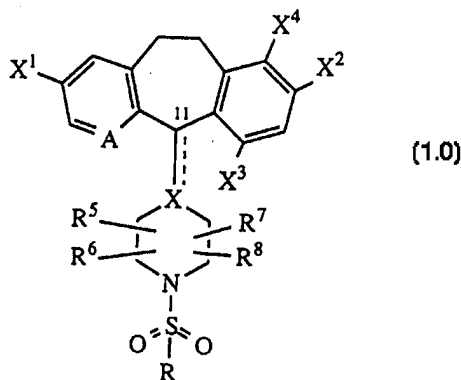




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<p>(21) International Application Number: PCT/US98/11508</p> <p>(22) International Filing Date: 15 June 1998 (15.06.98)</p> <p>(30) Priority Data: 08/877,050 17 June 1997 (17.06.97) US</p> <p>(71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US).</p> <p>(72) Inventors: NJOROGÉ, F., George; 2597 Juliat Place, Union, NJ 07083 (US). VIBULBHAN, Bancha; 201 North 24th Street, Kenilworth, NJ 07033 (US). TAVERAS, Arthur, G.; 43 Crestwood Road, Rockaway, NJ 07866 (US). DOLL, Ronald, J.; 126 Union Avenue, Maplewood, NJ 07040 (US). GIRIJAVALLABHAN, Viyyoor, M.; 10 Maplewood Drive, Parsippany, NJ 07054 (US).</p> <p>(74) Agents: MAJKA, Joseph, T. et al.; Schering-Plough Corporation, Patent Dept., K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).</p>		<p>(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b></p> <p><i>With international search report.</i></p> <p><i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>

**(54) Title:** NOVEL TRICYCLIC SULFONAMIDE INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE



**(57) Abstract**

Novel tricyclic sulfonamide compounds of formula (1.0) and pharmaceutical compositions are disclosed which are inhibitors of the enzyme, farnesyl protein transferase. Also disclosed is a method of inhibiting Ras function and therefore inhibiting the abnormal growth of cells. The method comprises administering the novel sulfonamide compound to a biological system. In particular, the method inhibits the abnormal growth of cells in a mammal such as a human.

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## NOVEL TRICYCLIC SULFONAMIDE INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

5 BACKGROUND

Patent application WO 95/00497 published 5 January 1995 under the Patent Cooperation Treaty (PCT) describes compounds which inhibit the enzyme, farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. Oncogenes frequently encode protein components of signal  
10 transduction pathways which lead to stimulation of cell growth and mitogenesis. Oncogene expression in cultured cells leads to cellular transformation, characterized by the ability of cells to grow in soft agar and the growth of cells as dense foci lacking the contact inhibition exhibited by non-transformed cells. Mutation and/or overexpression of certain oncogenes is frequently associated  
15 with human cancer.

To acquire transforming potential, the precursor of the Ras oncoprotein must undergo farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase, have therefore been suggested as anticancer agents for  
20 tumors in which Ras contributes to transformation. Mutated, oncogenic forms of Ras are frequently found in many human cancers, most notably in more than 50% of colon and pancreatic carcinomas (Kohl et al., Science, Vol. 260, 1834 to 1837, 1993).

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

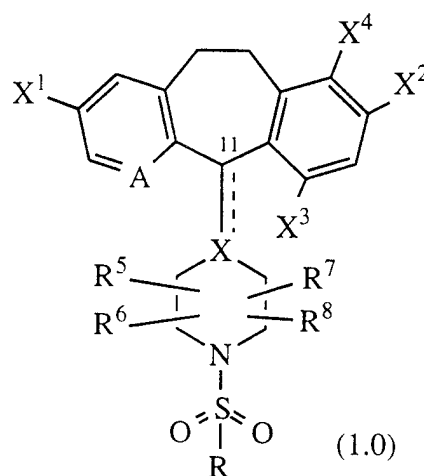
SUMMARY OF THE INVENTION

30 Inhibition of farnesyl protein transferase by 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  
35 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 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.

Compounds useful in the claimed methods are represented by Formula 1.0:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

A represents N or N-oxide;

X represents N, CH or C, such that when X is N or CH, there is a single bond to carbon atom 11 as represented by the solid line; or when X is C, there is a double bond to carbon atom 11, as represented by the solid and dotted lines;

X¹ and X² are independently selected from bromo, iodo or chloro;

X³ and X⁴ are independently selected from bromo, iodo, chloro, fluoro or hydrogen provided only one of X³ or X⁴ is hydrogen;

R⁵, R⁶, R⁷ and R⁸ each independently represents hydrogen, alkyl, aryl, or -CONR²⁰R²¹ wherein R²⁰ and R²¹ independently represent hydrogen, alkyl, alkoxy, aryl, aralkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl and heterocycloalkylalkyl, and further wherein R⁵ may be

combined with R<sup>6</sup> to represent =O or =S and/or R<sup>7</sup> may be combined with R<sup>8</sup> to represent =O or =S;

R can represent alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl or -NR<sup>10</sup>R<sup>11</sup>,

5 wherein R<sup>10</sup> and R<sup>11</sup> can independently represent hydrogen, alkenyl, alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl or heterocycloalkylalkyl.

Preferably in compound (1.0), there is a single bond at carbon atom 11; X is CH; R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are hydrogen; X<sup>1</sup>, X<sup>2</sup> and X<sup>3</sup> are bromo or chloro and  
10 X<sup>4</sup> is hydrogen; and R is alkyl, trifluoromethyl, alkenyl, aryl, heteroaryl or -NR<sup>10</sup>R<sup>11</sup> wherein R<sup>10</sup> and R<sup>11</sup> are independently selected from hydrogen and alkyl. When R is alkyl, an optional substituent on the alkyl group may be trifluoromethyl. When R is heteroaryl, optional substituents on the heteroaryl group may include alkyl or heteroaryl. Preferred compounds include those of  
15 Examples 1, 3, 4, 5, 6, 9, 10, 11 and 13.

In another embodiment, the present invention is directed toward a pharmaceutical composition for inhibiting the abnormal growth of cells comprising an effective amount of compound (1.0) in combination with a pharmaceutically acceptable carrier.

20 In another embodiment, the present invention is directed toward a method for inhibiting the abnormal growth of cells, including transformed cells, comprising administering an effective amount of compound (1.0) to a mammal (e.g., a human) in need of such treatment. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition).  
25 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; (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs, and (4) benign or malignant cells that are activated by mechanisms other than the Ras  
30 protein. Without wishing to be bound by theory, it is believed that these compounds may function either 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, or through inhibition of ras farnesyl protein transferase, thus making them useful for their  
35 antiproliferative activity against ras transformed cells.

The cells to be inhibited can be tumor cells expressing an activated ras oncogene. For example, the types of cells that may be inhibited include pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells, prostate tumor cells, breast tumor cells or colon tumors cells. Also, the inhibition of the abnormal growth of cells by the treatment with compound (1.0) may be by inhibiting ras farnesyl protein transferase. The inhibition may be of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene. Alternatively, compounds (1.0) may inhibit tumor cells activated by a protein other than the Ras protein.

This invention also provides a method for inhibiting tumor growth by administering an effective amount of compound (1.0) to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a method for inhibiting 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 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, prostate carcinoma and breast carcinoma and epidermal carcinoma.

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 N-substituted urea compounds (1.0) 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 N-substituted urea compounds (1.0).

In another embodiment, the present invention is directed toward a method for inhibiting ras farnesyl protein transferase and the farnesylation of the oncogene protein Ras by administering an effective amount of compound (1.0) to mammals, especially humans. 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.

5

### DETAILED DESCRIPTION OF THE INVENTION

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

M<sup>+</sup> -represents the molecular ion of the molecule in the mass spectrum;

10 MH<sup>+</sup> -represents the molecular ion plus hydrogen of the molecule in the mass spectrum;

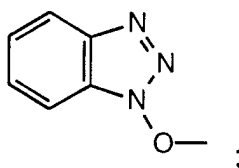
Bu-represents butyl;

Et-represents ethyl;

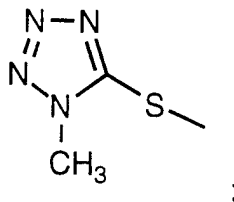
Me-represents methyl;

15 Ph-represents phenyl;

benzotriazol-1-yloxy represents



1-methyl-tetrazol-5-ylthio represents



20 alkyl-(including the alkyl portions of alkoxy, alkylamino and dialkylamino)-represents straight and branched carbon chains and contains from one to twenty carbon atoms, preferably one to six carbon atoms; for example methyl, ethyl, propyl, iso-propyl, n-butyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; wherein said alkyl group may be optionally and independently substituted

25 with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano, -CF<sub>3</sub>, oxy (=O), aryloxy, -OR<sup>10</sup>, -OCF<sub>3</sub>, heterocycloalkyl, heteroaryl, -NR<sup>10</sup>R<sup>12</sup>, -NHSO<sub>2</sub>R<sup>10</sup>, -SO<sub>2</sub>NH<sub>2</sub>, -SO<sub>2</sub>NHR<sup>10</sup>, -SO<sub>2</sub>R<sup>10</sup>, -SOR<sup>10</sup>, -SR<sup>10</sup>, -NHSO<sub>2</sub>, -NO<sub>2</sub>, -CONR<sup>10</sup>R<sup>12</sup>, -NR<sup>12</sup>COR<sup>10</sup>, -COR<sup>10</sup>, -OCOR<sup>10</sup>, -OCO<sub>2</sub>R<sup>10</sup> or -COOR<sup>10</sup>, wherein R<sup>10</sup> and R<sup>12</sup> can independently represent hydrogen, alkyl, alkoxy, aryl, aralkyl,

30 heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

alkenyl-represents straight and branched carbon chains having at least one carbon to carbon double bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms and most preferably from 3 to 6 carbon atoms; wherein said alkenyl group may be optionally and independently

5 substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano,  $-\text{CF}_3$ , dialkylamino, hydroxy, oxy, phenoxy,  $-\text{OCF}_3$ , heterocycloalkyl,  $-\text{SO}_2\text{NH}_2$ ,  $-\text{NHSO}_2\text{R}^{10}$ ,  $-\text{SO}_2\text{NHR}^{10}$ ,  $-\text{SO}_2\text{R}^{10}$ ,  $-\text{SOR}^{10}$ ,  $-\text{SR}^{10}$ ,  $-\text{NHSO}_2$ ,  $-\text{NO}_2$ ,  $-\text{CONR}^{10}$ ,  $-\text{NCOR}^{10}$  or  $-\text{COOR}^{10}$ ;

10 alkoxy-an alkyl moiety of one to 20 carbon atoms covalently bonded to an adjacent structural element through an oxygen atom, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy and the like; wherein said alkoxy group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano,  $-\text{CF}_3$ , oxy ( $=\text{O}$ ), aryloxy,  $-\text{OR}^{10}$ ,  $-\text{OCF}_3$ , heterocycloalkyl, heteroaryl,  $-\text{NR}^{10}\text{R}^{12}$ ,  $-\text{NHSO}_2\text{R}^{10}$ ,  $-\text{SO}_2\text{NH}_2$ ,  
15  $-\text{SO}_2\text{NHR}^{10}$ ,  $-\text{SO}_2\text{R}^{10}$ ,  $-\text{SOR}^{10}$ ,  $-\text{SR}^{10}$ ,  $-\text{NHSO}_2$ ,  $-\text{NO}_2$ ,  $-\text{CONR}^{10}\text{R}^{12}$ ,  $-\text{NR}^{12}\text{COR}^{10}$ ,  $-\text{COR}^{10}$ ,  $-\text{OCOR}^{10}$ ,  $-\text{OCO}_2\text{R}^{10}$  or  $-\text{COOR}^{10}$ , wherein  $\text{R}^{10}$  and  $\text{R}^{12}$  are as defined hereinabove;

20 aryl (including the aryl portion of arylalkyl)-represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is phenyl), wherein said aryl group optionally can be fused with aryl, cycloalkyl, heteroaryl or heterocycloalkyl rings; and wherein any of the available substitutable carbon and nitrogen atoms in said aryl group and/or said fused ring(s) may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano,  $-\text{CF}_3$ , oxy ( $=\text{O}$ ), aryloxy,  
25  $-\text{OR}^{10}$ ,  $-\text{OCF}_3$ , heterocycloalkyl, heteroaryl,  $-\text{NR}^{10}\text{R}^{12}$ ,  $-\text{NHSO}_2\text{R}^{10}$ ,  $-\text{SO}_2\text{NH}_2$ ,  $-\text{SO}_2\text{NHR}^{10}$ ,  $-\text{SO}_2\text{R}^{10}$ ,  $-\text{SOR}^{10}$ ,  $-\text{SR}^{10}$ ,  $-\text{NHSO}_2$ ,  $-\text{NO}_2$ ,  $-\text{CONR}^{10}\text{R}^{12}$ ,  $-\text{NR}^{12}\text{COR}^{10}$ ,  $-\text{COR}^{10}$ ,  $-\text{OCOR}^{10}$ ,  $-\text{OCO}_2\text{R}^{10}$  or  $-\text{COOR}^{10}$ , wherein  $\text{R}^{10}$  and  $\text{R}^{12}$  are as defined hereinabove;

30 arylalkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms of the alkyl moiety have been substituted with one or more aryl groups; wherein said aralkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano,  $-\text{CF}_3$ , oxy ( $=\text{O}$ ), aryloxy,  $-\text{OR}^{10}$ ,  $-\text{OCF}_3$ , heterocycloalkyl, heteroaryl,  $-\text{NR}^{10}\text{R}^{12}$ ,  $-\text{NHSO}_2\text{R}^{10}$ ,  $-\text{SO}_2\text{NH}_2$ ,  $-\text{SO}_2\text{NHR}^{10}$ ,  $-\text{SO}_2\text{R}^{10}$ ,  $-\text{SOR}^{10}$ ,  
35  $-\text{SR}^{10}$ ,  $-\text{NHSO}_2$ ,  $-\text{NO}_2$ ,  $-\text{CONR}^{10}\text{R}^{12}$ ,  $-\text{NR}^{12}\text{COR}^{10}$ ,  $-\text{COR}^{10}$ ,  $-\text{OCOR}^{10}$ ,  $-\text{OCO}_2\text{R}^{10}$  or  $-\text{COOR}^{10}$ , wherein  $\text{R}^{10}$  and  $\text{R}^{12}$  are as defined hereinabove;



aryloxy - represents an aryl group, as defined above, wherein said aryl group is covalently bonded to an adjacent structural element through an oxygen atom, for example, phenoxy, wherein said aryl group optionally can be fused with aryl, cycloalkyl, heteroaryl or heterocycloalkyl rings; and wherein any of the  
 5 available substitutable carbon and nitrogen atoms in said aryloxy group and/or said fused ring(s) may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano,  $-CF_3$ , oxy ( $=O$ ), aryloxy,  $-OR^{10}$ ,  $-OCF_3$ , heterocycloalkyl, heteroaryl,  $-NR^{10}R^{12}$ ,  $-NHSO_2R^{10}$ ,  $-SO_2NH_2$ ,  $-SO_2NHR^{10}$ ,  $-SO_2R^{10}$ ,  $-SOR^{10}$ ,  $-SR^{10}$ ,  $-NHSO_2$ ,  $-NO_2$ ,  $-CONR^{10}R^{12}$ ,  
 10  $-NR^{12}COR^{10}$ ,  $-COR^{10}$ ,  $-OCOR^{10}$ ,  $-OCO_2R^{10}$  or  $-COOR^{10}$ , wherein  $R^{10}$  and  $R^{12}$  are as defined hereinabove;

cycloalkyl-represents saturated carbocyclic rings branched or unbranched of from 3 to 20 carbon atoms, preferably 3 to 7 carbon atoms; wherein said cycloalkyl group may be optionally and independently substituted  
 15 with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano,  $-CF_3$ , oxy ( $=O$ ), aryloxy,  $-OR^{10}$ ,  $-OCF_3$ , heterocycloalkyl, heteroaryl,  $-NR^{10}R^{12}$ ,  $-NHSO_2R^{10}$ ,  $-SO_2NH_2$ ,  $-SO_2NHR^{10}$ ,  $-SO_2R^{10}$ ,  $-SOR^{10}$ ,  $-SR^{10}$ ,  $-NHSO_2$ ,  $-NO_2$ ,  $-CONR^{10}R^{12}$ ,  $-NR^{12}COR^{10}$ ,  $-COR^{10}$ ,  $-OCOR^{10}$ ,  $-OCO_2R^{10}$  or  $-COOR^{10}$ , wherein  $R^{10}$  and  $R^{12}$  are as defined hereinabove;

cycloalkylalkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms of the alkyl moiety have been substituted with one or more cycloalkyl groups; wherein said cycloalkylalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano,  $-CF_3$ , oxy ( $=O$ ), aryloxy,  $-OR^{10}$ ,  $-OCF_3$ ,  
 20 heterocycloalkyl, heteroaryl,  $-NR^{10}R^{12}$ ,  $-NHSO_2R^{10}$ ,  $-SO_2NH_2$ ,  $-SO_2NHR^{10}$ ,  $-SO_2R^{10}$ ,  $-SOR^{10}$ ,  $-SR^{10}$ ,  $-NHSO_2$ ,  $-NO_2$ ,  $-CONR^{10}R^{12}$ ,  $-NR^{12}COR^{10}$ ,  $-COR^{10}$ ,  $-OCOR^{10}$ ,  $-OCO_2R^{10}$  or  $-COOR^{10}$ , wherein  $R^{10}$  and  $R^{12}$  are as defined hereinabove;

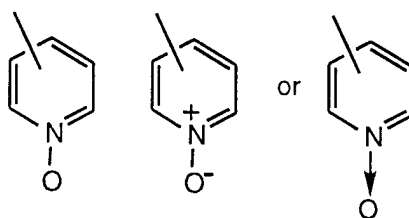
halo-represents fluoro, chloro, bromo and iodo;

heteroalkyl-represents straight and branched carbon chains containing from one to twenty carbon atoms, preferably one to six carbon atoms interrupted by 1 to 3 heteroatoms selected from  $-O-$ ,  $-S-$  and  $-N-$ ; wherein any of the available substitutable carbon and nitrogen atoms in said heteroalkyl chain may be  
 30 optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano,  $-CF_3$ , oxy ( $=O$ ), aryloxy,  $-OR^{10}$ ,  $-OCF_3$ , heterocycloalkyl, heteroaryl,  $-NR^{10}R^{12}$ ,  $-NHSO_2R^{10}$ ,  $-SO_2NH_2$ ,  $-SO_2NHR^{10}$ ,  $-SO_2R^{10}$ ,  $-SOR^{10}$ ,  $-SR^{10}$ ,  $-NHSO_2$ ,  $-NO_2$ ,  $-CONR^{10}R^{12}$ ,  
 35  $-NR^{12}COR^{10}$ ,  $-COR^{10}$ ,  $-OCOR^{10}$ ,  $-OCO_2R^{10}$  or  $-COOR^{10}$ , wherein  $R^{10}$  and  $R^{12}$  are as defined hereinabove;

-NR<sup>12</sup>COR<sup>10</sup>, -COR<sup>10</sup>, -OCOR<sup>10</sup>, -OCO<sub>2</sub>R<sup>10</sup> or -COOR<sup>10</sup>, wherein R<sup>10</sup> and R<sup>12</sup> are as defined hereinabove;

heteroaryl-represents cyclic groups having at least one heteroatom selected from O, S and N, said heteroatom(s) interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups containing from 2 to 14 carbon atoms, wherein said heteroaryl group optionally can be fused with one or more aryl, cycloalkyl, heteroaryl or heterocycloalkyl rings; and wherein any of the available substitutable carbon or nitrogen atoms in said heteroaryl group and/or said fused ring(s) may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano, -CF<sub>3</sub>, oxy (=O), aryloxy, -OR<sup>10</sup>, -OCF<sub>3</sub>, heterocycloalkyl, heteroaryl, -NR<sup>10</sup>R<sup>12</sup>, -NHSO<sub>2</sub>R<sup>10</sup>, -SO<sub>2</sub>NH<sub>2</sub>, -SO<sub>2</sub>NHR<sup>10</sup>, -SO<sub>2</sub>R<sup>10</sup>, -SOR<sup>10</sup>, -SR<sup>10</sup>, -NHSO<sub>2</sub>, -NO<sub>2</sub>, -CONR<sup>10</sup>R<sup>12</sup>, -NR<sup>12</sup>COR<sup>10</sup>, -COR<sup>10</sup>, -OCOR<sup>10</sup>, -OCO<sub>2</sub>R<sup>10</sup> or -COOR<sup>10</sup>, wherein R<sup>10</sup> and R<sup>12</sup> are as defined hereinabove.

Representative heteroaryl groups can include, for example, furanyl, imidazolyl, pyrimidinyl, triazolyl, 2-, 3- or 4-pyridyl or 2-, 3- or 4-pyridyl N-oxide wherein pyridyl N-oxide can be represented as:

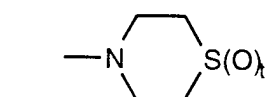
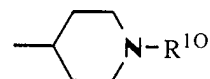


heteroarylalkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms have been replaced by one or more heteroaryl groups; wherein said heteroarylalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano, -CF<sub>3</sub>, oxy (=O), aryloxy, -OR<sup>10</sup>, -OCF<sub>3</sub>, heterocycloalkyl, heteroaryl, -NR<sup>10</sup>R<sup>12</sup>, -NHSO<sub>2</sub>R<sup>10</sup>, -SO<sub>2</sub>NH<sub>2</sub>, -SO<sub>2</sub>NHR<sup>10</sup>, -SO<sub>2</sub>R<sup>10</sup>, -SOR<sup>10</sup>, -SR<sup>10</sup>, -NHSO<sub>2</sub>, -NO<sub>2</sub>, -CONR<sup>10</sup>R<sup>12</sup>, -NR<sup>12</sup>COR<sup>10</sup>, -COR<sup>10</sup>, -OCOR<sup>10</sup>, -OCO<sub>2</sub>R<sup>10</sup> or -COOR<sup>10</sup>, wherein R<sup>10</sup> and R<sup>12</sup> are as defined hereinabove;

heterocycloalkyl-represents a saturated, branched or unbranched carbocyclic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 heteroatoms selected from -O-, -S- and -N-, wherein optionally, said ring may contain one or two unsaturated bonds which do not impart aromatic character to the ring; and wherein any of the available substitutable carbon and nitrogen atoms in the ring

- may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano,  $-\text{CF}_3$ , oxy ( $=\text{O}$ ), aryloxy,  $-\text{OR}^{10}$ ,  $-\text{OCF}_3$ , heterocycloalkyl, heteroaryl,  $-\text{NR}^{10}\text{R}^{12}$ ,  $-\text{NHSO}_2\text{R}^{10}$ ,  $-\text{SO}_2\text{NH}_2$ ,  $-\text{SO}_2\text{NHR}^{10}$ ,  $-\text{SO}_2\text{R}^{10}$ ,  $-\text{SOR}^{10}$ ,  $-\text{SR}^{10}$ ,  $-\text{NHSO}_2$ ,  $-\text{NO}_2$ ,  $-\text{CONR}^{10}\text{R}^{12}$ ,  $-\text{NR}^{12}\text{COR}^{10}$ ,  $-\text{COR}^{10}$ ,  $-\text{OCOR}^{10}$ ,  $-\text{OCO}_2\text{R}^{10}$  or  $-\text{COOR}^{10}$ , wherein  $\text{R}^{10}$  and  $\text{R}^{12}$  are as defined hereinabove. Representative heterocycloalkyl groups can include 2- or 3-tetrahydrofuranyl, 2- or 3- tetrahydrothienyl, 1-, 2-, 3- or 4-piperidinyl, 2- or

3-pyrrolidinyl, 1-, 2- or 3-piperizinyl, 2- or 4-dioxanyl, morpholinyl,

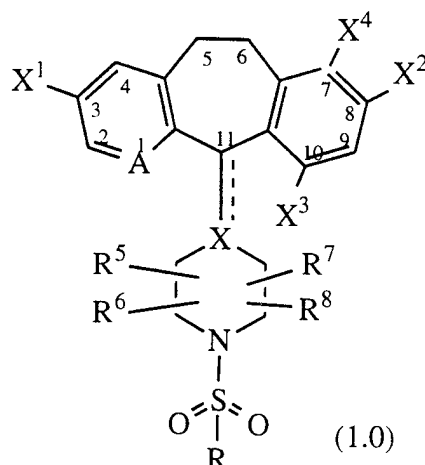


or wherein  $\text{R}^{10}$  is defined hereinbefore and  $t$  is 0, 1 or 2.

- heterocycloalkyl- represents an alkyl group, as defined above, wherein one or more hydrogen atoms have been replaced by one or more heterocycloalkyl groups; wherein optionally, said ring may contain one or two unsaturated bonds which do not impart aromatic character to the ring; and wherein said heterocycloalkylalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano,  $-\text{CF}_3$ , oxy ( $=\text{O}$ ), aryloxy,  $-\text{OR}^{10}$ ,  $-\text{OCF}_3$ , heterocycloalkyl, heteroaryl,  $-\text{NR}^{10}\text{R}^{12}$ ,  $-\text{NHSO}_2\text{R}^{10}$ ,  $-\text{SO}_2\text{NH}_2$ ,  $-\text{SO}_2\text{NHR}^{10}$ ,  $-\text{SO}_2\text{R}^{10}$ ,  $-\text{SOR}^{10}$ ,  $-\text{SR}^{10}$ ,  $-\text{NHSO}_2$ ,  $-\text{NO}_2$ ,  $-\text{CONR}^{10}\text{R}^{12}$ ,  $-\text{NR}^{12}\text{COR}^{10}$ ,  $-\text{COR}^{10}$ ,  $-\text{OCOR}^{10}$ ,  $-\text{OCO}_2\text{R}^{10}$  or  $-\text{COOR}^{10}$ , wherein  $\text{R}^{10}$  and  $\text{R}^{12}$  are as defined hereinabove.

- 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-hydroxybenzotriazole (HOBt); m-chloroperbenzoic acid (MCPBA); triethylamine ( $\text{Et}_3\text{N}$ ); diethyl ether ( $\text{Et}_2\text{O}$ ); ethyl chloroformate ( $\text{ClCO}_2\text{Et}$ ); and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (DEC).

Reference to the position of the substituents  $\text{X}^1$ ,  $\text{X}^2$ ,  $\text{X}^3$  and  $\text{X}^4$  is based on the numbered ring structure:



Certain compounds of the invention may exist in different stereoisomeric forms (e.g., enantiomers, diastereoisomers and atropisomers). The invention contemplates all such stereoisomers both in pure form and in mixture, including racemic mixtures. For example, the carbon atom at the C-11 position can be in the S or R stereoconfiguration.

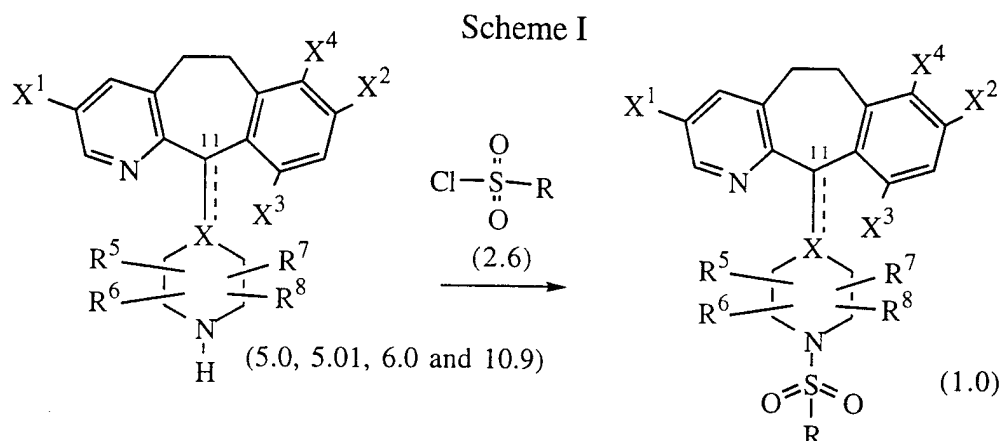
Certain tricyclic compounds will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated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

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

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

5

Compounds of the present invention can be prepared according to the following Scheme I:



wherein X, X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, R, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, and the solid and dotted lines are as defined hereinbefore.

10

Referring to the Scheme I, compounds of formula (1.0) can be prepared by reacting the compound of formula (5.0, 5.01, 6.0 or 10.9) with the corresponding sulfonyl chloride reagent of formula (2.6) with a base and aprotic solvent such as THF, dioxane, toluene, methylene chloride (CH<sub>2</sub>Cl<sub>2</sub>), acetonitrile, or DMF at temperatures which can range from 0° to 100°C, or reflux of the reaction mixture. The amount of sulfonyl chloride (2.6) can range from 1 to about 10 moles per mole of compound (5.0, 5.01, 6.0 or 10.9).

15

In an alternative procedure, the compounds of formula (1.0) wherein R is -NR<sup>10</sup>R<sup>11</sup> can be prepared by reacting the compound of formula (5.0, 5.01, 6.0 or 10.9) with thionyl chloride in an aprotic solvent as described above, in the presence of a base, followed by reaction with an amine of the formula HNR<sup>10</sup>R<sup>11</sup> (2.8) in an aprotic solvent wherein R<sup>10</sup> and R<sup>11</sup> are defined hereinbefore, at a temperatures from 0° to 100°C or reflux of the reaction mixture. The amount of the thionyl chloride or amine (2.8) can range from about 1 to 10 moles per mole of compound (5.0, 5.01, 6.0 or 10.9).

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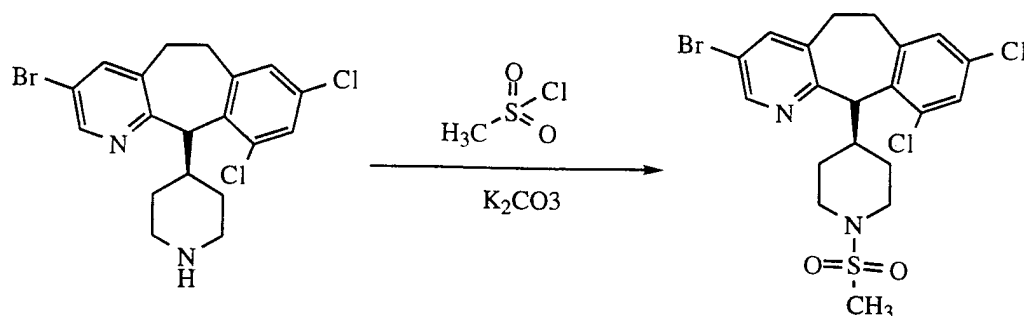
In another alternative procedure, the compounds of formula (1.0) wherein R is  $-NH_2$  can be prepared by reacting compound (2.0) with the sulfonamide  $SO(NH_2)_2$  in a protic solvent such as water at temperatures ranging from  $50^\circ$  to  $100^\circ C$ .

- 5           Compounds of formula (1.0) can be isolated from the reaction mixture using conventional procedures, such as, for example, extraction of the reaction mixture from water with organic solvents, evaporation of the organic solvents, followed by chromatography on silica gel or other suitable chromatographic media. Alternatively, compounds (1.0) can be dissolved in a water-miscible solvent, such as methanol, the methanol solution is added to water to precipitate the compound, and the precipitate is isolated by filtration or centrifugation.

- 15           (+)-Isomers of compounds of formula (5.0, 6.0 and 10.9) wherein X is CH can be prepared with high enantioselectivity by using a process comprising enzyme catalyzed transesterification. Preferably, a racemic compound of formula (5.0, 6.0 and 10.9), wherein X is C, the double bond is present and  $X^3$  is not H, is reacted with an enzyme such as Toyobo LIP-300 and an acylating agent such as trifluoroethyl 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 and  $R^3$  is not H. Alternatively, a racemic compound of formula (5.0, 6.0 and 10.9), wherein X is C, the double bond is present and  $R^3$  is not H, is first reduced to the corresponding racemic compound of formula (5.0, 6.0 and 10.9) 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.

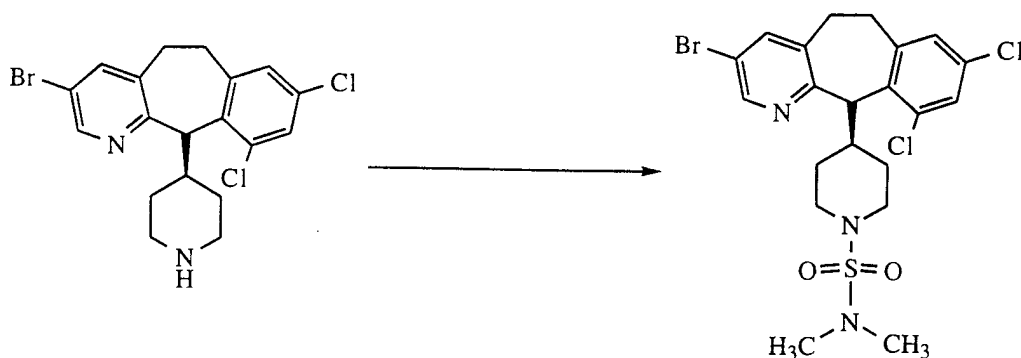
Compounds of the present invention and preparative starting materials thereof, are exemplified by the following examples, which should not be construed as limiting the scope of the disclosure.

30           Example 1 (+)-4-(3-Bromo-8,10-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-(methylsulfonyl)piperidine



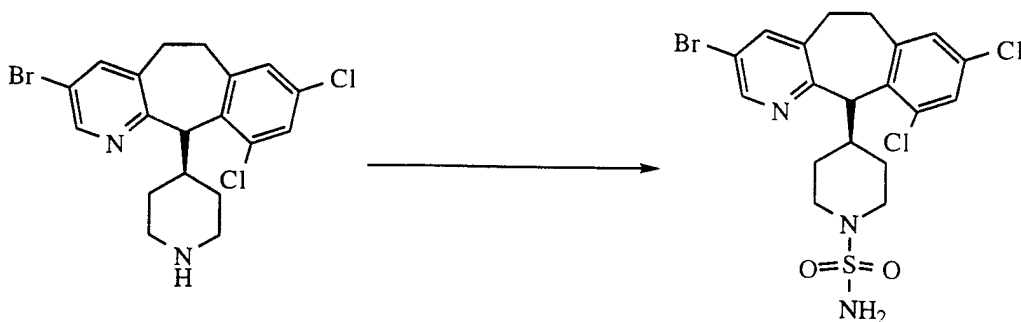
Dry anhydrous potassium carbonate (0.23g, 1.7 mmol) was suspended in 6 mL of anhydrous toluene. To this mixture was added the title compound of Preparative Example 10 (0.2g, 0.47 mmol), methane sulfonyl chloride (0.055g, 40  $\mu$ L, 0.47 mmol) and stirred at room temperature for ~ 72h. The reaction mixture was then filtered, and washed with  $\text{CH}_2\text{Cl}_2$ . The filtrate was washed with saturate  $\text{NaHCO}_3$ , dried over  $\text{MgSO}_4$ , filtered and concentrated to dryness to afford 0.23g of the title compound as a white solid: mp = 160-163°C, FAB-MS:  $\text{MH}^+$  = 505 (97% Yield),  $\text{COS IC}_{50}$  = 0.420 ( $\mu\text{M}$ ).

Example 2 (+)-4-(3-Bromo-8,10-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N,N-dimethyl-1-piperidinesulfonamide



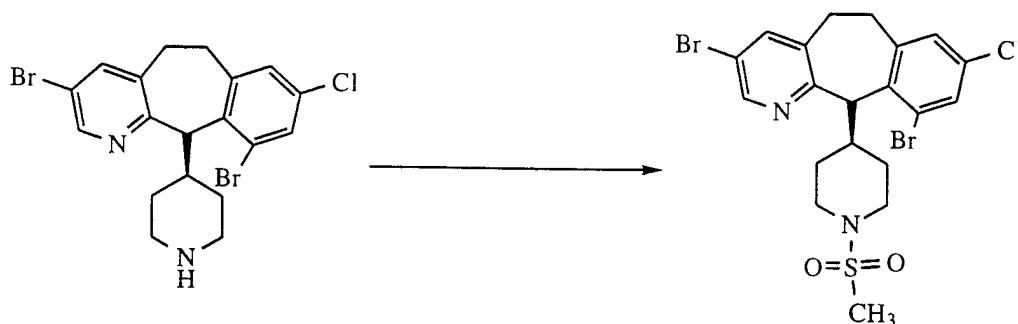
The title compound is prepared following essentially the same procedure as described in Example 1 except that N,N-dimethyl sulfonyl chloride was used instead of methane sulfonyl chloride to obtain a solid, FAB-MS:  $\text{MH}^+$  = 534, mp= 202-203°C; (65% Yield).

Example 3 (+)-4-(3-Bromo-8,10-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-(aminosulfonyl)piperidine



The title compound of Preparative Example 10 (0.2g, 0.47 mmol), and sulfamide (0.45g, 4.7 mmol) are dissolved in 7 mL of H<sub>2</sub>O and the reaction mixture heated to reflux for 72h. The reaction mixture was then cooled and filtered. The filtrate was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over MgSO<sub>4</sub> and concentrated. Purification by flash chromatography on silica gel eluting with 5% MeOH(sat. with ammonia)-CH<sub>2</sub>Cl<sub>2</sub> afforded 0.035g (15% yield) of the title compound, as a white solid. FAB-MS: MH<sup>+</sup> = 506. mp=133-134°C .

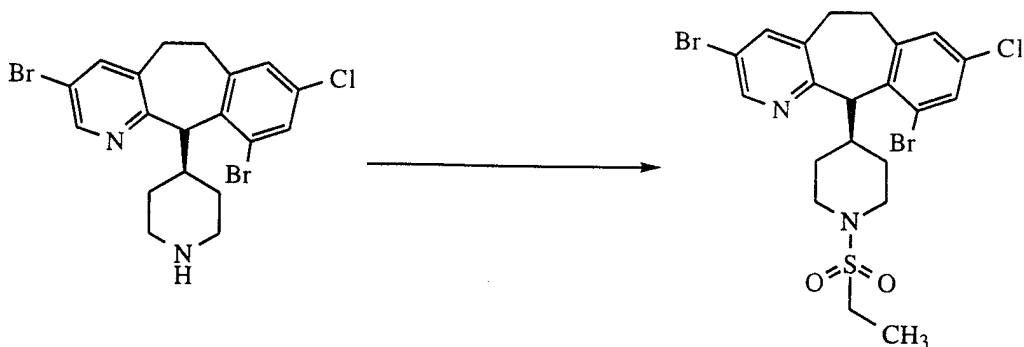
- 10 Example 4 (+)-4-(3,10-Dibromo-8-chloro-11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-(methanesulfonyl)piperidine



The title compound is prepared following essentially the same procedure as described in Example 1 except that the title compound of Preparative Example 3 (+)-4-(3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclo-hepta[1,2-b]pyridin-11-yl)-1-piperidine) was used instead of (+)-4-(3-bromo-8,10-dichloro-6,11-dihydro-5H-benzo[5,6]cyclo-hepta[1,2-b]pyridin-11-yl)-1-piperidine to obtain the title compound, a solid. FAB-MS: MH<sup>+</sup> = 549, mp= 216-217°C, yield = 74%, COS IC<sub>50</sub> = 0.015 (μM).

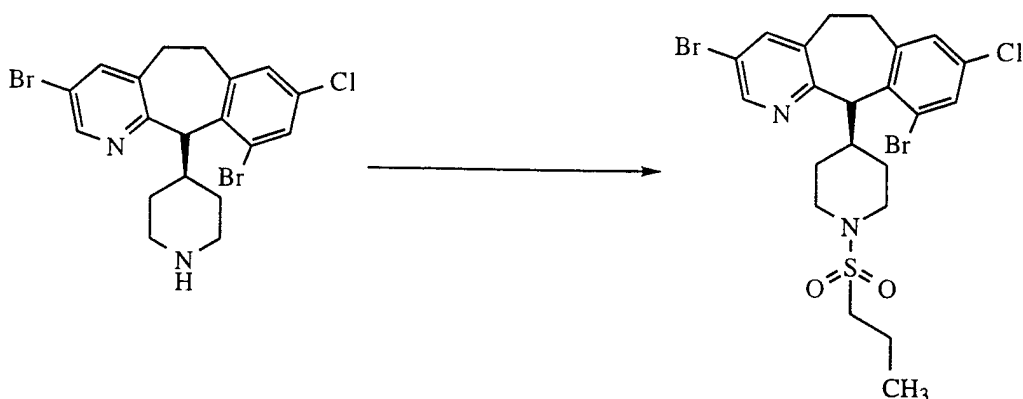
Example 5 (+)-4-(3,10-Dibromo-8-chloro-11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-(ethanesulfonyl)piperidine





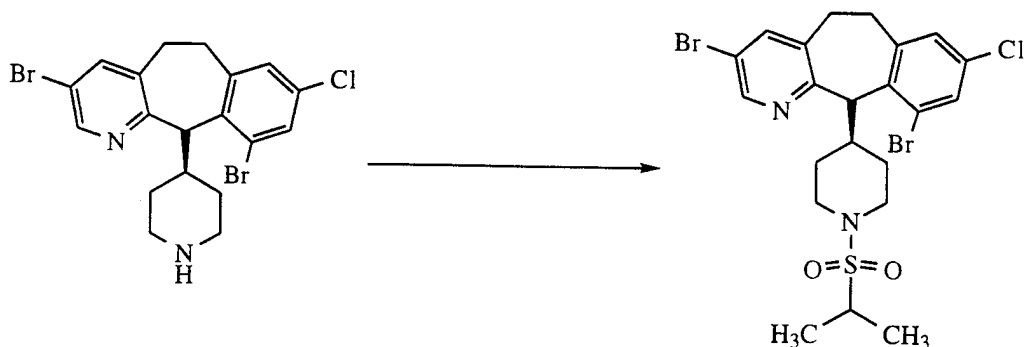
The title compound is prepared following essentially the same procedure as described in Example 4 except that ethane sulfonyl chloride was used instead of methane sulfonyl chloride to obtain a solid FAB-MS:  $MH^+ = 563$ . mp= 202-203°C  
 5 yield = 90 %

Example 6 (+)-4-(3,10-Dibromo-8-chloro-11-dihydro-5H-  
 10 benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-(propylsulfonyl)piperidine



The title compound is prepared following essentially the same procedure as described in Example 4 except that propane sulfonyl chloride was used instead of methane sulfonyl chloride to obtain a solid FAB-MS:  $MH^+ = 577$ . mp= 97-98°C  
 15 yield = 95 %

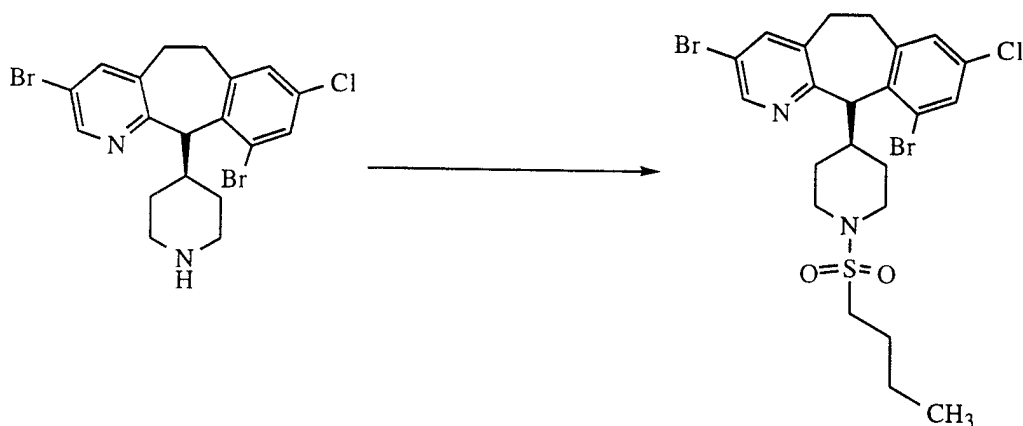
Example 7 (+)-4-(3,10-Dibromo-8-chloro-11-dihydro-5H-  
 benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-(isopropylsulfonyl)piperidine



The title compound is prepared following essentially the same procedure as described in Example 4 except that isopropane sulfonyl chloride was used instead of methane sulfonyl chloride to obtain a solid FAB-MS: MH<sup>+</sup> = 577. mp= 203-205°C (yield = 65 %).

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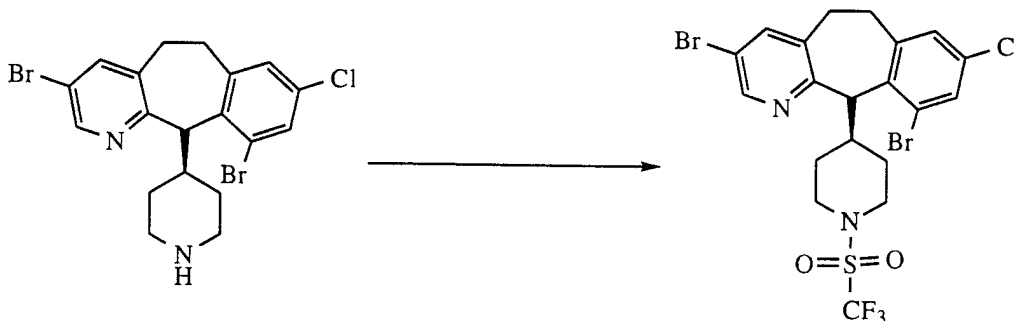
Example 8 (+)-4-(3,10-Dibromo-8-chloro-11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-(butylsulfonyl)piperidine



The title compound is prepared following essentially the same procedure as described in Example 4 except that butane sulfonyl chloride was used instead of methane sulfonyl chloride to obtain a solid FAB-MS: MH<sup>+</sup> = 591. mp= 73-74°C yield = 28 %

20

Example 9 (+)-4-(3,10-Dibromo-8-chloro-11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-(trifluoromethyl sulfonyl)piperidine

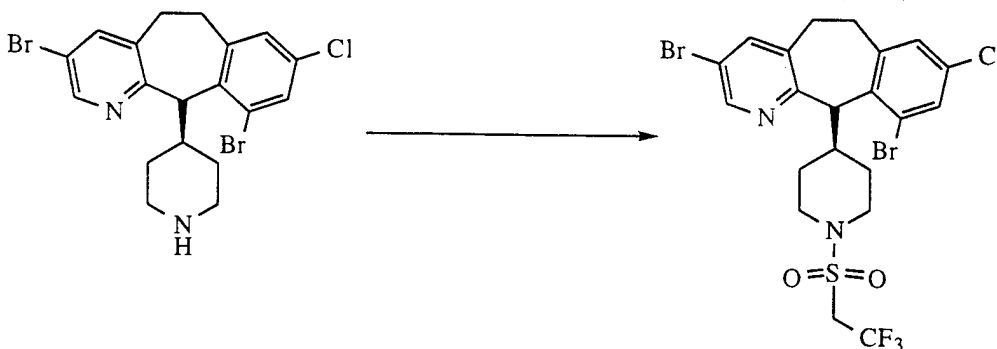


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The title compound is prepared following essentially the same procedure as described in Example 4 except that trifluoromethane sulfonyl chloride was used instead of methane sulfonyl chloride to obtain a solid FAB-MS:  $MH^+ = 603$ . mp= 111-112°C yield = 47 %

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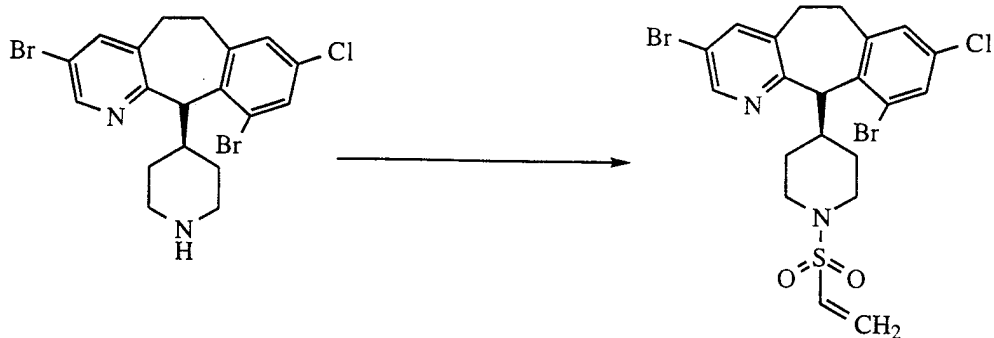
15 Example 10 (+)-4-(3,10-Dibromo-8-chloro-11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-(trifluoroethyl sulfonyl)piperidine



20

The title compound is prepared following essentially the same procedure as described in Example 4 except that trifluoroethane sulfonyl chloride was used instead of methane sulfonyl chloride to obtain a solid FAB-MS:  $MH^+ = 617$ . mp= 174-175°C yield = 46 %

Example 11 (+)-4-(3,10-Dibromo-8-chloro-11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-(vinylsulfonyl)piperidine

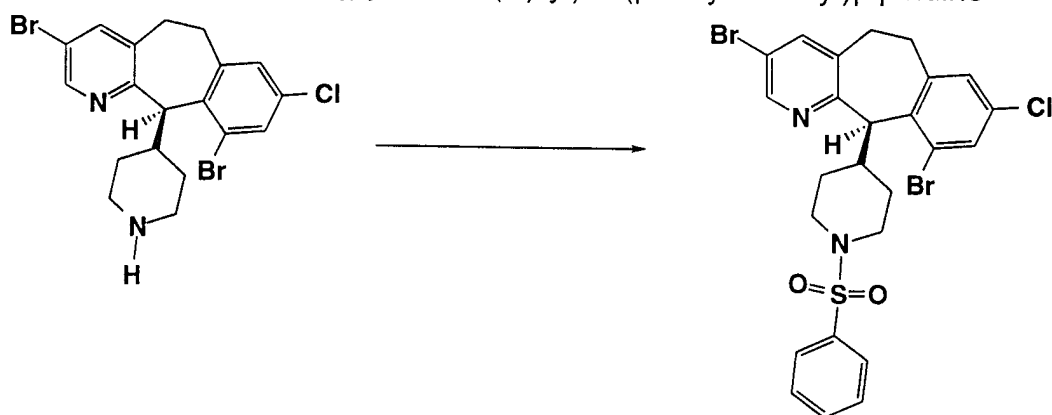


The title compound is prepared following essentially the same procedure as described in Example 4 except that 2-chloro-ethane sulfonyl chloride was used instead of methane sulfonyl chloride to obtain a solid FAB-MS: MH<sup>+</sup> = 514. mp=

5 129-130°C yield = 35 %

10

Example 12 (+) -4-(3,10-Dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(R)-yl)-1-(phenylsulfonyl)piperidine

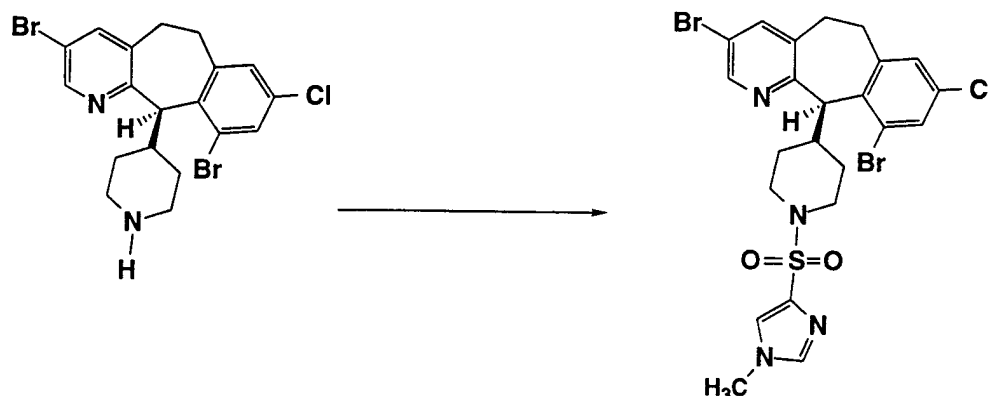


To the title compound of Preparative Example 3 (0.05 g, 0.11 mmol) and

15 triethylamine (0.015 mL, 1.5 eq) dissolved in anhydrous dichloromethane (10 mL) was added benzenesulfonyl chloride (0.015 mL, 1.1 eq). After stirring at room temperature overnight, the solution was diluted with dichloromethane, washed with 1 M hydrochloric acid, then washed with 1N aqueous sodium hydroxide and dried over anhydrous magnesium sulfate. Filtration and concentration *in vacuo* afforded

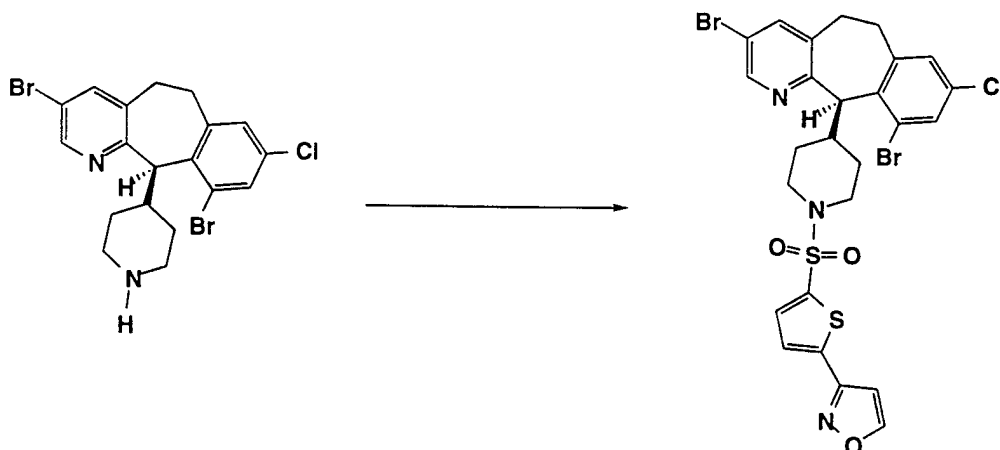
20 the title compound (0.064 g, 99% yield, mp=124.3-129°C).

Example 13 (+) -4-(3,10-Dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(R)-yl)-1-[(1-methyl-1H-imidazol-4-yl)sulfonyl]piperidine



- 5 To the title compound of Preparative Example 3 (0.05 g, 0.11 mmol) and triethylamine (0.015 mL, 1.5 eq) dissolved in anhydrous dichloromethane (10 mL) was added 1-methylimidazole-4-sulfonyl chloride (0.021 g, 1.1 eq). After stirring at room temperature overnight, the solution was diluted with dichloromethane, washed with 1 M hydrochloric acid, then washed with 1 N aqueous sodium
- 10 hydroxide and dried over anhydrous magnesium sulfate. Filtration and concentration in vacuo afforded the title compound (0.054 g, 82% yield, mp 157.5-161.2°C).

Example 14 (+) -4-(3,10-Dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(R)-yl)-1-[(5-(3-isoxazolyl)-2-thienyl)sulfonyl]piperidine



- To the title compound of Preparative Example 3 (0.05 g, 0.11 mmol) and triethylamine (0.015 mL, 1.5 eq) dissolved in anhydrous dichloromethane (10 mL) was added 5-(isoxazol-3-yl)thiophen-2-sulfonyl chloride (0.029 g, 1.1 eq). After
- 20 stirring at room temperature overnight, the solution was diluted with

dichloromethane, washed with 1 *M* hydrochloric acid, then washed with 1 *N* aqueous sodium hydroxide and dried over anhydrous magnesium sulfate. Filtration and concentration *in vacuo* afforded the title compound (0.069 g, 94%, mp 131.7-134.8°C).

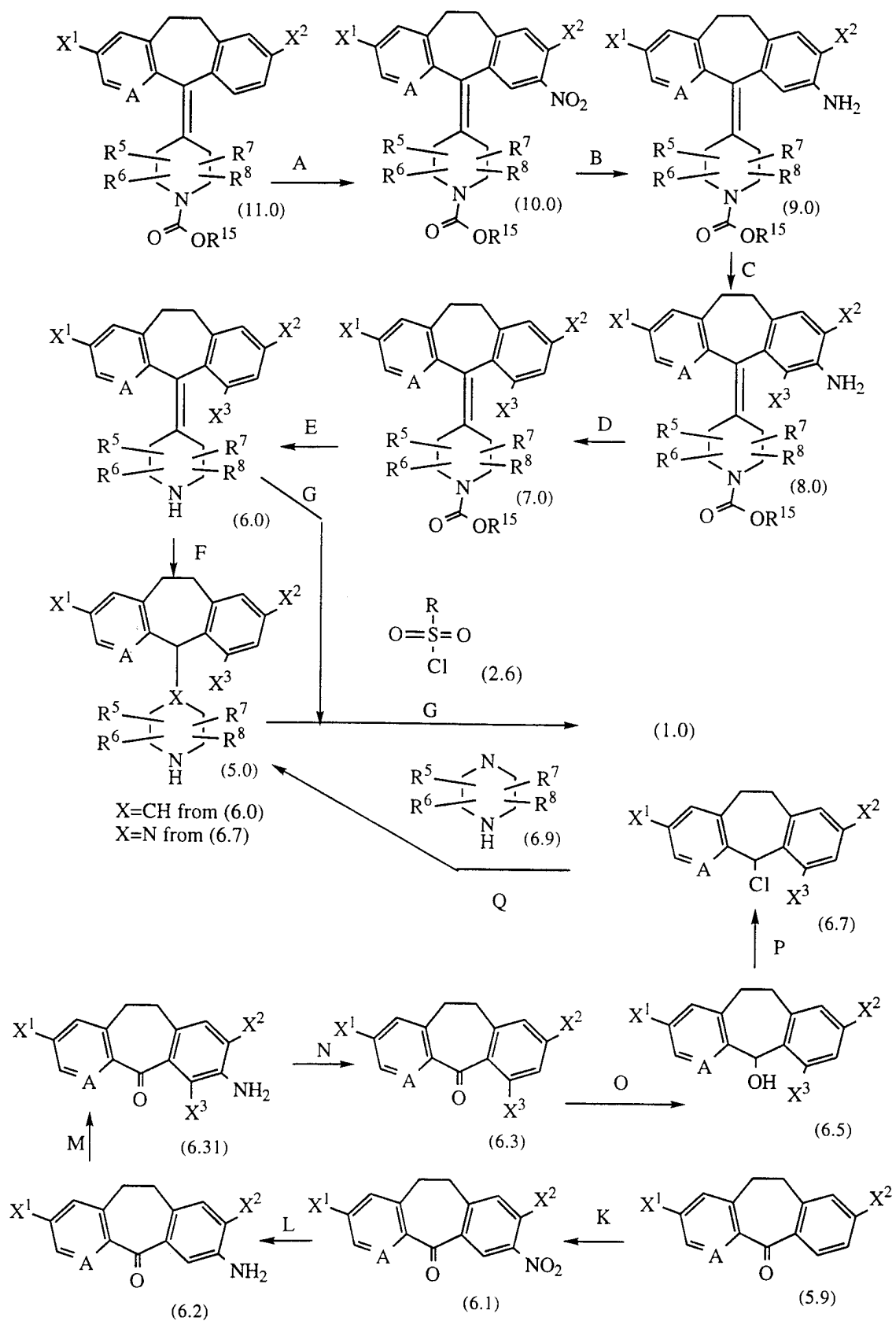
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### PREPARATION OF STARTING MATERIALS

Starting materials useful in preparing the compounds of the present invention are exemplified by the following preparative examples, which should not be construed to limit the scope of the disclosure. The tricyclic compounds used as starting materials, such as compound (11.0), inorganic and organic bases, and alcohols can be prepared using known methods in the art, such as taught in See J. K. Wong et al., Bioorganic & Medicinal Chemistry Letters, Vol. 3, No. 6, pp. 1073-1078, (1993); U.S. Patents 5,089,496; 5,151,423; 4,454,143; 4,355,036; PCT /US94/11390 (WO95/10514); PCT/US94/11391 (WO 95/10515); PCT/US94/11392 (WO95/10516); Stanley R. Sandler and Wolf Karo, Organic Functional Group Preparations, 2nd Edition, Academic Press, Inc., San Diego, California, Vol. 1-3, (1983), and in J. March, Advanced Organic Chemistry, Reactions & Mechanisms, and Structure, 3rd Edition, John Wiley & Sons, New York, 1346 pp. (1985). Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

Starting materials used to prepare the compounds of the present invention are depicted in Scheme IV:

Scheme IV





wherein for Scheme IV,  
A, X, X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, R, Z, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> the solid and dotted lines are as defined hereinbefore; and R<sup>15</sup> can represent any of the values for R<sup>10</sup> or R<sup>12</sup> as defined hereinbefore.

5           In Step A (Scheme IV), compounds of formula (10.0) can be prepared by reacting the compounds of formula (11.0) with a nitrating agent and/or optional protic or aprotic solvent such as those described hereinbefore. In a first procedure, compound (11.0) is reacted with about an equimolar amount of a  
10           nitrate salt, such as potassium nitrate, and acid, such as sulfuric acid at temperatures ranging from about -20° to +5° C. In a second procedure, compound (11.0) is treated with a mixture comprised of about two equivalents of trifluoromethanesulfonic acid and about one equivalent nitric acid in a solvent such as trifluoromethanesulfonic acid. In a third procedure, compound (11.0) is treated with a mixture comprised of about one equivalent of fuming nitric acid and  
15           about ten equivalents of trifluoromethanesulfonic anhydride in a solvent such as nitromethane. In a fourth procedure, compound (11.0) is treated with a nitronium salt, such as nitronium tetrafluoroborate, in a solvent, such as sulfolane. In a fifth procedure, compound (11.0) is reacted with fuming nitric acid at temperatures ranging from about -20° to +50° C.

20           In Step B(Scheme IV), compounds of formula (9.0) can be prepared by reacting compounds of the formula (10.0) with a reducing agent. In a first procedure, compound (10.0) can be reacted with about ten equivalents of a metal, such as iron, in a solvent, such as ethanol, in the presence of a salt, such as calcium chloride, at temperatures ranging from about 0° to +80° C. In a  
25           second procedure, compound (10.0) can be reacted with about ten equivalents of a metal, such as zinc, in a solvent, such as ethanol, in the presence of an acid, such as acetic acid at temperatures ranging from about 0° to +80° C. In a third procedure, compound (10.0) can be reacted with about five equivalents of stannous chloride hydrate in a solvent, such as ethyl acetate. In a fourth  
30           procedure, compound (10.0) can be reacted with about ten equivalents of a metal, such as tin, in a solvent, such as ethanol, in the presence of an acid, such as hydrochloric acid.

          In Step C(Scheme IV), compounds of formula (8.0) can be prepared by reacting compounds of the formula (9.0) with a halogenating agent. In a first  
35           procedure, compound (9.0) can be reacted with an excess of an elemental halogen, such as bromine, in a suitable solvent, such as acetic acid at temperatures ranging from about 0° to 20° C. In a second procedure, compound

(9.0) can be reacted with a salt, such as pyridinium bromide perbromide, in a solvent, such as THF, at temperatures from about 0° to +40° C. In a third procedure, compound (9.0) can be reacted with a halogen, such as chlorine, in the presence of a Lewis acid, such as iron(III) chloride, in a suitable solvent, such as dichloromethane.

In Step D(Scheme IV), compounds of formula (7.0) can be prepared by reacting compounds of the formula (8.0) with an oxidizing agent followed by a reducing agent, or by reacting compounds of the formula (8.0) with an oxidizing agent in the presence of a hydrogen atom source. In a first procedure, compound (8.0) can be reacted with a diazotizing agent, such as t-butyl nitrite, in a solvent and hydrogen atom source, such as DMF at temperatures from about 0° to +100° C. In a second procedure, compound (8.0) can be reacted with a diazotizing agent, such as sodium nitrite, and an acid, such as hydrochloric acid, and a reducing agent, such as hypophosphorous acid at temperatures from about -15° to +50° C. In a third procedure, compound (8.0) can be reacted with a diazotizing agent, such as sodium nitrite, and an acid, such as aqueous sulfuric acid, followed by treatment with a metal, such as copper. In a fourth procedure, compound (8.0) can be reacted with a diazotizing agent, such as sodium nitrite, and an acid, such as fluoboric acid, followed by treatment with a reducing agent, such as sodium borohydride.

In Step E(Scheme IV), compounds of formula (6.0) can be prepared by reacting compounds of the formula (7.0) under hydrolysis conditions. In a first procedure, compound (7.0) can be reacted with an acid, such as hydrochloric acid, at temperatures from about 20° to +90° C. In a second procedure, compound (7.0) can be reacted with a base, such as aqueous sodium hydroxide, in a suitable solvent, such as ethanol, at temperatures from about 20° to +90° C. In a third procedure, compound (7.0) can be reacted with a nucleophile, such as hydrazine hydrate, in a solvent, such as ethanol, with an optional base, such as sodium hydroxide, at temperatures from about 20° to +90° C. In a fourth procedure, compound (7.0) can be reacted with a silyl chloride, such as trimethylsilyl chloride, in a solvent, such as THF or CH<sub>2</sub>Cl<sub>2</sub> at temperatures ranging from about 0°C to reflux. In a fifth procedure, compound (7.0) can be reacted with an acid, such as trifluoroacetic acid, in an aprotic solvent, such as CH<sub>2</sub>Cl<sub>2</sub>.

In Step F(Scheme IV), compounds of formula (5.0) wherein X = CH can be prepared by reacting compounds of the formula (6.0) under reducing conditions. Compound (6.0) can be reacted with an alkyl-metal hydride, such as diisobutyl

aluminum hydride or lithium aluminum hydride (LAH), in a solvent, such as toluene or THF, at temperatures from about 0° to +90° C.

In Step G(Scheme IV), compounds of formula (1.0) can be prepared as described previously for Scheme I.

5        In Step K(Scheme IV), compounds of formula (6.1) can be prepared by reacting the compound of formula (5.9) with a nitrating agent and/or optional protic or aprotic solvent according to the procedures described in Step A (Scheme IV).

10       In Step L (Scheme IV), compounds of formula (6.2) can be prepared by reacting the compound of formula (6.1) with a reducing agent according to the procedures described in Step B (Scheme IV).

In Step M (Scheme IV), compounds of formula (6.31) can be prepared by reacting the compound of formula (6.2) with a halogenating agent according to the procedures described in Step C (Scheme IV).

15       In Step N (Scheme IV), compounds of formula (6.3) can be prepared by reacting the compound of formula (6.31) with an oxidizing agent followed by a reducing agent, or by reacting compounds of the formula (6.31) with an oxidizing agent in the presence of a hydrogen atom source according to the procedures described in Step D (Scheme IV).

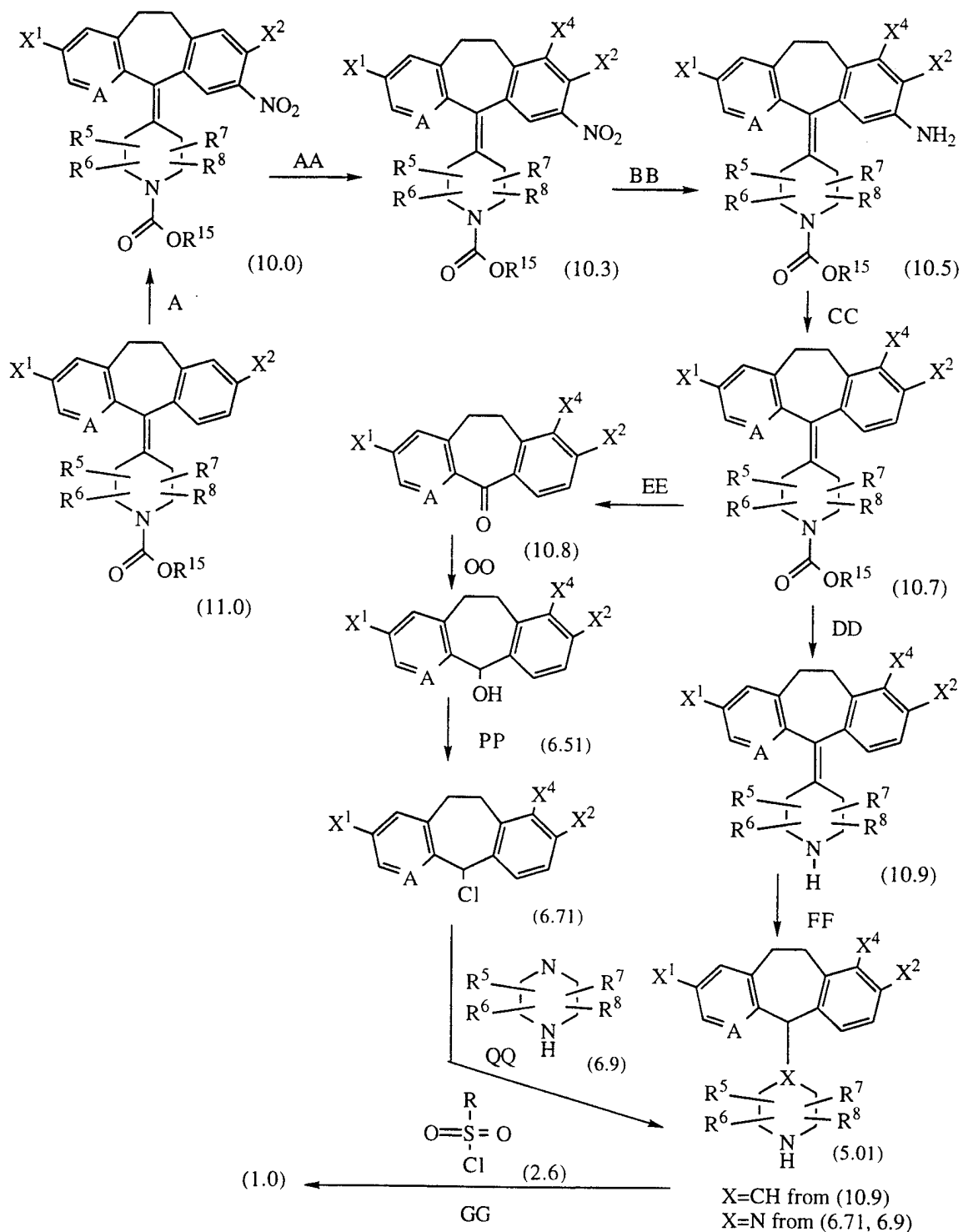
20       In Step O(Scheme IV), compounds of formula (6.5) can be prepared by reacting compounds of formula (6.3) with sodium borohydride ( $\text{NaBH}_4$ ) in a solvent such as ethanol/toluene under reflux conditions for 10 minutes or at 25°C for two hours or more.

25       In Step P (Scheme IV), compounds of formula (6.7) can be prepared by reacting compounds of formula (6.5) with  $\text{SOCl}_2$  in a solvent such as  $\text{CH}_2\text{Cl}_2$  at a temperature of about 25°C for about 4 hours or more.

30       In Step Q (Scheme IV), compounds of formula (5.0) wherein  $X = \text{N}$ , can be prepared by reacting compounds (6.7) with an excess amount of the piperazine compound of formula (6.9) in a solvent such as THF at 25°C or reflux for one hour or more.

Additional starting materials which can be used to prepare the compounds of the present invention are depicted in Scheme V.

Scheme V



In Step A (Scheme V), compounds of formula (10.0) can be prepared from compound of formula (11.0) using the procedures described in Scheme IV, Step A.

In Step AA(Scheme V), compounds of formula (10.3) can be prepared by  
5 reacting compound of formula (10.0) with 1,3-dibromo-5,5-dimethylhydantoin in

an acid, such as trifluoromethane sulfonic acid or sulfuric acid for about 24 h or more at 25°C.

5 In Step BB (Scheme V), compounds of the formula (10.5) can be prepared by treating the compounds of formula (10.3) with a reducing agent, using the procedures taught in Scheme IV, Step B.

10 In Step CC (Scheme V), compounds of formula (10.7) can be prepared by reacting compounds of formula (10.5) with sodium nitrite ( $\text{NaNO}_2$ ) in concentrated aqueous HCl at temperatures ranging from about -10°C to 0°C for about 2 h or more, then treating the reaction mixture with phosphorous acid ( $\text{H}_3\text{PO}_2$ ) at 0°C for 4 h or more.

15 In Step DD (Scheme V), compounds of formula (10.9) can be prepared by reacting compounds of formula (10.7) with concentrated aqueous HCl at about 85°C for about 18 h or more. Compound (10.9) can be reacted using the same procedures described in Scheme IV for treating compound (5.0) and (6.0) and subsequent intermediates therefrom, in order to obtain the desired compounds of formula (1.0).

In Step EE (Scheme V), compounds of formula (10.8) can be prepared by reacting compound of formula (10.7) with  $\text{NaIO}_4$  and  $\text{RuO}_2$  in acetonitrile and water for about 18 to 24 h or more at 25°C.

20 In Step FF (Scheme V), compounds of formula (5.01) wherein  $X = \text{CH}$  can be prepared by reacting compounds of the formula (10.9) under reducing conditions. Compound (10.9) can be reacted with an alkyl-metal hydride, such as diisobutyl aluminum hydride, in a solvent, such as toluene, at temperatures from about 0° to +90° C.

25 In Step GG (Scheme V), compounds of formula (1.0) can be prepared using the methods as described in Scheme I, hereinbefore.

30 In Step OO (Scheme V), compounds of formula (6.51) can be prepared by reacting compounds of formula (10.8) with sodium borohydride ( $\text{NaBH}_4$ ) in a solvent such as ethanol/toluene under reflux conditions for 10 minutes or at 25°C for two hours or more.

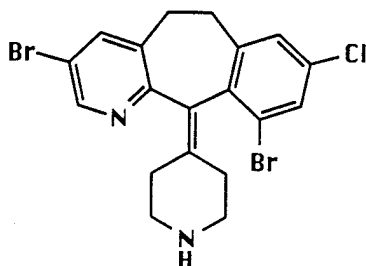
In Step PP (Scheme V), compounds of formula (6.71) can be prepared by reacting compounds of formula (6.51) with  $\text{SOCl}_2$  in a solvent such as  $\text{CH}_2\text{Cl}_2$  at a temperature of about 25°C for about 4 hours or more.

35 In Step QQ (Scheme V), compounds of formula (5.01) wherein  $X = \text{N}$ , can be prepared by reacting compounds (6.71) with an excess amount of the piperazine compound of formula (6.9) in a solvent such as THF at 25°C or reflux for one hour or more.

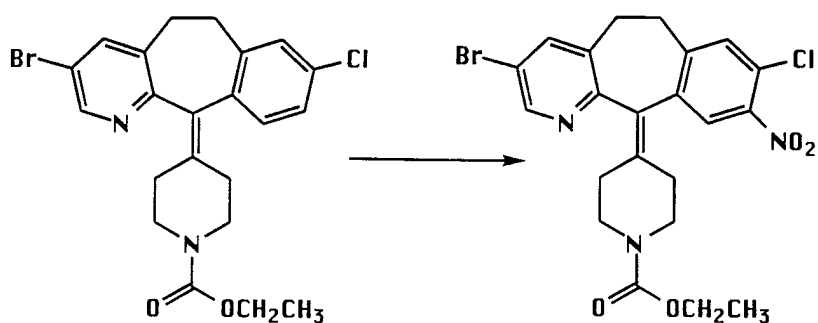
Referring to the Schemes IV and V, except as noted otherwise, temperatures can range from 0° to 100°C, or reflux of the reaction mixture and amounts of the reagents (e.g. compound 2.6) can range from 1 to about 10 moles per mole of reactant (e.g. compound 5.0 or 6.0).

- 5 The following preparative examples are intended to exemplify selected starting materials for preparing compounds of the present invention.

Preparative Example 1

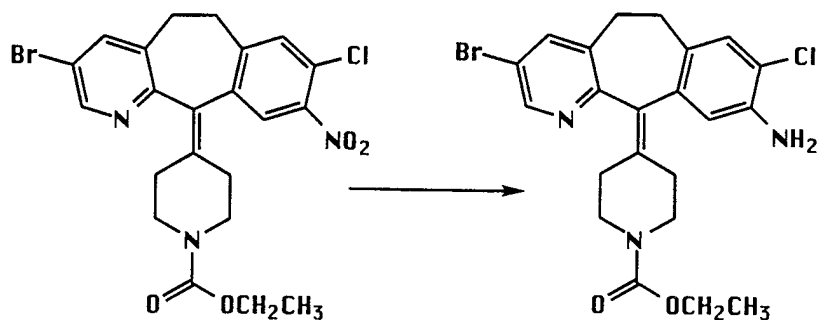


10 Step A:



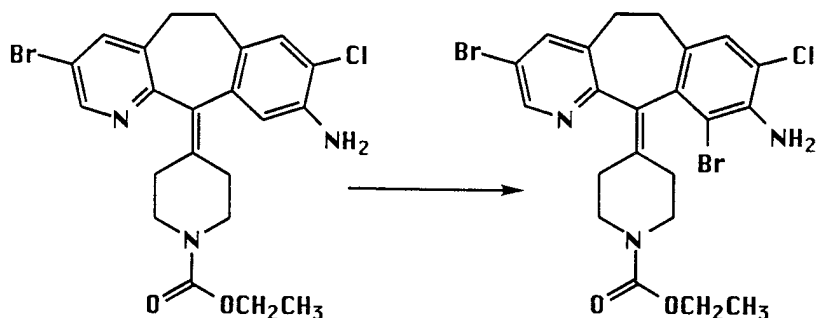
- Combine 15 g (38.5 mmol) of 4-(8-chloro-3-bromo-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester (as taught in Preparative Example 47 of PCT/US 94/11392) and 150 mL of concentrated H<sub>2</sub>SO<sub>4</sub> at -5°C, then add 3.89 g (38.5 mmol) of KNO<sub>3</sub> and stir for 4 hours. Pour the mixture into 3 L of ice and basify with 50% NaOH (aqueous). Extract with CH<sub>2</sub>Cl<sub>2</sub>, dry over MgSO<sub>4</sub>, then filter and concentrate *in vacuo* to a residue. Recrystallize the residue from acetone to give 6.69 g of the product.

20 Step B:



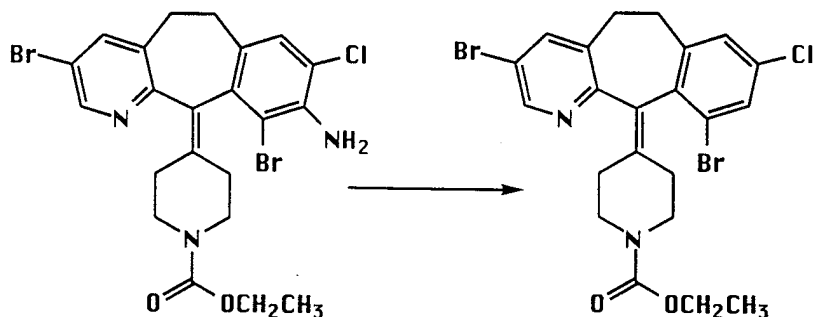
Combine 6.69 g (13.1 mmol) of the product of Step A and 100 mL of 85% EtOH/water, then add 0.66 g (5.9 mmol) of  $\text{CaCl}_2$  and 6.56 g (117.9 mmol) of Fe and heat the mixture at reflux overnight. Filter the hot reaction mixture through  
 5 Celite® and rinse the filter cake with hot EtOH. Concentrate the filtrate *in vacuo* to give 7.72 g of the product.

Step C:



Combine 7.70 g of the product of Step B and 35 mL of HOAc, then add 45 mL of a  
 10 solution of  $\text{Br}_2$  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  $\text{MgSO}_4$  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).

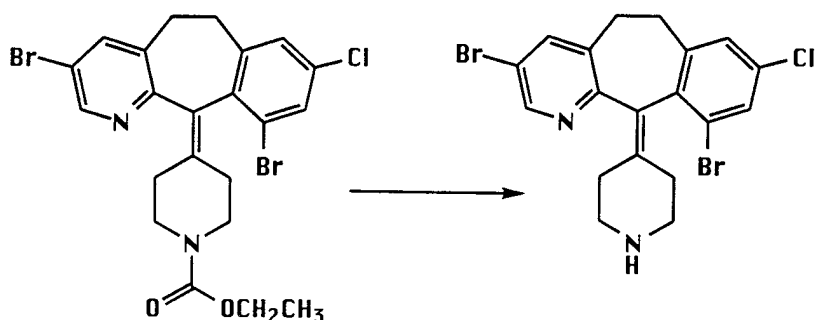
Step D:



Combine 0.557 g (5.4 mmol) of t-butylnitrite and 3 mL of DMF, and heat the mixture at to 60°-70°C. Slowly add (dropwise) a mixture of 2.00 g (3.6 mmol) of

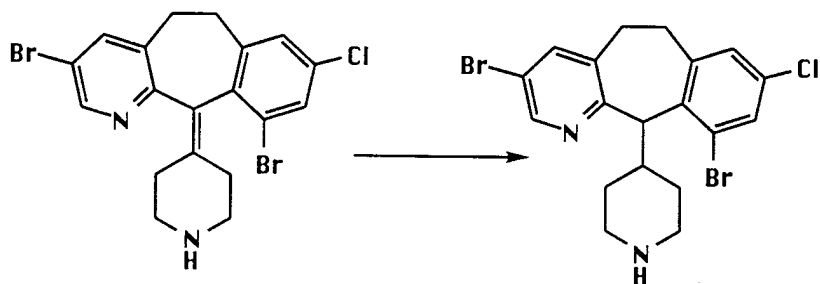
- the product of Step C and 4 mL of DMF, then cool the mixture to room temperature. Add another 0.64 mL of t-butyl nitrite at 40°C and reheat the mixture to 60°-70°C for 0.5 hrs. Cool to room temperature and pour the mixture into 150 mL of water. Extract with CH<sub>2</sub>Cl<sub>2</sub>, dry the extract over MgSO<sub>4</sub> and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 10%-20% EtOAc/hexane) to give 0.74 g of the product.

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<sub>2</sub>Cl<sub>2</sub>. Dry the extract over MgSO<sub>4</sub> and concentrate *in vacuo* to give 0.59 g of the title compound.

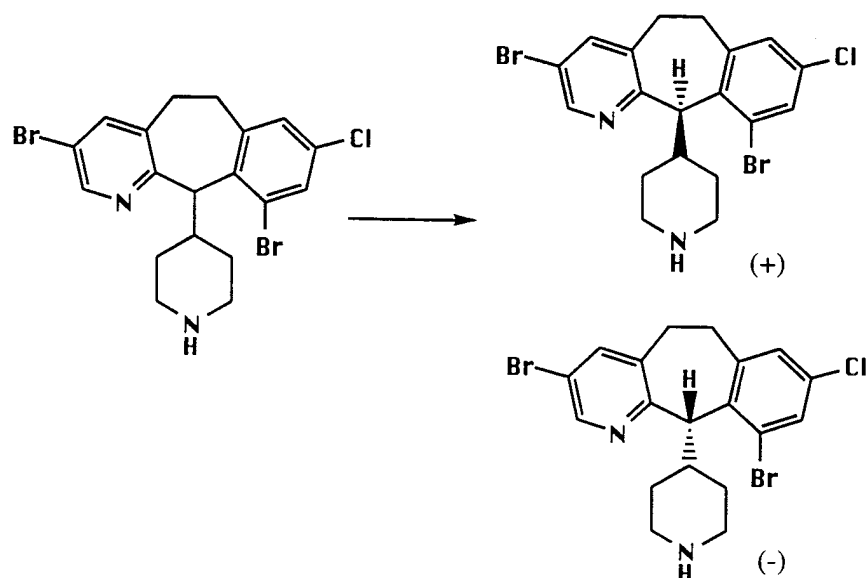
Preparative Example 2



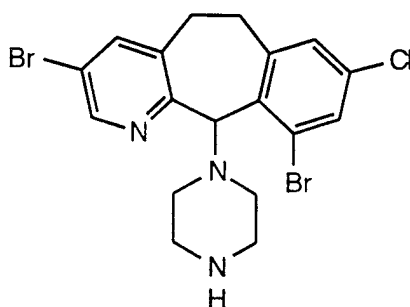
[racemic as well as (+)- and (-)-isomers]

- 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 (diisobutyl aluminum hydride) 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<sub>2</sub>Cl<sub>2</sub>, discard the extract, then basify the aqueous phase by adding 50% NaOH (aqueous). Extract with CH<sub>2</sub>Cl<sub>2</sub>, dry the extract over MgSO<sub>4</sub> and concentrate *in vacuo* to give 7.30 g of the title compound, which is a racemic mixture of enantiomers.



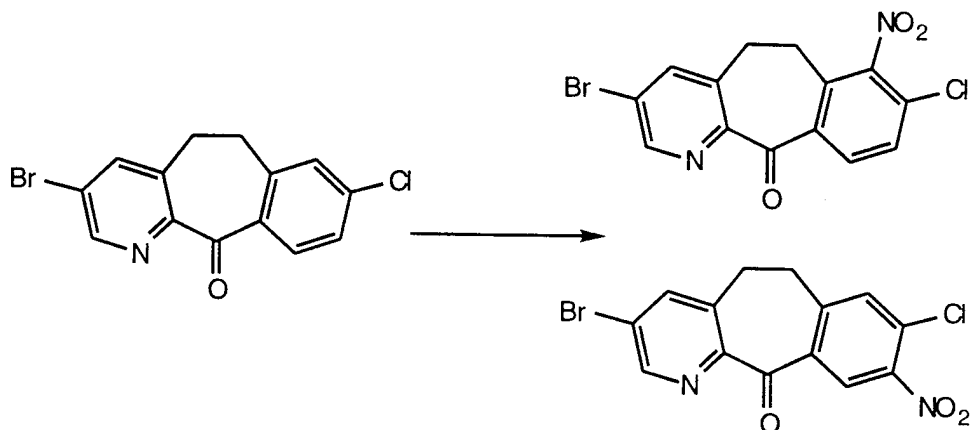
Preparative Example 3 - Separation of Enantiomers:

The racemic title compound of Preparative Example 1 is separated by preparative  
 5 chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, using 20%  
 iPrOH/hexane + 0.2% diethylamine), to give the (+)-isomer and the (-)-isomer of  
 the title compound. Alternatively, the enantiomers can also be separated by  
 crystallization with an amino acid such as N-acetylphenylalanine.

10 Preparative Example 6

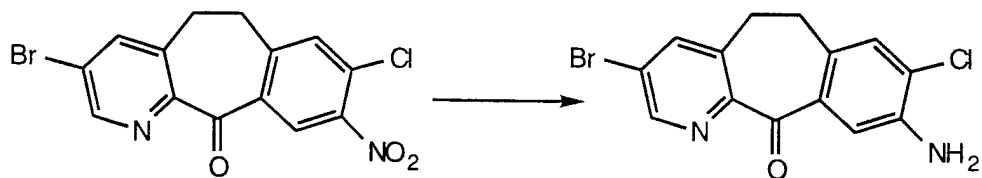
[racemic as well as (+)- and (-)-enantiomer]

Step A:



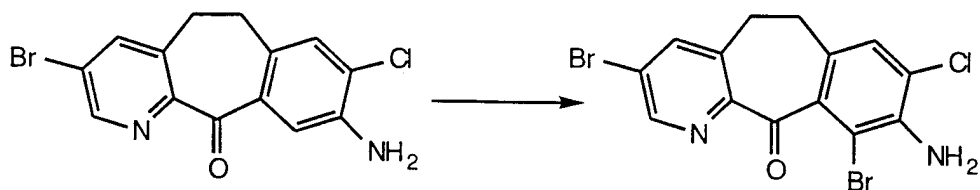
Combine 40.0 g (0.124 mole) of the starting ketone (as taught in Preparative Example 20 of PCT/US 94/11392) and 200 mL of  $\text{H}_2\text{SO}_4$  and cool to  $0^\circ\text{C}$ . Slowly add 13.78 g (0.136 mole) of  $\text{KNO}_3$  over a period of 1.5 hrs., then warm to room temperature and stir overnight. 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.  $\text{MH}^+$  (9-nitro) = 367.

#### 10 Step B:



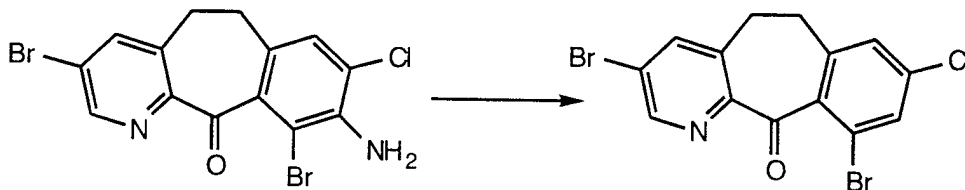
React 28 g (76.2 mmol) of the 9-nitro product of Step A, 400 mL of 85% EtOH/water, 3.8 g (34.3 mmol) of  $\text{CaCl}_2$  and 38.28 g (0.685 mole) of Fe at  $50^\circ\text{C}$ . Heat the mixture at reflux overnight, filter through Celite® and wash the filter cake with 2 X 200 mL of hot EtOH. Combine the filtrate and washes, and concentrate *in vacuo* to a residue. Extract the residue with 600 mL of  $\text{CH}_2\text{Cl}_2$ , wash with 300 mL of water and dry over  $\text{MgSO}_4$ . Filter and concentrate *in vacuo* to a residue, then chromatograph (silica gel, 30% EtOAc/ $\text{CH}_2\text{Cl}_2$ ) to give 24 g of the product.

#### Step C:



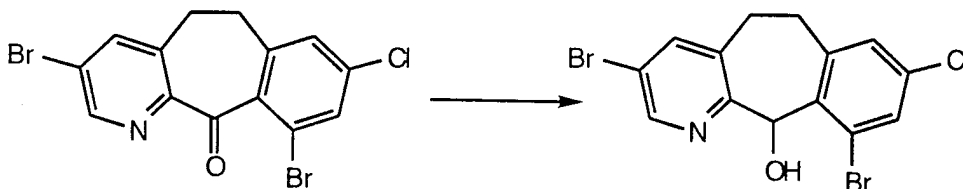
Combine 13 g (38.5 mmol) of the product of Step B, 140 mL of HOAc and slowly add a solution of 2.95 mL (57.8 mmol) of Br<sub>2</sub> in 10 mL of HOAc over a period of 20 min. Stir the reaction mixture at room temperature, then concentrate *in vacuo* to a residue. Add CH<sub>2</sub>Cl<sub>2</sub> and water, then adjust to pH = 8-9 with 50% NaOH (aqueous). Wash the organic phase with water, then brine and dry over Na<sub>2</sub>SO<sub>4</sub>. Concentrate *in vacuo* to give 11.3 g of the product.

Step D:



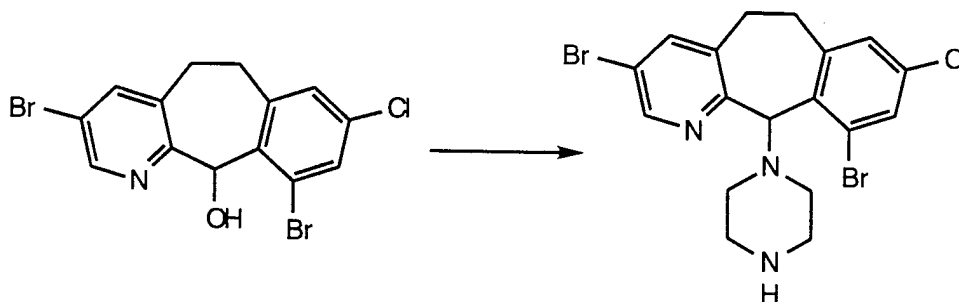
- 10 Cool 100 mL of concentrated HCl (aqueous) to 0°C, then add 5.61 g (81.4 mmol) of NaNO<sub>2</sub> and stir for 10 min. Slowly add (in portions) 11.3 g (27.1 mmol) of the product of Step C and stir the mixture at 0°-3°C for 2.25 hrs. Slowly add (dropwise) 180 mL of 50% H<sub>3</sub>PO<sub>2</sub> (aqueous) and allow the mixture to stand at 0°C overnight. Slowly add (dropwise) 150 mL of 50% NaOH over 30 min., to  
15 adjust to pH = 9, then extract with CH<sub>2</sub>Cl<sub>2</sub>. Wash the extract with water, then brine and dry over Na<sub>2</sub>SO<sub>4</sub>. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2% EtOAc/ CH<sub>2</sub>Cl<sub>2</sub>) to give 8.6 g of the product.

Step E:



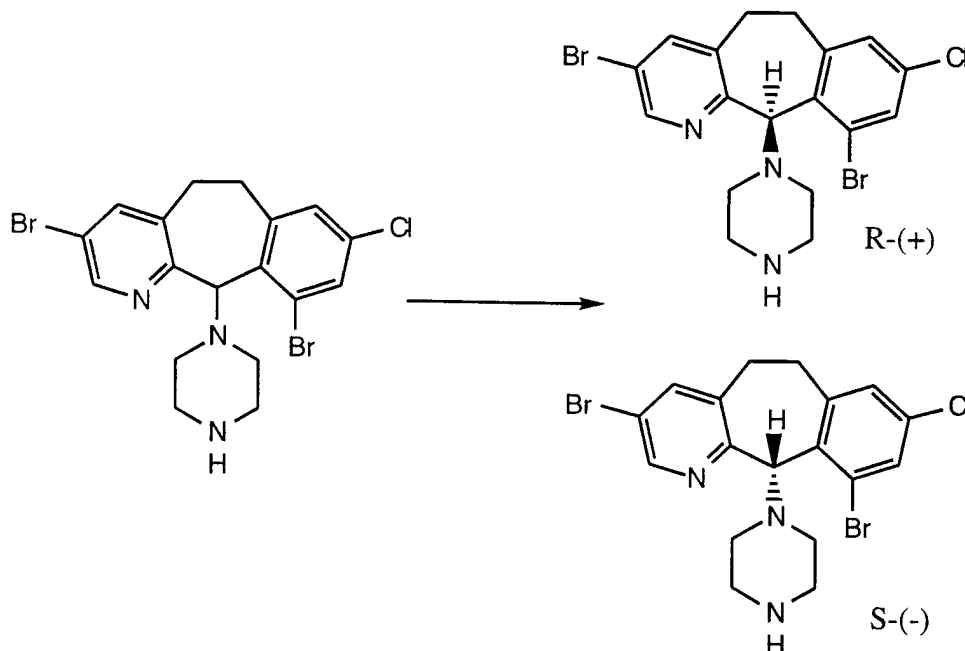
- 20 Combine 8.6 g (21.4 mmol) of the product of Step D and 300 mL of MeOH and cool to 0°-2°C. Add 1.21 g (32.1 mmol) of NaBH<sub>4</sub> and stir the mixture at ~0°C for 1 hr. Add another 0.121 g (3.21 mmol) of NaBH<sub>4</sub>, stir for 2 hr. at 0°C, then let stand overnight at 0°C. Concentrate *in vacuo* to a residue then partition the  
25 residue between CH<sub>2</sub>Cl<sub>2</sub> and water. Separate the organic phase and concentrate *in vacuo* (50°C) to give 8.2 g of the product.

Step F:

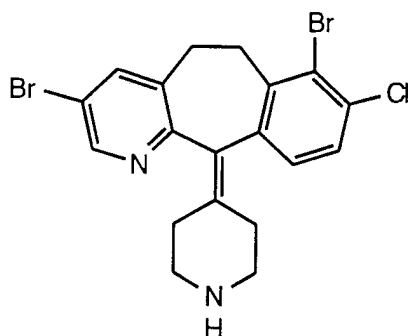
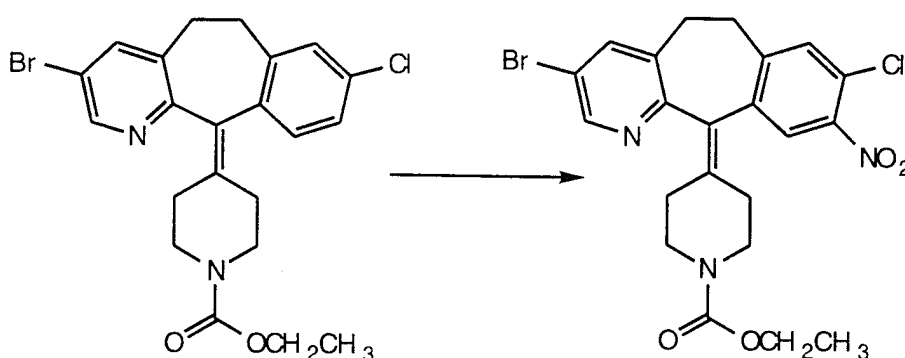


- Combine 8.2 g (20.3 mmol) of the product of Step E and 160 mL of  $\text{CH}_2\text{Cl}_2$ , cool to  $0^\circ\text{C}$ , then slowly add (dropwise) 14.8 mL (203 mmol) of  $\text{SOCl}_2$  over a 30 min. period. Warm the mixture to room temperature and stir for 4.5 hrs., then
- 5 concentrate *in vacuo* to a residue, add  $\text{CH}_2\text{Cl}_2$  and wash with 1 N NaOH (aqueous) then brine and dry over  $\text{Na}_2\text{SO}_4$ . Concentrate *in vacuo* to a residue, then add dry THF and 8.7 g (101 mmol) of piperazine and stir at room temperature overnight. Concentrate *in vacuo* to a residue, add  $\text{CH}_2\text{Cl}_2$ , and wash with 0.25 N NaOH (aqueous), water, then brine. Dry over  $\text{Na}_2\text{SO}_4$  and concentrate *in vacuo* to
- 10 give 9.46 g of the crude product. Chromatograph (silica gel, 5% MeOH/ $\text{CH}_2\text{Cl}_2$  +  $\text{NH}_3$ ) to give 3.59 g of the title compound, as a racemate.

#### Step G - Separation of Enantiomers:

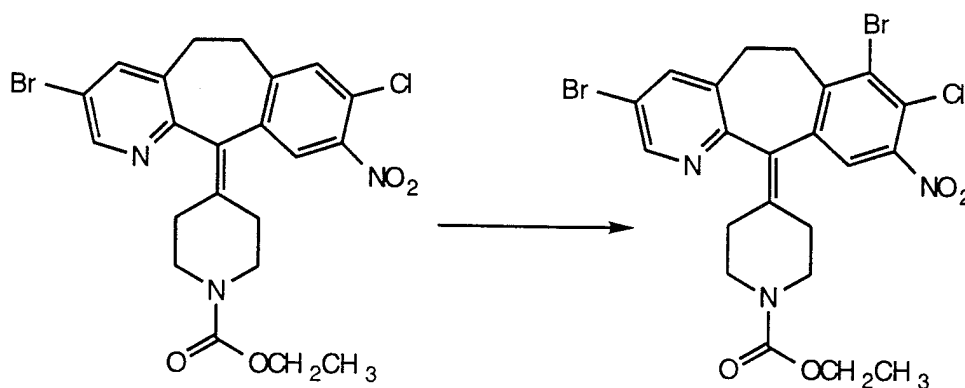


- 15 The racemic title compound from Step F (5.7 g) is chromatographed by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, flow rate 100 mL/min) using 30% iPrOH/hexane + 0.2% diethylamine, to give 2.88 g of the R-(+)-enantiomer and 2.77 g of the S-(-)-enantiomer of the title compound.

Preparative Example 75 Step A:

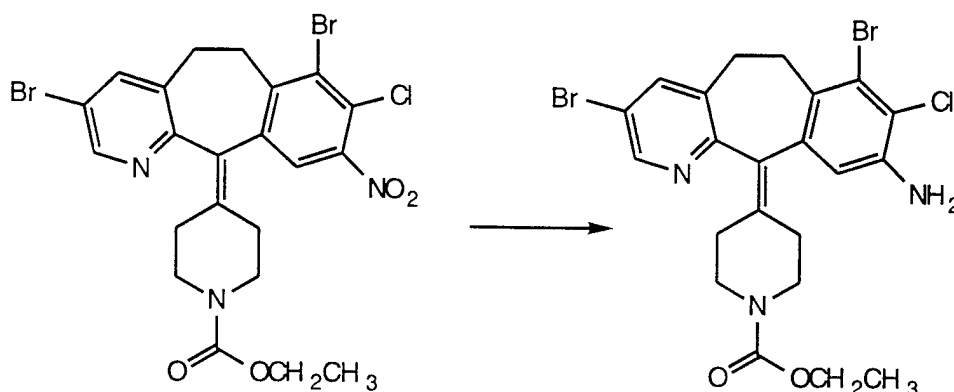
- Combine 25.86 g (55.9 mmol) of 4-(8-chloro-3-bromo-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester and 250 mL of concentrated  $\text{H}_2\text{SO}_4$  at  $-5^\circ\text{C}$ , then add 4.8 g (56.4 mmol) of  $\text{NaNO}_3$  and stir for 2 hours. Pour the mixture into 600 g of ice and basify with concentrated  $\text{NH}_4\text{OH}$  (aqueous). Filter the mixture, wash with 300 mL of water, then extract with 500 mL of  $\text{CH}_2\text{Cl}_2$ . Wash the extract with 200 mL of water, dry over  $\text{MgSO}_4$ , then filter and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 10% EtOAc/  $\text{CH}_2\text{Cl}_2$ ) to give 24.4 g (86% yield) of the product. m.p. =  $165\text{--}167^\circ\text{C}$ .

Step B:



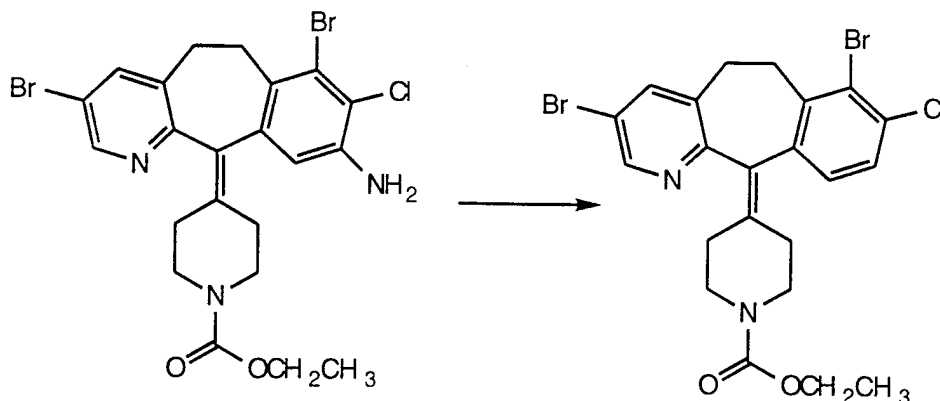
Combine 20 g (40.5 mmol) of the product of Step A and 200 mL of concentrated H<sub>2</sub>SO<sub>4</sub> at 20°C, then cool the mixture to 0°C. Add 7.12 g (24.89 mmol) of 1,3-dibromo-5,5-dimethyl-hydantoin to the mixture and stir for 3 hours at 20°C. Cool to 0°C, add an additional 1.0 g (3.5 mmol) of the dibromohydantoin and stir at 20°C for 2 hours. Pour the mixture into 400 g of ice, basify with concentrated NH<sub>4</sub>OH (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.

#### Step C:



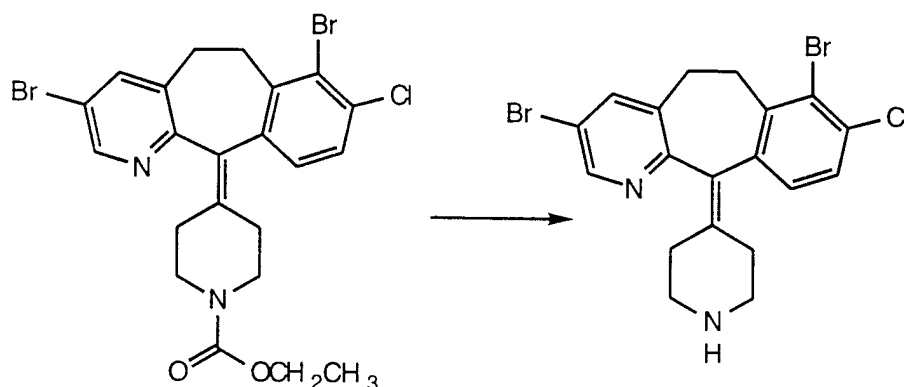
Combine 25 g (447 mmol) of Fe filings, 10 g (90 mmol) of CaCl<sub>2</sub> and a suspension of 20 g (34.19 mmol) of the product of Step B in 700 mL of 90:10 EtOH/water at 50°C. Heat the mixture at reflux overnight, filter through Celite® and wash the filter cake with 2 X 200 mL of hot EtOH. Combine the filtrate and washes, and concentrate *in vacuo* to a residue. Extract the residue with 600 mL of CH<sub>2</sub>Cl<sub>2</sub>, wash with 300 mL of water and dry over MgSO<sub>4</sub>. Filter and concentrate *in vacuo* to a residue, then chromatograph (silica gel, 30% EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) to give 11.4 g (60% yield) of the product.

#### Step D:



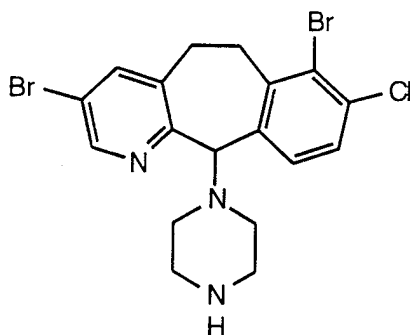
Slowly add (in portions) 20 g (35.9 mmol) of the product of Step C to a solution of 8 g (116 mmol) of NaNO<sub>2</sub> in 120 mL of concentrated HCl (aqueous) at -10°C. Stir the resulting mixture at 0°C for 2 hours, then slowly add (dropwise) 150 mL (1.44 mole) of 50% H<sub>3</sub>PO<sub>2</sub> at 0°C over a 1 hour period. Stir at 0°C for 3 hours, then pour into 600 g of ice and basify with concentrated NH<sub>4</sub>OH (aqueous). Extract with 2 X 300 mL of CH<sub>2</sub>Cl<sub>2</sub>, dry the extracts over MgSO<sub>4</sub>, 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.

#### Step E:



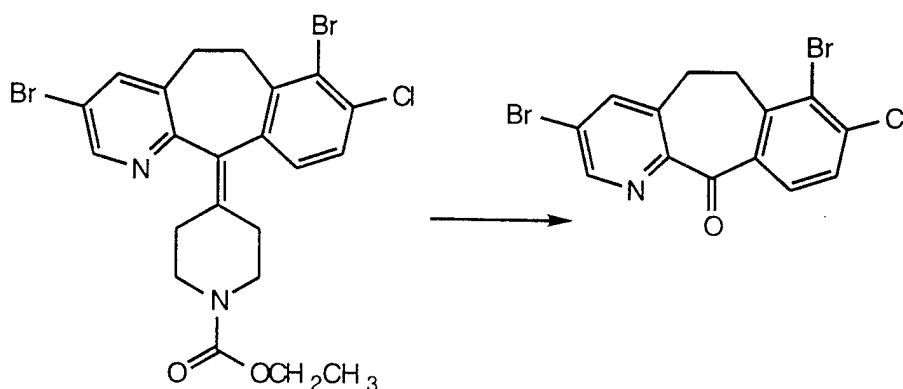
Combine 6.8 g (12.59 mmol) of the product of Step D and 100 mL of concentrated HCl (aqueous) and stir at 85°C overnight. Cool the mixture, pour it into 300 g of ice and basify with concentrated NH<sub>4</sub>OH (aqueous). Extract with 2 x 300 mL of CH<sub>2</sub>Cl<sub>2</sub>, then dry the extracts over MgSO<sub>4</sub>. Filter, concentrate *in vacuo* to a residue, then chromatograph (silica gel, 10% MeOH/EtOAc + 2% NH<sub>4</sub>OH (aqueous)) to give 5.4 g (92% yield) of the title compound.

#### Preparative Example 8



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

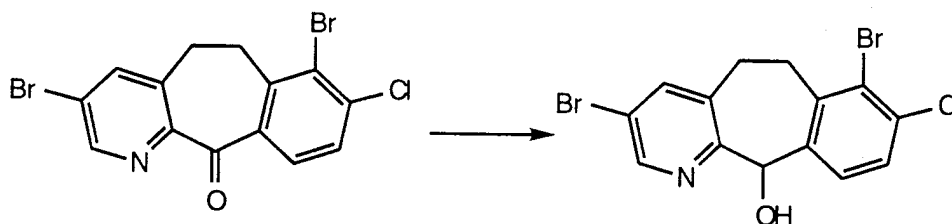
Step A:



- 5 Combine 16.6 g (0.03 mole) of the product of Preparative Example 7, Step D, with a 3:1 solution of CH<sub>3</sub>CN and water (212.65 mL CH<sub>3</sub>CN and 70.8 mL of water) and stir the resulting slurry overnight at room temperature. Add 32.833 g (0.153 mole) of NaIO<sub>4</sub> and then 0.31 g (2.30 mmol) of RuO<sub>2</sub> and stir at room temperature (the addition of RuO<sub>2</sub> is accompanied by an exothermic reaction and the
- 10 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<sub>2</sub>Cl<sub>2</sub>. Concentrate the filtrate *in vacuo* to a residue and dissolve the residue in CH<sub>2</sub>Cl<sub>2</sub>. Filter to remove insoluble solids and wash the solids with CH<sub>2</sub>Cl<sub>2</sub>. Wash the filtrate with water, concentrate to a volume of about
- 15 200 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<sub>2</sub>Cl<sub>2</sub>, dry over MgSO<sub>4</sub> 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
- 20 solids *in vacuo* to give 7.95 g of the product.

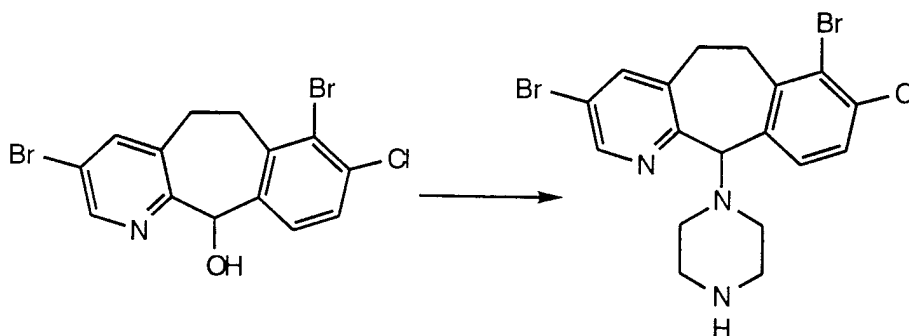
Step B:





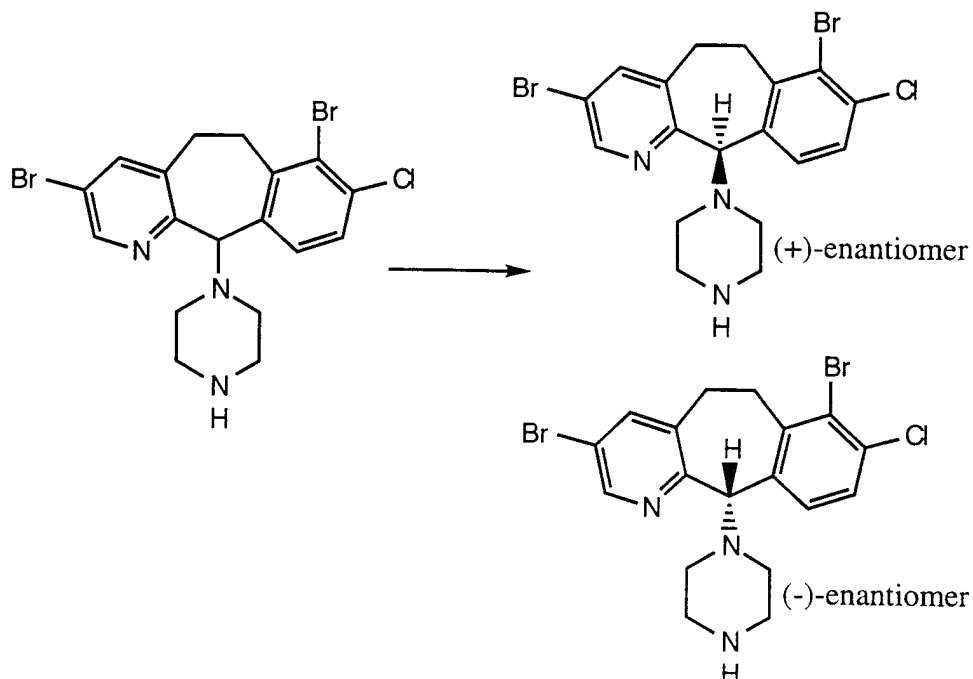
Combine 21.58 g (53.75 mmol) of the product of Step A and 500 mL of an anhydrous 1:1 mixture of EtOH and toluene, add 1.43 g (37.8 mmol) of NaBH<sub>4</sub> and heat the mixture at reflux for 10 min. Cool the mixture to 0°C, add 100 mL of water, then adjust to pH≈ 4-5 with 1 M HCl (aqueous) while keeping the temperature <10°C. Add 250 mL of EtOAc and separate the layers. Wash the organic layer with brine (3 X 50 mL) then dry over Na<sub>2</sub>SO<sub>4</sub>. Concentrate *in vacuo* to a residue (24.01 g) and chromatograph the residue (silica gel, 30 % hexane/CH<sub>2</sub>Cl<sub>2</sub>) to give the product. Impure fractions were purified by rechromatography. A total of 18.57 g of the product is obtained.

#### Step C:



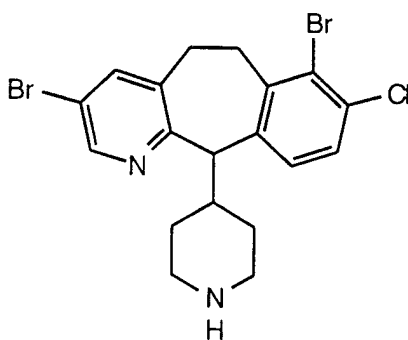
Combine 18.57 g (46.02 mmol) of the product of Step B and 500 mL of CHCl<sub>3</sub>, then add 6.70 mL (91.2 mmol) of SOCl<sub>2</sub>, and stir the mixture at room temperature for 4 hrs. Add a solution of 35.6 g (0.413 mole) of piperazine in 800 mL of THF over a period of 5 min. and stir the mixture for 1 hr. at room temperature. Heat the mixture at reflux overnight, then cool to room temperature and dilute the mixture with 1 L of CH<sub>2</sub>Cl<sub>2</sub>. Wash with water (5 X 200 mL), and extract the aqueous wash with CHCl<sub>3</sub> (3 X 100 mL). Combine all of the organic solutions, wash with brine (3 X 200 mL) and dry over MgSO<sub>4</sub>. Concentrate *in vacuo* to a residue and chromatograph (silica gel, gradient of 5%, 7.5%, 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> + NH<sub>4</sub>OH) to give 18.49 g of the title compound as a racemic mixture.

#### Step D - Separation of Enantiomers:



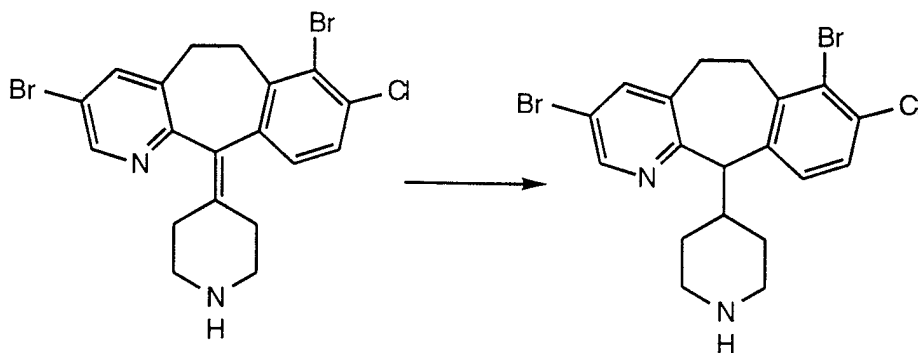
The racemic title compound of Step C is separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, flow rate 100 mL/min., 20% iPrOH/hexane + 0.2% diethylamine), to give 9.14 g of the (+)-enantiomer and 9.30 g of the (-)-enantiomer.

#### Preparative Example 9



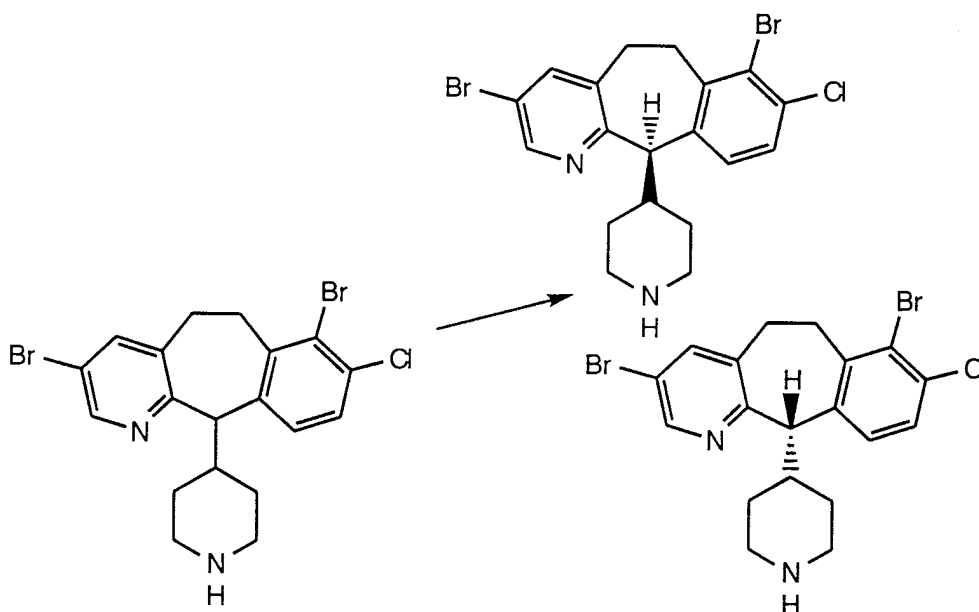
[racemic as well as (+)- and (-)-enantiomer]

#### 10 Step A:



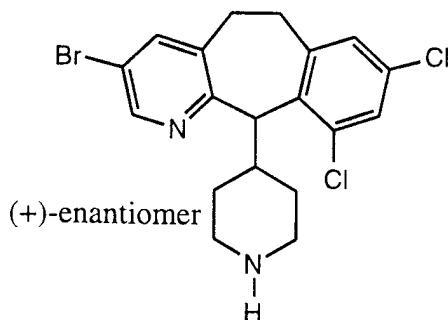
Combine 13 g (33.3 mmol) of the title compound from Preparative Example 7, and 300 mL of toluene at 20°C, then add 32.5 mL (32.5 mmol) of a 1 M solution of DIBAL in toluene. Heat the mixture at reflux for 1 hr., cool to 20°C, add another 32.5 mL of 1 M DIBAL solution and heat at reflux for 1 hr. Cool 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<sub>2</sub>Cl<sub>2</sub> (3 x 200 mL), dry the organic layers over MgSO<sub>4</sub>, then concentrate *in vacuo* to a residue. Chromatograph (silica gel, 12% MeOH/CH<sub>2</sub>Cl<sub>2</sub> + 4% NH<sub>4</sub>OH) to give 10.4 g of the title compound as a racemate.

#### Step B - Separation of Enantiomers:

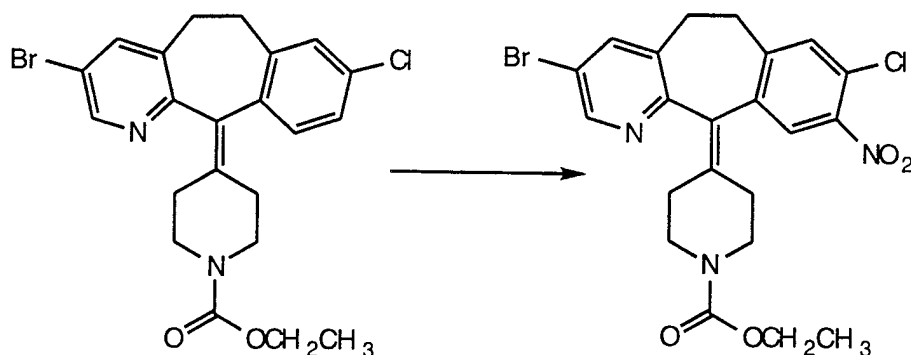


The racemic title compound of Step A is separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, using 5% iPrOH/hexane + 0.2% diethylamine), to give the (+)-enantiomer and the (-)-enantiomer of the title compound.

#### Preparative Example 10

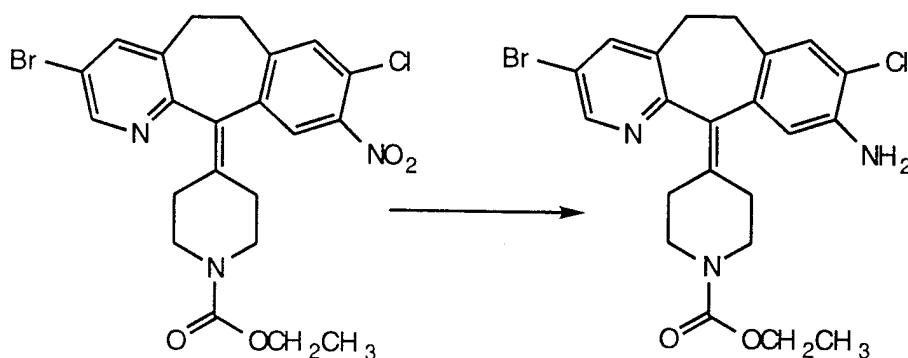


#### Step A:



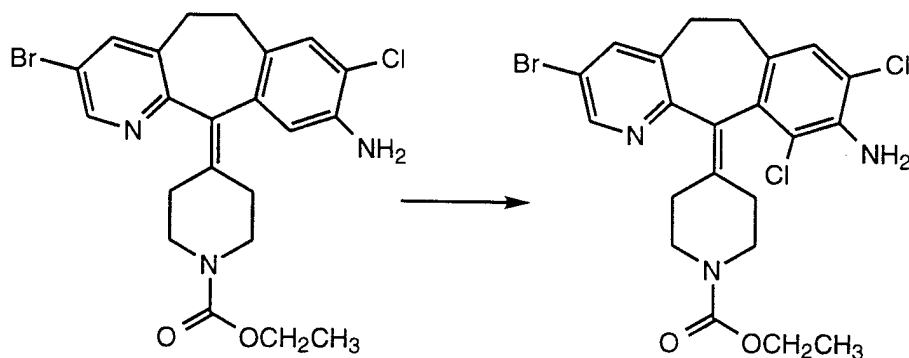
Combine 15 g (38.5 mmol) of 4-(8-chloro-3-bromo-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester and 150 mL of concentrated H<sub>2</sub>SO<sub>4</sub> at -5°C, then add 3.89 g (38.5 mmol) of KNO<sub>3</sub> and stir for 4 hours. Pour the mixture into 3 L of ice and basify with 50% NaOH (aqueous). Extract with CH<sub>2</sub>Cl<sub>2</sub>, dry over MgSO<sub>4</sub>, then filter and concentrate *in vacuo* to a residue. Recrystallize the residue from acetone to give 6.69 g of the product.

#### Step B:



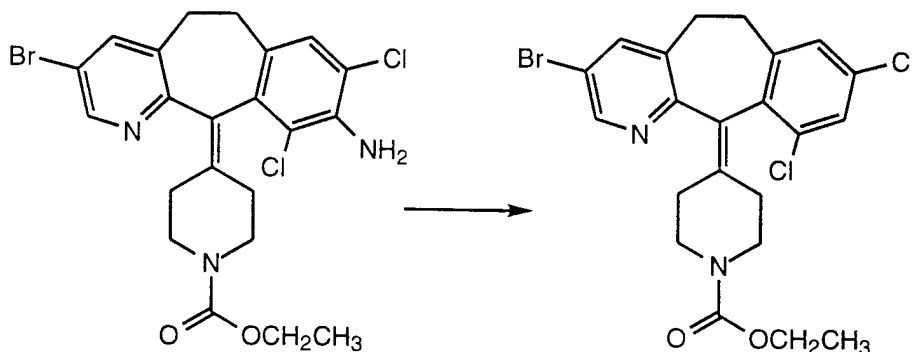
Combine 6.69 g (13.1 mmol) of the product of Step A and 100 mL of 85% EtOH/water, then add 0.66 g (5.9 mmol) of CaCl<sub>2</sub> and 6.56 g (117.9 mmol) of Fe and heat the mixture at reflux overnight. Filter the hot reaction mixture through Celite® and rinse the filter cake with hot EtOH. Concentrate the filtrate *in vacuo* to give 7.72 g of the product.

#### Step C:



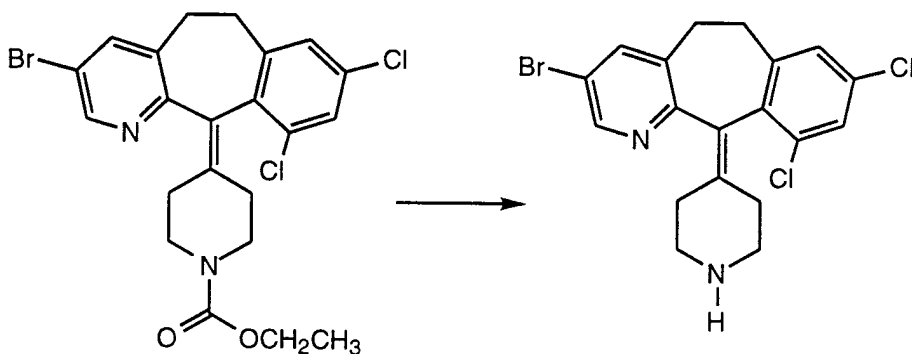
Dissolve 9.90 g (18.9 mmol) of the product of Step B, in 150 mL CH<sub>2</sub>Cl<sub>2</sub> and 200 mL of CH<sub>3</sub>CN and heat to 60°C. Add 2.77 g (20.8 mmol) N-chlorosuccinimide and heat to reflux for 3 h., monitoring the reaction by TCL (30%EtOAc/H<sub>2</sub>O). Add an additional 2.35 g (10.4 mmol) of N-chlorosuccinimide and reflux an additional 45 min. Cool the reaction mixture to room temperature and extract with 1N NaOH and CH<sub>2</sub>Cl<sub>2</sub>. Dry the CH<sub>2</sub>Cl<sub>2</sub> layer over MgSO<sub>4</sub>, filter and purify by flash chromatography (1200 mL normal phase silica gel, eluting with 30% EtOAc/H<sub>2</sub>O) to obtain 6.24 g of the desired product. M.p. 193-195.4°C.

#### Step D:



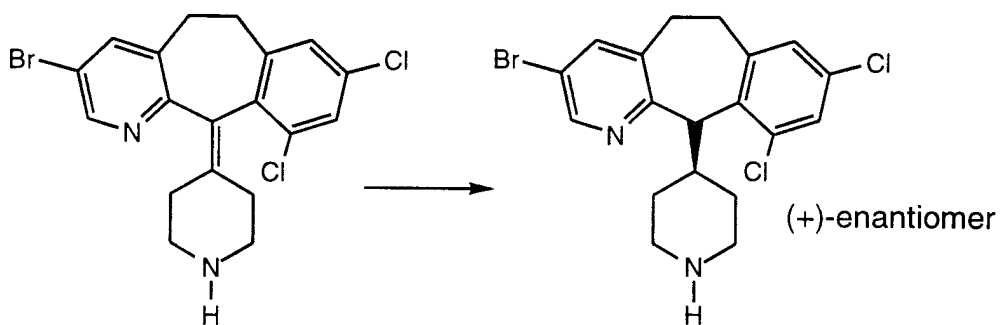
To 160 mL of conc. HCl at -10°C add 2.07 g (30.1 mmol) NaNO<sub>2</sub> and stir for 10 min. Add 5.18 g (10.1 mmol) of the product of Step A and warm the reaction mixture from -10°C to 0°C for 2 h. Cool the reaction to -10°C, add 100 mL H<sub>3</sub>PO<sub>2</sub> and let stand overnight. To extract the reaction mixture, pour over crushed ice and basify with 50% NaOH/ CH<sub>2</sub>Cl<sub>2</sub>. Dry the organic layer over MgSO<sub>4</sub>, 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.

#### Step E:



Dissolve 3.9 g of the product of Step D in 100 mL conc. HCl and reflux overnight. Cool the mixture, basify with 50 % w/w NaOH and extract the resultant mixture with CH<sub>2</sub>Cl<sub>2</sub>. Dry the CH<sub>2</sub>Cl<sub>2</sub> layer over MgSO<sub>4</sub>,  
 5 evaporate the solvent and dry under vacuum to obtain 3.09 g of the desired product.

Step F:



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

ASSAYS

1. In vitro enzyme assays: FPT IC<sub>50</sub> (inhibition of farnesyl protein transferase, in vitro enzyme assay) are determined by the methods disclosed in WO/10515 or WO 95/10516. The data demonstrate that the compounds of the invention are inhibitors of Ras-CVLS farnesylation by partially purified rat brain farnesyl protein transferase (FPT). The data also show that there are compounds of the invention which can be considered as potent (IC<sub>50</sub> <10 μM) inhibitors of Ras-CVLS farnesylation by partially purified rat brain FPT.

2. Cell-based assay. COS IC<sub>50</sub> values refer to the COS cells activity inhibition of Ras processing, are determined by the methods disclosed in WO/10515 or WO 95/10516.

Example No.	H-ras FPT IC <sub>50</sub> (μM)	
1	0.0080	
2	0.1640	
3	0.0260	
4	0.0070	
5	0.0154	
6	0.0320	
7	0.1100	
8	0.3200	
9	0.0340	
10	0.0890	
11	0.0320	
12	0.1790	
13	0.0850	
14	0.2760	

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.

5 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  
10 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 ExamplesEXAMPLE 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	<u>3</u>	<u>7</u>
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	<u>7</u>	<u>7</u>
Total		253	700

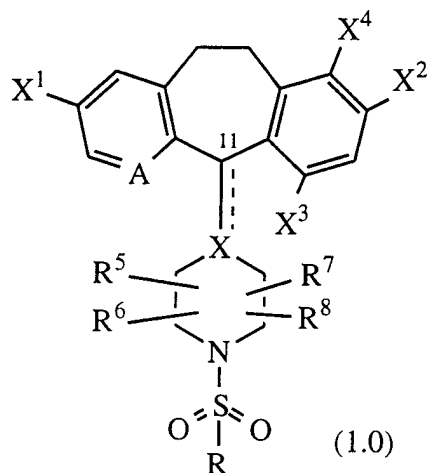
10 Method of Manufacture

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.

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

WHAT IS CLAIMED IS:

1. A compound of the formula:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

- 5 A represents N or N-oxide;

X represents N, CH or C, such that when X is N or CH, there is a single bond to carbon atom 11 as represented by the solid line; or when X is C, there is a double bond to carbon atom 11, as represented by the solid and dotted lines;

X¹ and X² are independently selected from bromo, iodo or chloro;

- 10 X³ and X⁴ are independently selected from bromo, iodo, chloro, fluoro or hydrogen provided only one of X³ or X⁴ is hydrogen;

R⁵, R⁶, R⁷ and R⁸ each independently represents hydrogen, alkyl, aryl, or -CONR²⁰R²¹ wherein R²⁰ and R²¹ independently represent hydrogen, alkyl, alkoxy, aryl, aralkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl and heterocycloalkylalkyl, and further wherein R⁵ may be combined with R⁶ to represent =O or =S and/or R⁷ may be combined with R⁸ to represent =O or =S;

R can represent alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl or -NR¹⁰R¹¹,

- 20 wherein R¹⁰ and R¹¹ can independently represent hydrogen, alkenyl, alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl or heterocycloalkylalkyl.

2. The compound of claim 1 wherein there is a single bond at carbon atom 11, X is CH and R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are hydrogen.
3. The compound of claim 2 wherein X<sup>1</sup>, X<sup>2</sup> and X<sup>3</sup> are bromo or chloro and  
5 X<sup>4</sup> is hydrogen.
4. The compound of claim 3 wherein R is alkyl, trifluoromethyl, alkenyl, aryl, heteroaryl or -NR<sup>10</sup>R<sup>11</sup> wherein R<sup>10</sup> and R<sup>11</sup> are independently selected from hydrogen and alkyl.  
10
5. The compound of claim 4 wherein R is alkyl and the alkyl group is substituted with trifluoromethyl.
6. The compound of claim 4 wherein R is heteroaryl and the heteroaryl group  
15 is substituted with alkyl or heteroaryl.
7. The compound of claim 1 selected from any of Examples 1-14.
8. The compound of claim 1 selected from Examples 1, 3, 4, 5, 6, 9, 10, 11  
20 and 13.
9. A pharmaceutical composition for inhibiting the abnormal growth of cells comprising an effective amount of compound of claim 1 in combination with a pharmaceutically acceptable carrier.  
25
10. A method for inhibiting the abnormal growth of cells comprising administering an effective amount of a compound of claim 1.
11. The method of Claim 10 wherein the the cells inhibited are tumor cells  
30 expressing an activated ras oncogene.
12. The method of Claim 10 wherein the cells inhibited are pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder  
35 carcinoma tumor cells or prostate tumor cells, breast tumor cells or colon tumors cells.

13. The method of Claim 10 wherein the inhibition of the abnormal growth of cells occurs by the inhibition of ras farnesyl protein transferase.
14. The method of Claim 10 wherein the inhibition is of tumor cells wherein the  
5 Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 98/11508

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 6 C07D401/04 A61K31/55 A61K31/435 A61K31/445 C07D221/16 C07D401/14 //(C07D401/14, 333:00, 261:00, 221:00), (C07D401/04, 233:00, 221:00)				
According to International Patent Classification (IPC) or to both national classification and IPC				
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07D				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)				
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>				
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	W0 95 10514 A (SCHERING CORP) 20 April 1995 see the whole document	1-14		
Y	NJOROGE F G ET AL: "NOVEL TRICYCLIC AMINOACETYL AND SULFONAMIDE INHIBITORS OF RAS FARNESYL PROTEIN TRANSFERASE" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 6, no. 24, 1996, pages 2977-2982, XP002056550 see the whole document	1-14		
-/--				
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.				
° Special categories of cited documents : <table border="0"> <tr> <td style="vertical-align: top;">           "A" document defining the general state of the art which is not considered to be of particular relevance            "E" earlier document but published on or after the international filing date            "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)            "O" document referring to an oral disclosure, use, exhibition or other means            "P" document published prior to the international filing date but later than the priority date claimed         </td> <td style="vertical-align: top;">           "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention            "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone            "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.            "&amp;" document member of the same patent family         </td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family			
Date of the actual completion of the international search		Date of mailing of the international search report		
1 October 1998		23. 10. 98		
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer  Stellmach, J		

# INTERNATIONAL SEARCH REPORT

In tional Application No  
PCT/US 98/11508

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NJOROGE F G ET AL: "DISCOVERY OF NOVEL NENPEPTIDE TRICYCLIC INHIBITORS OF RAS FARNESYL PROTEIN TRANSFERASE" BIOORGANIC & MEDICINAL CHEMISTRY, vol. 5, no. 1, 1997, pages 101-113, XP002056551 see the whole document ---	1-14
Y	BUSS J E ET AL: "FARNESYL TRANSFERASE INHIBITORS: THE SUCCESSES AND SURPRISES OF A NEW CLASS OF POTENTIAL CANCER CHEMOTHERAPEUTICS" CHEMISTRY AND BIOLOGY, vol. 118, no. 2, December 1995, pages 787-791, XP002056549 see the whole document ---	1-14
Y	WO 96 31505 A (PHARMACOPEIA INC) 10 October 1996 see the whole document ---	1-14
Y	WO 96 31478 A (SCHERING CORP ;PHARMACOPEIA INC (US)) 10 October 1996 see the whole document -----	1-14

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 98/11508

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

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 10 - 14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int: ional Application No

PCT/US 98/11508

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