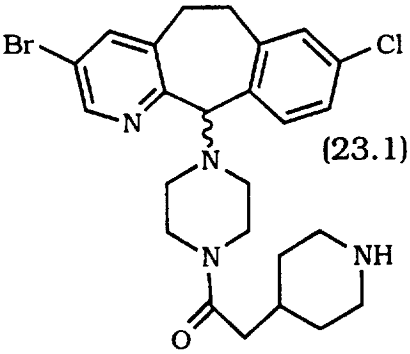


(23.0)

,

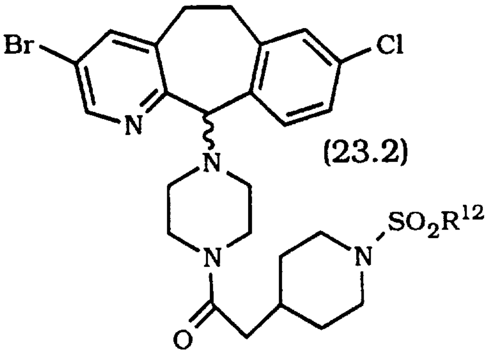
respectively.

Similarly, reaction of the compound of the formula:



(23.1)

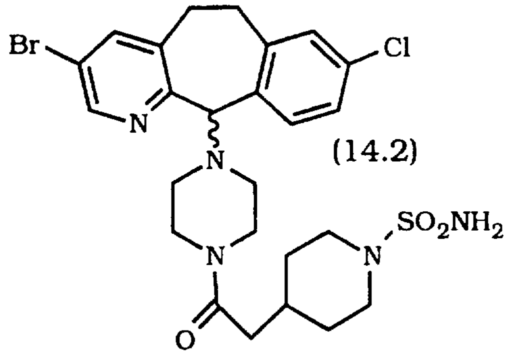
with $R^{12}SO_2Cl$ in dichloromethane and triethylamine yields compounds of the formula:



(23.2)

.

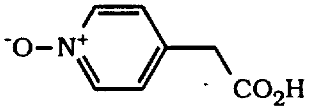
Alternatively, reaction of the compound of Formula 23.1 preferably with an excess of sulfamide in water at about 100°C, or with sulfamide in a melt at about 150°C, or with sulfamide in isopropanol at about 86°C, yields a compound of the formula:



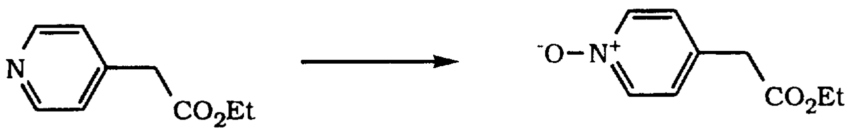
(14.2)

Compounds of the invention are exemplified by the following examples, which should not be construed to limit the scope of the disclosure.

PREPARATIVE EXAMPLE 1

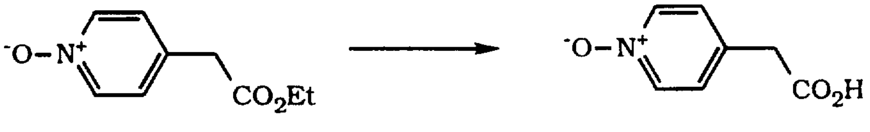


Step A:



Combine 10 g (60.5 mmol) of ethyl 4-pyridylacetate and 120 mL of dry CH_2Cl_2 at -20°C, add 10.45 g (60.5 mmol) of MCPBA and stir at -20°C for 1 hour and then at 25°C for 67 hours. Add an additional 3.48 g (20.2 mmoles) of MCPBA and stir at 25°C for 24 hours. Dilute with CH_2Cl_2 and wash with saturated $NaHCO_3$ (aqueous) and then water. Dry over $MgSO_4$, concentrate in vacuo to a residue, and chromatograph (silica gel, 2%-5.5% (10% NH_4OH in MeOH)/CH_2Cl_2)to give 8.12 g of the product compound. Mass Spec.: $MH^+ = 182.15$

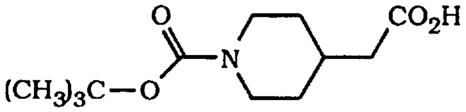
Step B:



Combine 3.5 g (19.3 mmol) of the product of Step A, 17.5 mL of EtOH and 96.6 mL of 10% NaOH (aqueous) and heat the

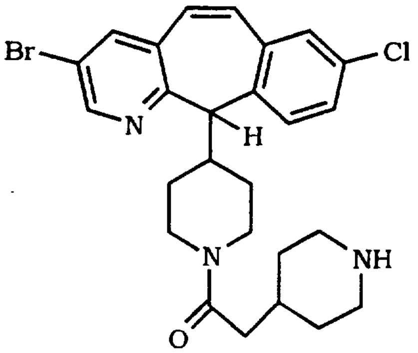
mixture at 67°C for 2 hours. Add 2 N HCl (aqueous) to adjust to pH = 2.37 and concentrate in vacuo to a residue. Add 200 mL of dry EtOH, filter through celite® and wash the filter cake with dry EtOH (2X50 ml). Concentrate the combined filtrates in vacuo to give 2.43 g of the title compound.

PREPARATIVE EXAMPLE 2

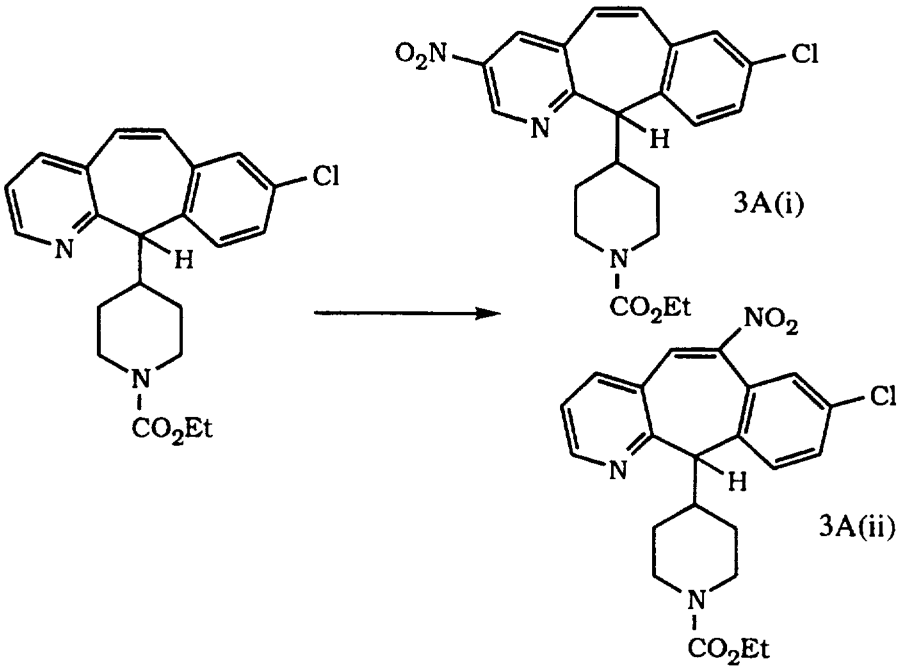


The title compound is prepared via the process disclosed in PCT International Publication No. WO95/10516.

PREPARATIVE EXAMPLE 3



Step A:

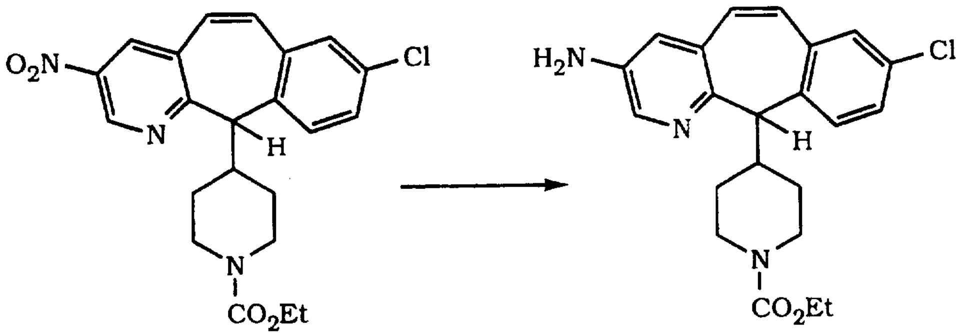


Combine 14.95 g (39 mmol) of 8-chloro-11-(1-ethoxycarbonyl-4-piperidinyl)-11H-benzo[5,6]cyclohepta[1,2-b]pyridine and 150 mL of CH_2Cl_2, then add 13.07 g (42.9 mmol) of $(nBu)_4NNO_3$ and cool the mixture to 0°C. Slowly add (dropwise) a solution of 6.09 mL (42.9 mmol) of TFAA in 20 mL of CH_2Cl_2 over 1.5 hours. Keep the mixture at 0°C overnight, then wash successively with saturated $NaHCO_3$ (aqueous), water and brine. Dry the organic solution over Na_2SO_4, concentrate in vacuo to a residue and chromatograph the residue (silica gel, EtOAc/hexane gradient) to give 4.32 g and 1.90 g of the two product compounds 3A(i) and 3A(ii), respectively.

Mass Spec. for compound 3A(i): $MH^+ = 428.2$;

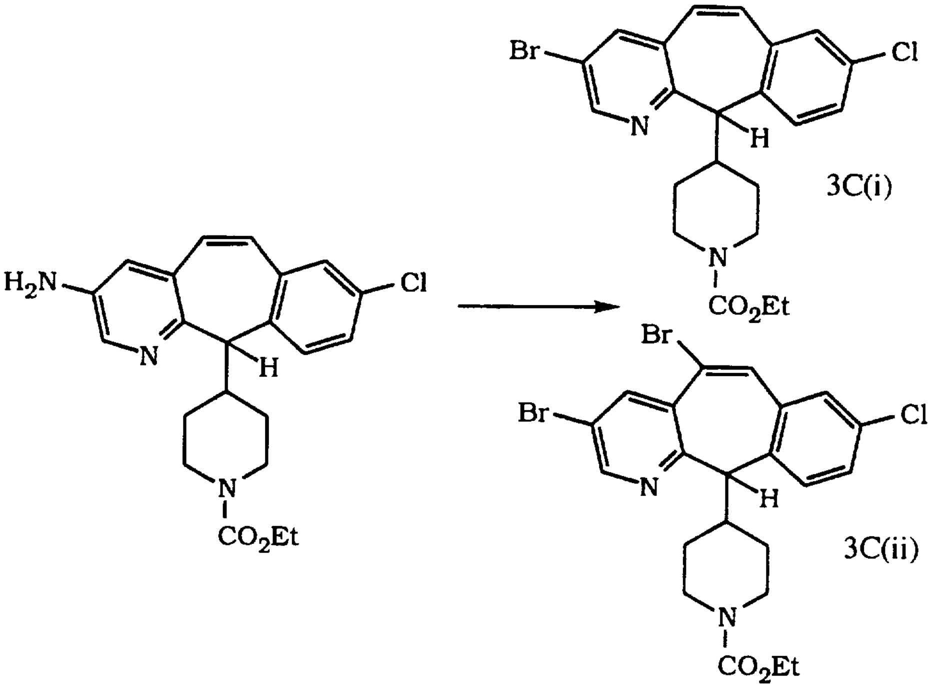
Mass Spec. for compound 3A(ii): $MH^+ = 428.3$.

Step B:



Combine 22.0 g (51.4 mmol) of the product 3A(i) from Step A, 150 mL of 85% EtOH (aqueous), 25.85 g (0.463 mole) of Fe powder and 2.42 g (21.8 mmol) of $CaCl_2$, and heat at reflux overnight. Add 12.4 g (0.222 mole) of Fe powder and 1.2 g (10.8 mmol) of $CaCl_2$ and heat at reflux for 2 hours. Add another 12.4 g (0.222 mole) of Fe powder and 1.2 g (10.8 mmol) of $CaCl_2$ and heat at reflux for 2 hours more. Filter the hot mixture through celite®, wash the celite® with 50 mL of hot EtOH and concentrate the filtrate in vacuo to a residue. Add 100 mL of anhydrous EtOH, concentrate to a residue and chromatograph the residue (silica gel, $MeOH/CH_2Cl_2$ gradient) to give 16.47 g of the product compound.

Step C:



3C(i)

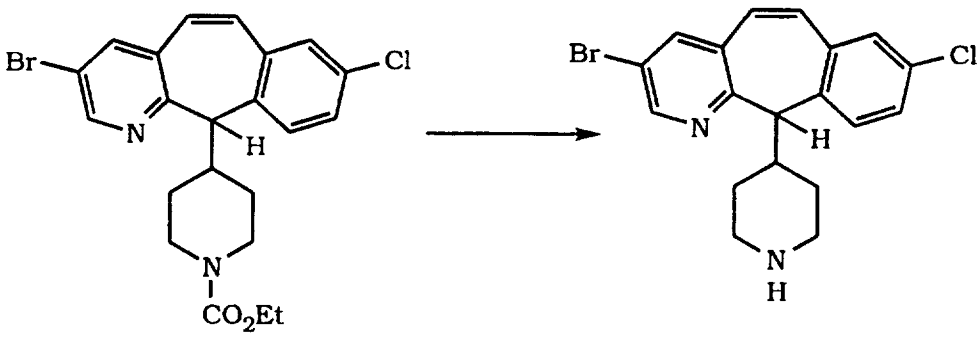
3C(ii)

Combine 16.47 g (41.4 mmol) of the product from Step B, and 150 mL of 48% HBr (aqueous) and cool to -3°C. Slowly add (dropwise) 18 mL of bromine, then slowly add (dropwise) a solution of 8.55 g (0.124 mole) of $NaNO_2$ in 85 mL of water. Stir for 45 minutes at -3° to 0°C, then adjust to pH = 10 by adding 50% NaOH (aqueous). Extract with EtOAc, wash the extracts with brine and dry the extracts over Na_2SO_4. Concentrate to a residue and chromatograph (silica gel, EtOAc/hexane gradient) to give 10.6 g and 3.28 g of the two product compounds 3C(i) and 3C(ii), respectively.

Mass Spec. for compound 3C(i): $MH^+ = 461.2$;

Mass Spec. for compound 3C(ii): $MH^+ = 539$.

Step D:

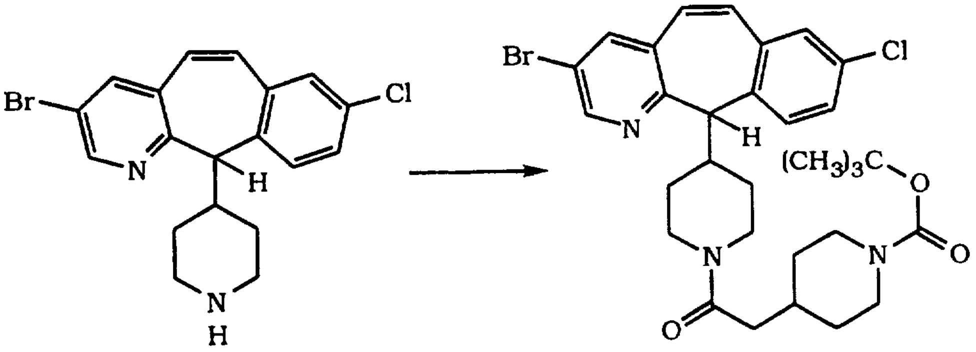


Hydrolyze the product 3C(i) of Step C by dissolving in concentrated HCl and heating to about 100°C for @ 16 hours.

Cool the mixture, the neutralize with 1 M NaOH (aqueous). Extract with CH_2Cl_2, dry the extracts over $MgSO_4$, filter and concentrate in vacuo to the title compound.

Mass Spec.: $MH^+ = 466.9$.

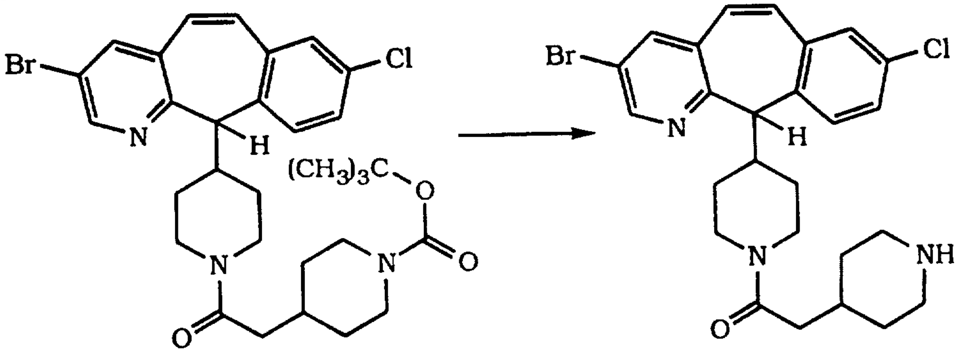
Step E:



Dissolve 1.160 g (2.98 mmol) of the title compound from Step D in 20 mL of DMF, stir at room temperature, and add 0.3914 g (3.87 mmol) of 4-methyl-morpholine, 0.7418 g (3.87 mmol) of DEC, 0.5229 g (3.87 mmol) of HOBT, and 0.8795 g (3.87 mmol) of 1-N-t-butoxycarbonyl-piperidinyl-4-acetic acid. Stir the mixture at room temperature for 2 days, then concentrate in vacuo to s residue and partition the residue between CH_2Cl_2 and water. Wash the organic phase successively with saturated $NaHCO_3$ (aqueous), 10% NaH_2PO_4 (aqueous) and brine. Dry the organic phase over $MgSO_4$, filter and concentrate in vacuo to a residue. Chromatograph the residue (silica gel, 2% MeOH/ CH_2Cl_2 + NH_3) to give 1.72 g of the product. m.p. = 94.0-94.5°C, Mass Spec.: $MH^+ = 616.3$,

elemental analysis: calculated - C, 60.54; H, 6.06; N, 6.83
found - C, 59.93; H, 6.62; N, 7.45.

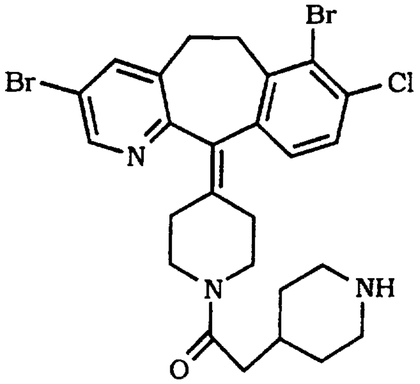
Step F:



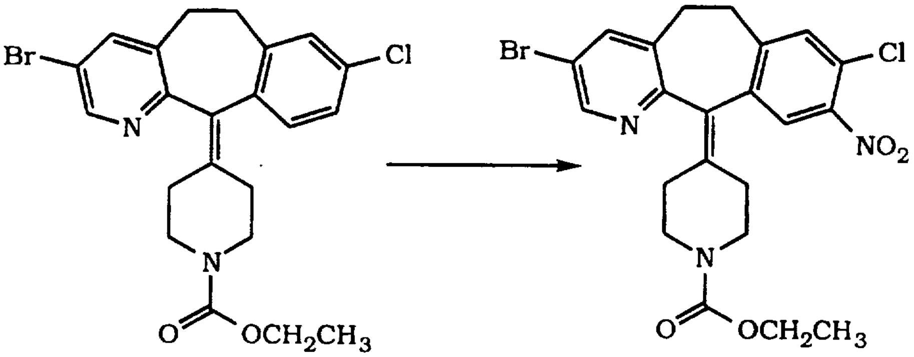
Combine 1.67 g (2.7 mmol) of the product of Step E and 20 mL of CH_2Cl_2 and stir at 0°C. Add 20 mL of TFA, stir the mixture

for 2 hours, then basify the mixture with 1 N NaOH (aqueous). Extract with CH_2Cl_2, dry the organic phase over $MgSO_4$, filter and concentrate in vacuo to give 1.16 g of the product. m.p. = 140.2-140.8°C, Mass Spec.: $MH^+ = 516.2$.

PREPARATIVE EXAMPLE 4



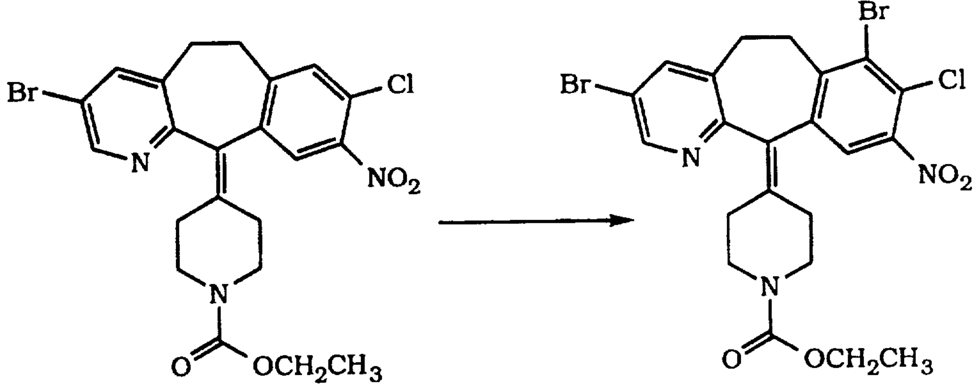
Step A:



Combine 25.86 g (55.9 mmol) of 4-(8-chloro-3-bromo-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester and 250 mL of concentrated H_2SO_4 at -5°C, then add 4.8 g (56.4 mmol) of $NaNO_3$ and stir for 2 hours. Pour the mixture into 600 g of ice and basify with concentrated NH_4OH (aqueous). Filter the mixture, wash with 300 mL of water, then extract with 500 mL of CH_2Cl_2. Wash the extract with 200 mL of water, dry over $MgSO_4$, then filter and concentrate in vacuo to a residue. Chromatograph the residue (silica gel, 10% EtOAc/ CH_2Cl_2) to give 24.4 g (86% yield) of the product. m.p. = 165-167°C, Mass Spec.: $MH^+ = 506$ (CI),

elemental analysis:	calculated - C, 52.13; H, 4.17; N, 8.29
	found - C, 52.18; H, 4.51; N, 8.16.

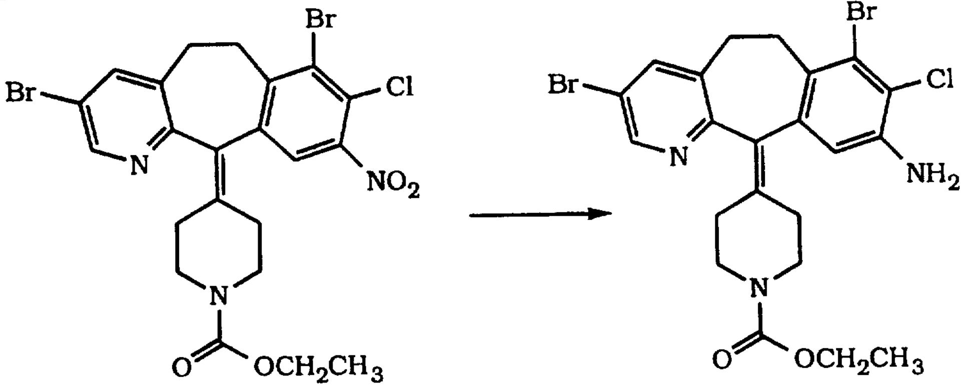
Step B:



Combine 20 g (40.5 mmol) of the product of Step A and 200 mL of concentrated H_2SO_4 at 20°C, then cool the mixture to 0°C. Add 7.12 g (24.89 mmol) of 1,3-dibromo-5,5-dimethylhydantoin to the mixture and stir for 3 hours at 20°C. Cool to 0°C, add an additional 1.0 g (3.5 mmol) of the dibromohydantoin and stir at 20°C for 2 hours. Pour the mixture into 400 g of ice, basify with concentrated NH_4OH (aqueous) at 0°C, and collect the resulting solid by filtration. Wash the solid with 300 mL of water, slurry in 200 mL of acetone and filter to provide 19.79 g (85.6% yield) of the product. m.p. = 236-237°C, Mass Spec.: MH^+ = 584 (CI),

elemental analysis:	calculated - C, 45.11; H, 3.44; N, 7.17
	found - C, 44.95; H, 3.57; N, 7.16.

Step C:

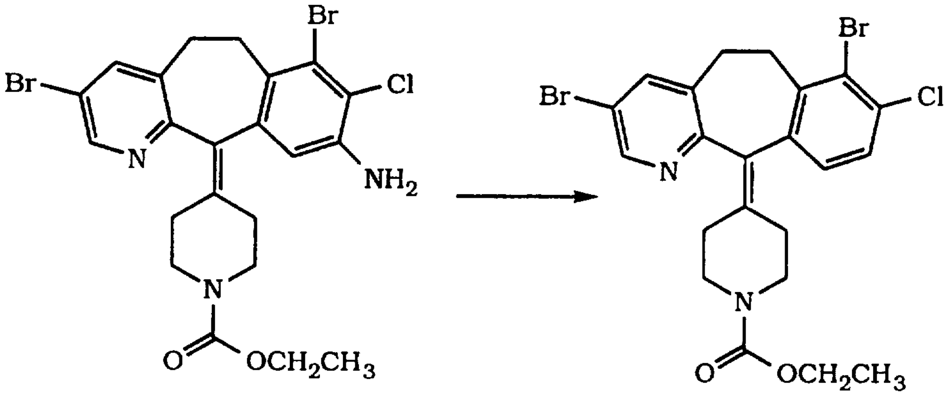


Combine 25 g (447 mmol) of Fe filings, 10 g (90 mmol) of $CaCl_2$ and a suspension of 20 g (34.19 mmol) of the product of Step B in 700 mL of 90:10 EtOH/water at 50°C. Heat the mixture at reflux overnight, filter through Celite® and wash the filter cake with 2 X 200 mL of hot EtOH. Combine the filtrate and washes, and concentrate in vacuo to a residue. Extract the residue with

600 mL of CH_2Cl_2, wash with 300 mL of water and dry over $MgSO_4$. Filter and concentrate in vacuo to a residue, then chromatograph (silica gel, 30% EtOAc/CH_2Cl_2) to give 11.4 g (60% yield) of the product. m.p. = 211-212°C, Mass Spec.: MH^+ = 554 (CI),

elemental analysis: calculated - C, 47.55; H, 3.99; N, 7.56
found - C, 47.45; H, 4.31; N, 7.49.

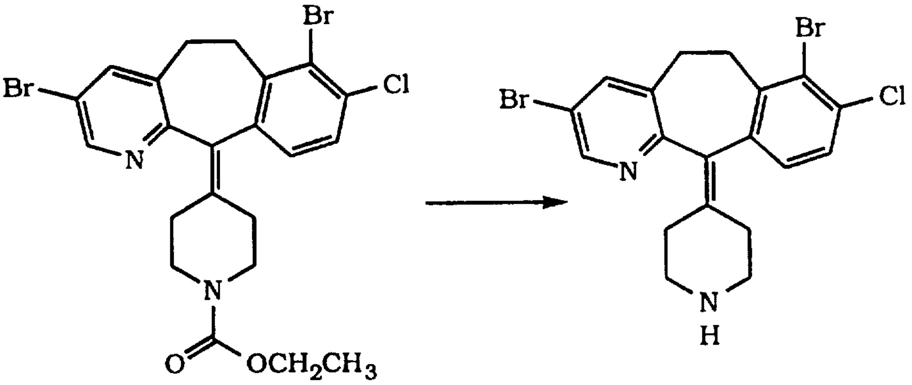
Step D:



Slowly add (in portions) 20 g (35.9 mmol) of the product of Step C to a solution of 8 g (116 mmol) of $NaNO_2$ in 120 mL of concentrated HCl (aqueous) at -10°C. Stir the resulting mixture at 0°C for 2 hours, then slowly add (dropwise) 150 mL (1.44 mole) of 50% H_3PO_2 at 0°C over a 1 hour period. Stir at 0°C for 3 hours, then pour into 600 g of ice and basify with concentrated NH_4OH (aqueous). Extract with 2 X 300 mL of CH_2Cl_2, dry the extracts over $MgSO_4$, then filter and concentrate in vacuo to a residue. Chromatograph the residue (silica gel, 25% EtOAc/hexanes) to give 13.67 g (70% yield) of the product. m.p. = 163-165°C, Mass Spec.: MH^+ = 539 (CI),

elemental analysis: calculated - C, 48.97; H, 4.05; N, 5.22
found - C, 48.86; H, 3.91; N, 5.18.

Step E:

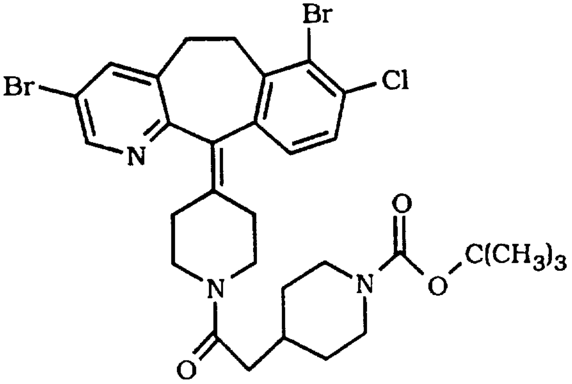


Combine 6.8 g (12.59 mmol) of the product of Step D and 100 mL of concentrated HCl (aqueous) and stir at 85°C overnight. Cool the mixture, pour it into 300 g of ice and basify with concentrated NH_4OH (aqueous). Extract with 2 x 300 mL of CH_2Cl_2, then dry the extracts over $MgSO_4$. Filter, concentrate in vacuo to a residue, then chromatograph (silica gel, 10% MeOH/EtOAc + 2% NH_4OH (aqueous)) to give 5.4 g (92% yield) of the title compound. m.p. = 172-174°C, Mass Spec.: $MH^+ = 467$ (FAB),

elemental analysis: calculated - C, 48.69; H, 3.65; N, 5.97
found - C, 48.83; H, 3.80; N, 5.97.

Step F:

Following essentially the same procedure as Step C of Preparative Example 5 below, the title compound from Step E above is reacted with 1-N-t-butoxycarbonylpiperidinyl-4-acetic acid to produce the compound



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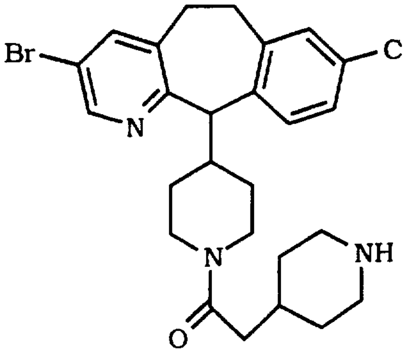
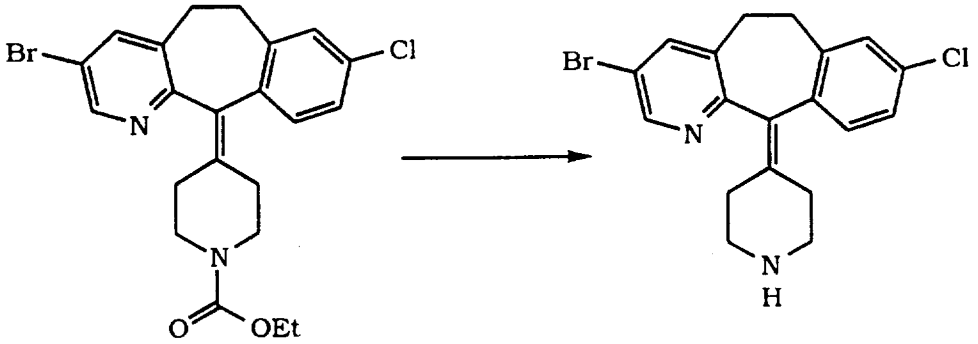
Step G:

Following essentially the same procedure as Step D of Preparative Example 5 below, the title compound from Step F above is deprotected to yield the title compound of Preparative Example 4.

PREPARATIVE EXAMPLE 5

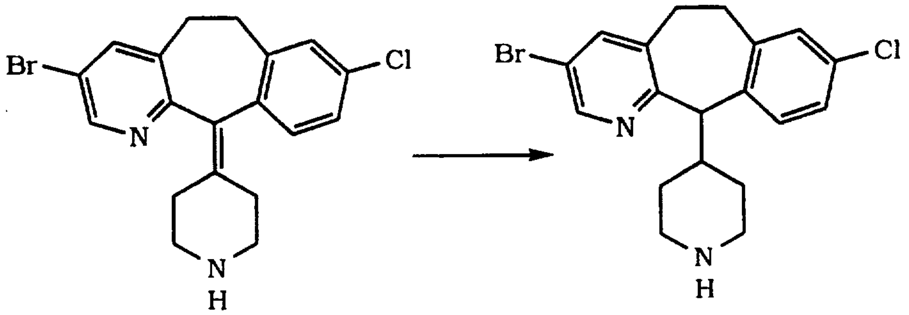


Step A:



Hydrolyze 2.42 g of 4-(8-chloro-3-bromo-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester via substantially the same procedure as described in Preparative Example 3, Step D, to give 1.39 g (69% yield) of the product.

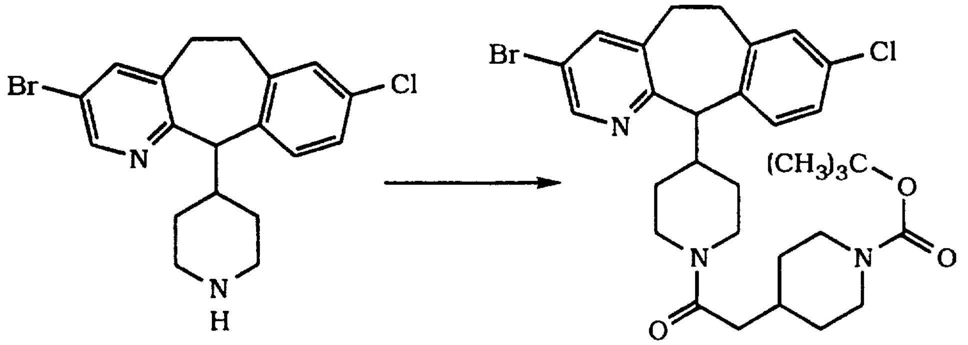
Step B:



Combine 1 g (2.48 mmol) of the product of Step A and 25 mL of dry toluene, add 2.5 mL of 1 M DIBAL in toluene and heat the mixture at reflux. After 0.5 hours, add another 2.5 mL of 1 M DIBAL in toluene and heat at reflux for 1 hour. (The reaction is monitored by TLC using 50% $MeOH/CH_2Cl_2$ $+NH_4OH$ (aqueous).)

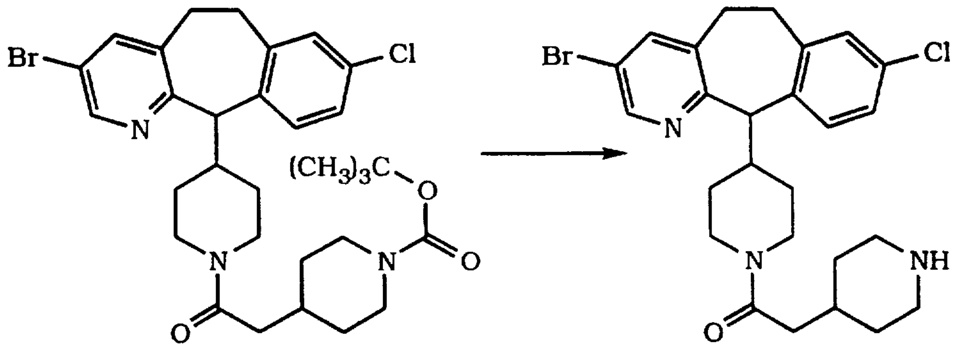
Cool the mixture to room temperature, add 50 mL of 1 N HCl (aqueous) and stir for 5 min. Add 100 mL of 1 N NaOH (aqueous), then extract with EtOAc (3 X 150 mL). Dry the extracts over $MgSO_4$, filter and concentrate in vacuo to give 1.1 g of the title compound.

Step C:



Combine 0.501 g (1.28 mmol) of the title compound of Step B and 20 mL of dry DMF, then add 0.405 g (1.664 mmol) of 1-N-t-butoxycarbonylpiperidinyl-4-acetic acid, 0.319 g (1.664 mmol) of DEC, 0.225 g (1.664 mmol) of HOBT, and 0.168 g (1.664 mmol) of 4-methylmorpholine and stir the mixture at room temperature overnight. Concentrate the mixture in vacuo to a residue, then partition the residue between 150 mL of CH_2Cl_2 and 150 mL of saturated $NaHCO_3$ (aqueous). Extract the aqueous phase with another 150 mL of CH_2Cl_2. Dry the organic phase over $MgSO_4$, and concentrate in vacuo to a residue. Chromatograph the residue (silica gel, 500 mL hexane, 1 L of 1% $MeOH/CH_2Cl_2$ + 0.1% NH_4OH (aqueous), then 1 L of 2% $MeOH/CH_2Cl_2$ + 0.1% NH_4OH (aqueous)) to give 0.575 g of the product. m.p. = 115°-125°C; Mass Spec.: $MH^+ = 616$.

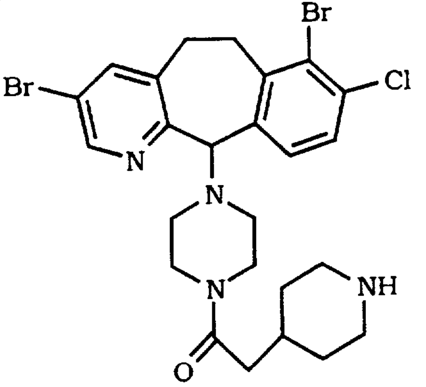
Step D:



Combine 0.555 g (0.9 mmol) of the product of Step C and 15 mL of CH_2Cl_2 and cool the mixture to 0°C. Add 15 mL of TFA

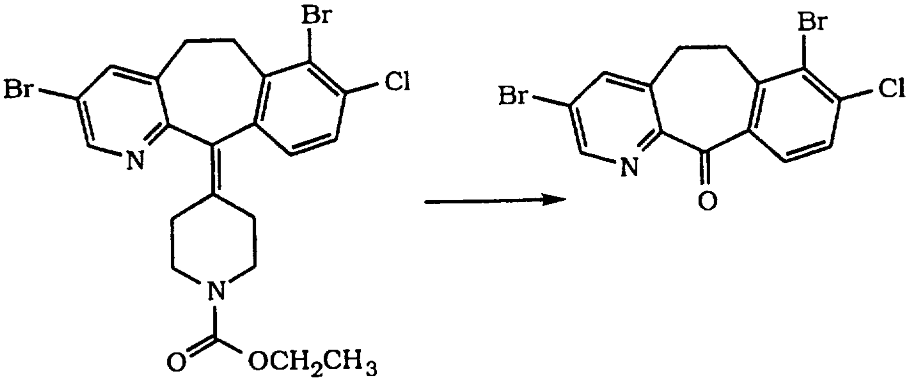
and stir at 0°C for 2 hours. Concentrate *in vacuo* at 40-45°C to a residue, then partition the residue between 150 mL of CH_2Cl_2 and 100 mL of saturated $NaHCO_3$ (aqueous). Extract the aqueous layer with 100 mL of CH_2Cl_2, combine the extracts and dry over $MgSO_4$. Concentrate *in vacuo* to give 0.47 g of the product. m.p. = 140°-150°C; Mass Spec.: $MH^+ = 516$.

PREPARATIVE EXAMPLE 6



[racemic as well as (+)- and (-)-isomers]

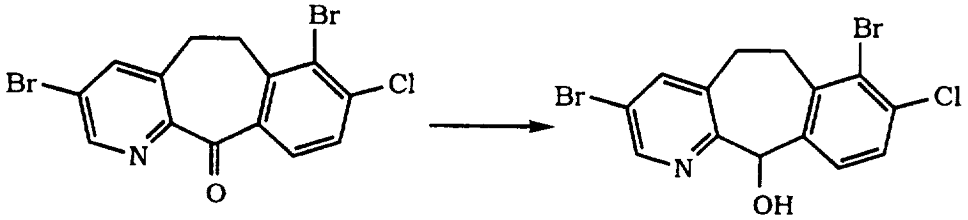
Step A:



Combine 16.6 g (0.03 mole) of the product of Preparative Example 4, Step D, with a 3:1 solution of CH_3CN and water (212.65 mL CH_3CN and 70.8 mL of water) and stir the resulting slurry overnight at room temperature. Add 32.833 g (0.153 mole) of $NaIO_4$ and then 0.31 g (2.30 mmol) of RuO_2 and stir at room temperature give 1.39 g (69% yield) of the product. (The addition of RuO is accompanied by an exothermic reaction and the temperature climbs from 20° to 30°C.) Stir the mixture for 1.3 hrs. (temperature returned to 25°C after about 30 min.), then filter to remove the solids and wash the solids with CH_2Cl_2. Concentrate the filtrate *in vacuo* to a residue and dissolve the

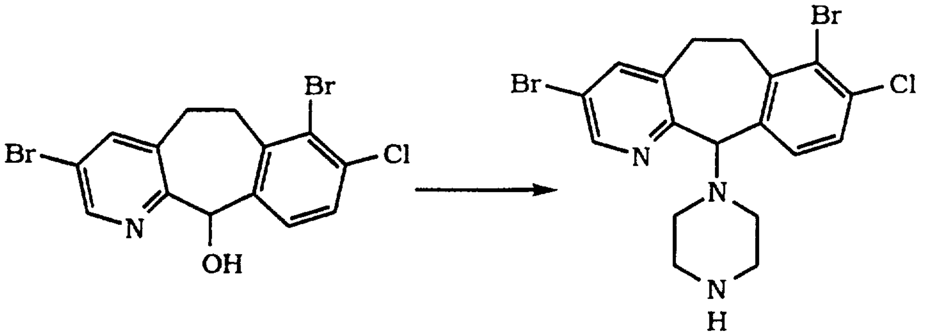
residue in CH_2Cl_2. Filter to remove insoluble solids and wash the solids with CH_2Cl_2. Wash the filtrate with water, concentrate to a volume of about 200 mL and wash with bleach, then with water. Extract with 6 N HCl (aqueous). Cool the aqueous extract to 0°C and slowly add 50% NaOH (aqueous) to adjust to pH = 4 while keeping the temperature <30°C. Extract twice with CH_2Cl_2, dry over $MgSO_4$ and concentrate *in vacuo* to a residue. Slurry the residue in 20 mL of EtOH and cool to 0°C. Collect the resulting solids by filtration and dry the solids *in vacuo* to give 7.95 g of the product. ^1H NMR ($CDCl_3$, 200 MHz): 8.7 (s, 1H); 7.85 (m, 6H); 7.5 (d, 2H); 3.45 (m, 2H); 3.15 (m, 2H).

Step B:



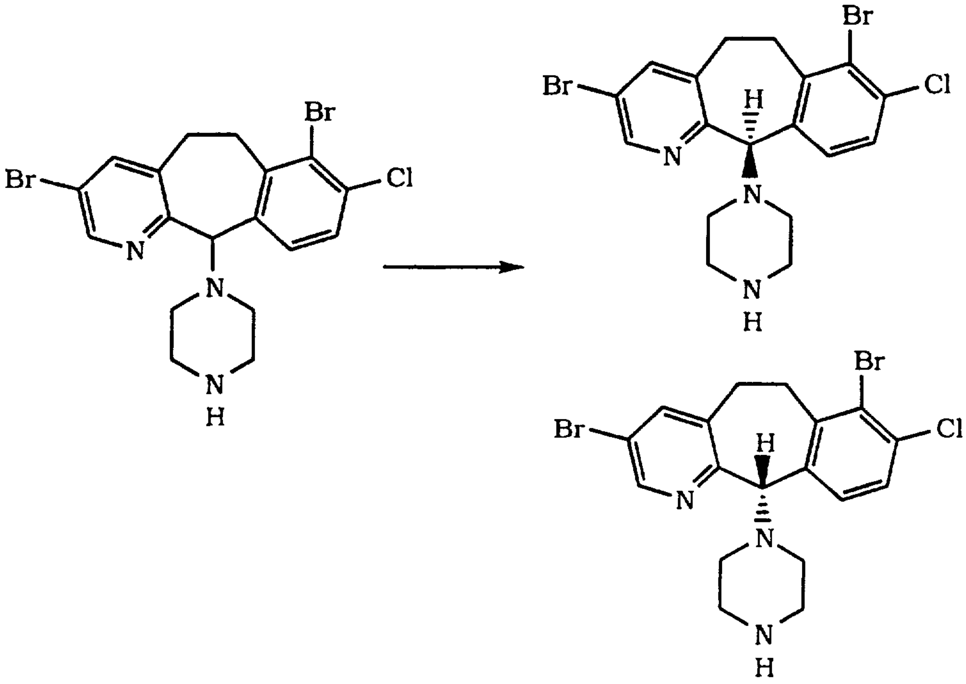
Combine 21.58 g (53.75 mmol) of the product of Step A and 500 mL of an anhydrous 1:1 mixture of EtOH and toluene, add 1.43 g (37.8 mmol) of $NaBH_4$ and heat the mixture at reflux for 10 min. Cool the mixture to 0°C, add 100 mL of water, then adjust to pH≈ 4-5 with 1 M HCl (aqueous) while keeping the temperature <10°C. Add 250 mL of EtOAc and separate the layers. Wash the organic layer with brine (3 X 50 mL) then dry over Na_2SO_4. Concentrate *in vacuo* to a residue (24.01 g) and chromatograph the residue (silica gel, 30 % hexane/CH_2Cl_2) to give the product. Impure fractions were purified by rechromatography. A total of 18.57 g of the product was obtained. ^1H NMR (DMSO-d_6, 400 MHz): 8.5 (s, 1H); 7.9 (s, 1H); 7.5 (d of d, 2H); 6.2 (s, 1H); 6.1 (s, 1H); 3.5 (m, 1H); 3.4 (m, 1H); 3.2 (m, 2H).

Step C:



Combine 18.57 g (46.02 mmol) of the product of Step B and 500 mL of $CHCl_3$, then add 6.70 mL (91.2 mmol) of $SOCl_2$, and stir the mixture at room temperature for 4 hrs. Add a solution of 35.6 g (0.413 mole) of piperazine in 800 mL of THF over a period of 5 min. and stir the mixture for 1 hr. at room temperature. Heat the mixture at reflux overnight, then cool to room temperature and dilute the mixture with 1 L of CH_2Cl_2. Wash with water (5 X 200 mL), and extract the aqueous wash with $CHCl_3$ (3 X 100 mL). Combine all of the organic solutions, wash with brine (3 X 200 mL) and dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, gradient of 5%, 7.5%, 10% $MeOH/CH_2Cl_2$ + NH_4OH) to give 18.49 g of the title compound as a racemic mixture.

Step D - Separation of Enantiomers:

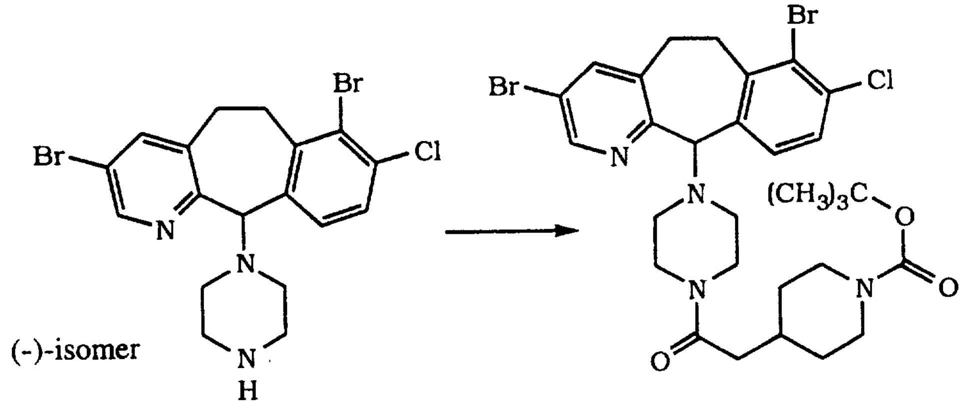


The racemic title compound of Step C is separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, flow rate 100 mL/min., 20% iPrOH/hexane + 0.2% diethylamine), to give 9.14 g of the (+)-isomer and 9.30 g of the (-)-isomer.

Physical chemical data for (+)-isomer: m.p. = 74.5°-77.5°C; Mass Spec. MH^+ = 471.9; $[\alpha]_D^{25}$ = +97.4° (8.48 mg/ 2mL MeOH).

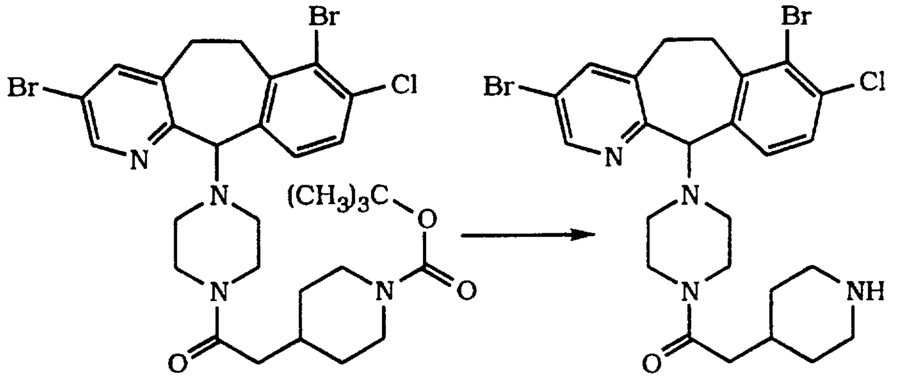
Physical chemical data for (-)-isomer: m.p. = 82.9°-84.5°C; Mass Spec. MH^+ = 471.8; $[\alpha]_D^{25}$ = -97.4° (8.32 mg/ 2mL MeOH).

Step E:



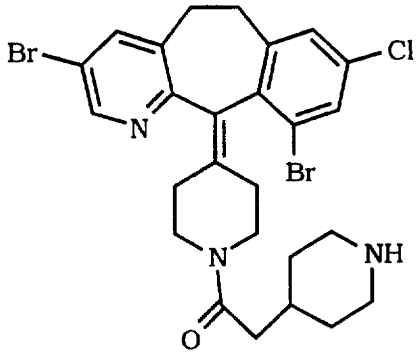
Combine 3.21 g (6.80 mmol) of the (-)-isomer product of Step D and 150 mL of anhydrous DMF. Add 2.15 g (8.8 mmol) of 1-N-t-butoxycarbonylpiperidinyl-4-acetic acid, 1.69 g (8.8 mmol) of DEC, 1.19 g (8.8 mmol) of HOBT and 0.97 mL (8.8 mmol) of N-methylmorpholine and stir the mixture at room temperature overnight. Concentrate *in vacuo* to remove the DMF and add 50 mL of saturated $NaHCO_3$ (aqueous). Extract with CH_2Cl_2 (2 X 250 mL), wash the extracts with 50 mL of brine and dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2% $MeOH/CH_2Cl_2$ + 10% NH_4OH) to give 4.75 g of the product. m.p. = 75.7°-78.5°C; Mass Spec.: MH^+ = 697; $[\alpha]_D^{25}$ = -5.5° (6.6 mg/2 mL MeOH).

Step F:

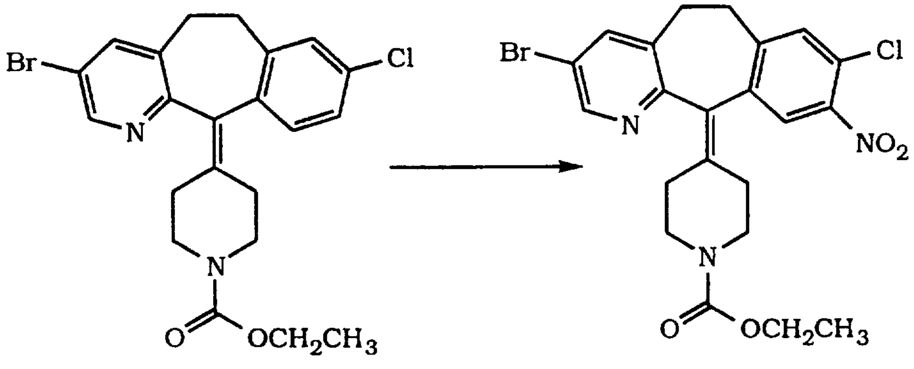


Combine 4.70 g (6.74 mmol) of the product of Step E and 30 mL of MeOH, then add 50 mL of 10% H_2SO_4/dioxane in 10 mL aliquots over a 1 hr. period. Pour the mixture into 50 mL of water and add 15 mL of 50% NaOH (aqueous) to adjust to pH≈ 10-11. Filter to remove the resulting solids and extract the filtrate with CH_2Cl_2 (2 X 250 mL). Concentrate the aqueous layer *in vacuo* to remove the MeOH and extract again with 250 mL of CH_2Cl_2. Dry the combined extracts over $MgSO_4$ and concentrate *in vacuo* to give the product. m.p. = 128.1°-131.5°C; Mass Spec.: $MH^+ = 597$; $[\alpha]_D^{25} = -6.02°$ (9.3 mg/2 mL MeOH).

PREPARATIVE EXAMPLE 7

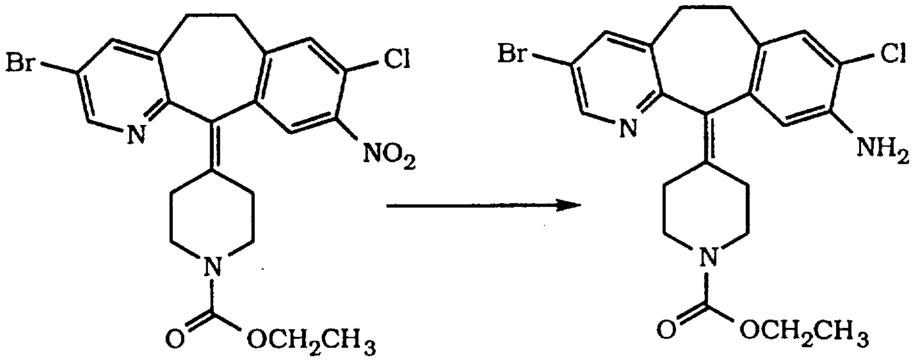


Step A:



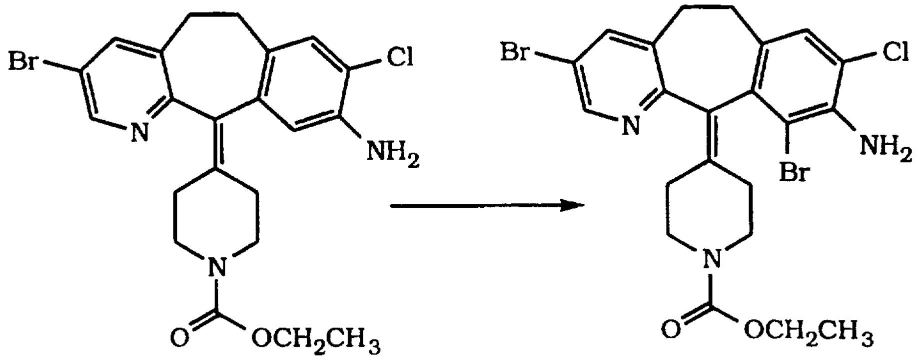
Combine 15 g (38.5 mmol) of 4-(8-chloro-3-bromo-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester and 150 mL of concentrated H_2SO_4 at -5°C, then add 3.89 g (38.5 mmol) of KNO_3 and stir for 4 hours. Pour the mixture into 3 L of ice and basify with 50% NaOH (aqueous). Extract with CH_2Cl_2, dry over $MgSO_4$, then filter and concentrate *in vacuo* to a residue. Recrystallize the residue from acetone to give 6.69 g of the product. ^{1}H NMR ($CDCl_3$, 200 MHz): 8.5 (s, 1H); 7.75 (s, 1H); 7.6 (s, 1H); 7.35 (s, 1H); 4.15 (q, 2H); 3.8 (m, 2H); 3.5-3.1 (m, 4H); 3.0-2.8 (m, 2H); 2.6-2.2 (m, 4H); 1.25 (t, 3H).

Step B:



Combine 6.69 g (13.1 mmol) of the product of Step A and 100 mL of 85% EtOH/water, then add 0.66 g (5.9 mmol) of $CaCl_2$ and 6.56 g (117.9 mmol) of Fe and heat the mixture at reflux overnight. Filter the hot reaction mixture through celite® and rinse the filter cake with hot EtOH. Concentrate the filtrate *in vacuo* to give 7.72 g of the product. Mass Spec.: $MH^+ = 478.0$

Step C:

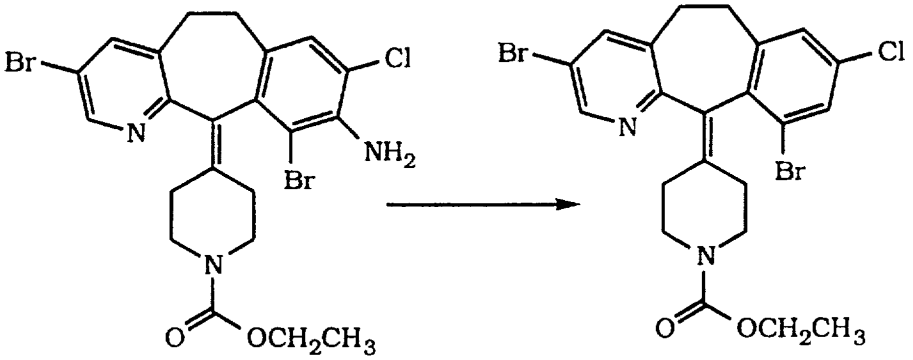


Combine 7.70 g of the product of Step B and 35 mL of HOAc, then add 45 mL of a solution of Br_2 in HOAc and stir the mixture at room temperature overnight. Add 300 mL of 1 N

NaOH (aqueous) , then 75 mL of 50% NaOH (aqueous) and extract with EtOAc. Dry the extract over $MgSO_4$ and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 20%-30% EtOAc/hexane) to give 3.47 g of the product (along with another 1.28 g of partially purified product). Mass Spec.: MH^+ = 555.9.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.5 (s, 1H); 7.5 (s, 1H); 7.15 (s, 1H); 4.5 (s, 2H); 4.15 (m, 3H); 3.8 (br s, 2H); 3.4-3.1 (m, 4H); 9-2.75 (m, 1H); 2.7-2.5 (m, 2H); 2.4-2.2 (m, 2H); 1.25 (m, 3H).

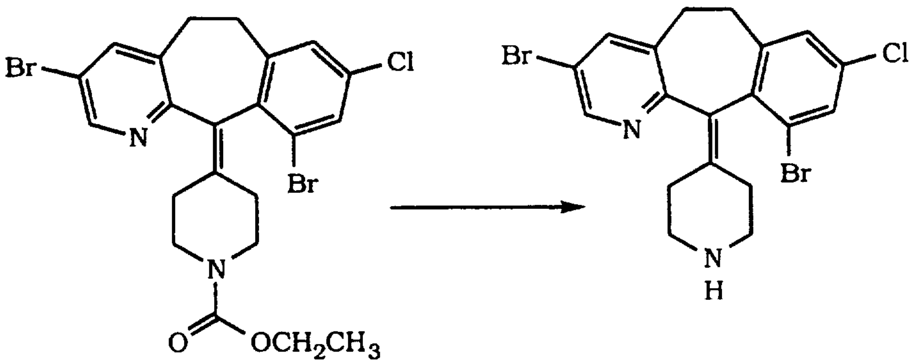
Step D:



Combine 0.557 g (5.4 mmol) of t-butylnitrite and 3 mL of DMF, and heat the mixture at to 60°-70°C. Slowly add (dropwise) a mixture of 2.00 g (3.6 mmol) of the product of Step C and 4 mL of DMF, then cool the mixture to room temperature. Add another 0.64 mL of t-butylnitrite at 40°C and reheat the mixture to 60°-70°C for 0.5 hrs. Cool to room temperature and pour the mixture into 150 mL of water. Extract with CH_2Cl_2, dry the extract over $MgSO_4$ and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 10%-20% EtOAc/hexane) to give 0.74 g of the product. Mass Spec.: MH^+ = 541.0.

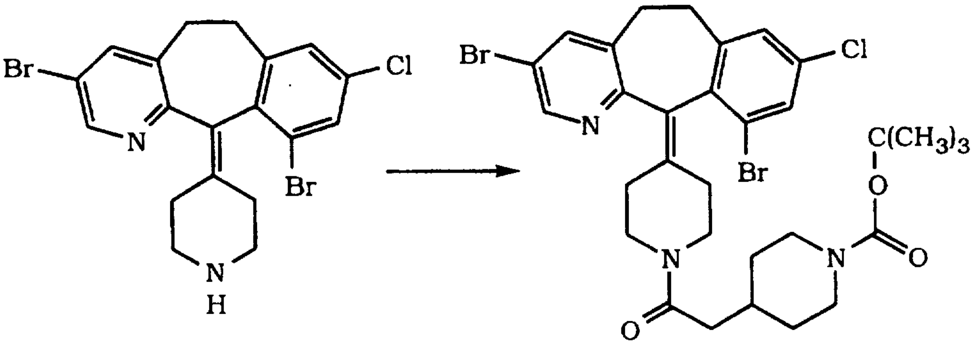
^{1}H NMR (CDC13, 200 MHz): 8.52 (s, 1H); 7.5 (d, 2H); 7.2 (s, 1H); 4.15 (q, 2H); 3.9-3.7 (m, 2H); 3.5-3.1 (m, 4H); 3.0-2.5 (m, 2H); 2.4-2.2 (m, 2H); 2.1-1.9 (m, 2H); 1.26 (t, 3H).

Step E:



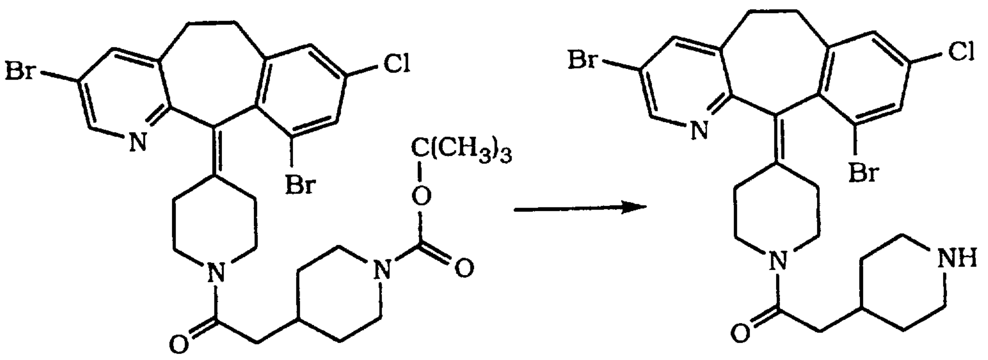
Combine 0.70 g (1.4 mmol) of the product of Step D and 8 mL of concentrated HCl (aqueous) and heat the mixture at reflux overnight. Add 30 mL of 1 N NaOH (aqueous), then 5 mL of 50% NaOH (aqueous) and extract with CH_2Cl_2. Dry the extract over $MgSO_4$ and concentrate *in vacuo* to give 0.59 g of the title compound. Mass Spec.: $M^+ = 468.7$. m.p. = 123.9°-124.2°C.

Step F:



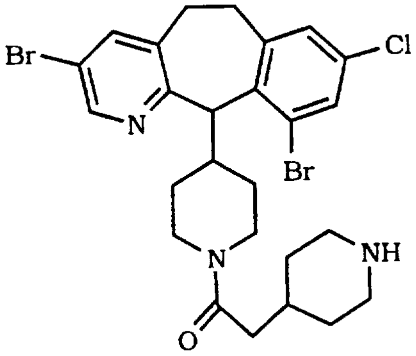
React 6.0 g (12.8 mmol) of the title compound from Step E and with 3.78 g (16.6 mmol) of 1-N-t-butoxycarbonylpiperidinyl-4-acetic acid using substantially the same procedures as described for Preparative Example 5, Step C, to give 8.52 g of the product. Mass Spec.: $MH^+ = 694.0$ (FAB). ^1H NMR ($CDCl_3$, 200 MHz): 8.5 (d, 1H); 7.5 (d, 2H); 7.2 (d, 1H); 4.15-3.9 (m, 3H); 3.8-3.6 (m, 1H); 3.5-3.15 (m, 3H); 2.9 (d, 2H); 2.8-2.5 (m, 4H); 2.4-1.8 (m, 6H); 1.8-1.6 (br d, 2H); 1.4 (s, 9H); 1.25-1.0 (m, 2H).

Step G:



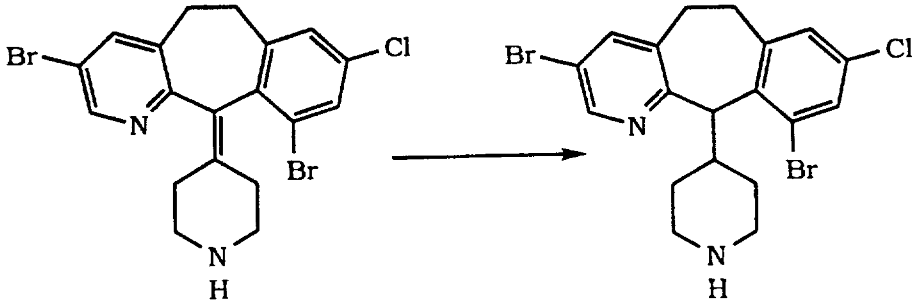
Combine 8.50 g of the product of Step F and 60 mL of CH_2Cl_2, then cool to 0°C and add 55 mL of TFA. Stir the mixture for 3 h at 0°C, then add 500 mL of 1 N NaOH (aqueous) followed by 30 mL of 50% NaOH (aqueous). Extract with CH_2Cl_2, dry over $MgSO_4$ and concentrate *in vacuo* to give 7.86 g of the product. Mass Spec.: M^+ = 593.9 (FAB). ^1H NMR ($CDCl_3$, 200 MHz): 8.51 (d, 1H); 7.52 (d of d, 2H); 7.20 (d, 1H); 4.1-3.95 (m, 2H); 3.8-3.65 (m, 2H); 3.5-3.05 (m, 5H); 3.0-2.5 (m, 6H); 2.45-1.6 (m, 6H);1.4-1.1 (m, 2H).

PREPARATIVE EXAMPLE 8



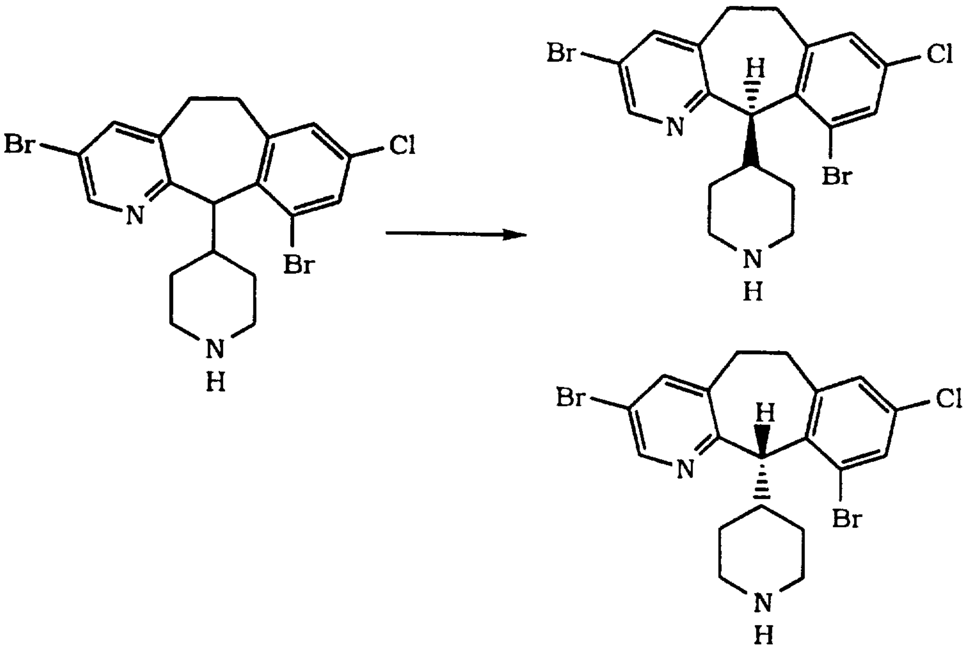
[racemic as well as (+)- and (-)-isomers]

Step A:



Prepare a solution of 8.1 g of the title compound from Preparative Example 7, Step E, in toluene and add 17.3 mL of a 1M solution of DIBAL in toluene. Heat the mixture at reflux and slowly add (dropwise) another 21 mL of 1 M DIBAL/toluene solution over a period of 40 min. Cool the reaction mixture to about 0°C and add 700 mL of 1 M HCl (aqueous). Separate and discard the organic phase. Wash the aqueous phase with CH_2Cl_2, discard the extract, then basify the aqueous phase by adding 50% NaOH (aqueous). Extract with CH_2Cl_2, dry the extract over $MgSO_4$ and concentrate *in vacuo* to give 7.30 g of the title compound, which is a racemic mixture of enantiomers.

Step B - Separation of Enantiomers:

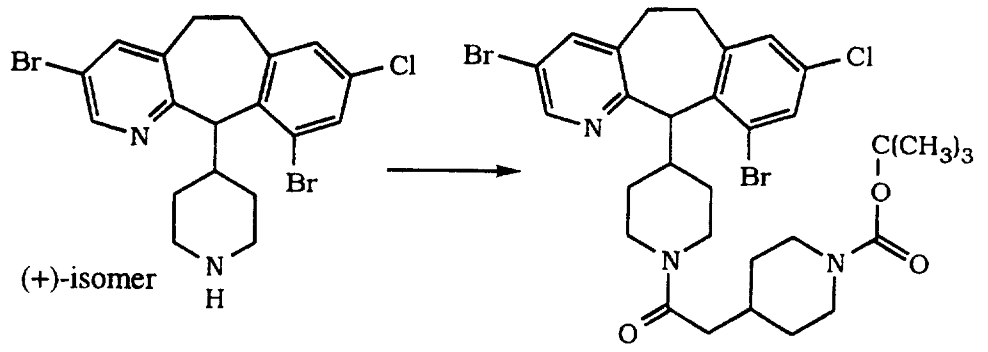


The racemic title compound of Step A is separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, using 20% iPrOH/hexane + 0.2% diethylamine), to give the (+)-isomer and the (-)-isomer of the title compound.

Physical chemical data for (+)-isomer: m.p. = 148.8°C; Mass Spec. $MH^+ = 469$; $[\alpha]_D^{25} = +65.6°$ (12.93 mg/ 2mL MeOH).

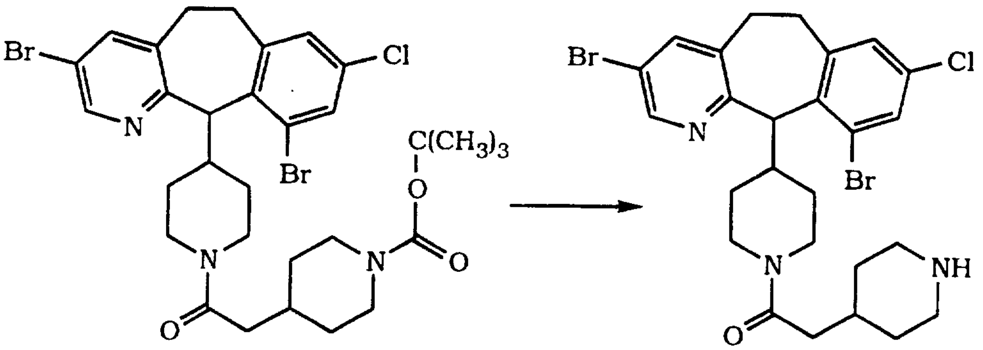
Physical chemical data for (-)-isomer: m.p. = 112°C; Mass Spec. $MH^+ = 469$; $[\alpha]_D^{25} = -65.2°$ (3.65 mg/ 2mL MeOH).

Step C:



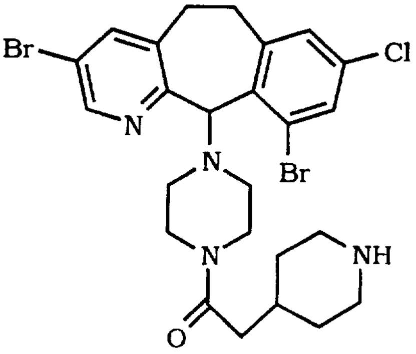
React 1.33 g of the (+)-isomer of the title compound of Preparative Example 8, Step B, with 1.37 g of 1-N-t-butoxycarbonylpiperidinyl-4-acetic acid using substantially the same procedures as described for Preparative Example 5, Step C, to give 2.78 g of the product. Mass Spec.: $MH^+ = 694.0$ (FAB); $[\alpha]_D^{25} = +34.1°$ (5.45 mg/2 mL, MeOH).

Step D:



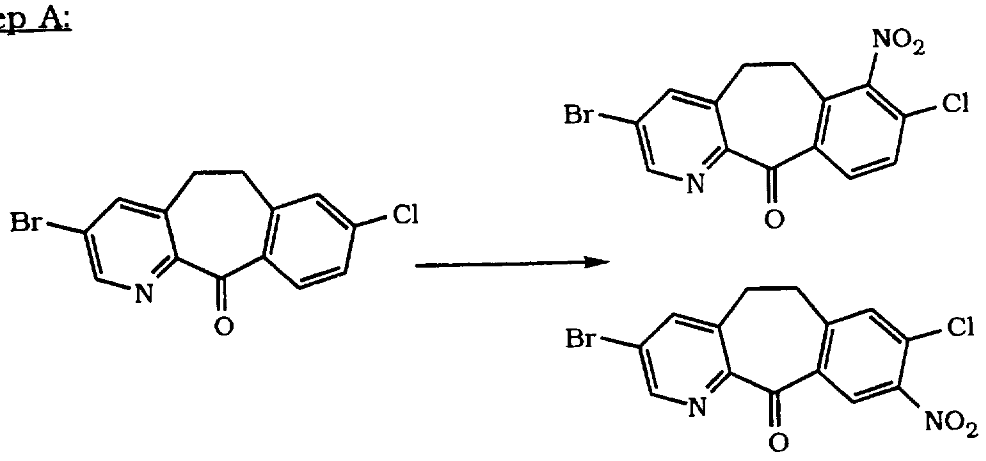
Treat 2.78 g of the product of Step C via substantially the same procedure as described for Preparative Example 5, Step D, to give 1.72 g of the product. m.p. = 104.1°C; Mass Spec.: $MH^+ = 594$; $[\alpha]_D^{25} = +53.4°$ (11.42 mg/2 mL, MeOH).

PREPARATIVE EXAMPLE 9



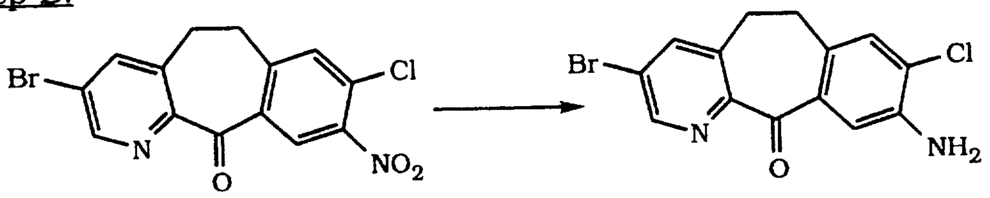
[racemic as well as (+)- and (-)-isomers]

Step A:



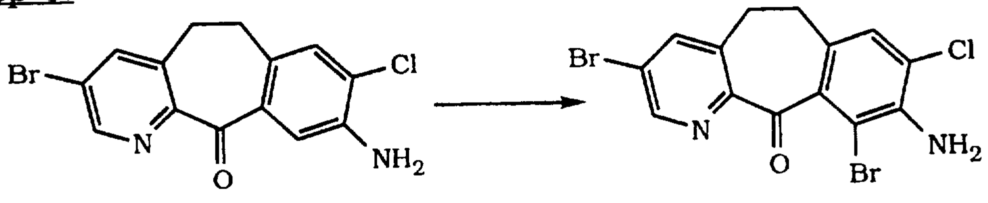
Combine 40.0 g (0.124 mole) of the starting ketone and 200 mL of H_2SO_4 and cool to 0°C. Slowly add 13.78 g (0.136 mole) of KNO_3 over a period of 1.5 hrs., then warm to room temperature and stir overnight. Work up the reaction using substantially the same procedure as described for Preparative Example 4, Step A. Chromatograph (silica gel, 20%, 30%, 40%, 50% EtOAc/hexane, then 100% EtOAc) to give 28 g of the 9-nitro product, along with a smaller quantity of the 7-nitro product and 19 g of a mixture of the 7-nitro and 9-nitro compounds.

Step B:



React 28 g (76.2 mmol) of the 9-nitro product of Step A, 400 mL of 85% EtOH/water, 3.8 g (34.3 mmol) of $CaCl_2$ and 38.28 g (0.685 mole) of Fe using substantially the same procedure as described for Preparative Example 4, Step C, to give 24 g of the product

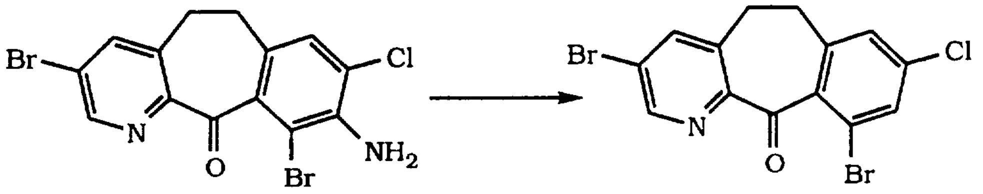
Step C:



Combine 13 g (38.5 mmol) of the product of Step B, 140 mL of HOAc and slowly add a solution of 2.95 mL (57.8 mmol) of

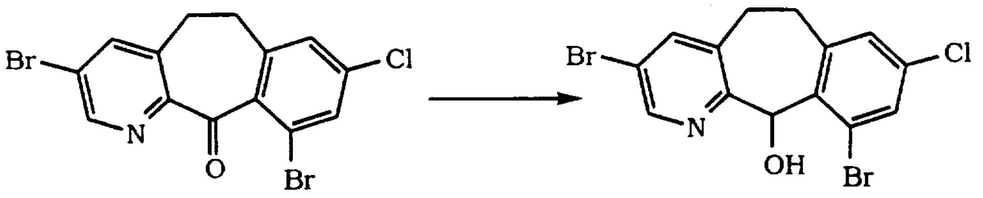
Br_2 in 10 mL of HOAc over a period of 20 min. Stir the reaction mixture at room temperature, then concentrate *in vacuo* to a residue. Add CH_2Cl_2 and water, then adjust to pH = 8-9 with 50% NaOH (aqueous). Wash the organic phase with water, then brine and dry over Na_2SO_4. Concentrate *in vacuo* to give 11.3 g of the product.

Step D:



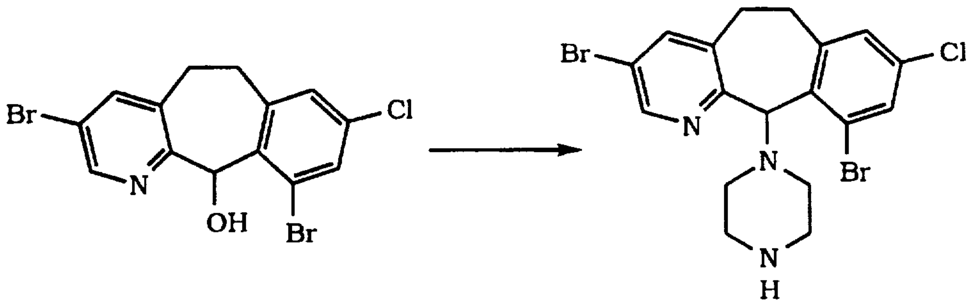
Cool 100 mL of concentrated HCl (aqueous) to 0°C, then add 5.61 g (81.4 mmol) of $NaNO_2$ and stir for 10 min. Slowly add (in portions) 11.3 g (27.1 mmol) of the product of Step C and stir the mixture at 0°-3°C for 2.25 hrs. Slowly add (dropwise) 180 mL of 50% H_3PO_2 (aqueous) and allow the mixture to stand at 0°C overnight. Slowly add (dropwise) 150 mL of 50% NaOH over 30 min., to adjust to pH = 9, then extract with CH_2Cl_2. Wash the extract with water, then brine and dry over Na_2SO_4. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2% EtOAc/ CH_2Cl_2) to give 8.6 g of the product.

Step E:



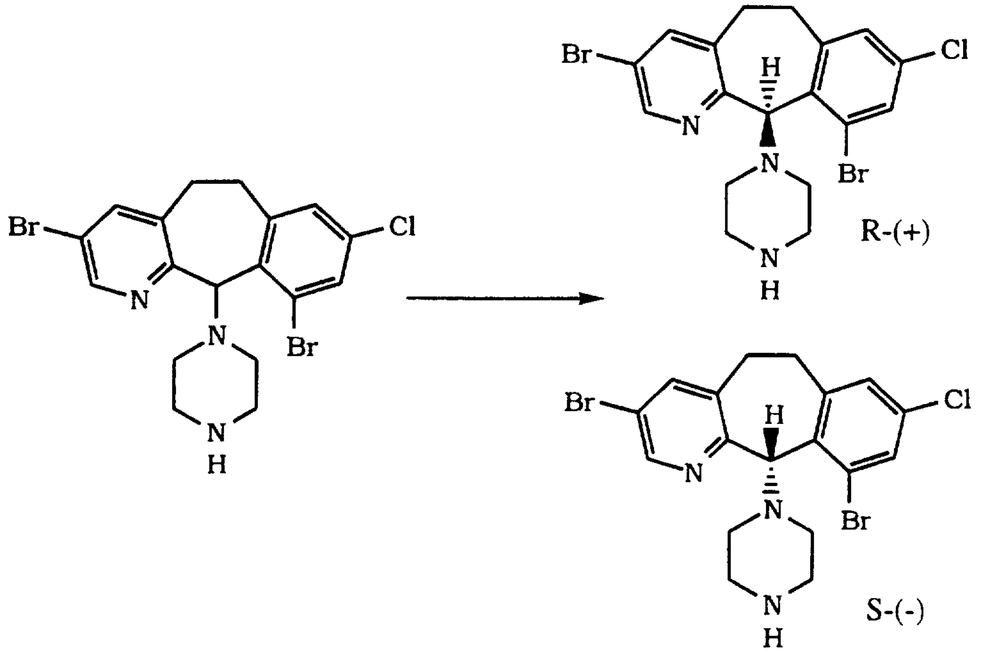
Combine 8.6 g (21.4 mmol) of the product of Step D and 300 mL of MeOH and cool to 0°-2°C. Add 1.21 g (32.1 mmol) of $NaBH_4$ and stir the mixture at ~0°C for 1 hr. Add another 0.121 g (3.21 mmol) of $NaBH_4$, stir for 2 hr. at 0°C, then let stand overnight at 0°C. Concentrate *in vacuo* to a residue then partition the residue between CH_2Cl_2 and water. Separate the organic phase and concentrate *in vacuo* (50°C) to give 8.2 g of the product.

Step F:



Combine 8.2 g (20.3 mmol) of the product of Step E and 160 mL of CH_2Cl_2, cool to 0°C, then slowly add (dropwise) 14.8 mL (203 mmol) of $SOCl_2$ over a 30 min. period. Warm the mixture to room temperature and stir for 4.5 hrs., then concentrate *in vacuo* to a residue, add CH_2Cl_2 and wash with 1 N NaOH (aqueous) then brine and dry over Na_2SO_4. Concentrate *in vacuo* to a residue, then add dry THF and 8.7 g (101 mmol) of piperazine and stir at room temperature overnight. Concentrate *in vacuo* to a residue, add CH_2Cl_2, and wash with 0.25 N NaOH (aqueous), water, then brine. Dry over Na_2SO_4 and concentrate *in vacuo* to give 9.46 g of the crude product. Chromatograph (silica gel, 5% MeOH/CH_2Cl_2 + NH_3) to give 3.59 g of the title compound, as a racemate. ^1H NMR ($CDCl_3$, 200 MHz): 8.43 (d, 1H); 7.55 (d, 1H); 7.45 (d, 1H); 7.11 (d, 1H); 5.31 (s, 1H); 4.86-4.65 (m, 1H); 3.57-3.40 (m, 1H); 2.98-2.55 (m, 6H); 2.45-2.20 (m, 5H).

Step G - Separation of Enantiomers:



The racemic title compound from Step F (5.7 g) is chromatographed as described for Preparative Example 6, Step D, using 30% iPrOH/hexane + 0.2% diethylamine, to give 2.88 g of the R-(+)-isomer and 2.77 g of the S-(-)-isomer of the title compound.

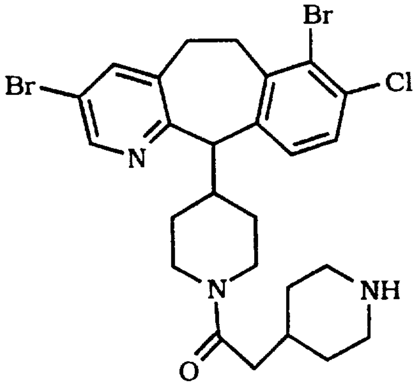
Physical chemical data for the R-(+)-isomer: Mass Spec. $MH^+ = 470.0$; $[\alpha]_D^{25} = +12.1°$ (10.9 mg/ 2mL MeOH).

Physical chemical data for the S-(-)-isomer: Mass Spec. $MH^+ = 470.0$; $[\alpha]_D^{25} = -13.2°$ (11.51 mg/ 2mL MeOH).

Step H:

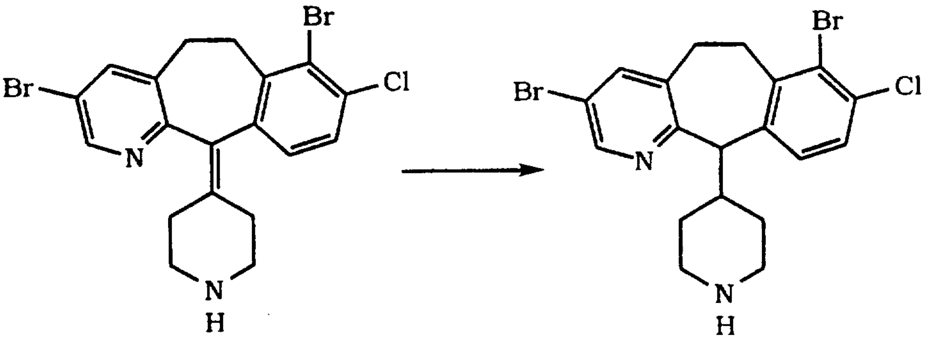
Following essentially the same procedure as Preparative Example 5, Steps C and D, the racemic title compound of Preparative Example 9 is obtained from the racemic compound of Step F. Similarly, using the (-)- or (+)- isomer from Step G, the (-)- or (+)-isomer of the title compound of Preparative Example 9 is obtained, respectively.

PREPARATIVE EXAMPLE 10



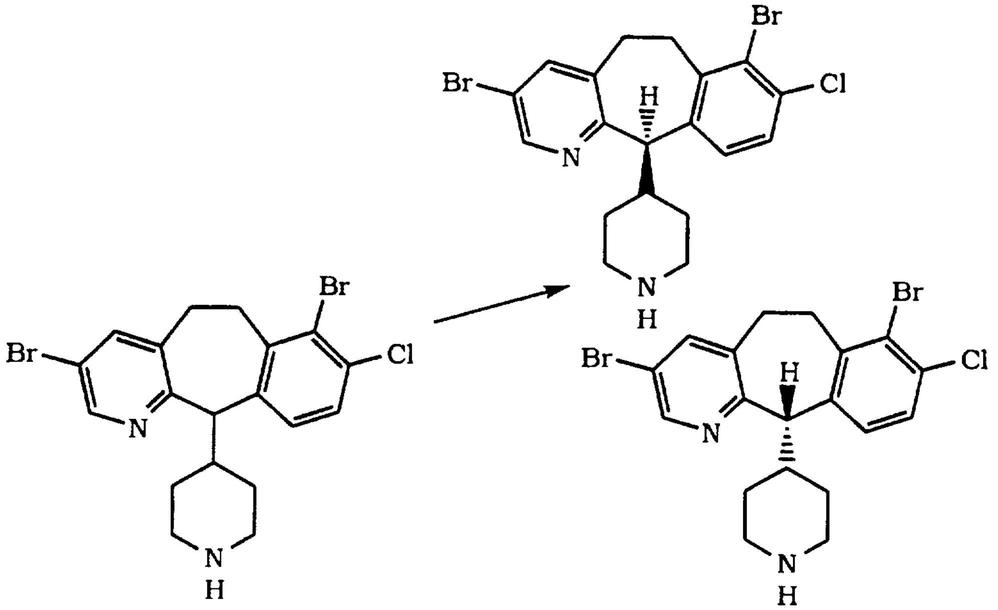
[racemic as well as (+)- and (-)-isomers]

Step A:



Combine 13 g (33.3 mmol) of the title compound from Preparative Example 4, Step E, and 300 mL of toluene at 20°C, then add 32.5 mL (32.5 mmol) of a 1 M solution of DIBAL in toluene. Heat the mixture at reflux for 1 hr., cool to 20°C, add another 32.5 mL of 1 M DIBAL solution and heat at reflux for 1 hr. Cool the mixture to 20°C and pour it into a mixture of 400 g of ice, 500 mL of EtOAc and 300 mL of 10% NaOH (aqueous). Extract the aqueous layer with CH_2Cl_2 (3 x 200 mL), dry the organic layers over $MgSO_4$, then concentrate *in vacuo* to a residue. Chromatograph (silica gel, 12% $MeOH/CH_2Cl_2$ + 4% NH_4OH) to give 10.4 g of the title compound as a racemate. Mass Spec.: $MH^+ = 469$ (FAB). partial ^1H NMR ($CDCl_3$, 400 MHz): 8.38 (s, 1H); 7.57 (s, 1H); 7.27 (d, 1H); 7.06 (d, 1H); 3.95 (d, 1H).

Step B - Separation of Enantiomers:



The racemic title compound of Step A is separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, using 5% iPrOH/hexane + 0.2% diethylamine), to give the (+)-isomer and the (-)-isomer of the title compound.

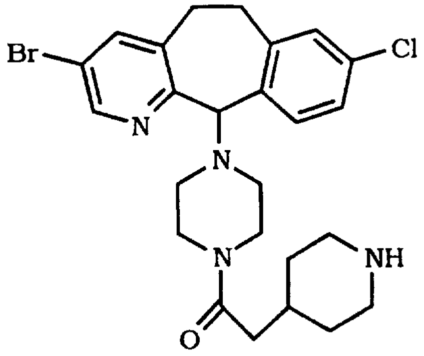
Physical chemical data for (+)-isomer: Mass Spec. $MH^+ = 469$ (FAB); $[\alpha]_D^{25} = +43.5°$ (c=0.402, EtOH); partial ^1H NMR ($CDCl_3$, 400 MHz): 8.38 (s, 1H); 7.57 (s, 1H); 7.27 (d, 1H); 7.05 (d, 1H); 3.95 (d, 1H).

Physical chemical data for (-)-isomer: Mass Spec. $MH^+ = 469$ (FAB); $[\alpha]_D^{25} = -41.8°$ (c=0.328 EtOH); partial ^1H NMR ($CDCl_3$, 400 MHz): 8.38 (s, 1H); 7.57 (s, 1H); 7.27 (d, 1H); 7.05 (d, 1H); 3.95 (d, 1H).

Step C:

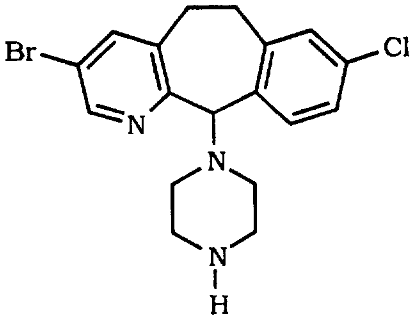
Following the procedure of Preparative Example 9, Step H, the racemic compound, the (+)-isomer or the (-)-isomer of the title compound of Preparative Example 10 can be obtained.

PREPARATIVE EXAMPLE 11



[racemic as well as R-(+)- and S-(-)-isomers]

The compound



is prepared according to the procedures of Preparative Example 40 of WO 95/10516 (published April 20, 1995), by following the procedures described in Example 193 of WO 95/10516.

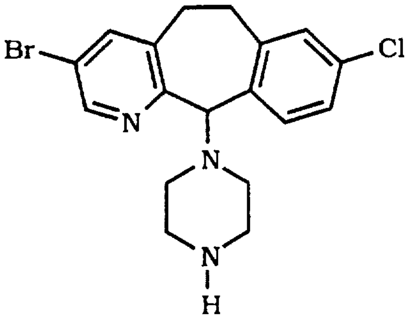
The (+)- and (-)-isomers can be separated by following essentially the same procedure as Step D of Preparative Example 6.

Physical chemical data for the R-(+)-isomer: ^{13}C NMR ($CDCl_3$): 155.8 (C); 146.4 (CH); 140.5 (CH); 140.2 (C); 136.2 (C); 135.3 (C); 133.4 (C); 132.0 (CH); 129.9 (CH); 125.6 (CH); 119.3 (C); 79.1 (CH); 52.3 (CH_2); 52.3 (CH); 45.6 (CH_2); 45.6 (CH_2); 30.0 (CH_2); 29.8 (CH_2). $[\alpha]_D^{25}$ = +25.8° (8.46 mg/2 mL MeOH).

Physical chemical data for the S-(-)-isomer: ^{13}C NMR ($CDCl_3$): 155.9 (C); 146.4 (CH); 140.5 (CH); 140.2 (C); 136.2 (C); 135.3 (C); 133.3 (C); 132.0 (CH); 129.9 (CH); 125.5 (CH); 119.2 (C); 79.1 (CH); 52.5 (CH_2); 52.5 (CH); 45.7 (CH_2); 45.7 (CH_2); 30.0 (CH_2); 29.8 (CH_2). $[\alpha]_D^{25}$ = -27.9° (8.90 mg/2 mL MeOH).

Following essentially the same procedure as Preparative Example 5, Steps C and D, the racemic compound, (+)-isomer or

(-)-isomer of the title compound of Preparative Example 11 can be obtained from the corresponding racemic compound, (+)-isomer or (-)-isomer of the compound



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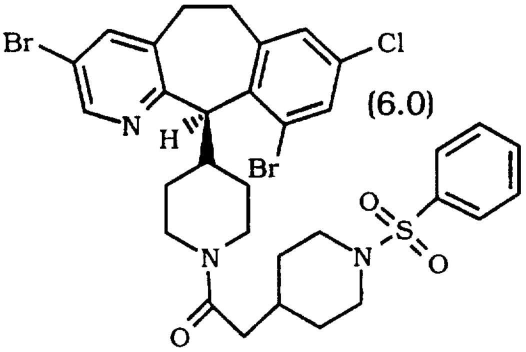
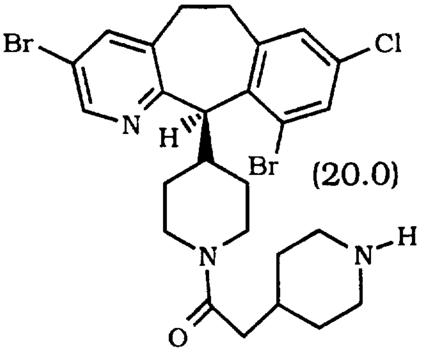
EXAMPLE 1



(6.0)

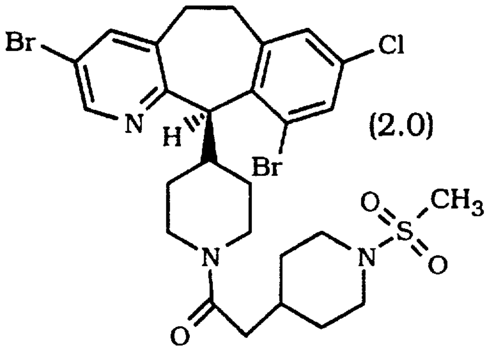
To the compound of Formula 20.0



(20.0)

(Preparative Example 8) (0.10 g, 0.17 mmol) and triethylamine (0.04 mL, 0.26 mmol) dissolved in anhydrous dichloromethane (10 mL) was added benzenesulfonyl chloride (0.03 mL, 1.2 eq). After stirring at room temperature overnight, the solution was diluted with dichloromethane, washed with 1 *M* hydrochloric acid, then washed with 1 *N* aqueous sodium hydroxide and dried over anhydrous magnesium sulfate. Filtration and concentration *in vacuo* afforded the compound of Formula 6.0 (0.11 g, 89%, mp 102-105°C).

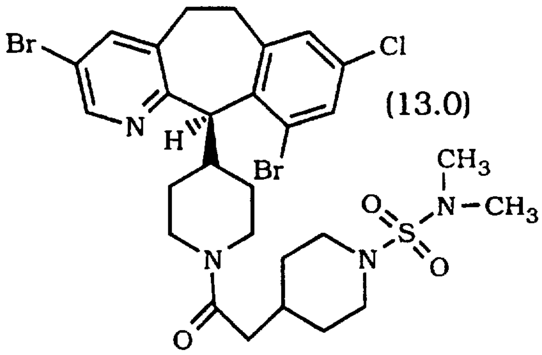
EXAMPLE 2



(2.0)

To the compound of Formula 20.0 (Preparative Example 8) (0.11 g, 0.19 mmol) and triethylamine (0.04 mL, 0.28 mmol) dissolved in anhydrous dichloromethane (10 mL) was added methanesulfonyl chloride (0.02 mL, 1.2 eq). After stirring at room temperature overnight, the solution was diluted with dichloromethane, washed with 1 *M* hydrochloric acid, then washed with 1 *N* aqueous sodium hydroxide and dried over anhydrous magnesium sulfate. Filtration and concentration *in vacuo* afforded the compound of Formula 2.0 (0.10 g, 80%, mp 133-136°C).

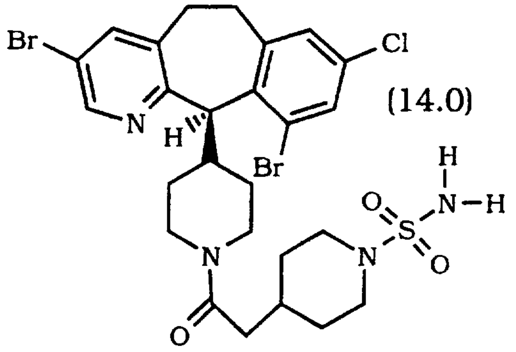
EXAMPLE 3



(13.0)

To the compound of Formula 20.0 (Preparative Example 8) (0.20 g, 0.34 mmol) and triethylamine (0.08 mL, 0.50 mmol) dissolved in anhydrous dichloromethane (10 mL) was added N,N-dimethylsulfamoyl chloride (0.04 mL, 1.2 eq). After stirring at room temperature overnight, the solution was diluted with dichloromethane, washed with 1 *M* hydrochloric acid, then washed with 1 *N* aqueous sodium hydroxide and dried over anhydrous magnesium sulfate. Filtration and concentration *in vacuo* afforded the compound of Formula 13.0 (0.22 g, 93%, mp 107.4-109.5°C).

EXAMPLE 4



(14.0)

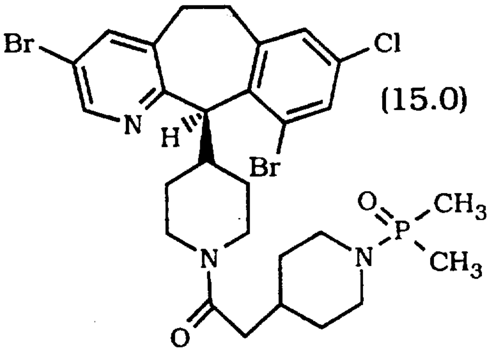
PROCEDURE 1:

To the compound of Formula 20.0 (Preparative Example 8) (0.30 g, 0.50 mmol) and triethylamine (0.22 mL, 3 eq) dissolved in anhydrous acetonitrile (10 mL) at 0°C was slowly added an acetonitrile solution (2 mL) of sulfamoyl chloride (0.12 g, 2 eq) (Chem. Ber.,Vol. 91, p. 1339 (1958)). After stirring at 0°C for 1 h, then at room temperature for 72 h, the mixture was concentrated *in vacuo*, diluted with dichloromethane, washed with 1 *M* hydrochloric acid, then washed with 1 *N* aqueous sodium hydroxide and dried over anhydrous magnesium sulfate. Filtration and concentration *in vacuo* afforded a solid which was purified by preparative plate chromatography (silica gel) using 5% methanol-dichloromethane and concentrated ammonium hydroxide to provide the compound of Formula 14.0 (0.05 g, 14%, mp 151.5-155.6 °C).

PROCEDURE 2:

Anhydrous pyridine (2 mL, 24.8 mmol) was cooled in an ice-water bath. SO_2Cl_2 (0.3 mL, 3.8 mmol) was added dropwise over about 5 minutes, and the resulting mixture was stirred for about 5 minutes. The compound of Formula 20.0 (Preparative Example 8) (150 mg) as a dichloromethane solution was added dropwise over about one minute, and the mixture was stirred at about 0°C for about 10 minutes. Concentrated NH_4OH (40 mL) was added dropwise and the mixture was stirred at room temperature for about 1 hour. Dichloromethane was added and the mixture was stirred at room temperature. The phases were separated, and 1M HCl was added to the organic phase, and the resulting mixture was stirred. The phases were separated, and the organic phase was washed with 1M HCl (aq), and the phases were separated. The organic phase was washed with saturated $NaHCO_3$ (aq), dried over anhydrous $MgSO_4$, filtered and concentrated by rotovap. The residue was purified by preparative plate chromatography (silica) using 5%$MeOH/CH_2Cl_2$ + NH_4OH to give the compound of Formula 14.0 (18 mg, 14%). MS-FAB DMSO: 673 (MH^+); mp = 151.5 - 155.6°C.

EXAMPLE 5

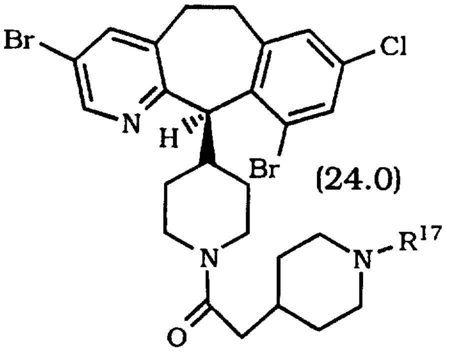


(15.0)

To the compound of Formula 20.0 (Preparative Example 8) (0.15 g, 0.25 mmol) and triethylamine (0.14 mL, 1.0 mmol) dissolved in anhydrous dichloromethane (5 mL) was added dimethylphosphinyl chloride (0.12 g, 4 eq). After stirring at room temperature for 48 h, the solution was diluted with dichloromethane, washed with 1 *M* hydrochloric acid, then washed with 1 *N* aqueous sodium hydroxide and dried over anhydrous magnesium sulfate. Filtration and concentration *in vacuo* afforded an oil which was purified by preparative plate chromatography (silica gel) using 2% methanol-dichloromethane and concentrated ammonium hydroxide to provide the compound of Formula 15.0 (0.03 g, 18%)

EXAMPLE 6-14

Following procedures similar to those of Example1, but using the sulfonyl chlorides in Column 1 of Table 1 instead of benzenesulfonyl chloride, the compounds of Formula 24:



(24.0)

were obtained wherein R^{17} is defined in Column 3 of Table 1. The number in parenthesis in Column 3 is the formula number of the compound obtained.

TABLE 1

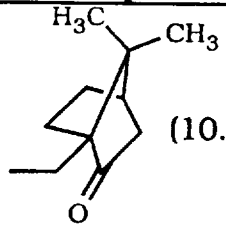
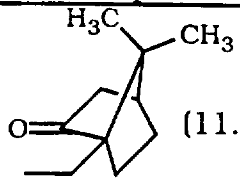
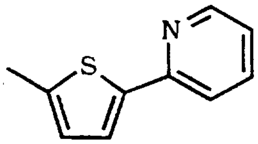
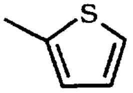
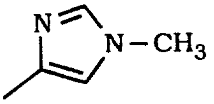
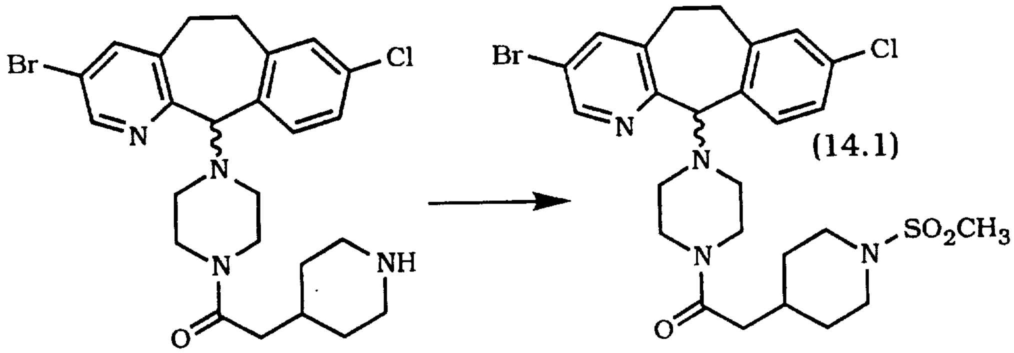
Ex.	Sulfonyl chloride	R^{17}
6	ethanesulfonyl chloride	$—SO_2CH_2CH_3$ (3.0) Yield:83%, mp 119-124°C
7	1-propanesulfonyl chloride	$—SO_2CH_2CH_2CH_3$ (4.0) Yield:78%, mp 111-119°C
8	isopropylsulfonyl chloride	$—SO_2CH(CH_3)_2$ (5.0) Yield:43%, mp 95-103°C
9	phenylmethylsulfonyl chloride	$—SO_2CH_2C_6H_5$ (9.0) Yield:69%, mp 116-123°C
10	(1S)-(+)-10-camphorsulfonyl chloride	 (10.0) Yield:60%, mp 144-152°C
11	(1R)-(-)-10-camphorsulfonyl chloride	 (11.0) Yield:50%, mp 143-150°C
12	2-(pyrid-2-yl)thiophene-5-sulfonyl chloride	 (8.0) Yield:36%, mp 135.3°C

TABLE 1 - continued

Ex.	Sulfonyl chloride	R^{17}
13	2-thiophenesulfonyl chloride	 (7.0) Yield:46%, mp 114.2°C
14	1-methylimidazole-4-sulfonyl chloride	 (12.0) Yield:46%, mp 117°C (dec)

EXAMPLE 15

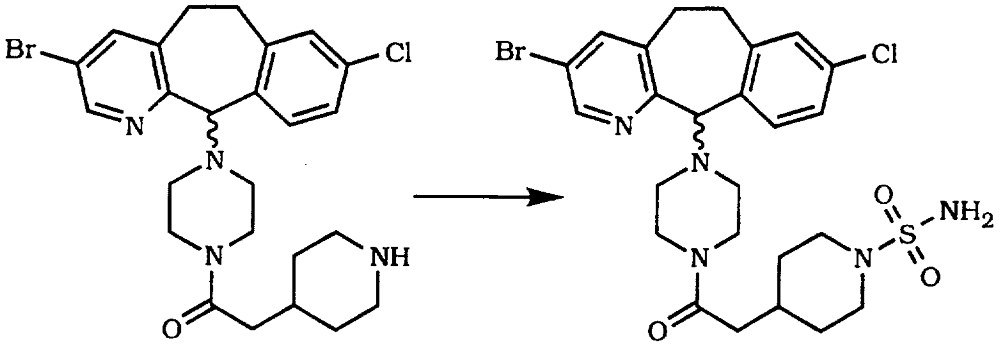


(14.1)

1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-4-(4-piperidinylacetyl)piperazine (1.5g) (1 equivalent) (prepared as described in Preparative Example 11) was dissolved in anhydrous dichloromethane (50ml) and triethylamine (0.8792g) (1.211ml) (3 equivalents) and methanesulfonyl chloride (0.498g) (0.336ml) (1.5 equivalents) were added. The mixture was stirred at 25°C under argon for 18h. Additional methanesulfonyl chloride (0.259g) (0.118ml) (0.75 equivalents) was added and the stirring was continued for a further 6h. Additional methanesulfonyl chloride (0.259g) (0.118ml) (0.75 equivalents) and triethylamine (0.8792g) (1.211ml) (3 equivalents) were added and the stirring was continued for a total of 90h. The mixture was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate and then with water. The dichloromethane layer was dried over magnesium sulfate, filtered and evaporated to dryness The resulting product was chromatographed on a silica gel column (60X2.5cm) using 1% (10% concentrated ammonium hydroxide in methanol as the eluant to give the title compound (Formula 14.1) (1.2505g; 72%), FABMS: m/z 595.1 (MH^+).

		δ_C ($CDCl_3$) for Formula 14.1
Tricyclic	CH_2:	30.0, 30.1
	CH:	146.6, 140.8, 132.0, 125.8, 130.0, 78.5
	C:	119.6, 140.4, 133.8, 134.8, 136.3, 155.0
Piperazine	CH_2:	41.1, 50.9, 51.4, 45.1
Piperazine N-substituent	CH_3	33.9
	CH_2:	45.7, 45.7, 31.3, 31.3, 38.4
	CH:	31.9
	C:	169.0

EXAMPLE 16



PROCEDURE 1:

1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-4-[(4-piperidinyl)acetyl]piperazine (0.555g) (1 equivalent) (prepared as described in Preparative Example 11) and sulfamide (1.03g) (10 equivalents) were added to water (20ml) and the mixture was heated under reflux at 100°C for 43h. The resulting solution was evaporated to dryness. The solid was taken up in methanol-water-dichloromethane and silica gel was added. The mixture was evaporated to dryness. The resulting solid was introduced onto a silica gel column (60X2.5cm) and the column was eluted with 3% increasing to 7% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (Formula 14.2) (0.5282g; 83%), FABMS: m/z 596.0 (MH^+).

δ_C (d6-DMSO) for Formula 14.2		
Tricyclic	CH_2:	29.3, 29.7
	CH:	146.4, 141.1, 132.8, 125.8, 130.3, 78.0
	C:	119.5, 141.4, 132.8, 135.8, 137.1, 155.8
Piperazine	CH_2:	41.0, 51.1, 51.7, 45.0
Piperazine N-substituent	CH_2:	46.1, 46.1, 30.8, 30.8, 38.2
	CH:	32.0
	C:	169.2

PROCEDURE 2:

1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-4-[(4-piperidinyl)acetyl]piperazine (1.25g) (1 equivalent) (prepared as described in Preparative Example 11) and sulfamide (2.32g) (10 equivalents) were heated at 150°C in a flask equipped with a reflux condenser. The solids melted and the mixture was stirred for 73h. and then cooled. The solid was taken up in methanol-water-dichloromethane and silica gel was added. The mixture was evaporated to dryness. The resulting solid was introduced onto a silica gel column (60X2.5cm) and the column was eluted with 2% increasing to 7% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (Formula 14.2) (0.3788g; 26%).

PROCEDURE 3:

1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-4-[(4-piperidinyl)acetyl]piperazine (1.5g) (1 equivalent) (prepared as described in Preparative Example 11) and sulfamide (2.79g) (10 equivalents) were added to isopropanol (100ml) and the mixture was heated under reflux at 86°C for 241h. The solution was evaporated to dryness. The solid was taken up in methanol-water-dichloromethane and silica gel was added. The mixture was evaporated to dryness. The resulting solid was introduced onto a silica gel column (60X2.5cm) and the column was eluted with 0.5% increasing to 7% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (Formula 14.2) (0.088g; 5%).

ASSAYS

FPT IC_{50} (inhibition of farnesyl protein transferase, in vitro enzyme assay) and COS Cell IC_{50} (Cell-Based Assay) were determined following the assay procedures described in WO 95/10516, published April 20, 1995. GGPT IC_{50} (inhibition of geranylgeranyl protein transferase, in vitro enzyme assay), Cell Mat Assay, and anti-tumor activity (in vivo anti-tumor studies) could be determined by the assay procedures described in WO 95/10516. The disclosure of WO 95/10516 is incorporated herein by reference thereto.

Additional assays can be carried out by following essentially the same procedure as described above, but with substitution of alternative indicator tumor cell lines in place of the T24-BAG cells. The assays can be conducted using either DLD-1-BAG human colon carcinoma cells expressing an activated K-ras gene or SW620-BAG human colon carcinoma cells expressing an activated K-ras gene. Using other tumor cell lines known in the art, the activity of the compounds of this invention against other types of cancer cells could be demonstrated.

Soft Agar Assay:

Anchorage-independent growth is a characteristic of tumorigenic cell lines. Human tumor cells are suspended in growth medium containing 0.3% agarose and an indicated concentration of a farnesyl transferase inhibitor. The solution is overlayed onto growth medium solidified with 0.6% agarose containing the same concentration of farnesyl transferase inhibitor as the top layer. After the top layer is solidified, plates are incubated for 10-16 days at 37°C under 5% CO_2 to allow colony outgrowth. After incubation, the colonies are stained by overlaying the agar with a solution of MTT (3-[4,5-dimethyl-thiazol-2-yl]-2,5-diphenyltetrazolium bromide, Thiazolyl blue) (1 mg/mL in PBS). Colonies can be counted and the IC_{50}'s can be determined.

The results are given in Table 1. In Table 1 "Ex. No." stands for "Example Number".

TABLE 1

Ex No.	Formula No.	FPT IC_{50} (nM) (H-ras)	COS Cell IC_{50} (nM)
1	6.0	72	----
2	2.0	2.1	30
3	13.0	7.3	9
4	14.0	2.9	35
6	3.0	3.7	12
7	4.0	5	30
8	5.0	5.8	----
9	9.0	17.5, 8.0	350
10	10.0	34.1	----
11	11.0	34.8	----
12	8.0	34%@73 nM	----
13	7.0	20	50
14	12.0	5.7	400
15	14.1	54	----
16	14.2	80	----

The following compounds had the following FPT IC_{50} (K-ras) results: 2.0, 8.2nM; 3.0, 16.4nM; 4.0, 14.2nM; 5.0, 22.9nM; 10.0, 52.5nM; 12.0, 23nM; and 13.0, 10nM.

The following compounds had the following Soft Agar IC_{50} results: 2.0, 50nM; 3.0, 100nM; 4.0, 250nM; 7.0, >250nM; and 13.0, 100nM.

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 300 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 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to block tumor growth. The compounds are non-toxic when administered within this dosage range.

The following are examples of pharmaceutical dosage forms which contain a compound of the invention. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

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	7	7
	Total	253	700

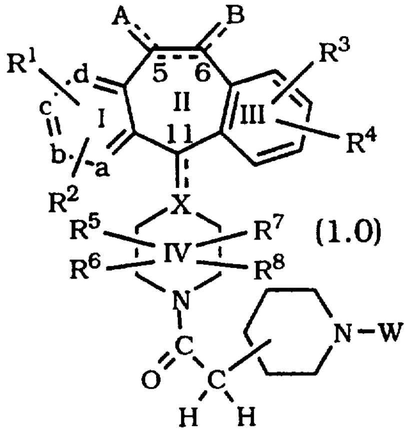
Method of Manufacture

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:



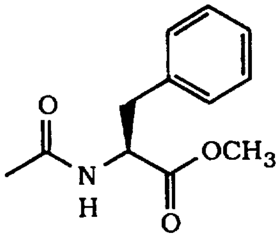
(1.0)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

one of a, b, c and d represents N or NR^9 wherein R^9 is O^-, $-CH_3$ or $-(CH_2)_nCO_2H$ wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR^1 or CR^2; or

each of a, b, c, and d are independently selected from CR^1 or CR^2;

each R^1 and each R^2 is independently selected from H, halo, $-CF_3$, $-OR^{10}$, $-COR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$ (wherein t is 0, 1 or 2), -SCN, $-N(R^{10})_2$, $-NR^{10}R^{11}$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, -CN, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-CONHR^{10}$, $-CONHCH_2CH_2OH$, $-NR^{10}COOR^{11}$,



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$-SR^{11}C(O)OR^{11}$, $-SR^{11}N(R^{75})_2$ wherein each R^{75} is independently selected from H and $-C(O)OR^{11}$, benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, $-OR^{10}$ or $-CO_2R^{10}$;

R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2, or R^3 and R^4 taken together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring (Ring III);

R^5, R^6, R^7 and R^8 each independently represents H, $-CF_3$, $-COR^{10}$, alkyl or aryl, said alkyl or aryl optionally being substituted with $-OR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$, $-NR^{10}COOR^{11}$, $-N(R^{10})_2$, $-NO_2$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{11}$, $-CO_2R^{10}$, OPO_3R^{10} or R^5 is combined with R^6 to represent =O or =S and/or R^7 is combined with R^8 to represent =O or =S;

R^{10} represents H, alkyl, aryl, or aralkyl;

R^{11} represents alkyl or aryl;

X represents N, CH or C, which C may contain an optional double bond (represented by the dotted line) to carbon atom 11;

the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent $-R^{10}$, halo, $-OR^{11}$, $-OCO_2R^{11}$ or $-OC(O)R^{10}$, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2, $-(OR^{11})_2$; H and halo, dihalo, alkyl and H, $(alkyl)_2$, -H and $-OC(O)R^{10}$, H and $-OR^{10}$, =O, aryl and H, $=NOR^{10}$ or $-O-(CH_2)_p-O-$ wherein p is 2, 3 or 4; and

W represents a group selected from: $-SO_2R^{12}$ or $-P(O)R^{13}R^{14}$;

R^{12} is selected from:

(1) alkyl;

(2) aralkyl;

(3) cycloalkyl;

(4) aryl;

(5) heteroaryl;

(6) substituted heteroaryl wherein said heteroaryl is as defined above and said substituents are selected from: (a) heteroaryl, (b) alkyl, (c) aryl, (d) aralkyl, (e) $-OR^{10}$, and (f) $N(R^{10})_2$;

(7) camphor; or

(8) $-NR^{15}R^{16}$ wherein R^{15} and R^{16} are independently selected from the group consisting of: (a) H, (b) alkyl, (c) aryl, (d) aralkyl, (e) heteroaryl, and (f) heterocycloalkyl; and

R^{13} and R^{14} are independently selected from:

(1) H;

(2) alkyl;

(3) aryl;

(4) aralkyl; or

(5) -OR^{13} wherein R^{13} is as defined above.

2. The compound of Claim 1 wherein R^2 is H; R^1 is selected from: Br or Cl; R^3 is selected from: Br or Cl; R^4 is selected from: H, Br or Cl; R^5, R^6, R^7 and R^8 are H; A and B are each H_2; and the optional bond between C5 and C6 is absent.

3. The compound of Claim 1 or 2 wherein W is selected from:

(A) -SO_2R^{12} wherein R^{12} is selected from the group consisting of: (1) alkyl, (2) aryl, (3) heteroaryl, (4) substituted heteroaryl, (5) aralkyl, (5) camphor, and (6) -$NR^{15}R^{16}$; or

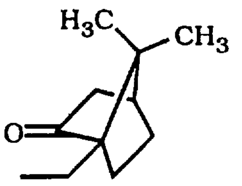
(B) -$P(O)R^{13}R^{14}$, wherein R^{13} is alkyl and R^{14} is alkyl.

4. The compound of any of Claims 1-3 wherein R^4 is H.

5. The compound of any of Claims 1-3 wherein R^4 is selected from the group consisting of: Cl or Br.

6. The compound of any of Claims 1-5 wherein X is CH.

7. The compound of any of Claims 1-6 wherein R^{12} is selected from the group consisting of: methyl, ethyl, n-propyl, iso-propyl, phenyl, thienyl,



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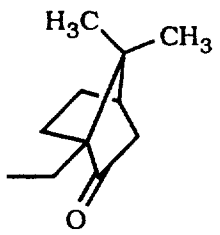

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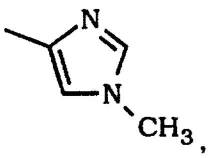

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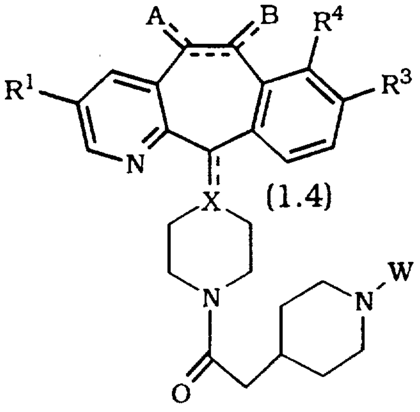
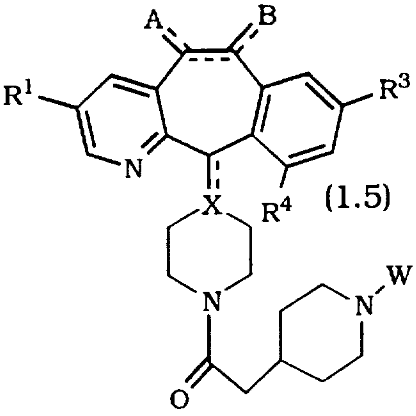
benzyl, -NH_2 and -$N(CH_3)_2$; and R^{13} and R^{14} are methyl.

8. The compound of any of Claims 1-7 selected from:



(1.4)

or

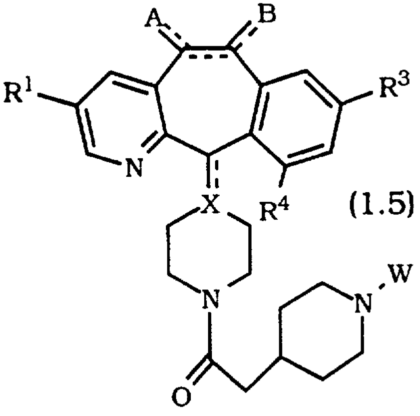


(1.5)

wherein R^1, R^3 and R^4 are each independently selected from halo.

9. The compound of any of Claims 1-8 wherein R^1 is Br; and R^3 is Cl; and R^4 is Br.

10. The compound of any of Claims 1-9 wherein said compound is a compound of the formula:



(1.5)

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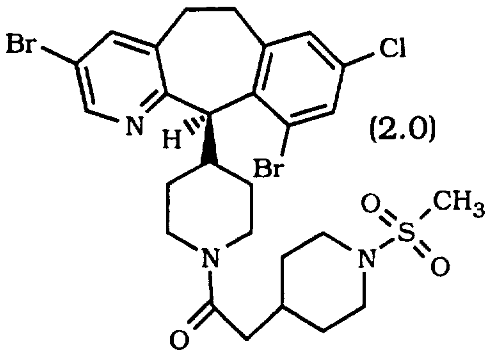
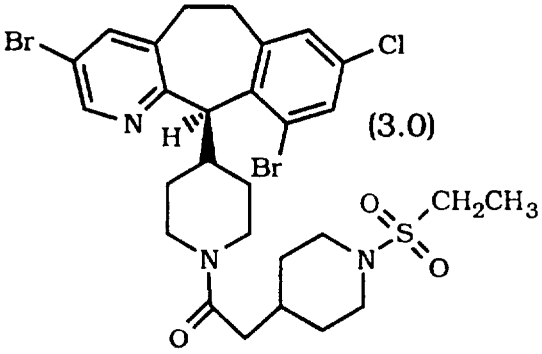
11. The compound of Claim 1 selected from:


Br
Cl
N
H
Br
N
O
N
O
S
O
CH3

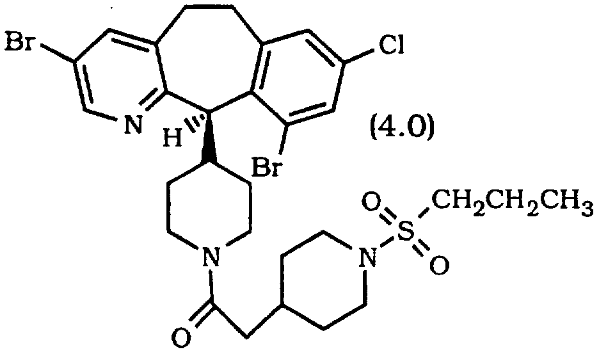
(2.0)

;


Br
Cl
N
H
Br
N
O
N
O
S
O
CH2CH3

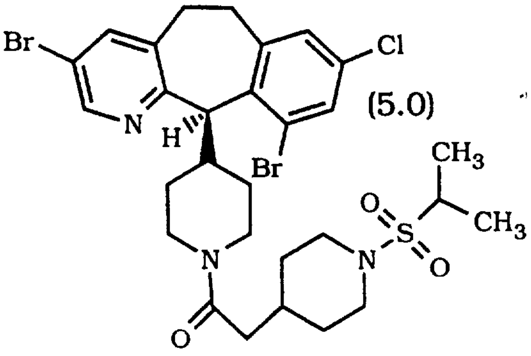
(3.0)

;


Br
Cl
N
H
Br
N
O
N
O
S
O
CH2CH2CH3

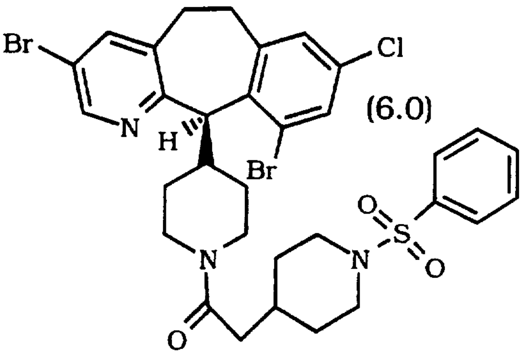
(4.0)

;


Br
Cl
N
H
Br
N
O
N
O
S
O
CH3
CH3

(5.0)

;



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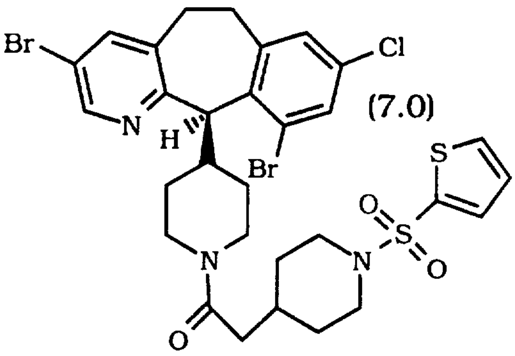

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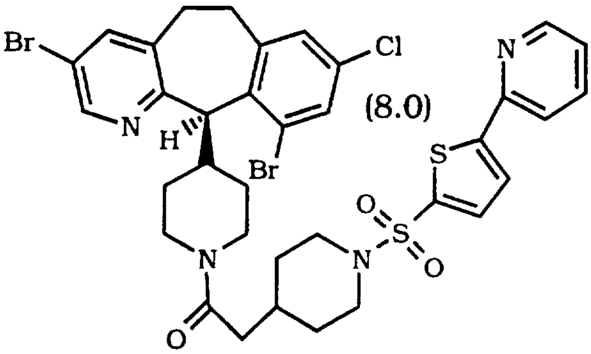

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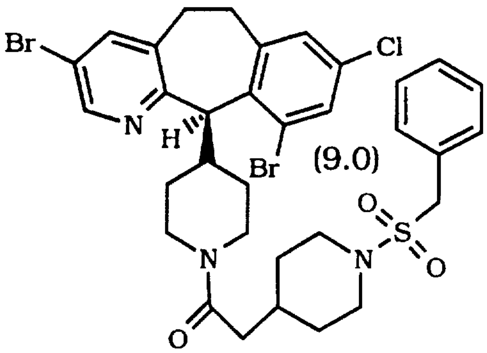

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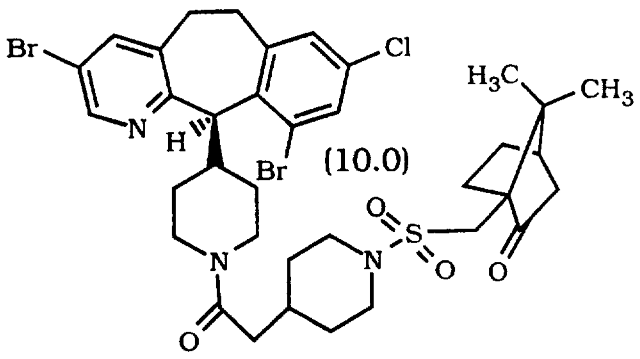

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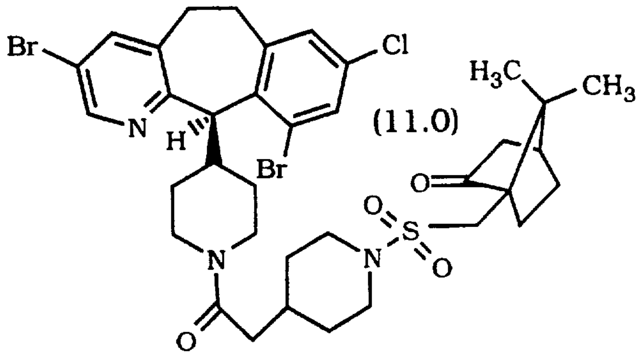

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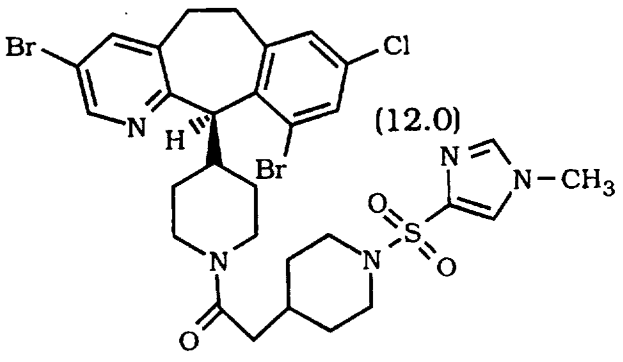

(12.0)

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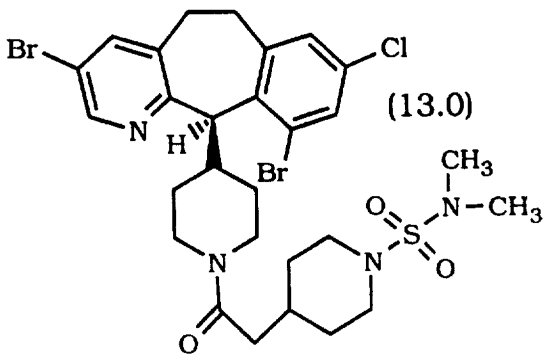

(13.0)

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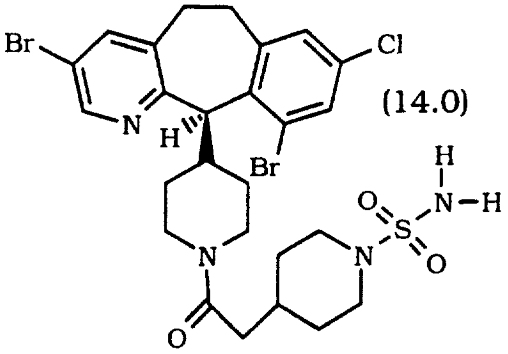

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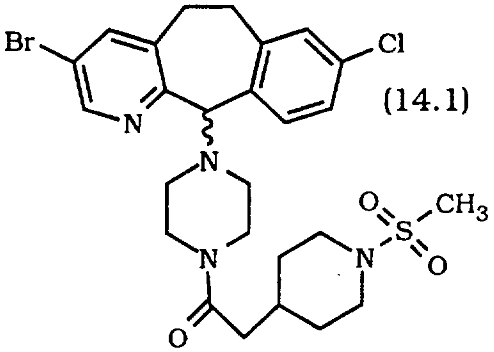

(14.1)

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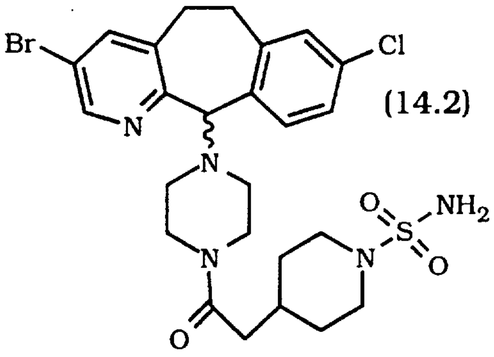
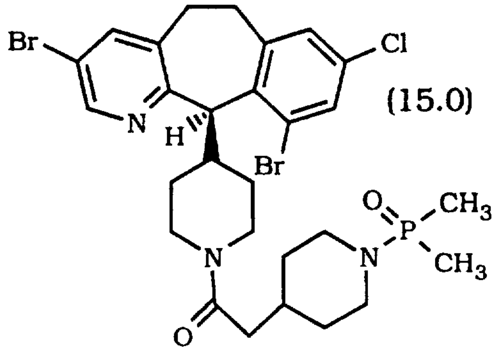


(14.2)

or



(15.0)

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12. A method of treating tumor cells comprising administering an effective amount of a compound of any of Claims 1-11.

13. The method of Claim 12 wherein the cells treated are pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells, colon tumors cells, breast tumor cells and prostate tumor cells.

14. A method of inhibiting farnesyl protein transferase comprising the administration of an effective amount of the compound of any of Claims 1-11.

15. A pharmaceutical composition comprising an effective amount of compound of any of Claims 1-11 in combination with a pharmaceutically acceptable carrier.

16. The use of a compound of any of Claims 1-11 for the treatment of tumor cells.

17. The use of a compound of any of Claims 1-11 for the manufacture of a medicament for the treament of tumor cells.

18. The use of a compound of any of Claims 1-11 for the inhibition of farnesyl protein transferase.

19. The use of a compound of any of Claims 1-11 for the manufacture of a medicament for the inhibition of farnesyl protein transferase.

INTERNATIONAL SEARCH REPORT

Intern. ɔnal Application No
PCT/US 97/15906

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/14 C07F9/6558 C07D409/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 10516 A (SCHERING CORP) 20 April 1995 cited in the application see claims ---	1,12-19
Y	WO 95 10514 A (SCHERING CORP) 20 April 1995 see claims ---	1,12-19
Y	US 4 282 233 A (VILANI FRANK J) 4 August 1981 see the whole document -----	1,12-19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

"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

1

Date of the actual completion of the international search 25 November 1997	Date of mailing of the international search report 02.12.97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Henry, J

International application No.
PCT/US 97/15906

INTERNATIONAL SEARCH REPORT

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. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ 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 searched 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claims 12-14 are directed to a method of treatment of the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 97/15906

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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