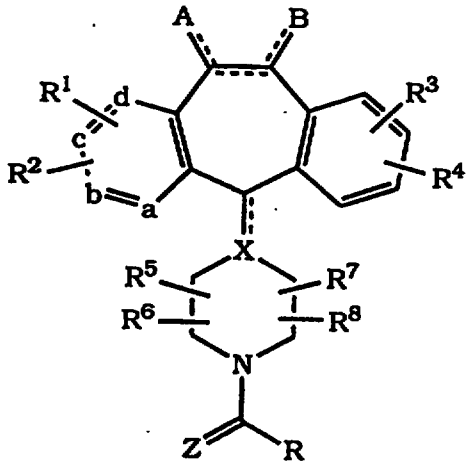
BENZO(5,6)CYCLOHEPTA(1,2-B)PYRIDINE DERIVATIVES FOR THE INHIBITION OF FARNESYL PROTEIN TRANSFERASE

BACKGROUND

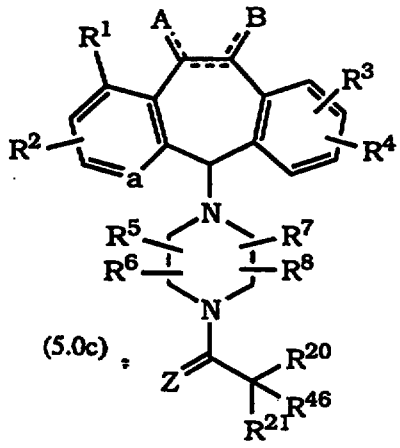
The biological significance of the Ras oncogene, and the role of both Ras and the enzyme known as farnesyl protein transferase in the conversion of normal cells to cancer cells, are described in PCT International Publication Nos. WO95/00497 and WO95/10516. Each of those publications also describes a distinct class of compounds which inhibit the activity of the enzyme farnesyl protein transferase, and thereby the farnesylation of the Ras protein.

PCT International Publication No. WO95/10516 relates to tricyclic amide and urea compounds of the general formula (1.0)

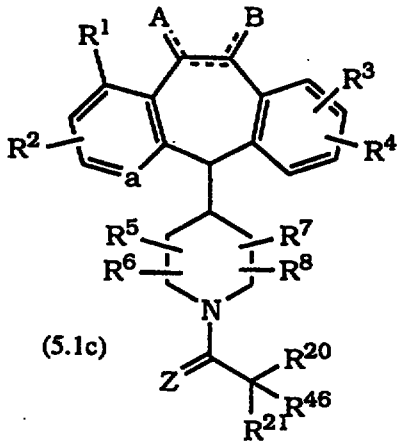


(1.0)

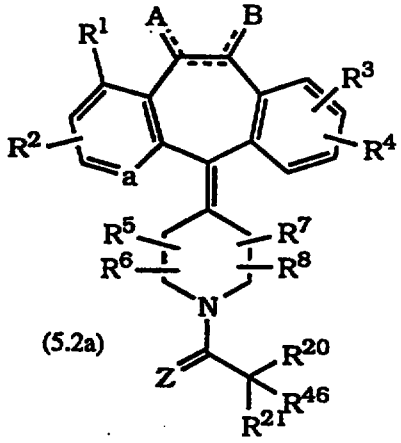
and their use in a method for inhibiting Ras function and the abnormal growth of cells. A number of sub-generic classes of compounds of formula (1.0) are described, which include compounds of the formulae (5.0c), (5.1c) and (5.2a)



(5.0c),



(5.1c),

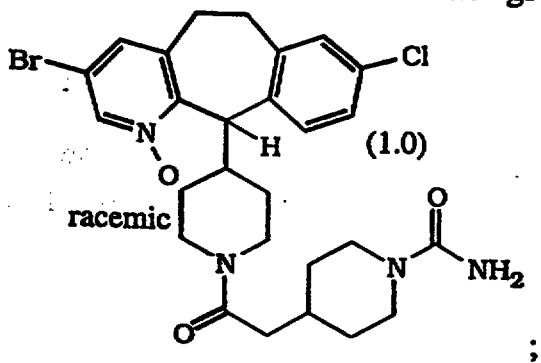


(5.2a),

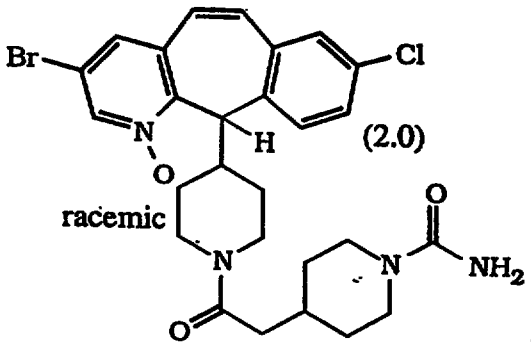
as well as the 11-R-isomer and 11-S-isomers of compounds (5.0c) and (5.1c). A number of specific compounds within each such sub-genus are also described therein, as is the biological activity of those compounds.

SUMMARY OF THE INVENTION

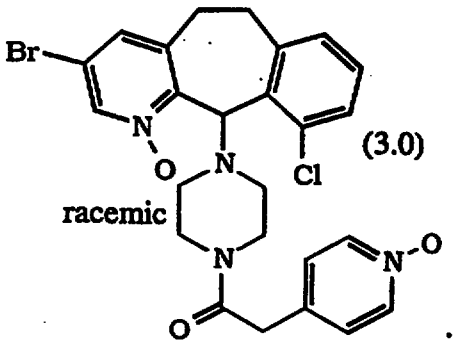
The present invention provides novel tricyclic amide compounds selected from the group consisting of:



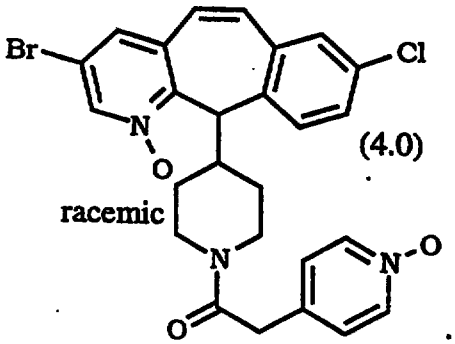
(1.0);



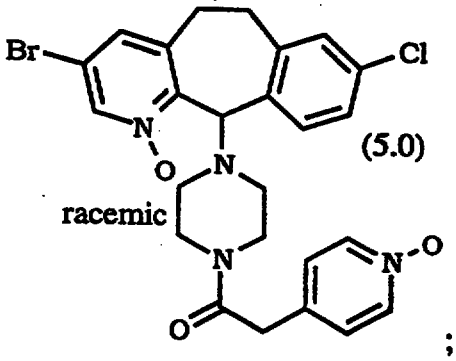
(2.0);


Br
Cl
racemic
(3.0)

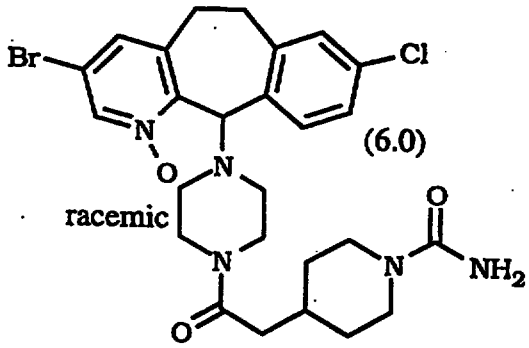
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Br
Cl
racemic
(4.0)

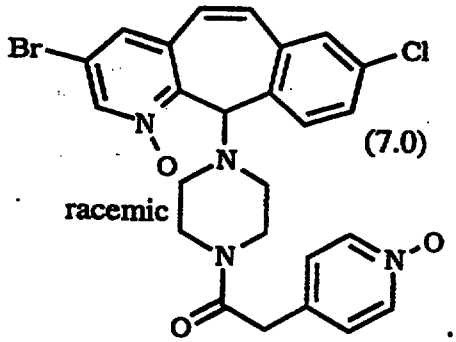
;


Br
Cl
racemic
(5.0)

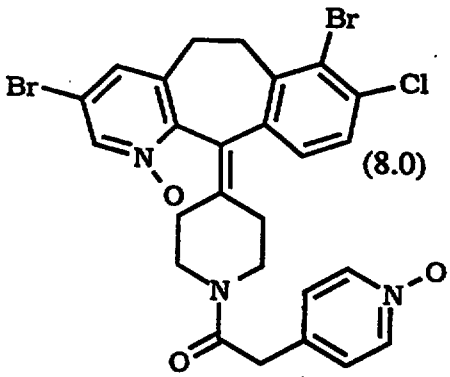
;


Br
Cl
racemic
(6.0)
NH2

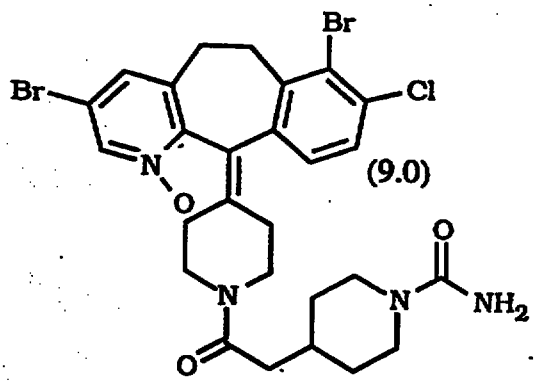
;


Br
Cl
racemic
(7.0)

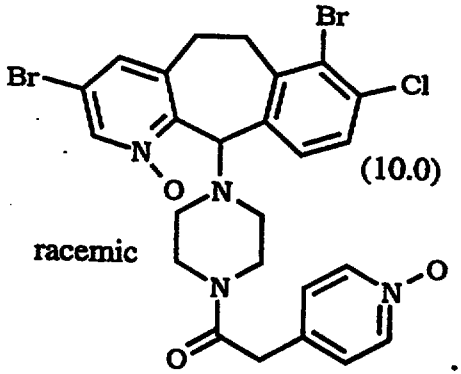
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Br
Br
Cl
(8.0)

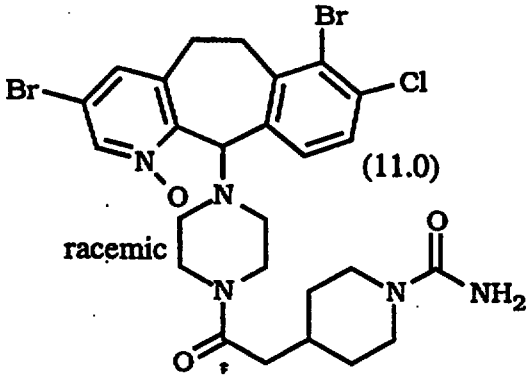
;


Br
Br
Cl
(9.0)
NH2

;

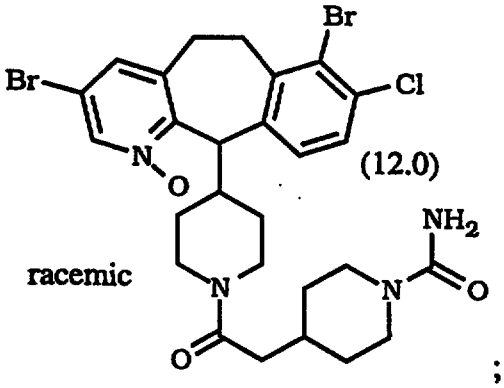

Br
Br
Cl
(10.0)
racemic

;



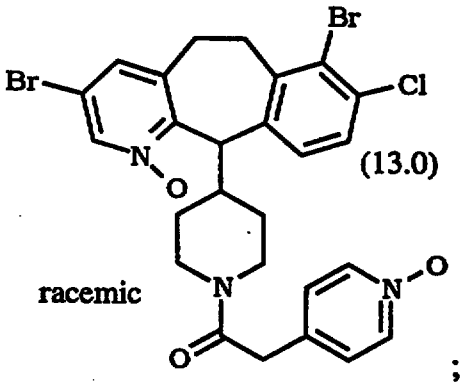
(11.0)

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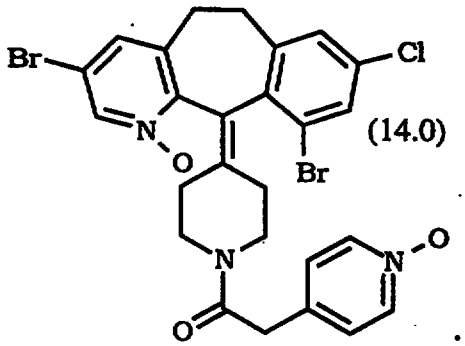
(12.0)

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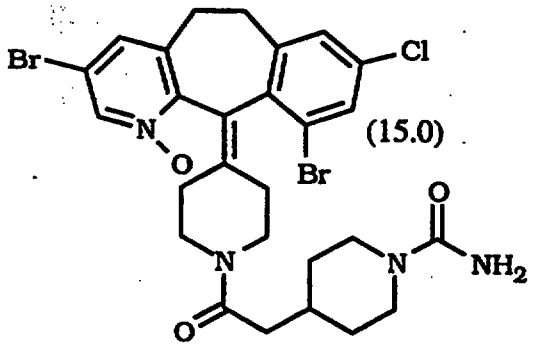
(13.0)

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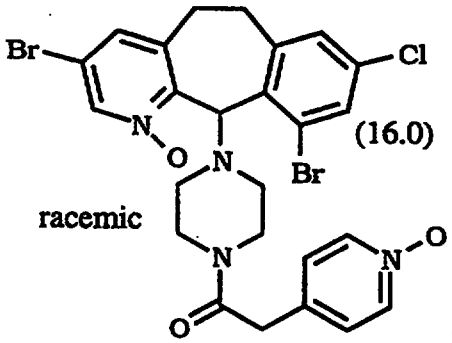
(14.0)

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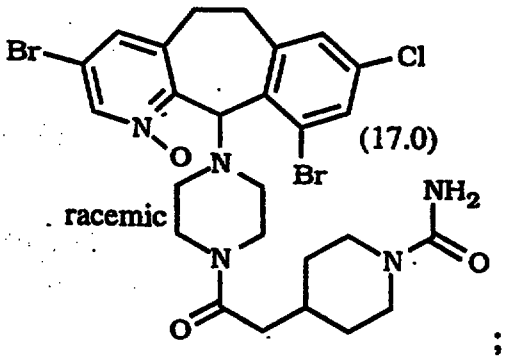
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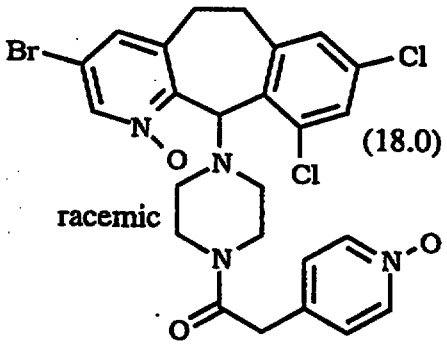
(16.0)

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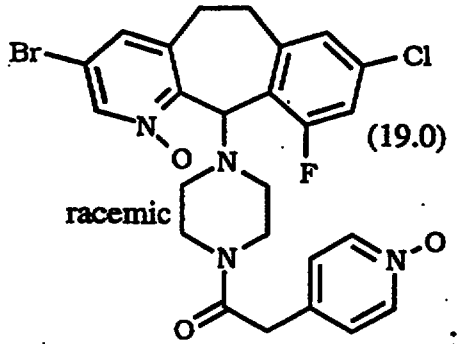
(17.0)

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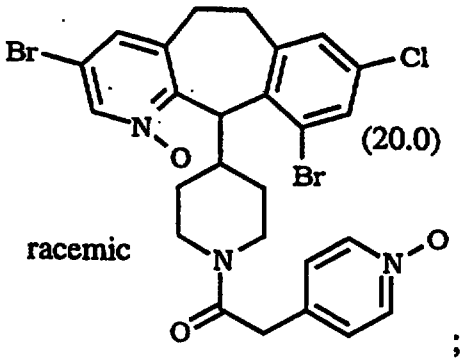


(18.0)

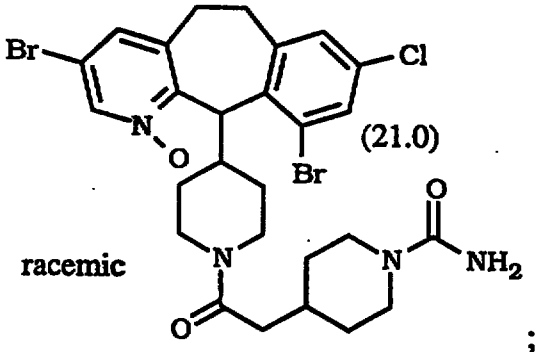
;


Br
Cl
F
(19.0)
racemic

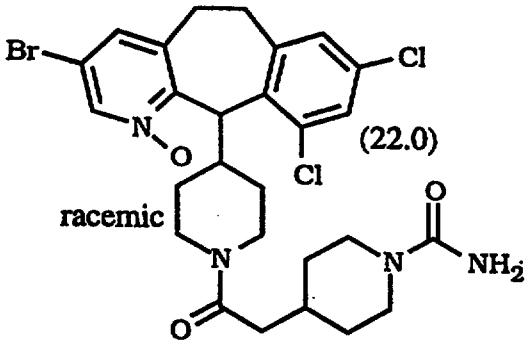
;


Br
Cl
Br
(20.0)
racemic

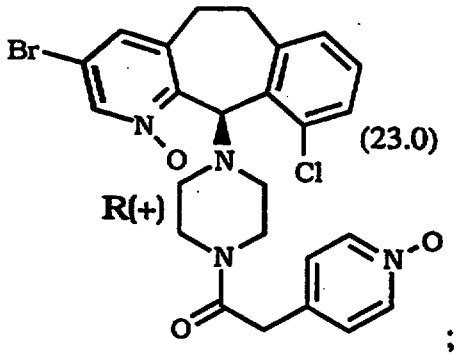
;


Br
Cl
Br
(21.0)
racemic
NH2

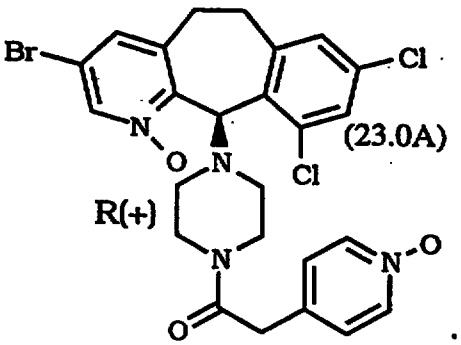
;


Br
Cl
Cl
(22.0)
racemic
NH2

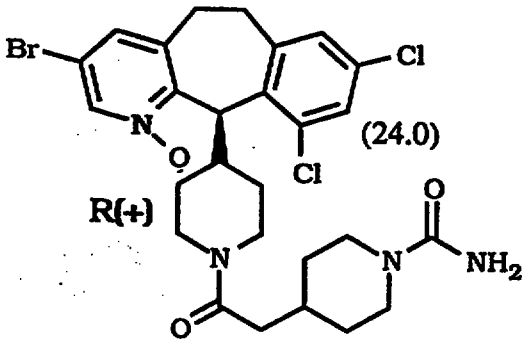
;


Br
Cl
(23.0)
R(+)

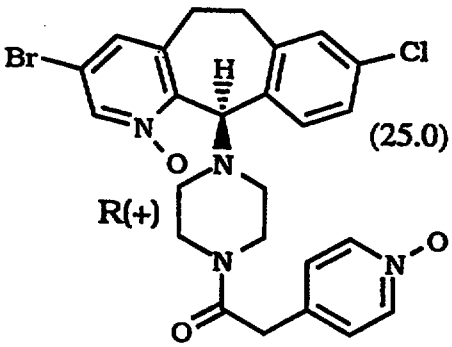
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Br
Cl
Cl
(23.0A)
R(+)

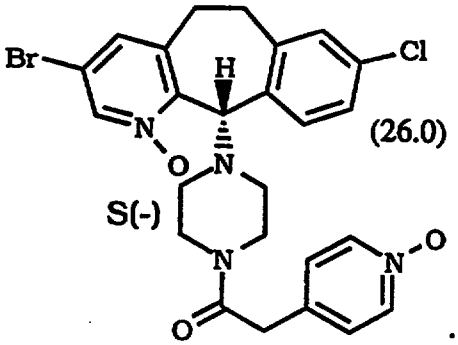
;


Br
Cl
Cl
(24.0)
R(+)
NH2

;

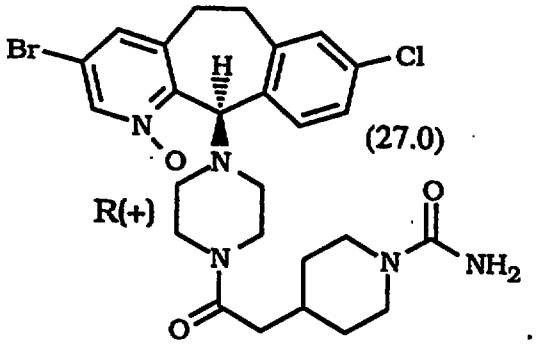

Br
Cl
H
(25.0)
R(+)

;



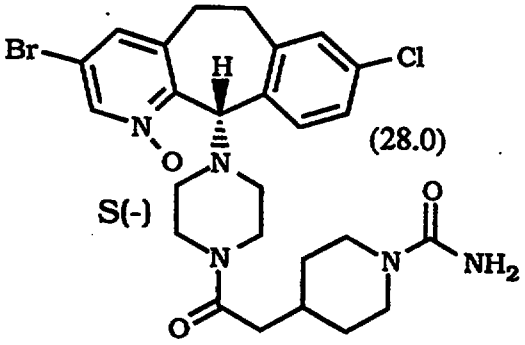
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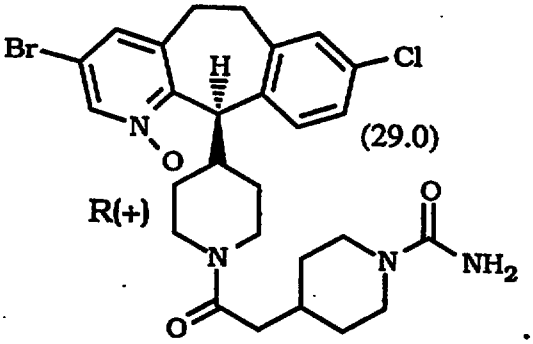
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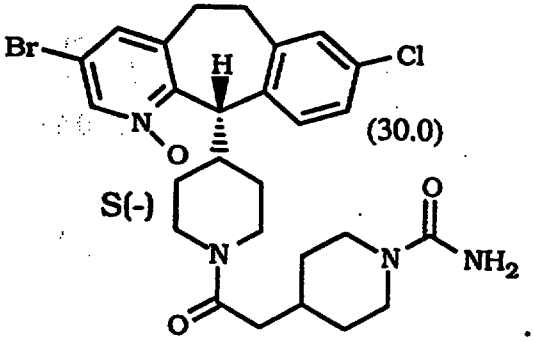
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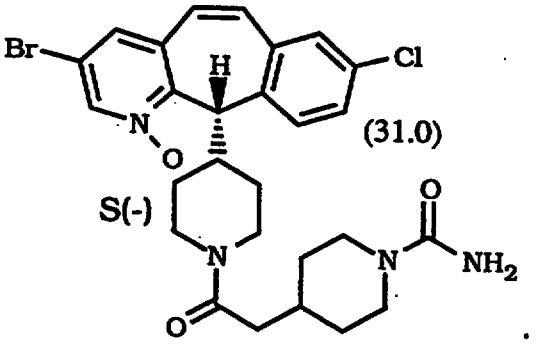
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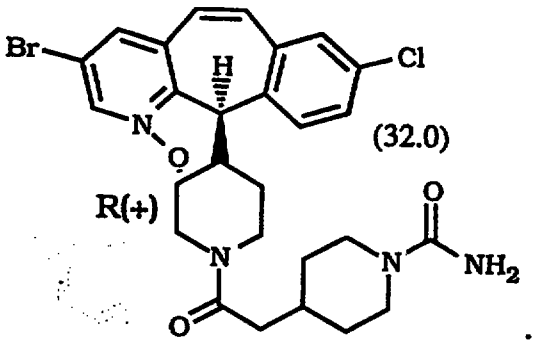
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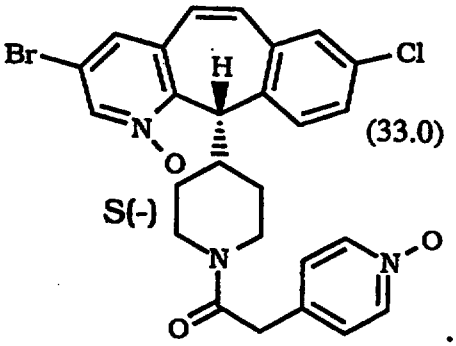
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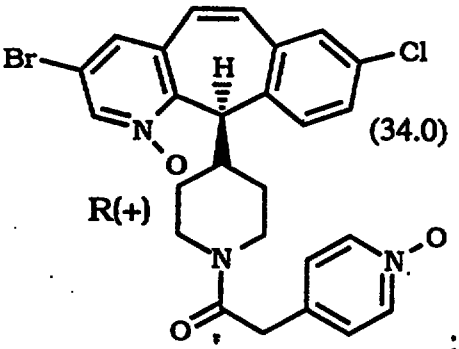
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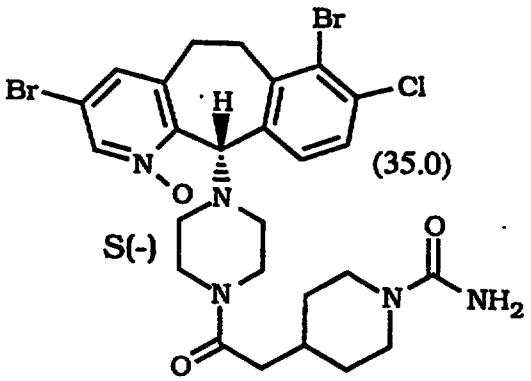


(33.0)

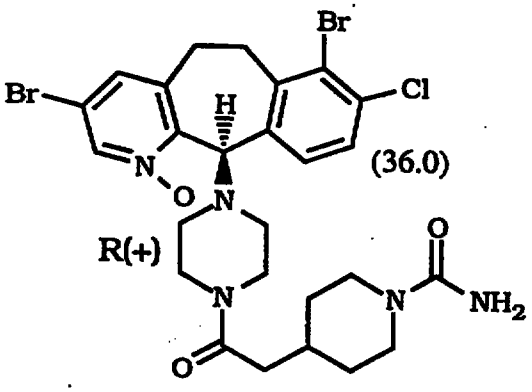
;


Br
Cl
H
N
O
(34.0)
R(+)
N
O
O

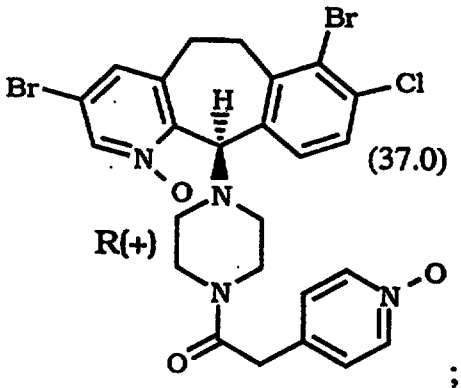
;


Br
Br
Cl
H
N
O
N
(35.0)
S(-)
O
N
NH2
O

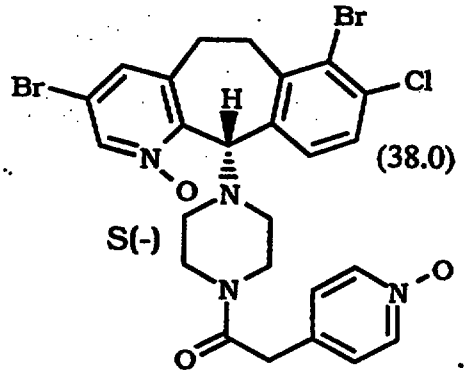
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Br
Br
Cl
H
N
O
N
(36.0)
R(+)
O
N
NH2
O

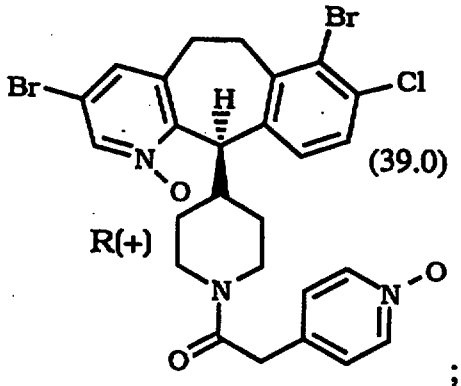
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Br
Br
Cl
H
N
O
N
(37.0)
R(+)
N
O
O

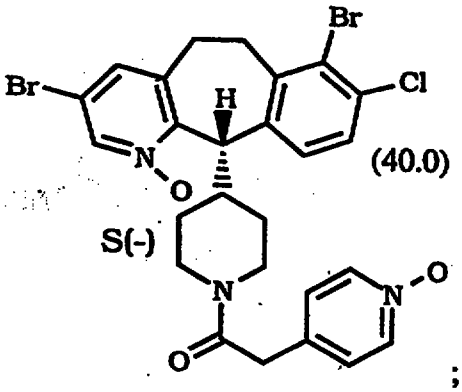
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Br
Br
Cl
H
N
O
N
(38.0)
S(-)
N
O
O

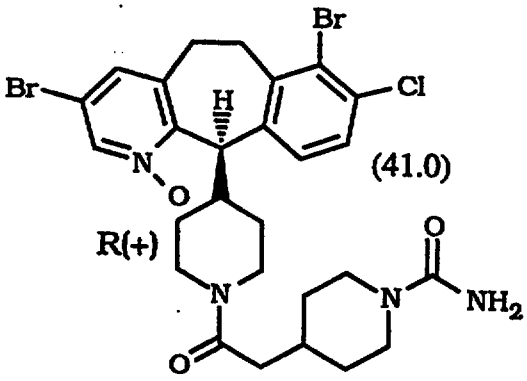
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Br
Br
Cl
H
N
O
(39.0)
R(+)
N
O
O

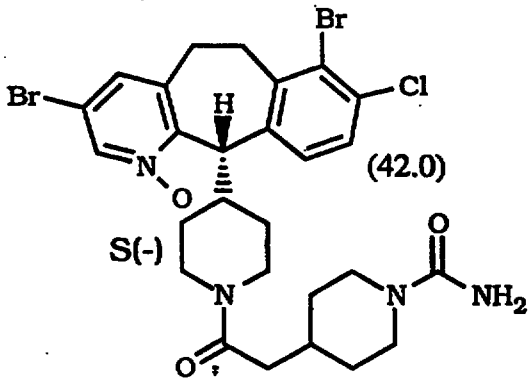
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Br
Br
Cl
H
N
O
(40.0)
S(-)
N
O
O

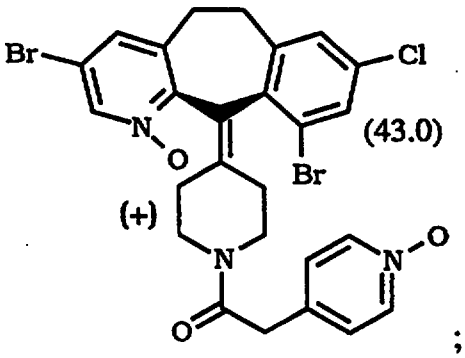
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Br
Br
Cl
H
N
O
(41.0)
R(+)
O
N
NH2
O

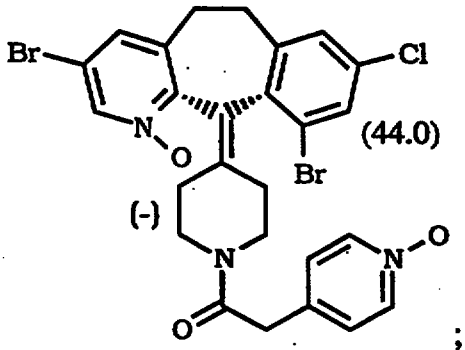
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Br
Br
Cl
H
N
O
(42.0)
S(-)
O
N
NH2
O

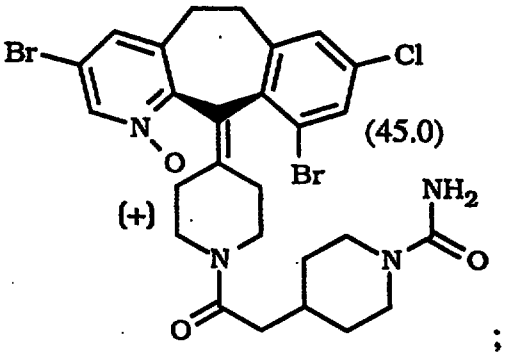
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Br
Cl
N
O
(43.0)
Br
(+)
N
O
O

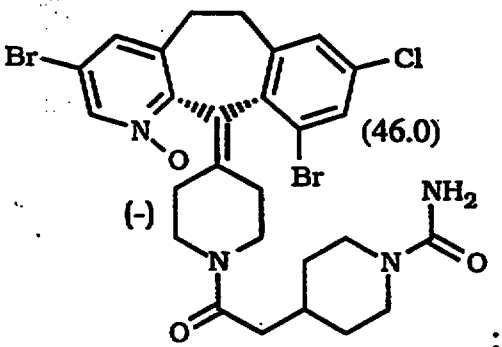
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Br
Cl
N
O
(44.0)
Br
(-)
N
O
O

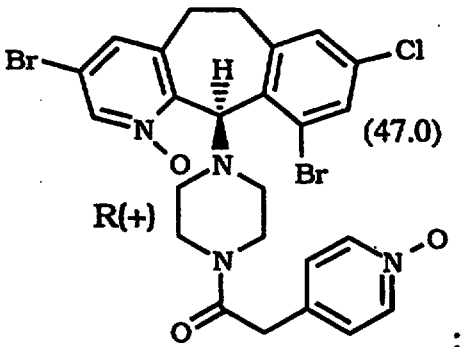
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Br
Cl
N
O
(45.0)
Br
(+)
NH2
N
O
O

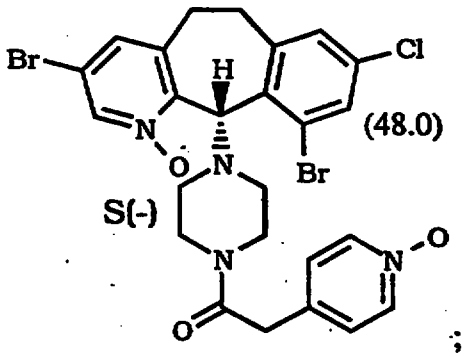
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Cl
N
O
(46.0)
Br
(-)
NH2
N
O
O

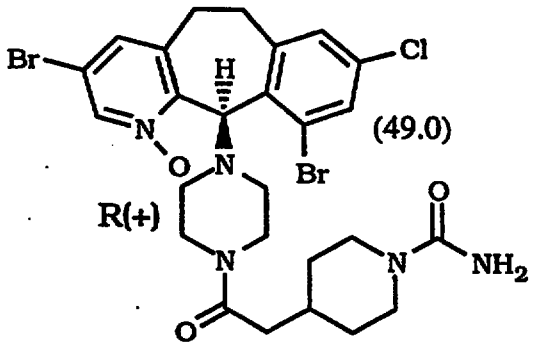
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H
N
O
(47.0)
Br
R(+)
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N
O
O

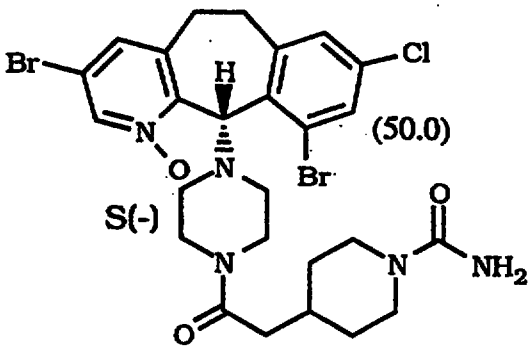
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Br
Cl
H
N
O
(48.0)
Br
S(-)
N
N
O
O

;

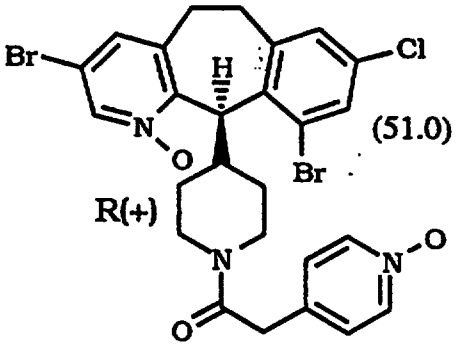

Br
Cl
H
N
O
(49.0)
Br
R(+)
N
N
O
NH2
O

;



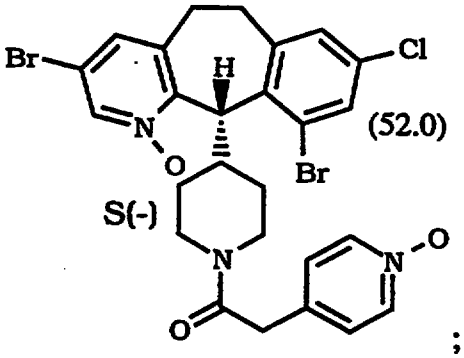
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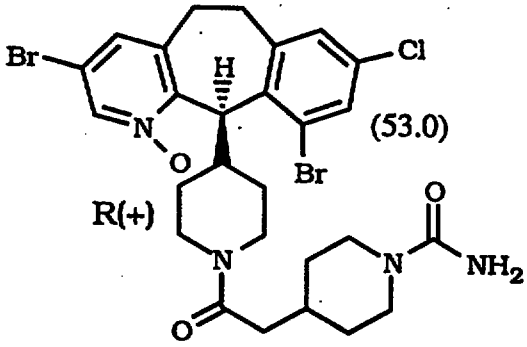
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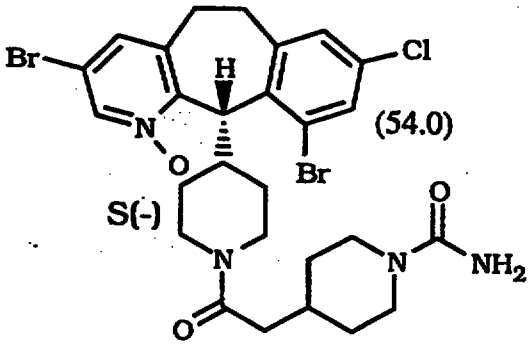
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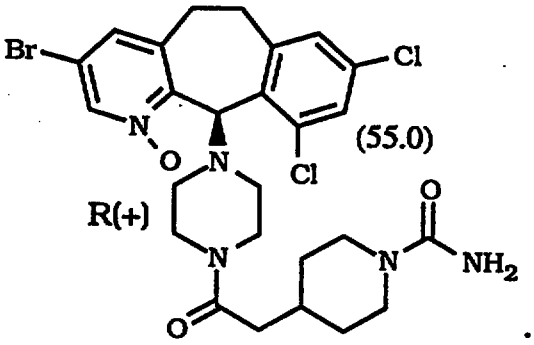
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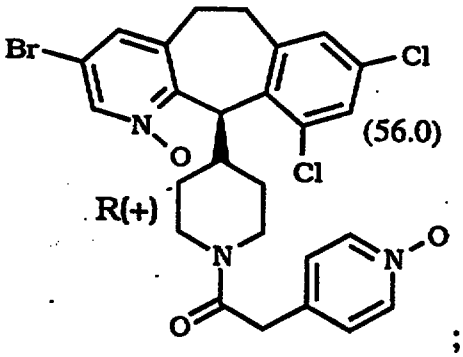
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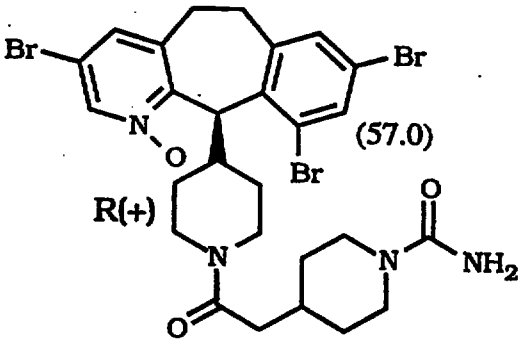
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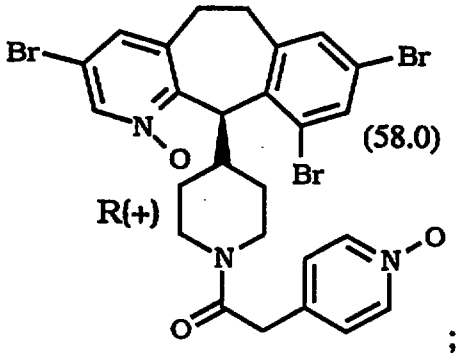
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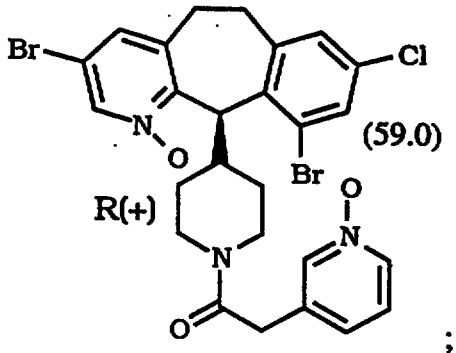


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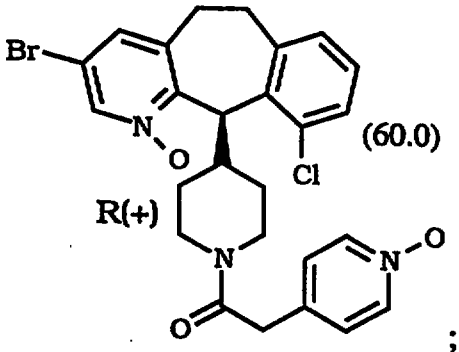
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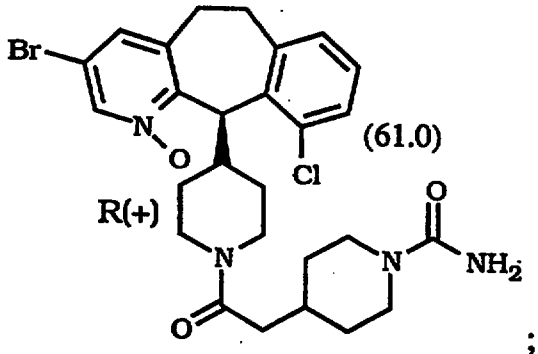
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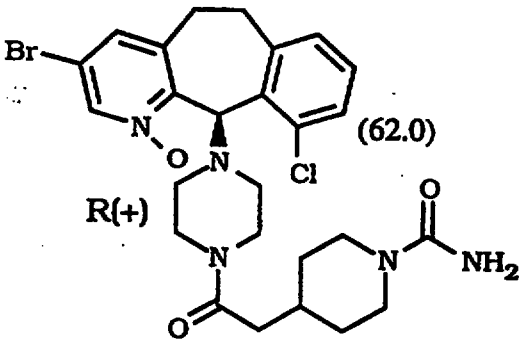
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(60.0)

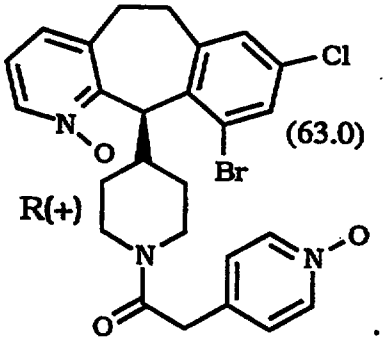
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(61.0)

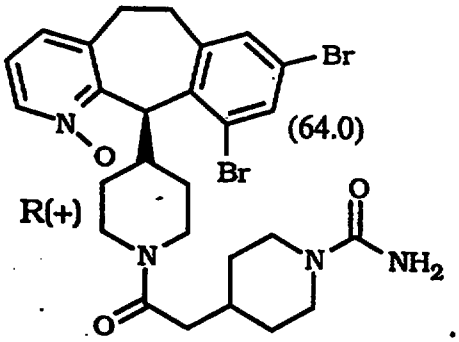
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(62.0)

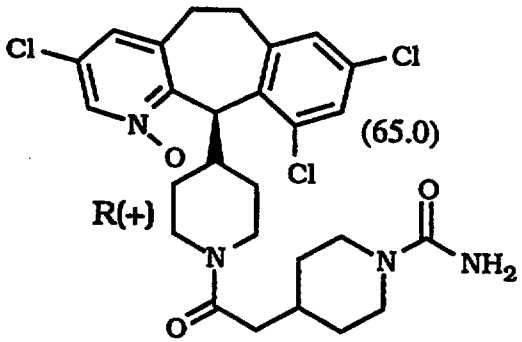
;


(63.0)

;


(64.0)

; and


(65.0)

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.

Thus, compounds of this invention include compounds selected from the group consisting of: Compounds 1.0, 2.0, 3.0, 4.0, 5.0, 7.0 and 6.0, or pharmaceutically acceptable salts thereof, wherein said compounds are as defined above.

Compounds of this invention also include compounds selected from the group consisting of: Compounds 10.0, 11.0, 12.0, 13.0, 16.0, 17.0, 18.0, 19.0, 20.0, 21.0, and 22.0, or pharmaceutically acceptable salts thereof, and wherein said compounds are as defined above.

Compounds of this invention also include compounds selected from the group consisting of: Compounds 8.0, 9.0, 14.0, and 15.0, or pharmaceutically acceptable salts thereof, and wherein said compounds are as defined above.

Compounds of this invention also include compounds selected from the group consisting of: Compounds 23.0, 25.0, 26.0, 27.0, 28.0, 29.0, 30.0, 31.0, 32.0, 33.0, 34.0, 60.0, 61.0, 62.0, 63.0, and 64.0, or pharmaceutically acceptable salts thereof, and wherein said compounds are as defined above.

Compounds of this invention also include compounds selected from the group consisting of: Compounds 23.0A, 24.0, 35.0, 36.0, 37.0, 38.0, 39.0, 40.0, 41.0, 42.0, 47.0, 48.0, 49.0, 50.0, 51.0, 52.0, 53.0, 54.0, 55.0, 56.0, 57.0, 58.0, 59.0, and 65.0, or pharmaceutically acceptable salts thereof, and wherein said compounds are as defined above.

Compounds of this invention also include compounds selected from the group consisting of: Compounds 43.0, 44.0, 45.0 and 46.0, or pharmaceutically acceptable salts thereof, and wherein said compounds are as defined above.

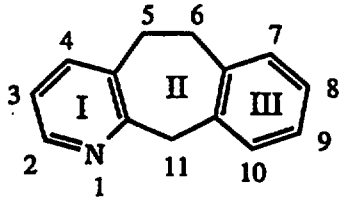
The preferred compounds include Compounds 5.0, 7.0, 25.0, 27.0, 29.0, and 34.0.

The preferred compounds also include Compounds 51.0 and 53.0

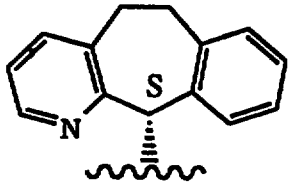
The preferred compounds also include Compounds 40.0 and 42.0.

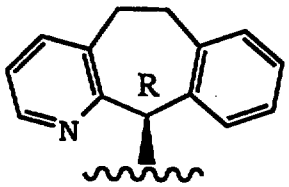
More preferred compounds are Compounds 25.0, 27.0, 51.0 and 53.0.

Those skilled in the art will appreciate that the tricyclic ring system is numbered:



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





Inhibition of farnesyl protein transferase by the tricyclic compounds of this invention has not been reported previously. Thus, this invention provides a method for inhibiting farnesyl protein transferase using tricyclic compounds of this invention which: (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.

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 (cancer) 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 cancers and prostate cancers.

It is believed that this invention also provides a method for inhibiting 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 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 by the tricyclic compounds described herein.

The compounds of this invention inhibit farnesyl protein transferase and the farnesylation of the oncogene protein Ras. This invention further provides a method of inhibiting 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 above.

The tricyclic compounds useful in the methods of this invention inhibit 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.

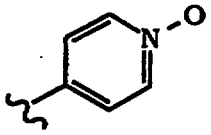
DETAILED DESCRIPTION OF THE INVENTION

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

M^+-represents the molecular ion of the molecule in the mass spectrum;

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

Pyridyl N-oxides are herein represented by the group



The following solvents and reagents are referred to herein by the abbreviations indicated: tetrahydrofuran (THF); ethanol (EtOH); methanol (MeOH); acetic acid (HOAc or AcOH); ethyl acetate (EtOAc); N,N-dimethylformamide (DMF); trifluoroacetic acid (TFA); trifluoroacetic anhydride (TFAA); 1-hydroxy-benzotriazole (HOBT); m-chloroperbenzoic acid (MCPBA); triethylamine (Et_3N); diethyl ether (Et_2O); ethyl chloroformate ($ClCO_2Et$); 1-(3-dimethylaminopropyl)-3-ethyl carbodiimde hydrochloride (DEC); diisobutylaluminum hydride (DIBAL); isopropanol (iPrOH); dimethylsulfoxide (DMSO)

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.

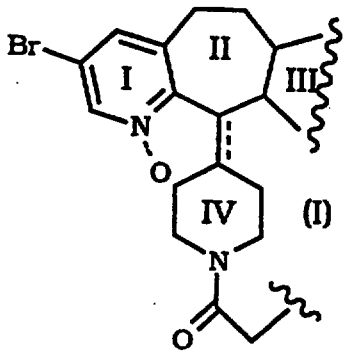
Certain basic tricyclic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, 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 salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

The compounds of the present invention can be prepared by the procedures described below.

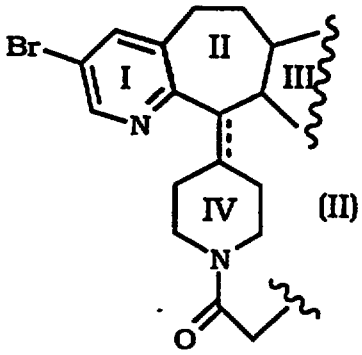
Preparation Of Piperidine Compounds

The compounds of the invention having a piperidine ring (Ring IV):



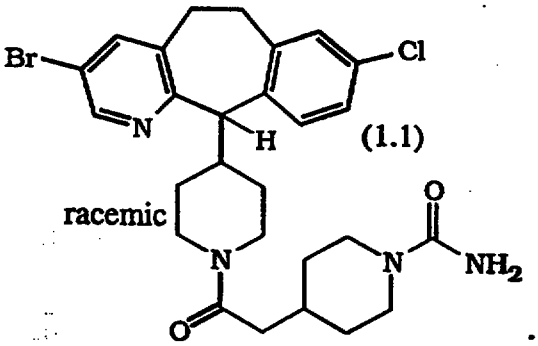
(I)

can be prepared, by techniques well known in the art, from the corresponding unoxidized pyridyl compounds:

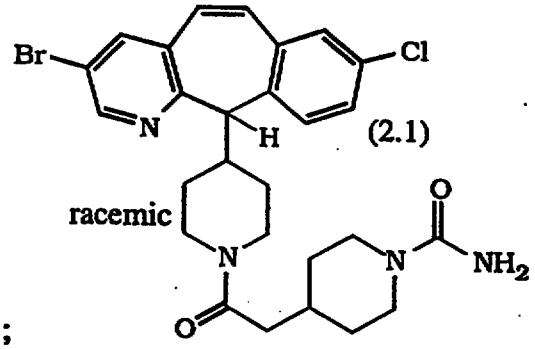


(II)

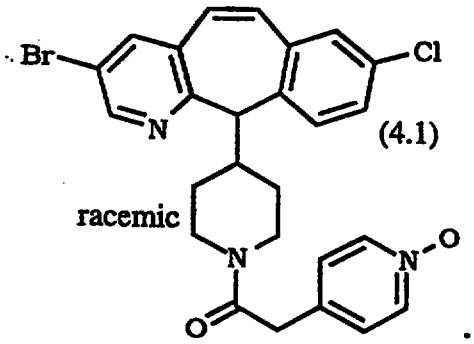
Thus, the compounds of the invention can be prepared from:



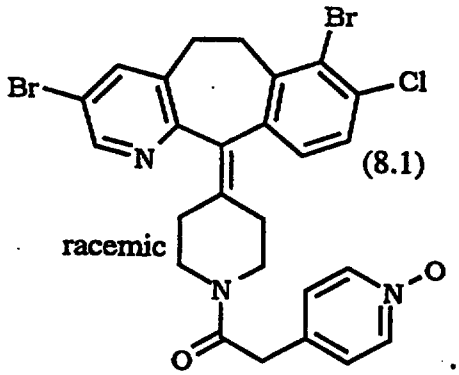
(1.1) ;



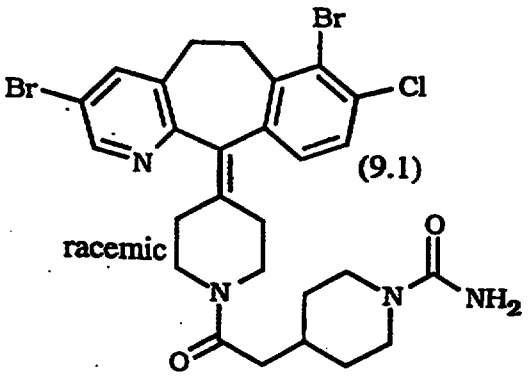
(2.1) ;



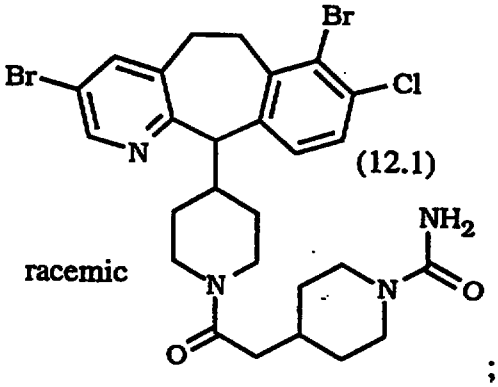
(4.1) ;



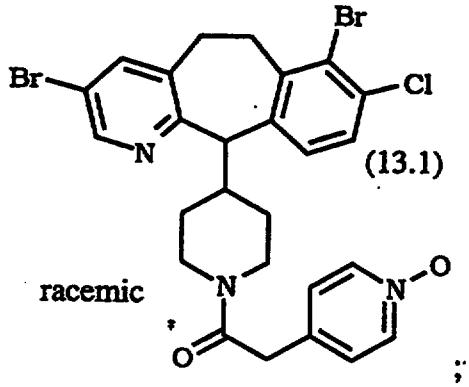
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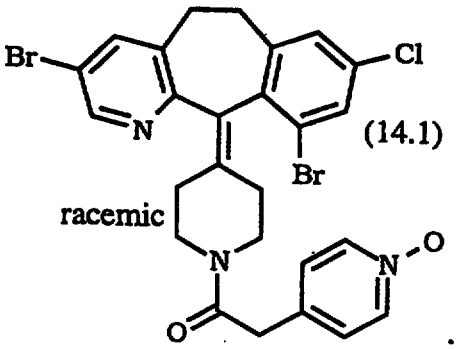
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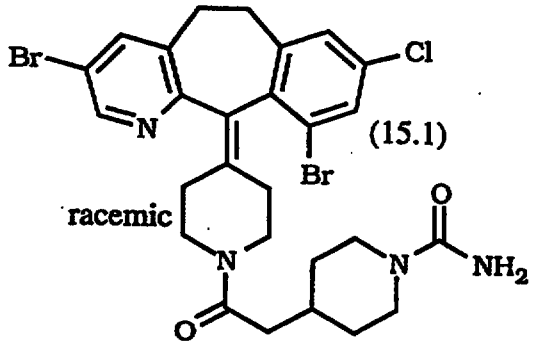
(12.1) ;


Br
Br
Cl
N
(13.1)
racemic
N
O
N
O

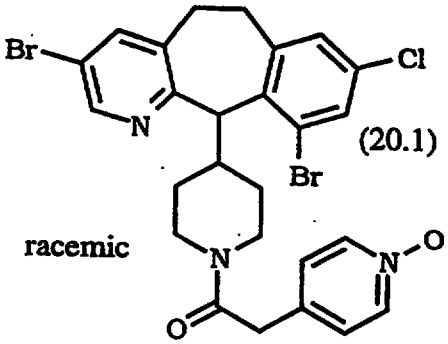
;


Br
Cl
N
(14.1)
Br
racemic
N
N
O
O

;

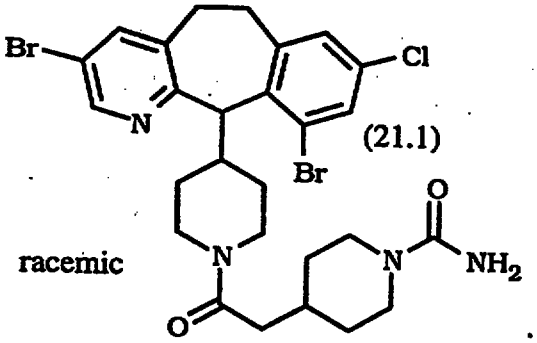

Br
Cl
N
(15.1)
Br
racemic
O
N
NH2
N
O

;

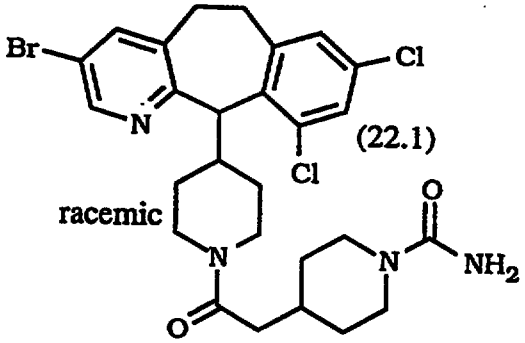

Br
Cl
N
(20.1)
Br
racemic
N
N
O
O

;

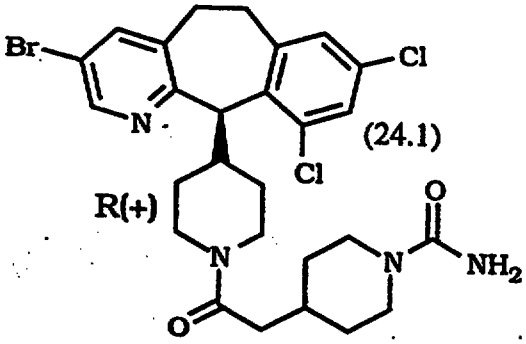
5


Br
Cl
N
(21.1)
Br
racemic
O
N
NH2
N
O

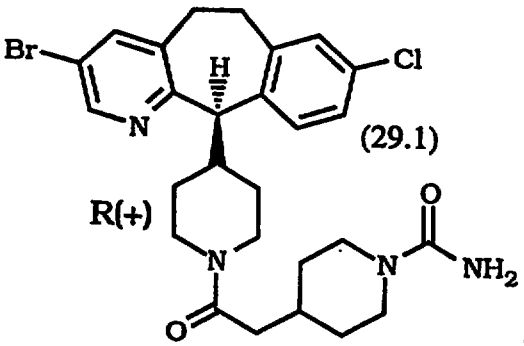
;


Br
Cl
N
(22.1)
Cl
racemic
O
N
NH2
N
O

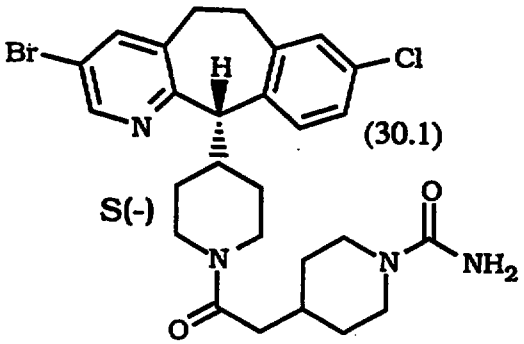
;


Br
Cl
N
(24.1)
Cl
R(+)
O
N
NH2
N
O

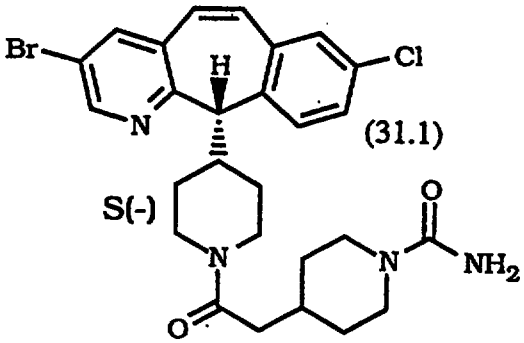
;


Br
H
Cl
N
(29.1)
R(+)
O
N
NH2
N
O

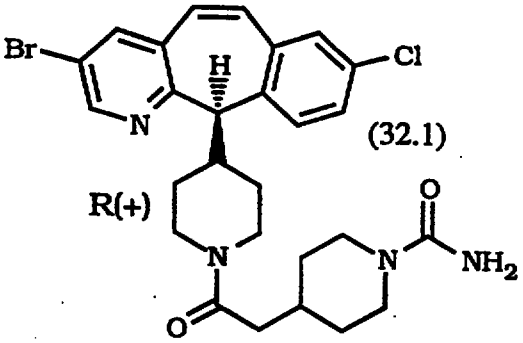
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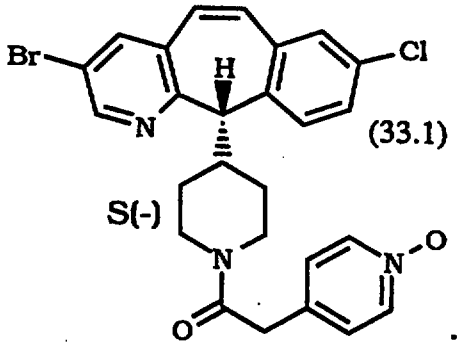
(30.1) ;



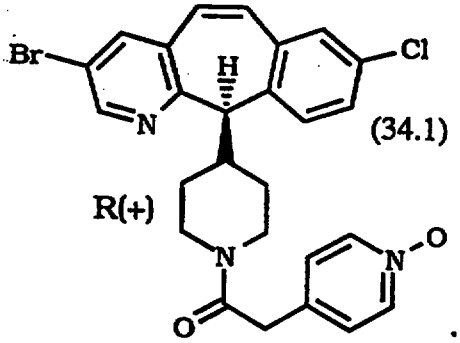
(31.1) ;



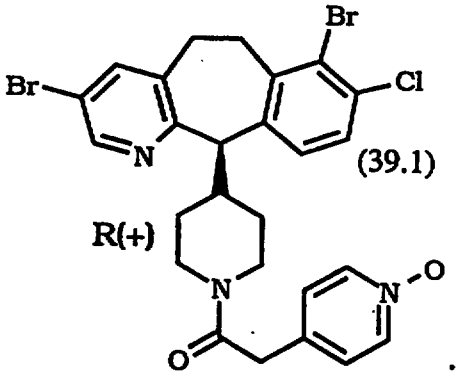
(32.1) ;



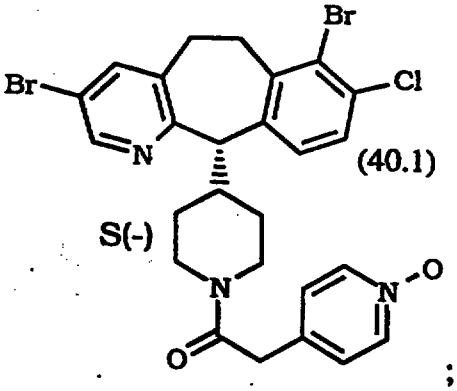
(33.1) ;



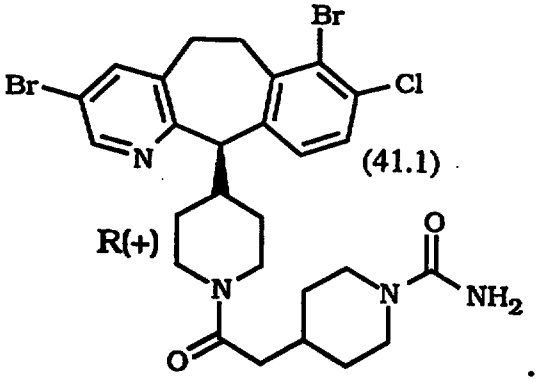
(34.1) ;



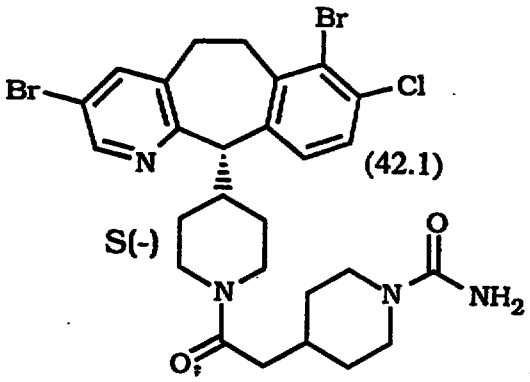
(39.1) ;



(40.1) ;

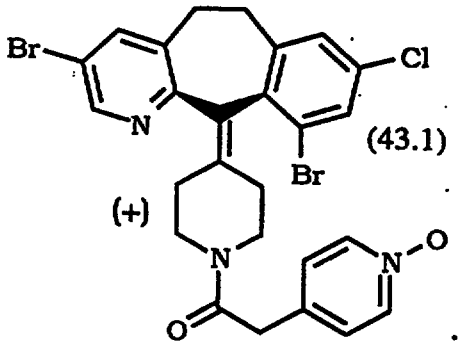


(41.1) ;



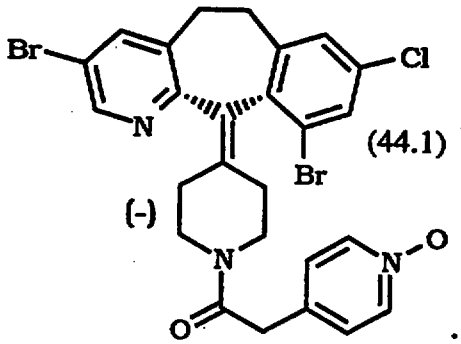
(42.1)

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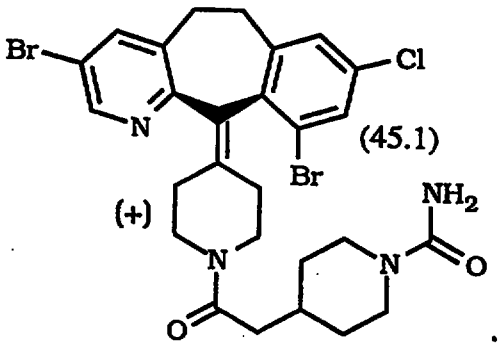
(43.1)

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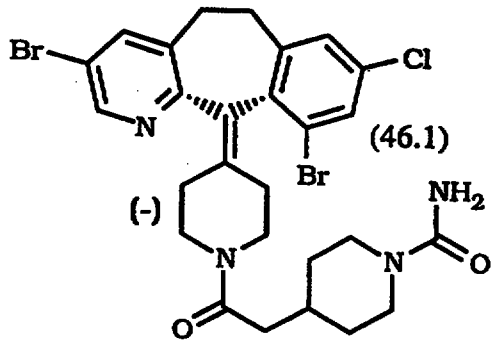
(44.1)

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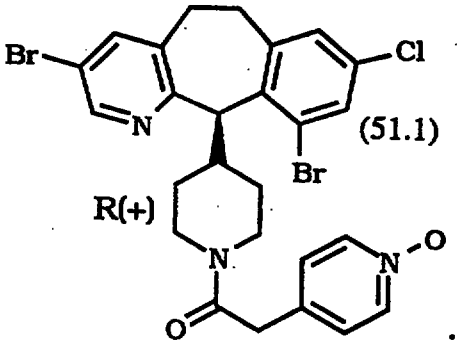
(45.1)

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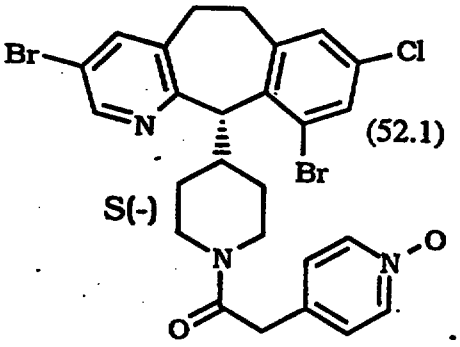
(46.1)

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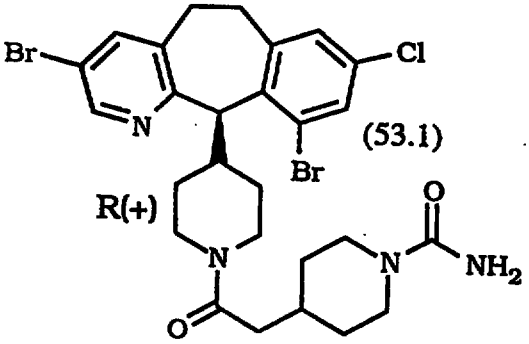
(51.1)

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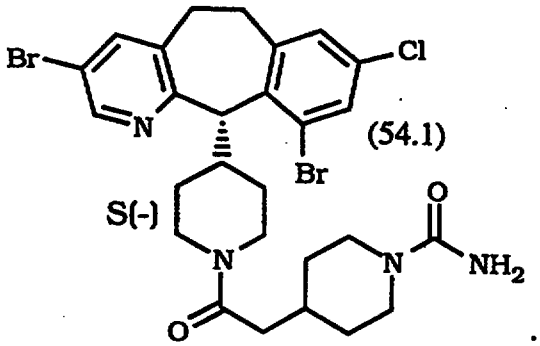


(52.1)

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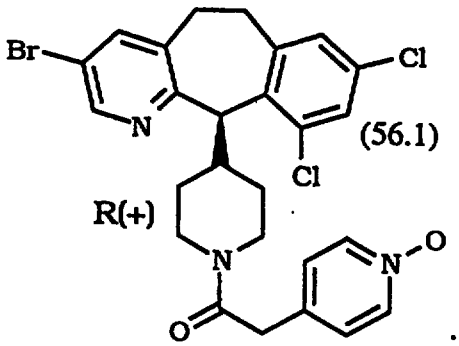


(53.1)



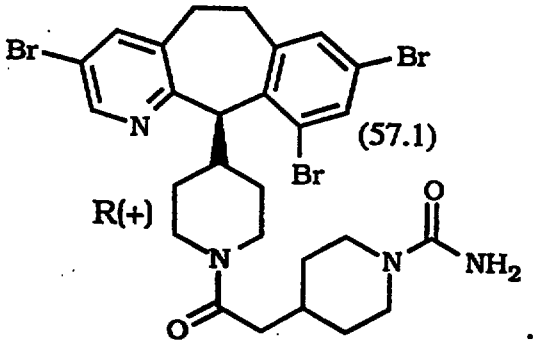
(54.1)

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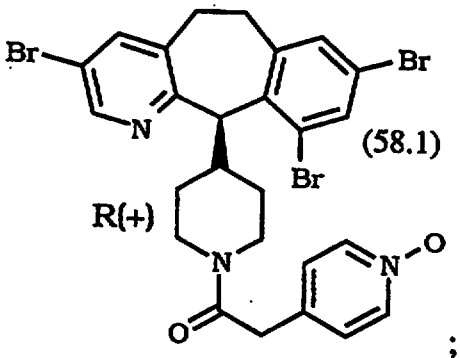
(56.1)

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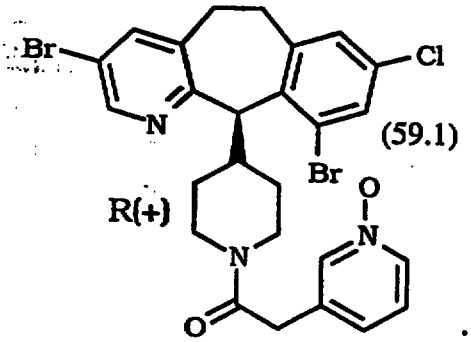
(57.1)

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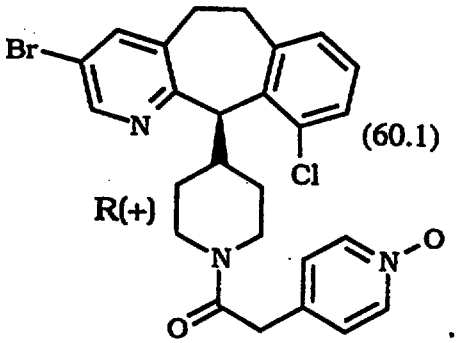
(58.1)

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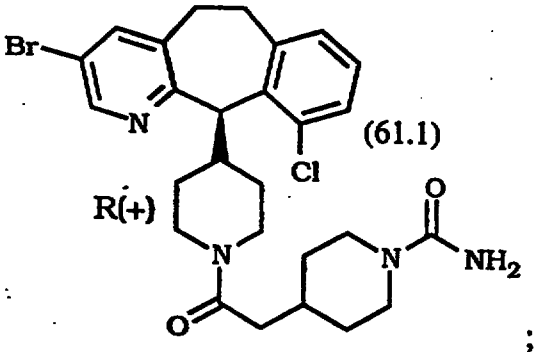
(59.1)

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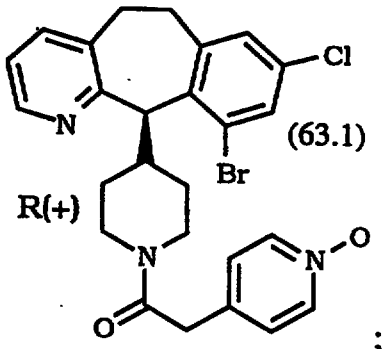
(60.1)

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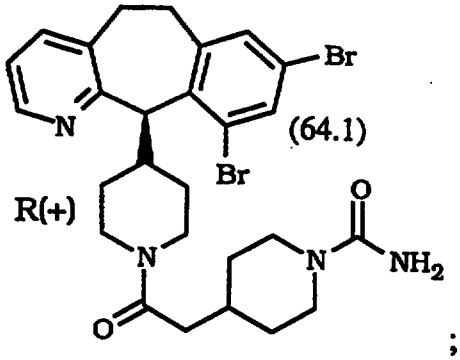
(61.1)

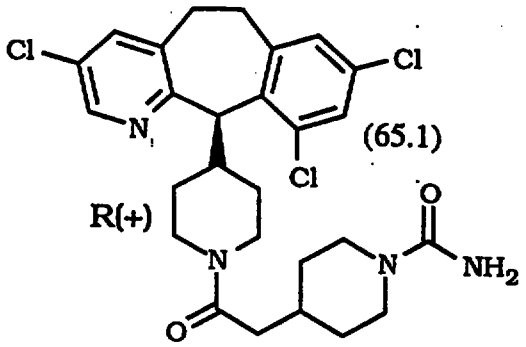
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(63.1)

;



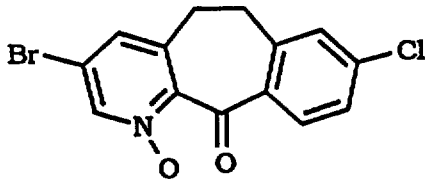


; and

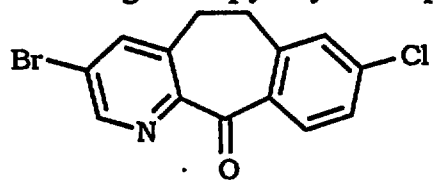
The piperidine compounds (Formula I) of the invention can be prepared from the above pyridyl compounds by oxidation with meta-chloroperoxybenzoic acid. This reaction is conducted in a suitable organic solvent, e.g., dichloromethane (usually anhydrous) or methylene chloride, at a suitable temperature, 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, the piperidine compounds (Formula I) of the invention can be made from intermediate compounds of Formulas 1.1 to 65.1 using the oxidation procedure with m-chloroperoxybenzoic acid. The oxidized intermediate compounds are then reacted to produce the compounds of the invention by methods known in the art. For example, the 3,8-dihalo compounds can be produced from the intermediate:

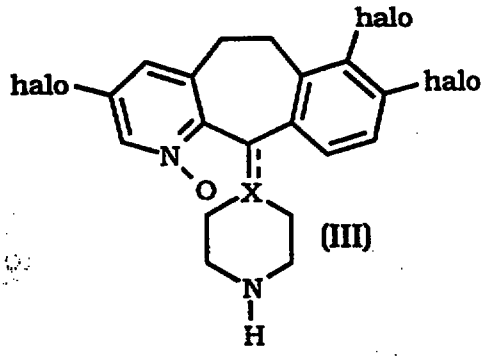


which is made by oxidizing the pyridyl compound

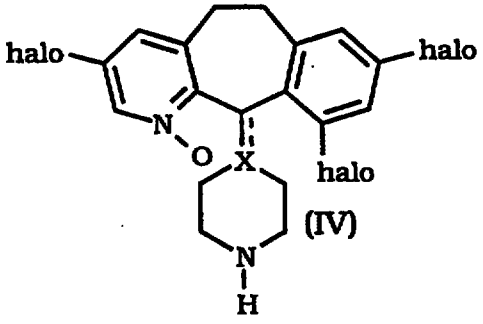


with m-chloroperoxybenzoic acid.

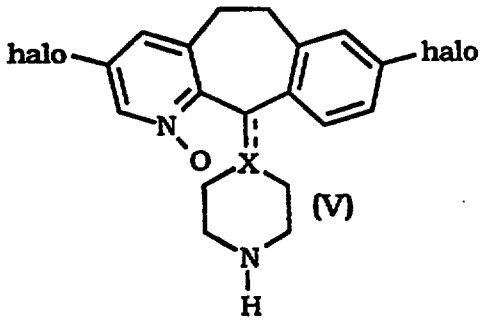
The 3,7,8-trihalo compounds, 3,8,10-trihalo compounds, 3,8-dihalo compounds and the 3,10-dihalo compounds can be produced from the intermediates



(III)

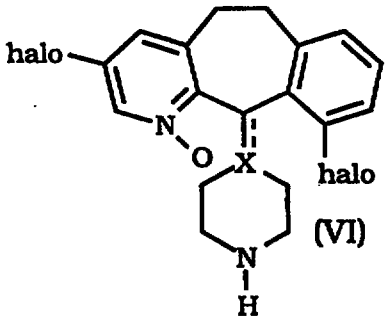


(IV)



(V)

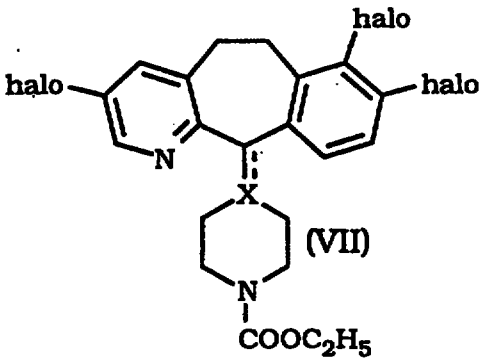
and



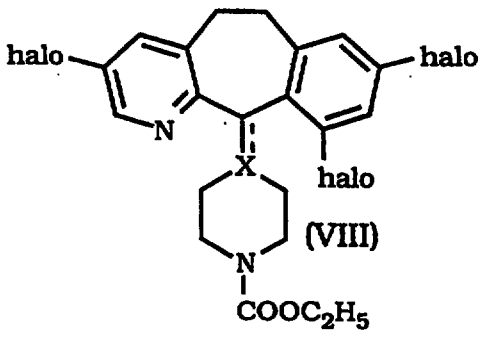
(VI)

respectively.

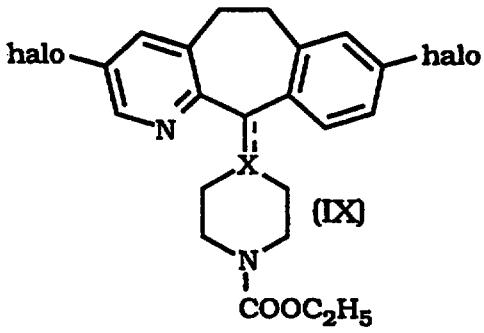
Compounds III to VI can be prepared using the above oxidation procedure with m-chloro-peroxybenzoic acid and the pyridyl compounds



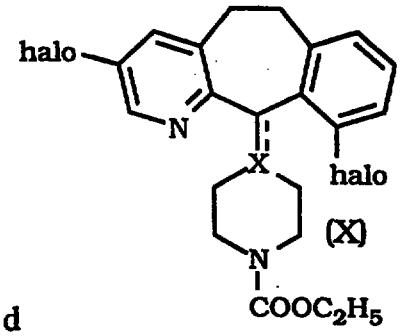
(VII),



(VIII),



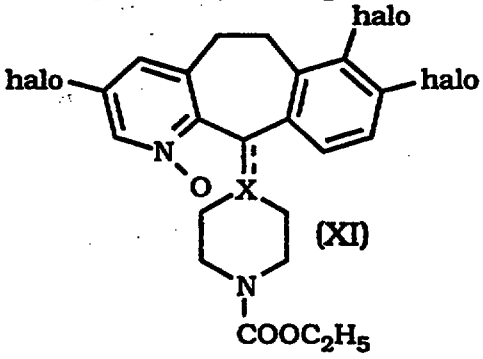
(IX)



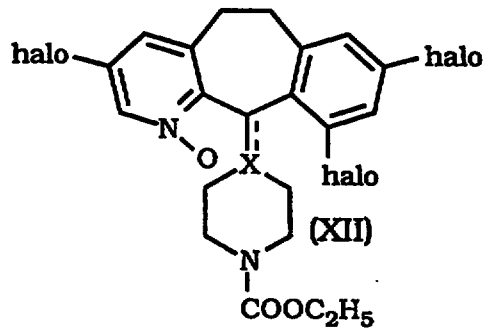
(X),

and

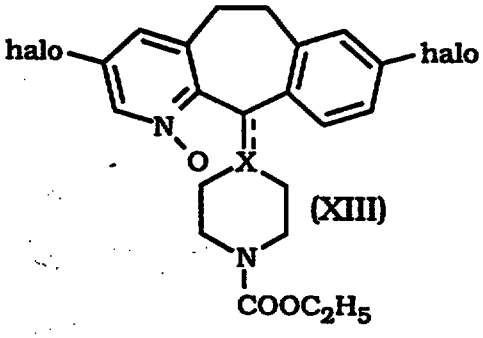
respectively, to produce the compounds



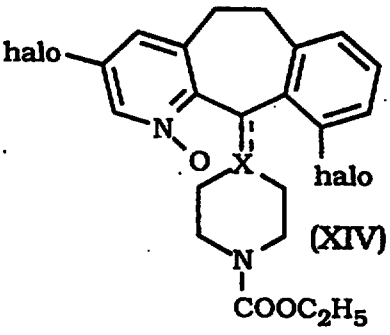
(XI),



(XII),



(XIII)



(XIV),

and

respectively. Compounds XI to XIV can then be converted to Compounds III to VI, respectively, by methods well known in the art.

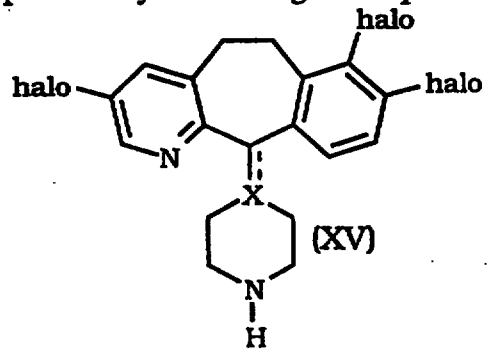
In the above compounds the dotted line (---) represents an optional bond, and X represents CH when the optional bond is

absent, and when the optional bond is present X represents C. The N-O intermediates are then reacted further to produce the compounds of the invention.

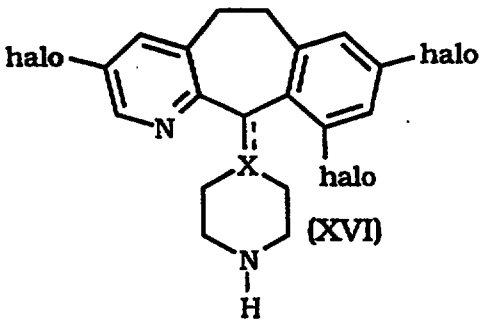
Those skilled in the art will appreciate that the oxidation reaction can be conducted on racemic mixtures and the isomers can then be separated by know techniques, or the isomers can be separated first and then oxidized to the corresponding N-oxide.

Those skilled in the art will appreciate that it is preferable to avoid an excess of m-chloroperoxybenzoic acid when the oxidation reaction is carried out on the compounds having a C-11 double bond to piperidine Ring IV (e.g., compounds 5.1, 6.1, 9.1, and the like). In these reactions an excess of m-chloro-peroxybenzoic acid can cause epoxidation of the C-11 double bond.

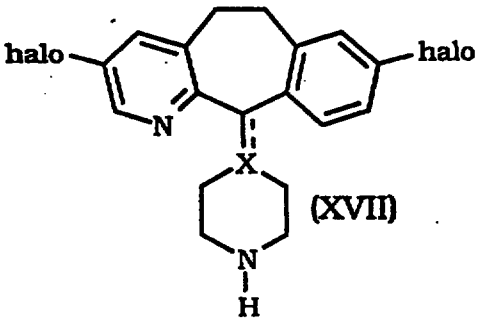
Intermediate compounds VII, VIII, IX and X are prepared by methods known in the art, for example by methods disclosed in WO 95/10516, in U.S. 5,151,423 and those described below. For example, Compounds VII to X can be prepared by reacting compounds



(XV),

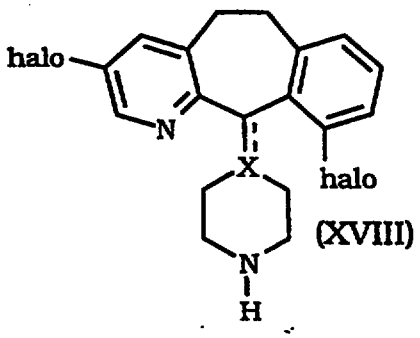


(XVI),



(XVII)

and

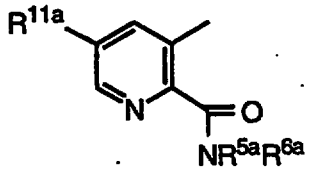


(XVIII),

respectively, with C_2H_5OCOCl and Et_3N in an inert solvent (e.g., CH_2Cl_2).

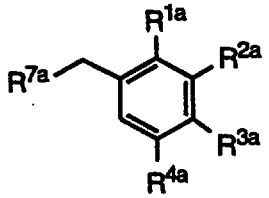
Intermediate Compounds XV, XVI, XVII and XVIII wherein the C-3 postion of the pyridine ring in the tricyclic structure is substituted by bromo can also be prepared by a procedure comprising the following steps:

(a) reacting an amide of the formula

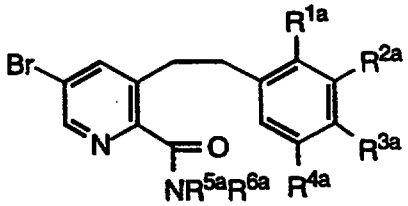


wherein R^{11a} is Br, R^{5a} is hydrogen and R^{6a} is C_1-C_6 alkyl, aryl or heteroaryl; R^{5a} is C_1-C_6 alkyl, aryl or heteroaryl and R^{6a} is hydrogen; R^{5a} and R^{6a} are independently selected from the group consisting of C_1-C_6 alkyl and aryl; or R^{5a} and R^{6a}, together with the nitrogen 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

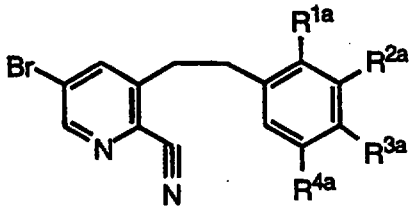


wherein R^{1a}, R^{2a}, R^{3a} and R^{4a} are are independently selected from the group consisting of hydrogen and halo and R^{7a} is Cl or Br, in the presence of a strong base to obtain a compound of the formula



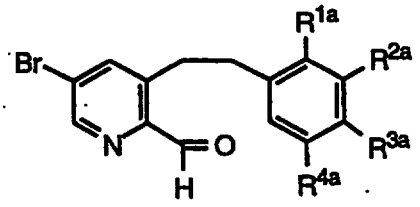
(b) reacting a compound of step (a) with

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



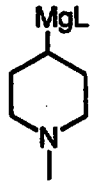
; or

(ii) DIBALH to obtain an aldehyde of the formula

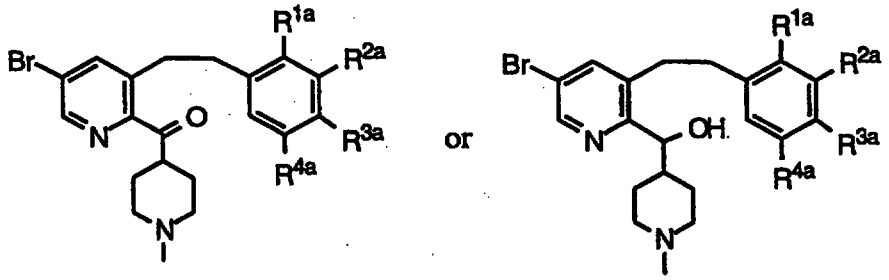


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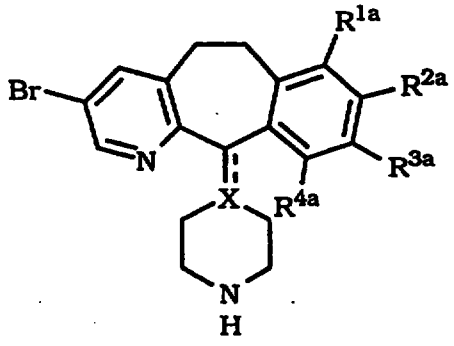
(c) reacting the cyano compound or the aldehyde with a piperidine derivative of the formula



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:



(d)(i) cyclizing the ketone with CF_3SO_3H to obtain a compound of the formula

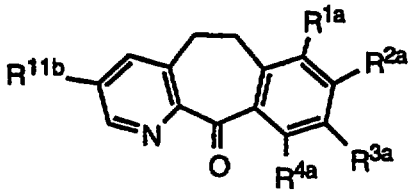


wherein the dotted line represents a double bond; or

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

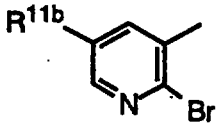
Methods for preparing the Intermediate compounds disclosed in WO 95/10516, U.S. 5,151,423 and described below

employ a tricyclic ketone intermediate. Such intermediates of the formula

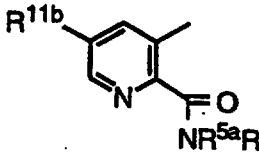


wherein R^{11b}, R^{1a}, R^{2a}, R^{3a} and R^{4a} are independently selected from the group consisting of hydrogen and halo, can be prepared by the following process comprising :

(a) reacting a compound of the formula

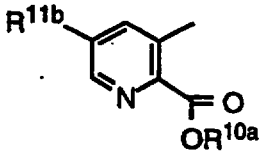


(i) with an amine of the formula $NHR^{5a}R^{6a}$, wherein R^{5a} and R^{6a} are as defined in the process above; in the presence of a palladium catalyst and carbon monoxide to obtain an amide of the formula:



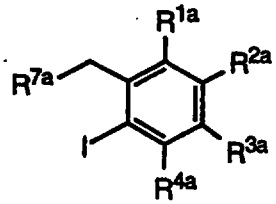
; or

(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

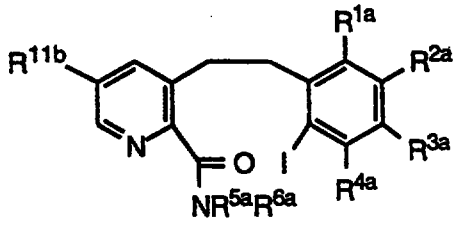


followed by reacting the ester with an amine of formula $NHR^{5a}R^{6a}$ to obtain the amide;

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



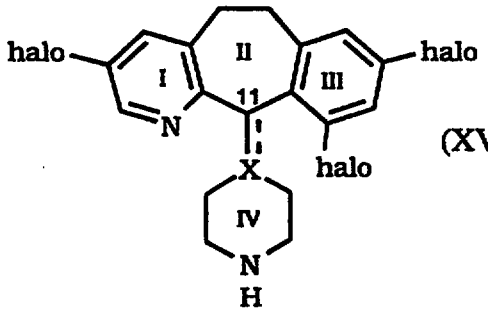
wherein R^{1a}, R^{2a}, R^{3a}, R^{4a} and R^{7a} are as defined above, in the presence of a strong base to obtain a compound of the formula



; 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 XVI



(XVI)

wherein X is CH can be prepared with high enantioselectivity by using a process comprising enzyme catalyzed transesterification. Preferably, a racemic compound of Formula XVI, wherein X is C and the double bond is present, is reacted with an enzyme such as Toyobo LIP-300 and an acylating agent such as trifluoroethly isobutyrate; the resultant (+)-amide is then hydrolyzed, for example by refluxing with an acid such as H_2SO_4, to obtain the corresponding optically enriched (+)-isomer wherein X is CH. Alternatively, a racemic compound of Formula XVI, wherein X is C and the double bond is present, is first reduced to the corresponding racemic compound of Formula XVI wherein X is CH. 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.

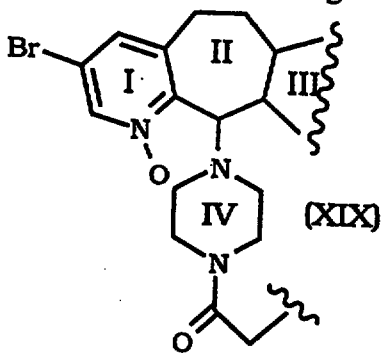
The compound of Preparative Example 21 is obtained in the crystalline state. Those skilled in the art will appreciate that compounds obtained in the amorphous state can be obtained in the crystalline state by crystallizing the amorphous materials

from solvents or solvent mixtures such as acetone, diethyl ether, ethyl acetate, ethanol, 2-propanol, tert-butyl ether, water and the like according to procedures well known in the art.

Those skilled in the art will also appreciate that the racemic mixture of Compound 11.0 can be made according to the procedures described below. For Example, the intermediate of Preparative Example 6 can be used to prepare Compound 11.0.

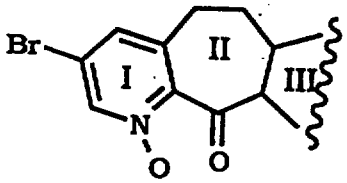
Preparation Of Piperazine Compounds

Compounds of the invention having a piperazine ring



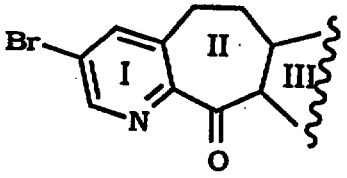
(XIX)

can be prepared from the tricyclic ketone:



(XX)

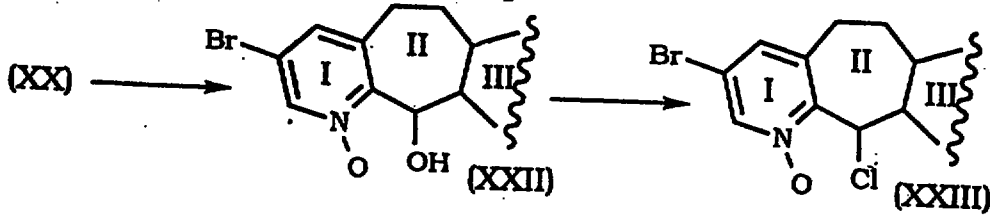
Ketone XX can be prepared by oxidation of the corresponding pyridyl compound:



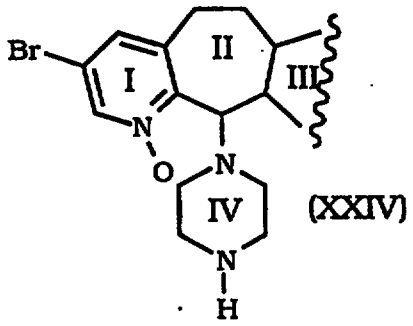
(XXI)

with m-chloroperoxybenzoic acid.

Ketone XX can be converted to the corresponding C-11 hydroxy compound which in turn can be converted to the corresponding C-11 chloro compound



Compound XXIII can then be reacted with piperazine to produce the intermediate:



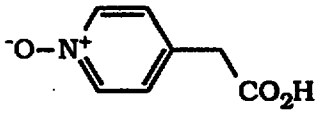
(XXIV)

Intermediate XXIV can then be reacted with the reagents which will provide the desired final product.

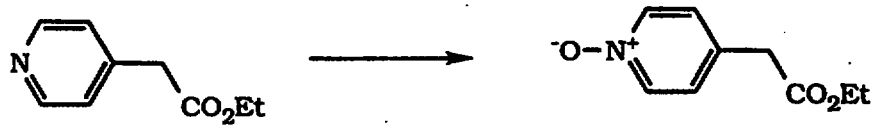
The above reactions are well known in the art and are illustrated in the examples below.

The examples that follow are intended to exemplify the claimed invention, and such examples should not be construed as limiting the disclosure or the claimed invention.

PREPARATIVE EXAMPLE 1

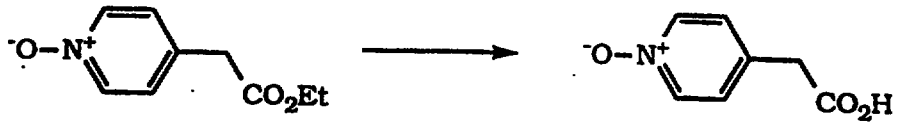


Step A:



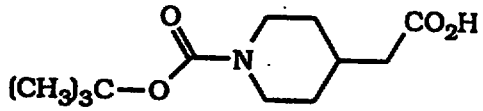
Combine 10 g (60.5 mmol) of ethyl 4-pyridylacetate and 120 mL of dry CH_2Cl_2 at -20°C, add 10.45 g (60.5 mmol) of MCPBA and stir at -20°C for 1 hour and then at 25°C for 67 hours. Add an additional 3.48 g (20.2 mmoles) of MCPBA and stir at 25°C for 24 hours. Dilute with CH_2Cl_2 and wash with saturated $NaHCO_3$ (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:



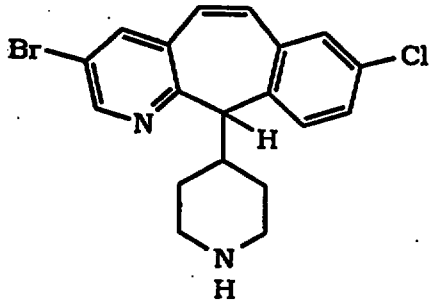
Combine 3.5 g (19.3 mmol) of the product of Step A, 17.5 mL of EtOH and 96.6 mL of 10% NaOH (aqueous) and heat the mixture at 67°C for 2 hours. Add 2 N HCl (aqueous) to adjust to pH = 2.37 and concentrate *in vacuo* to a residue. Add 200 mL of dry EtOH, filter through celite® and wash the filter cake with dry EtOH (2X50 ml). Concentrate the combined filtrates *in vacuo* to give 2.43 g of the title compound.

PREPARATIVE EXAMPLE 2

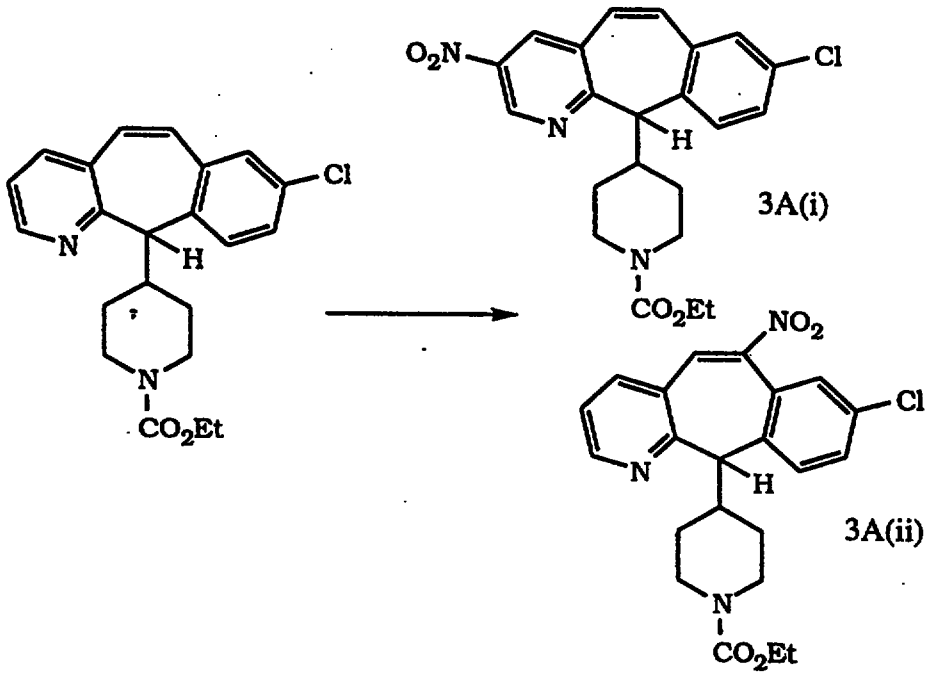


The title compound is prepared via the process disclosed in PCT International Publication No. WO95/10516.

PREPARATIVE EXAMPLE 3



Step A:

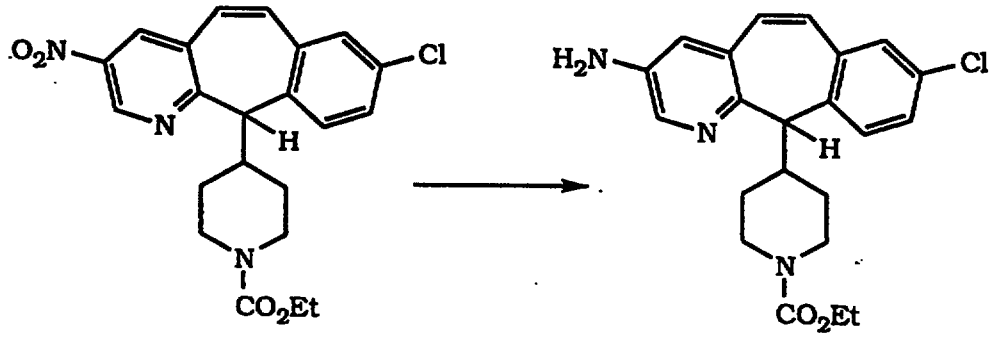


Combine 14.95 g (39 mmol) of 8-chloro-11-(1-ethoxy-carbonyl-4-piperidinyl)-11H-benzo[5,6]cyclohepta[1,2-b]-pyridine and 150 mL of CH_2Cl_2, then add 13.07 g (42.9 mmol) of $(nBu)_4NNO_3$ and cool the mixture to 0°C. Slowly add (dropwise) a solution of 6.09 mL (42.9 mmol) of TFAA in 20 mL of CH_2Cl_2 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): $MH^+ = 428.2$.

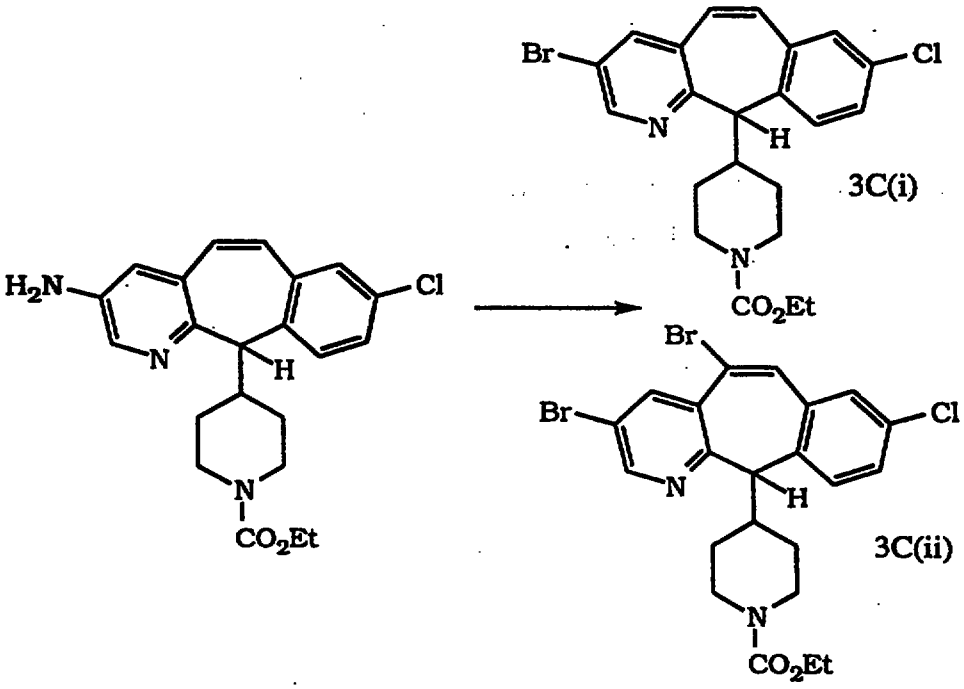
Mass Spec. for compound 3A(ii): $MH^+ = 428.3$.

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. $MH^+ = 398$.

Step C:



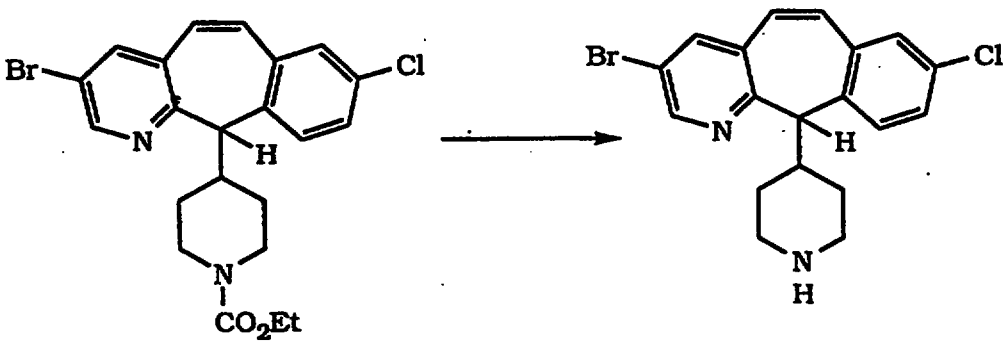
Combine 16.47 g (41.4 mmol) of the product from Step B, and 150 mL of 48% HBr (aqueous) and cool to -3°C. Slowly add (dropwise) 18 mL of bromine, then slowly add (dropwise) a solution of 8.55 g (0.124 mole) of $NaNO_2$ in 85 mL of water. Stir for 45 minutes at -3° to 0°C, then adjust to pH = 10 by adding 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): $MH^+ = 539$.

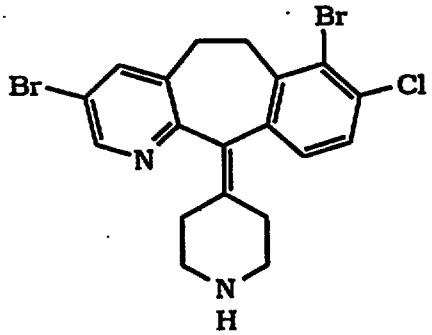
Step D:



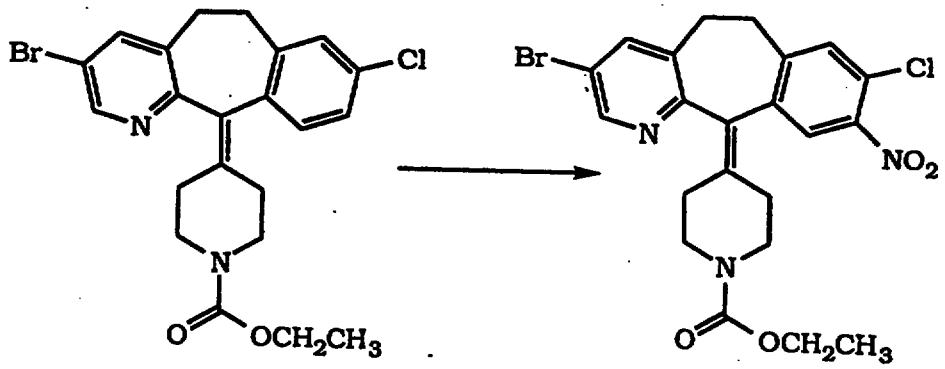
Hydrolyze the product 3C(i) of Step C by dissolving in concentrated HCl and heating to about 100°C for 16 hours. Cool the mixture, then neutralize with 1 M NaOH (aqueous). Extract with CH_2Cl_2, dry the extracts over $MgSO_4$, filter and concentrate *in vacuo* to the title compound.

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

PREPARATIVE EXAMPLE 4

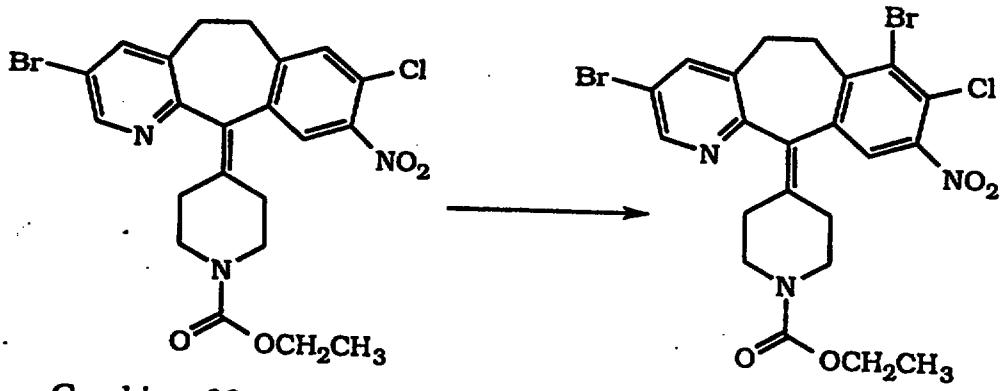


Step A:



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:

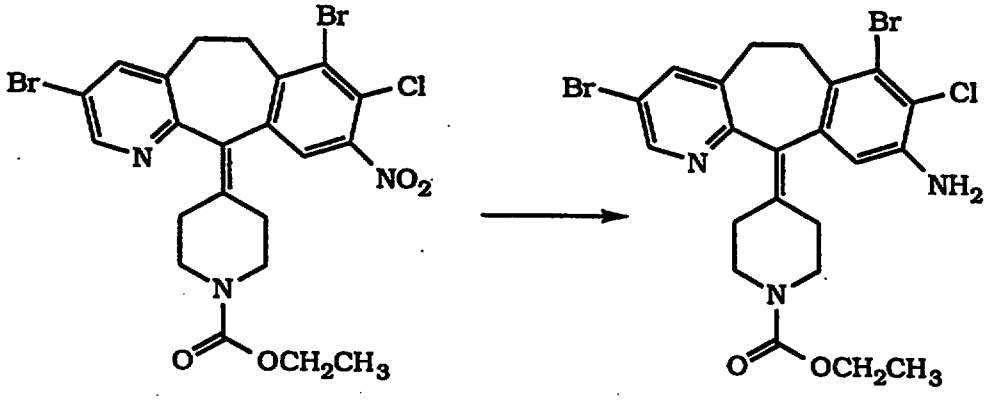


Combine 20 g (40.5 mmol) of the product of Step A and 200 mL of concentrated H_2SO_4 at 20°C, then cool the mixture to 0°C. Add 7.12 g (24.89 mmol) of 1,3-dibromo-5,5-dimethyl-hydantoin to the mixture and stir for 3 hours at 20°C. Cool to 0°C, add an additional 1.0 g (3.5 mmol) of the dibromohydantoin 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.

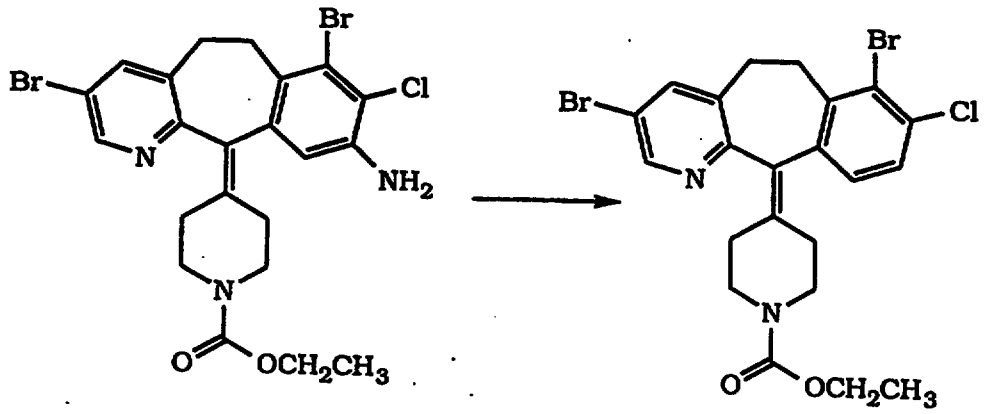
Step C:



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.

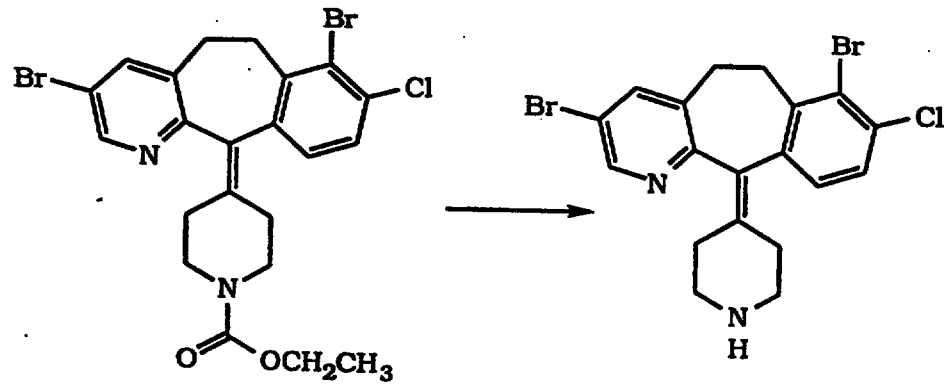
Step D:



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.

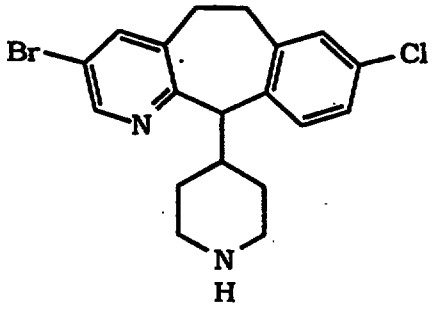
Step E:



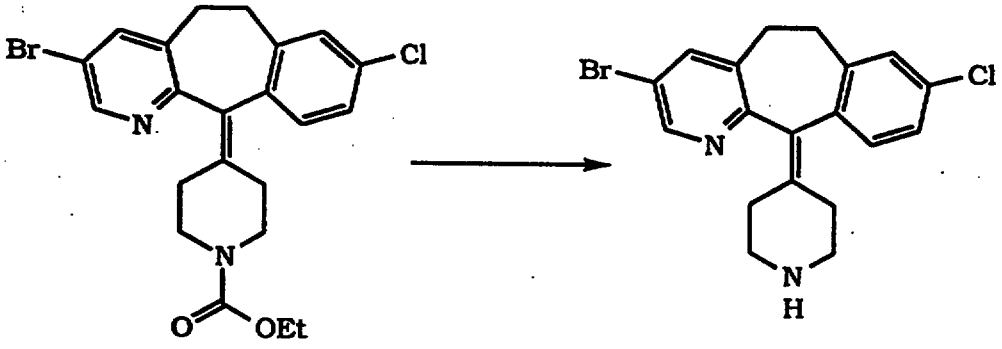
Combine 6.8 g (12.59 mmol) of the product of Step D and 100 mL of concentrated HCl (aqueous) and stir at 85°C overnight. Cool the mixture, pour it into 300 g of ice and basify with concentrated NH_4OH (aqueous). Extract with 2 x 300 mL of CH_2Cl_2, then dry the extracts over $MgSO_4$. Filter, concentrate *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. Elemental analysis: calculated - C, 48.69; H, 3.65; N, 5.97 found - C, 48.83; H, 3.80; N, 5.97.

PREPARATIVE EXAMPLE 5

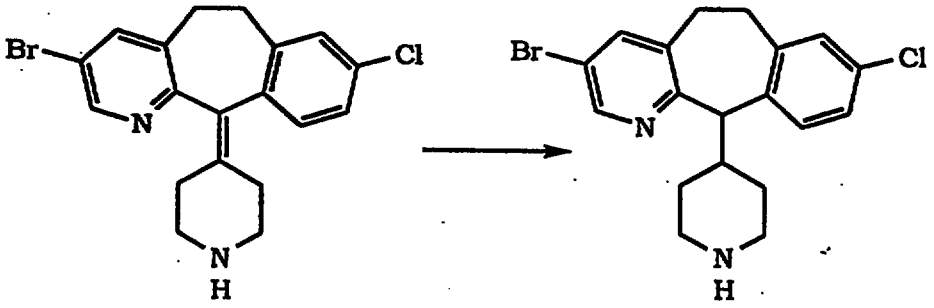


Step A:



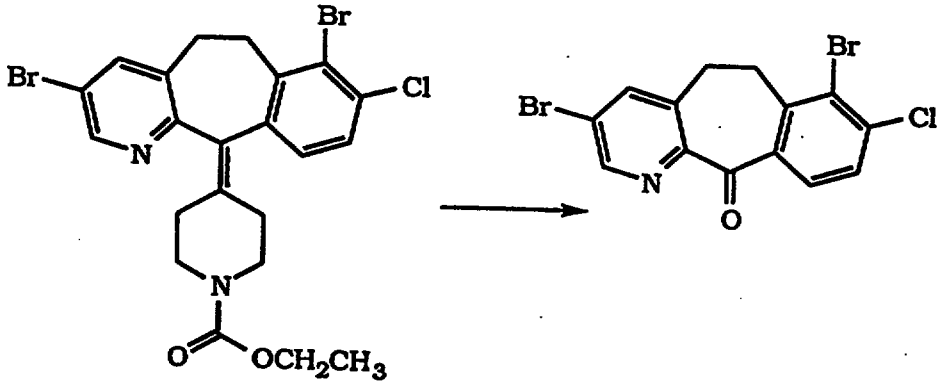
Hydrolyze 2.42 g of 4-(8-chloro-3-bromo-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester via substantially the same procedure as described in Preparative Example 3, Step D, to give 1.39 g (69% yield) of the product. MH^+ = 389.

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. MH^+ = 391.

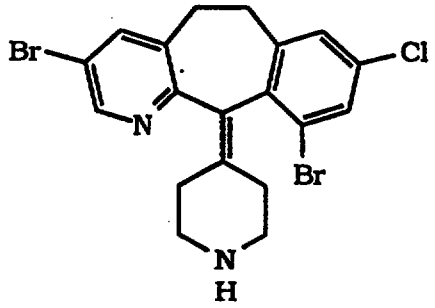
PREPARATIVE EXAMPLE 6



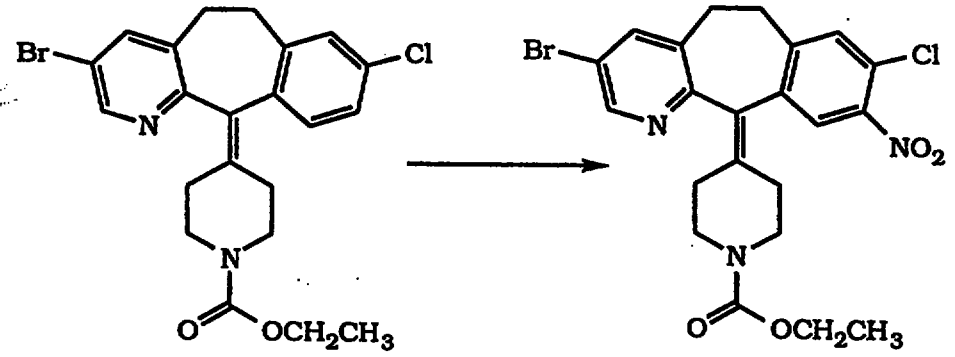
Combine 16.6 g (0.03 mole) of the product of Preparative Example 4, Step D, with a 3:1 solution of CH_3CN and water (212.65 mL CH_3CN and 70.8 mL of water) and stir the resulting slurry overnight at room temperature. Add 32.833 g (0.153 mole) of $NaIO_4$ and then 0.31 g (2.30 mmol) of RuO_2 and stir at room temperature (the addition of RuO_2 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. ^{1}H 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).

PREPARATIVE EXAMPLE 7

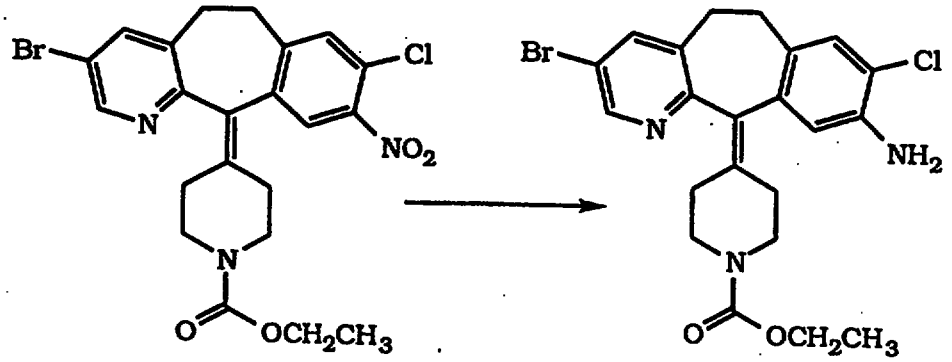


Step A:



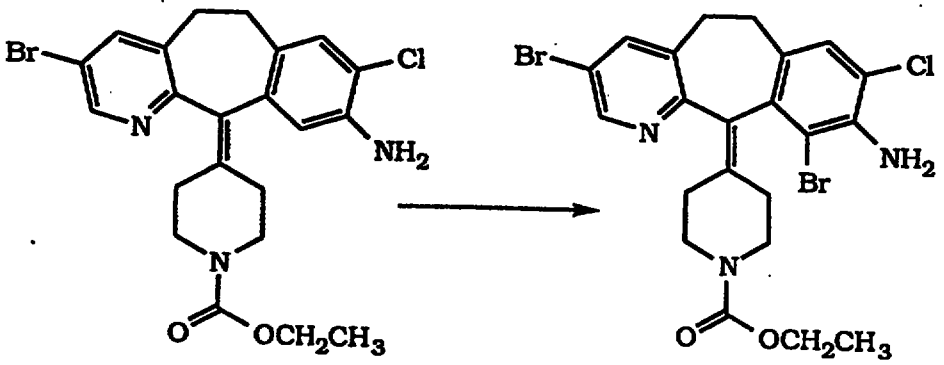
Combine 15 g (38.5 mmol) of 4-(8-chloro-3-bromo-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester and 150 mL of concentrated H_2SO_4 at -5°C, then add 3.89 g (38.5 mmol) of KNO_3 and stir for 4 hours. Pour the mixture into 3 L of ice and basify 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). MH^+ = 506.

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^+ = 476.0.

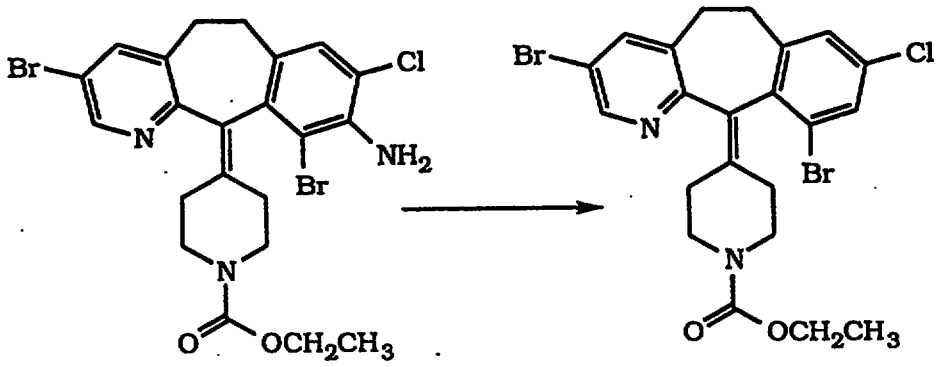
Step C:



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^+ = 554.

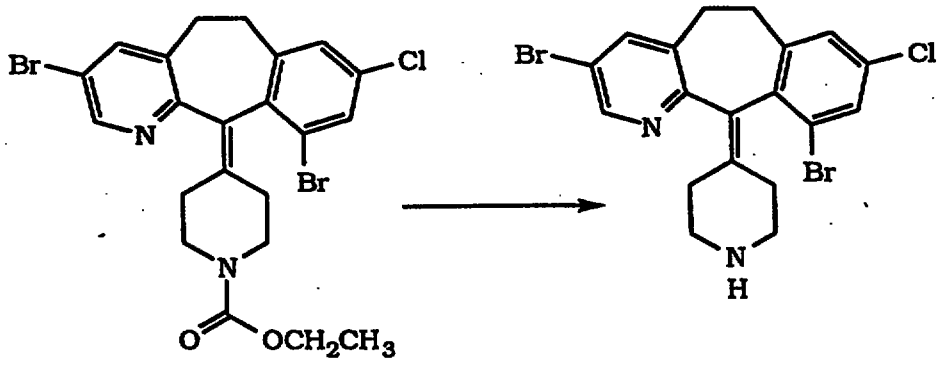
^1H NMR ($CDCl_3$, 300 MHz): 8.5 (s, 1H); 7.5 (s, 1H); 7.15 (s, 1H); 4.5 (s, 2H); 4.15 (m, 3H); 3.8 (br s, 2H); 3.4-3.1 (m, 4H); 9-2.75 (m, 1H); 2.7-2.5 (m, 2H); 2.4-2.2 (m, 2H); 1.25 (m, 3H).

Step D:



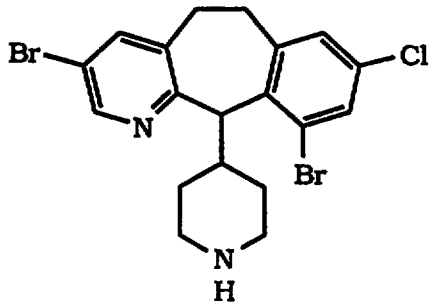
Combine 0.557 g (5.4 mmol) of t-butylnitrite and 3 mL of DMF, and heat the mixture at 60°-70°C. Slowly add (dropwise) a mixture of 2.00 g (3.6 mmol) of the product of Step C and 4 mL of DMF, then cool the mixture to room temperature. Add another 0.64 mL of t-butylnitrite at 40°C and reheat the mixture 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^+ = 539.0. ^1H NMR (CDCl3, 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:



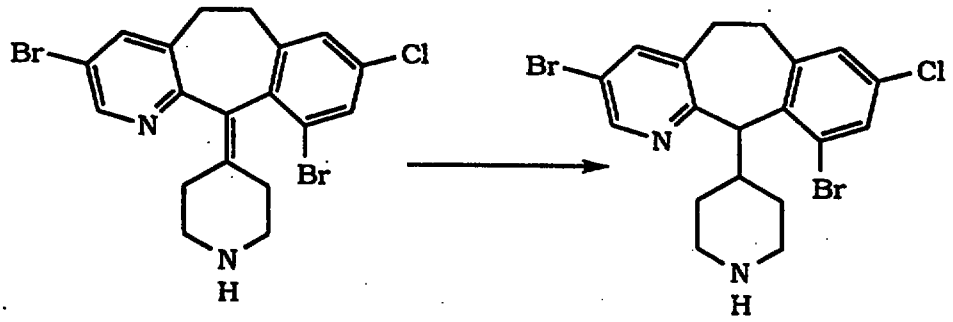
Combine 0.70 g (1.4 mmol) of the product of Step D and 8 mL of concentrated HCl (aqueous) and heat the mixture at reflux overnight. Add 30 mL of 1 N NaOH (aqueous), then 5 mL of 50% NaOH (aqueous) and extract with CH_2Cl_2. Dry the extract over $MgSO_4$ and concentrate *in vacuo* to give 0.59 g of the title compound. Mass Spec.: MH^+ = 467. m.p. = 123.9°-124.2°C.

PREPARATIVE EXAMPLE 8



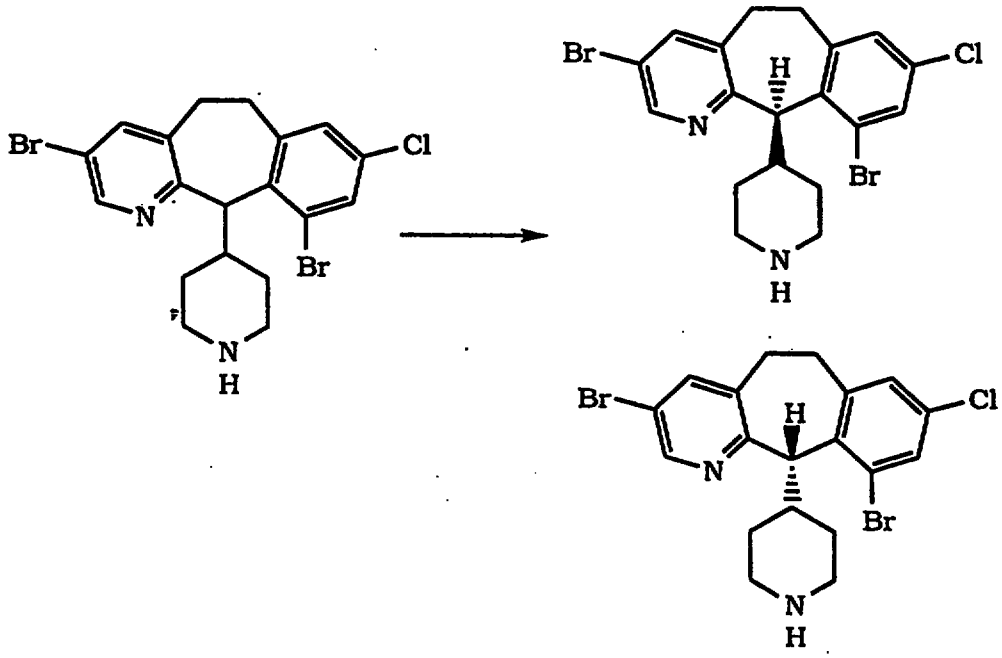
[racemic as well as (+)- and (-)-enantiomers]

Step A:



Prepare a solution of 8.1 g of the title compound from Preparative Example 7 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. MH^+ = 469.

Step B - Separation of Enantiomers:

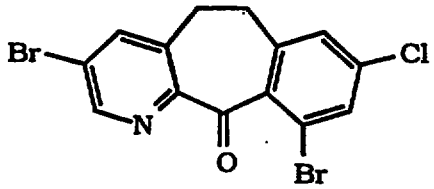


The racemic title compound of Step A is separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, using 20% iPrOH/hexane + 0.2% diethylamine), to give the (+)-enantiomer and the (-)-enantiomer of the title compound.

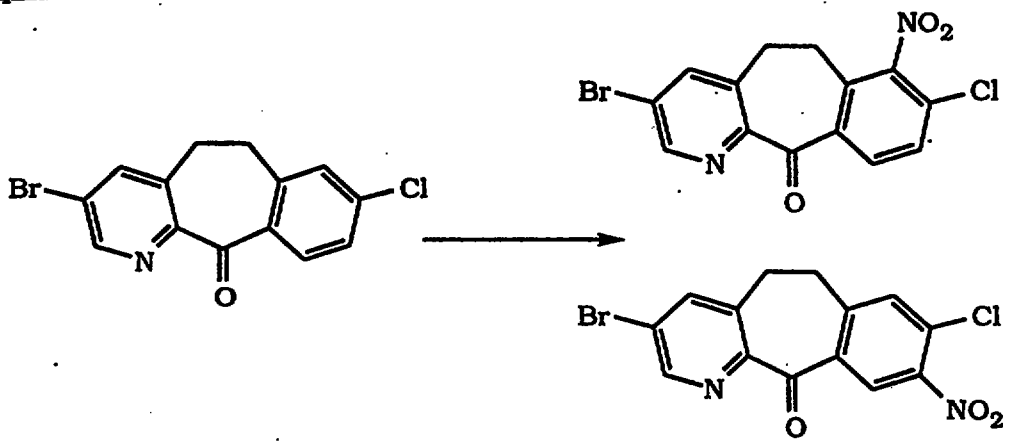
Physical chemical data for (+)-enantiomer: m.p. = 148.8°C; Mass Spec. $MH^+ = 469$; $[\alpha]_D^{25}$ = +65.6° (12.93mg/2mL MeOH).

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

PREPARATIVE EXAMPLE 9

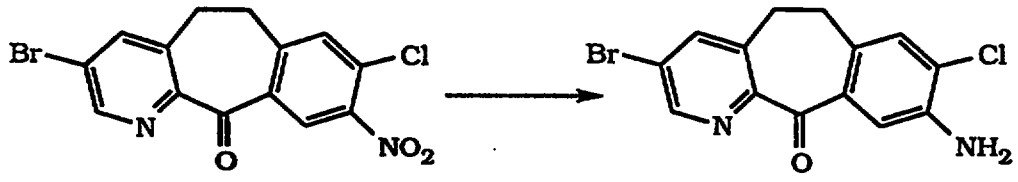


Step A:



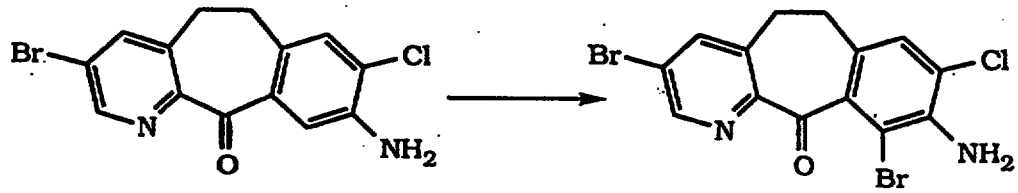
Combine 40.0 g (0.124 mole) of the starting ketone and 200 mL of H_2SO_4 and cool to 0°C. Slowly add 13.78 g (0.136 mole) of KNO_3 over a period of 1.5 hrs., then warm to room temperature and stir overnight. Work up the reaction using substantially the same procedure as described for Preparative Example 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. MH^+ (9-nitro) = 367.

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. MH^+ = 337.

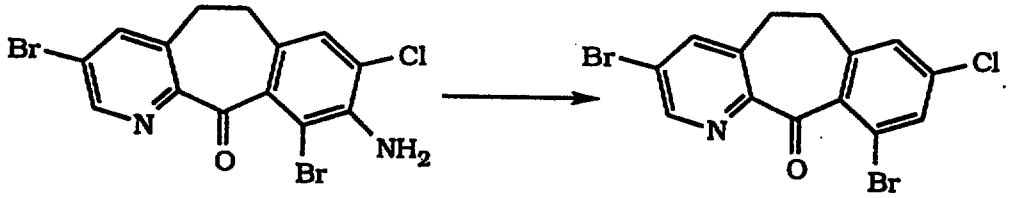
Step C:



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.

^1H NMR (200 MHZ, $CDCl_3$): 8.73 (d, 1H); 7.74 (d, 1H); 7.14 (s, 1H); 4.63 (s, 2H); 3.23-3.15 (m, 2H); and 3.07-2.98 (m, 2H).

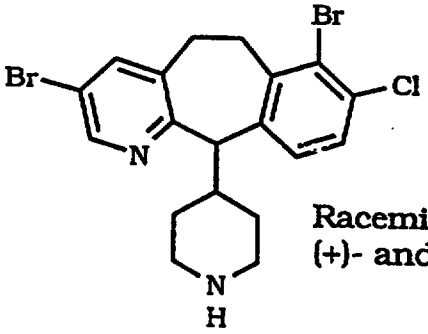
Step D:



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. MH^+ = 399.9.

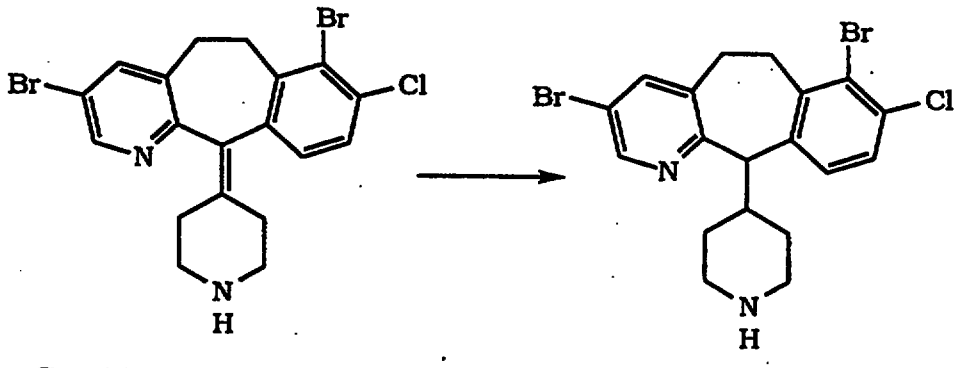
^1H NMR (200 MHZ, $CDCl_3$): 8.75 (d, 1H); 7.77 (d, 1H); 7.56 (d, 1H); 7.21 (d, 1H); and 3.3-3.0 (m, 4H).

PREPARATIVE EXAMPLE 10



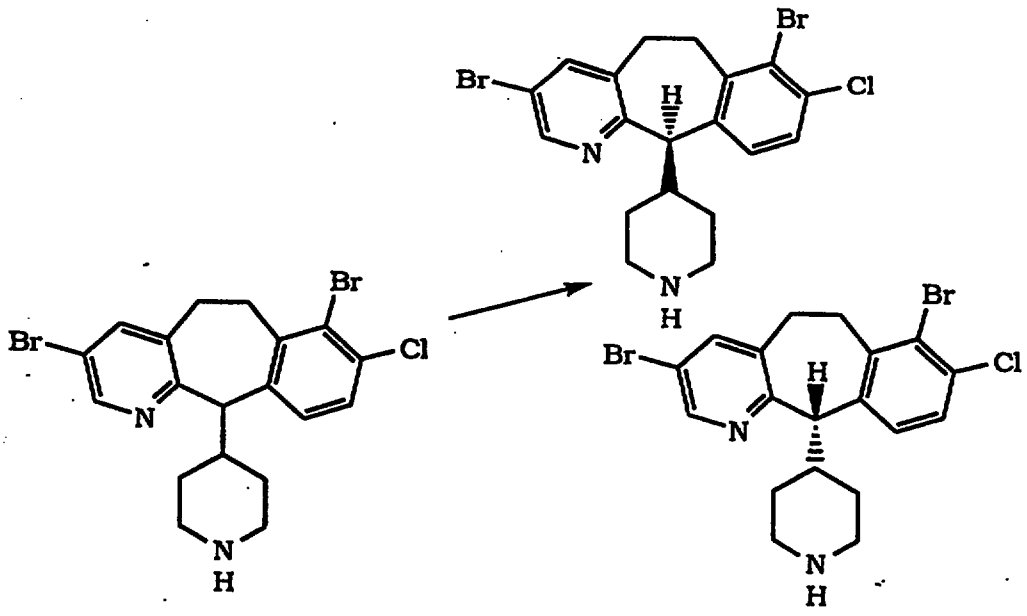
Racemic as well as (+)- and (-)- enantiomer

Step A:



Combine 13 g (33.3 mmol) of the title compound from Preparative Example 4, Step D, 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:

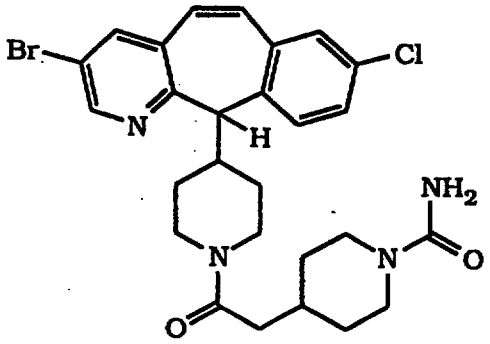


The racemic title compound of Step A is separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, using 5% iPrOH/hexane + 0.2% diethylamine), to give the (+)-enantiomer and the (-)-enantiomer of the title compound.

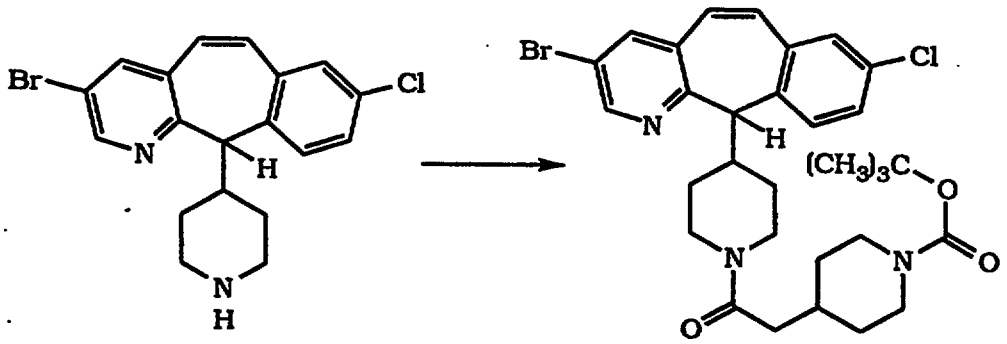
Physical chemical data for (+)-enantiomer: Mass Spec. $MH^+ = 469$ (FABS); $[\alpha]_D^{25} = +43.5°$ (c=0.402, EtOH); partial ^1H NMR ($CDCl_3$, 400 MHz): 8.38 (s, 1H); 7.57 (s, 1H); 7.27 (d, 1H); 7.05 (d, 1H); 3.95 (d, 1H).

Physical chemical data for (-)-enantiomer: 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).

PREPARATIVE EXAMPLE 11



Step A:

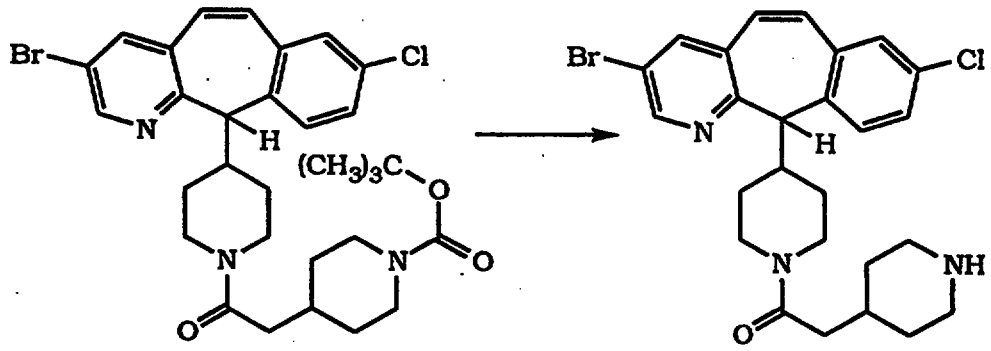


Dissolve 1.160 g (2.98 mmol) of the title compound from Preparative Example 3 in 20 mL of DMF, stir at room temperature, and add 0.3914 g (3.87 mmol) of 4-methyl-morpholine, 0.7418 g (3.87 mmol) of DEC, 0.5229 g (3.87 mmol) of HOBT, and 0.8795 g (3.87 mmol) of 1-N-t-butoxycarbonyl-piperidinyl-4-acetic acid. Stir the mixture at room temperature

for 2 days, then concentrate *in vacuo* to a 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^+ = 614.

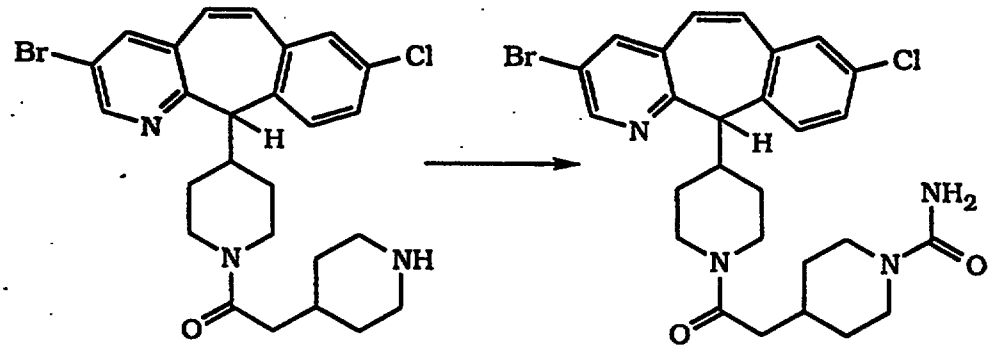
Elemental analysis: calculated - C, 60.54; H, 6.06; N, 6.83
found - C, 59.93; H, 6.62; N, 7.45.

Step B:



Combine 1.67 g (2.7 mmol) of the product of Step A 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^+ = 514.

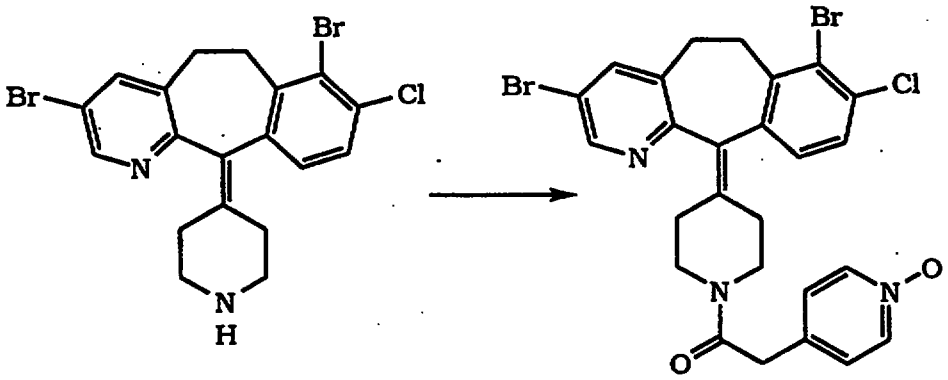
Step C:



Combine 0.50 g of the product of Step B, 20 mL of CH_2Cl_2 and 4.5 equivalents of $(CH_3)_3SiNCO$ and stir at room temperature for 3 hours. Extract the mixture with saturated $NaHCO_3$ (aqueous) and dry the organic phase over $MgSO_4$. Filter and concentrate *in vacuo* to give 0.8 g of the crude product.

Chromatograph the crude product (silica gel, 5% MeOH/CH_2Cl_2 + NH_3) to give 0.26 g of the product. m.p. = 170.2-170.5°C, Mass Spec.: MH^+ = 557.

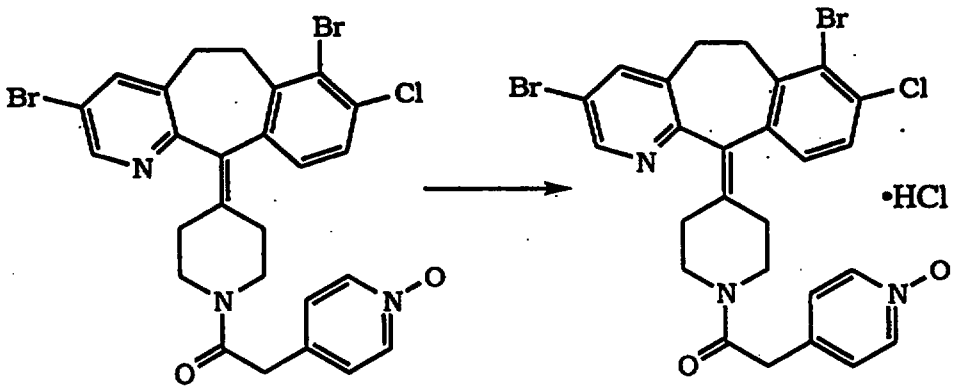
PREPARATIVE EXAMPLE 12



Combine 0.5 g (1.06 mmol) of the title compound of Preparative Example 4, 0.4 g (2.61 mmol) of the title compound of Preparative Example 1, 5 mL of dry DMF, and 0.5 mL (4.53 mmol) of 4-methylmorpholine, at 0°C, then add 0.6 g (3.12 mmol) of DEC and 0.4 g (2.96 mmol) of HOBT and stir the mixture overnight at 20°C. Concentrate *in vacuo* to a residue and extract the residue with CH_2Cl_2 (2 X 50 mL). Wash the extracts with 25 mL of water, dry over $MgSO_4$, then concentrate *in vacuo* to a residue and chromatograph (silica gel, 10% MeOH/EtOAc + 2% NH_4OH (aqueous)) to give 0.6 g (93.7% yield) of the title compound. Mass Spec.: MH^+ = 602 (FABS); partial ^1H NMR ($CDCl_3$, 300 MHz): 8.48 (s, 1H); 8.16 (d, 2H); 7.61 (s, 1H); 7.29 (m, 1H); 7.18 (d, 2H); 7.04 (d, 1H); 3.71 (s, 2H).

Elemental analysis: calculated - C, 48.81; H, 4.10; N, 6.57
found - C, 49.10; H, 3.79; N, 6.74.

PREPARATIVE EXAMPLE 13

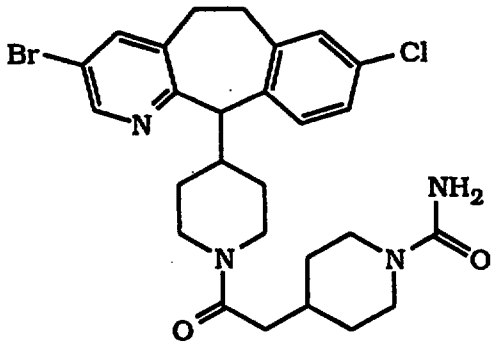


Dissolve 5.9 g (9.78 mmol) of the title compound of Preparative Example 12 in 300 mL of 1:5 CH_2Cl_2/EtOAc at 0°C. Slowly add (dropwise) 3 mL of 4 N HCl (aqueous) and stir the mixture at 0°C for 5 min. Add 200 mL of Et_2O, collect the resulting solids by filtration and wash the solids with 50 mL of Et_2O. Dry the solids at 20°C and 0.2 mm Hg to give 5.9 g (96% yield) of the title compound. Mass Spec.: MH^+ = 602 (FAB).

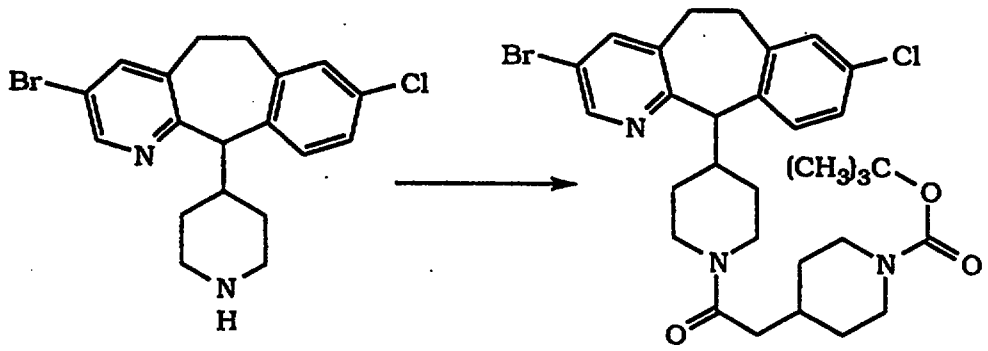
partial ^1H NMR (DMSO-d_6, 300 MHz): δ 8.66 (d, 2H); 8.51 (s, 1H); 7.95 (s, 1H); 7.67 (d, 2H); 7.47 (m, 1H); 7.15 (m, 1H); 3.99 (s, 2H).

Elemental analysis: calculated - C, 48.77; H, 3.62; N, 6.56
found - C, 48.34; H, 3.95; N, 6.84.

PREPARATIVE EXAMPLE 14

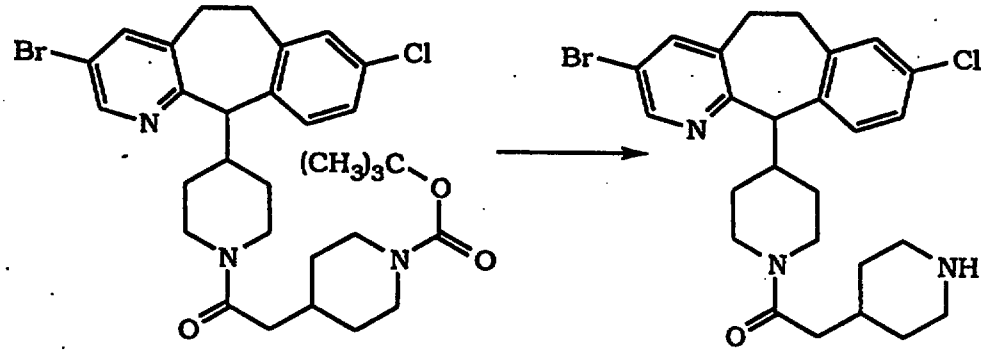


Step A:



Combine 0.501 g (1.28 mmol) of the title compound of Preparative Example 5 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.

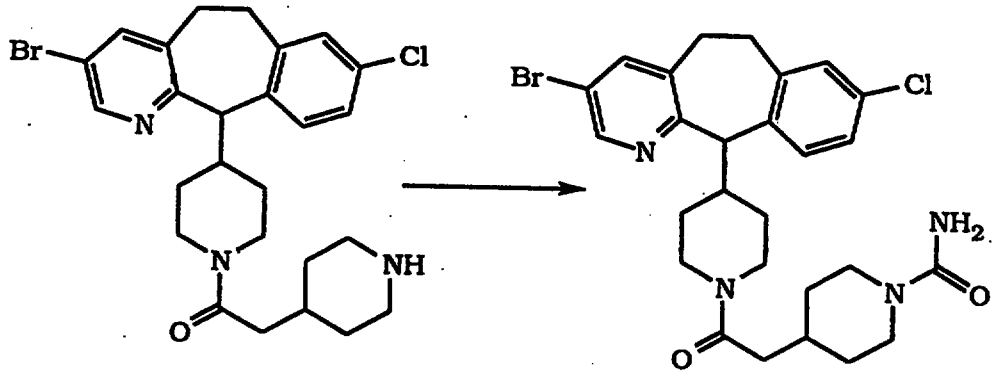
Step B:



Combine 0.555 g (0.9 mmol) of the product of Step A 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

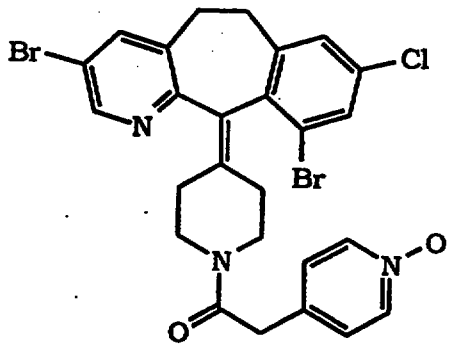
and 100 mL of saturated $NaHCO_3$ (aqueous). Extract the aqueous layer with 100 mL of CH_2Cl_2, combine the extracts and dry over $MgSO_4$. Concentrate *in vacuo* to give 0.47 g of the product. m.p. = 140°-150°C; Mass Spec.: MH^+ = 516.

Step C:



Combine 0.449 g (0.87 mmol) of the product of Step B, 20 mL of CH_2Cl_2 and 0.501 g (0.59 mmol) of $(CH_3)_3SiNCO$ and stir at room temperature overnight. Add 50-75 mL of saturated $NaHCO_3$ (aqueous) and stir for 0.5 hours. Dilute with CH_2Cl_2, separate the layers and extract the aqueous layer with 2 X 100 mL of CH_2Cl_2. Dry the combined CH_2Cl_2 extracts over $MgSO_4$ and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 500 mL CH_2Cl_2; 1 L of 1% MeOH/CH_2Cl_2 + 0.1% NH_4OH; 1 L of 2% MeOH/CH_2Cl_2 + 0.2% NH_4OH; then with 3% MeOH/CH_2Cl_2 + 0.3% NH_4OH) to give 0.33 g of the title compound. m.p. = 145°-155°C; Mass Spec.: MH^+ = 559.

PREPARATIVE EXAMPLE 15

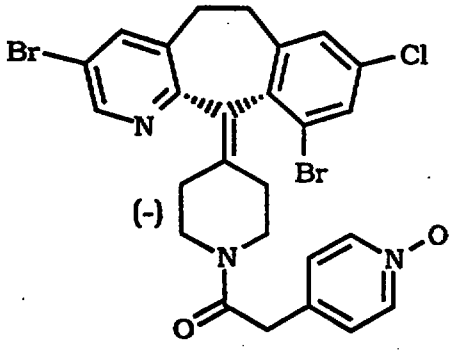


React the title compound of Preparative Example 7 and the title compound of Preparative Example 1 using substantially the same procedure as described for Preparative Example 12, to

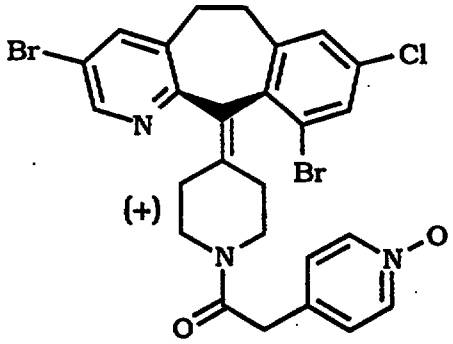
give 0.25 g of the title compound, which is a racemic mixture of atropisomers. Mass Spec.: MH^+ = 602. m.p. = 167.2°-167.8°C.

The HCl salt of the title compound of Preparative Example 15 is prepared by stirring for 1 hr. with HCl/CH_2Cl_2, then concentrating *in vacuo* to give the salt.

PREPARATIVE EXAMPLES 16A & 16B



Preparative Example 16A



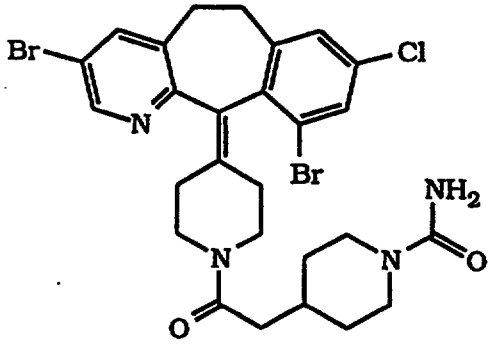
Preparative Example 16B

The title compound of Example 15 is a racemic mixture of atropisomers. Those atropisomers are separated by preparative chromatography (HPLC), using an Chiralpack AD column (5 cm x 50 cm) and 40% i-PrOH/ hexane + 0.2% diethylamine as the mobile phase to give the (+)- and (-)-enantiomers, Examples 16B and 16A, respectively.

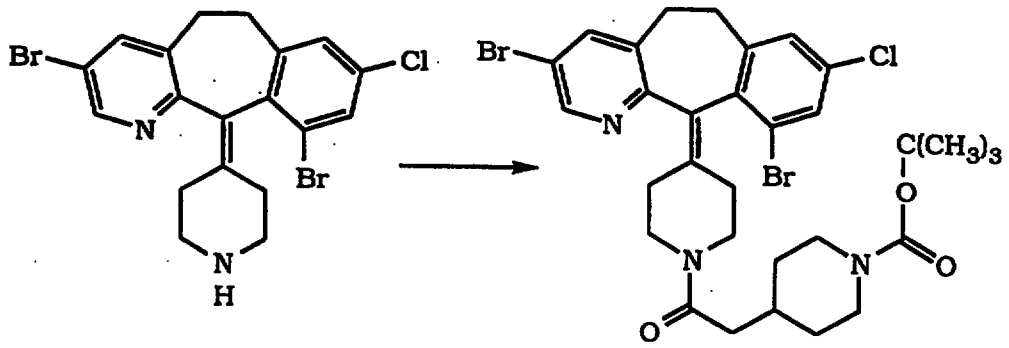
Physical chemical data for (-)-enantiomer, Example 16A: m.p. = 114.2°-114.8°C; $[\alpha]_D^{25}$ = -154.6° (8.73 mg/2 mL, MeOH).

Physical chemical data for (+)-enantiomer, Example 16B: m.p. = 112.6°-113.5°C; $[\alpha]_D^{25}$ = +159.7° (10.33 mg/2 mL, MeOH).

PREPARATIVE EXAMPLE 17

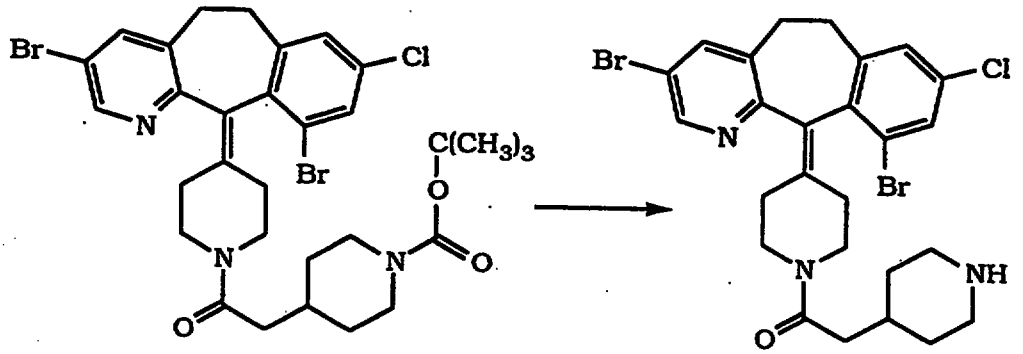


Step A:



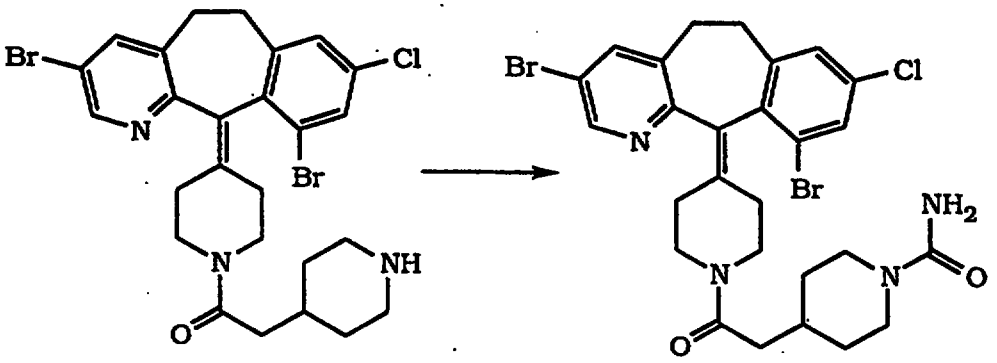
React 6.0 g (12.8 mmol) of the title compound of Preparative Example 7 and with 3.78 g (16.6 mmol) of 1-N-t-butoxycarbonylpiperidinyl-4-acetic acid using substantially the same procedures as described for Preparative Example 14, Step A, to give 8.52 g of the product. Mass Spec.: MH^+ = 692 (FAB). ^1H 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 B:



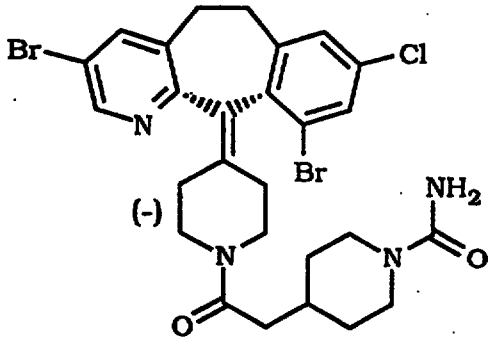
Combine 8.50 g of the product of Step A and 60 mL of CH_2Cl_2, then cool to 0°C and add 55 mL of TFA. Stir the mixture for 3 h at 0°C, then add 500 mL of 1 N NaOH (aqueous) followed by 30 mL of 50% NaOH (aqueous). Extract with CH_2Cl_2, dry over $MgSO_4$ and concentrate *in vacuo* to give 7.86 g of the product. Mass Spec.: MH^+ = 592 (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).

Step C:

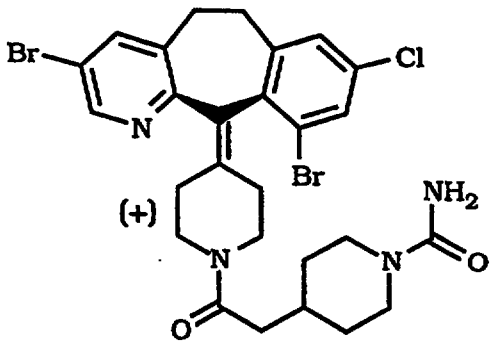


Treat 7.80 g (13.1 mmol) of the product of Step B with 12.1 g (105 mmol) of $(CH_3)_3SiNCO$ using substantially the same procedure as described for Preparative Example 14, Step C, to give 5.50 g of the title compound, which is a racemic mixture of atropisomers. m.p. = 163.6°-164.0°C. Mass spec.: MH^+ = 635 (FAB). ^1H NMR ($CDCl_3$, 200 MHz): 8.5 (d, 1H); 7.52 (d, 1H); 7.48 (d, 1H); 7.21 (d, 1H); 4.54, (s, 2H); 4.1-3.6 (m, 4H); 3.45-3.15 (m, 4H); 3.0-2.5 (m, 5H); 2.45-1.6 (m, 7H); 1.4-1.0, (m, 2H).

PREPARATIVE EXAMPLES 18A & 18B



Preparative Example 18A



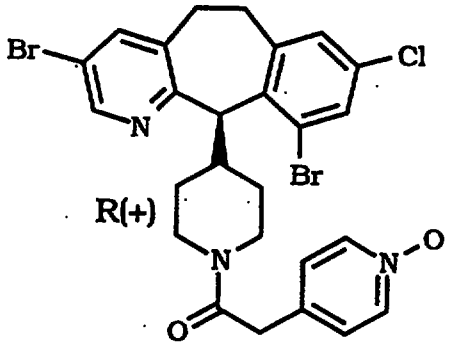
Preparative Example 18B

The title compound of Preparative Example 17 is a racemic mixture of atropisomers. Those atropisomers are separated by preparative chromatography (HPLC), using an Chiralpack AD column (5 cm x 50 cm) and 20% i-PrOH/ hexane + 0.2% diethylamine as the mobile phase, at a flow rate of 100 mL/min., to give the (+)- and (-)-enantiomers, Examples 18B and 18A, respectively.

Physical chemical data for (-)-enantiomer, Example 18A: m.p. = 142.9°-143.5°C; $[\alpha]_D^{25}$ = -151.7° (11.06 mg/2 mL, MeOH).

Physical chemical data for (+)-enantiomer, Example 18B: m.p. = 126.5°-127.0°C; $[\alpha]_D^{25}$ = +145.6° (8.38 mg/2 mL, MeOH).

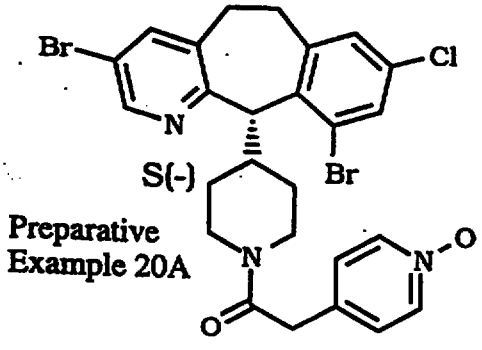
PREPARATIVE EXAMPLE 19



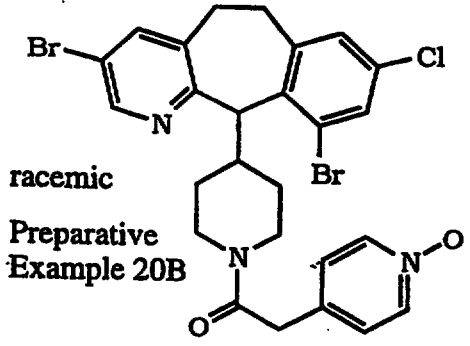
Combine 3.32 g of the (+)-enantiomer of the title compound of Preparative Example 8, Step B, 2.38 g of the title compound of Preparative Example 1, 1.92 g of HOBT, 2.70 g of DEC, 1.56 mL of N-methylmorpholine and 50 mL of dry DMF and stir at 25°C for 24 hrs. Concentrate *in vacuo*, then dilute the residue with CH_2Cl_2. Wash with 1 N NaOH (aqueous), then with saturated NaH_2PO_4 (aqueous) and dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2% $MeOH/CH_2Cl_2$ + NH_4OH) to give 3.82 g of the title compound. Mass Spec.: MH^+ = 604 (FAB).

The hydrochloride salt was prepared by dissolution of the title compound from Preparative Example 19 in dichloromethane saturated with hydrogen chloride. Concentration *in vacuo* provided the title compound from Preparative Example 19 as the HCl salt. m.p. = 166.5°C; $[\alpha]_D^{22}$ = +70.8° (9.9mg/2mL MeOH).

PREPARATIVE EXAMPLES 20A & 20B



Preparative Example 20A



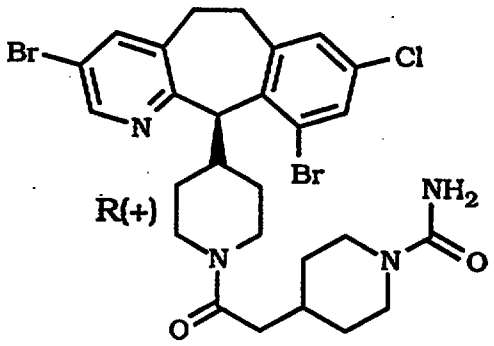
Preparative Example 20B

The (-)-enantiomer of the title compound of Preparative Example 8, Step B, (3.38 g) is reacted with 2.20 g of the title compound of Preparative Example 1, via substantially the same procedure as described for Preparative Example 19 to give 3.58 g of the title compound of Preparative Example 20A.

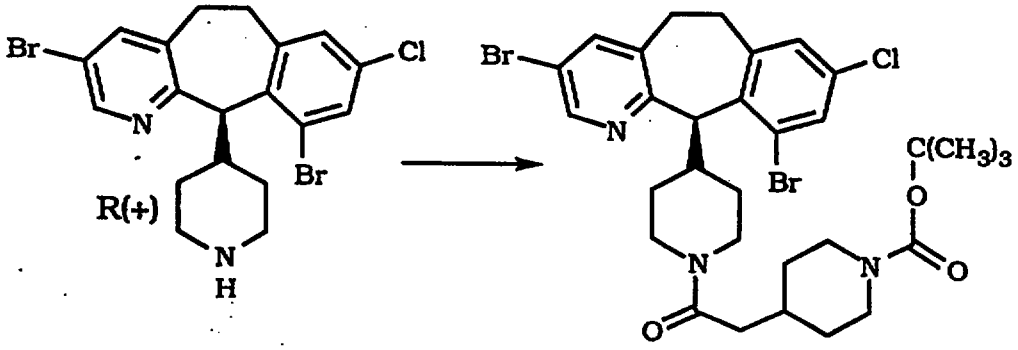
The HCl salt of the title compound of Preparative Example 20A is prepared by dissolving of the title compound in CH_2Cl_2, adding 6M HCl (g) in CH_2Cl_2, then concentrating *in vacuo* to give the salt. m.p. = 129°C; $[\alpha]_D^{25}$ = -72.3° (3.32mg/2mL MeOH).

The racemic title compound of Preparative Example 8, Step A, is reacted with the title compound of Preparative Example 1, via substantially the same procedure as described for Preparative Example 20A to give the title compound of Preparative Example 20B. m.p. = 145.0°C.

PREPARATIVE EXAMPLE 21



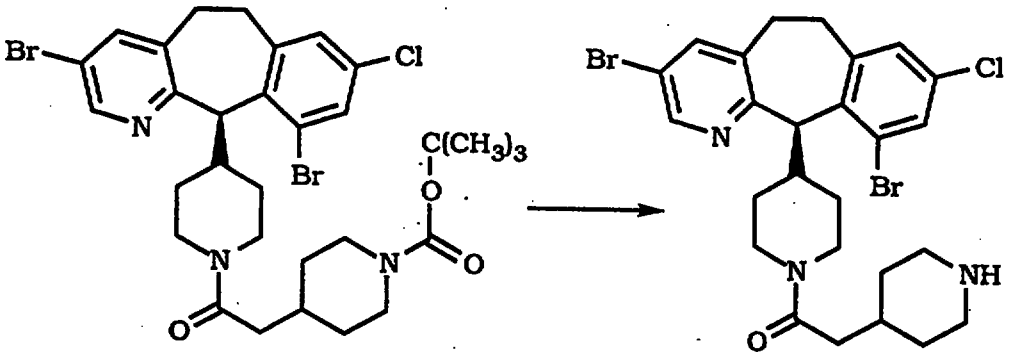
Step A:



React 1.33 g of the (+)-enantiomer of the title compound of Preparative Example 8, Step B, with 1.37 g of 1-N-t-butoxy-carbonylpiperidinyl-4-acetic acid using substantially the same procedures as described for Preparative Example 14, Step A, to

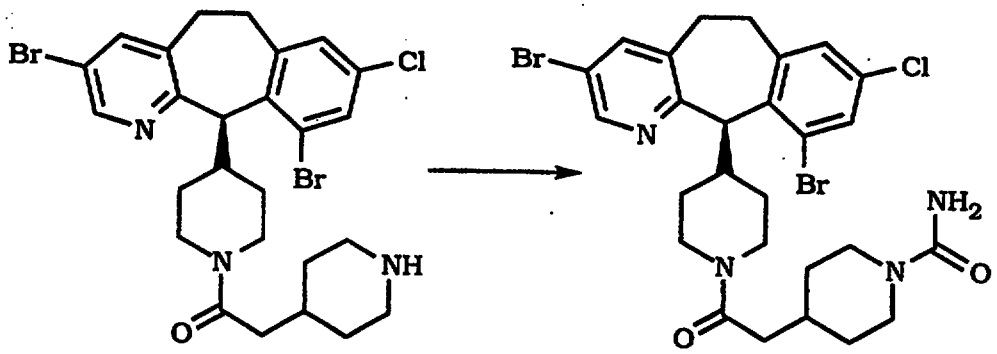
give 2.78 g of the product. Mass Spec.: MH^+ = 694.0 (FAB); $[\alpha]_D^{25}$ = +34.1° (5.45 mg/2 mL, MeOH).

Step B:



Treat 2.78 g of the product of Step A via substantially the same procedure as described for Preparative Example 17, Step B, 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).

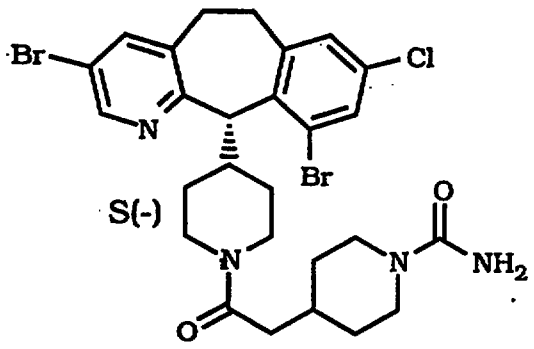
Step C:



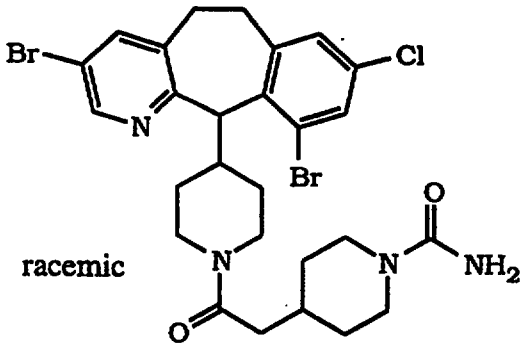
Treat 1.58 g of the product of Step B with 6 mL of $(CH_3)_3SiNCO$ using substantially the same procedure as described for Preparative Example 14, Step C, to give 1.40 g of the title compound. m.p. = 140°C; Mass spec.: MH^+ = 637; $[\alpha]_D^{25}$ = +49.1° (4.24mg/2 mL, MeOH).

Recrystallization from acetone provided the title compound as a solid. m.p. = 214.5-215.9°C.

PREPARATIVE EXAMPLES 22A & 22B



Preparative Example 22A

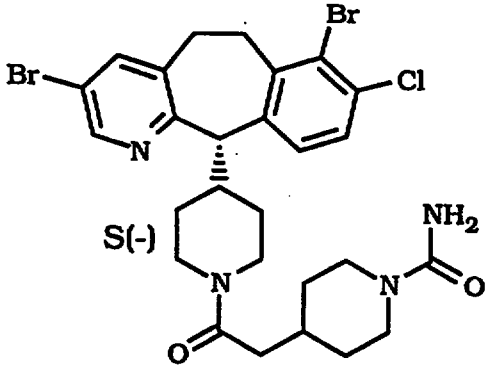


Preparative Example 22B

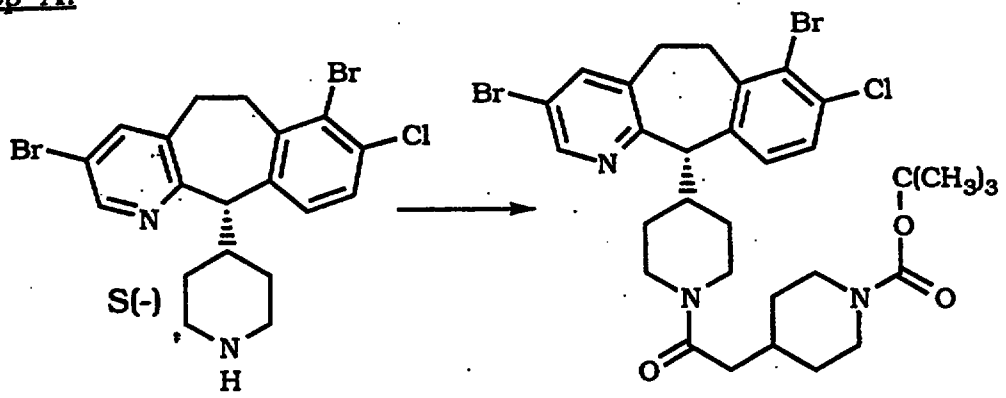
The (-)-enantiomer of the title compound of Preparative Example 8, Step B, (3.38 g) is converted to the title compound (Preparative Example 22A) via substantially the same procedure as described for Preparative Example 21, Steps A-C, to give the title compound Preparative Example 22A. m.p. = 152°C; Mass spec.: $MH^+ = 637$; $[\alpha]_D^{25}$ = -62.5° (1,12mg/2mL MeOH).

The racemic title compound of Preparative Example 8, Step A, is converted to the title compound (Preparative Example 22B) via substantially the same procedure as described for Preparative Example 10, Steps A-C to give the title compound Preparative Example 22B. m.p. = 111.2°C (dec).

PREPARATIVE EXAMPLE 23

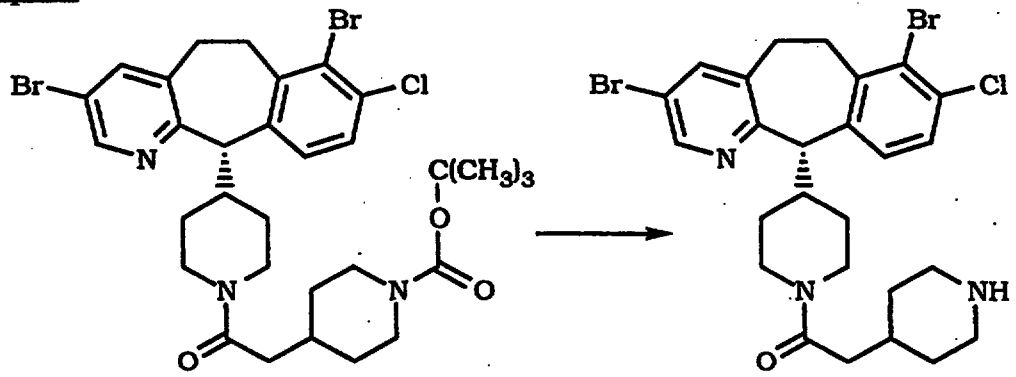


Step A:



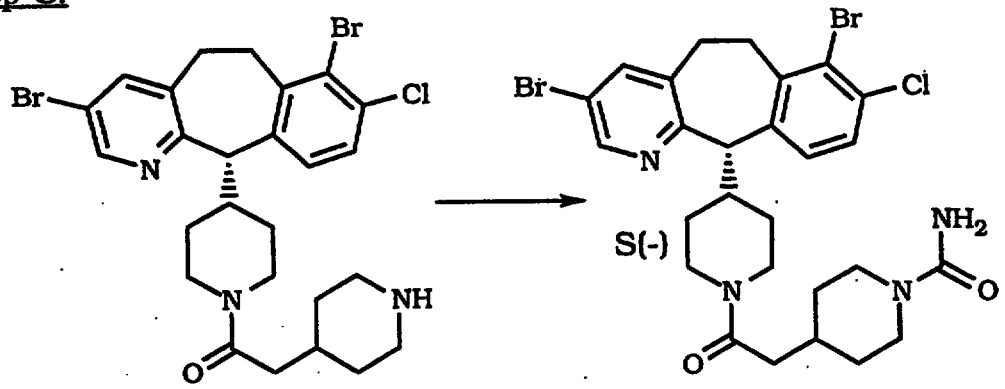
React 1.35 g of the (-)-enantiomer of the title compound of Preparative Example 10, Step B, with 1.4 g of 1-N-t-butoxy-carbonylpiperidinyl-4-acetic acid following substantially the same procedures as described for Preparative Example 14, Step A, to give 2.0 g of the product. Mass Spec.: MH^+ = 694 (FAB). partial ^1H NMR ($CDCl_3$, 300 MHz): 8.38 (s, 1H); 7.60 (s, 1H); 7.25 (d, 1H); 7.05 (m, 1H); 1.45 (s, 9H).

Step B:



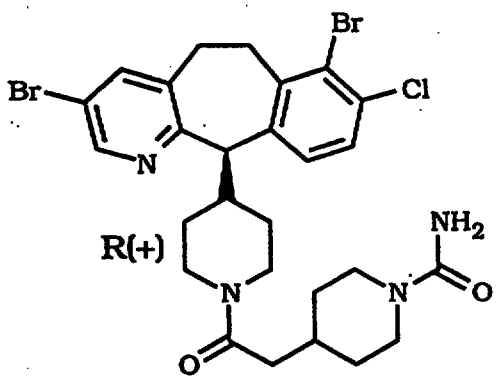
Treat 1.95 g of the product of Step A via substantially the same procedure as described for Preparative Example 17, Step B, to give 1.63 g of the product. Mass Spec. MH^+ = 594 (FAB). Partial ^1H NMR ($CDCl_3$, 300 MHz): 8.38 (s, 1H); 7.60 (s, 1H); 7.25 (d, 1H); 7.03 (m, 1H); 4.64 (d, 1H); 3.90 (m, 2H).

Step C:

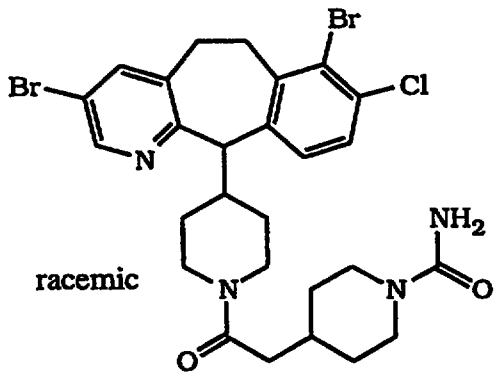


Treat 1.6 g of the product of Step B with 1.3 mL of $(CH_3)_3SiNCO$ using substantially the same procedure as described for Preparative Example 14, Step C, to give 1.27 g of the title compound. Mass spec.: MH^+ = 637 (FABS); $[\alpha]_D^{25}$ = -33.1° (c=0.58, EtOH). partial ^1H NMR ($CDCl_3$, 400 MHz): 8.38 (s, 1H); 7.59 (s, 1H); 7.25 (d, 1H); 7.04 (m, 1H); 4.60 (d, 1H); 4.41 (s, 2H).

PREPARATIVE EXAMPLES 24A & 24B



Preparative Example 24A



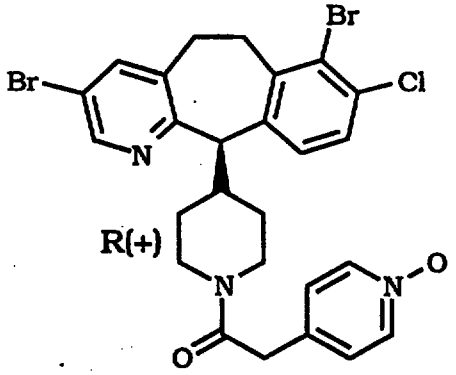
Preparative Example 24B

The (+)-enantiomer of the title compound from Preparative Example 10, Step B, (2.1 g) is converted to the title compound via substantially the same procedure as described for Preparative Example 21, Steps A-C, to give the title compound, Preparative Example 24A. Mass spec.: MH^+ = 637 (FABS); $[\alpha]_D^{25}$ = +32.4° (c=0.57, EtOH). Partial ^1H NMR ($CDCl_3$, 400 MHz): 8.39 (s, 1H); 7.59 (s, 1H); 7.25 (d, 1H); 7.04 (m, 1H); 4.60 (d, 1H); 4.41 (s, 2H). partial ^1H NMR (DMSO-d_6, 400 MHz): 8.42 (s, 1H);

7.88 (s, 1H); 7.41 (d, 1H); 7.29 (m, 1H); 5.85 (s, 2H); 4.20 (d, 1H).

The racemic title compound from Preparative Example 10, Step A, is converted to the racemic title compound, Preparative Example 24B, in an analogous manner. Partial ^{1}H NMR ($CDCl_3$, 400 MHz): 8.38 (s, 1H); 7.59 (s, 1H); 7.25 (d, 1H); 7.04 (m, 1H); 4.60 (d, 1H); 4.41 (s, 2H). partial ^{1}H NMR (DMSO-d_6, 400 MHz): 8.42 (s, 1H); ,7.88 (s, 1H); 7.41 (d, 1H); 7.29 (d, 1H); 5.85 (s, 2H); 4.20 (d, 1H).

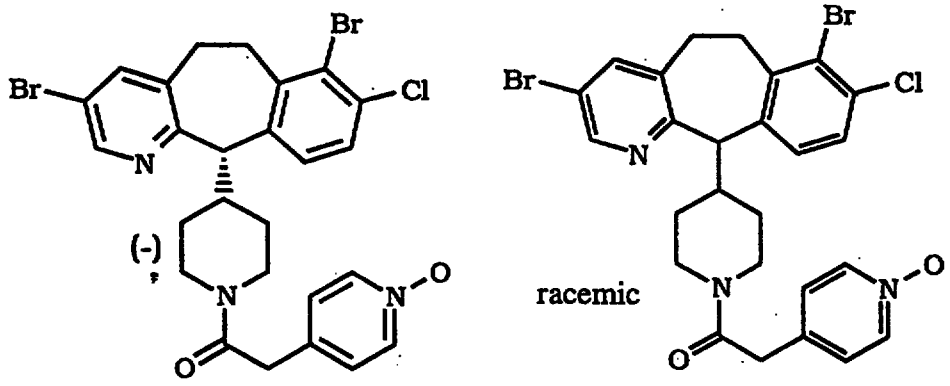
PREPARATIVE EXAMPLE 25



React 2.6 g of the (+)-enantiomer of the title compound of Preparative Example 10, Step B, and 1.68 g of the title compound of Preparative Example 1 following substantially the same procedure as described for Preparative Example 19 to give 2.10 g of the title compound. Mass spec.: MH^+ = 604 (FAB); $[\alpha]_D^{25}$ = +34.1° (10.98 mg/2 mL, EtOH). partial ^{1}H NMR ($CDCl_3$, 400 MHz): 8.38 (s, 1H); 8.15 (d, 2H); 7.58 (s, 1H); 7.26 (d, 1H); 7.15 (d, 2H); 7.03 (d, 1H); 4.57 (d, 1H).

To prepare the HCl salt of the title compound of Preparative Example 25 dissolve 700 mg of the title compound in 4 mL of CH_2Cl_2, add 4 mL of Et_2O, cool to 0°C and slowly add (dropwise) 1 mL of HCl (g) in dioxane. Add 2 mL of Et_2O and stir at 0°C for 7 min. Dilute with 30 mL of Et_2O, filter to collect the solid product and wash with 30 mL of Et_2O. Dry the solids *in vacuo* to give 0.836 g of the HCl salt of Example 14. $[\alpha]_D^{25}$ = +64.8° (9.94 mg/2 mL, EtOH).

PREPARATIVE EXAMPLE 26A & 26B



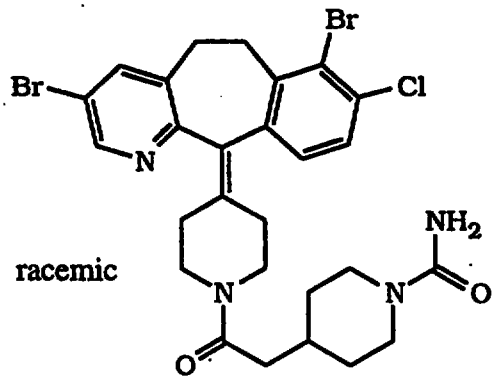
Preparative Example 26A Preparative Example 26B

The (-)-enantiomer of the title compound of Preparative Example 10, Step B, (0.60 g) is reacted with 0.39 g of the title compound of Preparative Example 1, via substantially the same procedure as described for Preparative Example 19 to give 0.705 g of the title compound. Mass spec.: MH^+ = 604 (FABS); $[\alpha]_D^{25}$ = -41.8° (EtOH). Partial ^1H NMR ($CDCl_3$, 300 MHz): 8.38 (s, 1H); 8.15 (d, 2H); 7.58 (s, 1H); 7.26 (d, 1H); 7.15 (d, 2H); 7.03 (d, 1H); 4.57 (d, 1H).

The HCl salt of the title compound of Preparative Example 26A is prepared via substantially the same procedure as described for Preparative Example 25. $[\alpha]_D^{25}$ = -63.2° (EtOH).

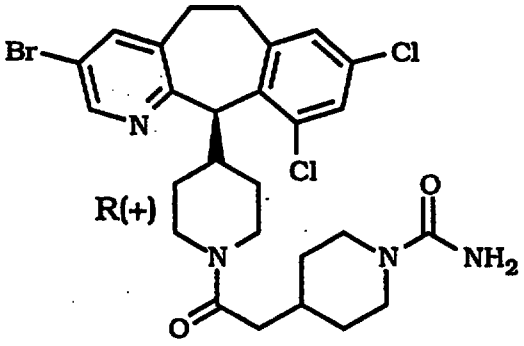
The racemic title compound of Preparative Example 10, Step A, is converted to the racemic title compound of Preparative Example 26B following substantially the same procedure as described for Preparative Example 19. Partial ^1H NMR ($CDCl_3$, 400 MHz): 8.38 (s, 1H); 8.15 (d, 2H); 7.58 (s, 1H); 7.26 (d, 1H); 7.15 (d, 2H); 7.03 (d, 1H); 4.57 (d, 1H). Partial ^1H NMR (DMSO-d_6, 400 MHz): 8.77 (d, 2H); 8.47 (s, 1H); 7.95 (s, 1H); 7.74 (d, 2H); 7.43 (m, 1H); 7.27 (d, 1H); 4.35 (d, 1H).

PREPARATIVE EXAMPLE 27

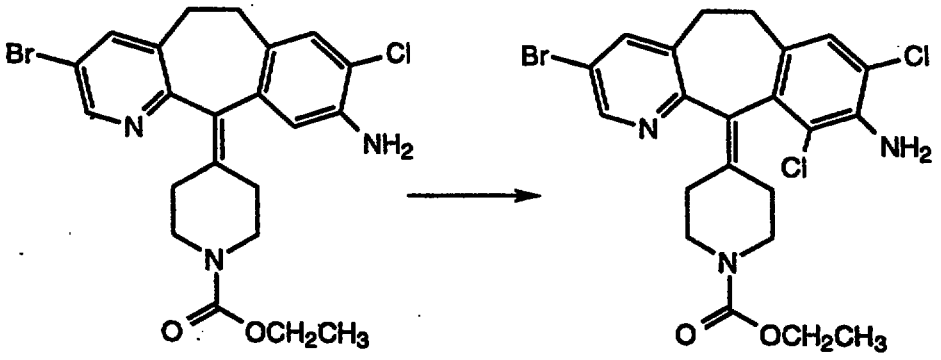


The title compound of Preparative Example 4 is reacted via substantially the same methods as described for Preparative Example 17, Steps A-C, to give the title compound, which is a racemate. Mass Spec.: MH^+ = 635 (FAB). Partial ^1H NMR ($CDCl_3$): 8.45 (s, 1H); 7.60 (s, 1H); 7.35 (d, 1H); 7.05 (d, 1H); 4.45 (s, 1H).

PREPARATIVE EXAMPLE 28



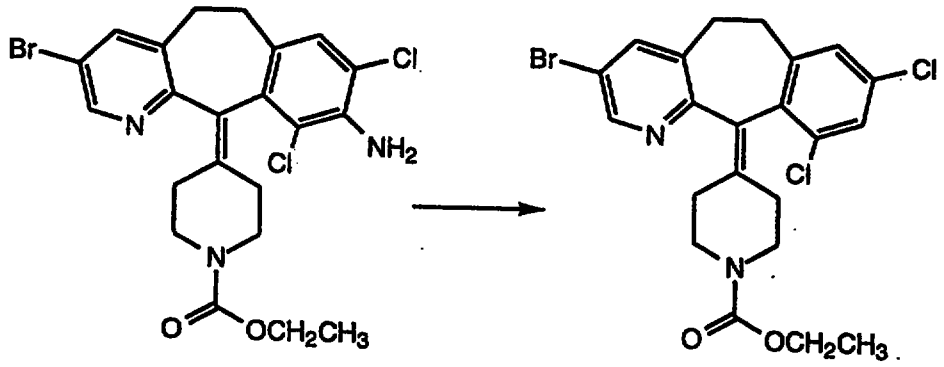
Step A:



Dissolve 9.90 g (18.9 mmol) of the product of Preparative Example 7, Step B, in 150 mL CH_2Cl_2 and 200 mL of CH_3CN and heat to 60°C. Add 2.77 g (20.8 mmol) N-chlorosuccinimide and

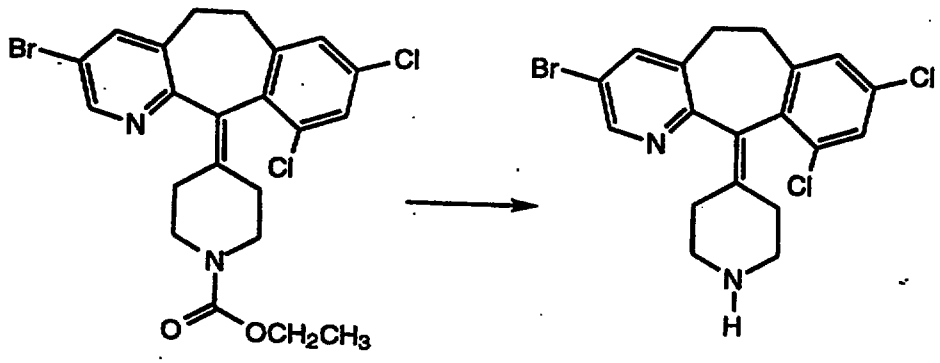
heat to reflux for 3 h., monitoring the reaction by TCL (30%EtOAc/H_2O). Add an additional 2.35 g (10.4 mmol) of N-chlorosuccinimide and reflux an additional 45 min. Cool the reaction mixture to room temperature and extract with 1N NaOH and CH_2Cl_2. Dry the CH_2Cl_2 layer over $MgSO_4$, filter and purify by flash chromatography (1200 mL normal phase silica gel, eluting with 30% EtOAc/H_2O) to obtain 6.24 g of the desired product. M.p. 193-195.4°C. MH^+ = 510.

Step B:



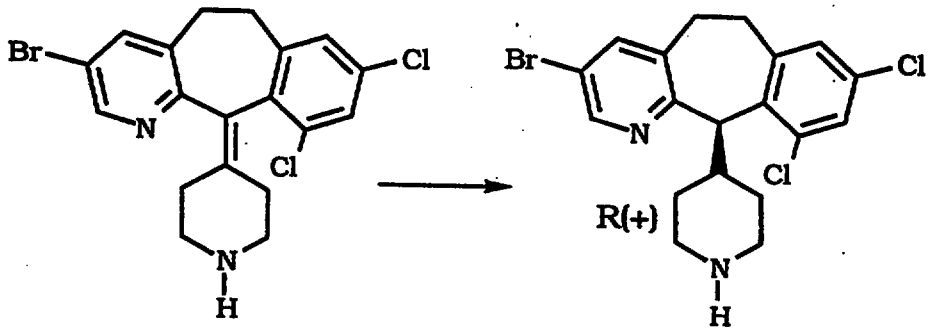
To 160 mL of conc. HCl at -10°C add 2.07 g (30.1 mmol) $NaNO_2$ and stir for 10 min. Add 5.18 g (10.1 mmol) of the product of Step A and warm the reaction mixture from -10°C to 0°C for 2 h. Cool the reaction to -10°C, add 100 mL H_3PO_2 and let stand overnight. To extract the reaction mixture, pour over crushed ice and basify with 50% NaOH/ CH_2Cl_2. Dry the organic layer over $MgSO_4$, filter and concentrate to dryness. Purify by flash chromatography (600 mL normal phase silica gel, eluting with 20% EtOAc/hexane) to obtain 3.98 g of product. Mass spec.: MH^+=495.

Step C:



Dissolve 3.9 g of the product of Step B in 100 mL conc. HCl and reflux overnight. Cool the mixture, basify with 50 % w/w NaOH and extract the resultant mixture with CH_2Cl_2. Dry the CH_2Cl_2 layer over $MgSO_4$, evaporate the solvent and dry under vacuum to obtain 3.09 g of the desired product. Mass spec.: MH^+=423.

Step D:

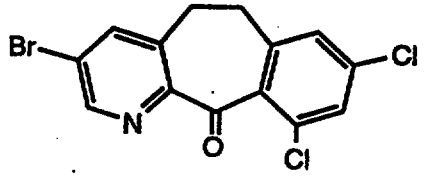


Using a procedure similar to that described in Preparative Example 8, obtain 1.73 g of the desired product, m.p. 169.6-170.1°C; $[\alpha]_D^{25}$ = +48.2° (c=1, MeOH). MH^+ = 425.

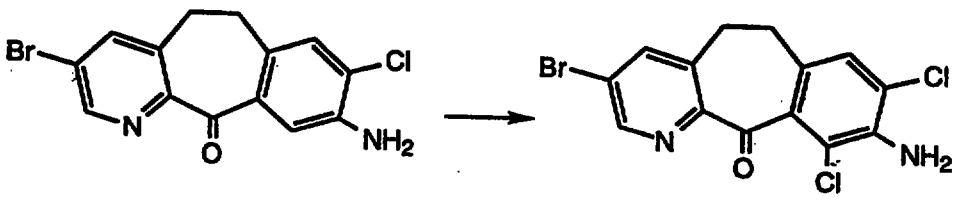
Step E:

Use a procedure similar to that of Preparative Example 14 with the product of Step D as the starting material to obtain the title compound. M.p. 152.3-153.3°C; $[\alpha]_D^{25}$ = +53.0° (c=1, MeOH). MH^+ = 593.

PREPARATIVE EXAMPLE 29

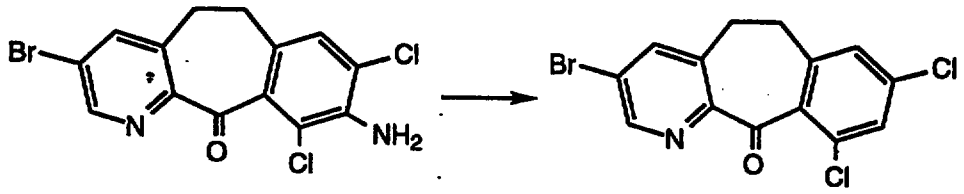


Step A:



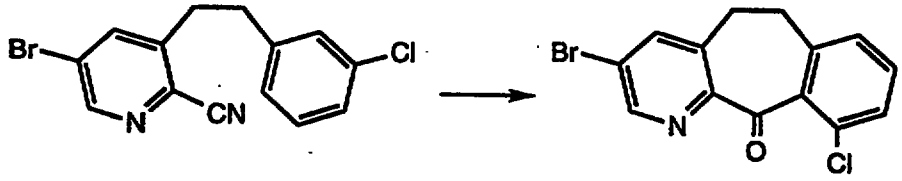
Treat 15.0 g (44.4 mmol) of the product of Preparative Example 9, Step B, with 6.52 g (48.9 mmol) of N-chloro-succinimide in a manner similar to that described in Preparative Example 28 Step A and extract as described to obtain 16.56 g of the desired product, m.p. 234.7-235.0°C. MH^+ = 370.

Step B:



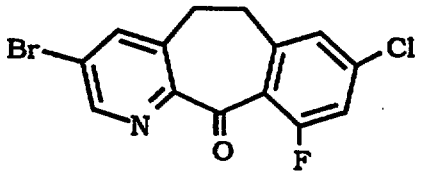
Treat 16.95 g (45.6 mmol) of the product of Step A in the manner described in Preparative Example 28, Step B, to obtain 13.07 g of the desired product, m.p. 191.7-192.1°C. MH^+ = 356.

PREPARATIVE EXAMPLE 30

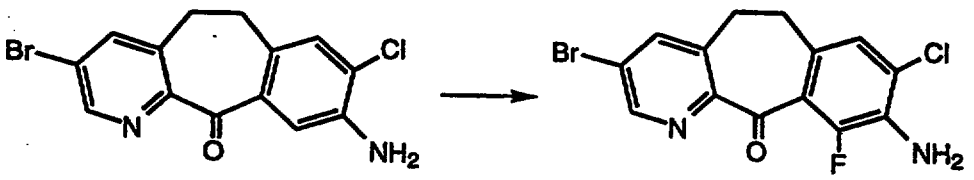


Heat 200 mg of the cyano starting material in 17 g polyphosphoric acid at 190-200°C for 45 min. Pour the resultant mixture into ice, add 30% HCl and stir for 30 min. Extract with CH_2Cl_2, wash with brine, dry over Na_2SO_4, filter and concentrate. Purify by preparative TLC, eluting with EtOAc/hexane to obtain 21 mg of the desired product (also obtained 59 mg of the 10-chloro product).

PREPARATIVE EXAMPLE 31

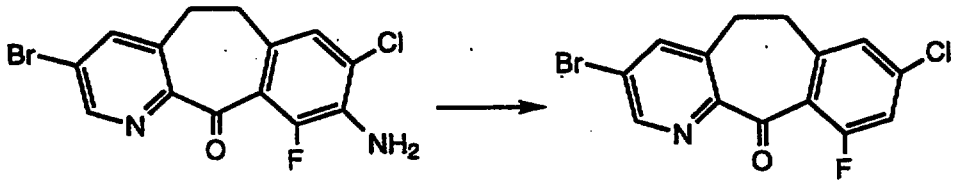


Step A:



Dissolve 10.0 g (29.6mmol) of the product of Preparative Example 9, Step B, in 150 mL CH_2Cl_2 and 200 mL CH_3CN at room temperature. Heat the mixture to 60°C, add 10.45 g (32.6 mmol) of 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2,2,2]octane bis-(tetrafluoroborate) and heat to reflux for 4 h. Cool the mixture to room temperature, extract with CH_2Cl_2 and 1 N NaOH. Dry the CH_2Cl_2 layer over $MgSO_4$, filter and concentrate to dryness. Purify the resultant residue by flash chromatography using 1400 mL normal phase silica gel eluted with 10% EtOAc-CH_2Cl_2 + 2 drops NH_4OH to obtain 2.00 g of product, m.p. 103.2-103.5°C. $MH^+ = 355$.

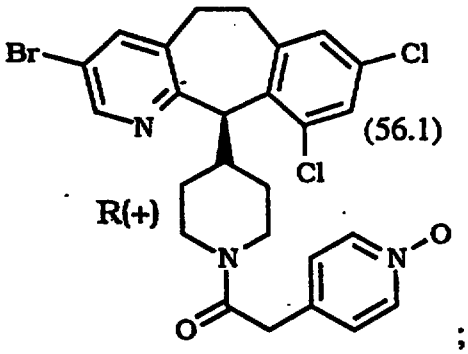
Step B:



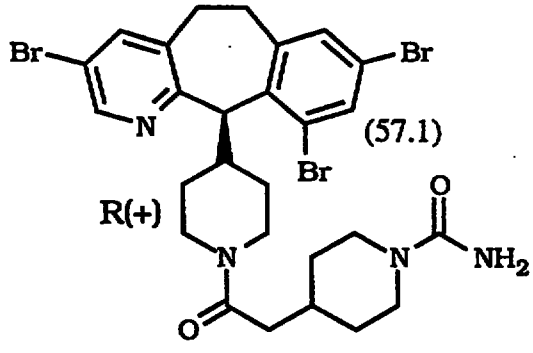
Using a procedure substantially as described in Preparative Example 9, Step D, treat 1.80 g (5.1 mmol) of the product of Step A. Purify the crude product by flash chromatography using 200 mL normal phase silica gel eluted with 20% EtOAc/hexane. Mass spec.: $MH^+ = 339$.

PREPARATIVE EXAMPLE 32

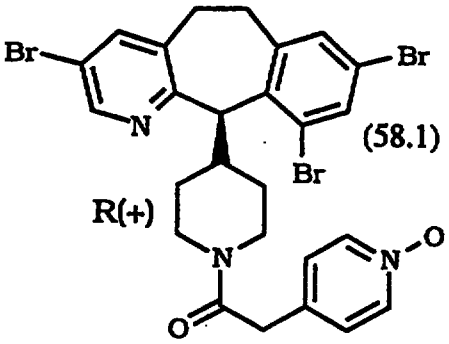
Using appropriate starting materials and procedures as described above, the following compounds could be made:



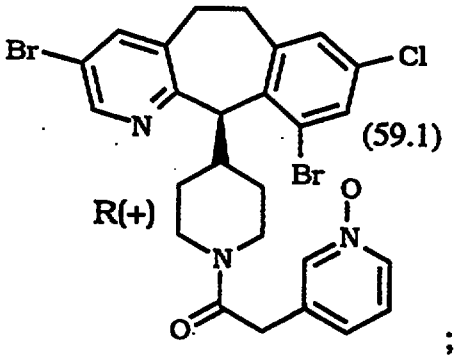
;



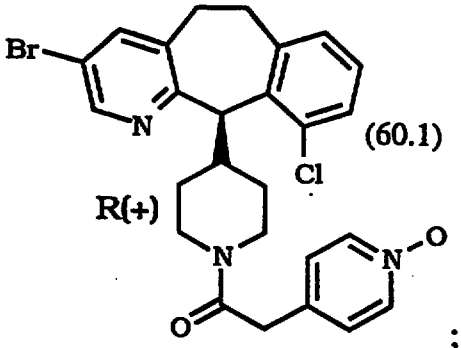
;



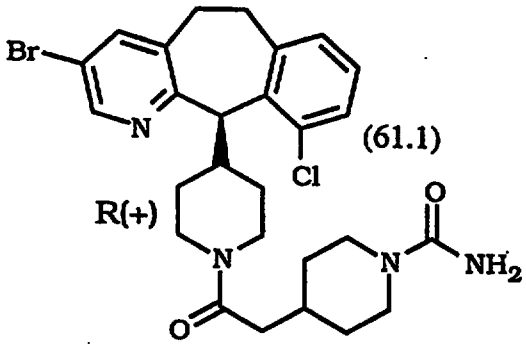
(58.1) ;



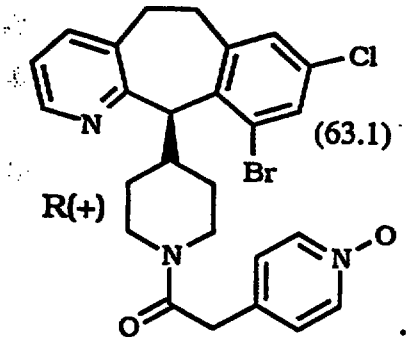
(59.1) ;



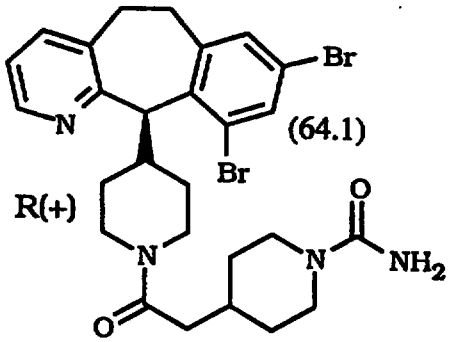
(60.1) ;



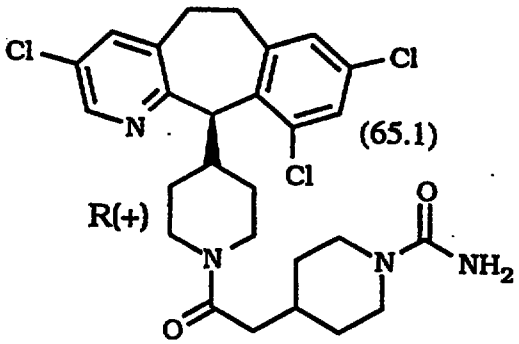
(61.1) ;



(63.1) ;



(64.1) ;

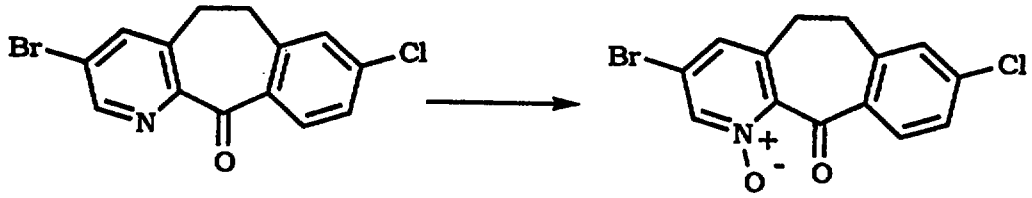


(65.1)

and

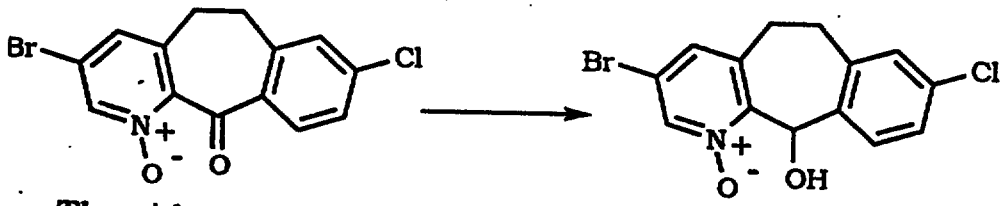
PREPARATIVE EXAMPLE 33

Step A



To a solution of 3-bromo-8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one (2g) (6.2mmoles) in anhydrous dichloromethane (14ml) at 0°C and under an argon atmosphere, was added a solution of 3-chloroperbenzoic acid (1.76g) (10.4mmoles) in anhydrous dichloromethane (35ml) dropwise over a period of 30 minutes. The mixture was allowed to warm to room temperature and after 18h additional 3-chloroperbenzoic acid (0.88g) (5.2mmoles) in anhydrous dichloromethane (25ml) was added and the mixture was stirred for a total of 42h. The mixture was diluted with dichloromethane and washed with 1N NaOH (200ml). The aqueous layer was extracted with additional dichloromethane (2X200ml) and the combined organic layers were dried over magnesium sulfate, filtered and evaporated to dryness. The product was chromatographed on silica gel using 0.25%-0.5%-1% (10% conc. NH_4OH in methanol)dichloromethane as the eluant to give the title compound (Yield:1.386g, 66%): ESIMS; m/z 338.1 (MH^+); δ_C ($CDCl_3$) CH_2: 30.5, 34.0; CH: 126.9, 127.6, 130.3, 132.5, 140.4; C: 121.0, 135.1, 138.3, 139.7, 141.6, 145.3, 188.0ppm.

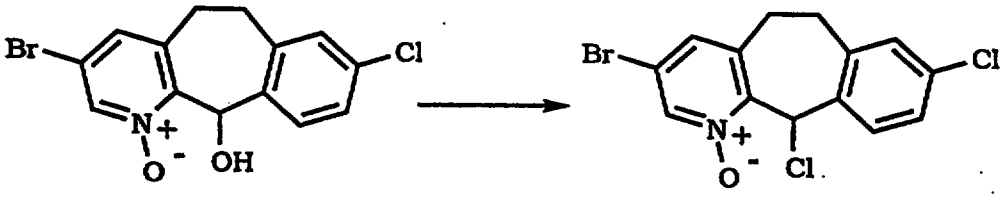
Step B



The title compound of Preparative Example 33A (1.3422g) (3.96mmoles) was dissolved in methanol (18ml) and dichloromethane (20ml) and sodium borohydride (0.219g) (5.79mmoles) was added. The mixture was stirred under argon at 0°C for 1h and then allowed to warm up to 25°C over a period of 1h. The mixture was diluted with dichloromethane (800ml)

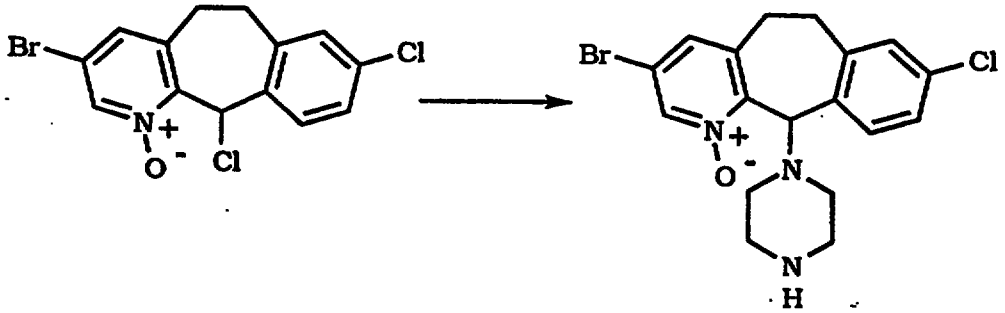
and washed with 1N NaOH (150ml). The aqueous layer was extracted with dichloromethane (2X100ml) and the combined organic layers were dried over magnesium sulfate, filtered and evaporated to dryness. The product was chromatographed on silica gel using 1% (10% conc. NH_4OH in methanol)dichloromethane as the eluant to give the title compound (Yield: 1.24g, 92%): ESIMS: m/z 340.1 (MH^+); δ_C ($CDCl_3$) CH_2: 31.2, 32.0; CH: 69.1, 126.8, 129.5, 131.7, 131.7, 136.7; C: 118.3, 134.7, 135.2, 139.7, 141.0, 148.9ppm.

Step C



The title compound of Preparative Example 33B (1.19g) (3.49mmoles) was dissolved in anhydrous toluene (22.5ml) and the solution was cooled to 0°C under argon. Thionyl chloride (0.472ml) (6.46mmoles) in anhydrous toluene (5ml) was added and the mixture was stirred at 0°C for 1h. The mixture was allowed to warm to 25°C over a period of 2.5h. The solution was poured into a 20% solution of ethyl acetate in dichloromethane (800ml) and the mixture was washed with 1N NaOH. The aqueous layer was extracted with dichloromethane (2X200ml) and the combined organic layers were dried over magnesium sulfate, filtered and evaporated to give the product which was used without further purification.

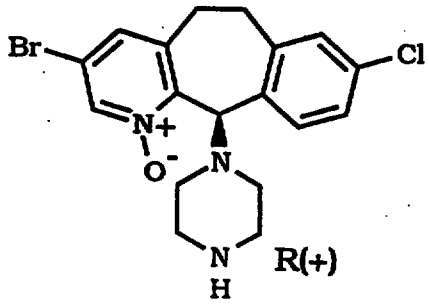
Step D



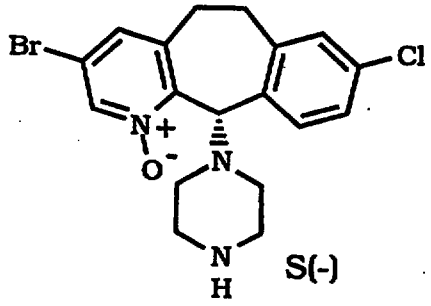
The title compound from Preparative Example 33C (3.49mmoles) was dissolved in anhydrous THF (10ml) and a

solution of piperazine (1.505g) (17.47mmoles) in anhydrous THF (20ml) was added and the mixture was stirred under argon at 25°C for 69h. The mixture was poured into dichloromethane (800ml) and washed with 1N NaOH (125ml). The aqueous layer was extracted with dichloromethane (2X200ml) and the combined organic layers were dried over magnesium sulfate, filtered and evaporated to dryness. The product was chromatographed on silica gel using 5% (10% conc. NH_4OH in methanol)dichloromethane as the eluant to give the title compound (Yield: 1.2772g, 89%): FABMS: m/z 408 (MH^+); δ_C ($CDCl_3$) CH_2: 30.1, 30.4, 46.2, 46.2, 52.3, 52.3; CH: 64.6, 126.3, 130.3, 130.6, 133.6, 138.5; C: 118.0, 133.9, 134.5, 139.8, 140.8, 148.8ppm.

STEP E

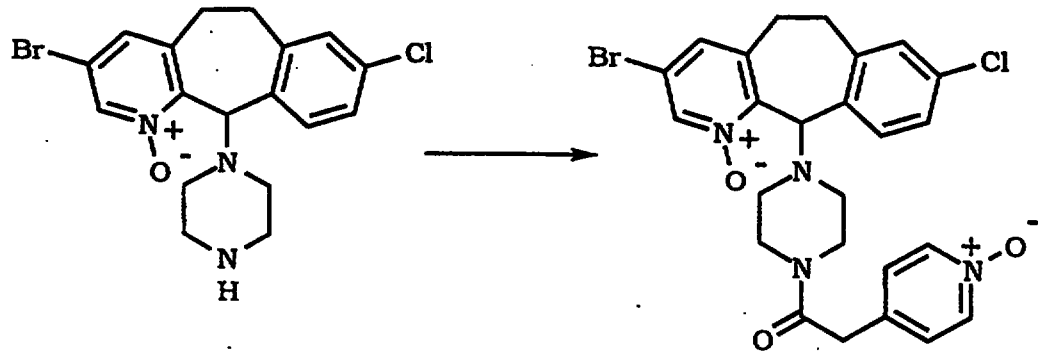


and



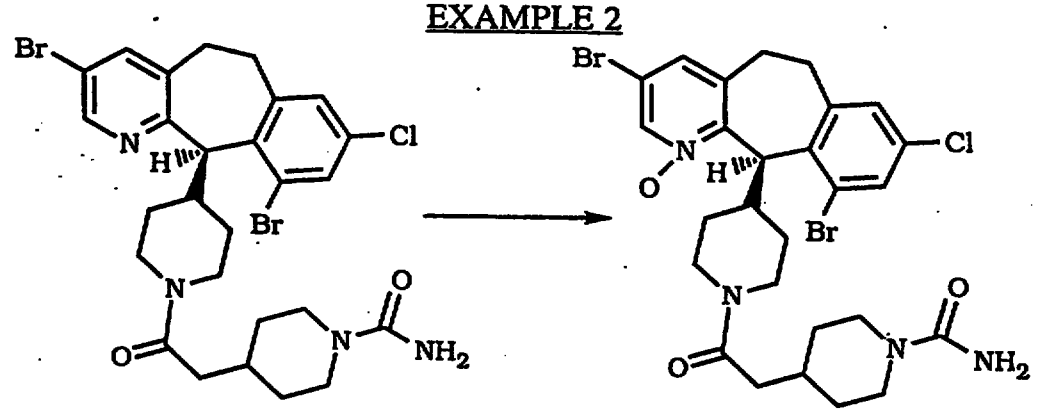
The title racemic compound from Step D above (1g) was separated on a Chiralpak AD HPLC column (5cm ID and 50cm long; particle size 20μ) using 2-propanol : hexane : diethylamine :: 30 : 70 : 0.2 stepped up to 40 : 60 ; 0.2 after passage of 2L, as the eluant to give the R(+) enantiomer as the first eluting fraction (0.486g): FABMS: m/z 408 (MH^+), δ_C ($CDCl_3$) CH_2: 30.1, 30.4, 46.3, 46.3, 52.5, 52.5; CH: 64.7, 126.2, 130.4, 130.6, 133.6, 138.5; C: 118.0, 133.9, 134.4, 139.8, 140.8, 148.9; $[\alpha]_D^{23°C}$ +90.9° (10.34mg/2mL, MeOH), followed by the S(-) enantiomer as the second eluting fraction (0.460g): FABMS: m/z 408.1 (MH^+), δ_C ($CDCl_3$) CH_2: 30.1, 30.4, 46.2, 46.2, 52.4, 52.4; CH: 64.6, 126.3, 130.4, 130.6, 133.6, 138.5; C: 118.1, 133.9, 134.4, 139.8, 140.8, 148.8; $[\alpha]_D^{23°C}$ -85.9° (8.61mg/2mL, MeOH).

EXAMPLE 1



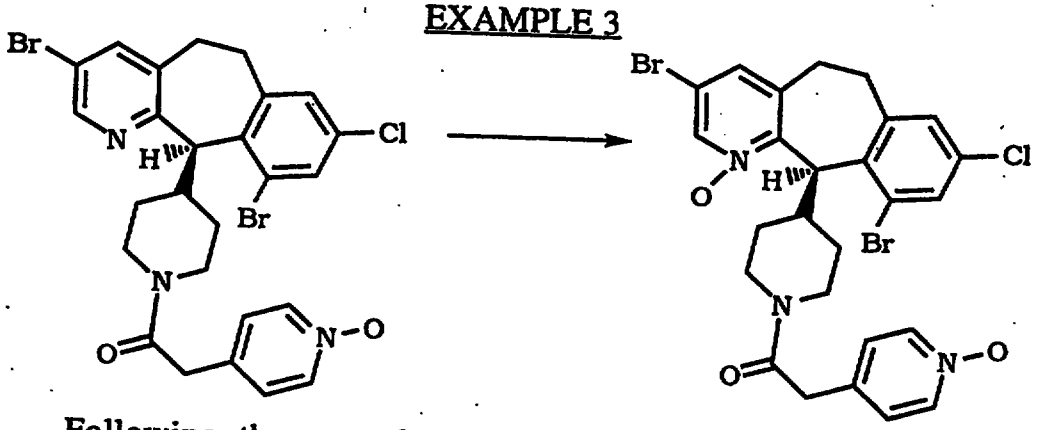
The title compound from Preparative Example 33D (0.4g) (0.979mmoles), 4-pyridylacetic acid N1-oxide (0.1948g) (1.27mmoles), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.244g) (1.27mmoles), 1-hydroxybenzotriazole (0.172g) (1.27mmoles) and 4-methylmorpholine (0.14ml) (1.27mmoles) were dissolved in anhydrous DMF (15ml) and the mixture was stirred at 25°C for 18h. The solution was poured into dichloromethane (800ml) and washed with 1N NaOH. The aqueous layer was extracted with dichloromethane (2X200ml) and the combined organic layers were evaporated to dryness. The residue was chromatographed on silica gel using 3.5% (10% conc. NH_4OH in methanol)dichloromethane as the eluant to give the title compound (Yield: 0.4806g, 90%): LSIMS: m/z 543 (MH^+); δ_C ($CDCl_3$) CH_2: 30.1, 30.5, 38.4, 42.1, 45.9, 50.4, 50.6; CH: 63.8, 126.5, 126.8, 126.8, 130.4, 130.5, 133.4, 138.4, 139.0, 139.0; C: 118.4, 133.4, 133.9, 134.8, 139.8, 141.0, 148.8, 167.0ppm. PMR data: δ_H ($CDCl_3$): 5.78 (s,1H,H_{11}), 7.14 (d,2H,Ar-H), 7.15 (s,2H,Ar-H), 7.20 (d,1H,Ar-H), 7.22 (d,1H,Ar-H), 8.16 (d,2H,Ar-H), 8.29 (s,1H,Ar-H).

EXAMPLE 2



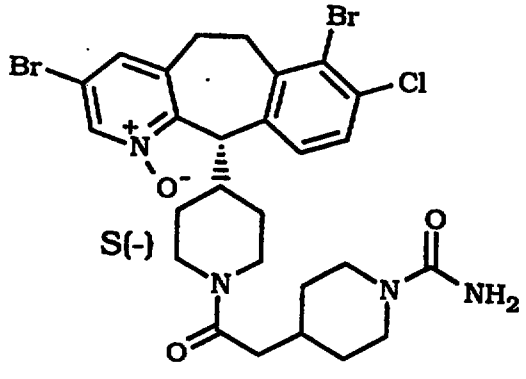
To a dichloromethane solution (50 mL) of the product of Preparative Example 21, Step C, (1.06 g, 1.65 mmol) was added meta-chloroperoxybenzoic acid (0.5 g of 57-86% purity, 1 eq). After stirring at room temperature for 5 hours, an additional 0.23 g of meta-chloroperoxybenzoic acid was added and the resulting mixture was stirred at room temperature overnight. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford a light yellow foam. Purification by flash column chromatography (silica gel) using 5% methanol-dichloromethane saturated with ammonium hydroxide provided the title compound (0.60 g, 56% yield, mp 170.5 - 175°C). $[a]_D^{21°C}$ = +116.2° (c = 0.113, methanol).

EXAMPLE 3



Following the procedure of Example 2, with the exception that the product of Preparative Example 19 was used instead of the product of Preparative Example 21, Step C, gave the product as a white solid, mp = 174.2°C.

EXAMPLE 4

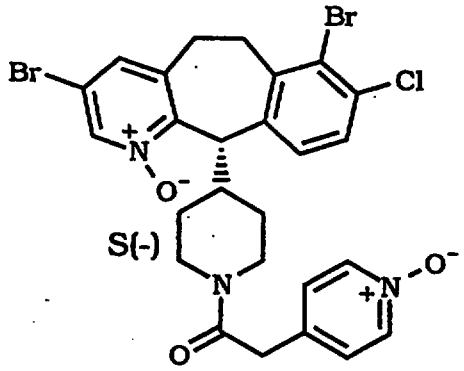


Added m-Chloroperbenzoic acid (50% 1.5g,4.36mmol) to a solution of the product from Preparative Example 23, Step C, (1.0g,1.48mmol) in methylene chloride (15ml) at 0°C, then stirred at 0°C for 5 hours, and room temperature for 3 hours. Water (50ml), ammonium hydroxide (10ml, conc) were added, and the mixture was extracted with methylene chloride (2x200ml). The organic layer was separated, dried over magnesium sulfate, filtered, and solvent evaporated yielding a solid, which chromatographed on silica gel eluting with 10% v/v methanol: methylene chloride containing 2% ammonium hydroxide yielding the title product as a white solid (700mg, 70%)$[\alpha]_D^{24.°C}$ = -68.9° (c = 0.352, ethanol).

MS (FAB, MH,653) HRMS Calc(C27H32N4O3BrCl(81)Br) 655.0509 Measured 655.0518

1H NMR(CDCL3) δ 8.31(s,1H), 7.28(s,1H), 7.19(d,1H), 7.11(d,1H), 5.37(m,1H), 4.60(d,1H), 4.42(s,2H), 3.86(m,3H), 3.41(m,3H), 2.89(m,4H), 2.42(m,1H), 2.20(m,3H), 2.04(m,1H), 1.78(m,2H), 1.66(m,1H), 1.48(m,2H), 1.16(m,3H).

EXAMPLE 5



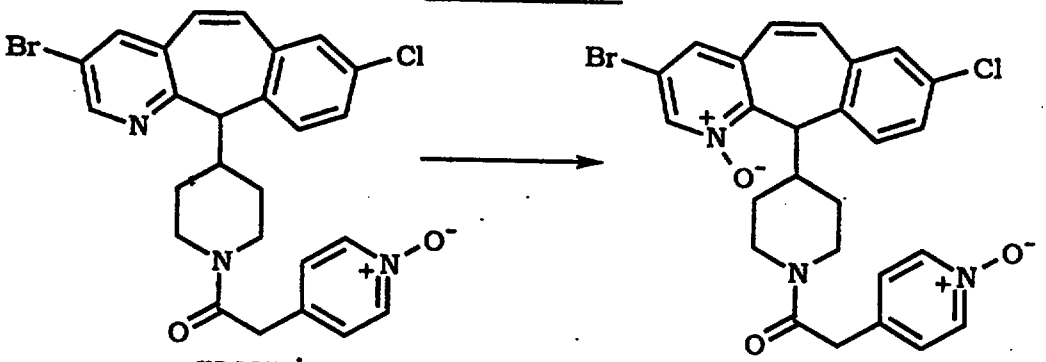
Following the same procedure as in Example 4, with the exception that an equivalent quantity of the product of Preparative Example 26A is used instead of the product from Preparative Example 23, Step C,. the title product was obtained as a white solid (73% yield). $[\alpha]_D^{24.°C}$ = -76.6° (c = 0.197, ethanol).

MS (FAB, MH 620) HRMS Calc MH C26H25N3O3BrCl(81)Br (621.9931) Measured 621.9942.

1H NMR(CDCL3)δ 8.32(s,1H), 8.22(d,2H), 7.29(s,1H), 7.19(d,1H), 7.18(d,2H), 7.10(d,1H), 5.37(m,1H), 4.58(d,1H),

,3.78(d,1H), 3.66(d,2H), 3.41(s,2H), 3.38(m,1H), 2.95(m,3H), 2.50(m,1H), 2.28(m,1H), 1.63(m,1H), 1.45(m,2H).

EXAMPLE 6



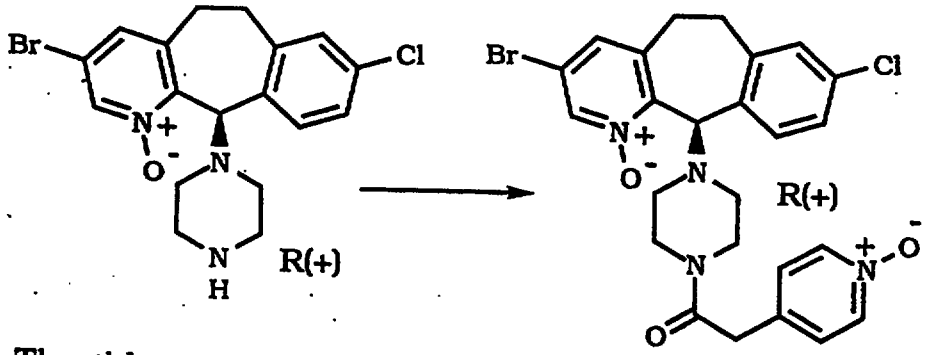
racemic racemic

Following the procedure of Preparative Example 12, except that the product of Preparative Example 3, Step D, is used instead of the compound of Preparative Example 4, the starting reactant is obtained. Following the procedure of Example 4, with the exception that the above reactant was used instead of the product from Preparative Example 23, Step C, yielded the title compound as a white solid (100%).

MS (FAB,MH 540) HRMS Calc MH C26H24N3O3BrCl (540.0690), Measured (540.0691)

1H NMR(CDCL3)δ 8.45(s,1H), 8.14(d,2H), 7.26-7.34(m,3H), 7.11(d,2H), 7.03,d1H), 6.73(d,1H), 5.55(d,1H), 4.40(m,1H), 3.70(m,2H), 3.59(s,2H), 2.85(m,1H), 2.45(m,1H), 2.15(m,1H), 1.35(m,1H), 1.15(m,3H).

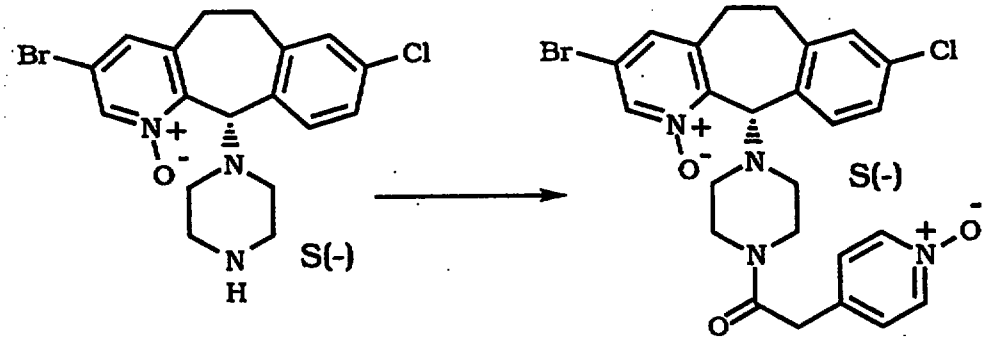
EXAMPLE 7



The title compound from Preparative Example 33, Step E, R(+) enantiomer (360.4mg, 0.882mmoles), 4-pyridylacetic acid N1-oxide (175.5mg, 1.146mmoles), 1-(3-dimethylaminopropyl)-

3-ethylcarbodiimide hydrochloride (220mg, 1.146mmoles), 1-hydroxybenzotriazole (155mg, 1.146mmoles) and 4-methylmorpholine (0.126mL, 1.146mmoles) were dissolved in anhydrous DMF 11mL) and the mixture was stirred at 25°C for 18h. The reaction was worked up as described in Example 1 and the product was chromatographed on silica gel using 4% (10% conc. NH_4OH in methanol)dichloromethane as the eluant to give the title compound (Yield: 441.1mg, 92%): LCMS: m/z 543.1 (MH^+); δ_C ($CDCl_3$) CH_2: 30.1, 30.6, 38.5, 42.1, 46.0, 50.5, 50.9; CH: 63.9, 126.5, 126.9, 126.9, 130.5, 130.6, 133.5, 138.5, 139.0, 139.0,: C: 118.4, 134.0, 134.0, 134.9, 139.9, 141.0, 147.8, 167.1; δ_H ($CDCl_3$): 5.74 (s,1H,H_{11}), 7.12 (d,2H,Ar-H), 7.13 (s,2H,Ar-H), 7.19 (d,1H,Ar-H), 7.21 (d,1H,Ar-H), 8.14 (d,2H,Ar-H), 8.27 (s,1H,Ar-H); $[\alpha]_D^{23°C}$ +69.2° (10mg/2mL, MeOH).

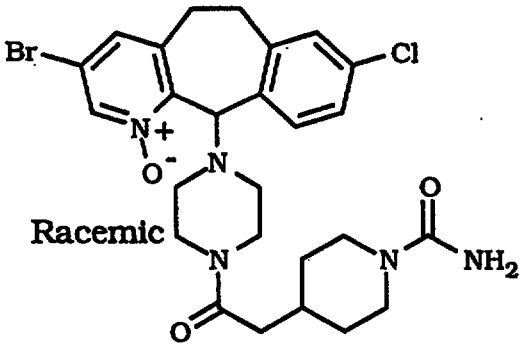
EXAMPLE 8



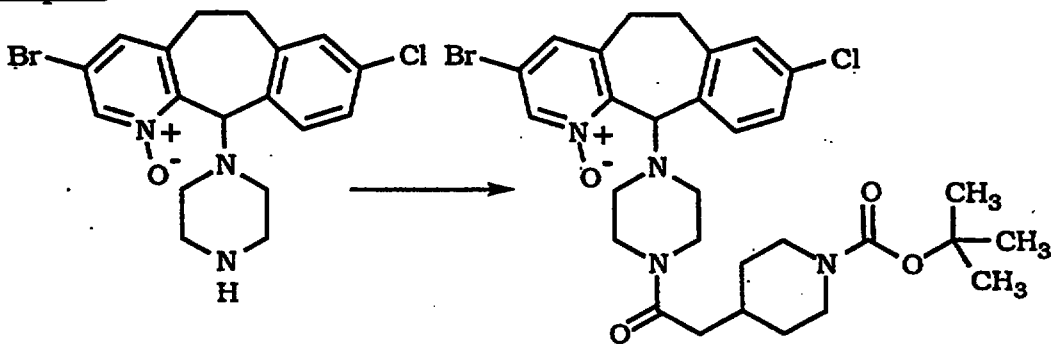
The title compound from Preparative Example 33, Step E, S(-) enantiomer (374.8mg, 0.917mmoles), 4-pyridylacetic acid N1-oxide (182.6mg, 1.192mmoles), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (229mg, 1.192mmoles), 1-hydroxybenzotriazole (161mg, 1.192mmoles) and 4-methylmorpholine (0.131mL, 1.192mmoles) were dissolved in anhydrous DMF (11mL) and the mixture was stirred at 25°C for 18h. The reaction was worked up as described in Example 1 and the product was chromatographed on silica gel using 4% (10% conc. NH_4OH in methanol)dichloromethane as the eluant to give the title compound (Yield: 467.3mg, 94%): LCMS: m/z 543.1 (MH^+); δ_C ($CDCl_3$) CH_2: 30.0, 30.5, 38.4, 42.0, 45.9, 50.4, 50.8; CH: 63.8, 126.5, 126.8, 126.8, 130.4, 130.6, 133.4, 138.4, 138.9, 138.9,: C: 118.4, 134.0, 134.0, 134.8, 139.8, 140.9, 147.7, 167.0;

δ_H ($CDCl_3$): 5.76 (s,1H,H_{11}), 7.13 (d,2H,Ar-H), 7.15 (s,2H,Ar-H), 7.21 (d,1H,Ar-H), 7.23 (d,1H,Ar-H), 8.16 (d,2H,Ar-H), 8.29 (s,1H,Ar-H); $[\alpha]_D^{23.4°C}$ -65.5° (10.4mg/2mL, MeOH).

EXAMPLE 9

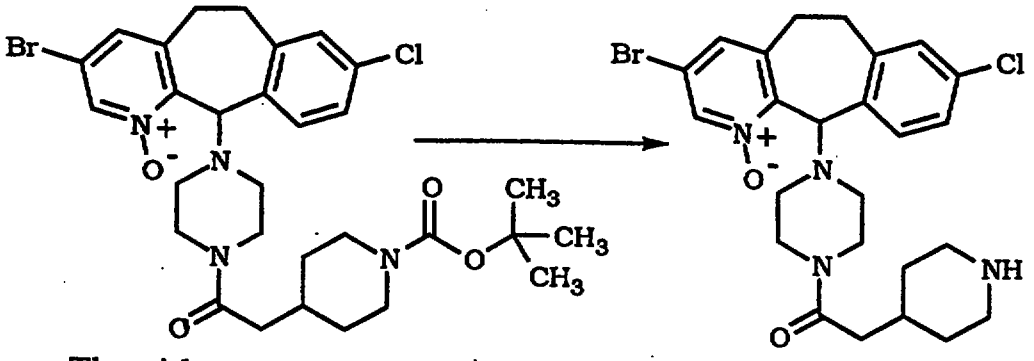


Step A



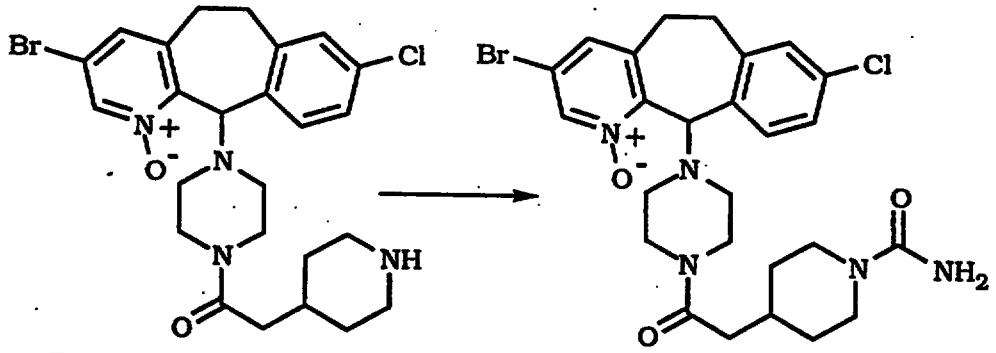
The title compound from Preparative Example 33, Step D, (±) (789.1mg, 1.93mmoles), 1-tert-butoxycarbonyl-4-piperidinylacetic acid (610.6mg, 2.51mmoles), 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (481.2mg, 2.51mmoles), 1-hydroxybenzotriazole (339.2mg, 2.51mmoles) and 4-methylmorpholine (0.276mL, 2.51mmoles) were dissolved in anhydrous DMF (30mL) and the mixture was stirred at 25°C for 21h. The reaction was worked up as described in Example 1 and the product was chromatographed on silica gel using 0.5%-1% (10% conc. NH_4OH in methanol)dichloromethane as the eluant to give the title compound (Yield: 1.22g, 100%): FABMS: m/z 633.3 (MH^+); δ_C ($CDCl_3$) CH_3: 28.5, 28.5, 28.5; CH_2: 30.2, 30.5, 32.2, 32.2, 39.5, 41.7, 43.8, 43.8, 45.8, 50.8, 51.2; CH: 33.3, 64.0, 126.5, 130.6, 130.6, 133.5, 138.5; C: 79.3, 118.3, 133.6, 134.8, 139.9, 140.9, 148.1, 154.8, 170.0; δ_H ($CDCl_3$): 1.46 (s,9H,-CMe_3), 5.75 (s,1H,H_{11}), 7.13 (d,1H,Ar-H), 7.16 (s,1H,Ar-H), 7.19 (s,1H,Ar-H), 7.23 (d,1H,Ar-H), 8.29 (s,1H,Ar-H).

Step B



The title compound from Step A above (1.21g, 1.91mmoles) was dissolved in methanol (10.6mL) and 10% (v/v) conc. H_2SO_4 in dioxane (26mL) and the mixture was stirred under argon at 25°C for 1.5h. The solution was concentrated and diluted with CH_2Cl_2 and basified with 1N aqueous NaOH. The CH_2Cl_2 extract, containing only part of the product due to its water solubility, was dried ($MgSO_4$), filtered and evaporated to dryness. The product was chromatographed on silica gel using 10% (10% conc NH_4OH in MeOH)dichloromethane as the eluant to give the title compound (Yield: 87.7mg, 10%): FABMS: m/z 533.1 (MH^+), δ_C ($CDCl_3$): CH_2: 30.2, 30.4, 32.4, 32.4, 39.6, 41.6, 45.7, 45.9, 45.9, 50.7, 51.2; CH: 32.7, 64.0, 126.5, 130.6, 130.6, 133.5, 138.5; C: 118.3, 133.5, 134.7, 139.9, 140.9, 148.1, 169.8; δ_H ($CDCl_3$): 5.73 (s,1H,H_{11}), 7.12 (d,1H,Ar-H), 7.15 (s,1H,Ar-H), 7.18 (s,1H,Ar-H), 7.21 (d,1H,Ar-H), 8.28 (s,1H,Ar-H).

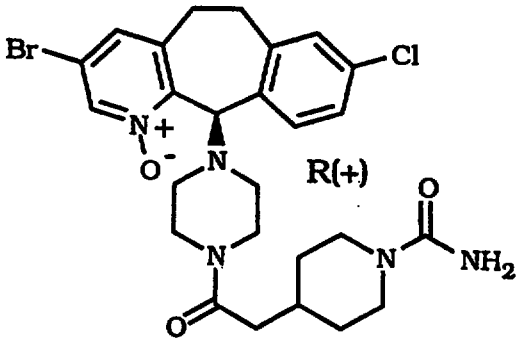
Step C



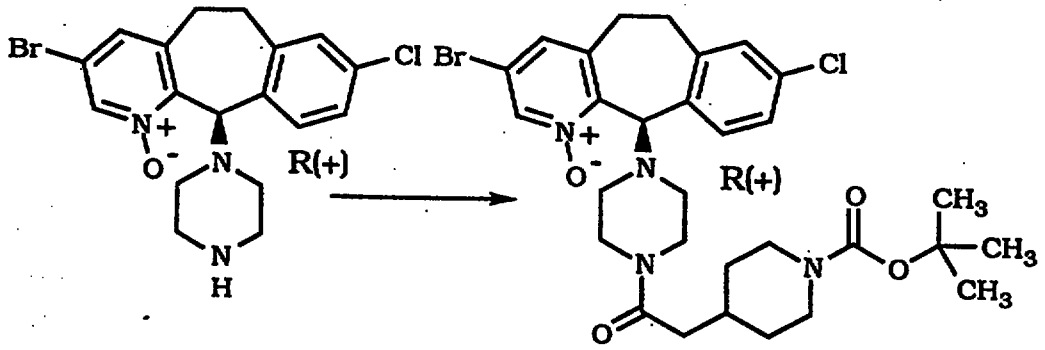
The title compound from Step B above (99.1mg, 0.189mmoles) and trimethylsilyl isocyanate (0.384mL, 2.83mmoles) were dissolved in anhydrous dichloromethane (3mL) and the mixture was stirred at 25°C under argon for 20h. Additional trimethylsilyl isocyanate (0.0768mL, 0.567mmoles)

was added and the reaction was allowed to proceed for an additional 5h. The mixture was diluted with dichloromethane and washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and evaporated to dryness. The product was chromatographed on silica gel using 3.5% (10% conc. NH_4OH in methanol)dichloromethane as the eluant to give the title compound (Yield: 80.4mg, 81%): FABMS: m/z 576.1 (MH^+); δ_C ($CDCl_3$): CH_2: 30.1, 30.4, 32.0, 32.0, 39.2, 41.6, 44.4, 44.3, 45.7, 50.7, 51.1; CH: 32.9, 63.9, 126.4, 130.5, 130.6, 133.4, 138.4; C: 118.3, 133.5, 134.7, 139.8, 140.9, 148.0, 169.7; δ_H ($CDCl_3$): 5.74 (s,1H,H_{11}), 7.12 (d,1H,Ar-H), 7.15 (s,1H,Ar-H), 7.19 (s,1H,Ar-H), 7.22 (d,1H,Ar-H), 8.28 (s,1H,Ar-H).

EXAMPLE 10



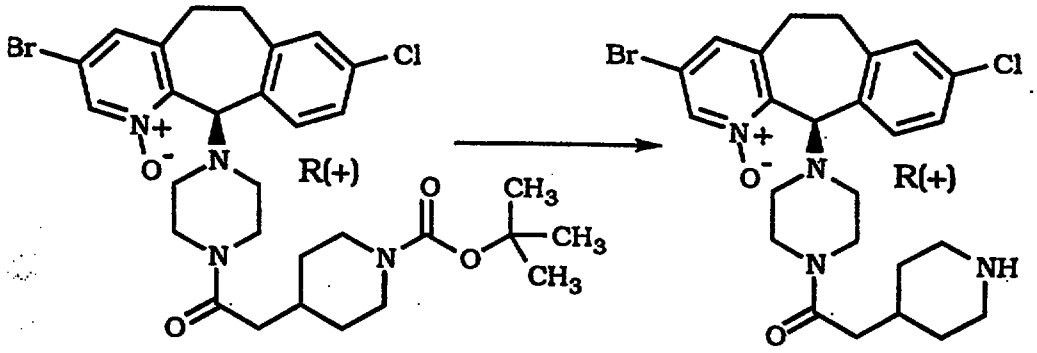
Step A



The title compound from Preparative Example 33, Step E, R(+) enantiomer (1g, 2.45mmoles), 1-tert-butoxycarbonyl-4-piperidinylacetic acid (487mg, 3.181mmoles), 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (610mg, 3.181mmoles), 1-hydroxybenzotriazole (430mg, 3.181mmoles) and 4-methylmorpholine (0.35mL, 3.181mmoles) were dissolved in anhydrous DMF (30.5mL) and the mixture was stirred at 25°C for 66h. The reaction was worked up as

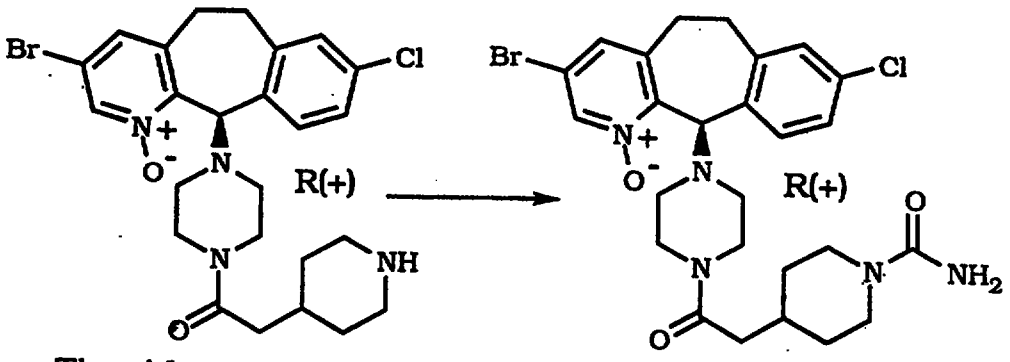
described in Example 1 and the product was chromatographed on silica gel using 1% (10% conc. NH_4OH in methanol)dichloromethane as the eluant to give the title compound (Yield: 1.25g, 81%): LCMS: m/z 633.1 (MH^+); δ_C ($CDCl_3$) CH_3: 28.5, 28.5, 28.5; CH_2: 30.2, 30.5, 32.2, 32.2, 39.4, 41.7, 43.6, 43.6, 45.8, 50.7, 51.2; CH: 33.3, 64.0, 126.5, 130.6, 130.6, 133.5, 138.5; C: 79.3, 118.3, 133.6, 134.8, 139.9, 140.9, 148.1, 154.9, 170.0; δ_H ($CDCl_3$): 1.46 (s,9H,-CMe_3), 5.74 (s,1H,H_{11}), 7.12 (d,1H,Ar-H), 7.16 (s,1H,Ar-H), 7.19 (s,1H,Ar-H), 7.23 (d,1H,Ar-H), 8.29 (s,1H,Ar-H); $[\alpha]_D^{23.4°C}$ +56.4° (9.05mg/2mL, MeOH).

Step B



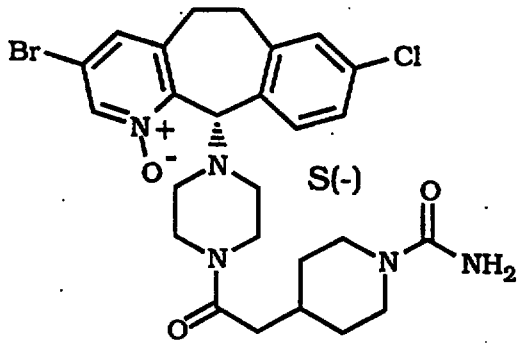
The title compound from Step A above (1.149g, 1.812mmoles) was dissolved in methanol (9.5mL) and 10% (v/v) conc. H_2SO_4 in dioxane (24.7mL) and the mixture was stirred under argon at 25°C for 1h. The mixture was passed over a bed of BioRad AG1-X8(OH^- form) ion exchange resin and the resin was washed with methanol. The combined eluates were evaporated to dryness and the product was chromatographed on silica gel using 10% (10% conc NH_4OH in MeOH)dichloromethane as the eluant to give the title compound (Yield: 762.9mg, 79%): LSIMS: m/z 533 (MH^+), δ_C ($CDCl_3$): CH_2: 30.2, 30.5, 33.2, 33.2, 40.1, 41.7, 45.9, 46.4, 46.4, 50.8, 51.2; CH: 33.4, 64.0, 126.5, 130.6, 130.6, 133.6, 138.6; C: 118.4, 133.6, 134.8, 139.9, 140.9, 148.2, 170.2; δ_H ($CDCl_3$): 5.73 (s,1H,H_{11}), 7.11 (d,1H,Ar-H), 7.14 (s,1H,Ar-H), 7.19 (s,1H,Ar-H), 7.22 (d,1H,Ar-H), 8.28 (s,1H,Ar-H; $[\alpha]_D^{23.2°C}$ +66.4° (10.90mg/2mL, MeOH).

Step C

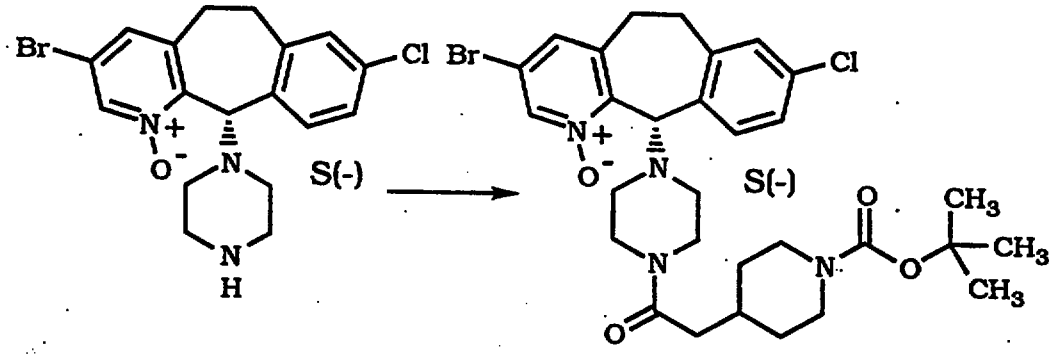


The title compound from Step B above (550mg, 1.03mmoles) and trimethylsilyl isocyanate (2.092mL, 15.45mmoles) were dissolved in anhydrous dichloromethane (16.4mL) and the mixture was stirred at 25°C under argon for 18h. The mixture was diluted with dichloromethane and washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and evaporated to dryness. The product was chromatographed on silica gel using 3.5% (10% conc. NH_4OH in methanol)dichloromethane as the eluant to give the title compound (Yield: 570.3mg, 99%): FABMS: m/z 576.3 (MH^+); δ_C ($CDCl_3$): CH_2: 30.2, 30.5, 32.1, 32.1, 39.3, 41.7, 44.4, 44.5, 45.8, 50.8, 51.2; CH: 33.0, 64.0, 126.5, 130.6, 130.6, 133.5, 138.6; C: 118.4, 133.5, 134.8, 139.9, 141.0, 148.1, 157.9, 169.8; δ_H ($CDCl_3$): 5.73 (s,1H,H_{11}), 7.12 (d,1H,Ar-H), 7.14 (s,1H,Ar-H), 7.19 (s,1H,Ar-H), 7.21 (d,1H,Ar-H), 8.28 (s,1H,Ar-H); $[\alpha]_D^{23.4°C}$ +60.2° (10.28mg/2mL, MeOH).

EXAMPLE 11

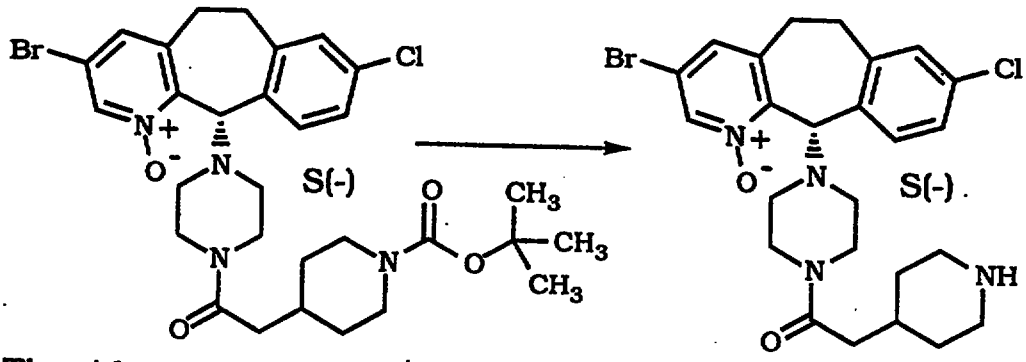


Step A



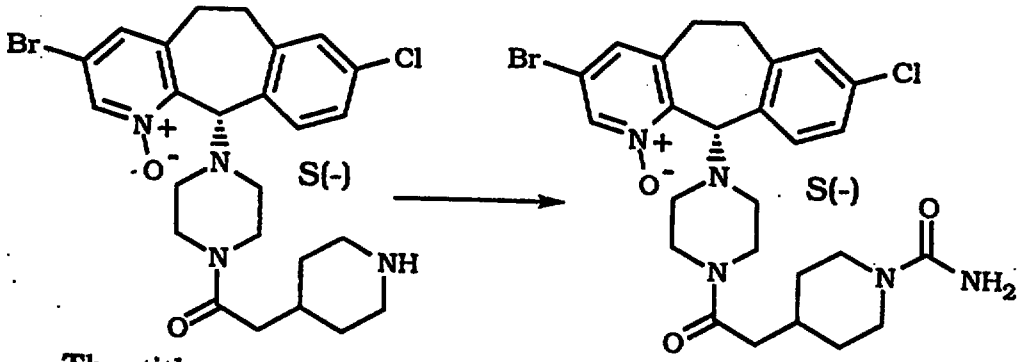
The title compound from Preparative Example 33, Step E, S(-) enantiomer (1g, 2.45mmoles), 1-tert-butoxycarbonyl-4-piperidinylacetic acid (487mg, 3.181mmoles), 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (610mg, 3.181mmoles), 1-hydroxybenzotriazole (430mg, 3.181mmoles) and 4-methylmorpholine (0.35mL, 3.181mmoles) were dissolved in anhydrous DMF (30.5mL) and the mixture was stirred at 25°C for 66h. The reaction was worked up as described in Example 1 and the product was chromatographed on silica gel using 1% (10% conc. NH_4OH in methanol)dichloro-methane as the eluant to give the title compound (Yield: 1.204g, 78%): LSIMS: m/z 633.5 (MH^+); δ_C ($CDCl_3$) CH_3: 28.5, 28.5, 28.5; CH_2: 30.2, 30.5, 32.2, 32.2, 39.4, 41.7, 43.6, 43.6, 45.8, 50.7, 51.2; CH: 33.3, 64.0, 126.5, 130.5, 130.5, 133.6, 138.5; C: 79.3, 118.3, 133.6, 134.8, 139.9, 140.9, 148.1, 154.8, 170.0; δ_H ($CDCl_3$): 1.46 (s,9H,-CMe_3), 5.74 (s,1H,H_{11}), 7.12 (d,1H,Ar-H), 7.15 (s,1H,Ar-H), 7.19 (s,1H,Ar-H), 7.22 (d,1H,Ar-H), 8.28 (s,1H,Ar-H); $[\alpha]_D^{23.7°C}$ -57.2° (9.09mg/2mL, MeOH).

Step B



The title compound from Step A above (1.104g, 1.741mmoles) was dissolved in methanol (9.13mL) and 10% (v/v) conc. H_2SO_4 in dioxane (23.75mL) and the mixture was stirred under argon at 25°C for 1h. The mixture was passed over a bed of BioRad AG1-X8(OH^- form) ion exchange resin and the resin was washed with methanol. The combined eluates were evaporated to dryness and the product was chromatographed on silica gel using 10% (10% conc NH_4OH in MeOH)dichloromethane as the eluant to give the title compound (Yield: 771.6mg, 83%): LSIMS: m/z 533 (MH^+), δ_C ($CDCl_3$): CH_2: 30.3, 30.5, 33.0, 33.0, 40.0, 41.7, 45.8, 46.2, 46.2, 50.8, 51.2; CH: 33.3, 64.0, 126.5, 130.6, 130.6, 133.6, 138.6; C: 118.4, 133.6, 134.8, 139.9, 140.9, 148.2, 170.1; δ_H ($CDCl_3$): 5.73 (s,1H,H_{11}), 7.12 (d,1H,Ar-H), 7.14 (s,1H,Ar-H), 7.19 (s,1H,Ar-H), 7.22 (d,1H,Ar-H), 8.28 (s,1H,Ar-H); $[\alpha]_D^{23.1°C}$ -66.9° (10.29mg/2mL, MeOH).

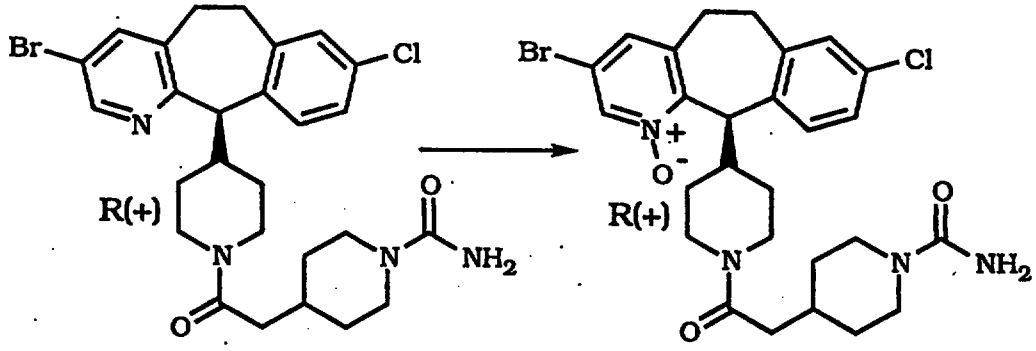
Step C



The title compound from Step B above (550mg, 1.03mmoles) and trimethylsilyl isocyanate (2.092mL, 15.45mmoles) were dissolved in anhydrous dichloromethane (16.4mL) and the mixture was stirred at 25°C under argon for 18h. The mixture was diluted with dichloromethane and

washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and evaporated to dryness. The product was chromatographed on silica gel using 3.5% (10% conc. NH_4OH in methanol)dichloromethane as the eluant to give the title compound (Yield: 571.5mg, 99%): FABMS: m/z 576.3 (MH^+); δ_C ($CDCl_3$): CH_2: 30.2, 30.5, 32.0, 32.0, 39.3, 41.7, 44.4, 44.5, 45.7, 50.7, 51.2; CH: 33.0, 64.0, 126.5, 130.6, 130.6, 133.5, 138.5; C: 118.4, 133.6, 134.8, 139.9, 141.0, 148.1, 157.9, 169.8; δ_H ($CDCl_3$): 5.73 (s,1H,H_{11}), 7.12 (d,1H,Ar-H), 7.15 (s,1H,Ar-H), 7.20 (s,1H,Ar-H), 7.22 (d,1H,Ar-H), 8.28 (s,1H,Ar-H); $[\alpha]_D^{23.1°C}$ -62.5° (9.54mg/2mL, MeOH).

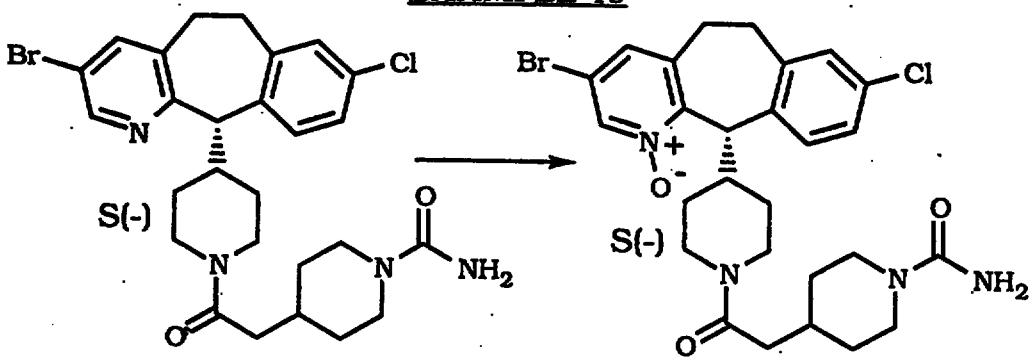
EXAMPLE 12



The starting reactant (0.1g, 0.18mmol), was disssolved in CH_2Cl_2 (5mL) and then cooled to -18°C. m-Chloroperoxybenzoic acid (0.18g, 1.07mmol) was then added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between CH_2Cl_2 and saturated $NaHCO_3$ (aqueous). The aqueous phase was extracted further with CH_2Cl_2. Combined CH_2Cl_2 fractions were dried over $MgSO_4$ and concentrated in vacuo to give a residue that was chromatographed on a silica plate eluting with 10% MeOH (saturated NH_3)-CH_2Cl_2 eluent to give the title compound as a white solid (0.013g, 13% yield, mp = 146.8-147.4°C, MH^+ = 577).

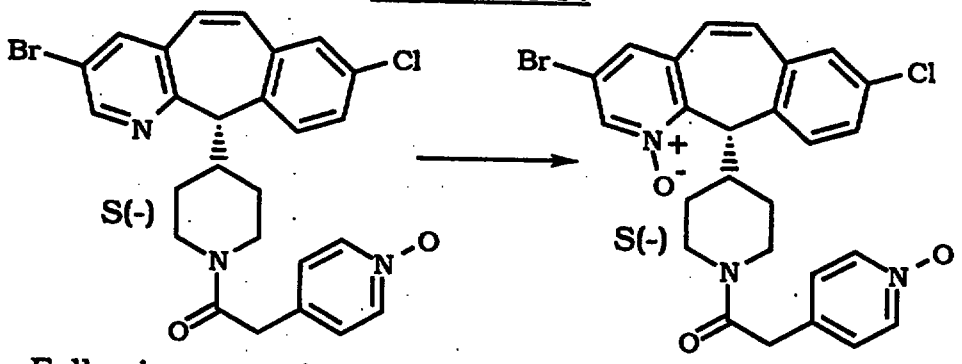
The starting reactant is obtained by the procedure of Preparative Example 14, and the chiral chromatography separation procerdures described above.

EXAMPLE 13



The title compound was prepared by essentially the same procedure as described in Example 12 (mp = 120-121°C, MH^+ = 577).

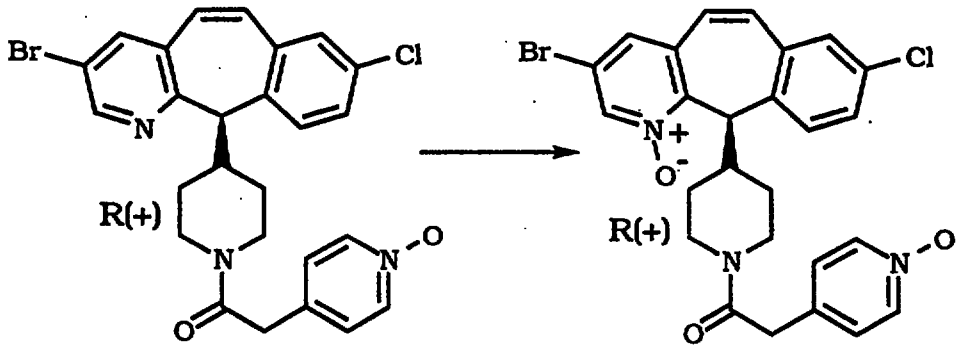
EXAMPLE 14



Following essentially the same oxidation procedure as in Example 12, the starting reactant is oxidized with m-chloro-peroxybenzoic acid to yield the title compound (mp = 109-110°C, MH^+ = 542).

The starting reactant is obtained by reacting the S(-) isomer of the title compound of Preparative Example 3 with title compound of Preparative Example 1 by essentially the same procedure as described in Preparative Example 12. The S(-) isomer of the racemate of Preparative Example 3 is obtained by the chiral chromatography separation procerdures described above.

EXAMPLE 15



The title compound was prepared by essentially the same procedure as described in Example 14 (mp = 125.5-126.3°C, MH^+ = 542).

ASSAYS

FPT IC_{50} (inhibition of farnesyl protein transferase, in vitro enzyme assay) was 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), COS Cell IC_{50} (Cell-Based 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 can be suspended in growth medium containing 0.3% agarose and an indicated concentration of a farnesyl transferase inhibitor. The solution can be 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 can be incubated for 10-16 days at 37°C under 5% CO_2 to allow colony outgrowth. After incubation, the colonies can be 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.

FPT pM IC_{50} Assay:

The enzymatic reaction is performed in 50 mM Tris, 5 µM $ZnCl_2$, 5 mM $MgCl_2$, 0.01 % Triton X-100, 5 mM dithiolthreitol (DTT), pH 7.7 (Buffer R) at 37° C for 1 hour. The purified human FPT (> 95 % pure) was derived from a Baculovirus/Sf-9 expression system. The peptide substrate used was biotin-CVLS (SynPep Corp., Dublin, CA) and (1-^{3}H)-FPP (21.5 Ci/mmol) was obtained from New England Nuclear Life Science Products (Boston, MA). Compounds were initially dissolved to a final concentration of 4 mg/ml in 100 % DMSO and then to 0.25 µg/ml in 100 % DMSO. Subsequent dilutions of the compound were performed in Buffer R.

The enzymatic reaction is performed in a final volume of 100 µl. Reactions are carried out in a 96 well plate format. The final concentrations of human FPT, FPP and biotin-CVLS are 30 pM, 176 nM and 100 nM, respectively, in a volume of 100 µl. A typical reaction involves the prequilibration of FPT and FPP in 40 µl at room temperature for 15 minutes followed by the addition of 40 µl of a solution containing test compound. This is further equilibrated for 15 minutes at room temperature. The enzymatic reaction is initiated by adding 20 µl of the biotin-CVLS peptide substrate and allowed to proceed at 37° C for 1 hour. The reaction is stopped using 150 µl of the Stop Solution consisting of 1.3 mg/ml scintillation beads (strepavidin-coated scintillation proximity beads from Amersham (Arlington Heights, IL), 250 mM EDTA, pH 8.0 and 0.5 % BSA. The radioactivity is measured after 20 minutes at room temperature.

Compounds are evaluated for their ability to inhibit the reaction by measuring the concentration-dependent percent inhibition of the reaction. Compound stocks at 0.25 µg/ml (DMSO) were diluted into Buffer R and then into the reaction mixture as described above to give a final concentration of 0.01, 0.003, 0.001, 0.0003, 0.0001 and 0.00003 µg/ml in the reaction

mixture. The enzymatic activity was recorded by measuring the CPM/well using a Wallac 1204 Betaplate BS liquid scintillation counter. Control experiments were performed without inhibitors to provide a CPM value for the non-inhibited reaction. In addition, reactions were performed without biotin-CVLS to provide a signal for background CPM values. After correcting the signals for background the percent inhibition would be calculated for each inhibitor concentration and an IC_{50} value would be interpolated from a least squares analysis of the data within the linear region of inhibition.

The compounds of Examples 1-15 and Compound 54.0 had an FPT IC_{50} within the range of 0.7nM to >174nM.

The compound of Example 7 had an FPT pM IC_{50} of 0.44nM and the compound of Example 10 had an FPT pM IC_{50} of 0.41nM.

The compounds of Examples 2, 3 and 7 had a COS Cell IC_{50} within the range of 9nM to 85nM, and a Soft Agar IC_{50} within the range of 25nM to 183nM.

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

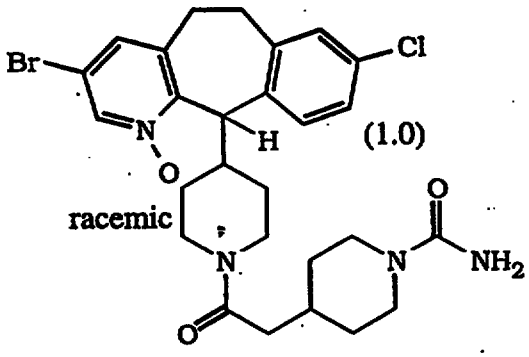
Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

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.

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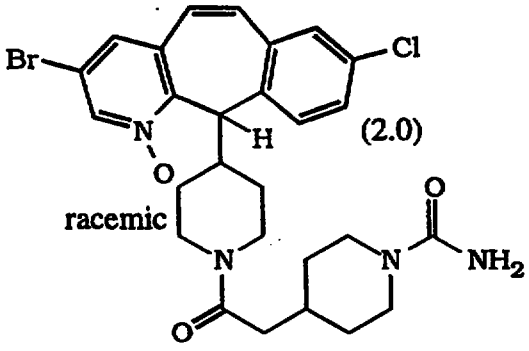
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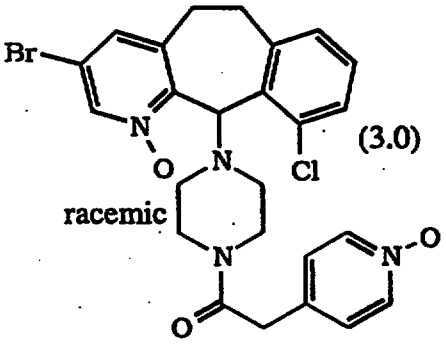
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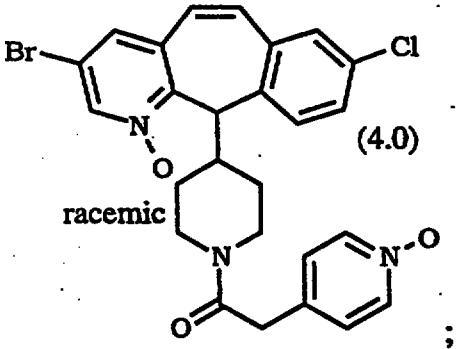
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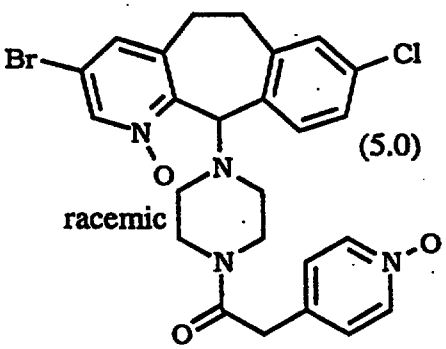
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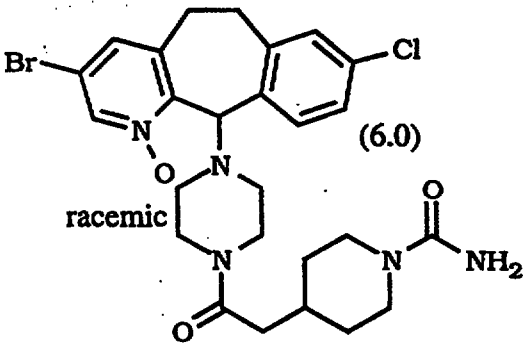
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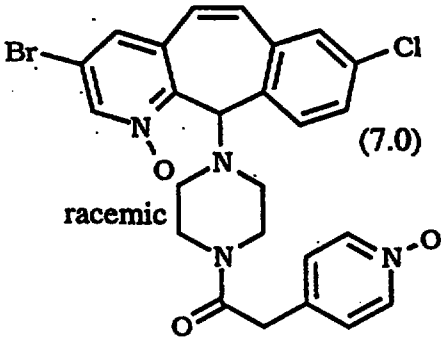
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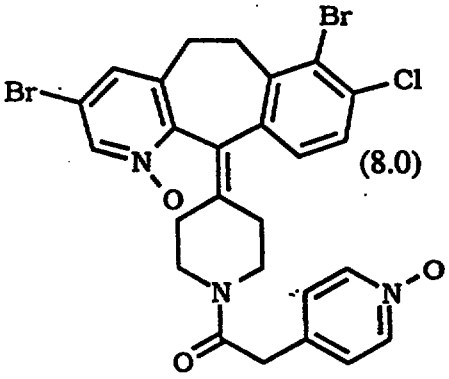
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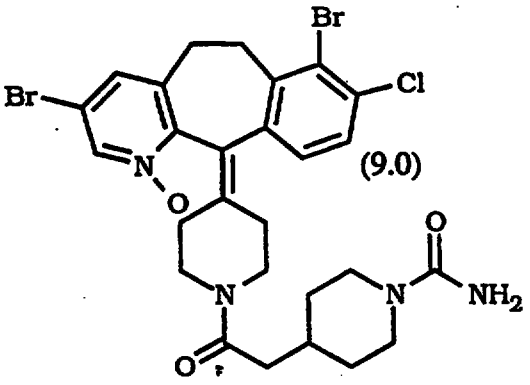


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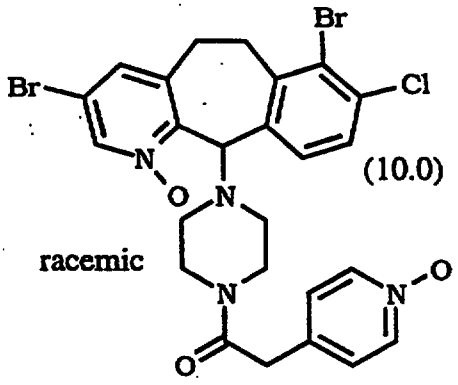
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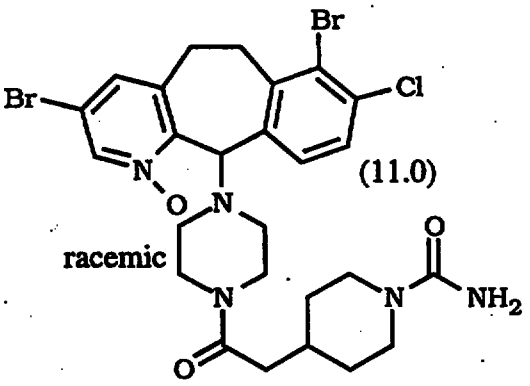

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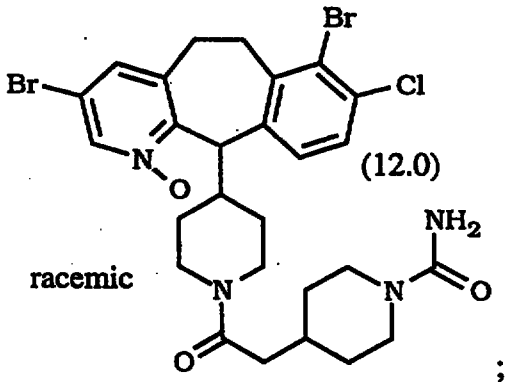
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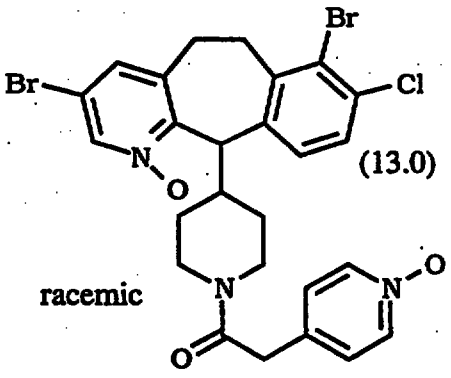
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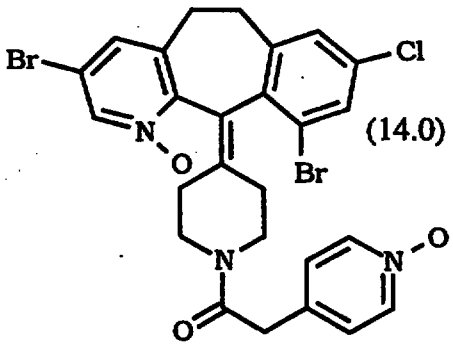
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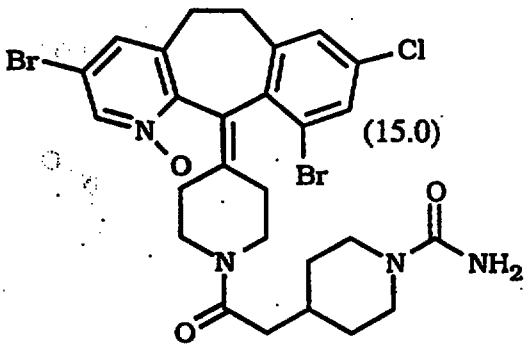

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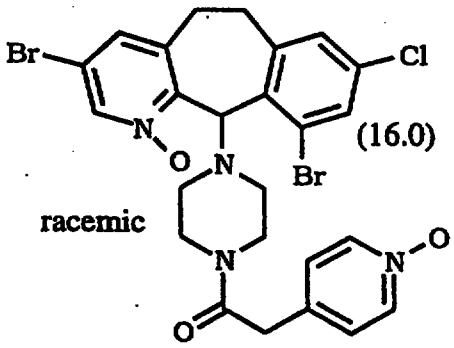
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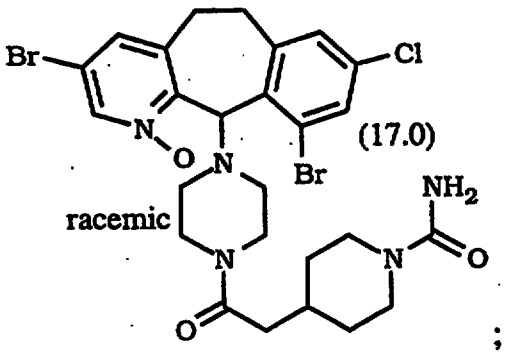

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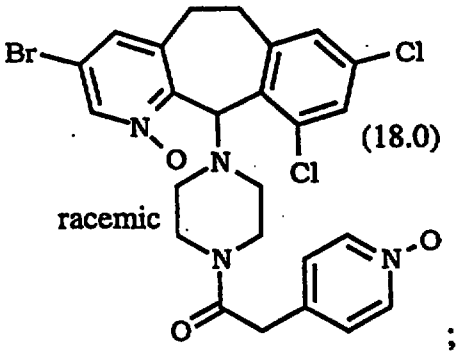
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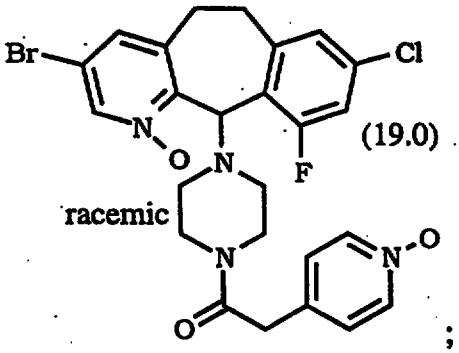
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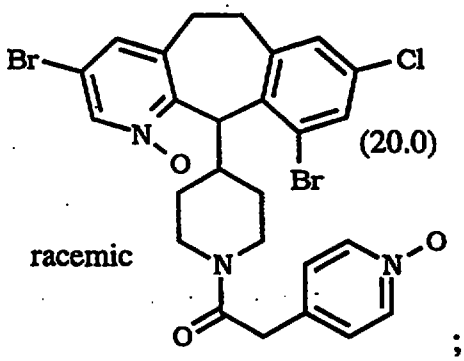
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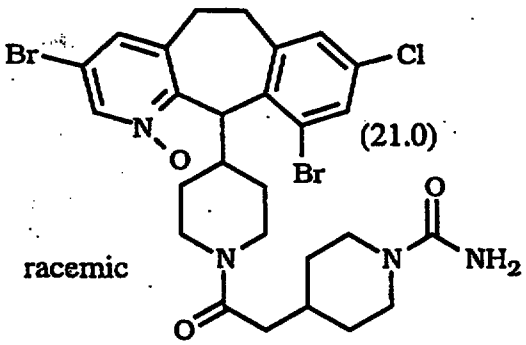
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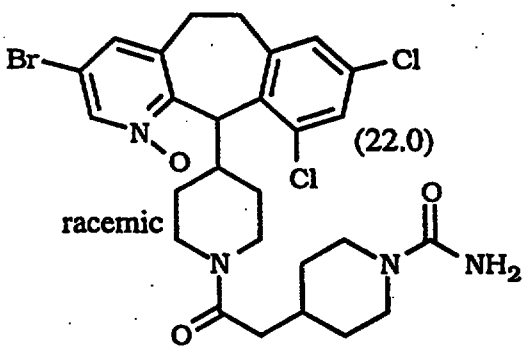
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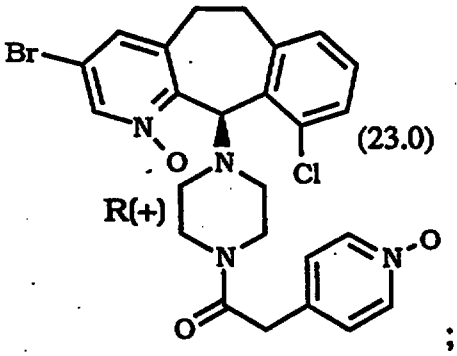
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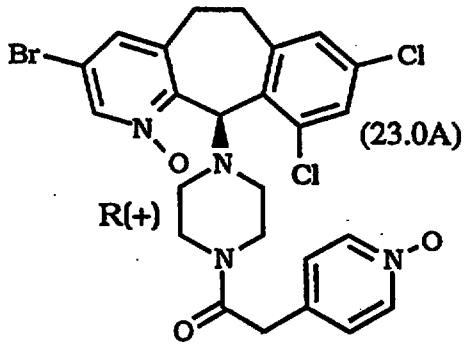
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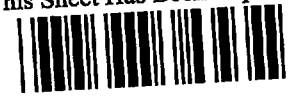


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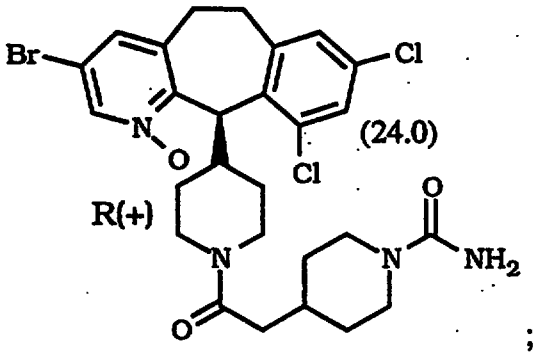
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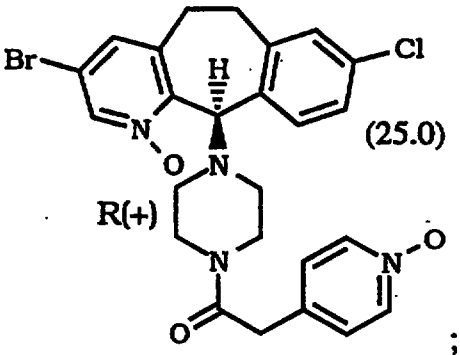




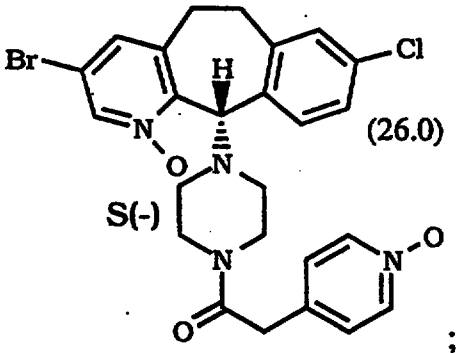
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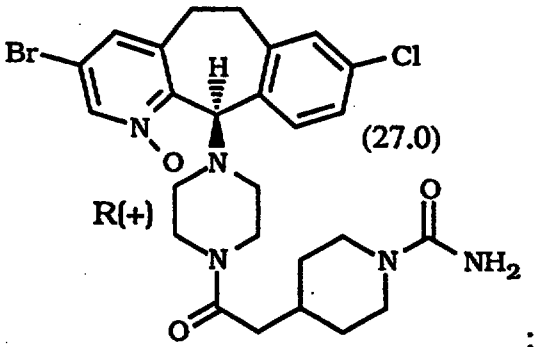
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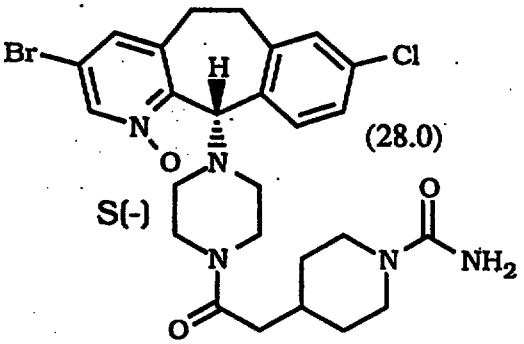
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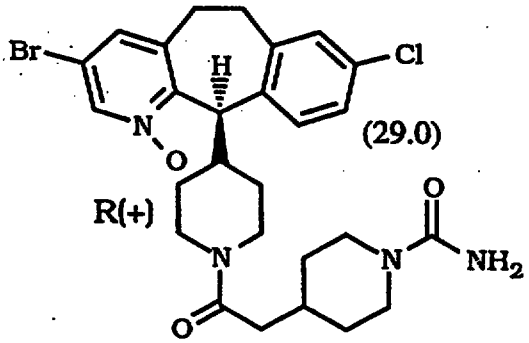
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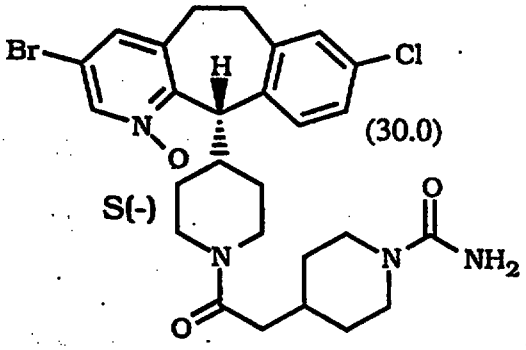
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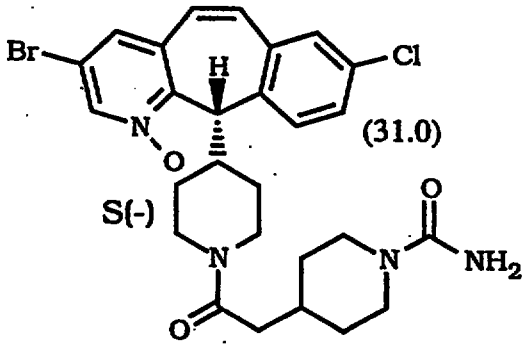
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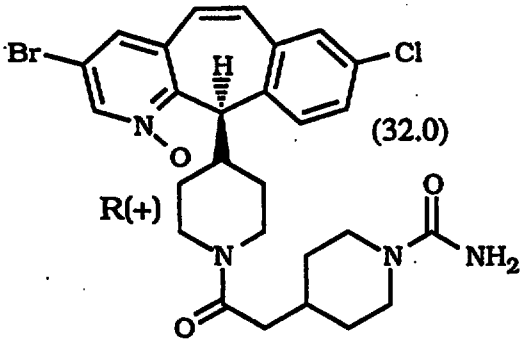
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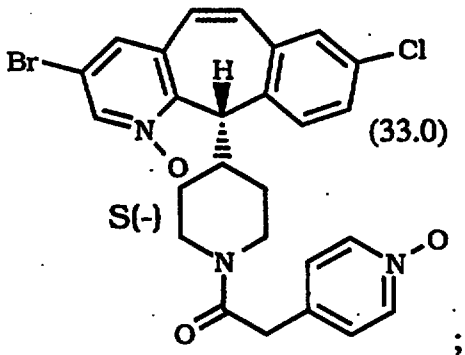




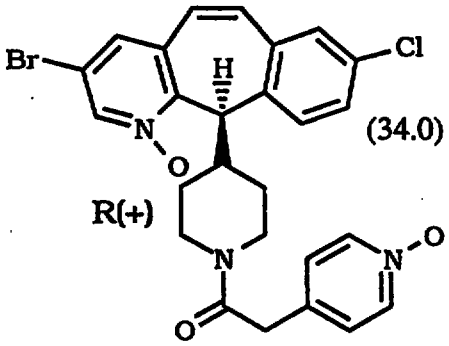
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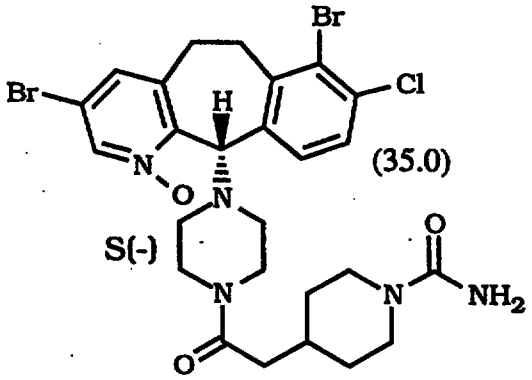
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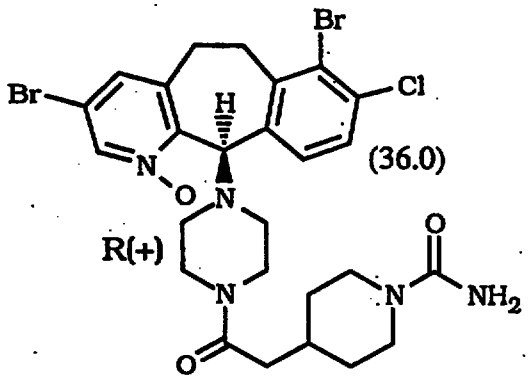
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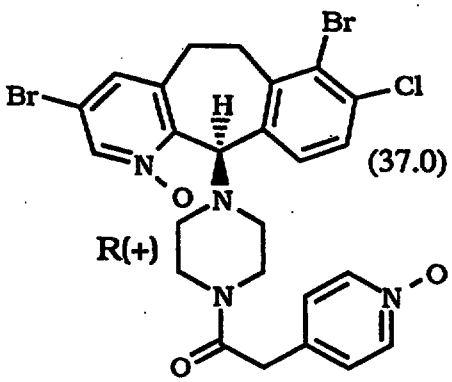
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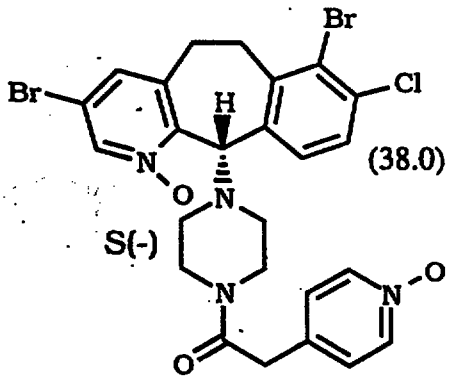
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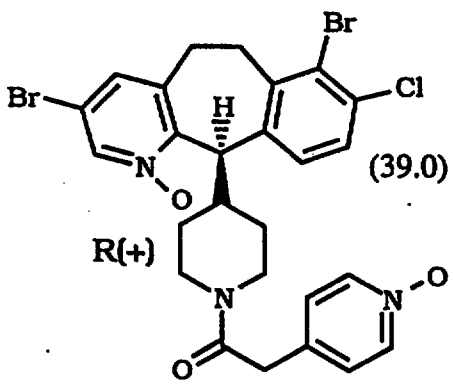
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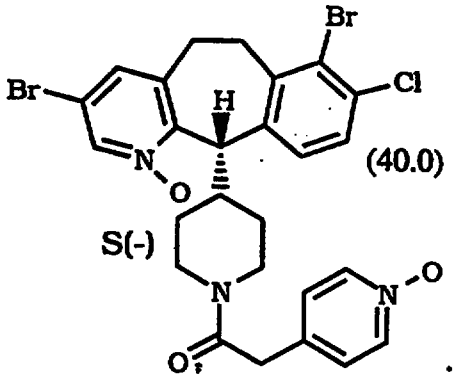
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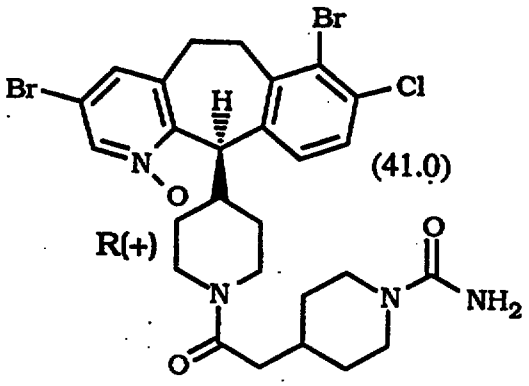
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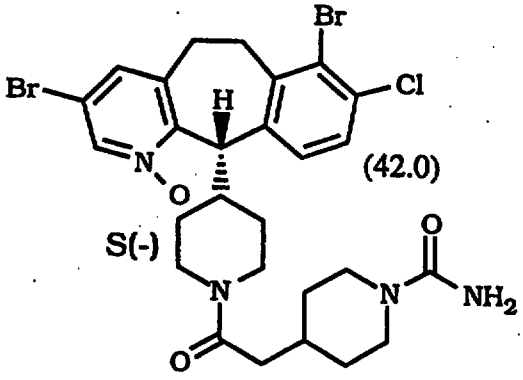
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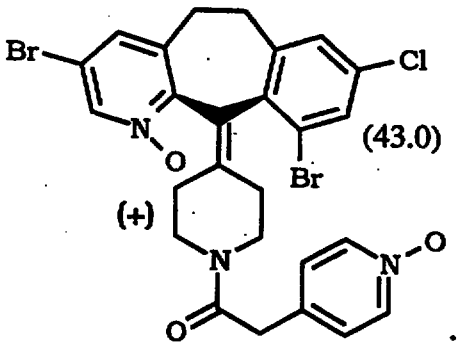
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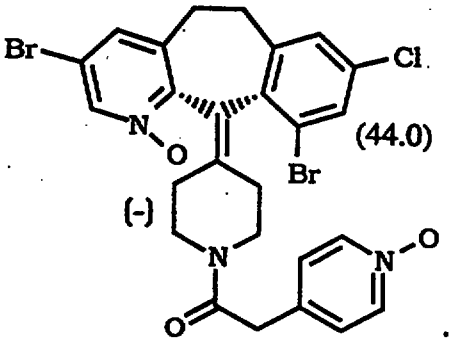
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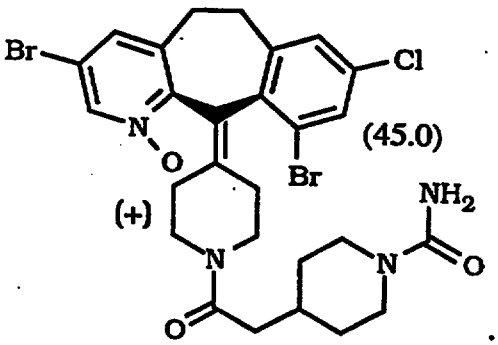
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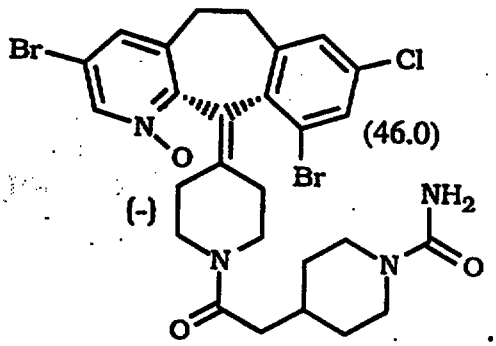
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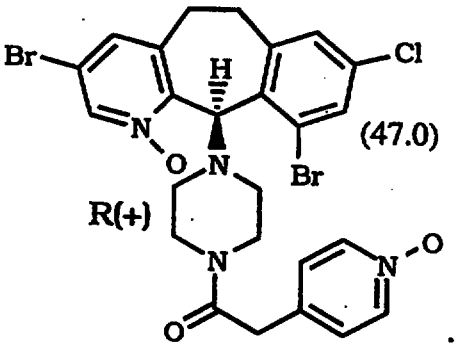
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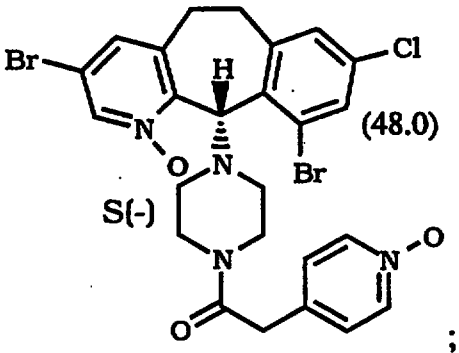
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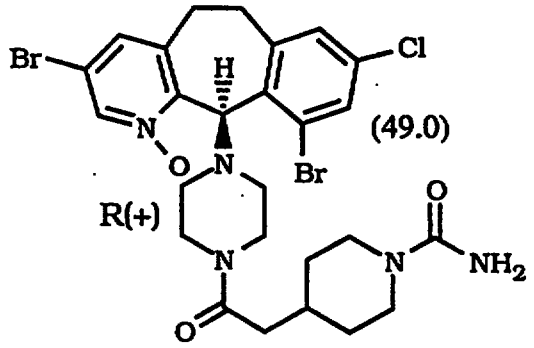




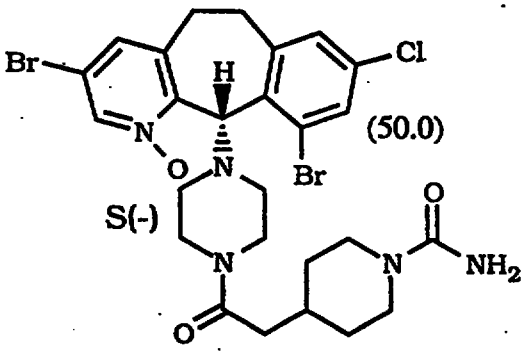
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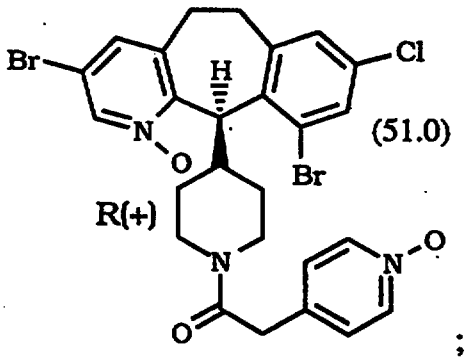
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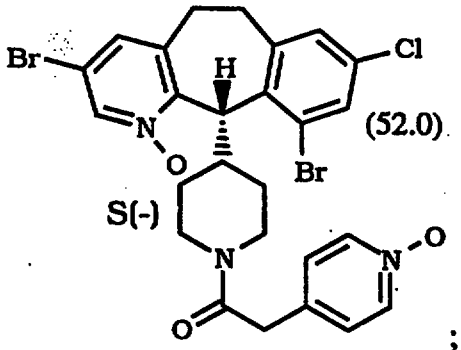
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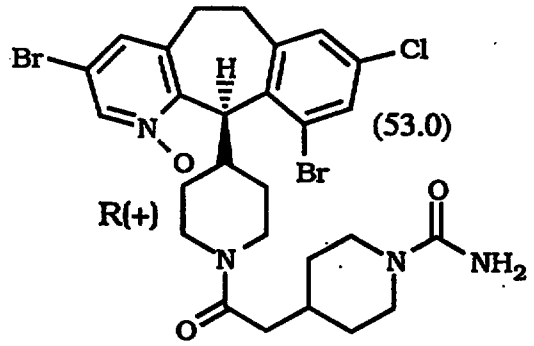
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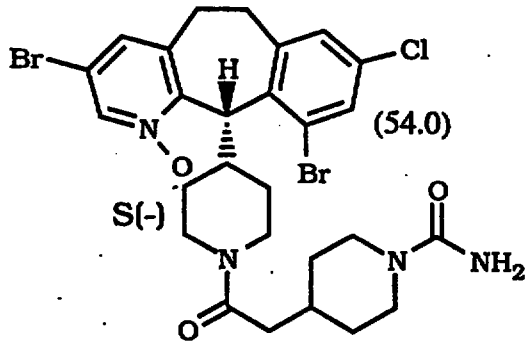
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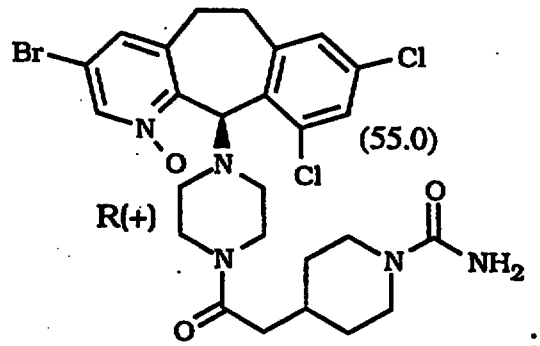
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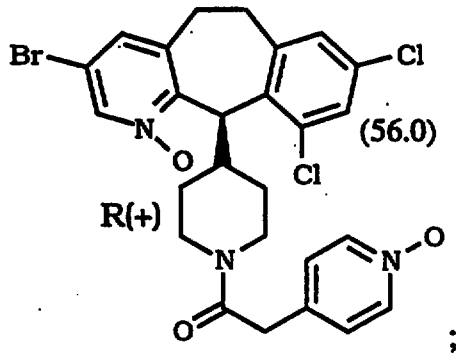
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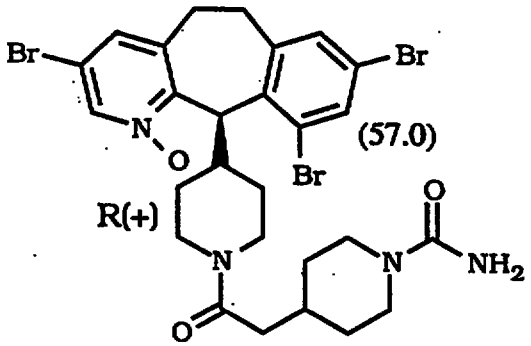




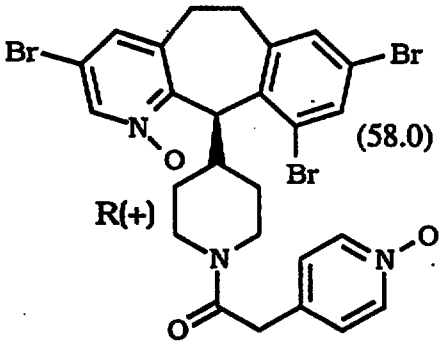
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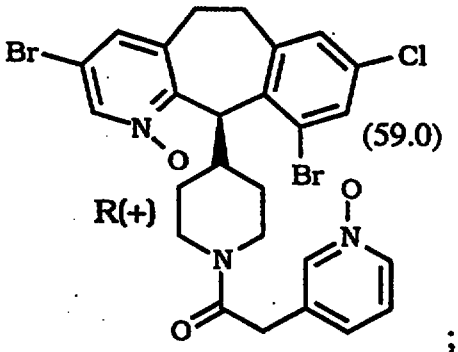
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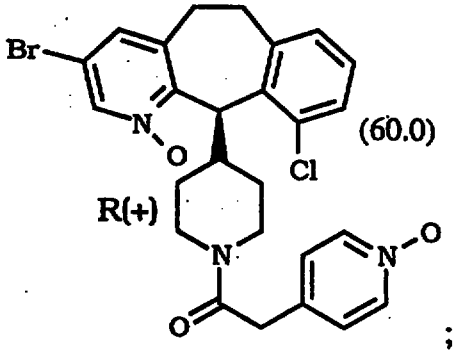
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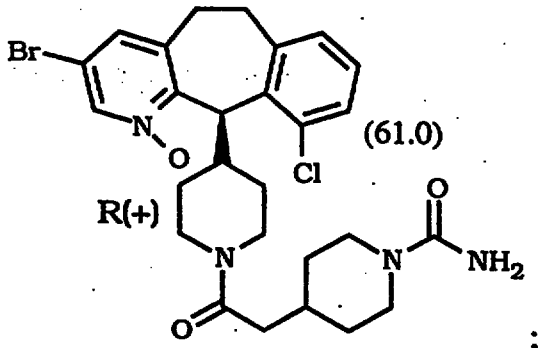
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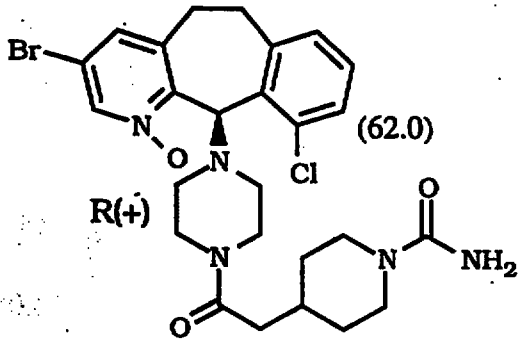
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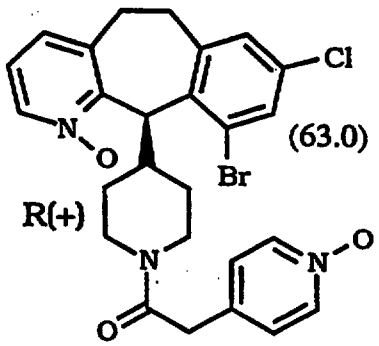
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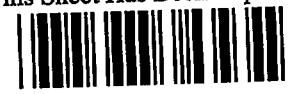


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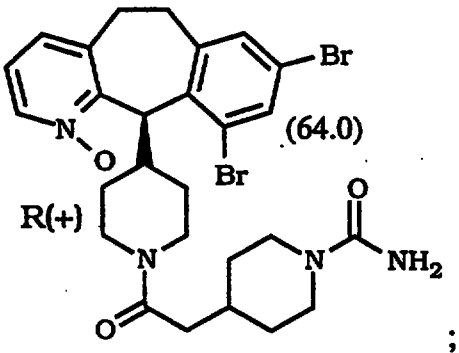
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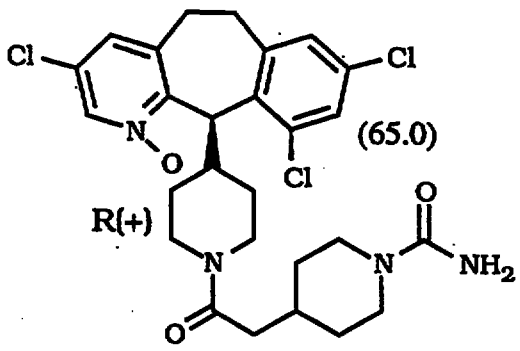




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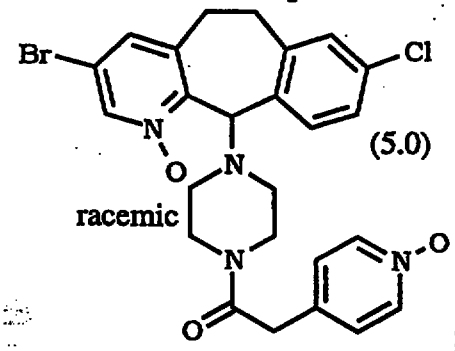


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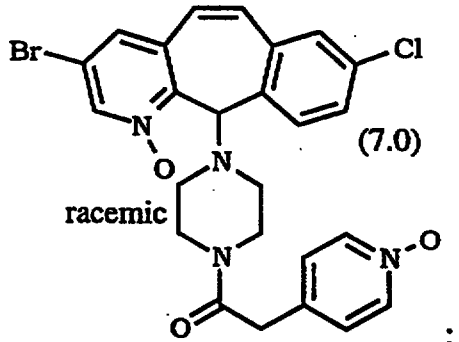


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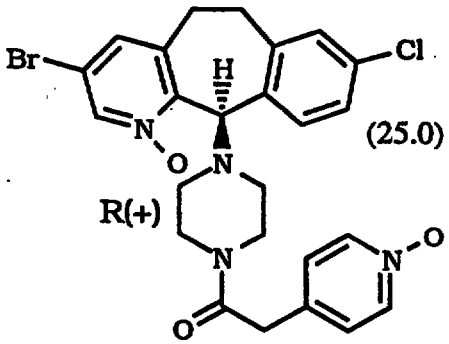
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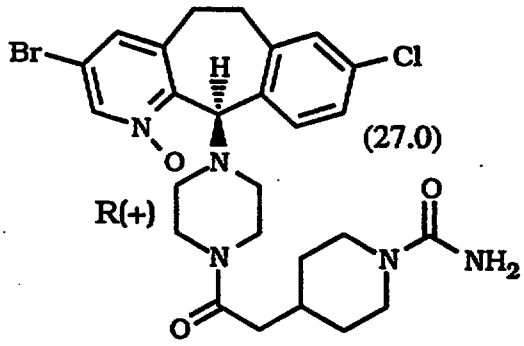
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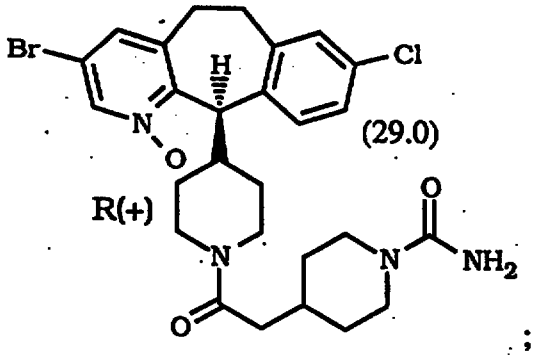
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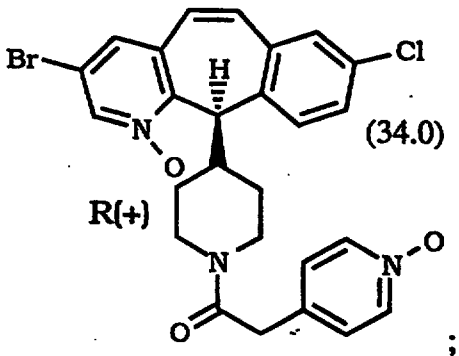
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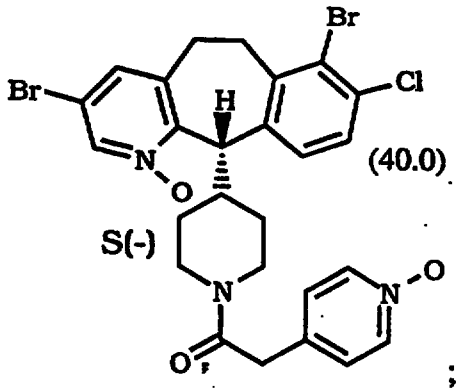
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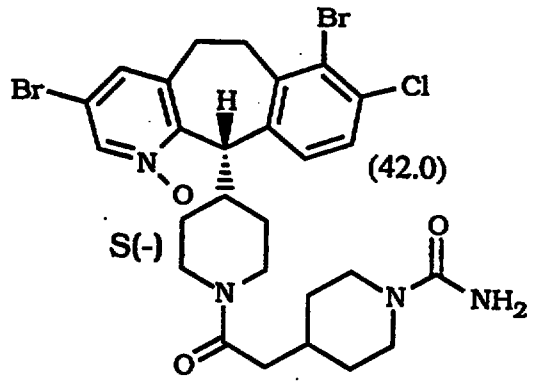
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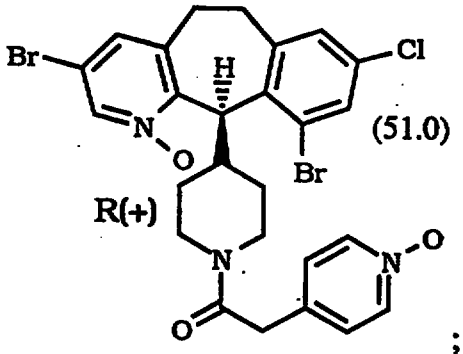
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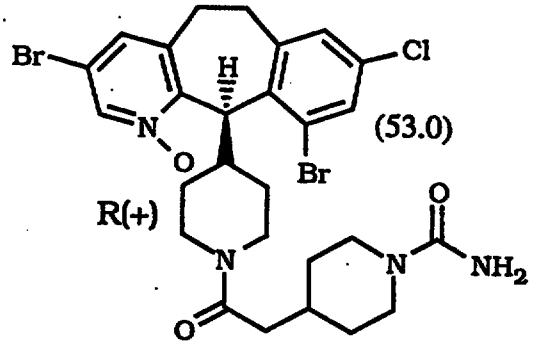
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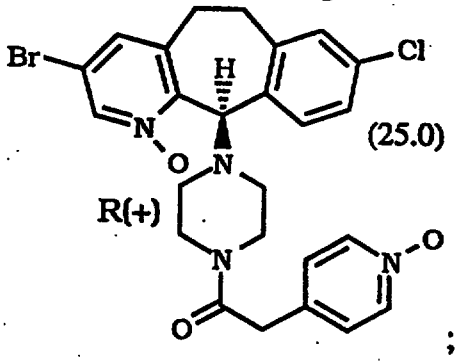
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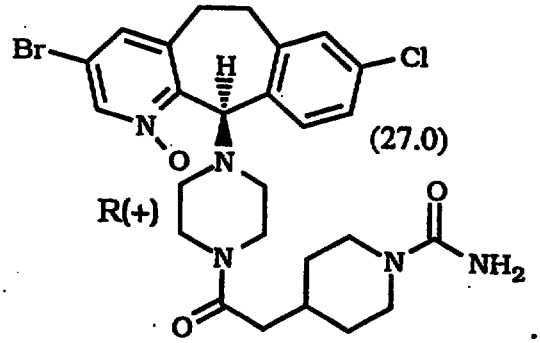
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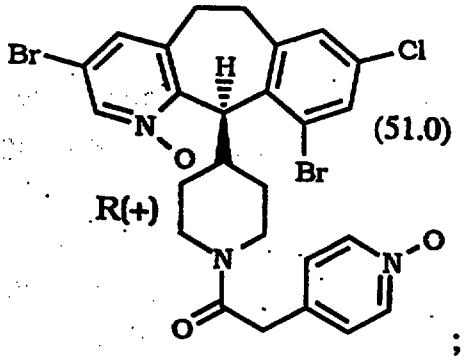
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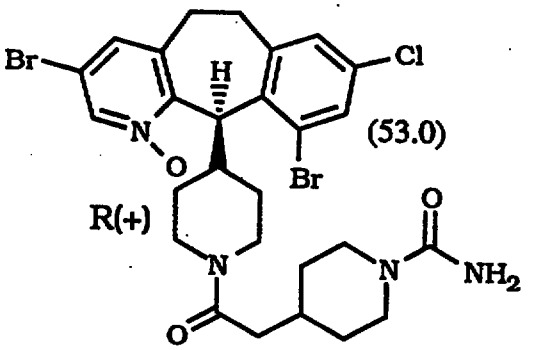
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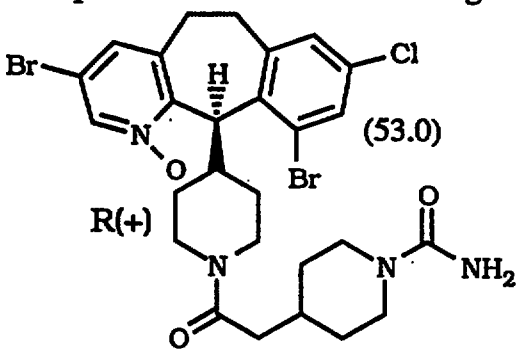
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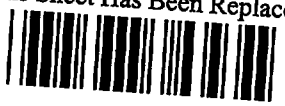
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4. The compound of Claim 1 having the formula:



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5. A method for inhibiting the abnormal growth of cells comprising administering an effective amount of a compound of Claim 1.

6. The method of Claim 5 wherein the cells inhibited are tumor cells expressing an activated ras oncogene.

7. The method of Claim 5 wherein the inhibition of the abnormal growth of cells occurs by the inhibition of farnesyl protein transferase.

8. The method of Claim 5 wherein the inhibition is of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene.

9. A method of inhibiting farnesyl protein transferase in a patient in need of such treatment comprising administering an effective amount of a compound of Claim 1.

10. A method of inhibiting farnesyl protein transferase in a patient in need of such treatment comprising administering an effective amount of a compound of Claim 3.

11. A method of treating pancreatic cancer, lung cancer, myeloid leukemia, thyroid follicular cancer, myelodysplastic syndrome, epidermal carcinoma, bladder carcinoma, colon cancer, breast cancer or prostate cancer in a patient in need of



such treatment comprising administering an effective amount of a compound of Claim 1.

12. A method of treating pancreatic cancer, lung cancer, myeloid leukemia, thyroid follicular cancer, myelodysplastic syndrome, epidermal carcinoma, bladder carcinoma, colon cancer, breast cancer or prostate cancer in a patient in need of such treatment comprising administering an effective amount of a compound of Claim 3.

13. A pharmaceutical composition comprising an effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable carrier.

14. A pharmaceutical composition comprising an effective amount of a compound of Claim 3 in combination with a pharmaceutically acceptable carrier.

15. The use of a compound of Claim 1 for the manufacture of a medicament for use in inhibiting growth of abnormal cells.

16. The use of a compound of Claim 1 for inhibiting the growth of abnormal cells.

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